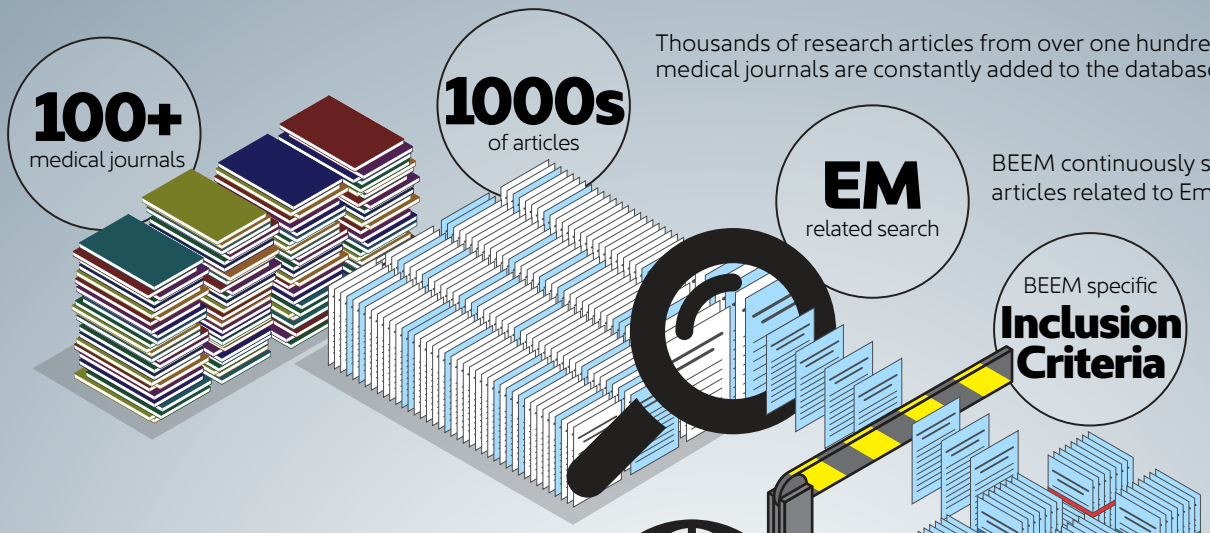

Recent
Relevant
Reliable
Unbiased
The 2021
complete edition
Better Outcomes Require
The Best Evidence
BEEM.ca
Best Evidence in Emergency Medicine
Number Needed to Read
1
NNR

The BEEM Process

Identifying the Best Evidence



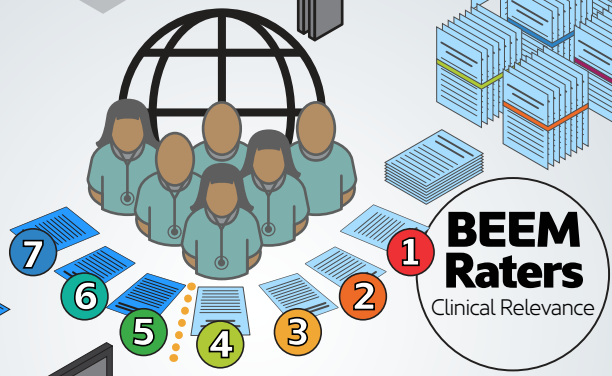
Thousands of research articles from over one hundred medical journals are constantly added to the database.

EM
related search

BEEM continuously scans for the latest articles related to Emergency Medicine.

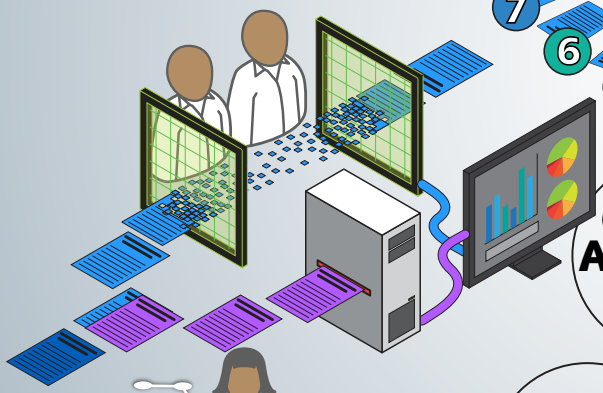
BEEM specific
Inclusion Criteria

Articles meeting the inclusion criteria are sorted by discipline and study design.



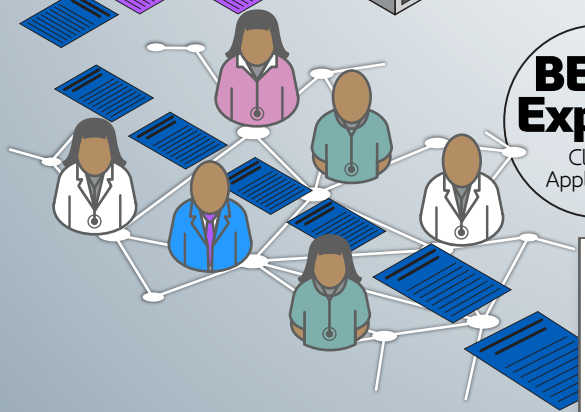
BEEM Raters
Clinical Relevance

Using only their titles and conclusions, articles are rated for their relevance to clinical practice by BEEM's international network of Emergency Physicians. Articles with a median score of 5 or better are selected for Critical Appraisal.



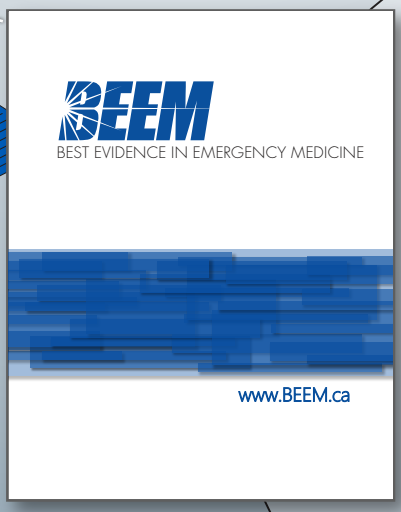
Critical Appraisal
Validity

Our in-house team of clinical epidemiologists appraises each article to identify errors and sources of bias and determine the validity of each study's results.



BEEM Experts
Clinical Applicability

Articles and critical appraisals are sent to select physicians with relevant subspecialty expertise for consensus on clinical applicability.



BEEM Manual & Events

- ☑ Recent
- ☑ Relevant
- ☑ Reliable
- ☑ Unbiased

The best evidence-based guidance for clinical practice in Emergency Medicine

Dear BEEM Attendee,

BEEM is a well-established conference that is designed to provide you with the highest levels of evidence for high impact articles related to the practice of Emergency Medicine. The sessions are categorized in different areas to cover a breadth of papers that include trauma, critical care, pediatrics, infectious diseases and cardiology to name a few. Each article is reviewed using the BEEM critical appraisal methodology to equip you with an unbiased critique.

During the conference, you will learn from experts in the field of Emergency Medicine and critical appraisal / methodology. You will have multiple opportunities to interact with the other participants as well as faculty. Please feel free to ask them any questions you have.

Sincerely,

Dr. Rahim Valani
Chair, BEEM

Dr. Suneel Upadhye
Co-Chair, Ski BEEM

Dr. Marcel Emond
Co-Chair, QueBEEM

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TRAUMA / CRITICAL CARE I

TRAUMA / CRITICAL CARE II

BEEM BITs (PART I)

Research Question

What ED interventions are beneficial to improve health outcomes in homeless patients?

BEEM Bottom Line

Why is this study important? Homeless patients suffer from more chronic illnesses, poorer health outcomes and access to primary care compared to housed citizens. They use the ED (frequently) for many primary care concerns, and may not benefit from continuity of care for chronic conditions. Getting such patients into stable housing and access to health services can optimize health outcomes and resource utilization.

Which, if any, threats to validity are most likely to have an impact on the results and how? The heterogeneity of ED interventions and outcomes precludes the ability to pool study results. There is also inherent and variable risk of bias associated with these challenging pragmatic study designs. There is some concern for bias regarding data extraction and risk bias assessment probably slightly favouring intervention.

How do the key results compare with the current evidence? Congruence with prior studies/reviews showing a benefit for early ED interventions to connect homeless patients with stable housing and essential community social services.

How should this study impact the care of ED patients? Intensive case management that focusses on stable housing and connection to primary care services can lead to optimal social/health outcomes. This will require sustained significant funding, resources, and interprofessional collaboration. The costs of such, however, may be offset by improved health outcomes and less ED utilization.

Suneel Upadhye, MD MSc FRCPC
Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact (HEI), McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Chloe Bedard, PhD
Health Research Methods, Evidence & Impact (HEI), McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Formosa EA, Kishimoto V, Orchanian-Cheff A, *et al.* Emergency department interventions for homelessness: a systematic review. CJEM 2021, 23: 111-122. https://doi.org/10.1007/s43678-020-00008-4

Design: Systematic review of intervention trials. *A priori* decision NOT to meta-analyze results due to anticipated clinical and methodological heterogeneity.

Population: *Included:* Patients experiencing homelessness in >50% of study populations.
Excluded: Studies with ED return visits and/or hospital costs

Intervention: Interventions initiated in the ED aimed at social determinants of health. All studies in North America.

Comparison: Usual care (not all studies).

Outcomes: *Changes in housing status, substance use disorder variables, access to primary care.*

Key Results: *13 studies included; 6 RCTs, 3 non-randomized studies, 4 pre/post interventional studies*

Case-management with an emphasis on “housing first” resulted in successful housing in >90% recipients (8 studies).

Case-management targeting substance use had variable results, from zero change in opioid risk to 70% alcohol use reduction.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓
3. The search for studies was unbiased and reproducible.	✓	X
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	X
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	X
7. The quality of the primary studies is high.	?	X
8. The methods used to combine the included primary studies were reported and valid.	X	✓
9. The outcomes are clinically relevant.	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	n/a

A1 = S. Upadhye A2 = C Bedard

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: None.

Selection Bias: While the search strategy appears sufficiently comprehensive, the specific search terms were not provided prohibiting reproducibility.

Measurement Bias: Data extraction and risk of bias assessment was conducted by only one author, therefore there is some concern for bias. No raw data available from individual studies for quantitative analyses. Mixed results of quality assessments for study risk of bias. Small sample sizes for most studies.

Analysis Bias: The short length of interventions and follow-ups make it difficult to ascertain sustainability of interventions (1-24mo).

Confounding: Practical limitations in conducting trials with homeless populations and relevant interventions (e.g. Blinding, co-interventions). Heterogeneity in interventions and other study elements make it difficult to pool/aggregate study results.

Administrative Details

Key Words: Social health determinants, homelessness

Appraisers: Upadhye S, Bedard C.

Reference(s): Formosa EA, Kishimoto V, Orchanian-Cheff A, Hayman K. Emergency department interventions for homelessness: a systematic review. CJEM 2021, 23: 111-122. https://doi.org/10.1007/s43678-020-00008-4

Research Question

Is there

BEEM Bottom Line

Why is this study important? Patient care equity in ED is paramount, yet is often lacking in various areas of care (eg. Analgesia, Dx testing, etc.). This study explores equity differences in ED imaging based on race/ethnicity.

Which, if any, threats to validity are most likely to have an impact on the results and how? Substantial heterogeneity amongst included studies precluded pooling of data for summary estimates. Limited search for articles may have missed some important studies (non-English, non-USA).

How do the key results compare with the current evidence? The results of this review mirror other studies showing disparities in patient care based on race/ethnicity (eg. ED analgesia/opioid use). These results also seem to extend to imaging decisions for children, although the drivers for such decisions may be different between adults & children.

How should this study impact the care of ED patients? Unconscious implicit bias and other motivators may influence how ED practitioners manage their patients. It is critical for ED staff to be aware of unconscious/other biases in evaluating and treating patients, in order to optimize equitable patient outcomes.

Suneel Upadhye, MD MSc FRCPC
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Shan A, Baumann G, Gholamrezanezhad A. Patient Race/Ethnicity and Diagnostic Imaging Utilization in the Emergency Department. J Am Coll Radiol 2020; 18(6): P795-808. https://doi.org/10.1016/j.jacr.2020.12.016

Design: "Systematic" review of observational studies exploring ethnicity/race associations with ED imaging. The methodology is more consistent with a scoping review, not full systematic review.

Population: *Included:* Imaging rates for ED adult and pediatric patients.
Excluded: Non-primary literature, case reports, non-English publications.

Intervention: Imaging rates between white and non-white/Hispanic patients (various indications).

Comparison: N/A

Outcomes: *Primary:* Imaging rates in various ethnic/race groups.
Secondary: Subgroup analyses based on disease severity, triage levels, clinical scenarios (eg. Abdominal pain, chest pain, headache/head injury, etc.), adult vs. pediatric.

Key Results: 42 studies included (41 US, 1 Canada). Sample sizes 155-2 million pts.

Sig.	*Outcome*	
NSS	Secondary	Mixed results on race/ethnicity differential imaging rates for head injury (adults & pediatric). Disease severity, triage level, insurance status not necessarily associated with differential imaging rates. No imaging differences amongst adults with stroke. Less associations with differential utilization of US, MRI (various indications).
SS	Primary	71% of included studies reported various degrees of decreased imaging rates for non-white and Hispanic patients (10-50% less likely); OR range 0.21-0.92. Adult black patients less likely to receive ED imaging relative to Hispanics, depending on clinical condition; more likely different for abdo pain, less for head injury/stroke. Strong association of decreased imaging for non-white/Hispanic/black children across various clinical conditions (abdo pain, trauma). Strong associations with differential utilization of CT, Xray.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	X
7. The quality of the primary studies is high.	?
8. The methods used to combine the included primary studies were reported and valid.	X
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None declared.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None?

Selection Bias: Limited search of English language studies from 3 electronic databases. No analysis for publication bias. Nearly all studies conducted in USA (31/32).

Measurement Bias: No quality assessments for included studies described/reported.

Analysis Bias: Heterogeneity of classification categories of race/ethnicity in included studies. No quantitative reporting of imaging rates from individual studies, no pooled data analysis.

Confounding: Various biases associated with different study designs, survey samples, etc. Lack of information of provider-level decision-making, or on availability of primary care services for white vs non-white populations, language barriers/cultural differences or parental values/preferences for imaging children.

Administrative Details

Key Words: Diagnostic imaging, ethnicity/race, health equity, utilization.

Appraisers: Upadhye S.

Reference(s): Shan A, Baumann G, Gholamrezanezhad A. Patient Race/Ethnicity and Diagnostic Imaging Utilization in the Emergency Department. J Am Coll Radiol 2020; 18(6): P795-808.

https://doi.org/10.1016/j.jacr.2020.12.016

Research Question

What is the prevalence and impact of work-place violence (WPV) in the emergency department?

BEEM Bottom Line

Why is this study important? Workplace violence (WPV) in the ED is a serious threat to ED staff health and well-being.

Which, if any, threats to validity are most likely to have an impact on the results and how? Limited search, data abstraction & quality assessment cause uncertainty in the thoroughness and fidelity of analyses completed. Lack of universal definitions of different types of WPV can lead to classification heterogeneity.

How do the key results compare with the current evidence? The current results mirror similar past studies looking at WPV in different workplaces.

How should this study impact the care of ED patients? Workplace violence is a common and serious problem in the ED, against both nurses and physicians. There is an urgent need for more standardized research into WPV causes/instigators and solutions to mitigate risks of injury/burnout amongst ED staff victims.

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Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact (HEI), McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Aljohani B, Burkholder J, Tran QK, *et al*. Workplace violence (WPV) in the emergency department: a systematic review and meta-analysis. Public Health 2021; 196: 186-197. DOI: 10.1016/j.puhe.2021.02.009

Design: Systematic review and meta-analysis of survey studies on WPV prevalence and causes.

Population: *Included:* Studies of adult patients with WPV against ED staff, and instigators of such ED WPV.
Excluded: Studies not reporting WPV against ED staff, prehospital personnel. Also excluded studies reporting domestic violence prior to ED arrival, or involving drugs/alcohol/psychiatric illness. Case reports, editorials and opinion articles also excluded.

Intervention: N/A.

Comparison: N/A.

Outcomes: *Primary:* Prevalence of WPV violence.
Secondary: Countries of origin, types of WPV, instigators, WPV victim professions (physicians, nurses, other).

Key Results: *26 studies included, 5792 health care workers (HCWs) survey respondents.*

Outcome	*Studies*	*Prevalence (95% CI)*	I^2
Verbal violence (overall)	21	0.77 (0.72-0.82); physicians 0.74 (0.520-0.88), nurses 0.75 0.67-0.82)	97%
Patient instigator	13	0.24 (0.18-0.31); 0.28 (0.19-0.38) vs nurses, 0.15 (0.09-0.24) vs physicians	93%
Types of WPV	21	Verbal 72.5%, physical 18.1%, other 9.5% (stalking, sexual harassment)	
Overall instigators	13	Family members 52%, patients 27.2%, "others" 20.8% (other relatives/friends)	

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	?
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	?
7. The quality of the primary studies is high.	?
8. The methods used to combine the included primary studies were reported and valid.	✓
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (declared).

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: None?

Selection Bias: None or enter text here (incomplete search, publication bias, etc.). Limited search of electronic databases (PubMed, SCOPUS). Unclear data abstraction process/personnel.

Measurement Bias: All studies based on surveys of health care worker WPV victims. No universal definition of abuse/assault/bullying between various studies. No quality assessment tools reported for included studies.

Analysis Bias: Random effects models used for pooled data analysis, esp with high heterogeneity studies.

Confounding: Risk of recall bias when surveying victims for WPV experiences. Interpersonal bias based on different perceptions of threat/confrontation based on age/gender/race/other attributes, which may affect objective reporting of WPV incidents.

Administrative Details

Key Words: Instigator, healthcare workers, workplace violence.

Appraisers: Upadhye S.

Reference(s): Aljohani B, Burkholder J, Tran QK, Chen C, Beisenova K, Pourmand A. Workplace violence in the emergency department: a systematic review and meta-analysis. Public Health 2021; 196: 186-197. DOI: 10.1016/j.puhe.2021.02.009

Research Question

Is supplemental hearing assistance useful to ED geriatric patients ?

BEEM Bottom Line

Why is this study important? The emergency department (ED) presents one of the most challenging listening situations in clinical medicine, especially for the older hearing-impaired patient. Poor communication is a barrier to care for older people with hearing loss.

Which, if any, threats to validity are most likely to have an impact on the results and how? This pilot study isn't powered to detect small differences in the validated outcome instruments. Veterans may benefit from different health care resources than regular ED population. Unblinding of professionals could have modified their approach to the patient with personal amplifier.

How do the key results compare with the current evidence? As a first study on PA in the ED, these results correlate with similar study in other settings as reported in a review by Mamo *et al*.

How should this study impact the care of ED patients? The benefit of PA in the ED is mainly about decreasing "cognitive fatigue or competition". The listening efforts without PA can engage cognitive resources and competes with other cognitive task such as memory and language processing. The latter are prerequisite to a good understanding of the older patient health conditions or treatment.

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Associate professor, Université Laval.
No conflicts of interest/Identify conflicts (ICMJE)

AUTHOR 2 Enter name and credentials here
Enter professional positions held here
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Chodosh J, Goldfeld K, Weinstein BE, et al. The HEAR-VA Pilot Study: Hearing Assistance Provided to Older Adults in the Emergency Department. J Am Geriatr Soc. 2021 Apr;69(4):1071-1078. doi: 10.1111/jgs.17037. Epub 2021 Feb 11.

Design: Prospective, randomized controlled pilot study.

Population: *Included:* Adults ≥ 60, English speaking, Emergency Severity Index category 4 and 5 (3 on occasion). Handicap Inventory (HHI-S)> 10 or self-reported hearing difficulties.
Excluded: patients with unstable and life-threatening situation.

Intervention: Personal amplifier (PA) during ED length of stay (as early as possible).

Comparison: Standard care.

Outcomes: *Primary:* Three validated instruments (Hearing and Understanding Questionnaire (HUQ), Care Transitions Measures (CTM-3), Patient Understanding of Discharge Information (PUDI).
Secondary: Return to ED (up to 30 days).

Key Results: *N* = 133 patients (Intervention=66, Control= 67).

Sig.	*Outcome*	*Intervention*	*Control*	*ARR (95% CI)*	*NNT (95% CI)*
NSS	Voices "clearer"	62/66	60/67	4.9 (-4.3; 13.7)	Not estimable
SS	Understand without effort	50/66	38/67	19.0 (3.3; 34.7)	5
SS	Understand management of health	64/66	56/67	10.8 (1.4; 20.1)	9
NSS	3-days RTED	2/66	6/67	6.2 (-1.9;14.4)	Not estimable
NSS	30-days RTED	15/66	18/67	3.4 (-11.2; 17.8)	Not estimable

ARR = absolute risk reduction (if the CI includes the value 0, there is no difference in risk between the groups and the NNT is not estimable); CI = confidence interval; *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.
*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	X	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	?✓X	?✓X
3. The allocation sequence was adequately concealed.	✓	?✓X	?✓X
4. The patients in all groups were similar with respect to prognostic factors.	X	?✓X	?✓X
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	?✓X	?✓X
6. All groups were treated equally except for the intervention.	✓	?✓X	?✓X
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	?✓X	?✓X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	?✓X	?✓X
9. All patient-important outcomes were considered.	✓	?✓X	?✓X
10. The effect size of the primary outcome is clinically significant.	?	?✓X	?✓X

A1 = M. Émond A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Private foundation & Veteran's merit award

Conflicts of Interest: None reported

Potential Threats to Validity

Chance: None

Selection Bias: Using self-reported hearing difficulties as eligibility criteria and discharged patient could lead to a lower handicap group of patients.

Measurement Bias: Unblinding of ED professionals could introduce a Hawthorne bias. Validated tools used for main outcome. Some surveys done post-discharge during a phone follow-up call.

Analysis Bias: ITT, No power calculation – pilot study.

Confounding: Presence of family in ED was more prevalent in the intervention group.

Administrative Details

Key Words: Older patients; Hearing disabilities; Discharge instructions.

Appraisers: Emond, M;

Reference(s):

1. Vincent CA, Wears RL. Communication in the emergency department. MedJ Aust. 2002;176(9):409-410.
2. Baevsky R. Sound levels in the emergency department setting. Acad Emerg Med. 2006;13(2):233.
3. Mamo SK, Reed NS, Nieman CL, Oh ES, Lin FR. Personal Sound Amplifiers for Adults with Hearing Loss. *Am J Med*. 2016;129(3):245-250.

Research Question

Are self-obtained vaginal swabs sufficiently accurate for diagnosing sexually transmitted diseases in the ED?

BEEM Bottom Line

Why is this study important? Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) testing is often performed in ED, and can be challenging in busy/overcrowded situations, or where patient privacy/preference is compromised. Self-obtained vaginal swab (SOVS) could improve patient and ED management since they are non-inferior to physician-performed endocervical sampling (PPES). In this study, 75% of patients preferred SOVS to PPES.

Which, if any, threats to validity are most likely to have an impact on the results and how? The study was conducted in ED with a convenience sample of specific US population (English and Spanish speaking) leading to its application in a similar setting.

How do the key results compare with the current evidence? SOVS performed as well as PPES in this ED setting. The results are congruent with previous reports in family medicine/gynecologic clinics where SOVS was validated for NG/CT screening.

How should this study impact the care of ED patients? SOVS can be used alternatively to obtain NG/CT testing in the ED when a pelvic clinical examination may not be warranted or nor useful to patient care. Sensitivities of the SOVS are non-inferior to the PPES ones, and the diagnostic likellihood ratios are outstanding for ruling in/out disease.

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Associate professor, Université Laval
No conflicts of interest

S. Upadhye, MD MSc FRCPC
Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest (ICMJE)

Study Summary

Article: Chinnock B, Yore M, Mason J, et al. Self-obtained vaginal swabs are not inferior to provider-performed endocervical sampling for emergency department diagnosis of Neisseria gonorrhoeae and Chlamydia trachomatis. Acad Emerg Med. 2021 Jun;28(6):612-620. doi: 10.1111/acem.14213. Epub 2021 Mar 24. PMID: 33460481.

Design: Prospective observational cohort study. Non-inferiority design.

Population: *Included:* Female (English and Spanish speaking) patients ≥ 18 years old needing NG/CT testing as per the ED physician. 2018 to 2020
Excluded: Inmates, acute psychiatric conditions, non-English/Spanish language, and use of NG/CT treatment in the preceding 4 weeks.

Index Test(s): Self-obtained vaginal swab (SOVS) following a brief one-page instruction form (no additional assistance by ED staff). NG/CT tests by rapid nucleic acid amplification test (NAAT).

Reference Test(s): Provider-performed endocervical sampling (PPES). NG/CT tests by NAAT assay.

Outcomes: *Primary:* Sensitivity of no less than 90% for the composite NG/CT diagnosis by SOVS compare to PPES.
Secondary: Sensitivity for NG and CT specifically. Patients' acceptability of SOVS.

Key Results: *N* = 515 out of 533 enrolled (86 (17%) positive to NG, CT or both).

Sig.	*Outcome*	*Result Report LR, Sens & Spec*
SS	Composite NG/CT	Sensitivity = 95 (95% CI: 88 to 99)
SS	Composite NG/CT	Specificity = 99 (95% CI: 97 to 100)
		***LR+ 83 (34-198), LR- 0.05 (0.02-0.13)**
SS	NG only	Sensitivity = 97 (95% CI: 87 to 100)
SS	NG only	Specificity = 100 (95% CI: 99 to 100)
SS	CT only	Sensitivity = 94 (95% CI: 84 to 99)
SS	CT only	Specificity = 99 (95% CI: 98 to 100)
	AUC: not available	
SS	Patients' preference SOVS vs PPES	P = 75%

AUC = Area Under the Curve; CI = Confidence Interval; LR = Likelihood Ratio; *N* = number of patients; NA = not applicable; NSS = Not Statistically Significant; *p* = probability; Sig. = Significance; SS = Statistically Significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The patients were representative of those likely to undergo testing in the ED.	✓	✓
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	X	?
3. All patients underwent the same diagnostic evaluation.	✓	✓
4. All tests were conducted within similar time frames to preclude changes in disease status.	✓	✓
5. The reference standard criteria for the candidate diagnoses are explicit and reproducible.	?	?
6. The reference standard was applied regardless of and blinded to the index test result.	✓	✓
7. The assignment of the candidate diagnoses was explicit and reproducible.	✓	✓
8. Most (> 80%) patients received a diagnosis.	✓	✓
9. Undiagnosed patients received adequate clinical follow-up.	?	?
10. The estimates of disease probability are clinically significant.	✓	✓

A1 = M. Émond A2 = S. Upadhye

Funding & Conflicts of Interest

Funding: Local funding – University of California San Francisco-Fresno research fund

Conflicts of Interest: None.

Potential Threats to Validity

Chance: None.

Selection Bias: Convenient sample; may lead to sampling bias (missing different patients/demographics during night hours?). Patient were eligible by MD need to test. Refusal were more prone to have PPES.

Measurement Bias: Low: 15/533 patients were removed for incomplete samples. 3 for indeterminate results. Overall enrollment goal was not met (due to COVID19 pandemic cessation of study), but required sample size of 80+ positive cases was met.

Analysis Bias: Low: To be a true positive at the composite outcome NG/CT, concordance needed to be 100%

Confounding: Patients who declined enrollment : Too unwell/painful (36%), 26% procedural uncertainty (uncomfortable with SOVS, concerned about procedural error, prefer PPES = 17%).

Administrative Details

Key Words: Sexually transmitted disease (STD); vaginal swab.

Appraisers: Emond M, Upadhye S.

Reference(s):

1. Lunny C, Taylor D, Hoang L, et al. Self-Collected versus Clinician-Collected Sampling for Chlamydia and Gonorrhea Screening: A Systemic Review and Meta-Analysis. PLoS One. 2015 Jul 13;10(7):e0132776. doi: 10.1371/journal.pone.0132776. PMID: 26168051; PMCID: PMC4500554.

Research Question

Is antacid therapy alone more effective than combined with lidocaine in relieving epigastric pain?

BEEM Bottom Line

Why is this study important? Epigastric pain is a common presenting problem in the emergency department (ED). With a broad differential, the clinician has to exclude several life-threatening causes and manage the patient's symptoms while awaiting test results. Not infrequently, a trial of antacids with or without local anesthetic is used for pain relief. This study looked at monotherapy antacid versus combination with lidocaine for symptom management.

Which, if any, threats to validity are most likely to have an impact on the results and how? This study is limited by the small sample size which makes possible chance imbalances in prognostic factors between the trial arms. There is also potential for selection bias caused by insufficient blinding of patients and confounding due to differences in doses of antacid between the arms. Further, the results of the trial are too imprecise to allow any confident conclusions regarding the non-inferiority of antacid and antacid/lidocaine mixtures, as inferred by the trial authors.

How do the key results compare with the current evidence? While combined antacid and local anesthetic therapy has been used to relieve patient symptoms, this should not be used as a diagnostic tool to rule out other causes of epigastric pain. In this study, 14% of patients were found to have cardiac pathology. The last published study for treatment of acute dyspepsia in the ED similar to this was a randomized trial of 113 patients that compared three treatments: antacid alone, antacid with Donnatal and antacid with Donnatal and viscous lidocaine.[1] The result showed no statistically significant difference in pain relief i.e., change in visual analog scale (VAS), between the three groups after 30 minutes.

How should this study impact the care of ED patients? This study reconfirms that antacid monotherapy is just as effective for epigastric pain relief as combination therapy. The clinic must be cognizant of other factors causing the patients symptoms, and in particular be aware of cardiac causes for the pain.

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No conflicts of interest (ICMJE)

Study Summary

Article: Warren J, Cooper B, Jermakoff A, et al. Antacid Monotherapy Is More Effective in Relieving Epigastric Pain Than in Combination With Lidocaine: A Randomized Double-blind Clinical Trial [published online ahead of print, 2020 Jun 29]. Acad Emerg Med. 2020;10.1111/acem.14069. doi:10.1111/acem.14069

Design: Single-center (Melbourne, Australia), blinded, randomized, controlled, superiority trial

Population: *Included:* Adults (≥ 18 years) prescribed an antacid/lidocaine mixture in ED for epigastric discomfort.

Excluded: Patients unable to consent.

Intervention: 1) Gastrogel (Aspen Pharma: aluminum hydroxide gel equivalent to 500 mg, magnesium trisilicate 240 mg and magnesium hydroxide 240 mg per 500 ml) 10 ml and lidocaine 2% viscous gel (Perrigo) 10 ml given as a single oral dose together or 2) Gastrogel 10 ml and lidocaine 2% solution (Pfizer) 10 ml given as a single oral dose together.

Comparison: Gastrogel 20 mL (i.e. double intervention dose) as a single oral dose. (NB: recommended dose is 10 to 20 mL)

Outcomes: *Primary:* Pain reduction 30 minutes post treatment via 100 mm VAS from baseline (minimum clinically important difference = 13 mm).
Secondary: Pain reduction and medication palatability (taste, bitterness, texture, and overall acceptability) using a VAS and change in pain score 60 minutes post treatment.

Key Results: *N* = 89 patients (30 lidocaine viscous; 31 lidocaine solution; 28 Gastrogel 20 mL).

Sig.	*Outcome*	*+ Lido Viscous*	*+ Lido Solution*	*Gastrogel 20 mL*	**P-value*
NSS	Change in pain VAS (IQR) @ 30 min	9 (3 to 26)	17 (7 to 27)	20 (7 to 36)	0.30
NSS	Change in pain VAS (IQR) @ 60 min	21 (3 to 31)	26 (9 to 41)	32 (13 to 42)	0.18
SS	Taste VAS (IQR)	37 (12 to 62)	29 (15 to 50)	76 (34 to 88)	<0.01
SS	Overall acceptability VAS (IQR)	50 (32 to 79)	57 (50 to 73)	75 (50 to 89)	0.01

CI = confidence interval; IQR = interquartile range; Lido = lidocaine 2%; min = minutes; *N* = number of patients; NSS = not statistically significant; *P* = probability; Sig. = significance; SS = statistically significant. *P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	X	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	?	?	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Royal Melbourne Hospital, Victoria, Australia.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: The trial is small and hence chance imbalances in prognostic factors between trial arms is plausible.

Selection Bias: Patients were eligible if they were prescribed an antacid/lidocaine mixture. Physicians' decision to prescribe an antacid/lidocaine mixture vs. antacid only may be affected by the suspected effectiveness in the particular patient. This may have biased results in favor of the antacid/lidocaine mixtures.

Measurement Bias: Outcomes were patient-reported and patients were not sufficiently blind to the intervention.

Analysis Bias: The trial is powered for a superiority analysis but concludes non-inferiority of antacid to antacid/lidocaine mixtures. The results of this trial are too imprecise to allow confident conclusions on non-inferiority.

Confounding: The antacid group received twice the dose of antacid in comparison to the antacid/lidocaine mixture groups.

Administrative Details

Key Words: Antacid; dyspepsia; epigastric pain; lidocaine; xylocaine.

Appraisers: Zeraatkar D; Worster A; Valani R.

Reference(s):

1. Berman DA, Porter RS, Graber M. The GI Cocktail is no more effective than plain liquid antacid: a randomized, double blind clinical trial. J Emerg Med. 2003;25(3):239-244.

Research Question

What are the effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding?

BEEM Bottom Line

Why is this study important? Tranexamic acid (TXA) has been studied to control bleeding in trauma, postpartum hemorrhage and surgery. Small randomized controlled trials (RCT) have examined TXA as an adjunctive therapy in gastrointestinal bleeding (GIB). This HALT-IT RCT aimed to definitively determine the safety and efficacy of TXA for GIB with mortality as the primary outcome.

Which, if any, threats to validity are most likely to have an impact on the results and how? The investigators amended the primary outcome during the trial from all-cause mortality to mortality secondary to re-bleeding at 5 days. Although the change was disclosed, there is a direct impact to the outcome but with minimal impact on the validity of the results. Second, TXA is most effective when given < 3 hours of bleeding onset as previously exemplified.[1,2] However, in this HALT-IT trial, > 80% of patients presented > 3 hours after bleeding onset. Last, half of the participants in HALT-IT had variceal bleeding and accounted for three-quarters of the deaths. Even though, there was no significant subgroup effect, patients with liver disease may respond differently to anti-fibrinolytics and may have driven the trial results.

How do the key results compare with the current evidence? A Cochrane systematic review and meta-analysis of 8 RCTs including 1,701 participants showed a large reduction in mortality (relative risk [RR] = 0.61; 95% confidence interval [CI] 0.42 to 0.87) with TXA in GIB with no difference in venous thromboembolic (VTE) events.[3] Compared with HALT-IT, these trials were smaller and underpowered. The TXA dose used in HALT-IT was higher and administration longer than in other TXA for GIB trials. In contrast, HALT-IT provides robust evidence that TXA does not impact mortality (RR 0.99; 95% CI 0.82 to 1.18) or transfusion (RR 0.99; 95% CI 0.97 to 1.02) in patients with GIB. In addition, TXA led to an increased risk of VTE (RR 1.85; 95% CI 1.15 to 2.98) and seizures (RR 1.73; 95% CI 1.03 to 2.93).

How should this study impact the care of ED patients? In adults with severe GIB, the balance of risks and benefits does not support routine administration of TXA.

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No conflicts of interest (ICMJE)

Study Summary

Article: HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10241):1927-1936.

Design: Multicenter (164 hospitals in 15 countries), randomised, blinded, placebo-controlled, superiority trial.

Population: *Included:* Adults (≥ 16 years) with severe gastrointestinal bleeding at risk of bleeding to death (i.e. unstable vital signs or likely to need transfusion or urgent endoscopy or surgery).
Excluded: Patients were only enrolled if the responsible clinician was substantially uncertain whether to use TXA; all other patients were excluded.

Intervention: TXA 1 g in sodium chloride 0.9% solution 100 ml intravenously (IV) over 10 minutes then TXA 3 g in 1 L of any isotonic IV solution at 125 mg/hour(h) for 24 h.

Comparison: Sodium chloride 0.9% solution 100 ml intravenously (IV) over 10 minutes then any isotonic IV solution at same rate as above for 24 h.

Outcomes: *Primary:* Death due to bleeding within 5 days (d) of randomization.
Secondary: Death due to bleeding within 24 h and within 28 d; all-cause and cause-specific mortality at 28 d; rebleeding within 24 h, 5 and 28 d; thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction).

Key Results: *N* = 12,009 patients.

Sig.	*Outcome*	*Intervention*	*Control*	*RR (95% CI)*
NSS	Death due to bleeding ≤ 5 d	222 (3.7%)	226 (3.8%)	0.99 (0.82 to 1.18)
NSS	Death due to bleeding ≤ 28 d	253 (4.2%)	262 (4.4%)	0.97 (0.82 to 1.15)
NSS	Rebleeding ≤ 5 d	287 (4.8%)	315 (5.3%)	0.91 (0.78 to 1.07)
NSS	Rebleeding ≤ 28 d	410 (6.8%)	448 (7.5%)	0.92 (0.81 to 1.05)
NSS	Any thromboembolic event	86/5952 (1.4%)	72/5977 (1.2%)	1.20 (0.88 to 1.64)

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference between the groups and the NNT is not estimable); Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	?	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	?	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: UK National Institute for Health Research Health Technology Assessment Programme.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: While this study appears to have met the sample size target, there were too few events to establish clinical equivalence, thus it cannot rule out possible modest positive or negative treatment effects.

Selection Bias: Details regarding the sampling method are missing, therefore, it is uncertain whether patients were recruited consecutively.

Measurement Bias: The primary outcome involves a degree of subjectivity with respect to determining the cause of bleeding, therefore, misclassification error is a risk; however, given that the randomization assignment was blinded it is unlikely to be biased towards either group.

Analysis Bias: The primary analysis was a modified intention-to-treat analysis, excluding patients who did not receive either treatment as well as those who did not have outcome data. However, the proportion of those excluded from the modified ITT were equal between groups, therefore, it is unlikely to have biased the results. This was a multi-centre international trial without any indication that the analyses accounted for clustering at any level; hence, the precision of the effects may be overestimated.

Confounding: The timing of TXA administration with the onset of gastrointestinal bleeding and the predominance of patients with liver disease in the population may be potential confounders.

Administrative Details

Key Words: Antifibrinolytic; gastrointestinal bleeding; tranexamic acid; venous thromboembolism.

Appraisers: Bedard C; Worster A; Dionne JC.

Reference(s):

1. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.
2. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial [published correction appears in Lancet. 2017 May 27;389(10084):2104]. Lancet. 2017;389(10084):2105-2116.
3. Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database Syst Rev 2012;1: CD006640.

Research Question

From a patient's perspective, are antibiotics "just as good as" surgery for appendicitis?

BEEM Bottom Line

Why is this study important? Large, high quality randomized controlled trials (RCTs) have demonstrated the safety of antibiotic treatment for uncomplicated (without rupture or localized peritonitis) appendicitis, yet this approach has not been adopted in North American practice.[1,2] With the COVID-19 pandemic, treatment options without hospitalization are being more widely considered.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this study were limited by the open-label nature of the study, a short follow-up period (only 90 days) and selection bias (only 30% of eligible patients were enrolled). This could have influenced the results if patients were preferentially offered one treatment over another by different providers. Additionally, complications after 90 days are not captured.

How do the key results compare with the current evidence? This study's results are comparable to previously published series as they had similar rates of perforated appendicitis.[1,2] However, in this trial, laparoscopic procedures were used more frequently, and almost 50% of patients in antibiotic group were discharged home after single dose of intravenous (IV) antibiotics in the emergency department (ED) and 70% avoided surgery and, hence, receive treatment at home, and return to work faster.

How should this study impact the care of ED patients? Much like the management of acute diverticulitis shifted away from surgical treatment decades ago, we may see a trend towards outpatient antibiotic therapy for acute uncomplicated appendicitis. At a minimum, ED providers should engage in a shared decision with patients about what matters to them. This can occur in conjunction with surgeons or prior to their involvement. This trial adds good evidence that out-patient treatments may be reasonable for providers and patients, as long as both parties understand the potential risks and benefits.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: CODA Collaborative, Flum DR, Davidson GH, et al. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. N Engl J Med. 2020 Oct 5. doi: 10.1056/NEJMoa2014320.

Design: Multicenter (25 USA emergency departments), pragmatic, nonblinded, noninferiority, randomized controlled trial.

Population: *Included:* Consecutive English- or Spanish-speaking adults (≥ 18 years) with clinical signs of acute, uncomplicated appendicitis (AUA) confirmed by imaging (computed tomography [CT], ultrasound [US], and/or magnetic resonance imaging [MRI]).
Excluded: Evidence of sepsis; altered immune response or at risk for bacterial seeding; uncompensated liver failure; actively treated inflammatory bowel disease, malignancy, dialysis, bacterial infection, illness requiring hospital admission, allergy to all proposed antibiotics; abdominal or pelvic surgery ≤ 90 days; surgical implant insertion ≤ 90 days; possible or planned pregnancy; imaging evidence of suspicious mass; prior enrollment; prisoner; unable or unavailable to participate.

Intervention: Antibiotics (Cefoxitin, Ertapenem, Moxifloxacin, Tigecycline, Ticarcillin-Clavulanic Acid, Metronidazole plus Cefazolin, Cefuroxime, Ceftriaxone, Cefotaxime, Ciprofloxacin, or Levofloxacin) for ≥ 24 hours IV (e.g. q8, q12, or q24 hour with or without concurrent oral antibiotics) followed by oral antibiotics for maximum 10 days.

Comparison: Appendectomy via open or laparoscopic approach and a single dose of antibiotics as per current standards.

Outcomes: *Primary:* Mean difference (MD) in patient-reported quality of life, as measured by the European Quality of Life–5 Dimensions (EQ-5D) at 30 days.
Secondary: Days until resolution of appendicitis; rates of perforated appendicitis; complications from treatment including National Surgical Quality Improvement Program (NSQIP)–defined complications.

Key Results: *N* = 1552 adults (mean age 38 years; 37% female; 414 [26.7%] with an appendicolith).

Sig.	*Outcome*	*Antibiotics*	*Appendectomy*	*Measure (95% CI)*
NSS	30-day EQ-5D scores	0.92 +/− 0.13	0.92 +/− 0.13	MD = 0.01 (−0.001 to 0.03)
NSS	30-day symptom resolution	462/676 (68%)	466/663 (70%)	RR = 0.97 (0.91 to 1.04)
SS	≥ 1 NSQIP-defined complication	37/676 (5%)	21/656 (3%)	RR = 1.72 (1.02 to 2.90)
SS	≥ 1 NSQIP-defined complication + appendicolith	26/183 (14%)	5/169 (3%)	RR = 4.80 (1.89 to 12.22)

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X	X	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser; ITT= intention to treat.

Funding & Conflicts of Interest

Funding: Patient-Centered Outcomes Research Institute.

Conflicts of Interest: None listed.

Potential Threats to Validity

Chance: The study appears to be sufficiently powered for a non-inferiority analysis on the primary outcome.

Selection Bias: The participants were recruited consecutively however, about 3% of eligible participants were not enrolled because they could not be approached within 7 hours. Another 96 participants were considered ineligible at the discretion of the clinical team, however it is unclear what criteria were used other than the prespecify exclusion criteria. Nonetheless, these factors likely only limited generalizability rather than selection bias since randomization was executed appropriately and allocation was concealed.

Measurement Bias: The nonblinded nature of the study in combination of the subjectivity of the primary outcome increases the risk of detection bias. Additionally, the management of pain and/or recurrent appendicitis or symptoms was not standardized nor measured, and it may have differed between study arms, therefore the risk of performance bias is also high.

Analysis Bias: Approximately 11% of patients in the antibiotic group crossed over into the appendectomy group thereby biasing the results towards the null; this is particularly problematic in a non-inferiority trial. However, the per-protocol analysis was robust to this contamination so it may not have resulted in a large bias.

Confounding: There may have been differences in care provided in the ED or during admission related to the allocated treatment especially considering that appendectomy has been the standard of care for appendicitis.

Administrative Details

Key Words: Antibiotics, appendectomy, appendicitis, appendicolith.

Appraisers: Bedard C; Worster A; Rosenfield D.

Reference(s):

1. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015; 313: 2340-8.
2. Ehlers AP, Talan DA, Moran GJ, et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis. J Am Coll Surg. 2016 Mar;222(3):309-14.

Research Question

Which variables are most associated with potentially missed appendicitis in the emergency department?

BEEM Bottom Line

Why is this study important? Diagnostic errors are a source of a preventable harm, and appendicitis is the most common surgical emergency to be assessed in the emergency department (ED). Identifying factors in systematic diagnostic error in a large cohort may yield useful information to prevent future misdiagnosis of appendicitis and ultimately, prevent harm.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this study are primarily limited by the lack of detailed individual patient data to differentiate between those who did not have appendicitis at the index visit and those whose appendicitis was missed. Misclassification of diagnostic codes and symptoms are also possible. Importantly, the study evaluated a symptom-based algorithm using discreet fields from an insurance database to test its hypothesis, excluding historical and clinical exam variables known to have high likelihood ratios for appendicitis.[1] Finally, the study used data from a single private insurance provider and so may have limited geographical generalizability.

How do the key results compare with the current evidence? This study's results are comparable to previously published series on missed appendicitis.[1–3] Unlike previous literature, this study did not show that extremes of age are independent risk factors for missed appendicitis.[4]

How should this study impact the care of ED patients? The presence of constipation should not dissuade a work-up for appendicitis in adults (odds ratio [OR] = 1.51) and (OR = 2.43) in children. The absence of abdominal pain was found to be associated with missed appendicitis on index presentation in adults (OR 3.57) and in children (OR = 2.99). This may represent natural disease progression, or atypical presentations.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Mahajan P, Basu T, Pai CW, et al. Factors Associated With Potentially Missed Diagnosis of Appendicitis in the Emergency Department. JAMA Netw Open. 2020 Mar 2;3(3):e200612.

Design: Administrative insurance claims database (USA) cohort study.

Population: *Included:* Adults (≥ 18 years) and children (< 18 years) who visited the ED in the 0 to 30 days before a diagnosis of appendicitis.
Excluded: Patients with appendectomy or ED visits > 30 days or prior to appendicitis diagnosis.

Exposure: The presence of the following symptoms alone or in combination: abdominal pain; constipation; nausea and or vomiting; fever.

Comparison: The absence of the above symptoms alone or in combination.

Outcomes: *Primary:* Potentially missed appendicitis.
Secondary: Independent variables associated with potentially missed appendicitis including sex, age, race, comorbidity, symptom, diagnostic tests.

Key Results: *N* = 187,461 (101,375 Adults; 22,336 Children). Potentially missed appendicitis = 7,033 (6,060 [6.0%] Adults; 973 [4.4%] Children).

Sig.	*Population*	*Predictor of Missed Appendicitis*	*Adjusted Odds Ratio (95% CI)*
SS	Adults	No Abdominal Pain	3.57 (3.22 to 3.95)
SS	Adults	Abdominal Pain and Constipation	1.51 (1.31 to 1.75)
SS	Children	No Abdominal Pain	2.99 (2.25 to 3.96)
SS	Children	Abdominal Pain and Constipation	2.43 (1.86 to 3.17)
SS	Women	Abdominal Pain Only	1.68 (1.58 to 1.78)
SS	Girls	Abdominal Pain Only	1.64 (1.43 to 1.88)

CI = confidence interval; *N* = number of patients; Odds ratio is a ratio and so if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	✓	✓	✓
7. The follow-up was complete.	✓	✓	✓
8. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Department of Emergency Medicine at the University of Michigan.

Conflicts of Interest: None reported.

Potential Threats to Validity

Chance: The association between several factors and the likelihood of a missed appendicitis diagnosis was imprecise (e.g., abdominal pain, nausea and/or vomiting, fever, and constipation).

Selection Bias: None detected.

Measurement Bias: Appendicitis was retrospectively identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Coding errors may have led to patients being missed or inappropriately included in the study. Further, a complete list of symptoms (i.e. abdominal pain, constipation, diarrhea, fever, and nausea and/or vomiting) was likely not captured for every patient.

Analysis Bias: As above, coding errors are likely as well as missing information about laboratory and imaging results given that the database included only a subset of laboratory test results.

Confounding: Without all of the individual patient data, it is impossible to know how the results of laboratory and imaging investigations influenced the discharge diagnoses.

Administrative Details

Key Words: Abdominal pain; appendectomy; appendicitis; constipation.

Appraisers: Zeraatkar D; Worster A; Bhatt M.

Reference(s):

1. Benabbas R, Hanna M, Shah J, Sinert R. Diagnostic Accuracy of History, Physical Examination, Laboratory Tests, and Point-of-care Ultrasound for Pediatric Acute Appendicitis in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2017;24(5):523-51.
2. Galai T, Beloosesky OZ, Scolnik D, Rimon A, Glatstein M. Misdiagnosis of Acute Appendicitis in Children Attending the Emergency Department: The Experience of a Large, Tertiary Care Pediatric Hospital. Eur J Pediatr Surg. 2017;27(2):138-41.
3. Leung YK, Chan CP, Graham CA, Rainer TH. Acute appendicitis in adults: Diagnostic accuracy of emergency doctors in a university hospital in Hong Kong. Emerg Med Australas. 2017;29(1):48-55.
4. Omari AH, Khammash MR, Qasaimeh GR, Shammari AK, Yaseen MK, Hammori SK. Acute appendicitis in the elderly: risk factors for perforation. World J Emerg Surg. 2014;9(1):6.

BEEM BITs (PART II)

Research Question

Can ED physicians use bedside POCUS to diagnose acute cholecystitis?

BEEM Bottom Line

Why is this study important? Acute cholecystitis can be a challenging diagnosis in the ED. A validated ED risk score, using elements of history symptoms, physical examination signs, and bedside POCUS findings, can help make a definitive diagnosis.

Which, if any, threats to validity are most likely to have an impact on the results and how? There is concern about convenience sampling that could introduce a selection bias in test performance outcomes. Lack of reported blinding for final outcomes adjudication also introduces risk of classification bias.

How do the key results compare with the current evidence? As with other ED POCUS studies, the main elements of diagnostic POCUS test performance are strongly dependent on operator experience.

How should this study impact the care of ED patients? The Bedside SAC score may be useful to successfully rule out/in acute cholecystitis (without lab studies), but further validation is likely required to make this a level II/I CDR.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Graglia S, Shokoohi H, Loesche MA, *et al*. Prospective validation of the bedside sonographic acute cholecystitis score in emergency department patients. Am J Emer Med 2021; 42: 15-19. https://doi.org/10.1016/j.ajem.2020.12.085

Design: Validation of a previously derived clinical prediction or decision rule.

Population: *Included:* Adults (≥ 18years) in ED with suspected cholecystitis and being considered for RUQ POCUS. *Excluded*: Known diagnosis, pregnant, prisoners, declined/unable to give consent, non-English speaking, unable to complete follow-up (1 month later).

Predictors: Bedside SAC Score elements: postprandial symptoms (1pt), RUQ tenderness (1pt), Murphy's sign (2pts), gallbladder thickening (2pts), presence of gallstones (3pts); score range 0-9pts.

Comparison: Medical record review of patient outcomes up to 1mo ED visit (discharge diagnosis, additional abdo imaging, lab tests, surgical pathologies). If no MRR information, patients were emailed/called to ascertain outcomes (3 attempts). If no outcomes information confirmed, patients deemed to be negative for acute cholecystitis.

Outcomes: *Primary:* Performance of the Bedside SAC score; predictive value to diagnose acute cholecystitis. *Secondary:* Score performance at different cutoffs.

Key Results: *N* = 153 patients included in the analysis. 24% (56/153) had a confirmed Dx acute cholecystitis. Avg age 43.5yrs, 34% males. AUC for score = 0.874 (0.813-0.936).

Table 2
Test performance of the Bedside SAC Score at all possible thresholds. Operating characteristics for each threshold include scores below but not including the score

Score	Sensitivity	Specificity	Accuracy	PPV	NPV	LR+	LR-
1	100% (90–100%)	9% (4–15%)	30% (23–38%)	25% (18–33%)	100% (69–100%)	1.09 (1.03–1.16)	0
2	100% (90–100%)	35% (27–44%)	50% (42–59%)	32% (24–42%)	100% (91–100%)	1.54 (1.35–1.76)	0
3	92% (78–98%)	55% (45–64%)	63% (55–71%)	38% (28–50%)	96% (88–99%)	2.02 (1.62–2.53)	0.15 (0.05–0.46)
4	89% (74–97%)	68% (58–76%)	73% (65–79%)	46% (34–58%)	95% (88–99%)	2.74 (2.06–3.64)	0.17 (0.06–0.42)
5	69% (52–84%)	88% (81–93%)	84% (77–89%)	64% (47–79%)	90% (83–95%)	5.8 (3.39–9.93)	0.35 (0.21–0.57)
6	67% (49–81%)	92% (85–96%)	86% (79–91%)	71% (53–85%)	90% (83–95%)	7.8 (4.13–14.7)	0.36 (0.23–0.58)
7	44% (28–62%)	96% (90–99%)	84% (77–89%)	76% (53–92%)	85% (78–91%)	10.4 (4.09–26.4)	0.58 (0.43–0.78)
8	17% (6–33%)	98% (94–100%)	79% (72–85%)	75% (35–97%)	79% (72–86%)	9.75 (2.06–46.2)	0.85 (0.73–0.98)
9	14% (5–30%)	100% (97–100%)	80% (73–86%)	100% (48–100%)	79% (72–86%)	∞	0.86 (0.76–0.98)

PPV/NPV = positive/negative predictive values, LR+/LR− = positive/negative likelihood ratios. Confidence intervals are included in parentheses.

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were representative of those with the problem.	✓
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	?
3. All patients underwent the same clinical evaluation.	?
4. All important predictor variables were included in the clinical evaluation and explicitly defined.	✓
5. Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	?
6. Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	✓
7. All outcome variables were included in the clinical evaluation and explicitly defined.	✓
8. All patient-important outcomes were considered.	?
9. The follow-up was complete.	X
10. The point estimates and respective precisions are clinically significant.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: 3 authors disclosed funding support for unrelated research from GE/EMF (HS, CKH, ASL).

Potential Threats to Validity

Chance: None?

Selection Bias: Convenience sampling used at 2 study sites introduces risk of selection bias. No comments on standardized history/physical exam for clinical assessment.

Measurement Bias: Close agreement between ED POCUS and formal radiology diagnoses for gallstones (Kappa 88.4%), wall thickening (K 86.7%), pericholecystic fluid (90.7%), and sonographic Murphys sign (77.6%). AUC for different BedSAC scores was 0.874 (90.3-100%). 9/162 patients lost to follow-up (6%).

Analysis Bias: Final ED physician adjudication may/may not have been blinded to initial SAC assessments? Risk of classification bias.

Confounding: POCUS image acquisition/interpretation will be strongly dependent on operator training/experience; no extra training provided for ED staff in this study.

Administrative Details

Key Words: Acute cholecystitis, clinical decision rules, emergency department POCUS

Appraisers: Upadhye S.

Reference(s): Graglia S, Shokoohi H, Loesche MA, Dante D, Haney RM, Huang CK, Morone CC, Springer C, Kimberly HH, Liteplo AS. Prospective validation of the bedside sonographic acute cholecystitis score in emergency department patients. Am J Emer Med 2021; 42: 15-19. https://doi.org/10.1016/j.ajem.2020.12.085

Research Question

For drainage of skin abscesses, how does loop drainage compare to traditional I&D?

BEEM Bottom Line

Why is this study important? Treating skin abscess in the ED is common, yet potentially painful with traditional I&D, with unproven repeated packing thereafter (also painful), and associated with 10% treatment failures. Loop drainage technique provides a minimally invasive, less painful single intervention that can improve abscess outcomes.

Which, if any, threats to validity are most likely to have an impact on the results and how? The analysis combined studies of different designs therefore the results are confounded by inherent variability in risk of bias; even within the randomized trials high risk of bias could not be ruled out. There is also concern for imprecision given low event rates and wide confidence intervals.

How do the key results compare with the current evidence? These findings support prior trials/reviews that loop drainage results in less Tx failures compared to traditional I&D. This augments the benefits of lesser pain for patients, reduced follow-up visits for packing changes, and better cosmetic outcomes.

How should this study impact the care of ED patients? Loop drainage is a superior abscess drainage technique with better outcomes compared to traditional I/D, less pain, less follow-up visits and better cosmetic outcomes. This should be the preferred technique for simple skin abscess drainage in the ED.

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Study Summary

Article: Gottlieb M, Schmitz G, Peksa GD. Comparison of the Loop Technique with Incision and Drainage for Skin and Soft Tissue Abscesses: A Systematic Review and Meta-analysis. Acad Emerg Med 2020; 1-9. doi: 10.1111/acem.14151

Design: Systematic review and meta-analysis of all comparative studies.

Population: *Included:* All articles (retro/prospective) comparing Loop Drainage technique (LDT) with traditional I&D (TID).
Excluded: Case reports/series, review articles.

Intervention: Loop drainage technique (LDT)

Comparison: Traditional I&D (TID)

Outcomes: *Primary:* Treatment failure (defined as per original studies, but could include repeat I/D, additional antibiotics use, need for hospitalization/operative management)
Secondary: Pre-defined subgroups analyses = pediatrics vs adults, RCTs only.

Key Results: *8 studies, 910 patients included for final meta-analysis*

Sig.	*Outcome*	*N/Studies*	*Measure NNT (95% CI)*	I^2
NSS	OR Tx failure in adults only; OR 1.54 (95%CI 0.79-3.00)	524/4	N/A	
NSS	OR Tx failure in children only; OR 3.23 (0.92-11.36)	386/5	N/A	
SS	OR Tx failure 2.02 (1.29-3.18) against TID	910/8	14 (7 to 47)	0

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓
7. The quality of the primary studies is high.	?	X
8. The methods used to combine the included primary studies were reported and valid.	✓	X
9. The outcomes are clinically relevant.	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	✓	✓

A1 = S. Upadhye A2 = C. Bedard

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: Appears sufficiently powered to detect statistical differences in relative effects, but it is unknown whether these differences are clinically important as there was no defined minimal important difference threshold and event rates are low. Subgroup analyses between pediatric and adult populations are likely underpowered.

Selection Bias: No evidence of publication bias on funnel plot testing, however this analysis is underpowered.

Measurement Bias: The majority of the risk of bias judgements were unclear, however these were often within highly relevant domains that could bias results (i.e. allocation concealment, blinding of outcome assessors). No statistical heterogeneity amongst included studies.

Analysis Bias: The primary meta-analysis combined both randomized and non-randomized design which is not recommended. While a sensitivity analysis was performed, the confidence intervals were wider with the lower bound closer to no difference. Funnel plot analyses are underpowered to detect publication bias with fewer than 10 trials. Finally, the authors stated that a random-effect model was to be used, but presented the results of a fixed effects model which showed larger effects.

Confounding: Possibly some minimal concerns about variable definitions used in primary trial outcomes (single vs composite).

Administrative Details

Key Words: Skin abscess, loop technique, incision & drainage.

Appraisers: S Upadhye, Bedard C.

Reference(s): Gottlieb M, Schmitz G, Peksa GD. Comparison of the Loop Technique with Incision and Drainage for Skin and Soft Tissue Abscesses: A Systematic Review and Meta-analysis. Acad Emerg Med 2020; 1-9. doi: 10.1111/acem.14151

Research Question

What is the diagnostic accuracy for different clinical and laboratory findings for Giant Cell Arteritis (GCA)?

BEEM Bottom Line

Why is this study important? Giant cell arteritis is a rare but "can't miss" diagnosis in the ED, as a missed diagnosis could lead to vision loss.

Which, if any, threats to validity are most likely to have an impact on the results and how? Patient selection bias was unclear/high with majority of studies. Considerable risk of bias also associated with differential use/reporting of reference standards. Both of these will skew the overall results of the index tests. No analysis done with combining clinical features to improve diagnostic accuracy. There is some overlap in the cutoffs used for lab tests (ie. ESR=60) to confirm/exclude a GCA diagnosis.

How do the key results compare with the current evidence? These results update a prior meta-analysis on diagnostic utility of individual clinical & laboratory features, with increase precision. There is overall confirmation of no single finding to definitively confirm/exclude a GCA diagnosis.

How should this study impact the care of ED patients? No single demographic, clinical nor laboratory test is definitive enough to rule in or out a GCA diagnosis, but it may influence subsequent diagnostic testing (imaging, biopsy) or decisions to initiate glucocorticoid therapy with specialist follow-up. "Classic" features for GCA (eg. Headache, scalp tenderness, constitutional symptoms) have limited utility in raising/lowering risk of GCA. The authors suggest an ESR cutoff of 60mm/hr to differentiate "positive" vs "negative" results (in isolation).

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic Accuracy of Symptoms, Physical Signs and Laboratory Tests for Giant Cell Arteritis: A Systematic Review and Meta-analysis. JAMA Intern Med 2020; 180(10): 12995-1304. doi:10.1001/jamainternmed.2020.3050

Design: Systematic review and meta-analysis of diagnostic accuracy studies

Population: *Included:* Consecutive patients being evaluated for GCA in the included studies (with at least 5 true positives and negatives), with an appropriate reference standard(s), and raw data available for meta-analysis.
Excluded: Case-control studies, case reports, conference abstracts. Also excluded cases of previously confirmed GCA or closely related condition (eg. PMR). Excluded reporting of composite findings.

Index Test: Symptoms, physical signs, and laboratory tests for GCA.

Reference Test: Temporal artery biopsy (TAB), imaging, or clinical diagnosis of GCA (based on definite clinical criteria, or agreement of 2+ physicians). Where multiple reference standards available, the clinical Dx was considered for the main study analyses.

Diagnosis of Interest: Giant cell arteritis.

Key Results: *N* = 14037 patients in 68 included studies; 4277 (30.5%) confirmed with GCA. 71% observational studies, 82% completed at academic centers. Pre-defined cutoffs for significance: LR+ >2.0 or LR- <0.50 (CI not including 1.00).

Index Test	*Positive Likelihood Ratio (95% CI)*	*Negative Likelihood Ratio (95% CI)*
Symptoms, Demographics	Limb claudication = 6.01 (1.38-26.16)	Age > 70 = 0.48 (0.27-0.86)
	Jaw claudication = 4.90 (3.73-6.41)	
Physical Signs, Lab tests	TA thickening = 4.70 (2.65-8.33)	ESR > 40 = 0.18 (0.08-0.44)
	Loss of TA pulsations = 3.25 (2.49-4.23)	ESR > 50 = 0.42 (0.38-0.62)
	TA tenderness = 3.14 (1.14-8.65)	ESR > 60 = 0.42 (0.28-0.61)
	Abnormal TA = 2.29 (1.61-3.26)	CRP > 2.5mg/dl = 0.38 (0.25-0.59)
	Anterior ischemic optic neuropathy = 2.15 (1.53-3.03)	CRP > ref value = 0.40 (0.29-0.56)
	ESR > 60 mm/hr = 2.40 (1.71-3.36)	
	ESR > 80 = 2.79 (1.78-4.37)	
	ESR > 100 = 3.11 (1.43-6.78)	
	Platelets > $400x10^3$/ul = 3.75 (2.12-6.64).	

CI: Confidence Interval; TA: Temporal Artery; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	?	X
3. The search for studies was unbiased and reproducible.	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	X
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓	✓
7. The quality of the primary studies is high.	?	X
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	?	✓
9. The subgroups were stated a priori and appropriate.	✓	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓	✓

A1 = S. Upadhye A2 = C. Bedard

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: This study was supported by TARGET partnership grant MR/N011775/1 from the Medical Research Council (Dr Mackie) and the Mandema Stipend from the University Medical Center Groningen (Dr van der Geest). Funding bodies had no roles in any part of study planning, conduct, data analyses, nor publication.

Conflicts of Interest: 1. van der Geest: speaker fees from Roche. 2. Brouwer: speaker/consultancy fees from Roche (paid to university). 3. Mackie: Grant meeting support from Roche, consultancy fees from Roche/Sanofi, trial investigator for Sanofi/GSK. No other conflicts disclosures.

Potential Threats to Validity

Chance: There were several features with insufficient data to reliably pool studies; however, the primary meta-analyses appear to have an adequate number of cases resulting in moderately precise confidence intervals.

Selection Bias: Search terms were comprehensive, but the search was limited to certain electronic databases, reference lists and was restricted to English-language only. However, there was minimal evidence of publication bias on funnel plot testing.

Measurement Bias: Data extracted singly by one author, then validated independently by another (not parallel independent abstractions). Clinical diagnosis of GCA as a reference standard is subjective and is strongly related to the experience of the individual diagnosing physician. Many symptoms lacked a clear definition in included studies (e.g., Jaw claudication).

Analysis Bias: Dichotomizing continuous variables (e.g., age, lab results) could artificially skew index test results. Uncertainty of the validity of the reference standard (particularly TAB) may have led to lowered estimates of accuracy of the individual index tests.

Confounding: No study was low risk of bias; of particular concern was the frequent use of clinical diagnosis as both the index and reference tests may have inflated accuracy estimates. Concurrent treatment of glucocorticoid during assessment of laboratory features may have lowered the accuracy of these variables.

Administrative Details

Key Words: Giant cell arteritis, diagnostic test accuracy.

Appraisers: Upadhye S, Bedard C, ; LAST NAME OF FIRST AUTHOR & FIRST INITIAL. Do not separate last name and first name initial with commas.

Reference(s): van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic Accuracy of Symptoms, Physical Signs and Laboratory Tests for Giant Cell Arteritis: A Systematic Review and Meta-analysis. JAMA Intern Med 2020; 180(10): 12995-1304. doi:10.1001/jamainternmed.2020.3050

Research Question

What is the benefit of pictorial ED discharge materials, compared to standard discharge advice?

BEEM Bottom Line

Why is this study important? Providing adequate discharge advice for patients leaving the ED is an essential activity to optimize patient outcomes. Use of pictorial materials may facilitate this process.

Which, if any, threats to validity are most likely to have an impact on the results and how? There are limited, and somewhat dated, studies examining the benefit of ED pictorial interventions. Limited generalizability as all included studies were US-based. No information provided on costs of production/implementation of ED pictorial discharge materials, which require multidisciplinary inputs.

How do the key results compare with the current evidence? There is limited evidence on the utility of ED pictorial discharge advice materials with which to compare these results.

How should this study impact the care of ED patients? Pictorial ED discharge materials increase comprehension, compliance and patient satisfaction. More research, with broad stakeholder inputs (including patients/caregivers) would likely make such materials more impactful.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Dermody S, Hughes M, Smith V. The Effectiveness of Pictorial Discharge Advice vs Standard Advice Following Discharge from the Emergency Department: A Systematic Review and Meta-Analysis. J Emerg Nurs 2021; 47: 66-75. https://doi.org/10.1016/j.jen.2020.07.005

Design: Systematic review and meta-analysis of randomized controlled trials (RCTs).

Population: *Included:* Adults/children sent home from ED with any type of pictorial information.
Excluded: Other modes of communicating discharge information (texts, recordings, videos), non-ED settings, non-English languages used.

Intervention: Use of pictorial information for discharge advice (line drawings, pictures, photographs, paintings, cartoons).

Comparison: Standard written/verbal discharge information.

Outcomes: *Primary:* Patient/caregiver comprehension of discharge advice.
Secondary: Compliance/adherence to discharge advice, patient satisfaction with ED visit/discharge advice, ED reattendance within 28days with same complaint.

Key Results: *4 studies, 1397 patients included.* All studies conducted at US study sites (mixed rural/community/urban teaching hospitals).

Sig.	*Outcome*	*N/Studies*	*Outcome Measure (95% CI)*	*I^2*
NSS	ED visit satisfaction	1 study, 205 pts	RR 1.02 (0.92-1.14)	N/A
SS	Comprehension	3 studies, 389 pts	RR 2.53 (1.19-5.35) favouring pictorial ED discharge; results stable to sensitivity analysis	89%
	Compliance	2 studies, 298 pts	RR 1.44 (1.22-1.68) favouring intervention	0%
	Completed meds course	1 study, 93 pts	RR 1.72 (1.11-2.50) favouring intervention	N/A
	Satisfaction with discharge advice	1 study, 205 pts	RR 1.48 (1.28-1.71) favouring intervention	N/A

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

Research Question

What is the risk of overcorrection of symptomatic hyponatremia with rapid intermittent bolus (RIB) versus slow continuous infusion (SCI) of hypertonic saline?

BEEM Bottom Line

Why is this study important? Hyponatremia is the most common electrolyte imbalance seen in the emergency department (ED) and, if overcorrected, can induce osmotic demyelination syndrome (ODS). This trial compares the rates of overcorrection of symptomatic hyponatremia with rapid intermittent bolus (RIB) to slow continuous infusion (SCI) of hypertonic saline.

Which, if any, threats to validity are most likely to have an impact on the results and how? There is a concern for selection and performance biases since treatment allocation was not concealed from those enrolling patients or from physicians and this may have caused the observed differences in comorbidities, causes of hypernatremia, and rate of cointerventions between groups. Moreover, the outcomes were not assessed for different categories of hyponatremia severity.

How do the key results compare with the current evidence? This study adds modest results using a weight-based approach to other small studies on hyponatremia correction using a fixed-dose regimen of hypertonic saline.[1]

How should this study impact the care of ED patients? The study results do not guide us on the best way to resolve life-threatening hyponatremic symptoms or to prevent overcorrection and ODS. Both RIB and SIC hypertonic saline therapies can be safe and effective for treating hyponatremia but close monitoring of serum sodium (sNa) is advised.

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Study Summary

Article: Baek SH, Jo YH, Ahn S, et al. Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia: The SALSA Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 26:e205519.

Design: Multicenter (South Korea), open-label, randomized controlled trial.

Population: *Included:* Adults (> 18 years) with moderate (nausea, headache, drowsiness, general weakness, and malaise) to severe (vomiting, stupor, seizure, and Glasgow Coma Scale [GCS] score ≤ 8) symptoms of hyponatremia (i.e. glucose-corrected sNa ≤ 125 mmol/L.
Excluded: Patients with primary polydipsia; pregnant or breastfeeding; anuria; hypotension; liver disease; diabetes; history of cardiac surgery; myocardial infarction; ventricular dysrhythmia; acute coronary syndrome or increased intracranial pressure.

Intervention: RIB saline 3% 2 ml/kg intravenous (IV) bolus every 6 hours (h) with the treatment goal for both arms to increase sNa level by 5 to 9 mmol/L and to achieve symptom relief ≤ first 24 h, and to increase sNa level by 10 to 17 mmol/L or ≥ 130 mmol/L and to achieve symptom relief ≤ 48 h.

Comparison: SCI saline 3% 0.5 ml/kg/h if moderate hyponatremia and 1.0 ml/kg/h if severe hyponatremia.

Outcomes: *Primary:* Overcorrection (sNa > 12 mmol/L ≤ 24 hours or sNa > 18 mmol/L ≤ 48 h).
Secondary: Rapid improvement of symptoms; change of symptoms from baseline to 24 h post treatment; time from treatment initiation to sNa increase ≥ 5 mmol/L; target correction ≤ 1 h; time to sNa >130 mmol/L.

Key Results: *N* = 178 subjects (mean age = 73.1 years; 44.9% male.

Sig.	*Outcome*	*RIB (%)*	*SCI (%)*	*ARD (95% CI)*	*NNT*
NSS	sNa Overcorrection	15/87 (17.2)	22/91 (24.2)	− 6.9% (-18.8 to 4.9)	NA
SS	sNa Relowering treatment	36/87 (41.4)	52/91 (57.1)	−15.8% (−30.3 to −1.3)	7
SS	sNa Target correction ≤ 1 h	28/87 (32.2)	16/91 (17.6)	14.6% (2.0 to 27.2)	7

ARD = absolute risk difference; CI = confidence interval; *N* = number of patients; NA = not applicable; NNT = number needed to treat; NSS = not statistically significant; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	X	X	X
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	?
3. The allocation sequence was adequately concealed.	X	X	?
4. The patients in all groups were similar with respect to prognostic factors.	X	X	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	X	X	X
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT= Intention to treat.

Funding & Conflicts of Interest

Funding: National Research Foundation of Korea.

Conflicts of Interest: None reported.

Potential Threats to Validity

Chance: Very wide confidence intervals suggest that the study was underpowered to provide precise estimates of effects. Furthermore, secondary analyses and post-hoc outcomes are exclusively exploratory and as such may be at risk of type I error.

Selection Bias: The authors noted that the randomized sequence was not concealed from those enrolling patients. While there were no significant differences in baseline or demographic factors between groups, there appears to be more cases of hyponatremia due to thiazide use in the SCI group and more cases due to decreased extracellular fluid and adrenal insufficiency in the RIB group; more comorbid cases of adrenal insufficiency in the RIB group; and slightly more patients recruited in the ED in the RIB group. There are more differences between groups than expected due to chance which could confound the results.

Measurement Bias: The non-blinded nature of the study also provided opportunities for differential treatment and care between groups in the ED and general ward; particularly since the RIB protocol was highly complex physicians may have altered their treatment plan to compensate. The RIB group received significantly higher cumulative amounts of hypertonic saline in the first 6 h compared to the SCI. Also, the SCI group received more hypotonic fluids and less isotonic fluids compared to the RIB group. Finally, the primary outcome is a surrogate outcome for ODS and therefore cannot be used to directly infer the effect of RIB vs SCI on ODS.

Analysis Bias: Given that the study is multi-centered it may have been worthwhile to assess the presence of cluster effects. While the results appear robust to the protocol violations there are likely too few patients in the sample to accurately evaluate the influence of drop-outs on the results.

Confounding: Some differences in cointerventions and baseline clinical characteristics (e.g. causes of hypernatremia) may have confounded the results. It would have been useful to have categories of baseline hyponatremia to know if patients with severe hyponatremia (< 110 mmol/L), or those outside the seizure risk range ()>120 mmol/L reported different outcomes to different administration speed.

Administrative Details

Key Words: Hypernatremia; hypertonic saline; hyponatremia; osmotic demyelination syndrome (ODS).

Appraisers: Bedard C; Worster A; Gosselin, S.

Reference(s): 1. Garrahy A, Dineen R, Hannon AM, et al. Continuous Versus Bolus Infusion of Hypertonic Saline in the Treatment of Symptomatic Hyponatremia Caused by SIAD. J Clin Endocrinol Metab. 2019 Sep 1;104(9):3595-3602.

Research Question

Is there an association between pain, opioid treatment, and delirium in older adults in the emergency department?

BEEM Bottom Line

Why is this study important? Delirium is an acute state of transient confusion with a fluctuating course and occurs frequently in emergency department (ED) patients.[1] Delirium also is associated with adverse outcomes and is an independent predictor of increased 6-month mortality.[1,2] Pain and delirium often occur together. However, there are limited data investigating interactions between pain and delirium across settings. In this Canadian prospective multicenter cohort study, the authors examine whether pain, opioids or both are associated with the development of delirium during an ED stay in an older ED population.

Which, if any, threats to validity are most likely to have an impact on the results and how? This study enrolled a non-consecutive sample of high-functioning elderly patients who were able to articulate their pain levels. There was a high rate of missed patients who might differ from those in the study on unmeasured factors. In addition, different opioids with potentially different "deliriogenic" properties were included. The incidence rates of delirium are determined, in part, by the frequency of delirium assessments. Lastly, the limited cases of delirium resulted in a minimally adjusted model with only four confounding factors controlled for; therefore, the results are imprecise and are unable to account for unmeasured confounders.

How do the key results compare with the current evidence? The result that severe pain, not opioids, is associated with the development of delirium is in line with findings of a systematic review which found that in acute severe pain lower doses of opioids may be associated with a higher risk of delirium (moderate quality evidence).[3] Similar results were found in several observational studies in mostly post-operative settings.[4] The atypical opioids, tramadol and meperidine, have both been associated with delirium but are rarely used for pain management in the ED.[5]

How should this study impact the care of ED patients? Pain in older ED patients is common, often undertreated and appears to increase the risk of delirium especially for those in severe pain. Hence, adequate (multimodal) pain management including opioids can provide more than just symptom relief for these patients at risk of delirium.

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No conflicts of interest (ICMJE)

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Study Summary

Article: Daoust R, Paquet J, Boucher V, et al. Relationship between pain, opioid treatment, and delirium in older emergency department patients [published online ahead of print, 2020 May 22]. Acad Emerg Med. 2020;10.1111/acem.14033. doi:10.1111/acem.14033

Design: Preplanned substudy of a multicenter (Quebec, Canada), prospective, cohort study.

Population: *Included:* Adults (≥ 65 years) who were independent or semi-independent (i.e., able to perform 5/7 activities of daily living according to the OARS) and waiting in the ED ≥ 8 hours for hospital admission.
Excluded: Patients with delirium within the first 8 hours of ED stay; a history of psychiatric disorders (i.e., schizophrenia, psychotic symptoms and bipolar disorder); who required admission to the intensive or palliative care units; were unable to consent or speak French or English; and or living (or in transition) in long-term care.

Exposure: Opioids (e.g. codeine, hydromorphone, meperidine, oxycodone, methadone, fentanyl, tramadol, pentazocine, and or morphine alone or in combination with acetaminophen).

Comparison: Not applicable.

Outcomes: *Primary:* Delirium in the ED or ≤ 24 hours of the hospital stay as determined by the Confusion Assessment Method (CAM) with the sensitive (SENS) method for interpreting the CAM.
Secondary: Potential predictors of delirium including demographics, level of pain, received opioids in ED, triage priority, time of day presentation, ED length of stay, medical interventions, etc.

Key Results: *N* = 338 subjects (41 had delirium; mean age 77years; 51% female; mean ED length of stay 32 hours).

Sig.	*Clinical Predictor*	*Subjects with Delirium (%)*	*Adjusted OR (95% CI)*
SS	Age ≥ 85 years	16/60 (26.7%)	3.04 (1.16 to 7.94)
SS	Level of pain ≥ 65 on VAS	12/47 (25.5%)	3.29 (1.38 to 7.88)
NSS	Received opioids in ED	20/202 (9.9%)	1.25 (0.55 to 2.83)

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; OR = odds ratio (because this is a ratio, if the value of the range includes 1, there is no difference; adjusted for 7 independent variables); Sig. = significance; SS = statistically significant; VAS = visual analog scale.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	X	X	X
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	X	X	X
7. The follow-up was complete.	✓	✓	✓
8. The effect size of the primary outcome is clinically significant.	?	?	?

A = appraiser.

Funding & Conflicts of Interest

Funding: Fonds de recherche des urgentistes de l'Hôpital du Sacré-Coeur de Montréal and the Fonds de recherche du Québec – Santé (FRQS 29307), Canada.

Conflicts of Interest: Authors had none to disclose.

Potential Threats to Validity

Chance: Only 41/338 (12%) patients experienced delirium, therefore the analysis is underpowered, resulting in wide confidence intervals around the estimates of risk.

Selection Bias: Non-consecutive sampling resulted in a proportion of patients that were eligible but not enrolled into the study; though the demographic characteristics were reportedly similar to those included, there is a possible risk of selection bias that is undetected.

Measurement Bias: The reliability and validity of the ED environmental information measurements are unknown. It is also unknown how the administrative data were extracted, therefore there is possible non-differential measurement error in the length of stay and opioid consumption data. In addition, timing, dosing, selection of medication is unknown. Finally, assessment of delirium was performed by non-blinded research assistants, therefore there is a substantial risk of detection bias.

Analysis Bias: Though the final model used a hypothesis-driven approach, the bivariate logistic regressions conducted between the outcome and various predictor variables has increased the risk of type I error. Given that only 41 patients experienced delirium, the model may be overfit as it included 5 confounding variables in addition to the 2 variables of interest (presence of severe pain and opioid consumption).

Confounding: The small number of cases subsequently led to limited adjustment for measured confounding factors; results may be confounded by differences in patient hydration, triage priority, and frailty. Also, there is residual confounding as with all observational studies because of unmeasured and unknown prognostic factors that cannot be controlled.

Administrative Details

Key Words: Analgesia; delirium; geriatric; older adults; opioid; pain; senior.

Appraisers: Bedard C; Worster A; Nickel C.; Dreher T

Reference(s):

1. Han JH, Shintani A, Eden S, et al. Delirium in the emergency department: an independent predictor of death within 6 months. Ann Emerg Med. 2010;56(3):244-252.e1.
2. Han JH, Vasilevskis EE, Chandrasekhar R, et al. Delirium in the Emergency Department and Its Extension into Hospitalization (DELINEATE) Study: Effect on 6-month Function and Cognition. J Am Geriatr Soc. 2017;65(6):1333-1338.
3. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011;40(1):23-29.
4. Sampson EL, West E, Fischer T. Pain and delirium: mechanisms, assessment, and management. Eur Geriatr Med. 2020;11(1):45-52.
5. Swart LM, van der Zanden V, Spies PE, et al. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. Drugs Aging. 2017;34(6):437-443.

Research Question

In patients presenting with cannabis hyperemesis syndrome (CHS), is haloperidol more effective compared to ondansetron for reducing pain and nausea?

BEEM Bottom Line

Why is this study important? Cannabis Hyperemesis Syndrome (CHS) is increasingly common in the emergency department (ED), with chronic cannabis users presenting with episodic cycles of nausea and abdominal pain refractory to traditional anti-emetics. Case reports support the use of typical anti-psychotics (Haloperidol).[1,2] This is the first trial to compare the effectiveness of haloperidol versus ondansetron for CHS.

Which, if any, threats to validity are most likely to have an impact on the results and how? A primary limitation of this study is the small sample size, and the risk of bias for chance baseline imbalances in prognostic factors between groups. Furthermore, the comparative effectiveness of each anti-emetic beyond 2 hours (h) is uncertain due to the high loss to follow-up at 48 h. Finally, the trial was terminated early for benefit, which may produce overestimated effect estimates.

How do the key results compare with the current evidence? Haloperidol 1 mg intravenous (IV) was reported as non-inferior to ondansetron 4 mg IV in post-operative nausea and vomiting at 0 to 4 hour (h) and 0 to 24 h periods.[3] These results further support haloperidol's anti-emetic effects, specifically for CHS.

How should this study impact the care of ED patients? In ED patients presenting with suspected CHS, IV haloperidol (0.05 to 0.1 mg/kg) is a reasonable first line agent in treatment of nausea and pain. The lower haloperidol dose of 0.05 mg/kg IV is less likely to induce precipitate akathisia and acute dystonia.

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No conflicts of interest (ICMJE)

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Study Summary

Article: Ruberto AJ, Sivilotti MLA, Forrester S, et al. Intravenous Haloperidol Versus Ondansetron for Cannabis Hyperemesis Syndrome (HaVOC): A Randomized, Controlled Trial. Ann Emerg Med. 2020 Nov 5:S0196-0644(20)30666-1.

Design: Multicenter (2 Academic EDs in Ontario, Canada) superiority, randomized, triple-blind, double-crossover trial.

Population: *Included:* Adults (≥ 18 years) with hyperemesis (>2 h of ongoing witnessed emesis), caused by cannabis use (near-daily inhalational use ≥ 6 months), defined as ≥ 3 episodes of emesis in a cyclic pattern separated by > 1 month within ≤ 2 years.
Excluded: Pregnant, received an antiemetic/anticholinergic/antipsychotic agent (except dimenhydrinate) intravenously (IV) in ≤ 24 h, daily opioid use, allergy/intolerance to either study drug, deemed unreliable for follow-up, or to return for crossover.

Intervention: Ringer's solution 1 L IV over 30 minutes and recorded baseline nausea and abdominal pain each on a 10-cm visual analog scale (VAS; 0 = none, 10 = worst possible) for both groups. Haloperidol (0.05 or 0.1 mg/kg) IV with IV crystalloid at 250 ml/hour. After 7-day washout allocated to Ondansetron (8mg) IV for period 2.

Comparison: Ondansetron (8 mg) IV with IV crystalloid solution at a rate of 250 ml/hour. After 7-day washout period, allocation to haloperidol (0.05 or 0.1 mg/kg) IV for period 2.

Outcomes: *Primary:* Mean changes in abdominal pain and nausea scores at 2 h from baseline.
Secondary: Changes in either abdominal pain or nausea score over time; treatment success (i.e., both abdominal pain and nausea < 2 cm at ≥ 2 h): readiness for ED discharge at 2 h; use of rescue antiemetics before discharge; time to discharge; ED length of stay > 12 h; and unscheduled return visits ≤ 7 days. Safety outcomes were any adverse events related to study drug (i.e. acute dystonia, or moderate to severe akathisia).

Key Results: *N* = 30 subjects (aged 18 to 66 years; 14 females; ondansetron 8 mg = 17; haloperidol 0.1 mg/kg = 7; and haloperidol 0.05 mg/kg = 6), mean daily Cannabis use 1.5g.

Sig.	*Outcome*	*Haloperidol*	*Ondansetron*	*Difference (95% CI)*
SS	Mean change in combined scores at 2 h	–4.6 (2.5)	–2.3 (2.4)	–2.3 (–4.2 to –0.5)
SS	Mean change in nausea scores at 2 h	–5.0 (2.7)	–2.4 (2.4)	–2.5 (–4.4 to –0.6)
NSS	Mean change in abdominal pain scores at 2 h	–4.3 (3.0)	–2.1 (2.8)	–2.2 (–4.4 to 0)
NSS	Treatment success, *N* (%)	7 (53.8)	5 (29.4)	24% (–16 to 59)

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	?	X	X
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X	X	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser; ITT= intention to treat.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The trial is small with few included patients. Small trials are at risk for chance baseline imbalances in prognostic factors across arms. Due to the small study sample, results are imprecise and consistent with both the potential for an important or negligible difference between haloperidol and ondansetron.

Selection Bias: The effects of haloperidol (either dose) vs. ondansetron beyond 2 h is highly uncertain since only 9/30 patients reported outcome data at 24 and 48 h.

Measurement Bias: None detected.

Analysis Bias: The trial was terminated early for benefit. Trials that are terminated based on interim analyses indicating benefit are at high risk of overestimating the treatment effect.

Confounding: None detected.

Administrative Details

Key Words: Antiemetic; antipsychotic; benzodiazepine; cannabis hyperemesis syndrome (CHS); haloperidol; ondansetron.

Appraisers: Zeraatkar D; Worster A; Trajkovski A, Lang E.

Reference(s):

1. Hickey JC, Witsil JC, Mycyk M. Haloperidol for treatment of cannabinoid hyperemesis syndrome. The American Journal of Emergency Medicine. 2013. 31(6):1003.e5-1003.e6 [epub, doi: 10.1016/j.ajem.2013.02.021]
2. Jones J, Abernathy K. Successful Treatment of Suspected Cannabinoid Hyperemesis Syndrome Using Haloperidol in the Outpatient Setting. Case Rep Psychiatry. 2016. 3614053. [epub, doi: 10.1155/2016/3614053]
3. Yazbeck-Karam VG, Siddik-Sayyid SM, Barakat HB, et al. Haloperidol Versus Ondansetron for Treatment of Established Nausea and Vomiting Following General Anesthesia: A Randomized Clinical Trial. Anesth Analg. 2017 Feb;124(2):438-444.

Research Question

Are older adults taking direct oral anticoagulants at higher risk of hospital admission for hemorrhage with clarithromycin than with azithromycin?

BEEM Bottom Line

Why is this study important? Antibiotics and direct oral anticoagulants (DOACs) are frequently prescribed medications in emergency departments (EDs). This combination is seen especially in the older population who are at risk for polypharmacy, drug interactions and increased risk of bleeding. In fact, the rate of anticoagulant-associated hemorrhage requiring hospitalization doubles those older than 75 years.[1] DOACs are metabolized primarily via P-glycoprotein (P-gp) cell transporters or the cytochrome P450 enzyme CYP3A4.[2] Clarithromycin is a greater inhibitor of P-gp and CYP3A4 than azithromycin and while many studies report drug-drug interactions as effects on area under the curve (AUC) or peak drug levels, this study compares the adverse effects of clarithromycin to azithromycin in patients prescribed DOACs for the clinical outcome of major hemorrhage.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this study are limited by the potential for residual confounding and confounding by indication. Errors in the classification of exposures and the outcome may have overestimated or underestimated the reported association between clarithromycin and hemorrhage outcomes. However, the very likely scenario of noncompliance with medications (antibiotics and or DOACs) would cause an overestimation of the association.

How do the key results compare with the current evidence? The anticoagulant effects of DOACs are dependent upon their serum levels and clarithromycin has been reported to increase these by 20% to 100%.[3,4] Not all studies have reported associated bleeding risks, but those that do, have shown that elevated levels of DOACs are associated with increased rates of hemorrhage.

How should this study impact the care of ED patients? Although there was a small increased rate of bleeding in patients prescribed clarithromycin compared to azithromycin, the overall low rate of major hemorrhage seen in both groups suggests that either macrolide would be acceptable when prescribed in context with the patients' co-morbidities and other medications. However, given that azithromycin has a minimum effect on P-gp and CYP3A4, it is much less likely to interfere with DOACs or the multitude of other drugs that rely on these proteins. Hence, the safest macrolide prescribing approach is to use azithromycin as the first line with consideration of local antibiotic resistance patterns.

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No conflicts of interest (ICMJE)

Study Summary

Article: Hill K, Sucha E, Rhodes E, et al. Risk of Hospitalization With Hemorrhage Among Older Adults Taking Clarithromycin vs Azithromycin and Direct Oral Anticoagulants. JAMA Intern Med. 2020;180(8):1-10.

Design: Administrative health care database retrospective cohort study using population-based health care databases.

Population: *Included:* Adults (≥ 66 years) in Ontario, Canada, prescribed a DOAC (apixaban, dabigatran, or rivaroxaban) and also prescribed clarithromycin or azithromycin.
Excluded: Kidney transplant recipients and subjects undergoing dialysis or prescribed other potent CYP3A4 or P-gp inhibitors (e.g. conazole antifungals, tacrolimus, cyclosporine, quinines, and rifampin) within 90-days to the index look-back period.

Exposure: Clarithromycin prescription.

Comparison: Azithromycin prescription.

Outcomes: *Primary:* Hospital admission or ED visit ≤ 30 days after antibiotic dispensed for major (i.e., gastrointestinal or nontraumatic intracranial) hemorrhage as identified using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes in the Canadian Institute for Health Information Discharge Abstract Database.
Secondary: Any hemorrhage or receipt of packed red blood cell (pRBC) transfusion.

Key Results: *N* = 24,943 (36.2% of all patients were between 66 and 75 years old and 50.1% female).

Sig.	Outcome	Clarithromycin (%)	Azithromycin (%)	Adjusted HR (95% CI)	NNH (95% CI)
NSS	*Primary*	51/6,592 (0.77)	79/18,351 (0.43)	1.71 (1.20 to 2.45)	333 (167 to 1000)
NSS	*Secondary*	109/6,592 (1.65)	199/18,351 (1.08)	1.53 (1.21 to 1.94)	167 (100 to 500)

CI = confidence interval; HR = hazard ratio (because this is a ratio, if the value of the range includes 1, there is no difference; adjusted for proton pump inhibitors, DOAC type, and daily DOAC dose.); *N* = number of patients; NNH = number needed to harm (if the value of the range includes infinity, there is no difference; NSS = not statistically significant; Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	?	?	✓
7. The follow-up was complete.	✓	✓	✓
8. The effect size of the primary outcome is clinically significant.	?	X	?

A = appraiser.

Funding & Conflicts of Interest

Funding: Heart and Stroke Foundation of Canada, Ontario Ministry of Health and Long-Term Care, University of Ottawa and The Ottawa Hospital Research Institute.

Conflicts of Interest: Two of the authors received fees from the pharmaceutical industry.

Potential Threats to Validity

Chance: Although the study population is large, there were few observed bleeding events in both groups.

Selection Bias: None detected.

Measurement Bias: Administrative data may contain errors in the classification of exposures and the occurrence of outcomes.

Analysis Bias: None detected.

Confounding: Residual confounding, as with all observational studies, due to imbalances in unknown confounding factors is possible. Further, results may be confounded by indication whereby patients prescribed clarithromycin may have had greater risk of hemorrhage than patients prescribed azithromycin.

Administrative Details

Key Words: Antibiotic; azithromycin; clarithromycin; direct oral anticoagulant (DOAC); emergency department (ED); hemorrhage.

Appraisers: Zeraatkar D; Worster A; Rigg K.

Reference(s):

1. Canadian Institute for Health Information. Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011. Canadian Institute for Health Information; 2013.
2. Voukalis C, Lip GY, Shantsila E. Drug-drug interactions of non-vitamin K oral anticoagulants. Expert Opin Drug Metab Toxicol. 2016;12(12):1445-1461.
3. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost. 2018;16(5):842-848.
4. Hill K, Sucha E, Rhodes E, et al. Risk of Hospitalization With Hemorrhage Among Older Adults Taking Clarithromycin vs Azithromycin and Direct Oral Anticoagulants. JAMA Intern Med. 2020;180(8):1-10.

CARDIO-RESP (PART I)

Research Question

What risk score most accurately identifies high-risk ED syncope patients?

BEEM Bottom Line

Why is this study important? Syncope is a common ED visit (1%), that may lead to over-hospitalization and low-value advanced testing (30-50%; 33% non-diagnostic) for potential serious causes (7-23% event rate of arrhythmia, MI, bleeding or death at 30d). Accurate risk-stratification of such patients is necessary to determine those high-risk patients needing admission vs. lower-risk patients who can be discharged with outpatient follow-up.

Which, if any, threats to validity are most likely to have an impact on the results and how? Limited search/language restrictions could have missed important studies/results. Not all patients received the same workup, so those "sicker" patients with higher risk scores would be more thoroughly investigated, leading to a "workup" bias that would over-inflate score performance accuracy.

How do the key results compare with the current evidence? The results here support prior reviews suggesting that the CSRS is the most methodologically sound and validated risk stratification tool for ED syncope patients.

How should this study impact the care of ED patients? The CSRS is the most accurate rule for differentiating high- vs. low-risk ED syncope patients who may warrant admission for more intensive workups in hospital.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Sweanor RAL, Redelmeier RJ, Simel DL, *et al*. Multivariable risk scores for predicting short-term outcomes for emergency department patients with unexplained syncope: A systematic review. Acad Emerg Med; 2021, 0-9. DOI: 10.1111/acem.14203.

Design: Systematic review of CDR validation studies.

Population: *Included:* Patients evaluated for ED syncope age 12+ (not studies with all patients <18yo).
Excluded: Studies with risk score results that could not be blinded from study outcomes.

Index Test: Multivariate risk scores for syncope.

Reference Test: Clinical outcomes at 30d post-ED visit.

Diagnosis of Interest: Causes of syncope with a 30d adverse effect.

Key Results: *N* = 24234 patients in 17 studies. 7.5% of ED syncope patients had 30d adverse event rate.

Rule	*Diagnostic Measures*	I^2
San Francisco Syncope Rule (9 studies, 6311 pt visits). 1.4-11% event rate	LR+ = 1.1-2.2, LR- = 0.03-0.63 (Positive score ≥ 1/5)	
OESIL Rule (1 study, 187 pts), 6.4% event rate at 7days (AMI)	LR+ = 1.0 (0.68-1.6) LR- = 0.94 (0.41-2.1) (Positive score ≥ 2/4)	
Boston Syncope Rule (3 studies, 757 pts.), 6.4-25% event rate	LR+ = 1.3-2.6 LR- = 0.01-0.48 (Positive score ≥ 1/8)	
ROSE Rule (2 studies, 1254 pts), 6.4-7.6% event rate	LR+ = 1.2-3.5 LR- = 0.1-0.2 (Positive score ≥ 1/8)	
Cdn Syncope Risk Score (CSRS; 2 studies, 7849 pts), 3.6-3.7% event rate at 30d	LR+ (score>4) = 11 (8.9-14) LR- (score≤0) = 0.10 (0.06-0.20)	

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	?
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	X
9. The subgroups were stated a priori and appropriate.	X
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	X

A1 = S.Upadhye

ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: Not reported.

Conflicts of Interest: Not reported.

Potential Threats to Validity

Chance: None or enter text here.

Selection Bias: None or specify comprehensive searches; publication bias. Reasonable electronic search, screening of reference lists. Limited to English language. No gray literature used. No comment on publication bias.

Measurement Bias: No distinct quality assessment tool used to assess included studies; authors used an amalgam of QUADAS, QIPS and TRIPOD criteria. No included reporting of final quality assessments.

Analysis Bias: No meta-analysis due to likely heterogeneity of outcomes measures (between scores, and within same-score studies).

Confounding: Inclusion of pre-syncope patients who are less well defined, and whose outcomes may confuse the rule accuracy calculations of true syncope patients.

Administrative Details

Key Words: syncope predictors, risk scores, outcomes

Appraisers: Upadhye S; LAST NAME OF FIRST AUTHOR & FIRST INITIAL. Do not separate last name and first name initial with commas.

Reference(s): Sweanor RAL, Redelmeier RJ, Simel DL, Albassam OT, Shadowitz S, Etchells EE. Multivariable risk scores for predicting short-term outcomes for emergency department patients with unexplained syncope: A systematic review. Acad Emerg Med; 2021, 0-9. DOI: 10.1111/acem.14203.

PMID: 33382159

Research Question

What are the predictors and frequency of spontaneous conversion (SCV) back to sinus rhythm in ED patients with acute atrial fibrillation?

BEEM Bottom Line

Why is this study important? Many patients with acute atrial fibrillation (AAF) in the ED will spontaneously revert prior to medical/electrical cardioversion. This study aimed to identify predictors of spontaneous reversion.

Which, if any, threats to validity are most likely to have an impact on the results and how? Some variability in determinants of SCV (eg. Time of symptom onset, use of anti-arrhythmic meds) confound accurate classification of AAF patients, and the predictor values associated with SCV.

How do the key results compare with the current evidence? N/A

How should this study impact the care of ED patients? A better understanding of SCV predictors can facilitate ED discharge planning with rate control strategies and subsequent follow-up management.

Suneel Upadhye MD MSc FRCPC
Associate Professor, Emergency Medicine/ Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Pluymaekers N, Hermans A, Linz DK, *et al*. Frequency and Determinants of Spontaneous Conversion to Sinus Rhythm in Patients Presenting to the Emergency Department with Recent-onset Atrial Fibrillation: A Systematic Review. Arrhtym Electrophys Rev 2020; 9(4): 195-201. DOI: https://doi.org/10.15420/aer.2020.34

Design: Systematic review of all studies examining SCV to sinus rhythm in ED.

Population: *Included:* Patients in ED with AAF who spontaneously converted (SCV) to sinus rhythm.
Excluded: Patients with AAF seen in outpt clinics.

Intervention: N/A

Comparison: N/A

Outcomes: *Primary:* Rate of SCV in ED patients.
Secondary: Determinants of ED SCV, adverse events.

Key Results: *25 studies* = 4885 patients. **Definition:** conversion was defined as spontaneous if the patient converted to sinus rhythm without active cardioversion (meds/electricity), with rate control and/or placebo medication allowed. If patients were treated with placebo, digoxin, beta blockers or non-dihydropyridine calcium channel blockers and converted to sinus rhythm, it was considered SCV for this review.

Outcome	
Primary:	SCV rate varied from 9-83% in included studies. The most important SCV predictors were: shorter duration of AAF (<24hrs, <48hrs or longer), fewer prior AAF episodes, normal atrial dimensions, absence of prior heart failure/other underlying heart disease. There was insufficient data to differentiate “early vs late” SCV predictors.
Secondary:	Bleeding and stroke events were rare.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The methods used to combine the included primary studies were reported and valid.	N/A
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Not reported.

Conflicts of Interest: None (disclosed).

Potential Threats to Validity

Chance: None?

Selection Bias: Broad search for articles, English language only. No comments on publication bias assessment.

Measurement Bias: Some variance in outcomes based on inclusion/exclusion of first-time AAF vs all-comers, and whether pts were on anti-arrhythmic meds/digoxin. Studies varied in when they defined the duration of AAF (pt-reported symptom onset vs ED registration time).

Analysis Bias: Higher risk of bias with included smaller observational studies.

Confounding: Inclusion of consecutive patient sampling.

Administrative Details

Key Words: Spontaneous conversion, AF, determinants, emergency care

Appraisers: Upadhye S.

Reference(s): Pluymaekers N, Hermans A, Linz DK, Dudink E, Luermans J, Weijs B, Vernooy K, Crijns H. Frequency and Determinants of Spontaneous Conversion to Sinus Rhythm in Patients Presenting to the Emergency Department with Recent-onset Atrial Fibrillation: A Systematic Review. Arrhtym Electrophys Rev 2020; 9(4): 195-201. DOI: https://doi.org/10.15420/aer.2020.34

Research Question

Is a Drug-Shock treatment strategy (compared to Shock-Only) superior for ED acute atrial flutter conversion to sinus rhythm?

BEEM Bottom Line

Why is this study important? Although rare, treatment of symptomatic ED acute atrial flutter can be achieved via a Drug-Shock vs. Shock-Only strategy.

Which, if any, threats to validity are most likely to have an impact on the results and how? This is a planned substudy of a larger ED acute AFib trial; may have been under-powered to detect an MCID of 10% between the two strategies.

How do the key results compare with the current evidence? Results are congruent with prior (Canadian) studies that show excellent outcomes for immediate rhythm control strategies can be achieved, with high ED discharge rates and sustained NSR.

How should this study impact the care of ED patients? There is no statistical difference between either treatment strategy, both during the ED visit, and at 14day follow-up. Procainamide is NOT recommended as the Drug choice for acute Aflutter. Shared decision-making with patients are needed to make an appropriate management decision.

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Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Stiell IG, Sivilotti MLA, Taljaard M, *et al*. A randomized, controlled comparison of electrical versus pharmacological cardioversion for emergency department patients with acute atrial flutter. CJEM. 2021 May;23(3):314-324. doi: 10.1007/s43678-020-00067-7.

Design: Enter text here. State true design not what the investigators call it.

Population: *Included:* Stable patient with symptomatic acute atrial flutter ≥3hrs duration with onset within last 48hrs, onset within 7days with adequate anticoagulation ≥4 weeks, or onset within 7days with no left atrial thrombus on TEE.
Excluded: Hemodynamic instability, required immediate emergency cardioversion (sBP <100), rapid ventricular pre-excitation, acute coronary syndrome, pulmonary edema), spontaneous reversion prior to randomization, previously enrolled in study, non-arrhytmia primary presentation (eg. CAP, PE, sepsis). Other patient safety concerns (listed in online Appendix).

Intervention: Attempted pharmacological cardioversion with IV procainamide (15 mg/kg over 30 min, max 1500mg) followed by electrical cardioversion (≥ 200J x3) if necessary. Infusion was stopped if patient converted to NSR, QTc prolongation >35%, QRS interval >120ms, HR <60bpm or sBP <100mmHg not responsive to IV fluid bolus. (Drug-Shock)

Comparison: Placebo infusion followed by electrical cardioversion. (Shock Only)

Outcomes: *Primary:* Conversion to/maintenance of NSR for 30+ minutes post randomization/3 shocks. Verified by blinded Adjudication committee (2 ED physicians/1 electrophysiology cardiologist).
Secondary: ED length of stay, cardiac rhythm at disposition, adverse events during ED visit. 14day ECG rhythm, recurrence of atrial fibrillation, ED return visits, hospital admissions, stroke, and survival.

Key Results: *N* = 76 patients. Drug-Shock 33 pts, Shock-Only 43 pts.

Sig.	*Outcome*	*Intervention*	*Control*	*AD (95% CI)*	*NNT (95% CI)*
NSS	Primary conversion to NSR	33 (100%)	40 (93%)	7% (-6 to 14%) (p=0.25)	N/A
	ED LOS	9.4hrs	7.5hrs	1.9hrs (-1.2 to 5) (p=0.50)	
	NSR at disposition	100%	100%	N/A	N/A
	14day NSR	92%	91%	N/A	
	14d Rec AFib	0	2.9%	NS	
	14d Return ED visits	21.2%	18.6%	NS	
	14d admission	3%	0	NS	
	Stroke or death	0	0	NS	
SS	Transient ED hypotension	24%	2.3%	21.7% (p=0.004)	

ARR = absolute risk reduction (if the CI includes the value 0, there is no difference in risk between the groups and the NNT is not estimable); CI = confidence interval; *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	X
2. The patients were adequately randomized (allocation sequence adequately generated).	✓
3. The allocation sequence was adequately concealed.	✓
4. The patients in all groups were similar with respect to prognostic factors.	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	X

A1 = S. Upadhye

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Grants from CIHR, Heart & Stroke Foundation of Canada.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: Planned for 50pts enrolled (part of a larger AFib study); eventually screened 165 and enrolled 76.

Selection Bias: Some differences noted between both groups at baseline. Convenience sampling strategy may have resulted in missed eligible patients.

Measurement Bias: None? Under-powered to adequately rule out MCID 10%.

Analysis Bias: Primary ITT. Secondary modified ITT excluding rhythm converters prior to study infusion. Eleven patients were excluded post hoc for an actual AFib Dx (not Aflutter).

Confounding: Independent factors affecting the outcome; clinicians to comment. Despite block randomization, the two groups were not evenly balanced for baseline demographics.

Administrative Details

Key Words: Atrial flutter, cardioversion, emergency department, procainamide

Appraisers: Upadhye S.

Reference(s): Stiell IG, Sivilotti MLA, Taljaard M, Birnie D, Vadeboncouer A, Hohl CM, McRae AD, Morris J, Mercier E, Macle L, Brison RJ, Thiruganasambandamoorthy V, Rowe BH, Borgundvaag B, Clement CM, Brinkhurst J, Brown E, Nemnon MJ, Wells GA, Perry JJ. A randomized, controlled comparison of electrical versus pharmacological cardioversion for emergency department patients with acute atrial flutter. CJEM. 2021 May;23(3):314-324. doi: 10.1007/s43678-020-00067-7.

Research Question

What is the diagnostic accuracy of ED POCUS in assessing acute adult dyspnea?

BEEM Bottom Line

Why is this study important? Enter text here. Notes: Overall, this review supports the use of adjunct POCUS in assessing ED dyspnea to improve diagnostic accuracy, but not as a substitute for standard testing. None of the studies addressed potential harms of false negatives/positives of ED POCUS and unnecessary follow-up testing.

Which, if any, threats to validity are most likely to have an impact on the results and how? Different prevalences of target diseases could cause spectrum bias, and influence the diagnostic performance of index POCUS testing. Heterogeneity due to differential reference standards, variable "indeterminate" results reporting/analyses and overall high risk of bias in included studies (55%) precluded the ability to pool results for meta-analyses (except for CHF).

How do the key results compare with the current evidence? Overall these results support the growing role of ED POCUS as a diagnostic ADJUNCT in assessing acute ED dyspnea patients, but not as a replacement for current standardized testing.

How should this study impact the care of ED patients? For ED physicians who are trained and experienced, adding POCUS to the bedside testing of acute dyspnea patients can improve diagnostic accuracy.

Suneel Upadhye, MD MSc FRCPC

Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University

Study Summary

Article: Gartlehner G, Wagner G, Affengruber L, Chapman A, Dobrescu A, Klerings I, Kaminski-Hartenthaler A, Speil AO. Point-of-Care Ultrasonography in Patients with Acute Dyspnea: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. Annals Int Med 2021; doi:10.7326/M20-5504

Design: State true design not what the investigators call it. Systematic narrative review and meta-analysis of

Population: Adult patients with acute dyspnea attributable to: Congestive heart failure (CHF), pleural effusion, pneumonia , pulmonary embolism (PE)

Index Test: Point-of-care US (POCUS)

Reference Test: Standard diagnostic testing for each clinical condition.

Diagnosis of Interest: Congestive heart failure (CHF), pleural effusion, pneumonia , pulmonary embolism (PE).

Key Results:

N/Studies	*Measure (95% CI)*	*I^2*
572/3 (Low/unclear risk of bias)	POCUS ADDED to Standard Dx Pathways: Sensitivity (Range): 0.70-1.00 (0.52-1.00) for all target conditions Specificity (Range): 0.63-1.00 (0.52-1.00) for all target conditions	N/A
8626/49 (unclear/high risk of bias	POCUS to REPLACE Std Dx Pathways: Sensitivity (CHF; 5 studies) = 0.76 (0.48–0.91) Specificity (CHF; 5 studies) = 0.96 (0.90–0.98)	

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	?
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	?
9. The subgroups were stated a priori and appropriate.	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	X

A1 = S Upadhye

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: Internal funding from American College of Physicians (ACP).

Conflicts of Interest: None reported (available online).

Potential Threats to Validity

Chance: None.

Selection Bias: Insufficient number of studies to assess for publication bias. Studies selected were all conducted in countries with High Development Index scores.

Measurement Bias: High heterogeneity between studies precluded formal meta-analyses for most clinical outcomes (except CHF). Lack of reporting of POCUS "indeterminate" results; introduces bias in subsequent calculations of index test performance.

Analysis Bias: Many of the included studies (55%) were deemed to have high risk of bias.

Confounding: Different prevalences of confirmed cases for different conditions may have led to spectrum bias in assessing Dx test accuracy. Based on POCUS provider experience and patterns of use, there was minimal impact on sensitivity, but variable changes in specificity. Different studies used different reference standards beyond chart reviews, discharge diagnoses, CXR results, chest CT results, or mixed standards; this can have an influence on the index test performance metrics.

Administrative Details

Key Words: Point-of-care ultrasonography (POCUS), CHF, pleural effusion, pneumonia, pulmonary embolism.

Appraisers: Upadhye S, ; LAST NAME OF FIRST AUTHOR & FIRST INITIAL. Do not separate last name and first name initial with commas.

Reference(s): Gartlehner G, Wagner G, Affengruber L, Chapman A, Dobrescu A, Klerings I, Kaminski-Hartenthaler A, Speil AO. Point-of-Care Ultrasonography in Patients with Acute Dyspnea: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. Annals Int Med 2021; doi:10.7326/M20-5504.

Research Question

What is the utility of using ED POCUS in the assessment of acute dyspnea?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? This guideline is very relevant to the increasingly prevalent practice of ED POCUS for various bedside diagnostic tests. This CPG confirms that there is utility in adding ED POCUS for diagnosing acute dyspnea related to CHF/pleural effusion/pneumonia/PE as an additional adjunct to usual Dx testing strategies, but NOT as a substitute for these. Addition of ED POCUS with lower false positives/negatives associated with standard testing. No direct complications noted for using ED POCUS. Access to formal US devices, and training/experience with ED POCUS for dyspnea will be obvious (but surmountable) barriers.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? There were no significant validity threats in how this CPG group constructed this guidance document. All key steps for "trustworthy" CPG production were followed (IOM 2011 Standards). Authors used the GRADE methodology framework appropriately, and reported all steps explicitly. Outcomes were limited to diagnostic accuracy, but did not examine the following: quality of life, ICU admissions, disease-specific outcomes (unnecessary antibiotics use, respiratory support, referral times, use of lung CT). There was insufficient information to analyze the impact of POCUS on mortality, ED time to diagnosis nor time to treatment.

How should this guideline, and specifically which recommendations should impact the care of ED patients? For ED physicians trained/experienced with ED POCUS, this modality can be a valuable **adjunct** to standard testing modalities for acute dyspnea due to CHF/pleural effusion/CAP/PE in the ED.

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Guidelines Methodologist, CAEP/SAEM-GRACE groups (non-profit)
Curator, EMGuidelines website (non-profit)

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Assisstant Professor, Department of Medicine, Division of Emergency Medicine
Emergency & Critical Care Physician, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Qaseem A, Etxeandia-Ikobaltzeta I, Mustafa RA, Kansagara D, Fitterman N, Wilt TJ. for Clinical Guidelines Committee of the American College of Physicians. Appropriate Use of Point-of-Care Ultrasonography in Patients with Acute Dyspnea in Emergency Department or Inpatient Settings: A Clinical Guideline from the American College of Physicians. Annals Int Med 2021. doi:10.7326/M20-7844.

Design: Clinical Practice Guideline.

Population: Adult ED patients with acute dyspnea, later confirmed with 1 of the following: acute CHF +/- pulmonary edema, pulmonary embolism (PE), pleural effusion, pneumonia, or pneumothorax (PTX).

Scope: This guideline is intended for ED clinicians who take care of adult dyspnea patients.

Key Results: **Overall, the addition of ED POCUS (to standard Dx pathway) increased the proportion of correct ED dyspnea diagnoses from 59-91% (ARD 31.9%, 95%CI 22.4-53.8%); moderate certainty evidence.**

Recommendation	*Strength*	*Quality of Evidence*
Clinicians may use point-of-care ultrasonography **in addition to the standard diagnostic pathway** when there is diagnostic uncertainty in patients with acute dyspnea in the ED.	Conditional	Low
There was insufficient evidence to make a recommendation for use of ED POCUS to **replace** standard Dx pathway (no direct results for health outcomes of interest).	None	No direct Evidence

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓	✓
2. Systematic methods were used to search for evidence.	✓	✓
3. The criteria for selecting the evidence are clearly described.	✓	✓
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓	✓
7. Experts externally reviewed the guideline prior to its publication.	✓	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓	✓

A1 = S. Upadhye A2 = S. Sharif

Funding & Conflicts of Interest

Funding: Provided exclusively by American College of Physicians (ACP).

Conflicts of Interest: Full disclosure/management of CoI. No significant concerns noted.

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **YES; 2 patient stakeholders included among various clinical participants.**

Presentation: Well organized with easy to find recommendations? **YES**

Comprehensive: Was the information to inform decision-making complete? **YES**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **YES. NOT applicable to handheld devices.**

Administrative Details

Key Words: Acute dyspnea; CHF; ED POCUS; pleural effusion; pneumonia; pulmonary embolism.

Appraisers: Upadhye S, Sharif S.

Reference(s):

1. See Article above.
2. Supporting Systematic Review (see BEEM manual). Ann Intern Med. doi:10.7326/M20-5504. PMID: 33900798.

Research Question

Which of the 4 published decision aids provides the highest sensitivity to rule-out myocardial infarction and major adverse cardiac events?

BEEM Bottom Line

Why is this study important? Multiple decision aids to risk stratify emergency department (ED) patients with suspected acute coronary syndromes (ACS) currently are in use. This study compares the diagnostic performance of the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid, the Emergency Department Assessment of Chest Pain (EDACS) score, the History, ECG, Age, Risk factors and Troponin (HEART) score, and the Thrombolysis in Myocardial Infarction (TIMI) risk score.[1-4]

Which, if any, threats to validity are most likely to have an impact on the results and how? There is concern for incorporation bias because cardiac troponin (cTn) levels were used to diagnose acute myocardial infarction (AMI) in both the decision aids and the outcomes. The HEART, TIMI, and EDACS decision aids were all slightly modified in their use, which may have introduced a disadvantage to their performance against the reference standard and the T-MACS decision aid. The results are based on a small number of outcomes that were adjudicated and, therefore, not completely objective. As such, a change in just a single outcome could have a significant impact on the final results. Finally, the analysis excluded patients without a complete set of data which may have had greater impact on the HEART and TIMI scores because of the number and subjective nature of their variables.

How do the key results compare with the current evidence? This study affirms that newer, ED data-driven decision aids (T-MACS and EDACS) can rule-out a larger number of patients than the HEART and TIMI scores. These results are congruent with a retrospective study of 118,822 adult ED patients evaluated for possible ACS in a United Kingdom (UK) integrated health care system comparative study of the EDACS (original and simplified) and modified HEART risk scores using a contemporary cTnI at the lower limit of quantitation (LoD < 0.02 ng/ml) cutoff.[5] The authors reported that the original EDACS identified the largest proportion of patients as low risk of a major adverse cardiac event (MACE) at 60 days. Data from the current study also confirm a single high-sensitivity cTn (hs-cTn) value below the LoD provides high clinical sensitivity to rule-out AMI.

How should this study impact the care of ED patients? The T-MACS and EDACS are the preferred decision aids for ED use and together with a single hs-cTn at the LoD can both rule out AMI and identify those at low risk of subsequent MACE. However, caution should be taken in assessing patients with recent symptom onset.

Pete Kavsak, PhD, FCACB, FCCS
Professor, Department of Pathology and Molecular Medicine
McMaster University
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Conflict of Interest (ICMJE): Dr. Kavsak has received speaker honoraria and unrestricted grants from cTn assay manufacturers and has a patent pending.

Andrew Worster, MD, CCFP(EM), MSc, FCFP
Professor, Division of Emergency Medicine, Departments of Medicine & Health Research Evidence & Impact, McMaster University
Hamilton, ON, Canada
Conflict of Interest (ICMJE): Dr. Worster has a patent pending.

Study Summary

Article: Body R, Morris N, Reynard C, et al. Comparison of four decision aids for the early diagnosis of acute coronary syndromes in the emergency department. Emerg Med J. 2020 Jan;37(1):8–13.

Design: Nested (Bedside Evaluation of Sensitive Troponin [BEST] study), multicenter (UK EDs), prospective, cohort study.

Population: *Included:* Presumably adults (age unspecified) presenting to the ED with discomfort in the chest epigastrium, arms, shoulders or neck of apparent non-cardiac cause and suspected to be from ACS.
Excluded: Unable or unwilling to provide written informed consent; evidence of ST elevation myocardial infarction; another medical condition requiring hospital admission (including type 2 AMI); peak symptoms > 12 hours before ED presentation.

Index Test(s): T-MACS decision aid; EDACS score; HEART score; TIMI risk score, and a single cTn measurement using the Siemens ADVIA Centaur hs-cTnI assay.

Reference Test(s): Serial hs-cTnI measurements upon ED arrival and 3 hours later if using a hs-cTn assay and 6 hours later if using a contemporary cTn assay.

Outcomes: *Primary:* Adjudicated diagnosis of type 1 AMI as defined by the 3rd Universal Definition of Myocardial Infarction.
Secondary: MACE including AMI, all-cause mortality and revascularization.

Key Results: *N* = 999 (AMI = 132; no AMI = 867).

CDR	*Sensitivity (95% CI)*	*Specificity (95% CI)*	*LR+ (95% CI)*	*LR– (95% CI)*	*False Negatives*
T-MACS	99.2 (95.7 to 100.0)	53.3 (49.9 to 56.7)	1.48 (1.37 to 1.56)	0.02 (0.14 to 0.00)	1 (0.11 %)
EDACS	96.2 (92.2 to 99.4)	55.1 (51.4 to 58.7)	2.14 (1.90 to 2.41)	0.07 (0.15 to 0.01)	5 (0.59%)
HEART	91.8 (85.0 to 96.2)	38.6 (35.1 to 42.2)	1.50 (1.31 to 1.66)	0.21 (0.43 to 0.09)	11 (1.24%)
TIMI	97.5 (92.9 to 99.5)	22.2 (19.4 to 25.2)	1.25 (1.15 to 1.33)	0.11 (0.37 to 0.02)	3 (0.35%)

CDR = clinical decision rule; CI = Confidence Interval; LR = Likelihood Ratio; *N* = number of patients.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were representative of those likely to undergo testing in the ED.	✓	✓	✓
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	?	?	X
3. All patients underwent the same diagnostic evaluation.	?	X	X
4. All tests were conducted within similar time frames to preclude changes in disease status.	✓	✓	✓
5. The reference standard criteria for the candidate diagnoses are explicit and reproducible.	✓	✓	✓
6. The reference standard was applied regardless of and blinded to the index test result.	✓	✓	✓
7. The assignment of the candidate diagnoses was explicit and reproducible.	✓	✓	✓
8. Most (> 80%) patients received a diagnosis.	✓	✓	✓
9. Undiagnosed patients received adequate clinical follow-up.	✓	✓	✓
10. The estimates of disease probability are clinically significant.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Manchester University NHS Foundation Trust with cTn reagents provided Siemens without charge.

Conflicts of Interest: The senior author has received speaker fees from multiple cTn assay manufacturers.

Potential Threats to Validity

Chance: The analyses did not include the full sample and, therefore, the study was underpowered to achieve the desired precision parameter range of 5%.

Selection Bias: It is unclear whether patients were enrolled consecutively, and given that there were more AMIs than expected, it's possible that the sample enrolled higher risk patients. However, the patients were enrolled prospectively so there is no reason to suspect a high risk of selection bias.

Measurement Bias: There is a risk of incorporation bias despite outcome adjudicators being blinded to the results of the hs-cTnI level and decision aid results given that they were provided with cTn levels routinely collected as part of clinical practice. All decision aids except T-MACS were modified slightly from their original intended use, which may have biased the diagnostic accuracy results against the other 3 decision aids.

Analysis Bias: The authors used a complete case analysis and, therefore, excluded patients with incomplete data on any of the decision aids or reference standard. This differentially affected the HEART and TIMI decision aids because there were more variables required to apply these aids and, therefore, were more likely to have missing data. While the authors conclude that those excluded 405 patients without sample data for the hs-cTnI assay did not bias the results, there is no comparison of demographic characteristics to those included in the analysis to support this claim.

Confounding: There is no standardization of cTn tests and differences between cTnT and cTnI are expected as these are 2 different proteins.

Administrative Details

Key Words: Acute myocardial infarction (AMI); ED Assessment of Chest Pain Score (EDACS); History, ECG, Age, Risk factors and Troponin score (HEART); Troponin-only Manchester Acute Coronary Syndromes (T-MACS); Thrombolysis in Myocardial Infarction (TIMI); Troponin.

Appraisers: Bedard C; Worster A; Kavsak P.

Reference(s):

1. Body R, Almashali M, Morris N, et al. Diagnostic accuracy of the T-MACS decision aid with a contemporary point-of-care troponin assay. Heart 2019;105:768–74.
2. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicentre validation of the heart score. Critical Pathways in Cardiology 2010;9:164–9.
3. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker. J Am Coll Cardiol 2012;59:2091–8.
4. Than M, Flaws D, Sanders S, et al. Development and validation of the Emergency Department Assessment of Chest pain Score and 2 h accelerated diagnostic protocol. Emerg Med Australas 2014;26:34–44.
5. Reaney PDW, Elliott HI, Noman A, et al. Risk stratifying chest pain patients in the emergency department using HEART, GRACE and TIMI scores, with a single contemporary troponin result, to predict major adverse cardiac events. Emerg Med J. 2018 Jul;35(7):420–427.

Research Question

Is a single troponin measurement below the level of detection superior to serial troponin measurements for the safe discharge of chest pain patients?

BEEM Bottom Line

Why is this study important? The rapid and safe discharge of chest pain patients who do not have acute coronary syndrome (ACS) or another serious etiology is a long-term holy grail of emergency medicine. If a single blood test could rule out ACS in a high percentage with a high negative predictive value, it would come near to that holy grail. This trial compares a strategy of a single undetectable below the limit of detection (< LoD) high-sensitivity cardiac troponin (hs-cTn) and non-ischemic electrocardiogram (ECG) to the current standard emergency department (ED) care of serial measurements a hs-cTn to rule out ACS.

Which, if any, threats to validity are most likely to have an impact on the results and how? Although the estimated 9% difference in outcome rates between the two arms was met, the outcome rates were several times higher than anticipated in the sample size calculations and so the estimated 9% difference in outcome rates became a much smaller proportional difference. Multiple comparators in the control arm, other unexplained variability between sites, and probable contamination between study arms led to imprecise estimates of effect.

How do the key results compare with the current evidence? In a meta-analysis of hs-cTnT measurements in 9241 patients, 31% of initial values were < LoD (5 ng/L) with a negative predictive value (NPV) of 99.5% (95% confidence interval [CI]: 99.1 to 99.7).[1] In a pooled analysis of 3155 patients using a hs-cTnI (Abbott) assay, 19% of initial values were < LoD (5 ng/L) with a NPV of 99.5% (95% CI: 98.4 to 99.9).[2] An analysis of used stored samples collected in 2 prospective observational studies of 1871 patients using a hs-cTnI (Beckman) assay, 34% of patients had an initial value < LoD (2 ng/L) with an NPV of 99.5% (95% CI: 98.4 to 99.9).[3] Hence, previous research using all 3 hs-cTn assays used in this trial strongly supports the use of a single hs-cTn measurement < LoD to safely rule out 30-day death or myocardial infarction. However, the hs-cTn measurements were < LoD in only 19 to 34% of cases compared to the 46% reported in this randomized controlled trial (RCT).

How should this study impact the care of ED patients? The results of this study provide evidence that using the LoDED strategy is safe and could have a modest effect on ED length of stay (LOS). However, emergency physicians would do well to note that chest pain in the context of a high pretest probability, even with a hs-cTn below the LoD and non-ischemic ECG might still be due to ACS.

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No conflicts of interest (ICMJE)

Study Summary

Article: Carlton EW, Ingram J, Taylor H, et al. Limit of detection of troponin discharge strategy versus usual care: randomised controlled trial. Heart. 2020 Oct;106(20):1586-1594.

Design: Multicenter (8 UK hospitals), open-label, superiority, RCT.

Population: *Included:* Adults (≥ 18 years) presenting with chest pain peak symptoms < 6 hours (h) prior requiring investigations to rule out acute coronary syndrome (ACS) and non-ischaemic ECG (no new T-wave inversion of > 3 mm or ST depression of > 1 mm).
Excluded: Clear chest pain due to arrhythmia or other non-ACS condition at presentation; initial hs-troponin result known to treating clinician; hospital admission indicated for other medical/social reasons; lack of written informed consent; follow-up impossible; previous study inclusion; prisoner; pregnant; renal failure requiring dialysis.

Intervention: Limit of detection and ECG discharge (LoDED) strategy - eligible for discharge if undetectable hs-cTn level at presentation (irrespective of symptom onset time), non-ischemic ECG, no ongoing clinical concern.

Comparison: Usual rule-out strategies (control) - eligible for discharge if hs-cTn level at presentation and at 1 to 6 h normal (< 99th percentile) and low risk GRACE, TIMI or HEART score or non-ischemic ECG.

Outcomes: *Primary:* Discharge from hospital within 4 h of ED arrival without any major adverse cardiac event (MACE: cardiac death, type I acute myocardial infarction or emergency revascularization) within 30 days (d).
Secondary: ED LOS; hospital admission; hospital LOS; MACE 30-d incidence; comparative costs.

Key Results: *N* = 629 patients (mean age 53.8 years; 41% female).

Sig.	*Outcome*	*LoDED (%)*	*Usual Care (%)*	*OR (95% CI)*
NSS	Discharge ≤ 4 h without MACE ≤ 30 d	141/309 (46%)	114/311 (37%)	1.58 (0.84 to 2.98)

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; OR = odds ratio (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X	✓

A = appraiser: ITT= intention to treat.

Funding & Conflicts of Interest

Funding: UK National Institute for Health Research (NIHR).

Conflicts of Interest: One author received research funding and education honoraria from 2 of the hs-cTn bioassay manufacturers.

Potential Threats to Validity

Chance: Despite the increase in occurrence of the primary outcome, the study is at risk of type II error because the relative difference between groups was smaller than anticipated.

Selection Bias: The randomization and allocation procedures enabled a low risk of selection bias; however, the sample appears to have low generalizability to higher risk patients since the majority of enrolled patients were deemed low risk by treating physicians. Also, only about 50% of enrolled patients presented < 3 h from chest pain to blood draw (equivalent to 2 h from chest pain to presentation), which is the critical group to study; early presentation has been associated with a lower NPV, consistent with face validity. Lastly, it is unclear if all consecutive eligible patients were enrolled: over 9 months at 8 centers, there were only 632 enrolled, though another 1599 were excluded after assessment.

Measurement Bias: While detection bias is low, it is possible that physicians applied the LoDED strategy to patients randomized to usual care given the non-blinded nature of the study and the "usual care" already included the LoDED strategy at 4 of the 8 study centers. The control arm contained multiple different rule-out strategies contributing heterogeneity.

Analysis Bias: Potential contamination between study arms may have diluted a possible intervention effect. Substantial variability between sites also likely diluted effects and this could not be fully explained by different control rule-out strategies.

Confounding: None noted.

Administrative Details

Key Words: Acute myocardial infarction (AMI); high-sensitivity cardiac troponin (hs-cTn); limit of detection (LoD); major adverse cardiac event (MACE).

Appraisers: Bedard C; Worster A; Smith SW.

Reference(s):

1. Pickering JW, Than MP, Cullen L, et al. Rapid Rule-out of Acute Myocardial Infarction With a Single High-Sensitivity Cardiac Troponin T Measurement Below the Limit of Detection: A Collaborative Meta-analysis. Ann Intern Med. 2017 May 16;166(10):715-724.
2. Carlton E, Greenslade J, Cullen L, et al. Evaluation of High-Sensitivity Cardiac Troponin I Levels in Patients With Suspected Acute Coronary Syndrome. JAMA Cardiol. 2016 Jul 1;1(4):405-12.
3. Greenslade J, Cho E, Van Hise C, et al. Evaluating Rapid Rule-out of Acute Myocardial Infarction Using a High-Sensitivity Cardiac Troponin I Assay at Presentation. Clin Chem. 2018 May;64(5):820-829.

Research Question

What is the diagnostic utility of troponin testing in elderly patients with nonspecific complaints?

BEEM Bottom Line

Why is this study important? The study is one of the first to question the utility of troponin testing to diagnose acute coronary syndrome (ACS) in elderly patients presenting to emergency department (ED) with nonspecific complaints.

Which, if any, threats to validity are most likely to have an impact on the results and how? Almost half of the initial cohort was excluded as it comprised of patients whose triage note listed a nonspecific complaint, but the ED chart was subsequently found to list a primary focal complaint. This selection bias most likely resulted in underestimation of the true troponin testing frequency as providers may have overemphasized a focal complaint after viewing the troponin result, despite the triage presentation of nonspecific symptoms. Restriction to in-hospital outcomes may have missed some adverse events after hospital discharge. Without a comparison group of patients presenting with nonspecific complaints who did not receive a troponin test, these results are unable to associate the rate of troponin testing with any patient outcomes. Limitations inherent to retrospective chart reviews led to overestimation of both the prevalence of ACS in this population and the sensitivity and specificity of troponin testing.

How do the key results compare with the current evidence? In this study, troponin elevation was present in 19.9% of patients, with a positive predictive value of 6.1% for ACS. Other observational studies have also found a high false positive rate of troponin testing for ACS in elderly patients, attributable to the significant prevalence of comorbidities in this population.[1,2]

How should this study impact the care of ED patients? Troponin testing may be low yield in our geriatric patients with nonspecific complaints. It remains unclear whether elderly patients without ACS symptoms benefit from troponin testing.

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No conflicts of interest

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No conflicts of interest

Study Summary

Article: Wang AZ, Schaffer JT, Holt DB, et al. Troponin Testing and Coronary Syndrome in Geriatric Patients With Nonspecific Complaints: Are We Overtesting? Acad Emerg Med. 2020 Jan;27(1):6-14.

Design: Single-center (Indianapolis, IN, USA), database review, cohort study.

Population: *Included:* Adults (≥ 65 years) presenting with vague or nonspecific complaints including weakness, dizziness, fatigue, lethargy, altered mental status, light-headed, medical problem, examination requested, failure to thrive, or "multiple complaints" and had a troponin level measured in the ED.
Excluded: Patients with a focal chief complaint identified by the provider or fever ≥ 38.0°C at triage.

Exposure: Troponin I (Access, Beckman Coulter using 99th percentile cutoff of 0.04 ng/L) measurement in the ED.

Comparison: No troponin measurement.

Outcomes: *Primary:* Proportion of patients with verified nonspecific complaints who underwent troponin testing.
Secondary: Proportion of patients with elevated troponin levels; proportion of patients with ACS (as defined by the American Heart Association guidelines including: ST-elevation myocardial infarction, coronary revascularization or demonstration of acute occlusion, stenosis ≥ 70%, or inducible, troponin rise and fall in a pattern typical of ACS without an obvious alternative cause or unstable angina, i.e. cardiac chest pain without elevation in biomarkers[1]) at the index visit or within 30 days; the frequency of other causes of troponin elevation.

Key Results: *N* = 412 patients (239 [58%] female).

Outcome	*Criterion*	*Proportion (%)*	*Criterion*	*Proportion (%)*
Troponin Level	> 0.04 ng/L	82/412 (19.9)	≤ 0.04 ng/L	330/412 (80.1)
ACS Diagnosed	At Index	5/82 (6.09)	At 30 days	0/82 (0)
Non-ACS Diagnoses	Sepsis (#1)	22/77 (28.6)	Dehydration (#2)	7/77 (9.1)

N = number of patients.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	?	?	?
4. The outcome criteria were clinically appropriate for the research question.	X	X	X
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	✓	✓	✓
7. The follow-up was complete.	✓	?	X
8. The effect size of the primary outcome is clinically significant.	?	?	?

A = appraiser.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: Very low event rate therefore, likely underpowered to provide a precise estimate of ACS in this population.

Selection Bias: Given the screening procedures of the chart review, there may be missing cases of patients who were recorded at triage to present with a focal complaint but the provider then noted a nonspecific complaint or patients who presented to triage with a nonspecific complaint not listed in the EMR screening search. The presentation of 'nonspecific complaint' is diverse, therefore, it is uncertain how similar the sample is in terms of their prognostic risk. Furthermore, there is no comparison group of patients with nonspecific complaints without a troponin test. Without a comparison group, these results are unable to associate the rate of troponin testing with any patient outcomes.

Unstable angina (UA) was included as an ACS diagnosis but yet the diagnosis requires a specific complaint, i.e. chest pain. Hence, patients with UA should have been excluded as their inclusion could have falsely elevated the ACS proportion without even being included in the denominator.

Measurement Bias: Adjudication of ACS was limited to tests recorded in the EMR ordered at the discretion of the physician; therefore, a uniform gold standard was not applied to all patients. Follow-up data was also limited to information recorded in regional databases and may be subject to misclassification errors

Analysis Bias: The results of the utility of the troponin testing are likely overestimated given the high risk of verification bias since troponin results were often the only indication for a final diagnosis of ACS.

Confounding: Residual confounding as with all observational studies because of unknown prognostic factors that cannot be controlled for.

Administrative Details

Key Words: Acute coronary syndrome (ACS); elderly; myocardial infarction; nonspecific complaint; troponin.

Appraisers: Bedard C; Worster A; Chopra, S.

Reference(s):

1. Sedighi SM, Prud'Homme P, Ghachem A, et al. Increased level of high-sensitivity cardiac Troponin T in a geriatric population is determined by comorbidities compared to age. Int J Cardiol Heart Vasc. 2019 Mar 8;22:187-191.
2. Boeddinghaus J, Nestelberger T, Twerenbold R, et al. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. Eur Heart J. 2018 Nov 7;39(42):3780-3794.

Research Question

What are the latest guidelines for the diagnosis of acute aortic syndrome?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Acute aortic syndromes (AAS) represents a rare yet life-threatening problem for emergency department (ED) physicians and there is sparse evidence supporting diagnostic strategies with high sensitivity and or specificity. This clinical practice guideline (CPG) synthesizes the current evidence with clinical expertise in guiding ED physicians in the assessment and management of AAS. The document is authored primarily by ED physicians, ensuring its utility in ED practice.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? The clinical stratification of risk factors lacks supporting evidence and, therefore, is based on committee expert opinion. As such, the scoring of different features in the decision aid may lack validity and reliability. The performance of these clinical risk factors in this proposed algorithm await future validation. The integration of D-dimer testing into the decision-making process is a novel concept for most ED physicians and will likely require specific education and discussion to optimize uptake.

How should this guideline, and specifically which recommendations should impact the care of ED patients? This CPG offers concrete practical guidance for ED physicians to assess patients for potential AAS diagnosis by integrating D-dimer testing and minimizing the risk of unnecessary imaging radiation exposure. ED physicians can refer to the published clinical decision aid and an online tool soon to follow.

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No conflicts of interest (ICMJE)

Study Summary

Article: Ohle R, Yan JW, Yadav K, et al. Diagnosing acute aortic syndrome: a Canadian clinical practice guideline. CMAJ. 2020 Jul 20;192(29):E832-E843.

Design: Clinical Practice Guideline.

Population: Adults (≥ 18 years) with suspected AAS.
Exclusions: Pregnancy; recent (< 24 hr) cocaine use, leaky and or ruptured aortic aneurysms.

Scope: This is a guide for emergency medicine physicians, family physicians, internists, radiologists, vascular surgeons, cardiothoracic surgeons, critical care physicians, patients and decision-makers to select a diagnostic strategy for AAS (excluding ruptured or leaking aortic aneurysms) that is most likely to yield a diagnostic result with the minimum number of diagnostic tests and radiation exposure.

Key Results:

Recommendation	*Strength*	*CoE*
1a. Assess risk of AAS in patients with non-traumatic chest, abdominal, back pain and/or perfusion deficit, syncope, interarm blood pressure differential > 20 mm Hg or systolic blood pressure > 180 mm Hg. AAS risk factors include connective tissue and aortic valve diseases, recent aortic manipulation, thoracic or abdominal aortic aneurysm and history of AAS. High-risk AAS pain and physical exam features include abrupt onset, severe, tearing or migrating pain and new aortic regurgitation, pulse deficit, neurological deficit, hypotension or pericardial effusion respectively.	Strong	Low
1b. Assess AAS probability as low (≤ 0.5%), moderate (0.5 to 5%) or high (> 5 %).	Conditional	Low
2. If low (≤ 0.5%) probability of AAS, do not test.	Conditional	Low
3a. If moderate (0.5 to 5%) AAS probability, use D-dimer to rule out. If D-dimer positive, use ECG-gated CT.	Conditional	Moderate
3b. If moderate (0.5 to 5%) AAS probability and D-dimer or ECG-gated CT negative, no further testing.	Conditional	Low
4a. If high (> 5%) AAS probability, start with ECG-gated CT.	Strong	Moderate
4b. If high (> 5%) AAS probability, do not perform D-dimer testing.	Conditional	Moderate

CoE = certainty of Evidence; ECG-gated CT= ECG timed CT image capture.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓	✓	✓
2. Systematic methods were used to search for evidence.	✓	✓	✓
3. The criteria for selecting the evidence are clearly described.	✓	✓	✓
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓	✓	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓	✓	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓	✓	✓
7. Experts externally reviewed the guideline prior to its publication.	✓	✓	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓	✓	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓	✓	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Alternate Funding Plan Innovation grant from the Northern Ontario Academic Medical Association. No influence in CPG development process, nor creating recommendations.

Conflicts of Interest: None declared. Reported using Guideline International Network frameworks.

Potential Threats to Validity

Development: The stakeholders participating in the CPG development included ED physicians and nurses (academic, community, rural), surgeons (cardiothoracic and vascular), cardiac anaesthesiologists, cardiologists, critical care physicians, radiologists and patient representatives. Training and contributions of patient participants was not reported.

Presentation: The presentation is well organized with easy to find recommendations including a table that outlines the scoring of risk factors. Aggregate scoring levels for low/moderate/high pre-test probability are also presented along with a clinical algorithm to follow which is easy and linear.

Comprehensive: The information to inform decision-making was complete.

Clincal Validity: The recommendations are clinically sound and appropriate for the intended patients. The recommendations are laid out in a systematically intuitive manner and give concrete guidance for ED physicians assessing potential AAS patients.

Administrative Details

Key Words: Acute aortic syndrome; aortic dissection; D-dimer; computed tomography.

Appraisers: Worster A; Robichaud L; Upadhye S.

Reference(s): None.

CARDIO-RESP (PART II)

Research Question

What is the diagnostic accuracy of the EDACS score for ED chest pain assessment?

BEEM Bottom Line

Why is this study important? Rapid yet accurate risk stratification of ED chest pain patients can be useful in appropriately determining patients who can be safely discharged for outpatient follow-up vs. those patients requiring admission.

Which, if any, threats to validity are most likely to have an impact on the results and how? It is unclear how modification of the QUADAS-2 tool may have impacted study quality scores, and subsequent inclusion/exclusion for SR/MA. The lower sensitivity of EDACS in North American studies (96%) may lead to unacceptable high false negative rates (tolerance limit 1% for missed cases).

How do the key results compare with the current evidence? Multiple ED chest pain tools have been tested/validated to different degrees for ED use (eg. EDACS, HEART, Vancouver, etc.), so clinicians should choose that which makes most clinical sense/validated in their local practice.

How should this study impact the care of ED patients? Use of the EDACS risk tool may improve decision making in ED chest pain patients.

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Conflicts of interest: Inventor/Patent holder of Clinical Chemistry Score

Study Summary

Article: Boyle RSJ, Body R. The Diagnostic Accuracy of the Emergency Department Assessment of Chest Pain (EDACS) Score: A Systematic Review and Meta-analysis. Annals Emerg Med 2021 Apr;77(4):433-441. doi: 10.1016/j.annemergmed.2020.10.020. Epub 2021 Jan 16.

Design: Systematic review and meta-analysis of the EDACS risk tool for ED chest pain.

Population: *Included:* Studies including ED adult patients with minimum 5min chest pain or other ACS-like symptoms.
Excluded: Tests using a single troponin test or tests >3hrs after ED arrival.

Index Test: Use of EDACS score and hs-troponin levels.

Reference Test: Cardiac events adjudicated by 2 independent clinicians, using 3rd Universal AMI definitions.

Diagnosis of Interest: Major adverse cardiac events (MACE = STEMI, NSTEMI, CV death, cardiac arrest, ventricular arrhythmia, cardiogenic shock, high-grade AV block, emergency revascularization) at 30days.

Key Results: *N* = 11578 patients in 8 included studies. MACE rate 10.5% overall.
Missed MACE rate with EDACS score: 0.5%.

	Measure (95% CI)	I^2
	Sensitivity = 0.96 (0.90-0.99)	97%
	Specificity = 0.61 (0.56-0.66)	
	LR+ 2.47 (2.21-2.76), LR- = 0.06 (0.03-0.16); Diagnostic OR 38 (16-91)	
	AUC = 0.77 (0.73-0.80)	

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓
4. The selection of studies was unbiased and reproducible.	?	?
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	?	?
7. The quality of the primary studies is high.	✓	✓
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	X	X
9. The subgroups were stated a priori and appropriate.	✓	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓	✓

A1 = S. Upadhye A2 = A. Worster

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: Both authors have disclosed industry funding for research and other commercial activities.

Potential Threats to Validity

Chance: None?

Selection Bias: Low risk of publication bias (reported Deek's funnel plot).

Measurement Bias: Significant heterogeneity in different diagnostic assays used and threshold cutoffs between various studies.

Analysis Bias: Both authors worked together to assess study quality using a "modified" versions of QUADAS-2 tool?

Confounding: None or enter independent factors affecting the outcome; clinicians to comment.

Administrative Details

Key Words: EDACS score, chest pain, emergency department

Appraisers: Upadhye S, Worster A.

Reference(s): Boyle RSJ, Body R. The Diagnostic Accuracy of the Emergency Department Assessment of Chest Pain (EDACS) Score: A Systematic Review and Meta-analysis. Annals Emerg Med 2021 Apr;77(4):433-441. doi: 10.1016/j.annemergmed.2020.10.020. Epub 2021 Jan 16.

Research Question

What is the optimal use of high-sensitivity troponins to rule out myocardial infarction in ED chest pain?

BEEM Bottom Line

Why is this study important? This study confirms the diagnostic utility of using hs-troponins in ED chest pain pathways to rapidly rule-out NSTEMI and facilitate earlier safe discharge.

Which, if any, threats to validity are most likely to have an impact on the results and how? Minimal. The study authors used test cutoff thresholds that are congruent with most clinically acceptable miss rates. Most hospital laboratories cannot reliably measure troponin concentrations at the level of detection (LoD) required for some single test rule out pathways.

How do the key results compare with the current evidence? These results mirror 2 recent "real-world" RCTs suggesting that hs-troponin assays (many platforms), either singly or serially, can be useful to safely rule-out NSTEMI and facilitate rapid ED discharge. However, most hospital laboratories cannot reliably measure troponin concentrations at the level of detection (LoD) required for some single test rule out pathways. Single troponin measurement can miss NSTEMI in early presenters and those with lingering symptoms. Both rule and rule out strategies can be optimized with serial troponin measurements in combination with validated clinical decision tools.[1,2]

How should this study impact the care of ED patients? ED physicians should know what hs-troponin test is used in their hospital, and how to interpret single vs. serial results for individual patients, ideally in a structured pathway (that may or may not include an incorporated risk score).

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Conflicts of interest: Inventor/Patent holder of Clinical Chemistry Score

Study Summary

Article: Westwood ME, Armstrong N, Worthy G, *et al*. Optimizing the Use of High-Sensitivity Troponin Assays for the Early Rule-out of Myocardial Infarction in Patients Presenting with Chest Pain: A Systematic Review. Clin Chem 2021; 67 (1): 237-244. DOI: 10.1093/clinchem/hvaa280

Design: Systematic review; meta-analysis if 4+ studies available for the same assay index test.

Population: *Included:* Adults (_18 years) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source' (10) due to a suspected, but not proven, AMI
Excluded: Patients with STEMI

Index Test: Hs-troponin (multiple assays)

Reference Test: Case adjudication using the 3rd Universal AMI Definition (including measurement of troponin T or I (using any method) on presentation and 3-6 hours later or occurrence of MACE (any definition used in identified studies) during 30-day follow-up.

Diagnosis of Interest: Myocardial infarction (NSTEMI)

Key Results: *N* = 37 studies included.

N/Studies	*Measure (95% CI)*	I^2
Single Test	***Assay (cutoff): Sens/Spec***	
6 studies	Roche Elecsys (5ng/ml): 0.99 (0.98-100)/0.35 (0.25-0.46)	
3 studies	Abbott ARCHITECT (5ng/ml): 0.97 (0.95-0.98)/0.58 (0.57-0.59)	
1 study	Seimens (5ng/ml): 0.99 (0.97-1.00)/0.52 (0.50-0.55); two combined assays	
	Abbott ARCHITECT (2ng/ml): 1.00 (0.99-1.00)/0.21 (0.16-0.26)	
	Seimens (2ng/ml): 1.00 (0.99-1.00)/ 0.23-0.26 (0.21-0.28); two combined assays	
Multiple Tests	***Strategy (Assay): Sens/Spec (RoR = rule out rate)***	
1 study	ESC 0/1hr rule out pathway (Roche Elecsys): 0.99 (0.98-1.00)/0.68 (0.67-0.70); NSTEMI miss rate 0.67%	
2 studies	ESC 0/1hr rule out pathway (Abbott ARCHITECT): 0.99 (0.98-1.00)/0.57 (0.56-.059); overall RoR = 71%	
	ESC 0/1hr rule out pathway (Beckman Coulter): 0.99 (0.98-1.00)/0.70 (0.66-.74); overall RoR = 60%, miss rate 1.04%	
	ESC 0/1hr rule out pathway (Quidel TriageTrue): 1.00 (0.97-1.00)/0.66 (0.62-0.70); overall RoR = 55%	
	ESC 0/1hr rule out pathway (Siemens assays): 0.99 (0.95-1.00)/0.56 (0.52-0.60); overall RoR = 16%, miss rate 0.88%	
	High-STEACS (Abbott ARCHITECT): 0.99 (0.97-1.00)/0.76 (0.73-0.79); overall RoR = 65%, miss rate 0.73%	
	High-STEACS (Siemens Atellica): 0.98 (0.95-0.99)/0.74 (0.72-0.76); overall RoR = 65%, miss rate 1.45%	

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?	?
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓	✓
7. The quality of the primary studies is high.	?	?
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	✓	✓
9. The subgroups were stated a priori and appropriate.	✓	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓	✓

A1 = S. Upadhye A2 = A Worster

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: Multiple research grants/fellowships. No industry. Sponsor had no role in any research planning/conduct/reporting.

Conflicts of Interest: One author disclosed industry consultant/advisory fees, and speaking honoraria (R. Body)

Potential Threats to Validity

Chance: None?

Selection Bias: Unable to access online search strategy/selection details. No comment on publication bias assessments.

Measurement Bias: Unable to access online study quality assessment details.

Analysis Bias: All articles were data abstracted by one author, then double-checked by 2nd author.

Confounding: Incomplete literature on the utility of hs-troponins incorporated into clinical risk scores.

Administrative Details

Key Words: Chest pain, high-sensitivity troponins, myocardial infarction

Appraisers: Upadhye S; Worster A.

Reference(s):

1. Liu L, Mathias A, Kwong T, Worster A, Kavsak PA. Clinical chemistry score misses fewer deaths as compared to troponin T alone in a United States emergency department population. Clin Biochem. 2021 Jun 12:S0009-9120(21)00171-5. doi: 10.1016/j.clinbiochem.2021.06.002.

2. Kavsak PA, Cerasuolo JO, Ko DT, Ma J, Sherbino J, Mondoux SE, Perez R, Seow H, Worster A. High-Sensitivity Cardiac Troponin I vs a Clinical Chemistry Score for Predicting All-Cause Mortality in an Emergency Department Population. CJC Open. 2020 Mar 20;2(4):296-302. doi: 10.1016/j.cjco.2020.03.004.

Research Question

What are the latest guidelines for the management of recurrent low-risk ED chest pain?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? This guideline attempts to address the ED management of recurrent low-risk chest pain patients.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Lack of direct high-quality evidence led to "conditional" recommendations for many key questions. A single patient participant provided some patient values/preferences/outcomes prioritization.

How should this guideline, and specifically which recommendations should impact the care of ED patients? Guideline recommendations provide some reassurance and "warranty" information on low-risk recurrent patients who have had normal/non-significant coronary imaging within the prior 2 years, and otherwise negative high-sensitivity troponin tests during ED visit. They also provide the evidence behind which patients would be suitable for a single high-sensitivity troponin testing.

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Guidelines Methodologist, CAEP/SAEM-GRACE groups (non-profit)
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No conflicts of interest/Identify conflicts (ICMJE)

**Author on this original publication

Study Summary

Article: Musey Jr PI, Bellolio F, **Upadhye S**, *et al*. Guidelines for reasonable for appropriate care in the emergency department (GRACE): Recurrent low-risk chest pain in the emergency department. Acad Emerg Med 2021; 00:1-27. DOI: 10.1111/acem.14296

Design: Clinical Practice Guideline.

Population: Adult patients with recurrent low risk chest pain.

Scope: This guideline is intended for ED physicians assessing adult recurrent chest pain patients.

Key Results: See Specific Guideline Questions (below)

Recommendatio	*Strength*	*Quality of Evidence*
None	None	High
Rec 6.	In adult patients with recurrent, low-risk chest pain and prior CCTA <2 years with no coronary stenosis, we **suggest** no further diagnostic testing other than a single, high-sensitivity troponin below a validated threshold to exclude ACS within that 2-year time frame. (Conditional)	Moderate
Rec 1	In adult patients with recurrent, low-risk chest pain, for >3 h duration we **suggest** a single, high-sensitivity troponin below a validated threshold to reasonably exclude ACS within 30 days. (Conditional)	Low
Rec 2	In adult patients with recurrent, low-risk chest pain, and a normal stress test within the previous 12 months, we **do not recommend** repeat routine stress testing as a means to decrease rates of MACE at 30 days. (Conditional)	
Rec 4	In adult patients with recurrent, low-risk chest pain and non-obstructive (<50% stenosis) CAD on prior angiography within 5 years, we **suggest** referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional)	
Rec 5	In adult patients with recurrent, low-risk chest pain and no occlusive CAD (0% stenosis) on prior angiography within 5 years, we **recommend** referral for expedited outpatient testing as warranted rather than admission for inpatient evaluation. (Conditional)	
Rec 7	In adult patients with recurrent, low-risk chest pain, we **suggest** the use of depression and anxiety screening tools as these might have an effect on healthcare use and return ED visits. (Conditional)	
Rec 8	In adult patients with recurrent, low-risk chest pain, we **suggest** referral for anxiety or depression management, as this might have an impact on healthcare use and return ED visits. (Conditional)	

Rec 3	In adult patients with recurrent, low-risk chest pain, there is **insufficient evidence** to recommend hospitalization (either standard inpatient admission or observation stay) versus discharge as a strategy to mitigate major adverse cardiac events within 30 days. (No evidence)	Very Low

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓	✓
2. Systematic methods were used to search for evidence.	✓	✓
3. The criteria for selecting the evidence are clearly described.	✓	✓
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓	✓
7. Experts externally reviewed the guideline prior to its publication.	✓	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓	✓
10. Thestrength and certainty of the key recommendations are clearly identified.	✓	✓

A1 = S. Upadhye A2 = S. Sharif

Funding & Conflicts of Interest

Funding: Society of Academic Emergency Medicine. Sponsor had no role in any stage of CPG development.

Conflicts of Interest: Reported. Some authors had research funding from gov't agencies/industry.

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? Single stakeholder with lived experiences involved with panel discussions (not a trained CPG panelist). Majority of evidence Very Low/Low/Moderate and often indirectly related to PICOT questions.

Presentation: Well organized with easy to find recommendations? **YES**

Comprehensive: Was the information to inform decision-making complete? **YES**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **YES?** Recommendation utility will vary based on local clinical work environment.

Administrative Details

Key Words: Recurrent chest pain, risk stratification

Appraisers: Upadhye S, Sharif S.

Reference(s):

1. Musey Jr PI, Bellolio F, Upadhye S, Chang AM, Diercks DB, Gottlieb M, Hess EP, Kontos MC, Mumma BE, Probst MA, Stahl JH, Stopyra JP, Kline JA, Carpenter CR. Guidelines for reasonable for appropriate care in the emergency department (GRACE): Recurrent low-risk chest pain in the emergency department. Acad Emerg Med 2021; 00:1-27. DOI: 10.1111/acem.14296

Research Question

What are the risks of outpatient treatment of pulmonary embolism with direct anticoagulants?

BEEM Bottom Line

Why is this study important? Outpatient treatment of low-risk pulmonary embolism (PE) patients is an important stewardship effort, provided that the discharge oral anticoagulants (OACs) prescribed are safe in the short-term future.

Which, if any, threats to validity are most likely to have an impact on the results and how? Paucity of direct evidence comparing outpatient management strategies between different anticoagulant classes limit generalizability of findings.

How do the key results compare with the current evidence? There are ongoing prospective trials examining the efficacy/safety of OACs in treating low-risk PE patients in outpatient settings.

How should this study impact the care of ED patients? There are rare major/minor adverse outcomes with treating low-risk PE patients with OACs over 30-90days.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Maughan BC, Frueh L, McDonagh MS, Casciere B, Kline JA. Outpatient Treatment of Low-risk Pulmonary Embolism in the Era of Direct Oral Anticoagulants: A Systematic Review. Acad Emerg Med 2021; 28: 226-239. doi: 10.1111/acem.14108

Design: Systematic review of prospective trials (randomized/non-randomized).

Population: *Included:* Adult patients with acute symptomatic PE discharged from ED/within 48hrs. Randomized and prospective non-randomized studies included. "Low-risk" PE patients defined using Hestia, PESI or sPESI criteria. *Excluded*: Retrospective studies, case reports, editorials, other publication types. Studies re: VTE prophylaxis, no clearly defined outpt cohort, populations with higher risk comorbidities (eg. cancer), or unusual outpt scenarios (eg. patient hotels, hospital-in-the-home).

Intervention: Direct oral anticoagulants (DOACs), any medication/dosage. 863 patients; 97% received rivaroxaban in trials that reported specific drug choices (remainder received apixaban).

Comparison: LMWH or VKA's (1018)

Outcomes: *Major:* All-cause mortality, PE-related mortality, recurrent VTE, major bleeding (ISTH definition).
Minor: ED return visit, hospital readmission, clinically relevant nonmajor bleeding (CRNMB)

All outcomes to be reported at 30 and 90days.

Key Results: *12 studies, 3191 patients included. 4 RCTs, 8 non-randomized studies. Avg age 41-62yo.*

Outcome	*Median rates (range)*	
All-Cause Mortality	30days 0% (range 0-1.7%, 11 studies)	90days: 0.4% (0-3.3%, 10 studies)
PE Mortality	30days: 0% (range 0-0.6%, 12 studies)	90days: 0% (0-0.4%, 10 studies)
Recurrent VTE	30days: 0% (0-1.4%, 10 studies)	90days: 0.3% (0-2.2%, 10 studies)
Major Rebleeds	30days: 0% (0-1.2%, 11 studies)	90days: 0% (0-1.8%, 9 studies)
	**No statistically significant difference with high-quality studies comparing VKAs vs DOACs for individual major outcomes, nor 90day composite of all 4 major outcomes.	
Minor CRNMB	Median 2% (0.2-5.1%)	
Return ED visits	Median 15.5% (range 14.9-16.0%; 2 studies at 30days); 21.1% (1 study, 90days)	
Hospital Readmissions	30days: 2.4% (1.5-3.0%, 3 studies)	90days: 9.4% (8.2-10.5%, 2 studies)

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	?
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	X
8. The methods used to combine the included primary studies were reported and valid.	✓
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: BCM has received national grant funding. JAK has received public grant and institutional industry grant funding (not personal). No other conflicts reported.

Potential Threats to Validity

Chance: None?

Selection Bias: Broad search (electronic, contacted authors, screened reference lists). English-language articles only. No reported assessment of publication bias.

Measurement Bias: Overall quality of studies: 4 RCT's low risk of bias, NonRCTs = moderate quality (6 Mod, 2 Serious RoB)

Analysis Bias: None. No reporting of heterogeneity, nor attempted meta-analysis.

Confounding: Low variation in patient comorbidity of CHF (0-3.6%), prior VTE (15.1-26.5%), and chronic lung disease (0-12.5%). Varied rates of malignancy in included studies (0-45.5%), and DOACs are not recommended in cancer patients d/t higher risk of bleeding.

Administrative Details

Key Words: Direct oral anticoagulants, outpatient, pulmonary embolism

Appraisers: Upadhye S.

Reference(s): Maughan BC, Frueh L, McDonagh MS, Casciere B, Kline JA. Outpatient Treatment of Low-risk Pulmonary Embolism in the Era of Direct Oral Anticoagulants: A Systematic Review. Acad Emerg Med 2021; 28: 226-239. doi: 10.1111/acem.14108

PMID: 32779290

Research Question

For cardioversion of atrial fibrillation, is a strategy of drug–shock more effective than a shock-only and does pad placement make a difference?

BEEM Bottom Line

Why is this study important? There exists a high degree of variation in management approaches for recent-onset atrial fibrillation and flutter (RAFF) patients treated in academic emergency departments (EDs).[1] This study sought to identify the most effective strategy of cardioversion by comparing 2 protocols: 1) procainamide followed by electrical (DC) cardioversion (drug–shock); and 2) DC cardioversion alone (shock-only) with anteroposterior and anterolateral pad positions.

Which, if any, threats to validity are most likely to have an impact on the results and how? The trial is limited by potential compromises in the blinding procedure in Protocol 1 (drug–shock) and the absence of blinding in Protocol 2 (DC cardioversion). The sample size also precludes the precise estimation of the prevalence of adverse events with each approach. Finally, the results may not be similar in other health systems such as in Europe or in developing countries.

How do the key results compare with the current evidence? A similar Canadian trial reported an electrical-first strategy results in a significantly shorter ED length-of-stay.[2] However, in this trial, the drug infusion cardioverted approximately 50% of patients and thereby avoided the resource-intensive procedural sedation required for DC cardioversion. Hence, the findings are congruent with existing recommendations: 1) pharmacological conversion with procainamide is safe in stable patients; 2) biphasic defibrillator DC cardioversion will effectively cardiovert regardless of pad position.[3]

How should this study impact the care of ED patients? First attempting cardioversion with procainamide (or with other drugs such as flecainide, or propafenone) followed by shock for refractory AF should minimize patient discomfort and resource use.

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No conflicts of interest (ICMJE)

Study Summary

Article: Stiell IG, Sivilotti MLA, Taljaard M, et al. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2). Lancet. 2020 Feb 1;395(10221):339-349.

Design: Multicenter (11 EDs in Canada) partial factorial, superiority, randomised, blinded, placebo-controlled trial with a nested randomised, open-label, active comparator-controlled trial.

Population: *Included:* ED patients (≥ 16 years) presenting with RAFF ≥ 3 hours duration and onset ≤ 48 hours or onset ≤ 7 days and anticoagulated for > 4 weeks or no left atrial thrombus on transesophageal echocardiogram.
Excluded: Patients with another primary presentation; permanent AF; hemodynamic instability; Wolff-Parkinson-White syndrome; acute coronary syndrome; pulmonary edema; left ventricular ejection fraction < 30%); heart rate < 55/min; 3° atrioventricular (AV) or complete left bundle branch block or a history of 2° or 3° AV block without a pacemaker or implantable cardioverter-defibrillator; QTc > 460 ms; Brugada syndrome; myocardial infarction (< 3 months); procainamide, procaine, other ester-type local anesthetic hypersensitivity; taking class I or III antiarrhythmics except amiodarone; estimated glomerular filtration rate < 60 mL/min/1.73m^2; breast feeding; pregnant; converted before randomization; or previously enrolled.

Intervention: Protocol 1 – procainamide (15 mg/kg/30 min) infusion then DC cardioversion as needed (≤ 3 shocks, ≥ 200 J).
Protocol 2 – anteroposterior or anterolateral pad position for DC cardioversion.

Comparison: Protocol 1 – placebo infusion (30 min) then DC cardioversion as needed (≤ 3 shocks of ≥ 200 J).
Protocol 2 – anteroposterior or anterolateral pad position for DC cardioversion.

Outcomes: *Primary:* Conversion (including spontaneous) to sinus rhythm after randomization and maintenance ≥ 30 min.
Secondary: Normal sinus rhythm (NSR) at the time of ED disposition; admission; ED Length-of-stay (LOS); time to sinus rhythm conversion; adverse events; AF recurrence; return ED visits; stroke; survival.

Key Results: *N* = 396 patients.

Sig.	*Analysis*	*Outcome*	*Drug-Shock (%)*	*Shock Only (%)*	*RR (95% CI)*
NSS	ITT	DC Home	198 (97)	183 (95)	1.02 (0.98 to 1.06)
NSS	ITT	NSR Conversion	196 (96)	176 (92)	1.05 (0.99 to 1.10)
SS	m-ITT	NSR Conversion	192 (97)	166 (92)	1.08 (1.03 to 1.13)
Sig.	*Analysis*	*Outcome*	*Ant.-Lat. (%)*	*Ant.-Post (%)*	*RR (95% CI)*
NSS	ITT	NSR Conversion	119 (94)	108 (92)	1.02 (0.95 to 1.09)

Ant.-Lat. = anterior-lateral; Ant.-Post. = anterior-posterior; CI = confidence interval; ITT = intention-to-treat; m-ITT = modified intention-to-treat (i.e. excluded patients who converted to sinus rhythm before the study infusion was started); *N* = number of patients; NSS = not statistically significant (SS); RR = relative risk (if the value of the CI range includes 1, there is no difference); Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	X	X	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	?	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	?	?	?
6. All groups were treated equally except for the intervention.	?	?	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	?	?

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Funding Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: The sample size is not sufficiently large to allow estimation of the prevalence of adverse events with each protocol.

Selection Bias: None detected.

Measurement Bias: None detected.

Analysis Bias: None detected.

Confounding: Although there was an attempt to blind healthcare providers in Protocol 1, the bags of procainamide and placebo were semi-opaque, which may have compromised blinding.

Protocol 2 was unblinded, which may have resulted in confounding caused by imbalances in cointerventions.

Administrative Details

Key Words: Atrial fibrillation (AF); atrial flutter; cardioversion; procainamide.

Appraisers: Zeraatkar D; Worster A; Peschanski N.

Reference(s):

1. Stiell IG, Clement CM, Brison RJ, et al. Variation in management of recent-onset atrial fibrillation and flutter among academic hospital emergency departments. Ann Emerg Med. 2011 Jan;57(1):13-21.
2. Scheuermeyer FX, Andolfatto G, Christenson J, et al. A Multicenter Randomized Trial to Evaluate a Chemical-first or Electrical-first Cardioversion Strategy for Patients With Uncomplicated Acute Atrial Fibrillation. Acad Emerg Med. 2019 Sep;26(9):969-981.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-2962.

Research Question

Can application of the YEARS algorithm safely exclude pulmonary embolism?

BEEM Bottom Line

Why is this study important? The YEARS diagnostic algorithm is a novel, simplified diagnostic management approach for patients with suspected pulmonary embolism (PE) that was developed, in part, to reduce ccomputed tomography pulmonary angiography (CTPA) imaging.[1] The YEARS strategy combines items from the Well's score with an increased D-dimer cutoff at presentation and has been prospectively tested in a multicentre, cohort study in the Netherlands. In an attempt to externally validate this strategy in an independent cohort, the authors of this study retrospectively applied the YEARS algorithm to the patients with suspected PE from 3 published prospective cohort studies and then conducted a meta-analysis.

Which, if any, threats to validity are most likely to have an impact on the results and how? Of the 17 cases of missed PE, 2 were diagnosed by the finding of a deep vein thrombosis (not PE), which may have inflated the false negative rate. Many of the PE cases were of distal, smaller emboli and we do not know whether patients would have come to harm without diagnosis and treatment. This study combined data from three multi-site cohort studies which varied in their assessment of clinical probability of PE and CTPA testing; left uncorrected these differences may have led to inflated precision and may have produced variable outcomes. Also, since the YEARS algorithm was applied retrospectively, positive outcomes may be due to the original cohort procedures rather than the use of the algorithm.

How do the key results compare with the current evidence? The results of this analysis indicate that the YEARS algorithm is a simple approach to PE testing and reduces CT scanning for PE. The YEARS algorithm was previously assessed in a prospective cohort study of 498 pregnant women with suspected PE.[2] The patients were assessed with the 3 Well's criteria i.e., clinical signs of deep-vein thrombosis (DVT), hemoptysis, and PE as the most likely diagnosis prior to D-dimer measurements. If 0/3 criteria were met and the D-dimer < 1000 ng/ml or if any criteria were met and the d-dimer level was < 500 ng per milliliter, PE was ruled out. Adaptation of the YEARS algorithm for pregnant women involved compression ultrasonography (US) if there were symptoms of deep-vein thrombosis (DVT). All those in whom PE had not been ruled out underwent CTPA unless the US results were positive. The results showed that the pregnancy-adapted YEARS diagnostic algorithm safely ruled out PE across all trimesters of pregnancy and that CTPA was avoided in 32 to 65% of patients.

How should this study impact the care of ED patients? Emergency physicians should be familiar with an evidence-based approach for PE testing. The YEARS algorithm is a safe and simple approach to PE testing and reduces CT scanning for PE. Using age-adjusted D-dimer in patients who score <4.5 points on the Wells score is another option.

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Associate Professor, Department of Medicine, McMaster University
Dr de Wit is active in diagnostic PE research.

Study Summary

Article: Eddy M, Robert-Ebadi H, Richardson L, et al. External validation of the YEARS diagnostic algorithm for suspected pulmonary embolism. J Thromb Haemost. 2020 Aug 31. doi: 10.1111/jth.15083.

Design: Meta-analysis of 3 prospective, multicenter (Belgium, France, and Switzerland), management outcome studies.

Population: *Included:* Adults emergency department patients with acute onset of new or worsening shortness of breath or chest pain and clinically suspected PE.
Excluded: Not stated.

Predictors: Can rule out a PE if D-dimer < 500 ng/mL or if < 1000 ng/mL and no YEARS items, i.e., no clinical signs of DVT, no hemoptysis, and PE not the most likely diagnosis. Also applied age-adjusted D-dimer (AADD = D-dimer < age x 10).

Comparison: A mix of three diagnostic strategies including the Geneva score, D-dimer +/- CT +/- ultrasound.

Outcomes: *Primary:* PE on CT or via follow-up at ≤ 3 months.
Secondary: Not applicable (NA).

Key Results: *N* = 3,314

YEARS Items (n)	*D-dimer (n)*	*AADD (n)*	*PE (n)*
0 (n = 1,783)	< 1,000 ng/mL (n = 1,142)	D-dimer < AADD (n = 870)	0
0 (n = 1,783)	< 1,000 ng/mL (n = 1,142)	D-dimer > AADD (n = 272)	17
0 (n = 1,783)	> 1,000 ng/mL (n = 641)	NA	134
≥ 1 (n = 1,531)	< 500 ng/mL (n = 281)	NA	0
≥ 1 (n = 1,531)	> 500 ng/mL (n = 1,250)	NA	580

N = number of subjects; n = number of subjects in sample.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were representative of those with the problem.	✓	✓	✓
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	✓	✓	✓
3. All patients underwent the same clinical evaluation.	X	X	X
4. All important predictor variables were included in the clinical evaluation and explicitly defined.	✓	✓	✓
5. Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	✓	✓	✓
6. Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	✓	✓	✓
7. All outcome variables were included in the clinical evaluation and explicitly defined.	✓	✓	✓
8. All patient-important outcomes were considered.	✓	✓	✓
9. The follow-up was complete.	X	?	?
10. The point estimates and respective precisions are clinically significant.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Swiss national Research Foundation.

Conflicts of Interest: The authors report no conflicts of interest relevant to this work.

Potential Threats to Validity

Chance: There appears to be a sufficient number of cases to produce relatively narrow confidence intervals; however stratified analyses examined age-adjusted cut-off are less precise.

Selection Bias: Study was conducted in European emergency departments 10 to 20 years ago with a 22% prevalence of PE. In Canada, prevalence of PE in the same cohort is 4%.

Measurement Bias: There are slight differences between the three cohorts with respect to the type of CTPA imaging and assessment of clinical probability; these were minor differences; however, it is unclear if they may have reduced the validity of combining the cohorts. Given that this was a retrospective analysis of a cohort study, the outcomes cannot be attributed to the use of the YEARS algorithm.

Analysis Bias: Despite noted clinical heterogeneity between cohorts (and likely inter-site variability within each cohort) there was no investigation or subsequent correction for potential cluster effects. A small amount of data is missing, however there appears to be sufficient cases to minimize the risk of over-fitting.

Confounding: The authors noted that the prevalence of PE was greater than expected; higher prevalence may have influenced the third YEARS criteria requiring clinical judgment of whether PE is the most probable diagnosis.

Administrative Details

Key Words: Computed tomography (pulmonary angiography (CTPA); deep vein thrombosis (DVT); pulmonary embolism (PE); YEARS diagnostic algorithm.

Appraisers: Bedard C; Worster A; De Wit K.

Reference(s):

1. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017;390:289-297.
2. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. N Engl J Med. 2019 Mar 21;380(12):1139-1149.

Notes for BEEM Presentations

Authors' Conclusion(s)

"In summary, we were able to externally validate the YEARS algorithm. Overall, the rule appears to safely exclude PE. However, caution is required in patients with no YEARS items and a D-dimer greater than their age-adjusted D-dimer cutoff, especially in centers with a higher prevalence of PE. A large international individual patient level data meta-analysis of available diagnostic studies for PE is currently being undertaken and will shed further light on tailoring diagnostic strategies."

Clinical Teaching Points

1) The YEARS protocol excluded PE without imaging 43% of emergency patients tested for PE.
2) The YEARS protocol was safe when applied to a cohort of patients with a high prevalence of PE (22%).
3) Age-adjusted D-dimer is a safe approach in patients with a low probability of PE (either Wells score < 4.5 or no YEARS components).
4) Most cases of missed PE are in patients who were never tested for PE (rather than patients who were tested with YEARS/ ag-adjusted D-dimer etc).

EBM Teaching Point

Level I Clinical Decision Rules can be used in a wide variety of settings with confidence to change clinician behavior and improve patient outcomes. At this level, rules must have at least one prospective validation in a different population plus one impact analysis, along with a demonstration of change in clinician behavior with beneficial consequences.

Jeopardy Question

Answer: This diagnostic algorithm can safely rule out PE and reduce CTPA.
Question: What is YEARS?

Research Question

Does oxygen via high-flow nasal cannula improve symptom relief compared to conventional oxygen therapy in palliative patients presenting with acute hypoxemic respiratory failure?

BEEM Bottom Line

Why is this study important? Room air and conventional oxygen therapy (COT) via nasal cannula may be ineffective at relieving dyspnea severity in palliative patients.[1] High-flow nasal cannula (HFNC) has been shown to be noninferior to bilevel positive airway pressure (BIPAP) at relieving dyspnea in palliative patients, but it is unknown whether it is superior to COT.[2]

Which, if any, threats to validity are most likely to have an impact on the results and how? This is a small single center study with very limited external validity. The results are at high risk of performance bias (due to lack of blinding) and selection bias (due to the exclusion of participants from the analysis for reasons that may be related to the efficacy of the interventions) as well as different oxygen titration standards and morphine amounts for each group which clearly favoured the HFNC group.

How do the key results compare with the current evidence? A systematic review and meta-analysis found that HFNC is superior to COT at reducing intubation and escalation of oxygen therapy in acute hypoxemic respiratory failure patients, but did not improve patient reported comfort or dyspnea.[3] The improved dyspnea with HFNC in this trial might have been be a function of reversal of respiratory failure rather than improved comfort/symptoms.

How should this study impact the care of ED patients? While HFNC likely does not relieve dyspnea severity over COT for hypoxemic respiratory failure overall, it may be an effective intervention for relief of dyspnea in palliative care patients with hypoxemic respiratory failure in the emergency department (ED) who have no symptom relief with COT.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Ruangsomboon O, Dorongthom T, Chakorn T, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Relieving Dyspnea in Emergency Palliative Patients With Do-Not-Intubate Status: A Randomized Crossover Study. Ann Emerg Med. 2019 Dec 18. pii: S0196-0644(19)31227-2.

Design: Single-center (Bangkok, Thailand) superiority, randomized, nonblinded, crossover trial.

Population: *Included:* Adults (≥ 18 years) with palliative and do-not-intubate status presenting to the ED with hypoxemic respiratory failure (i.e. oxygen saturation by pulse oximetry [SpO_2] < 90% on room air, respiratory rate ≥ 30 breaths/minute [min], accessory muscle use, a modified Borg scale ≥ 4 [self-report dyspnea scale ranging from 0, nothing at all to 10, maximal] and competent status Kelly score < 4 ([mental status assessment ranging from 1, follows complex 3-step command to 6, comatose with brain stem dysfunction]).
Excluded: Refusal; agitation or noncooperation; or contraindication to opioids or NHFC.

Intervention: HFNC by an Optiflow™ cannula using an AIRVOTM2 humidified high-flow system (Fisher & Paykel Healthcare, Auckland, NZ) with titrated fraction of inspired oxygen (FiO_2) to achieve SpO_2 ≥ 95% and flow rate 30 to 60 L/min for 60 min. All subjects in both groups received standard treatments including morphine for respiratory distress.

Comparison: Nasal cannula or nonrebreather mask with titrated flow rate to achieve SpO_2 ≥ 95% for 60 min.

Outcomes: *Primary:* Modified Borg scale score at 60 min with 1 point (standard deviation [SD] 1.8) as clinically significant.
Secondary: Numeric rating scale score of dyspnea (0 = no dyspnea, 10 = worst dyspnea), respiratory rate, SpO_2, pulse rate, mean arterial pressure, HFNC–associated adverse event rate, and inhospital mortality rate.

Key Results: *N* = 48 patients (24 per group).

Sig.	*Outcome at 60 min*	*Control (n = 22)*	*HFNC (n = 22)*	*Difference (95% CI)*
NSS	Mean modified Borg scale	4.9	2.9	2.0 (1.4 to 2.6)
SS	Mean numeric rating scale	5.1	2.9	2.2 (1.6 to 2.9)
SS	Mean respiratory rate	30.9	25.1	5.9 (3.5 to 8.3)
SS	Mean SpO_2	96.9	98.2	–1.3 (–2.3 to –0.3)

CI = confidence interval; *N* = number of patients; n = sample; NSS = not statistically significant; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	?	?	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	X
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	X	X	X
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	?	?	?

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Siriraj Research and Development Fund with HFNC equipment provided in kind by Fisher & Paykel Healthcare independent of the trial design, data collection, data analysis and article preparation.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The trial includes few participants and so chance imbalances in prognostic factors are possible.

Selection Bias: Participants were excluded from analysis for reasons that may be related to the efficacy of the interventions.

Measurement Bias: Because blinding is not possible, results may be affected by performance and measurement bias. The Borg scale is a subjective measurement tool which may not be reproducible. Further, the validity of the outcome measures in palliative populations is unclear.

Analysis Bias: The possibility of a carryover effect cannot be ruled out.

Confounding: The flow rates in the HFNC group were titrated to patient dyspnea, i.e. the primary outcome, while the flow rates in the COT group were titrated to $SpO_2 \geq 95\%$ and patients in the HFNC group received significantly more morphine-equivalents (55mg/day) than the COT group (25mg/day). Either of these factors could have confounded the results in favour of the HFNC group.

Administrative Details

Key Words: Dyspnea; high-flow nasal cannula (HFNC); Optiflow; oxygen; palliative; respiratory.

Appraisers: Zeraatkar D; Worster A; Nikolla DA.

Reference(s):

1. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*. 2010;376(9743):784-93.

2. Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage*. 2013 Oct;46(4):463-73.

3. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019 May;45(5):563-572.

INFECTIONS

Research Question

What is the accuracy of various signs & symptoms in the diagnosis of adult community-acquired pneumonia (CAP)?

BEEM Bottom Line

Why is this study important? A clinical assessment of CAP is important in determining who needs a CXR to confirm the diagnosis, and who may need antibiotics (in order to rationalize CXR ordering and Abx stewardship).

Which, if any, threats to validity are most likely to have an impact on the results and how? Most included studies had low risk of bias (some moderate). Some heterogeneity between study definitions, settings & inclusion criteria acknowledged (not a serious threat to results). All studies used CXR as a reference standard (not always confirmed on CT scan?).

How do the key results compare with the current evidence? Various clinical signs/symptoms for CAP have some moderate pre-CXR diagnostic accuracy, but no single item is definitive enough to obviate a CXR and proceed directly to Abx treatment (LR+ values ranging from 0.5-2.0). Various S/S, when present, increased the likelihood of CAP Dx, but the absence of such did not reduce the risk as much. Presence of acute cough was useless for Dx accuracy, and should not prompt CXR ordering. The absence of abnormal VS was helpful to exclude CAP Dx. Based on Dx OR values, the most useful findings were overall clinical impression, egophony, any abnormal VS, any abnormal lung finding, tachypnea, and objective fever.

How should this study impact the care of ED patients? This updated review reinforces that the overall clinical impression of an experienced ED physician is the best "test" for clinically diagnosing CAP, ordering confirmatory CXR, and treating with Abx.

S. Upadhye, MD MSc FRCPC

Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact (HEI), McMaster University

No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Ebell MH, Chupp H, Cai X, Bentivegna M, Kearney M. Accuracy of Signs and Symptoms for the Diagnosis of Community-acquired Pneumonia: A Meta-analysis. Acad Emerg Med 2020; 27: 542-553.

doi: 10.1111/acem.13965

Design: Systematic review and meta-analysis of diagnostic accuracy of CAP signs & symptoms.

Population: *Included:* Adults/adolescents with signs/symptoms of CAP being managed in outpatient settings (including ED). *Excluded*: Patients with dyspnea NYD or sepsis, patients in specialized nursing facilities, immunocompromised patients, known chronic lung diseases, hospital/ventilator-acquired pneumonia, or pathogen-specific diagnostic studies. Case control studies also excluded.

Index Test: Clinical assessment of signs/symptoms of CAP.

Reference Test: Imaging confirmation of CAP (CXR used in all included studies)

Diagnosis of Interest: CAP

Key Results: *N* = 8544 patients in 17 studies. Prevalence of CAP: 10% in primary care studies, 20% in ED studies

N/Studies	*Measure (95% CI)*	I^2
	Clinical Symptom (studies/patients): Sens/Spec/LR+/LR-/Dx test OR/AUROC	
	Overall Clinical impression (7/5081): 0.50/0.92/6.32/0.54/11.5/0.741	
	Hx of COPD (3/748): 0.19/0.91/ 2.37/0.88/2.74/Not calc	
	Subjective Fever (8/4097): 0.63/0.55/1.47/0.68/2.10/0.623	
	Chills (7/2453): 0.55/0.62/1.44/0.73/2.00/0.610	
	Dyspnea (10/5626): 0.63/0.51/1.30/0.75/1.75/0.598	
	Chest Pain (8/5031): 0.51/0.58/1.21/0.86/1.41/0.549	
	Clinical Sign (studies/patients): Sens/Spec/LR+/LR-/Dx test OR/AUROC	
	Egophony (3/1116): 0.05/0.99/6.17/0.96/6.46/NC	
	Percussion dullness (7/1932): 0.14/0.94/2.62/0.94/2.29/NC	
	Confusion (4/1596): 0.11/0.95/2.15/0.94/2.29/NC	
	Crackles (12/5898): 0.42/0.79/ 2.00/ 0.74/2.70/0.611	

Dec breath sounds (6/4322): 0.25/0.87/1.96/0.87/2.29/NC
Any abnormal lung exam (8/2875): 0.60/0.67/1.90/0.61/3.18/0.669
Rhonchi (5/2375): 0.23/0/87/1.76/0.89.1.99/NC
Toxic appearance (5/4162): 0.42/0.70/1.46/0.83/1.77/NC
Any abnormal VS (3/604): 0.93/0.30/1.37/0.25/6.01/NC

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	?
4. The selection of studies was unbiased and reproducible.	?
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	X
9. The subgroups were stated a priori and appropriate.	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓

A1 = S. Upadhye

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: No commercial support reported.

Conflicts of Interest: Declared (as per publisher guidelines) but not reported.

Potential Threats to Validity

Chance: None.

Selection Bias: No reporting of publication bias evaluation.

Measurement Bias: None.

Analysis Bias: None.

Confounding: Most included studies examined individual clinical CAP S/S, but not necessarily combinations.

Administrative Details

Key Words: Community-acquired pneumonia, signs, symptoms, diagnosis

Appraisers: Upadhye S.

Reference(s): Ebell MH, Chupp H, Cai X, Bentivegna M, Kearney M. Accuracy of Signs and Symptoms for the Diagnosis of Community-acquired Pneumonia: A Meta-analysis. Acad Emerg Med 2020; 27: 542-553.

doi: 10.1111/acem.13965

Research Question

What are the latest guidelines for the early management of community-acquired pneumonia (CAP)?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? This Policy updates the prior 2009 ACEP Policy (addressed low-value routine blood cultures for low-risk CAP patients). CAP is still a leading cause of death and hospital admission worldwide, so it is important for ED physicians to hone their clinical decision-making in risk-stratifying CAP patients for certain ED tests, admission and treatment.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Lack of patient/public stakeholders to ensure patient-relevant outcomes for CPG questions. This is a common flaw with ACEP Policy processes. Limited English-electronic electronic database searches for evidence risk missing important information from other sources (eg. Grey literature).

How should this guideline, and specifically which recommendations should impact the care of ED patients? Enter text here. Notes:

Suneel Upadhye, MD MSc FRCPC

Guidelines Methodologist, CAEP/SAEM GRACE (non-profit)

Curator, EMGuidelines website (non-profit)

Study Summary

Article: Smith MD, Fee C, Mace SE, Maughan B, Perkins JC, Kaji A, Wolf SJ. Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department with Community-Acquired Pneumonia (CAP). Annals Emerg Med 2021; 77: e1-e57. https://doi.org/10.1016/j.annemergmed.2020.10.024.

Design: Clinical Practice Guideline.

Population: Adult ED patients with a Dx of CAP. CAP defined is as an acute pulmonary parenchymal infection (new infection), usually bacterial that are treatable with anitbiotics (Abx). Causes may be community-, hospital- or ventilator-acquired. Exclusion = Pregnant, pediatric patients

Scope: This guideline is intended for physicians working in the ED who evaluate/treat CAP.

Key Results: **Key Questions:**

Q1. In the adult ED patient diagnosed with community-acquired pneumonia, what clinical decision aids can inform the determination of patient disposition?

Q2. In the adult ED patient with community-acquired pneumonia, what biomarkers can be used to direct initial antimicrobial therapy?

Q3. In the adult ED patient diagnosed with community-acquired pneumonia, does a single dose of parenteral antibiotics in the ED followed by oral treatment versus oral treatment alone improve outcomes?

Recommendation	*Strength*
Q1. The Pneumonia Severity Index (PSI) and CURB-65 decision aids can support clinical judgement by identifying patients at low risk of mortality who may be appropriate for outpatient treatment. PSI is supported by a larger body of evidence and is preferred by other society guidelines (ATS/IDSA 2019 guidelines).	Level B
Q3. Given the lack of evidence, the decision to administer a single dose of parenteral antibiotics prior to oral therapy should be guided by patient risk profile and preferences.	Level C
Q2. Do not rely upon any current laboratory test(s), such as procalcitonin and/or C-reactive protein (CRP), to distinguish a viral pathogen from a bacterial pathogen when deciding on administration of antimicrobials in ED patients who have CAP.	Level C
Q1. Do not routinely use biomarkers to augment the performance of clinical decision aids to guide the disposition of ED patients with CAP.	Consensus

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The guideline development group includes all of the relevant stakeholders, including patients.	?
2.	Systematic methods were used to search for evidence.	X
3.	The criteria for selecting the evidence are clearly described.	✓
4.	The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓
5.	The health benefits, side effects, and risks were considered in formulating the recommendations.	✓
6.	There is an explicit approach linking the evidence to formulate the recommendations.	✓
7.	Experts externally reviewed the guideline prior to its publication.	✓
8.	The content of the guideline is free of influence by the views of the funding body.	✓
9.	Competing interests of guideline development group members have been recorded and managed.	✓
10.	The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: ACEP. No role in collecting/analyzing literature, nor crafting recommendations.

Conflicts of Interest: None reported.

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **As with long-standing ACEP Policy processes, the working group rarely includes patient/public stakeholders (which is problematic). The evidence search was limited to English language articles from electronic databases.**

Presentation: Well organized with easy to find recommendations? **Yes**

Comprehensive: Was the information to inform decision-making complete? **Variable; CURB-65 and PSI tools provided (available with online apps also). No shared decision-making tools provided.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes? Mostly low-level recommendations with weak/absent supporting evidence.**

Administrative Details

Key Words: Community-acquired pneumonia; decision aids; biomarkers; intravenous antibiotics

Appraisers: Upadhye S.

Reference(s): Free Policy download: Downloadable at: https://www.acep.org/patient-care/clinical-policies/community-acquired-pneumonia/ (free PDF version)

The ATS/IDSA 2019 CPG updates CAP recommendations (available free at https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST).

The NICE (UK) 2019 CPG update is available at: https://www.nice.org.uk/guidance/ng138.

CADTH Rapid Review (2020) is freely accessible at: https://cadth.ca/management-patients-presenting-pneumonia-emergency-department-guidelines.

Research Question

What are the determinants of ED physician prescribing of antibiotics for respiratory tract infections?

BEEM Bottom Line

Why is this study important? This review explores those factors associated with ED antibiotic prescribing for adult respiratory tract infections.

Which, if any, threats to validity are most likely to have an impact on the results and how? There is a somewhat limited search of articles, which could have led to selection bias. There is no quality assessment of included articles reported, nor is there an attempt to quantify the magnitude of different predictors of Abx prescribing determinants.

How do the key results compare with the current evidence? The results support a proactive strategy of multimodal education strategies for providers/patients in order to improve RTI Abx prescribing practices.

How should this study impact the care of ED patients? There is a need to recognize personal biases in prescribing Abx for adult RTI's where they may not be warranted. Structured education for both providers and patients can optimize Abx stewardship.

S. Upadhye, MD MSc FRCPC
Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Lim DW, Htun HL, Ong LS*, et al*. Systematic review of determinants influencing antibiotic prescribing for uncomplicated acute respiratory tract infections in adult patients in the emergency department. Inf Cont Hosp Epid 2020; 1-10. doi:10.1017/ice.2020.1245

Design: Systematic review of ED-based trials for antibiotic prescribing determinants. No meta-analysis.

Population: *Included:* Adult ED patients with uncomplicated respiratory tract infections (RTIs).
Excluded: Studies including mixed populations, non-ED settings, complicated RTIs (eg. Abscess, other)

Intervention: Factors associated with ED Abx prescribing

Comparison: Appropriate versus inappropriate antibiotic prescribing behaviours (if intervention is available)

Outcomes: *Primary:* antibiotic prescribing rates and antibiotic use

Key Results: *12 studies* = 150 to >37million visits analyzed in various studies. Most predictors addressed only in 1-2 studies.

Abx Rx Determinants
NEGATIVE Predictors: 1) Provider factors: co-management with house staff 2) Patient factors (Symptoms, Comorbidities): Prior URTI in last 6 weeks 3) Investigations: Normal CRP value, positive rapid influenza test
POSITIVE Predictors: 1) Provider: Older age, non-physician (NP, PA), non-EM/IM, patient expectations. Clinical Dx bronchitis, AECOPD, sinusitis, pharyngitis, CAP. 2) Patient: Older male, CHF comorbidity, patient satisfaction score, ED LOS. Symptoms = Purulent sputum, dyspnea, symptoms >2days. Signs = Abnormal resp exam, fever? 3) Investigations: Blood culture ordered

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	?
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	X
7. The quality of the primary studies is high.	?
8. The methods used to combine the included primary studies were reported and valid.	N/A
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None?

Selection Bias: *Search: English articles only. Electronic databases; no gray literature mentioned. No assessment of publication bias.*

Measurement Bias: *No quality assessment for included studies reported.*

Analysis Bias: *No attempt to quantify magnitude of predictor determinants of Abx prescribing (qualitative descriptions only).*

Confounding: None?

Administrative Details

Key Words: Antibiotic prescribing, emergency department, respiratory infections

Appraisers: Upadhye S.

Reference(s): Lim DW, Htun HL, Ong LS, Guo H, Chow A. Systematic review of determinants influencing antibiotic prescribing for uncomplicated acute respiratory tract infections in adult patients in the emergency department. Inf Cont Hosp Epid 2020; 1-10. doi:10.1017/ice.2020.1245

Research Question

What are the overall effects of delaying antibiotics for respiratory tract infections (RTI)?

BEEM Bottom Line

Why is this study important? Antibiotic stewardship is critical in the growing challenge of increased antibiotic resistance. Antibiotic over-use is most common in primary care for respiratory infections, representing the single largest opportunity for stewardship interventions.

Which, if any, threats to validity are most likely to have an impact on the results and how? No validity threats. No study included use of POC testing, decision aids nor specific HCP training to de-implement Abx use. This group also used a 10-member patient/public stakeholder panel to help with study design, implementation and data interpretation. This group also advised on how to use these results in knowledge translation strategies. Three stakeholders included as authors.

How do the key results compare with the current evidence? This IPDMA reinforces prior Cochrane study-level SR/MA's that support a delayed vs immediate/no Abx strategy for common RTIs.

How should this study impact the care of ED patients?

Suneel Upadhye MD MSc FRCPC
Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Stuart B, Hounkpatin H, Becque T, *et al*. Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis. BMJ 2021;372:n808. http://dx.doi.org/10.1136/bmj.n808

Design: Individual patient data meta-analysis. Only RCTs/observational cohort studies included.

Population: *Included:* Patients treated for RTI in a community setting.
Excluded: Patients treated in hospital. Non-RCTs/observational studies.

Intervention: Delayed antibiotics for RTI.

Comparison: Immediate or no Abx.

Outcomes: *Primary:* Average symptom severity 2-4 days after initial consultation.
Secondary: Duration of illness after initial consultation, illness complications resulting in hospitalization/death, reconsultation for same/worsening symptoms, patient satisfaction (4 pt Likert scale).

Key Results: *IPD available from 13 studies (n=55682 patients)*

Sig.	*Outcome*	*N/Studies*	*Outcome Measure (95% CI)*	*I^2*
NSS	Avg duration of symptoms with delayed vs. no Abx	7/3907 pts	Mean Diff 7pt scale: 0.003 (-0.12 to 0.11)	N/A
NSS	Avg duration of symptoms with delayed vs. immediate Abx	8/3752 pts	0.02 (-0.11 to 0.15)	N/A
NSS	Reconsultation rates: delayed vs immediate Abx		OR 0.95 (0.74-1.22)	N/A
NSS	Complications (hospitalization/ death) with delayed vs no Abx, nor delayed vs immediate Abx		OR 0.62 (0.30-1.27) OR 0.78 (0.53-1.13)	N/A
NSS	Patient satisfaction delayed vs no Abx		Mean Diff 0.09 (0.06-0.11)	
SS	Children <5yo with higher symptom severity at 2-4d follow up		Mean Diff 7pt scale: 0.10 (0.03-0.18)	N/A
SS	Longer time to symptom resolution with delayed vs immediate Abx		HR 1.04 (1.01-1.08)	N/A
SS	Lower reconsultation rates with delayed vs no Abx		OR 0.72 (0.60-0.87)	N/A

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

No other pre-specified subgroups had any effectiveness differences between Abx groups.

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The methods used to combine the included primary studies were reported and valid.	✓
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	N/A

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: This work was funded by the NIHR Research for Patient Benefit (RfPB) Programme (grant No PB-PG-0416-20005). The funder had no role in interpretation/publication of study results.

Conflicts of Interest: None (explicit disclosure).

Potential Threats to Validity

Chance: None.

Selection Bias: The included studies for IPD included 93% of all potential eligible study populations.

Measurement Bias: None.

Analysis Bias: None. Use of one- and two-stage random effects analyses for pre-defined sensitivity analyses.

Confounding: Unclear impact of findings from LMIC countries (higher probability of serious illness/complications), or different pathogens or access to reconsultation care/secondary care if clinical deterioration. Authors did use propensity scores to mitigate potential confounding of observational data sets (much larger than RCT IPD sets).

Administrative Details

Key Words: Delayed antibiotics, lower respiratory infections

Appraisers: Upadhye S.

Reference(s): Stuart B, Hounkpatin H, Becque T, Yao G, Zhu S, Alonso-Coello P, Altiner A, Arroll B, Bohning D, Bostock J, Bucher HC, Chao J, de la Poza M, Francis N, Gillespie D, Hay AD, Kenealy T, Loffler C, McCormick DP, Mas-Dalmau G, Munoz L, Samuel K, Moore M, Little P. Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis. BMJ 2021;372:n808

http://dx.doi.org/10.1136/bmj.n808

PubMed ID: 33910882

Research Question

What are the latest guidelines for the management of acute rheumatic fever/heart disease?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Acute rheumatic fever/heart disease (ARF/AHD) is more prevalent in women and native populations, and these particular vulnerable populations merit special attention to avoid catastrophic cardiac complications. This guideline updates prior 2012 guidance on diagnosing/managing ARF/AHD in general and specific populations.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Lack of an explicit literature search, detailed quality assessment of included studies limits reproducibility of evidence reviews.

How should this guideline, and specifically which recommendations should impact the care of ED patients? This updated CPG has a strong culturally competent focus to address ARF/AHD in high-risk populations, and makes clear recommendations with support tables on acute and ongoing management of ARF/AHD for ED clinicians.

Suneel Upadhye, MD MSc FRCPC

Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)

Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: Ralph AP, Noonan S, Wade V, Currie BJ. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Med J Aust. 2021 Mar;214(5):220-227. doi: 10.5694/mja2.50851. Epub 2020 Nov 15.

Design: Clinical Practice Guideline.

Population: Patients (adult, pediatric) diagnosed with acute rheumatic fever (ARF) or rheumatic heart disease (RHD).

Scope: This guideline is intended for physicians who diagnose/manage ARF or AHD.

Key Results:

Recommendation	*Strength*	*Quality of Evidence*
GAS skin infections should be treated with Cotrimoxazole or IM PenG.	Strong.	High
Population-based screening for RHD using auscultation is NOT recommended.	Strong.	
ECHO screening of patients at risk of undiagnosed RHD is recommended.	Strong.	
Patients diagnosed with RHD should be referred to specialist cardiology services for possible anticoagulant Rx.	Weak.	
Pregnant women with high risk of ARF/AHD with worsening dyspnea, orthopnea, wheeze or worsening fatigue should be investigated with ECHO.	Strong.	
Patients at high-risk of ARF with sore throat should be treated with 1st line PenV. (Box 3)	Weak.	Moderate
Identification/treatment of GAS skin infections may decrease the burden of ARF.	Weak.	
All patients with ARF should be hospitalized for cardiac investigations (ECG, ECHO) and other diagnoses excluded.	Strong.	
There may be a role for corticosteroids for severe rheumatic carditis or Syndenhams chorea.	Weak.	

BEEM Critique

Risk of Bias Assessment

	A1
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓
2. Systematic methods were used to search for evidence.	?
3. The criteria for selecting the evidence are clearly described.	X
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	X
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	X
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓
7. Experts externally reviewed the guideline prior to its publication.	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: National Heart Foundation of Australia. No comments in role of sponsor in evaluating evidence or generating recommendations.

Conflicts of Interest: Various authors employed by RHDAustralia (nationally funded organization).

Potential Threats to Validity

Development: Explicit and broad representation of various stakeholders, including Aboriginal/native stakeholders, was included elicit lived experiences, and to ensure culturally competent recommendations. Literature review is minimally described, and no specific details provided re: quality assessment of evidence or risk of bias assessments. Use of GRADE methods to write recommendations (no explicit info on GRADE methods used, or Summary of Evidence/Findings Tables provided). Quality of evidence rated as A-D scale (A = high, D = very low), and recommendations were Strong (1) or Weak (2).

Presentation: Well organized with easy to find recommendations? **Yes**

Comprehensive: Was the information to inform decision-making complete? **Yes; useful tables provided.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes**

Administrative Details

Key Words: Acute rheumatic fever, rheumatic heart disease.

Appraisers: Upadhye S.

Reference(s): Ralph AP, Noonan S, Wade V, Currie BJ. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Med J Aust. 2021 Mar;214(5):220-227. doi: 10.5694/mja2.50851. Epub 2020 Nov 15.

Research Question

Does antibiotic treatment of asymptomatic bacteriuria in pregnancy reduce the development of pyelonephritis and associated risk of low birthweight and preterm birth?

BEEM Bottom Line

Why is this study important? Asymptomatic bacteriuria, the finding of urinary bacteria in the absence of urinary tract infection (UTI) symptoms, is common during pregnancy and more so in women from low-income countries and those with previous antepartum UTI.[1] While the prevalence of asymptomatic bacteriuria is similar between pregnant and non-pregnant women, the risk of progression to symptomatic cystitis or pyelonephritis is increased in pregnancy due to common physiologic changes. These changes include increased bladder volume with decreased detrusor tone, ureteric dilatation from direct uterine pressure and progestogenic relaxation of ureteric smooth muscle, and glycosuria in up to 70% of pregnant individuals.[2,3] Association of asymptomatic bacteria with subsequent preterm birth and low birth weight is controversial, and the benefits versus harms of treatment (e.g., antibiotics [Abx]) to eradicate bacteria is unknown.

Which, if any, threats to validity are most likely to have an impact on the results and how? The included studies are severely methodologically flawed and at high risk of bias, including selection, measurement, attrition, and selective reporting bias. Both clinical and statistical variability between studies reduces the consistency of the average effect of Abx treatment. Of the 15 included studies, 11 enrolled women prior to 1970 and these may not be representative of the screening and diagnostic methods and treatments now available. Overall there is low certainty in the quality of evidence in this review.

How do the key results compare with the current evidence? Very little evidence exists to support current practice recommendations of screening for asymptomatic bacteriuria at least once during early pregnancy. However, the risk of potential harm (pyelonephritis, preterm birth and low birth weight) from lack of treatment is thought to outweigh risk of Abx therapy in pregnancy.

How should this study impact the care of ED patients? The risks and benefits of Abx therapy should be discussed with the patient. Where there is suspicion of pyelonephritis, consultation with obstetrics should occur. Inpatient management with intravenous (IV) Abx is usually indicated due to approximately 10% risk of endotoxin-induced alveolar injury and the potential for progression to pulmonary edema and acute respiratory distress syndrome (ARDS).[4,5]

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Study Summary

Article: Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2019 Nov 25;2019(11).

Design: Systematic review and meta-analysis of randomized and quasi-randomized controlled trials.

Population: *Included:* Pregnant women (age unspecified) with asymptomatic bacteriuria.
Excluded: Not applicable.

Intervention: Abx.

Comparison: Placebo or no treatment.

Outcomes: *Primary:* Development of pyelonephritis.
Secondary: Preterm birth < 37 weeks; birthweight < 2,500 g; bacteriuria persisting at the time of delivery; neonatal mortality or other serious adverse neonatal outcome; maternal side effects.

Key Results: *N* = > 2,000 patients in 15 studies.

Sig.	*Outcome*	*N/Studies*	*RR (95% CI)*	*I^2*	*C of E*
SS	Development of pyelonephritis	2,017/12	0.24 (0.13 to 0.41)	60%	Low
SS	Preterm birth < 37 weeks	327/3	0.34 (0.13 to 0.88)	32%	Low
SS	Birthweight < 2500 g	1,437/6	0.64 (0.45 to 0.93)	28%	Low
SS	Persistent bacteriuria	596/4	0.30 (0.18 to 0.53)	76%	?

C of E = certainty of evidence; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	?	?	X
3. The search for studies was unbiased and reproducible.	X	X	X
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	?	?	?
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: Cochrane Collaboration.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The primary analyses are imprecise with the absolute effects ranging widely among the primary outcomes. The subgroup analyses on treatment duration also are underpowered.

Selection Bias: The authors contacted the Information Specialist of the Cochrane Pregnancy and Childbirth's Trials registry but did not provide specific details on how the Specialist searched by topic. This search strategy may have been overly specific and subsequently may have introduced publication bias. Furthermore, the authors note that the original review and previous updates lacked a predefined protocol; therefore, the searches run previously may also be incomplete.

Measurement Bias: There are missing details on how precision was assessed for each outcome during the GRADE assessment. There is no other suspected measurement bias introduced from the review process. However, the included studies had severe measurement issues specifically with respect to defining pyelonephritis, preterm birth, and persistent bacteriuria.

Analysis Bias: Data was meta-analyzed despite a substantial amount of clinical variability between studies with respect to the type of Abx used and treatment regimen, and methodological variability (randomized vs non-random allocation). Many of the Abx used in the included studies are now contraindicated during pregnancy, which would limit the applicability of the results to current treatment practices.

Confounding: The included studies did not measure or report on the balance of prognostic variables such as maternal smoking, socioeconomic status, or co-occurring genital infections. Most included studies are at high risk of bias which confounds the results and lowers the certainty of evidence.

Administrative Details

Key Words: Antibiotics (Abx); asymptomatic; bacteriuria; pregnancy; pyelonephritis; urinary tract infection (UTI).

Appraisers: Bedard C; Worster A; Ghate G.

Reference(s):

1. Ajayi AB, Nwabuisi C, Aboyeji AP, et al. Asymptomatic bacteriuria in antenatal patients in Ilorin, Nigeria. Oman Medical Journal 2012;27(1):31–5.
2. Patterson TF, Andriole VT. Bacteriuria in pregnancy. Infect Dis Clin North Am 1987;1:807–22.
3. Asscher AW, Sussman M, Waters WE, et al. Urine as a medium for bacterial growth. Lancet. 1966 Nov 12;2(7472):1037–41.
4. Hill JB, Sheffield JS, McIntire DD, et al. Acute pyelonephritis in pregnancy. Obstet Gynecol. 2005 Jan;105(1):18–23.
5. Sheffield JS, Cunningham FG. Urinary tract infection in women. Obstet Gynecol. 2005 Nov;106(5 Pt 1):1085–92.

Research Question

Do patients with severe COVID-19 benefit from the addition of dexamethasone to usual care?

BEEM Bottom Line

Why is this study important? As the coronavirus disease 2019 (COVID-19) pandemic has spread across the globe, multiple therapies have been studied. This trial assesses whether dexamethasone significantly impacts mortality in these patients with severe disease.

Which, if any, threats to validity are most likely to have an impact on the results and how? This was an open label trial and, as such, physicians might have treated those allocated to dexamethasone differently than those with usual care leading to biased results. Furthermore, 8% of patients randomized to the usual care group received open-label dexamethasone as part of their clinical care which could have impacted the results as well; however, this would lead to an underestimation of the treatment effect of dexamethasone.

How do the key results compare with the current evidence? These results are consistent with a systematic review and meta-analysis of randomized trials of 2,095 patients with non-COVID-19 acute respiratory distress syndrome (ARDS) that showed glucocorticoids reduced mortality (risk ratio [RR] = 0.72 [95% confidence interval [CI] = 0.55 to 0.93]).[1] Dexamethasone also was shown to reduce mortality compared to usual care in a more recent randomized trial of 277 mechanically ventilated patients with ARDS.[2]

How should this study impact the care of ED patients? For COVID-19 patients requiring mechanical ventilation or any oxygen support, corticosteroids should be the standard of care. In resource poor settings, it may be applicable to administer corticosteroids to severe COVID-19 patients not on oxygen due to lack of availability. If a patient has suspected or confirmed severe COVID-19, a short course of dexamethasone (5 to 7 days) should be part of the treatment plan in addition to good supportive care. Dexamethasone should not be used in patients with non-severe COVID-19.

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No conflicts of interest (ICMJE)

Study Summary

Article: RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020;10.1056/NEJMoa2021436. doi:10.1056/NEJMoa2021436.

Design: Multi-center (176 hospitals in the United Kingdom), open-label, randomized (1:2 ratio) controlled trial.

Population: *Included:* Initially, hospitalized adults (≥ 18 years) with clinically suspected or laboratory confirmed SARS-CoV-2 infection; age limit removed in May 2020. Pregnant patients were also included.
Excluded: Patients with medical history who, in the opinion of the attending clinician, might be at increased risk by participating.

Intervention: Dexamethasone 6 mg orally or intravenously daily for ≤ 10 days (d).

Comparison: Usual standard of care.

Outcomes: *Primary:* All-cause 28-d mortality in all patients and subgroups.
Secondary: Length of hospital stay; receipt and duration of invasive mechanical ventilation (IMV; including extracorporeal membrane oxygenation) post randomization; cause-specific mortality; receipt of hemodialysis; major cardiac arrhythmia.

Key Results: *N* = 6,425 patients with mean age 66.1 ± 15.7 years and of whom 36% were female. Shorter hospitalization in dexamethasone group (12 vs 13 d). The risk of progression to IMV was lower in the dexamethasone group (RR 0.77; 95% CI, 0.62 to 0.95).

Sig.	*28- d Mortality*	*Dexamethasone (%)*	*Usual Care (%)*	*RR (95% CI)*	**NNT (95% CI)*
SS	All subjects	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75 to 0.93)	23 (16 to 56)
SS	IMV	95/324 (29.3)	283/683 (41.4)	0.64 (0.51 to 0.81)	7 (5 to 13)
SS	Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72 to 0.94)	21 (14 to 64)
NSS	No oxygen	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91 to 1.55)	N/A

CI = confidence interval; IMV = invasive mechanical ventilation; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant. *Because NNT (and NNH) refers to people, the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X	✓

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: National Institute for Health Research Clinical Research Network.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: The primary analysis showed a statistical difference in favour of dexamethasone. These results are unlikely due to chance alone.

Selection Bias: It is unknown whether patients were consecutively recruited. While there was a small age difference between groups this was likely due to chance and analyses were adjusted appropriately; other reported prognostic factors were well-balanced.

Measurement Bias: Physicians retained discretion to alter the treatment plan and, given the non-blinded nature of the study, this may have led to performance bias. The risk of detection bias is low since the outcomes are objectively determined, though, lack of data verification procedures allows for potential measurement error.

Analysis Bias: Multiple analyses were conducted without adjusting the overall significance level; this would impact the believability of the subgroup analyses.

Confounding: Of the usual care group, 8% received dexamethasone as part of their clinical care. However, this would lead to an underestimation of the treatment effect of dexamethasone in the intervention arm.

Administrative Details

Key Words: COVID-19; dexamethasone; glucocorticoids; mechanical ventilation; oxygen.

Appraisers: Bedard C; Worster A; Rochwerg B; Sharif S.

Reference(s):

1. Ye Z, Wang Y, Enrique L, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ. 2020;192(27): E756-E767.
2. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020; 8: 267-76.

Research Question

How do N95 respirators compare to medical masks for preventing viral respiratory infections in healthcare workers?

BEEM Bottom Line

Why is this study important? With the rapid worldwide spread of COVID-19, appropriate use and conservation of personal protective equipment (PPE), particularly N95 respirators, has become a major concern. Unlike standard medical masks, N95 respirators are specifically designed to prevent inhalation of small airborne particles by their tight fit to optimize facial seal and the filtration test requirements. For these reasons, the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control, and the Public Health Agency of Canada (PHAC) all recommend the N95 respirators for high-risk exposures such as aerosol-generating procedures including intubation and bronchoscopy. This review compares N95 respirators to medical masks for preventing viral respiratory infections in healthcare workers.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this systematic review and meta analysis are primarily limited by the restriction to English language studies and the imprecision caused by small trials with too few observed events. The results are further limited by indirectness as most trials reported on non-coronavirus infections contrary to the title of the study. There is also evidence in the trials of both performance and detection bias due to lack of blinding.

How do the key results compare with the current evidence? This systematic review adds one new trial to a 2016 review and accounted for the use of cluster randomisation in the primary trials in their analysis.[1] It provides some further support that standard (medical) masks are likely adequate protection for most medical care for patients with viral respiratory infections including COVID-19. This thereby allows for conservation of limited N95 mask supplies for high-risk exposures. Since the included studies were done before the current pandemic, none of the trials specifically focussed on COVID-19 infections and so the existing evidence does not rule out superiority of either N95 or medical masks. Interestingly, a case report from Singapore revealed that 41 health care workers wearing medical masks during high-risk procedures of a patient with severe COVID-19 did not contract the illness.[2]

How should this study impact the care of ED patients? This review provides some support for the worldwide recommendation for droplet/contact precautions for the standard care of patients with possible COVID-19. Specifically, standard medical masks should be worn in proximity of patients with suspected viral respiratory infections including COVID-19 and N95 respirators should be reserved for high-risk exposures.

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No conflicts of interest (ICJME)

Study Summary

Article: Bartoszko JJ, Farooqi MAM, Alhazzani W, et al. Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: A systematic review and meta-analysis of randomized trials. Influenza Other Respir Viruses. 2020 Apr 4. doi: 10.1111/irv.12745.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* Healthcare workers with risk of exposure to a patient with acute respiratory illness.
Excluded: None.

Intervention: N95 respirator.

Comparison: Standard surgical/medical mask.

Outcomes: *Primary:* laboratory-confirmed viral (including but not limited to coronaviruses) respiratory infection by polymerase chain reaction (PCR), serology, or viral culture.
Secondary: Laboratory confirmed coronavirus infection, laboratory-confirmed influenza infection, influenza-like illness, clinical respiratory illness, workplace absenteeism.

Key Results: *N* = 4 trials including 8736 subjects (4779 N95 respirators and 3957 medical masks).

Sig.	*Outcome*	*Odds Ratio (95% CI)*	*Certainty of Evidence*	*I^2*
NSS	Laboratory-confirmed viral respiratory infection	1.06 (0.90 to 1.25)	Low	0%
NSS	Clinical respiratory illness	1.49 (0.98 to 2.28)	Very low	78%

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); NSS = not statistically significant; Odds Ratio is a ratio that, if the value of the range includes 1, there is no difference; Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	?	?
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	X
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	X	?	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: None reported.

Potential Threats to Validity

Chance: The included trials were small with too few observed events, due to which the results are imprecise with the lower and upper bounds of the confidence intervals indicating both superiority and inferiority of medical masks to N95 masks.

Selection Bias: This review was limited to English language studies only.

Measurement Bias: The trials reporting on clinical respiratory infections are at high risk of detection bias due to lack of blinding.

Analysis Bias: None of the trials included COVID19 patients specifically.

Confounding: Confounding cannot be ruled out due to lack of blinding.

Administrative Details

Key Words: Coronavirus; COVID-19; healthcare workers; N95 respirators; pandemic; polymerase chain reaction (PCR); SARS-CoV-2; surgical masks; viral respiratory infection.

Appraisers: Zeraatkar D; Worster A; Edmonds M.

Reference(s):

1. Smith JD, MacDougall CC, Johnstone J et al. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: a systematic review and meta-analysis. MAJ 2016:188(8):657-74. DOI:10.1503/cmaj.1508.35.

2. Ng K, Poon BH, Kiat Pur TH et al. COVID-19 and the risk to health care workers: a case report. Ann Intern Med 2020; https://doi.org/10.7326/L20-O175.

Research Question

What is the risk of cardiovascular death among adults within days of a dispensed azithromycin prescription?

BEEM Bottom Line

Why is this study important? The macrolide antibiotics such as azithromycin and clarithromycin are commonly prescribed to emergency department (ED) patients but, in some people, are also believed to cause QT prolongation.[1] These people are then at significant risk of fatal cardiac arrhythmias. This administrative health care database cohort study measures the association between unexpected death from multiple (albeit primarily cardiovascular) causes within days of being dispensed an azithromycin prescription in almost 2 million adults.

Which, if any, threats to validity are most likely to have an impact on the results and how? This study provides very low certainty evidence that outpatient azithromycin use may be associated with increased risk of cardiovascular death and non-cardiovascular death. The accuracy of the results is severely limited due the potential for residual confounding and misclassification of antibiotic use and mortality. Further, the absolute effect is very small and unlikely to be clinically important.

How do the key results compare with the current evidence? Previous studies have shown conflicting results. In 2012, Ray et al. found a cardiovascular deaths rate of 85.2 per 1 millions[2] courses while a year later Svanstrom found a cardiovascular deaths rate of 15.4 per 1 million courses of azithromycin.[3]

How should this study impact the care of ED patients? It is unlikely that the results of this study should influence prescribing of macrolides at all. Patients prescribed azithromycin have a 0.002% absolute risk of cardiovascular death in the first 5 days compared to amoxicillin. Hence, the impact on the ED patients is very small with a number needed to harm of > 76,000.

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No conflicts of interest (ICMJE)

Study Summary

Article: Zaroff JG, Cheetham TC, Palmetto N, et al. Association of Azithromycin Use With Cardiovascular Mortality. JAMA Netw Open. 2020;3(6):e208199.

Design: Administrative health care database (California, USA) retrospective cohort study.

Population: *Included:* Adults (≥ 30 and ≤ 74 years) dispensed outpatient prescription for azithromycin or amoxicillin.
Excluded: No prescription benefit coverage on the index date; receipt of > 1 study antibiotic (azithromycin or amoxicillin) ≤ 10 days of index date; hospital admission ≤ 30 days of index date; nursing home residence ≥ 30 days in ≤ 365 days of index date; serious underlying medical condition (e.g. cancer ≤ 3 years of index date or human immunodeficiency virus infection [HIV]) prior to index date.

Exposure: Outpatient dispensed prescriptions for oral azithromycin.

Comparison: Outpatient dispensed prescriptions for oral amoxicillin (with or without clavulanate).

Outcomes: *Primary:* Cardiovascular (CV) and sudden cardiac death (e.g. death from myocardial infarction, heart failure, arrhythmia, stroke) ≤ 0 to 5 and 6 to 10 days after the index (prescription) date.
Secondary: All-cause death and noncardiovascular (non-CV) death identified via International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10) codes from state death certificates.

Key Results: *N* = 7,824,681 antibiotic exposures (1,736,976 azithromycin [22.2%]; 6,087,705 amoxicillin [77.8%]) among 2,929,008 individuals (mean age, 50.7 years; 61.8% women)

Sig.	*Death (0 to 5 d)*	*Azithromycin (%)*	*Amoxicillin (%)*	*Adjusted HR (95% CI)*	*NNH (95%)*
SS	CV	62 (0.0036)	95 (0.0016)	1.82 (1.23 to 2.67)	76,923 (38,461 to 250,000)
NSS	Sudden CV	21 (0.0012)	39 (0.0006)	1.59 (0.90 to 2.81)	N/A
SS	All-cause	145 (0.0083)	163 (0.0027)	2.00 (1.51 to 2.63)	37,037 (22,727 to 71,429)
SS	Non-CV	83 (0.0048)	68 (0.0011)	2.17 (1.44 to 3.26)	76,923 (40,000 to 200,000)

CI = confidence interval; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; NNH = number needed to harm (because NNH [and NNT} refers to people, the estimates have been rounded to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups); Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	?	?	?
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	?	?	?
7. The follow-up was complete.	✓	✓	✓
8. The effect size of the primary outcome is clinically significant.	?	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: Pfizer.

Conflicts of Interest: 2 authors were (non- Pfizer) industry employees.

Potential Threats to Validity

Chance: None detected.

Selection Bias: None detected.

Measurement Bias: Misclassification of prescriptions and outcome data is possible and may have attenuated the association between azithromycin and mortality. Misclassification of causes of death may explain the association between azithromycin prescription and non-cardiovascular mortality.

Analysis Bias: None detected.

Confounding: Residual confounding due to unknown or unadjusted prognostic factors (e.g., varying diseases and disease severity) is possible. The association between azithromycin prescriptions and increased risk for non-cardiovascular mortality suggests residual confounding is likely. Prescription doesn't guarantee the patients did take the medication as prescribed or at all.

Potential inaccuracies in medical records on confounding factors may have increased confounding.

Administrative Details

Key Words: Amoxicillin; antibiotic; azithromycin; cardiovascular death; sudden death.

Appraisers: Zeraatkar D; Worster A; Gosselin S.

Reference(s):

1. Ray WA, Murray KT, Meredith S, et al. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med. 2004;351(11):1089-1096.
2. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death, N Engl J Med. 2012;366(20):1881-1890.
3. Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. N Engl J Med. 2013;368(18):1704-1712.

NEURO/STROKE

Research Question

What is the utility of the Canadian TIA Score (compared to ABCD2 or ABCD2i) to predict subsequent stroke?

BEEM Bottom Line

Why is this study important? Accurate risk-stratification of ED TIA patients as Low vs. High risk allows for appropriate disposition decisions. This study compares the discriminative abilitiy of the Canadian TIA Score with the ABCD2/ABCD2i scores.

Which, if any, threats to validity are most likely to have an impact on the results and how? None.

How do the key results compare with the current evidence? These results build on prior work that assesses ED physician stroke risk tolerances, and the accuracy of prior risk stratification tools to guide ED disposition decisions.

How should this study impact the care of ED patients? The Canadian TIA Score is more discriminating than prior tools to risk-stratify ED TIA patients for short-term stroke risk, and can be used to make appropriate resource-optimizing decisions.

AUTHOR 1
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Perry JJ, Sivilotti MLA, Emond M, *et al*. Prospective validation of Canadian TIA Score and comparison with ABCD2 and ABCD2i for subsequent stroke risk after transient ischemic attack: a multicentre prospective cohort study. BMJ 2021; 372:n49. http://dx.doi.org/10.1136/bmj.n49

Design: Prospective cohort study to implement/validate the Canadian TIA Score.

Population: *Included:* Adults ≥ 18yrs with an ED discharge Dx of TIA or minor stroke.
Excluded: Neuro deficits >24hrs, decreased LOC (GCS <15 in previously normal patients), alternative neuro Dx (eg. migraines, seizure, hypoglycemia, electrolyte imbalance), ED presentation >7 days after onset of symptoms, or reperfusion (tPA, embolectomy) for acute ED stroke.

Predictors: Canadian TIA Score.

Comparison: ABCD2 and ABCD2i score variables.

Outcomes: *Primary:* Stroke or carotid endarterectomy/stenting with 7days of ED TIA visit. Total 182 outcome events (1.4% strokes, 1.1% carotid intervention).
Secondary: Stroke with 7days of ED TIA visit (with/without carotid endarterectomy or stenting).

Key Results: *N* = 7607 pts consecutively enrolled via ED over 5yrs. Mean age 68.5yrs, 52.3% female; 75% first reported TIA. 96.5% had CT head and 91% ECG during ED visit. Majority of discharged patients continued/started on ASA, clopidogrel, or both in ED. Predefined risk thresholds for primary outcome: Low = <1%, Med = 1-5%, High>5%.

Cdn Risk Score	Low Risk (-3 to 3) Med Risk (4-8) High Risk (≥9)	Interval LR 0.20 (0.09-0.44) 0.94 (0.85-1.04) 2.56 (2.02-3.25)	Est. Risk 0.7% 2.1% 6.3%	Observed Risk 0.5% 2.3% 6.3%
ABCD2 /ABCD 2i	Low risk = 0 Med Risk = 3-97% High Risk = 3-7%	Neither score correctly correctly classified any patients as Low risk.		
	Cdn TIA Score ABCD2 ABCD2i	AUC 0.70 (0.66-0.73) AUC 0.60 (0.56-0.64) AUC 0.64 (0.59-0.68)	Cdn TIA Score able to correctly risk-stratify TIA patients for stroke risk compared to ABCD2/I scores.	Absolute net reclassification index between Cdn TIA Score and ABCD2i = 8.5%.

CI = confidence interval; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; *p* = probability; OR = odds ratio (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were representative of those with the problem.	✓
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	✓
3. All patients underwent the same clinical evaluation.	✓
4. All important predictor variables were included in the clinical evaluation and explicitly defined.	✓
5. Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	✓
6. Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	✓
7. All outcome variables were included in the clinical evaluation and explicitly defined.	✓
8. All patient-important outcomes were considered.	✓
9. The follow-up was complete.	✓
10. The point estimates and respective precisions are clinically significant.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: CIHR grant.

Conflicts of Interest: Two authors supported by public grants (JJ, JL); otherwise no CoI declared.

Potential Threats to Validity

Chance: Study nurses reviewed all ED visits to identify potential/missed patients.

Selection Bias: Consecutive sampling over 5yrs at 13 Cdn Eds (10 university hospitals, 3 community); no time limitations. 80.6% of all screened patients were enrolled; patients not enrolled were demographically similar to enrollees, but more frequently admitted [18.4% vs 5.8%]). Only 34 patients (0.4%) were lost to 7d follow-up.

Measurement Bias: All ED physicians formally trained and applied the data collection forms for all 3 scores compared. Telephone follow-up of patients at 7 and 90days, using validated Questionnaire for Verifying Stroke Free Status tool.

Analysis Bias: All outcomes adjudicated by site committees (neurologists, ED physician) blinded to index ED visit management.

Confounding: None?

Administrative Details

Key Words: Canadian TIA Score, carotid endarterectomy/stenting, stroke

Appraisers: Upadhye S.

Reference(s): Perry JJ, Sivilotti MLA, Emond M, Stiell IG, Stotts G, Lee J, Worster A, Morris J, Cheung KW, Jin AY, Oczkowski WJ, Sahlas DJ, Murray HE, Mackey A, Verreault S, Camden MC, Yip S, Teal P, Gladstone DJ, Boulos MI, Chagnon N, Shouldice E, Atzema C, Slaoui T, Teitlebaum J, Abduzlaziz K, Nemnom MJ, Wells GA, Sharma M. Prospective validation of Canadian TIA Score and comparison with ABCD2 and ABCD2i for subsequent stroke risk after transient ischemic attack: a multicentre prospective cohort study. BMJ 2021; 372:n49. http://dx.doi.org/10.1136/bmj.n49

Table 1 | Canadian TIA Score	
Items	**Points**
Clinical findings:	
1) First transient ischaemic attack (in lifetime)	2
2) Symptoms ≥10 minutes	2
3) Past history of carotid stenosis	2
4) Already on antiplatelet therapy	3
5) History of gait disturbance	1
6) History of unilateral weakness	1
7) History of vertigo	−3
8) Initial triage diastolic blood pressure ≥110 mm Hg	3
9) Dysarthria or aphasia (history or examination)	1
Investigations in emergency department:	
1) Atrial fibrillation on electrocardiogram	2
2) Infarction (new or old) on computed tomography	1
3) Platelet count $\geq 400 \times 10^9$/L	2
4) Glucose ≥15 mmol/L	3
Total score (−3 to 23):	X

Research Question

How useful is the HINTS exam to rule out stroke in ED patients with acute vestibular syndrome (AVS)?

BEEM Bottom Line

Why is this study important? Determining which ED patients with acute vertigo/vestibular syndromes may have central causes (ie. stroke) is very important to avoid critical misses. The HINTS exam has been proposed as a test with good discriminative value for central vs. peripheral vertigo.

Which, if any, threats to validity are most likely to have an impact on the results and how? Overall, the review and meta-analysis was conducted without bias, however it is likely that the spectrum and detection bias in the included studies has lead to an inflated estimate of diagnostic accuracy. Only one included study incorporated the HINTS exam performance by ED physicians (with neurology/vascular fellowship training), and even with such advanced credentialling, the HINTS exam did not perform with sufficient accuracy to include/exclude central stroke.

How do the key results compare with the current evidence? There is a lack of evidence supporting the use of HINTS exam by ED physicians.

How should this study impact the care of ED patients? The HINTS exam is insufficient to rule in/out central stroke in ED AVS patients.

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No conflicts of interest/Identify conflicts (ICMJE)

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Ohle R, Montpellier RA, Marchadier V, *et al*. Can Emergency Physicians Accurately Rule Out a Central Cause of Vertigo Using the HINTS Examination? A Systematic Review and Meta-analysis. Acad Emerg Med 2020; 27: 887-896. doi: 10.1111/acem.13960

Design: Systematic review of the HINTS diagnostic test studies.

Population: *Included:* Adult patients with acute vestibular syndrome/vertigo.
Excluded: Not reported.

Index Test: HINTS exam.

Reference Test: CT or MRI imaging.

Diagnosis of Interest: Central cause of vertigo (ie. stroke).

Key Results: *N* = 617 patients in 5 studies. Prevalence of stroke in ED AVS patients: 9.3-44%

N/Studies	*Measure (95% CI)*	I^2
	Neurologists/Neuro-ophthalmologists only (4 studies) LR+ = 16-63.9 LR– = 0.01-0.38 Sensitivity = 96.7 (93.1-98.5) Specificity = 94.8 (91-97.1)	0
	ED physicians with vascular/neurology fellowship training (1 study) Sensitivity = 83.3 (63.1-93.6) Specificity = 43.8 (36.7-51.2) LR+ = 1.48, LR- = 0.007	N/A

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓	✓
7. The quality of the primary studies is high.	X	X
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	?	✓
9. The subgroups were stated a priori and appropriate.	?	n/a
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓	✓

A1 = S. Upadhye A2 = C. Bedard

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: None (not reported).

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: The meta-analysis overall appears to have narrow confidence intervals but there is insufficient data to address their objective to compare the diagnostic accuracy between emergency physicians and neurologists/neurootologists. The individual studies included in the review did not report study sampling strategies and many were suspected at risk of spectrum bias.

Selection Bias: Comprehensive unlimited searches limit the risk of missing relevant studies, though there are too few studies found to statistically determine the probability of publication bias.

Measurement Bias: Risk of bias assessment was reliable. However, the overall risk of bias for included studies was high.

Analysis Bias: The meta-analysis had low risk of bias; however, possible detection bias was present in many included studies, in addition to suspected spectrum bias, this likely lead to inflated sensitivity and specificity.

Confounding: It is likely that the above stated spectrum and detection bias lead to an inflated estimate of diagnostic accuracy.

Administrative Details

Key Words: Acute vestibular syndrome, HINTS exam, stroke

Appraisers: Upadhye S, Bedard C.

Reference(s): Ohle R, Montpellier RA, Marchadier V, Wharton A, McIsaac S, Anderson M, Savage D. Can Emergency Physicians Accurately Rule Out a Central Cause of Vertigo Using the HINTS Examination? A Systematic Review and Meta-analysis. Acad Emerg Med 2020; 27: 887-896. doi: 10.1111/acem.13960

Research Question

What is the effectiveness of dimenhydrinate vs metoclopramide in treating ED vertigo/nausea?

BEEM Bottom Line

Why is this study important? Vertigo (ED incidence 3.3%) can be associated with intense nausea, and needs effective treatment in the ED. Both dimenhydrinate (DMH) and metoclopramide (MCP) are common anti-nauseants in ED care.

Which, if any, threats to validity are most likely to have an impact on the results and how? This study was designed based on equality of DMH vs MCP, yet reported equivalence based on non-significance; further data is required from an equivalence-designed trial to conclude equal efficacy. The patient sampling strategy is not reported, which may have introduced an element of selection bias. Finally, the minimal clinical important difference (MCID) on the VAS measurements is inconsistently reported.

How do the key results compare with the current evidence? Both agents are helpful for reducing vertigo/nausea intensity as monotherapy, consistent with prior trials cited.

How should this study impact the care of ED patients? Either DMH or MCP can be effective IV monotherapy for treating ED acute vertigo/nausea within 30min.

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No conflicts of interest/Identify conflicts (ICMJE)

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Ercin D, Erdur B, Turkcuer I, *et al*. Comparison of efficacy dimenhydrinate and metoclopramide in the treatment of nausea due to vertigo: a randomized study. Am J Emerg Med 2021; 40: 77-82. https://doi.org/10.1016/j.ajem.2020.12.010

Design: Single center prospective DB-RCT

Population: *Included:* Adults (≥ 18 and ≤ 65 years) with an ED Dx of vertigo/motion sickness.
Excluded: Consent refused, hypersensitivity/other CI for either agent, pregnant/breast-feeding, suspected/proven GI bleed, bowel obstruction/perforation, prior Hx psychiatric/neurologic disorder, renal failure, or mild nausea from vertigo (<4cm on VAS).

Intervention: Dimenhydrinate (DMH) 50mg in 150ml NS solution, infused over 15min.

Comparison: Metoclopramide (MCP) 10mg in 150ml NS solution, infused over 15min.

Outcomes: *Primary:* Reduction of vertigo intensity at 30min (on VAS 1-10 scale).
Secondary: Reduction in nausea intensity on VAS, and change in 30min VAS scores for vertigo & nausea.

Key Results: *N* = 200 patients (100 per group; mean age 31 years, 72% female).

Sig.	*Outcome*	*DMH (mean ± SD)*	*MCP (mean ± SD)*	*Mean/Risk Difference (95% CI)*
NSS	Vertigo intensity at 30min	2.46 ± 2.39	2.31 ± 1.96	0.15 (-0.46 to 0.76)
NSS	Nausea intensity at 30min	2.27 ± 2.24	2.70 ± 2.48	-0.43 (-1.09 to 0.23)
NSS	Adverse effects at 30min	21 (21%)	28 (28%)	-0.07 (-0.19 to 0.05)
NSS	Need for rescue meds	25 (25%)	23 (23%)	0.02 (-0.10 to 0.14)

SD = standard deviation; CI = confidence interval; *N* = number of patients; NSS = not statistically significant; Sig. = significance; SS = statistically significant

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The patients were recruited consecutively.	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓
6. All groups were treated equally except for the intervention.	✓	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓
9. All patient-important outcomes were considered.	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X

A1 = S. Upadhye A2 = C. Bedard

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Research supported by Pamukkale University Faculty of Medicine Research Fund, grant number (2012TPF034).

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: Sample size calculation for equality design met/exceeded.

Selection Bias: The patient sampling/recruiting strategy (eg. Convenience, consecutive, etc.) is not reported. The DMH group appears to be slightly older with higher proportion of patients noted with ‘disease’, ‘allergy’ and on medication; however, these differences are small and likely due to chance.

Measurement Bias: Use of 1-10 VAS scales administered by blinded staff; MCID (meaningful clinically important difference) had been defined as 1.5 however this MCID was not supported by evidence.

Analysis Bias: None.

Confounding: In addition to study meds, patients were treated with Epley maneuver, betahistine or piracetam tabs (co-interventions not reported), however the authors did not indicate if these were administered equally across groups. Patients also received a rescue dose of diazepam 5m for insufficient vertigo relief, or 5mg granisetron for insufficient nausea relief.

Administrative Details

Key Words: Dimenhydrinate, emergency department, metoclopramide, nausea, vertigo.

Appraisers: Upadhye S, ; Bedard C.

Reference(s): Ercin D, Erdur B, Turkcuer I, Seyit M, Ozen M, Yilmaz A, Ercins DOZ. Comparison of efficacy dimenhydrinate and metoclopramide in the treatment of nausea due to vertigo: a randomized study. Am J Emerg Med 2021; 40: 77-82. https://doi.org/10.1016/j.ajem.2020.12.010
PMID: 33360021

Research Question

What is the effectiveness of dimenhydrinate (DMH) + metoclopramide (MCP) in the treatment of ED acute posttraumatic headache?

BEEM Bottom Line

Why is this study important? Acute posttraumatic headaches can be common and debilitating after traumatic head injury. Effective treatment of such in the ED can have immediate and sustained benefits.

Which, if any, threats to validity are most likely to have an impact on the results and how? Despite statistical significance for the primary outcome, the trial cannot conclude superiority because the range of treatment effects includes non-clinically important differences. There some concern for selection bias as the sampling strategy was not reported and slight imbalances between groups may have skewed the results. Finally, comparing active treatments to placebos (as opposed to standard therapies) generally with favour the active therapy.

How do the key results compare with the current evidence? The results are congruent with prior cited trial evidence for similar headache syndromes.

How should this study impact the care of ED patients? Combination DMH+MCP may be useful for short-term relief of acute posttraumatic headache intensity, but less so for other sustained post-concussive symptoms.

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No conflicts of interest/Identify conflicts (ICMJE)

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Friedman BW, Irizarry E, Cain D, Caradonna A, Minen MT, Solorzano C, Zias E, Zybert D, McGregor M, Bijur PE, Gallagher EJ. Randomized Study of Metoclopramide Plus Diphenhydramine for Acute Posttraumatic Headache. Neurol 2021; 96; e2323-22331. doi:10.1212/WNL.0000000000011822

Design: Multi-site DB-RCT.

Population: *Included:* Adults (≥ 18) meeting Int Classification of Headache Disorders criteria for acute posttraumatic headache. Moderate/severe intensity.
Excluded: Headache >10days elapsed since initial injury, already treated with antidopaminergic meds, study meds allergies/other Cis, or pregnancy. Pre-trauma headache syndrome with similar headache features.

Intervention: DMH 25mg + MCP 20mg IV over 15min.

Comparison: Placebo (normal saline IV over 15min).

Outcomes: *Primary:* Headache intensity on VAS 0-10 scale at baseline and 1hr.
Secondary: Headache intensity on IHS ordinal scale (4pts) at 0, 1, 2 & 48hrs. Patient satisfaction with ED care, willingness to repeat same Tx, and headache symptoms up to 7d post-ED visit. Patients also asked to rate Post Concussion Symptom Scale (PCSS) scores with RA coaching (22 items, 0-6 Likert scales) at 48hrs & 7days.

Key Results: *N* = 160 patients (n = 81 in DMH, n = 79 in placebo; mean age 45 years; 67% females)

Sig.	*Outcome*	*DMH*	*Placebo*	*ARR/Mean Difference (95% CI)*	*NNT (95% CI)*
NSS	48-hr headache relief	24/78	18/76	0.07 (-0.07 to 0.21)	N/A
SS	Rescue Medication in ED	8/81	20/79	0.15 (0.04 to 0.27)	6 (4 to 28)
SS	Mean 1-hr PCSS	16	25	9 (3 to 15)	N/A
NSS	Mean 1-week PCSS	14	21	7 (0 to 15)	N/A
SS	Adverse Events	35/81	22/79	0.15 (0.01 to 0.30)	7 (3 to 189)
SS	1-hr Pain Improvement (mean ± SD)	5.2 ± 2.3	3.8 ± 2.6	1.4 (0.7 to 2.2)	N/A

ARR = absolute risk reduction; CI = confidence interval; *N* = number of patients; NA = not applicable; NNT = number needed to treat; NSS = not statistically significant; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The patients were recruited consecutively.	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	X
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓
9. All patient-important outcomes were considered.	✓	✓
10. The effect size of the primary outcome is clinically significant.	?	✓

A1 = S. Upadhye A2 = C. Bedard

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Publication was supported in part by the Harold and Muriel Block Institute for Clinical and Translational Research at Einstein and Montefiore grant support (UL1TR001073).

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: The primary analyses were sufficiently powered to detect statistical but not clinically significant differences.

Selection Bias: The sampling strategy (consecutive, convenience, etc.) was not clearly reported, though consecutive recruitment is probable. The study was conducted in an urban, socioeconomically depressed area, which could influence post-ED headache outcomes and investigators excluded patients with mild headaches, both of which limit generalizability. Patients in the placebo group had longer duration of symptoms and were less likely to have taken medications before their ED visit.

Measurement Bias: It is unclear how the MCID was determined for different scales used. It is unknown if various previously published scales have been validated for ED use/reliability or if data collected via telephone was reliable.

Analysis Bias: ITT.

Confounding: DMH may have some anticholinergic effects that can be confused with postconcussive symptoms. IV placebo effects likely higher than oral.

Administrative Details

Key Words: Acute posttraumatic headache, dimenhydrinate, metoclopramide, post-concussive.

Appraisers: Upadhye S, Bedard C.

Reference(s): Friedman BW, Irizarry E, Cain D, Caradonna A, Minen MT, Solorzano C, Zias E, Zybert D, McGregor M, Bijur PE, Gallagher EJ. Randomized Study of Metoclopramide Plus Diphenhydramine for Acute Posttraumatic Headache. Neurol 2021; 96; e2323-22331. doi:10.1212/WNL.0000000000011822

Research Question

What is the most effective/safe agent for use in acutely agitated ED patients?

BEEM Bottom Line

Why is this study important? It is important to achieve reduction of agitation without risk of deep sedation/respiratory depression/hypoxemia in ED agitated patients. This study compares 3 common medications used (at 4 different doses).

Which, if any, threats to validity are most likely to have an impact on the results and how? This trial was originally conducted in 2005, but is only being published now. Majority of agitated patients were intoxicated with alcohol, so it may be difficult to generalize these results to other contemporary "agitators" (eg. Bath salts, methamphetamines, etc.).

How do the key results compare with the current evidence? The results are congruent with recent trials examining similar comparisons (listed in Table 5).

How should this study impact the care of ED patients? Use of droperidol is quickly effective and safe in reducing acute agitation in the ED, with less risk of deep sedation/respiratory depression/hypoxemic events.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Martel ML, Driver BE, Miner JR, *et al*. Randomized Double-Blind Trial of Intramuscular Droperidol, Ziprasidone and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department. Acad Emerg Med 2021; 28: 421-434. doi: 10.1111/acem.14124

PMID: 32888340

Design: 4 arm parallel RCT.

Population: *Included:* Adult patients with acute undifferentiated agitation in ED. Consent exemption approved under REB review.
Excluded: Police custody, pregnant/breast-feeding, previously enrolled in study, or documented allergy to any of the study medications.

Intervention: 4 different arms: Droperidol 5mg, Ziprasidone 10 & 20mg, and lorazepam 2mg. All doses given intra-muscularly.

Comparison: Inter-arm comparisons above

Outcomes: *Primary:* proportion of patients adequately sedated at 15min (defined as Altered Mental Status Scale [AMSS] score of ≤ 0 [range -4 to +4]). Cross-correlated with BARS scores (Behavioural Activity Rating Scale).
Secondary: Need for additional rescue sedation, ED LOS, respiratory depressions events (SpO_2 <90, requiring supplemental oxygen, or ETCO2>15mm).

Key Results: *N* = 115 patients.

Outcome	*Droperidol 5mg*	*Ziprasidone 10mg*	*Ziprasidone 20mg*	*Lorazepam 2mg*
AMSS 45min	21 (84%)	22 (79%)	24 (77%)	18 (56%)
Total ED LOS	563min (477-615)	540min (438-720)	551min (455-640)	611min (439-782)
Hypoxemia	2 (8%)	2 (7%)	6 (19%)	7 (23%)
Rescue Sed	5 (20%)	7 (25%)	5 (16%)	12 (39%)
Primary (15min)	**16 (64%)**	7 (25%)	11 (35%)	9 (29%)
Resp Dep	**3 (12%)**	10 (36%)	12 (39%)	15 (48%)

ARR = absolute risk reduction (if the CI includes the value 0, there is no difference in risk between the groups and the NNT is not estimable); CI = confidence interval; *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.
*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	?
3. The allocation sequence was adequately concealed.	?
4. The patients in all groups were similar with respect to prognostic factors.	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	?
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	✓

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Unknown?

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None?

Selection Bias: No details on randomization process, nor allocation concealment. 149 patients, 34 rejected for unknown reasons (selection bias?). Patients balanced on baseline demographic factors (Table 2).

Measurement Bias: What is the MCID for the AMSS scale? Respiratory depression differences driven by change in $ETCO_2$ measurements; no differences in hypoxia rates in 4 arms.

Analysis Bias: All patients analyzed in their assigned groups. Paired comparisons reported.

Confounding: Majority of patients in each arm equally agitated with alcohol intoxication (approx. 80%).

Administrative Details

Key Words: Acute ED agitation, droperidol, lorazepam, ziprasidone

Appraisers: Upadhye S.

Reference(s): Martel ML, Driver BE, Miner JR, Biros MH, Cole JB. Randomized Double-Blind Trial of Intramuscular Droperidol, Ziprasidone and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department. Acad Emerg Med 2021; 28: 421-434. doi: 10.1111/acem.14124

Research Question

Does the addition of N-terminal pro–B-type natriuretic peptide measurement to the Canadian Syncope Risk Score improve the prediction of 30-day serious adverse events in emergency department patients presenting with syncope?

BEEM Bottom Line

Why is this study important? Syncope is a common emergency department (ED) complaint that presents clinicians with the challenge of identifying patients at risk for serious adverse events (SAEs). Cardiac biomarkers such as natriuretic peptides and high-sensitivity troponin have demonstrated some prognostic value in risk stratification of ED patients with syncope.[1,2] This study evaluated whether adding N-terminal pro–B-type natriuretic peptide (NT-proBNP) to the Canadian Syncope Risk Score (CSRS) improves prediction of 30-day SAEs in ED patients with syncope.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results are limited by the potential non-representativeness of the study sample (patients included had higher prevalence of comorbidities and SAEs) and the low prevalence of SAEs in the sample (which may affect the reliability of model estimates).

How do the key results compare with the current evidence? The findings were consistent with other studies in that NT-proBNP values among study patients with SAEs were higher than those without SAE's.[3,4] In a recent multicenter study that enrolled patients from thirteen hospitals in 8 countries, authors noted that the prognostic accuracy of the NT-proBNP was inferior to the CSRS[4].

How should this study impact the care of ED patients? When evaluating ED patients with syncope (who meet criteria for application of the CSRS), the addition of an NT-proBNP to the CSRS does not appear to provide any prognostic benefit for 30-day SADs. Clinicians should exercise selective use of the NT-proBNP.

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No conflicts of interest (ICMJE)

Study Summary

Article: Thiruganasambandamoorthy V, McRae AD, Rowe BH, et al. Does *N*-Terminal Pro-B-Type Natriuretic Peptide Improve the Risk Stratification of Emergency Department Patients With Syncope? *Ann Intern Med*. 2020;172(10):648-655.

Design: Prospective, multicenter (6 Canadian EDs), cohort substudy.

Population: *Included:* Adults (≥ 16 years) presenting to the ED within 24 hours of syncope.
Excluded: Patients with prolonged (i.e. > 5 minutes) loss of consciousness, mental status changes from baseline, witnessed seizure, head trauma leading to loss of consciousness, requiring hospitalization for traumatic injuries, questionable accurate history, or adjudicated to have a serious underlying condition identified at index ED visit.

Exposure: Addition of the NT-proBNP to the CSRS.

Comparison: The CSRS alone.

Outcomes: *Primary:* SAE ≤ 30 days. SAE defined by the CSRS as death, serious non-arrhythmic outcomes (i.e. myocardial infarction, serious structural heart disease, aortic stenosis, hypertrophic cardiomyopathy; left atrial myxoma or thrombus pericardial effusion or tamponade, aortic dissection, pulmonary embolism, severe pulmonary artery hypertension, subarachnoid hemorrhage, significant hemorrhage, procedural interventions to treat arrhythmia any other serious condition, any interventions used to treat a non-arrhythmic cause of syncope, serious arrhythmic outcomes.
Secondary: Arrhythmic SAEs include arrhythmia; interventions for arrhythmia, such as cardioversion or pacemaker or defibrillator insertion; or death due to an unknown cause. Cardiac SAEs include patients with arrhythmic SAEs, serious structural heart disease, myocardial infarction, acute coronary syndrome, or surgery for valvular or structural heart disease.

Key Results: *N* = 1,452 (mean age 58.1 years; 51.6% female).

Sig.	*SAE (n)*	*CSRS AUC (95% CI)*	*+NT-proBNP AUC (95% CI)*	*P-value*
NSS	All (152)	0.892 (0.867 to 0.916)	0.900 (0.878 to 0.922)	0.12
NSS	Arrhythmic (84)	0.932 (0.910 to 0.954)	0.936 (0.917 to 0.956)	0.35
NSS	Cardiac (109)	0.938 (0.920 to 0.956)	0.942 (0.926 to 0.958)	0.22

AUC = area under the receiver operating characteristic curve; CI = confidence interval; *N* = number of patients; *n* = number of patients in subgroup; NSS = not statistically significant; *p* = probability; Sig. = significance. P-values = probability-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	X	X	?
2. The patients were representative of those with the problem.	X	X	X
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	?
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	✓	✓	✓
7. The follow-up was complete.	✓	✓	✓
8. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: Physicians' Services Incorporated Foundation, Canadian Institutes of Health Research, and The Ottawa Hospital Academic Medical Organization.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: None detected.

Selection Bias: Patients who did not have blood tests or cardiac troponin measurements were not included in the study. These patients were younger, had a low prevalence of comorbid conditions, and very few had serious outcomes. Approximately 19.5% of all eligible patients in index population were not included or “missed”.

Measurement Bias: None detected.

Analysis Bias: There were few patients in the study who experienced SAEs, which may adverse impact the reliability of model estimates.

Confounding: None detected.

Administrative Details

Key Words: Arrhythmia; Canadian Syncope Risk Score; *N*-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP); syncope.

Appraisers: Zeraatkar D; Worster A; Graffeo CS.

Reference(s):

1. Thiruganasambandamoorthy V, Ramaekers R, Rahman M, et al. Prognostic Value of Cardiac Biomarkers in the Risk Stratification of Syncope: A Systematic Review Intern Emerg Med. 2015 Dec;10(8):1003-14.
2. Clark C, Gibson T, Weiss R, et al. Do High Sensitivity Troponin and Natriuretic Peptide Predict Death or Serious Cardiac Outcomes After Syncope? Acad Emerg Med. 2019 May; 26(5): 528–538.
3. Probst M, Gibson T, Weiss E, et al. Risk Stratification of Older Adults Who Present to the Emergency Department With Syncope: The FAINT Score Ann Emerg Med. 2020 Feb;75(2):147-158.
4. Du Fay de Lavallaz J, Badertscher P, Nestelberger T, et al. B-Type Natriuretic Peptides and Cardiac Troponins for Diagnosis and Risk-Stratification of Syncope. Circulation. 2019; 139:2403–2418
5. Albassam O, Redelmeier R, Shadowitz S, et al. Did This Patient Have Cardiac Syncope?: The Rational Clinical Examination Systematic Review JAMA. 2019 Jun 25;321(24):2448-2457.
6. Shen W, Sheldon R, Benditt D et al 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society Circulation. 2017 Aug 1;136(5):e25-e59
7. Brignole M, Moya A, de Lange F et al. 2018 ESC Guidelines for the Diagnosis and Management of Syncope Eur Heart J. 2018 Jun 1;39(21):1883-1948.

Research Question

Is the Canadian Syncope Risk Score a valid clinical prediction tool for use in the emergency department?

BEEM Bottom Line

Why is this study important? Syncope is a common emergency department (ED) presentation but there is a need for robust evidence to guide risk stratification for serious outcomes. This study aimed to prospectively validate the Canadian Syncope Risk Score (CSRS) to predict which patients were at risk of a serious outcome within 30 days of the index ED visit as well as to determine the patient's immediate disposition, i.e., discharge home or admit to hospital. If validated, the use of CSRS will be able to improve patient safety and health care efficiency.

Which, if any, threats to validity are most likely to have an impact on the results and how? There is a substantial concern for selection bias since 19.5% of eligible patients were missed for unknown reasons and high-risk patients were excluded from enrollment. The 4% lost to follow-up were younger and generally at a lower risk of a serious outcome.

How do the key results compare with the current evidence? The San Francisco Syncope Rule (SFSR) and the Risk of Syncope in the ED (ROSE) have assessed the risk of short-term serious outcomes in patients presenting with Syncope in the ED.[1,2] The short-term serious mortality for ED syncope was very low and similar to previously reported studies. Interestingly, the SFRS performed poorly on external validity and the ROSE used B-type natriuretic peptide (BNP) not widely used in the ED outside of the USA. Unlike other syncope risk stratification models, the CSRS excluded patients at high risk of serious outcomes on ED presentation. The authors acknowledged that the use of CSRS will be more applicable to the lower risk patient who may be safely discharged home.

How should this study impact the care of ED patients? ED clinicians now have further data to justify discharging the very low and low risk syncopal patients who fit the criteria. However, for medium, high and very high-risk patients, the model's sensitivity becomes notably lower. Shared decision-making regarding admission to hospital and the need of for further investigations for medium risk patients is reasonable, high-risk patients should be admitted.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Thiruganasambandamoorthy V, Sivilotti MLA, Le Sage N, et al. Multicenter Emergency Department Validation of the Canadian Syncope Risk Score. JAMA Intern Med. 2020 Mar 23. doi: 10.1001/jamainternmed.2020.0288.

Design: Prospective, multicenter (9 Canadian EDs), cohort study reported according to TRIPOD guidelines.

Population: *Included:* Adults (≥ 16 years) presenting to the ED within 24 hours of syncope.
Excluded: Patients with prolonged (i.e. > 5 minutes) loss of consciousness, mental status changes from baseline, witnessed seizure, head trauma leading to loss of consciousness, requiring hospitalization for traumatic injuries, questionable accurate history, or adjudicated to have a serious underlying condition identified during the index ED evaluation.

Predictors: 2 points for QTc > 480 ms, any systolic pressure reading <90 or >180 mm Hg, cardiac syncope, elevated troponin; 1 point for abnormal QRS axis (< −30° or > 100°), QRS duration > 130 ms, or history of heart disease; −1 point for predisposition to vasovagal syncope; −2 points for vasovagal syncope diagnosed in the ED.

Comparison: None.

Outcomes: *Primary:* Death, serious non-arrhythmic outcomes (i.e. myocardial infarction, serious structural heart disease, aortic stenosis, hypertrophic cardiomyopathy; left atrial myxoma or thrombus pericardial effusion or tamponade, aortic dissection, pulmonary embolism, severe pulmonary artery hypertension, subarachnoid hemorrhage, significant hemorrhage, procedural interventions to treat arrhythmia any other serious condition, any interventions used to treat a non-arrhythmic cause of syncope, serious arrhythmic outcomes.
Secondary: Outcomes by risk level.

Key Results: *N* = 3,817 (mean age 53.9 years; 2088 [54.7%] female; 139 outcomes; 32 nonrhythmic outcomes; 13 deaths)

Risk Level (CSRS Score)		Number of Patients (%)	All Outcomes	Nonarrhythmic (%)	All Deaths (%)
Very High	(6 to 11)	78 (20.4)	40 (51.3)	7 (9.0)	7 (9.0)
High	(4 to 5)	167 (43.8)	32 (19.2)	6 (3.6)	5 (3.0)
Medium	(1 to 3)	687 (18.0)	55 (8.0)	15 (2.2)	1 (0.1)
Low	(0 to –1)	1254 (32.9)	9 (0.7)	3 (0.2)	0
Very Low	(–3 to –2)	1631 (42.7)	3 (0.2)	1 (0.1)	0

N = number of patients.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were representative of those with the problem.	✓	?	?
2. The patients were enrolled consecutively or in a way to ensure a representative sample.	✓	✓	✓
3. All patients underwent the same clinical evaluation.	?	X	X
4. All important predictor variables were included in the clinical evaluation and explicitly defined.	✓	✓	✓
5. Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	✓	✓	✓
6. Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	?	?	?
7. All outcome variables were included in the clinical evaluation and explicitly defined.	✓	✓	✓
8. All patient-important outcomes were considered.	✓	✓	✓
9. The follow-up was complete.	X	X	X
10. The point estimates and respective precisions are clinically significant.	?	?	?

A = appraiser.

Funding & Conflicts of Interest

Funding: The Heart and Stroke Foundation of Canada and the Cardiac Arrhythmia Network of Canada.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The study met the recommended minimum of 100 events and a minimum of 100 nonevents for prediction tool validation studies.

Selection Bias: Despite the intended consecutive enrolment procedures, the sample missed approximately 20% of potentially eligible patients, raising some concern for selection bias; there is minimal data presented to compare those missed and those included in the sample to determine the extent or direction of the bias. Also, race and ethnicity are not mentioned in this study, which may affect generalizability to certain ethnic groups.

Measurement Bias: The authors noted that ED physicians were trained on how to complete the CSRS after its publication. The derivation cohort published before showed that the tool has a robust performance in predicting short term serious outcomes. Based on this, the risk of measurement error or bias is likely low.

Analysis Bias: 114 patients (3.0%) did not have an electrocardiogram performed, and 1566 patients (41.0%) did not have troponin concentrations measured during the ED evaluation and their data was imputed as 'normal'. However, sensitivity analyses showed that the results were robust to this assumption. This is not surprising as these were mostly in young adults who, by the clinicians' judgement, did not require these tests. If clinicians tested this low-risk population in practice they might be committing errors of commission.
The analyses excluded those lost to follow-up (approximately 4%) who appeared to be younger and more often arrived at the ED by ambulance, though the authors noted that overall they were at a lower risk; therefore, the results may be slightly biased towards a higher risk demographic.

Confounding: None identified.

Administrative Details

Key Words: Arrhythmia; Canadian Syncope Risk Score; syncope.

Appraisers: Bedard C; Worster A; Smith-Gorvie T.

Reference(s):

1. Quinn JV, Stiell IG, McDermott DA, et al. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. Ann Emerg Med. 2004 Feb;43(2):224-32
2. Reed MJ, Newby DE, Coull AJ, et al. The ROSE (risk stratification of syncope in the emergency department) study. J Am Coll Cardiol. 2010 Feb 23;55(8):713-21.

Research Question

What is the clinical impact of the Ottawa subarachnoid hemorrhage rule and the 6-hour-computed tomography rule on investigation rates?

BEEM Bottom Line

Why is this study important? Subarachnoid hemorrhage (SAH) represents approximately 1% of all headaches seen in the emergency department (ED).[1] Given the severe consequences of a missed diagnosis, patients with suspected SAH often undergo invasive tests such as lumbar puncture (LP) or computed tomography angiography (CTA). These investigations increase patient risk as well as healthcare costs and delays to ED discharge. This study assesses the impact of the combined Ottawa SAH and the 6-Hour-Computed Tomography (CT) rules on reducing investigations in those headache patients at low risk of SAH.

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this study are primarily limited by the potential for confounding from the before-and-after design and the small observed difference in the application of the Ottawa SAH Rule between the control and intervention phases, which may have attenuated any potential differences in outcomes. All of the study sites were urban, teaching hospitals having taken part in the derivation phases of the rule. This raises the question about external validity especially in other ED settings and among physicians who are less familiar with the rule.

How do the key results compare with the current evidence? The sensitivity of the Ottawa SAH rule is similar to what has been assessed in other validation studies.[2,3] However, the 6-hour-CT rule has a lower sensitivity and wider 95% confidence interval (95.5% [89.8 to 98.5]) than in the original study assessing this diagnostic test.[4] The 6-hour-CT rule in the present study missed 5 SAHs: 1 radiology misread, 2 incidental aneurysms, 1 nonaneurysmal cause, and 1 profoundly anemic patient.

How should this study impact the care of ED patients? These combined rules can rule out SAH and limit additional invasive testing in a subset of headache patients with suspected SAH. However, physicians must be aware of a potential increase in diagnostic testing given the low specificity of the rule and given the subjectivity of some of the clinical criteria if the rule is not applied correctly.

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No conflicts of interest (ICMJE)

Study Summary

Article: Perry JJ, Sivilotti MLA, Émond M, et al. Prospective Implementation of the Ottawa Subarachnoid Hemorrhage Rule and 6-Hour Computed Tomography Rule. Stroke. 2020 Feb;51(2):424-430.

Design: Multicenter (Canada), before and after, interventional, cohort study.

Population: *Included:* Adults (> 15 years) with ED presenting complaint of nontraumatic, acute (maximal intensity in < 1 hour) headache, or syncope associated with headache, ≤ 14 days duration and Glasgow Coma Scale of 15/15.
Excluded: Patients with ≥ 3 similar headaches over > 6 months; brain neoplasm, intracranial aneurysm or SAH diagnosis or CT and LP for the same headache prior to ED arrival; papilledema; new focal neurological deficit; cerebroventricular shunt; headache ≤ 72 hours post-LP.

Exposure: (After phase) Application of: 1) Ottawa SAH rule which indicates investigation for ≥ 1 of: symptoms of neck pain or stiffness; age ≥ 40 years old; witnessed loss of consciousness; onset during exertion; thunderclap headache (peaking intensity immediately); limited neck flexion on exam; and 2) 6-hour-CT rule ruling out SAH if modern CT scan performed ≤ 6 hours of symptom onset and read by an attending radiologist as negative.

Comparison: (Before phase) Standard care.

Outcomes: *Primary:* ED investigation rate for CT, LP, CTA and additional testing post-CT (i.e. CTA or LP).
Secondary: Ottawa SAH rule sensitivity with SAH defined as: subarachnoid blood on CT, xanthochromia in the cerebrospinal fluid (CSF), or (>1x10^6/L) red blood cells in the final CSF tube and an aneurysm on angiography. For subjects with no investigations, SAH was confirmed or ruled out with health records review at 6 months.

Key Results: *N* = 3,672

Sig.	*Test/Outcome*	*Before (N = 1,743)*	*After (N = 1,929)*	*P-value*
NSS	CT (%)	1534 (88.0)	1688 (87.5)	0.643
SS	LP (%)	678 (38.9)	500 (25.9)	<0.0001
SS	CTA (%)	328 (18.8)	419 (21.7)	0.029
SS	CTA or LP (%)	894 (51.3)	813 (42.2)	<0.0001
NSS	SAH (%)	100 (5.7)	88 (4.6)	0.22

N = number of patients; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant. P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	?	?	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	?	?	?
7. The follow-up was complete.	✓	✓	?
8. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Canadian Institutes of Health Research.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: None detected.

Selection Bias: None detected.

Measurement Bias: The difference in the application of the Ottawa SAH Rule between the control and intervention phases was small (77.5% vs. 85.6%), which may have attenuated any differences in outcomes.

The failure to blind investigators who reviewed patients' health records may have biased the reported sensitivity and specificity of the 6-hour-CT and the Ottawa SAH rules.

Analysis Bias: None detected.

Confounding: Given the before-after design, the results may be confounded by time-varying factors (e.g., nature of injuries).

Administrative Details

Key Words: Computed tomography angiography (CTA); lumbar puncture (LP); subarachnoid hemorrhage (SAH).

Appraisers: Zeraatkar D; Worster A; Morris J.

Reference(s):

1. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med. 2000 Jan 6;342(1):29-36.
2. Kimura A, Kobayashi K, Yamaguchi H et al. New clinical decision rule to exclude subarachnoid haemorrhage for acute headache: a prospective multicentre observational study. BMJ Open. 2016 Sep 9;6(9).
3. Bellolio MF, Hess EP, Gilani WI et al. External validation of the Ottawa subarachnoid hemorrhage clinical decision rule in patients with acute headache. Am J Emerg Med. 2015 Feb;33(2):244-9.
4. Perry JJ, Stiell IG, Sivilotti ML et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. BMJ. 2011 Jul 18;343

Research Question

What are the latest guidelines for the early management of acute ischemic stroke?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? These guidelines are an update of the 2018 acute ischemic stroke (AIS) guidelines and include several new recommendations for the management of AIS.[1]

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? The guideline panel is over-represented by stroke neurologists whose programs of clinical care are dependent on insured patients eligible for aggressive and costly care. Hence, there is a trend towards treatment recommendation even if the certainty in evidence is low or very low. There is incongruity between study design criteria and strength of recommendation and a gross neglect of cost and resource considerations.

How should this guideline, and specifically which recommendations should impact the care of emergency department (ED) patients? The recommendations need to be reviewed by a multidisciplinary team at each hospital to determine which should be implemented, rejected, or modified (e.g., GRADE adolopment).

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Intellectual Conflict of Interest (ICMJE): Chair of CAEP Stroke Practice Committee

Study Summary

Article: Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344–e418.

Design: Clinical Practice Guideline.

Population: Adults (≥ 18 years) with symptomatic AIS.

Scope: Intended for prehospital care providers, physicians, allied health professionals, and hospital administrators.

Key Results: The newest and most relevant to emergency care of 130 recommendations.

Recommendation	*Strength*	*Quality of Evidence*
1. Establish systems for urgent brain imaging for IV fibrinolysis & mechanical thrombectomy candidates.	Strong	Moderate NR
2. Correct hypotension and hypovolemia to maintain systemic perfusion levels for organ function.	Strong	Low EO
3. Consider telestroke/teleradiology evaluations of AIS patients for correct IV alteplase eligibility decision making.	Moderate	Moderate R
4. Consider telestroke/teleradiology guidance for IV alteplase administration.	Moderate	Moderate NR
5. Proceed with computed tomographic angiography without a serum creatinine concentration in patients with suspected intracranial large vessel occlusion and no history of renal impairment who meet criteria for mechanical thrombectomy.	Moderate	Moderate NR
6. Consider alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) IV ≤ 4.5 hours of stroke symptom recognition in patients with AIS who awake with stroke symptoms or have unclear time of onset and who have a DW-MRI lesion smaller than 1/3 of the MCA territory and no visible signal change on FLAIR.	Moderate	Moderate R
7. Consider telestroke networks to triage patients with AIS who may be eligible for interfacility transfer for mechanical thrombectomy.	Weak	Moderate NR
8. Consider alteplase IV for eligible patients with mild disabling stroke symptoms who can be treated within 3 and 4.5 hours of AIS symptom onset or patient last known well or at baseline state.	Weak	Moderate NR
9. Consider tenecteplase 0.4 mg/kg single IV bolus as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	Weak	Moderate R
10. Consider alteplase decision-making support via telephone consultation if no access to either an in-person stroke team or a telestroke system.	Weak	Low LD

DW-MRI = diffusion-weighted magnetic resonance imaging; EO = expert opinion; FLAIR = fluid-attenuated inversion recovery; IV = intravenous; LD = limited data; MCA = middle cerebral artery; NR = nonrandomized trial(s); R = randomized trial(s).

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The guideline development group includes all of the relevant stakeholders, including patients.	X	X	X
2. Systematic methods were used to search for evidence.	✓	✓	✓
3. The criteria for selecting the evidence are clearly described.	✓	✓	✓
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	X	X	X
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	X	X	X
6. There is an explicit approach linking the evidence to formulate the recommendations.	X	X	X
7. Experts externally reviewed the guideline prior to its publication.	✓	✓	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓	✓	✓
9. Competing interests of guideline development group members have been recorded and managed.	X	X	X
10. The strength and certainty of the key recommendations are clearly identified.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: American Heart Association/American Stroke Association.

Conflicts of Interest: Panel members were not allowed to participate in discussions or vote on topics relevant to their relations with industry.

Potential Threats to Validity

Development: There is an over-representation of stroke neurologists but no reporting of patient or other non-clinical stakeholders in either the evidence review or writing groups.

Presentation: All 240 recommendations are presented in clear tabular form within the manuscript with color codes for level of evidence and strength of recommendation. The recommendations are subgrouped according to clinical area or healthcare system.

Comprehensive: There are 240 different recommendations aimed at all levels of early acute stroke care, but there are no clinical support pathways or algorithms to assist ED physician work flow. The feasibility and cost of implemeting the recommendations is not specifically addressed. Given the time-sensitive nature of the treatment and its efficacy, it is disappointing that the recommendations do not address comprehensive strategies to reduce door-to-needle (for thrombolysis or thrombectomy) times.

Clincal Validity: The recommendations appear to be clinically sound and appropriate for intended ED patient care. There are no specific discussions of benefits, side effects, and/or risks around the recommendations.

Administrative Details

Key Words: Guideline; endovascular therapy; ischemic stroke; thrombolysis; thrombectomy.

Appraisers: Worster A; Lang E; Upadhye S.

Reference(s):

1. Powers WJ, Rabinstein AA, Ackerson T, et al on behalf of the American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:e46–e99.

Research Question

Does the addition of ticagrelor to aspirin reduce the risk of ischemic events following mild acute ischemic stroke or high-risk transient ischemic attack?

BEEM Bottom Line

Why is this study important? Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin (ASA) given within 24 hours of acute onset minor acute ischemic stroke (AIS) or high-risk transient ischemic attack (TIA) reduces the risk of subsequent stroke during the next 30 to 90 days (number needed to treat [NNT] = 53).[1,2] Unlike clopidogrel, ticagrelor is a direct platelet inhibitor and, therefore, potentially more effective. This trial assesses DAPT with ticagrelor and ASA for mild acute, non-embolic AIS or high-risk TIA.

Which, if any, threats to validity are most likely to have an impact on the results and how? The study does not appear to be powered to demonstrate superiority. The sampling was likely non-consecutive and restricted to high-risk patients. The use of a composite endpoint (stroke or death) to justify the use of ticagrelor can be misleading as the components of the composite outcome were not equally affected, and statistical significance was only demonstrated for stroke, not death.

How do the key results compare with the current evidence? This trial did not compare ticagrelor with clopidogrel. This study instead evaluated the use of ticagrelor in addition to aspirin compared to aspirin alone, and it failed to show the same benefits that the addition of clopidogrel to aspirin has had in previous trials. In this trial, there were fewer strokes, more deaths and more bleeding in the ticagrelor plus ASA arm than in the ASA alone arm, and no difference in overall disability between the two groups.

How should this study impact the care of ED patients? Given the lack of clinical superiority of ticagrelor in addition to aspirin, this study does not change current practice. Therefore, DAPT with clopidogrel and ASA remains the preferred treatment for high-risk patients with non-cardioembolic strokes.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. N Engl J Med. 2020;383(3):207-217.

Design: Multicenter (414 sites in 28 countries), superiority, blinded, placebo-controlled, randomized trial.

Population: *Included:* Adults (≥ 40 years) with either a mild-to-moderate acute noncardioembolic ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤ 5/42) or a high-risk TIA (ABCD2 score ≥ 6/7) or symptomatic intracranial or extracranial arterial stenosis (≥ 50% narrowing of lumen diameter).
Excluded: Patients with planned thrombolysis, mechanical thrombectomy, anticoagulation or specific antiplatelet therapy other than aspirin ≤ 24 hours before randomization; ticagrelor or ASA hypersensitivity; possible cardioembolic cause; bleeding disorder; history of major bleeding ≤ 6 months, or major surgery ≤ 30 days.

Intervention: DAPT with ticagrelor 180 mg (2 tablets) once then 90 mg every 12 hours orally and ASA 300 to 325 mg once then 75 to 100 mg orally every 24 hours for 30 days.

Comparison: Matching placebo (2 tablets) once then 1 tablet every 12 hours orally and ASA 300 to 325 mg once then 75 to 100 mg orally every 24 hours for 30 days.

Outcomes: *Primary:* A composite of stroke (ischemic or hemorrhagic) or all-cause mortality.
Secondary: First subsequent ischemic stroke, disability (modified Rankin scale > 1; 0 to 1 = no disability, 2 to 5 = increasing disability, and 6 = death) ≤ 30 days. Severe bleeding (defined according to the GUSTO criteria: intracerebral hemorrhage or resulting in substantial hemodynamic compromise requiring treatment).

Key Results: *N* = 11,016 patients (mean age = 65 years; 39% female; 5,523 in DAPT group and 5,493 in ASA group).

Sig.	*Outcome*	*DAPT (%)*	*ASA*	*HR (95% CI)*	*NNT/NNH* (95% CI)*
SS	Composite	303 (5.5)	362 (6.6)	0.83 (0.71 to 0.96)	26 (13 to 133)
SS	Stroke	284 (5.1)	347 (6.3)	0.81 (0.69 to 0.95)	23 (12 to 107)
NSS	Death	36 (0.7)	27 (0.5)	1.33 (0.81 to 2.19)	N/A
NSS	Disability	1281(23.8)	1284 (24.1)	0.98 (0.89 to 1.07)	N/A
SS	Severe bleeding	28 (0.5)	7 (0.1)	3.99 (1.74 to 9.14)	264 (170 to 589)

CI = confidence interval; *N* = number of patients; N/A = not applicable; NNT/NNH = number needed to treat/harm; NSS = not statistically significant; *p* = probability; HR = hazard ratio (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant. *Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.[3]

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	?	X	X

A = appraiser; ITT= intention to treat.

Funding & Conflicts of Interest

Funding: Astra Zeneca.

Conflicts of Interest: Several authors received support from Astra Zeneca.

Potential Threats to Validity

Chance: The study is powered to determine a statistical difference between ticagrelor and aspirin, however, it does not appear to be powered to demonstrate superiority with respect to any threshold of clinical significance; thus, the upper bound of the CI is nearing no effect.

Selection Bias: It is unclear whether patients were recruited consecutively; in absence of this information, it may be assumed that patients were enrolled during weekday/daytime hours, thus may not be entirely generalizable to the target population. Note that all patients were from Europe, Asia or Australia, a very small proportion was from North America (0.2%)

Measurement Bias: There is no indication that data collection procedures were adjudicated or completed in duplicate; while systematic bias is not suspected, nondifferential measurement error may have occurred.

Analysis Bias: The components of the composite outcome, stroke and death, were not equally likely. The difference in the primary outcome was mostly driven by a difference in stroke events (284/5523 [5.1%) in the ticagrelor arm vs. 347/5493 [6.3%] in controls). There were more deaths in the ticagrelor arm (36/5523, 0.7%) than in controls (27/5493, 0.5%). Despite study hypotheses stating the superiority of ticagrelor over aspirin, the statistical plan did not include thresholds of clinical superiority; therefore, only statistical significance can be inferred.

Confounding: None.

Administrative Details

Key Words: Acute ischemic stroke (AIS); aspirin (ASA); clopidogrel; dual antiplatelet therapy (DAPT); stroke; ticagrelor; transient ischemic attack (TIA).

Appraisers: Bedard C; Worster A; Bellolio M F.

Reference(s):

1. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018;379(3):215-225.

2. Hao Q, Tampi M, O'Donnell M, et al. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. BMJ. 2018 Dec. 18;363:k5108.

3. Altman DG & Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ (Clinical research ed.). 1999;319(7223):1492–1495.

PEDIATRICS (PART I)

Research Question

Can infants/young children with fractures be identified for potential maltreatment?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Identification of abuse is essential to ensuring child safety in the ED. Certain fractures may be predictive of child abuse.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Lack of patient/caregiver stakeholder involvement and external review risk missing key patient-related outcomes. Search strategies seem limited, and no explicit quality assessment methods/results erode confidence in evidence base supporting recommendations.

How should this guideline, and specifically which recommendations should impact the care of ED patients? Specific fractures in infants/young children (ribs, humerus, femur) should prompt further investigations for suspected child abuse.

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Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: Mitchell IC, Norat BJ, Auerbach M, *et al*. Identifying Maltreatment in Infants and Young Children Presenting with Fractures Does Age Matter? Acad Emerg Med 2021 Jan;28(1):5-18. doi: 10.1111/acem.14122

Design: Systematic Review/Clinical Practice Guideline

Population: Children with various fractures, suspected victims of child abuse.

Scope: This guideline is intended for practitioners/facilities who evaluate injured children for potential child abuse.

Key Results:

Recommendation	*Strength*	*Quality of Evidence*
"In children presenting to a health care facility with a **rib fracture**, who were not in an independently verified incident, we strongly recommend routine child abuse evaluations for patients younger than 3 years of age."	Recommendation (Strong); incidence of abuse 96% (random effects); RE)	Moderate
"In children presenting to a health care facility with a **humeral fracture**, who were not in an independently verified incident, we strongly recommend routine child abuse evaluations for patients younger than 18 months of age."	Recommendation (Strong); 48% incidence of abuse (RE)	Moderate
""In children presenting to a health care facility with a **femoral fracture** aged less than 18 months, who were not in an independently verified incident, we strongly recommend routine evaluation to identify child abuse."	Recommendation (Strong); Abuse incidence (<12mo) 34%, incidence <18mo 25% (RE)	Moderate

BEEM Critique

Risk of Bias Assessment

	A1
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓
2. Systematic methods were used to search for evidence.	X
3. The criteria for selecting the evidence are clearly described.	?
4. The strengths and limitations of the body of evidence are clearly described (e.g., **GRADE**, Cochrane, etc.).	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓
7. Experts externally reviewed the guideline prior to its publication.	X
8. The content of the guideline is free of influence by the views of the funding body.	?
9. Competing interests of guideline development group members have been recorded and managed.	✓
10. Thestrength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None reported?

Conflicts of Interest: None (reported).

Potential Threats to Validity

Development: **Limited search of electronic databases, English only articles. Unclear quality assessment of included articles. No parents/caregiver stakeholders included on CPG panels.**

Presentation: Well organized with easy to find recommendations? **No? EM physicians prefer all CPG Recs to be summarized at beginning of publications (Aboulsoud et al 2011).**

Comprehensive: Was the information to inform decision-making complete? **Yes.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes**

Administrative Details

Key Words: Child abuse, fractures, risk stratification.

Appraisers: Upadhye S.

Reference(s): Mitchell IC, Norat BJ, Auerbach M, Bressler CJ, Como JJ, Escobar Jr MA, Flynn-O'Brien KT, Lindberg DM, Nickoles T, Rosado N, Weeks K, Maguire S. Identifying Maltreatment in Infants and Young Children Presenting with Fractures: Does Age Matter? Acad Emerg Med 2021 Jan;28(1):5-18. doi: 10.1111/acem.14122

Research Question

What is the utility of the Infant Scalp Score for infants with traumatic scalp hematoma for risk of traumatic brain injury?

BEEM Bottom Line

Why is this study important? Risk stratification of infants with isolated scalp hematoma for potential traumatic brain injury is important determine which infants need CT scanning, and which can be spared unnecessary ionizing radiation.

Which, if any, threats to validity are most likely to have an impact on the results and how? This is a secondary exploratory analysis of the original PECARN database to generate a CDR relevant to infants <12mo.; predictor variables limited to those data points already collected (may be missing other important predictors).

How do the key results compare with the current evidence? This is a new CDR that is just derived using administrative data. Future prospective validation is required. This CDR is not appropriate for infants who are victims of potential child abuse (higher incidence of CT TBI).

How should this study impact the care of ED patients? The new ISS may be a useful tool to risk stratify CT imaging needs for infants <12mo with isolated traumatic scalp hematoma.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Schutzman SA, Nigrovic LE, Mannix R. The Infant Scalp Score: A Validated Tool to Stratify Risk of Traumatic Brain Injury in Infants with Isolated Scalp Hematoma. Acad Emerg Med. 2021 Jan;28(1):92-97. doi: 10.1111/acem.14087. PMID: 32673432.

Design: This is a CDR derivation study using the original PECARN TBI database as source material.

Population: *Included:* Infants <1yo with an isolated scalp hematoma (ISH) without other clinical findings/bulging fontanel. *Excluded*: Missing clinical variables, uncertain Dx of ISH.

Predictors: Age (months), hematoma size, hematoma location.

Comparison: CT findings, or structured follow-up for clinical status 7d after initial ED head injury assessment (not scanned).

Outcomes: *Primary:* Clinically important TBI (ciTBI) = death from TBI, need for neurosurgical procedure, intubation for 24hrs, or hospitalization for 2+ nights. Incidence: 2.1% of imaged children, 0.9% of all infants.
Secondary: Any TBI on CT scan = any intracranial bleed, pneumocephalus, cerebral edema, depressed skull fracture, or skull diastasis. Incidence: 12.7% imaged infants, 4.6% total cohort.

Key Results: *N* = 1289 infants included (43904 in parent study, 5441 infants <1yo). 36% of infants had cranial CT

Outcome	*Area Under Curve*	*Outcomes*
ciTBI	0.916	Cutoff 4/8: No ciTBI/any TBI missed. 52% infants imaged (669/1289)
Any CT TBI	0.807	Cutoff 5/8: No ciTBI/3 any TBI missed. 32% infants imaged (417/1289)

CI = confidence interval; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; *p* = probability; OR = odds ratio (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The patients were representative of those with the problem.	✓
2.	The patients were enrolled consecutively or in a way to ensure a representative sample.	X
3.	All patients underwent the same clinical evaluation.	✓
4.	All important predictor variables were included in the clinical evaluation and explicitly defined.	✓
5.	Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	?
6.	Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	✓
7.	All outcome variables were included in the clinical evaluation and explicitly defined.	✓
8.	All patient-important outcomes were considered.	✓
9.	The follow-up was complete.	✓
10.	The point estimates and respective precisions are clinically significant.	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None?

Selection Bias: Publicly available PECARN TBI dataset was sampled.

Measurement Bias: Successful follow-up in 79% of parent study.

Analysis Bias: No CI's around individual ROC point estimates.

Confounding: Long-term impact of any CT TBI on future developmental/neurocognitive outcomes not clear.

Administrative Details

Key Words: Clinical decision rule, infant scalp hematoma, traumatic brain injury.

Appraisers: Upadhye S.

Reference(s): Schutzman SA, Nigrovic LE, Mannix R. The Infant Scalp Score: A Validated Tool to Stratify Risk of Traumatic Brain Injury in Infants with Isolated Scalp Hematoma. Acad Emerg Med. 2021 Jan;28(1):92-97. doi: 10.1111/acem.14087. PMID: 32673432

Research Question

Can bruising patterns be useful in predicting abuse in young children?

BEEM Bottom Line

Why is this study important? Bruising is a common injury in child abuse, and may be a missed opportunity to identify children at risk of abuse prior to a near-/fatality abuse event. Distinct differences in bruising patterns of abuse vs non-abuse injuries may help identify abused children.

Which, if any, threats to validity are most likely to have an impact on the results and how? Spectrum bias may attenuate CDR performance corrects, since all patients recruited from 5 Peds ED study sites (ie. higher prevalence of abuse?).

How do the key results compare with the current evidence? An earlier version of the TEN4 rule had a Sens 81%, unacceptably missing 19% of abused children. The refined rule performs much better, and is congruent with prior abuse bruise reports.

How should this study impact the care of ED patients? The refined TEN4-FACESp bruising CDR has strong discriminatory ability for differentiating abuse from non-abused children <4yo.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Pierce MD, Kaczor K, Lorenz DJ, *et al*. Validation of a Clinical Decision Rules to Predict Abuse in Young Children Based on Bruising Characteristics. JAMA Netw Open 2021; Apr 1;4(4):e215832. doi: 10.1001/jamanetworkopen.2021.5832.

Design: Prospective refinement and validation of a bruising CDR for children seen in Peds ED (5 test sites).

Population: *Included:* Children <4yo.
Excluded: Children with injuries from MVA, known coagulopathy, preexisting neuromuscular dz from known spasticity, severe skin disorders that may distort bruising characteristics.

Predictors: TEN4-FACESp score (torso/ear/neck/any bruising on infant<4.99mo., frenulum, angle of jaw, cheek [fleshy], eyelids, subconjunctiva). Any positive criterion is considered "positive" for abuse classification. Patterned bruising = bite, loop, hand slap, squeeze/grab, or multilinear.

Comparison: Expert consensus panel (98% agreement).

Outcomes: *Primary:* Performance characteristics of refined TEN4-FACESp rule.

Key Results: *N* = 21123 children screened, 2161 enrolled. Mean age 2.1yrs, 60% male. 410 cases determined as abuse (19%). Higher likelihood of abuse in non-white or Hispanic ethnicity, and have gov't insurance compared to non-abused children.
Median bruise count in abused children = 3; generally higher in all age strata. Patterned bruising generally uncommon (8%), but much higher in abused children (39%) vs non-abused (0.6%). Children with patterned bruising were highly categorized as abuse (94%).

CDR	*Outcome*	*Sensitivity (95% CI)*	*Specificity (95% CI)*
TEN4-FACESp	Child abuse	95.6% (93-97.3%) LR+ 7.41	87.1% (85.4-88.6) LR- 0.05

Test characteristics did not vary significantly based on skin tone.

TEN bruises alone correctly identified 81% of abuse patients.

Most specific bruises for abuse = buttocks, perineum/anus, jaw angle, neck, subconjunctiva.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The patients were representative of those with the problem.	✓
2.	The patients were enrolled consecutively or in a way to ensure a representative sample.	✓
3.	All patients underwent the same clinical evaluation.	✓
4.	All important predictor variables were included in the clinical evaluation and explicitly defined.	✓
5.	Clinicians interpreted the predictor variables and scored prospectively and blinded to the outcome.	✓
6.	Clinicians interpreted the predictor variables and scored the rule reliably and accurately.	?
7.	All outcome variables were included in the clinical evaluation and explicitly defined.	✓
8.	All patient-important outcomes were considered.	✓
9.	The follow-up was complete.	✓
10.	The point estimates and respective precisions are clinically significant.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Not specifically reported.

Conflicts of Interest: Most authors have NIH grant support. One author (JML) reported being a medicolegal expert/court testimony.

Potential Threats to Validity

Chance: Not every child in the cohort may have received a complete head2toe examination, which may lead to misclassification bias.

Selection Bias: Children recruited from Peds ED's, where prevalence of abuse may be higher than general ED settings.

Measurement Bias: None?

Analysis Bias: CDR outcomes performed better with actual study data than boot-strapping with 10000 iterations (Sens 91.5%, Spec 84.5%, LR+ 5.90, LR- 0.11).

Confounding: Non-abused children with darker skin tone had significantly lower bruise counts than those with lighter tone; risk of under-estimating abuse in darker skin children?

Administrative Details

Key Words: Enter up to 5 key words here (in alphabetical order, separated by semicolons and a period at the end).

Appraisers: Upadhye S.

Reference(s): Pierce MD, Kaczor K, Lorenz DJ, Bertocci G, Fingarson AK, Makaroff K, Berger RP, Bennett B, Magana J, Staley S, Ramaiah V, Fortin K, Currie M, Herman BE, Herr S, Hymel KP, Jenny C, Sheehan K, Zuckerbraun N, Hickey S, Meyers G, Leventhal JM. Validation of a Clinical Decision Rules to Predict Abuse in Young Children Based on Bruising Characteristics. JAMA Netw Open 2021; Apr 1;4(4):e215832. doi: 10.1001/jamanetworkopen.2021.5832.

Research Question

Is POCUS useful to diagnose skull fractures in children?

BEEM Bottom Line

Why is this study important? Children with low-risk of traumatic brain injury may still have a clinically important skull fracture. ED POCUS may be a useful modality to identify such injuries.

Which, if any, threats to validity are most likely to have an impact on the results and how? ED POCUS skills/experience will influence test performance characteristics.

How do the key results compare with the current evidence? Most clinical decision rules (CATCH, CHALICE, PECARN, NICE) include skull fracture as a predictor variable. A contemporary review publication confirmed findings of this study (Gordon 2020).

How should this study impact the care of ED patients? ED POCUS can be a valuable adjunct for diagnosing childhood skull fracture, and CT-sparing for children with a negative scan.

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Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact (HEI), McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Alexandridis G, Verschuuren EW, Rosendaal AV, Kanhai DA. Evidence base for point-fo-care ultrasound (POCUS) for diagnosis of skull fractures in children: a systematic review and meta-analysis. Emerg Med J 2020 Dec 3:emermed-2020-209887. doi: 10.1136/emermed-2020-209887.

Design: Systematic review and meta-analysis of prospective studies evaluating POCUS diagnosis for child skull fracture.

Population: *Included:* Children <18yo diagnosed with skull fracture using point-of-care ultrasound (POCUS).
Excluded: Studies not using CT scan as reference standard. Also excluded review articles, conference abstracts and case reports.

Index Test: POCUS. All scans performed by ED physicians/fellows (varied levels of training).

Reference Test: CT scan of skull.

Diagnosis of Interest: Pediatric skull fracture.

Key Results: *N* = 7 studies, 925 patients included. ALL PATIENTS RECRUITED FROM ED SETTINGS ☺ Age range 2mo-17yrs; average 7-17yrs.
Fracture incidence 10-77%. 75% injuries due to mechanical fall.

Measure (95% CI)		I^2
Sensitivity = 91% (67-100)	Specificity = 96% (85-100)	32%
LR+ = 22.75 LR– = 0.09	*2.9% false positives, 2.2% false negatives	
AUC = Not calculated	**Results similar with high vs low fracture incidence groups, ages	

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	?
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	✓
9. The subgroups were stated a priori and appropriate.	?
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓

A1 = S. Upadhye

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: None?

Selection Bias: None or specify comprehensive searches; publication bias. Search of various electronic databases, reference lists of included articles. No language restrictions. Assessment of publication bias by Egger's test; none detected.

Measurement Bias: Overall risk of bias (RoB) for included studies: 2/7 low RoB, 5/7 some RoB (patient selection domain).

Analysis Bias: Two subgroups (based on high vs low fracture %) assigned during study visual inspection. Moderate heterogeneity amongst included studies (I^2 = 32%).

Confounding: Most studies (5/7) used convenience sampling, which may lead to recruiting bias. Knowledge of anatomic suture lines is essential to avoid false positives.

Administrative Details

Key Words: Blunt childhood head injury, point-of-care ultrasound, skull fracture.

Appraisers: Upadhye S.

Reference(s):

Alexandridis G, Verschuuren EW, Rosendaal AV, Kanhai DA. Evidece base for point-fo-care ultrasound (POCUS) for diagnosis of skull fractures in children: a systematic review and meta-analysis. Emerg Med J 2020 Dec 3:emermed-2020-209887. doi: 10.1136/emermed-2020-209887.

Gordon I, Sinert R, Chao J. The utility of ultrasound in detecting skull fractures after pediatric blunt head trauma: systematic review and meta-analysis. Pediatr Emerg Care 2020. doi:10.1097/PEC.0000000000001958. [Epub ahead of print: 28 Feb 2020].

Research Question

Do children with a stable distal radial buckle need primary care physician follow-up?

BEEM Bottom Line

Why is this study important? Most pediatric distal radial buckle fractures have excellent healing, and there is little value added of orthopedic follow-up. This study examined the benefits/outcomes of primary care physician follow-up vs. self-care.

Which, if any, threats to validity are most likely to have an impact on the results and how? Minimal crossover between groups that may have biased results towards confirming noninferiority; mitigated by similar results in ITT vs per protocol analyses.

How do the key results compare with the current evidence? These results build on prior work suggesting that simple distal radial buckle fractures in children do not require physician follow-up.

How should this study impact the care of ED patients? ED physicians can educate patients/parents on the post-immobilization care of distal radial buckle fractures, and provide specific instructions on when physician follow-up may be needed (otherwise just complete home management).

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Colaco K, Willan A, Stimec J, *et al*. Home Management Versus Primary Care Physician Follow-up of Patients with Distal Radius Buckle Fractures: A Randomized Controlled Trial. Annals Emerg Med 2021; 77: 163-173. https://doi.org/10.1016/j.annemergmed.2020.07.039

Design: Parallel 2-arm double-blinded randomized noninferiority trial. (Single urban tertiary children's hospital {Toronto Hospital for Sick Children], sees approximately 300 buckle fractures annually).

Population: *Included:* Children (5-17yo) within 3days of isolated wrist injury and confirmed diagnosis of distal radial buckle fracture (with/without ulnar buckle/styloid fracture). All children treated with prefabricated removable splint.
Excluded: Ipsilateral forearm fracture in preceding 3mo, risk of pathologic fractures or known congenital wrist anomalies. Significant cognitive/developmental delay, insurmountable language barrier or no phone/email access for follow-up.

Intervention: Home removal of splint and self/parental assessment.

Comparison: Primary care physician (PCP) follow-up 1-2 weeks after ED visit.

Outcomes: *Primary:* Change in modified ASKp-38 score from ED visit to 3 weeks.
Secondary: Functional recovery, use of splint, parental satisfaction. Data on health care use.

Key Results: *N* = 149 patients; mean age 9.5yrs, 54% male, 40% injury to dominant wrist. 73 pts home mgt, 76 to PCP. 86% completed the study protocol by 6 weeks.

Sig.	*Outcome*	*Intervention*	*Control*	*Outcome Measure (95% CI)*
NSS	Primary modASKp-38 ITT	N/A	N/A	Mean Diff -0.5% (**-2.6** to 1.3)
	Primary (Per Protocol, PP)	N/A	N/A	Mean Diff 0.4% (**-1.9** to 2.8)
	PP, radiologically confirmed buckle fractures	N/A	N/A	Mean Diff 0.8% (**-1.4** to 2.9)
	Splint Use, Parental satisfaction			No significant differences for all secondary outcomes. No differences in child care or medications costs.
SS	Total costs (Cdn$)			-122.30 (-169.1 to -75.5) favouring home mgt
	Total health system costs			-100.1 (-130.0 to -70.2) favouring home mgt
	Total parental costs			- 28.2 (-49.6 to -7.0) favouring home mgt
	Parental wage loss			-29.6 (-45.0 to -14.2) favouring home mgt

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓
3. The allocation sequence was adequately concealed.	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	X

A1 = S. Upadhye

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: PSI (gov't) grant.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: Allowances made for ED Xray discrepancies and management change at ED physician discretion; patients still included in final analyses. 4 missed Salter-Harris II fractures later treated in orthopedics clinic/ED.

Selection Bias: Patients recruited during Research Assistant working hours (0830-2300) daily. Recruited to exceed calculated sample size by 20% (SS 110, recruited 140). Patient groups otherwise properly balanced for clinical features and parental education level.

Measurement Bias: Non-inferiority (NI) margin set a 5% difference between two mgt options, based on prior research. Impossible to blind patients to intervention allocation, but 3wk outcomes assessment blinded.

Analysis Bias: ITT, Per Protocol, As Treated for radiologically confirmed distal buckle fracture. Noninferiority margin was not crossed in any calculation variation.

Confounding: Crossover: 8/66 (12.1%) home mgt pts visited PCP for minor splint issues/misunderstanding of discharge follow-up instructions. 56/67 (83.6%) of PCP follow-up patients actually complied; remaining 11 did not bother. No impact on final ITT or per protocol outcomes.

Two extra Xrays ordered within home mgt group, 8 extra in PCP group; no changes in subsequent management.

Administrative Details

Key Words: Buckle fracture, distal radius, follow-up, primary care physician

Appraisers: Upadhye S.

Reference(s): Colaco K, Willan A, Stimec J, Barra L, Davis A, Howard A, Boutis K. Home Management Versus Primary Care Physician Follow-up of Patients with Distal Radius Buckle Fractures: A Randomized Controlled Trial. Annals Emerg Med 2021; 77: 163-173. https://doi.org/10.1016/j.annemergmed.2020.07.039

Research Question

Is ibuprofen superior to acetaminophen for treatment of fever in children younger than 2 years?

BEEM Bottom Line

Why is this study important? Despite that antipyretics are the most frequent medications used in pediatric, recommendations for the use of acetaminophen and ibuprofen in young children are variable, particularly for ibuprofen. Moreover, superiority of ibuprofen as an antipyretic may be not applicable for younger children.

Which, if any, threats to validity are most likely to have an impact on the results and how? The review presents moderate certainty evidence that ibuprofen is superior to acetaminophen for the relief of fever in children younger than 2 years in the first 24 hours. The superiority of ibuprofen as an antipyretic was not demonstrated beyond 24 hours. The results of the review are primarily limited by potential for confounding in the primary studies due to suboptimal randomization and blinding as well as insufficient number of studies and events to provide precise effect estimates for some outcomes. On this matter, few patients were less than 6 months in the studies reviewed, which preclude the authors to conclude for these patients. Further, the comprehensiveness of the search is unclear as the search strategy was not reported and some studies may have been missed since the title and the abstract screening was done by only one reviewer. Finally, the meta-analytic model (fixed effect vs. random effects) was selected based on the magnitude of observed heterogeneity, a practice that is strongly discouraged due to the low reliability of such statistics.

How do the key results compare with the current evidence? Despite this, the results of this study are concordant to previous systematic reviews in reporting that ibuprofen was more efficacious than acetaminophen to treat fever in children in the first 24 hours with no difference in adverse event incidence.[1,2]

How should this study impact the care of ED patients? The similar safety profile in children 6 months and older (including severe adverse effects, kidney impairment, GI bleeding, hepatotoxicity and wheeze at 28 days or less) makes ibuprofen an interesting first line choice. Ibuprofen is more likely to reduce fever in the first 24h of illness in children aged 6 months to 2 years old as it is superior to acetaminophen. However, because the superiority on comfort is not established, acetaminophen could be added if the desired level of comfort is not achieved after the use of ibuprofen. Acetaminophen could also be used as a first line antipyretic if a child presents a contraindication to ibuprofen or if the child is less than 6 months. Further studies are still needed to confirm safety for infant younger than 6 months, and to address the concern that ibuprofen might increase the risk of serious bacterial infection.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of Acetaminophen (Paracetamol) With Ibuprofen for Treatment of Fever or Pain in Children Younger Than 2 Years: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Oct 1;3(10):e2022398.

Design: Systematic review and meta-analysis of trials, cohort and case-control studies.

Population: *Included:* Children (< 2 years) with fever or pain requiring acetaminophen (paracetamol) or ibuprofen. *Excluded*: Children treated with both medications.

Intervention: Acetaminophen (paracetamol).

Comparison: Ibuprofen.

Outcomes: *Primary:* Fever or pain ≤ 4 hours of treatment onset.
Secondary: Fever or pain at 4 to 24 hours (h), 1 to 3 days (d), and > 3 d; renal impairment; gastrointestinal bleeding; hepatoxicity; severe soft tissue infection; empyema; and asthma or wheeze all at ≤ and > 28 d.

Key Results: *N* = 11 randomized with 28,450 participants. Data from 8 nonrandomized trials not included.

Sig. (Favors)	*Outcome (categorical)*	*N/ Studies*	*Odds Ratio (95% CI)*	*RD (/1000) (95% CI)*	I^2
SS (Ibuprofen)	Afebrile at < 4 h	587/5	1.86 (1.01 to 3.44)	152 more (2 to 281)	60%
SS (Ibuprofen)	Afebrile at 4 to 24 h	538/4	2.22 (1.55 to 3.17)	196 more (107 to 280)	0%
NSS (None)	Afebrile at 1 to 3 days	150/1	2.95 (0.75 to 11.58)	69 more (-31 to 98)	NA
SS (Ibuprofen)	Improved pain score 4 to 24 h	102/1	2.86 (1.27 to 6.45)	252 more (59 to 395)	NA
NSS (None)	Improved pain score 1 to 3 d	210/2	0.70 (0.20 to 2.44)	89 fewer (-338 to 207)	76%
NSS (None)	Serious adverse events	27,932/7	1.08 (0.87 to 1.33)	2 more (-3 to 6)	0%

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; NA = not applicable; NSS = not statistically significant; RD = risk difference using the medial risk in the acetaminophen group as the baseline risk Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X	X
3. The search for studies was unbiased and reproducible.	?	?	?
4. The selection of studies was unbiased and reproducible.	?	?	?
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	X	X	X
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: University of Auckland, New Zealand and Health Research Council of New Zealand.

Conflicts of Interest: One author received support for attendance at meetings from industry.

Potential Threats to Validity

Chance: Results for afebrile at <4 hours, afebrile at 1 to 3 days, and improved pain scores at 1 to 3 days were imprecise, with confidence intervals including both appreciable benefit, negligible benefit, and harm. There was insufficient studies and events for adverse events of interest, due to which results were inconclusive.

Selection Bias: None detected.

Measurement Bias: None detected.

Analysis Bias: The meta-analytic model (fixed effect vs. random effects) was selected based on the magnitude of observed heterogeneity—a practice that is strongly discouraged due to the low reliability of such statistics.

Confounding: 5/11 RCTs were at high risk of bias due to the randomization process, which may result in baseline imbalances in prognostic factors and produce confounding. 2/11 and 1/11 RCTs were at some concerns and high risk of bias, respectively, due to deviations from the intended intervention, which may also produce confounding.

Administrative Details

Key Words: Acetaminophen; fever; ibuprofen; paracetamol.

Appraisers: Zeraatkar D; Worster A; Trottier ED.

Reference(s):

1. Pierce CA, Voss B: Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother 2010, 44(3):489-506.

2. Perrott DA, Piira T, Goodenough B, et al: Efficacy and Safety of Acetaminophen vs Ibuprofen for Treating Children's Pain or Fever: A Meta-analysis. Arch Pediatr Adolesc Med 2004;158(6):521-526.

Research Question

Is intranasal ketamine effective for the treatment of acute pain in children?

BEEM Bottom Line

Why is this study important? While ketamine is widely accepted as the safest and most commonly used agent for procedural sedation in children, its use for moderate to severe pain management is less well-described.[1] Use of the intranasal (IN) route for administration allows for earlier pain management, and in some cases, avoidance of a potentially distressing medical procedure, i.e., intravenous (IV) insertion. This study attempts to synthesize available evidence regarding IN ketamine and determine how its safety and effectiveness compared to other analgesic agents.

Which, if any, threats to validity are most likely to have an impact on the results and how? Only 6 small studies were identified with a total of 261 patients included, this limits the ability to draw any robust conclusions, as included studies were under-powered to definitively answer the research question. The search strategy was very limited, and records were selected by only 1 reviewer, therefore, key evidence may be missing from this review. Only 2 of the 3 randomized controlled trials (RCTs) included were rated as high quality (results below) but this was using the outdated Jadad scale.

How do the key results compare with the current evidence? The results of this systematic review are, not unsurprisingly, congruent with the findings of two of the individual, included clinical trials, which were both conducted in the ED setting.[2,3] Another recent systematic review and meta-analysis of IN ketamine for pain treatment in children has yielded similar results, suggesting that IN ketamine provides similar analgesic effectiveness as IN fentanyl, with more non-serious adverse events.[4]

How should this study impact the care of ED patients? Ketamine given IN has potential for use in pediatric patients who are hypotensive or in situations where opioids should be avoided for airway or other concerns. With mounting concerns and resistance to accept opioids for children's moderate to severe pain, IN ketamine represents a reasonable alternative, especially for children with challenges to obtaining vascular access. Given the small size and number of studies to date, IN ketamine requires further study, with a focus on opioid-sparing effects, adverse events, and long-term misuse potential.

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No conflicts of interest (ICMJE)

Study Summary

Article: Ferguson CL, Beckett RD. Intranasal Ketamine for Treatment of Acute Pain in Pediatrics: A Systematic Review. Pediatr Emerg Care. 2020;36(8):e476-e481.

Design: Systematic review of observational studies and randomized trials.

Population: *Included:* Children (≤ 17 years) requiring treatment for acute pain.
Excluded: Patients who received ketamine for sedation, anesthetic premedication or via any route other than IN.

Intervention: Ketamine IN.

Comparison: Any or none (Fentanyl IN & paracetamol IV found).

Outcomes: *Primary:* Pain relief by reported pain scale scores.
Secondary: Adverse effects, sedation, patient satisfaction, and need for additional analgesia.

Key Results: *N* = 2 RCTs (double-blinded) comparing ketamine 1 mg/kg IN to fentanyl 1.5 mcg/kg IN

RCT	*N*	*Pain Scores (Years Old)*	*Pain Score Reduction*	*Adverse Events*
Reynolds (2017)	87	FPS-R (4 to 10) VAS (11 to 17)	Mean @ 20 min: Ketamine 44 ± 36 mm Fentanyl 35 ± 29 mm	Ketamine 100% Fentanyl 61%
Graudins (2015)	73	FPS-R (3 to 6) VAS (≥ 7)	Median @ 30 min, Ketamine 45 mm Fentanyl 40 mm	Ketamine 78% Fentanyl 40%

FPS-R = Faces Pain Scale–Revised; min = minutes; *N* = number of patients; VAS = visual analog scale.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	?
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X	X
3. The search for studies was unbiased and reproducible.	?	X	X
4. The selection of studies was unbiased and reproducible.	X	X	X
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	X	X	X
6. The assessment of the quality of the primary studies was unbiased and reproducible.	X	X	X
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	?	?	?
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	N/A	N/A	N/A

A = appraiser; N/A= not applicable.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: The authors declare no conflict of interest.

Potential Threats to Validity

Chance: Individual studies contained within the review are small and therefore subject to type II error due to being underpowered

Selection Bias: There are too few details reported to fully evaluate the search strategy (e.g., no report of search terms); however, there appears to be a risk of publication bias because only 2 databases were searched, and the search was conducted 2 years prior. The authors identified ongoing trials in their search of the registries, therefore it is possible that these ongoing trials in 2018 have been completed and their evidence is missing from this review. Furthermore, the article selection process was completed by only a single reviewer, therefore increasing the risk that relevant evidence may be missing.

Measurement Bias: Risk of bias assessment was only completed for the randomized controlled trials, and this was completed using an out-of-date tool (Jadad scoring system) which primarily assessing reporting rather than risk of bias. It is assumed that this was also completed by a single reviewer.

Analysis Bias: While the evidence collected precluded a meta-analysis, the methods for their 'qualitative analysis' were not clear. The includable studies are described sequentially with limited synthesis of results.

Confounding: High risk of confounding in the non-comparative studies included in the review. The different study designs included in the review confound the overall conclusions.

Administrative Details

Key Words: Acute pain; fentanyl; intranasal (IN); ketamine.

Appraisers: Bedard C; Worster A; Ali S.

Reference(s):

1. Bhatt M, Johnson DW, Chan J, et al. Sedation Safety Study Group of Pediatric Emergency Research Canada (PERC). Risk Factors for Adverse Events in Emergency Department Procedural Sedation for Children. JAMA Pediatr. 2017 Oct 1;171(10):957-964.
2. Reynolds SL, Bryant KK, Studnek JR, et al. Randomized controlled feasibility trial of intranasal ketamine compared to intranasal fentanyl for analgesia in children with suspected extremity fractures. Acad Emerg Med. 2017;24:1430–1440.
3. Graudins A, Meek R, Egerton-Warburton D, et al. The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Ann Emerg Med. 2015;65(3):248-254.e1.
4. Oliveira J E Silva L, Lee JY, Bellolio F, et al. Intranasal ketamine for acute pain management in children: A systematic review and meta-analysis. Am J Emerg Med. 2020 Sep;38(9):1860-1866.

Research Question

Which is the optimum second-line therapy for adults and children with benzodiazepine-refractory convulsive status epilepticus?

BEEM Bottom Line

Why is this study important? The most common paediatric neurological emergency in the world is convulsive status epilepticus and the recommended first-line treatment is a benzodiazepine.[1] However, for benzodiazepine-refractory status epilepticus (BRSE), the optimum therapy is unclear, and recommendations vary. This randomized controlled trial (RCT) compares the potential efficacy and safety of the second-line anticonvulsants levetiracetam, fosphenytoin, and valproate for the treatment of BRSE among children and adults in the emergency department (ED).

Which, if any, threats to validity are most likely to have an impact on the results and how? The results of this trial are severely limited by the low statistical power which precludes the ability to draw any conclusions regarding the comparative efficacy and safety of the study drugs. The findings of this trial are further limited by the choice of primary outcome of seizure cessation, which is a surrogate with uncertain correlation with patient-oriented outcomes, such as survival and neurologic function.

How do the key results compare with the current evidence? Although the most appropriate second-line therapy for BRSE has not been established, all three anticonvulsants (fosphenytoin, levetiracetam and valproate), have been proven safe and effective.[2–3] The currently recommended second-line treatments for BRSE are intravenous phenytoin in the UK and Europe, fosphenytoin in the USA, and Canada.

How should this study impact the care of ED patients? In BRSE among all age groups, second line agents can be effective in nearly 50% of cases. Levetiracetam (Keppra) may be preferentially used in pediatric patients for BRSE as well as initial seizure therapy because of its ease of administration and its mild side effect profile with less neurologic and respiratory depression. Pediatric advanced life support (PALS) recommends treating seizures aggressively with a number of recommended therapeutics, including benzodiazepines, fosphenytoin, levetiracetam and, if these fail, barbiturates.[5]

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No conflicts of interest (ICMJE)

Study Summary

Article: Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020 Apr 11;395(10231):1217-1224.

Design: Multicentre (58 EDs in USA), double-blind, response-adaptive, randomised controlled trial.

Population: *Included:* ED patients (≥ 2 years) with persistent or recurrent convulsions ≥ 5 and ≤ 30 minutes (min) after the last dose of benzodiazepine for generalized convulsive seizure lasting > 5 min.
Excluded: Patients known to be pregnant, unable to tolerate any study medication, in custody, postanoxic, suffering traumatic-, hypoglycemic- or hyperglycemic-precipitated seizures, or just received non-benzodiazepine anticonvulsant medications.

Intervention: Levetiracetam 60 mg/kg (maximum 4500 mg), or fosphenytoin 20 mg phenytoin equivalents per kg (maximum 1500 mg PE), or valproate 40 mg/kg (maximum 3000 mg) infused intravenously (IV) over 10 min.

Comparison: Each of the above.

Outcomes: *Primary:* Seizure-free with improving responsiveness at 60 min after the start of study drug infusion.
Secondary: A composite of life-threatening hypotension or cardiac arrhythmia; need for endotracheal intubation within 60 min of start of study drug infusion; acute seizure recurrence 60 min to 12 h after the start of study drug infusion; acute respiratory depression at any time; and mortality.

Key Results: *N* = 462 patients (225 children; 186 adults; 51 elderly).

Sig.	*Seizure-free @ 60 min*	*Levetiracetam*	*Fosphenytoin*	*Valproate*	*P-value*
NSS	Children (2 to 18 years)	85/225	71/225	69/225	0.22
NSS	Adults (18 to 65 years)	71/186	54/186	61/186	0.17
NSS	Elderly (> 65 years)	19/51	17/51	15/51	0.70

N = number of patients; NSS = not statistically significant; Sig. = significance; *P* = probability; P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	?	?
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	X	X	X
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Funding National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The confidence intervals around estimates of the primary outcome are wide and do not exclude the possibility of a clinically important difference between the study drugs. There were too few participants in the trial to produce reliable estimates of secondary and safety outcomes.

Selection Bias: Nearly a quarter of patients had protocol violations and these were primarily related to eligibility.

Measurement Bias: Seizures were not confirmed via EEGs. However, due to blinding of study investigators, this is unlikely to have biased results. The trial reports on seizure cessation rather than more patient-oriented outcomes such as survival and neurologic function.

Analysis Bias: None detected.

Confounding: Some patients who did not reach the primary outcome might have not done so because of the sedative effects of treatments.

Administrative Details

Key Words: Benzodiazepine; convulsion; fosphenytoin; levetiracetam; seizure; status epilepticus; valproate.

Appraisers: Zeraatkar D; Worster A; Laskowski U.

Reference(s):

1. Novorol CL, Chin RF, Scott RC. Outcome of convulsive status epilepticus: a review. Arch Dis Child. 2007;92(11):948-951.
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Research Question

What is the effect of prednisolone in preschool children with wheeze associated with acute respiratory illness?

BEEM Bottom Line

Why is this study important? The British Thoracic Society and others recommends a 3-day course of oral prednisolone for preschool children with moderate-severe wheeze.[1] However, wheezing in this population is impacted by different factors than in older children and adults and the recommended treatment with corticosteroids is controversial.[2]

Which, if any, threats to validity are most likely to have an impact on the results and how? The heterogenous sample (asthmatics, atopic individuals, children exposed to passive cigarette smoke, and roughly 40% of whom were not responsive to bronchodilators) had 20% missing outcome data. The trial was designed with an equivalence hypothesis and used a minimal clinically important difference in the Pediatric Respiratory Assessment Measure (PRAM) score of 1, rather than the recommended 3. Hence, the between-group differences seen (e.g. PRAM score at 4 hours) are not necessarily clinically meaningful. The authors did not determine viral etiology or viral load which has been shown to be a predictor of outcome and responsiveness to oral prednisolone.[3]

How do the key results compare with the current evidence? In a randomized trial of 74 children (mean age 13 months) with a first acute, moderate-to-severe wheezing episode and polymerase chain reaction confirmed rhinovirus, those with the highest viral loads showed decreased symptoms and recurrence following prednisolone (2 mg/kg/day for 3 days) compared to placebo.[3]

How should this study impact the care of ED patients? The results do not eliminate the possibility that corticosteroids reduce symptoms prior to 24 hours and prevent deterioration and need for further medical intervention. The potential benefits and risks of corticosteroids in this population should be discussed with the caregivers prior to prescribing.

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University of Western Ontario, London, ON, Canada
No conflicts of interest (ICMJE)

Study Summary

Article: Wallace A, Sinclair O, Shepherd M, et al. Impact of oral corticosteroids on respiratory outcomes in acute preschool wheeze: a randomised clinical trial. Arch Dis Child. 2020: Archdischild-2020-318971.

Design: Multi-center (3 New Zealand EDs), blinded, placebo-controlled equivalence randomized trial.

Population: *Included:* Children ($\geq$ 24 and $\leq$ 59 months) with acute wheeze associated with any respiratory illness and initial Preschool Respiratory Assessment Measure (PRAM; scores the presence and or severity of combined wheeze, air entry, scalene retraction, suprasternal indrawing and oxygen saturation from 0 to maximum of 12) score $\geq$ 3. *Excluded*: Patients with any condition causing respiratory distress other than non-life-threatening asthma; contraindication to corticosteroids or taken in $\leq$ 7 days; previous study enrolment; and inability for follow-up.

Intervention: Prednisolone (2 mg/kg, maximum 40 mg) per os daily x 3 days and salbutamol 600 mcg inhaled via spacer q 20 minutes x 3 and continued as needed.

Comparison: Placebo once daily and salbutamol 600 mcg inhaled via spacer q 20 minutes x 3 and continued as needed.

Outcomes: *Primary:* PRAM mean score change from baseline to 24 hours (h).
Secondary: PRAM mean score change at 4 h; hospital admission; ED and hospital median length-of-stays (LOS); salbutamol amount in 48 h and 7 days; additional prednisolone; and adverse events.

Key Results: *N* = 477 patients (238 in prednisolone group and 239 in placebo group).

Sig.	*Outcome*	*Prednisolone*	*Placebo*	*Difference (95% CI)*	*P-value*
NSS	PRAM change at 24 h	−5.12	−4.73	−0.39 (−0.84 to 0.06)	0.09
NSS	PRAM change at 4 h	−4.18	−3.51	−0.67 (−1.18 to −0.16)	0.01
Sig.	*Outcome*	*Prednisolone*	*Placebo*	*Difference (IQR)*	*P-value*
NSS	ED LOS (hours)	5.6	6.0	−0.57 (−1.15 to 0.02)	0.06
NSS	Hospital LOS (hours)	26.3	29.2	−2.9 (−7.8 to 2.4)	0.27

CI = confidence interval; IQR = interquartile range; *N* = number of patients; NSS = not statistically significant; *p* = probability; Sig. = significance. P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	?	?	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X	X	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	?	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = Intention to treat.

Funding & Conflicts of Interest

Funding: Health Research Council of New Zealand.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: None detected.

Selection Bias: Only 80% of patients initially randomized had primary outcome data available. Patients with missing outcome data may have outcomes that are appreciably different from those with complete follow-up.

Measurement Bias: Results of the trial suggest that corticosteroids probably do not improve respiratory symptoms at 24 h possibly because symptoms resolve in most children without intervention. The results of the trial, however, do not eliminate the possibility that corticosteroids may reduce symptoms prior to 24 h and prevent deterioration and need for further medical intervention.

Analysis Bias: None detected.

Confounding: None detected.

Administrative Details

Key Words: Corticosteroids; prednisolone; preschool; respiratory illness; steroids; wheeze.

Appraisers: Zeraatkar D; Worster A; Poonai N.

Reference(s):

1. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. sign 153, 2016. Available: https://www.sign. ac. uk/ assets/ sign153. pdf
2. Beigelman A, Durrani S, Guilbert TW. Should a Preschool Child with Acute Episodic Wheeze be Treated with Oral Corticosteroids? A Pro/Con Debate. J Allergy Clin Immunol Pract 2016;4:27–35.
3. Jartti T, Nieminen R, Vuorinen T, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. J Allergy Clin Immunol. 2015 Mar;135(3):691-8.e9.

PEDIATRICS (PART II)

Research Question

Can parental medical education improve safety of fever medications administered to children?

BEEM Bottom Line

Why is this study important? Dosing errors are common (70%) amongst parents with febrile children with acetaminophen and ibuprofen, leading to health-care overutilization (both under- and over-dosing). A multimodal teaching intervention at ED discharge could reduce the risk of medication errors.

Which, if any, threats to validity are most likely to have an impact on the results and how? Substantial loss to follow-up threatens the statistical significance of primary outcome (explored in online appendices). Unclear how long it takes to deliver the teaching intervention, which may be a barrier to implementation.

How do the key results compare with the current evidence? These results build on prior work that support the same conclusions.

How should this study impact the care of ED patients? A multimodal caregiver teaching intervention on appropriate antipyretic medication administration for febrile children reduces early dosing errors. Further confirmation in larger settings, and analyzing time requirements for intervention delivery, are warranted.

Suneel Upadhye, MD MSc FRCPC
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Naureckas C, Camargo CA, Faridi M, *et al*. Medication Education for Dosing Safety: A Randomized Controlled Trial. Annals Emerg Med 2020; 76: 637-645. https://doi.org/10.1016/j.annemergmed.2020.07.007

Design: Randomized trial of an educational intervention.

Population: *Included:* Parents of febrile children (age 90d-11.9yrs) being discharged from ED with plan to use liquid antipyretics, fluent in English/Spanish, and reachable for telephone follow-up within 7days.
Excluded: Children with complex chronic medical conditions, planned use of nonstandard weight-based meds, children not accompanied by parent/legal guardian.

Intervention: Standard discharge teaching PLUS child-specific dosing algorithm, demonstration of meds loading in syringe by RA, "teach-back" cycles where parent demonstrated appropriate skills acquisition of meds loading/ administration, then parent sent home with same syringe.

Comparison: Standard discharge teaching.

Outcomes: *Primary:* Parent/guardian report of safe dosing at first f/u call (defined as within 20% of weight-based dose at ED discharge). Correction of dosing information by RA if needed.
Secondary: Safe dosing report at 2nd f/u call.

Key Results: *N* = 149 patients. 66 allocated to intervention, 83 to controls. 35 analyzed at both calls in Int group; 62 and 41 analyzed at 1st and 2nd calls in controls.

Sig.	*Outcome*	*Intervention*	*Control*	*Outcome Measure (95% CI)*
NSS	Secondary: Call 2			aRR* 0.97 (0.74-1.27)
SS	Primary: Call 1			RR 1.58 (1.12-2.24) aRR* 1.50 (1.06-1.23) favouring intervention

*aRR = adjusted relative risk for health literacy, parental language

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓
3. The allocation sequence was adequately concealed.	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	?
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	?

A1 = S. Upadhye

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: This work was supported by the Massachusetts General Hospital Department of Emergency Medicine Fellowship Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine, the National Center for Advancing Translational Sciences, and National Institutes of Health Award UL 1TR002541.

Conflicts of Interest: None (not explicitly reported?).

Potential Threats to Validity

Chance: Appropriate sample size calculations based on prior research done in investigators workplace. Low response to initial follow-up calls led to protocol change to send text messages before phone calls; improved call responses seen thereafter. Single site intervention may limit generalizability to other workplaces.

Selection Bias: Patients recruited during work hours when bilingual research assistants available.

Measurement Bias: None?

Analysis Bias: ITT vs per protocol analyses not specified. **Substantial loss to follow-up in both arms**; first phone call responses = 53% in Int arm, 75% in control arm. Various impacts of LTFU explored in online Appendices.

Confounding: Unable to blind patients/RA's to allocation, but treating providers & outcomes assessors were blinded.

Administrative Details

Key Words: Enter up to 5 key words here (in alphabetical order, separated by semicolons and a period at the end).

Appraisers: Upadhye S.

Reference(s): Naureckas C, Camargo CA, Faridi M, Espinola JA, Hayes BD, Porter S, Cohen A, Sameuls-Kalow M. Medication Education for Dosing Safety: A Randomized Controlled Trial. Annals Emerg Med 2020; 76: 637-645. https://doi.org/10.1016/j.annemergmed.2020.07.007

Research Question

What are the predictors of severe illness in community children with fever?

BEEM Bottom Line

Why is this study important? Recognition of febrile children at risk of serious illness is important to avoid significant morbidity/ mortality and manage resources wisely, especially in low/middle income countries.

Which, if any, threats to validity are most likely to have an impact on the results and how? Most studies were too heterogeneous to pool results. Spectrum bias with mostly hospitalized children limit generalizability to community settings (validity in ED?).

How do the key results compare with the current evidence? These results are congruent with prior reviews, especially with children from low/middle-income countries.

How should this study impact the care of ED patients?

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Chandna A, Tan R, Carter M, *et al*. Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies. BMJ Global Health 2021;6:e003451. doi:10.1136/bmjgh-2020-003451.

Design: Systematic review of prognostic studies in pediatric febrile illness severity.

Population: *Included:* Prognostic studies with children >28days and <19yrs old with community acute febrile illness and suspected sepsis.
Excluded: No pediatric prognostic data reported in included studies, or patients recruited from admitted inpatients. No specific clinical syndromes or pathogens included. Variables not available at time of presentation also excluded.

Index Test: Various clinical predictor variables for febrile illness at community presentation.

Reference Test: Hospital/ICU admission, mortality.

Diagnosis of Interest: Suspected sepsis/severe illness requiring admission, death.

Key Results: *N* = 18 studies, 24530 children evaluated.

Prognostic Group	*Prognostic Variable (n=studies), Likelihood Ratios (95% CI)*	
Clinical	Malnutrition; n=5	LR+ 1.56-11.13, LR- 0.87-0.95
	Prostration; n=2	LR+ 0.87-3.88, LR- 0.18-1.23
	Resp distress; n=5	LR+ 1.36-7.71, LR- 0.28-0.64
	Jaundice; n=1	LR+ 5.42 (3.65-8.06), LR- 0.78 (0.70-0.88)
	Comorbidity; n=6 (4 HIV+)	LR+ 1.35-12.48, LR- 0.12-0.97
	Oxygen Sat (<90%); n=3	LR+ 2.10-9.49, LR- 0.73-0.86
	Bradycardia (80-105bpm); n=3	LR+ 5.95-14.59, LR- 0.91-0.94
	Peripheral hypoperfusion; n=6	LR+ 1.78-17.38, LR- 0.61-0.93
	Hypotension; n=4	LR+ 1.89-9.57, LR- 0.79-0.92
	Decreased LOC; n=11	LR+ 0.95-14.02, LR- 0.27-1.04
Lab	Elevated Lactate (>4mM); n=6	LR+ 2.28-5.13, LR- 0.13-0.87
	Hypoglycemia (<2.5mM); n=3	LR+ 5.10-13.36, LR- 0.75-0.87
	Hyperkalemia; n=1	LR+ 6.64 (4.46-9.89), LR- 0.84 (0.78-0.89)
Clinical prediction models	Outcome: Mortality, organ support, PICU admit (n=28)	AUROC 0.55-0.97
	Hospital LOS, symptom duration (n=5)	AUROC 0.49-0.64

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	X
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	X
9. The subgroups were stated a priori and appropriate.	X
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓

A1 = S. Upadhye

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: Gov't/university research trust funding.

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: Most of the studies included hospitalized children, not community-based (spectrum bias).

Selection Bias: Search of electronic databases (no language restrictions) with "snowballing" of reference lists. No gray literature/conference abstracts mentioned. No mention of publication bias analysis.

Measurement Bias: Quality assessment completed independently using QUIPS/PROBAST tools. Only two studies considered low risk of bias.

Analysis Bias: High heterogeneity precluded meta-analysis.

Confounding: A number of studies from sub-Saharan Africa (higher rates of malaria, HIV) contributed to specific predictor variables (eg. malnutrition) that may not be generalizable to higher-income countries.

Administrative Details

Key Words: Community, febrile illness, severity prediction.

Appraisers: Upadhye S.

Reference(s): Chandna A, Tan R, Carter M, Van Den Bruel A, Verbakel J, Koshiaris C, Salim N, Lubell Y, Turner P, Keitel K. Predictors of disease severity in children presenting from the community with febrile illnesses: a systematic review of prognostic studies. BMJ Global Health 2021;6:e003451. doi:10.1136/bmjgh-2020-003451.

Research Question

What exam features or diagnostic tests are useful to diagnose septic arthritis in limping children?

BEEM Bottom Line

Why is this study important? Septic arthritis is a rare yet critical diagnosis to exclude in the limping child. This study updates current evidence on clinical examination and investigations for SA in limping children.

Which, if any, threats to validity are most likely to have an impact on the results and how? Inconsistent definitions and reporting of clinical findings, spectrum bias, and uncertain time intervals between index and reference tests erode the already weak performance characteristics of various clinical, lab and imaging modalities for diagnosing pediatric septic arthritis.

How do the key results compare with the current evidence? These results mirror the relative paucity of reliable clinical markers for adult septic arthritis (Carpenter *et al*, 2011).

How should this study impact the care of ED patients? There are almost no clinical/lab/imaging features that can reliably rule out SA in febrile limping children without an alternate infection source. This may necessitate moving onto diagnostic joint aspiration.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Tu J, Gowdie P, Cassar J, Craig S. Test characteristics of history, examination and investigations in the evaluation for septic arthritis in the child presenting with acute non-traumatic limp: A systematic review. BMJ Open 2020;10:e038088. doi:10.1136/bmjopen-2020-038088.

Design: Systematic review of diagnostic studies for pediatric septic arthritis.

Population: *Included:* All studies describing pediatric patients with monoarticular complaints (limp, altered gait, non-weight bearing, limb pain/swelling) with suspicion of septic arthritis (SA).
Excluded: Patients without monoarticular complaint, adult/mixed populations, no extractable data determining test characteristics, no reference standard for SA Dx.

Index Test: History/physical exam findings, lab investigations, imaging results.

Reference Test: Abnormal synovial fluid findings (macroscopic appearance, elevated WBC count, fluid/blood culture results).

Diagnosis of Interest: Septic arthritis.

Key Results: *N* = 18 studies, 2672 children; 560 confirmed septic arthritis.

	Index Test Likelihood Ratio (95% CI)
Useful	Fever (any level): LR+ 2 to 25.2 (1.7-78), LR- 0.2-0.8 Joint tenderness: LR+ 11.4 (5.9-22.0), LR- 0.3 (0.2-0.5); single study Labs (7 studies): ESR LR+ 2 to 12, LR- 0.1-0.9; CRP LR+ 1.2-12.3, LR- 0.1-0.7 Imaging: US joint effusion LR+ 8.4 (4.1-17.1), LR- 0.2 (0.1-0.3); single study n=30 kids
Not useful	Clinical: Male gender, history of tick bites, prior antibiotic use, history of chills, joint pain, recent illness Laboratory: WBC count, procalcitonin (single small study) Imaging: Plain radiographs of joint
Unknown	Kocher CDR (non-weightbearing status, fever, WBC>12, ESR>40mm/hr): AUC 0.96 derivation, 0.80 and 0.86 on validation. Caird CDR (Kocher criteria + CRP>20mg/L): PPV (5 criteria positive) 98% derivation, 60% external validation?

AUC = area under the curve; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); LR = likelihood ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant.
P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	X
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓
7. The quality of the primary studies is high.	X
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	X
9. The subgroups were stated a priori and appropriate.	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓

A1 = S. Upadhye

QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: Spectrum bias likely had an impact (over-estimation) of index test performance in study samples.

Selection Bias: Limited electronic search (MedLine, EMBASE); no mention of gray literature, conference abstracts, article reference lists. English language articles only. No mention/reporting of publication bias analysis.

Measurement Bias: Lack of blinding in outcome assessors between index and reference tests. Unknown times between index and reference tests can affect index test performance (eg. CRP, ESR).

Analysis Bias: Unable to pool data for meta-analysis due to widespread heterogeneity between included studies.

Confounding: A number of clinical, exam and radiographic variables did not share the same definition, which could affect how variable outcomes are interpreted. Also, there was variability in the definition of SA, which would affect diagnostic test outcomes. No time interval reporting between index and reference tests.

Administrative Details

Key Words: Limping child, septic arthritis

Appraisers: Upadhye S.

Reference(s): Tu J, Gowdie P, Cassar J, Craig S. Test characteristics of history, examination and investigations in the evaluation for septic arthritis in the child presenting with acute non-traumatic limp: A systematic review. BMJ Open 2020;10:e038088. doi:10.1136/bmjopen-2020-038088.

Research Question

What are the latest guidelines for the management of a well looking febrile infant (aged 8-60days)?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Evaluation of febrile infants is a daunting challenge for most ER physicians, and clear guidance on the risk of serious bacterial illness and intensity of investigations are welcome.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? This is a strong guideline that meets NEATS trustworthiness standards. The involvement of parents/caregivers in the guideline development process would have made this publication even more credible. Defining QI performance metrics would make these pathways easier to implement, and monitor for audit/feedback purposes.

How should this guideline, and specifically which recommendations should impact the care of ED patients? Three clear evidence-based evaluation/management algorithms for 3 different age strata are clearly outlined, and should help

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Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: Pantell RH, Roberts KB, Adams WG, *et al*, for the Subcommittee on Febrile Infants. Pediatrics 2021; 148(2):e2021052228

Design: Clinical Practice Guideline.

Population: Well-looking febrile infants (temp ≥ 38°C/100.4°F) aged 8-60days, with gestational birth age of 37-42 weeks. Guideline not to be used with infant is not "well-appearing." Excluded = preterm infants (<37weeks GA), infants <2weeks age with complicated perinatal course (infection/surgery), high suspicion of HSV, focal bacterial infection identified (treat as indicated), clinical bronchiolitis, documented/suspected immune compromise, congenital/chromosomal anomalies, tech intervention to sustain life, immunized within last 48hrs.

Scope: This guideline is intended for clinicians taking care of febrile infants aged 8-60days.

Key Results: 42 recommendations total, stratified for infants 8-21d, 22-28d, and 29-60d.

Strength of Recommendations (Grade of Evidence Quality*) – "Clinicians should…"

Infant Age Group	Strong	Moderate	Weak
8-21days	**KAS 1**: Should obtain urine specimen by catheterization or suprapubic aspiration (SPA) of bladder for urinalysis and, if urinalysis result is positive, for culture. (A) **KAS 2**: Should obtain a blood culture. (A) **KAS 4**: Should obtain CSF for analysis (WBC, protein, glucose, Gram stain) and culture for bacteria. (A) **KAS 5**: Should initiate parenteral antimicrobial therapy. (A) **KAS 7b**: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. (A)	**KAS 6**: Should actively monitor infants while awaiting results of bacterial cultures in a hospital setting with nurses and staff experienced in the care of neonates/young infants. (B) **KAS 7a**: Should discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following criteria are met: (1) culture results are negative for 24–36 h or only positive for contaminants; (2) the infant continues to appear clinically well or is improving (eg, fever, feeding); (3) there no other reasons for hospitalization. (B)	**KAS 3**: May assess IM**s. (B)
22-28days	**KAS 8**: Should obtain urine specimen by catheterization or	**KAS 10**: Should assess IMs. (B/Strong)	**KAS 11a**: Clinicians may obtain a CSF

	SPA of bladder forurinalysis and, if urinalysis result is positive, for culture OR Should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture. (A) **KAS 9**: Should obtain a blood culture. (A) **KAS 12a**. Should administer parenteral antimicrobial therapy in a hospital if either of the following apply: (1) CSF analysis suggests bacterial meningitis; (2) urinalysis result is positive. (A) **KAS 14c**: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. (A)	**KAS 11b**. Should obtain CSF for analysis (WBC, protein, glucose, Gram stain), and bacterial culture if any IM obtained is positive. (B) **KAS 12b**. May administer parenteral antimicrobial therapy in a hospital if ALL of the following apply: (1) CSF analysis is normal; (2) urinalysis is normal; (3) Any IM obtained is abnormal. (B) **KAS 12c**. May administer parenteral antimicrobial therapy to hospitalized infants even if ALL of the following are met: (1) urinalysis is normal; (2) no IM obtained is abnormal; (3) CSF analysis is normal or enterovirus-positive. (B/Weak) **KAS 13a**: May manage infants at home if all of the following criteria are met: (1) Urinalysis is normal; (2) No IM obtained is abnormal. (3) CSF analysis is normal or enterovirus-positive. (4) Verbal teaching and written instructions have been provided for monitoring throughout the period of time at home. (5) Follow-up plans for reevaluation in 24 h have been developed and are in place. (6) Plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care. (B) **KAS 13b**: Should hospitalize infants in a facility with nurses and staff experienced in the care of neonates/young infants when CSF is not obtained or is uninterpretable. (B/Weak) **KAS 14a**: Should discontinue antimicrobial agents and discharge hospitalized infants after 24 to 36 h of negative culture results if both of the following are met: (1) the infant is clinically well or improving (eg, fever, feeding); (2) there are no other reasons for hospitalization. (B/Strong) **KAS 14b**: Should discontinue antimicrobial agents on infants managed at home when all of the following criteria are met: (1) infant is clinically well or improving (eg, fever, feeding) at time of reassessment; (2) all culture results are negative at 24–36 h; (3) there is no other infection requiring treatment (eg, otitis media). (B/Strong)	analysis on infants 22–28 d of age even if all of the following criteria are met: (1) urinalysis result is negative or positive; (2) no IM obtained is abnormal; (3) blood and urine cultures have been obtained; (4) infant is hospitalized. (C/Mod) **KAS 12d**: Should administer parenteral antimicrobial therapy for infants who will be managed at home even if ALL of the following are met: (1) urinalysis is normal; (2) No IM obtained is abnormal; (3) CSF analysis is normal. (C/Mod)
29-60days	**KAS 15**: Should obtain urine specimen by bag, spontaneous void, or stimulated void for urinalysis and, if urinalysis result is positive, obtain a catheterization or SPA specimen for culture, OR Should obtain urine specimen by catheterization or SPA of bladder for urinalysis and, if result is positive, for culture. (A) **KAS 19a**: Should use parenteral antimicrobial therapy if CSF analysis suggests bacterial meningitis. (A) **KAS 20a**: Should hospitalize infants in a unit with nurses and staff experienced in the care of	**KAS 16:** Should obtain a blood culture. (B) **KAS 17:** Should assess IMs. (B) **KAS 18b**: Need not obtain CSF for analysis and culture if all IMs obtained are normal. (B) **KAS 19b**: May use parenteral antimicrobial therapy if both of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) any IM obtained is abnormal. (B) **KAS 19c**: Should initiate oral antimicrobial therapy if all of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) urinalysis result is positive; (3) no IM obtained is abnormal. (B) **KAS 19d**: Need not use antimicrobial therapy while awaiting bacterial culture results if all of the following are met: (1) CSF analysis, if obtained, or normal or enterovirus-positive; (2) urinalysis result is negative; (3) no IM obtained is abnormal. (B)	**KAS 18a**: May obtain CSF for analysis (WBC, differential, protein, glucose, Gram stain), culture for bacteria, and test for enterovirus when CSF pleocytosis is detected or during enterovirus season if any IM is abnormal. (C) **KAS 20e**: Need not treat with antimicrobial therapy if all of the following apply: (1) CSF analysis (if CSF obtained) is normal; (2) urinalysis result is negative; (3)

	29- to 60-d-old infants if CSF analysis, if obtained, is abnormal. (A) **KAS 21d**: Should treat infants' positive bacterial pathogens in urine, blood, or CSF with targeted antimicrobial therapy for the duration of time consistent with the nature of the disease, responsible organism, and response of the infant to treatment. (A)	**KAS 20b**: May hospitalize infants in a unit with nurses and staff experienced in the care of 29- to 60d-old infants if any IM obtained is abnormal. (B) **KAS 20c**: Should manage patients at home if all of the following criteria are met: (1) CSF analysis, if CSF obtained, is normal; (2) urinalysis result is negative; (3) all IMs obtained are normal; (4) appropriate parental education has been provided; (5) follow-up plans for reevaluation in 24 h have been developed and are in place (6) plans have been developed and are in place in case of change in clinical status, including means of communication between family and providers and access to emergency medical care. (B) **KAS 20d**: May manage infants without antimicrobial treatment at home without having obtained interpretable CSF if all of the following are met: (1) urinalysis result is negative; (2) all IMs obtained are normal; (3) parents can return promptly if there is a change in infant condition and agree to follow-up in 24 to 36 h. Infants monitored at home should be reassessed in the following 24 h. (B) **KAS 21a**. Should discontinue antimicrobial agents when all of the following are met: (1) all bacterial culture results are negative at 24–36 h; (2) infant is clinically well or improving (eg, fever, feeding); (3) there is no other infection requiring treatment (eg, otitis media). (B/Strong) **KAS 21b**: Should discharge hospitalized patients with positive urine culture (UTI) results if all of the following are met: (1) blood culture result is negative; (2) result of CSF culture, if obtained, is negative; (3) infant is clinically well or improving (eg, fever, feeding); (4) there are no other reasons for hospitalization. (B/Strong) **KAS 21c**: Should discontinue parenteral antibiotics (if started) and begin or continue oral antimicrobial for infants with UTIs managed at home when all of the following are met: (1) urine culture result is positive; (2) all other bacterial culture results are negative at 24–36 h; (3) infant is clinically well or improving (eg, fever, feeding). (B/Strong).	no IM obtained is abnormal. (C/Mod)

*Evidence Quality: A=Strong, B=Moderate, C=Weak unless otherwise specified.
**IM = Inflammatory Mediators (CRP, Procalcitonin, WBC/ANC)

BEEM Critique

Risk of Bias Assessment

		A1
1.	The guideline development group includes all of the relevant stakeholders, including patients.	✓
2.	Systematic methods were used to search for evidence.	✓
3.	The criteria for selecting the evidence are clearly described.	✓
4.	The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓
5.	The health benefits, side effects, and risks were considered in formulating the recommendations.	✓
6.	There is an explicit approach linking the evidence to formulate the recommendations.	✓
7.	Experts externally reviewed the guideline prior to its publication.	✓
8.	The content of the guideline is free of influence by the views of the funding body.	✓
9.	Competing interests of guideline development group members have been recorded and managed.	✓
10.	The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: 3 subcommittee members had some commercial/industry disclosures. No members of the writing committee had reported conflicts.

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **Extensive 2021 systematic review (300pgs) published in support of these CPG recommendations. No patient/parent stakeholders in working groups.**

Presentation: Well organized with easy to find recommendations? **Yes; Key Action Statements summarized in Table 1.**

Comprehensive: Was the information to inform decision-making complete? **Yes; benefits, harms/risks, costs detailed for each Key Action Statement.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes**

Administrative Details

Key Words: Clinical practice guideline, febrile illness, infants 8-60days.

Appraisers: Upadhye S.

Reference(s): Pantell RH, Roberts KB, Adams WG, Dreyer BP, Kupperman N, O'Leary ST, Okechukwu K, Woods CR, for the Subcommittee on Febrile Infants. Pediatrics 2021; 148(2):e2021052228 PMID: 34281996

Hui C, Neto G, Tsertsvadze A, et al. Diagnosis and management of febrile infants (0-3 months). Evid Rep Technol Assess (Full Rep). 2012;205(205):1–297.

Research Question

How frequently do emergency physician pediatric musculoskeletal radiograph interpretations differ from radiologist interpretations and lead to adverse events?

BEEM Bottom Line

Why is this study important? Pediatric musculoskeletal (MSK) injuries are one of the most common emergency department (ED), presentations of this age group. However, the rate of interpretation discrepancy between emergency physicians (EPs) and radiologists as well as the impact of these discrepancies are unknown. This study measures the interpretation discrepancy rate and the associated predictors and adverse events (AEs).

Which, if any, threats to validity are most likely to have an impact on the results and how? The sample selection is at high risk of bias being from a single center and excluding patients with serious injuries and those presenting at night. The authors independently reviewed 100% of discordant cases, but only 17% of concordant interpretations. The short follow-up period and the significant loss to follow-up most likely underestimate the results.

How do the key results compare with the current evidence? This prospective study reports a 7.8% rate of AEs (confidence interval [CI] reaching up to 9%) with inaccurate reading of pediatric MSK radiographs. A retrospective review of 25,304 plain radiographs at a single center revealed a discrepancy rate of 1.0% of which (82.1%) were false negatives.[1] Most (41.7%) discrepancies were misinterpretations of chest radiographs due to missed pneumonia, while misinterpretations of extremity radiographs accounted for another 43.7% discrepancies. The authors considered only 0.41% of all radiographs as clinically significant. Other research has reported diagnostic error rates of pediatric MSK radiographs ranging from 5% to 15%.[2,3]

How should this study impact the care of ED patients? The rates of radiograph misinterpretation and resulting AEs likely vary widely. However, awareness of radiographs with highest risk and that require special attention, as well as developing cognitive skills and requesting radiological consultations can help reduce the misinterpretation rates.

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Study Summary

Article: Al-Sani F, Prasad S, Panwar J, et al. Adverse Events from Emergency Physician Pediatric Extremity Radiograph Interpretations: A Prospective Cohort Study. Acad Emerg Med. 2019 Nov 8. doi: 10.1111/acem.13884.

Design: Single-center (Saskatchewan, Canada), prospective cohort study.

Population: *Included:* Children (≤ 18 years) presenting to a pediatric ED with an extremity injury and requiring radiographic imaging.
Excluded: Children with imaging prior to the ED visit; already included in the study; presented as a Level I trauma patient; had orthopedics/plastics/radiology consultation prior to enrolment; radiology inconclusive ED radiograph diagnosis; whose parents were not able or available to communicate.

Exposure: MSK radiograph interpretations by EPs.

Comparison: MSK radiograph interpretations by radiologists.

Outcomes: *Primary:* Frequency of discordant EP radiograph interpretations that led to an AE (defined as "clinical sequelae and/or repeat health care visits due to a delay in correct radiograph interpretation") determined by telephone follow-up ≤ 3 weeks of ED discharge.
Secondary: Variables associated with the outcome including: trainee present; pediatric emergency medicine credentialed attending physician; ≥ 10 years postgraduation from all training; patient age, sex, fall, injury location; ≤ 20% pretest probability of a fracture/dislocation; severity assessment of injury; pain score ≤2; review of the radiograph before patient examination; EP uncertainty in diagnostic interpretation; season; day shift.

Key Results: *N* = 2,302.

EP Interpretation				
False –ve	29 Minor	88 Moderate	6 Severe	123 Total
Most frequent false –ve	Distal radius	Finger	Distal tibia (SH)	
False +ve	N/A	N/A	N/A	57 Total
Most frequent false +ve	Finger	Distal fibula (SH)	Toe	

N = number of patients; N/A = not applicable; SH = Salter Harris misclassification.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	X	X	X
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	X	X	X
7. The follow-up was complete.	X	X	X
8. The effect size of the primary outcome is clinically significant.	?	?	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The primary analyses appear to be sufficiently powered as evidenced by relatively narrow CIs; however, the multivariable logistic regression is overfit and results are likely subject to type I error.

Selection Bias: The participants were not sampled consecutively, rather enrolled only between 08:30 and 23:00 hours. Therefore, those cases presenting overnight are not represented. Further limitations to generalizability result from sampling from only a single center and excluding those cases with an inconclusive diagnosis or language barrier. Also, there is limited generalizability to general ED physicians as most physicians included in the study were pediatric emergency faculty.

Measurement Bias: There is no information about the validity or reliability of the assessment of the presence or absence of an AE. Only a sample of concordant interpretation cases were evaluated for AEs. Therefore, it is unknown how accurate the rate of AEs is in this group or the comparability of those followed-up to those not followed-up. Determination of concordant or discordant interpretations also is suspected of measurement bias given that only discordant cases were reviewed in duplicate.

Analysis Bias: The analyses did not appear to be corrected for multiple comparisons despite pretesting variables prior to entering them into the multivariable logistic regression model. This data-driven approach increases the likelihood of a type I error. There is also a significant loss to follow-up which not only reduces power but possibly underestimates rates of AEs.

Confounding: Residual confounding as with all observational studies because of unknown prognostic factors that cannot be controlled for; independent factors affecting the outcome.

Administrative Details

Key Words: Adverse event (AE); extremity injury; musculoskeletal (MSK); radiograph; x-ray.

Appraisers: Bedard C; Worster A; Al Raisi M.

Reference(s):

1. Taves J, Skitch S, Valani R. Determining the clinical significance of errors in pediatric radiograph interpretation between emergency physicians and radiologists. CJEM. 2018 May;20(3):420–424.
2. Mounts J, Clingenpeel J, McGuire E, et al. Most frequently missed fractures in the emergency department. Clin Pediatr (Phila) 2011;50:183–6.
3. Smith JE, Tse S, Barrowman N, et al. Missed fractures on radiographs in a pediatric emergency department. CJEM 2016;18:S119.

Research Question

Does irrigation with 20 minutes of cool running water reduce the need for skin grafts in children with burns?

BEEM Bottom Line

Why is this study important? Current guidelines for the management of acute thermal burns include recommendations for irrigation with cool running water for variable duration of time ranging from 5 to > 20 minutes (mins.).[1,2] The evidence for cool running water comes mainly from animal and adult human studies. As children have smaller body surface area (BSA) ratios, skin thickness, and volumes compared to adults, this prospective database study attempts to determine whether children with acute burns also benefit from cool running water for 20 mins. within 3 hours of a burn injury.[3,4]

Which, if any, threats to validity are most likely to have an impact on the results and how? In this single-center study, 90% of the burns were < 5% BSA; hence, any findings of association with larger burns require validation. This study was an observational analysis of primary and secondary data. As such, it is subject to recall bias and bias caused by imbalances in unknown or unadjusted confounders. This study is not a trial; therefore, conclusions of causation should be avoided. However, a randomized trial on this topic is unlikely given the access to point-of-care first-aid treatments, questionable equipoise, and practical challenges.

How do the key results compare with the current evidence? The findings support existing evidence in the adult burn literature that cool water first aid is associated with improved burn outcome.[3,4] This study uniquely confirmed these associations in a dedicated pediatric cohort. It also found a dose-response relationship of stronger effect with longer durations of cool running water up to 20 mins.

How should this study impact the care of ED patients? For most pediatric burns, cool running water first aid is associated with improved burn outcomes. A cumulative 20 mins. in the first 3 hours post-injury is superior to shorter durations. However, caution must be taken not to induce hypothermia especially in smaller children.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Griffin BR, Frear CC, Babl F, et al. Cool Running Water First Aid Decreases Skin Grafting Requirements in Pediatric Burns: A Cohort Study of Two Thousand Four Hundred Ninety-five Children. Ann Emerg Med. 2020 Jan;75(1):75–85.

Design: Single center (Queensland, Australia), prospective, observational cohort study.

Population: *Included:* Children (≤ 16 years old) presenting to a single center with an acute burn.
Excluded: Friction burns; electrical burns; chemical burns; burns of unknown mechanism; children with unknown first aid treatment.

Exposure: Cool running water ≥ 20 mins. delivered either cumulatively or continuously ≤ 3 hours of injury.

Comparison: Any other form of first aid, including still water, ice, aloe vera; < 20 minutes of cool running water.

Outcomes: *Primary:* Need for skin grafting.
Secondary: Time to re-epithelialization (i.e., number of days between injury and outpatient treatment completion); wound depth; hospital admission; length-of-stay (LOS); requirements for any operating room interventions.

Key Results: *N* = 2,495 subjects; 1,780 (71.3%) received running water ≥ 20 minutes (vs. all other forms of first aid).

Sig.	*Outcome*	*Odds Ratio or Hazard Ratio (95% CI)*	*NNT* (95% CI)*
SS	Skin graft	0.59 (0.44 to 0.79)	20 (13 to 41)
SS	Full-thickness depth	0.37 (0.24 to 0.59)	23 (17 to 35)
SS	Hospital admission	0.69 (0.33 to 0.90)	21 (8 to 67)
SS	Operating room interventions	0.66 (0.50 to 0.88)	25 (15 to 77)
NSS	Time to re-epithelialization (all burns)	1.10 (0.99 to 1.22)	N/A
NSS	Hospital length of stay	0.92 (0.73 to 1.16)	N/A

CI = confidence interval; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; Odds ratio (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.
*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	✓	✓	✓
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	?	?	?
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	?	?	?
7. The follow-up was complete.	?	?	?
8. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: None detected.

Selection Bias: None detected.

Measurement Bias: The primary outcome (skin grafting) is a decision made by clinicians, which in the absence of blinding, may be biased by their knowledge of the intervention (the type and extent of first aid).

Analysis Bias: It is not clear that the primary outcome was selected a priori.

Confounding: This is an observational study, not a trial and therefore, unknown confounders or causative factors can still exist and remain undetected. The authors analyze mechanism of injury and socio-economic status as covariates; however, others may exist.

Administrative Details

Key Words: Burn; first aid; pediatric; skin graft; water.

Appraisers: Zeraatkar D; Worster A; Kam A.

Reference(s):

1. American Burn Association. Initial First Aid Treatment for Minor Burns.Chicago, IL: The Association; 2017. Available at: http://ameriburn.org/prevention/prevention-resources/#1493037731300-e4bd5ba9-3769. Accessed January 17, 2020.
2. Stiles K, Goodwin N. First Aid Clinical Practice Guidelines. London, UK: British Burn Association; 2018. Available at: https://www.britishburnassociation.org/pre-hospital-approach-to-burns-patientmanagement/. Accessed January 17, 2020.
3. Wood FM, Phillips M, Jovic T, et al. Water first aid is beneficial in humans post-burn: evidence from a bi-national cohort study. PLoS One. 2016;11:e0147259.
4. Harish V, Tiwari N, Fisher OM, et al. First aid improves clinical outcomes in burn injuries: evidence from a cohort study of 4918 patients. Burns. 2018;45:433–439.

Research Question

Is the combination of ibuprofen and acetaminophen for pediatric pain superior to either analgesic alone?

BEEM Bottom Line

Why is this study important? Ibuprofen and acetaminophen are two of the three most commonly used analgesics in the world, along with opioid medications.[1] Given the current opioid crisis and unclear lifetime risks of opioid misuse after therapeutic use, determining ways to optimize pediatric pain management without opioids is of high importance for health practitioners caring for children. This trial compares the combination of oral ibuprofen and acetaminophen with each analgesic alone for pediatric emergency department (ED) patients with acute pain.

Which, if any, threats to validity are most likely to have an impact on the results and how? Pain in children < 8 years was measured using a 6-point scale that is fraught with cultural biases; scores were then directly equated to an 11-point numerical rating scale; this conversion is not validated. Measures were not made beyond 60 minutes; pain relief is most effective when it is sustained, and this was not measured in this study. The results may not be appliable to all children, as patients were enrolled during limited hours and at a single center. Authors report that the trial was underpowered to demonstrate the analgesic superiority of the ibuprofen and acetaminophen combination in comparison with each analgesic alone, with respect to safety outcomes.

How do the key results compare with the current evidence? Acetaminophen's additive value to ibuprofen has been demonstrated in many conditions, including acute post-operative pain, where ibuprofen and acetaminophen combinations provided better analgesia than either drug alone in 64% (ibuprofen) and 85% (acetaminophen) of studies.[2] Ibuprofen is as or more efficacious than acetaminophen for pain and fever in both adults and children and is equally safe.[1,3] A 2016 systematic review supports ibuprofen as a first choice for mild-moderate musculoskeletal injury pain, but recognizes that ibuprofen, alone, is inadequate for moderate-severe pain.[4] Finally, a recent systematic review, including only children, concluded that while both acetaminophen and ibuprofen were effective for short-term pain relief, the combination of acetaminophen and ibuprofen for ear infection pain required further study.[5]

How should this study impact the care of ED patients? Using ibuprofen, alone or in combination with acetaminophen, remains a prudent choice over the addition of opioids to the pain treatment of most children with acute pain in the ED. Future studies will need to confirm the utility of combination acetaminophen/ibuprofen therapy in children, as well as the ideal opioid, when needed.

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No conflicts of interest (ICMJE)

Study Summary

Article: Motov S, Butt M, Masoudi A, et al. Comparison of Oral Ibuprofen and Acetaminophen with Either Analgesic Alone for Pediatric Emergency Department Patients with Acute Pain. J Emerg Med. 2020;58(5):725-732.

Design: Single center (USA), superiority, blinded, randomized controlled trial.

Population: *Included:* Children (≥ 3 and ≤ 17 years) with acute (traumatic and nontraumatic) pain and a pain score of ≥ 1 (Wong-Baker FACES Pain Scale pain score for patients aged < 8 years and verbal numeric rating scale [NRS] 0 to 10 for patients aged ≥ 8 years) who required oral ibuprofen or acetaminophen.
Excluded: Patients allergic to or unable to tolerate oral ibuprofen or acetaminophen, received analgesics ≤ 4 hours prior, possibly pregnant, refused or unable to participate.

Intervention: Ibuprofen (10 mg/kg) plus acetaminophen (15 mg/kg) orally.

Comparison: Either ibuprofen (10 mg/kg) or acetaminophen (15 mg/kg) orally.

Outcomes: *Primary:* Mean reduction in pain scores and mean pain scores in each group at 60 minutes (min).
Secondary: Adverse events and the need for rescue analgesia at 60 min.

Key Results: *N* = 90 patients (30 per group; mean age 11.4 years; 63% male).

Sig.	*Mean Pain Score @ 60 min*	*Acetaminophen*	*Ibuprofen*	*Combination*	*P-value*
NSS	Reduction from baseline	2.83 (2.12 to 3.81)	2.77 (1.48 to 3.18)	3.1 (1.87 to 3.46)	0.93
NSS	Actual	2.97 (2.18 to 3.76)	2.33 (1.51 to 3.15)	2.67 (1.91 to 3.43)	0.78

NB: No clinically important adverse effects and no required rescue analgesia at 60 min. CI = confidence interval; *N* = number of patients; NSS = not statistically significant; *p* = probability; P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	X	?	?
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	X	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓	✓	✓
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	X	X	X
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Maimonides Research and Development Foundation.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: The primary outcome was sufficiently powered, however the secondary outcomes regarding adverse effects and need for rescue analgesics were not.

Selection Bias: Non-consecutive recruitment increases the risk that the results may not be generalizable to the target population, particularly those patients that present to the ED during evening hours and on weekends. However, concealed allocation of treatment assignment minimizes the risk of selection bias.

Measurement Bias: Details regarding the validity and reliability of the NRS and Wong-Baker FACES pain assessment tools were not provided. It is unclear how pain was assessed in those less than 8 years of age since their referenced tool was validated on a sample of children 8 to 17 years of age. Given that the study enrolled patients as young as 3 years, there is concern regarding the quality of the data collected from young children on their rating of pain.

Analysis Bias: It is not clear if age was used to stratify or adjust the analyses. Given the wide age range considered in the eligibility criteria, it may be problematic if age was not controlled for; however, the age range of the enrolled participants was not reported therefore it is unclear whether this impacted the results.

Confounding: Study subjects were heterogenous for the source of pain which likely caused imbalance between the groups given the small group sizes.

Administrative Details

Key Words: Acetaminophen; analgesia; ibuprofen; pain.

Appraisers: Bedard C; Worster A; Ali S.

Reference(s):

1. Hartling L, Ali S, Dryden DM, et al. How Safe Are Common Analgesics for the Treatment of Acute Pain for Children? A Systematic Review. Pain Res Manag. 2016:5346819.
2. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110(4):1170-1179.
3. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. Ann Pharmacother. 2010;44(3):489-506.
4. Le May S, Ali S, Khadra C, et al. Pain Management of Pediatric Musculoskeletal Injury in the Emergency Department: A Systematic Review. Pain Res Manag. 2016;2016:4809394.
5. Sjoukes A, Venekamp RP, van de Pol AC, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database Syst Rev. 2016;12(12):CD011534.

Research Question

Is first attempt at pediatric lumbar puncture more successful with ultrasound guidance?

BEEM Bottom Line

Why is this study important? Lumbar puncture (LP) is a routine emergency department (ED) procedure whether obtaining cerebrospinal fluid (CSF) to diagnose meningitis or measuring opening pressure to diagnose benign intracranial hypertension. Regardless of the clinical scenario, first attempt LP failures are common and can lead to repeat LP attempts, delays to diagnosis, unnecessary antibiotic therapy and even hospital admission. This study aimed to determine if ultrasound-assisted-LP (UALP) has a higher probability of first-attempt success of obtaining a non-bloody CSF sample compared to standard LP (SLP) using palpation for landmark identification.

Which, if any, threats to validity are most likely to have an impact on the results and how? The trial was performed at two tertiary academic hospitals by select physicians trained in UALP therefore the results may not be generalizable. The exclusion of patients with spine abnormalities might have favoured the SLP group. The study's results are further limited by confounding, chance imbalances between groups with respect to important prognostic factors, and the small sample size which could not rule out a clinically important benefit, i.e., type 2 error.

How do the key results compare with the current evidence? Pediatric studies have shown that point-of-care-ultrasound (POCUS) can be used to measure the interspinous space and to determine how the measurement changes in different positions.[1] In neonates, ultrasound (US) can identify the level of conus medullaris as well as anatomic reasons for failed LP attempts.[2] Results from a meta-analysis suggest that POCUS has no effect in increasing LP success (relative risk [RR] 0.58; 95% confidence interval [CI] 0.15 to 2.28).[3] However, it was beneficial in reducing the risk of traumatic LPs in neonates and infants (RR = 0.33; 95% CI 0.13 to 0.82). The key results of this current trial are consistent with the current available evidence.

How should this study impact the care of ED patients? In this study, UALP did not significantly increase the first LP attempt success rate compared to SLP. However, given that POCUS has no reported adverse effects, physicians adept at POCUS should consider it to identify LP landmarks if it is difficult to find them by standard palpation.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Zummer J, Desjardins MP, Séguin J, et al. Emergency physician performed ultrasound-assisted lumbar puncture in children: A randomized controlled trial. Am J Emerg Med. 2020 Feb 19. pii: S0735-6757(20)30109-1. doi: 10.1016/j.ajem.2020.02.036.

Design: Two-center (Montreal, Canada), superiority, open, randomized controlled trial.

Population: *Included:* Children (< 19 years) requiring a LP during their ED visit and physician trained in UALP present.
Excluded: Patients with known spine or spinal cord abnormalities, ventricular shunts, hemodynamic instability, significant bleeding risk or unattainable consent.

Intervention: POCUS of the spine by a UALP-trained pediatric ED physician (using Sonosite Edge, Fujifilm Sonosite or Zonare Z.One Pro, ZONARE Medical Systems with either a linear or curvilinear probe) to mark the preferred puncture site. LP with the patient in either a lateral decubitus or sitting position.

Comparison: Standard landmark-based LP (SLP) with the patient in either a lateral decubitus or sitting position.

Outcomes: *Primary:* First-attempt lumbar puncture success, i.e. at least 0.5 mL CSF and nontraumatic (red blood cell count < 1000/mm^3).
Secondary: Overall LP success rate; first-attempt LP failure rate; overall LP failure rate.

Key Results: *N* = 186 (approximately 50% < 1 month old).

Sig.	*LP Outcome*	*UALP (n = 84)*	*SLP (n = 82)*	*Difference (95% CI)*
NSS	1st-attempt success (%)	57 (68)	49 (60)	8.1 (−6.4 to 22.2)
NSS	Overall success (%)	73 (87)	70 (85)	1.5 (−9.1 to 12.3)
NSS	Overall failure (%)	11 (13)	12 (15)	−1.5 (−12.3 to 9.2)

CI = confidence interval; *N* = number of patients; n = sample size; NSS = not statistically significant); Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	X	X	X
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	?	X	X
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	X	X
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	?	?	X
10. The effect size of the primary outcome is clinically significant.	?	?	?

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: The authors have no financial relationships to disclose.

Potential Threats to Validity

Chance: The study was powered to detect a difference of 20% in first attempt success rate, this was decided based on expert opinion without patient input. This statistically insignificant results are likely from a type 2 error because of the small sample size. If true, the difference that was found (8.1% higher success rate in UALP) is still likely a clinically important difference (number needed to treat = 12.5).

Selection Bias: Since the study required the participation of a physician trained in UALP, a convenience sample was used, which may not be representative of the target population.

Measurement Bias: None detected.

Analysis Bias: There was no attempt to adjust for important prognostic factors like patient age (50% were neonates) or experience level of provider (40% completed ≤10 prior LPs).

Confounding: Various technical variables that may influence success, such as amount and type of local anesthetic and depth of needle insertion, were not standardized and may have varied across trial arms.

Administrative Details

Key Words: Cerebrospinal fluid; lumbar puncture (LP); pediatric; point of care ultrasound (POCUS).

Appraisers: Zeraatkar D; Worster A; Eltorki M.

Reference(s):

1. Abo A, Chen L, Johnston P, et al. Positioning for lumbar puncture in children evaluated by bedside ultrasound. Pediatrics. 2010 May;125(5):e1149-53.
2. Coley BD, Shiels WE 2nd, Hogan MJ. Diagnostic and interventional ultrasonography in neonatal and infant lumbar puncture. Pediatr Radiol. 2001 Jun;31(6):399-402.
3. Olowoyeye A, Fadahunsi O, Okudo J, et al. Ultrasound imaging versus palpation method for diagnostic lumbar puncture in neonates and infants: a systematic review and meta-analysis. BMJ Paediatr Open. 2019 Mar 15;3(1):e000412.

PEDIATRICS (PART III)

Research Question

What is the utility in using intranasal ketamine for pediatric ED acute analgesia?

BEEM Bottom Line

Why is this study important? Having analgesic alternatives in pediatric acute ED pain care is important, especially if there are potential safety concerns, and a desire to avoid parenteral opioids.

Which, if any, threats to validity are most likely to have an impact on the results and how? Minimal.

How do the key results compare with the current evidence? There is a growing body of evidence supporting ketamine acute analgesia options in the ED for all age groups, especially in the era of opioid stewardship.

How should this study impact the care of ED patients? Intranasal ketamine is an effective and safe alternative to opioids in acute pediatric ED pain, especially when oral/parenteral routes may be impractical.

Suneel Upadhye, MD MSc FRCPC
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: de Silva LOJ, Lee JY, Bellolio F, *et al*. Intranasal ketamine for acute pain management in children: A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 1860-1866.

https://doi.org/10.1016/j.ajem.2020.05.094

Design: Systematic review and meta-analysis of randomized controlled trials (RCTs).

Population: *Included:* RCTs of children (age <18yo) needing ED acute analgesia (moderate/severe pain).
Excluded: Chronic pain conditions with recurrent exacerbations (eg. sickle cell disease), non-ED settings. Ketamine given for ED PSA, or alternative routes (IM, po, IV) also excluded.

Intervention: Intranasal ketamine (INK) at low/sub-dissociative doses (1-1.5mg/kg).

Comparison: Intranasal fentanyl (INF) 1.5-2ug/kg.

Outcomes: *Primary:* Pain reduction using validated pain scales at 10-15min, 30min and 60min time intervals.
Secondary: Need for rescue analgesia, adverse events, sedation rates (UMSS scale). Minor AE's = nausea, vomiting, dizziness, drowsiness, sleepiness, dysphoria/dissociation, unpleasant taste, pruritis, visual changes, headache, rash, light-headedness, nystagmus, salivation, vivid dreams, trouble concentrating, sore throat, hallucinations. Major AE's = dysrhythmias, seizures, apnea, resp depression, anaphylaxis, hypotension, cardiac arrest.

Key Results: *4 trials included, 276 patients randomized (138 to INK, 138 to INF). 3 studies included acute extremity pain, 4th study included extremity & abdominal pain.*

Sig.	*Outcome*	*OutcomeMeasure (95% CI)*	I^2
NSS	Primary: pain reduction (10-15min)	WMD -1.42pts (-9.95 to 7.10)	60%
	30min	WMD 0.40 (-6.29 to 7.10)	24%
	60min	WMD -0.64 (-6.76 to 5.47) **INK was non-inferior to INF all times (based on 10pt NI margin)	0%
	Need for rescue analgesia	RR 0.74 (0.44-1.25); INK 0-25%, INF 0-34%	25%
SS	Adverse events (minor)	RR 2.00 (1.43-2.00) favouring INF **1 serious AE in INF group, none in INK	49%
	Sedation	RR 1.81 (1.24-2.62) favouring INF; none were deep/unarousable	0%

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	?
3. The search for studies was unbiased and reproducible.	?
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The methods used to combine the included primary studies were reported and valid.	✓
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	?

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Mayo Clinic Small Grant program.

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: None? No children <3yo in any included studies.

Selection Bias: Limited search of 3 electronic databases, hand search of reference lists from retrieved articles. Contacted authors for missing data if needed. Unable to complete publication bias analysis due to small number of included articles.

Measurement Bias: Use of Cochrane Risk of Bias (RoB) tool for study quality assessments, and overall outcomes evidence evaluated using GRADE methods. All included studies had low RoB, and High GRADE certainty of evidence.

Analysis Bias: Three of 4 studies reported per-protocol analyses (rather than ITT). Use of random effects models for higher heterogeneity studies appropriate.

Confounding: All patients received ibuprofen or acetaminophen prior to study drug Rx (balanced co-interventions between study groups).

Administrative Details

Key Words: Acute analgesia, intranasal, fentanyl, ketamine.

Appraisers: Upadhye S.

Reference(s): de Silva LOJ, Lee JY, Bellolio F, Homme JL, Anderson JL. Intranasal ketamine for acute pain management in children: A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 1860-1866. https://doi.org/10.1016/j.ajem.2020.05.094

Research Question

What is the efficacy of nebulized magnesium in the treatment of severe pediatric asthma?

BEEM Bottom Line

Why is this study important? While IV magnesium is useful in reducing hospitalizations in refractory pediatric asthma, there are persistent concerns around invasive Rx and safety. This study examined the utility of nebulized magnesium in severe asthma.

Which, if any, threats to validity are most likely to have an impact on the results and how? There may be a selection bias as participants vs non-participants are not clearly compared. Early high-dose initial aggressive asthma treatments may have opened airways substantially, and attenuated the effects of nebulized magnesium.

How do the key results compare with the current evidence? This study clarifies prior mixed results on the utility (or lack thereof?) of nebulized magnesium in refractory pediatric asthma.

How should this study impact the care of ED patients? Nebulized asthma had no incremental benefit over SABA's in reducing pediatric hospitalizations, and clinical improvement of symptoms.

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Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Schuh S, Sweeney R, Rumantir M, *et al*, for the Pediatric Emergency Research Canada (PERC) Network. JAMA 2020;324(20):2038-2047. doi:10.1001/jama.2020.19839

Design: Parallel 2 arm, placebo-controlled, double-blinded RCT.

Population: *Included:* Children 2-17yo with moderate/severe refractory asthma AFTER an initial 1hr asthma treatment period (including oral steroid and 3 rounds of inhaled albuterol/ipratropium via MDI). Mod/severe asthma = PRAM score ≥ 5pts.
Excluded: Children requiring immediate airway intervention, IV magnesium prior to enrollment, chronic lung/CV/renal/neurologic/other systemic comorbidities, known hypersensitivity to magnesium. Also excluded families without language competencies (English, French), no telephone/email contact or previously enrolled.

Intervention: 3 consecutive treatments of nebulized magnesium (600mg/1.2ml) with albuterol 5mg/1ml, topped up to 5ml total with sterile water

Comparison: 3 consecutive treatments of placebo 1.2ml of 5.5% saline with same albuterol/sterile water mix

Outcomes: *Primary:* ED physician decision to hospitalize children for persistent resp distress/need for supplemental oxygen within 24hrs of visit.
Secondary: Change in PRAM score (clinically significant = 3/12 pt improvement), resp rate, oxygen saturation (room air) up to 4hrs, BP changes, and number of rescue albuterol Rx needed (up to 4hrs). Adverse events also measured; hypotension needing intervention, apnea, ICU admissions.

Key Results: *N* = 818 patients.

Sig.	*Outcome*	*Intervention*	*Control*	*Outcome Measure (95% CI)*	*NNT (95% CI)*
NSS	Primary	372/816	178/409	RD -4.2% (-11 to 2.8)*	N/A
	Secondary PRAM			RD 0.14pts (-0.23 to 0.51)	N/A
	Resp Rate			RD 0.31 breaths/min (-1.17 to 1.79)	N/A
	Oxygen Sat			RD -0.05% (-0.54 to 0.45%)	N/A
	SBP			RD 0.61mmHg (-1.64 to 2.85)	N/A
	Rescue albuterol			ARR 0.94 (0.78-1.14)	N/A

*No differences based on prespecified analyses for age strata, sites, age, gender, PRAM cutoffs, history of atopy/preschool wheezer. No differences in 72hr revisits, or use of IV magnesium after intervention Rx.

ADVERSE EVENTS: Infrequent (total 33 mild, 3 moderate) and none attributable to experimental Rx.

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓
3. The allocation sequence was adequately concealed.	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	X

A1 = S. Upadhye

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Grants from CIHR, PSI, Thrasher fund, and Toronto Hospital for Sick Children. No role in study management or publication.

Conflicts of Interest: Many authors disclosed grants from public agencies/hospitals/foundations. One author (Ducharme) disclosed industry grants/speaking fees unrelated to this study work.

Potential Threats to Validity

Chance: Change in sample size from initial 284 to 816pts, based on under-estimated primary outcomes. Lack of standardized hospitalization criteria may have contributed to null result; decision to hospitalize may be influenced by various physician/patient/system factors.

Selection Bias: None? 4332 excluded, 696 declined/unable to participate for various reasons; demographically different from those included?

Measurement Bias: None.

Analysis Bias: None; ITT and per protocol analyses showed similar results (7% of intervention arm children did not receiv all 3 nebs).

Confounding: Higher doses of nebulized albuterol after initial MDI Rx may have improved with high-efficiency delivery of albuterol to airways, which may have masked any benefits of neb magnesium?

Administrative Details

Key Words: Asthma, nebulized magnesium, pediatric emergency department.

Appraisers: Upadhye S.

Reference(s): Schuh S, Sweeney R, Rumantir M, Coates AL, Willan AR, Stephens D, Atenafu EG, Finkelstein Y, Thompson G, Zemek R, Plint AC, Gravel J, Ducharme FM, Johnson DW, Black K, Curtis S, Beer D, Klassen TP, Nicksy D, Freedman SB, for the Pediatric Emergency Research Canada (PERC) Network. JAMA 2020;324(20):2038-2047. doi:10.1001/jama.2020.19839

Research Question

What are the latest guidelines for the management of neonatal resuscitation?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Early effective respiratory/cardiac support is essential to reduce neonatal mortality, as 10% of neonates need respiratory support at birth, and 1% require intensive resuscitative measures to restore cardiopulmonary function at birth.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Minimal. Lack of patient/parent/public engagement is problematic to maintain focus on patient-relevant outcomes (PRO's). Use of multiple strata of recommendation classes (1-2a-2b-3Mod-3Harm)/levels of evidence (A-BR-BNR-CLD-CEO may leave readers confused, as opposed to a more intuitive framework (eg. GRADE).

How should this guideline, and specifically which recommendations should impact the care of ED patients? Enter text here. Notes:

Suneel Upadhye, MD MSc FRCPC. Assoc Prof, EM/HEI, McMaster University
Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: See Ref below
Design: CPG
Population: Neonates (up to 28days)
Scope: See below

Key Results:

Recommendation	*LoE*
Neonates >36weeks GA with evolving moderate/severe hypoxic-ischemic encephelopathy should be offered therapeutic hypothermia under clearly defined protocols.	A
Every birth should be attended by at least 1 person who can provide initial NR and initiate PPV, whose sole responsibility is care of the newborn.	B-NR
Before each birth a standardized risk factors assessment tool should be used, and a qualified team assembled based on risk stratification.	B-NR
In neonates with apnea>60sec or persistent bradycardia <100bpm despite initial stimulation, PPV should be initiated ASAP (40-60 breaths/minute, insufflation <1sec, avoid sustained/peak pressures).	B-NR, B-R
Avoid 100% oxygen in neonates >35weeks GA with PPV (CoR 3). Limit oxygen to 21-30%.	B-R
Neonatal temperature should be routine recorded, and hypothermia <36C should be prevented.	B-NR
All standardized equipment should be available (checklist) to ensure all necessary supplies are ready for complete resuscitation. Consider a preresuscitation team briefing to prepare.	C-LD
Glucose levels should be monitored ASAP after advanced resuscitation, and treated as indicated.	C-LD
If NR fails after 20min, cessation of efforts should be discussed with team/family.	C-LD
Individual/team training should be reinforced <2yrs to ensure knowledge/skills retention.	C-LD
During CPR, HR assessment should be done with an ECG.	C-EO
For neonates requiring vascular access, the umbilical vein is the recommended route (or IO if unavailable).	C-EO
Neonates receiving prolonged PPV/advanced resuscitation should be transferred/maintained in appropriate monitoring environment.	C-EO
Non-initiation of, or discontinuation of failed NR should be considered ethically equivalent.	C-EO

Only Class 1 or 3 (Strong) recommendations summarized here. See publication for Level 2a/2b/3 Mod recommendations

Class of Recommendation (CoR)	*Level of Supporting Evidence (LoE)*
1 (Strong): Benefits >>> Risk. "Recommended, indicated, useful, effective, beneficial." 2a (Moderate): Benefits >> Risk. "Reasonable, can be useful/ effective/beneficial." 2b (Weak): Benefit ≥ Risk. "May/might be reasonable, considered. Unknown/unclear/uncertain usefulness or effectiveness 3 No Benefit (Moderate): Benefit = Risk. "Not recommended/indicated/ useful/effective/beneficial. Should not be performed/administered." 3 Harm (Strong): Risk > Benefit. "Potential/actual harm, excessive morbidity/mortality, should not be performed/ administered."	Level A = High quality evidence from >1 RCT, meta-analyses of high quality RCTs, corroborating registry studies Level B-R (Randomized) = Moderate quality evidence from 1+ RCTs, SR/MA of moderate quality RCTs Level B-NR (Nonrandomized) = Mod quality evidence from 1+ nonrandomized/observational studies, or registries Level C-LD (Limited Data) = non/randomized (or registry) studies with design/execution limitations, or SR/MA of same. Physiologic/mechanistic studies of human subjects. Level C-EO (Expert Opinion) = Consensus of expert opinion based on clinical experience.

Scope: "This guideline is designed for North American healthcare providers who are looking for an up-to-date summary for clinical care, as well as for those who are seeking more in-depth information on resuscitation science and gaps in current knowledge."

NB. Cannot exceed 1 page.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The guideline development group includes all of the relevant stakeholders, including patients.	✓
2.	Systematic methods were used to search for evidence.	✓
3.	The criteria for selecting the evidence are clearly described.	✓
4.	The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓
5.	The health benefits, side effects, and risks were considered in formulating the recommendations.	✓
6.	There is an explicit approach linking the evidence to formulate the recommendations.	✓
7.	Experts externally reviewed the guideline prior to its publication.	✓
8.	The content of the guideline is free of influence by the views of the funding body.	✓
9.	Competing interests of guideline development group members have been recorded and managed.	✓
10.	The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None reported. All volunteers with no conflicts of interest.

Conflicts of Interest: None (reported in Appendices 1&2).

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **No patient/parent stakeholders involvement reported. Linkage of evidence base with strength of recommendations is explicit.**

Presentation: Well organized with easy to find recommendations? **Yes; key recommendations summarized at top of article (Top Ten list). Coloured recommendation boxes scattered throughout manuscript.**

Comprehensive: Was the information to inform decision-making complete? **Yes. Clinical pathways/algorithms included in body of text.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes.**

Administrative Details

Key Words: Guidelines, neonatal cardiopulmonary resuscitation.

Appraisers: Upadhye S.

Reference(s): Aziz K, Lee HC, Escobedo MB, Hoover AV, Kamath-Rayne BD, Kapadia VS, Magid DJ, Niermeyer S, Schmolzer GM, Szyld E, Weiner GM, Wyckoff MH, Yamada NK, Zaichkin J. Part 5: Neonatal Resuscitation 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2021 Jan;147(Suppl 1):e2020038505E. doi: 10.1542/peds.2020-038505E.

Research Question

What are the latest guidelines for the management of pediatric cardiac arrest?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? These guidelines update prior recommendations on the management of pediatric cardiac arrest, in order to optimize survival to hospital discharge with meaningful neurologic recovery.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Minimal. Lack of patient/parent/public engagement is problematic to maintain focus on patient-relevant outcomes (PRO's). Use of multiple strata of recommendation classes (1-2a-2b-3Mod-3Harm)/levels of evidence (A-BR-BNR-CLD-CEO may leave readers confused, as opposed to a more intuitive framework (eg. GRADE).

How should this guideline, and specifically which recommendations should impact the care of ED patients? Enter text here. Notes:

Suneel Upadhye, MD MSc FRCPC. Assoc Prof, EM/HEI, McMaster University
Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: Topjian AA, Raymond TT, Atkins D, *et al*, on behalf of the Pediatric Basic and Advanced Life Support Collaborators. Part 4: pediatric basic and advanced life support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2021 Jan;147(Suppl 1):e2020038505D. doi: 10.1542/peds.2020-038505D.

Design: Clinical Practice Guideline.

Population: Infants/children in pre/intra/post-arrest states. Excludes neonates up to 28days.

Scope: This guideline is intended to be a resource for lay rescuers and healthcare providers to identify and treat infants and children in the pre-arrest, intra-arrest, and post-arrest states.

Key Results: Enter text here, separated by semicolons and a period at the end.

Recommendation	*LoE*
Provide continuous core temp measurement during TTM post-arrest	A
Initiate bystander chest compressions (+/- rescue breaths) in out-of-hospital arrest.	B-NR
Avoid sodium bicarb, unless known hyperkalemia/Na channel blocker OD (eg TCA). **CoR 3 Harm**	B-NR
Avoid calcium administration (routine) unless known hypocalcemia/CCB OD/hypermagnesemia or hyperkalemia. **CoR 3 Harm**	B-NR
Provide family members the option of being present during resuscitation, and designate a team member to provide answers, comfort and support.	B-NR
Use inhaled nitric oxide/prostacyclin for initial Rx of pulmonary HTN crises/acute right heart failure d/t increased pulmonary vascular resistance. Provide ongoing respiratory monitoring/care.	B-R
Lay rescuers should start CPR in unresponsive/nonbreathing/VSA children (no pulse check).	C-LD
Use 2 finger sternum (single)/2 thumb encircling hands (2 rescuers) for infants.	C-LD
Activate "CPR mode" to stiffen mattress bed during in-hospital arrest.	C-LD
Use a head-tilt/chin-lift maneuver to open airway (unless suspected C spine injury; use jaw thrust)	C-LD
Use a pediatric attenuator for AED on infants/child <8yo.	C-LD
Use parenteral fluids/vasopressors to maintain sBP >5th percentile for age after ROSC.	C-LD
Use continuous EEG monitoring for seizure detection in post-arrest persistent encephalopathy (if resources available). Trat clinical seizures post arrest.	C-LD
If family presence is detrimental during resuscitation, ask respectfully to leave the room.	C-LD
Reassess patient after each fluid bolus for response/signs of volume overload.	C-LD
In severe foreign body airway obstruction, perform abdominal thrusts/5 back-blow cycles repeatedly until object expelled or victim goes unresponsive; once unresponsive, start CPR and clear visible obstructions when opening airway. Do not perform blind finger sweeps.	C-LD
Provide rescue breathing/BVM support until spont breathing restored in opioid-related arrest, and use standard BLS/ALS protocols prior to naloxone administration (C-EO).	C-LD
Discontinue cricoid pressure during intubation if it interferes with ventilation/intubation (**Cor 3 Harm).** For intubated children with perfusing rhythm, use colorimeter/capnography to confirm ETT placement.	C-LD
For bradycardia <60bpm with CV compromise & effective ventilation/oxygenation, start CPR. If due to primary AV block or increased vagal tone, give atropine.	C-LD

Give IV/IO adenosine for SVT treatment. If refractory SVT to adenosine/vagal maneuvers, seek expert consultation (C-EO).	C-LD
For stable wide-complex tachycardia, seek expert advice prior to administering antiarrhythmic meds.	C-LD
Consider ICU transfer for children with acute myocarditis showing arrhythmias, ST changes or low cardiac output.	C-LD
With each chest compression, allow chest to recoil completely.	C-EO
Use child weight-based dosing for resuscitation drug dosing (not exceed adult doses).	C-EO
Use a manual defibrillator for shockable rhythms in infants under trained HCP care. Use largest paddles/self-adhering electrodes on child's chest while maintaining good separation. Continue CPR between shocks (minimize interruption of chest compressions).	C-EO
Use continuous arterial pressure monitoring (if resources available) to identify/treat hypotension.	C-EO
For non-survivors of unexpected arrest, provide access to pathologist/autopsy and preserve biological materials for genetic analysis/inherited cardiac disease testing.	C-EO
For survivors of unexpected cardiac arrest, get a new ECG/compare to prior ECG's, and get a complete personal/family history of syncopal events/arrhythmias/other cardiac disease.	C-EO
For patients with cardiogenic shock, get early expert consultation.	C-EO
Provide rescue breathing for patients with a pulse but inadequate/absent respiratory efforts.	C-EO
Pay attention to cuffed ETT size, position & inflation pressure.	C-EO
Give epinephrine IV/IO/ETT if persistent bradycardia (after correcting hypoxia)	C-EO
Provide analgesia/sedation/neuromuscular blockade for children at high risk of pulmonary HTN crisis.	C-EO
In traumatic arrest, evaluate/treat correctible causes (eg. bleeding, tamponade, tension PTX).	C-EO

*****Only Class 1 or 3 (Strong) recommedations summarized here. See publication for CoR 2a/2b/3 Mod recommendations***

Class of Recommendation (CoR)	***Level of Supporting Evidence (LoE)***
1 (Strong): Benefits >>> Risk. "Recommended, indicated, useful, effective, beneficial."	Level A = High quality evidence from >1 RCT, meta-analyses of high quality RCTs, corroborating registry studies
2a (Moderate): Benefits >> Risk. "Reasonable, can be useful/ effective/beneficial."	Level B-R (Randomized) = Moderate quality evidence from 1+ RCTs, SR/MA of moderate quality RCTs
2b (Weak): Benefit ≥ Risk. "May/might be reasonable, considered. Unknown/unclear/uncertain usefulness or effectiveness	Level B-NR (Nonrandomized) = Mod quality evidence from 1+ nonrandomized/observational studies, or registries
3 No Benefit (Moderate): Benefit = Risk. "Not recommended/indicated/ useful/effective/beneficial. Should not be performed/administered."	Level C-LD (Limited Data) = non/randomized (or registry) studies with design/execution limitations, or SR/MA of same. Physiologic/mechanistic studies of human subjects.
3 Harm (Strong): Risk > Benefit. "Potential/actual harm, excessive morbidity/mortality, should not be performed/ administered."	Level C-EO (Expert Opinion) = Consensus of expert opinion based on clinical experience.

BEEM Critique

Risk of Bias Assessment

	A1
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓
2. Systematic methods were used to search for evidence.	✓
3. The criteria for selecting the evidence are clearly described.	✓
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓
7. Experts externally reviewed the guideline prior to its publication.	✓
8. The content of the guideline is free of influence by the views of the funding body.	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None reported. All volunteers with no conflicts of interest.

Conflicts of Interest: None (reported in Appendix 1 & 2).

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **No patient/parent stakeholders involvement reported. Linkage of evidence base with strength of recommendations is explicit.**

Presentation: Well organized with easy to find recommendations? **Yes; key recommendations summarized at top of article (Top Ten list). Coloured recommendation boxes scattered throughout manuscript.**

Comprehensive: Was the information to inform decision-making complete? **Yes. Clinical pathways/algorithms included in body of text.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes**

Administrative Details

Key Words: Guidelines, advanced/basic life support, pediatric resuscitation.

Appraisers: Upadhye S.

Reference(s): Topjian AA, Raymond TT, Atkins D, Chan M, Duff JP, Joyner BL Jr, Lasa JJ, Lavonas EJ, Levy A, Mahgoub M, Meckler GD, Roberts KE, Sutton RM, Schexnayder SM; on behalf of the Pediatric Basic and Advanced Life Support Collaborators. Part 4: pediatric basic and advanced life support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2021 Jan;147(Suppl 1):e2020038505D. doi: 10.1542/peds.2020-038505D.

Research Question

What is the utility of sodium bicarbonate in pediatric in-hospital cardiac arrest?

BEEM Bottom Line

Why is this study important? Sodium bicarbonate (SB) is commonly used in pediatric cardiac arrest as a buffer Rx for presumed metabolic acidosis/deleterious effects with prolonged arrest times, although the evidence for such practice is unclear.

Which, if any, threats to validity are most likely to have an impact on the results and how? A limited number of included observational studies, with evidence of publication bias and other unreported confounders, limit the strength/generalizability of findings.

How do the key results compare with the current evidence? These results reinforce recommendations NOT to use routine SB in pediatric cardiac arrest situations.

How should this study impact the care of ED patients? Use of sodium bicarbonate in pediatric cardiac arrest is NOT routinely recommended. There was insufficient information to guide practice in specific subgroups of interest (eg. hyperkalemia, TCA overdose, metabolic acidosis).

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Chang CY, Wu PH, Hsiao CT, *et al*. Sodium bicarbonate administration during in-hospital pediatric cardiac arrest: A systematic review and meta-analysis. Resusc 2021; 162: 188-197. https://doi.org/10.1016/j.resuscitation.2021.02.035

Design: Systematic review and meta-analysis of observational trials.

Population: *Included:* Patients <18yo with in-hospital cardiac arrest, given IV sodium bicarbonate (SB) during arrest. *Excluded*: Adults >18yo, out-of-hospital cardiac arrest (OHCA), respiratory arrest with pulse, special populations (congenital heart disease, inherited metabolic disorders). Also excluded case reports/series, unpublished reports, and animal studies.

Intervention: Sodium bicarbonate (SB) IV infusion.

Comparison: Usual PALS-driven care.

Outcomes: *Primary:* Rate of survival to hospital discharge.
Secondary: Survival at 24hrs, and neurologic outcomes (measured by Pediatric Cerebral Performance Scale). PCPS score of 1-3 at discharge was considered a "good" neuro outcome.

Key Results: *7 studies, 4877 pts included. 3168 pts received SB (65.6%).*

Sig.	*Outcome*	*N/Studies*	*Outcome Measure (95% CI)*	*I^2*
NSS	Secondary (24hr survival, neuro outcomes)	1	**Insufficient data to meta-analyze outcomes	N/A
SS	Primary: survival to hospital discharge	7	OR 0.40 (0.25-0.63) **AGAINST SB** infusion; no difference in studies before/after 2010	73%

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The research question is sensible and answerable.	✓
2.	The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	?
3.	The search for studies was unbiased and reproducible.	?
4.	The selection of studies was unbiased and reproducible.	?
5.	The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6.	The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7.	The quality of the primary studies is high.	✓
8.	The methods used to combine the included primary studies were reported and valid.	✓
9.	The outcomes are clinically relevant.	✓
10.	The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None? Limited number of included studies for primary outcomes, only 1 study for secondary; overall did not meet Optimal Information Size (OIS).

Selection Bias: Limited electronic databases search (Pubmed, EMBASE, Cochrane Trials Registry), and bibliographies/reference lists of retrieved articles. No gray literature searches. No language or study design restrictions. Screening/selection of articles not clearly described. Publication bias analysis in Supp material; some evidence of plot asymmetry with smaller studies.

Measurement Bias: Use of Newcastle-Ottawa scale to appraise observational studies; 1 moderate, 6 high quality studies included. Overall GRADE certainty of evidence was low/very low.

Analysis Bias: Use of random effects analyses for high heterogeneity studies was appropriate. Insufficient studies for prespecified subgroup analyses (hyperkalemia, metabolic acidosis, TCA overdose).

Confounding: No randomized studies, so use of SB was at clinician discretion which may have led to biased interventions. Pre-existing medical conditions preceding cardiac arrest are not described in included studies, which may also lead to different eventual outcomes. Similarly, intra- and post-arrest management was not necessarily standardized within/between studies, so these variables also have potential impact on review outcomes.

Administrative Details

Key Words: Sodium bicarbonate, cardiac arrest, pediatric, systematic review/meta-analyses.

Appraisers: Upadhye S.

Reference(s): Chang CY, Wu PH, Hsiao CT, Chang CP, Chen YC, Wu KH. Sodium bicarbonate administration during in-hospital pediatric cardiac arrest: A systematic review and meta-analysis. Resusc 2021; 162: 188-197. https://doi.org/10.1016/j.resuscitation.2021.02.035

Research Question

What is the optimal management of stable/non-critical pediatric intussusception?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? This review updates evidence/recommendations on antibiotics stewardship, imaging, ED discharge advice and non-surgical management for stable non-critical pediatric intussusception.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? This "systematic review" actually meets some of the standards of a clinical practice guideline (CPG). Various key elements on the evidence review and transformation into CPG recommendations are missing.

How should this guideline, and specifically which recommendations should impact the care of ED patients? ED physicians can avoid prophylactic antibiotics in children with intussusception, and if observed in ED after successful enema reduction, can be sent home after 4hrs of observation/successful trial of oral intake.

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Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
Curator, EmergencyGuidelines.ca website (nonprofit)

Study Summary

Article: Kelley-Quon LI, Arthur LG, Williams RF, *et al*. Management of intussusception in children: A systematic review. J Peds Surg 2021; 56: 587-596. DOI: 10.1097/PEC.0000000000002224.

Design: Clinical Practice Guideline.

Population: Children with clinical features of intussusception.

Scope: Not specified. Presumably intended for emergency physicians/other clinicians who manage children with acute abdominal pain/potential surgical emergencies.

Key Results: Grade ABCD recommendations, Level of Evidence (LoE) 1-5. ED-relevant recommendations only listed.

Recommendation	*Strength*	*LoE*
None	Grade A	1
None	Grade B	2
Prophyllactic antibiotics are unnecessary prior to enema reduction.	Grade C	3-4
Children with successful enema reduction can be discharged from ED after 4hrs of observation, with appropriate parental education on recurrence symptoms*/RTER criteria.	Grade C	3-4
Have a physician present to handle pneumoperitoneum/CPR at time of enema reduction.	Grade D	5
An interval of 30min-4hrs may be reasonable/safe for delayed repeated enemas (needs further study).	Grade D	5

*Children >2yo may have a slightly higher recurrence risk compared to children <2yo.

Explanations for GRADE ABCD/Level of Evidence 1-5 strata not provided in manuscript.

BEEM Critique

Risk of Bias Assessment

	A1
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓
2. Systematic methods were used to search for evidence.	X
3. The criteria for selecting the evidence are clearly described.	X
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	X
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	?
6. There is an explicit approach linking the evidence to formulate the recommendations.	?
7. Experts externally reviewed the guideline prior to its publication.	X
8. The content of the guideline is free of influence by the views of the funding body.	✓
9. Competing interests of guideline development group members have been recorded and managed.	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Author LIK supported by NIH NCATS grant.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Development: **Limited evidence search (electronic databases only), no gray literature/article reference lists/abstracts; excluded non-English studies, animal studies, case reports, and protocol papers. Stated use of Oxford Centre for EBM Levels of Evidence for included study review. No details on quality assessment of included trials? Unclear how evidence review was linked to formulated recommendations.**

Presentation: Well organized with easy to find recommendations? **No.**

Comprehensive: Was the information to inform decision-making complete? **Somewhat limited ED-relevant recommendations?**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes.**

Administrative Details

Key Words: Antibiotics, enema, intussusception, outpatient.

Appraisers: Upadhye S.

Reference(s):

1. Kelley-Quon LI, Arthur LG, Williams RF, Goldin AB, St. Peter SD, Beres AL, Hu YY, Renaud EJ, Ricca R, Slidell MB, Taylor A, Smith CA, Miniati D, Sola JE, Valusek P, Berman L, Raval MV, Gosain A, Dellinger MB, Somme S, Downard CD, McAteer JP, Kawaguchi A. Management of intussusception in children: A systematic review. J Peds Surg 2021; 56: 587-596. DOI: 10.1097/PEC.0000000000002224.
2. Hom J, Kaplan C, Fowler S, Messina C, Chandran L, Kunkov S. Evidence-Based Diagnostic Test Accuracy of History, Physical Examination, and Imaging for Intussusception. A Systematic Review and Meta-analysis. Ped Emerg Care 2020; DOI: 10.1097/PEC.0000000000002224. PMID: 32941364

Research Question

What is the safety profile of ceftriaxone in pediatric patients, as determined by the frequency and type of adverse drug reactions documented in the published literature?

BEEM Bottom Line

Why is this study important? As a third-generation cephalosporin, ceftriaxone is a broad-spectrum antibiotic that is used for a wide range of indications in the pediatric emergency department. However, despite its common use, the frequency and severity of associated adverse drug reactions (ADRs) has not been widely studied in pediatric patients.

Which, if any, threats to validity are most likely to have an impact on the results and how? There was no subgroup analysis by age, drug dosage, or duration, which limits extrapolation of results. Risk difference was inappropriately calculated from studies of different designs. Given that the included studies were not primarily intended to identify ADRs and the flawed assumptions regarding zero events, the reported risk of ADR is likely underestimated.

How do the key results compare with the current evidence? The Surviving Sepsis campaign recommends third generation cephalosporins for septic children because, compared to other generations, they have the widest spectrum of activity including against gram-negative organisms.[1] The report on Evidence-Based Management of Sickle Cell Disease recommends empiric parental antibiotics with gram positive and negative coverage for febrile patients.[2]

How should this study impact the care of ED patients? Gastrointestinal (GI) disorders (37.4%) and hepatobiliary disorders (24.6%) are frequent ADRs. Physicians should be aware of possible severe hemolytic anemia, particularly in patients with Sickle Cell Disease.

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No conflicts of interest (ICMJE)

Study Summary

Article: Zeng L, Wang C, Jiang M, et al. Safety of ceftriaxone in paediatrics: a systematic review. Arch Dis Child. 2020 Oct;105(10):981-985.

Design: Systematic review and meta-analysis of randomized controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case series and case reports.

Population: *Included:* Children (≥ 1 month and ≤ 18 years) who received ceftriaxone intravenously (IV).
Excluded: None described.

Intervention: Ceftriaxone IV (any dosage and duration).

Comparison: Placebo and or other antibiotics.

Outcomes: *Primary:* ADRs.
Secondary: ADRs requiring specific investigations.

Key Results: *N* = 5,717 patients in 112 studies.

ADR (n = 4,928)	*Events*	*PI ADR/100*	*ADR from Specific Investigations*	*Event Rate*	*PI ADR/100*
Diarrhea	150	3.0	Thrombocytosis	19/61	31.2
Nausea & Vomiting	84	1.7	Biliary pseudolithiasis	89/430	20.7
Fever	85	1.7	Cholelithiasis	62/329	18.8
Pain @ IV site	74	1.5	Biliary Sludge	32/441	7.1
Rash	57	1.2			

PI ADR/100 = pooled incidence of ADRs per 100 patients.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?	?	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	?	?	?
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	X	X	X
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: Key Program of Science and Technology Agency, Sichuan Province (No. 2017JY0067).

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: As this review is examining the impact of ceftriaxone on adverse drug reaction the number of events is low resulting in underpowered analyses and imprecise results.

Selection Bias: While the authors conducted a fairly comprehensive search of published literature, grey literature is absent from the review. Additionally, while spontaneous ADR reporting databases were searched, they were ultimately not included due to reporting issues identified by the authors. It is unclear how much unpublished data or data from these databases would be relevant to this review, however their exclusion places the study at a risk of publication bias. Finally, since the search was completed in 2018, it is possible that new evidence is available to inform this research question.

Measurement Bias: The published protocol provided additional details on review's methodology; however, it was not reported if data extraction or risk of bias were completed in duplicate, therefore increasing the risk of measurement bias. Within the individual studies, there is a high risk of measurement bias: The ADR diagnostic criteria and timing of assessment with respect to ceftriaxone administration are unclear; ADRs diagnosed via specific investigations (e.g., biliary) were more likely to be conducted in patients known to be receiving ceftriaxone and or at higher risk (detection bias).

Analysis Bias: Risk cannot be accurately calculated from combined studies of different designs. No subgroup analysis of different age groups, despite a relatively wide age range of participants. The authors assumed zero events in studies that measured ADRs but did not report any events; these studies may be subject to selective reporting bias and therefore may bias the results to underestimated risk of ADR.

Confounding: Presumably the adverse events are most likely to occur with higher dosages and durations and in this review, daily ceftriaxone dosage and duration was variable ranging from 30 to 120 mg/kg/day and 2 to 50 days respectively.

Administrative Details

Key Words: Adverse drug reactions; antibiotics; ceftriaxone; cephalosporin.

Appraisers: Bedard C; Worster A; Bechard M.

Reference(s):

1. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pedatr Crit Care Med. 2020;21(2):e52-e106.
2. US Department of Health and Human Services. Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014. National Institutes of Health. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf

Research Question

Is repeated antibiotic exposure associated with an increased body mass index by 4.5 years old?

BEEM Bottom Line

Why is this study important? The increase in obesity in children and young people is considered a public health crisis.[1] This national study adds to the published evidence that the gut microbiome is associated with the development of disease risks including childhood obesity.

Which, if any, threats to validity are most likely to have an impact on the results and how? Those children excluded because of missing data were more likely to be obese thereby possibly underestimating the true measure of association. This association is confounded by the increased infection risk in the New Zealand (NZ) population with a high incidence of socio-economic deprivation particularly in those of Maori and Pacific Island heritage. The number of antibiotics dispensed is a surrogate for actual antibiotic exposure/consumption. Finally, the observational nature of the study gives rise to potential confounding of the results and precludes assertions of causality.

How do the key results compare with the current evidence? The findings of this study are consistent with multiple population based studies linking pre-natal and early childhood antibiotic exposure to the development of childhood obesity.[2-4] However, association is not necessarily causation and it is not clear if the association is mediated by a direct effect on gut microbiome.

How should this study impact the care of ED patients? Balancing the significant risk of failure to treat invasive bacterial infections in at-risk subpopulations versus the unnecessary use of antibiotics for infections not requiring treatment remains a clinical dilemma. Clinicians should follow local clinical practice guidelines and antibiotic stewardship programs when treating young children with infections particularly when the likely aetiology is not bacterial.

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No conflicts of interest (ICMJE)

Study Summary

Article: Chelimo C, Camargo CA Jr, Morton SMB, et al. Association of Repeated Antibiotic Exposure Up to Age 4 Years With Body Mass at Age 4.5 Years. JAMA Netw Open. 2020 Jan 3;3(1):e1917577.

Design: National, prospective, cohort (Growing Up in NZ) study.

Population: *Included:* NZ children born during 2009 to 2010 from singleton pregnancies who had documented prescription data and 54-month weight and height measurements.
Excluded: gestational age < 28 weeks or missing documentation; birth weight missing; or congenital anomalies.

Exposure: Dispensed penicillin, macrolide, cephalosporin, and or co-trimoxazole between birth and age 48 months.

Comparison: No antibiotic dispensed between birth and age 48 months.

Outcomes: *Primary:* World Health Organization (WHO) body mass index (BMI)-for-age standardized (i.e. z) scores and International Obesity Task Force (IOTF) overweight (BMI ≥ 25 and <30) and obesity (BMI ≥ 30).
Secondary: Not applicable.

Key Results: *N* = 5128 (2622 [51%] male)

Sig.	*Category*	*Unexposed (n = 242)*	*Exposed (n = 4886)*	*P-value*
	≤ Normal Weight	192 (5%)	3448 (95%)	
SS	Overweight	41 (4%)	1010 (96%)	0.004
	Obese	< 10 (2%)	428 (98%)	
SS	Mean (SD) BMI Z score	0.65 (1.02)	0.95 (1.20)	< 0.001

N = number of patients; n= sample size; *P* = probability; SD = standard deviation; Sig. = significance; SS = statistically significant. P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were selected consecutively or randomly (i.e., without bias).	X	X	X
2. The patients were representative of those with the problem.	✓	✓	✓
3. The patients were sufficiently homogeneous with respect to prognostic risk.	✓	✓	✓
4. The outcome criteria were clinically appropriate for the research question.	✓	✓	✓
5. The outcome criteria were explicit.	✓	✓	✓
6. The outcome criteria were applied without bias.	✓	✓	✓
7. The follow-up was complete.	X	X	X
8. The effect size of the primary outcome is clinically significant.	?	?	?

A = appraiser.

Funding & Conflicts of Interest

Funding: New Zealand government and Health Research Council, University of Auckland, and Auckland UniServices Limited.

Conflicts of Interest: None reported.

Potential Threats to Validity

Chance: The study appears to have sufficient power and the models are hypothesis-driven, therefore, reducing the risk of type I error for the effect of antibiotic dispensing. However, some associations between perinatal, social and environmental factors and BMI may be spurious due to the large sample size.

Selection Bias: Children without complete data or consent for prescription data linkage were disproportionally of NZ subpopulations with higher obesity prevalence rates and from families with socioeconomic deprivation; this might have underestimated the association between antibiotic exposure and body mass.

Measurement Bias: BMI was measured validly and reliably with low risk of bias or measurement error. However, all confounding variables were self-reported (i.e. child screen time, household income, pregnancy weight and height, and diet), which are subject to social-desirability bias and are often incompletely reported. Measurement of antibiotic dispensing did not include in-hospital prescriptions and furthermore was a proxy to actual antibiotic consumption.

Analysis Bias: The models appeared to have been generated without bias; however, variance estimates were not adjusted. Therefore, precision is overestimated due to a high sampling rate. Additionally, given that sampling took place within 3 District Health Boards[1], it is unclear if the data is subject to clustering effects (no adjustments were made in the analyses).

Confounding: Maternal diabetes during or before pregnancy was associated with children's body mass (unknown if also related to antibiotic exposure) but was not included in the adjusted model. Physical activity levels of both the mother and child were not measured/adjusted for in the model. There is residual confounding as with all observational studies because of unknown prognostic factors that cannot be controlled.

Administrative Details

Key Words: Antibiotic; body mass index (BMI); child; obesity.

Appraisers: Bedard C; Worster A; Borland M.

Reference(s):

1. Lobstein T, Baur L, Uauy R; IASO International Obesity TaskForce. Obesity in children and young people: a crisis in public health. Obes Rev. 2004 May;5 Suppl 1:4-104.
2. Morton SMB, Atatoa Carr PE, Grant CC, et al. Cohort Profile: Growing Up in New Zealand. Int J Epidemiol. 2013 Feb 1;42(1):65–75.
3. Li DK, Ferber J, Odouli R. Infection and antibiotic use in infancy an drisk of childhood obesity: a longitudinal birth cohort study. Lancet Diabetes Endocrinol. 2017 Jan;5:18-25.
4. Rasmussen SH, Shrestha S, Bjerregaard LG et al. Antibiotic exposure in early life and childhood overweight and obestiy: a systemic review and meta-analysis. Diabetes Obes Metab. 2018;20:1508-1514.

Research Question

Which antibiotics commonly prescribed for acute otitis media are associated most with adverse events?

BEEM Bottom Line

Why is this study important? Acute otitis media (AOM) is extremely common, with ¾ of children experiencing this diagnosis before beginning school. As antibiotics remain the most common treatment, along with analgesia, reviews reporting on adverse events (AEs) related to effective interventions needed to inform family-centred decision-making.

Which, if any, threats to validity are most likely to have an impact on the results and how? The review was not registered nor was the protocol published at inception. The methodology is poorly reported. For most of the results, the heterogeneity is exceedingly high; hence, the pooled prevalence is likely distorted.

How do the key results compare with the current evidence? The Canadian Pediatric Society recommends a 5-day course of amoxicillin (high or low dose) for children ≥ 2 years with uncomplicated otitis media, a duration of treatment that was excluded from this review.[1] As such, this review does not directly inform the management of cases where we use shorter duration of penicillins.[2] An all-ages study of amoxicillin/clavulanate-associated harms demonstrated an overall number needed to harm of 10 for diarrhea; amoxicillin alone was not associated with this risk. Mean duration of treatment in this study was 7 days.[3]

How should this study impact the care of emergency department (ED) patients? Of the four antibiotics included in this review, high dose amoxicillin (≥ 80 mg/kg/day and amoxicillin/clavulanate ≥ 7 days have the highest association with the most common adverse effects of rash and diarrhea. Physicians' choice of antibiotic should be made considering the child's baseline health (e.g. pre-existing chronic gastrointestinal issues) and include counseling regarding the frequency of common adverse events and possible prevention therapy (e.g. probiotics).[4,5]

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No conflicts of interest (ICMJE)

Study Summary

Article: Hum SW, Shaikh KJ, Musa SS, et al. Adverse Events of Antibiotics Used to Treat Acute Otitis Media in Children: A Systematic Meta-Analysis. J Pediatr. 2019 Dec;215:139-143.e7.

Design: Systematic review and meta-analysis of randomized controlled trials, cross-sectional and cohort studies.

Population: *Included:* Children (≥ 0 and ≤ 19 years) prescribed antibiotics for uncomplicated AOM.
Excluded: No descriptors provided.

Intervention: Amoxicillin, amoxicillin/clavulanate (90/6.4 mg/kg/day), cefdinir all for ≥ 7 days and azithromycin ≥ 5 days.

Comparison: Placebo in 9 studies and antibiotic in the remainder.

Outcomes: *Primary:* Common adverse events (AEs) including diarrhea, generalized rash, diaper rash, or candida diaper dermatitis.

Key Results: *N* = 19,634 patients 82 studies.

Antibiotic	*Adverse Event*	*n/Studies*	*Pooled Prevalence % (95% CI)*	I^2
Amoxicillin/clavulanate	Diarrhea	3519/14	18.9 (14.7 to 23.1)	91.0%
Amoxicillin HD	Diarrhea	179/2	13.8 (4.7 to 22.9)	57.3%
Cefdinir	Diarrhea	1388/7	13.0 (11.2 to 14.7)	00.0%
Placebo	Diarrhea	1022/9	6.9 (2.8 to 12.4)	88.0%
Amoxicillin HD	Generalized Rash	231/2	6.5 (0.0 to 15.3)	81.8%
Amoxicillin/clavulanate	Generalized Rash	1631/7	4.9 (2.4 to 7.4)	87.2%
Placebo	Generalized Rash	782/6	2.3 (0.3 to 5.5)	79.4%
Amoxicillin/clavulanate	Diaper Rash	2673/8	14.8 (8.7 to 20.9)	97.2%
Cefdinir	Diaper Rash	159/1	10.1 (5.4 to 14.7)	N/A
Placebo	Diaper Rash	305/2	4.6 (2.4 to 7.3)	N/A

CI = confidence interval; HD = high-dose (amoxicillin ≥80 mg/kg/day); I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X	X
3. The search for studies was unbiased and reproducible.	X	X	X
4. The selection of studies was unbiased and reproducible.	X	X	X
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	X	X	X
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	X	X	X
9. The outcomes are clinically relevant.	X	?	?
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: None reported.

Conflicts of Interest: The authors declare no conflicts of interest.

Potential Threats to Validity

Chance: There is considerable heterogeneity in 76% of the pooled estimates making the review under-powered to detect true estimates of AEs (high chance of type II error).

Selection Bias: The search was confined to English language studies in a single database. The time period of publication was > 50 years yet the number of retrieved articles was not high and more than 81% were then excluded raising concerns about the search strategy used.

Measurement Bias: The included studies did not include measures of antibiotic compliance which undoubtedly impacts on the risk of adverse effects. The review has narrow case definitions for AEs which may have excluded relevant studies. Also, measurement and reporting biases were the most detected among the included studies.

Analysis Bias: Risk is determined from prospective cohort studies; pooling the results of studies of different designs obscures the true risk and so sensitivity analyses based on study designs should have been performed. Due to high heterogeneity, subgroup analysis could have been more insightful (e.g. categorized by study design, methods of ascertainment of AEs). Also, some AEs are better extracted as counts than as dichotomous data (e.g. diarrhea). The denominator for prevalence was determined differently depending on the available data.

Confounding: Although most included studies are randomized, important confounder domains that most likely biased the reported estimates were not investigated in the review: e.g. compliance and drop outs, form of administration, age, sex, differences in study populations and type of health care, etc.

Administrative Details

Key Words: Acute otitis media; adverse events; antibiotics; diarrhea; rash.

Appraisers: Khalifa D; Worster A; Ali S.

Reference(s):

1. Le Saux N, Robinson JL; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Management of acute otitis media in children six months of age and older. Paediatr Child Health. 2016 Jan-Feb;21(1):39-50.
2. Kozyrskyj A, Klassen TP, Moffatt M, et al. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev. 2010;(9):CD001095.
3. Gillies M, Ranakusuma A, Hoffmann T, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015;187(1):E21-E31.
4. Suzuki HG, Dewez JE, Nijman RG, et al. Clinical practice guidelines for acute otitis media in children: a systematic review and appraisal of European national guidelines. BMJ Open. 2020;10(5):e035343.
5. Guo Q, Goldenberg JZ, Humphrey C, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2019;4:CD004827.

Research Question

Does application of the Feverkidstool reduce antibiotic prescritions for children with respiratory infections?

BEEM Bottom Line

Why is this study important? Although most lower respiratory tract infections (RTIs) are caused by viruses, children with RTI symptoms are commonly prescribed antibiotics in the emergency department (ED).[1] The Feverkidstool is a validated clinical decision rule that calculates the risk of serious bacterial infections in children based on the following predictors: age (years); sex; respiratory rate; temperature (°C); heart rate; fever duration (days); C-reactive protein (CRP; mg/l); capillary refill (< 2 seconds [sec]; 2–4 sec; > 4 sec); chest wall retractions; ill appearance; and oxygen (O_2) saturation (< 94%).[2] This trial assessed whether application of this tool in the ED would reduce antibiotic prescribing for children identified as low (< 3%) or intermediate risk (4–10%) of bacterial pneumonia.

Which, if any, threats to validity are most likely to have an impact on the results and how? Given the stepped-wedge design, the results may be confounded by temporal factors. The wide confidence intervals (CIs) indicate an inadequate sample size and the composite outcome is driven by secondary outcomes.

How do the key results compare with the current evidence? Study clinicians followed the Dutch/British Thoracic Society guideline, which unlike the Canadian Pediatric Society, the Pediatric Infectious Disease Society of America (PIDSA) and IDSA do not support chest radiography for inpatients; this is a barrier to employing this strategy in North America.[3,4] The admission rate (50%), O_2 use (72%), and referred into ED (66%) were all higher than seen in North American EDs.

How should this study impact the care of ED patients? The applicability and generalizability of the Feverkidstool in populations with lower admission rates is unclear. Withholding antibiotics in children with intermediate (4–10%) predicted risk of pneumonia may not be acceptable to some practitioners.

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Study Summary

Article: van de Maat JS, Peeters D, Nieboer D, et al. Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in The Netherlands: A stepped-wedge cluster randomised trial. PLoS Med. 2020 Jan 31;17(1):e1003034.

Design: Multicenter (The Netherlands) stepped-wedge cluster, superiority and noninferiority, randomized trial.

Population: *Included:* Children (≥ 1 and ≤ 60 months) with fever (on history or > 38.5°C in ED) and symptoms of potential lower RTI (i.e., cough or dyspnea). Clusters consisted of 8 tertiary and general hospitals with 500–13,000 annual pediatric ED admissions in 6 cities of the southwest and central Netherlands.
Excluded: Children with antibiotic use in previous week; amoxicillin allergy; alternate infection; O_2 saturation < 85%; respiratory insufficiency; empyema; sepsis; immunodeficiency; congenital heart defect; chronic pulmonary disease; multiple handicaps; prematurity.

Intervention: The risk of bacterial pneumonia was calculated using the Feverkidstool and, if low (≤ 3%) or intermediate (4–10%), antibiotics were withheld. If at high risk (> 10%), antibiotics were prescribed at the discretion of the physician as per usual care. Amoxicillin was the first line antibiotic for community acquired pneumonia.

Comparison: Usual care included a clinical assessment and investigations at the discretion of the treating physician and initiation of therapy according to the Dutch and UK guidelines for febrile children.

Outcomes: *Primary:* Antibiotic prescription at ED discharge (superiority) and treatment failure (non-inferiority) (i.e., hospital admission, new antibiotic or complications ≤ 7 days, or fever up to day 7).
Secondary: Compliance with Feverkidstool recommendations; complications (i.e., pleural empyema, parapneumonic effusion, pulmonary abscess, or need for mechanical ventilation by day 7).

Key Results: *N* = 999 patients in 8 clusters.

Sig.	*Outcome*	*Intervention*	*Usual Care*	*aOR (95% CI)*	*NNT (95% CI)*
NSS	Abx prescribed: ITT	101/402	179/597	1.07 (0.57 to 2.01)	N/A
NSS	Abx prescribed: PP	83/359	179/597	0.96 (0.49 to 1.88)	N/A
SS	Treatment failure: ITT	61/381	131/572	0.53 (0.32 to 0.88)	15 (8 to 58)
SS	Treatment failure: PP	57/340	131/572	0.56 (0.34 to 0.93)	16 (9 to 138)
SS	Complications	1/381	1/572	NR	N/A

Abx = antibiotic; aOR = adjusted odds ratio (if the CI includes the value 1, there is no difference in odds between the groups); ITT = intention to treat; *N* = number of patients; N/A = not applicable; NNT = number needed to treat (rounded up to the next whole number); NR = not reported; NSS = not statistically significant; PP = per protocol; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	?
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	?	?	✓
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Netherlands Organisation for Health Research and Development (ZonMW, grant number 836041001) and Innovatiefonds Zorgverzekeraars (B14-205, dosier 2818).

Conflicts of Interest: None.

Potential Threats to Validity

Chance: For the outcome antibiotic prescribed, the CIs suggest that the Feverkidstool may be plausibly associated with either increased or decreased antibiotic prescription. Hence, the results are too imprecise to draw conclusions.

Selection Bias: None detected.

Measurement Bias: The composite outcome of treatment failure is primarily driven by secondary antibiotic prescriptions rather than more the important components of the composite, such as hospitalizations or the need for O_2.

Analysis Bias: The groups might not have been equal as there was a large difference (17 vs. 5%) in prolonged capillary refill between them.

Confounding: The results of this trial are limited by the stepped-wedge design, which is susceptible to confounding by temporal factors.

Administrative Details

Key Words: Antibiotic; bacteria; Feverkidstool; pneumonia; respiratory tract infection (RTI); virus.

Appraisers: Zeraatkar D; Worster A; Lim R.

Reference(s):

1. Tramper-Stranders GA. Childhood community-acquired pneumonia: A review of etiology- and antimicrobial treatment studies. Paediatr Respir Rev. 2018 Mar;26:41–48.
2. Nijman RG, Vergouwe Y, Thompson M, et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ. 2013; 346:f1706.
3. Saux N, Robinson JL. Uncomplicated pneumonia in healthy Canadian children and youth: Practice points for management Le Canadian Pediatric Society Infectious Diseases and Immunization Committee, updated online Oct 31, 2018. https://www.cps.ca/en/documents/position/pneumonia-management-children-youth.
4. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011;53(7):e25–76.

Research Question

Is the time to recovery from influenza-like illness reduced by adding oseltamivir to usual care?

BEEM Bottom Line

Why is this study important? Clinical practice guidelines recommend that patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or, who are at high risk for influenza-associated complications should receive treatment as soon as possible with antiviral medications.[1,2] It can also be considered for symptomatic outpatients with suspected influenza (i.e., influenza-like illness [ILI]), if initiated within 48 hours of symptom onset.[1,2] Oseltamivir has been shown to reduce time to symptom resolution.[3] This trial evaluated the effect of oseltamivir added to usual therapy on patient-reported time to return to usual daily activity.

Which, if any, threats to validity are most likely to have an impact on the results and how? The trial is significantly limited by its open-label design hence, the superiority of oseltamivir may be due to a placebo effect. The findings that patients with a longer duration of illness were more likely to benefit also contradicts the biological notion that the greatest benefit of a reverse transcriptase inhibitor is during the early phase of illness, when viral replication is occurring.[4] Stratification of children < or > age 12 years may have resulted in a loss of power to see benefit or harm in children < 5 years, with highest influenza morbidity.

How do the key results compare with the current evidence? The results are consistent with 2 systematic reviews.[5,6]

How should this study impact the care of ED patients? The utility of this study's findings appears to lie primarily in patients > 65 years of age with more severe illness, comorbidities, and longer duration of illness as the treatment effect in children was minimal.

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Study Summary

Article: Butler CC, van der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. Lancet. 2019 Dec 12. pii: S0140–6736(19)32982-4. doi: 10.1016/S0140-6736(19)32982–4.

Design: Multicenter (15 European countries), open-label, pragmatic, adaptive, superiority, randomized controlled trial.

Population: *Included:* Patients (≥ 1 year old) with ILI (i.e., sudden onset of self-reported fever, with at least one respiratory symptom [cough, sore throat, or running or congested nose] and one systemic symptom [headache, muscle ache, sweats or chills, or tiredness]); ≤ 72 hours during a seasonal influenza epidemic.
Excluded: Patients with chronic renal failure; impaired immunity; requiring immediate antiviral treatment or immediate hospitalization; allergy to oseltamivir; requiring general anesthesia ≤ 2 weeks; life expectancy < 6 months; severe hepatic impairment; requiring live viral vaccine ≤ 7 days; pregnant, lactating, breastfeeding.

Intervention: Oseltamivir (5 days of twice daily, oral dose based on body weight (BW): 75 mg if BW > 40 kg; 60 mg if BW >23 to 40 kg; 45 mg if BW >15 to 23 kg; 30 mg if BW 10–15 kg) plus usual care.

Comparison: Usual care.

Outcomes: *Primary:* Patient-reported time to recovery (i.e., return to usual activities with minor or absent fever, headache, and muscle ache. For non-verbal children, minor or absent clinginess.
Secondary: Hospital admissions, ILI-related complications, repeat MD visits, time to alleviation of symptoms.

Key Results: *N* = 3,266 patients (Oseltamivir = 1,629; Usual Care = 1,637).

Sig.	*Oseltamivir benefit*	*HR (95% CI)*
SS	All Patients (*n* = 3,059)	1.29 (1.20 to 1.39)
SS	Non-influenza patients only (*n* = 1,469)	1.31 (1.18 to 1.46)
SS	Influenza patients only (*n* = 1,590)	1.27 (1.15 to 1.41)
		Difference (95% CI)
NSS	Hospital attendance Week 1–2	0.6% (–0.7 to 2.0)
NSS	Hospital attendance Week 3–4	0.2% (–0.7 to 1.2)

CI = confidence interval; HR = hazard ratio (because this is a ratio, if the value of the range includes 1, there is no difference); *N* = number of patients; n = sample size; NSS = not statistically significant; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	✓	✓	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X	X	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	?	X	?

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: European Commission's Seventh Framework Programme.

Conflicts of Interest: Several of the authors reported receiving research grants, consultancy fees, and honoraria from industry.

Potential Threats to Validity

Chance: None detected.

Selection Bias: The low vaccination rate is based on local guidelines, which are different compared to other regions.

Measurement Bias: The Canadian Acute Respiratory Illness Flu Scale was modified for children < 12 years, possibly rendering ascertainment of the primary outcome in this demographic less valid.

Analysis Bias: Patients were stratified into 3 age groups: < 12, 12–64, and ≥ 65 years. Children < 4 years are at increased risk of hospitalization, and the Center for Disease Control recommends vaccinating children under the age of 2 years. The low number of pediatric patients as well as clumping all children into the first tercile can impact the analysis. In addition, patients > 65 years constituted the smallest proportion of enrollments, calling into question the generalizability of the findings to this demographic as a whole.

Confounding: The trial was open-label and, hence, the observed results may be at least partially or even completely attributed to a placebo effect. There may have been a benefit of other drugs such as respiratory agents in patients with chronic respiratory illness.

Administrative Details

Key Words: Antibiotic (Abx); antiviral; influenza-like illness; oseltamivir.

Appraisers: Zeraatkar D; Worster A; Poonai N.

Reference(s):

1. Xu X, Blanton L, Elal AI, et al. Update: Influenza Activity in the United States During the 2018–19 Season and Composition of the 2019–20 Influenza Vaccine. MMWR Morb Mortal Wkly Rep 2019;68:544–551.
2. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(No. RR–1).
3. National Institute for Health and Care Excellence. Amantadine, oseltamivir and zanamivir for the treatment of influenza: technology appraisal guidance [TA168]. National Institute for Health and Care Excellence, 2009. https://www.nice.org.uk/guidance/ta168.
4. Centres for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. Centres for Disease Control and Prevention, 2018.
5. Dobson J, Whitley RJ, Pocock S, et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 2015; 385: 1729–37.
6. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2014; 4: CD008965.

TRAUMA/CRITICAL CARE (PART I)

Research Question

What is the benefit of using peripheral nerve blocks in ED patients with hip fracture?

BEEM Bottom Line

Why is this study important? Adult hip fracture is a common painful condition encountered in the ED. Having effective and safe alternatives for analgesia is important to optimize patient comfort. Peripheral nerve blockade (PNB) offers an attractive local effective, safe and opioid-sparing alternative to traditional ED parenteral analgesia strategies.

Which, if any, threats to validity are most likely to have an impact on the results and how? Minimal. Use of fixed effects analyses for moderate/high heterogeneity pooled data may over-estimate benefits.

How do the key results compare with the current evidence? This review updates prior Cochrane reviews on the utility of PNB for acute hip fracture analgesia.

How should this study impact the care of ED patients? PNB for hip fracture is a safe and effective alternative for acute analgesia, allowing for less pain with early movement, lower chest infections, less opioid use and reduced confusional states.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Guay J, Kopp S. Peripheral nerve blocks for hip fractures in adults. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD001159. DOI: 10.1002/14651858.CD001159.pub3.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* Adults (≥ 18years) with acute hip fracture.
Excluded: "Quasi" RCTs, cross-over trials. Many included studies excluded dementia patients.

Intervention: Peripheral nerve blockade (PNB) administered pre/intra/post-operatively.

Comparison: Sham injection.

Outcomes: *Primary:* Pain on movement 30min after block placement. Acute confusional states or AMI (0-30days).
Secondary: Chest infections (0-30days), all-cause mortality (0-6mo), time to first mobilization after surgery, costs of analgesic regimens

Key Results: *43 trials included (18 new): 1368 pts received PNB, 1352 sham blocks. Average age: 59-89yrs, avg ASA category 1-4, females 33-95%. 22 trials conducted a 3-in-1 femoral nerve block. 15 trials each used US-guided PNB or blind landmarking technique.*

Sig.	*Outcome*	*Studies (pts)*	*Outcome Measure (95%CI)*
NSS	Mortality reduction (6mo)	11 (617)	RR 0.87 (0.47-1.60); low certainty evidence
	MI (30days)	1 (31)	Insufficient events detected
	Cost of analgesics	1 (75)	4 Euros difference (not economically significant)
SS	30min Pain on movement	11 (503)	SMD -1.05 (-1.25 to -0.86); equivalent to -2.5 on 0-10 Likert scale [High certainty evidence]. Benefit proportional to amount of local anesthetic used (p=0.0003).
	Reduced acute confusional states	13 (1072)	RR 0.67 (0.50-0.90); NNT=12 (7-47); high evidence certainty
	Reduced chest infections	3 (131)	RR 0.41 (0.19-0.89); NNT=7 (5-72); mod certainty of evidence
	Time to first mobilization	3 (208)	Mean Diff -10.80hrs (-12.83 to -8.77hrs); mod certainty of evidence

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The methods used to combine the included primary studies were reported and valid.	✓
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: None? Optimal information size was met for primary outcome.

Selection Bias: Publication bias analysis by funnel plot; some PB evident for different outcomes.

Measurement Bias: The authors show that the primary outcome is improved by 2.5pts on 0-10 Likert scale, but do not identify/justify the minimal important clinical difference for pain scales used (usually 13mm on 100mm scale in general pain literature).

Analysis Bias: None or enter text here (e.g., fixed vs. random effects, combined results of studies of different design). Use of fixed effects models for high heterogeneity meta-analyses? May under-estimate the impact of error in pooling data.

Confounding: Blinding of patients/treating physicians likely impossible. It is feasible, however, to blind outcome assessors and data analysts.

Administrative Details

Key Words: Hip fracture, peripheral nerve blockade.

Appraisers: Upadhye S.

Reference(s): Guay_J, Kopp_S. Peripheral nerve blocks for hip fractures in adults. Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD001159. DOI: 10.1002/14651858.CD001159.pub3.

Research Question

What are the most effective interventions for ED sciatica/nonspecific low back pain?

BEEM Bottom Line

Why is this study important? Low back pain (LBP) is a leading cause of disability and health-care costs worldwide. It is a common chief complaint in the ED, and is frequently treated with opioid analgesics. Finding effective treatments for ED LBP is important to optimize patient outcomes and reduce ED length of stay.

Which, if any, threats to validity are most likely to have an impact on the results and how? An incomplete analysis using GRADE quality domains makes the evidence evaluations and subsequent conclusions suspect. No clear definition of minimal clinically important differences on standardized pain scales make it hard to interpret clinical significance of mean score reductions.

How do the key results compare with the current evidence? The results in this review are congruent with prior literature suggesting variable comparable benefits of different medications (NSAIDs, opioids) in nonspecific LBP and sciatica, and little value in using corticosteroids and muscle relaxants.

How should this study impact the care of ED patients? Different medications (NSAIDs, opioids) may be of some use to reduce ED pain intensity in LBP (nonspecific, sciatica), but more research is needed. Interventional treatments involving trigger point injections hold considerable promise for efficacy, safety and rapid mobilization/ED discharge.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Oliveira CB, Amorim HE, Coombs DM, *et al*. Emergency department interventions for adults with low back pain: a systematic review of randomised controlled trials. Emerg Med J 2021; 38: 59-68. doi:10.1136/emermed-2020-209588

Design: Systematic review of randomized controlled trials.

Population: *Included:* Enter text here, separated by semicolons. Adults (≥ 18years) with nonspecific low back pain (nLBP) or sciatica (Sci).
Excluded: Patients with spinal stenosis, other "red flag" conditions (infection, fracture, neoplasm, cauda equina syndrome, axial spondylarthritis), mixed studies with different diagnoses (unless 75% nonspecific LBP/sciatica).

Intervention: Mixed analgesics (NSAIDs, opioids, muscle relaxants, corticosteroids, combinations).

Comparison: Placebo, NSAIDs, "usual ED care" (variable at ED physician discretion), walking aids.

Outcomes: *Primary:* Pain outcomes during ED visit, as measured by VAS (visual analog scale) or NRS (numeric rating scale). Some trials divided into various 15min/hourly time intervals.
Secondary: ED length of stay (LOS), functional assessment/ability to walk, adverse events, ED recidivism <48hrs.

Key Results: *15 trials included = 1802 patients*. Mean age 31.5-45.1yrs old. No trials reported ED recidivism rates.

Sig.	*Outcome*	*Mean Difference (0-100pt scale) [95%CI]*
NSS	Primary nLBP	Oral ketorolac vs oral acetaminophen/codeine
		IM vs oral phenarydol muscle relaxant; LoE moderate
		IV desketoprofen vs IV paracetamol
		Oral prednisone vs. placebo (ED discharge); LoE moderate
	Primary (Sci)	IV ketorolac vs IV lidocaine; LoE moderate
		IV dexamethasone vs placebo (ED discharge); LoE moderate
	Functional Walk	IV morphine vs IV morphine/promethazine; LoE moderate
	Adverse effects	Some trends towards A/E's with opioids (nausea, vomiting, sedation)
SS	Primary nLBP	Ketoprofen gel vs placebo (30min); -15pts [-21.0 to -9.0]
		Intradermal thiocolchicoside/tenoxicam/lidocaine vs IV desketoprofen (all time points); -8.1 to -17.1
		IV morphine vs IV desketoprofen (15 & 30min); -15.3 to -11.2
		Trigger point injections vs IV desketoprofen (5-60min); -21.8 to -37.7
		Physiotherapy vs std care (ED discharge): -16.0 (-22.4 to -9.6)
	Primary (Sci)	IV paracetamol vs placebo (15 to 30min): -8.8 to -15.7, LoE moderate

	IV morphine vs placebo (15 to 30min): -24.5 to -39.3
	IV morphine vs IV paracetamol (15 to 30min): -15.7 to -23.6
ED LOS	IV dexamethasone vs placebo; -15.3min (-18.4 to -12.2)
	IV morphine vs IV morphine/promethazine; -78min (-140 to -16); LoE moderate

BEEM Critique

Risk of Bias Assessment

	A1
1. The research question is sensible and answerable.	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3. The search for studies was unbiased and reproducible.	✓
4. The selection of studies was unbiased and reproducible.	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7. The quality of the primary studies is high.	✓
8. The methods used to combine the included primary studies were reported and valid.	X
9. The outcomes are clinically relevant.	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Some authors supported by public research grants. No industry funding.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: None?

Selection Bias: Electronic searches, citation reference lists, no language restrictions. No mention of publication bias assessment.

Measurement Bias: Missing data managed by contacting authors for extra information, or by Cochrane handbook methods. Quality assessments done using PEDrO scale (majority low RoB), and GRADE overall evidence methods (limited domains?).

Analysis Bias: All trial outcomes reframed to 0-100 scales, and no statement/standardization of MCID (minimal clinically important difference) for pain intensity. Overall GRADE quality of evidence for primary/secondary outcomes was low/moderate. No definition of clinically important ED LOS reduction.

Confounding: Possible lack of generalizability of results of direct head-2-head comparisons of medications that not be readily available worldwide.

Administrative Details

Key Words: Emergency department, interventions, low back pain

Appraisers: Upadhye S.

Reference(s): Oliveira CB, Amorim HE, Coombs DM, Richards B, Reedyk M, Maher CG, Machada GC. Emergency department interventions for adults with low back pain: a systematic review of randomised controlled trials. Emerg Med J 2021; 38: 59-68. doi:10.1136/emermed-2020-209588

Research Question

What is the efficacy of methoxyflurane (MTxF) in the treatment of emergency trauma pain?

BEEM Bottom Line

Why is this study important? Inhalational analgesia using methoxyflurane (MTxF) has been recommended for moderate/severe trauma pain in Europe and Australasia. It is considered a fast-acting effective analgesia alternative to standard treatments.

Which, if any, threats to validity are most likely to have an impact on the results and how? Effect estimates showed statistical significance favouring MTxF at certain time points, but not necessarily clinically important effects. Lack of standardized analgesia comparisons may distort/attenuate the measured benefits of MTxF. No cost data provided for MTxF vs. standard analgesia.

How do the key results compare with the current evidence? These results attenuate the conclusions of industry-sponsored trials/reviews that may over-embellish analgesic efficacy.

How should this study impact the care of ED patients? Inhaled MTxF may be a useful analgesic strategy for prehospital/ED trauma care, but more research is needed to prove clinically important benefit, and cost comparisons.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Liu H, Fu X, Ren YF, *et al*. Does Inhaled Methoxyflurane Implement Fast and Efficient Pain Management in Trauma Patients? A Systematic Review and Meta-Analysis. Pain Ther 2021; 10: 651-674. DOI: 10.1007/s40122-021-00258-9

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* RCTs with trauma pain randomized to receiving methoxyflurane (MTxF) inhalation vs placebo/standard analgesia Rx in ED or prehospital settings.
Excluded: Protocol papers, missing data on outcomes.

Intervention: Inhaled MTxF (3ml in all included studies).

Comparison: Placebo/standard analgesic treatment (varied between trials).

Outcomes: *Primary:* Change in baseline pain scores during first 30minutes of treatment (5min intervals).
Secondary: Time to first pain relief, proportion of patients experiencing pain relief, rescue analgesia rates, treatment satisfaction (patients/investigators), MTxF Tx-emergency adverse events (TEAE's during ED visit, 14day follow-up).

Key Results: *9 studies* = 1806 patients.

Sig.	*Outcome*	*N/Studies*	*Outcome Measure (95% CI)*	*I^2*
NSS	Primary 25min	2 studies	WMD -0.36 (-0.85 to 0.13)	3%
	30min	2 studies	WMD -0.39 (-0.97 to 0.19)	0%
SS	Primary 5min	6 studies	WMD -0.93 (-1.14 to -0.71)	28%
	10min	6 studies	WMD -1.11 (-1.56 to -0.66)	65%
	15min	6 studies	WMD -1.23 (-1.99 to -0.47)	85%
	20min	6 studies	WMD -1.12 (-1.75 to –0.49)	75%
	Time to pain relief	6 studies	-5.29min (-6.97 to -3.82) favouring MTxF	100%
	Overall pain relief	6 studies	RR 1.41 (1.17 to 1.70) favouring MTxF	85%
	Need for rescue analgesia	7 studies	RR 0.32 (0.21 to 0.49) favouring MTxF	38%
	Analgesia satisfaction	4-8 studies	Patients RR 1.31 (1.07-1.60, 7 studies, I^2 86%), MD RR 1.50 (1.29-1.74, 6 studies, I^2 58%) nurses RR 1.89 (1.37-2.62, 3 studies, I^2 80%) all favouring MTxF	
	Total TEAEs	7 studies	RR 3.09 (1.72-5.57) against MTxF	87%

BEEM Critique

Risk of Bias Assessment

		A1
1.	The research question is sensible and answerable.	✓
2.	The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓
3.	The search for studies was unbiased and reproducible.	✓
4.	The selection of studies was unbiased and reproducible.	✓
5.	The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6.	The assessment of the quality of the primary studies was unbiased and reproducible.	✓
7.	The quality of the primary studies is high.	X
8.	The methods used to combine the included primary studies were reported and valid.	✓
9.	The outcomes are clinically relevant.	✓
10.	The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: Provincial Development Grant from Traditional Chinese Medicine – Key Discipline of TCM. Journal Rapid Service fee paid by authors.

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: None?

Selection Bias: Thorough search of all electronic databases, trial registries, gray literature, conference proceedings, reference lists. Contacted authors as needed. No language restrictions. Unable to measure publication bias (too few studies to do a funnel plot analysis).

Measurement Bias: Minimum clinically important difference (MCID) for pain scale improvements clearly defined (1.5cm on 10cm VAS scale). Quality assessment of RCTs done with Cochrane risk of bias (RoB) tool; 4 DB-RCTs low RoB, 5 open label trials high RoB. Overall quality of evidence was low/very low for most outcomes.

Analysis Bias: Fixed effects analyses for low heterogeneity outcomes (I^2 <50%), and random effects if >50%. Sensitivity/subgroup analyses performed for sources of high heterogeneity; found mostly due to open label designs (higher RoB). A priori sensitivity analysis to exclude studies with high RoB, and post hoc analysis to exclude 1 study (PenASAP). No differences in effect estimates found after planned sensitivity analyses. Subgroup analyses found attenuation of benefits based on control group interventions, reducing the benefit of MTxF at 15 and 20min.

Confounding: No costing data provided for MTxF vs. standardized analgesia.

Administrative Details

Key Words: Acute trauma analgesia, inhaled methoxyflurane.

Appraisers: Upadhye S.

Reference(s):

1) Liu H, Fu X, Ren YF, Tan SY, Xiang SR, Zheng C, You FM, Shi W, Li LJ. Does Inhaled Methoxyflurane Implement Fast and Efficient Pain Management in Trauma Patients? A Systematic Review and Meta-Analysis. Pain Ther 2021; 10: 651-674. DOI: 10.1007/s40122-021-00258-9

2) Fabbri A, Borobia AM, Ricard-Hibon A, Coffey F, Caumont-Prim A, Montestruc F, Soldi A, Lugilde ST, Dickerson S. Low-Dose Methoxyflurane versus Standard of Care Analgesics for Emergency Trauma Pain: A Systematic Review and Meta-Analysis of Pooled Data. J Pain Res 2021; 14: 93-105. doi: 10.2147/JPR.S292521

Research Question

What is the benefit of therapeutic hypothermia (TH) in improving neurologic outcomes in cardiac arrest survivors?

BEEM Bottom Line

Why is this study important? Improving neurological outcomes in cardiac arrest survivors is a critical goal, and early therapeutic hypothermia (TH) may be helpful to preserve brain function. Recent trials show conflicting results on TH benefits.

Which, if any, threats to validity are most likely to have an impact on the results and how? A limited electronic search may have missed important articles/abstracts/information that may influence final effect estimates. Absent reporting of quality assessments of included trials may leave readers uncertain about the trustworthiness of individual trials and summaries presented here. Heterogeneity in TH intervention delivery likely led to different magnitudes of effect.

How do the key results compare with the current evidence? These results are congruent with prior reviews, and includes an updated RCT (HYPERION).

How should this study impact the care of ED patients? The pooled studies are heterogeneous, and the pooled TH effect estimate suggests a small potential benefit of providing TH to cardiac arrest survivors, especially those who had an initial shockable rhythm.

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Rout A, Singh S, Sarkar S, *et al*. Meta-analysis of the Usefulness of Therapeutic Hypothermia After Cardiac Arrest. Am J Cardiol 2020; Oct 15;133:48-53. doi: 10.1016/j.amjcard.2020.07.038.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* RCTs of adults surviving in- or out-of hospital cardiac arrest (IHCA, OHCA) treated with TH.
Excluded: Nonrandomized studies, in-hospital vs pre-hospital comparisons of TH initiation only.

Intervention: Therapeutic hypothermia, and reporting of one outcome of interest. Duration of cooling 24hr, with target temp range 32-34°C.

Comparison: Usual care, with maintenance of body temp ≥36°C.

Outcomes: *Primary:* Neurological outcome (based on Cerebral performance category scores) at 14-180days, or hospital discharge.
Secondary: Mortality

Key Results: *8 RCTs included; 2026 pts in TH arm, 1001 in controls. Mean age 64yo, 72% males. 40% nonshockable rhythm at initial presentation.*

Sig.	*Outcome*	*Studies*	*Measure NNT (95% CI)*	*I^2*
NSS	Mortality reduction	7 studies (1167 deaths in 1972 pts)	RR 0.94 (0.85-1.03)	28%
SS	Poor neurological outcome (overall)	8 studies	RR 0.87 (0.77-0.98) favouring HT	64%
	Poor neuro outcome (initial shockable rhythm)	4 studies	RR 0.81 (0.67-0.99) favouring HT	49%
	Mortality (initial shockable rhythm)	4 studies	RR 0.85 (0.73-0.99) favouring HT	72%

CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; n = sample size; N/A = not applicable; NNT = number needed to treat; NSS = not statistically significant; *p* = probability; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number. If the value '∞' is included in the CI, then there is no difference in outcomes between the intervention and control groups.

BEEM Critique

Risk of Bias Assessment

		A1
1.	The research question is sensible and answerable.	✓
2.	The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X
3.	The search for studies was unbiased and reproducible.	✓
4.	The selection of studies was unbiased and reproducible.	✓
5.	The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓
6.	The assessment of the quality of the primary studies was unbiased and reproducible.	?
7.	The quality of the primary studies is high.	?
8.	The methods used to combine the included primary studies were reported and valid.	✓
9.	The outcomes are clinically relevant.	✓
10.	The statistical heterogeneity of the primary outcome is low (< 25%).	X

A1 = S. Upadhye

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (declared).

Potential Threats to Validity

Chance: Some differences in the TH intervention arms of different studies (techniques, duration of cooling, time to initiate TH, etc.) may have impacted the final trial outcomes.

Selection Bias: Search limited to electronic databases only. No publication bias analysis reported.

Measurement Bias: No reporting of quality assessments tools used (nor results) to analyze included trials. One comment in discussion that half of included trials had low risk of bias, but no details on what tools used and individual study scores.

Analysis Bias: Random effects analyses for high heterogeneity pooled studies.

Confounding: Inclusion/exclusion of a single large negative trial (TTM) can influence the pooled effect estimate considerably (ie. excluded = pooled estimate significantly positive towards TH, included = weaker positive effect, almost nonsignificant).

Administrative Details

Key Words: Cardiac arrest, neurological outcome, therapeutic hypothermia.

Appraisers: Upadhye S.

Reference(s): Rout A, Singh S, Sarkar S, Munawar I, Garg A, D'Adamo CR, Tantry US, Dharmadhikari A, Gurbel PA. Meta-analysis of the Usefulness of Therapeutic Hypothermia After Cardiac Arrest. Am J Cardiol 2020; Oct 15;133:48-53. doi: 10.1016/j.amjcard.2020.07.038.

Research Question

How do NSAIDs compare with other oral analgesics for treating acute soft tissue injuries?

BEEM Bottom Line

Why is this study important? Acute soft tissue injuries including sprains, strains, lacerations, contusions and hematomas are among the most common presenting complaints to emergency departments (EDs) worldwide. Pain is the most common symptom and the most common reason for oral analgesics including non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol) and opioids. NSAIDs are often favored as the analgesics of choice because of their combined analgesic and anti-inflammatory effects but are not without adverse effects. This systematic review and meta-analysis is an update of the summary evidence of analgesia and other outcomes associated with NSAIDs compared to opioids and acetaminophen.[1]

Which, if any, threats to validity are most likely to have an impact on the results and how? The review presents moderate to high certainty evidence that NSAIDs result in little to no difference in pain reduction compared to acetaminophen and opioids but may increase the risk of gastrointestinal adverse events compared to paracetamol and reduce the risk of adverse events compared to opioids. The evidence was primarily limited due to the potential for confounding bias caused by suboptimal randomization and allocation concealment and performance and detection bias due to lack of blinding of trial personnel and participants.

How do the key results compare with the current evidence? This is an update of a previous review by the same authors that included 16 trials (2 with only children) and 2144 participants.[1] The evidence was generally low- or very low-quality but consistent in the finding of no clinically important difference in analgesic efficacy between NSAIDs and other oral analgesics. The results of this review show a number needed to harm for adverse gastrointestinal events of 9 (95% confidence interval: 8 to 13).

How should this study impact the care of ED patients? The evidence does not show NSAIDs to be superior to other oral analgesics as is commonly believed. The need for, type and dose of analgesia is best determined by a thorough clinical assessment of the patient's injuries, risk of adverse effects and expectations. Combination analgesics are an option but carry the potential for increased risk of adverse effects.

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No conflicts of interest (ICMJE)

Study Summary

Article: Jones P, Lamdin R, Dalziel SR. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. Cochrane Database Syst Rev. 2020 Aug 12;8(8):CD007789.

Design: Systematic review and meta-analysis of randomized and quasi-randomized controlled trials.

Population: *Included:* Patients (no age specifications) with acute soft tissue injuries.
Excluded: None specified.

Intervention: Oral non-steroidal anti-inflammatory drugs (NSAIDs).

Comparison: Oral paracetamol (acetaminophen), opioids, combined paracetamol and opioids.

Outcomes: *Primary:* Pain.
Secondary: Swelling, function, adverse effects, and early re-injury.

Key Results: *N* = 20 studies with 3305 participants.

Sig.	*Outcome*	*Comparator*	*N/Studies*	*Mean Difference (95% CI)*	*Certainty of Evidence*	I^2
NSS	Pain < 24 hours	Paracetamol	11/1853	-0.12 (-2.27 to 2.03)	High	0%
NSS	Pain < 24 hours	Opioids	4/1058	-0.49 (-3.05 to 2.07)	Moderate	34%
Sig.	*Outcome*	*Comparator*	*N/Studies*	*Relative Risk (95% CI)*	*Certainty of Evidence*	I^2
NSS	GI Adverse Events	Paracetamol	10/1504	1.34 (0.97 to 1.86)	Low	0%
SS	GI Adverse Events	Opioids	5/1151	0.48 (0.36 to 0.62)	Moderate	55%
NSS	GI Adverse Events	Combined	3/141	0.21 (0.03 to 1.74)	Low	0%

CI = confidence interval; GI = gastrointestinal; I^2 = inconsistency index (measure of statistical heterogeneity); *N* = number of patients; NSS = not statistically significant; *R*elative Risk is a ratio, therefore, if the value of the range includes 1, there is no difference; Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓	?
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	?
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	?	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X	?

A = appraiser.

Funding & Conflicts of Interest

Funding: Cochrane Collaboration; Department of Emergency Medicine, Auckland City Hospital, Auckland District Health Board, New Zealand; Auckland District Health Board Charitable Trust, New Zealand.

Conflicts of Interest: One author is an advisor for the Pharmaceutical Management Agency (PHARMAC).

Potential Threats to Validity

Chance: None detected.

Selection Bias: Of the 20 included trials, 4 are at unclear or high risk of bias for missing outcome data.

Measurement Bias: Of the 20 included trials, 9 were at high risk of bias for blinding of participants and outcome assessors. Suboptimal blinding or the lack of blinding of participants (for patient-reported outcomes) and outcome assessors (for other outcomes) may produce detection bias.

Analysis Bias: Categorical measures of pain were analyzed by dichotomization based on the number of response options included as part of the measurement tool regardless of the description of the response options or the characteristics of the tool. The proportion of patients categorized as experiencing pain relief may not actually be reflective of the proportion experiencing pain relief.

Confounding: Of the 20 included trials, 11 were at unclear or high risk of bias for randomization and allocation concealment and 8 trials were at unclear or high risk of bias for blinding of treatment providers. Suboptimal randomization, allocation concealment, and blinding of healthcare providers may produce confounding bias.

Administrative Details

Key Words: Acetaminophen; acute soft tissue injury; analgesia; non-steroidal anti-inflammatory drugs (NSAIDs).

Appraisers: Zeraatkar D; Worster A; Upadhye S.

Reference(s):

1. Jones P, Dalziel SR, Lamdin R, Miles-Chan JL, Frampton C. Oral non-steroidal anti-inflammatory drugs versus other oral analgesic agents for acute soft tissue injury. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD007789.

Research Question

Is low-dose ketamine as effective and safe as morphine for analgesia in the emergency department?

BEEM Bottom Line

Why is this study important? Pain is a common symptom of patients presenting to the emergency department (ED). Adequate analgesia is important for appropriate assessment and management of ED patients. While opioid analgesia has been the mainstay of treatment for severe pain in the ED, it is not without risk and side effects. This systematic review and meta-analysis compared low dose ketamine to morphine for pain management in the ED.

Which, if any, threats to validity are most likely to have an impact on the results and how? The overall quality of the evidence is low because the included studies vary widely in their results, and there are too few patients to produce reliable estimates of effect. The dose of ketamine was not standard across all trials questioning the true analgesic dose of ketamine. There is a risk that not all relevant trials were included due to the restrictive search strategy. Finally, the resulting conclusions of equivalence between low-dose ketamine and morphine are likely overstated.

How do the key results compare with the current evidence? Ketamine has been shown to have great analgesic properties and has been used in the prehospital and ED setting in Europe and Australasia.[1] Slow intravenous infusion has been shown to reduce side effects.[2] This study affirms the utility of low dose ketamine as an effective alternative to opioids.

How should this study impact the care of ED patients? The use of alternative analgesic agents to opioids are important in the ED given the opioid crisis, use of antagonists and partial antagonists in chronic opioid users, and tolerance for high doses. Ketamine is an excellent alternative for pain control and can be used safely in these patients.

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No conflicts of interest (ICMJE)

Study Summary

Article: Balzer N, McLeod S, Walsh C, et al. Low-dose ketamine for acute pain control in the emergency department: A systematic review and meta-analysis. Acad Emerg Med. 2020 Oct 24. doi: 10.1111/acem.14159.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* Adults (≥ 18 years) requiring intravenous (IV) analgesia for acute pain management for any condition in the ED or pre-hospital setting.
Excluded: Ketamine for uses other than acute pain analgesia (e.g. procedural sedation, intubation, perioperative, psychiatric, chronic pain) or combined with other medications.

Intervention: Ketamine (< 0.5 mg/kg) IV bolus or infusion < 30 minutes).

Comparison: Morphine 0.1 mg/kg IV.

Outcomes: *Primary:* Mean difference in numeric pain scores (NPS; from 0 to 10, maximum) at different time points.
Secondary: Need for rescue analgesia; adverse events; nausea and hypoxia.

Key Results: *N* = 1191 patients in 8 RCTs (LDK = 598; morphine = 593).

Sig.	*Outcome*	*Difference (95% CI)*	*CoE*
NSS	Mean difference in NPS @ 60 to 90 min.	0.12 higher (0.03 to 0.22)	Low
NSS	Mean difference in NPS @ 90 to 120 min.	0.08 higher (0.05 to 0.11)	Low
NSS	Need for rescue analgesia	29/1000 more (from 56 fewer to 240 more)	Low
NSS	Nausea	3/1000 fewer (from 41 fewer to 55 more)	Low
NSS	Hypoxia	89/1000 fewer (from 130 fewer to 59 more)	Low

CoE = certainty of evidence; CI = confidence interval; *N* = number of patients; NSS = not statistically significant; Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X	X
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?	?	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X	X

A = appraiser.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None declared.

Potential Threats to Validity

Chance: The meta-analyses are underpowered to both detect statistical significance and to determine equivalence.

Selection Bias: Search strategy appears very restrictive by applying and combining search terms not recommended in a systematic search (e.g. including terms related to the comparison and setting); the search also included study design filters that are not evidence-based. The search was also restricted to the English language.

Measurement Bias: It is unknown if data extraction was completed in duplicate, independently. The GRADE assessment did not define thresholds for determining imprecision nor did they define a clinically important difference.

Analysis Bias: There are missing details regarding their analysis, specifically with respect to handling missing data and whether data was analysed according to intention to treat. Conclusions of equivalence were made despite low certainty evidence (downgrading due to imprecision and inconsistency).

Confounding: The doses and durations of analgesics could vary.

Administrative Details

Key Words: Analgesia; ketamine; pain; morphine.

Appraisers: Bedard C; Worster A; Valani R.

Reference(s):

1. Bansal A, Miller M, Ferguson I, et al.. Ketamine as a Prehospital Analgesic: A Systematic Review. Prehosp Disaster Med. 2020 Jun;35(3):314-321.
2. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med. 2017 Aug;35(8):1095-1100.

Research Question

Does tranexamic acid reduce mortality from acute traumatic brain injury?

BEEM Bottom Line

Why is this study important? Traumatic brain injury (TBI) is a major cause of mortality and morbidity especially among young people in lower income countries. Most TBI patients have intracranial hemorrhage (ICH) and hematoma expansion portends a poor prognosis and death. Tranexamic acid (TXA) is a safe and effective antifibrinolytic agent with many clinical indications and evidence for improving outcomes in patients with known or suspected significant hemorrhage.[1] The administration of TXA in the emergency department (ED) is simple, rapid and inexpensive but its role in TBI management is still controversial. This is a systematic review and meta-analysis of the collective evidence for TXA in the management of TBI.

Which, if any, threats to validity are most likely to have an impact on the results and how? The certainty of evidence ranges from moderate to low and is primarily limited by imprecision. There were too few trials, patients, and events included in the meta-analysis to detect any clinically important harm or benefit with sufficient certainty. The included studies were also at high risk of bias due to unblinded outcome adjudication and potential for confounding caused by imbalances in co-interventions across trial arms.

How do the key results compare with the current evidence? Potential mortality benefit of TXA in TBI patients (relative risk [RR] 0.91; 95% confidence interval [CI] 0.85 to 0.97) has been reported in a previous meta-analysis but no effect on neurological outcome using Glasgow Outcome Scale (GOS) (RR 0.72; 95% CI: 0.47 to 1.11).[2] Two subsequent studies evaluating TXA in TBI were published with almost opposite conclusions. The CRASH-3 study, although touted as a positive study, raised many questions in large part because the authors changed their primary outcome during the study and, despite this, concluded that TXA reduced the mortality in TBI patients.[3] Contrary to CRASH-3, another trial showed no benefit in TXA in the management of TBI patients.[4] This meta-analysis included these two studies in its pooled summary measures.

How should this study impact the care of ED patients? All efforts in the initial management of acute TBI patients in the ED should emphasize the prevention of secondary brain injury. Based on current evidence, although the use of TXA in hemorrhagic TBI could potentially attenuate hemorrhagic progression, it likely has no effect on mortality and morbidity.

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No conflicts of interest (ICMJE)

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No conflicts of interest (ICMJE)

Study Summary

Article: Lawati KA, Sharif S, Maqbali SA, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. Intensive Care Med. 2020 Oct 20. doi: 10.1007/s00134-020-06279-w.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* Adolescents (≥ 15 years) and adults presenting with acute TBI.
Excluded: No exclusions listed.

Intervention: TXA intravenously at any dose in TBI.

Comparison: Placebo or no TXA.

Outcomes: *Primary:* All-cause mortality (at longest time point reported).
Secondary: Head injury-related death in hospital at 28 days; disability (GOS < 4 and the GOS-extended ≤ 4 indicating a poor outcome); neurosurgical intervention; hospital and intensive care unit length-of-stay (LOS); hematoma expansion; adverse events (a composite outcome variably defined by individual study authors including deep vein thrombosis, vascular occlusive events, stroke, seizure).

Key Results: *N* = 14,747 patients in 9 trials.

Sig.	*Outcome*	*RR (95% CI)*	*RD/1000 (95% CI)*	*I^2*
NSS	All-cause mortality	0.95 (0.88 to 1.02)	10 fewer (25 fewer to 4 more)	0%
NSS	Disability	0.90 (0.69 to 1.17)	30 fewer (110 fewer to 60 more)	58%
NSS	Neurosurgical intervention	1.11 (0.89 to 1.39)	17 more (17 fewer to 59 more)	0%
NSS	Hematoma expansion	0.77 (0.58 to 1.03)	36 fewer (66 fewer to 5 more)	0%
NSS	Adverse events	0.97 (0.85 to 1.11)	0 fewer (2 fewer to 1 more)	6%

CI = confidence interval; I^2 = inconsistency index (statistical heterogeneity); *N* = number of patients; NSS = not statistically significant; RD = risk difference; RR = relative risk; Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: The authors declare no competing interests.

Potential Threats to Validity

Chance: There were too few patients and events to detect clinically important benefit or harm with sufficient certainty. Trial sequential analysis also indicated that the optimal information size was not met.

Selection Bias: None detected.

Measurement Bias: Of the 9 included trials, 4 were at high risk of bias for measurement of the outcome; probably due to unblinded outcome adjudication.

Analysis Bias: None detected.

Confounding: Of the 9 included trials, 3 were at high risk of bias for imbalances in co-interventions or care that may have confounded results.

Administrative Details

Key Words: Intracranial hemorrhage (ICH); Tranexamic acid (TXA); traumatic brain injury (ATBI).

Appraisers: Zeraatkar D; Worster A; Nemeth J.

Reference(s):

1. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013 Mar;17(10):1-79.
2. Chen H, Chen M. The efficacy of tranexamic acid for brain injury: A meta-analysis of randomized controlled trials. Am J Emerg Med. 2020 Feb;38(2):364-370.
3. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):1713-1723.
4. Rowell SE, Meier EN, McKnight B, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. JAMA. 2020 Sep 8;324(10):961-974.

TRAUMA/CRITICAL CARE (PART II)

Research Question

What is the effectiveness of topical tetracaine in the treatment of corneal abrasions?

BEEM Bottom Line

Why is this study important? There is controversy over the historic efficacy & safety of topical tetracaine for ED corneal abrasion analgesia, although this has been recently challenged.

Which, if any, threats to validity are most likely to have an impact on the results and how? This is a single center study that had some relevant co-analgesic interventions that could have been confounding (opioid use), but likely wasn't.

How do the key results compare with the current evidence? Current results are congruent with recent trials supporting the safe use of tetracaine for corneal abrasions for 24hrs.

How should this study impact the care of ED patients? For uncomplicated corneal abrasions, topical tetracaine is an efficiacious and safe analgesic strategy for 24hrs.

Suneel Upadhye, MD MSc FRCPC
Associate Professor, Emergency Medicine/Health Research Methods, Evidence & Impact, McMaster University
No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Shipman S, Painter K, Keuchel M, Bogie C. Short-Term Topical Tetracaine is Highly Efficacious for the Treatment of Pain Caused by Corneal Abrasions: A Double-Blind Randomized Clinical Trial. Ann Emerg Med. 2021;77:338-344. https://doi.org/10.1016/j.annemergmed.2020.08.036

Design: Randomized controlled trial (RCT).

Population: *Included:* Adults (≥ 18 and ≤ 80 years) with an uncomplicated corneal abrasion.
Excluded: Contact lens wearer, prior corneal surgery/transplanted in affected eye, >36hrs after injury, retained/contaminated foreign bodies present, co-existing ocular infection, pregnancy, penetrating eye injury, immunosuppression, allergy to study medication, unable to attend follow-up, unable to speak/read English or Spanish, or injury requiring urgent ED ophthalomology consultation (lacerations, ulcers, vision loss).

Intervention: 1 vial of tetracaine 0.5% in a single 2ml bottle.

Comparison: 4 vials of balanced artificial tears solution.

Outcomes: *Primary:* Numeric Rating Scale score (0-10cm) at initial ED follow-up visit (24hrs after initial visit, and 48hrs).
Secondary: Breakthrough opioid use, adverse events.

Key Results: *N* = 118 patients (59 each arm).

Sig.	*Outcome*	*Intervention*	*Control*
SS	Primary	Median score (n=56) 1 (IQR 1-2); 6pt diff from baseline	Median score (n=55) 8 (7-8); 0pt difference from baseline
	Opioid tabs used	1	7
	Adverse events (%)	2 (3.6)	6 (11)

****NO DIFFERENCE:** Residual abrasion on slit lamp exam at 24hrs (18% Int vs 11% Ctrl).

BEEM Critique

Risk of Bias Assessment

	A1
1. The patients were recruited consecutively.	✓
2. The patients were adequately randomized (allocation sequence adequately generated).	✓
3. The allocation sequence was adequately concealed.	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	✓
6. All groups were treated equally except for the intervention.	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓
9. All patient-important outcomes were considered.	✓
10. The effect size of the primary outcome is clinically significant.	✓

A1 = S. Upadhye

ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Study was funded in part by a grant from the Foundation of Osteopathic Emergency Medicine Young Investigator's Award.

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: "Blinded" opaque envelopes had 1 vial of tetracaine (Int) vs. 4 vials of balanced artificial tears (placebo); loss of blinding amongst treating staff?

Selection Bias: None. Consecutive sampling 24hrs a day by all ED staff.

Measurement Bias: NRS minimal clinical important difference (MCID) was 1.5cm (SD 2.5cm); justification for this?

Analysis Bias: Calculated need for 60pts per arm, recruited 59pts/arm. ITT analysis; 3/59 LFTU in Int arm (5%), 4/59 LTFU in Ctrl arm (6%). Majority of patients did not attend 1wk f/u appt with ophthalmology (<20% each arm). Study under-powered for safety outcomes. Raw data for group outcomes not provided to calculate ARR/NNT.

Confounding: Patients were also treated with antibiotic drops in both groups for same 24hr period. They also all received a prescription for hydrocodone/acetaminophen #12 (1-2 tabs q6h prn) for breakthrough pain.

Administrative Details

Key Words: Corneal abrasions, emergency department, tetracaine.

Appraisers: Upadhye S.

Reference(s): Shipman S, Painter K, Keuchel M, Bogie C. Short-Term Topical Tetracaine is Highly Efficacious for the Treatment of Pain Caused by Corneal Abrasions: A Double-Blind Randomized Clinical Trial. Ann Emerg Med. 2021;77:338-344. https://doi.org/10.1016/j.annemergmed.2020.08.036

Research Question

What are the complications risk with use of peripheral IV vasopressors?

BEEM Bottom Line

Why is this study important? Rapid vasopressor (VP) infusion is important in time-dependent critical care scenarios (eg. septic shock). Using peripheral intravenous (IV) catheters can achieve such treatment faster than central venous line placement/ confirmation.

Which, if any, threats to validity are most likely to have an impact on the results and how? High suspicion of publication bias given both the limited search and nature of adverse event/complication reporting in published literature. Varied study designs with high heterogeneity makes outcome data pooling unreliable (even with more conservative random effects analysis). Lack of weight-based dosing limits comparisons/generalizability of results.

How do the key results compare with the current evidence? These results show congruence with past trials, especially those using larger peripheral IV catheters in ED settings.

How should this study impact the care of ED patients? Use of peripheral IV catheters for vasopressor infusion is faster, effective and safe.

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No conflicts of interest/Identify conflicts (ICMJE)

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Tran QK, Mester G, Bzhilyanskaya V,*et al*. Complications of vasopressor infusion through peripheral venous catheters: A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 2434-2443. https://doi.org/10.1016/j.ajem.2020.09.047

Design: Systematic review and meta-analysis of trials using peripheral IV vasopressor (VP) infusions.

Population: *Included:* All trials (prospective RCTs, observational studies, retrospective studies) with adults (≥ 18years) receiving VPs.
Excluded: Case reports.

Intervention: All trials (prospective RCTs, observational studies, retrospective studies) using peripheral IV VP infusions.

Comparison: N/A.

Outcomes: *Primary:* Any VP-related complication at longest time of VP infusion. *"Minor" complications = extravasation, infiltration, cellulitis, thrombophlebitis. "Major" complications = limb ischemia, tissue necrosis, deep venous thrombosis.*
Secondary: Treatments for complications = amputations, debridements, hot/cold compresses, analgesia, observation, local phentolamine infiltration.

Key Results: *9 studies, 1835 patients (1 RCT). Mean age 63yrs, 48% female. Two studies set in ED (275pts). Most common catheter size 18-20G. Most common VP: norepinephrine (NE; 65%), epinephrine (Epi; 12%), phenylephrine (PhEpi; 12%). Mean infusion time 9.7-49hrs.*

Outcome	*Events/n*	*Pooled Proportion (95% CI)*	*I^2*
Primary	122/1835	0.086 (95%CI 0.031-0.21).	96%
Secondary	None; no treatments reported?		

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X
3. The search for studies was unbiased and reproducible.	?	X
4. The selection of studies was unbiased and reproducible.	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓
7. The quality of the primary studies is high.	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	X
9. The outcomes are clinically relevant.	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X

A1 = S. Upadhye A2 = C. Bedard

Funding & Conflicts of Interest

Funding: None (reported).

Conflicts of Interest: None (reported).

Potential Threats to Validity

Chance: There was only 1 prospective RCT included and the remainder of studies were heterogeneous designs. As expected ,there were very few events to provide a precise estimate of the complications related to PIV.

Selection Bias: Limited search to few electronic databases, and selected article reference lists. There were no extended searches (for unpublished materials), and the review excluded non-English language studies. The search only included generic index terms and not specific free text. The review also noted that they did not contact authors for more data. All the above increases the risk of publication bias because complication/adverse event reporting is highly variable and indexing techniques are limited.

Measurement Bias: Risk of bias assessments used the Cochrane Risk of Bias (RCTs) and Newcastle-Ottawa scale (observational studies). All included studies rated as Moderate quality (inter-rater agreement Kappa scores 70%). Only 1 study reported objective measurements of complications; therefore comparisons across studies may not be appropriate. There was no assessment of quality across the collection of evidence (i.e. GRADE).

Analysis Bias: None or enter text here (e.g., fixed vs. random effects, combined results of studies of different design). Subgroup analyses appear to be mostly driven by the information reported in the included studies (i.e. not a priori) with the exception of presence of explicit safety guidelines. Random effects analyses were used appropriately for highly heterogeneous studies; the majority of heterogeneity due to study designs with different patient populations (97%). The use of prediction intervals is not recommended when there are fewer than 10 studies meta-analysed and when there is risk of publication bias as it can lead to spurious confidence intervals.

Confounding: Insufficient information to determine risk factors for complications. Lack of weight-based dosing limits inter-study comparisons/generalizability of results.

Administrative Details

Key Words: Complications, peripheral intravenous vasopressors

Appraisers: Upadhye S, Bedard C.

Reference(s): Tran QK, Mester G, Bzhilyanskaya V, Afridi LZ, Andhavarapu S, Alam Z, Widjaja A, Andersen B, Matta Ann, Pourmand A. Complications of vasopressor infusion through peripheral venous catheters: A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 2434-2443. https://doi.org/10.1016/j.ajem.2020.09.047

Research Question

What are the latest guidelines for the management of acute anaphylaxis?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? This guideline updates prior 2008 guidance on emergency anaphylaxis treatment, and provides detailed evidence reviews about effective treatments for acute anaphylaxis.

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Enter text here. Notes: Top 3 fatal flaws in order of priority. Explain in simple terms for clinician readers. No description of the littérature search strategy is presented. Absence of selection bias thus cannot be confirmed. The recommendations are based on mostly low and the very low quality evidence. The lack of description of the populations included in the studies could threaten the external validity of the results.

How should this guideline, and specifically which recommendations should impact the care of ED patients? This evidence update supports the Resuscitation Council UK May 2021 update on emergency anaphylaxis treatment, which contains useful charts, algorithms, dosing tables, etc. for ready adaptation into ED practice.

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Curator, EmergencyGuidelines.ca website (nonprofit)

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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Dodd A, Hughes A, Sargant N, Whyte AF, Soar J, Turner PJ. Evidence update for the treatment of anaphylaxis. Resuscitation 2021; 86-96. https://doi.org/10.1016/j.resuscitation.2021.04.010. PMID: 33895231

Design: Clinical Practice Guideline.

Population: Not specified; guidance for adults and children with anaphylaxis.

Scope: This guideline is intended for ED practitioners who treat anaphylaxis.

Key Results: *Updated recommendations for 2021

Recommendation	*Strength*	*Quality of Evidence*
We recommend adrenaline as the first line treatment for anaphylaxis.	Strong	Moderate
Intramuscular adrenaline should be administered at the doses listed in Table 4.	Strong	Low
Where respiratory and/or cardiovascular features of anaphylaxis persist despite 2 appropriate doses of adrenaline (administered by IM or IV route), seek urgent expert help (e.g. from experienced critical care clinicians) to establish an intravenous adrenaline infusion to treat refractory anaphylaxis.	Strong	
*We suggest that antihistamines are not used as part of the initial emergency treatment for anaphylaxis.	Low	
Adrenaline should be administered early once symptoms of anaphylaxis have been recognized or suspected.	Weak	Very Low
The intramuscular (IM) route is recommended for initial adrenaline treatment for anaphylaxis.	Strong	
Titrate the administration of adrenaline (by any route) against clinical response.	Strong	
*Subsequent doses of adrenaline should be given every 5 min, titrated to clinical response, in patients whose symptoms are refractory to initial treatment.	Weak	
Low dose intravenous adrenaline infusions appear to be effective and safe to treat refractory anaphylaxis.	Weak	
For anaphylaxis refractory to initial treatment with adrenaline, an IV fluid bolus (crystalloid) is recommended as an adjunt to improve drug distribution	Weak	
*We suggest against the routine use of corticosteroids to treat anaphylaxis.	Weak	
*Beta-2 agonists (such as salbutamol) may be useful as an adjunct treatment for lower respiratory symptoms caused by anaphylaxis, following initial treatment with IM adrenaline.	Weak	
*In the presence of persisting respiratory symptoms in anaphylaxis, beta-2 agonists (whether inhaled or parenteral) should not be used as an alternative to further parenteral treatment with adrenaline.	Strong	
*We suggest a risk-stratified approach to the discharge of patients following anaphylaxis (Table 5)	Weak	

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓	X
2. Systematic methods were used to search for evidence.	?	?
3. The criteria for selecting the evidence are clearly described.	?	?
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	?	?
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓	✓
7. Experts externally reviewed the guideline prior to its publication.	✓	?
8. The content of the guideline is free of influence by the views of the funding body.	?	?
9. Competing interests of guideline development group members have been recorded and managed.	✓	✓
10. The strength and certainty of the key recommendations are clearly identified.	✓	✓

A1 = S. Upadhye A2 = J. Morris

Funding & Conflicts of Interest

Funding: None stated.

Conflicts of Interest: Declared. Some authors had govt/non-industry grants, and other academic allergy affiliations. Senior author did have some industry fees and nonfinancial supports.

Potential Threats to Validity

Development: Consider appropriate stakeholders, systematic evidentiary base & recommendations consistent with the literature? Transparent and reproducible? **This was a GRADE-Adolopment exercise in adapting/updating pre-existing systematic reviews and guidelines (not a *de novo* literatue search). Search strategy for source materials not included in this report. The roles and the reason for choosing the internal reviewers are not detailed.**

Presentation: Well organized with easy to find recommendations? **Questions and recommendations scattered throughout the text (not summarized separately at beginning of manuscript).**

Comprehensive: Was the information to inform decision-making complete? **Yes; GRADE Adolopment framework provided.**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **Yes**

Administrative Details

Key Words: Anaphylaxis, adrenaline, antihistamine, corticosteroids, resuscitation

Appraisers: Upadhye S, Morris J.

Reference(s):

1. Dodd A, Hughes A, Sargant N, Whyte AF, Soar J, Turner PJ. Evidence update for the treatment of anaphylaxis. Resuscitation 2021; 86-96. https://doi.org/10.1016/j.resuscitation.2021.04.010. PMID: 33895231
2. Working Group of Resuscitation Council UK (May 2021). Emergency treatment of anaphylaxis. Available at: https://www.resus.org.uk/library/additional-guidance/guidance-anaphylaxis/emergency-treatment.
3. Beardsall I. Anaphylaxis – a Guideline Update. St. Emlyn's Emergency Medicine #FOAMed. Available at: https://www.stemlynsblog.org/anaphylaxis-a-guideline-update/

Research Question

What are the latest guidelines for the management of biphasic anaphylaxis?

BEEM Bottom Line

Why is this guideline and at least some of its recommendations important? Biphasic anaphylaxis occurs in 1-20% of patients, which may occur from 1-72hrs after initial anaphylaxis episode, but has been reported up to 78hrs. Risk factors for severe anaphylaxis include the following: older age, asthma Hx, and comorbid CV/other diseases. It is not clear what the optimal length of ED observation should be after initial anaphylaxis treatment to avoid biphasic reactions, but summary literature suggests that the range should be 1-5hrs (NPV range 95-97.3%).

Which, if any, threats to validity or applicability are most likely to have an impact on the recommendations and how? Lack of an explicit reported search strategy, limited to English language articles (risk of missing important information). No declaration of funding body, nor influence on guideline development/reporting. Many authors have considerable industry relationships, and it is not clear how these were managed.

How should this guideline, and specifically which recommendations should impact the care of ED patients? This guideline updates information on use of epinephrine for acute anaphylaxis, and observation for biphasic recurrence. It refutes the utility of antihistamines and glucocorticoids for biphasic anaphylaxis prevention and also recommends against routine use of those medications in patients with history of radiocontrast HSRs to prevent anaphylaxis before a radiocontrast study.

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Guidelines Methodologist, CAEP/SAEM GRACE (nonprofit)
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Shaker MS, Wallace DV, Golden DBK, *et al*. Anaphyllaxis – a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020; 145(4): 1082-1123.

Design: Clinical Practice Guideline.

Population: Not specified.

Scope: This guideline is intended for ED physicians who treat anaphylaxis

EM-Relevant Questions Addressed in Guideline:

Q1. What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?
Q2. Should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis?
Q3. Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent HSRs to RCM?

Key Results:

Recommendation	*Strength*	*Quality of Evidence*
Rec1a: We suggest that a clinician incorporate severity of anaphylaxis presentation and/or the administration of >1 dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis.	Conditional	Very Low
Rec1b: We suggest extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need >1 dose of epinephrine.	Conditional	Very Low
Rec2: We suggest **against** administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis.	Conditional	Very Low
Rec3: We suggest **against** routinely administering glucocorticoids and/or antihistamines to prevent anaphylaxis in patients with prior radiocontrast HSRs when readministration of a low- or iso-osmolar, nonionic RCM agent is required.	Conditional	Very Low

Additional Good Practice Statements

GPS1: Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.
GPS2: Do not delay the administration of epinephrine for anaphylaxis, as doing so may be associated with higher morbidity and mortality.
GPS3: After diagnosis and treatment of anaphylaxis, all patients should be kept under observation in a setting capable of managing anaphylaxis until symptoms have fully resolved.

GPS4: All patients with anaphylaxis should receive education on anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine, and the use of epinephrine auto-injectors, and they should be referred to an allergist.

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The guideline development group includes all of the relevant stakeholders, including patients.	✓	?
2. Systematic methods were used to search for evidence.	?	?
3. The criteria for selecting the evidence are clearly described.	X	?
4. The strengths and limitations of the body of evidence are clearly described (e.g., GRADE, Cochrane, etc.).	✓	✓
5. The health benefits, side effects, and risks were considered in formulating the recommendations.	✓	✓
6. There is an explicit approach linking the evidence to formulate the recommendations.	✓	✓
7. Experts externally reviewed the guideline prior to its publication.	✓	✓
8. The content of the guideline is free of influence by the views of the funding body.	?	?
9. Competing interests of guideline development group members have been recorded and managed.	✓	?
10. The strength and certainty of the key recommendations are clearly identified.	✓	✓

A1 = S. Upadhye A2 = J. Morris

Funding & Conflicts of Interest

Funding: Not specified.

Conflicts of Interest: Reported. Many industry relationships declared.

Potential Threats to Validity

Development: The steering group and support collaborators all seem to be appropriate healthcare/ER/allergy experts. No patient/public stakeholders reported. The search strategy was limited and only partially reported (ie not reproducible). Use of GRADE methods to evaluate evidence and formulate recommendations is explicitly described for each relevant question.

Presentation: Well organized with easy to find recommendations? **YES**

Comprehensive: Was the information to inform decision-making complete? **YES**

Clincal Validity: Are the recommendations clinically sound and appropriate for the intended patients? **YES**

Administrative Details

Key Words: anaphylaxis, epinephrine, antihistamines, glucocorticoids

Appraisers: Upadhye S, Morris J, ; LAST NAME OF FIRST AUTHOR & FIRST INITIAL. Do not separate last name and first name initial with commas.

Reference(s):

1. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Greenhawt M, Khan DA, Lang DM, Lang ES, Lieberman JA, Portnoy J, Rank MA< Stukus DR, Wang J. Anaphyllaxis – a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020; 145(4): 1082-1123.

Research Question

What are the factors associated with the need for longer ED observations periods in anaphylaxis?

BEEM Bottom Line

Why is this study important? This study reviews the literature on predictive factors associated with need for longer ED observation periods after initial anaphylaxis Rx.

Which, if any, threats to validity are most likely to have an impact on the results and how? Limited electronic database/language-restricted search (by a single searcher) could have led to missed relevant studies. The qualitative nature of data gathering precludes any concrete recommendations re: ED observation times.

How do the key results compare with the current evidence? The results of this review are congruent with similar recent reviews and guidelines addressing the ED management of severe anaphylaxis.

How should this study impact the care of ED patients? ED physicians should understand key predictors for biphasic anaphylaxis, and combine this with individual patient safety factors in making discharge decisions and in giving discharge patient instructions after treating initial severe anaphylaxis.

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No conflicts of interest/Identify conflicts (ICMJE)

Judy Morris MD MSc FRCPC
Associate Professor, Family and Emergency Medicine Department
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No conflicts of interest/Identify conflicts (ICMJE)

Study Summary

Article: Simard D, Bouchard V, Plourde A, *et al*. Factors influencing emergency department observation time following anaphylaxis: a systematic review. Can J Emerg Med 2021; 23: 480-493. DOI: 10.1007/s43678-021-00112-z

Design: Systematic review of studies examining factors associated with anaphylaxis severity and ED observation time.

Population: *Included:* Studies including ED patients being treated/observed after initial anaphylaxis Rx. No age restrictions.
Excluded: Case studies.

Intervention: Epinephrine, glucocorticoids.

Comparison: N/A

Outcomes: *Primary:* Factors associated with longer ED observation times.
Secondary: Variance in anaphylaxis/biphasic definitions across studies.

Key Results: *N* = 21 primary studies, 22707 patients. 14 retrospective, 9 pediatric, 3 adult studies, 9 reviews, 15 guidelines/expert opinion papers

Sig.	*Outcome*	*N/Studies*	*Details*	I^2
Not SIgnificant	Use of glucocorticoids in initial anaphylaxis Rx	N/A	Mixed results on the utility of glucocorticoids as an effective Rx, and independent predictor of biphasic anaphylaxis	
Significant	Biphasic anaphylaxis	N/A	Risk factors for BA = initial anaphylaxis severity, need for multiple epinephrine initial doses, delay in initial epinephrine dose, Hx of prior anaphylaxis, unknown triggers, and young age.	
Significant	Use of NIAID/FAAN criteria for defining anaphylaxis/BA	N/A	Most studies used these criteria; authors recommend adoption of same criteria for all future studies	

BEEM Critique

Risk of Bias Assessment

	A1	A2
1. The research question is sensible and answerable.	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	X	X
3. The search for studies was unbiased and reproducible.	?	?
4. The selection of studies was unbiased and reproducible.	X	X
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	?	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	?
7. The quality of the primary studies is high.	✓	?
8. The methods used to combine the included primary studies were reported and valid.	?	?
9. The outcomes are clinically relevant.	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	X	X

A1 = S. Upadhye A2 = J. Morris

Funding & Conflicts of Interest

Funding: None.

Conflicts of Interest: None (reported as such).

Potential Threats to Validity

Chance: None?

Selection Bias: Search limited to specific electronic databases, and 2 EM textbooks. Articles in English/French only included. Search period limit 2008-2018 for a disease with little changes in disease characteristics and treatments over the years. Articles selected by a single author. Lack of detailed study review may have led to inclusion of primary studies that were also part of review articles/guidelines also included (ie. double inclusion?).

Measurement Bias: Data extracted singly by one author, then validated independently by another (not parallel independent abstractions with 3rd party resolution). Use of Cochrane RoB tool for study quality (reported). No attempt to quantify or pool risk factors.

Analysis Bias: Qualitative analysis of predictors factors based on frequency of reporting, not actual patient outcome numbers (ie. no quantitative data analyzed).

Confounding: Potential confounding in the initial study themselves especially given the high number of retrospective studies included and some studies including the same study population.

Administrative Details

Key Words: Anaphylaxis, Biphasic, ED Observation, Risk/prognostic factors

Appraisers: Upadhye S, Morris J.

Reference(s):

1. Simard D, Bouchard V, Plourde A, Lefebvre S, Herman-Lemelin A, Lapointe S, Tremblay L, Desmeules C, Gagne A, Bouchard J. Factors influencing emergency department observation time following anaphylaxis: a systematic review. Can J Emerg Med 2021; 23: 480-493. DOI: 10.1007/s43678-021-00112-z

Research Question

How does chest ultrasonography compare to supine chest radiography for the diagnosis of pneumothorax in trauma patients?

BEEM Bottom Line

Why is this study important? Supine chest x-ray (CXR) is recommended in the current Advanced Trauma Life Support guidelines for the emergency department (ED) assessment of the trauma patient.[1] Bedside chest ultrasound (CUS) allows timely and accurate diagnosis of pneumothorax which is important in trauma care. This systematic review evaluates the evidence comparing CXR and CUS for the diagnosis of pneumothorax in supine trauma patients.

Which, if any, threats to validity are most likely to have an impact on the results and how? The review presents low certainty evidence that the diagnostic accuracy of CUS is superior to CXR for diagnosing pneumothorax. The results of the review are primarily limited by most primary studies being at high or unclear risk of bias and the observed heterogeneity in the sensitivity of CXR across trials. There was a high or unclear risk of bias in patient selection which could mean CUS might not perform as well in certain patient populations. The minimal level of operator training required is unknown which threatens generalizability of the results to clinicians who may not have a solid background in POCUS.

How do the key results compare with the current evidence? The findings of this review are consistent with the results of current studies regarding the sensitivity and specificity of CUS in detecting pneumothorax in adult trauma centre patients.[2] However, a lower sensitivity has been observed in pediatric trauma and in pre-hospital settings.[3,4]

How should this study impact the care of ED patients? CUS should be considered a first line tool in detecting traumatic pneumothorax in the supine trauma patient. CXR and CT should continue to be used as additional diagnostic tests in stable trauma patients with a moderate-to-high pretest probability of pathology.

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No conflicts of interest (ICMJE)

Study Summary

Article: Chan KK, Joo DA, McRae AD, et al. Chest ultrasonography versus supine chest radiography for diagnosis of pneumothorax in trauma patients in the emergency department. Cochrane Database Syst Rev. 2020;7(7):CD013031. Published 2020 Jul 23.

Design: Systematic review and meta-analysis of prospective, paired comparative accuracy studies.

Population: *Included:* Trauma patients with suspected traumatic pneumothorax (age range unspecified).
Excluded: hemodynamically unstable patients; CUS unavailable; chest wall injuries precluding CUS; CT not indicated.

Index Test: Supine CUS and CXR.

Reference Test: Computed tomography (CT) of the chest or clinical findings of a rush of air or bubbling in chest drain after tube thoracostomy (TT).

Diagnosis of Interest: Traumatic pneumothorax of any severity.

Key Results: *N* = 1,271 patients in 9 studies.

Sig.	*Measure*	*CUS*	*CXR*	*Difference*	**P-value*
SS	Sensitivity (95% CI)	0.91 (0.85 to 0.94)	0.47 (0.31 to 0.63)	0.44 (0.27 to 0.61)	< 0.001
NSS	Specificity (95% CI)	0.99 (0.97 to 1.00)	1.00 (0.97 to 1.00)	−0.007 (−0.018 to 0.005)	0.35

CI = confidence interval; *N* = number of patients; NSS = not statistically significant; *p* = probability; Sig. = significance; SS = statistically significant. *P-values express the probability of observing differences that are as or more extreme than the observed differences when no true differences exist between the tested quantities. These are usually compared against an arbitrary cutoff value such as 0.05 (5%). We encourage readers to instead rely on effect sizes and confidence intervals for clinical decision-making, which communicate magnitude and precision of observed differences.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	?	?
2. The search included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	?	?	?
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The quality assessment of the primary studies used QUADAS, was unbiased, and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The populations, cut-off thresholds, and reference standards were similar for combined studies.	✓	✓	✓
9. The subgroups were stated a priori and appropriate.	✓	✓	✓
10. The methods of meta-analyses are valid (e.g., summary ROC or bivariate random effects).	✓	✓	✓

A = appraiser; QUADAS = quality assessment of diagnostic accuracy studies; ROC = receiver operating characteristic curve.

Funding & Conflicts of Interest

Funding: Cochrane Collaboration.

Conflicts of Interest: The authors declare no conflicts of interest.

Potential Threats to Validity

Chance: None detected.

Selection Bias: Most studies were at high risk of selection bias because of inappropriate eligibility criteria making the sample unrepresentative of those that would typically be suspected of having a pneumothorax and candidate for CUS or CXR.

Measurement Bias: Most primary studies were at unclear risk of bias because blinding of outcome assessors to the results of the index/reference tests was not reported.

Analysis Bias: None detected.

Confounding: None detected.

Administrative Details

Key Words: Chest ultrasound (CUS); chest xray (CXR); diagnosis; pneumothorax; trauma; ultrasonography.

Appraisers: Zeraatkar D; Worster A; Hall G.

Reference(s):

1. ATLS Committee. Advanced Trauma Life Support Student Course Manual. 9th edition. Chicago: American College of Surgeons, 2012.

2. Jahanshir A, Moghari SM, Ahmadi A, et al. Value of point-of-care ultrasonography compared with computed tomography scan in detecting potential life-threatening conditions in blunt chest trauma patients. Ultrasound J. 2020;12(1):36.

3. Vasquez DG, Berg GM, Srour SG, et al. Lung Ultrasound for detecting pneumothorax in injured children: preliminary experience at a community-based Level II pediatric trauma center. Pediatric Radiology. 2020; 50:329-337.

4. Oliver P, Bannister P, Bootland D, et al. Diagnostic performance of prehospital ultrasound diagnosis for traumatic pneumothorax by a UK Helicopter Emergency Medical Service. European Journal of Emergency Medicine. 2020;27(3):202-206.

5. Bignucolo A, Acton C, Ohle R, et al. Traumatic pneumothorax mapping using computed tomography to assess optimal area to scan with POCUS. CJEM. 2020 Sep;22(5):708-711.

Research Question

What are the potential benefits and harms of suturing mammalian bite wounds?

BEEM Bottom Line

Why is this study important? The 2014 Infectious Disease Society of America (IDSA) guidelines for mammalian bite wounds recommend against primary wound closure.[1] The exception is facial wounds where closure is recommended following copious irrigation and antibiotic prophylaxis. The citations supporting these recommendations are between 30 and 48 years old and are low quality evidence. Wounds at high risk of rabies are a special case: they should not be closed or undergo delayed, loose approximation so that regionally infiltrated Rabies Immunoglobulin can take effect.[2] It is unknown whether suturing bite wounds not at risk for rabies increases the infection rate or changes the appearance of the scar.

Which, if any, threats to validity are most likely to have an impact on the results and how? This systematic review was well performed. An extensive search and careful application of eligibility found very few studies. The included studies all had some degree of bias (moderate to high risk). Outcome assessments for healing and infection were completed with non-blinded assessors; wound appearance may have been influenced by subjectivity. Finally, there were too few events for each outcome to provide a precise result with estimates ranging from potential harm to benefit from primary closure.

How do the key results compare with the current evidence? This review identified only 4 trials, all involving dog bites: 3 trials with 878 subjects comparing primary closure with no closure and a single trial with 120 patients comparing primary to delayed closure. Pooled estimates did not show a difference between primary closure and no closure, but this evidence is "low certainty" due to bias and small numbers. The pooled estimates are underpowered to detect a difference between primary and delayed/no closure.

How should this study impact the care of emergency department (ED) patients? The optimal management of mammalian bite wounds remains unknown. There is a large variety of host and wound factors impacting infection and healing rates, requiring large sample sizes with wide eligibility criteria in order to determine best practice. Focused research in this area should be a priority for wound care researchers.

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No conflicts of interest (ICMJE)

Study Summary

Article: Bhaumik S, Kirubakaran R, Chaudhuri S. Primary closure versus delayed or no closure for traumatic wounds due to mammalian bite. Cochrane Database Syst Rev. 2019 Dec 6;12:CD011822.

Design: Systematic review and meta-analysis of randomized controlled trials.

Population: *Included:* Patients of all ages with acute (i.e., ≤ 24 hours), uncomplicated, mammalian bite wounds.
Excluded: Patients with wounds with infection at presentation and/or involving non-soft tissues(e.g., nerves, tendon, joints, bones, etc.).

Intervention: Primary closure.

Comparison: No closure (i.e., no approximation); delayed closure (approximation > 48 hours after wound cleaning and debridement as needed).

Outcomes: *Primary:* Time to complete wound healing.
Secondary: From time of injury: healed within 7, 10 and 14 days; infection-free (i.e., no evidence of pus, cellulitis, or bacterial growth by culture in 7, 10 and 14 days); cosmesis measured using any validated score (e.g., Cosmetic Visual Analogue Score [CVAS], Wound Evaluation Score [WES]) at 7, 10 and 14 days.

Key Results: *N* = 998 patients in 4 studies.

Sig.	*Outcome*	*Comparators*	*N/Studies*	*Measure (95% CI)*	I^2	*C of E*
NSS	Infection-free	Primary vs. no closure	782/2	RR 1.01 (0.97 to 1.05)	0	Very Low
NSS	Infection-free	Primary vs. delayed closure	120/1	RR 0.98 (0.90 to 1.07)	N/A	Very Low
SS	Cosmesis	Primary vs. no closure	182/1	MD –1.31 (–2.03 to –0.59)	N/A	Moderate

C of E = certainty of evidence; CI = confidence interval; I^2 = inconsistency index (measure of statistical heterogeneity); MD = mean difference; *N* = number of patients; N/A = not applicable; NSS = not statistically significant; RR = relative risk (because this is a ratio, if the value of the range includes 1, there is no difference); Sig. = significance; SS = statistically significant.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The research question is sensible and answerable.	✓	✓	✓
2. The search for studies included all languages, databases, abstracts, bibliographies, and expert contact.	✓	✓	✓
3. The search for studies was unbiased and reproducible.	✓	✓	✓
4. The selection of studies was unbiased and reproducible.	✓	✓	✓
5. The data abstraction was unbiased (e.g., conducted independently by 2 researchers).	✓	✓	✓
6. The assessment of the quality of the primary studies was unbiased and reproducible.	✓	✓	✓
7. The quality of the primary studies is high.	X	X	X
8. The methods used to combine the included primary studies were reported and valid.	✓	✓	✓
9. The outcomes are clinically relevant.	✓	✓	✓
10. The statistical heterogeneity of the primary outcome is low (< 25%).	✓	✓	✓

A = appraiser.

Funding & Conflicts of Interest

Funding: Cochrane Collaboration.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: Both pooled outcomes were severely underpowered and were consequently downgraded for their imprecision.

Selection Bias: It is unclear why the authors selected a precision maximizing filter on their MEDLINE search. Publication bias could not be statistically or visually assessed; however, they performed an otherwise comprehensive search. Therefore bias is not suspected.

Measurement Bias: Assessments of risk of bias and certainty of evidence were completed well. The individual studies included in the review; however, were subject to detection bias due to the inability to blind outcome assessors.

Analysis Bias: None detected.

Confounding: High risk of bias present in the 4 included studies may have confounded the results (specifically detection, performance, and selection bias).

Administrative Details

Key Words: Bite wound; infection; mammalian; suture; wound closure.

Appraisers: Bedard C; Worster A; Murray H.

Reference(s):

1. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014 Jul 15;59(2):147–59.
2. WHO. WHO Expert Consultation on Rabies, third report: WHO Technical Series Report No.1012, Geneva, 2018, ISBN 978-92–4–121021–8.

Research Question

Is conservative treatment for primary spontaneous pneumothorax noninferior to interventional treatment?

BEEM Bottom Line

Why is this study important? Invasive management for primary spontaneous pneumothorax (PSP) has not been shown to be superior or even equal to conservative management. Most cases of PSP resolve spontaneously with reduced healthcare costs and patient discomfort. This trial assesses whether conservative treatment of moderate to large PSP is noninferior to interventional treatment.

Which, if any, threats to validity are most likely to have an impact on the results and how? The inability to blind treating physicians led to an overestimate of radiographic resolution in the intervention group. Furthermore, the results of a sensitivity analysis treating those with missing 8-week outcome data as treatment failures could not rule out inferiority of conservative management. Finally, the generalizability of the sample also is highly limited as only 45% of potentially eligible patients underwent randomization.

How do the key results compare with the current evidence? The British Thoracic Society and European Respiratory Society recommend conservative management for small PSP without significant breathlessness and selected asymptomatic large PSP.[1,2] There is very limited randomized control trial (RCT) data on PSP management with a 2014 Cochrane Review noting no completed RCTs.[3]

How should this study impact the care of emergency department (ED) patients? Patients with any size PSP should have a chest tube inserted if they are experiencing hemodynamic or respiratory compromise. Intervention; however, is not without risk as the number needed to harm is 5. In young patients with PSP who are asymptomatic with normal physiological parameters and good access to medical care, a conservative approach may be reasonable in combination with an informed discussion with the patient.

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Study Summary

Article: Brown SGA, Ball EL, Perrin K, et al. Conservative versus Interventional Treatment for Spontaneous Pneumothorax. N Engl J Med. 2020 Jan 30;382(5):405–415.

Design: Multicenter (39 centers in Australia & New Zealand), open-label, noninferiority, randomized controlled trial.

Population: *Included:* Patients (≥ 14 and ≤ 50 years) with a unilateral PSP ≥ 32% on chest radiography according to the Collins method (sum of interpleural distances, > 6 cm).
Excluded: Previous ipsilateral PSP; secondary pneumothorax; coexistent haemothorax; bilateral pneumothorax; tension pneumothorax and/or clinical instability including respiratory rate > 30 breaths/minute or oxygen saturation (SaO_2) < 90% breathing room air; pain or breathlessness; pregnancy; unlikely to re-attend hospital or present for study follow up; air travel within 12 weeks.

Intervention: Prior to treatment, all patients received O_2 (if SpO2 < 92% on room air) and analgesia (acetaminophen, ibuprofen, and oral or intravenous opioids as needed). Conservative management consisted of observation for 4 hours and discharge if no radiographic recurrence or clinical instability (patient walking comfortably on room air).

Comparison: Interventional management consisted of insertion of a Seldinger-style chest tube (≤ 12 French) attached to an underwater seal, without suction and repeat chest radiograph 1 hour later to confirm lung expansion. Drain removal and discharge if no radiographic recurrence or clinical instability at 4 hours. All others admitted.

Outcomes: *Primary:* Complete PSP radiographic resolution (i.e., full lung re-expansion) as determined by the treating physician ≤ 8 weeks.
Secondary: Complete PSP radiographic resolution as per-protocol (APP) analysis; complete PSP radiographic resolution as reviewed by blinded radiologists; time to complete resolution of symptoms; adverse events; hospital length-of-stay; number of days off work.

Key Results: *N* = 316 patients.

Sig.	*Outcome*	*Interventional*	*Conservative*	*ARR (95% CI)*	*NNT* (95% CI)*
NSS	PSP Resolution (ITT)	129/131	118/125	–4.1 (–8.6 to 0.5)	N/A
NSS	PSP Resolution (APP)	124/126	123/130	–3.8 (–8.3 to 0.7)	N/A
SS	Days off work	10.9 days	6.0 days	2.0 (1.0 to 3.0)	N/A
Sig.	*Outcome*	*Interventional*	*Conservative*	*ARI (95% CI)*	*NNH* (95% CI)*
SS	Adverse events	41/154	13/162	18.6 (10.5 to 26.7)	5 (10 to 4)

ARI = absolute risk increase; ARR = absolute risk reduction (if the CI includes the value 0, there is no difference in risk between the groups and the NNT is not estimable); CI = confidence interval; ITT = intention-to-treat; *N* = number of patients; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; NSS = not statistically significant; Sig. = significance; SS = statistically significant.
*Because NNT (and NNH) refer to people the estimates have been rounded off to the next highest whole number.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	?	?	X
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	X	X	X
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	?	?	X
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	X	X	X
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	✓	✓	✓

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Funded by the Emergency Medicine Foundation and others.

Conflicts of Interest: None.

Potential Threats to Validity

Chance: The study appears to have sufficient power; however, the significance levels for the secondary analyses were not adjusted for; therefore, the results are subject to type I error.

Selection Bias: Despite adequate randomization procedures, the intervention group had patients with longer symptom duration and higher number of pack per year of tobacco smoking compared with the conservative management group. The generalizability of the sample also is highly limited as only 45% of potentially eligible patients underwent randomization, with the majority of patients being male (> 80%) with a low BMI (average of 21). However, this may not be a true selection bias as it reflects the natural disease presentation.

Measurement Bias: High risk of both detection and performance bias due to the inability to mask treating physicians. Treating physicians were significantly more likely to report radiographic resolution than blinded radiologists.

Analysis Bias: The analysis used ITT procedures; however, there was contamination between groups: 15.4% randomized to conservative treatment received the intervention, which increased the adverse event rate in this group and biases the results towards noninferiority. Sensitivity analyses treating those missing outcome data at 8 weeks as treatment failures yielded a CI that crossed the margin of noninferiority.

Confounding: Differences between groups in their smoking history and symptom duration may have confounded the results.

Administrative Details

Key Words: Chest tube; primary spontaneous pneumothorax (PSP); thoracostomy.

Appraisers: Bedard C; Worster A; Sharif S.

Reference(s):

1. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. Thorax 2010;65:ii 18–ii31.
2. Tschopp J-M, Bincliffe O, Astoul P *et al*. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. European Respiratory Journal. 2015. 46: 321–335.
3. Ashby M, Haug G, Mulcahu P, *et al*. Conservative versus interventional management for primary spontaneous pneumothorax in adults. Cochrane Database Syst Rev. 2014;(12):Cd010565.
4. Collins CD, Lopez A, Mathie A, et al. Quantification of pneumothorax size on chest radiographs using interpleural distances: regression analysis based on volume measurements from helical CT. AJR Am J Roentgenol. 1995 Nov;165(5):1127–30.

Research Question

Does surgical repair within 6 hours of hip fracture diagnosis decrease mortality and major adverse events?

BEEM Bottom Line

Why is this study important? Hip fracture is a common emergency department (ED) presentation, especially in the older adult population, frail or fit. They are at increased risk of mortality and morbidities; therefore, many clinical guidelines recommend that surgery should happen in a timely manner. However, the best time to operate is still unknown.

Which, if any, threats to validity are most likely to have an impact on the results and how? Firstly, the convenience sample restricts generalizability of the results to a higher risk population of patients presenting to hospital outside of regular working hours. Secondly, most eligible patients were not enrolled with the most common reason being the inability to secure an operating room which suggests reduced applicability to hospitals with fewer surgical resources. Finally, despite an overall low risk of bias in the trial, there is some concern for performance bias because clinical personnel were aware of patients' group assignment; however, this is unlikely to substantially influence the results given the objective nature of the primary outcomes.

How do the key results compare with the current evidence? This study had an ambitious targeted time-to-surgery and achieved a median time from hip fracture diagnosis to surgery of 6 hours (h) (interquartile range [IQR] 4 to 9) in the rapid-care group and 24 h (IQR 10 to 42) in the standard-care group. A meta-analysis of observational studies showed a significant reduction in mortality when surgery was performed earlier rather than later with cut-offs of < 24 h, < 48 h and < 72 h.[1] An old (1998) randomized trial of 71 patients reported that patients with proximal femur fractures who underwent surgery within 24 h had a shorter length of hospital stay without an increase in mortality rate, deterioration in function or increase in need for social support than the standard care group.[2]

How should this study impact the care of ED patients? Hip fracture is a painful traumatism and surgical repair should occur as soon as possible. How soon? The answer is probably sometime within the first 24 h after the trauma. Rushing to surgery within 6 h does not seem to provide significant mortality or major morbidity benefit.

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No conflicts of interest (ICMJE)

Study Summary

Article: HIP ATTACK Investigators. Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial. Lancet. 2020 Feb 7. pii: S0140-6736(20)30058-1.

Design: Multicenter (69 hospitals in 17 countries), superiority, randomized, controlled trial.

Population: *Included:* Adults (≥ 45 years) with a closed hip fracture from a fall at standing height and requiring surgery. *Excluded*: Patients requiring emergent treatment for any reason; bilateral hip or peri-prosthetic fractures; intake of any non-reversible anticoagulants ≤ 24 h prior to enrolment; on vitamin K antagonist and history of heparin induced thrombocytopenia (HIT); refusing participation or previously enrolled.

Intervention: Rapid medical clearance and surgical repair ≤ 6 h of hip fracture diagnosis.

Comparison: Standard timing of medical clearance and surgical repair of hip fracture.

Outcomes: *Primary:* 1) Composite of mortality of major complications including nonfatal myocardial infarction (MI), pulmonary embolism, pneumonia, sepsis, stroke, and major bleeding; 2) all-cause mortality at 90 days (d). *Secondary:* All-cause mortality at 1 year; vascular and non- vascular mortality, and MI at 90 days and 1 year.

Key Results: *N* = 2,970 patients.

Sig.	*Outcome*	*Intervention*	*Control*	*HR (95% CI)*
NSS	Composite at 90 d	321/1487	331/1483	0.97 (0.83 to 1.13)
NSS	Mortality at 90 d	140/1487	154/1483	0.91 (0.72 to 1.14)
NSS	MI at 90 d	84/1487	80/1483	1.05 (0.77 to 1.43)

CI = confidence interval; HR = hazard ratio (if the CI includes the value 1, there is no difference in risk between the groups); *N* = number of patients; NSS = not statistically significant; Sig. = significance.

BEEM Critique

Risk of Bias Assessment

	A1	A2	A3
1. The patients were recruited consecutively.	X	X	X
2. The patients were adequately randomized (allocation sequence adequately generated).	✓	✓	✓
3. The allocation sequence was adequately concealed.	✓	✓	✓
4. The patients in all groups were similar with respect to prognostic factors.	✓	✓	✓
5. All clinicians, patients, and outcome assessors were unaware of group allocation.	X	X	X
6. All groups were treated equally except for the intervention.	✓	✓	✓
7. The follow-up was complete given the study duration (100% if in-hospital follow-up).	✓	✓	✓
8. The patients were analyzed in the groups to which they were randomized (ITT).	✓	✓	✓
9. All patient-important outcomes were considered.	✓	✓	✓
10. The effect size of the primary outcome is clinically significant.	X	X	X

A = appraiser; ITT = intention to treat.

Funding & Conflicts of Interest

Funding: Canadian Institutes of Health Research.

Conflicts of Interest: Multiple authors received fees and grants outside the submitted work.

Potential Threats to Validity

Chance: The analyses were slightly underpowered due to the exclusion of data from 3 study centres with poor data quality and the lower than expected event rate for both primary outcomes.

Selection Bias: The study recruited a convenience sample of patients which limits the generalizability of the results to those presenting to the ED outside of regular working hours (i.e. likely not applicable to higher risk patients). Additionally, over 60% of eligible patients were not enrolled, further restricting generalizability of the results. Otherwise, selection bias is low given adequate randomization methods and apparent balance in prognostic factors between groups.

Measurement Bias: There was no standardized measurement of health status prior to surgery. Some concern for performance bias given the inability to blind clinical personnel. There is low risk of detection bias because outcome assessors were blinded.

Analysis Bias: None identified.

Confounding: None identified.

Administrative Details

Key Words: Hip fracture; complication; mortality; surgery.

Appraisers: Bedard C; Worster A; Brousseau A-A.

Reference(s): 1. Simunovic N, Devereaux PJ, Sprague S, et al. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ. 2010;182(15):1609-16.
2. Swanson CE, Day GA, Yelland CE, et al. The management of elderly patients with femoral fractures. A randomised controlled trial of early intervention versus standard care. Med J Aust. 1998;169(10):515-8.