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Andrew Worster, MD
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The Most Relevant, Reliable, and Unbiased Continuing Medical Education for Emergency Medicine Practitioners

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ACEP Clinical Policy: Critical issues in the evaluation and management of adult patients presenting to the ED with seizures. ......................................................................................................................................... 93
Are alpha-blockers effective as medical expulsive therapy for ureteral stones?

The Bottom Line: Adult patients presenting with symptoms of ureteral stones and confirmation of a single stone <1 cm with no signs of infection, hydronephrosis, or renal tract abnormalities should be offered alpha-blocker medical expulsive therapy (tamsulosin 0.4 mg once daily).

Article Title: Alpha-blockers as medical expulsive therapy for ureteral stones.


PubMed ID: 24691989

Population: All randomized controlled trials in the Cochrane Renal Group’s Specialised Register (to 9 July 2012) from CENTRAL, MEDLINE and EMBASE, and including hand searches of conference proceedings and the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Intervention: Alpha-blockers as medical expulsive therapy for ureteral stones in adult patients.

Outcomes: Stone clearance.

Authors’ Conclusions: The use of alpha-blockers in patients with ureteral stones results in a higher stone-free rate and a shorter time to stone expulsion. Alpha-blockers should, therefore, be offered as part of medical expulsive therapy as one of the primary treatment modalities.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. No
7. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: In 25 of the 32 studies, there was only single blinding and blinding was not described in the methods or no blinding had taken place. Two studies had incomplete data and one reported a relatively high number of patients who withdrew from the study. The inconsistency index for heterogeneity ranged from 0% to 94% although was mostly >64% (high heterogeneity) for treatment outcomes. These combined factors limit the methodological strength of the evidence found.
Key Results:
- The results are based on 32 studies with 5,864 adult participants and showed that patients in the alpha 1-receptor blocker groups (compared to standard therapy, calcium channel blockers or placebo) had significantly higher stone-free rates (RR = 1.48 [95% CI: 1.3 to 1.6]; NNT = 3.99 [95% CI: 3.48 to 4.70]); passed a stone 2.9 days sooner (mean difference of -2.9 [95% CI: -4.0 to -1.8]); had fewer painful episodes (MD -0.48 [95% CI: -0.94 to -0.01]); and fewer hospital admissions (RR = 0.35 [95% CI: 0.1 to 1.00]). However, patients using alpha 1-receptor blockers were more likely to experience adverse effects (RR = 2.7 [95% CI: 1.4 to 5.5]) although most adverse effects were mild and did not lead to therapy discontinuation.

BEEM Commentary: In the ureter, alpha 1-receptor antagonists inhibit basal tone and decrease peristaltic activity resulting in reduced intra-ureteral pressure and increased fluid transport. It seems clinically sensible that these drugs would be effective at facilitating ureteric calculi passage perhaps especially in the lower ureter where alpha 1-receptors are predominant. The overall evidence from this review shows alpha 1-receptor antagonists (mostly tamsulosin 0.4 mg once daily) to be effective in facilitating ureteric calculi passage when compared to standard therapy, calcium channel blockers, or placebo. Although, given the methods of some of the studies and the heterogeneity of the results, the relative risk of the primary outcome is likely less than the cited 1.48 (NNT = 4). However, even a diminished effect that doubled the NNT to eight would still make it one of the most effective therapies offered by emergency physicians with only minor side effects. For example, thrombolytics (given within six hours) for STEMI, NNT = 43 for one life saved.
Should the initial imaging method for patients with suspected nephrolithiasis be computed tomography (CT), point of care ultrasonography (POCUS) or formal ultrasonography (FUS)?

**The Bottom Line:** Ultrasound as a first line test for suspected acute renal stone disease is reasonable. There appear to be multiple benefits to both the patient and the healthcare system.

**Article Title:** Ultrasonography versus computed tomography for suspected nephrolithiasis.


**PubMed ID:** 25229916

**Population:** ED patients 18 to 76 years of age with suspected nephrolithiasis. All pregnant patients were excluded, even if renal stone disease was the primary diagnosis in the differential.

Excluded: Men weighing >129 kg; women weighing >113 kg; on dialysis; with a single kidney; renal transplant recipient; or pregnant.

**Intervention:** Initial diagnostic ultrasonography performed by an emergency physician (point-of-care ultrasonography (POCUS)), ultrasonography (US) performed by a radiologist, i.e. formal US (FUS), or abdominal computed tomography (CT).

**Outcomes:**
- **Primary:** 30-day incidence of high-risk diagnoses with complications that could be related to missed or delayed diagnosis and the six-month cumulative radiation exposure.
- **Secondary:** Serious adverse events; related serious adverse events (deemed attributable to study participation); pain (assessed on an 11-point visual-analogue scale, with higher scores indicating more severe pain); return ED visits; hospitalizations; and diagnostic accuracy.

**Authors’ Conclusions:** Initial ultrasonography (both point of care and formal ultrasonography) was associated with lower cumulative radiation exposure than initial CT, without significant differences in high-risk diagnoses, complications, serious adverse events, pain scores, return ED visits, or hospitalizations.

**Quality Checklist:**
1. The study population included or focused on those in the ED. **Yes**
   **Comment:** Only emergency presentations were included, though initial inclusion criteria and exclusion selection was at the discretion of the emergency physician.
2. The patients were adequately randomized. **Yes**
3. The randomization process was concealed. **No**
4. The patients were analyzed in the groups to which they were randomized. **Yes**
5. The study patients were recruited consecutively (i.e. no selection bias). **No**
6. The patients in both groups were similar with respect to prognostic factors. **Yes**

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **No**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** Patients were only randomized if all three imaging tests were available in the department. Both the patient and the treating physician would be aware of which imaging test was being used to rule in/out primary renal stone disease. Because of the availability of imaging modalities and the variation in inclusion criteria for renal stone disease being primary in the differential, subject selection was not continuous and randomization could not be concealed. The weight exclusion criteria was not explained, which is important because no approved definition of obese outside of objective weight was used to exclude patients. Therefore, the author’s weight-based exclusion criteria may not reflect adipose tissue or impaired imaging with either US or CT modality.

**Key Results:**
- 2,759 patients randomized: 908 to POCUS; 893 to RUS; and 958 to CT. The incidence of high-risk diagnoses with complications in the first 30 days (0.4%) did not differ between the three groups. The mean six-month cumulative radiation exposure was significantly lower in the US groups than in the CT group (p <0.001). Serious adverse events occurred in 12.4% of the patients assigned to POCUS, 10.8% of those assigned to FUS, and 11.2% of those assigned to CT (p = 0.50). Related adverse events were infrequent (incidence, 0.4%) and similar across groups. Return emergency department visits, hospitalizations, and diagnostic accuracy did not differ significantly among the groups.

**BEEM Commentary:** The author’s comments are reasonable, though they did not comment on the characteristics of stone diagnosis on US, actual stone visualization, hydronephrosis, ureteral jets, free fluid, etc. Comments were made that POCUS in higher subsequent CT use compared to formal radiology scans. They hypothesized that this was because of provider confidence but do not detail sonography equipment used, sonographer experience, or actual ultrasound findings.
Is there a set of clinical features that can be used to rule out appendicitis in patients with suspected acute appendicitis and nondiagnostic ultrasound?

The Bottom Line: If validated, this CDR may assist in reducing wait times and unnecessary ED imaging. Notably, it applies only to the exclusion of acute appendicitis after sonography and requires next day follow-up and reassessment.

Article Title: A simple clinical decision rule to rule out appendicitis in patients with nondiagnostic ultrasound results.


PubMed ID: 24842498

Population: Patients with suspected appendicitis and negative or inconclusive radiology-performed ultrasound (US) from six (2 university, 6 large teaching) Dutch hospitals. The development data set obtained from May 2005 through December 2006 included 422 adult patients with suspected acute appendicitis based on both CT and US results. The validation data set obtained from March 2010 through September 2010 included 211 patients with suspected acute appendicitis.

Intervention: Derivation and validation of a clinical decision rule to identify patients at low risk of appendicitis who are theoretically safe to forego immediate further imaging after negative or inconclusive US. The gold standard used by the investigators was expert assessment (2 surgeons and 1 radiologist) using all available data (clinical, CT, MRI, US) with at least three months follow-up.

Outcomes: Diagnostic accuracy of the new CDR (ROC AUC, sensitivity, specificity, negative predictive value, positive predictive value).

Authors’ Conclusions: The decision rule presented here could assist in lowering the number of imaging investigations in patients with suspected appendicitis. Before final recommendations can be made, its feasibility and utility should be further explored. This could be done in a so-called management study, in which the rule is implemented in a protocol and its performance closely monitored over time by carefully collecting patient outcomes. An alternative study design, requiring a higher number of patients to be included, would be to randomly allocate patients with suspected appendicitis and a negative or inconclusive US to the decision rule or to standard additional imaging.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: Unselected patients presenting to six Dutch academic and teaching hospitals.

2. The patients were representative of those with the problem. Yes

3. All important predictor variables and outcomes were explicitly specified. No
4. This is a prospective, multicentre study including a broad spectrum of patients and clinicians (level II).  
   **Yes**

5. Clinicians interpret individual predictor variables and score the clinical decision rule reliably and accurately.  
   **Unsure**

6. This is an impact analysis of a previously validated CDR (level I).  
   **No**

7. For Level I studies, impact on clinician behavior and patient-centric outcomes is reported.  
   **No**

8. The follow-up was sufficiently long and complete.  
   **Yes**

9. The effect was large enough and precise enough to be clinically significant.  
   **Yes**

**Methodological Critique:** This paper describes development and validation of a CDR, and is not an impact analysis. Overall, this is a high quality ED-based study that evaluates a population of direct interest to ED providers: abdominal pain patients with suspected appendicitis and non-diagnostic US imaging. Nonetheless, there are some concerns.

First, US was obtained by radiologists, not emergency physicians. Many contemporary adult EDs lack access to radiology-performed US for appendicitis. Future studies ought to evaluate the diagnostic accuracy of this CDR on patients with clinical uncertainty after ED-performed bedside US, although it is unlikely that the CDR would be less accurate in this population.

Second, in deriving a CDR it is essential that an exhaustive list of candidate variables be generated. The investigators only referenced two sources from which they derived 14 candidate variables. One of the best resources for diagnostic accuracy, the JAMA Rationale Clinical Exam (JAMA 1996; 276: 1589-1594), was ignored so the authors likely neglected several potentially important predictor variables like the psoas sign and the obturator sign.

Third, it is unclear whether clinicians who “prospectively collected data with a web-based digital case record form” did so with knowledge of the CT or US findings. Multiple forms of diagnostic research bias exist (see Acad Emerg Med 2013; 20: 1194-1206) so understanding what bedside clinicians did and did not know when they recorded their findings is essential to understanding the risk and skew of bias.

Fourth, the dichotomous outcomes of ‘discharge or next day reassessment’ may not be viable in many contexts where social or institutional factors render next day reassessment unrealistic. Further, appendicitis is usually considered against other differential diagnoses, and especially in females, is often not the only pathology being evaluated by imaging.

Finally, there was an unusually large proportion of inconclusive US results (22% in the development group and 47% in validation). The authors postulate this may be related to radiologist cognizance of study participation, and not wanting to miss a diagnosis, they instead classified some studies as ‘inconclusive’ when they may have otherwise called them negative. Either way, patient outcomes would be unaffected as both conclusions lead to CT evaluation.

**Key Results:**
- From the derivation data set, 199 patients with negative or inconclusive US for acute appendicitis were included in the development of this CDR. To rule out appendicitis in this group (with negative or inconclusive US), less than two of the following criteria could be met (males, migration of pain to the right lower quadrant, vomiting, and elevated white blood cell count).
Application of the CDR in the development arm selected 63% of patients as low risk and suitable for discharge after negative or inconclusive US for acute appendicitis. Using a validation cohort of 120 patients (of which 12% had appendicitis), the CDR found 72 patients (of which 6% had appendicitis) for early discharge and next day out-patient reassessment with the following diagnostic accuracy: sensitivity 83% [95% CI: 64% to 94%], specificity 71% [95% CI: 66% to 74%], positive likelihood ratio 2.86 [95% CI: 1.99 to 4.09], and negative likelihood ratio 0.24 [95% CI: 1.99 to 4.09]. The authors report a negative predictive value (NPV) for the CDR of 94% [95% CI: 87% to 98%]. In comparison, the negative predictive value of CT was 99% [95% CI: 93% to 100%; p = 0.14] and for MRI was 99% [95% CI: 94% to 100%; p = 0.12].

**BEEM Commentary:** Before modifying clinical behaviour, we should await evaluation of feasibility and utility. This would require a larger number of patients, as well as random allocation between the CDR and standard imaging approach (which is variable between institutions). If ultimately supported, this CDR can help reduce ED wait times by reducing imaging, without compromising patient safety. If validated in a separate population of patients, this CDR may assist in safe discharge of patients who are suspected to have appendicitis after negative or inconclusive US.
### Does trimethoprim–sulfamethoxazole increase risk of sudden death among patients taking spironolactone?

<table>
<thead>
<tr>
<th><strong>The Bottom Line:</strong></th>
<th>Careful consideration should be given to the choice and duration of antibiotic prescribed to older patients especially those on spironolactone.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Article Title:</strong></th>
<th>Trimethoprim–sulfamethoxazole and risk of sudden death among patients taking spironolactone.</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th><strong>PubMed ID:</strong></th>
<th>25646289</th>
</tr>
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<table>
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<tr>
<th><strong>Population:</strong></th>
<th>Patients ≥65 years old listed in the Ontario Drug Benefit Database and receiving continuous spironolactone. Cases defined as patients who died of sudden death within 14 days after being prescribed antibiotic. For each case, four controls were matched by sex and age at the index date (within one year) and sex.</th>
</tr>
</thead>
</table>

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<tr>
<th><strong>Intervention:</strong></th>
<th>A prescription for trimethoprim–sulfamethoxazole (TMP-SMZ), ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin (without clavulanic acid).</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th><strong>Outcomes:</strong></th>
<th>Sudden death within 14 days after being prescribed one of the antibiotics.</th>
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**Authors’ Conclusions:** We found that TMP-SMZ was associated with a marked increase in the risk of sudden death among older patients receiving spironolactone, a finding that we speculate reflects trimethoprim-induced hyperkalemia. We also found a less pronounced but clinically important association with ciprofloxacin, and possibly nitrofurantoin. When clinically appropriate, clinicians should consider alternative antibiotics for patients receiving spironolactone.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **No**
   - **Comment:** Since this is a case control study from a large administrative database, all clinical settings would have been included.

2. The patients were representative of those with the problem. **Yes**

3. The patients were sufficiently homogeneous with respect to prognostic risk. **Yes**

4. Objective and unbiased outcome criteria were used. **Yes**

5. The follow-up was sufficiently long and complete. **Yes**

6. The effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** This population-based, nested case control study was funded by the Canadian Drug Safety and Effectiveness Research Network and the Ontario Ministry of Health and Long-Term Care. Given the harmful nature and rarity of outcome events of the research question, the case control design is appropriate but the study is still subject to the biases of this type of retrospective study. The hypothesis is that the combination of spironolactone and TMP-SMZ leads to fatal hyperkalemia. However, serum
potassium levels and renal function were not collected and there were no corresponding indications for the antibiotics, hence, patients who died might have been suffering more severe infections or more severe degrees of comorbidities.

**Key Results:**

- The 17-year study period identified 11,968/206,319 patients who experienced sudden death while on spironolactone and 349/11,968 who died within 14 days after receiving one of the study antibiotics. Of the 349 patients, 328 (94.0%) were matched to at least one control. 210/328 cases were ≥85 years and had more comorbidities and medications than the controls.

- TMP-SMZ treatment was associated with significantly more sudden deaths than amoxicillin (OR = 2.46 [95% CI: 1.55 to 3.90], ciprofloxacin (OR = 1.55 [95% CI: 1.02 to 2.38], and nitrofurantoin (OR = 1.70 [95% CI: 1.03 to 2.79]) during spironolactone therapy. There was no risk of sudden death with norfloxacin (OR = 0.86 [95% CI: 0.47 to 1.58]).
  - 14-Day Sudden Death Rate with Spironolactone:
    - TMP-SMZ 0.74%
    - Ciprofloxacin 0.54%
    - Nitrofurantoin 0.39%
    - Amoxicillin 0.35%
    - Norfloxacin 0.31%

**BEEM Commentary:** These antibiotics are commonly prescribed to elderly patients especially for urinary tract infections. Patients taking spironolactone are more likely to be older and, by association, have more comorbidities and medications and, therefore, be at greater risk of medication interaction and sudden death from any cause. Hence, these results might not apply to younger, healthier patients. Regardless, if hyperkalemia is the actual cause of sudden death in these patients as hypothesized, then presumably the patient’s renal function and the duration as well as type of antibiotic are contributing factors. This is one more reason to think twice about whether antibiotic therapy is really necessary and, if so, which one and for how long.

These overall findings are consistent with other BEEM-reported studies on the dangerous interactions between antibiotics and other medications (Gandhi S, Fleet JL, Bailey DG, McArthur E, Wald R, Rehman F, Garg AX. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. JAMA. 2013 Dec 18;310(23):2544-53.)
Can icatibant reduce the time to resolution of symptoms for patients with ACE-inhibitor–induced angioedema?

The Bottom Line: Validation of these results followed by widespread availability of icatibant could make a significant difference to many patients.

Article Title: A randomized trial of icatibant in ACE-inhibitor–induced angioedema.


PubMed ID: 25629740

Population: Patients 18 to 95 years old presenting to the ED with ACE-inhibitor–induced angioedema affecting the upper aerodigestive tract (face, lips, cheeks, tongue, soft palate or uvula, pharynx, and larynx).

Excluded: Patients with angioedema due to other causes; history of angioedema before initiation of ACE-inhibitor therapy; acute urticaria; unstable angina; acute myocardial ischemia; acute heart failure (NYHA III or IV) pregnancy; and lactation.

Intervention: Icatibant 30 mg SC into the abdominal wall and normal saline IV (placebo) within 10 hours after symptom onset, or Prednisolone 500 mg plus Clemastine (Tavegil, Novartis) 2 mg IV and normal saline SC within 10 hours after symptom onset.

Outcomes: Primary: Time to the complete resolution of edema after treatment.

Secondary: Proportion of patients requiring rescue therapy; the proportion of patients with complete resolution of edema four hours after treatment; adverse events.

Authors’ Conclusions: Among patients with ACE-inhibitor–induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: All ED patients.

2. The patients were adequately randomized. Yes

3. The randomization process was concealed. Yes

4. The patients were analyzed in the groups to which they were randomized. Yes

5. The study patients were recruited consecutively (i.e. no selection bias). Unsure

6. The patients in both groups were similar with respect to prognostic factors. Yes

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. Yes

8. All groups were treated equally except for the intervention. Yes
9. Follow-up was complete (i.e. at least 80% for both groups). Yes

10. All patient-important outcomes were considered. Yes

11. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: This well-designed and executed multicentre, double-blind, double-dummy, randomized phase two trial was funded by Shire and the Federal Ministry of Education and Research of Germany. The outcomes were a composite of investigator-assessed and patient-assessed symptom scores rather than the validated Angioedema Activity Score. Given that in the clinical setting, emergency physicians use subjective methods of assessment, there is no reason to believe that these evaluations are not valid. The analysis was as per protocol rather than intention-to-treat although the final analysis included all 27 randomized patients.

Key Results:
- The median time to complete resolution was eight hours (interquartile range (IQR): 3.0 to 16.0) with icatibant compared 27.1 hours (IQR: 20.3 to 48.0) with standard therapy (p = 0.002). Three standard therapy patients required rescue intervention with icatibant and prednisolone; one patient required tracheotomy. Significantly more patients in the icatibant group than in the standard-therapy group had complete resolution of edema within four hours after treatment (5 of 13 vs. 0 of 14). According to a composite investigator-assessed symptom score and to patient-assessed symptom scores, the median time to the onset of symptom relief was significantly shorter with icatibant (approximately two hours) vs. standard therapy (approximately 12 hours).

BEEM Commentary: ACE-inhibitor-induced angioedema can be a life-threatening condition with upper airway obstruction occurring in 10% of cases. Our treatment options in the ED are limited in range and effectiveness. Validation of these results using other standard therapies as controls followed by widespread availability of icatibant could make a significant difference to many patients.
### Does the addition of low-dose ketamine improve pain control with ED acute pain patients receiving IV opioids?

#### The Bottom Line:
Low-dose ketamine (0.15 mg/kg) IV could be a useful adjunct to morphine IV in treating acute pain conditions in the ED but further validation in other settings is needed.

#### Article Title:
Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial.

#### Reference:

#### PubMed ID:
25377395

#### Population:
English-speaking adults (18 to 65 years old), moderate to severe pain (NRS >5/10) for <7 seven days, deemed appropriate for IV opioid analgesia by ED physician. Excluded: Neuro/resp/hemodynamic compromise; known or suspected allergy to ketamine or morphine; acute psych illness; history of stroke; renal insufficiency; liver failure; CAD; pregnant; breastfeeding; pain not moderate; severe with just IV opioids/other adjuncts; or unable to provide consent.

#### Intervention:
Morphine + ketamine (Group 1 = 0.15 mg/kg, Group 2 = 0.3 mg/kg). 10-minute interval between meds to ensure no adverse reactions.

#### Outcomes:
**Primary:** Summed pain-intensity difference (SPID) at two hours (measured q30min).

**Secondary:** Numeric rating scale (NRS) score at each time point (0-10), total pain relief (5 point scale); amount of rescue analgesia needed, time to rescue analgesia, global analgesia effectiveness (Silverman integrated analgesic [SIA] assessment score = SPID + rescue analgesia usage). Adverse events also noted.

#### Authors’ Conclusions:
Low-dose ketamine is a viable analgesic adjunct to morphine for the treatment of moderate to severe acute pain. Dosing of 0.3 mg/kg is possibly more effective than 0.15 mg/kg, but may be associated with minor adverse events. Future studies should evaluate additional outcomes, optimum dosing, and use in specific populations.

#### Quality Checklist:
1. The study population included or focused on those in the ED. **Yes**  
   **Comment:** Large urban academic ED Rhode Island, Level I trauma, >100,000 adult ED visits/year.

2. The patients were adequately randomized. **Yes**

3. The randomization process was concealed. **Yes**

4. The patients were analyzed in the groups to which they were randomized. **Yes**
5. The study patients were recruited consecutively (i.e. no selection bias). **Unsure**

6. The patients in both groups were similar with respect to prognostic factors. **Unsure**

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **Yes**

8. All groups were treated equally except for the intervention. **Unsure**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **Unsure**

**Methodological Critique:** Superiority design, power based on expected 33% difference in SPID scores, targets met (20 per group). Patients recruited by trained RA's from 08:00 to midnight (based on RA availability). Study sample too small to ensure similar clinical diagnoses between groups. Unclear if patients may have had other nonopioid analgesics (i.e. acetaminophen, NSAIDs, muscle relaxants, etc.). Randomized computerized blocks of six patients. Randomization, allocation, meds dispensing overseen by pharmacist not involved in patient care (everyone else blinded); MDs/nurses made aware of pain assessments to determine need for rescue analgesia. Patients discharged prior to two-hour final assessment had imputed final scores.

**Key Results:**
- 78 patients enrolled, 60 completed (20 per group).
- Primary: Overall improvement in SPID scores in ketamine/morphine groups (Group 1: 50%, Group 2: 70%) vs. morphine alone (25%; overall p = 0.02). No difference between higher vs. lower dose ketamine groups.
- Secondary: Similar numbers of patients received rescue analgesia: standard care group, 7/20, 35%; group 1, 4/20, 20%; and group 2, 4/20, 20% (p = 0.48). Among those receiving rescue analgesia, those in the standard care group received analgesia sooner than either low-dose ketamine group, on average. More participants in the low-dose ketamine groups reported dysphoria and dizziness.

**BEEM Commentary:** Combining analgesics in the ED is not new and neither is the concept of low-dose ketamine (0.15 mg/kg) IV as an adjunct to morphine IV in treating acute pain conditions in the ED. While further validation in other settings is needed, this is a reasonable and relatively safe option for patients who do not achieve analgesia with high doses of morphine or are unable to tolerate them.
What are the appropriate quality indicators for assessing and managing pain in the ED?

**The Bottom Line:** Pain measurement is a tedious and possibly unreliable process, still in its infancy.

**Article Title:** Quality indicators for the assessment and management of pain in the emergency department: a systematic review.


**PubMed ID:** 25337856

**Population:** Original research that described the development or collection of data on one or more quality indicators relevant to the assessment or management of pain in ED in adult and pediatric ED patients.

Excluded: Studies outside of ED; hospital in-patients

**Intervention:** Pain assessment tools.

**Outcomes:** Type and use of different ED pain management quality indicators, indicator data sources, operational indicators, pain diagnoses.

**Authors’ Conclusions:** Gaps in the existing literature include a lack of measures reflecting procedural pain, patient outcomes and the pediatric population. Future efforts should focus on developing indicators specific to these key areas.

**Quality Checklist:**

1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **No**
4. The assessments of studies were reproducible. **Yes**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **Unsure**
7. The treatment effect was large enough and precise enough to be clinically significant. **Unsure**

**Methodological Critique:** Duplicated broad electronic searches, English-only language, single data abstraction. Study quality of observational studies based on Newcastle-Ottawa Scale; mixed quality levels. Qualitative synthesis of data outcomes, so no impact of heterogeneity, no treatment effects relevant. This study clarifies the many areas of pain control in the ED that can be operationalized and optimized. The vast majority of studies to date deal with initial pain presentations. There was a marked lack of indicators dealing with procedural pain, pediatric pain assessments and patient-oriented outcomes. Other barriers to
adequate indicator use were gender, language, and US insurance status. Majority of studies were retrospective in nature, so the inherent problems with such data collection were evident.

**Key Results:**
- 23 articles included: 15 observational studies, three before/after, three audits, one QI development study, one survey. Median 302 patients per study, majority adults, one pediatric study. Eleven studies in North America (one Canada), UK five, Australia four, France one. Methodological quality was moderate, with weaknesses in the reporting of study design and methodology.
- Most common indicators were those for pain assessment times, reassessments, and time to analgesia order/administration to patient (i.e. process indicators).
- 80% (16/20) of indicators focused on care processes, 3/20 measured structures (i.e. education programs), one on patient outcomes.
- Initial pain assessments ranged from 57% to 95%, but reassessments only 32% to 50%.
- Analgesia time for patients with "severe" pain ranged from 20 minutes to >1 hour post-triage.
- Median times to analgesia varied by diagnosis: hip fracture 141 minutes, renal colic 48 minutes, sickle cell pain crisis 90 minutes. Delayed analgesic times were observed with children and elderly patients.
- Only 34% to 39% patients reported "excellent" pain management satisfaction (one study).

**BEEM Commentary:** Appropriate analgesia in painful conditions has been designated a priority by the WHO and Institute of Medicine quality of care standards. In Canada, a national EM consensus document on prioritized quality indicators included pain management, specifically around documented pain assessments and times to initial analgesia (Schull et al, CJEM 2011). There is evidence also that ED overcrowding leads to increased delays in providing adequate analgesia to patients in pain. A variety of barriers to appropriate pain management in the ED have been previously outlined (Motov et al, J Pain Research 2009).

Instituting pain management protocols and education programming could be an achievable reality with the goal of optimizing rapid and competent patient analgesia in the ED, given the recent work on quality indicators and the results of this review. There is enough recent literature supporting protocol development for acute painful conditions in ED. As with most institutional process development plans, however, there is tedious work in creating appropriate protocols with all vested stakeholders, funding support, and institutional commitment to make ED pain management a priority. Whether this is a priority, however, in current busy ED practice, especially in the face of uninvested stakeholders or noncommittal institutions/funding, is another matter.

There is much work to do in optimizing pain measurement tools in the ED, which can then be used to actually change practice and measure the change outcomes reliably.
Which high sensitivity cardiac troponin assay is more accurate for diagnosing non-ST-elevation myocardial infarction (NSTEMI)?

The Bottom Line: The newer high sensitivity assays are more sensitive and precise than the previous generation assays and, therefore, likely more clinically useful in ruling out NSTEMI, especially when the results of two serial measurements are available. However, we still require clinical judgement to rule out acute coronary syndrome.

Article Title: Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction.


PubMed ID: 24842285

Population: Consecutive ED patients with suspected acute myocardial infarction in nine different study centres in Switzerland, Spain, and Italy.

Intervention: Measurement of cTnI and cTnT using clinically available high-sensitivity assays (hs-cTnI Abbott and hs-cTnT Roche).

Outcomes: Adjudicated non-ST-elevation myocardial infarction (NSTEMI).

Authors’ Conclusions: Both hs-cTnI and hs-cTnT provided high diagnostic and prognostic accuracy. The direct comparison revealed small but potentially important differences that might help to further improve the clinical use of hs-cTn in the management of patients presenting with suspected AMI.

Quality Checklist:

1. The clinical problem is well defined. Yes
   Comment: It is unknown whether cardiac troponin (cTn) I or cTnT is the preferred biomarker in the early diagnosis of acute myocardial infarction without ST segment elevation (NSTEMI).

2. The study population represents the target population that would normally be tested for the condition including (i.e. no spectrum bias). Yes

3. The study population included or focused on those in the ED. Yes

4. The study patients were recruited consecutively (i.e. no selection bias). Yes

5. The diagnostic evaluation was sufficiently comprehensive and applied equally to all patients (i.e. no evidence of verification bias). Yes

6. All diagnostic criteria were explicit, valid and reproducible (i.e. no incorporation bias). Yes

7. The reference standard was appropriate (i.e. no imperfect gold-standard bias). No

8. All undiagnosed patients underwent sufficiently long and comprehensive follow-up (i.e. no double gold-standard bias). Yes
9. The likelihood ratio(s) of the test(s) in question is presented or can be calculated from the information provided. **No**

10. The precision of the measure of diagnostic performance is satisfactory. **Yes**

**Methodological Critique:** Differences in diagnostic accuracy are difficult to interpret because diagnostic accuracy incorporates both sensitivity and specificity. In most cases, ED physicians are using cardiac troponin tests to rule out AMI hence the AUC diagnostic accuracy of the two tests might be very similar but the sensitivities significantly different. According to the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines (see http://www.equator-network.org/reporting-guidelines/stard/), diagnostic accuracy should be reported as positive and negative likelihood ratios (see http://pmid.us/10216335) so that clinicians can interpret research findings for bedside use.

**Key Results:**
- The diagnostic accuracy for NSTEMI of the two assays assessed at presentation as measured by the AUC (area under the receiver-operating-characteristics (ROC) curve) was not statistically significantly different: hs-cTnI AUC = 0.93 [95% CI: 0.92 to 0.94] and hs-cTnT AUC = 0.94 [95% CI: 0.92 to 0.94].

**BEEM Commentary:** The authors report that there are small but potentially important differences that might help to further improve the clinical use of high-sensitivity cardiac troponin assays. This might be true, but there are still many aspects of the pathophysiology of acute coronary syndrome (ACS) and the role of troponins that we don't understand. The diagnosis of NSTEMI is based on cardiac troponin levels and has no independent reference, hence any study that evaluates the diagnostic performance of a cardiac troponin assay for NSTEMI has a degree of incorporation bias (see http://pmid.us/18371254). The newer high sensitivity assays are both more sensitive and precise than the previous generation assays and, therefore, likely more clinically useful in ruling out NSTEMI, especially when the results of two serial measurements are available. However, regardless of diagnostic accuracy, we cannot determine with precision the clinical benefit associated with either hs-cTnI or hs-cTnT without conducting a randomized controlled trial directly comparing the two (see http://pmid.us/9867891) and we require clinical judgement to rule out acute coronary syndrome.
How well do high-sensitivity troponin assays diagnose acute myocardial infarction?

<table>
<thead>
<tr>
<th>The Bottom Line:</th>
<th>High-sensitivity troponin assays are here to stay and might have a clinical advantage for some patients in some situations but this has yet to be clearly defined.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article Title:</td>
<td>Performance of the high-sensitivity troponin assay in diagnosing acute myocardial infarction: systematic review and meta-analysis.</td>
</tr>
<tr>
<td>PubMed ID:</td>
<td>25295240</td>
</tr>
<tr>
<td>Population:</td>
<td>Studies of adult patients presenting to the emergency department with symptoms such as chest pain that were suggestive of acute myocardial infarction (AMI).</td>
</tr>
<tr>
<td>Intervention:</td>
<td>High-sensitivity troponin T or troponin I measurements between two and 24 hours apart.</td>
</tr>
<tr>
<td>Outcomes:</td>
<td>The final diagnosis of AMI based on adjudication using all medical records from the hospital visit.</td>
</tr>
</tbody>
</table>

**Authors’ Conclusions:** For patients presenting to the emergency department, the high-sensitivity assay for cardiac troponin has higher sensitivity but lower specificity than the conventional assay and, thus, may be useful in triaging patients. Over six hours, the area under the curve for both high-sensitivity troponin T and conventional troponin assays was similar. Future studies are needed to determine the potential benefits of earlier treatment and the economic consequences of the use of the high sensitivity assay.

**Quality Checklist:**

1. The diagnostic question is clinically relevant with an established criterion standard. **No**  
   **Comment:** The only established criterion standard for non-ST-elevation MI is a troponin concentration above the 99th percentile.

2. The search for studies was detailed and exhaustive. **No**

3. The methodological quality of primary studies was assessed for common forms of diagnostic research bias. **Yes**

4. The assessments of studies were reproducible. **Yes**

5. There was low heterogeneity for estimates of sensitivity or specificity. **Yes**

6. The summary diagnostic accuracy is sufficiently precise to improve upon existing clinical decision making models. **Yes**

**Methodological Critique:** Only English-language studies were included in the analysis and so relevant studies in other languages may have been omitted. Meta-analysis of troponin studies in particular is very difficult because of the multiple laboratory assay analyzers, various assay cut-off points, variation in
intervals between initial measurements and retesting and subjective timing of symptom onset, each of which will contribute to heterogeneity. All these issues aside, troponin measurement elevation can occur in the absence of acute myocardial infarction and this is supported by the relatively low specificity of these assays. Regardless, perhaps the greatest problem is verification of the outcome and the imprecise (if not completely arbitrary) definition of acute myocardial infarction. Finally, the results are reported in terms of sensitivity and specificity which are not clinically intuitive as they refer to the probability of positive and negative test results in patients with and without the disease respectively rather than the probability of disease in patients with and without positive results. To that end, it would have been much more helpful to report the results as likelihood ratios. Given the multiple challenges to meta-analyses of troponin studies, the heterogeneity is surprisingly low.

Key Results:
- Nine studies assessed the use of high-sensitivity troponin T assays (n = 9,186 patients): The summary sensitivity of these tests in diagnosing acute MI at presentation to the ED was estimated to be 0.94 [95% CI: 0.89 to 0.97], compared with 0.72 [95% CI: 0.63 to 0.79] for conventional tests. The summary specificity was 0.73 [95% CI: 0.64 to 0.81] for the high-sensitivity assay compared with 0.95 [95% CI: 0.93 to 0.97] for the conventional assay.
- The differences in estimates of the summary sensitivity and specificity between the high-sensitivity and conventional assays were statistically significant (p < 0.01). The area under the curve was similar for both tests carried out three to six hours after presentation. Three studies assessed the use of high-sensitivity troponin I assays and showed similar results.

BEEM Commentary: The reporting of the results as sensitivity and specificity is not helpful to clinicians although these results suggest emergency physicians will have to deal with many more false positives. Since the troponin assay can only be used to diagnose and rule out NSTEMI but not to rule out acute coronary syndrome (ACS), the greatest problem with the high sensitivity assays is with patients with low clinical probability of ACS but an elevated troponin level. Furthermore, these tests should not be used as a single measure and repeat measure should be conducted three to six hours after the first.
What is the optimum duration of systemic corticosteroid (SCS) therapy for exacerbations of chronic obstructive pulmonary disease (COPD)?

**The Bottom Line:** Oral corticosteroids for five to seven days duration is probably as effective and produces fewer side effects than longer treatment durations.

**Article Title:** Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease.


**PubMed ID:** 25491891

**Population:** Adults with an acute exacerbation of chronic obstructive pulmonary disease (COPD). The definition of an acute exacerbation could include any combination of an increase in breathlessness, sputum volume, sputum purulence, cough, or wheeze.

**Intervention:** Systemic corticosteroids (SCS) given for a period of seven or fewer days (SCS ≤7) compared to standard durations (>7 days).

**Outcomes:**

- **Primary:** Treatment failure (i.e. the need for additional treatment; hospital admission/re-admission for index episode; return to ED; unscheduled physician visit for the index episode); relapse after treatment (i.e. treatment for new acute exacerbation; re-admission for COPD); adverse drug effects.
- **Secondary:** Mortality; lung function; length of hospital stay; arterial blood gases; and symptom scores.

**Authors’ Conclusions:** Information from a new large study has increased our confidence that five days of oral SCS is likely to be sufficient for treatment of adults with acute exacerbations of COPD, and this review suggests that the likelihood is low that shorter courses of SCS (of around five days) lead to worse outcomes than are seen with longer (10 to 14 days) courses. We graded most available evidence as moderate in quality because of imprecision; further research may have an important impact on our confidence in the estimates of effect or may change the estimates. The studies in this review did not include people with mild or moderate COPD; further studies comparing short-duration SCS vs. conventional longer-duration SCS for treatment of adults with acute exacerbations of COPD are required.

**Quality Checklist:**

1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **Yes**
4. The assessments of studies were reproducible. **Yes**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. Yes

7. The treatment effect was large enough and precise enough to be clinically significant. Yes

**Methodological Critique:** In this typically high quality Cochrane systematic review and meta-analysis of five studies conducted in hospitals with N = 519 participants, the methodological quality of the published included trials was good with minimum bias.

**Key Results:**
- Between short-duration and longer-duration of SCS treatment, there was no difference in risk of treatment failure (n = 457; odds ratio (OR) = 0.72 [95% CI: 0.36 to 1.46]); no difference in risk of relapse (a new event) (n = 457; OR = 1.04 [95% CI: 0.70 to 1.56]); no difference in time to the next COPD exacerbation (n = 311; hazard ratio = 0.95 [95% CI: 0.66 to 1.37]); no difference in the likelihood of an adverse event (n = 503; OR = 0.89 [95% CI: 0.46 to 1.69]); no difference in length of hospital stay (n = 421; mean difference (MD) = -0.61 days [95% CI: -1.51 to 0.28]); and no difference in lung function at the end of treatment (n = 185; MD FEV1 -0.04 L [95% CI: -0.19 to 0.10]).

**BEEM Commentary:** Systemic corticosteroids have been demonstrated to be effective in the treatment of COPD exacerbations but are not without adverse side effects. While guidelines have recommended treatment durations from seven to 10 days, the optimum duration of steroid treatment for benefit and minimum adverse drug effects is unknown. The results indicate that five days of oral SCS is likely to be sufficient for treatment of adults with acute exacerbations of COPD.
Is out-of-hospital noninvasive positive-pressure support ventilation effective in adult patients in respiratory distress?

The Bottom Line: Non-invasive positive-pressure support ventilation is a reasonable out-of-hospital treatment to consider for adult patients with severe respiratory distress.

Article Title: Effect of out-of-hospital noninvasive positive-pressure support ventilation in adult patients with severe respiratory distress: a systematic review and meta-analysis.


PubMed ID: 24342819

Population: Randomized controlled trials of adult patients with out-of-hospital, severe respiratory distress (suspected acute cardiogenic pulmonary edema, acute exacerbation of COPD, acute asthma exacerbation or pneumonia).

Intervention: Non-invasive positive-pressure ventilation (NIPPV) or standard therapy.

Outcomes:
- Primary: In-hospital mortality.
- Secondary: Need for invasive ventilation; hospital and ICU lengths-of-stay (LOS); and complications.

Authors’ Conclusions: Out-of-hospital administration of NIPPV appears to be an effective therapy for adult patients with severe respiratory distress. When EMS providers are faced with a patient presenting with undifferentiated dyspnea who is likely to require intubation, a trial of out-of-hospital NIPPV appears to be an effective and safe therapy that may decrease need for invasive ventilation and mortality, given there are no contraindications to its use. In light of this evidence, it is reasonable to consider NIPPV for the treatment of adults with severe respiratory distress in the out-of-hospital setting. EMS agencies and individual out-of-hospital care providers should incorporate NIPPV into the treatment of severe respiratory distress, if feasible.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. No
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Yes
7. The treatment effect was large enough and precise enough to be clinically significant. Yes
Methodological Critique: The search was restricted to studies published in the English language. This is a common limitation of systematic reviews conducted with limited resources but not necessarily an acceptable limitation. The authors neither reference nor use the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (http://www.equator-network.org/reporting-guidelines/prisma/), including structured reporting of their quality assessment of the studies included (http://guides.mclibrary.duke.edu/content.php?pid=166533&sid=2305787). Therefore, it is hard to determine if the primary studies were of high methodological quality. Grossly inspecting the data provided, the individual studies appear to be reasonable, but insufficient detail prevents a definitive answer. Five of the studies were judged to be low risk of bias using the Cochrane Collaboration tool for assessing risk of bias. Allocation was concealed in five of the studies. There was no blinding in any of the studies. Overall, they had very good follow-up with only eight patients being lost.

Only five of the studies commented on complications. This is a well-recognized limitation of RCTs which tend to under report harm (see http://pmid.us/24401468 and http://pmid.us/24607768).

Key Results:

- Seven studies were included in the analysis. Six of the seven studies used CPAP and one trial used BiPAP. The vast majority of patients (>80%) were suspected to be of acute cardiogenic pulmonary edema:
  - Acute cardiogenic pulmonary edema (n = 522, 82.6%)
  - Acute exacerbation of COPD (n = 81, 12.8%)
  - Pneumonia (n = 19, 3.0%)
  - Severe Asthma (n = 10, 1.6%)

- Primary outcome: Reduction in in-hospital mortality with the use of NIPPV (RR = 0.58 [CI: 0.35 to 0.95] (NNT = 18 [95% CI: 10 to 170]).

- Secondary Outcome: Need for Invasive ventilation (RR = 0.37 [95% CI: 0.24 to 0.58]); (NNT = 8 [95% CI: 6 to 14]). ICU and hospital LOS could not be pooled. Complications were reported in three patients with emesis.

BEEM Commentary: Acute respiratory distress is a very common presentation. These patients present undifferentiated. In-hospital data suggests NIPPV to be an effective treatment to reduce mortality and need for invasive ventilation. It is reasonable to ask whether providing NIPPV to these patients in the pre-hospital setting could result in similar positive results. A variety of commercial NIPPV products were used in the various RCTs. Given the overall positive effects demonstrated this would add confidence to the conclusion that the intervention works. In addition, there was no accepted standard dose for starting or stopping NIPPV, which adds credence to the concept that this therapy benefits some patients. The results of this study apply predominantly to pre-hospital systems that include an on-scene physician, suspected CHF, and CPAP as NIPPV. However, the results are sufficiently impressive and convincingly reproduced from study-to-study so the authors’ conclusion that “NIPPV appears to be an effective therapy for adult patients with severe respiratory distress” seems compelling. Lacking sufficient safety data, EMS protocols should cautiously monitor for adverse events and unintended consequences of NIPPV for undifferentiated dyspnea.
In treating uncontrolled atrial fibrillation, is it best to control the rate or the rhythm?

**The Bottom Line:** Both rate- and rhythm-control strategies seem to be equally efficacious in AF outcomes but in the ED setting, a rate-control approach will likely be more achievable.

**Article Title:** Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review.


**PubMed ID:** 24887617

**Population:** English-language studies in PubMed, EMBASE, and the Cochrane Database of Systematic Reviews between January 2000 and November 2013 of adult patients with uncontrolled atrial fibrillation (AF).

**Intervention:** Pharmacologic treatment for rate- or rhythm-control of AF.

**Outcomes:** Primary: Conversion to sinus rhythm, maintenance of normal sinus rhythm (NSR), AF recurrence at 12 months, functional outcomes (AF symptom control, quality of life, functional status), complications of AF (death, myocardial infarction, cardiomyopathy, cardiovascular hospitalizations, congestive heart failure, control of AF symptoms, quality of life, functional status, stroke/other embolic events) and adverse effects of therapy.

**Authors’ Conclusions:** Pharmacologic rate- and rhythm-control strategies have comparable efficacy across outcomes in primarily older patients with mild AF symptoms. Pulmonary vein isolation is better than antiarrhythmic medications at reducing recurrences of AF in younger patients with paroxysmal AF and mild structural heart disease. Future research should address uncertainties related to subgroups of interest and the effect of different therapies on long-term clinical outcomes.

**Quality Checklist:**

1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **No**
3. The primary studies were of high methodological quality. **Unsure**
4. The assessments of studies were reproducible. **Unsure**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **Unsure**
7. The treatment effect was large enough and precise enough to be clinically significant. **Yes**
Methodological Critique: Searches were restricted to electronic databases 2000 to 2013 (updates the previous AHRQ 2000 report); no hand-searches; no gray literature or conference abstract searches; no expert author inquiries. Searches were limited to English language only. Quality assessments were based on AHRQ criteria, some applicability limitation factors examined; no overall assessment of good/moderate/low quality for included studies. No comments on duplicated quality assessments. There were no specific heterogeneity discussion/calculation in either the paper or the supplement, however, blanket heterogeneity was commented on as a limitation in the main abstract.

Key Results:
- Included 162 studies, n = 28,836 patients. Visual inspection of Forest plots demonstrate considerable heterogeneity based on trial size, effect size and direction, and dominance of certain outcomes by largest trials (not in restoration of sinus rhythm subgroup analysis). It is not clear how the exclusion of heavily-weighted trials would influence robustness of summary effect estimate in other outcomes (overall death, CV death, stroke rates).
- There was no difference in the rate- vs. rhythm-control for all patient-oriented outcomes examined.

BEEM Commentary: The information here reinforces other recent evidence that rate control is an appropriate goal (achievable in the ED setting) compared to rhythm control (which may be difficult or impossible to achieve in the ED setting). The 2012 Canadian Cardiovascular Society (CCS) AF guideline updates comment on choices for rate control suggesting beta-blockers (be cautious in patients >60 years old with hypertension as per the Canadian Hypertension Education Program guidelines) or low-dose nonhydropyridine calcium channel blockers (i.e. not nifedipine or amlodipine; use diltiazem or verapamil). The 2011 CCS guidelines for management of AF in Canadian ED’s (Stiell IG, Macle L; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol. 2011 Jan-Feb;27(1):38-46.) present appropriate recommendations for the common AF presentations in ED (i.e. unstable, rate control, conversion). The results of this systematic review are consistent with other recent reviews and guidelines supporting the lack of difference in important outcomes using rate-vs. rhythm-control strategies. In the ED setting, it is more appropriate to pursue a rate-control strategy first, and consider a rhythm conversion approach if clinically appropriate.
What is the sensitivity and specificity of ultrasound (US) using B-lines in diagnosing acute cardiogenic pulmonary edema (ACPE) in patients presenting to the Emergency Department (ED) with acute dyspnea?

The Bottom Line: The evaluation of B-lines by bedside point of care ultrasonography may have value in the diagnosis of ACPE. This may depend on factors such as the method of scanning used and the training of the operator.

Article Title: Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis.


PubMed ID: 25176151

Population: Prospective cohort and prospective case-control studies published in PubMed, EMBASE, Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and the Cochrane Database of Systematic Reviews that recruited patients presenting to hospital with symptomatic, acute dyspnea, or where there was a clinical suspicion of congestive heart failure, and reported the sensitivity and specificity of B-lines in diagnosing ACPE.

Excluded: Studies of asymptomatic individuals or in patients where there was no suspicion of ACPE.

Intervention: Beside ultrasonography for ACPE (final diagnosis of ACPE) and evaluating B-lines.

Outcomes: ACPE is 94.1% [95% CI: 81.3% to 98.3%] and the specificity is 92.4% [95% CI: 84.2% to 96.4%]. Preplanned subgroup analyses did not reveal statistically significant changes in the overall summary estimates, nor did exclusion of three potential outlier studies.

Authors’ Conclusions: Point of care ultrasound to diagnose ACPE using B-lines exceeds the tools currently available to clinicians at the bedside.

Quality Checklist:

1. The diagnostic question is clinically relevant with an established criterion standard. Yes
   Comment: The question is relevant but no established criterion for either diagnosis of ACPE or for B-line assessment in point of care (POC) ultrasound are fully explained. They are mentioned in brief such as Volpicelli method for ultrasound or in the discussion BNP is referenced.

2. The search for studies was detailed and exhaustive. Yes

3. The methodological quality of primary studies was assessed for common forms of diagnostic research bias. Yes
4. The assessments of studies were reproducible. Yes

5. There was low heterogeneity for estimates of sensitivity or specificity. Yes

6. The summary diagnostic accuracy is sufficiently precise to improve upon existing clinical decision making models. Yes

**Methodological Critique:** This study was exhaustive in searching for ultrasound diagnostics performed at the bedside for ACPE but were not restrictive in settings, patient demographics, or ultrasound training of provider. The reference standard was not fully explained, and in the conclusion, reference to laboratory testing was included. There were multiple analyses of bias when excluding studies.

**Key Results:**
- Seven studies included 1,075 patients. Of the seven studies, two were in the ED, two in the ICU, two in a hospital ward, and one study was in the pre-hospital setting. The summary sensitivity of point-of-care lung US using B-lines to diagnosis ACPE is 94.1% [95% CI: 81.3% to 98.3%], and the summary specificity is 92.4% [95% CI: 84.2% to 96.4%]. The positive likelihood ratio is 12.4 [95% CI: 5.7 to 26.8] and the negative likelihood ratio is 0.06 [95% CI: 0.02 to 0.22]. The diagnostic odds ratio is 195.35 [95% CI: 36.4 to 1,049.8]. Analysis of the Cook's Distance measure revealed Three out of seven studies that might significantly alter the overall summary estimates for sensitivity and specificity. The study by Liteplo et al. (Cook’s Distance = 1.22) and the two studies by Lichtenstein et al (Cook’s Distance = 2.03 and 3.84) were excluded from the primary meta-analysis to examine the effects on the overall summary estimates. The resultant sensitivity (minus these two studies) was 93.4% [95% CI: 81.8% to 97.8%] and the specificity was 88.8% [95% CI: 78.6% to 94.5%].

**BEEM Commentary:** The review was too heterogeneous and had no definitive gold standard fully explained. The conclusion that B-line on ultrasound exceeds current tools is overstated. The evaluation of B-lines has value but the method to define a B-line on POC scanning was not defined in this review. The gold standard was not directly compared or further subdivided.
**Is EGDT or other protocol-based care superior to usual care for septic shock patients in the ED?**

| The Bottom Line: | Effective care for septic shock hinges on early recognition, lactate screening, IV crystalloid resuscitation, and early broad spectrum antibiotics. |
| Article Title: | A randomized trial of protocol-based care for early septic shock. |
| PubMed ID: | 24635773 |

### Population:
Adult patients ≥18 years old with at least two SIRS criteria and refractory hypotension (sBP <90 mm Hg after fluid challenge or requiring vasopressors) or lactate <4 mMol/L. Recruited in 31 US tertiary hospital ED's.

Excluded: Patients with acute CVA/ACS/CHF/arrhythmia/seizure/GI bleed/status asthmaticus/overdose/burn/trauma/need for immediate surgery; known CD4 count <50/mm³; advanced directive against resuscitation; CI to CVP line placement; high likelihood of refusing blood transfusion (i.e. Jehovah's witness); resuscitation deemed futile; pregnancy; transfer from other hospital; or participant in another ongoing study.

### Intervention:
Six-hour protocol of early goal-directed therapy (EGDT) vs. other protocol-based care.

### Outcomes:
- **Primary:** In-hospital death any cause at 60 days.
- **Secondary:** Any death at 90 days, cumulative death at 90 days and one year, duration of CV failure, respiratory failure, and acute RF, hospital and ICU LOS, and hospital discharge disposition (eg. home, nursing/other long-term care).

### Authors’ Conclusions:
In a multicentre trial conducted in the tertiary care setting, protocol-based resuscitation of patients in whom septic shock was diagnosed in emergency departments did not improve outcomes.

### Quality Checklist:
1. The study population included or focused on those in the ED. **Yes**
   - **Comment:** Exclusive ED populations.

2. The patients were adequately randomized. **Yes**

3. The randomization process was concealed. **Yes**

4. The patients were analyzed in the groups to which they were randomized. **Yes**

5. The study patients were recruited consecutively (i.e. no selection bias). **Unsure**

6. The patients in both groups were similar with respect to prognostic factors. **Yes**
7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **Unsure**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** Well-executed three-arm RCT looking at three likely resuscitation scenarios. Block randomization 1:1:1 to ensure adequate numbers in each group. Sequential recruiting not reported. Blinding not explicitly described in paper or Supp Appendix; but outcomes data locked until December 2013, so clinical investigators unaware of different arm outcomes. No industry sponsorship. Near perfect follow-up for outcomes. Initial sample size calculation modified at first planned interim analysis due to less observed mortality in control arm (attributed to the changing trend in improved sepsis care over last decade); reduced from 1,950 to 1,350 patients with preserved power metrics. The limitations discussed are appropriate and likely irrelevant to the overall conclusions.

**Key Results:**
- 1,341 patients, of whom 439 were randomly assigned to protocol-based EGDT, 446 to protocol-based standard therapy, and 456 to usual care.
- Primary outcome: (in-hospital death 60 days): No difference (EGDT 21%, Protocol 18.2%, usual care 18.9%).
- Secondary outcome: Death 90 days: No difference (31.9%/30.8%/33.7%).
- ICU admissions: More EGDT admissions (91.3% vs. 85.4% vs. 86.2%).
- Hospital LOS: No difference (11.1 days vs. 12.3 vs. 11.3).
- Adverse organ system failures: No difference for CV/resp/renal; slight increase in ARF requiring dialysis in Protocol group.
- Adverse Rx events: No difference (5.2% vs. 4.9% vs. 8.1%).
- Disposition destinations: No differences.

**BEEM Commentary:** This landmark ED-based study further refines the revolutionary care pioneered in the original Rivers EGDT paper in 2001 and the results are consistent with subsequent large EGDT trials. It refutes the need for universal invasive monitoring, which will be welcome for most ED clinicians in smaller/rural settings who may not have the full technical support/expertise to fully execute the original EGDT protocol. This study also reaffirms the importance of early antibiotics, IV crystalloid resuscitation, and following serial lactates to monitor resuscitation success. The options outlined here can likely be extrapolated easily to those patients with severe sepsis as well as septic shock. Importantly, this article does not refute the value of bundled care, which has been proven in prior trials/metaanalyses to be of significant benefit to reduce patient mortality/morbidity, but does suggest that an all-or-nothing super-invasive strategy (a la EGDT) is not universally required. Furthermore, the emphasis on crystalloids for IV resuscitation is congruent with SSC guidelines (update 2013) and a 2013 Cochrane update on fluid resuscitation of critically patients. Finally, although no vasopressor is specified, the results here again are
congruent with use of norepinephrine vs. dopamine recommendations from the SSC 2013 update and a recent metaanalysis published supporting NE over DA (De Backer et al, Crit Care Med 2012).
Does an ED patient with septic shock need aggressive early goal-directed therapy (EGDT) or "usual" resuscitation?

<table>
<thead>
<tr>
<th>The Bottom Line:</th>
<th>Invasive EGDT-based sepsis resuscitation treatment and monitoring are not required compared to early recognition and liberal IV fluid resuscitation and empiric antibiotics prescription in ED septic patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article Title:</td>
<td>Goal-directed resuscitation for patients with early septic shock.</td>
</tr>
<tr>
<td>PubMed ID:</td>
<td>25272316</td>
</tr>
<tr>
<td>Population:</td>
<td>Adults ≥ 18 years old presenting to one of 51 EDs in Australia, New Zealand, Finland, Hong Kong, and Ireland within six hours with suspected or confirmed infection, two or more SIRS criteria, and evidence of refractory hypotension (sBP &lt; 90 mm Hg or MAP &lt; 65 after intravenous fluids &gt; 1000 ml within the first hour) or hypoperfusion (lactate &lt; 4 mMol/L). Excluded: Patients &lt; 18 years old, contraindications to central venous catheterization (CVC)/blood products; imminent/inevitable death; underlying disease with &lt; 90 days life expectancy; transfer from another facility; confirmed/suspected pregnancy; unable to randomize or start EGDT within six hours of ED arrival. Study sites in Australia/New Zealand (45 sites), six sites in Finland, Hong Kong, Ireland; mixed rural and metropolitan centres.</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Full EGDT provided by a trained study team using a standardized EGDT delivery protocol or usual care.</td>
</tr>
<tr>
<td>Outcomes:</td>
<td>Primary: All-cause death at 90 days. Secondary/Tertiary: 90 days survival time, ICU mortality, 28-day mortality, in-hospital 60-day mortality, cause-specific 90-day mortality, length-of-stay in ED/ICU/hospital, use of critical interventions (mechanical ventilation, vasopressor support, renal dialysis), discharge destination of survivors, adverse events. A priori subgroup analyses for demographics, APACHE scores, mech ventilation, refractory hypotension, lactate level, and intravenous fluid resuscitation volume (&lt;20 cc/kg vs. &gt; 20 cc/kg).</td>
</tr>
</tbody>
</table>

**Authors’ Conclusions:** In critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days.

**Quality Checklist:**
1. The study population included or focused on those in the ED. **Yes**
   **Comment:** All patients recruited from ED.

2. The patients were adequately randomized. **Yes**
3. The randomization process was concealed. **Yes**

4. The patients were analyzed in the groups to which they were randomized. **Yes**

5. The study patients were recruited consecutively (i.e. no selection bias). **Yes**

6. The patients in both groups were similar with respect to prognostic factors. **Yes**

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **No**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** This publicly-sponsored, randomized controlled trial was conducted in multiple healthcare systems with nearly identical demographic and clinical characteristics in both cohorts.

**Key Results:**

- (EGDT n = 796, usual care n = 804) showed no difference in the primary outcome, 90-day all cause mortality (EGDT 18.6% vs. usual care 18.8%), nor survival time.

- Significant differences between the two groups in terms of ICU admissions (EGDT 87% vs. usual care 76.9%); fluid given in first six hours (EGDT 250 ml > usual care); vasopressors (EGDT 66.6% vs. usual care 57.8%); and blood transfusions (EGDT 13.6% vs. usual care 7.0%).

**BEEM Commentary:** This is the second largest 2014 sepsis resuscitation trial (ProCESS spring 2014) suggesting that aggressive EGDT protocols are not necessary to increase survival in septic shock patients, compared to “usual” care involving early recognition, IV fluid resuscitation and empiric antibiotics treatment. This information confirms (as did ProCESS 2014) what many clinicians without EGDT resources/capabilities have hoped for and believed; invasive resuscitation is not needed beyond liberal IV crystalloid resuscitation (>30 cc/kg), broad-spectrum antibiotics, and serial lactate monitoring.
Does early goal-directed therapy improve outcomes in septic shock patients more than current standard care?

**The Bottom Line:** There is no need to provide invasive expensive EGDT in the ED for septic shock patients.

**Article Title:** Trial of early, goal-directed resuscitation for septic shock.


**PubMed ID:** 25776532

**Population:** Adult patients in ED with septic shock (two or more SIRS criteria with refractory sBP <90 mm Hg despite fluid resuscitation 1L within 60 minutes, or hyperlactemia <4 mMol/L). Patients recruited from 56 UK hospitals. Excluded: Age <18 years, pregnant, primary acute diagnosis (CVA, ACS, CHF, status asthmaticus, arrhythmia, seizure, OD, burn/trauma); unstable GIB; need immediate surgery; history of AIDS; DNR; other advanced directives restricting resuscitation; contraindications to line placement/blood transfusions; transfer from another in-hospital setting not able to commence within one hour of ED arrival or complete six-hour protocol, physician discretionary exclusion.

**Intervention:** Early goal-directed therapy (EGDT) or usual care (UC). All patients received antibiotics before randomization.

**Outcomes:** Primary: 90-day all-cause mortality. Secondary: SOFA scores (6, 72 hours); advanced life support (CV, Resp, Renal) in first 28 days; Length-of-Stay (LOS) (ED, ICU, hospital); all-cause mortality 28-day hospital discharge; one year, survival duration; health-related quality of life (HRQOL, measured on EQ-5D), resource usage, costs at 90 days and one year.

**Authors’ Conclusions:** In patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **Yes**
   
   **Comment:** The final ED-based comparison of EGDT vs. usual care.

2. The patients were adequately randomized. **Yes**

3. The randomization process was concealed. **Yes**

4. The patients were analyzed in the groups to which they were randomized. **Yes**

5. The study patients were recruited consecutively (i.e. no selection bias). **Yes**
6. The patients in both groups were similar with respect to prognostic factors. Yes

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. No

8. All groups were treated equally except for the intervention. Yes

9. Follow-up was complete (i.e. at least 80% for both groups). Yes

10. All patient-important outcomes were considered. Yes

11. The treatment effect was large enough and precise enough to be clinically significant. No

Methodological Critique: This was a parallel arm, pragmatic, superiority trial, 1:1 randomization in permuted blocks of 4/6/8. 1,260 patients needed for sample size, 1,243 completed trial (>98% follow-up) for primary outcome. Baseline characteristics well matched in both arms, including infection sources. Unable to blind physicians to intervention allocation for obvious reasons. Only one-third patients screened were successfully recruited (poorly recruited on weekends, nights).

Economic evaluation: resources cost on 2012 GB pound/US dollar values. Cost effectiveness determined on threshold willingness to pay (WTP) for QALY gains as per NICE guidelines (GBP20,000/USD$28430 per QALY).

Trifecta completed - the final nail in the coffin for EGDT for adult septic shock in the ED. It is rare to have simultaneous real-time economic evaluations done in large RCTs, so when they are done (and done properly as it was here), the results are even more informative.

Key Results:
- No statistically significant differences in any clinical outcomes.
- Primary: 90-day mortality: EGDT 29.5%, UC 29.2%.
- Secondary: Mortality 28 days: 24.8% vs. 24.5%; Mortality at hospital discharge: 25.6% vs. 24.6%; ED LOS: 1.5 hours vs. 1.3 hours; ICU LOS: 2.6 days vs. 2.2 days; Hospital LOS: 9 days vs. 9 days; Days on life support: CV 37.0% vs. 30.9%, Resp 28.9% vs. 28.5%, Renal 14.2% vs. 13.2%; Days free of life support: CV 20.3 vs. 20.6, Resp 19.6 vs. 19.8, Renal 20.6 both; HRQOL: No difference either arm; QALY up to 90 days: No difference.
- Costs up to 90 days: $17,647 EDGT vs. $16,239 UC (probability of EGDT cost effectiveness <20%)
- Serious adverse events: 4.8% vs. 4.2%. No significant differences based on preplanned subgroups: age, MEDS score, SOFA score, randomization time, degree of protocolization in UC arm.

BEEM Commentary: It is now clear that an expensive and invasive care for these patients is not necessary. The failure to reproduce the original 2001 EGDT results in all three trials likely reflects the increased attention and aggressive treatments (albeit non-invasively) that most ED physicians now use worldwide in treating septic shock patients. Hence, this is not a refutation of any protocolized care, but only of EGDT in its original 2001 version. Every study group and the Survive Sepsis Campaign still recommend the use of sepsis protocols that emphasize early recognition, lactate screening, copious IV crystalloid resuscitation, and targeted (or at least broad-spectrum) antibiotics.
What is the optimal target blood pressure for the resuscitation of patients in septic shock?

The Bottom Line: There is no mortality difference in targeting a MAP of 70 to 90 mm Hg in septic shock patients.

Article Title: High versus low blood-pressure target in patients with septic shock.


PubMed ID: 24635770

Population: Adult patients (>18 years old) with fluid-refractory or vasopressor-dependent septic shock in 29 centres in France from March 2010 to December 2011.

Excluded: Unable to gain consent; pregnant; recent enrollment in another similar trial; physician ‘do not resuscitate’ (DNR) determination; or not enrolled in French healthcare system.

Intervention: Resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group).

Outcomes: Primary: Mortality at 28 days.

Secondary: Mortality at 90 days; days alive and free of organ dysfunction by day 28; ICU/hospital length-of-stay (LOS). Serious adverse events (cardiac, ischemic, other).

Funded by French Ministry of Health.

Authors’ Conclusions: Targeting a MAP of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at 28 or 90 days.

Quality Checklist:

1. The study population included or focused on those in the ED. Unsure
   
   Comment: Patient recruitment/treatment locations not specified.

2. The patients were adequately randomized. Yes

3. The randomization process was concealed. Yes

4. The patients were analyzed in the groups to which they were randomized. Yes

5. The study patients were recruited consecutively (i.e. no selection bias). Yes

6. The patients in both groups were similar with respect to prognostic factors. Yes

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. Unsure

8. All groups were treated equally except for the intervention. Yes

9. Follow-up was complete (i.e. at least 80% for both groups). Yes
10. All patient-important outcomes were considered. Yes

11. The treatment effect was large enough and precise enough to be clinically significant. No

**Methodological Critique:** This is a well-conducted, multicentre RCT examining an important hemodynamic measure in sepsis resuscitation. This study was a superiority design and met the sample size requirements. The analyses were performed according to intention-to-treat. Appropriate blinding: unable to blind physicians who were titrating treatments to target mean arterial pressure (MAP). A large number of patients were screened and rejected (approximately 4,100 screened, 798 randomized, 22 did not complete 90-day follow-up). Baseline characteristics and co-interventions were nearly identical in both groups. Patients were also stratified based on the history of chronic hypertension (HTN). There were more failures in attaining and maintaining target MAP in the higher group vs. lower; no effect on overall mortality outcomes (although lack of compliance in both arms then favour the null hypothesis being confirmed). Both groups attained and maintained average MAPs that were higher than specified in each arm protocol by an average of five mm Hg, but the overall differences were maintained so no exclusions were needed. It is not clear how many patients were recruited from or treated in the ED. The study was powered to show a 10% difference in primary outcome of superiority, which was not demonstrated; a noninferiority margin, however, was not determined, so it is not clear if one group had worse outcomes than the other, or was this really equivalent treatment. Also, there were no comments on the management and complications associated with the significantly higher rates of atrial fibrillation patients found in the higher MAP group. There was a high use of glucocorticoids (high MAP 80% vs. low MAP 85%), and activated protein C (6.8% and 7.5% respectively), which may have also influenced clinical outcomes, and may limit generalizability of results (authors acknowledge this).

**Key Results:**
- Norepinephrine vasopressor of choice (94% to 96%). At 28 days, no significant between-group difference in mortality in the high-target group compared to the low-target group (HR = 1.07 [95% CI: 0.84 to 1.38]; p = 0.57). There was also no significant difference in mortality at 90 days (HR = 1.04 [95% CI: 0.83 to 1.30]; p = 0.74). The occurrence of serious adverse events did not differ significantly between the two groups, p = 0.64. The incidence of newly diagnosed atrial fibrillation (AF) was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

**BEEM Commentary:** The clear imperative of maintaining vascular perfusion pressures to end-organs is critical in correcting septic shock. The original mandate for a target MAP of >65 mm Hg in the Surviving Sepsis Campaign (SSC) guidelines was not necessarily evidence based, and did not necessarily account for the issue of chronic hypertension and concerns about the need to maintain higher overall MAPs in these patient subgroups. This trial answers that question quite well, confirming no need to treat these patients differently. If the treating physician is concerned, however, with maintaining cerebral perfusion pressure (CPP) in chronic HTN patients with septic shock, a higher target MAP is not unreasonable. The need to invasively monitor MAP during sepsis resuscitation has been recently refuted with the publication of the three major non-invasive sepsis resuscitation trials (ProCESS, ARISE, ProMISE), making the question of MAP titration in the ED essentially moot. The authors conclusions are accurate, in that the superiority design failed to show reduced mortality at 28 and 90 days from a higher MAP target vs. lower MAP.
Which sepsis scoring system has the best predictive performance for ED septic patients for adverse outcomes?

**The Bottom Line:** The Predisposition Insult Response and Organ failure (PIRO) the Sequential Organ Failure Assessment (SOFA) and Mortality in ED Sepsis (MEDS) scores can be useful to risk stratify individual patient sepsis mortality in the days following an episode of ED care, but none have been validated to guide treatment decisions or disposition destinations yet.

**Article Title:** Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock.


**PubMed ID:** 25377403

**Population:** Septic patients recruited from ED in Perth, Western Australia (n = 240 patients). Sub-study of the Critical Illness and Shock Study (CISS). Patients were recruited by a research nurse from 07:00 to 22:00 daily (7 days per week). Excluded: Patients transferred from other facilities.

**Intervention:** Data collection to calculate PIRO, SOFA and MEDS scores.

**Outcomes:** 30-day mortality after ED presentation.

**Authors' Conclusions:** The PIRO model, taking into account comorbidities and septic source as well as physiologic status, performed better than the SOFA score and similarly to the MEDS score for predicting mortality in ED patients with severe sepsis and septic shock. These findings have implications for identifying and managing high-risk patients and for the design of clinical trials in sepsis.

**Quality Checklist:**

1. The clinical problem is well defined. **Yes**
   
   **Comment:** Risk stratification of ED septic patients.

2. The study population represents the target population that would normally be tested for the condition including (i.e. no spectrum bias). **Yes**

3. The study population included or focused on those in the ED. **Yes**

4. The study patients were recruited consecutively (i.e. no selection bias). **No**

5. The diagnostic evaluation was sufficiently comprehensive and applied equally to all patients (i.e. no evidence of verification bias). **Yes**

6. All diagnostic criteria were explicit, valid and reproducible (i.e. no incorporation bias). **Unsure**

7. The reference standard was appropriate (i.e. no imperfect gold-standard bias). **Yes**
8. All undiagnosed patients underwent sufficiently long and comprehensive follow-up (i.e. no double gold-standard bias). **Yes**

9. The likelihood ratio(s) of the test(s) in question is presented or can be calculated from the information provided. **Yes**

10. The precision of the measure of diagnostic performance is satisfactory. **Yes**

**Methodological Critique:** One challenge with this study is that the scores have not been tested in their native derivation, but in modified versions due to limitations of the lab at the study hospital as described. As such, this study is examining locally modified scores that may not be generalizable to the rest of the ED world. Patients were not recruited consecutively, only when research RN was present to recruit in the ED. All data was explicitly defined, but abstracted from the medical records by one author. Some score variables were modified as follows: SOFA score respiratory factor modified to either fraction of inspired oxygen-to-peripheral capillary oxygen saturation ratio or inspired oxygen concentration (since the majority of ED patients were not intubated), MEDS neutrophil count excluded (since not collected in that hospital lab), and PIRO BUN >8 mmol/L (instead of >20 mg/dl) and no neutrophil band counts. However, all three scores have area under the curve (AUC) values around 0.80, which is indicative of a diagnostic test that has potential utility for the outcomes of interest. There is insufficient data provided to calculate likelihood ratios.

The authors acknowledge the limitations of case selection as a subgroup analysis of a broader sepsis study, and may not therefore be representative of the full spectrum of ED cases. Scores were not calculated in real time in the ED (so may be missing some data points), and not used to guide clinical care (which is appropriate).

Overall, the difficulty in using any scoring risk stratification tool in the ED is one of generalizability and applicability. The MEDS score has been validated up to a Level II CDR (Jalayer/SU, CAEP 2011). There are no studies, as of yet, that have implemented these scores in an ED care pathway dictating treatment and disposition decisions (required to elevate to Level I CDR). The fact that the PIRO and MEDS scores predict higher mortality in higher quintiles is rather intuitive and not surprising.

**Key Results:**

- Overall 30-day mortality was 20%; 44% admitted to ICU beds. Most frequent sepsis causes were respiratory (40%), GU (19%), skin/soft tissue (13%), abdominal (12%), bloodstream (7%).

- Diagnostic test performance as defined by the area under the receiver-operating characteristic curve, i.e AUC of ROC:
  - ROC PIRO = 0.86 [95% CI: 0.80 to 0.92]
  - ROC MEDS = 0.81 [0.74 to 0.88]
  - ROC SOFA = 0.78 [0.71 to 0.85]

- Results were similar in the ICU-only subgroup, although the PIRO score was superior to the MEDS score in the ICU setting (p = 0.02).

- Higher death rates noted in those patients who were older, had higher comorbidity scores, and higher PIRO/SOFA/MEDS scores. Increased mortality was seen in higher quintiles of PIRO and MEDS scores.
BEEM Commentary: The findings of this study suggest that PIRO and MEDS may be useful to risk stratify ED septic patients to estimate 30-day mortality risk. The SOFA score is not practical if patients are not intubated.
Does this patient presenting with a viral syndrome have early HIV?

| The Bottom Line: | If unsure about the possibility of acute HIV infection, forget the clinical exam and order the screening test. |
| Article Title: | Does this adult patient have early HIV infection?: The Rational Clinical Examination systematic review. |
| PubMed ID: | 25027143 |
| Population: | Adult patients presenting to primary care/ED with possible acute retroviral syndrome symptoms. |
| Intervention: | Clinical evaluation for HIV. |
| Outcomes: | HIV detection. |

Authors’ Conclusions: The limited utility of clinical examination to detect or rule out early HIV infection highlights the importance of routine testing for HIV infection among adults.

Quality Checklist:

1. The diagnostic question is clinically relevant with an established criterion standard. **Unsure**
   Comment: Gold standard test not specified; presumably HIV screening.

2. The search for studies was detailed and exhaustive. **Yes**

3. The methodological quality of primary studies was assessed for common forms of diagnostic research bias. **Yes**

4. The assessments of studies were reproducible. **Unsure**

5. There was low heterogeneity for estimates of sensitivity or specificity. **No**

6. The summary diagnostic accuracy is sufficiently precise to improve upon existing clinical decision making models. **No**

Methodological Critique: The prevalence of early HIV detection in some US EDs ranges from 0.05% to 1.0%. It is not precisely clear how many patients present with early HIV symptoms, but it is reported that as many as 90% will be symptomatic with acute HIV. The majority of new HIV patients are unaware of their status, but once diagnosed, will usually reduce high-risk behaviours voluntarily. Furthermore, early identification allows for early aggressive anti-retroviral therapy, which can reduce viral load, transmission rates, complications, and morbidity/mortality. In 2006, the CDC recommended routine ED HIV testing for all potential patients without separate consent or counselling that may be a barrier to testing (Self WH, EM Clinics North America 2010). Risk factors to consider include a history of STDs, multiple sex partners, receptive anal intercourse, active genital ulcers (self/partner), traumatic sex, IV drug use/needle sharing, or recent occupational blood exposure.
There is considerable diversity in local prevalence of HIV, so this would impact pretest probability for clinical assessment and subsequent HIV testing in your practice locale. Many of these results are from high-prevalence sub-Saharan African studies with a high prevalence of certain findings (i.e. genital ulcers). Many of the North American studies also had heterogeneous populations including IV drug users, sex-trade workers, MSM, and general population patients, all of whom may self-report symptoms differently. Overall, the results of this review suggest that there is no single or combined set of clinical findings that can adequately rule out early HIV infection as the LR- values don’t approach the ideal 0.05 or less value that is useful for a diagnostic test to rule out a disease of interest. No single symptom or sign has a strong enough LR+ value to rule in early HIV either, although various combinations of signs and symptoms may be helpful to make a formal screening decision.

There is evidence that routine screening in certain higher risk environments is more clinically efficacious and cost-effective for detecting early HIV and instituting appropriate therapy. Implementation of point-of-care HIV screening in Canadian EDs has been proven to be easy and rapid to perform, and acceptable by patients (Stenstrom et al, CJEM 2011).

**Key Results:**
- Unclear (or unstated) gold standard test for clinical variables examined. Study quality assessed using the QUADAS tools; reproducible assessments not reported. Significant variable heterogeneity based on outcomes measured and study settings.
- 16 studies included: 24,745 patients; 1,253 with early HIV (5.1%).
- Reported interrater reliability for various clinical features was variable modest to poor (kappa ranging from 0.36 to 0.58).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>(Studies)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital ulcers</td>
<td>(3)</td>
<td>5.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight loss</td>
<td>(7)</td>
<td>4.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Vomiting</td>
<td>(4)</td>
<td>4.6</td>
<td>0.90</td>
</tr>
<tr>
<td>Swollen LNs</td>
<td>(7)</td>
<td>4.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>(10)</td>
<td>3.9</td>
<td>0.94</td>
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<tr>
<td>Arthralgia</td>
<td>(4)</td>
<td>3.7</td>
<td>0.88</td>
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<tr>
<td>Fever</td>
<td>(12)</td>
<td>3.4</td>
<td>0.74</td>
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<tr>
<td>Oral ulcers</td>
<td>(5)</td>
<td>3.4</td>
<td>0.91</td>
</tr>
<tr>
<td>Nausea</td>
<td>(3)</td>
<td>3.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>(10)</td>
<td>3.1</td>
<td>0.89</td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>(4)</td>
<td>2.9</td>
<td>0.79</td>
</tr>
<tr>
<td>Night sweats</td>
<td>(10)</td>
<td>2.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Fatigue</td>
<td>(8)</td>
<td>2.6</td>
<td>0.85</td>
</tr>
<tr>
<td>Headaches</td>
<td>(9)</td>
<td>2.1</td>
<td>0.90</td>
</tr>
<tr>
<td>Genital warts</td>
<td>(3)</td>
<td>2.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Rash</td>
<td>(7)</td>
<td>1.5</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Different studies have looked at different combinations of signs and symptoms with better diagnostic proficiency.

- Having four or more signs and symptoms gave a positive LR ranging from 6.9 to 12, whereas the summary negative LR for no signs or symptoms was 0.47.

**BEEM Commentary:** Clinicians should not count on any single or combination of clinical signs and symptoms to rule in or out early HIV infection. If in doubt with a non-low-risk patient, proceed to formal HIV testing.

<table>
<thead>
<tr>
<th>Signs</th>
<th>(Studies)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any lymphadenopathy</td>
<td>(5)</td>
<td>3.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Inguinal LNs</td>
<td>(5)</td>
<td>3.1</td>
<td>0.82</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>(6)</td>
<td>2.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Cervical LNs</td>
<td>(3)</td>
<td>2.2</td>
<td>0.95</td>
</tr>
<tr>
<td>Rash</td>
<td>(4)</td>
<td>1.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Axillary LNs</td>
<td>(3)</td>
<td>1.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Genital warts</td>
<td>(3)</td>
<td>1.4</td>
<td>0.98</td>
</tr>
</tbody>
</table>
In critically ill patients requiring intubation, does ketamine increase intracranial pressure or worsen neurologic outcomes?

<table>
<thead>
<tr>
<th>The Bottom Line:</th>
<th>There is no convincing evidence that ketamine increases intracranial pressure or worsen neurologic outcomes in critically ill patients requiring intubation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article Title:</td>
<td>The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review.</td>
</tr>
<tr>
<td>PubMed ID:</td>
<td>25064742</td>
</tr>
<tr>
<td>Population:</td>
<td>Randomized controlled trials and prospective controlled studies that reported human data in patients &gt;16 years who had previously been intubated or who were being intubated at data collection and reported at least one outcome of interest, and include a comparison group treated with an intravenous drug that might be used for rapid sequence intubation in the ED. Excluded: Non-intubated patients, that lacked a comparison group, or if not written in English.</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Intravenous ketamine used as an infusion or bolus dose.</td>
</tr>
</tbody>
</table>

Authors’ Conclusions: According to the available literature, the use of ketamine in critically ill patients does not appear to adversely affect patient outcomes.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Yes
7. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: This review was limited to English language only studies although no non-English studies were found and the search was otherwise comprehensive. There was a large degree of variability in the quality and clinical data points and only one study was deemed at low risk of bias in all quality assessment domains while the remaining studies were at high risk in at least one domain. These
findings precluded a valid meta-analysis. Also, the results would have been driven by one single-blinded RCT (Jabre P, Combes X, Lapostolle F, et al. Etomidate vs. ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomized controlled trial. Lancet. 2009;374:293-300.) that enrolled more patients than all of the others combined. Hence, biases from this study would carry over to the overall conclusions.

**Key Results:**
- Ten of 4,896 studies reporting data on 953 patients met the inclusion criteria. two of the eight studies reporting intracranial pressure within 10 minutes of ketamine administration showed small reductions and two studies reported an increase. None of the studies reported significant differences in cerebral perfusion pressure, neurologic outcomes, ICU length of stay, or mortality.

**BEEM Commentary:** In the absence of known space-occupying lesions or obstructive hydrocephalus, the use of ketamine for endotracheal intubation is unlikely to cause any adverse neurologic outcome.
Is intensive blood pressure (BP) reduction in patients with acute-onset intracerebral hemorrhage (ICH) safe and effective?

<table>
<thead>
<tr>
<th>The Bottom Line:</th>
<th>While intensive BP reduction in patients with acute-onset ICH might be safe, there is no evidence that it improves clinical outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article Title:</td>
<td>Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis.</td>
</tr>
<tr>
<td>PubMed ID:</td>
<td>25239836</td>
</tr>
<tr>
<td>Population:</td>
<td>Randomized controlled trials of patients with acute intracerebral hemorrhage (ICH).</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Intensive BP-reduction protocol to a target of &lt;150 mm Hg systolic BP (SBP) or 110 mean arterial pressure (MAP).</td>
</tr>
<tr>
<td>Outcomes:</td>
<td>Unfavourable 3-month outcome (death or dependence) and hematoma growth.</td>
</tr>
</tbody>
</table>

Authors’ Conclusions: Our findings indicate that intensive BP management in patients with acute ICH is safe. Fewer intensively treated patients had unfavourable three-month functional outcomes although this finding did not reach significance. Moreover, intensive BP reduction appears to be associated with a greater attenuation of absolute hematoma growth at 24 hours that may reflect a plausible underlying mechanism linking aggressive BP control with potentially improved clinical outcomes.

Quality Checklist:
1. The clinical question is sensible and answerable. **Unsure**
2. The search for studies was detailed and exhaustive. **No**
3. The primary studies were of high methodological quality. **Yes**
4. The assessments of studies were reproducible. **Unsure**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **Yes**
7. The treatment effect was large enough and precise enough to be clinically significant. **No**

Methodological Critique: The clinical question is not specific in terms of objectives in that the safety and efficacy outcomes were not each explicitly defined, the search was limited to MEDLINE and the Cochrane Database of Systematic Reviews but did not include EMBASE or the grey literature. The authors claim to have completed quality control using low, high, or unclear risk of bias as described by Higgins. However, the authors fail to report the "quality control" results. Even though the lack of blinding of the included studies favoured the intervention groups, the results of the clinically relevant outcomes are statistically insignificant and only the results of the surrogate outcome (hematoma growth) is statistically significant.
Key Results:
- There were four eligible studies with 3,315 patients. Death rates were similar between patients randomized to intensive BP-lowering treatment and those receiving guideline BP-lowering treatment (OR = 1.01 [95% CI: 0.83 to 1.23]) as were the three-month death or dependency (modified Rankin Scale grades 3 to 6) compared with guideline treatment (OR = 0.87 [95% CI: 0.76 to 1.01]). There was no evidence of heterogeneity between estimates (I² = 0%) or publication bias in the funnel plots (p = 0.993) was detected. Intensive BP reduction was associated with a greater attenuation of absolute hematoma growth at 24 hours (p = 0.038).

BEEM Commentary: The continuing hypothesis is that BP-reduction following acute ICH leads to reduced hematoma size and perihematoma edema, which in turn leads to improved clinical outcomes. The lowering of BP for these patients continues to be practiced and promoted dogmatically by neurologists and neurosurgeons but has yet to be unequivocally demonstrated as clinically effective even in this most recent meta-analysis.
**What is the role for zolmitriptan for acute migraines in adults?**

| The Bottom Line: | An ED-dosing protocol of oral/nasal zolmitriptan 5 mg followed by observation for one to two hours can be a useful and resource-effective alternative to IV medication bolus therapies for acute migraine treatment. |
| Article Title: | Zolmitriptan for acute migraine attacks in adults. |
| PubMed ID: | 24848613 |
| Population: | Randomized controlled studies assessing the acute treatment of adults ≥18 years old with episodic migraines (as defined by the International Headache Society). Excluded: Studies for chronic migraine therapy or prophylaxis. |
| Intervention: | Single dose zolmitriptan. |
| Outcomes: | Primary: Pain-free at two hours (without need for rescue medications); Headache (HA) reduction in pain at two hours (moderate/severe reduced to mild/none, without use of rescue medications). Secondary: Pain-free at 24 hours; Sustained headache relief at 24 hours; adverse events; pain intensity measured on a four-point categorical scale (none/mild/moderate/severe) or 100 mm visual analog scale (VAS); pain relief measured on a five-point categorical scale or 100 mm VAS; 30 mm on VAS used as cutoff for mild none vs. moderate/severe headache. |

**Authors’ Conclusions:** Zolmitriptan is effective as an abortive treatment for migraine attacks for some people, but is associated with increased adverse events compared to placebo. Zolmitriptan 2.5 mg and 5 mg benefited the same proportion of people as sumatriptan 50 mg, although not necessarily the same individuals, for headache relief at two hours.

**Quality Checklist:**

1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **Unsure**
4. The assessments of studies were reproducible. **Unsure**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **Yes**
7. The treatment effect was large enough and precise enough to be clinically significant. **Yes**
Methodological Critique: Typically thorough Cochrane systematic review including extensive original study search using electronic databases, reference lists, clinical trial databases (3), and AstraZeneca trial database. The data abstraction was duplicated. The quality assessment used the Cochrane risk of bias and Jadad criteria. The study included a pre-planned subgroup analysis for migraine with and without aura.

Key Results:

- The results were based on 25 studies (all RCTs) that included 20,162 patients and evaluated multiple zolmitriptan formulations and placebo comparisons. In the majority of studies, the risk of bias was uncertain. Overall heterogeneity was low to moderate, depending on the outcome assessed.

- Primary (HA free at two hours): Benefit with zolmitriptan
  - Zolmitriptan 1 mg vs. placebo: RR = 2.7 [95% CI: 2.0 to 3.7]; n = 4 studies, 1,200 attacks, NNT = 7.1
    Oral Rx alone: RR = 1.9 [95% CI: 1.1 to 3.3]; NNT = 14
  - Zolmitriptan 2 mg vs. placebo: RR = 3.0 [95% CI: 2.6 to 3.5]; 11 studies, 5,825 attacks, NNT = 5.1
    Oral Rx alone: RR = 3.0 [95% CI: 2.6 to 3.5], NNT = 5.0
  - Zolmitriptan 2.5 mg was more beneficial vs. 1 mg (z = 3.933, p = 0.0001)
  - Zolmitriptan 5 mg vs. placebo: RR = 3.0 [95% CI: 2.8 to 3.3]; 11 studies, 9,391 attacks, NNT = 4.5
    Oral Rx alone: RR = 3.2 [95% CI: 2.7 to 3.7], NNT 4.8
  - Zolmitriptan 10 mg vs. placebo: RR = 7.8 [95% CI: 4.2 to 14.5], NNT 3.1
    Oral 10 mg dose was significantly better than 5 mg (z = 3.882, p = 0.0001)
  - Primary (HA reduced at two hours): Benefit with zolmitriptan similar to above
  - Secondary (HA free at 24 hours): Benefit with zolmitriptan
  - Secondary (HA relief at 24 hours): Benefit with zolmitriptan
  - Relief of functional disability at two hours: Benefit with zolmitriptan 5 mg, NNT 4.8
  - Need for rescue medications: Significantly less with zolmitriptan vs. placebo, NNT 3.3 to 4.7
  - Adverse Events: Majority well tolerated, self-limited, mild/moderate severity
    - Any adverse events: NNH 2.6 to 16 (higher rates with higher doses)
    - Serious events: Overall rate <0.33% for all Zolmitriptan doses >1 mg (placebo rate 0.20%).
      No evidence of dose response, majority neurologic (dizzy, asthenia, somnolence, paresthesias), chest heaviness (not cardiac), nausea, some flushing

BEEM Commentary: Prior studies have supported the use of IV metoclopramide (BEEM 2012), IV prochlorperazine (BEEM 2010) or high-dose ASA (1000 mg; BEEM 2011) in acute migraine care, and ketorolac/diphenhydramine for secondary acute medical management (BEEM 2014). Since this review did not report study settings, it is not clear how many may have recruited ED patients. However, the applicability of the results to ED care of migraines should be generalizable and easy since there were similar benefits between oral, nasal or IV routes. The resource implications are significant if this could work in the ED. Patients would likely be HA-free or significantly reduced at two hours, and functionally
improved with dosing of at least 5 mg. The NNT values are impressively low to achieve ED-relevant outcomes. Adverse event rates are minimal and transient.
How safe and effective are the new oral anticoagulants (NOACs) in the elderly?

The Bottom Line: We cannot definitively conclude there is no difference in bleeding risk between elderly people using NOACs vs. anticoagulation conventional therapy.

Article Title: New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials.


PubMed ID: 24786913

Population: All randomized controlled trials published through March 30, 2013 identified in the PubMed, Cochrane Library, EMBASE, Web of Science, or CINAHL databases. Eligible studied enrolled males and females over the age of 75 years and reported specific data for these elderly adults.

Intervention: New NOACs (rivaroxaban, apixaban, and dabigatran) and conventional therapy.

Outcomes: Major or clinically relevant bleeding, stroke or systemic embolism (in patients with atrial fibrillation), venous thrombo-embolism or VTE-related death (in patients without atrial fibrillation).

Authors’ Conclusions: In elderly adults enrolled in randomized trials, bleeding with new oral anticoagulants (NOACs) was not different from that with conventional anticoagulants. NOACs might be more effective than conventional agents in this population. An individualized approach matching the particular NOAC to the participant profile, taking into consideration the risk of bleeding and other comorbidities, should be taken rather than a generalized "one size fits all" approach in the elderly adults.

Quality Checklist:

1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Unsure
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. No
7. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: This is an important topic with relevance to emergency medicine. There are however, some important considerations.

First, there was high heterogeneity between studies in the main outcome measure of major or clinically significant bleeding. Other threats to validity include the pooling of data from studies that had different
protocols, definitions and baseline participant characteristics. Participants in the included studies were healthier, had fewer comorbidities and better functional status than the typical elderly population seen in the ED, so healthy skepticism dictates that one question the applicability of study findings to the patients seen in such a setting. Safety data for one of the NOACs (dabigatran) was inconsistently reported in the included studies, making it difficult to form conclusions on one of the main outcomes.

Finally, one of the authors has close ties to multiple pharmaceutical companies both as a consultant and as a speaker, particularly to the companies producing the three NOACs considered in this meta-analysis. Before the conclusions of this meta-analysis can be applied, it is important to first conduct the research with more homogenous studies using comparable protocols and definitions. Ideally, these studies would include pragmatic, real-world patients with multiple comorbidities and polypharmacy, to reflect the reality of our clinical context.

**Key Results:**

- There were 10 RCTs with a total of 25,031 patients over 75 years of age: five evaluated rivaroxaban, three apixaban, and two dabigatran. The majority of patients (55% or 13,779/25,031) were anticoagulated for atrial fibrillation and enrolled in one of four trials (ROCKET-AF, ARISTOTLE, AVERROSE, RE-LY). Other indications for anticoagulation included acute VTE, extended treatment of VTE, or “medically ill participants.”

- The risk of major or clinically significant bleeding was not significantly different between any NOAC and conventional therapy (OR = 1.02 [95% CI: 0.73 to 1.43]) although significant heterogeneity was identified with the index of inconsistency 86%.

- In atrial fibrillation groups, various NOACs were more effective than conventional therapy for prevention of stroke or systemic embolism (OR = 0.65 [95% CI: 0.48 to 0.87]; NNT = 72 [95% CI: 52 to 117]). Although each trial consistently demonstrated benefit, significant heterogeneity was identified in the meta-analysis pooled estimate Odds Ratio with the index of inconsistency 73%.

- In the non-atrial fibrillation group, NOACs had significantly lower risk of VTE or VTE-related death than conventional therapy.

**BEEM Commentary:** Given the heterogeneity between studies, in addition to other methodological concerns, it may be premature to conclude that there is no difference in bleeding risk between NOACs and conventional therapy.
**Do bronchodilators help children with bronchiolitis?**

**The Bottom Line:** Bronchodilators such as albuterol or salbutamol do not improve any patient-important outcomes.

**Article Title:** Bronchodilators for bronchiolitis.


**PubMed ID:** 24937099

**Population:** Infants ≤24 months old with acute bronchiolitis.

**Intervention:** Bronchodilator therapy including nebulized, oral, and subcutaneous albuterol, salbutamol, terbutaline, ipratropium bromide, adrenergic agents excluding epinephrine.

**Outcomes:**
- Primary: Oxygen saturation.
- Secondary: Improvement in clinical score; hospital admission; duration of hospitalization; time to resolution of illness; pulmonary function testing.

**Authors’ Conclusions:** Bronchodilators such as albuterol or salbutamol do not improve oxygen saturation, do not reduce hospital admission after outpatient treatment, do not shorten the duration of hospitalization, and do not reduce the time to resolution of illness at home. Given the adverse side effects and the expense associated with these treatments, bronchodilators are not effective in the routine management of bronchiolitis.

**Quality Checklist:**
1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **Yes**
4. The assessments of studies were reproducible. **Yes**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **No**
7. The treatment effect was large enough and precise enough to be clinically significant. **No**

**Methodological Critique:** Another high quality systematic review from the CDSR. This is a well-performed and fair assessment of bronchodilators for bronchiolitis in children. Some of the studies included recurrent wheezers, which would have biased in favour of treatment effect. The heterogeneity is likely from a combination of inpatient and outpatient studies as well as a variety of different medications and modalities used.
Key Results:

- For the primary outcome, oxygen saturation, there was no significant difference noted: mean difference = -0.43 [95% CI: -0.92 to 0.06]. There was significant heterogeneity for this comparison (I² = 81%). When the subgroup of outpatients treated with inhaled albuterol or salbutamol were examined, there was low heterogeneity and no significant differences noted: mean difference = -0.19 [95% CI: -0.59 to 0.21].

- There was a small but significant improvement in clinical score noted, but there were no significant differences in admission rates, length of hospitalization, or time to illness resolution. Pulmonary function tests showed no significant differences, except in intubated PICU patients, for whom there was a small decrease in airway resistance identified.

- There were significant adverse effects noted in the trials which included tachycardia, flushing, hyperactivity, tremor, and mild hypertension.

BEEM Commentary: Clinicians are often stuck with what to do with the masses of children presenting with this complaint. Bronchodilators are often tried, without much success. This study further solidifies the notion that, for the average infant with bronchiolitis, there is no role for bronchodilators. They are expensive, have little to no benefit, and cause significant side effects.
Does giving nebulized hypertonic saline improve respiratory distress in infants with bronchiolitis in the emergency department?

The Bottom Line: There is insufficient evidence to promote the use of hypertonic saline for the treatment of bronchiolitis.

Article Title: Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial.


PubMed ID: 24862623

Population: Children <24 months old diagnosed with bronchiolitis (November to April).

Excluded: Children with a prior illness with wheeze responsive to bronchodilators; premature; cyanotic congenital heart disease; chronic lung disease; or tracheostomy.

Intervention: 2.5 mg of nebulized albuterol followed by four cc of nebulized 3% hypertonic saline (HS) or 0.9% normal saline (NS) repeated twice as needed in the ED and continued q8h if admitted.

Outcomes: Admission rate; length of stay; RDAI (Respiratory Distress Assessment Instrument); RACS (Respiratory Assessment Change Score); adverse effects.

Authors’ Conclusions: Hypertonic saline given to children with bronchiolitis in the ED decreases hospital admissions. We can detect no significant difference in Respiratory Distress Assessment Instrument score or length of stay between the HS and NS groups.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: Patients were recruited from two tertiary urban children's hospital EDs

2. The patients were adequately randomized. Yes

3. The randomization process was concealed. Yes

4. The patients were analyzed in the groups to which they were randomized. Yes

5. The study patients were recruited consecutively (i.e. no selection bias). No

6. The patients in both groups were similar with respect to prognostic factors. No

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. Yes

8. All groups were treated equally except for the intervention. Yes

9. Follow-up was complete (i.e. at least 80% for both groups). Yes

10. All patient-important outcomes were considered. Yes

11. The treatment effect was large enough and precise enough to be clinically significant. Yes
Methodological Critique: This study was designed for N = 700 but fell short at 408. This is concerning and much has been written about trials that have ended prematurely and the erroneous results that they have generated. The primary outcome of hospital admission is subjective in the sense that different physicians have different thresholds for referral and admission and as the authors admit 'We found significant differences in admission rate and length of stay by site.' These findings further the skepticism about the validity of the results. As an added note, the 2 groups differed in that the HS group had higher rates of tobacco exposure (13.5% vs. 9.1%) as well as higher levels of atopy (8.1% vs. 4.1%) although the impact of this is unclear.

Key Results:

- Admission rate: 42.6% patients in the NS group were admitted compared to 28.9% in the HS group (odds ratio (OR): 0.55 [95% CI: 0.36 to 0.83]). This difference was statistically significant even after controlling for differences in baseline clinical predictors. The absolute risk reduction (ARR) was 13.7 and the number needed to treat (NNT) was seven to prevent hospitalization.
- Length of stay: The mean length of stay was 3.92 (5.24) days for the NS group and 3.16 (2.11) days for the HS group (p = 0.24) was not statistically significant (p = 0.24) even after controlling for differences in baseline clinical predictors.
- No significant difference in the RACS was noted and no differences in supplemental treatments used between the two groups. There were no significant differences in adverse effects.

BEEM Commentary: The results of this study need to be taken in context with the results of the Cochrane Database Systematic Review on the same topic by Zhang (2013) that showed no difference in admission rates with HS treatment.
Does giving nebulized hypertonic saline improve respiratory distress in infants with bronchiolitis?

**The Bottom Line:** This small study fails to demonstrate that nebulized 3% HS compared with normal saline improves respiratory distress in infants with bronchiolitis not responding to standard treatments in the ED.

**Article Title:** Nebulized hypertonic saline for bronchiolitis in the emergency department: a randomized clinical trial.


**PubMed ID:** 24862342

**Population:** Infants two to 24 months old with first episode of acute bronchiolitis and moderate to severe respiratory distress after nebulized albuterol and nasal suctioning.

**Intervention:** Nebulized 3% hypertonic saline (4 cc) or normal saline (NS)

**Outcomes:**
- Primary: Respiratory Assessment Change Score (RACS);
- Secondary: Changes in heart rate, respiratory rate and oxygenation; hospitalization rate; physician clinical impression; parental impression of breathing and feeding; adverse events.

**Authors’ Conclusions:** Infants with bronchiolitis and persistent respiratory distress after standard treatment in the emergency department had less improvement after receiving 3% HS compared with those who received NS. Based on these results and the existing evidence, administration of a single dose of 3% HS does not appear to be indicated to treat bronchiolitis in the acute care setting.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **Yes**
   
   Comment: Patients were recruited from an urban tertiary care pediatric emergency department.

2. The patients were adequately randomized. **Unsure**

3. The randomization process was concealed. **Yes**

4. The patients were analyzed in the groups to which they were randomized. **Yes**

5. The study patients were recruited consecutively (i.e. no selection bias). **Unsure**

6. The patients in both groups were similar with respect to prognostic factors. **No**

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **Yes**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**
11. The treatment effect was large enough and precise enough to be clinically significant. **Unsure**

**Methodological Critique:** This is a very small study with significant methodological issues including the fact that the two groups were not similar at the beginning of the study, with the hypertonic saline group being exposed to more smokers in the home (17 vs. 13), having more previous ICU admissions (6 vs. 4) and presenting at 3.7 days vs. 2.4 days. The hypertonic saline group was also older by one month. With such a small sample size, minimal differences like these can have a huge impact on the final results. The authors also state, regarding the primary outcome, that "These results were limited by missing data (23 per group)." Given these and other issues, no reliable conclusions can be made.

**Key Results:**
- The HS group demonstrated significantly less improvement in the median RACS compared with the NS group at one hour after the intervention: (HS RACS = -1 [IQR: -5 to -1] vs. NS RACS = -5 [IQR: -6 to -2]; p = 0.01).
- No significant differences were noted in changes in heart rate or oxygen saturation, rate of hospitalization, or parental perception of breathing or feeding status. No adverse events occurred in the study.

**BEEM Commentary:** The authors have made inappropriate conclusions about an inadequately reported, small study.
What are the effects of over-the-counter medications for acute cough in children and adults?

**The Bottom Line:**
The results of this review reveal no convincing evidence that over-the-counter medications for cough do anything other than possibility causing adverse effects.

**Article Title:** Over-the-counter (OTC) medications for acute cough in children and adults in community settings.


**PubMed ID:** 25420096

**Population:** Children and adults with acute cough in the outpatient setting presenting to an acute care centre.

**Intervention:** Non-prescription OTC oral cough medications divided into specific groups: Antitussives; expectorants; mucolytics, antihistamine-decongestant combinations; other drug combinations; antihistamines.

**Outcomes:**
- **Primary:** Cough related outcomes including frequency, severity, sputum production, and improvement.
- **Secondary:** Adverse effects.

**Authors’ Conclusions:** The results of this review have to be interpreted with caution because the number of studies in each category of cough preparations was small. Availability, dosing and duration of use of over-the-counter cough medicines vary significantly in different countries. Many studies were poorly reported making assessment of risk of bias difficult and studies were also very different from each other, making evaluation of overall efficacy difficult. There is no good evidence for or against the effectiveness of OTC medicines in acute cough. This should be taken into account when considering prescribing antihistamines and centrally active antitussive agents in children; drugs that are known to have the potential to cause serious harm.

**Quality Checklist:**
1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **No**
4. The assessments of studies were reproducible. **No**
5. The outcomes were clinically relevant. **No**
6. There was low statistical heterogeneity for the primary outcome. **No**
7. The treatment effect was large enough and precise enough to be clinically significant. **No**
Methodological Critique: This systematic review uses the same high quality and comprehensive approach as all Cochrane reviews. There were small numbers of trials in each category, the quantitative data available was limited and the heterogeneity between trials in terms of populations, interventions and outcomes that precluded pooling of the results. Finally, assessment of the risk of bias of the included studies was limited by poor reporting. In short, excellent study methods but poor quality primary studies.

Key Results:
This study included 19 trials involving 3,799 adults and 10 trials of 1,036 children:

- 3/10 pediatric trials revealed antihistamines to be no more effective than placebo;
- 3/10 pediatric trials revealed antitussives to be no more effective than placebo;
- 2/10 pediatric trials revealed antihistamine-decongestants to be no more effective than placebo;
- 1/10 pediatric trial revealed antitussive/bronchodilator combinations to be no more effective than placebo;
- 1/10 pediatric trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group;
- 1/29 trial indicated that three types of honey were more effective than placebo; and,
- 21/29 studies reported adverse effects.

BEEM Commentary: There continues to be no great evidence that OTC medications for cough have any significant benefit and their routine use cannot be justified on the current state of the evidence. In addition the potential for adverse effects from accidental overdose in the pediatric population make purchasing these products of questionable safety.
Does giving honey to children with cough provide symptomatic relief?

**The Bottom Line:** In children over one year of age, honey is a safe and effective way to improve acute cough from URTI as well as improve sleep and parental sleep.

**Article Title:** Honey for acute cough in children.


**PubMed ID:** 25536086

**Population:** RCTs studying children one to 18 years old with acute cough from an upper respiratory infection.

**Intervention:** Honey (with or without antibiotics).

**Outcomes:**
- Primary: Duration of cough; symptomatic relief of cough.
- Secondary: Improvement in child's sleep; improvement in caregiver sleep; improvement in quality of life; adverse effects; improvement in appetite; cost.

**Authors’ Conclusions:** Honey may be better than 'no treatment', diphenhydramine and placebo for the symptomatic relief of cough, but it is not better than dextromethorphan. None of the included studies assessed the effect of honey on 'cough duration' because intervention and follow-up were for one night only. There is no strong evidence for or against the use of honey.

**Quality Checklist:**
1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **No**
4. The assessments of studies were reproducible. **Yes**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **Yes**
7. The treatment effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** This is another high quality CDSR and an update of a CDSR performed in 2012 with the only difference being the addition of Cohen’s 2012 RCT. Of the three studies included, only one (Cohen 2012) has a low risk of bias. For this reason the inclusion of the data from the other two studies renders conclusions dubious at best. As Cohen’s study was the only one with proper blinded control, we should look there for high quality results and ignore results from the other two included trials.
Key Results:

- This review included three RCTs of which two had high risk of bias. The studies compared the effect of honey with dextromethorphan, diphenhydramine and 'no treatment' on symptomatic relief of cough using the seven-point Likert scale. Honey was better than 'no treatment' in reducing frequency of cough (mean difference (MD) = -1.07 [95% CI: -1.53 to -0.60]). Moderate quality evidence suggests honey did not differ significantly from dextromethorphan in reducing cough frequency (MD = -0.07 [95% CI: -1.07 to 0.94]). Low quality evidence suggests honey may be slightly better than diphenhydramine in reducing cough frequency (MD = -0.57 [95% CI: -0.90 to -0.24]). Adverse events included mild reactions (nervousness, insomnia and hyperactivity) experienced by seven children (9.3%) from the honey group and two (2.7%) from the dextromethorphan group; the difference was not significant (risk ratio (RR) = 2.94 [95% CI: 0.74 to 11.71]). Three children (7.5%) in the diphenhydramine group experienced somnolence (RR = -0.14 [95% CI: 0.01 to 2.68]; one study) but there was no significant difference between honey vs. dextromethorphan or honey vs. diphenhydramine. No adverse event was reported in the 'no treatment' group.

- Severity of coughing was significantly less with honey and significantly better than all other groups. Additionally, honey was found to significantly improve the quality of sleep for both children and parents and this improvement was significantly better than that found in the dextromethorphan, diphenhydramine, placebo and 'no treatment' groups. There were no significant differences in adverse effects found in any of the studies. None of the three included studies did not examine quality of life, changes in appetite or cost of treatments.

BEEM Commentary: The authors have undervalued their results. In saying that there is "no strong evidence for or against the use of honey" ignores their significant findings of improved cough, improved sleep and improved parental sleep with honey.
What is the safety and efficacy of opioids in children with acute abdominal pain?

The Bottom Line: Intravenous opioid analgesia for children with acute abdominal pain may be useful but the supporting evidence is weak.

Article Title: Opioid analgesia for acute abdominal pain in children: A systematic review and meta-analysis.


PubMed ID: 25377394

Population: All randomized controlled trials (RCTs) of children aged <18 years with acute abdominal pain that compared any opioid analgesic to placebo identified through electronic searches of MEDLINE (1946-2013), EMBASE (1980-2013), Cochrane Central Register of Controlled Trials (2013), CINAHL (1981-2013), and Google Scholar (2013).

Intervention: Any opioid analgesia (compared to non-analgesic placebo). Most studies used morphine IV (0.05 to 0.15 mg/kg).

Outcomes: Primary: Pre- and post-intervention pain scores (self-reported, 100 mm VAS scales, measured at 15 to 30 minutes).

Secondary: Differences in intestinal perforations/abscesses (up to 3 days), side effects (up to 3 weeks), and rates of missed appendicitis (up to 3 weeks).

Authors’ Conclusions: The use of opioids in undifferentiated acute abdominal pain in children is associated with no difference in pain scores and an increased risk of mild side effects. However, there is no increased risk of perforation or abscess. The overall quality of evidence is low, suggesting the need for larger, high-quality trials that are powered to detect both serious complications of appendicitis and determine the most efficacious opioid dosing for children.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. No
7. The treatment effect was large enough and precise enough to be clinically significant. No
Methodological Critique: This systematic review reported no industry funding. The search was broad including electronic & manual searches unrestricted by language or date. There were too few studies for a funnel plot analysis. There were high kappa agreements for the searches and inclusion decisions. The risk of bias was assessed using the Cochrane Risk of Bias tool and was generally low. The overall quality of evidence low (GRADE evidence profile).

Key Results:

- **Six studies included 324 children. Acute appendicitis was the most common pathology reported.**
- **Primary:** There was no significant difference in the pooled mean pre/post difference in self-reported pain scores (19.61 mm [95% CI: -1.16 to 40.37]) or significant increase in the risk of perforation or abscess associated with opioids in cases of appendicitis (RR = 1.03 [95% CI: 0.55 to 1.93]). However, the risk of side effects was significantly greater in patients who received opioids (RR = 6.06 [95% CI: 1.10 to 33.49]). A sensitivity analysis excluding one study eliminated the heterogeneity and the pooled MD was 8.88 (4.68-13.08); includes MCID (13mm) at upper bound (MCID = minimal clinically important difference). The use of a fixed vs. random effects analysis, however, did yield a smaller pooled effect estimate (MD 6.55 mm, 5.53 to 7.58), but the upper bound then excluded the MCID.
- **Secondary:** There was no difference in perforations/abscesses (RR = 1.03 [95% CI: 0.55 to 1.93]), heterogeneity moderate at 39%). The two missed cases of appendicitis were both in the placebo arm (RR = 0.31 [95% CI: 0.03 to 2.86]). All reported adverse events (most commonly pruritus, emesis, drowsiness, nausea, dizziness) were in the opioid group (RR = 6.06 [95% CI: 1.1 to 33.5]).

BEEM Commentary: It is somewhat surprising that the use of presumably strong analgesics (i.e. opioids such as morphine) were not significantly better than nonanalgesic placebos (this would be more understandable compared to nonopioid analgesic alternatives). The preplanned subgroup analysis (removing one outlier study), however, did reveal a statistically significant result, with a 95% CI including the MCID (13 mm), suggesting that opioid analgesia may, in fact, be superior to saline placebo. A key concern is that use of different analysis models to account for heterogeneity (fixed vs. random effects) yields different results with respect to the MCID, limiting the clinical utility of these results. An MCID of 13 mm on a 100 mm VAS is typically considered clinically significant. There were no meaningful differences in missed appendicitis rates or adverse events, and event rates were low in both groups anyway.

Results are likely generalizable worldwide in developing countries, as studies included both males and females, age range five to 18 years (mean age 11 to 12 years).

Most studies used 0.1 mg/kg IV morphine, which is readily available in most EDs. Results limited by small numbers of patients and outcome events, leading to imprecision of pooled results with predictable heterogeneity. Future studies should be powered with higher numbers, and use nonopioid analgesic comparators (as use of saline placebos likely currently unethical).
Is oral morphine superior to oral ibuprofen for the management of post fracture pain management in children?

The Bottom Line: Oral morphine 0.5 mg/kg every six hours does not appear to be superior to oral ibuprofen 10 mg/kg every six hours for post-fracture pain in children but causes more adverse effects. Hence, first line treatment of post-fracture pain with ibuprofen and Tylenol does not seem unreasonable and might be better tolerated by the patient.

Article Title: Oral administration of morphine versus ibuprofen to manage post fracture pain in children: a randomized trial.


PubMed ID: 25349008

Population: Children aged five to 17 years old with a nonoperative, radiographically evident extremity fracture sustained within the preceding 24 hours. Excluded: Known hypersensitivity to either ibuprofen or morphine; chronic use of nonsteroidal anti-inflammatory drugs (NSAIDS) or opioids; associated injuries requiring analgesia; known renal disease; bleeding disorders; poor fluency in English; sleep apnea; and pregnancy.

Intervention: Morphine 0.5 mg/kg (max. 10 mg) PO or ibuprofen 10 mg/kg (max. 600 mg) every six hours as needed for pain for 24 hours after discharge (max. four doses).

Outcomes: Primary: Pain scale scores before and after the first dose of analgesic. Secondary: Type and frequency of adverse effects and the number of participants who required acetaminophen.

Authors’ Conclusions: We found no significant difference in analgesic efficacy between orally administered morphine and ibuprofen. However, morphine was associated with a significantly greater number of adverse effects. Our results suggest that ibuprofen remains safe and effective for outpatient pain management in children with uncomplicated fractures.

Quality Checklist:
1. The study population included or focused on those in the ED. Yes
   Comment: All ED patients.
2. The patients were adequately randomized. Yes
3. The randomization process was concealed. Yes
4. The patients were analyzed in the groups to which they were randomized. Yes
5. The study patients were recruited consecutively (i.e. no selection bias). No
6. The patients in both groups were similar with respect to prognostic factors. Yes
7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **Yes**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **No**

**Methodological Critique:** This single-centre, parallel-group, randomized, double-dummy, blinded superiority trial was funded by a grant from the University of Western Ontario. The enrolled subjects were from a convenience sample of eligible patients presenting to a single pediatric ED. The six-hour dosing regimen of the morphine is less than the recommended two to four hours and favoured the ibuprofen group for the primary outcome but might also have favoured the morphine group for the secondary outcome of adverse events. The analysis was based on a modified intention-to-treat principle in which included subjects were required to receive at least one dose of the intervention.

**Key Results:**
- Of the 183 patients randomized, data from 66 subjects in the morphine group and 68 in the ibuprofen group revealed no significant inter-group difference in the primary outcome (0.2 [95% CI: -0.2 to 0.6]) or in the change in pain scores between the groups at any of the four time points (p = 0.6). Participants in the morphine group had significantly more adverse effects than those in the ibuprofen group (56.1% vs. 30.9%, p <0.01).

**BEEM Commentary:** This well-designed and executed pragmatic trial failed to show morphine at subtherapeutic intervals was superior to ibuprofen for post-fracture pain in children but caused significantly more adverse effects. Ideally, we will see confirmation of these results from other centres with more frequent dosing of morphine. Until then, these findings are consistent with another recently published RCT on pediatric analgesia (Kelly LE, Sommer DD, Ramakrishna J, Hoffbauer S, Arbab-Tafti S, Reid D et al. Morphine or Ibuprofen for post-tonsillectomy analgesia: a randomized trial. Pediatrics. 2015 Feb;135(2):307-13.). Hence, first line treatment of post-fracture pain with ibuprofen and Tylenol does not seem unreasonable and might be better tolerated by the patient.
How does a radiation-free strategy of ultrasound/MRI compare to CT for children with suspected appendicitis?

The Bottom Line: US +/- MRI appears to be a good diagnostic strategy for some patients with appendicitis. Further prospective research is required to clarify the answer to this question before MRI will be routinely used. Until then, MRI should be seen as an option that may be limited by its immediate availability and the need for sedation in pediatric patients.

Article Title: Ultrasonography/MRI versus CT for diagnosing appendicitis.


PubMed ID: 24590746

Population: Pediatric patients <18 years old presenting to the ED with abdominal pain who had a computed tomography (CT), ultrasound (US), or magnetic resonance imaging (MRI).

Intervention: Imaging for suspected acute appendicitis between: CT was used as the primary imaging modality (group A); US was the primary imaging modality followed by MRI for equivocal findings (group B).

Outcomes: Primary: Negative appendectomy rates; perforation rates.
Secondary: Time from ED triage to diagnosis, antibiotic administration, appendectomy incision and hospital discharge, diagnostic test sensitivity and specificity.

Authors’ Conclusions: In children with suspected acute appendicitis, a radiation-free diagnostic imaging of ultrasonography selectively followed by MRI is feasible and comparable to CT, with no difference in time to antibiotic administration, time to appendectomy, negative appendectomy rate, perforation rate, or length of stay.

Quality Checklist:

1. The clinical problem is well defined. Yes
   Comment: Children presenting with abdominal pain are often investigated for appendicitis. There are concerns around the radiation risk of abdominal CT scans in children.

2. The study population represents the target population that would normally be tested for the condition including (i.e. no spectrum bias). Yes

3. The study population included or focused on those in the ED. Yes

4. The study patients were recruited consecutively (i.e. no selection bias). Yes

5. The diagnostic evaluation was sufficiently comprehensive and applied equally to all patients (i.e. no evidence of verification bias). Unsure
6. All diagnostic criteria were explicit, valid and reproducible (i.e. no incorporation bias). **Unsure**

7. The reference standard was appropriate (i.e. no imperfect gold-standard bias). **Yes**

8. All undiagnosed patients underwent sufficiently long and comprehensive follow-up (i.e. no double gold-standard bias). **Unsure**

9. The likelihood ratio(s) of the test(s) in question is presented or can be calculated from the information provided. **Yes**

10. The precision of the measure of diagnostic performance is satisfactory. **Unsure**

**Methodological Critique:** This is a retrospective study which opens the door to innumerable bias concerns. The two groups are not mutually exclusive in terms of strategies used. Group A had some children receiving MRI and Group B had some children receiving CT. There was no control of which patients received CT strategy vs. US vs. MRI, and as such we cannot trust that the patients in the two time-frames can be properly compared.

**Key Results:**
- Group A: 15.1% US, 92% CT, 1.5% MRI. Group B: 92% US, 13.6% CT, 38.8 MRI. All differences were significant p <0.0001.
- Rates of complicated appendicitis by operative findings were not significantly different: 27.1% (A) vs. 22.4% (B), p = 0.4. Rates of complicated appendicitis by pathology were not significantly different: 14.4% (A) vs. 12.2% (B), p = 0.7. Negative appendectomy rates were not significantly different: 2.5% (A) vs. 1.4% (B), p = 0.7.
- Diagnostic test evaluations (95% CI). Group A: Sensitivity = 100% (97% to 100%); specificity = 98% (93% to 99%); PPV = 98% (93% to 99%); NPV = 100% (96% to 100%). Group B: Sensitivity = 100% (97% to 100%); specificity = 99% (97% to 100%); PPV = 99% (95% to 100%); NPV = 100% (98% to 100%).
- Time to antibiotics was 8.7 hours (SD 4.1) in Group A and 8.2 hours (SD 4.8) in Group B, p = 0.14.
- Time to appendectomy was 13.2 hours (SD 7.2) in Group A and 13.9 hours (SD 6.7) in Group B, p = 0.41.
- Length of stay was 52.2 hours (SD 79.7) in Group A and 43.4 hours (SD 63) in Group B, p = 0.18.

**BEEM Commentary:** If the result of this study have any validity, it does appear that for some patients, of which we are unsure specifically which ones, the use of US +/- MRI appears to offer very good diagnostic capabilities while avoiding the long-term radiation risks associated with abdominal CT. Moving forward, we will need to see a prospective randomized trial before this strategy can be employed across the board. In the meantime, we can begin to ask the question whether MRI would be a reasonable option some patients. Unfortunately, pediatric patients may require sedation for MRI, which may hamper the utility of this test from the ED. This may be the future of appendicitis workups in children!
How does intranasal fentanyl compare to other forms of analgesia in children with acute pain presenting to the ED?

The Bottom Line: Intranasal fentanyl is a safe and viable option for acute pain control in children.

Article Title: Intranasal fentanyl for the management of acute pain in children.


PubMed ID: 25300594

Population: RCTs and quasi-RCTs examining children three months to 18 years old with acute pain.

Intervention: Intranasal fentanyl (INF) vs. other pharmacological/non-pharmacological analgesic.

Outcomes: Primary: Reduction in pain score.

Secondary: Adverse events; tolerance; use of rescue analgesia; patient/parent satisfaction; cost; mortality.

Authors’ Conclusions: INF may be an effective analgesic for the treatment of patients with acute moderate to severe pain, and its administration appears to cause minimal distress to children.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Yes
7. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: Overall this is a very well performed systematic review. The search was very thorough and the studies are of reasonable quality. Given that there were only three studies found, and that each study had different comparisons (INF vs. IV morphine (IVM); INF vs. IM morphine (IMM); two different concentrations of INF), pooling of data was not possible. Therefore, it is impossible to comment on heterogeneity.

The primary outcome measure, reduction in pain, is clinically relevant and INF was shown to improve children’s pain rating.
Key Results:
- This study included three studies with 313 participants and all three reported a reduction in pain score with INF and INF produced a greater reduction in pain score at 10 minutes compared with Intramuscular morphine (IMM) (INF group pain score: 1/5 vs. IMM group pain score: 2/5; p = 0.014). No other statistically significant differences in pain scores were reported at any other time point.
- No adverse events or deaths were reported in any of the studies.

BEEM Commentary: The three studies were all from Australia and did not include patients younger than three years. As well, all three studies examined children with orthopedic injuries, not pain from non-traumatic etiologies. Therefore, it is difficult to know whether this data can be generalized to different ages and different populations and different etiologies of pain.
In children with pyelonephritis, what antibiotic should we use, via what route, at what dose, and for how long?

The Bottom Line: Oral antibiotics can be used for treating pediatric pyelonephritis as long as care is taken to ensure that antibiotics match local microbial resistance patterns.

Article Title: Antibiotics for acute pyelonephritis in children.


PubMed ID: 25066627

Population: Randomized controlled trials and quasi-RCTs studying inpatient and outpatient children ≤18 years old with acute pyelonephritis.

Intervention: Antibiotics - all doses and routes.

Outcomes: Primary: Duration of fever; symptom persistence; dimercaptosuccinic acid (DMSA) renal scan evidence of renal parenchymal damage; length of hospital stay for inpatients; persistent bacteriuria; recurrence of UTI; adverse events; economic costs.

Secondary: Persistent renal damage; hypertension; chronic renal disease.

Authors’ Conclusions: Results suggested that children aged over one month with acute pyelonephritis can be treated effectively with oral antibiotics (cefixime, cefituben, or amoxicillin/clavulanic acid) or with short courses (2 to 4 days) of intravenous (IV) therapy followed by oral therapy. If IV therapy with aminoglycosides is needed, single daily dosing is safe and effective.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. No
4. The assessments of studies were reproducible. Yes
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Yes
7. The treatment effect was large enough and precise enough to be clinically significant. No

Methodological Critique: This typically high standard Cochrane systematic review included 27 studies in the meta-analysis. However, the actual number of studies answering any individual question is low. In addition, as seen in the risk of bias tool, the quality of the included studies was not high. There was no appropriate blinding in any of the studies and there were problems with incomplete data in at least seven of the 27 studies. Given that many of the outcome measures were objective, for example persistence of UTI, the lack of blinding would have minimally biased the results. In addition, as outlined in the text of the
paper, nine of the included studies used a urine bag for specimen collection, a method well known to be misleading in diagnosing urinary infections in children. In some of the analyses (i.e. 1.1, 1.6, 2.4, 5.1, 10.2) there was a failure to show benefit of one treatment over the other, which is not the same as showing equivalency. A long-standing problem with research papers is concluding that two treatments are equal when we have failed to show a difference.

Given the above mentioned reasons coupled with the limitations posed by the quality of the included studies, it is difficult to make definitive conclusions based on the study findings. Having said that, the best evidence available does point to being able to use oral medication for children presenting with pyelonephritis. Extreme caution is advised in making an antibiotic choice given the regional differences in pathogen sensitivities to antibiotics. In some areas, for example, E-coli resistance to sulfamethoxazole-trimethoprim is quite high.

**Key Results:**
- The 27 included studies evaluated 12 different comparisons.
- No significant differences were found in duration of fever (2 studies, 808 children: Mean difference (MD) = 2.05 hours [95% CI: -0.84 to 4.94]; persistent UTI at 72 hours after commencing therapy (2 studies, 542 children: RR = 1.10 [95% CI: 0.07 to 17.41]) or persistent kidney damage at six to 12 months (4 studies, 943 children: RR = 0.82 [95% CI: 0.59 to 1.12]) between oral antibiotic therapy (10 to 14 days) and intravenous (IV) therapy (3 days) followed by oral therapy (10 days).
- Similarly, no significant differences in persistent bacteriuria at the end of treatment (4 studies, 305 children: RR = 0.78 [95% CI: 0.24 to 2.55]) or persistent kidney damage (4 studies, 726 children: RR = 1.01 [95% CI: 0.80 to 1.29]) were found between IV therapy (3 to 4 days) followed by oral therapy and IV therapy (7 to 14 days).
- No significant differences in efficacy were found between daily and thrice daily administration of aminoglycosides (1 study, 179 children: Persistent clinical symptoms at three days: RR = 1.98 [95% CI: 0.37 to 10.53]).
- Adverse events were mild and uncommon and rarely resulted in discontinuation of treatment.

**BEEM Commentary:** The question of the best antibiotic treatment for pyelonephritis in children remains an ongoing issue. Although the quality of the evidence is poor, there appears to be little difference between oral antibiotics and intravenous antibiotics for the treatment of pediatric pyelonephritis. The selection of antibiotics should be based on local resistance patterns.
Which previously established decision rule for identifying children requiring a CT scan post-head injury has the best diagnostic accuracy?

**The Bottom Line:** The clinical judgement of experienced emergency physicians continues to be the best method for assessing risk of clinically-important injury in children with a minor head trauma although the PECARN rule is a useful tool for less experienced clinicians.

**Article Title:** Comparison of PECARN, CATCH, and CHALICE rules for children with minor head injury: a prospective cohort study.


**PubMed ID:** 24635987

**Population:** Children <18 years old presenting to the ED within 24 hours of a minor head injury and a GCS of 13 or more.

**Intervention:** The PECARN, CATCH and CHALICE rules.

**Outcomes:** Test characteristics including sensitivity, specificity and likelihood ratios predicting clinically important traumatic brain injuries.

**Authors’ Conclusions:** Of the five modalities studied, only physician practice and PECARN identified all clinically important traumatic brain injuries, with PECARN being slightly more specific. CHALICE was incompletely sensitive but the most specific of all the rules. CATCH was incompletely sensitive and had the poorest specificity of all modalities.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **Yes**
   - **Comment:** The patients were recruited from an urban ED.

2. The patients were representative of those with the problem. **Yes**

3. All important predictor variables and outcomes were explicitly specified. **Yes**

4. This is a prospective, multicentre study including a broad spectrum of patients and clinicians (level II). **No**

5. Clinicians interpret individual predictor variables and score the clinical decision rule reliably and accurately. **Unsure**

6. This is an impact analysis of a previously validated CDR (level I). **No**

7. For Level I studies, impact on clinician behavior and patient-centric outcomes is reported. **Yes**

8. The follow-up was sufficiently long and complete. **Yes**

9. The effect was large enough and precise enough to be clinically significant. **Yes**
Methodological Critique: This is a well-designed study trying to answer an important question in pediatric emergency care. The primary outcome is relevant to patients. The execution of the study design was well done as well. There was overall good follow-up of patients (90%) and the researchers were careful to try to catch all patients with clinically-important injury.

There were some limitations of the study design. Firstly, the sample size for clinical decision rule studies is typically based on the number of outcomes needed and this was not the case for this study, hence the number of patients with significant injury was only 21. This limited number results in the wider confidence intervals seen around point estimates. Secondly, the inter-rater reliability during data collection was only moderate.

Key Results:
- Among the 1,009 children, 21 (2%; 95% confidence interval [CI] 1% to 3%) had clinically important traumatic brain injuries. Only physician practice and PECARN identified all clinically important traumatic brain injuries.
- PECARN: Sensitivity = 100% [95% CI: 84 to 100], specificity = 62% [95% CI: 59 to 66], LR + 2.7 [95% CI: 2.5 to 2.9], LR - 0 [95% CI: 0 to ?].
- CATCH: Sensitivity = 91% [95% CI 70 to 99], specificity = 44% [95% CI: 41 to 47], LR + 1.6 [95% CI: 1.4 to 1.9], LR - 0.2 [95% CI: 0.1 to 0.8].
- CHALICE: Sensitivity = 84% [95% CI: 60 to 97], specificity = 85% [95% CI: 82 to 87], LR + 5.5 [95% CI: 4.3 to 7.1], LR - 0.2 [95% CI: 0.1 to 0.5].
- Physician practice: Sensitivity = 100% [95% CI: 84 to 100], specificity = 50% [95% CI: 47 to 53], LR + 2.0 [95% CI: 1.9 to 2.1], LR - 0 [95% CI: 0 to ?].

BEEM Commentary: Overall, this study supports the use of the PECARN rule for the assessment of children with head injuries. The high sensitivity ensures that no children are sent home with a clinically important injury. The moderate specificity helps ensure that less unnecessary scans are done. We are limited in our definitive conclusions from this single-centre trial by the wide confidence intervals noted. These findings however, should be taken into consideration with the fact that clinical decision rules are meant to help clinicians make clinical decisions in difficult cases and, in doing so, perform better than clinical gestalt. While the PECARN showed a small increase in specificity over physician judgment, the area under the receiver operating characteristic (ROC) curve was considerably less (81%) than physician practice (94%). We agree with the authors’ conclusions and recognize the limitations of the conclusions based on the wider confidence intervals.
In children with minor head injuries, does isolated loss of consciousness predict clinically-important traumatic brain injury?

The Bottom Line: Children with minor head injury and an isolated history of loss of consciousness who have no other risk factors for clinically-important head injuries can safely be sent home with appropriate discharge instructions. A period of observation in the ED may be warranted depending on comfort level, but CT scans should not be routinely used.

Article Title: Isolated loss of consciousness in children with minor blunt head trauma.


PubMed ID: 25003654

Population: Children <18 years old with non-trivial blunt head injuries.

Excluded: Patients with penetrating head injury, pre-existing neurologic disease, syncope or seizure preceding the head injury, as well as neuro-imaging post-injury prior to presentation.

Intervention: Presence of isolated loss of consciousness (LOC).

Outcomes: Clinically important traumatic brain injury (ciTBI); traumatic brain injury on CT.

Authors’ Conclusions: Children with minor blunt head trauma presenting to the emergency department with isolated LOC are at very low risk for ciTBI and do not routinely require computed tomographic evaluation.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: Patients were recruited from 25 EDs.

2. The patients were representative of those with the problem. Yes

3. The patients were sufficiently homogeneous with respect to prognostic risk. Yes

4. Objective and unbiased outcome criteria were used. Yes

5. The follow-up was sufficiently long and complete. Unsure

6. The effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: This is a secondary analysis of the data from the Kuppermann (2009) study that established the PECARN head-injury rule for children. The methodology of the original study, and therefore this study, is robust. Follow-up, although not specified in this paper, is described in the original paper and included ensuring that patients who were sent home were followed up by phone. Those not reached by phone were searched for to ensure they did not re-present to healthcare or the morgue.
Key Results:

- The primary focus examined children with LOC but no other PECARN predictors of head injury (PECARN-isolated LOC). There were 2780 PECARN-isolated LOC patients of which 38 (1.9% [95% CI: 1.4 to 2.6]) had a TBI on CT and 13 (0.5% [95% CI: 0.2 to 0.8]) had a clinically important TBI (ciTBI). This was significantly lower than the patients who had additional PECARN ciTBI predictors (see Table 2 in the text).

- The secondary focus examined children with LOC but no other clinical predictor found in a pediatric TBI study (Expanded-isolated LOC). Of the 576 patients in this group, only one (0.2% [95% CI: 0.0 to 1.0]) had a clinically-important TBI. Of the 326 patients in this group who had a CT scan, three had TBI noted (0.9% [95% CI: 0.2 to 2.7]).

BEEM Commentary: The number of patients in this study is impressive and the value of this is seen in the narrow confidence intervals around the data points. It is unlikely that a primary cohort study of this magnitude will ever be conducted to specifically answer this question and so this might continue to be the best evidence that emergency physicians ever have.

The results of this study indicate that the child with a head injury who has isolated LOC and no other concerning history, signs or symptoms of injury is at extremely low risk of clinically-important injury and can safely be sent home in the charge of reliable caregivers with appropriate instructions. Periods of observation in the ED are valuable and appropriate in place of head CT if there are concerns.
In children with minor head injuries, does isolated vomiting predict clinically-important traumatic brain injury?

**The Bottom Line:** Children with isolated vomiting after a head injury can be safely sent home with appropriate discharge instructions. A period of observation in the ED may be warranted depending on comfort level, but CT scans should not be routinely used.

**Article Title:** Association of traumatic brain injuries with vomiting in children with blunt head trauma.


**PubMed ID:** 24559605

**Population:** Children <18 years old with non-trivial blunt head injuries.
Excluded: Patients with penetrating head injury; pre-existing neurologic disease; syncope or seizure preceding the head injury; as well as neuro-imaging post-injury prior to presentation.

**Intervention:** Presence of isolated vomiting.

**Outcomes:** Clinically important traumatic brain injury; traumatic brain injury on CT.

**Authors’ Conclusions:** Traumatic brain injury on CT is uncommon and clinically important traumatic brain injury is very uncommon in children with minor blunt head trauma when vomiting is their only sign or symptom.

**Quality Checklist:**

1. The study population included or focused on those in the ED.  **Yes**  
   **Comment:** Patients were recruited from 25 EDs.

2. The patients were representative of those with the problem.  **Yes**

3. The patients were sufficiently homogeneous with respect to prognostic risk.  **Yes**

4. Objective and unbiased outcome criteria were used.  **Yes**

5. The follow-up was sufficiently long and complete.  **Unsure**

6. The effect was large enough and precise enough to be clinically significant.  **Yes**

**Methodological Critique:** This is a secondary analysis of the data from the database of the PECARN head-injury rule for children cohort study. The methodology of the original study and, therefore, very good. Follow-up, although not specified in this paper, is described in the original paper and included ensuring that patients who were sent home were followed up by phone. The authors were unable to complete telephone or mail follow-up on the 831 patients (17.8%) for whom isolated vomiting status was known, which could have led to an underestimation of the prevalence of clinically important traumatic brain injury.
brain injury or traumatic brain injury on CT. Those not reached by phone were searched for to ensure they did not re-present to healthcare or the morgue.

Key Results:

- Clinically important traumatic brain injury (ciTBI) occurred in 2/815 patients (0.2% [95% CI: 0% to 0.9%]) with isolated vomiting post-injury compared to 114/4577 patients (2.5% [95% CI: 2.1% to 3.0%]) in the non-isolated vomiting group. Risk difference = -2.3% [95% CI: -2.8% to -1.5%].

- Traumatic brain injury (TBI) on CT occurred in 5/298 patients (1.7% [95% CI: 0.5% to 3.9%]) with isolated vomiting compared to 211/3284 patients (6.4% [95% CI: 5.6% to 7.3%]) in the non-isolated vomiting group. Risk difference = -4.7% [95% CI: -6.0% to -2.4%].

- None of the patients with TBI and isolated vomiting post-injury required neurosurgery. The two patients with ciTBI required two days of observation as inpatients.

BEEM Commentary: The number of patients in this study is impressive and the value of this is seen in the narrow confidence intervals around the data points. It is unlikely that a primary cohort study of this magnitude will ever be conducted to specifically answer this question and so this might continue to be the best evidence that emergency physicians ever have. The results of this study indicate that the child with a head injury who has isolated vomiting and no other concerning history, signs or symptoms of injury is at extremely low risk of clinically-important injury and can safely be sent home in the charge of reliable caregivers with appropriate instructions. Periods of observation in the ED are valuable and appropriate in place of head CT if there are concerns.
Is there benefit to recommending strict rest after a child has a concussion?

The Bottom Line: In children with concussion, two days of rest followed by a gradual return to activity is preferred over five days of rest followed by a gradual return to activity. The longer strict rest period appears to cause more post-concussive symptoms.

Article Title: Benefits of strict rest after acute concussion: a randomized controlled trial.


PubMed ID: 25560444

Population: Patients aged 11 to 22 years old presenting to the ED with acute (<24 hours) diagnosis of concussion.

Excluded: Unable to speak English, couldn’t consent; pre-existing intellectual disability or mental health issue; previously diagnosed intracranial injury; being admitted; lived >1 hour from the investigation centre or at the discretion of the recruiting physician.

Intervention: Strict rest at home for five days (no school, work or activity) followed by stepwise return to activity.

Outcomes: Compliance with physical and mental activity recommendations; symptoms; neurocognitive performance (ImPACT); balance.

Authors’ Conclusions: Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: The patients were aged 11 to 22 years, so not strictly pediatric by most standards. The patients were, however, recruited from the ED.

2. The patients were adequately randomized. Yes

3. The randomization process was concealed. Yes

4. The patients were analyzed in the groups to which they were randomized. Yes

5. The study patients were recruited consecutively (i.e. no selection bias). No

6. The patients in both groups were similar with respect to prognostic factors. No

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. No

8. All groups were treated equally except for the intervention. Unsure

9. Follow-up was complete (i.e. at least 80% for both groups). Yes

10. All patient-important outcomes were considered. No
11. The treatment effect was large enough and precise enough to be clinically significant. Yes

Methodological Critique: This is a novel, single-centre study examining a topic that we often struggle with in the ED, specifically, how long to keep someone resting post-concussion. The patients were aged 11 to 22 years and so it is questionable whether this study can be generalized to younger pediatric patients. The two groups did differ significantly in terms of age with the strict rest group being older. The impact of this difference is unknown. The outcome measures such as representation to ED and proportion of patients with symptoms beyond 10 days were not described; 11% of patients were lost to follow-up.

Key Results:
- Both groups reported an ~20% decrease in physical activity and energy expenditure for the five days post-injury. There was more reported high and moderate mental activity on days two to five in the usual care group on days two to five (8.33 vs. 4.86 hours, \( p = 0.03 \)).
- Efficacy: 67% of patients in the usual care group experienced symptom resolution during follow-up compared to 63% in the strict group (\( p = 0.82 \)). It took three days longer for 50% of patients in the strict group to report symptom resolution. The strict group had more post-concussive symptoms compared to the usual care group over the 10 day follow-up period (70.4 vs. 50.2, \( p < 0.03 \)) and had greater post-concussive symptom scale (PCSS) scores (187.9 vs. 131.9, \( p < 0.03 \)).
- There were no significant differences noted in computer-based neurocognitive tests and balance scores noted and no significant differences in neuropsychological assessments except for the Symbol Digit Modalities Test for which the usual group performed worse at day three and better at day 10.

BEEM Commentary: This study has opened the door to a very interesting line of inquiry, and further research will be very useful. For the time being, however, there is evidence to support a two-day rest period following a concussion with a gradual return to activity. Keeping a child at strict rest for five days post-concussion appears to offer no benefit, and there is evidence of harm from this strategy.
Do displaced proximal humerus fractures require surgery?

**The Bottom Line:** Surgical treatment of displaced proximal humerus fractures involving the humeral neck in adult patients is not superior to non-surgical treatment.

**Article Title:** Surgical vs nonsurgical treatment of adults with displaced fractures of the proximal humerus: the PROFHER randomized clinical trial.


**PubMed ID:** 25756440

**Population:** Adults (≥ 16 years) with a proximal humerus fracture involving the surgical neck <3 weeks old and displaced enough to justify surgery.

Excluded: Associated ipsilateral shoulder dislocation; open fracture; insufficient mental capacity to understand the trial or instructions for rehabilitation; unfit for surgery or anesthesia; clear need for surgery; multiple upper limb fractures; nonosteoporotic pathological fracture; terminal illness; or not a resident in the hospital catchment area.

**Intervention:** Internal fracture fixation (or humeral head replacement, i.e. hemiarthroplasty) or a sling for three weeks or as long as deemed necessary followed by active rehabilitation.

**Outcomes:**

Primary: Oxford Shoulder Score (OSS = 0 to 48), a validated shoulder-specific outcome measure at six, 12, and 24 months.

Secondary: Short-Form 12 (SF-12) health survey; complications related to surgery and shoulder fracture (eg, surgical site infection, symptomatic malunion, and avascular necrosis of the humeral head); complications requiring secondary surgery or treatment; medical complications during inpatient stay; and mortality.

**Authors’ Conclusions:** Among patients with displaced proximal humeral fractures involving the surgical neck, there was no significant difference between surgical treatment compared with nonsurgical treatment in patient-reported clinical outcomes over two years following fracture occurrence. These results do not support the trend of increased surgery for patients with displaced fractures of the proximal humerus.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **No**
   
   **Comment:** Although these patients were recruited from fracture clinics and orthopedic wards, they all likely entered the hospital system through the ED.

2. The patients were adequately randomized. **Yes**

3. The randomization process was concealed. **Yes**
4. The patients were analyzed in the groups to which they were randomized. **Yes**

5. The study patients were recruited consecutively (i.e. no selection bias). **Unsure**

6. The patients in both groups were similar with respect to prognostic factors. **Yes**

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. **No**

8. All groups were treated equally except for the intervention. **Yes**

9. Follow-up was complete (i.e. at least 80% for both groups). **Yes**

10. All patient-important outcomes were considered. **Yes**

11. The treatment effect was large enough and precise enough to be clinically significant. **Yes**

**Methodological Critique:** This pragmatic, open, multicentre, parallel-group, superiority, randomized clinical trial at 32 acute UK National Health Service hospitals. Trial was funded by the UK National Institute for Health Research, Health Technology Assessment Programme. As expected, trial participants and clinicians were not blind to the interventions. However, neither were the outcome assessors which could result in bias favouring either group. Analyses were on based on intention-to-treat.

**Key Results:**

- Of the 1,250 patients screened, 563 met inclusion criteria of which 313 refused participation. 295/1000 were excluded because of comorbidities precluding surgery or lack of mental capacity. Approximately 54% to 59% of the enrolled patients were ≥65 years old. Data was analysed from the remaining 250 (125 per group). 16/125 in the surgery group and 2/125 in the nonsurgery group did not receive the assigned intervention. 114/125 in the surgery group and 117/125 in the nonsurgery group were included in the final analysis.

- Primary: There was no significant difference in the mean Oxford Shoulder Scores between the two groups over two years (0.75 points [95% CI, −1.33 to 2.84 points]; p = 0.48) or at individual time points.

- Secondary: There were no significant differences between the two groups over two years with respect to the following secondary outcomes: the mean SF-12 physical component score (p = 0.18); the mean SF-12 mental component score (p = 0.32); complications related to surgery or shoulder fracture (p = 0.28); requiring secondary surgery to the shoulder (11 in each group); increased or new shoulder-related therapy (p = 0.58); and mortality (p = 0.27). Ten medical complications in the surgical group during the postoperative hospital stay.

**BEEM Commentary:** This multicentre study of primarily older patients with a closed and otherwise uncomplicated proximal humerus fracture involving the surgical neck <3 weeks old and displaced enough to justify surgery failed to show that that surgical treatment provides better patient-important clinical outcome than conservative treatment but is associated with significant risk. The study was not powered to determine whether these results also apply to young healthy patients. Regardless, from an emergency medicine perspective, we can offer these patients appropriate analgesia, a comfortable sling, follow-up with orthopedic surgery and reassurance that they are unlikely to require surgery.
How should a reduced shoulder be immobilized in the ED to prevent dislocation recurrence?

The Bottom Line: It appears that immobilization in the abduction and external rotation (AbER) position after successful reduction of anterior shoulder dislocation has the best likelihood of return to functional goals, and reduced risk of 24-month recurrent dislocation.

Article Title: Immobilization in external rotation combined with abduction reduces the risk of recurrence after primary anterior shoulder dislocation.


PubMed ID: 24725898

Population: ED patients with anterior shoulder dislocation (ages 15 to 55) successfully reduced. Excluded: Prior surgical shoulder problems; current need for surgery; multidirectional instability; inability to complete 24-month follow-up.

Intervention: Immobilization in adduction and internal rotation using sling and swathe bandage or immobilization in abduction and external rotation with a stabilizer brace. Patients received a rehabilitation program three weeks after the intervention.

Outcomes: Primary: Recurrence of dislocation after 24 months. Secondary: Rates of positive apprehension tests, return to preinjury sport, functional outcomes on Western Ontario Shoulder Instability Index (WOSI), proportion of noncooperative patients.

Authors’ Conclusions: Immobilization with the shoulder in the AbER position is effective to reduce the risk of recurrence after primary anterior shoulder dislocation and should be preferred to the traditional method of immobilization in AdIR position in clinical practice.

Quality Checklist:

1. The study population included or focused on those in the ED. Yes
   Comment: Urban university ED; 68,000 visits regional level II trauma centre in Tehran, Iran.

2. The patients were adequately randomized. Yes

3. The randomization process was concealed. Yes

4. The patients were analyzed in the groups to which they were randomized. Yes

5. The study patients were recruited consecutively (i.e. no selection bias). Yes

6. The patients in both groups were similar with respect to prognostic factors. Yes

7. All participants (patients, clinicians, outcome assessors) were unaware of group allocation. No
8. All groups were treated equally except for the intervention. Yes
9. Follow-up was complete (i.e. at least 80% for both groups). Yes
10. All patient-important outcomes were considered. Yes
11. The treatment effect was large enough and precise enough to be clinically significant. Yes

**Methodological Critique:** Aside from obvious blinding problems with immobilization techniques, this is methodologically a well-executed RCT. The strong difference in favour of AdER is astonishing with a low NNT of 3.4 for preventing 24-month recurrence. The authors acknowledge significant noncompliance with the AdER brace due to unpleasant consequences for patient daily life (walking in doorways/crowds, sleep position). The authors reasonably justify the choice of a 10 degree angle for AdER, citing studies that higher angles are more cumbersome and compliance is worse.

**Key Results:**
- Randomized with computerized schemes, 1:1 blocks. Unable to blind physicians or patients to immobilization method for obvious reasons; no comments on blinding of final 24-month outcomes assessors. Planned superiority trial to show 30% difference favouring AbER group, sample size 102 patients achieved (91 males, 11 females). No loss to 24-month follow-up.
- Mean age 35.7 years, majority R shoulder dislocations (71%), etiologies sports (67.6%), accidental injury 32.4%. All ED reductions successful, no surgeries needed. Majority of recurrences with first 12 months.
- Primary: AbER recurrence rate 3.9%, AdIR rate 33.3% (p <0.001). The absolute risk reduction is 29.4%, yielding an NNT of 3.4.
- Secondary: No significant difference in apprehension tests between both groups. Significant difference in return to sports favouring AbER group (83.8%) vs. AdIR group (31.5%); ARR = 52.3, NNT = 2. Higher non-cooperative brace uses in AbER group (19.6%) vs. AdIR (5.8%). Improved WOSI scores in favour of AbER group vs. AdIR group (p = 0.004).

**BEEM Commentary:** The construction of the RCT, the achievement of recruiting proper sample size and complete follow up, in addition to the astonishingly large difference in the two groups, suggest that the AbER position, if tolerated for three weeks, followed by a structured rehabilitation program, will reduce the 24-month recurrence of dislocation substantially, compared to the traditional AdIR position. Important patient-oriented outcomes including return to sport and WOSI scores are also improved with initial AbER immobilization. Compliance might be a challenge with patients during the three week immobilization period. However, before this is standard practice in many EDs around the world, two changes must occur: studies at other centres will be needed to validate these results; and commercially manufactured devices for AbER will need to be available.
Should EMS providers have advanced trauma life support training?

The Bottom Line: The current evidence indicates that there is no benefit of advanced life support training for ambulance crews on patient outcomes.

Article Title: Advanced training in trauma life support for ambulance crews.


PubMed ID: 25144654

Population: Randomized controlled trials, controlled trials and non-randomized studies, including before-and-after studies and interrupted time series studies, comparing the impact of ALS-trained ambulance crews vs. crews without ALS training on the reduction of mortality and morbidity in adult (>18 years old) trauma patients.

Intervention: Advanced trauma life support training of ambulance crews.

Outcomes: Reduction in morbidity and mortality in trauma patients.

Authors' Conclusions: At this time, the evidence indicates that there is no benefit of advanced life support training for ambulance crews on patient outcomes.

Quality Checklist:
1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Yes
4. The assessments of studies were reproducible. Unsure
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Unsure
7. The treatment effect was large enough and precise enough to be clinically significant. No


Key Results:
- Three studies included, 4,763 patients (2,867 from Canadian OPALS Trauma study).
- No benefit was observed into two before/after implementation studies and one small RCT (n = 16) of having advanced trauma life support training for EMS providers.
- OPALS study suggests an increased mortality in patients with GCS <9 who received care from ALS-trained EMS personnel.
BEEM Commentary: This is another thorough review that refutes advanced training for EMS providers for critical care situations. There is no large RCT, however, definitively address this question, as there are suggestions that this may be unethical. The OPALS studies have answered many of the prehospital training utility questions over the past decade or so. For respiratory distress, there was a small benefit with mortality absolute risk reduction (ARR) 1.9% with ALS-trained EMS personnel vs. BLS. In cardiac arrest patients, however, there was no benefit of ALS interventions in a CPR/Defib optimized system. While it may seem intuitive that having higher trained personnel intervening earlier in life-threatening situations in out-of-hospital settings, the large OPALS datasets for various patient populations and critical diagnoses have definitively refuted this assumption. The results might vary; however, between geographic settings where transfer to definitive care differ significantly.
Is a liberal vs. restrictive fluid resuscitation strategy optimal for trauma patient outcomes?

The Bottom Line: No evidence-based guidance as to which resuscitation strategy is optimal; use your best clinical judgement.

Article Title: Liberal versus restricted fluid resuscitation strategies in trauma patients: a systematic review and meta-analysis of randomized controlled trials and observational studies.


PubMed ID: 24335443

Population: Randomized controlled trials and observational studies unrestricted for language, population or publications year comparing different fluid administration strategies in trauma patients (age range not specified).

Excluded: Patients with >10% burns, or studies comparing different fluid types. Included RCTs excluded patients with traumatic brain injury (TBI).

Intervention: Liberal fluid resuscitation strategies.

Outcomes: Restrictive fluid resuscitation (definitions of liberal vs. restrictive quantities not specified).

Authors' Conclusions: Current evidence indicates that initial liberal fluid resuscitation strategies may be associated with higher mortality in injured patients. However, available studies are subject to a high risk of selection bias and clinical heterogeneity. This result should be interpreted with great caution.

Quality Checklist:

1. The clinical question is sensible and answerable. Yes
2. The search for studies was detailed and exhaustive. Yes
3. The primary studies were of high methodological quality. Unsure
4. The assessments of studies were reproducible. Unsure
5. The outcomes were clinically relevant. Yes
6. There was low statistical heterogeneity for the primary outcome. Yes
7. The treatment effect was large enough and precise enough to be clinically significant. No

Methodological Critique: The searches were unrestricted, duplicate, independent electronic and manual. Investigator differences were resolved by consensus. There was no data on single vs. duplicated data abstraction, agreement. Quality of the included studies was assessed using Cochrane Risk of Bias tool (RCTs) or Newcastle-Ottawa scale (observational studies). It is undefined what constitutes "liberal" vs. "restrictive" fluid resuscitation in these studies. In some of the restrictive studies, a target SBP of 90 mm
Hg is defined for "permissive hypotension." Most of the included studies were performed in prehospital settings, so generalizability to the ED is unclear.

**Key Results:**
- Eleven studies identified (4 RCT [n = 2,107 patients], seven observational [n = 13,687 patients]). No evidence of publication bias. Heterogeneity was low in both study sets. Similar age and gender distributions in both trial sets. one RCT dropped due to high protocol violation rate and significant variation of study populations. RCTs had a higher proportion of penetrating and excluded TBI patients, whereas observational studies had more blunt traumas and TBI patients.

- The quantitative synthesis indicated that liberal fluid resuscitation strategies might be associated with higher mortality than restricted fluid strategies, both in RCTs (RR = 1.25 [95% CI: 1.01 to 1.55]); three trials; I², 0 and observational studies (OR = 1.14 [95% CI: 1.01 to 1.28]); seven studies; I², 21.4%. When only adjusted ORs were pooled for observational studies, odds for mortality with liberal fluid resuscitation strategies increased: OR = 1.19 [95% CI: 1.02 to 1.38]; six studies; I², 26.3%.

**BEEM Commentary:** The arguments remain as to whether or not aggressive vs. limited fluid resuscitation is appropriate in all trauma patients, those with specific injury patterns, or not at all. Opponents of liberal fluids cite increased bleeding from dislodged clots & dilutional coagulopathy, and the concept here is "permissive hypotension." The issue of permissive hypotension in the face of TBI or compromised cerebral perfusion is not addressed in this review. Furthermore, the majority of evidence on the outcomes of the two strategies is based on animal evidence, not human trials. There is not yet definitive evidence in human studies (with or without burns or TBI, blunt vs. penetrating trauma) as to whether or not liberal vs. restrictive fluid resuscitation is the correct strategy for mortality reduction. The majority of current evidence is from heterogeneous observational studies, therefore prone to the many biases to go with such study designs.
## Does ultrasound-guided subclavian catheterization reduced the frequency of adverse events compared with the landmark technique?

<table>
<thead>
<tr>
<th>The Bottom Line:</th>
<th>Compared with the conventional landmark technique, ultrasound-guided subclavian catheterization by trained and experienced users likely reduces the frequency of adverse events.</th>
</tr>
</thead>
</table>

**Article Title:** Ultrasound-Guided Subclavian Vein Catheterization: A Systematic Review and Metaanalysis.


**PubMed ID:** 25803646

**Population:** Peer-reviewed, randomized controlled trials of ultrasound-guided subclavian vein catheter insertion compared to the traditional landmark technique.

**Intervention:** Dynamic and static sonographic Doppler and imaging 2D ultrasound guidance of subclavian vein catheter insertion.

**Outcomes:**
- **Primary:** Catheterization failure.
- **Secondary:** Frequency of complications including, pneumothorax, arterial bleeding or arterial puncture, infection, thrombus, arrhythmias, malposition, hemothorax, cardiac tamponade, and nerve injuries. Time for cannulation and number of attempts.

**Authors’ Conclusions:** Ultrasound-guided subclavian catheterization reduced the frequency of adverse events compared with the landmark technique. Our findings support the use of dynamic 2D ultrasound for subclavian catheterization to reduce adverse events and failed catheterization.

**Quality Checklist:**

1. The clinical question is sensible and answerable. **Yes**
2. The search for studies was detailed and exhaustive. **Yes**
3. The primary studies were of high methodological quality. **No**
4. The assessments of studies were reproducible. **Yes**
5. The outcomes were clinically relevant. **Yes**
6. There was low statistical heterogeneity for the primary outcome. **No**
7. The treatment effect was large enough and precise enough to be clinically significant. **Yes**
Methodological Critique: This study was supported, in part, by institutional departmental funds from the Ottawa Hospital but no industry funding. The search was comprehensive and reproducible. The inter-rater agreement between abstractors was measured appropriately as were the assessments of bias and statistical analyses.

Key Results:
- Of the 10 included studies with a total of 2,168 participants, only one was conducted in the ED. No study fulfilled all six criteria for low risk of bias although it was low for most studies in most categories but unclear for allocation concealment allocation and unclear or high for blinding of outcome assessment. As expected, blinding to the procedure was not feasible. There was no significant difference in catheterization failure rates between the ultrasound and landmark groups (RR = 0.67 [95% CI: 0.36 to 1.27]) although the prevalence of complications was significantly less in the ultrasound group (OR = 0.53 [95% CI: 0.41 to 0.69]).

BEEM Commentary: Subclavian catheterization, while an excellent choice for the landmark approach is very challenging for the novice to perform using ultrasound due to overlying bone obstructing the beam. This has led to most clinicians who use ultrasound to access the internal jugular where feasible. Two factors limiting further potential benefit are the variable training of the clinicians enrolled (ultrasound is a user-dependent skill) and the inferior needle imaging quality of older machines. With mainly ICU studies, the results need validation in the ED setting.

This review reinforces that any clinician inserting central lines today should consider dynamic ultrasound guidance but only after obtaining adequate training for the appropriate approach. It is also important to realize even with ultrasound harm can occur and an understanding of when to use it is as important as how to use it.
ACEP Clinical Policy: Management of Adult ED Patient with Suspected Thoracic Aortic Dissection (TAD)

**Article Title:** Clinical policy: critical issues in the evaluation and management of adult patients with suspected acute nontraumatic thoracic aortic dissection.


**PubMed ID:** 25529153

**Population:** Adult patients seen in ED with suspected TAD.

Excluded: Traumatic TAD, pregnant or pediatric patients.

**Intervention:** Diagnostic and therapeutic interventions.

**Outcomes:** Diagnostic accuracy of different ED tests, hemodynamic control of confirmed TAD.

**Quality Checklist:**

1. The study population included or focused on those in the ED. **Yes**
   
   **Comment:** ACEP clinical policy for ED physicians.

2. Were all important options and outcomes clearly specified? **Yes**

3. Were all relevant stakeholders involved in guideline development? **Yes**

4. An explicit and sensible process was used to the relative value of different outcomes. **Unsure**

5. The guideline thoughtfully balances desirable and undesirable effects. **Yes**

6. The guideline accounts for important recent developments. **Yes**

7. The guideline has been peer-reviewed and tested. **No**

8. What is the impact of uncertainty associated with the evidence and values used in the guidelines? **Unsure**

9. The guideline authors’ conflicts of interest are fully reported, transparent, and unlikely to sway the recommendations of the guideline. **Yes**

10. Has an implementation strategy with readily usable workflow protocols been provided? **No**

**Methodological Critique:** Funding source = ACEP Clinical Policy Group.

Methodology unchanged since original 1993 Shriger article for ACEP policies.

**Levels of Evidence:**

- Level A: Generally accepted principles for patient care based on high degree of clinical certainty (strong supportive evidence).
• Level B: Recommendations may identify particular strategies that reflect moderate clinical certainty).

• Level C: Recommendations based on weak/absent evidence, and based on expert consensus.

Search for evidence: English language only, electronic databases (Medline, Cochrane CDSR/DARE databases, Web of Science, Scopus), bibliographic lists, recent expert papers.

External commentary by ED physicians, cardiologists, vascular surgeons (members of AHA, Soc Vascular Surgery). ACEP member review on website and EM Today (60-day review period). No comments on implementation utility.

Grading of evidence based on Evidence Classes I-IV, and Levels of Recommendations A-C.

Conflict of Interest: No "relevant" relationships.

No clear comments on uncertainty impact.

No implementation strategies with usable workflow protocols provided.

**Key Recommendations (Strength of Evidence):**

- In adult patients with suspected nontraumatic TAD, are there clinical decision rules that identify a group of patients at very low risk for the diagnosis of TAD?
  - Level A & B: No recommendations.
  - Level C: In an attempt to identify very low risk TAD patients, do not use any CDR alone (further workup at EM MD discretion).

- In adult patients with suspected nontraumatic TAD, is a negative serum D-Dimer sufficient to identify a group of patients at very low risk for the diagnosis of TAD?
  - Level A & B: No recommendations.

- In adult patients with suspected nontraumatic TAD, is the diagnostic accuracy of CTA at least equivalent to TEE or MRA to exclude TAD diagnosis?
  - Level A & C: No recommendations.
  - Level B: In adult patients with suspected nontraumatic TAD, ED physicians may use CTA to exclude TAD because it has similar accuracy to TEE or MRA. (See Shiga et al, Arch Int Med 2006; 166, 1350-1356).

- In adult patients with suspected nontraumatic TAD, does an abnormal bedside TTE establish the diagnosis of TAD?
  - Level A: No recommendations.
  - Level B: In adult patients with suspected nontraumatic TAD, do not rely on abnormal bedside TTE result to definitively establish diagnosis of TAD.
  - Level C: In adult patients with suspected nontraumatic TAD, immediate surgical consultation/transfer to higher level of care should be considered if TTE is suggestive of TAD.

- In adult patients with suspected nontraumatic TAD, does targeted HR and BP lowering reduce morbidity and mortality?
Level A & B: No recommendations.
Level C: In adult patients with suspected nontraumatic TAD, reduce BP and HR if elevated. However, there are no specific targets that have demonstrated a reduction in morbidity and mortality.

**BEEM Commentary:** ACEP continues to put out the most relevant EM CPG products consistently to date. Unfortunately, ACEP clings to an outdated and non-intuitive grading system for evidence evaluation and recommendations; should adopt GRADE methods.

This CPG updates key diagnostic strategies initially reviewed by Klompas et al (JAMA Rational Clinical Exam 2002), and summarized by S. Upadhye/K. Schiff (EM Clinics North America 2012: 307-327). The levels of recommendations, however, are stuck at Levels B & C, as the supporting evidence is generally weak. The review by Shiga et al (Arch Int Med 2006) supports the use of advanced imaging in ANY suspected TAD patient, as no clinical assessment, lab test, X-ray or US test is adequate to rule the diagnosis out with sufficient sensitivity.
ACEP Clinical Policy: Critical issues in the evaluation and management of adult patients presenting to the ED with seizures.

**Article Title:** Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures.

**Reference:**

**PubMed ID:** 24655445

**Population:** Adult ED patients with seizures.

Excluded: Pediatric patients, complex partial seizures, acute brain/multisystem trauma, known SOL/brain tumour, immunocompromised or preeclamptic patients.

**Intervention:** Use of antiepileptic meds; disposition from ED.

**Outcomes:** Seizure medications; disposition from ED.

**Quality Checklist:**
1. The study population included or focused on those in the ED. **Yes**
   
   Comment: Adult ED patients.

2. Were all important options and outcomes clearly specified? **Yes**

3. Were all relevant stakeholders involved in guideline development? **Yes**

4. An explicit and sensible process was used to the relative value of different outcomes. **Unsure**

5. The guideline thoughtfully balances desirable and undesirable effects. **Yes**

6. The guideline accounts for important recent developments. **Yes**

7. The guideline has been peer-reviewed and tested. **No**

8. What is the impact of uncertainty associated with the evidence and values used in the guidelines? **Unsure**

9. The guideline authors’ conflicts of interest are fully reported, transparent, and unlikely to sway the recommendations of the guideline. **Unsure**

10. Has an implementation strategy with readily usable workflow protocols been provided? **Unsure**

**Methodological Critique:** Funding source = ACEP Clinical Policy group.

**Levels of Evidence:**

Level A: Generally accepted principles for patient care based on high degree of clinical certainty (strong supportive evidence).

Level B: Recommendations may identify particular strategies that reflect moderate clinical certainty.
Level C: Recommendations based on weak/absent evidence, and based on expert consensus.

- Standard ACEP methodology for CPG Policy statements (initial 1993). Update of 2004 CPG.
- Search for evidence: English language only, electronic databases (Medline, Cochrane), bibliographic lists, recent expert papers.
- External commentary by American Epilepsy Society, American Academy of Neurology, and other epilepsy expert groups. ACEP member comments via EM Today. No comments on implementation utility.
- Grading of evidence based on Evidence Classes I-IV, and Levels of Recommendations A-C.
- Conflict of Interest: A. Jagoda declares "relevant" consultant/advisory board relationships with multiple pharmaceutical companies.
- Uncertainty impact not discussed.
- No implementation protocols provided. Two tables (2 & 3) outlining dosing for AEDs and meds for generalized status epilepticus.

**Key Recommendations (Strength of Evidence):**

- **In patients with first generalized convulsive seizure who have returned to baseline clinical status, should antiepileptic therapy be initiated in ED to prevent additional seizures?**
  - Level A & B: No recommendations.
  - Level C: ED Physician need not initiate antiepileptic prescription in ED with first provoked seizure or unprovoked seizure without prior brain disease/injury. Physician may initiate seizure prevention meds for first unprovoked seizure with a history of brain injury/disease (or defer to other care providers).

- **In patients with first unprovoked seizure who have returned to baseline status, should they be admitted to hospital to prevent adverse events?**
  - Level A & B: No recommendations.
  - Level C: Patient need not be admitted after return to baseline.

- **In patient with known seizure disorder in which resuming antiepileptic meds in ED is deemed appropriate, does the route of administration impact recurrence of seizures?**
  - Level A & B: No recommendations.
  - Level C: No - May administer meds via oral or IV routes.

- **In patients with generalized convulsive status epilepticus who continue to seize despite optimal Bzd loading, which agent(s) should be administered next to terminate seizures?**
  - Level A: Must administer additional antiepileptic meds for refractory status epilepticus if Bzds have failed.
  - Level B: Consider IV phenytoin, fosphenytoin or valproic acid as second line choice after Bzd loading. Authors recommend valproic acid over phenytoin derivatives due to faster infusion, better adverse event profile.
  - Level C: Consider IV levetiracetam, propofol or barbiturates as third line choices after Bzd loading.
BEEM Commentary: No Level A recommendations for non-emergent use of AEDs, or discharge destination. No Level A recommendations for refractory generalized status epilepticus post Bzd failure. ACEP continues to consistently put out the most relevant EM CPGs products to date but should adopt GRADE methodologies.