Systematic Reviews & Meta-analysis

Clay Bordley
Department of Pediatrics
Division of Hospital & Emergency Medicine

Jane P. Gagliardi
Department of Psychiatry and Behavioral Sciences
Department of Medicine
First a Case....
Assess
Ask
Acquire
Appraise
Apply
3 mo w/ sneezin’, wheezin’ and fever

- Congested for 4 days, fast breathing for past 24 hours
  - Breast and bottle fed, but having trouble sucking and breathing
  - Decreased wet diapers
- 3yr cousin with URI sx’s
- PMHx: 39 wk, unremarkable P/L/D
- SHx: 16yr mother (sucking her thumb), lives with MGM, mo and cousins
- PE
  - 38.0 186 64, 93% sat
  - Alert, obvious congestion and increased WOB’ing, nl TM’s, (+) retractions, defuse wheezing, no murmur, nl CR and pulses, abd soft, no HSM
- Your impression:
  - Bronchiolitis, fever, borderline sats

What Clinical Questions Do You Have?
Disclosures

Pharmacologic Treatment of Bronchiolitis in Infants and Children
A Systematic Review

Valerie J. King, MD, MPH; Meera Viswanathan, PhD; W. Clayton Bordley, MD, MPH; Sonya F. Sutter, BS; Kathleen N. Lohr, PhD; Timothy S. Carey, MD, MPH

Background: Bronchiolitis is the most common lower respiratory tract infection in infants. Up to 25% of all children in their first year of life are hospitalized with bronchiolitis. Bronchodilators and corticosteroids are commonly used treatments, but little consensus exists about optimal management strategies.

Objectives: To conduct a systematic review of the effectiveness of commonly used treatments for bronchiolitis in infants and children.

Data Sources: We searched MEDLINE and the Cochrane Controlled Trials Register for references to randomized controlled trials of bronchiolitis treatment published since 1980.

Study Selection: Randomized controlled trials of interventions for bronchiolitis in infants and children were included if they were published in English between 1980 and November 2003 and had a minimum sample size of 10.

Data Extraction: We abstracted data on characteristics of the study population, interventions used, and results of studies meeting entry criteria into evidence tables and analyzed them by drug category.

Data Synthesis: Interventions were grouped by drug category and qualitatively synthesized.

Results: Of 797 abstracts identified in the literature search, we included 54 randomized controlled trials. This review includes 44 studies of the most common interventions: epinephrine (n=40), β2-agonists bronchodilators (n=13), corticosteroids (n=13), and ribavirin (n=10). Studies were, in general, underpowered to detect statistically significant outcome differences between study groups. Few studies collected data on outcomes that are of great importance to parents and clinicians, such as the need for and duration of hospitalization.

Conclusions: Overall, little evidence supports a routine role for any of these drugs in treating patients with bronchiolitis. A sufficiently large, well-designed pragmatic trial of the commonly used interventions for bronchiolitis is needed to determine the most effective treatment strategies for managing this condition.


Testing in Bronchiolitis
A Systematic Review

W. Clayton Bordley, MD, MPH

Background: The diagnosis of bronchiolitis is based on typical history and results of a physical examination. The indications for and utility of diagnostic and supportive laboratory testing (eg, chest x-ray films, complete blood cell counts, and respiratory syncytial virus testing) are unclear.

Objectives: To review systematically the data on diagnostic and supportive testing in the management of bronchiolitis and to assess the utility of such testing.

Design: In conjunction with an expert panel, we generated feasibility criteria and derived relevant terms to search the literature published from 1980 to November 2002 in MEDLINE and the Cochrane Collaboration Database of Controlled Clinical Trials. Trained abstractors completed detailed data collection forms for each article. We summarized the data in tables after performing data integrity checks.

Results: Of the 797 abstracts identified, we present evidence from 82 trials that met our inclusion criteria (17 are primary articles on diagnosis of bronchiolitis and 65 are reports of treatment or prevention trials). Numerous studies demonstrate that rapid respiratory syncytial virus tests have acceptable sensitivity and specificity, but no data show that respiratory syncytial virus testing affects clinical outcomes in typical cases of the disease. Seventeen studies presented chest x-ray film data. Abnormalities on chest x-ray films ranged from 20% to 96%. Insufficient data exist to show that chest x-ray films reliably distinguish between viral and bacterial disease or predict severity of disease. Ten studies included complete blood cell counts, but most did not present specific results. In one study, white blood cell counts correlated with radiologically defined disease categories of bronchiolitis.

Conclusions: A large number of studies include diagnostic and supportive testing data. However, these studies do not define clear indications for such testing or the impact of testing on relevant patient outcomes. Given the high prevalence of this disease, prospective studies of the utility of such testing are needed and feasible.

Today’s Clinical Question

Is hypertonic saline effective in infants with bronchiolitis?
Assess
Ask
Acquire
Appraise
Apply
Exercise #1

Search in groups of 2

Time: 3-5 minutes

Be prepared to report to group

1. How did you do your search
2. What source did you choose?
3. Did you get an answer?
What Did You Find?
Hypertonic saline — Hypertonic saline theoretically has the potential to reduce airway edema and mucus plugging, the predominant pathologic features of acute bronchiolitis [77].

We do not suggest the use of hypertonic saline in children with bronchiolitis. Although there is evidence to suggest that hypertonic saline may shorten length of stay in hospitalized children, additional studies are needed to determine the optimal delivery interval, concentration, and delivery device (eg, ultrasonic versus jet nebulizer) [77-78].

A meta-analysis evaluating hypertonic saline for bronchiolitis in children included seven trials (591 patients) [77]. In pooled analysis of four trials (282 patients) [78-80,82] treatment of children hospitalized with nonsevere acute bronchiolitis with nebulized 3% saline (generally administered with bronchodilators) was associated with decreased mean length of stay (mean difference -1.16 days, 95% CI -1.55 to -0.77 days) and improved clinical scores during the first three days of admission compared with treatment with 0.9% saline [77]. In pooled analysis of three trials (282 patients) in the outpatient or emergency department setting [79,83,84] treatment with 3% versus 0.9% saline (administered with bronchodilators) was associated with a nonsignificant reduction in hospitalization (risk ratio 0.63, 95% CI 0.34-1.17) [77]. Subsequent outpatient trials (one using 5% saline) have had similar findings [85,86]. No significant adverse events related to hypertonic saline were reported [77].

Heliox — Heliox is a mixture of helium (70 to 80 percent) and oxygen (20 to 30 percent). It flows through airways with less turbulence and resistance than supplemental oxygen (nitrogen/oxygen), thus improving ventilation and decreasing the work of breathing [32]. (See "Physiology and clinical use of heliox.")

We do not suggest the routine use of heliox in the treatment of bronchiolitis in infants and children. The administration of heliox is cumbersome and results in a relatively small benefit in a limited group of infants. (See “Physiology and clinical use of heliox,” section on "Technical issues.")

A meta-analysis of four heterogeneous randomized and quasi-randomized trials of heliox for the treatment of moderate or severe bronchiolitis concluded that heliox may improve clinical score in the first hour, but did not reduce the rate of intubation, need for mechanical ventilation, or length of stay in the intensive care unit [87-91]. In a subsequent randomized trial comparing administration of nebulized epinephrine with heliox followed by administration of heliox by high-flow nasal cannula (HFNC) with administration of nebulized epinephrine with oxygen followed by administration of oxygen by HFNC, heliox did not result in
Bronchiolitis Treatment & Management

Overview  Presentation  DDx  Workup  Treatment  Medication

Approach Considerations

Hospital admissions for infants with bronchiolitis treated in the ED. In this trial, 800 infants were assigned to 1 of 4 treatment groups (nebulized albuterol and inhaled dexamethasone, nebulized epinephrine and oral placebo, nebulized placebo and oral dexamethasone, or nebulized albuterol and oral placebo). Only the infants in the epinephrine-dexamethasone group were significantly less likely to be admitted to the hospital within 7 days of treatment.

Admission Criteria

Sumner et al, using data from the Canadian Bronchiolitis Epinephrine Steroid Trial, found epinephrine and dexamethasone to be the most cost-effective treatment for bronchiolitis in infants aged 6 weeks to 12 months.

Supportive Therapy

Corticosteroids may be useful in patients with a history of reactive airway disease. Steroid treatment has not been shown to decrease the long-term incidence of wheezing or asthma after RSV infection. Nebulized steroid treatment has not been proven efficacious.

Pharmacologic Therapy

In a study by Croc et al, the mast cell inhibitor cromolyn had no beneficial effects. One study suggested that montelukast, a Cys-LT receptor antagonist, may reduce postbronchiolitis reactive airway disease, but this intervention cannot be recommended at this time.

Chest Physiotherapy

Nebulized hypertonic saline have been used for treating hospitalized, as well as ambulatory, children with viral bronchiolitis, with varying degrees of success. In a prospective, double-blinded, multicenter trial, the use of nebulized 3% hypertonic saline was a safe, inexpensive, and effective treatment for moderately ill hospitalized infants with viral bronchiolitis.

Complications of Therapy

In a randomized, double-blind trial of 187 infants younger than 18 months with acute bronchiolitis, Al-Ansari et al found that nebulization with 5% hypertonic saline was safe and superior to 0.9% saline, and possibly superior to 3% hypertonic saline, for early ambulatory treatment of bronchiolitis. A multicenter trial with a larger sample size may help establish the clinical benefits of this therapy.

Discharge Criteria

Prevention

Consultations

Long-Term Monitoring

Show All
Nebulized 3% Hypertonic Saline Solution Treatment in Hospitalized Infants With Viral Bronchiolitis

Axigdor Mandelberg, MD; Guy Tal, MD; Michaela Witzling, MD; Eli Soneck, MD; Sima Houri, MD; Ami Baitin, MD; and Israel E. Prid, MD, FCCP

Objective: To determine the utility of inhaled hypertonic saline solution to treat infants hospitalized with viral bronchiolitis.

Design: Randomized, double-blind, controlled trial. Fifty-two hospitalized infants (mean ± SD age, 2.9 ± 2.1 months) with viral bronchiolitis received either inhalation of epinephrine, 1.5 mg, in 4 mL of 0.9% saline solution (group 1; n = 26) or inhalation of epinephrine, 1.5 mg, in 4 mL of 3% saline solution (group 2; n = 27). This therapy was repeated three times every hospitalization day until discharge.

Results: The percentage improvement in the clinical severity scores after inhalation therapy was not significant in group 1 on the first, second, and third days after hospital admission (3.5%, 2%, and 4%, respectively). In group 2, significant improvement was observed on these days (7.3%, 8.9%, and 16%, respectively; p < 0.001). Also, the improvement in clinical severity scores differed significantly on each of these days between the two groups. Using 3% saline solution decreased the hospitalization stay by 25% from 4 ± 1.0 days in group 1 to 3 ± 1.2 days in group 2 (p < 0.05).

Conclusions: We conclude that in nonasthmatic, nonconcordantly ill infants hospitalized with viral bronchiolitis, aerosolized 3% saline solution/1.5 mg epinephrine decreases symptoms and length of hospitalization as compared to 0.9% saline solution/1.5 mg epinephrine.

(CHEST 2003; 123:481–487)

Key words: β2-agonist; epinephrine; hypertonic saline solution; respiratory syncytial virus; viral bronchiolitis

Abbreviations: CF = cystic fibrosis; NS = not significant; RSV = respiratory syncytial virus

Respiratory syncytial virus (RSV) is the chief cause of hospital admission for respiratory tract illness in young children. In the 1990s, an estimated 100,000 children were hospitalized with RSV infection in the United States annually, at a cost of $300 million.1–3 The magnitude of the cost is understandable, since virtually all children become infected with RSV within 2 years after birth,1 with 1% requiring hospitalization. Nearly two thirds of the cost related to annual RSV epidemics is attributable to hospitalization.1,4 Therefore, therapies that reduce hospital days could potentially greatly reduce healthcare expenditures. Despite 4 decades of efforts, there are no effective means to control RSV,1 and still the mainstay of treatment for RSV infection is supplemental oxygen and hydration.5 Controversy exists related to the available treatments for acute bronchiolitis.6,7 Antiviral agents are available, but their use in most patients is controversial and therefore not routinely indicated. The efficacy of ribavirin, the only specific drug available for the treatment of RSV infection,1 has not been demonstrated conclusively.1,5–10 Most of the studies using glucocorticoids in the treatment of bronchiolitis denied a positive therapeutic effect in previously normal children with bronchiolitis.5,11–14 The use of β2-agonists occasionally resulted in a short-term improvement in patients with bronchiolitis, especially when using epinephrine,15–16 while others failed to show a significant effect.3,17

Pathophysiologically, bronchiolitis is an infection of the bronchiolar epithelium, with subsequent pro-

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Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary

Edited by Bernard Foëx

BET 1
NEBULISED HYPERTONIC SALINE SIGNIFICANTLY DECREASES LENGTH OF HOSPITAL STAY AND REDUCES SYMPTOMS IN CHILDREN WITH BRONCHIOLITIS

Report by: Daniel Horner, ST3 Emergency Medicine/Critical Care
Search checked by: Rachel Jenner, Paediatric Emergency Medicine Consultant
Institution: Booth Hall Children’s Hospital, Manchester, UK

A short-cut review was carried out to establish whether nebulised hypertonic saline reduces length of stay and symptoms in children with bronchiolitis. One Cochrane review was found, which addressed this question. This review is summarised. The clinical bottom line is that nebulised hyper-

Best Evidence Topic reports (BETs) summarise the evidence pertaining to particular clinical questions. They are not systematic reviews, but rather contain the best (highest level) evidence that can be practically obtained by busy practising clinicians. The search strategies used to find the best evidence are reported in detail in order to allow clinicians to update searches whenever necessary. Each BET is based on a clinical scenario and ends with a clinical bottom line which indicates, in the light of the evidence found, what the reporting clinician would do if faced with the same scenario again. The BETs published below were first reported at the Critical Appraisal Journal Club at the Manchester Royal Infirmary or placed on the BestBETs website. Each BET has been constructed in the four stages that have been described elsewhere. The BETs shown here together with those published previously and those currently under construction can be seen at http://www.bestbets.org.


Hypertonic Saline

Recently, a randomized, double-blind, placebo-controlled trial was conducted at a single pediatric ED to determine whether nebulized 3% hypertonic saline with epinephrine is more effective than nebulized 0.9% saline with epinephrine in the treatment of infants younger than 12 months with mild-to-moderate bronchiolitis. The primary outcome measure was the change from baseline to 120 minutes in respiratory distress, as measured by the Respiratory Assessment Change Score (RACS). The change in oxygen saturation levels was also determined. Secondary outcome measures included the rates of hospital admission and return to the ED. A total of 46 patients were enrolled and their conditions evaluated. No improvements were noted in oxygen saturation levels and RACSs assessed at baseline and 120 minutes in the hypertonic saline group compared with the normal saline control group. In addition, rates of admission and return visits to the ED were similar between groups. The authors concluded that in the emergency setting, treatment of acute bronchiolitis with hypertonic saline and epinephrine did not improve clinical outcomes any more than treatment with normal saline and epinephrine. This finding differs from previously published results of outpatient and inpatient populations and merits further evaluation.
Nebulized hypertonic saline solution for acute bronchiolitis in infants

Liningie Zhang1, Basil A Mendoza-Sassi2, Claire Wainwright3, Terry P Klassen4

1Faculty of Medicine, Federal University of Rio Grande, Rio Grande, RS, Brazil. 2Department of Internal Medicine, Federal University of Rio Grande, Rio Grande, RS, Brazil. 3Department of Respiratory Medicine, Royal Children's Hospital, Brisbane, Australia. 4Manitoba Institute of Child Health, Winnipeg, Canada

Contact address: Liningie Zhang, Faculty of Medicine, Federal University of Rio Grande, Rua Visconde Paranaguá 102, Centro, Rio Grande, RS, 96201-900, Brazil. zhanglining@uol.com.br.

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ABSTRACT

Background
Airway edema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Nebulized hypertonic saline solution may reduce these pathological changes and decrease airway obstruction.

Objectives
To assess the effects of nebulized hypertonic saline solution in infants with acute viral bronchiolitis.

Search methods
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 2), which contains the Cochrane Acute Respiratory Infections Group Specialized Register, OLMEDLINE (1951 to 1965), MEDLINE (1966 to May Week 4, 2010), EMBASE (1974 to June 2010) and LILACS (1982 to June 2010).

Selection criteria
Randomized controlled trials (RCTs) and quasi-RCTs using nebulized hypertonic saline alone or in conjunction with bronchodilators as an active intervention in infants up to 24 months of age with acute bronchiolitis.

Data collection and analysis
Two review authors independently performed data extraction and study quality assessment. We performed meta-analyses using the Cochrane statistical package RevMan 5. We used the random-effects model for meta-analyses. We used mean difference (MD) and risk ratio (RR) as effect size metrics.

Main results
We included seven trials (581 infants) with mild to moderate acute viral bronchiolitis (282 inpatients, 65 outpatients and 234 emergency department patients). Patients treated with nebulized 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline (MD -1.16 days, 95% CI -1.55 to -0.77, P < 0.00001). The 3% saline group also had a significantly lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment (day 1: MD -0.95, 95% CI -1.55 to -0.34, P = 0.001; day 2: MD -1.01, 95% CI -1.68 to -0.33, P = 0.004; day 3: MD -1.10, 95% CI -1.68 to -0.52, P < 0.00001).

Nebulized hypertonic saline solution for acute bronchiolitis in infants (Review)
Did You Use PICOTT?

- Patient: Infants w/ bronchiolitis
- Intervention: Hypertonic saline
- Control: None
- Outcome: Effectiveness (?)
- Type of question: ?
- Type of study: ?
Exercise #2

• Connie searched and came up with 7 candidate studies
Exercise #2

• In the next FIVE MINUTES:
  – Critically appraise your article
    • Follow-up
    • Randomization
    • Intention to treat
    • Similar at baseline
    • Blinding
    • Equal treatment outside the intervention

• Summarize the methods and results

• Be ready to share your answers out loud
• 5 minutes to CAT the articles
  • **F**ollow-up
  • **R**andomization
  • **I**ntention to treat
  • **S**imilar at baseline
  • **B**linding
  • **E**qual treatment outside the intervention
What overall grade would you assign your study?

1. A (excellent, few sources of bias)
2. B (not bad, despite some bias)
3. C (mediocre, some obvious bias)
4. D (barely makes the cut, lots of bias)
5. F (may not even be worth reading)
Please remember the grade you assigned
(will return to this a bit later)
Learning Objectives

• Understand the distinction between reviews, systematic reviews and meta-analysis
• Understand the basic methods & outcomes reported in meta-analysis
• Interpret a forest plot
• Understand the critical appraisal elements that apply to systematic reviews
• Understand role systematic of reviews in guidelines and other publication types
• Use a systematic review to help guide clinical decision-making
Components of **Systematic** Reviews

- Specific objective(s)
- Clearly described, reproducible methods
  - Databases and search terms
- A priori inclusion / exclusion criteria
- Data extracted by more than one reviewer
- Consideration of quality
- Evidence table(s)
- Results
  - Qualitative and/or quantitative
Specific Objective(s)

• A focused clinical question
• (May look suspiciously like a PICOTT)
Clearly Described Methods

• LITERATURE SEARCH:
  – Search Terms
  – Database(s)
  – Time Frame
Inclusion/Exclusion Criteria

• This needs to be specified A PRIORI:
  – What types of studies will be included?
  – What characteristics of studies will be accepted?
  – Is there any consideration of QUALITY of the studies to be included?
Consideration of quality - Assessments of study quality should resemble:

1. PICOTT
2. Validity Criteria
3. Cochrane review
4. Performance Improvement
5. Systematic review
Data Abstraction

- How many reviewers?
- Should the reviewer(s) be aware of the study hypothesis?
- What sort of information should the reviewer(s) abstract?
- How are conflicts resolved?
Results

- Forest Plots

Impact of Diet Soda on Impulsivity

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly, 1994</td>
<td>0.590</td>
<td>0.096</td>
<td>3.634</td>
<td></td>
</tr>
<tr>
<td>Heajin, 1990</td>
<td>0.404</td>
<td>0.201</td>
<td>1.074</td>
<td></td>
</tr>
<tr>
<td>Leigh, 1992</td>
<td>0.394</td>
<td>0.076</td>
<td>2.055</td>
<td></td>
</tr>
<tr>
<td>Nosak, 1992</td>
<td>0.400</td>
<td>0.058</td>
<td>2.737</td>
<td></td>
</tr>
<tr>
<td>Sant, 1998</td>
<td>1.250</td>
<td>0.470</td>
<td>3.281</td>
<td></td>
</tr>
<tr>
<td>Pitteh, 1996</td>
<td>0.129</td>
<td>0.027</td>
<td>0.605</td>
<td></td>
</tr>
<tr>
<td>Day, 1990</td>
<td>0.313</td>
<td>0.054</td>
<td>1.885</td>
<td></td>
</tr>
<tr>
<td>Kelly, 1993</td>
<td>0.429</td>
<td>0.070</td>
<td>2.820</td>
<td></td>
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<tr>
<td>Singh, 2000</td>
<td>0.719</td>
<td>0.237</td>
<td>2.179</td>
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<tr>
<td>Silvash, 1994</td>
<td>0.143</td>
<td>0.082</td>
<td>0.250</td>
<td></td>
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<tr>
<td>Singh, 2000</td>
<td>0.328</td>
<td>0.233</td>
<td>0.462</td>
<td></td>
</tr>
</tbody>
</table>

*adapted from article addressing different question
Summarizing the Evidence
BREAK!
Which of the following is NOT a necessary part of a systematic review?

a) Focused clinical question
b) Reproducible search methods
c) Inclusion/exclusion criteria
d) Statistical analysis
e) Consideration of study quality
Meta-analysis
Meta-analysis

(definition): mathematical synthesis of the results of two or more primary studies that addressed the same hypothesis in the same way
The Basic Principles

• Each study reports a measure of effect
  – Rate, RR, OR, risk difference, others
• Summary (pooled) effect measure is calculated
  – \textit{weighted} average of the individual studies
  • Weighting may be based on sample size (usually) and/or study quality
• Confidence intervals
  – Communicates the \textit{precision} of the summary estimate,
  – Allows calculation of a P value
• Measure of variability among results (aka \textit{heterogeneity})
  – Is the variation compatible with random variation?
  – Is the variation sufficiently large to suggest the studies assessed different “truths” in their results?
  – Note: estimate of whether or not methods are similar enough to combine should have been done while compiling evidence table
Review, Systematic Review and Meta-analysis
<table>
<thead>
<tr>
<th></th>
<th>Unsystematic Review</th>
<th>Systematic Review</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(also known as)</td>
<td>Narrative Review</td>
<td>Qualitative Review</td>
<td>Quantitative Review</td>
</tr>
<tr>
<td>Evidence Summary?</td>
<td>Maybe (at the discretion of the author)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Is this review based on a focused clinical question?</td>
<td>No A narrative review is usually based on a clinical problem (e.g. Review of GI Bleeding)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Does this kind of review have a methods section?</td>
<td>No. Narrative reviews are written in the style suggested by the journal and the author without an explicit methodology.</td>
<td>Yes. Systematic Reviews have methodologies that include comment on the following core elements of article selection: How they found the evidence (comprehensive search strategy) How they determined the quality of the evidence (validity check)</td>
<td>Yes. Meta-analyses have methodologies that include everything in a Systematic Review (comprehensive search strategy and validity check) AS WELL AS a Summary Statistic (combining the data from individual studies based on precision including sample size and variability)</td>
</tr>
<tr>
<td>Who’s viewpoint is represented</td>
<td>The authors (Expert Model / Authority)</td>
<td>Evidence Model: this is simply a systematic collection and ‘grading’ of scientific data</td>
<td>Evidence Model: based on a systematic review with a combining of data from individual studies into a summary statistic</td>
</tr>
</tbody>
</table>
Exercise #3

• Who is familiar with Forest Plots?
• Create a Forest Plot
  – Based on the 7 RCT’s you reviewed
  – Each group come down and add their results to the Forest plot
Let’s Look at Some Prettier Examples
Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelberg 2003</td>
<td>3.0</td>
<td>1.2</td>
<td>0.00 (-1.87, -0.13)</td>
<td></td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6</td>
<td>1.4</td>
<td>-0.90 (-1.86, 0.06)</td>
<td></td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>2.6</td>
<td>1.9</td>
<td>-0.90 (-1.88, 0.08)</td>
<td></td>
</tr>
<tr>
<td>Luo 2010</td>
<td>6.0</td>
<td>1.2</td>
<td>-1.40 (-1.96, -0.84)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4.0</td>
<td>1.0</td>
<td>-1.16 (-1.55, -0.77)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.000001)
Forest Plots

- The data for each trial are represented, divided into experimental and control groups
- The calculated effect measure is presented numerically
- The % weight given to each study is reported

![Forest Plot Diagram]

Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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</thead>
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<tr>
<td>Mandelberg 2003</td>
<td>3 1.2</td>
<td>4 1.9</td>
<td>-1.00 [-1.87, -0.13]</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6 1.4</td>
<td>3.5 1.7</td>
<td>-0.90 [-1.96, 0.06]</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>2.6 1.9</td>
<td>3.5 2.9</td>
<td>-0.90 [-1.88, 0.08]</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>6 1.2</td>
<td>7.4 1.5</td>
<td>-1.40 [-1.96, -0.84]</td>
</tr>
</tbody>
</table>

Total (95% CI) 145 137 100.0% -1.16 [-1.55, -0.77]

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.000001)

Favors 3% saline Favors 0.9% saline
Forest Plots

- The result of each study is plotted graphically with a block.
- The size of the block for each study is proportional to the % weight.
- The horizontal line represents the confidence interval.

**Figure 1.** 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelberg 2003</td>
<td>Mean 3</td>
<td>Mean 4</td>
<td>-1.00 [-1.87, -0.13]</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>SD 1.2</td>
<td>SD 1.9</td>
<td>-0.90 [-1.86, 0.06]</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>Mean 2.6</td>
<td>Mean 3.5</td>
<td>-0.90 [-1.88, 0.08]</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>SD 1.9</td>
<td>SD 2.9</td>
<td>-1.40 [-1.96, -0.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145</td>
<td>137</td>
<td>-1.16 [-1.55, -0.77]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%

Test for overall effect: Z = 5.87 (P < 0.00001)
Forest Plots

- The label above the graph provides information about statistics
- The horizontal line at the bottom depicts the scale for the treatment effect

Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>3</td>
<td>1.2</td>
<td>27</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6</td>
<td>1.4</td>
<td>21</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>2.6</td>
<td>1.9</td>
<td>47</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>6.1</td>
<td>1.2</td>
<td>50</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145</td>
<td></td>
<td>137</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)

Favors 3% saline  Favors 0.9% saline
Forest Plots

- The vertical line in the middle is where treatment and control have the same effect – **THE LINE OF NO DIFFERENCE**

---

**Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>3.0</td>
<td>1.2</td>
<td>27</td>
<td>4.0</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6</td>
<td>1.4</td>
<td>21</td>
<td>3.5</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>2.6</td>
<td>1.9</td>
<td>47</td>
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</tr>
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<td>Luo 2010</td>
<td>6.1</td>
<td>1.2</td>
<td>50</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Total (95% CI): 145 137 100.0% -1.16 [-1.55, -0.77]

Heterogeneity: $\tau^2 = 0.00$; Chi² = 1.40, df = 3 ($P = 0.71$); $I^2 = 0$

Test for overall effect: $Z = 5.87$ ($P < 0.00001$)

Favors 3% saline Favors 0.9% saline
Forest Plots

• The pooled estimate is given as a diamond shape
  – The horizontal width of the diamond is the **confidence interval** of the pooled estimate
• The pooled estimate is also given numerically

---

**Figure 1.** 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<td>Mean</td>
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<td>Mandelberg 2003</td>
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<td>6</td>
<td>1.2</td>
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<td>7.4</td>
</tr>
</tbody>
</table>

**Total (95% CI)**
- 145
- 137
- 100.0%

-1.16 [-1.55, -0.77]

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)

Favors 3% saline  Favors 0.9% saline
Forest Plots

- Heterogeneity: The forest plot displays the results of the Chi square test and the p value

**Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>3</td>
<td>1.2</td>
<td>4</td>
<td>1.9</td>
<td>-1.00 [-1.87, -0.13]</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>2.6</td>
<td>1.4</td>
<td>21</td>
<td>1.7</td>
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<tr>
<td>Kuzik 2007</td>
<td>2.6</td>
<td>1.9</td>
<td>47</td>
<td>2.9</td>
<td>-0.90 [-1.88, 0.08]</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>6</td>
<td>1.2</td>
<td>50</td>
<td>1.5</td>
<td>-1.40 [-1.96, -0.84]</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td></td>
<td>197</td>
<td>100.0%</td>
<td>-1.16 [-1.55, -0.77]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)
Heterogeneity

• Inevitably, studies brought together in a systematic review will differ.
• The amount of variability in the results from studies in a systematic review is termed heterogeneity.
• What are some possible sources of heterogeneity?
Measures of Heterogeneity

• Eyeball test
• Chi Square
• $I^2$ Inconsistency
“eyeball test”

<table>
<thead>
<tr>
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<tr>
<td>Luo 2010</td>
<td>6</td>
<td>7.4</td>
<td>-1.40 [-1.96, -0.84]</td>
</tr>
<tr>
<td>Bordley 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
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Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)
Measures of Heterogeneity

✓ Eyeball test

• Chi Square
  – Assesses whether observed differences in results are compatible with chance alone.
  – A low P value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity (variation in effect estimates beyond chance).

• $I^2$ Inconsistency
  – Moves the focus away from testing whether heterogeneity is present to assessing its impact on the meta-analysis.
Back to Our Case
Assess
Ask
Acquire
Appraise
Apply
Validity Criteria for a Systematic Review

• Focused clinical question?
• Appropriate study inclusion criteria?
• Thorough search?
  – unlikely to miss relevant studies?
• Quality of included studies assessed?
• Heterogeneity?
• Sufficient follow-up (duration, subjects accounted for)?
• Generalizable to your clinical scenario?
It All Comes Back to the Search

THE TRUTH IS OUT THERE

Focused clinical question?
Appropriate study inclusion criteria?
Thorough search?
Assessing Quality of Included Studies

• Why
  – Garbage in leads to garbage out
  – Individual study bias affects meta-analysis result

• How: Quality Scores
  – 25 scales & 9 checklists (e.g., Jadad)
  – Cochrane method:
    • 7 domains and risk of bias for each
  – Sensitivity analysis
Exercise #4

APPRAISE THE SYSTEMATIC REVIEW

• Focused clinical question?
• Appropriate study inclusion criteria?
• Thorough search?
  – unlikely to miss relevant studies?
• Quality of included studies assessed?
• Heterogeneity?
• Sufficient follow-up (duration, subjects accounted for)?
• Generalizable to your clinical scenario?
What grade would you assign this systematic review?

1. A- nearly perfect minimal bias
2. B-not too bad; some bias
3. C-mediocre; may have biased results
4. D-garbage in…
5. F-garbage out…
Assess  
Ask  
Acquire  
Appraise  
Apply
3% saline versus 0.9% saline: Length of hospital stay (days)

Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)

<table>
<thead>
<tr>
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</tr>
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<tbody>
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<td>3 1.2</td>
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</tr>
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<td>Luo 2010</td>
<td>6 1.2</td>
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<td>Total (95% CI)</td>
<td>145</td>
<td>137</td>
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</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 5.87 (P < 0.00001)
3% saline versus 0.9% saline: Rate of Hospitalization

Analysis 1.5. Comparison 1 3% saline versus 0.9% saline, Outcome 5 Rate of hospitalization.

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 3% saline versus 0.9% saline

Outcome: 5 Rate of hospitalization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Anil 2010</td>
<td>1/75</td>
<td>1/74</td>
<td></td>
<td>5.0 %</td>
<td>0.99 [ 0.06, 15.48 ]</td>
</tr>
<tr>
<td>Grewal 2009</td>
<td>8/24</td>
<td>13/24</td>
<td></td>
<td>82.4 %</td>
<td>0.62 [ 0.31, 1.21 ]</td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>2/33</td>
<td>3/32</td>
<td></td>
<td>12.7 %</td>
<td>0.65 [ 0.12, 3.62 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>132</strong></td>
<td><strong>130</strong></td>
<td><strong>-</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.63 [ 0.34, 1.17 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 11 (3% saline), 17 (0.9% saline)

Heterogeneity: Tau² = 0.0; Chi² = 0.11, df = 2 (P = 0.95); I² =0.0%

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable
Given the information you have, would you give the baby nebulized saline?

1. No, just use humidified air (tell the kid's parents to keep the hot shower running in a closed bathroom)
2. No, just use the nebulized Xopenex
3. Yes, use 0.9% nebulized saline
4. Yes, use 3% nebulized saline
5. I prefer to conduct my own clinical trial
Summary Points

• All reviews are not Systematic Reviews
• Systematic review use explicit and reproducible methods to answer a focused question
• A meta-analysis is a mathematical synthesis of the results of two or more primary studies that addressed the same hypothesis in the same way
• Meta-analysis increases the precision of a result
  – Decision to perform involves judgment and quantitative assessment
Hierarchy of Evidence

Cochrane Database of Systematic Reviews
ACP Journal Club

PubMed (MEDLINE) – "AND" meta-analysis into your search. This will pick up Meta-Analysis as a MeSH term and as a publication type.

Evidence-Based Medicine Resources

Cochrane Database of Systematic Reviews / ACP Journal Club

PubMed (MEDLINE) – Use the "Find Systematic Reviews" filter under Clinical Queries, or "AND" systematic[sb] into your search. (Note: the systematic reviews subset includes meta-analyses.)

ACP Journal Club / Cochrane Central Register of Controlled Trials (CCRT)

PubMed (MEDLINE) – Use the "Therapy" filter under Clinical Queries, or "AND" randomized controlled trial into your search. This will pick up Randomized Controlled Trials as a MeSH term and Randomized Controlled Trial as a publication type.

PubMed (MEDLINE) – "AND" cohort study into your search. This will pick up the MeSH term Cohort Studies and the more specific MeSH terms Follow Up Studies, Longitudinal Studies, and Prospective Studies under it.

PubMed (MEDLINE) – "AND" case control study into your search. This will pick up the MeSH term Case-Control Studies and the more specific MeSH term Retrospective Studies under it.

PubMed (MEDLINE) – "AND" case report into your search. This will pick up Case Reports as a publication type.
Extra stuff

• Systematic reviews are the foundation of other evidence based tools

• Finding systematic reviews
Other Applications of Systematic Reviews

• Practice Guidelines
  – Combine quality of evidence with strength of recommendation

• Cost-benefit analyses (to derive ranges used in models)

• Decision analysis (to derive probabilities used in models)
Practice Guidelines

CLINICAL PRACTICE GUIDELINE

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation
Subcommittee on Hyperbilirubinemia

ABSTRACT

This policy is a revision of the policy posted on October 1, 1994.

CLINICAL PRACTICE GUIDELINE

Diagnosis and Management of Bronchiolitis
Subcommittee on Diagnosis and Management of Bronchiolitis

ABSTRACT

Bronchiolitis is a disorder most commonly caused in infants by viral lower respiratory tract infection. It is the most common lower respiratory infection in this age group, it is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm.

The American Academy of Pediatrics convened a committee composed of primary care physicians and specialists in the fields of pulmonology, infectious disease, emergency medicine, epidemiology, and medical informatics. The committee partnered with the Agency for Healthcare Research and Quality and the RTI International-Duke University of North Carolina Evidence-Based Practice Center to...
A Cost-effectiveness Analysis of Newborn Hearing Screening Strategies

Alex R. Kemper, MD, MPH; Stephen M. Downs, MD, MSc

Context: Congenital hearing loss affects between 1 and 3 out of every 1000 children. Screening of all neonates has been made possible by the development of portable automated devices. Universal screening is a 2-stage screening process using automated transient-evoked otoacoustic emissions, followed when indicated by automated auditory brain response testing. Targeted screening reserves the 2-stage screening process for those infants at risk for congenital hearing loss.

Objectives: To compare the expected costs and benefits of targeted screening with universal screening for the detection of significant bilateral congenital hearing loss.

Design: Cost-effectiveness analysis from the health care system perspective, including costs directly related to screening and initial follow-up evaluation.

Main Outcome Measures: Number of cases identified, number of false positives, and cost per case.

Results: For every 100,000 newborns screened, universal screening detects 86 of 110 cases of congenital hearing loss, at a cost of $11,650 per case identified. Targeted screening identifies 51 of 110 cases, at $3120 per case identified. Universal screening produces 320 false-positive results, 304 more than targeted screening. Switching to universal screening from targeted screening would cost an additional $23,930 for each extra case detected.

Conclusions: Universal screening detects more cases of congenital hearing loss, at the expense of both greater cost and more false-positive screening results. Little is known about the negative impact of false-positive screening and about the benefits of early intervention for congenital hearing loss. Those who advocate adoption of universal screening should be aware not only of the direct costs of universal screening, but of the indirect costs and strategies to increase the benefits of screening.
Other Systematic Reviews

“The Rational Clinical Examination”

CLINICIAN’S CORNER

Has This Prepubertal Girl Been Sexually Abused?

Molly Curtin Barkoff, MD, MPH; Adam J. Zoelstor, MD, MPH; Kathi L. Makroff, MD; Jonathan D. Thackeray, MD; Robert A. Shapiro, MD; Desmond K. Runyan, MD, DFPH

JAMA. 2008;300(23):2779-2792.

ABSTRACT

Context: The legal and social sequelae of interpreting genital findings as indicative of sexual abuse are significant. While the absence of genital trauma does not rule out sexual abuse, the physical examination can identify genital findings compatible with sexual abuse.

Objectives: To determine the diagnostic utility of the genital examination in prepubertal girls for identifying nonacute sexual abuse.

Data Sources: Published articles (1996-October 2008) that appeared in the MEDLINE database and were indexed under the search terms of child abuse, sexual or child abuse and either physical examination, genitalia, female, diagnosis; or sensitivity and specificity; and bibliographies of retrieved articles and textbooks.

Study Selection: Three of the authors independently reviewed titles of articles obtained from MEDLINE and selected articles for full-text review.

Data Extraction: Two authors independently abstracted data to calculate sensitivity, specificity, and likelihood ratios for the diagnosis of nonacute genital trauma caused by sexual abuse in prepubertal girls.

Results: Data were not pooled due to study heterogeneity. The presence of vaginal discharge (positive likelihood ratio, 2.7; 95% confidence interval, 1.2-6.0) indicates an increased likelihood of sexual abuse. In the posterior hymen, hymenal transactions, deep notches, and perforations prompt concerns for genital trauma from sexual abuse, but the sensitivity is unknown. Without a history of genital trauma from sexual abuse, the majority of prepubertal girls will not have a hymenal transaction (specificity close to 100%).

Conclusions: Vaginal discharge as well as posterior hymenal transactions, deep notches, and perforations raise the suspicion for sexual abuse in a prepubertal girl, but the findings do not independently confirm the diagnosis. Given the broad 95% confidence intervals around the likelihood ratios for the presence of findings along with the low or unknown sensitivity of all physical examination findings evaluated, the physical examination cannot independently confirm or exclude nonacute sexual abuse as the cause of genital trauma in prepubertal girls.
Locate systematic reviews using

- **Cochrane Database of Systematic Reviews** (CDSR)
  The CDSR is a full-text database containing systematic reviews and protocols (reviews still in progress) of the effects of health care interventions; mainly randomized controlled trials. "Gold Standard" for high quality, systematic reviews.

- **Database of Abstracts of Reviews of Effects (DARE)**
  Structured abstracts of good quality systematic reviews from around the world. Complements CDSR by offering a selection of quality assessed reviews in subjects with no Cochrane review. Also part of the Cochrane Library.

- **PubMed Systematic Reviews**
  PubMed Clinical Queries: Systematic Reviews combines your search term(s) with citations identified as systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. No evaluation of comparative quality of different reviews on a topic.

- **PubMed | Search Tips**
  Hint: you can limit to Publication Type: Meta-Analysis

- **CINAHL Plus | Search Tips**
  Hint: you can limit with Publication Types: Systematic Review
Effective Ways to Keep Up

<table>
<thead>
<tr>
<th>#</th>
<th>Article Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ</td>
</tr>
<tr>
<td>3</td>
<td>Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev</td>
</tr>
<tr>
<td>4</td>
<td>Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. JAMA</td>
</tr>
<tr>
<td>5</td>
<td>Neonatal outcomes after gestational exposure to nitrofurantoin. Obstet Gynecol</td>
</tr>
<tr>
<td>6</td>
<td>Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. JAMA</td>
</tr>
<tr>
<td>7</td>
<td>Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ</td>
</tr>
<tr>
<td>8</td>
<td>Prevention of contrast-induced nephropathy with Na/K citrate. Eur Heart J</td>
</tr>
</tbody>
</table>

Just click on the titles to review the abstract and/or PubMed record.
Increasing Utility of Systematic Reviews

• Cochrane—standardizing methodology
• The PRISMA statement
  – reporting systematic reviews and meta-analyses of healthcare interventions
• Critical appraisal criteria
  – JAMA Users Guide to the Medical Literature
• DARE and PubMed filters
  – Finding systematic reviews can be easy!
Publishing Systematic Reviews

The **CONSORT** equivalent

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The aim of the PRISMA Statement is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.

We have adopted the definitions of systematic review and meta-analysis used by the Cochrane Collaboration [9]. A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies.

- Download a full-text copy of the PRISMA Statement [here](#).
- Download a full-text copy of the PRISMA Statement in [Spanish here](#).

The PRISMA Statement consists of a checklist and a flow diagram, and is intended to be accompanied by the PRISMA Explanation and Elaboration document.