Clin-IQ Preparation Workbook

by

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Clin-IQ FAQs

1. **WHAT** Clin-IQ (Clinical Inquiries) IS
   - A scholarly activity that finds the best answer to an important clinical question.
   - A brief, 1,000 word paper that answers a clinical question by evaluating published evidence from the medical literature.
   
   And **IS NOT**
   - Clin-IQ is **NOT** a case report. No Internal Review Board (IRB) or informed consent required.

2. **WHY** do it?
   - Introduces clinical trainees to the biomedical research literature.
   - Promotes life-long learning for medical professionals by teaching the skills to access, appraise and apply answers to clinical questions to improve patient care.
   - Increases scholarly activities and productivity for faculty and trainees to meet Accreditation Council for Graduate Medical Education (ACGME) scholarly activity requirements.
   - Creates opportunities for publications and presentations.

3. **WHO** participates in Clin-IQ?
   1) Trainees at all levels of clinical education.
   2) Academic faculty and clinicians from all disciplines and specialties.
   3) Community-based faculty and practice-based research network members.
   4) Trained professional medical librarians.

4. **HOW** does it work? Steps to Implementing Clin-IQ
   1) Gather questions from clinical settings.
   2) Format questions into PICO format (patient/population-intervention/indication-comparison/control and outcome of interest).
   3) START SMALL with QUESTIONS that are IMPORTANT AND RELEVANT.

**BASIC CLIN-IQ PROCESS**

- **Identify a clinical question**
- **Write question in PICO format**
- **Search evidence-based literature**
- **Evaluate the evidence**
- **Answer the question**
- **Share the answer**

**Examples of sharing:**
- Journal article
- Professional Meetings
- Presentation or Poster
EDUCATIONAL GOALS AND OBJECTIVES

OVERVIEW

Clin-IQ (Clinical Inquiries) was developed by the University of Oklahoma (OU) College of Medicine Department of Family Medicine Research Division to promote research and scholarly collaboration for the OU Family Medicine Residency Program. The Clin-IQ process has since been expanded to help meet the need for the rapid dissemination of clinically relevant and important information into clinical practice to improve patient outcomes of care. Since its inception in 2003, the process has been modified and refined continuously. This workbook is the result of that ongoing effort to incorporate feedback to improve Clin-IQ.

Evidence of collaborative scholarly activity is required by the Accreditation Council for Graduate Medical Education (ACGME) for reaccreditation for all graduate medical education training programs. The Clin-IQ process was designed to help clinical training programs meet the increasing level of scholarship required by ACGME. Since the first publication in 2006, Clin-IQ has currently yielded a total of 83 publications from 9 residency programs and medical students; 54 are indexed in PubMed (an important marker for the training programs). More than 60 Clin-IQs have been presented as posters at local and regional meetings. For trainees and faculty seeking fellowship training or academic promotion and tenure, Clin-IQ – a 1,000 word paper that answers a clinically relevant question – demonstrates an understanding of the evidence-based medical literature and adds a valued peer-reviewed publication to postgraduate applications and faculty vitae.

Most importantly, Clin-IQ answers to relevant clinical questions can result in better patient care.

OBJECTIVES. The Clin-IQ process teaches clinical trainees to:
1. Recognize and construct well-formulated, clinically relevant questions.
2. Access appropriate current literature of the highest level of evidence relevant to a clinical question.
3. Utilize Medical Reference Library consultants effectively.
4. Interpret the results from published literature.
5. Appraise the validity and strength of evidence of the literature selected.
6. Summarize the results for an audience of their peers, faculty mentors, and community clinicians.
7. Synthesize the literature in a written document.
8. Follow instructions for authors for scholarly writing.
9. Produce a publication ready document of their findings.

WHERE DO QUESTIONS COME FROM? Questions arise in clinical practice every day. Each program and clinician should develop a method for collecting questions. Talk to your program director or faculty mentor.

1. During clinic.
2. On hospital rounds.
3. From board exams or readings.
4. From community physicians/preceptors.
5. Listening to lectures and at meetings.
6. In discussion with other clinicians.
7. From the medical literature and texts.
**Faculty/Trainee Collaboration. Trainees should be paired with a faculty mentor to:**
1. Demonstrate the importance of the research process to the trainee.
2. Build a collegial relationship between faculty and trainee.
3. Support the trainee as he/she learns and works through a scholarly research process.

**Faculty and Fellows: Clin-IQ can**
1. Provide publication opportunities to meet the requirements of a fellowship training program or faculty promotion/tenure.
2. Serve as preliminary literature review for larger project (and be publishable).
3. Afford opportunities to interact with colleagues and trainees as part of a scholarly research process.
4. Contribute to the training program’s reaccreditation.

**Evaluation of Clin-IQ Projects:**
1. Each document should be peer-reviewed and revised as indicated.
2. Establish an in-house peer review process. This will facilitate publication and presentation.

**Follow the Instructions in This Manual Closely.** This process is based on real-world medical publishing. By following these guidelines, you will complete a document that is close to publication ready. Publication will depend on relevance and importance as determined by journal editors.
TEMPLATE: BUILD A CLIN-IQ

1: CHOOSE A QUESTION.

Write the question you have selected on the following lines.


2: DETERMINE IF THE QUESTION IS IN PICO FORMAT; REWRITE IT IF IT IS NOT.

P = patient/population: always your primary focus.
I = intervention/indication: what are you proposing to do (not do, e.g., watchful waiting).
C = comparison/control: some questions (e.g., causation) may not have a comparison.
O = outcome: what do you want to happen.

Read the two questions below.

Before – Not Specific

Do myringotomy tubes help children with recurrent otitis media?

After – Very Specific, Well-Built

In infants and children to age 3 (or 4 or 5) with chronic otitis media, are myringotomy tubes better than episodic or prophylactic antibiotics for reducing the incidence and/or severity of disease with fewer side effects (diarrhea, others?)

Re-write the question you have selected on the following lines.

P

I

C

O

3: DEVELOP SEARCH TERMS, LIMITS AND INCLUSION/EXCLUSION CRITERIA

Based on your PICO formatted question (above), select search terms for your literature search.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant or preschool child; chronic otitis media</td>
<td>myringotomy tubes</td>
<td>episodic or prophylactic antibiotics</td>
<td>Incidence or severity or side effects</td>
</tr>
</tbody>
</table>

*Adapted from Kerr J. Abdominal Imaging 33 (Sept): 31-33, 2008*
Search Terms:

Limits: (e.g., Human, English, Infants or Pre-School Children review, RCT)

Inclusion and Exclusion Criteria: A brief discussion of which articles you chose to include, e.g., all clinical trials in humans that compared tubes with other treatments or with watchful waiting that were published in the past 6 years and included an $n$ (number of subjects) of XX or greater) and articles you chose to exclude (children over age 5, adolescents, adults). (See Sample of Completed Clin-IQ, page 18)

4: SEARCH THE MEDICAL LITERATURE

Consulting with a Medical Reference Librarian: Consulting with a medical reference librarian before you do a literature search is most likely to yield the highest level of current evidence with the least amount of irrelevant retrieval. You may consult with a librarian or you perform the literature search yourself. If you choose to consult with a librarian, here are some tips to make that interaction more productive.

- Meet face-to-face. Medical reference librarians are trained in “reference interviews” and will ask you questions about your topic that you may not have considered. Ask your librarian for details about the reference and literature searching services they offer.
- Bring your project workbook with you to the consultation. The librarian will then understand the limited nature of your search and be better able to assist you.
- Most medical reference librarians will be able to search and locate relevant review articles as well as evidence articles.
- These trained professionals understand evidence-based medicine, levels of evidence and study types. They can assist you in identifying which type of study (or studies) will best answer your question.
- You may also consider consulting with a medical librarian about
  a) Inclusion and exclusion criteria
  b) Search terms and limits

The medical librarian must become an author on a Clin-IQ if he/she:

  a) a. Performs the literature search that yields the articles used for the Clin-IQ, and
  b) b. Reads the final document for publication.
5: Locate 1 or 2 Review/Background Articles. Based on search terms, locate 1 or 2 current (preferably 2008 or newer) review/background article available (you can do the search yourself or work with a librarian). Your review article should include:

- Clinical significance of the problem.
- Prevalence.
- Relevant issues.

6: Write a Draft of the Summary of Issues (Word count = 200-300)

Should include how prevalence and clinical significance relate back to your question. You have two examples to work from (see Sample of Completed Clin-IQ, page 18, and Example of Published Clin-IQ, page 30).

7: Locate 2 Current (preferably 2008 or newer) Highest Level Evidence Articles.

You can do this search yourself or consult with a trained medical librarian (item 4 above). Be sure to identify which type of study qualifies as the highest level of evidence. See Figure 1, pages 13, and Figure 2, page 15, for a discussion of levels of evidence.

- Find at least 2 articles relevant to your question that meet the highest level of evidence available as shown on Figures 1 and 2.
- Read the articles
- Send the articles to your faculty mentor

8: Write a Draft of the Summary of Evidence (Word count = 500-700)

- number of patients or papers, if meta-analysis or systematic review
- type of studies (include data on a table for clarity)
- statistical significance.*
- intervention of interest
- outcome(s) of interest (morbidity, mortality, quality of life, etc.)
- weaknesses or conflicts
- cite references

*An excellent Statistics tutorial can be found at http://web.med.unsw.edu.au/QMP/QMPHome.htm
9: **DETERMINE LEVEL OF EVIDENCE OF YOUR BODY OF LITERATURE** (See Figure 1, page 13 and Figure 2, page 15)

Level of evidence for the answer (A, B, or C, see figures): __________________________

10: **ANSWER THE QUESTION.**

   Answer: (Circle one): Yes   No   Inconclusive or 1-2 sentences if that is more responsive.

11: **(OPTIONAL BUT RECOMMENDED) ADD AN ORIGINAL TABLE, FIGURE, CHART OR GRAPH**
   - Tables, figures or charts can be added to elucidate data in the Summary of Evidence.
   - Tables, figures or charts must be original, created based on data available from the articles.
   - Place an citation within the text indicating the context of the graphical material (e.g., Figure 1, Table 2).

12: **WRITE A DRAFT CONCLUSION (WORD COUNT = 50-100)**
   - Conclusions (1-2 sentences), to include:
     - Summary of issue (relevance) linked to
     - Summary of evidence, linked to
     - The answer and how you would change your practice based on what you have learned.

13: **ADD REFERENCE LIST:** You must cite all the materials (books, journal articles, website, etc.) that you used to answer your question. You should only need 1-2 review articles and 2 evidence articles.

   1. Review article #1
   2. Review article #2 (optional)
   3. Evidence article #1
   4. Evidence article #2
14: WRITE AN ABSTRACT OF 250 WORDS OR LESS. The Abstract should be written last but placed before the Summary of Issues. The National Library of Medicine, which curates and indexes Medline, includes abstracts in the indexed record if an abstract is provided. Abstracts are required by most journals and increase the impact of your document.

15. COMPLETE CLIN-IQ CHECK LIST. Have you:

☐ Answered the question
☐ Prepared the reference list in proper format.
☐ Cited sources properly as shown in this Guidelines for Authors (above).
☐ If you included a table, figure or graphic, is it original or adapted sufficiently from the source to avoid potential copyright violation or plagiarism (item 16 below. A Word About Plagiarism).
☐ If you included a table, figure or graphic, have you noted in the text where the table material is discussed (Table 1, Figure 2, etc.).
☐ Shared your draft with your mentor/co-author(s) and addressed all comments and suggestions.
☐ Requested additional review from faculty or peers (review form, page 16)
☐ Revised draft until all authors agree it is publication or presentation worthy.
☐ Write a 250 abstract and insert into the publication/presentation ready document above the Summary of Issues.

16. A WORD ABOUT PLAGIARISM: Plagiarism and copyright infringement occur when an author extracts large portions of materials from a published document. Tables, figures, charts and graphs of any kind must be significantly altered or, preferably, created from data within a published study. Brief material (generally a sentence or two, less than a paragraph) may be quoted provided adequate citations are provided for the sources.

A consult with a medical librarian can help you be re-assured that you have not exceeded copyright limitations or plagiarized material.

REQUIRED SUPPORT ACKNOWLEDGMENT STATEMENT
Any materials, papers, presentations, etc., developed based on this document must acknowledge the grant. A copy of the material(s) should also be submitted to OSCTR (OSCTR@OUHSC.EDU) for the grant archives and reporting.

Please use the following statement:

“This [document, paper, presentation, etc.] was supported in part by Oklahoma Shared Clinical & Translational Resources, grant number NIGMS U54GM104938, NIGMS/NIH.”
Example Clin-IQ Article Review Worksheet

1. Name: ____________________________________________________________

2. Article citation (done in correct JAMA format as required by Clin-IQ and shown in your Clin-IQ Workbook).

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

3. What was the question the article/study was designed to answer?

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

4. Based on the information about the authors given in the article, does there appear to be any conflict of interest between the authors and the question being studied?
   □ Yes    □ No

5. What methods were used to answer the question? __________________________

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

6. What is the strength of evidence for this study (refer to the strength of evidence flow chart in your Clin-IQ workbook). __________________________

____________________________________________________________________
____________________________________________________________________

7. Briefly discuss the results and study findings. Include in your discussion how you or other physicians and health care professionals use this information in their clinical practice.

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
### Clin-IQ Guidelines for Authors

#### General Format

<table>
<thead>
<tr>
<th>Double space the entire document.</th>
<th>Indent the first line of each paragraph. Do not use extra blank lines between paragraphs.</th>
</tr>
</thead>
</table>

#### Create an Abstract

<table>
<thead>
<tr>
<th>An abstract is required for all peer reviewed, published papers. Your abstract should include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A brief statement of issues,</td>
</tr>
<tr>
<td>2. Your clinical question and a brief answer including recommendations,</td>
</tr>
<tr>
<td>3. Must be less than 250 words.</td>
</tr>
</tbody>
</table>

**Example (118 words)**

**Abstract:** About 40% of adults in the United States suffer from chronic pain. Over half will seek medical treatment for their discomfort. Chronic pain is often accompanied by co-morbidities such as functional disability and mental illness, including depression and anxiety, which can result in decreased productivity and overall reduced quality of life. A growing body of evidence suggests that yoga, and possibly other meditative movement therapies (MMTs), may reduce and perhaps eliminate symptoms associated with chronic pain. The studies examined here demonstrated that yoga instruction combined with at home practice often resulted in reduced pain, improved function and quality of life. Patients should be cautioned to seek professional yoga teachers for proper instruction to avoid further injury.

#### Citing Abbreviations

<table>
<thead>
<tr>
<th>The first time you use an abbreviation you must write the complete phrase first and follow the phrase with the abbreviation in parentheses. From then on, use only the abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Accreditation Council for Graduate Medical Education (ACGME) is the entity that accredits residency training programs. The ACGME requires programs to conduct faculty/residency collaborative scholarly activity to retain accreditation.</td>
</tr>
</tbody>
</table>

#### Numbers in Text

<table>
<thead>
<tr>
<th>Spell out numbers one through nine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unless percents (9%)</td>
</tr>
<tr>
<td>Medication dosages (15 mg BID)</td>
</tr>
<tr>
<td>Laboratory values (162.4 ml/min)</td>
</tr>
<tr>
<td>Dates (June 30, 2014)</td>
</tr>
<tr>
<td>Time frame (39 weeks, 3 years)</td>
</tr>
<tr>
<td>Ages (individuals 13 yrs or older).</td>
</tr>
<tr>
<td>More than one number in a sentence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In this study, nine children aged 4 months to 2 years received ear tubes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In this study, the first 8 children received ear tubes and the second 8 were placed on Bactrim for 2 weeks.</td>
</tr>
</tbody>
</table>

#### Articles from the Medical Literature

- **Recent** review article(s), no more than 2, on which to base your summary of issues.
- **Recent** evidence articles, 2, on which to base your Summary of Evidence and your answer.
- **All articles should be from medical journals preferably published in 2008 or newer.** If you have problems, consult a trained medical librarian. Be sure to bring this workbook and your Clin-IQ question with you when you consult with the librarian. (Some libraries offer online "Ask a Librarian" assistance. Talk to your medical librarians about services they offer.)

**Examples**

**Review article:**

**Evidence article:**
If you cite, paraphrase, mention or quote directly from a published article, book, website, etc. you must cite the material in the text (and include the citation information in the Reference List). Failure to do so constitutes plagiarism and copyright infringement.

Both the estrogen and progestogen of combined oral contraceptives contribute to the increased thrombotic risk. On top of this, smoking doubles the risk of venous thrombosis. Women over age 35 who smoke should not use combined oral contraceptives due to the risk for cardiovascular disease.

Both the estrogen and progestogen of combined oral contraceptives contribute to the increased thrombotic risk.

... in these 56 women when APC resistance was re-tested 3 months later (mean baseline 2.75 vs. mean three months later 2.47; difference -0.29; 95% CI -0.04 to -0.53).

Both the estrogen and progestogen of combined oral contraceptives contribute to the increased thrombotic risk.

Reference lists are placed at the end of the paper. References are listed in the order in which they are cited in the text of your article. TIP: Reference 1 is always 1 no matter how many times it is cited in the text.

Both the estrogen and progestogen of combined oral contraceptives contribute to the increased thrombotic risk.

Complete Reference Examples (based on the Uniform Requirements for Articles Submitted to Biomedical Journals)

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Book Chapter Example</td>
<td>2. Lim LL, Foldvary-Schaeger N. Sleep Disorders. Ch. 10 In: Carey WD, ed. Current Clinical Medicine, 2nd ed. New York: Elsevier (Saunders); 2010:914-921.</td>
</tr>
</tbody>
</table>

Acknowledgment: “This [document, paper, presentation, etc.] was supported in part by Oklahoma Shared Clinical & Translational Resources, grant number NIGMS U54GM104938, NIGMS/NIH.”

A sample completed Clin-IQ, which meets the style, formatting and publication requirements, can be found beginning on page 18.

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*A guide to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals can be found at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/*
1. **Systematic Review**: Level 1 Evidence  
   a. A comprehensive survey of a topic in which all the primary studies of the highest evidence (e.g., randomized controlled trials, prospective cohort studies; see below) are identified, appraised and summarized using explicit inclusion and exclusion criteria.  
   b. Results should be reproducible  

2. **Meta-analysis**: Level 1 Evidence  
   a. Similar to a systematic review in that a comprehensive search of the topic is conducted.  
   b. If the results of the review of all included studies are similar enough statistically, the results are combined and analyzed as if they were one study  
   c. Results should be reproducible.  

3. **Randomized Controlled Trial (RCT)**: Level 1 Evidence  
   a. 2 groups: 1 treatment group and 1 control group. Treatment group received treatment under investigation. Control group receives either no treatment (placebo) or gold standard treatment.  
   b. Patients are randomly assigned to each group.  
   c. Best type of study to answer questions about therapy.  
   d. Sometimes there can be 3 or even 4 groups (called arms) depending on the study question. Example of a 4-arm RCT: Allergy treatment.  
      i. Claritin alone  
      ii. Flonase alone  
      iii. Claritin + Flonase  
      iv. Placebo
4. **Cohort Study: Level 1 or 2 Evidence based on question and study design**
   a. A study in which patients who presently have a condition and/or receive a particular treatment are observed over time and compared with another group who do not have the condition being studied.
   b. Example:

   ![Diagram of Cohort Study Example]

   Examples adapted from SUNY Downstate Medical Center ([http://library.downstate.edu/EBM2](http://library.downstate.edu/EBM2))
**Figure 2.**
Algorithm for determining level of evidence for an individual study

Is the study a key citation for an important point of evidence under discussion?
- No Level of evidence not needed
- Yes

Is the key outcome of the study based on *patient-oriented evidence* (i.e., an improvement in morbidity, mortality, symptoms, quality of life, or cost)?
- No
- Yes Level of evidence = 3

Is the study based on opinion, bench research, a consensus guideline, usual practice, clinical experience, or a case series?
- No
- Yes

Is the study one of the following?
1. Systematic review/meta-analysis of high-quality studies with consistent findings.
2. High-quality randomized controlled trial
   - Allocation concealed
   - Blinding, if possible
   - Intention-to-treat analysis
   - Adequate size
   - Adequate follow-up (>80%)
3. High-quality cohort study for prognosis (prospective, with >80% follow-up)
4. Validated clinical decision rule in a relevant population
5. High-quality diagnostic cohort study
   - Adequate size
   - Adequate spectrum of patients
   - Blinding
   - Consistent reference standard
- Yes Level of evidence = 1
- No Level of evidence = 2

**Levels of Evidence**

A = Consistent level 1 studies
B = Consistent level 2 or 3 studies or extrapolations from level 1 studies
C = Level 4 studies or extrapolations from level 2 or 3 studies
D = Level 5 studies or troubling inconsistent or inconclusive studies of any level

Clin-IQ Peer Review Form

Reviewer:

Authors

Brief Title (first few words)

General Instructions to Reviewers

• Objective is to help authors improve the manuscript.
• Suggest how to make the manuscript more clear, concise and relevant.
• Identify possible areas of confusion for the reader and make specific suggestions.
• Verify that at least one reference is accurately interpreted.
• Identify any glaring grammatical or format problems, in a supportive manner.
• Sprinkle PRAISE along with recommendations for change.

Answer:

Does the answer accurately represent the evidence given? [ ] Needs improvement [ ] Yes

Reviewers Comments:

Level of Evidence:

Does the level of evidence accurately represent the references cited?

[ ] Needs improvement [ ] Yes

Reviewers Comments:

Summary of Issues: Clinical significance, prevalence and relevance based on recent review article(s).

Is the writing clear and logical? [ ] Needs improvement [ ] Ready to publish

Is the length appropriate (200-300 words)? [ ] Needs improvement [ ] Ready to publish

Reviewers Comments:
Clin-IQ Peer Review Form

Summary of Evidence: Describes studies, outcomes, interventions. A figure or table will be added. Evidence articles should be cited.

Is the writing clear and logical? [ ] Needs improvement [ ] Ready to publish

Is the length appropriate (500-700 words)? [ ] Needs improvement [ ] Ready to publish

Review at least one evidence article and comment:
- Is the information appropriately represented in the text? [ ] Needs improvement [ ] Yes
- Have the statistics been accurately represented and explained? [ ] Needs improvement [ ] Yes
- If present, do the figures or tables accurately present the data and contribute to your understanding of the material? [ ] Needs improvement [ ] Yes

Reviewers Comments:

Conclusions: Conclusion should be clinically relevant and wrap up evidence.

Is the writing clear and logical? [ ] Needs improvement [ ] Ready to publish

Is the length appropriate (50-100 words)? [ ] Needs improvement [ ] Ready to publish

Does the conclusion state clearly how the answer will impact practice?[ ] Needs improvement [ ] Yes

Reviewers Comments:

Reference List:
Are all references cited in the body of the report according to the instructions in the Workbook (superscripted numbers)? [ ] Needs improvement [ ] Yes

Is the reference list in order numerically according to the order the articles are cited in the text? [ ] Needs improvement [ ] Yes

Reviewers Comments:

Additional comments to the author
Sample of Completed Clin-IQ

Do SSRIs and SNRIs reduce the frequency and/or severity of hot flashes in menopausal women?


Chris Stubbs, MD (PGY-2), Lisa Mattingly, MD (PGY-3), Steven A. Crawford, MD, Elizabeth A. Wickersham, MD, Jessica L. Brockhaus, BA, Laine H. McCarthy, MLIS.

University of Oklahoma Health Sciences Center Family Medicine Residency Program, Oklahoma City, OK.

Abstract

Clinical Question: In menopausal women who experience regular hot flashes, does treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) reduce the frequency and/or severity of hot flashes?

Answer: Yes. Review of the literature suggests that treatment with SSRIs or SNRIs reduces the frequency and severity of hot flashes in menopausal and post-menopausal women. Studies demonstrated that paroxetine (Paxil), citalopram (Celexa) and escitalopram (Lexapro) were the most effective SSRIs, and venlafaxine (Effexor) was the most effective first line SNRI, with desvenlafaxine as a second option. The most common side effects reported for both SSRIs and SNRIs are nausea and constipation, with most resolving within the first week of treatment. SNRIs have been associated with increased blood pressure in some patients and should be used with caution in women with hypertension. Women with a history of breast cancer and taking tamoxifen should avoid SSRIs, which have been shown to interfere with tamoxifen metabolism. SNRIs are the safest drugs for this population. Treatment choice should be patient-specific and begin with the lowest dose available.
Level of Evidence for the Answer: A

Search Terms: SSRI, SNRI, hot flashes, vasomotor symptoms, menopause

Search Conducted: August 2014, February 2016 and August 2016

Inclusion Criteria: menopausal, perimenopausal or postmenopausal women 18 years of age or older with frequent and/or severe vasomotor symptoms, meta-analyses, systematic reviews, randomized controlled trials, cohort studies.

Exclusion Criteria: pre-menopause, anxiety, depression, panic disorder, bipolar disorder, co-morbid conditions.

Corresponding Author: Elizabeth Wickersham, MD, Assistant Professor, Research Division, Department of Family & Preventive Medicine, University of Oklahoma Health Sciences Center, 900 NE 10th St., Oklahoma City, OK 73104. (405) 271-2370. elizabeth-wickersham@ouhsc.edu

Acknowledgment: The authors thank Zsolt J. Nagykaldi, Ph.D., for reading and commenting on this paper. E.A.W. and L.H.M. are supported in part or in full by Oklahoma Shared Clinical & Translational Resources (OSCTR) grant NIGMS U54GM104938, NIGMS/NIH.

Summary of the Issues: Between 80% and 90% of perimenopausal and menopausal women will experience vasomotor symptoms (VMS), commonly called hot flashes. Depending on severity and frequency, hot flashes may adversely affect a woman’s quality of life from 5 to 7 years or more. Hot flashes are the result of decreased estrogen levels associated with menopause. Hormone replacement therapy (HRT) is considered the gold standard treatment for hot flashes. However, HRT is linked to increased risk of estrogen-dependent pathologies, including breast cancer, endometrial cancer, cardiovascular disease and thromboembolism. Women experiencing hot flashes who either cannot
take HRT or who would prefer other options are looking to nonhormonal therapies to control the frequency and severity of menopausal vasomotor symptoms.\textsuperscript{1-3}

Research into nonhormonal options has focused on two major categories of nonestrogen therapy: nonpharmaceutical and pharmaceutical. Nonpharmaceutical therapies include lifestyle changes, such as exercise weight loss; yoga and other mindfulness or relaxation techniques; cognitive behavioral therapy; a variety of vitamins and supplements; and over-the-counter herbal remedies, such as black cohosh, ginseng and combination botanical remedies. Although some of these therapies have demonstrated some degree of efficacy – weight loss and mindfulness stress reduction techniques, for example – in general, these options “may not be the best for women with severe VMS or those seeking immediate relief.”\textsuperscript{3}

Several nonestrogen pharmaceutical, or prescription, therapies have also been evaluated for hot flashes. These include clonidine, an alpha-adrenergic agonist, the anticonvulsant gabapentin, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Clonidine and gabapentin have both demonstrated some effectiveness. However, each have significant adverse side effects that may make them impractical options for many women. Gabapentin is associated with dizziness, drowsiness, peripheral edema, loss of balance and suicidal thoughts. Side effects from clonidine are similar and include dizziness, sedation, headache and a significant elevation in blood with abrupt cessation.\textsuperscript{1-4}

SSRIs and/or SNRIs have demonstrated promise for reducing both the frequency and severity of hot flashes without the risks of HRT or the more severe side effects of the other prescription drugs studied.\textsuperscript{1-4} This brief review examines the current evidence to determine if SSRIs and/or SNRIs may be effective and safe alternatives to HRT for reducing the frequency and/or severity of hot flashes in menopausal women.
Summary of the Evidence:

In 2013, Shams et al. published a systematic review and meta-analysis evaluating the effectiveness of five SSRIs – escitalopram, paroxetine, sertraline, citalopram and fluoxetine – for reducing vasomotor symptoms (hot flashes) in healthy perimenopausal women.\(^5\) The review analyzed 11 randomized controlled trials (RCTs) with rigorous methodology published between 2003 and 2012. The studies included 2,069 women between 36 and 76 years of age who were followed for a period of 1 to 9 months, depending on the study. Meta-analyses showed that treatment with an SSRI resulted in a significant decrease in the average number of daily hot flashes at 4 to 8 weeks, down from 10 per day to 9 (95% CI -1.49 to -0.37) compared to placebo. In this study, escitalopram (Lexapro) was the most effective SSRI for reducing the daily frequency of hot flashes. Participants in the SSRI group also reported a reduction in severity of residual hot flashes compared to placebo. The most common side effects reported included nausea, fatigue and drowsiness but were not significantly different from placebo. The investigators concluded that SSRIs are a reasonable substitute for HRT.\(^5\)

A 2015 systematic review by Handley and Williams examined 18 RCTs published between 2000 to 2012 that compared SSRIs/SNRIs to placebo for reducing peri- and postmenopausal hot flashes.\(^6\) Participants were healthy women between the ages of 27 and 78 years who reported experiencing an average of 46 to 76 hot flashes per week, depending on the study. All studies assessed hot flash frequency and severity using a self-reported daily hot flash diary. The severity rating and frequency were multiplied to yield a composite score, with higher scores representing more severe symptoms. SSRIs/SNRIs reduced hot flash symptoms by as much as 65% compared to placebo. Potential first line SSRIs were paroxetine (Paxil), paroxetine ER (Paxil CR), citalopram (Celexa) and escitalopram (Lexapro). Venlafaxine (Effexor XR) was identified as a potential first line SNRI.
Paroxetine ER demonstrated the greatest statistically significant reduction in hot flash frequency at both 12.5mg/day (62%, \( p=0.007 \)) and 25mg/day (64%, \( p=0.03 \)). Venlafaxine provided more immediate symptom relief than the SSRIs, but had a higher incidence of side effects, most notably nausea and constipation. SNRIs may increase blood pressure and should be used with caution in hypertensive patients.\(^6\)

In 2015, The North American Menopause Society (NAMS) released a position statement regarding nonhormonal management of menopause-associated vasomotor symptoms.\(^3\) Panel members searched five databases for high-level evidence articles (RCTs or systematic reviews) focused on nonhormonal therapies for hot flashes. The search identified 340 original research articles and 105 systematic reviews appropriate for further evaluation. NAMS panel members reviewed all articles and assigned levels of evidence. A limited number of head-to-head RCTs comparing HRT to other pharmacological agents were identified. One such study reported that the SNRI venlafaxine (Effexor) demonstrated similar effectiveness for reducing VMS symptoms compared to a low-dose estradiol. A limitation of that RCT was that the protocol did not include a comparison of the two therapies with up-dosing.

After evaluation of the evidence, the NAMS panel concluded that multiple nonhormonal therapies are appropriate considerations for menopausal and post-menopausal hot flashes. Recommendations include the following SSRIs and SNRIs: paroxetine salt 7.5mg/day (Brisdelle®); paroxetine or paroxetine ER 10-25mg/day; escitalopram 10-20mg/ day; citalopram 10-20mg/day; desvenlafaxine 50-150mg/day; and venlafaxine XR 37.5-150mg/ day. Patients should be started at the lowest available dose and titrated up as needed. Brisdelle® is only available in 7.5mg and is currently the only drug FDA-approved for hot flashes.\(^3\) The Table summarizes the efficacy, safety and costs associated with SSRI/SNRI treatment.
Conclusion

HRT is still considered the most effective treatment for reducing hot flashes in menopausal and post-menopausal women. However, concerns that HRT can increase the risks of estrogen-dependent pathologies have led to studies investigating other treatments for vasomotor symptoms. Based on the evidence reviewed, SSRIs and SNRIs reduce the frequency and severity of menopause-associated vasomotor symptoms by 10% to 64%, depending on the study. Side effects from SSRIs and SNRIs, which included nausea, constipation, and dry mouth, were generally not severe and often subsided within the first week.3,4 SSRIs escitalopram and paroxetine ER and SNRI venlafaxine XR were shown to be the most effective.3-5 Although less effective than HRT, SSRIs/SNRIs are demonstrated to reduce hot flashes and may be recommended for women who wish to avoid the risks of HRT. Additional placebo-controlled studies are needed to evaluate risks, benefits and dosing. Women with a history of breast cancer who are taking tamoxifen should avoid SSRIs. Studies have demonstrated that some SSRIs inhibit the activity of the enzyme CYP2D6, which can result in lower therapeutic levels of tamoxifen. The SNRIs venlafaxine and desvenlafaxine appear to have little or no impact on tamoxifen activity and should be considered as the first line therapy for these patients.5,6
References


Table. SSRI/SNRI Safety, Efficacy and Cost for Treatment of Hot Flashes.\textsuperscript{5,6} To avoid side effects, patients should be started on the lowest dose available and gradually increased as needed to control hot flashes. Drugs are listed by class in the order of demonstrated safety and effectiveness. Costs are for generic drugs where available and are for reference purposes only. Actual costs will vary dependent on pharmacy and insurance coverage.

<table>
<thead>
<tr>
<th>Generic (Brand Name)</th>
<th>Recommended First Line Medications for Hot Flashes</th>
<th>Daily Doses</th>
<th>Appropriate for Tamoxifen users</th>
<th>Approximate cost of 30 day supply</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. <strong>Paroxetine (Paxil)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine salt (Brisdelle\textsuperset{\textregistered}) (FDA approved for hot flashes)</td>
<td>7.5mg</td>
<td>No</td>
<td></td>
<td>$150-$200+</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10mg</td>
<td>No</td>
<td></td>
<td>$5.00+</td>
</tr>
<tr>
<td></td>
<td>20mg</td>
<td>No</td>
<td></td>
<td>$5.00+</td>
</tr>
<tr>
<td>Paroxetine ER (Paxil CR)</td>
<td>12.5mg</td>
<td>No</td>
<td></td>
<td>$40-$250</td>
</tr>
<tr>
<td></td>
<td>25mg</td>
<td>No</td>
<td></td>
<td>$40-$250</td>
</tr>
<tr>
<td>2. <strong>Citalopram (Celexa)</strong></td>
<td></td>
<td>20mg</td>
<td>No</td>
<td>$4.00-$12.00</td>
</tr>
<tr>
<td>3. <strong>Escitalopram (Lexapro)</strong></td>
<td></td>
<td>10mg</td>
<td>No</td>
<td>$8.00-$10.00</td>
</tr>
<tr>
<td><strong>Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. <strong>Venlafaxine (Effexor XR)</strong></td>
<td>37.5mg</td>
<td>Yes</td>
<td></td>
<td>$6.00-$12.00+</td>
</tr>
<tr>
<td>2. <strong>Desvenlafaxine ER (Pristiq)</strong></td>
<td>50mg</td>
<td>Yes</td>
<td></td>
<td>$140-$240+</td>
</tr>
</tbody>
</table>

CR, controlled release; ER, extended release; XR, extended release.
Examples of Published Clin-IQs

Can Bedside Ultrasound Inferior Vena Cava Measurements Accurately Diagnose Congestive Heart Failure in the Emergency Department? A Clin-IQ

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Abstract

Congestive heart failure (CHF) is a major cause of morbidity and mortality. Early diagnosis of CHF in patients presenting to the emergency department with undifferentiated dyspnea would allow clinicians to begin appropriate treatment more promptly. Current guidelines recommend B-type natriuretic peptide (BNP) levels for more accurate diagnosis of CHF in dyspneic patients. Although BNP levels are relatively inexpensive, the test is not usually performed at bedside and results may take up to an hour or more. BNP also may have a “gray zone” in which the values can neither confirm nor rule out CHF. BNP has a reported sensitivity of 97% and specificity of 74% at a cutoff of 400 pg/ml. Studies investigating bedside ultrasound inferior vena cava (IVC) measurements for identifying CHF report a specificity of 84% to 96% and sensitivity values ranging from 37% to 93%, depending on the study. Given that ultrasound IVC measurements are performed at bedside and results are available rapidly, it is reasonable to evaluate whether ultrasound IVC measurements obtained by appropriately trained emergency department clinicians, alone or in combination with BNP, may increase diagnostic accuracy of CHF. (J Patient Cent Res Rev. 2016;3:230-234.)

Keywords
ultrasound; heart failure; inferior vena cava; pro-B-type natriuretic peptide; emergency department

Clinical Question

In adults, 18 years of age and older, who present to the emergency department (ED) with dyspnea, are inferior vena cava (IVC) measurements using bedside ultrasound as accurate as B-type natriuretic peptide (BNP) levels for identifying heart failure?

Brief Answer

Yes. Bedside ultrasound measurement of the IVC is a highly specific and rapid tool for diagnosing heart failure in the ED setting compared with BNP. BNP costs less than bedside ultrasound but is less specific and may take up to one hour or more at a clinical juncture when rapid detection of volume overload can rule in or rule out heart failure. In the studies reviewed, the specificity of the IVC measurement was as good as, or better than, BNP values. Ultrasound IVC measurements may be especially useful for cases in which BNP values fall into a nondiagnostic “gray zone” range. Based on current evidence, it seems reasonable to conclude that ultrasound IVC measurements, taken by properly trained ED clinicians, alone or in combination with BNP, would likely increase accuracy of diagnosing heart failure, allow earlier initiation of appropriate treatment and potentially reduce morbidity and mortality.

Date of Literature Search: March/April 2016.

Level of Evidence: B.

Search Terms
Ultrasound, heart failure, inferior vena cava, pro-B-type natriuretic peptide, NR-PRoBNP, emergency department, diagnosis

Inclusion Criteria
Current systematic reviews, meta-analyses, cohort studies, clinical research trials investigating the
efficacy of ultrasound measurements of the IVC for diagnosing heart failure in the ED.

Exclusion Criteria
Children less than 18 years of age, renal failure, dialysis, mechanical ventilation, trauma, abdominal surgery within two weeks, pregnancy.

Summary of Issues
In 2003, congestive heart failure (CHF) affected more than 5.7 million adults in the United States, with a lifetime incidence of 1 in 5 for individuals over age 40 years. Heart failure has a mortality rate of 19% and is the primary hospital discharge diagnosis for adults over age 65. As the Baby Boomer generation continues to age, the American Heart Association estimates that 550,000 new cases of heart failure will be diagnosed each year at an estimated cost of $27 billion annually.

Approximately 80% of hospitalized heart failure patients are admitted from the ED. Current clinical guidelines recommend taking BNP levels to improve diagnostic accuracy of CHF in patients who present to the ED with undifferentiated dyspnea. BNP is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells. A normal level (< 100 pg/ml) rules out acute heart failure and an elevated level (> 500 pg/ml) in the absence of renal failure can be diagnostic. A study evaluating the efficacy of BNP in correctly diagnosing CHF reported a sensitivity of 96% and specificity of 26% at a cutoff level of 100 pg/ml, at a cutoff level of 400 pg/ml, BNP had a sensitivity of 87% and specificity of 74%. However, BNP levels can have a “gray zone” in which the values neither confirm nor rule out CHF. In addition, BNP levels are not generally done at the bedside and results can take up to an hour at a time when rapid recognition of volume overload is critical for early treatment.

Ultrasound IVC measurements, performed at bedside in the ED, are rapid and potentially more specific for diagnosing CHF. Measuring the IVC also may be more accurate for identifying alternative causes of dyspnea, such as pneumonia, chronic obstructive pulmonary disease (COPD), noncardiogenic pulmonary edema and lung cancer. This brief report examines the evidence for using bedside ultrasound IVC, alone or in addition to BNP, for accurately identifying heart failure versus other causes of dyspnea.

Summary of the Evidence
Studies show that bedside ultrasound measurements of the IVC correlate with central venous pressure and response to fluid administration. A small IVC (< 2 cm in diameter), with collapse greater than 50% on inspiration, corresponds to a central venous pressure < 10 cm of water, and vice versa. Published guidelines by the American Society of Echocardiography support the evaluation of IVC size and collapsibility in the assessment of central venous pressure. Studies in patients with heart failure used IVC measurements to estimate elevated cardiac filling pressures.

In 2009, Blehar et al. used IVC measurements to identify CHF in a convenience sample of 46 adults (age ≥ 18 years) who presented at the ED with the complaint of dyspnea. Patients who had received a liver transplant, were on mechanical ventilation, taking diuretics, bronchodilators or vasoactive medications, or who were pregnant were excluded. Study participants received ultrasound IVC measurements using a 3.5 MHz curvilinear probe at bedside prior to any interventions. Minimum diameter during inspiration and maximum diameter during expiration were measured. Variation was calculated as the difference between maximum and minimum divided by the maximum. Patients with CHF should have less variation in IVC diameter because volume overload does not allow as much IVC collapse as normally occurs during inspiration. Two physicians, blinded to the ultrasound results, used a standardized chart review to retrospectively determine the final diagnosis as CHF or an alternate diagnosis.

The study showed that respiratory variation of the IVC was smaller in patients with CHF (9.6%) than without CHF (46%). At the optimum cutoff value of 15% variation or less of the IVC diameter, the sensitivity was 93% (95% confidence interval [CI]: 76–99) and the specificity was 84% (95% CI: 77–88) for the diagnosis of CHF (Table 1). Four participants who presented with shortness of breath and BNP measurements > 100 pg/ml were correctly identified by ultrasound IVC measurements as non-CHF. The main limitations of this study were its small study size and the lack of echocardiogram to rule out confounding factors like tricuspid regurgitation.

In 2012, Miller et al. determined the sensitivity and specificity of a caval index for diagnosing acute heart failure in 89 adults (age ≥ 50 years), who
Table 1. Sensitivity and Specificity of IVC Measurements for Diagnosing Congestive Heart Failure

<table>
<thead>
<tr>
<th>Study (number of subjects)</th>
<th>IVC-CI diameter variation cutoff</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blehar et al. ³ (N=46)</td>
<td>&lt;15%</td>
<td>93% (76–99)</td>
<td>84% (77–86)</td>
</tr>
<tr>
<td>Miller et al. ³ (N=89)</td>
<td>&lt;15%</td>
<td>37% (22–55)</td>
<td>98% (88–96)</td>
</tr>
<tr>
<td>Anderson et al. ³ (N=101)</td>
<td>&lt;20%</td>
<td>52% (38–67)</td>
<td>88% (77–96)</td>
</tr>
<tr>
<td>Yamanoglu et al. ³ (N=74)</td>
<td>&lt;50.5%</td>
<td>84% (60–90)</td>
<td>91% (70–98)</td>
</tr>
</tbody>
</table>

CI, confidence interval; IVC-CI, inferior vena cava collapsibility index.

presented at the ED with undifferentiated dyspnea.³ Patients were excluded if they required mechanical ventilation, experienced recent trauma, had abdominal surgery within the past two weeks, had known portal hypertension or were pregnant. Two physicians took ultrasound measurements with a cardiac phased-array probe of the maximum IVC diameter during expiration and the minimum IVC during inspiration over three respiratory cycles prior to any interventions. A caval index was calculated as the difference between the IVC during expiration and inspiration divided by the IVC during expiration multiplied by 100 (IVCex - IVCi)/(IVCex × 100). This study found that a caval index of < 15% had a sensitivity of 37% (95% CI: 22–55) and a specificity of 96% (95% CI: 86–99); at a caval index of 33%, the sensitivity was 80% (95% CI: 63–91) and the specificity was 81% (95% CI: 68–90) (Table 1). A limitation of this study for the purposes of this review is that the diagnostic characteristics of BNP were reported but not directly compared to ultrasound measurements. The main limitation of this study was its small sample size.³

In a 2013 study, Anderson and colleagues investigated the accuracy of IVC collapsibility index (IVC-CI), left ventricular ejection fraction (LVEF) and lung B-lines measured by ultrasound for diagnosing acutely decompensated heart failure in the ED.¹ The prospective convenience cohort study enrolled 101 adults (age ≥ 18 years) who presented at the ED with acute dyspnea. BNP levels were ordered for all study participants. Clinical investigators, who were emergency ultrasound fellowship-trained and blinded to all clinical data, performed the ultrasound measurements of the IVC maximum and minimum, LVEF and lung B-lines. These measurements were compared to a final diagnosis as determined by chart review conducted by two emergency physicians blinded to the ultrasound results.¹

At a cutoff point of 20%, the IVC-CI had a sensitivity of 52% (95% CI: 38–67) and a specificity of 86% (95% CI: 77–95) for accurately diagnosing acutely decompensated heart failure (Table 1), similar to the specificity of BNP levels > 500 pg/ml (83% [95% CI: 67–92]).¹ When IVC-CI measurements were combined with both LVEF and lung B-lines, the specificity went up to 100% (95% CI: 92–100). These results suggest that ultrasound tests measuring IVC-CI, LVEF and lung B-lines may be the most accurate and effective means of diagnosing heart failure at bedside. This study was limited by its smaller size and possible selection bias from the convenience sampling methodology. There may have been some misclassifications based on the retrospective chart review and potential bias introduced by other test values recorded in charts from prior non-ED encounters. For example, a smaller IVC-CI variability may have been recorded because a low ejection fraction was already noted in the chart.¹

In a 2014 prospective, observational study, Yamanoglu et al. used IVC diameter measurements to differentiate between dyspnea of cardiac origin and pulmonary dyspnea.³ Inclusion criteria were met by 74 elderly adults (mean age: 72.8 years) who presented to the ED during the study time window. Patients with severe tricuspid regurgitation, cardiac tamponade, aortic dissection, abdominal surgery within the preceding two weeks, or those who had cardiopulmonary arrest, had been intubated or were pregnant were excluded. Of the 74 enrolled patients, 32 received a final diagnosis of cardiac-associated dyspnea. B-mode IVC diameter greater than 9 mm during inspiration had the greatest sensitivity (84.4%) and specificity...
(92.9%) for identifying dyspnea of cardiac origin; IVC-CI was similar, with a sensitivity of 84.4% and specificity 90.5% (Table 1). This study concluded that ultrasound IVC measurements were “rapid, readily available, inexpensive, reproducible techniques” for differentiating dyspnea due to cardiac etiology (acute heart failure) from dyspnea of pulmonary origin.7

Ultrasound technology is a common diagnostic tool in the ED4 and is a required competency in all U.S. Accreditation Council for Graduate Medical Education emergency medicine programs.5,9 Bedside ultrasound IVC measurement shows promise for use in appropriately diagnosing CHF. Diagnostic accuracy would be improved with standardization of the location of IVC diameter measurement and probe orientation (i.e. long vs short axis), which may vary depending on training and experience of ED physicians.9 Reports have documented the benefit of training targeting the specific skills required for accurate performance and reading ultrasound test results in the ED.10

Limitations

None of the studies reviewed in this report were randomized controlled trials of efficacy. However, a minority of studies of diagnostic tests meet this standard. The four studies reported1,5,7 were prospective. In three of the four,1,5,6 there was an independent blind comparison with reference standards. All of the studies used convenience samples, which increases the risk of selection bias. However, the papers reviewed included a broad spectrum of patients with characteristics generalizable to the ED population. Small sample sizes in each of the papers cited resulted in moderately wide confidence intervals. Larger studies or a meta-analysis combining the data of several studies could improve the precision of the estimates of sensitivity and specificity of IVC-CI. However, a meta-analysis may not be feasible due to differences in ultrasound technique, study protocols and other potential causes of study heterogeneity. Randomized controlled trials are needed to evaluate the efficacy of bedside ultrasound compared to BNP or the combination of BNP and bedside ultrasound in the management of CHF.

Conclusions

Bedside ultrasound inferior vena cava measurements in the presence of undifferentiated dyspnea in the emergency department may be as helpful as, and more rapid than, B-type natriuretic peptide values for diagnosing congestive heart failure. In the studies reviewed, IVC-CI (ranging from 15% to 55.5%) had a high specificity (84%–96%) for identifying heart failure, which would allow ED physicians to avoid prematurely treating patients who are not experiencing CHF and revise their plan while collecting additional data. In all instances, the specificity of ultrasound IVC was as good as or better than BNP values and may help achieve appropriate diagnosis for patients in which BNP values fall in the “gray zone.” Bedside ultrasound IVC assessment also may be useful for the early recognition of other causes of dyspnea and comorbid conditions — such as COPD and other respiratory illnesses — that are increasing in prevalence among elderly patients. Ultrasound IVC allows physicians to begin treating even unstable patients earlier, before results from more traditional tests like BNP become available.1

Now that the accuracy of bedside ultrasound has been established, the next step would be undertaking studies that evaluate the accuracy of ED physician-obtained IVC measurements by ultrasound. Ideally, an ED physician should be able to accurately and efficiently assess noncollapsibility, as can be done for collapsibility, by fluid resuscitation. If randomized controlled trials demonstrate the efficacy of bedside ultrasound compared to BNP in the management of CHF, cost-effectiveness studies comparing diagnostic methods and strategies should be undertaken to determine whether the additional cost of ultrasound (~$264 vs ~$88 for BNP, per Healthcare Bluebook mobile app) provides significant improvements in diagnostic accuracy, morbidity, mortality and quality of life.

Patient-Friendly Recap

• Heart failure is often diagnosed in the emergency department using a specific blood test that takes up to an hour to yield results.
• Bedside ultrasound technology, a common diagnostic tool used in emergency departments, has shown promise in measuring heart function.
• The authors reviewed findings from several published studies and concluded that measuring a patient’s inferior vena cava with ultrasound may help quickly and accurately diagnose congestive heart failure.
Conflicts of interest
None.

Funding Sources
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References
Clinical Question: Nasal saline or intranasal corticosteroids to treat allergic rhinitis in children.

Stefani Madison, MD (PGY-3), Elizabeth Aubrey Brown, MD (PGY-2), Rachel Franklin, MD, Elizabeth A. Wickersham, MD, Laine H. McCarthy, MLIS

ABSTRACT
Clinical Question: In pediatric populations, is nasal saline irrigation as effective as intranasal corticosteroids at relieving allergic rhinitis symptoms?
Answer: No. Intranasal steroids are more effective than nasal saline alone to reduce symptoms of allergic rhinitis (AR) in children. Combination therapy further improves symptom reduction.
Level of Evidence for the Answer: B
Search Terms: Allergic Rhinitis, Nasal Saline, Nasal corticosteroids, children younger than age 18.
Date Search Was Conducted: August and September 2014, October 2015.
Inclusion Criteria: Meta-analyses, randomized controlled trials, systematic reviews, cohort studies, nasal spray, hypertonic saline solution, nasal lavage, rhinitis, intranasal administration, nasal saline, human, English language.
Exclusion Criteria: Antihistamines, Adults, Articles older than 2008

SUMMARY OF THE ISSUES
Allergic Rhinitis (AR) is one of the most common diseases in pediatric patients, with a worldwide prevalence ranging from 2.2% to 45.5% in children between the ages of 6 and 14.1,2 Symptoms include nasal obstruction, rhinorrhea, nasal itching and sneezing, which can be disruptive to sleep and lead to negative impacts on daily function and performance.3 Avoidance of allergens is the first-line treatment but often is not feasible. Appropriate pharmacotherapy often includes intranasal corticosteroid sprays (INS), which is not without drawbacks.4 INS must be used daily to relieve symptoms effectively and do not provide long-term relief of symptoms once the course of therapy is completed.

Nasal saline has been investigated as an alternative to INS therapy. Nasal saline is a solution of 0.9% sodium chloride and sterile water that can be administered in a variety of delivery vehicles, including nasal mist or spray bottles, neti pots (to rinse nasal passages) and nasal saline irrigation machines, which use pulse action or suction to clear sinuses. Saline irrigation has been shown to assist with clearing potential allergens and mucus, improve the mucociliary transport function of the nasal mucosa and open nasal passages.4 Studies indicate that nasal saline is useful as an adjuvant treatment in children with AR,1,3 but can nasal saline be effective in treating AR when used alone? A study by Hong et al. on the compliance and efficacy of saline irrigation in pediatric patients with chronic rhinosinusitis found this to be an effective choice, with reported compliance as high as 60%.4 Therefore, it is reasonable to consider whether or not nasal saline irrigation could be effective in this population as an alternative treatment for AR symptoms in those who do not wish to use intranasal corticosteroids.

SUMMARY OF THE EVIDENCE
A prospective study by de Souza Fernandes et al. studied the usefulness of Peak Nasal Inspiratory Flow (PNIF) curves to assess treatment outcomes for children with AR.4 Forty eligible patients ages 8 to 15 with AR symptoms, diagnosed using the guidelines established in the Allergic Rhinitis and its Impact on Asthma (ARIA) study and confirmed by allergy testing, were monitored for 10 weeks. Classification of AR severity was based on PNIF. A clinical score was calculated based on a previously established set of six signs and symptoms of AR: nasal obstruction, rhinorrhea, sneezing, nasal itching, oropharyngeal itching and ocular itching. Each item was rated from 0 to 3, with 0=no symptoms and 3=intense, almost debilitating symptoms.

The participants were divided into two groups. The treatment group received fluticasone propionate corticosteroid nasal spray, 100 mg per day, and the placebo control group was treated with nasal sodium chloride, 0.9% once daily. Statistical analyses considered variation of clinical scores and PNIF between the two study groups. Overall results showed statistically significant reduction in the clinical symptoms score for the treatment group (p<0.001) compared with little change in the nasal saline placebo group (p>0.001) (Table). The INS treatment group also demonstrated increased PNIF percentages compared to the saline placebo group. The power of the study was limited by the small number of participants.

The results of a study by Chen et al. concurred with the de Souza study. This 2014 three-arm, randomized control study evaluated nasal saline compared with nasal steroids and with a combination of nasal saline and steroids. Sixty-one children...
Table. Mean Score and Percent Reduction in Clinical Symptoms of AR with INS Compared with Saline Over 8 Weeks.

<table>
<thead>
<tr>
<th>Week</th>
<th>Steroid Group</th>
<th>Saline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Clinical</td>
<td>Percent Reduction</td>
</tr>
<tr>
<td></td>
<td>Symptom Score</td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>11.2</td>
<td>--</td>
</tr>
<tr>
<td>Week 2</td>
<td>3.9</td>
<td>65%</td>
</tr>
<tr>
<td>Week 4</td>
<td>3.5</td>
<td>10%</td>
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<tr>
<td>Week 6</td>
<td>3.5</td>
<td>0%</td>
</tr>
<tr>
<td>Week 8</td>
<td>3.4</td>
<td>3%</td>
</tr>
<tr>
<td>Net Percent Reduction</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

Aged 2 to 15 years with confirmed diagnosis of moderate to severe AR were divided into three groups: nasal saline irrigation, INS, and a combination of nasal saline irrigation and INS. The patients in the corticosteroid groups were prescribed 200µg for weeks 1 through 4, 100µg for weeks 5 through 8, and 50µg for weeks 9 through 12. The nasal saline irrigation groups were instructed to use 4 to 6 sprays twice daily for 12 weeks. Patients and parents recorded nasal signs and symptoms as instructed. Nasal signs were scored as: 1=turbinate hypertrophy with little nasal blockage, 2=congestion with nasal blockage or 3=congestion with total nasal blockage limiting nasal breathing. Four nasal symptoms — nasal itching, rhinorrhea, nasal obstruction, sneezing — were rated on a 0 to 3 scale based on intensity with 0=no symptoms and 3=severe symptoms. Eosinophils were quantified for each patient via nasal smear.

Patients were evaluated at 4, 8 and 12 weeks of treatment. The signs and symptoms were recorded and eosinophil smears were reexamined at each follow-up visit. The study demonstrated that combination therapy with both intranasal steroids and saline nasal irrigation resulted in significant improvement in signs and symptoms (p<0.05) compared to those treated with saline irrigation alone or steroids alone. Clinical significance was demonstrated by decreased eosinophils in nasal secretions in the combination group when compared to saline alone or intranasal steroids alone (p<0.05) by 8 and 12 weeks of use. We were unable to compare statistical data from this report with other published reports due to the lack of numerical data accompanying the charts and figures. Visual review of the figures, however, supported their conclusion that daily nasal irrigation is an effective adjuvant treatment for allergic rhinitis “in combination with a reduced dose of a nasal corticosteroid.”

In 2013, the European Academy of Allergy and Clinical Immunology (EAACI) published recommendations for treatment of AR based on the highest level of evidence retrieved from a systematic review of the literature. The Group supported the use of multiple treatment modalities including intranasal corticosteroids and nasal saline irrigation. The EAACI also concluded that nasal saline irrigation is an effective adjuvant to intranasal corticosteroids therapy and indicated that nasal saline was effective at reducing the amount of INS required for symptom relief.

CONCLUSION

The studies reviewed herein concluded that intranasal steroids are more effective at reducing symptoms of AR when compared to nasal saline irrigation alone. Combination therapy with INS and nasal saline irrigation improves AR symptoms and maximizes the efficacy of intranasal corticosteroids. Concomitant use of intranasal corticosteroids and nasal saline irrigation is an effective treatment option that is well tolerated in a pediatric population. Based on clinical experience and patient preference, INS and adjunct nasal saline irrigation appear to be a good option for improving symptoms and quality of life for children suffering from AR.

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Clinical Question: Does Medical Evidence Support Routine Oronasopharyngeal Suction at Delivery?

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Search Terms: Neonate; oronasopharyngeal suction; oxygen saturation; vaginal delivery.

Conflict of Interest: None.

IRB Approval: Not required.

ABSTRACT

Oronasopharyngeal suction (ONPS) is regularly performed in neonates at delivery in many hospitals across the country today. Although ONPS is a technique that has essentially become habitual for most obstetricians, its theorized usefulness to help promote expeditious lung aeration after delivery by removal of amniotic fluid, meconium, mucus and blood that may otherwise be aspirated by the newborn, is currently not recommended. ONPS can cause vagal stimulation-induced bradycardia and thus hypercapnea, iatrogenic infection due to mucous membrane injury, and development of subsequent neonatal brain injury due to changes in cerebral blood flow regulation, particularly in premature infants. Multiple studies that have been performed comparing routine use of ONPS to no intervention controls indicate that newborns receiving ONPS took a longer time to achieve normal oxygen saturations, caused apneic episodes, and caused disturbances in heart rate (mainly bradycardia) compared to the control groups. Although the ONPS groups revealed no significantly different APGAR scores at 1 and 5 minutes, the ONPS groups took longer than the control group to reach an arterial oxygen saturation greater than or equal to 92% in the first minutes of life. Currently, Neonatal Resuscitation Program guidelines discourage the use of meconium-stained amniotic fluid and in the absence of obvious obstruction. Furthermore, this manuscript highlights various literature sources revealing that the routine use of ONPS at the time of delivery can cause more harm than good, if any good at all.

MANUSCRIPT

Oronasopharyngeal suction (ONPS) in neonates during and after delivery is a commonly performed practice in the field of obstetrics despite American Health Association and the International Neonatal Resuscitation Chapter Collaborators 2010 guidelines and recommendations. The technique is commonly passed down from attending physicians to residents based on the theory that ONPS helps improve aeration of the newborn lungs by removal of amniotic fluid, meconium, mucus, and blood that may otherwise be aspirated by the baby. This technique is also theorized to help improve oxygenation by means of establishing functional residual capacity more quickly. However, there are possible harmful effects of ONPS that cause concern for its routine use including vagal stimulation inducing bradycardia and thus apnea, mucous membrane trauma resulting in iatrogenic infection, and rebound nasal congestion. Several studies summarized by Velaphi and Vidyasagar evaluated whether or not ONPS immediately after delivery had an overall effect on morbidity and mortality in the newborn. This review reported that, although APGAR scores among vigorous newborns showed no statistically significant difference between newborns receiving ONPS compared with no intervention, newborns receiving ONPS took a longer time to achieve normal oxygen saturations, experienced apneic episodes, and had disturbances in heart rate (mainly bradycardia) compared to newborns without any intervention. It is even speculated that these delays in achieving optimal oxygen saturations after delivery might increase the risk of developing pulmonary hypertension in some neonates.

Additionally, there is conflicting data regarding the use of ONPS in neonates with meconium-stained amniotic fluid present. Vain et al. revealed in a large multicenter randomized study in which two thousand five hundred and fourteen term neonates with meconium-stained amniotic fluid were randomized into either utilizing ONPS or no intervention at all. It was found that intrapartum ONPS of term infants born with meconium-stained amniotic fluid did not prevent
meconium aspiration syndrome. Although this is a somewhat high-level study, more controlled studies are needed regarding ONPS in neonates with meconium-stained amniotic fluid.

Furthermore, a randomized equivalency study by Kelleher and colleagues investigated various sources stating that simply wiping of the face, nares, and mouth with a towel at the time of delivery is equally as effective as ONPS with a bulb syringe. Four hundred and eighty neonates with and without meconium-stained amniotic fluid were studied. Two hundred and forty six were randomized to the wipe group, and two hundred and forty two were randomized to the suction group. Neonatal outcomes were equivalent, suggesting that routine ONPS is not necessary. However, there is still a larger need for data before wiping of the face, nares, and mouth with a towel in place of ONPS can be recommended and implemented.

Nejad et al. evaluated the effects of ONPS versus no intervention on arterial oxygen saturation (SaO2) at the time of delivery. One hundred and seventy healthy term newborns that delivered vaginally without any complications in the vertex presentation with clear amniotic fluid present were randomized into either the ONPS group or the control group (no suction). Immediately after delivery, eighty five neonates were suctioned with a sterile polyethylene tube with no more than 30 cm H2O, and eighty five neonates only had visible material suctioned, if any at all. Therefore, if no obvious pooling of amniotic fluid within the oronasopharyngeal area, the neonates were not suctioned at all in the control group. Both groups were then evaluated routinely under a radiant warmer with oxygen saturation sensors attached to their right middle fingers to monitor arterial oxygen saturation and heart rate. Readings were recorded at the first minute after birth along with routine 1 and 5 minute APGAR scores to evaluate neonatal well being.

When comparing the routine umbilical cord arterial and venous blood gas values, this study found that the control group did have a statistically lower partial oxygen pressure (PaO2) and higher partial carbon dioxide pressure (PCO2) than the study group (p < 0.05), but the ranges in both groups were still considered within the normal range overall. Therefore, these values did not reveal a clinically significant difference. There was also no statistically significant difference in APGAR scores amongst the two groups at one and five minutes, and all neonates had an APGAR score between 8 and 10 at 1 and 5 minutes, respectively. The differences in PaO2 and PCO2 resulted in no difference in the overall pH in both groups. However, the primary end-point of the study was to determine the time it would take to reach 92% SaO2 between the two groups. The slowest time for a newborn to reach this level in the no suction group was 9 minutes of life, and the slowest time in the suction group was 11 minutes (p = 0.002). None of the neonates in the suction group achieved 92% SaO2 before 8 minutes of life. Additionnally, the ONPS group had lower SaO2 levels by 5 minutes of life than the control group. This study concluded that refraining from performing ONPS in normal term vaginal deliveries enabled the neonate to reach oxygen saturations greater than or equal to 92% quicker than routine suctioning of the airways and that routine ONPS is therefore not recommended.

A 2013 Cochrane Collaboration protocol review established guidelines for studying routine ONPS in term and preterm newborns. ONPS after birth was traditionally thought to help intrapulmonary fluid expulsion, improve oxygen saturation levels and prevent aspiration of mucus and blood from the trachea. However, ONPS has been associated with adverse effects such as bradycardia, iatrogenic infection due to mucous membrane injury, and development of subsequent neonatal brain injury due to changes in cerebral blood flow regulation. Endotracheal suction is still the standard of care in preterm neonates. Although the Cochrane Collaboration discusses that certain studies discourage the routine use of ONPS because of these adverse effects, completely abandoning this common delivery practice would require a large body of research that unfortunately has yet to be performed. This lack of evidence has been recognized, and a protocol for data review has been implemented, but is still underway. This review to be conducted by The Cochrane Collaboration will evaluate the effect of routine ONPS versus no intervention in term, preterm, and very preterm infants in order to evaluate morbidity and mortality in newborn infants born with and without meconium stained amniotic fluid. Kattwinkel et al. 2010 also discusses that current Neonatal Resuscitation Program guidelines state that the routine use of ONPS during delivery with clear or meconium-stained amniotic fluid and in the absence of obvious obstruction is not recommended.

Velaphi and Vidyasagar published a review in 2008 consisting of an electronic search of Medline, Cochrane reviews, and Embase for articles pertaining to the question at hand, ranging from 1971 to 2006. Their overall impression of the multiple studies that were reviewed was that routine ONPS of live and vigorous newborns at delivery reveals no positive benefits pertaining to the newborn's respiratory status, and “is more likely to cause harm than good,” and that ONPS should therefore be abandoned as a routine delivery technique. This includes newborns born by either vaginal or cesarean delivery.

CONCLUSION

Based on our review of literature and current national and international guidelines, we conclude that routine use of ONPS after delivery is not indicated for vigorous, term infants with clear or meconium-stained fluid and may actually be harmful. ONPS can cause vagal stimulation-induced bradycardia and thus hypventilation, iatrogenic infection due to mucous membrane injury, and development of subsequent neonatal brain injury due to changes in cerebral blood flow regulation, particularly in premature infants. However, ONPS compared to no intervention in the presence of excessive audible secretions or in the

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depressed newborn infant is still in need of further research. Endotracheal suction is still the recommended care in non-vigorous and preterm infants.\textsuperscript{1,3}

REFERENCES
Is 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Combined With 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) Superior to PPSV23 Alone for Reducing Incidence or Severity of Pneumonia in Older Adults? A Clin-IQ

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Abstract
Pneumonia infection is a significant cause of morbidity and mortality worldwide. In addition to the public health concerns, pneumonia also accounts for a significant cost to the health care system. Currently there are two leading vaccines targeted against Streptococcus pneumoniae: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Until recently, the recommendation for adult pneumonia vaccination has been a single dose of PPSV23 for all adults aged 65 years or older. However, concerns were raised regarding the vaccine’s efficacy due to the persistent burden of pneumococcal disease in the elderly population. This paper focuses on two trials that evaluated the safety and efficacy of PCV13 in the adult population. The first study reveals improved immune response with the addition of PCV13 to PPSV23, while the second shows PCV13 was effective in the prevention of vaccine-type community-acquired pneumonia. Both studies observed adequate safety profiles for PCV13 in series with PPSV23 and with PCV13 compared to placebo. (J Patient Cent Rev. 2016;3:111-115.)

Keywords
pneumococcal conjugate vaccine; pneumococcal polysaccharide vaccine; adults; PPSV23; PCV13

Clinical Question
In patients 65 years of age or older, is 13-valent pneumococcal conjugate vaccine (PCV13) combined with 23-valent pneumococcal polysaccharide vaccine (PPSV23) superior to PPSV23 alone for reducing the incidence or severity of pneumonia?

Answer
Probably, since PCV13 combined with PPSV23 yields improved immune titers compared to PPSV23 alone. More clinically relevant data showing reduction in incidence or severity of pneumonia is unlikely to become available because of the expense and ethics of conducting the research.

Date answer was determined: September 2015.

Level of evidence: A.

Search Terms
Adults age 65 and older, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, PPSV23, PCV13.

Inclusion Criteria
Humans, age 65 years and older, English language articles, 2008–2015 year of publication.

Exclusion Criteria
Children and adults younger than age 65 years.

Summary of the Issues
Pneumonia infection is a significant cause of morbidity and mortality worldwide, and Streptococcus pneumoniae is currently the most commonly identified pathogen in community-acquired pneumonia.1 In the United States, S. pneumoniae is responsible for 500,000 cases of pneumonia and 50,000 cases of bacteremia each year, with annual mortality rates of 5–7% and 20%, respectively.1 Pneumococcal disease in all of its forms is estimated to cause 1.6 million
deaths globally per year. In addition to the public health concerns, pneumonia also accounts for a significant cost to the health care system.

Currently there are two leading vaccines targeted against S. pneumoniae: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Pneumococci bacteria are contained within a polysaccharide capsule. The capsules contain antigenic variation, and more than 90 distinct capsular serotypes have been identified. PPSV23 contains antigens from 23 common serotypes, while PCV13 contains antigens from 13 serotypes. Although both vaccines aim to induce immunity against the most common serotypes that cause clinical disease, there is substantial overlap in the antigens contained within each vaccine. Specifically, 12 of the 13 serotypes included in PCV13 are common to PPSV23.

The other major difference between PPSV23 and PCV13 is the design of the vaccine itself. PPSV23 contains capsular polysaccharide antigens. These antigens elicit a T-cell–independent antibody response. The antibodies produced boost activity of phagocytic cells and thereby induce killing of pneumococcus. PCV13 is a conjugate vaccine that combines these capsular polysaccharides with a protein carrier. With the addition of the protein, PCV13 produces a T-cell–dependent immune response with antibody production and the potential for immune memory.

Until recently the recommendation for adult pneumonia vaccination has been a single dose of PPSV23 for all adults aged 65 years or older. However, concerns were raised regarding the vaccine’s efficacy due to the persistent burden of pneumococcal disease in the elderly population. PCV13 was introduced in the pediatric population in 2010 as a replacement for 7-valent pneumococcal conjugate vaccine (PCV7). The conjugated vaccines have proved to be successful at reducing the burden of pneumococcal disease in the pediatric population. New research has focused on PCV13 in the adult population to evaluate both safety and efficacy as well as determine the most appropriate vaccination strategy for prevention of pneumococcal disease.

Summary of the Evidence
A 2013 study examined the safety and effectiveness of PCV13 in elderly adults who had previously received vaccination with PPSV23. In this study, antipneumococcal opsonophagocytic activity (OPA) titers were measured to evaluate vaccine efficacy. The study, a randomized, modified double-blinded trial, included 936 adults aged 70 years or older who had been previously vaccinated with PPSV23 at least 5 years prior to the trial. Study participants were divided into two groups. One group received a second dose of PPSV23, whereas the other received PCV13. Both groups received a dose of PCV13 1 year later. OPA titers were measured prior to and at 1 month following each vaccine administration. Safety assessments also were performed at 2 weeks, 1 month, and 6 months postvaccination.

Study results revealed a significantly greater OPA response for 10 of the 12 common serotypes following vaccination with PCV13 as compared to PPSV23. The study then evaluated immune response following PCV13 administration in both groups 1 year following the initial PCV13 or PPSV23 vaccine. This was performed to assess the impact of initial vaccine choice on response of subsequent vaccinations. Using a 95% confidence interval, OPA titer responses were statistically significantly higher for 11 common serotypes in the group that received PCV13 at enrollment and at 1 year compared to the group receiving PPSV23 initially. The results suggest that a booster dose of PPSV23 given prior to PCV13 may not improve coverage, and it may be more beneficial to administer PCV13 following initial vaccination with PPSV23. PCV13 also had a satisfactory safety profile compared to PPSV23.

Though this report highlighted the limitations of PPSV23 alone in prevention of pneumococcal disease in the elderly, the study is limited by the fact that it was funded by Wyeth Vaccines Research, Wyeth Pharmaceuticals Inc. (Collegeville, PA) manufactures Pneumonea 13®, a PCV13. Additionally, while OPA titers are considered a measurement of functional immune response, it is difficult to extrapolate this data into prevention of clinical illness. The primary concern for health care providers is a vaccination strategy that will reduce morbidity and mortality in their patient population.
The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTAl) was developed to determine the clinical efficacy and safety of PCV13 in the adult population. The study included 84,496 pneumococcal vaccine-naïve adults aged 65 years or older. The randomized, double-blinded, placebo-controlled trial was conducted in the Netherlands, where there were no recommendations for routine pneumococcal vaccination in older adults. Participants were randomly divided into two groups in a 1:1 ratio, either receiving PCV13 or placebo injection. Study participants were then followed for an average of approximately 4 years.

The primary objective of the study was to demonstrate prevention of a first episode of vaccine-type community-acquired pneumonia (CAP). Secondary objectives included prevention of first-episode nonbacteremic and noninvasive vaccine-type CAP (negative cultures of sterile sites) and vaccine-type invasive pneumococcal disease (S. pneumoniae present in sterile site). Fifty-nine sentinel centers participated in the study. For patients presenting with symptoms of lower respiratory tract infection, routine diagnostic evaluation was performed. A database was searched for study participation if pneumonia was the suspected diagnosis. For study participants, a urine sample was obtained for testing of serotype-specific urinary antigen. Culture results were monitored for determination of invasive pneumococcal disease. Chest X-rays performed were read at a central location, and radiologists were not informed of patients’ vaccination status.

The CAPiTAl study concluded PCV13 was effective in preventing vaccine-type CAP and vaccine-type invasive pneumococcal disease in immunocompetent adults aged 65 years or older for a duration of at least 4 years. Vaccine efficacy was statistically significant in these groups and was found to be 46% in prevention of first-episode vaccine-type CAP, 45% in first-episode nonbacteremic and noninvasive vaccine-type CAP, and 75% in vaccine-type invasive pneumococcal disease (Table 1). PCV13 was also found to be safe in the adult population. While there were more local reactions and systemic events in the PCV13 group compared to placebo, there were no documented serious adverse events. Additional endpoints observed during the study included the first episode of nonbacteremic and noninvasive pneumococcal CAP, including nonvaccine serotypes, and the first episode of all-cause CAP. PCV13 efficacy was not found to be significantly different between these groups.

The trial was successful in establishing efficacy and safety for PCV13 in adults for prevention of vaccine-type pneumococcal disease, but this study does have several limitations. Funding and support was namely provided by Pfizer Inc. (New York, NY), which purchased Wyeth, the manufacturer of Prevmar 13, in October 2009. The study also was conducted within one country in a population with little variation in race (98.5% white). Vaccine efficacy may be altered in a more diverse patient population. Additionally, this population was pneumococcal vaccine-naïve. Unlike the Netherlands, the United States has a developed

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<th>Table 1. PCV13 efficacy in first-episode vaccine-type pneumococcal disease^6</th>
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<td>PCV13 (N=42,240)</td>
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<td>First-episode vaccine-type CAP</td>
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<td>First-episode vaccine-type invasive pneumococcal disease</td>
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CAP, community-acquired pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine.

vaccination strategy for pneumonia. Many adults aged 65 years or older have received PPSV23 according to current guidelines. Therefore, while this study shows effectiveness of PCV13, it does not address the question of superiority of PPSV23 in combination with PCV13 compared to PPSV23 alone.

Conclusions
Each pneumonia vaccine has its own set of benefits and limitations. PPSV23 covers a greater number of pneumococcal serotypes, but may not induce effective or lasting immunity. PCV13 seems to produce greater potential for immune memory. However, there are questions of necessity since introduction of PCV13 in the pediatric population has decreased the incidence of these pneumococcal strains in the population as a whole. Regardless, the current vaccination strategy has not been as successful as desired in prevention of pneumococcal disease in the adult population, prompting the U.S. Advisory Committee on Immunization Practices to update its recommendations for pneumococcal vaccination. Current updated guidelines recommend routine administration of PCV13 in series with PPSV23 in all adults 65 years of age or older (Table 2).

Based on studies currently available, the combination of PPSV23 with PCV13 should produce a superior immune response than with PPSV23 alone. Improving immune response should result in an overall reduction in clinical incidence and severity of pneumococcal disease.

Patient-Friendly Recap
• A relatively new vaccine called PCV13 has been effective in preventing pneumonia in children.
• The authors asked whether PCV13, in combination with the commonly used pneumonia vaccine PPSV23, is better at preventing pneumonia in older adults than PPSV23 alone.
• They determined that the research published to date, despite limitations regarding study funding, supports combined use of PCV13 and PPSV23.

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Conflicts of Interest
None.

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