TRANSLATING RESEARCH FOR POLICY IMPACT AND PRACTICE

DEVELOPING CLINICAL GUIDELINES: AN EVIDENCE BASED APPROACH

Peter Tugwell

[with help from Luis Gabriel Cuervo, Jeremy Grimshaw, Gordon Guyatt, Annette O’Connor, Andy Oxman, Jordi Pardo, Tamara Rader, Nancy Santesso, Holger Schunemann, Dawn Stacey, Vivian Welch and my Ottawa group.]
Clinical practice guidelines

‘Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances’.

International CPG Activities

Many countries have established clinical practice guideline programs including:
• US and Canadian Preventive Task Force
• Canadian provincial guidelines programs
• Dutch College of General Practitioners
• National Institute for Clinical Effectiveness
• Scottish Intercollegiate Guidelines Network
• New Zealand Guidelines Group
• National Health and Medical Research Council Australia
• US Agency for Health Care Policy and Research

? Caribbean Countries
Guidelines for Guidelines

Jamaica

http://www.moh.gov.jm/general/publication
Registration/Assessment Guidelines, Forms & Lists

Written by Administrator

Friday, 15 January 2010 15:38

Registration of Drugs and other Items

Registration of drugs and other products/items are major regulatory functions executed through the Pharmaceutical & Regulatory Affairs Department. It involves in-depth scientific evaluation of the technical documentation submitted in support of registration resulting in licensing of a drug or other related product. It is one of the primary mechanisms through which the quality, safety and efficacy of drugs, and other products mentioned in the Food and Drugs Act and Regulations are ensured.

‘Drug’ refers to any substance that conforms to the definition prescribed by the Act. Such substances generally require registration and include drugs, herbal preparations and some vitamins and supplements. Registration may also be required for any cosmetic, food or device making therapeutic claims.

In instances where products are deemed safe enough to be placed on the market without formal
Question for you -the audience!
Please discuss with your neighbour
Identify 1 of each of the following:

Think of

A] **Patients**: one benefit and one harm of guidelines to Patients

B] **Clinicians** : one benefit and one harm of guidelines to Clinicians.
Potential benefits and harms for patients?
Potential benefits for patients

- improve health outcomes
- improve consistency of care
- summarise benefits and harms of treatment options (consumer guidelines)
- empower patients to make informed treatment choices
- help patients to influence policy

Potential harms for patients

- flawed guidelines may result in sub optimal, ineffective or harmful practices
- inflexible guidelines may result in inappropriate care for individual patients
- consumer versions of guidelines may be inaccurate
- distort policy decisions

Potential benefits and harms for healthcare professionals?
Potential benefits for healthcare professionals

• summarise and synthesise evidence
• improve quality of clinical decisions
• support quality improvement activities
• identify future research needs

Guidelines: Potential harms for healthcare professionals

- provide inaccurate summaries and syntheses of evidence
- reduce professionalism (cookbook medicine)
- medico-legal concerns
- economic impact
- discourage research

Who here from the Caribbean has experience with guideline development?

- Please tell us about:
  - Composition of guideline development group
  - Methods of identifying and synthesising evidence
  - Methods of developing guidelines
2 of my recent guideline experiences using Cochrane Systematic Reviews

1. Primary Care for Immigrants and Refugees to Canada
2. Osteoarthritis management in Primary Care

After reviewing all the Guideline systems where we could use Cochrane SRs, we decided to use the ‘GRADE’ approach

GRADE (Grades of Recommendation, Assessment, Development and Evaluation)
Evaluation of evidence-based literature and formulation of recommendations for the clinical preventive guidelines for immigrants and refugees in Canada

Peter Tugwell MD MSc, Kevin Pottie MD MCSc, Vivian Welch MSc PhD, Erni Ueffing BHS C. MHSc, Andrea Chambers MSc, John Feighnerr MD MSc; for the Canadian Collaboration for Immigrant and Refugee Health (CIRH)

ABSTRACT

Background: This article describes the evidence review and guideline development method developed for the Clinical Preventive Guidelines for Immigrants and Refugees in Canada by the Canadian Collaboration for Immigrant and Refugee Health Committee.

Methods: The Appraisal of Guidelines for Research and Evaluation (AGREE) best-practice framework was combined with the recently developed Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to produce evidence-based clinical guidelines for immigrants and refugees in Canada.

Results: A systematic approach was designed to produce the evidence reviews and apply the GRADE approach, including building on evidence from previous systematic reviews, searching for and comparing evidence between general and specific immigrant populations, and applying the GRADE criteria for making recommendations. This method was used for priority health conditions that had been selected by practitioners caring for immigrants and refugees in Canada.

Interpretation: This article outlines the 14-step method that was defined to standardize the guideline development process for each priority health condition.

Key points:

- We combined the AGREE best practice framework with the recently developed GRADE approach to develop evidence-based clinical preventive guidelines for immigrants and refugees in Canada.
- This methods paper documents the systematic approach used to produce the evidence reviews and apply the GRADE approach.
- The 14-step approach included building on evidence from previous systematic reviews, searching for and comparing evidence between general and specific immigrant populations, and applying the GRADE criteria for making recommendations.
- For each recommendation, the basis (balance of benefit and harm, quality of evidence, and values) is stated explicitly to ensure transparency.

A variety of methods is used for developing clinical guidelines and practice recommendations. We used the recently developed approach of moving away from recommendations classified by letters and numbers to the simplified classification system recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group and applied this to clinical preventive actions. Our guideline development process followed the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (www.agreetrust.org), which is recognized internationally as providing best-practice criteria for evidence-based guideline development.

We developed the recommendations on the basis of a pre-defined process overseen by the CIRH Guideline Committee. Defining a methods process ensured that each guideline was developed in a systematic, reproducible manner and was based on the best evidence available. This process was based on a variety of methods used for developing clinical guidelines and practice recommendations.

From the Institute of Population Health (Tugwell, Pottie, Welch, Ueffing, Chambers), the Department of Medicine (Tugwell), the Department of Family Medicine (Pottie), University of Ottawa, Ottawa, Ont., and the Department of Family Medicine (Feighnerr), University of Western Ontario, London, Ont.


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Infectious Diseases
• MMR/DPTP-HIB
• Varicella (Chicken Pox)
• Hepatitis B
• Tuberculosis
• HIV/ AIDS*
• Hepatitis C
• Intestinal Parasites
• Malaria

NCD
• Diabetes
• Dental disease
• Contraception
• Cervical Cervix/HPV
• Iron Deficiency Anemia
• Mental Health and Maltreatment
  – Depression
  – Post Traumatic Stress Disorder
  – Child Maltreatment
  – Intimate Partner Violence
• Pregnancy Care
• Vision Disorders
American College of Rheumatology 2012
Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee
MARC C. HOCHBERG, ROY D. ALTMAN, KARINE TOUPIN APRIL, MARIA BENKHALT, GORDON GUYATT, JESSIE MCGOWAN, TANVEER TOWHEED, VIVIAN WELCH, GEORGE WELLS, AND PETER TUGWELL
ACR Proposal

• Pharmacologic and non-pharmacologic interventions for OA
Knee and Hip OA Treatments

NON-PHARMACOLOGIC
- Acupuncture
- Exercise
- Foot insole
- Knee brace
- Manual physio
- TENS
- Weight loss

PHARMACOLOGIC
- Acetaminophen
- Chondroitin Sulfate
- Cortico-steroid injection
- Glucosamine Sulfate
- Opioids
- Tramadol
- Oral NSAIDs
- Topical capsaicin
- Topical NSAIDs
- Hyaluronates injection
ACR Proposal

• Pharmacologic and non-pharmacologic interventions [incl weight loss, exercise, knee brace, foot insole]

• Use of the ‘GRADE’ Method
  – to create Summary of Findings tables and to make recommendations
Knee and Hip OA Treatments

NON-PHARMACOLOGIC
• Acupuncture
• Exercise
• Foot insole
• Knee brace
• Manual physio
• TENS
• Weight loss

PHARMACOLOGIC
• Acetaminophen
• Chondroitin Sulfate
• Cortico-steroid injection
• Glucosamine Sulfate
• Opioids
• Tramadol
• Oral NSAIDs
• Topical capsaicin
• **Topical NSAIDs**
• Hyaluronates injection
E.g. Topical NSAIDs vs. placebo

<table>
<thead>
<tr>
<th>Patient or population:</th>
<th>patients with knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Topical NSAIDs</td>
</tr>
<tr>
<td>Comparison:</td>
<td>placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks</th>
<th>Absolute difference</th>
<th>Relative effect</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group rate</td>
<td>Intervention rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Topical NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| WOMAC. Scale from: 0 to 100. (follow-up: 4 weeks) | 35% | 54% (47% to 60%) | 19% | 1.52 | 1378 (9)

(high) | 5 (4 to 7)

| Harms             |                     |                     |                |                             |                                |           |
| Dry skin number of patients with event (follow-up: 4 weeks) | 1% | 36% (5% to 258%) | 35% | RR 30 | 168 (1)

(high) | 3 (0 to 26) (reflects benefit in placebo)

Rash number of patients with event (follow-up: 4 weeks) | 4% | 13% (4% to 46%) | 9% | RR 3.67 | 168 (1)

(high) | 10 (2 to 463) (reflects benefit in placebo)

1 The study reported a weighted mean difference of change over placebo. We calculated the SMD using Excel and RevMan 5.

2 There is also another review done in 2008 by Dzau. However, they did not pool results. The chosen meta-analysis (Bjordal, 2006) includes more RCTs (from 1993 to 2004 including the studies by Bookman, 2004 and Roth, 2004 which were the newest studies in the Cochrane review).
ACR Proposal

• Pharmacologic and non-pharmacologic interventions [incl weight loss, exercise, knee brace, foot insole]

• Use of the ‘GRADE’ Method
  – to create Summary of Findings tables and to make recommendations

• ACR Panel Experience
  – Apply evidence base to patient Scenarios using Decision Aids
Case study: Paul, age 55, has Osteoarthritis of the knees.

- Shows good knowledge about the options.
- Is motivated to make a change.
- Had indicated pain relief is his objective.
- Decides to discuss NSAIDs with his doctor.
Stepped care Decision Aid

Based on Cochrane Reviews and GRADE –based Recommendations
What is Osteoarthritis?
It breaks down the cartilage in a joint. This causes joint pain, stiffness and swelling. It limits people from doing what they want and need to do. Usually the symptoms come on slowly, but get worse over time. There is no cure but symptoms can be controlled.

How is osteoarthritis affecting you? (Check ☑ the answer that shows how you felt IN THE PAST WEEK)

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all/No Pain</th>
<th>Mildly</th>
<th>Moderately</th>
<th>Severely</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>How intense has your joint pain been?</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>How much has your joint pain affected your sleep?</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>How much has your joint pain affected your overall quality of life?</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>How much has your joint pain made it DIFFICULT to do your daily activities such as errands, chores, hobbies, socializing, travel, and being physically active.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
These are the interventions

What are you doing now to manage your osteoarthritis? (Check ☐ those you use now)
The treatments are listed in levels ranging from simpler (0) to stronger (5). When simpler treatments no longer work, stronger ones with possible side effects are tried. Sometimes surgery is needed.

Level 0  □ Nothing yet  □ Hot pepper cream such as Capsaicin  □ Glucosamine  □ TENS- Electrical currents applied to skin
□ Chondroitin

Level 1  □ Exercise  □ Healthy weight  □ Acupuncture  □ Acetaminophen such as Tylenol
□ Insoles  □ Joint injection with steroid or viscosupplement

Level 2  □ Non-steroidal creams (NSAID) such as Pennsaid® lotion
□ Insoles  □ Joint injection with steroid or viscosupplement

Level 3  □ NSAID pills such as Advil

Level 4  □ Opioid (narcotic) painkillers such as oxycontin, oxycodone, morphine, demerol

Level 5  □ See a surgeon about joint replacement
List other things you have tried: __________________________________________________________

How often have you followed your current plan during the past week? (Circle the best answer)
I followed my exercise program  0 days  1-2 days  3-4 days  5-6 days  7 days  Does not apply
I did things to control my weight  0 days  1-2 days  3-4 days  5-6 days  7 days  Does not apply
I took my daily medicines  0 days  1-2 days  3-4 days  5-6 days  7 days  Does not apply

What are your options?
• Make no change. You continue as you are doing now.
• Make a change. You follow your plan more regularly or you try another option.

Working through the 4 steps of this decision aid may help you decide
Step 1: What are the benefits and harms of each treatment option?

Visual representation of what the research shows, includes the assessment of methodological quality of the evidence using GRADE.
Step 1: What are the benefits and harms of each option?

<table>
<thead>
<tr>
<th>Level 3</th>
<th>NSAID pills (such as Advil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>These options work better than a placebo. More people are harmed by the treatment than in level 2.</td>
<td></td>
</tr>
<tr>
<td>In 100 people:</td>
<td></td>
</tr>
<tr>
<td>30 improve on their own</td>
<td></td>
</tr>
<tr>
<td>21 improve due to treatment</td>
<td></td>
</tr>
<tr>
<td>49 don’t improve</td>
<td></td>
</tr>
<tr>
<td>NSAID pills can cause nausea, stomach bleeding or ulcers, or heart attack. In 100 people under 60 years with no history of a heart disease:</td>
<td></td>
</tr>
<tr>
<td>99 are not harmed</td>
<td></td>
</tr>
<tr>
<td>1 gets a heart attack due to NSAID pills</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 4</th>
<th>Opioid (narcotic) painkillers such as opioids, oxycontin, oxycodone, morphine, demerol</th>
</tr>
</thead>
<tbody>
<tr>
<td>These options work better than a placebo. More people are harmed by the treatment than level 3.</td>
<td></td>
</tr>
<tr>
<td>In 100 people:</td>
<td></td>
</tr>
<tr>
<td>30 improve on their own</td>
<td></td>
</tr>
<tr>
<td>21 improve due to treatment</td>
<td></td>
</tr>
<tr>
<td>49 don’t improve</td>
<td></td>
</tr>
<tr>
<td>Opioid painkillers can cause nausea, constipation, or withdrawal symptoms. More people get withdrawal symptoms when their Opioid painkillers are reduced:</td>
<td></td>
</tr>
<tr>
<td>23 more people get withdrawal symptoms</td>
<td></td>
</tr>
<tr>
<td>77 people avoid withdrawal symptoms</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 5</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>See a surgeon about joint replacement surgery if other options have not worked.</td>
<td></td>
</tr>
</tbody>
</table>

100 faces illustrate the benefits of the intervention
Discussion of options with patients based on what is important to them

### Step 2: Which reasons to choose each option matter most to you?

Common reasons to choose each option are listed below
- Show how much each reason matters to you by circling a number from 0 to 5
- ‘0’ means it is not important to you. ‘5’ means it is very important to you.
- If a reason is important to you, the options to consider are shown in the column on the right.

<table>
<thead>
<tr>
<th>How important is it to you ...</th>
<th>Not Important</th>
<th>Very Important</th>
<th>Options to consider if this reason is important to you</th>
</tr>
</thead>
<tbody>
<tr>
<td>To get better pain relief</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>Try other options in your current level or move to the next level.</td>
</tr>
<tr>
<td>To avoid taking pills?</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>Try options in Level 1 or 2.</td>
</tr>
<tr>
<td>To avoid needles?</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>Avoid acupuncture in Level 1 and joint injections in Level 2.</td>
</tr>
<tr>
<td>To avoid bleeding ulcers or heart attack?</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>Avoid NSAID pills in Level 3.</td>
</tr>
<tr>
<td>To avoid withdrawal symptoms?</td>
<td>0 1 2 3 4 5</td>
<td></td>
<td>Avoid OPIOID painkillers in Level 4.</td>
</tr>
</tbody>
</table>

List other reasons

|                                   | 0 1 2 3 4 5 |
Discuss of patient knowledge of the benefits and harms

### Step 3: What else do you need to prepare for decision making?

**Find out how well this decision aid helped you to learn the key facts.**
Check ☑ the best answer.

1. Which option has the highest chance of improving pain?
   - Steroid joint injection
   - Acetaminophen
   - Chondroitin
   - Don't know

2. Which option has the highest chance of bleeding stomach ulcers or heart attack?
   - Glucosamine
   - NSAID pills
   - Opioid painkillers
   - Don't know

3. Which option has the highest chance of withdrawal symptoms?
   - Glucosamine
   - NSAID pills
   - Opioid painkillers
   - Don't know

4. If 100 people take NSAID pills for 1 to 6 months, how many more people with no history of heart disease will have a heart attack from taking them?
   - 0
   - 1
   - 2-5
   - Don't know

5. Over time, the pain from osteoarthritis usually...
   - Gets worse
   - Stays the same
   - Gets better
   - Don't know

**Find out how comfortable you feel about deciding.**
Check ☑ the best answer

- Do you know enough on the benefits and harms of each option to make a choice?  □ Yes  □ No
- Are you clear about which benefits and harms matter most to you?  □ Yes  □ No
- Do you have enough support and advice from others to make a choice?  □ Yes  □ No
- Do you feel sure about the best choice for you?  □ Yes  □ No

If you answered ‘No’ to any of these, discuss with your practitioner.
Make a list of your next steps.

This information is not intended to replace the advice of a health care provider.
Answers for key facts: 1. Joint Injection; 2. NSAID pills; 3. Opioid painkillers; 4. 1; 5. Gets worse.

Content Editors: McGowan J, Toupin-April K, Hawker G, Rader T, Tugwell, P.
Conflict of interest declaration available from trader@uottawa.ca. Funded by the Canadian Institute for Health Research.
References to the evidence can be found at www.cochranemsk.org.
Publication Date 2011. Last reviewed: June 7, 2011.

* Adapted SURE test © O'Connor & Légaré
Physician receives a one page clinical summary of the patients answers.
LETS LOOK AT ‘GRADE’

Grades of Recommendation, Assessment, Development and Evaluation
Key features of GRADE
(Grades of Recommendation, Assessment, Development and Evaluation)

• Background on guidelines and GRADE
• Quality of evidence
• Going from evidence to recommendations
Key features of GRADE
(Grades of Recommendation, Assessment, Development and Evaluation)

• Background on guidelines and GRADE
• Quality of evidence
• Going from evidence to recommendations
Appraising evidence and developing recommendations

• To guide healthcare decision-making, a guideline (panel) should weight the desirable and undesirable consequences related to that decision for the relevant setting on the basis of the best available evidence and integrate values and preferences.

• Evidence = observations in the world

• Best available = implies hierarchy of evidence
Background

• WHO develops advice (recommendations) “all the time”
• Format differs, methods differ, much criticism
• May 2005 World Health Assembly resolution
  – WHO Director-General "to undertake an assessment of WHO's internal resources, expertise and activities in the area of health research, with a view to developing a position paper on WHO's role and responsibilities in the area of health research, and to report through the Executive Board to the next World Health Assembly."
WHO guidelines were considered

✓ not transparent

✓ not evidence based

Oxman et al, Lancet 2007;369:1883-9
In other words

- Systematic reviews
- Transparency about judgements
- Expert opinion confused with evidence
- Conflict of interest
- Adaptation of global guidelines to end users' needs
- Tension between time taken and when advice needed
- Resources
Which approach?

Recommendation for use of oral anticoagulation in patients with atrial fibrillation and rheumatic mitral valve disease

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Recommendation</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• B</td>
<td>Class I</td>
<td>➢ AHA</td>
</tr>
<tr>
<td>• A</td>
<td>1</td>
<td>➢ ACCP</td>
</tr>
<tr>
<td>• IV</td>
<td>C</td>
<td>➢ SIGN</td>
</tr>
</tbody>
</table>
GRADE Working Group

Grades of Recommendation Assessment, Development and Evaluation

• Aim: to develop (use and test) a common, transparent and sensible system for grading the quality of evidence and the strength of recommendations (over 100 systems)
• International group of guideline developers, epidemiologists, clinical researchers, public health officers, methodologists & clinicians from around the world (>300 contributors) – since 2000
GRADE Uptake

- World Health Organization
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- American Thoracic Society
- American College of Physicians
- European Respiratory Society
- European Society of Thoracic Surgeons
- British Medical Journal
- Infectious Disease Society of America
- American College of Chest Physicians
- UpToDate®
- National Institutes of Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- Cochrane Collaboration
- Infectious Disease Society of America
- Clinical Evidence
- Agency for Health Care Research and Quality (AHRQ)
- Partner of GIN
- Over 60 major organizations
Getting from evidence to recommendations - GRADE

Recommendations are judgments:
  – Quality of evidence
  – Trade off between benefits and harms
  – Values and preferences
  – Resource use

But judgments need to be based on the best available evidence and transparent
GRADE Quality of Evidence

In the context of making recommendations:

• The quality of evidence reflects the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation.
GRADE: quality of (a body of) evidence & recommendations

Clear separation, but *judgments* required:

1) 4 categories of quality of evidence:
   – methodological quality of evidence
   – likelihood of **bias** related to recommendation
   – by outcome and across outcomes

2) Recommendation: 2 grades – weak (aka conditional) or strong (for or against an action)?
   – balance of benefits and downsides
   – values and preferences
   – resource use
   – quality of evidence
# GRADE evidence profile

**Author(s):** YFY (update from CDSR version)

**Date:** 2009-10-09

**Question:** Should Antibiotics vs. no antibiotics be used for children with otitis media?

**Settings:** outpatient


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Pain at 24 hours (follow-up 24 hours)</td>
<td>5 randomized trials</td>
</tr>
<tr>
<td></td>
<td>223/624 (35.7%)</td>
</tr>
<tr>
<td>Pain at 2 to 7 days (follow-up 2-7 days)</td>
<td>10 randomized trials</td>
</tr>
<tr>
<td></td>
<td>228/1425 (16%)</td>
</tr>
<tr>
<td>Hearing - 1 month (follow-up 1 months; as measured by tympanometry)</td>
<td>4 randomized trials</td>
</tr>
<tr>
<td></td>
<td>153/467 (32.8%)</td>
</tr>
<tr>
<td>Hearing - 3 months (follow-up 3 months; as measured by tympanometry)</td>
<td>3 randomized trials</td>
</tr>
<tr>
<td></td>
<td>96/410 (23.4%)</td>
</tr>
<tr>
<td>Vomiting, diarrhea, or rash</td>
<td>5 randomized trials</td>
</tr>
<tr>
<td></td>
<td>110/690 (15.9%)</td>
</tr>
</tbody>
</table>

1. This is the median event rate.
2. Tympanometry surrogate for hearing
3. 95% CI interval includes clear benefit as well as harm
4. Relative study inconsistency is not present. However, the absolute rates of adverse effects ranged from 1 to 50% suggesting inconsistency.
<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at 24 hours (follow-up 24 hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
</tr>
<tr>
<td>Pain at 2 to 7 days (follow-up 2-7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
</tr>
<tr>
<td>Hearing - 1 month (follow-up 1 months; as measured by tympanometry)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious(^2)</td>
<td>serious(^3)</td>
<td>none</td>
</tr>
<tr>
<td>Hearing - 3 months (follow-up 3 months; as measured by tympanometry)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>serious</td>
<td>serious(^2)</td>
<td>no serious imprecision</td>
<td>none</td>
</tr>
<tr>
<td>Vomiting, diarrhea, or rash</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>very serious(^4)</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
</tr>
</tbody>
</table>

---

\(^1\) This is the median event rate.

\(^2\) Tymanometry surrogate for hearing

\(^3\) 95 CI interval includes clear benefit as well as harm

\(^4\) Relative study inconsistency is not present. However, the absolute rates of adverse effects ranged from...
## GRADE evidence profile

**Author(s):** YFY (update from CDSR version)
**Date:** 2009-10-09
**Question:** Should Antibiotics vs. no antibiotics be used for children with otitis media?  
**Settings:** outpatient

### Summary of findings

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>no antibiotics</td>
</tr>
<tr>
<td>Pain at 24 hours (follow-up 24 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 randomized trials</td>
<td>223/624</td>
<td>36.7% (^1)</td>
</tr>
<tr>
<td>Pain at 2 to 7 days (follow-up 2-7 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 randomized trials</td>
<td>228/1425</td>
<td>25% (^2)</td>
</tr>
<tr>
<td>Hearing - 1 month (follow-up 1 months; as measured by tympanometry)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 randomized trials</td>
<td>153/467</td>
<td>32.8%</td>
</tr>
<tr>
<td>Hearing - 3 months (follow-up 3 months; as measured by tympanometry)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 randomized trials</td>
<td>96/410</td>
<td>23.4%</td>
</tr>
<tr>
<td>Vomiting, diarrhea, or rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 randomized trials</td>
<td>110/690</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

\(^1\) This is the median event rate.  
\(^2\) Tympanometry surrogate for hearing  
\(^3\) 95% CI interval includes clear benefit as well as harm  
\(^4\) Relative study inconsistency is not present. However, the absolute rates of adverse effects ranged from 1 to 50% suggesting inconsistency.
# GRADE evidence profile

**Author(s):** YF Y (update from CDSR version)

**Date:** 2009-10-09

**Question:** Should Antibiotics vs. no antibiotics be used for children with otitis media?

**Settings:** outpatient


## Quality assessment

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Antibiotics</th>
<th>no antibiotics</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain at 24 hours (follow-up 24 hours)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>223/624 (35.7%)</td>
<td>36.7%¹</td>
<td>RR 0.9 (0.78 to 1.04)</td>
<td>37 fewer per 1000 (from 81 fewer to 15 more)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Pain at 2 to 7 days (follow-up 2-7 days)</strong></td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>228/1425 (16%)</td>
<td>25%²</td>
<td>RR 0.72 (0.62 to 0.83)</td>
<td>73 fewer per 1000 (from 44 fewer to 99 fewer)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Hearing - 1 month (follow-up 1 months; as measured by tympanometry)</strong></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious³</td>
<td>serious³</td>
<td>none</td>
<td>153/467 (32.8%)</td>
<td>158/400 (36.5%)</td>
<td>RR 0.89 (0.75 to 1.07)</td>
<td>40 fewer per 1000 (from 91 fewer to 26 more)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Hearing - 3 months (follow-up 3 months; as measured by tympanometry)</strong></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>serious</td>
<td>serious³</td>
<td>no serious imprecision</td>
<td>none</td>
<td>96/410 (23.4%)</td>
<td>96/398 (24.1%)</td>
<td>RR 0.97 (0.76 to 1.24)</td>
<td>7 fewer per 1000 (from 58 fewer to 58 more)</td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Vomiting, diarrhea, or rash</strong></td>
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</tr>
<tr>
<td>5</td>
<td>randomized trials</td>
<td>no serious limitations</td>
<td>very serious⁴</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>110/690 (15.9%)</td>
<td>83/711 (11.7%)</td>
<td>RR 1.38 (1.09 to 1.76)</td>
<td>44 more per 1000 (from 11 more to 89 more)</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

---

¹ This is the median event rate.

² Tymanometry surrogate for hearing

³ 95 CI interval includes clear benefit as well as harm

⁴ Relative study inconsistency is not present. However, the absolute rates of adverse effects ranged from 1 to 50% suggesting inconsistency.
Determinants of confidence

- **RCTs**
- **observational studies**

**5 factors that can lower quality**
1. limitations in detailed study design and execution (*risk of bias criteria*)
2. Inconsistency (*or heterogeneity*)
3. Indirectness (*PICO and applicability*)
4. Imprecision
5. Publication bias

**3 factors can increase quality**
1. large magnitude of effect
2. opposing plausible residual bias or confounding
3. dose-response gradient
Strength of recommendation

“The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects.”

• Strong or conditional
Implications of a strong recommendation

- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not.
- Clinicians: Most patients should receive the recommended course of action.
- Policy makers: The recommendation can be adapted as a policy in most situations.
Implications of a conditional/weak recommendation

• Patients: The majority of people in this situation would want the recommended course of action, but many would not

• Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making

• Policy makers: There is a need for substantial debate and involvement of stakeholders
### Systematic review

**Formulate question**
- Select outcomes
- Rate importance

**Outcomes across studies**

**Create evidence profile with GRADEpro**

**Rate quality of evidence for each outcome**
- High
- Moderate
- Low
- Very low

#### Grade overall quality of evidence

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

- Grade down
- Grade up

**Summary of findings & estimate of effect for each outcome**

#### Guideline development

**Grade recommendations**
- For or against (direction) ↓↑
- Strong or conditional/weak (strength)

- By considering balance of:
  - Quality of evidence
  - Balance benefits/harms
  - Values and preferences

- Revise if necessary by considering:
  - Resource use (cost)

**Formulate Recommendations (↓↑ | +...)**
- “We recommend using...” | “Clinicians should...”
- “We suggest using...” | “Clinicians might...”
- “We suggest not using...” | “Clinicians ... not...”
- “We recommend not using...” | “Clinicians should not...”
Conclusions

- Guidelines should be based on the **best available** evidence to be evidence based
- GRADE is the approach used by WHO and gaining acceptance internationally
  - combines what is known in health research methodology and provides a structured approach to improve communication
- Does not avoid judgments but provides framework
- Criteria for evidence assessment across questions and outcomes
- Criteria for moving from evidence to recommendations
- Transparent, systematic
  - four categories of quality of evidence
  - two grades for strength of recommendations
- Transparency in decision making and judgments is key
Thank you!

• Questions?
Desirable attributes of CPGs

- Validity
- Reliability
- Reproducibility
- Representative development
- Clinical applicability
- Clinical flexibility
- Clarity
- Meticulous documentation
- Scheduled review

Identifying evidence for guideline development

Possible methods include:

• Expert opinion
• Unsystematic reviews
• Systematic reviews.