Challenges in pediatric pharmacotherapy; development, growth, and suitability of therapy

- Faculty: Geert W. ‘t Jong
- Relationships with commercial interests:
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Objectives

- Understanding the lack of evidence, off-label use, and lack of proper formulations in pediatric pharmacotherapy
- Learning about the ontogeny of drugs in infants and children
- Learning about drug interactions, side effects, and pharmacogenomics
- Understanding appropriate prescribing, specifically antibiotics
Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing

• François-Marie Arouet de Voltaire (Voltaire) (1694-1778)
History of Drug Therapy for Children

• Drugs have been used to treat or relieve human disease since prehistoric times, largely conducted using what we currently consider folk or traditional medication and was largely anecdotal, unscientific, inexpensive and risky
  • *Drug News & Perspectives* 2010, 23(7)

<table>
<thead>
<tr>
<th>Country</th>
<th>Infant mortality rate$^a$</th>
<th>Child (under 5) mortality rate$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>165</td>
<td>257</td>
</tr>
<tr>
<td>Canada</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>China</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Cuba</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Haiti</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>
Providential Discoveries

• Two key discoveries in 1928 and 1935 changed this long established and uncomfortable paradigm
• 1928 - Sir Alexander Fleming takes a weekend off from his studies at Cambridge isolating *Staphylococcus*
• 1929 - Gerhard Domagk decides to see what azo dyes do in laboratory mice
• In the case of sulphonamides, these discoveries rapidly became part of clinical care, and change the care environment profoundly
Care Becomes Cure

• Rapid entry of drugs into clinical practice
• Major effect on practice - in UK, 1,000 children a year were saved from death from otherwise trivial infections
• “The major threats to human life were tuberculosis, tetanus, syphilis, rheumatic fever, pneumonia, meningitis, polio and septicaemia of all sorts - these worried us the way cancer, stroke and heart disease worried us today- the big problems of the 1930s and 1940s literally vanished” - Lewis Thomas
Two Tragedies

• One of the first formulations of sulphonamides used ethylene glycol as a vehicle (1937) which caused many cases of renal injury and 117 deaths, resulting in many of the regulations currently in place for drug safety.

• The Thalidomide tragedy of the early 1960’s pointed out the need for enhanced drug safety, notably for children but the response did not deliver the results that one might have expected.

• Kefauver-Harris amendments to the Food and Drug Act (passed unanimously by the House and Senate and signed into law by President Kennedy on October 10, 1962)
  • *Drug News & Perspectives* 2010, 23(7)
The Therapeutic Orphan

• Term coined by Dr. Harry Shirkey in 1968
• Referred to the lack of dosing, efficacy and safety data for drugs commonly used in children
• Despite the frequent paucity of data, drug use in children continued to expand, often with dramatic success
WE CAN’T TREAT CHILDREN LIKE ADULTS

- Increased Risk of Severe ADRs in Children
- >75% of approved drugs used in children are untested in pediatric populations
- Young children cannot evaluate or express their own response to medications
- Pediatric dosage forms not available
- Children metabolize drugs differently than adults
‘...no *adequate scientific* basis info for 80% of prescription medicines.’
Figure 1: Frequency of the Prescription of Drugs in a Children's Hospital during a Five-Week Period, According to Whether Use of the Drug Was Unapproved, Off Label, or Approved.

Published Pediatric Trials


Adverse Drug Events in Children

- While there are not many studies specific to children, the risk appears to be from 5 – 17%
- There is an increased risk for drug error
- In some groups of children and for some conditions, the risk of an ADE is significant
  - *BMC Med* 2013 Nov 7;11:237
Risk Factors for ADRs

- History of a previous ADR
- Large drug doses; measured formulations
- Polypharmacy
- Impairment of the organs of excretion (hepatic or renal dysfunction)
- Extremes of age
- Female sex
- Specific genetic polymorphisms
- General anaesthesia
History of a Previous ADR

• Suggested by a number of studies
• This is independent of drug class
• It speaks to the fact that immune and drug clearance mechanisms while having much in common on higher levels have considerable variability at the functional level
Large Drug Doses

- Alludes to the use of microgram rather than milligram dosing
- Clearly seen in child health care with respect to salbutamol (albuterol); systemic delivery requires much higher doses and is associated with significantly higher ADRS rates than targeted topical delivery

- Formulations often imprecise or hard to measure
- Tablet splitting, solutions etc.
Polypharmacy

• More than simple math (i.e. 5% +5% +5% = 15%)
• Modeling suggests that once the number of drugs exceeds 8 the chances of an adverse drug effect is nearly 100%
• Highly germane to certain groups of children
Impairment of the organs of excretion (hepatic or renal dysfunction)

• Speaks to a key tenet of Developmental Pharmacology, that children are not small adults
• Drug clearance is well known to be subject to ontogeny, notably in infancy and specifically in pre-term infants
• The impact of ontogeny on activation-mediated events is less well appreciated
Figure 1  Schematic depiction of drug-metabolising enzyme ontogeny (3). CYP, cytochrome P450; TPMT, thiopurine S-methyltransferase; UGT, UDP-glucuronosyltransferases; SULT, sulfotransferases; FMO, flavin-containing mono-oxygenase.
Extremes of age

- Children, infants – notably premature infants – have altered clearance mediated by ontogeny and also tend to receive a relatively large number of medications
Female Sex

• For older children (notably adolescents) drug utilization for girls and boys is not the same
• That being said, when this is corrected for being female is an independent risk factor for adverse drug reactions
• May be related to immunological differences between female and male immune function
• Similar observations for carriage of certain viral infections
Adolescents

- Changes hormonal influence
- Changes body composition
- Changes in disease processes
- Changes in adherence
- Changes in metabolism
Specific genetic polymorphisms

• While variations in risk have been recognized since Pythagoras (fava beans) and Sir Archibald Garrod over the past two decades is has been clearly demonstrated that genetics influences drug safety, for some drugs, in a very significant manner
Mother’s Genotype:

- **CYP2D6 gene duplication**
  - Increased formation of morphine

- **Homozygous for UGT2B7*2/*2**
  - Potentially increased formation of morphine-6-glucuronide

- **Outcome:**
  - Accumulation of morphine in breast milk
  - Breast milk fed to infant
  - Accumulation of morphine in infant caused CNS depression, respiratory failure, and death
  - Infants do not express CYP2D6 and UGT2B7 and do not metabolize morphine
Adverse Effects of Well Intentioned Acts

• Many hospitals in North America have abandoned the use of codeine
• The alternate opiate selected has been variable
  • Morphine, Hydrocodone, Oxycodone
• This has been accompanied by some interesting messaging
  • MORPHINE IS SAFER
• Although many clinicians have stopped using codeine this has not abolished opiate toxicity
• Increasing number of cases of morphine-related morbidity
• Many questions as to optimal therapy
Cardiotoxicity highest in first year but continues to increase over time in high risk groups

- High Risk (17%)
  - HR (95% CI): 29.4 (12.4 – 69.4)
  - $P_{\text{trend}} = 6.7 \times 10^{-25}$

- Intermediate Risk (37%)
  - HR (95% CI): 6.6 (2.7 – 15.8)

- Low Risk (46%)
General Anaesthesia

- ADRIC Project
  - Very large study at Alder Hey of children admitted to an academic child health care centre
  - Prospective
  - Careful case definition
  - Identifies a 17% risk of an ADR

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Risk factors for ADRs assessed by multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariate</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age on admission (in years)</td>
<td>1.06 (1.04-1.07)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>0.93 (0.80-1.08)</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>1.25 (1.22-1.28)</td>
</tr>
<tr>
<td>Received a GA</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>6.38 (5.30-7.68)</td>
</tr>
<tr>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.89 (1.36-2.63)</td>
</tr>
</tbody>
</table>
One-off or Key Missed Risk Factor?

• 2% chance of death if you have a GA
• Anaesthetic risk probably related to a combination of other factors
• Many children who receive general anaesthesia are:
  • Very young (Extremes of age)
  • Altered clearance (Age or disease)
  • Are on therapy with a number of drugs (Polypharmacy)
  • Are relatively ill
Drug Errors – A Special Risk for Children

- Wrong drug
- Wrong dose
- Special cases in childhood – 10 fold Errors

<table>
<thead>
<tr>
<th>Variables Associated with Medication Errors - Univariate analysis</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Trainee vs staff*</td>
<td>1.48</td>
<td>(1.03-2.11)</td>
</tr>
<tr>
<td>Beginning vs end of year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trainees*</td>
<td>1.67</td>
<td>(1.06-2.64)</td>
</tr>
<tr>
<td>Staff</td>
<td>1.30</td>
<td>(0.81-2.08)</td>
</tr>
<tr>
<td>All physicians</td>
<td>1.33</td>
<td>(0.95-1.86)</td>
</tr>
<tr>
<td>Severity of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe vs mild*</td>
<td>2.53</td>
<td>(1.18-5.41)</td>
</tr>
<tr>
<td>Moderate vs mild</td>
<td>1.48</td>
<td>(1.00-2.17)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
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<tr>
<td>&lt;3m</td>
<td>0.14</td>
<td>(0.03-0.57)</td>
</tr>
<tr>
<td>3m – 5y*</td>
<td>1.80</td>
<td>(1.20-2.61)</td>
</tr>
<tr>
<td>6-11y</td>
<td>0.96</td>
<td>(0.68-1.34)</td>
</tr>
<tr>
<td>12-18y</td>
<td>0.55</td>
<td>(0.30-0.91)</td>
</tr>
<tr>
<td>Waiting time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 hours</td>
<td>0.88</td>
<td>(0.54-1.43)</td>
</tr>
<tr>
<td>Weekends vs weekdays*</td>
<td>1.48</td>
<td>(1.04-2.11)</td>
</tr>
<tr>
<td>Patient seen between 4am &amp; 8am*</td>
<td>2.40</td>
<td>(1.27-4.52)</td>
</tr>
</tbody>
</table>

* p ≤ 0.05

Graph showing the percentage of errors and number of patients seen over time.
Electronic Order Entry

• Over the past decade electronic order entry has become routine
• Most of these systems will identify drug errors such as tenfold errors
• This is likely to change the types of drug errors
• However, it is not likely to abolish them
• In fact, this may change simple errors to arcane ones
Challenges – Drug Use in Children

- On average, Canadian children take 3.9 prescriptions per year; this is not a uniform distribution; 20% of children account for 70% of drug use
  - Paed Child Health 2003; 8 Suppl A

- Adolescents constitute one of the leading demographics for growth in prescription drug use in the US

- 30% of American children aged 10 – 18 take at least one prescription for control of a chronic condition
  - Medco Health Corp Annual Report 2010
Drug Use by US Patients (2010)

Pediatrics Vol. 130 No. 1 July 1, 2012
# Top 12 Drugs Prescribed to US Children

<table>
<thead>
<tr>
<th>Drug Molecule</th>
<th>Pediatric Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>18,292,768</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>10,171,046</td>
</tr>
<tr>
<td>Albuterol</td>
<td>7,343,063</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>4,454,926</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>4,308,857</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>4,009,275</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>3,144,844</td>
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<tr>
<td>Prednisolone sodium phosphate</td>
<td>2,932,124</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2,887,667</td>
</tr>
<tr>
<td>Montelukast</td>
<td>2,629,494</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>2,568,202</td>
</tr>
<tr>
<td>Codeine phosphate/acetaminophen</td>
<td>1,993,396</td>
</tr>
</tbody>
</table>

*Pediatrics Vol. 130 No. 1 July 1, 2012*
The Future

- Although there are many questions, there is considerable reason for optimism
- New tools and techniques offer great promise
  - Advances in clinical trial design
  - Pharmacometric modeling
  - New biomarkers, sampling techniques
  - Collaboration, networks
- The greatest challenge may be in providing access to the average clinician to this promise
Ambulatory ABx

• Est. 50 million Abx Rx annually
  • ~20% of all visits
  • ~50% (24.6 million) received broad-spectrum (azithromycin)
  • 70% for respiratory conditions
    • 23% for respiratory conditions not needing abx...
Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011

- NAMCS/NHAMCS survey data, 2010/11
  - Conditions Abx always indicated (CAP, UTI)
  - May be...(sinusitis, pharyngitis)
  - Not indicated (acute bronchitis)

- Rates of Rx per 1000 people
- 12.6% of all visits = Abx prescription
  - Sinusitis → 50/1000 people

- For all ages & Dx: 506 Rx/1000 people
  - Only 353 Rx estimated to be appropriate
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rates per 1000 Population</th>
<th>Potential Reduction in Annual Antibiotic Prescription Rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2010-2011 Weighted Mean Annual Rate of Antibiotic Prescriptions (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All acute respiratory conditions(^b)</td>
<td>421 (369 to 473)</td>
<td>-34</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>65 (51 to 79)</td>
<td>-9</td>
</tr>
<tr>
<td>Suppurative otitis media</td>
<td>154 (131 to 177)</td>
<td>-10</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>91 (76 to 105)</td>
<td>-34</td>
</tr>
<tr>
<td>Asthma or allergy; bronchitis or bronchiolitis; influenza; nonsuppurative otitis media; viral URI; and viral pneumonia(^e)</td>
<td>90 (71 to 108)</td>
<td>-100</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22 (16 to 27)</td>
<td>0</td>
</tr>
<tr>
<td>Other conditions(^d)</td>
<td>225 (197 to 252)</td>
<td>-20</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (17 to 28)</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous bacterial infections</td>
<td>20 (13 to 26)</td>
<td>0</td>
</tr>
<tr>
<td>Remaining other conditions(^g)</td>
<td>182 (160 to 205)</td>
<td>-25</td>
</tr>
<tr>
<td>Total(^h)</td>
<td>646 (571 to 721)</td>
<td>-29</td>
</tr>
</tbody>
</table>
Antibiotics and Sore Throat

Figure. Antibiotic Prescribing to Adults With Sore Throat in the United States, 1997-2010

A

All Visits

Emergency Department

Primary Care

Proportion of Sore Throat Visits, %

2-Year Period Ending in Year Above


JAMA Internal Medicine   January 2014   Volume 174, Number 1
Antibiotic Prescribing by Physicians Versus Nurse Practitioners for Pediatric Upper Respiratory Infections

Elisabeth H. Ference, MD, MPH¹, Jin-Young Min, MD¹, Rakesh K. Chandra, MD², James W. Schroeder, Jr., MD¹, Jody D. Ciolino, PhD⁴, Amy Yang, MS⁵, Jane Holl, MD, MPH⁴,⁶,⁷, and Stephanie Shintani Smith, MD, MS¹,⁶

Figure 1. Trends in percentage of visits with antibiotic prescription for pediatric patients with upper respiratory infections (URIs), by provider type and diagnosis.
Appropriateness of antibiotic prescribing for upper respiratory tract infections in general practice: Comparison between Denmark and Iceland

Nanna Rún Sigurðardóttir\textsuperscript{a}, Anni Brit Sternhagen Nielsen\textsuperscript{a}, Anders Munck\textsuperscript{b} and Lars Bjerrum\textsuperscript{a}

\textsuperscript{a}Section and Research Unit for General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; \textsuperscript{b}Audit Project Odense, Research Unit of General Practice, University of Southern Denmark, Odense, Denmark
Antibiotic Prescription Pattern for Viral Respiratory Illness in Emergency Room and Ambulatory Care Settings

M. Nadeem Ahmed, MD, PhD, Maria M. Muyot, PhD, Shahana Begum, MS, Patti Smith, RN, BSN, Charletta Little, BS, and Fernando J. Windemuller, MD

Figure 4. Rate of antibiotic prescriptions by emergency room physicians, family physicians, and pediatricians by different age-groups
Figure. Percentage of Visits in Which Antibiotics Were Prescribed That Are First-line and Non-First-line for Otitis Media, 2010-2011

A. Otitis media
B. Sinusitis
C. Pharyngitis

Choose wisely.

Antibiotics aren’t always the right tool for the job.

Antibiotics aren’t effective in treating most colds, coughs, or flu. Be #healthcareful – talk to your doctor about what you need, and what you don’t. To learn more, visit choosingwisely.nl.

GET SMART
Know When Antibiotics Work

Antibiotics are strong medicines. Keep them that way. Prevent antibiotic resistance. Antibiotics don’t fight viruses; they fight bacteria. Using antibiotics for viruses can put you at risk of getting a bacterial infection that is resistant to antibiotic treatment. Talk to your healthcare provider about antibiotics, visit www.cdc.gov/getsmart or call 1-800-CDC-INFO to learn more.

Antibiotic Resistance
Twitter Chats
November 18, 2014

Join @CDC_eHealth 3 pm EST #SaveAbx

Join the 24 hour global chat #AntibioticDay

www.cdc.gov/getsmart/week

WARNING: Antibiotics don’t work for viruses like colds and the flu. Using them for viruses will NOT make you feel better or get back to work faster.
A Psychological Dilemma?

Box. The Imbalance in Factors Related to Antibiotic Prescribing

Factors Driving Antibiotic Prescribing: Immediate and Emotionally Salient
- Belief that a patient wants antibiotics
- Perception that it is easier and quicker to prescribe antibiotics than explain why they are unnecessary
- Habit
- Worry about serious complications and "just to be safe" mentality

Factors Deterring Antibiotic Prescribing: More Remote and Less Emotionally Salient
- Risks of adverse reactions and drug interactions
- Recognizing the need for antibiotic stewardship
- Desire to deter low-value care and decrease unnecessary health care spending
- Prefer to follow guidelines
How do we tip the balance?
• 5 Los Angeles community clinics, adult patients
• Randomized to either:
  • Signed-commitment-poster in exam room x 12 weeks
  • vs. no poster in office
• Lay-person explanation to why using less Abx
• Baseline & intervention period Abx data analysis
• Patients with an acute respiratory infection (ARI) diagnosis
  • frame with one influenza season
• Looked at ARI Dx for which Abx inappropriate and appropriate
~20% ↓ Inappropriate Use

- MDs & NPs; in practice x 17.6 years
• Influence of interpersonal factors
  • Desire to remain “publically” consistent
  • To avoid disapproval by their peers
  • Commitment prompts people to later justify that behaviour
• Good way to have a low-cost sustained active engagement
• MD may perceive less patient demand even if none
Outpatient Audit & Feedback

• Network of 25 primary care pediatric practices
  • Cluster RCT
  • 9 control grps vs.9 intervention grps
  • Common EMR
• Clinical education sessions q4 months + 1 year personalized, quarterly audit & feedback on Abx Rx’s
• Not looking at Abx “Yes vs. No”, but rather **broad vs. narrow spectrum use**.
  • CAP; sinusitis; pharyngitis; “viral infection”

Gerber JS et al. JAMA 2013;309(22):2345-2352
Figure 2. Standardized Rates of Broad-Spectrum Antibiotic Prescribing at Acute Care Office Visits Over Time

$P=.01$
Durability & A Lasting Impression

Gerber JS et al. JAMA
2014(312):2569-70
Figure. Standardized Rates of Broad-Spectrum Antibiotic Prescribing Before, During, and After Audit and Feedback
Pediatrician Perceptions

• Ignoring of reports; distrust
  • Didn’t believe them
  • Data integrity

• “Gaming” behaviour
  • Adding bacterial Dx codes during ARTI

• Liked idea of guidelines, just not following them...

• Parental pressure

• Perceptions of antibiotic overuse
  • *It’s not me, it’s them...*
Meeker D et al. JAMA 2016;315(6);562-70

- RCT in 47 clinics, ~250 MDs
- Rx rates for Abx-inappropriate visits
- Effect of 3 behavioral interventions
  - Suggested alternatives
  - Accountable justification
  - Peer comparison
- 0, 1, 2, or 3 of these
• Decreased in all groups
• Significant only in accountability + peer comparison group

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**Figure 2. Adjusted Rates of Antibiotic Prescribing at Primary Care Office Visits for Antibiotic-Inappropriate Acute Respiratory Tract Infections Over Time**

**A** Accountable justification

**B** Peer comparison

**C** Suggested alternatives

Prescribing rates for each intervention are marginal predictions from hierarchical regression models of intervention effects, adjusted for concurrent exposure to other interventions and clinician and practice random effects. Error bars indicate 95% CIs. Model coefficients are available in eTable 3 in Supplement 2.
Urine C&S Follow-up

• QI study in Pediatric Urgent Care Network
• Improve F/U of negative UCs
• Multidisciplinary task force
  • Routine protocol
  • Documentation in EMR
• Monitored return visits for UTI x 14 days
FIGURE 2
The Shewhart p-chart demonstrates the monthly antibiotic discontinuation rates for patients who were treated empirically for a UTI but had a negative urine culture result. Interventions are indicated below the chart with arrows designating the time each intervention occurred.
Conclusion

Pediatric pharmacotherapy still hampered by
- Insufficient evidence
- Lack of appropriate formulations

Risk of ADRs high in children
- Please refer to my clinic for ADR characterization

Children’s Clinic, Children’s Hospital

Antibiotics prescribing in outpatient settings has to improve
Adultes, enfants, à chacun son médicament

Nous ne sommes pas des adultes en miniature !
Efficacy of Proton-Pump Inhibitors in Children With Gastroesophageal Reflux Disease: A Systematic Review

abstract

INTRODUCTION: Use of proton-pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD) in children has increased enormously. However, effectiveness and safety of PPIs for pediatric GERD are under debate.

OBJECTIVES: We performed a systematic review to determine effectiveness and safety of PPIs in children with GERD.

METHODS: We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for randomized controlled trials and crossover studies investigating efficacy and safety of PPIs in children aged 0 to 18 years with GERD for reduction in GERD symptoms, gastric pH, histologic aberrations, and reported adverse events.

RESULTS: Twelve studies were included with data from children aged 0–17 years. For infants, PPIs were more effective in 1 study (compared with hydrolyzed formula), not effective in 2 studies, and equally effective in 2 studies (compared with placebo) for the reduction of GERD symptoms. For children and adolescents, PPIs were equally effective (compared with alginates, ranitidine, or a different PPI dosage). For gastric acidity, in infants and children PPIs were more effective (compared with placebo, alginates, or ranitidine) in 4 studies. For reducing histologic aberrations, PPIs showed no difference (compared with ranitidine or alginates) in 3 studies. Six studies reported no differences in treatment-related adverse events (compared with placebo or a different PPI dosage).

CONCLUSIONS: PPIs are not effective in reducing GERD symptoms in infants. Placebo-controlled trials in older children are lacking. Although PPIs seem to be well tolerated during short-term use, evidence supporting the safety of PPIs is lacking. Pediatrics 2011;127:925–935