Off-Label Utilization of Antibiotics in Pediatrics

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Declaration of Interests

Presently on the Speakers’ Bureau

• Wyeth- piperacillin-tazobactam, pneumococcal vaccine
• MSD- rotavirus and HPV vaccine
• GSK- quality medicines
• Natrapharm- quality medicines
• Astra- pk/pd module
• Pediatrica- Cefixime module
• Westmont- ASK module
THOUGHTS FOR TODAY

• DEFINITIONS
• EXTENT OF OFF-LABEL USE
• WHY DOES IT OCCUR
• ISSUES- problems, legal
• ANTIBIOTIC EXAMPLES- Quinolones, Carbapenems, Daptomycin, Tigecycline, Tetracyclines, Macrolides
  (Characteristics, Status, Why off-label, acceptable off-label uses, dose)
• WHAT SHOULD WE DO NOW
OFF-LABEL USE OF REGISTERED MEDICINES

• refers to use that is not included in the approved label. (AAP Statement on THE USE OF DRUGS NOT DESCRIBED IN THE PACKAGE INSERT LABEL, Pediatrics 2002;10:181-183)

• prescriptions of registered medicine for a use that is not included in the prescribing information or that is disclaimed in the approved information (Working Group of NSW Therapeutics Advisory Group Inc, September 2003)
Unlicensed drug use

• Use of a drug without a product license or marketing authorization
# Reasons for Off-Label Use of Registered Medicines

<table>
<thead>
<tr>
<th>Reason Use is Off-label</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Low doses of amoxicilin for resp tract infection</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>valaciclovir – “safety and effectiveness in children has not been established”</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>azithromycin, used for anti-inflammatory effect in cystic fibrosis</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>tobramycin injection used as inhalation in cystic fibrosis</td>
</tr>
</tbody>
</table>
Why does it occur?

package insert/label - provide all info judged necessary for drug to be used safely and effectively

Therapeutic orphan

• For years, children were excluded from clinical trials - prudent to not to expose children to molecules
Why does it occur?

• many drugs marketed without pediatric safety and efficacy data, or pediatric formulations

• Pediatric clinical trials are costlier and logistically more challenging to undertake
EXTENT OF THE PROBLEM
<table>
<thead>
<tr>
<th>Country (year)</th>
<th>Setting</th>
<th>Methodology</th>
<th>Size</th>
<th>Unlicensed and off-label use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands (2000), Jong</td>
<td>Pedia hosp</td>
<td>Prospec, 5 wks</td>
<td>238 children, 2139 presc</td>
<td>Children: 92% Presc: 66%</td>
</tr>
<tr>
<td>Europe (2000) Conroy</td>
<td>5 gen peda wards in 5 countries</td>
<td>Prospec, 1 mo</td>
<td>624 children, 2262 presc</td>
<td>Children: 67% Presc: 46%</td>
</tr>
<tr>
<td>Israel (2000), Gavrilov</td>
<td>Gen pedia ambu hosp unit</td>
<td>Prospec, 2 mos</td>
<td>132 children, 222 presc</td>
<td>Children: 42% Presc: 42%</td>
</tr>
<tr>
<td>Australia (2000) Turner</td>
<td>2 gen ped and pedia surg wards</td>
<td>Prospec, 1 mo</td>
<td>200 children, 735 presc</td>
<td>Children: 36% Presc: 16%</td>
</tr>
</tbody>
</table>
### Most commonly used unlicensed and Off label drugs in General Pediatrics Clinic

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total No. of Presc</th>
<th>No. (%) of unlicensed or off label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>21</td>
<td>11 (52.4%)</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>8</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>10</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>21</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>6</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>5</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>

### Unlicensed and off label prescriptions

<table>
<thead>
<tr>
<th></th>
<th>No. of Presc</th>
<th>% of Total no. of prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlicensed</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Off label</td>
<td>40</td>
<td>27.2%</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>28.5%</td>
</tr>
</tbody>
</table>

### Categories and frequency (%) of off label medications use in PGH-OPD Gen. Pediatrics

<table>
<thead>
<tr>
<th>Category of off label use</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different indication</td>
<td>32 (62.7%)</td>
</tr>
<tr>
<td>Different dose</td>
<td>13 (25.5%)</td>
</tr>
<tr>
<td>Inappropriate age</td>
<td>6 (7.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
</tr>
</tbody>
</table>

### Incidence of Off-label Antibiotics Prescriptions (City Hospital in Russia)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>49%</td>
</tr>
<tr>
<td>Toddlers</td>
<td>28%</td>
</tr>
<tr>
<td>School-age</td>
<td>10%</td>
</tr>
<tr>
<td>Teenagers</td>
<td>11%</td>
</tr>
</tbody>
</table>

Ratchina, et al. Unlicensed and Off-label antibiotic use in a paediatric City hospital in Russia, presented at 2008 ESCMID, Spain
Reason for Off-label Antibiotics Prescriptions (City Hospital in Russia)

<table>
<thead>
<tr>
<th>Reason</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unproved indication</td>
<td>38</td>
</tr>
<tr>
<td>Diff dose and frequency of administration</td>
<td>36</td>
</tr>
<tr>
<td>Age limitations</td>
<td>26</td>
</tr>
</tbody>
</table>

Ratchina, et al. Unlicensed and Off-label antibiotic use in a paediatric City hospital in Russia, presented at 2008 ESCMID, Spain
## Use of Antibiotics per Age Group with Respect to Dosage (Scotland Primary Care setting)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Low Dose</th>
<th>High dose</th>
<th>Total no. of antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>11.8%</td>
<td>2.5%</td>
<td>9767</td>
</tr>
<tr>
<td>5-11</td>
<td>19.9%</td>
<td>1.4%</td>
<td>8055</td>
</tr>
<tr>
<td>12-16</td>
<td>30%</td>
<td>0.3%</td>
<td>6089</td>
</tr>
<tr>
<td>Total</td>
<td>19.2%</td>
<td>1.6%</td>
<td>23,911</td>
</tr>
</tbody>
</table>

Problems Resulting from off label/unlicensed Drug Use

1. Lack of appropriate formulations
   - only capsule or tablet formulations
   - need extemporaneous preparations;
   - usually add to juice or syrup
   - still need kinetic studies
   - may change absorption, metabolism, efficacy
Problems Resulting from off-label /unlicensed Drug Use

2. Choice of dose – inaccurate pharmacokinetics different in neonates and children may cause: underdosing/toxic dose leading to: lack of efficacy, toxicity

1950’s- Acute toxicity to CHLORAMPHENICOL- Gray baby syndrome caused by immature glucoronidation- USA and Europe
Problems Resulting from off label/unlicensed Drug Use

3. Adverse drug reactions

CHILDMREN \neq SMALL ADULTS

Pharmacodynamics/ kinetics are different
Developmental changes, responses unique
to children
ex. tetracycline
### Risk of ADRs related to off-label drug use (office practice in France)

<table>
<thead>
<tr>
<th>Off-label status</th>
<th>Patients N=1419</th>
<th>Percentage of total patients</th>
<th>Relative Risk of ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total off label</td>
<td>601</td>
<td>42.35</td>
<td>3.44</td>
</tr>
<tr>
<td>Contraindication</td>
<td>24</td>
<td>1.69</td>
<td>5.38</td>
</tr>
<tr>
<td>Different indication</td>
<td>391</td>
<td>27.55</td>
<td>4.42</td>
</tr>
<tr>
<td>Higher dose</td>
<td>89</td>
<td>6.27</td>
<td>1.65</td>
</tr>
<tr>
<td>Lower dose</td>
<td>105</td>
<td>7.4</td>
<td>1.12</td>
</tr>
<tr>
<td>Age</td>
<td>45</td>
<td>3.17</td>
<td>1.71</td>
</tr>
<tr>
<td>Route of admin</td>
<td>18</td>
<td>1.27</td>
<td>3.71</td>
</tr>
<tr>
<td>Inadvisable co-prescription</td>
<td>29</td>
<td>2.04</td>
<td>No ADR</td>
</tr>
</tbody>
</table>

Problems Resulting from off label/unlicensed Drug Use

4. Medication errors
   - Possible to measure 10-100 times overdose for a small baby when there is no dosage strength available

5. Product information- lacks information in which the caregiver may be alarmed

6. Lack of postmarketing surveillance
   - Pharmacovigilance for ADRs
Problems Resulting from off label/unlicensed Drug Use

7. Interface issues
   - Interruption of drug supply

8. Increased Antimicrobial resistance specially for too low doses
Other side of the coin

- Wrong to assume all off-label use is bad/wrong
- Lack of pediatric labeling does not mean that the drug is harmful, but simply lacks the clinical trial which satisfy FDA REQUIREMENTS

Statements from UK and US professional bodies highlight that unlicensed and off label drug use is a vital part of children’s drug therapy

(AAP Statement on THE USE OF DRUGS NOT DESCRIBED IN THE PACKAGE INSERT LABEL, Pediatrics 2002;10:181-183)
Other side of the coin

- Does not imply disapproval or the practice is improper
- Prerogative of physicians to use their professional judgment in treating patients
- Possible, no other available product for use in children specially in life-threatening situations

(AAP Statement on THE USE OF DRUGS NOT DESCRIBED IN THE PACKAGE INSERT LABEL, Pediatrics 2002;10:181-183)
Laying Down the Law

- BFAD/FDA- regulates the manufacturing, labeling and promotion of drugs
- It does not regulate the use of drugs by physicians
- It is not illegal to prescribe drugs OFF LABEL
- Responsibility of prescribing will lay in the prescriber
A doctor may be accountable for the negligent use of a drug whether or not the FDA has approved the use of that drug.

A prescriber could be subject to claims of malpractice if he/she denied a patient the best potential treatment just because it was unlicensed or off label.

(AAP Statement on THE USE OF DRUGS NOT DESCRIBED IN THE PACKAGE INSERT LABEL, Pediatrics 2002;10:181-183)
ANTIBIOTIC EXAMPLES

Quinolones
Carbapenems
Daptomycin
Tigecycline/Tetracycline
Macrolides
Quinolones

Characteristics

**synthetic fluorinated analogs of nalidixic acid**

- bind to the A subunit of DNA gyrase (topoisomerase) and prevent supercoiling of DNA, thereby inhibiting DNA synthesis
### Antimicrobial Spectrum - Quinolones

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid</td>
<td>Urinary pathogens, Shigella</td>
</tr>
<tr>
<td>Ciprofloxacin, Ofloxacin</td>
<td>Gram negative(Salmonella, Shigella, E. coli, other Enterobacteriaceae, Pseudomonas, few gram positive</td>
</tr>
<tr>
<td>Levofloxacin, Moxifloxacin</td>
<td>Same as Cipro +Respiratory and gram positive pathogens; less activity for Pseudomonas compared to Cipro</td>
</tr>
</tbody>
</table>
Quinolones

Status: NOT APPROVED FOR CHILDREN <18 YRS

Why off-label: studies in juvenile animals, specially canines showed arthropathies/cartilage toxicity

- fluid-filled blisters and erosions of the articular cartilage; degenerative lesions with fissures in the weight-bearing cartilage
Quinolones studies in children

>1700 children used Ciprofloxacin for an acute illness (in General Research Database, Group Health Cooperative of Puget Sound Database)
- no report of joint toxicities or kidney problems

634 Children treated with Ciprofloxacin on compassionate use
1.3% reported arthralgia, mostly self-limited and occurred exclusively in cystic fibrosis patients

Quinolones studies in children

Cipro vs pivmecillinam for shigellosis
Joint pain: cipro -18%
pivmecillanem (22%)

>2500 children from Bayer global drug safety database
arthralgia for smaller subgroup
cipro 1% vs control 2%
Maximum risk of chostochondritis= 0.04%
1 in 2348

Langley, Paediatr Child Health 2001; 6: 322-324
Acceptable Off label uses of Quinolones

Ciprofloxacin
- Shigellosis
- Switch therapy for Pseudomonas aeruginosa
- Exacerbations of cystic fibrosis
- MDR-TB
- Other infections resistant to beta-lactams and other classes

Levofloxacin/Moxifloxacin
- MDR-TB
# Quinolone Dose for Children

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Neonates: 7-40 mg/kg/day IV div q 12 hrs Children: oral: 20-30 mg/kg/day div q 12 hrs max dose: 1.5g/day IV: 20-30 mg/kg/day div q 12 hrs max dose: 800mg/day</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>6mos-5yrs: 10 mg/kg/dose q 12 hrs ≥5 yrs: 10 mg/kg/dose q 24 hrs max dose: 500 mg</td>
</tr>
</tbody>
</table>

Carbapenems

Spectrum of activity- most active beta-lactams against a wide variety of bacteria including G(+) MSSA only, G(-), and anaerobic bacteria; reserved for multi-drug resistant bacteria

Differences

Ertapenem- no activity for Pseudomonas aeruginosa

• Meropenem- less seizures reported; slightly better activity gram negative; good activity for Pseudomonas aeruginosa

• Imipenem- not recommended for CNS infections; slightly better activity for gram positive; good activity for Pseudomonas aeruginosa
Carbapenems- PRESENT STATUS

Ertapenem: approved for 3mos onwards for intraabdominal infections, CAP, complicated UTI, complicated skin and skin structures infection

Meropenem: approved for 3mos onwards for multi-drug resistant infections including CNS infections

Imipenem: approved for 3mos onwards for multi-drug resistant infections except CNS infections
Off label Uses-For neonates wherein only drug sensitive is the carbapenem

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Neonatal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>data (?)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&lt;7 days: 20mg/kg/dose q 12 hrs&lt;br&gt; &gt;7 days: 1200-2000g: 20mg/kg/dose q 12 hrs&lt;br&gt; 2000g: 20mg/kg/dose q 8 hrs</td>
</tr>
<tr>
<td>Imipenem+Cilastatin</td>
<td>0-4 wks: &lt;1200g : 20 mg/kg/dose q 18-24 hrs&lt;br&gt; ≤7 days: 1200-1500g: 40 mg/kg/day div q 12 hrs&lt;br&gt; ≥1500 g: 50 mg/kg/day div q 12 hrs&lt;br&gt; &gt;7 days: 1200-1500g: 40 mg/kg/day div q 12 hrs&lt;br&gt; &gt;1500 g: 75 mg/kg/day div q 12 hrs&lt;br&gt; 4 wks to 3mos: 100mg/kg/day div q 6 hrs</td>
</tr>
</tbody>
</table>
Daptomycin

- 1st cyclic lipopeptide, natural
- product from Streptomyces pristinaspiralis
- Unique mode of action, binds to cell membrane causing depolarization; causes inhibition of protein, DNA and RNA synthesis
- no cross resistance with other antimicrobials
- Rapidly bactericidal for gram positive organisms, including MRSA, VISA, VRSA
Daptomycin

- Indicated for treatment of complicated skin and skin structure infections, bacteremia and endocarditis MRSA, VISA, VRSA
- Not indicated for CAP - mortality higher in patients receiving daptomycin than comparator agents
- Daptomycin interacts with surfactants in the lungs leading to inhibition of antibacterial activity
Daptomycin

- **Current Status:** not approved for children
- **Why off label:** pharmacokinetics not well established
- Ongoing Phase 1-4 clinical trials in children
  - small trial- showed no adverse effect

**Acceptable Off-label use in children**
- MRSA, not responsive to vancomycin, linezolid,

**Dose:**
- 2-17 yrs: 4-6 mg/kg/dose IV infusion over 30 min once daily
Tigecycline

- injectable glycyldycline antibacterial
- semisynthetic derivatives of tetracycline antibiotics with a glycylamido moiety attached at the 9 position of the D-ring of the base molecule.
- modification maintains the antibacterial effect but provides stability against mechanisms of tetracycline resistance
- bacteriostatic
<table>
<thead>
<tr>
<th></th>
<th>Susceptible in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive</strong></td>
<td>Staph aureus (including MRSA), Staph epidermidis (including MRSE), Group B strep,</td>
</tr>
<tr>
<td></td>
<td>Strep pyogenes, E. faecalis (including vancomycin resistant), E. faecium (including</td>
</tr>
<tr>
<td></td>
<td>vancomycin resistant)</td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td>Acinetobacter baumanii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter</td>
</tr>
<tr>
<td></td>
<td>cloacae, E. coli, K oxytoca, K pneumoniae, Serratia, Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td>Bacteroides, including fragilis, Prevotella spp, Clostridium perfringens, Peptostrept</td>
</tr>
<tr>
<td></td>
<td>tococcus</td>
</tr>
</tbody>
</table>
Tigecycline

**Current Status**: not approved for patients <18 yrs old

**Why Off label**: tetracycline derivative; expected to have same ADRs

**Possible Off-label use**: polymicrobial infection with multidrug resistant gram positive and gram negative infection

**Dose**: no kinetic data; wild guess
12yrs and above: 100 mg initial dose, then 50 mg every 12 hrs IV infusion over 30-60 min
Tetracyclines

- **Current status:** not approved for children <8 yrs
- **Why Off label:** ADRs in less than 8 yrs teeth and bones - discoloration of teeth, hypoplasia of the enamel; binds to Ca and may cause deformity or growth inhibition of bone
- **Off label use**
  - Cholera
    - Dose: Tetracycline: 25-50 mg/kg/day div 6 hrs for 3 days
    - Doxycycline: 2-4 mg/kg/day div q 12-24 hrs; max dose: 200 mg/day for 3 days
Macrolides

- Other effects aside from antibacterial activity
  Anti-virulence effects against Pseudomonas aeruginosa
- At sub-MIC concentrations, have profound effects on the surface assembly of pili, thereby contributing to the inhibition of fimbriae surface translocation of opportunistic pathogens, such as *P aeruginosa* (*twitching motility*).
- retard the formation of a mature biofilm, increasing penetration of anti-pseudomonal drugs
Macrolides

Anti-inflammatory activity

- Mechanism of action involves down regulation of the local immune response as well as downgrading the virulence of colonizing bacteria.
- May be useful in asthma, chronic sinusitis
Macrolides

- Current status: approved only as antibacterial
  - In vitro data promising; clinical trials with good results
- Off label uses:
  - Adjunctive therapy in difficult cases of Pseudomonas aeruginosa for asthma with bacterial infections; macrolides might have advantages
What should we do?

Routine off label use can be justified if there is:

- high quality evidence supporting **efficacy** or effectiveness;

and

- sufficient evidence regarding the **safety** spectrum of the medicine to allow a reasonable evaluation of the **benefit:risk** ratio for any given clinical context.
What should we do?

- The available efficacy and safety data should be weighed against the seriousness of the underlying condition.
- **the less serious the clinical need, the higher the level of evidence needed to support use of the medicine.**
- Individual patient values and preferences should also be considered
Informed consent

• When there is high-quality evidence supporting off-label use of a medicine (ie, routine off-label use is justified)-the usual process of obtaining consent for treatment should be followed.

• includes discussing with the patient/parents the reason for using the medicine, possible alternative therapies and potential side effects.

• additional information about any uncertainties associated with such use should be given.

• Documentation of the consent process is recommended and, in some cases, obtaining written consent may be appropriate.

MJA 2006; 185 (10): 544-548
Informed consent

Written informed consent required:

• When there is no high-quality evidence supporting routine off-label use of a medicine, there may still be a case for its use in a particular patient, but there may be a higher level of risk—“exceptional use”.

• Context of a formal research proposal that has been evaluated and approved by an institutional research ethics committee.
Exceptional use- must fulfill all of the following

- There is a serious underlying disease or condition
- There is some evidence to support potential beneficial effect
- Potential benefits outweigh potential risks
- Standard therapy has been trialled or is inappropriate
- Use has been approved by institutional drug committee
- Written informed consent obtained
Last words

• Since many drugs have already been approved for use, many situations do not call for use of off label prescription.
• Off label drug use should be done in good faith, in the best interest of the patient, and without fraudulent intent.
• It should be based on sound scientific evidence, expert medical judgment, or published literature.
VII

Thou shalt not rush to use new antibiotics unless they hold clear advantages over existing agents

Lieberman J, 4th ACPID, Cebu, 2006
The sole purpose of use should be to benefit the individual patient.