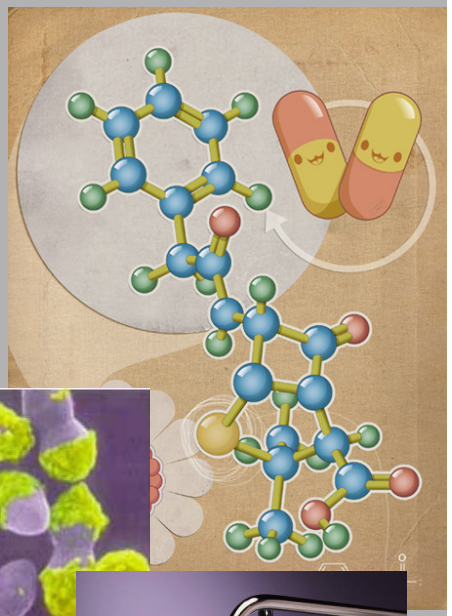
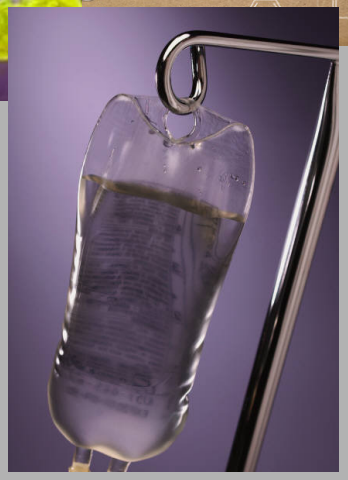
Off-Label Utilization of Antibiotics in Pediatrics





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PIDSP 16th Annual Convention

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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

Reason Use is Off-label	Examples
Dose	Low doses of amoxicilin for resp tract infection
Age	valaciclovir – “safety and effectiveness in children has not been established”
Indication	azithromycin, used for anti-inflammatory effect in cystic fibrosis
Route	tobramycin injection used as inhalation in cystic fibrosis

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

Extent of Use of off label/unlicensed drugs

Country (year)	Setting	Methodology	Size	Unlicensed and off-label use
Netherlands (2000), Jong	Pedia hosp	Prospec, 5 wks	238 children, 2139 presc	Children: 92% Presc: 66%
Europe (2000) Conroy	5 gen pedia wards in 5 countries	Prospec, 1 mo	624 children 2262 presc	Children: 67% Presc: 46%
Israel (2000), Gavrilov	Gen pedia ambu hosp unit	Prospec, 2 mos	132 children 222 presc	Children: 42% Presc: 42%
Australia (2000) Turner	2 gen ped and pedia surg wards	Prospec, 1 mo	200 children 735 presc	Children: 36% Presc: 16%
Montano (2006) Philippines	OPD (PGH)	Prospec, 2 wks	108 children 147 presc	Presc: 28.5%

Most commonly used unlicensed and Off label drugs in General Pediatrics Clinic

Medication	Total No. of Presc	No. (%) of unlicensed or off label
Paracetamol	21	11 (52.4%)
Cloxacillin	8	6 (75%)
Multivitamins	10	8 (80%)
Amoxicillin	21	4 (19%)
Cefuroxime	6	3 (50%)
Salbutamol	5	2 (40%)

Montano (2006) Philippines, unpublished

Unlicensed and off label prescriptions

	No. of Presc	% of Total no. of prescriptions
Unlicensed	2	1.4%
Off label	40	27.2%
Total	42	28.5%

Montano (2006) Philippines, unpublished

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

Category of off label use	No. (%)
Different indication	32 (62.7%)
Different dose	13 (25.5%)
Inappropriate age	6 (7.8%)
Total	51

Montano (2006) Philippines, unpublished

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

Age Group	Incidence
Neonates	49%
Toddlers	28%
School-age	10%
Teenagers	11%

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)

Reason	%
Unproved indication	38
Diff dose and frequency of administration	36
Age limitations	26

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)

Age (years)	Low Dose	High dose	Total no. of antibiotics
0-4	11.8%	2.5%	9767
5-11	19.9%	1.4%	8055
12-16	30%	0.3%	6089
Total	19.2%	1.6%	23,911

Elkins-Daukes, et al.Br J Clin Pharmacol 2003; **56:**92–95

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

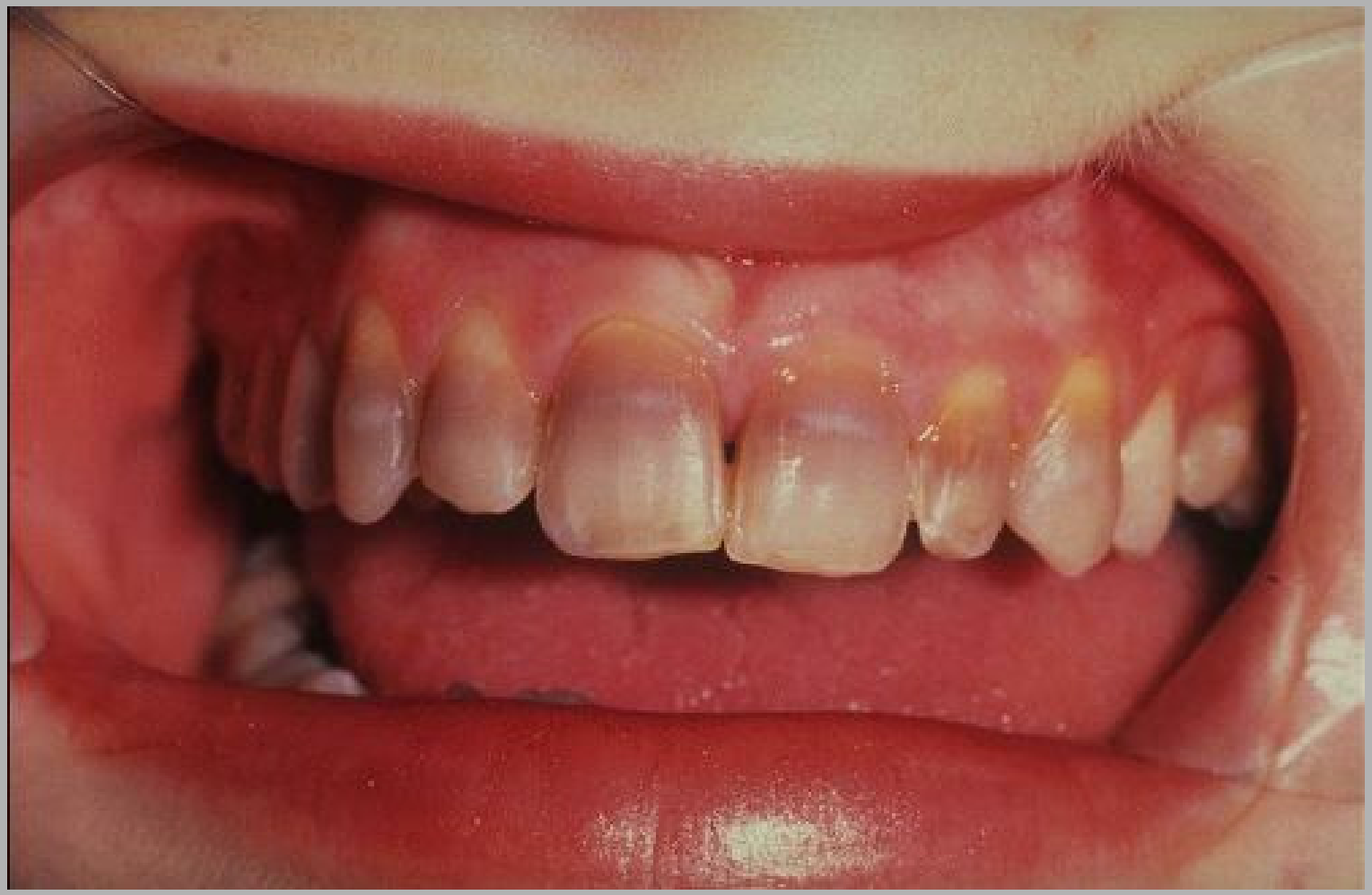
1950's- Acute toxicity to **CHLORAMPHENICOL-** Gray baby syndrome caused by immature glucoronidation- USA and Europe

Problems Resulting from off label/unlicensed Drug Use

3. Adverse drug reactions

CHILDREN $\neq$ **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)

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

B. Horen et al. *Br J Clin Pharmacol* 2002; 54: 665–670

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 dug 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

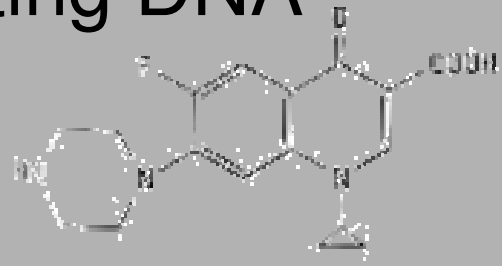
Quinolones
Carbapenems
Daptomycin
Tigecycline/Tetracycline
Macrolides

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



Ciprofloxacin

Antimicrobial Spectrum- Quinolones

Quinolone	Spectrum
Nalidixic acid	Urinary pathogens, Shigella
Ciprofloxacin, Ofloxacin	Gram negative(Salmonella, Shigella, E. coli, other Enterobacteriacae, Pseudomonas, few gram positive
Levofloxacin, Moxifloxacin	Same as Cipro +Respiratory and gram positive pathogens; less activity for Pseodomonas compared to Cipro

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

Grady. Ped Infect Dis Journ, 2003; 22: 1128-32

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

Quinolone	Dose
Ciprofloxacin	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
Levofloxacin	6mos-5yrs: 10 mg/kg/dose q 12 hrs ≥5 yrs: 10 mg/kg/dose q 24 hrs max dose: 500 mg

Taketomo, et al. Pediatric Dosage Handbook 2008-2009, Lexi Comp, 0hio, 2008

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

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

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

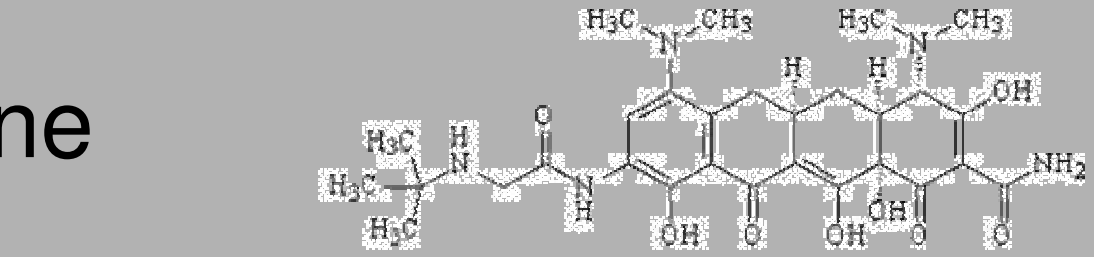
  small trial- showed no adverse effect

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 glycylcycline 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

Tigecycline- In vitro Spectrum of Activity

	Susceptible in vitro
Gram positive	Staph aureus (including MRSA), Staph epidermidis (including MRSE), Group B strep, Strep pyogenes, E. faecalis (including vancomycin resistant), E. faecium (including vancomycin resistant)
Gram negative	Acinetobacter baumanii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, E. coli, K oxytoca, K pneumoniae, Serratia, Stenotrophomonas maltophilia
Anaerobes	Bacteroides, including fragilis, Prevotella spp, Clostridium perfringens, Peptostreptococcus

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 for3 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 inapproriate
- 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
OFF LABEL
use should be to
benefit
the individual patient