



Antimicrobial Stewardship in Primary Care

Part III: Considerations for Special Populations in the Context of Antimicrobial Stewardship

This third and final part of our series of CPD articles on antimicrobial stewardship in primary care focuses on Considerations for Special Populations in the Context of Antimicrobial Stewardship.



Figure 1: Under the Weather stickers to encourage appropriate antibiotic use in children available from the HSE. They can be ordered through healthpromotion.ie



Key Principles for Management of Infection in Children

- Prescribing of any drug in children requires careful consideration of age, weight and pharmacology. Children are particularly susceptible to adverse drug reactions and dosing errors. This is compounded by the lack of paediatric labelling details for many common prescription drugs. The pharmacokinetics and pharmacodynamics of a given drug are frequently very different in children, compared to adults and may vary considerably depending on the child's age and stage of development.
- In general, drug dosing in children should be weight-based (mg/kg), though note that the recommended weight-based dose may vary according to age (for example, the half-life of many drugs is prolonged in young infants, compared to older children, resulting in lower recommended doses according to weight). Also, maximum dose limits must be taken into account and for most drugs the adult maximum dose should not be exceeded.
- The majority of childhood infections are caused by viruses (e.g. earache, sore throat) and in such cases antibiotics will provide no benefit. www.undertheweather.ie is a useful resource for parents and care-givers regarding management of common viral illnesses in children.

- Several severe bacterial infections are preventable by routine immunisation early in childhood.
- Children are less likely to carry resistant bacteria, compared to adults, unless they have had significant previous antibiotic exposure or healthcare contact.
- It is vital to ensure a child's weight is checked to ensure appropriate dose (risk of resistance and treatment failure if underdosed and risk of toxicity or side effects if overdosed). Dosing advice for children is available at www.antibioticprescribing.ie

Dispensing Antimicrobials in Pregnancy and Lactation

Before dispensing antimicrobials for pregnant or breast-feeding women, pharmacists should consider the safety of both the mother and the baby. The use of a 'safe-list' can be misleading as it implies that the agents on the list have been tested in humans for a full range of potential developmental toxicities including foetal death, structural malformations and functional deficits. Very few treatments have been evaluated to the extent required to state that they are completely safe in pregnancy. As older agents, more data is available for penicillin and cephalosporins in pregnancy than others and often they are first line agents in pregnant patients.

A risk/benefit assessment must often be made. It is worth noting that often the perception of both physicians and patients is that no amount of risk is acceptable.

At the dispensing level, consider the following:

- Allergy status of the woman;
- Trimester of pregnancy;
- Exposure of the foetus to the prescribed antimicrobial and its possible teratogenicity;
- Drug-Drug or Drug-Disease interactions;

- It is important to recognise that antibiotics should often be administered during pregnancy at the upper end of their suggested dosing ranges, as pregnant women often have an increased GFR and volume of distribution ranges are higher;
- Some useful resources for medication safety in pregnancy and lactation include:
 - Summary of Product Characteristics (SmPC);



- HSE Medication Guidelines for Obstetrics and Gynaecology: Antimicrobial Safety in Pregnancy and Lactation;
- UK Teratology Information Service;
- *LactMed*, a database by the National Institute of Health in the USA for drug safety in breastfeeding;
- UK Drugs in Lactation Advisory Service (Search for the drug name and click on 'Lactation Safety Information');
- www.antibioticprescribing.ie for suitable choices in pregnancy for common community infections.

■ Excretion of most drugs in breast milk is low but the possibility should be discussed with mothers and latest guidance checked on individual drugs SmPC or the resources listed above;

- That any female of childbearing age could be pregnant when dispensing medication, including antimicrobials;
- If still in doubt, consider seeking specialist advice from an infection or maternity expert.

See *Table 1* (Cautions in Pregnancy) for more information.

Table 1

Cautions in Pregnancy

Avoid, if possible, agents with a known teratogenic risk or reserve to instances where no alternative exists including:

- **Clarithromycin** in the first trimester unless a reasonable alternative is not an option or resistance spectrum requires them;
- **Nitrofurantoin** in first trimester unless no suitable alternative exists, and use should be avoided after week 36 (theoretical risk of haemolysis);
- **Ciprofloxacin** and other **fluoroquinolones**: Avoid if possible. Cartilage toxicity reported in animal studies (although no reports in humans);
- **Tetracyclines**: Avoid unless indication is compelling. Exposure in 2nd or 3rd trimester can cause discolouration of deciduous teeth and possible effects on bone growth. Some references contra-indicate use only after 15 weeks gestation;
- **Trimethoprim/ Co-trimoxazole**: Avoid in pregnancy unless no alternative. Association between trimethoprim exposure and congenital malformations.

Antimicrobial use in Renal Impairment

- Several commonly prescribed antimicrobials require dose adjustment in moderate to severe renal impairment (e.g. amoxicillin, co-amoxiclav and trimethoprim) (see *Table 2*);
- Some antimicrobials are contraindicated in renal impairment (e.g. nitrofurantoin and fosfomycin);
- It is important not to undertreat infections by adjusting doses downwards unnecessarily, however similarly not adjusting

downwards when recommended increases antibiotic exposure, can have limited benefit and can increase adverse drug effects;

- An excerpt of detailed guidance for individual agents is provided in *Table 2* but as a general rule of thumb, dose adjustment or avoidance of antimicrobials is not necessary unless creatinine clearance (CrCl) is ≤ 30 mL/min apart from nitrofurantoin for UTI prophylaxis, and levofloxacin;

- Specialist advice should be sought to identify suitable alternative agents if the drug to be prescribed is cautioned or contraindicated in the renal prescribing tables.
- For information on safety in renal impairment, always check the SmPC or www.antibioticprescribing.ie;
- It is important to remember that patients >65 years are likely to have some degree of renal impairment. Biochemistry results including serum creatinine may be available for residents in older persons residential care facilities. Pharmacists dispensing medication that need dose adjustment/ are contraindicated in renal impairment to older persons residing in residential care facilities. You are encouraged to check these results when conducting medication use reviews or dispensing medication. For information on how to estimate renal function by calculating CrCl or estimated glomerular filtration rate (eGFR), refer to the 'Renal Impairment Summary' on www.antibioticprescribing.ie.

History of Antibiotic Allergy

- Allergies and anaphylaxis can occur with any medication. Allergies to antimicrobials are most likely with penicillin and cephalosporins. The most common causes of fatal medication-related anaphylaxis are

"Several commonly prescribed antimicrobials require dose adjustment in moderate to severe renal impairment (e.g. amoxicillin, co-amoxiclav and trimethoprim)."

Table 2: Community Renal Impairment Prescribing Table for Antibacterials
(Source: www.antibioticprescribing.ie)

Renal Impairment Prescribing Table – ANTIBACTERIALS				
Dose adjustments recommended in this table are applicable to the infections detailed on www.antibioticprescribing.ie for the treatment of community infections only. All doses are oral and for adults unless otherwise stated				
Use either eGFR or calculated CrCl figure to direct to relevant dosing column in tables below.				
Drug	Stage 3A	Stage 3B	Stage 4	Stage 5
	eGFR (ml/min/1.73m ²) or calculated CrCl (ml/min)			
	30 - 50		10 - 30	<10
Amoxicillin	No adjustment required		Max. 500mg every 12 hours	Max. 500mg every 24 hours
Azithromycin	No adjustment required			Use with caution - systemic exposure may be increased 33%
Benzylpenicillin	No adjustment required for single stat dose			
Cefalexin	No adjustment required			Max 250mg every 8 hours
Cefotaxime	No adjustment required for single stat dose			
Ceftriaxone	No adjustment required			
Ciprofloxacin	500 mg every 12 hours		500mg every 24 hours	
Clarithromycin	No adjustment required		Use half normal dose. Contraindicated if severe hepatic impairment also present.	
Clindamycin	No adjustment required			Use with caution. No adjustment required.
Co-amoxiclav	No adjustment required		500mg/125 mg every 12 hours	500mg/125 every 24 hours
Co-trimoxazole	No adjustment required		15-30: Max. 80mg/400mg every 12 hours	<15: Seek specialist advise for alternative
Doxycycline	No adjustment required			Use with caution - no adjustment required
Flucloxacillin	No adjustment required			Consider dose reduction or extension of dose interval In high dose regimens the max. recommended dose is 1 g every 8-12 hours
Fosfomycin	No adjustment required			Not recommended
Levofloxacin 500mg every 12 hours	20-50: Initial dose 500mg, then 250mg every 12 hours		10-20: Initial dose 500 mg, then 125 mg every 12 hours	Initial dose 500 mg, then 125 mg every 24 hours
500mg every 24 hours	20-50: Initial dose 500mg, then 250mg every 24 hours		<20: Initial dose 500mg, then 125mg every 24 hours	
Lymecycline	No adjustment required		Seek specialist advice for alternative	
Metronidazole	No adjustment required			
Minocycline	No adjustment required			Seek specialist advice for alternative
Nitrofurantoin	45-60: Use with caution. Increased risk of treatment failure due to inadequate urine concentration and side effects. < 45: Long-term use contraindicated. May be used with caution if eGFR 30-44 as a short-course (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria if potential benefit outweighs risk.		Contraindicated	
Ofloxacin	20-50: 200mg every 24 hours		<20: 200mg every 48 hours	
Phenoxymethylpenicillin	No adjustment required			
Rifampicin	No adjustment required			
Spectinomycin	No adjustment required			
Trimethoprim	No adjustment required		15-30: Normal dose for 3 days, then 50% of normal dose <15: 50% of normal dose	50% of normal dose

penicillin/cephalosporins, neuromuscular blockers, radiocontrast media and NSAIDs;

■ Ensuring known allergens are avoided requires patient education and pharmacist caution,

aided by dispensing safety technology where available. Check allergy history immediately

before dispensing any antimicrobial:

- Ensure you understand which antimicrobials

are contra-indicated in which allergy e.g. which products are penicillin-based;

- Ensure allergies are entered to patient's record and that the computer system is configured to generate automated alerts, which cannot be overridden without amending the allergy status, if there is an attempt to dispense a known allergen;
- Ensure the patient understands the nature of their allergy, which medication they should not have and that they need to communicate this to all healthcare providers.
- Applying a label of 'Penicillin Allergy' to a patient is a significant issue and will impose restrictions for prescribing with multiple potentially adverse outcomes eg, sub-optimal antibiotic effectiveness, more expensive and potentially more harmful antibiotic regimens. It is important to discuss the significance with the patient before applying the label of penicillin allergy and also to ascertain as much detail as possible about the patient's previous experience and why they think they have penicillin allergy. It is important to explain that adverse reactions such as gastrointestinal upset is not a sign of penicillin allergy. It is important to document the exact nature and timing of reactions for future reference. De-labeling of

penicillin allergy is an aspect of antimicrobial stewardship of increasing global focus and concern but must be done by an expert and in a controlled manner.

- Prior tolerance to penicillin does not exclude risk of allergic reaction to future penicillin. Pharmacists should know how to recognise and treat anaphylaxis.

Elderly and Polypharmacy

- The presence of polypharmacy, dysphagia, renal impairment, antibiotic resistance and co-morbidities are more common in elderly patients. These factors are important considerations in selecting the optimal antibiotic agent and dosing regimen as they may influence the effects, side-effects and frequency of drug interactions of any antimicrobials.
- These are particularly important in the context of long courses and/or prophylactic courses of antibiotics. Nitrofurantoin for prophylaxis is contra-indicated in patients with renal impairment with $\text{CrCl} \leq 45 \text{ mL/min}$. Long term use carries a risk of pulmonary fibrosis and peripheral neuropathy. All nitrofurantoin prescriptions > 6 months should be reviewed with a view to de-prescribing. Azithromycin used for the prophylaxis of respiratory

infections in certain circumstances carries risks of cardiac arrhythmia, hepatotoxicity, hearing loss/tinnitus and antimicrobial resistance. Use of long term azithromycin should be reviewed by a specialist within a year to assess ongoing benefit versus risk. Evidence for its long-term safety and efficacy beyond this period is limited.

- Swallowing difficulty, or dysphagia, can occur in any age group but is more common in elderly populations. Community pharmacists can offer advice on alternative formulations if swallowing is a problem. This is important to prevent unnecessary avoidance of preferred 'green' agents in favour of non-preferred 'red' agents available in liquid formulation. For many antimicrobials, oral suspensions are available. For some antimicrobials, dispersible tablets are available (eg doxycycline). It is also important to identify patients with dysphagia and offer support and guidance on crushing/mixing with food/alternative formulations

to prevent absorption problems. Pharmacists are best placed to offer guidance on such formulation issues and availability. With access to Medicines Complete, the Handbook of Drug Administration via Enteral Feeding Tubes can be an excellent reference source.

- As with all medications, a thorough review of a patient's medication record should be undertaken at dispensing of antimicrobials, especially in patients with co-morbidities and/or polypharmacy. Drug-drug interactions are common in this cohort and their potential for harm should always be considered.
- Recurrent infections or multiple courses of antibiotics can indicate a resistant organism or perhaps an alternative diagnosis. It is important to discuss such trends or concerns with patients and prescribers. This is particularly important in patients where antibiotics have been prescribed by multiple prescribers who may not be aware of other recent antibiotics.

The national antibiotic prescribing guidelines for the community setting in Ireland, developed by multi-disciplinary teams of clinical and infection experts are updated regularly and are available at www.antibioticprescribing.ie.

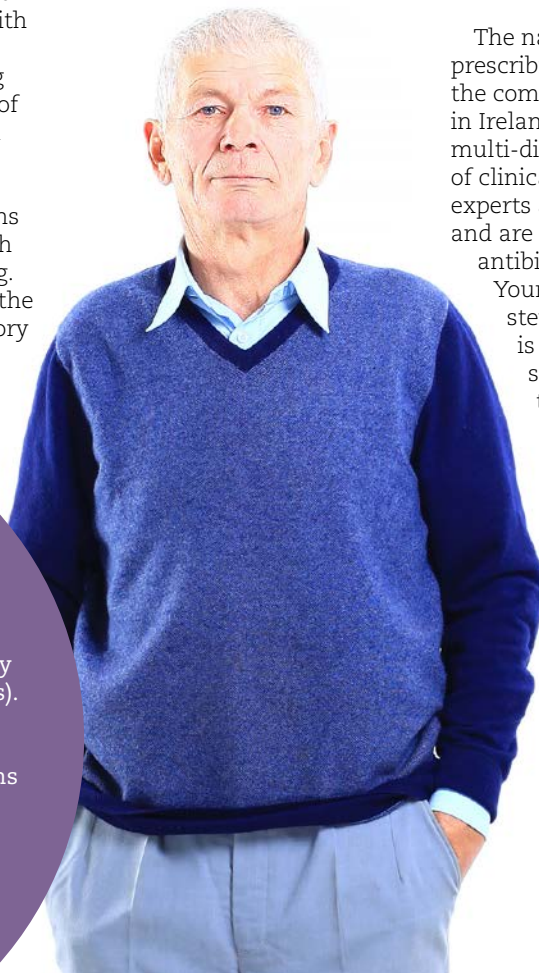
Your local antimicrobial stewardship pharmacist is available for support on any of the considerations detailed above. Their contact details are available on www.antibioticprescribing.ie on the 'About Us' page.

References available on request

How common is Penicillin Allergy?

Penicillin allergy is commonly reported either by patient or carer (between 10 – 20% of all patients).

Fewer than 10% of those who think they have an allergy to penicillin are truly allergic. Cross sensitivity between penicillin and cephalosporins has also been over-reported and is probably in the region of 2 – 3% for third generation cephalosporins, but closer to 10% for first generation cephalosporins.



CPD overview

Self-appraisal

- What do I know about the management of Special Populations in the Context of Antimicrobial Stewardship?
- Am I aware of dose adjustment in renal impairment?
- Am I aware of the antimicrobial considerations in pregnancy & lactation?
- Am I aware of the principle of management of infection in children?

Personal plan

Including a list of desired learning outcomes in a personal learning plan is a helpful self-analytical tool.

- Create a list of desired learning outcomes.
- How will I accomplish these learning outcomes?
- Identify resources available to achieve learning outcomes.
- Develop a realistic timeframe for the plan.

Action

Activities chosen should be outcomes based to meet learning objectives.

- Implement plan.
- Read this article on Considerations for Special Populations in the Context of Antimicrobial Stewardship.
- Evaluate professional resource materials available in the pharmacy and source additional material if necessary.
- Evaluate patient support material and source additional material if necessary.

Evaluate

Consider outcomes of learning and impact of learning.

- Have I met my desired learning outcomes?
- Do I now feel confident to engage with Special Populations in the Context of Antimicrobial Stewardship?
- Provide an example(s) of changes that I have implemented in my pharmacy practice.
- Have further learning needs been identified?

Document your learning

- Create a record in my ePortfolio.
- As part of this record, complete an evaluation, noting whether learning outcomes were achieved and identifying any future learning needs.

Your 5-minute assessment



Answer the following five questions:

1. Which of the following is TRUE in relation to antimicrobial use in children?
 - A. Children are less susceptible to adverse drug reactions and dosing errors.
 - B. The majority of childhood infections are caused by viruses, so antibiotics provide no benefit.
 - C. Children are more likely to carry resistant bacteria than adults and so broad-spectrum agents should be used first-line.
 - D. In general, the recommended duration of antibiotic therapy is longer in children than in adults.
2. Which of the following should a pharmacist check before dispensing an antimicrobial for use in pregnancy or lactation?
 - A. Allergy status of patient
 - B. Stage of pregnancy
 - C. Concurrent medication
 - D. Previous antimicrobial treatments
 - E. All of the above
3. Which of the following antibiotics are contraindicated in patients with $eGFR < 30 \text{ mL/min/1.73m}^2$ (Stage 4 - 5 renal insufficiency)?
 - A. Amoxicillin
 - B. Cefalexin
 - C. Nitrofurantoin
 - D. Co-amoxiclav
4. Which of the following statements is FALSE in relation to penicillin allergy?
 - A. Penicillin is one of the most common causes of fatal medication-related anaphylaxis.
 - B. It is important to record penicillin allergy on a patient's medication record.
 - C. Penicillin allergy is reported by patients/carers in approximately 10 - 20% of the population but the figure of actual penicillin allergy in the population is likely to be much higher than this.
 - D. Labelling of a patient with penicillin allergy should involve explaining the significance of this labelling to the patient and taking a detailed description of the exact nature of the allergic reaction.
5. What is the maximum timeline for review for a patient taking azithromycin for prophylaxis of COPD exacerbations?
 - A. 3 months
 - B. 6 months
 - C. 12 months
 - D. 18 months

Answers
1. B, 2. E, 3. C, 4. D, 5. C