42

Prescribing in infection: antibacterials

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Introduction

Antimicrobials are among the most commonly prescribed drugs in paediatric practice, across primary and hospital care. This chapter focuses on how to optimise antibiotic prescribing for children and neonates. Prescription of antibiotics in an appropriate and effective manner not only ensures adequate treatment of infections, but also avoids the emergence of resistance (personal and community), adverse reactions and unnecessary use of resources.

The learning objectives of this chapter are:

- to know the key classes of antibacterial drugs, common indications and cautions when prescribing
- to understand the key principles of antimicrobial stewardship, including that agent choice should be based on knowledge of the suspected pathogen(s) and local epidemiology
- to understand that consideration should also be given to the drug's ability to reach the site of infection, such as considering bone penetration in osteomyelitis
- to be aware of age related or disease related factors that can alter compliance with antibiotic therapy
- to recognise common and serious adverse reactions to antimicrobials.

Antibiotic prescribing: general principles

When prescribing antibiotics for children, there are a variety of practical factors that should always be taken into account.

Taste

Children are much less likely to take medication that tastes unpleasant. A taste test may be performed prior to prescription or discharge from hospital. A general guide to palatability of common antibiotics is included in Table 1.[1]

Number of doses

Children and parents are more likely to adhere to regimens requiring fewer doses per day or a shorter overall course. A regimen of fewer doses per day also improves the feasibility of outpatient/ambulant intravenous (IV) antibiotic treatment.

Route

Consider the best route of administration based on infection severity, drug pharmacokinetics and pharmacodynamics, and the patient's ability to tolerate/absorb oral medication. Use IV antibiotics first in systemically unwell patients and in serious infections, e.g. meningitis, bone and joint infection, endocarditis, and in high risk groups, e.g. neonates and neutropenic or immunodeficient patients.

Some parenteral regimens may be suitable for course completion at home while the patient remains under hospital supervision; paediatric outpatient parenteral antimicrobial therapy (OPAT) services are increasingly available. Advantages include improved patient experience, reduced inpatient stay (with associated economic benefits) and reduced risk of nosocomial infections. Different antimicrobials are more, or less, suitable for OPAT use, and this is summarised in Table 1 and Table 3.[2]

Timing

Start antimicrobial treatment as soon as possible following collection of microbiological samples, then try to organise dose timings to improve compliance. Where possible, prescribe oral medication during the child's waking hours, and ambulatory/OPAT doses during working hours. This might mean choosing a broader-spectrum agent given two or three times per day rather than a four times daily narrow-spectrum regimen. The following points can aid pragmatic prescribing.

- If a first dose of ceftriaxone has been given overnight, it can be moved to daytime by giving the second dose early, at any time from 12 hours following the initial dose.

  A regimen of 80 mg/kg with the first two doses being given at a 12-hourly interval was previously widely and effectively used for paediatric meningococcal sepsis, without adverse effects.

- Make sure parents are aware of time windows to give antimicrobials, for example a three times per day routine might be explicitly described as 'at 08:00 before school, at 16:00 on coming home and at midnight before parents go to sleep'.

Duration

There is little evidence for antimicrobial treatment course duration, which is currently based mainly on experience and expert opinion. Some evidence suggests an increased risk of resistance developing with longer courses of lower doses, and a reduced risk with higher doses for shorter courses.[3,4] Shorter courses also improve compliance and reduced the risk of adverse effects.[4] However, course duration needs to be sufficient to fully treat the infection, and is an area requiring further research.

Antimicrobial stewardship

This is the process of responsible planning and management of antimicrobial use with the aims of optimising treatment and minimising risk of adverse effects to the individual, and minimising the development of resistance at the individual and community level. Public Health England 2015 guidelines for antimicrobial prescribing, *Start Smart – Then Focus*,[5] include points relevant to paediatrics (see Figure 1).[6]

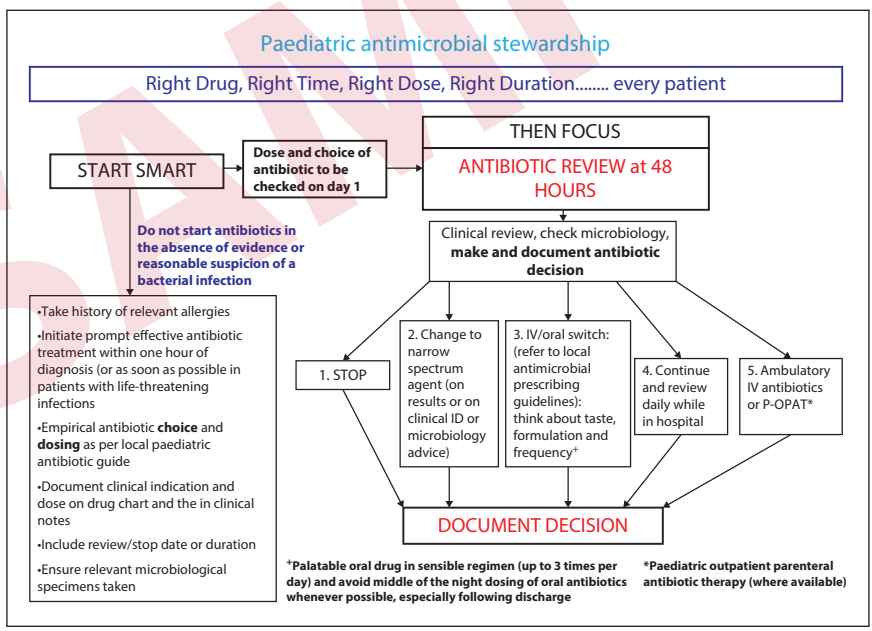

Figure 1 Principles of paediatric antimicrobial stewardship. Adapted for children from Public Health England's Start Smart – Then Focus[5]

Antibiotics

Beta-lactam antibiotics

- Large family of antibiotics (see Table 1)
- Characterised by presence of beta-lactam ring
  - Different ring structures and side chains confer differing activity
- Act by inhibition of cell wall synthesis
  - Mediated via penicillin-binding proteins[7]
- Therefore not effective against:
  - intracellular organisms
  - pathogens that lack a cell wall
  - organisms with impenetrable cell wall, i.e. mycobacteria[8]

Due to formularies frequently following formal drug licensing indications, many of which have inadequate evidence to guide them, many beta-lactams have a dose range for children or an option to double the dose in severe infection. Any patients requiring hospitalisation and IV antibiotics will typically be considered to have a severe infection and, if so, should be commenced on the highest formulary dose allowed for their weight/age. For example, we recommend that all patients commenced on ceftriaxone should start on 80 mg/kg IV (maximum 4 g once daily). Inadequate dosing can cause increased risk of treatment failure and resistance emerging, particularly when dealing with infections in difficult sites, e.g. central nervous system (CNS), bone and joint. Similarly, as most children presenting in primary care with infection have viral infections not requiring antibiotics, any child starting oral antibiotics in the community for a suspected bacterial infection should be given a high oral dose for the shortest possible course. The potential inadequacy of formulary oral beta-lactam age based oral dose recommendations was recognised for amoxicillin and ampicillin in April 2014;[9] the standard age band doses per kilogram of amoxicillin were subsequently doubled from those previously recommended, to the high dose alternative.[10] In primary or hospital care, all oral beta-lactam prescriptions should use the higher available dose recommendation with minimum course duration.

Resistance to beta-lactams

- Resistance to beta-lactams is increasingly significant globally, although uncommon in the UK.[11]
- Resistance can arise by beta-lactamase production.
- Beta-lactamase enzymes hydrolyse the beta-lactam ring.
  - Some beta-lactamases only cause resistance to penicillins.
  - Sensitivity is maintained to beta-lactamase resistant antibiotics, e.g. flucloxacillin.

- Other bacteria can produce extended spectrum beta-lactamase (ESBL).
  - Confers resistance to broader range of beta-lactams.
- Beta-lactamase inhibitors such as clavulanic acid and tazobactam have no specific antimicrobial activity themselves, but giving in combination with beta-lactam antibiotics can allow them to remain active against pathogens that would otherwise be resistant.[8]
- Another mechanism of resistance is a change in the penicillin-binding site seen with methicillin resistant *Staphylococcus aureus* (MRSA), which results in resistance to all members of the beta-lactam family of antibiotics.[8]

Macrolides

- Macrolides are bacteriostatic agents (Table 2)
- Bind to bacterial ribosomal RNA, blocking protein synthesis
- Similar spectrum of activity to beta-lactams
- Often used as an alternative in penicillin-allergic patients
- Widely distributed and achieve high tissue concentrations, particularly in bronchial tree and tonsils
- Concentrate in intracellular compartment – thus useful for intracellular infections, e.g. *M. pneumoniae*, Rickettsiae and Chlamydiae[7]
- Also active against some atypical mycobacteria
- Acquired resistance increasingly common in Staphylococci and group A Streptococci[7]

Glycopeptides

- Include vancomycin and teicoplanin (see Table 3)
- Inhibit peptidoglycan synthesis → inhibits bacterial cell wall synthesis
- Bactericidal and active against Gram positive organisms
- Often used when beta-lactams ineffective due to resistance (e.g. MRSA) or hypersensitivity
- Due to large molecular size, mostly inactive against Gram negative bacteria (except *Neisseria* spp.) as unable to penetrate outer membrane[8]
- Parenteral administration (as not absorbed via gastrointestinal tract)
  - Exception is oral vancomycin to treat *Clostridium difficile*-associated pseudomembranous colitis
- Do not cross intact blood–brain barrier
- Will cross in presence of meningeal inflammation[8]
- Vancomycin
  - Must be given by slow (> 1 hour) IV infusion

Table 1 Beta-lactam antibiotics – commonly used examples[1,2,7,8]

Class	Category	Parenteral drug	OPAT[a]	Enteral drug	Taste[b]	Active against	Excretion	Special notes
Penicillins	Natural penicillin	**Benzyl-penicillin (penicillin G)**	Use ceftriaxone instead due to dose frequency.	**Phenoxymethyl-penicillin (penicillin V)**	2	Gram positive – Strepto-cocci Gram negative – *Neisseria*	Rapid renal excretion	Inactivated by bacterial beta-lactamases (produced by most Staphylococci).
	Semi-synthetic (beta-lactamase resistant) penicillin	**Flucloxacillin**	Intermittent infusions not suitable due to frequency. Often successful use of ceftriaxone as alternative in UK. 24 hour infusion via elastomeric device is possible.	**Flucloxacillin**	4	Gram positive including Beta-lactamase producing Staphylococci.	Rapid renal excretion	
	Semi-synthetic (amino) penicillin	**Amoxicillin**	Use ceftriaxone instead due to dose frequency.	**Amoxicillin**	1	Gram positive – Strepto-cocci Gram negative – *Neisseria*, *Haemophilus*, *Listeria monocytogenes*, *Borrelia* (Lyme)	Renal	Inactivated by bacterial beta-lactamases Risk of non-allergy mediated rash in EBV infection.
		Amoxicillin and clavulanic acid (co-amoxiclav)		**Co-amoxiclav**	1	As above plus beta-lactamase producing Gram positive		Contains clavulanic acid – beta-lactamase inhibitor.
	Semi-synthetic (ureido) penicillin	**Piperacillin/ tazobactam (piptazo-bactam)**	Intermittent infusions not suitable due to frequency 24 hour infusion via elastomeric device is possible.			Gram positive Enhanced Gram negative particularly *Pseudomonas* and *Klebsiella*	Renal	Contains tazobactam – beta-lactamase inhibitor.

Cephalosporins	First generation			**Cefalexin**	1	Gram positive – Streptococci, Staphylococci Gram negative – *Neisseria haemophilus,* Enterobacteria (parenteral agents) Ceftazidime – *Pseudomonas*	Renal	
	Second generation	**Cefuroxime**	Use ceftriaxone instead due to dose frequency.	**Cefaclor**	1			
	Third generation	**Cefotaxime**						
		Ceftazidime	Intermittent infusions not suitable due to frequency. 24 hour infusion via elastomeric device is possible.					Antipseudomonal activity.
		Ceftriaxone	Suitable for daily infusion.				50–60% renal 40–50% biliary long half-life	Only use 80 mg/Kg IV. Second dose can be given any time from 12 hours following the initial dose. Do not use in neonates if IV calcium used concomitantly.[c]
Carbapenems		**Meropenem**	Not advised, as concerns about stability.			Gram positive and Gram negative	Renal	Not to be used first line due to increase in resistance.

[a] Suitability for outpatient parenteral antibiotic therapy

[b] Taste – ranked 1–4, where 1 is the most palatable.

[c] In neonates (up to 28 days of age), ceftriaxone is contraindicated if:

- jaundice (> 50 µmol/L)
- hypoalbuminaemia (albumin < 25 g/L)
- acidosis (pH < 7.35)

Notes:

In patients of any age, ceftriaxone must not be mixed or administered *simultaneously* with any calcium-containing IV solutions (such as total parenteral nutrition or Hartmann's), even via different infusion lines or at different infusion sites.

In patients older than 28 days of age, ceftriaxone and calcium-containing solutions may be administered *sequentially* one after another through a different IV site or through the same IV site if thoroughly flushed with normal saline.

Table 2 Macrolides[7,8,12]

Drug	Route	Activity	Excretion	Adverse effects	Special notes
Erythromycin	Oral IV	Gram positive cocci Intracellular bacteria ● Mycoplasmas ● Chlamydiae ● Rickettsiae ● *Legionella pneumophila* ● *Campylobacter jejuni*	Excreted in bile Some renal excretion	Nausea and vomiting	Poor taste and tolerability, Four times/day regimen so best avoided Good oral absorption Good tissue distribution
Clarithromycin	Oral IV	As erythromycin Improved activity against Gram positive bacteria and *Legionella pneumophila*		Reduced adverse effects	
Azithromycin	Oral	As erythromycin Improved activity against Gram negative bacteria			High tissue concentrations and post-antibiotic effect allow dose to be given once daily for just 3 consecutive days

- Minimises risk of red man syndrome (upper torso flushing, erythema and pruritis caused by rapid histamine release)
- More rarely, this can cause angio-oedema, anaphylactoid reactions and cardiovascular collapse
- Intramuscular (IM) injection causes pain and necrosis
- Can cause nephrotoxicity and ototoxicity
- Monitor plasma concentrations carefully (associated with risk of toxicity) (see chapter 35)
- Modify dose in renal failure (see chapter 47)
- Avoid using in combination with aminoglycosides or loop diuretics, to reduce risk of nephrotoxicity[7]
- High level acquired vancomycin resistance can occur
  - Arises following acquisition of resistance associated genes
- Notable problem in Enterococci (vancomycin resistant Enterococci; VRE)

  - Transfer of resistance genes to Staphylococci also observed
  - Some strains of VRE remain sensitive to teicoplanin[7,8]
- Teicoplanin
  - Less active against some coagulase negative Staphylococci
  - Less risk of nephrotoxicity and ototoxicity
  - Toxicity is not dose dependent; no need for therapeutic drug monitoring
  - Can be safely given intramuscularly or by IV bolus
  - Added advantage of longer half-life, allowing once daily dosing[7]

Aminoglycosides

- Include gentamicin, amikacin, tobramycin (see Table 3)
- Bind to bacterial ribosomal subunit → inhibit protein synthesis
- Potent, broad spectrum, bactericidal agents
- Used for serious Gram negative infections
  - Particularly if reduction in host defences
- They are active against most aerobic Gram negative pathogens (except *Neisseria* spp)
- Not active against anaerobes and most Gram positive bacteria (except Staphylococci)
- Must be given parenterally
  - Poorly absorbed from gastrointestinal tract
- Do not penetrate well into tissues and bone or via the blood–brain barrier
  - Thus often used in first stages of bacterial sepsis then stopped once there is clinical stability
- Act synergistically with beta-lactams
  - Often used in combination with them, especially if infection blood surface associated, e.g. endocarditis
- Risk of nephrotoxicity and ototoxicity
  - Necessitates careful monitoring of plasma concentrations (see chapter 35)
  - Dose adjust in renal impairment (see chapter 47)
- Acquired resistance is relatively rare[7,8]

The key features of several other commonly used classes of antibiotic are summarised below in Table 4.

Anti-mycobacterial agents

- Mycobacteria are challenging organisms to treat:
  - Impermeable cell wall
  - Intracellular location
  - Extremely slow growth

Table 3 Glycopeptides and aminoglycosides[2,7,8]

Family	Mechanism	Drug	Route	OPAT[a]	Uses / Activity	Excretion	Special notes
Glycopeptides	Inhibition of cell wall formation	**Vancomycin**	IV slow infusion	Intermittent infusions not suitable due to frequency. 24 hour infusion via elastomeric device is possible.	**Gram positive** ● Staphylococci ● Streptococci ● Enterococci (unless vancomycin resistant) **Gram negative** ● *Neisseria*	**Renal (glomerular)**	Risk of nephrotoxicity and ototoxicity – levels required Caution and reduced dose in renal impairment Risk of red man syndrome with rapid IV infusion
		Teicoplanin	IV or IM	Once-daily infusion via silicone-free syringe			Reduced risk of adverse effects Potentially reduced activity against coagulase-negative staphylococci
Aminoglycosides	Inhibitors of protein synthesis	**Gentamicin**	IV or IM	Once-daily infusion via syringe	**Gram negative aerobes** ● *E. coli* ● *Klebsiella* ● *Enterobacter* ● *Proteus* ● *Shigella* ● *Salmonella* ● *Serratia* ● *H. influenzae* ● *Pseudomonas* (particularly tobramycin) **Gram positive** ● Staphylococci	**Renal (glomerular)**	Use in severe infections, often in association with a beta-lactam in the early stages of sepsis treatment on paediatric intensive care unit
		Tobramycin	IV	Once-daily infusion via syringe			Similar to gentamicin but improved activity against *Pseudomonas aeruginosa* Often used in CF patients with *Pseudomonas*
		Amikacin	IV				Active against many gentamicin-resistant Gram negative rods

[a] Suitability for outpatient parenteral antibiotic therapy

Table 4 Other antibiotics[7,8]

Mechanism	Family	Drug	Route	Activity	Excretion	Adverse effects	Special notes
Inhibitors of protein synthesis	Tetracyclines	**Doxycycline**	Oral	*Chlamydiae* *Rickettsiae* Mycoplasmas *Borrelia* (Lyme) Spectrum of activity broad but acquired resistance common	Renal Faecal	GI upset Brown staining teeth Interference with bone development Risk of hepatotoxicity	UK formulary advises do not use < 9 years or in pregnancy / breast feeding. However evidence from the USA suggests short course therapy with doxycycline is not associated with long lasting adverse effects
	Chloram-phenicol	**Chloram-phenicol**	Oral – well absorbed IV – if NBM	*H. influenzae* meningitis Broad spectrum of activity but not used if alternative available due to toxicity	Metabolised in liver, excreted renally	Bone marrow toxicity – usually dose dependant and reversible Rarely idiosyncratic and irreversible	Achieves good CNS penetration High rates of resistance
	Lincosamides	**Clindamycin**	Usually oral IV or IM	Gram positive bacteria – particularly *Staphylococcus aureus* Anaerobic bacteria	Metabolised in liver, excreted in faeces	Not active against *Clostridium difficile* so risk of pseudomembranous colitis	Good bone penetration – useful in osteomyelitis Poor cerebrospinal fluid (CSF) penetration even via inflamed meninges
	Oxazolid-inones	**Linezolid**	Oral or IV	Gram positive bacteria including many multiresistant strains Resistance rare	Metabolised in liver	Bone marrow suppression and optic neuropathy following prolonged use	Reserve for use against multi-resistant pathogens

(continued)

Table 4 (*Continued*)

Mechanism	Family	Drug	Route	Activity	Excretion	Adverse effects	Special notes
Inhibitors of nucleic acid synthesis	Quinolones	**Ciprofloxacin**	Oral or IV	Gram positive ● Staphylococci Gram negative bacteria ● *Pseudomonas aeruginosa* Intracellular bacteria	Renal Some excreted in faeces	Avoid in patients with increased risk of seizures	Good oral absorption. Use IV only if unable to take orally
	Rifamycins	**Rifampicin**	Oral	Prophylaxis for contacts of *Haemophilus influenza* and *meningococcal meningitis*	Metabolised in liver Excreted in bile	Turns urine, sweat and saliva orange Rapid development of resistance if used as monotherapy	Well absorbed and distributed Crosses blood brain barrier Affinity for plastics – reported useful in adults for attempting treatment of infections associated with prostheses If used as anti-Staphylococcal agent never use as monotherapy
	Trimethoprim	**Trimethoprim**	Oral	Gram negative rods (not *Pseudomonas* spp.)	Renal excretion – more rapidly excreted in renal failure	Neutropenia Nausea and vomiting Adverse effects more common in HIV infection	Treatment and prophylaxis of urinary tract infections Often given in combination with sulfamethoxazole as co-trimoxazole – act synergistically
	Nitroimida-zoles	**Metronidazole**	Oral or IV	Anaerobes	Renal excretion	Peripheral neuropathy in prolonged use or high doses – rare	Good oral absorption, distribution to tissues and CSF

- Long treatment courses are required[8]
- Manage patients under guidance of paediatric infectious disease or tuberculosis (TB) specialists
- Standard recommended regimen for *M. tuberculosis* infection is:
  - Four drug regimen for the first 2 months (see Table 5)
    - Usually isoniazid, rifampicin, pyrazinamide and ethambutol
  - Followed by isoniazid and rifampicin for a further 4 months
- In meningeal involvement, continue isoniazid and rifampicin for a total of 12 months
- If meningeal or pericardial involvement, commence a glucocorticoid at treatment outset and wean off after the first 2–3 weeks[13]
- Multiple agents in combination are necessary to kill both replicating and dormant bacilli and to reduce the risk of resistance developing
- Majority of organisms will be killed in the early intensive phase of treatment, leaving a minority of persistently dormant organisms to be killed by rifampicin in continuation phase
- Isoniazid is also continued in case any rifampicin resistant organisms begin to replicate[7]

Multiple drug resistant TB

- Multiple drug resistance is an increasing problem worldwide
- Resistance can quickly develop
  - Exacerbated by monotherapy or poor compliance
- Patients must be counselled regarding risks
- Directly observed therapy is not currently routinely recommended in the UK
- Considered in patients at high risk of poor adherence[13]
- Other agents or regimens will be necessary for drug resistant strains
  - Treatment regimens are guided by isolate sensitivity patterns whenever available

Allergies and adverse drug reactions

Adverse events while taking antimicrobials (particularly beta-lactams) are common. A large proportion of children are labelled as antibiotic allergic as a result. Many of these events will be unrelated to the antibiotic or will not be a hypersensitivity reaction. Only 6–24% of children with a suspected antibiotic allergy will have a positive result on drug provocation testing.[14] This can have significant implications, limiting the range of potentially

Table 5 Antimycobacterials[7,8]

Drug	Mechanism of action	Absorption and distribution	Excretion	Adverse effects
Isoniazid	Inhibition of mycolic acid synthesis (mycobacterial cell wall component) Rapidly bactericidal against replicating organisms Minimal effect on dormant organisms	Good GI absorption	Metabolised by acetylation	Potential neurotoxicity – prevented by concomitant pyridoxine (ask child or young person to report pins and needles) Hepatitis – rare and reversible in children Can cause high levels of anticonvulsants in slow acetylators
Rifampicin	Blocks mRNA synthesis Active against nearly dormant organisms	Good GI absorption Well distributed and crosses blood–brain barrier	Metabolised in liver, excreted in bile	Orange urine/saliva/sweat – non-harmful and an indicator of compliance If used as anti-Staphylococcal agent never use as monotherapy
Pyrazinamide	Inhibition of mycolic acid synthesis Active against slowly replicating bacilli in acidic environments	Good GI absorption Well distributed and crosses blood–brain barrier	Metabolised in liver, excreted in urine	Potential hepatotoxicity but usually well tolerated
Ethambutol	Inhibits arabinogalactan polymerisation (mycobacterial cell wall component)	Good GI absorption Well distributed and crosses blood–brain barrier if meninges inflamed	Renal excretion	Optic neuritis – monitor visual acuity, and discontinue if any change. Can be irreversible if treatment continued

life-saving antibiotics available to them. Drug provocation testing can be helpful in patients with mild symptoms of suspected drug allergy, particularly those who will require further antibiotic therapy.[14,15]

It is very important to recognise true IgE mediated hypersensitivity reactions, which can be life-threatening. In patients with true penicillin hypersensitivity, there can be cross-sensitivity to other beta-lactams: 3–9% of penicillin-allergic patients may also be allergic to cephalosporins.[7] Due to the relatively low risk, intensive care clinicians may choose to use a third generation cephalosporin for treating community acquired sepsis, which can be appropriate; however, it is important to carefully assess any potential reaction to guide appropriate future use/avoidance of antibiotics. Table 6 summarises the key features of important adverse drug reactions.

When antibiotic allergy is suspected:

- Characteristics typical of type I (IgE mediated) hypersensitivity reactions are: early onset after exposure (usually 1–4 hours; range up to 72 hours), angio-oedema, urticaria, diffuse erythema, bronchospasm, laryngeal oedema and anaphylaxis.
- In type I hypersensitivity and severe non-IgE mediated reactions, all penicillins are absolutely contraindicated; other beta-lactams should only be used if there is no alternative, and then under expert guidance.
- In patients with mild non-IgE mediated reactions (e.g. non-urticarial rash), avoid penicillins unless there is no alternative; use other beta-lactams with caution.[6]

When penicillin allergy is suspected:

- Erythromycin is commonly prescribed but is not ideal because it:
  - is unpalatable
  - requires four times daily dosing
  - has a poor adverse effect profile.
- Clarithromycin has good anti-Staphylococcal activity but is less palatable than amoxicillin.
- Azithromycin is more palatable and has a useful pharmacokinetic profile:
  - High and persistent tissue concentration
  - Once-daily dosing for 3 consecutive days achieves therapeutic levels (sustained for up to 10 days[12])
  - Three days is a sufficient treatment course
  - Effective prophylactic agent in certain patient groups
  - For prophylaxis, prescribe for 3 consecutive days per week

Table 6 Adverse drug reactions

Allergic response	Timing	Symptoms	Immunological mechanism	Prognosis
Maculopapular eruption	6–10 days after first exposure < 3 days after second exposure	Widespread red macules / papules Variable in size and distribution Can resemble urticaria	T-cell mediated	Lesions last 5–10 days
Fixed drug eruption	6–10 days after first exposure < 3 days after second exposure	Localised inflamed skin – always at same site	T-cell mediated	Will recur with repeated use of drug Will resolve days to weeks after drug cessation
Urticaria/angio-oedema	< 1 hour after exposure	Urticaria – erythematous swollen lesions with brightest erythema at periphery and paler in centre. Distribution of lesions will change over hours to days Angio-oedema – swelling, typically of face, hands, feet If severe, can affect airway	IgE mediated mast cell degranulation	May last for several days May rapidly evolve into airway compromise or anaphylaxis Potential for late phase reaction
Anaphylaxis	< 1 hour after exposure	Severe systemic reaction Urticaria/angio-oedema/erythema + hypotension and/or bronchospasm	IgE mediated mast cell degranulation	Immediately life-threatening
Drug reaction with eosinophilia and systemic symptoms (DRESS)	2–6 weeks after first exposure < 3 days after Second exposure	Widespread maculopapular rash or erythroderma Eosinophilia Fever Lymphadenopathy Liver/renal/bone marrow dysfunction	T-cell mediated	Can result in prolonged symptoms even after cessation of drug Mortality up to 10%

Erythema multiforme (EM)	1–2 weeks after first exposure <3 days after second exposure	Distinct circular lesions 1–2 cm diameter, flat or raised Darker in centre, paler peripherally, may be concentric rings – target lesions May be associated blistering of lesions and systemic symptoms	T-cell mediated	Risk of mortality increases with increasing body surface area involvement, age, biochemical and haemodynamic instability Mortality up to 90% in most severe cases SJS/TEN likely to require intensive care
Stevens–Johnson syndrome (SJS)		As EM, with blistering/skin loss 1–10% of body surface area Mucosal involvement		
Toxic epidermal necrolysis (TEN)		Blistering/skin loss > 30% Mucosal involvement		
SJS/TEN overlap		Blistering/skin loss 10-30% Mucosal involvement		
Acute generalised exanthematous pustulosis (AGEP)	3–5 days after exposure	Widespread pustules Fever Neutrophilia	T-cell mediated	Will resolve within days of drug cessation

Conclusions

High quality antimicrobial prescribing can benefit both children and communities, and the benefits of antimicrobial stewardship are broad. However, changing antibiotic prescribing practices among physicians requires insights into behaviour as well as science. For complex cases, have a low threshold to discuss with specialists in paediatric infectious diseases and microbiology.

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