

# Penicillin – getting prescribing right for children

## SUMMARY

Penicillins are commonly prescribed to children. Recommendations in the product information may not be the most appropriate doses for children and may list clinical indications that are preferably treated with other antibiotics.

Reputable guidelines, for example Therapeutic Guidelines: Antibiotic, offer up-to-date advice on optimal choice, route, dosage and duration of oral penicillins in children.

In most instances, the child's weight should be used to calculate the dose in mg per kg without exceeding the maximum adult dose.

When prescribing higher weight-based doses of amoxicillin or flucloxacillin, check the volume of oral liquid required to complete a treatment course to ensure adequate supply.

## Introduction

Rates of antibiotic prescribing and dispensing for infants and young children are higher than for any other age group under 65 years.<sup>1</sup> Penicillins such as amoxicillin and the combination amoxicillin/clavulanate are among the most commonly dispensed antibiotics in primary care.

When indicated, it is critical that the optimal antibiotic choice, dosage, regimen and duration are prescribed for children. Australian guidelines, including Therapeutic Guidelines: Antibiotic,<sup>2</sup> provide up-to-date recommendations for prescribing oral penicillins in children. GPs may instead choose to order the dose recommended in the product information as this is freely available online and integrated into many electronic prescribing systems.<sup>3</sup> However, recommendations in the product information may not

be the most appropriate doses for children (see Box). It may only include indications and doses approved by the Therapeutic Goods Administration at registration. As most oral penicillin products in Australia have been used for more than 20 years and are generally off-patent, up-to-date dosing information may not be included in the product information, particularly for children.

## Prescribing in children

Many childhood infections do not require antibiotics at all, including:

- common self-limiting infections
- viral infections
- bacterial infections that require drainage or other physical treatment (e.g. cutaneous abscess, dental infections requiring timely dental treatment).

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## Box Examples of prescribing pitfalls for oral penicillins in children

### Amoxicillin

A 2-year-old child weighing 12 kg has mild-moderate pneumonia amenable to treatment with oral antibiotics. The dose recommended in Therapeutic Guidelines is 25 mg/kg/dose or 300 mg eight hourly.

The recommended dose in the product information would equate to 13.3 mg/kg/dose or 160 mg eight hourly. If this was followed the child would receive approximately half of the dose recommended by current guidelines.

### Amoxicillin/clavulanic acid

A 5-year-old child weighing 20 kg has otitis media refractory to amoxicillin alone and is treated with amoxicillin/clavulanic acid. The dose recommended in Therapeutic Guidelines is a 7:1 ratio of 22.5 mg/kg of amoxicillin (450 mg) with 3.2 mg/kg clavulanic acid given 12 hourly.

The product information recommends the 4:1 formulation of amoxicillin:clavulanic acid at a dose of 13.3 mg/kg of amoxicillin (265 mg) and 3.3 mg/kg of clavulanic acid given eight hourly. This dosing and frequency is different from current guidelines and the excess clavulanic acid increases the risk of gastrointestinal adverse effects.

### Flucloxacillin

A 3-year-old child weighing 15 kg is receiving oral flucloxacillin as step-down therapy for osteomyelitis after discharge from hospital. Therapeutic Guidelines recommend 25 mg/kg/dose or 375 mg six hourly.

The product information recommends 125 mg flucloxacillin six hourly which is approximately a third of the dose recommended in current guidelines.

Shared decision making with parents is an effective approach to appropriately using antibiotics and reducing antibiotic overuse.

‘Children are not little adults’ is a common comment from those working in paediatrics. The epidemiology, clinical presentation and prognosis of some infections differ in children compared to adults. Understanding this is key to timely diagnosis and good antimicrobial stewardship. In addition, pharmacokinetics can be different in children. This was evident with oral penicillins from the very beginning – gastric acid secretion, intestinal motility and drug pH all affect absorption. Depending on age and whether a child is unwell, these can result in net increased or decreased absorption compared to an adult. However, the magnitude of these effects are greatest during the first two years of life.<sup>4</sup>

In paediatric studies, dosage requirements often exceeded the expected dose for body size.<sup>4,5</sup> Direct comparisons between paediatric studies were complicated by incomplete information about the age or weight of patients, use of different product strengths, teaspoon measures, and the ‘rounding’ of doses for convenient administration.<sup>4,6</sup>

Empiric prescribing should ideally be based on the likely pathogen and the pharmacokinetics and pharmacodynamics of the antibiotic. Dosing information for children is included in Therapeutic Guidelines, the AMH Children’s Dosing Companion, and guidelines from children’s hospitals.

When a penicillin is required, it should be prescribed at doses that are expected to safely maximise the time that the drug remains above the minimum inhibitory concentration for the pathogen. If available, reviewing cultures and the results of susceptibility testing ensures the correct drug with the narrowest spectrum is used.

Narrow-spectrum penicillins are active against *Streptococcus pyogenes* (Group A streptococcus). Phenoxymethylpenicillin has been used extensively for erysipelas, streptococcal tonsillitis and dental infections that require antibiotics.

Amoxicillin is active against susceptible *Escherichia coli*. Adding the beta-lactamase inhibitor clavulanic acid increases the ability to treat certain Gram-negative organisms.

For *Streptococcus pneumoniae* infections (other than meningitis) with reduced susceptibility to penicillin, increasing the penicillin or amoxicillin dose may be effective. Using amoxicillin/clavulanic acid does not provide additional benefit in this case, as penicillin resistance in *Streptococcus pneumoniae* is not

mediated by a beta-lactamase.<sup>7</sup> For mild to moderate pneumonia, oral amoxicillin is recommended in Therapeutic Guidelines at 25 mg/kg dose eight hourly and in World Health Organization guidelines<sup>8</sup> at 40 mg/kg 12 hourly. It is non-inferior to parenteral options for this condition.

Amoxicillin/clavulanic acid is appropriate for treating beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. If a higher amoxicillin dose is required, children aged two months and over should be prescribed a formulation with a lower dose of clavulanic acid.

Duration of therapy varies by indication. Many common, uncomplicated infections may be treated with shorter antibiotic courses than are commonly given.<sup>9</sup>

### Dosing by age or weight – practical problems

In many instances it is unclear if dosing principles and recommended age bands in the product information are based on convenience or arise for other reasons – these fail to account for growth and metabolic development occurring within each age band. At the margins of age bands, for example at age six or 12 years, the average child<sup>10</sup> might receive phenoxymethylpenicillin doses that either exceed the maximum or fail to meet the minimum dose for weight. For amoxicillin, this leads to substantial differences for children slightly above or below 20 kg.

Dose ranges are further widened for patients at the lowest and highest percentile weights for age, most obviously among 10–14 year-olds where the difference between the 5th and 90th percentile is greatest. Achieving adequate drug concentrations in overweight and obese patients is an increasing concern in countries such as Australia where around a quarter of children and adolescents (5–17 years) fall into this category.<sup>11</sup> Doses based only on age may be sub-therapeutic and result in treatment failure and an increased risk of resistance, or be excessively large doses based on a higher age band.<sup>12</sup> In most instances, the child’s weight should be used to calculate the dose in mg per kg without exceeding the maximum adult dose.

### Volume and pack size

Discrepancies between the dose and duration recommended in the product information and guidelines introduce new problems.<sup>13</sup> Older children may need additional tablets, and younger children may need a larger volume of oral liquid compared to what is provided in standard packs.<sup>14</sup>

## Phenoxymethylpenicillin

When phenoxymethylpenicillin became available, doses in the range of 60 to 120 mg 3–6 hourly were commonly used for adults.<sup>15–17</sup> Doses were generally halved for children, but for severe paediatric infections these half doses were often doubled.<sup>17–19</sup> In the Australian product information, the same general principles continue to apply, which allow for a wide dose range. Twice-daily doses of phenoxymethylpenicillin for tonsillitis in children are not listed in the product information, even though this simplified regimen is commonly prescribed and reportedly achieves similar outcomes.<sup>20</sup> Therapeutic Guidelines recommends 15 mg/kg (up to 500 mg) 12-hourly phenoxymethylpenicillin for pharyngitis or tonsillitis requiring antibiotics.

## Amoxicillin

Recommendations in the product information for amoxicillin suspensions – 250 mg/5 mL and 125 mg/5 mL – are generally unchanged from doses used in trials conducted in the 1970s. Paediatric doses are provided only for children weighing less than 20 kg.<sup>21</sup> The product information recommends doses of 6.6 mg/kg eight hourly (20 mg/kg/day) with doubling of the dose for severe infections, for infections with less susceptible organisms or for lower respiratory tract infections. It is likely doses this low are often inadequate – data from the USA on acute otitis media suggest 83% of *Streptococcus pneumoniae* are susceptible to amoxicillin at 40 mg/kg/day.<sup>22</sup> Twice-daily dosing at 60 mg/kg/day (given as 30 mg/kg/dose up to a maximum of 1 g 12 hourly) is licensed for use in acute otitis media in Australia. Prescribing amoxicillin for neonates remains off label in Australia, as are higher amoxicillin doses even though they have been studied and licensed overseas.<sup>23</sup> Therapeutic Guidelines<sup>2</sup> recommends 15 mg/kg doses eight hourly for urinary tract infections (with susceptible organisms) and 25 mg/kg eight hourly for pneumonia.

## Amoxicillin/clavulanic acid

Clavulanic acid (clavulanate), a beta-lactamase inhibitor, is added to an amoxicillin backbone. Paediatric formulations of this combination in a

7:1 ratio (400 mg:57 mg in 5 mL) provide a higher amoxicillin component for indications such as acute otitis media. This optimises efficacy and minimises diarrhoea associated with too much clavulanic acid.<sup>24</sup> Despite this, products with a greater proportion of clavulanic acid (4:1, 125 mg:31.25 mg in 5 mL) continue to be recommended for children in the product information.

## Flucloxacillin

Approved indications in Australia for flucloxacillin include pneumonia, and skin and bone infections. For children, the product information recommends prescribing half or a quarter of the adult dose depending on age. In early studies, flucloxacillin doses of 12.5 mg/kg for children produced similar concentrations to adults given doses of 500 mg. However, neonates had higher absorption than older children,<sup>25</sup> and infants aged under six months had better absorption than older children with liquid formulations.<sup>26</sup> Higher doses and weight-based doses that are recommended in many guidelines for bone infections in children are not included in the product information.

## Conclusion

Evidence supporting optimal penicillin prescribing remains limited for children compared to adults. Dose recommendations available in the product information provide guidance which has often been superseded by regularly updated, evidence-based sources, such as Therapeutic Guidelines.

Prescribers should have access to evidence and updated guidelines to make decisions for children. Cooperation between regulators, pharmaceutical companies and software vendors is needed to improve this and support appropriate use of penicillins and other antimicrobials in the community. ◀

*Brendan McMullan, Greg Rowles and Mona Mostaghim contributed to the most recent edition of eTG.*

*Brendan McMullan and Mona Mostaghim have also provided advice for sections of the AMH Children's Dosing Companion.*

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