

# Antibiotic Doses Table: Editorial comments

The following comments and excerpts from discussions are a summary of the editorial committee's rationale and reasoning behind the changes and developments in the fourth edition of the CARPA STM antibiotic table. Some sections are quite detailed and included to preserve this important front-line debate, particularly about using amoxicillin twice a day. This topic will most likely be the subject of further development in future editions of the STM and evidence base. The antibiotic table was expanded to include virtually all the antimicrobials used in the manual so all doses can be checked in the one place. There was an extensive process of re-drafting, review and debate.

We acknowledge the valuable input of members of the Antibiotic Guidelines Writing Group (simultaneously working on the twelfth edition of the well-known Antibiotic Guidelines published by Therapeutic Guidelines Limited Victoria) as well as 'regular' CARPA contributors. The key commentators were: Bart Currie (main link to ABG group), Christine Connors, Peter Morris, Jo Wright, Dan Ewald, Frank Shann, Jenny Johnstone, Jonathan Carapetis, John Turnidge, Jonathan Dartnell and Jeni Simpson.

As a result of this collaboration, we expect the tables of 'practical dosing' in the twelfth edition of the antibiotic guidelines and the CARPA STM will be virtually the same. This should minimise confusion that could result from conflicting guidelines.

All the antibiotics recommended have wide therapeutic ranges, with gentamycin the main exception where more detailed dose-for-weight information is given. Because we are aware of high rates of serious disease from bacterial infections in the CARPA area population, and often poor medication adherence, the doses recommended are calculated for the high end of the weight range.

Peter Morris (Menzies School of Health Research) has reviewed the evidence around the twice-a-day (bd) vs three-times-a-day (tds) amoxicillin doses for otitis media, and this underpins the recommendation for that condition. His summary (with references) follows.

## **Twice-daily dosing for AOM: What's the evidence?**

Compliance is a big problem for us in our otitis media (OM) studies in remote Aboriginal communities. Our aim is to increase the dose of amoxicillin and reduce the frequency of treatment in order to improve compliance without any loss of effectiveness. In our studies, we treat children with acute otitis media (AOM) with amoxicillin 25 mg/kg bd initially and increase this to 50 mg/kg bd in children who are treatment failures (or children we think are highly likely to be treatment failures). In the evidence-based guidelines we produced for the Office of Aboriginal and Torres Strait Islander Health, we recommended 50 mg/kg/day given bd or tds, increased to 90 mg/kg/day given bd or tds for treatment failures or in areas with high rates of resistance-Level III evidence (i.e. very similar doses to what we are actually using but more consistent with expert recommendations from USA and Australia).

Looking at the literature to see if this was reasonable, I checked PubMed using the following topic strategy:

((“otitis”[MeSH Terms] OR otitis[Text Word]) AND (“amoxicillin”[MeSH Terms] OR amoxicillin[Text Word]) OR amox\*) combined with: (clinical trial [ptyp] OR “clinical trial\*”[text word] OR random\*[text word] OR “double blind”[text word] OR “single blind”[text word] OR placebo\*[text word])

This identified five RCTs involving more than 1500 children comparing amoxicillin or amoxycillin/clavulanate bd with amoxicillin or amoxycillin/clavulanate tds.<sup>1-5</sup> The outcomes in the studies were very similar for both groups. A quick (and very rough) statistical summary suggests that around 90% of children in the bd group were clinically cured after treatment. This was slightly higher than the tds group, combined risk difference -2% (95%CI -5, 1). Benefits of greater than 1% in the tds group are unlikely.

The search also identified a longitudinal study of 500 children treated with amoxycillin/clavulanate 45 mg/kg bd. Two hundred and ninety-five had bacteriologically proven infections and 90% of these were cured with the bd regimen. Of the 295 bacterial infections, 125 were pneumococcal. Ninety-eight per cent of the pneumococcal infections were bacteriologically cured, including 91% of the 34 resistant isolates (MICs 2-4).<sup>6</sup>

The pharmacodynamic data is more difficult to sort out. Based on the published OM studies that had cultured middle ear fluid before and after treatment and regression analysis, Craig and Andes estimated that time above the MIC of 40% for amoxicillin would result in a bacteriological cure rate of 80-85%.<sup>7</sup> (However, while the correlation between time above MIC and bacteriologic cure was very strong, it did not explain 43% of the variance in cure rates. Also, bacteriologic cure is not necessary for clinical cure and around 50% of pneumococcal infections will resolve without antibiotics). Craig and Andes also used regression analysis to estimate that a beta-lactam MEF (middle ear fluid concentration) to MIC ratio of >3.2 was also correlated with a bacterial cure rate >80%. The authors then estimated that amoxicillin 13 mg/kg tds would provide T>MIC of 100% for susceptible pneumococci, T>MIC of 59% for intermediate resistance (MIC 1 mic/ml), and T>MIC 46% for resistant pneumococci (MIC 2 mic/ml). The only antibiotic that provided better T>MIC was ceftriaxone, so this paper was important in the USA in the move back to amoxicillin as first-line treatment for AOM.

Others authors in the USA (where there are high rates of penicillin resistance) have made estimates of T>MIC for higher doses of amoxycillin given bd. From the previous data, it would appear than even modest increases in dose are likely to be sufficient to provide T>MIC of 40% for susceptible and intermediate resistant organisms. While SmithKline Beecham also have some pharmacodynamic data to support their application to the FDA for twice-daily dosing, this has not been published (as far as I am aware). Since 1996, I have only been able to identify three further relevant studies of higher doses of amoxycillin.<sup>8-10</sup>

All studies were small (20-30 children with AOM). Canafax et al. measured serum and MEF levels of amoxicillin after a dose of 25 mg/kg and estimated that plasma levels would be above 2 mic/ml for around five hours. MEF levels would be above 1 mic/ml for around four hours. Seikel et al. measured plasma and MEF levels after doses of amoxicillin/clavulanate of 35 mg and 45 mg/kg. Mean plasma concentration was 7.7 mic/ml at three hours for 35 mg/kg and 13 mic/ml for 45 mg/kg. MEF levels exceeded 1 mic/ml in 90% specimens and 4 mic/ml in 40% of specimens. Harrison et al. compared a

dose of 13 mg/kg of amoxicillin with 30 mg/kg. Mean MEF after two hours was 4.3 mic/ml for 30 mg/kg and 0.68 mic/ml for 13 mg/kg. All authors concluded that higher doses more likely to be appropriate for infection with resistant pneumococci. A dose of 25 mg/kg bd would appear to remain above MIC for long enough to provide bacteriologic cure for susceptible and intermediate resistant strains and some fully resistant strains. Higher doses were estimated to provide bacteriologic cure in around 2/3 of resistant pneumococci.

## References

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3. Hoberman A, Paradise JL, Burch DJ, Valinski WA, Hedrick JA, Aronovitz GH et al. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin) for treatment of acute otitis media in children. *Pediatr Infect Dis J* 1997; 16(5):463-70.
4. Jacobsson S, Fogh A, Larsson P, Lomborg S. Evaluation of amoxicillin clavulanate twice daily versus thrice daily in the treatment of otitis media in children. Danish-Swedish Study Group. *Eur J Clin Microbiol Infect Dis* 1993; 12(5):319-24.
5. Principi N, Marchisio P, Bigalli L, Massironi E. Amoxicillin twice daily in the treatment of acute otitis media in infants and children. *Eur J Pediatr* 1986; 145(6):522-525.
6. Dagan R, Hoberman A, Johnson C, Leibovitz EL, Arguedas A, Rose FV et al. Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. *Pediatr Infect Dis J* 2001; 20(9):829-37.
7. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J* 1996; 15(3):255-259.
8. Canafax DM, Yuan Z, Chonmaitree T, Deka K, Russlie HQ, Giebink GS. Amoxicillin middle ear fluid penetration and pharmacokinetics in children with acute otitis media. *Pediatr Infect Dis J* 1998; 17(2):149-56.
9. Seikel K, Shelton S, McCracken GH, Jr. Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. *Pediatr Infect Dis J* 1998; 17(10):969-70.
10. Harrison CJ, Welch DF. Middle ear effusion amoxicillin concentrations in acute otitis media. *Pediatr Infect Dis J* 1998; 17(7):657-8.

## Editorial comments continued

By way of further explanation, Augmentin is amoxicillin plus clavulanic acid. Clavulanic acid inactivates beta-lactamase, making beta-lactamase-producing bacteria sensitive to penicillin. Clavulanic acid has no antibacterial action on its own. Pneumococci don't produce beta lactamases (while 15-30% of Haemophilus and 80-90% of Moraxella do). This means amoxicillin and amoxicillin-clavulanic acid will be equivalent in the treatment of pneumococci and amoxicillin-clavulanic acid provides a theoretical advantage in the treatment of Haemophilus and Moraxella. Since these infections often resolve spontaneously anyway, amoxicillin has generally remained first-line treatment.

Peter Morris further adds:

Interestingly there has only been one study comparing amoxicillin vs amoxicillin-clavulanic acid that I am aware of (Stenstrom C, Lundgren K, Ingvarsson L, Bertilson SO. Amoxicillin/clavulanate versus amoxicillin in recurrent otitis media and therapeutic failure in children. *Acta Otolaryngol* 1991; 111(1):120-9.) and this didn't describe any difference. Also, there have been lots of trials comparing antibiotics with beta-

lactamase activity with antibiotics without it and these also show no difference.

The area where we don't have much information concerns which dosing regimen results in more antibiotic resistance. I think the bd regimen needs to be included as an option and will be surprised if it's not eventually included in the Antibiotic Guidelines.

It is worth noting that establishing equivalence of two antibiotics for a clinical condition that in many instances may have a viral cause has some limitations for our population where there are generally higher rates of bacterial infection. If there is some advantage of tds over bd amoxicillin it may be more apparent in settings where the cause is more likely to be bacterial infection.

### **Concerns about increased resistance with bd amoxicillin**

John Turnidge offered the following expert comments:

The resistance problem is twofold: that of adequate dosing to ensure efficacy; and also adequate dosing to reduce the risk of colonisation with resistant bacteria (especially resistant (R) pneumococci). We have some good pharmacodynamic/pharmacokinetic (PK/PD) information on the former but little on the latter, as far as I can tell just two studies.

The retrospective study from France<sup>a</sup> examined the relationship between carriage and dose + duration of treatment or a range of antibiotics. These investigators demonstrated that R pneumococci carriage is less likely with higher doses and shorter courses, especially for amoxicillin. Higher dose amoxicillin was defined as greater than 50 mg/kg/day; shorter courses were defined as five days or less.

The study from CDC (performed in Dominican Republic<sup>b</sup>) conducted a prospective study of carriage of pneumococci after either 20 mg/kg bd for 10 days or 45 mg/kg bd of amoxicillin for five days. Carriage of non-susceptible pneumococci was significantly lower in the high/short group (24% vs 32%).

Using my pharmacodynamic calculator I have calculated various bd and tds amoxicillin dosing schedules to see what gives a (plasma) T>MIC of 1µg/ml of around 50%. This assumes MEF levels are similar, which is inaccurate of course, but still provides a basis for comparison. This is what you get:

#### **Dosing options and % of time above the minimum inhibitory concentration of 1µg/ml**

<b>Twice daily dosing</b>		<b>Three times a day dosing</b>	
12.5 mg/kg (= 500 mg adult) bd	32%	12.5 mg/kg (= 500 mg adult) tds	48%
25 mg/kg (= 1 g adult) bd	41%	25 mg/kg (= 1 g adult) tds	61%
50 mg/kg (= 2 g adult) bd	49%	50 mg/kg (= 2 g adult) tds	73%

Given that these relate to average PK, then half of the patients would have percentages lower than this. It also shows how much you need to change the bd dose to get a reasonable increase in MIC.

#### **References**

a Guillermot et al. JAMA 1998; 279:365-70.

b Schrag et al. JAMA 2001; 286:49-56.

#### **Adult COAD and amoxicillin**

There is also evidence from a RCT of the clinical equivalence of twice-a-day amoxicillin (1 g bd) to 500 mg tds for exacerbations of chronic bronchitis in adults (Georgopoulos A, Borek M, Ridl W. Randomised, double-blind, double-dummy study comparing the efficacy and safety of amoxicillin 1 g bd with amoxicillin 500 mg tds in the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother* 2001; 47(1):67-76.) As mentioned above, if a lot of the symptoms in the study population were due to viral infection, we would not expect this type of trial to demonstrate any difference between the two regimens. The side effect profile was very similar in the two groups.

However, in 2002 twice-a-day amoxicillin was approved by the Therapeutic Goods Administration Committee for this use.

**In summary:** We believe the likely advantages of better compliance with twice-a-day amoxicillin and the evidence of clinical efficacy warrant recommending twice-a-day dosing for otitis media and exacerbations of COAD. The concerns about possibly increasing the prevalence of resistant organisms, particularly pneumococci, have restrained the extrapolation as first-line treatment regimen for other clinical conditions where amoxicillin might be used (e.g. ARI). Twice-a-day dosing is recommended for other conditions if the clinician believes that there will be a major improvement in compliance over three-times-a-day dosing. In this case the higher (double) doses should be used.

#### **Phenoxymethyle penicillin: Include or not?**

There is a very limited role for phenoxymethyle penicillin (penicillin V) in the CARPA STM. It is included for those situations where benzathine is refused for one reason or another. This will be for rheumatic fever prophylaxis, skin sores, treatment of sore throat. For skin sores people can be given once a day roxithromycin, which should have better compliance. Oral penicillin is included for sore throat rather than going straight to roxithromycin in an attempt to decrease the general use of roxithromycin and the possible increase in resistant organisms that may result.

#### **Probenecid with antibiotics**

Probenecid is not an antibiotic itself. It delays the renal excretion of penicillin-type antibiotics (including amoxicillin, flucloxacillin, dicloxacillin). This can be used to reduce the number of times the antibiotic needs to be taking each day, or in the case of treatment for gonorrhoea, allows single-dose supervised treatment. Probenecid should not be used if the aim is to have the antibiotic in the urine (treating UTI), or if the person's kidney function is very poor. People with poor renal

function will already have slower excretion of these antibiotics and only need twice-a-day doses.

There is no need to increase the size of each dose, so the dose of antibiotic when given with probenecid is the same size, but given half as often (bd instead of qid).

The main indication for using probenecid will be with flu/dicloxacillin for skin infections not responding to benzathine.

### **Probenecid and children**

Jeni Simpson, Remote Pharmacist, Alice Springs Hospital, prepared the following comments on probenecid suspensions for children:

To follow up on your request for information regarding stability and compatibility of amoxicillin/ flucloxacillin suspension combined with crushed probenecid tablets, the following drug information sources were accessed:

- Royal Adelaide Children's Hospital drug information service, pharmacy department and pharmacy manufacturing
- Royal Adelaide Hospital drug information service and pharmacy manufacturing
- Royal Melbourne Children's Hospital drug information service, pharmacy department and pharmacy manufacturing
- Princess Margaret Children's Hospital pharmacy and pharmacy manufacturing
- Internet resources including Medline, Pharmaceutical texts and guides including APP guide, Martindale, Mims, AHFS drug info, Paediatric pharmacopoeia, APF, AMH, Goodman and Gilman, etc.
- Orion Pharmaceuticals, staff pharmacist (the Australian distributor of probenecid tablets)

There appears to be no information at all in the literature regarding the use of, or stability and compatibility of, probenecid in suspension, either alone or in combination with amoxicillin or flucloxacillin.

Royal Adelaide Children's Hospital does prepare a probenecid suspension mixture which is given a month's expiry, though they have no clinical information to back up this choice of expiry date. Royal Melbourne Children's Hospital simply crush probenecid tablets and give a rounded-up quantity i.e. one quarter of a tablet. Princess Margaret Hospital pharmacy manufacturing department, although having no direct experience with probenecid, were exceptionally helpful and looked into the matter very thoroughly. Upon discussion with Garry Thompson the following points were covered:

Probenecid is virtually insoluble in water and in the buffered acidic amoxicillin/flucloxacillin suspension. (In an alkaline environment would expect some slight solubility which could then start to affect stability etc.) Hence, the stability of the probenecid in these suspensions would not appear to be a problem. As such the two suspensions would be coexisting within the mixture rather than interacting. There appeared to be no apparent reason why they would not be compatible.

It is thought that the suspending agent used in the amoxicillin/flucloxacillin would also suspend the probenecid, though there was some discussion that it may be overwhelmed by the quantity of probenecid (an estimate of maximal probenecid doses was ascertained using the 10 mg/kg dose of probenecid recommended in the paediatric pharmacopoeia).

A number of ingredients in probenecid tablets (such as the maize starch and colloidal silica) tend to expand and have gel-like properties in solution and may aid suspension, but this effect would be very minimal. Other ingredients would have no effect.

Due to the increased powder mass associated with combining probenecid into these suspensions the amount of water that needs to be added to make the mixtures up to volume may also have to be adjusted. Quite vigorous shaking may also be necessary.

All of this information is, as discussed, theoretical and it would be necessary to run some tests and trials on the mixing of these products together before introducing this as a standard procedure. Expiry dates for the reconstituted solution would also have to be discussed. However, it does to some degree appear possible.

Further to the above input we found that few if any clinicians had actually been using probenecid with children as indicated in the third edition of the CARPA STM.

Dan Ewald and Jeni Simpson did some trials of making a probenecid suspension.

In brief, it proved fairly impractical, as you need to add 14 finely crushed probenecid tablets to one bottle of amoxicillin suspension. You need to reduce the amount of water added by 10 ml to retain the concentration of amoxicillin per mL as it was. It becomes a thick porridge-like mixture with a dreadful taste that is difficult to get rid of and leaves a gritty texture in the mouth.

Using probenecid in children is restricted in practical terms to those old enough to swallow probenecid tablets.

### **Retaining erythromycin**

Generally, roxithromycin can be used in situations where erythromycin has been used in the past. Roxithromycin has the advantage of a longer half-life, allowing once-a-day dosing regimens. Erythromycin has been retained as some practitioners found it more acceptable for children. However, some clinics no longer stock it and have not found this to be a problem. There are a few situations where erythromycin is still recommended (e.g. trachoma in the very young), mainly because the original evidence of efficacy was established with erythromycin and has not been replicated with roxithromycin or other longer acting macrolides.

### **Tinidazole and metronidazole both included**

Tinidazole is a better alternative to metronidazole as it has advantages of simpler dosing and fewer side effects. However, metronidazole is retained as there is no liquid preparation of tinidazole available and metronidazole has a better safety rating for use in pregnancy and lactation.

### **Recommending higher concentration liquid preparations of antibiotics**

Based on our clinical experience we believe that it is easier to give a child a small volume of a medicine they don't like than a larger volume, hence a preference for the 50 mg/mL strength of antibiotics over 25 mg/mL. Using the lower strength of antibiotic often necessitates giving out two

bottles to cover the entire period of treatment. This is added work in dispensing and added cost, probably making up for the higher cost of the stronger preparation.