

Antibiotic prescribing in children – top-tips

1) Fever in children is extremely common and results in over 50% of primary care activity in children under 5 years of age. Although parental anxiety about missing a serious infection is driving this increasing activity, the absolute risk of a child having a serious bacterial infection has markedly reduced since the introduction of conjugate vaccines against strep pneumo, HiB and meningococcus.

2) Parents seek a consultation because:

- It provides a proper ‘health-check’ and in their opinion, removes any ‘health-threat’
 - Parents lack confidence to distinguish self-limiting illnesses from serious ones but believe that clinicians can
- They want advice on what symptoms to look out for and when to seek help
- They do not generally seek antibiotics (although this is something that can be clarified during the consultation). Parents generally believe that Abs are required to treat ‘severe’ infections rather than to treat bacterial infections:
 - parents often believe that features suggesting a severe infection include high fever, prolonged duration of symptoms and degree of impact on the child (sleep / school)
 - Parents perception of susceptibility also plays a role in their expectation for Abs (younger, underlying health issues)

3) The factors associated with clinicians prescribing antibiotics include:

- Perceived vulnerability of children, especially young children.
- Seeking safety in the face of uncertainty (especially if re-presentation)
 - Uncertainty is driven by the difficulty in distinguishing bacterial and viral infections.
 - Perceived risk of suppurative complications from an untreated bacterial respiratory tract infection, especially in young children.
- Repercussions of ‘missing something’ in a child
 - The media are inclined to pick up on any cases where significant morbidity/death in a child that has resulted from a healthcare professional ‘missing’ a severe infection.
 - Staff with little experience of seeing unwell children are less confident at ruling out severe infection.

4) Young children have far lower rates of suppurative complications than older children, even when antibiotics are not prescribed:

- Rate of mastoiditis following otitis media (age 0-4 years versus 5-15 years): 1.33 vs 2.39 per 10,000
- Rate of quinsy after tonsillitis (age 0-4 years versus 5-15 years): 1.59 vs 5.99 per 10,000

5) There is good evidence to show that addressing parental concerns during a consultation results in significant reductions in future reconsultation rates, as well as marked reductions in Ab prescribing (Francis NA, BMJ 2009):

- Focus on the reasons the parent sought a consultation (rather than the distinction between viral and bacterial infections).
- Reassure the family that although their child has an infection that is having an impact on their sleep/feeding, their symptoms are not indicative of a severe infection in terms of objective parameters / 'red-flags'. Parents should also be provided with information about the likely duration of symptoms and advice on how to manage them.
- Most importantly, one must clearly explain the symptoms that parents should look out for and the actions required if they were to occur. All this information should ideally be provided both verbally and in writing - see Healthier Together safety netting sheet: <http://www.what0-18.nhs.uk/health-professionals/primary-care-staff/safety-netting-parents/fever-children-less-5-years-age/>

6) One of the major challenges facing clinicians is distinguishing whether a child presenting with an RTI has a bacterial or viral infection. It is often extremely difficult to make this decision clinically and there are few reliable diagnostic tests that can assist in a community based setting. This uncertainty often results in clinicians prescribing "just in case". However, there is an increasing body of evidence to show that antibiotics do not significantly reduce severity or duration of symptoms in the majority of children with RTIs, irrespective of the aetiology:

i) Acute otitis media (AOM)

A systematic review of 13 RCTs (3401 children and 3938 AOM episodes) from high-income countries demonstrated that antibiotics have no early effect on pain, a slight effect on pain in the days following and only a modest effect on the number of children with tympanic perforations, contralateral otitis episodes and abnormal tympanometry findings at two to four weeks and at six to eight weeks compared with placebo. This suggests that in high-income countries, most cases of AOM spontaneously remit without complications. Even in children with AOM under 2 years of age, there is evidence to suggest that antibiotics make very little difference to the severity of symptoms in the majority of children.

ii) Tonsillitis

There is data, albeit limited, to suggest that antibiotics have little or no impact in reducing the severity of symptoms in the majority of children with acute tonsillitis

iii) Lower respiratory tract infections (LRTIs)

The lack of evidence around the benefits of Abs in children with LRTIs is demonstrated by the fact that there is currently a randomised controlled trial recruiting children between 6 months and 12 years of age presenting with an acute uncomplicated lower respiratory infection (LRTI), defined as an acute cough judged to be infective in origin, lasting <21 days. Patients will be randomised to either an antibiotic arm (amoxicillin) or placebo for 7 days and the primary outcome being evaluated is the duration of significant symptoms

7) Ensuring consistent prescribing approaches across the urgent care pathway is paramount – inconsistent approaches drive parental anxiety and promote health seeking behaviour. Consistent approaches for identifying children requiring Ab treatment for RTIs are being implemented across primary (SCAN) and secondary care (PIER) in Wessex:

i) Acute otitis media

Consider starting oral antibiotics **only if any of the following criteria are met** in a child presenting with AOM (bulging ear drum or discharge): -

- Symptoms for 4 days or more
- Purulent discharge from ear canal (not due to otitis externa)
- Systemically unwell
- Under 6 months of age with presumed acute OM.
- In child 6 months - 2 years old, consider starting Abs if the following features are present:-
 - Bilateral OM
 - Unilateral OM and symptom score of >8 in child 6 months-2 years old (0=no symptoms, 1=a little, 2=a lot) for the following criteria: -
 - fever (>39 degrees = score of 2)
 - tugging ears
 - crying more
 - irritability
 - difficulty sleeping
 - less playful
 - eating less.

ii) Tonsillitis

Base decision to treat on FeverPAIN score (Fever, Purulence, Attend within 3 days of onset or less, severely Inflamed tonsils, No cough or coryza):

- score 0-1 = 18% streptococci: use no antibiotics
- score 2-3: 34-40% streptococci, use back up/delayed antibiotic
- score ≥4: 62-65% streptococci, use immediate Ab

This score is validated in children aged 3 years and older. However, younger children are less likely to have a bacterial aetiology and are less likely to develop complications.

iii) LRTIs

There is a paucity of evidence to guide antibiotic prescribing decisions in children and most national guidelines tend to focus on LRTIs in adults. Prior to the results of the [ARTIC PC study](#) being made available, a pragmatic approach seems most appropriate, with consideration of antibiotics if persistent/recurrent fever over preceding 24-48 hours with chest wall recession and tachypnoea.

8) Compliance with treatment re taste of oral antibiotic suspensions and frequency of dosing. Aim to use an antibiotic that is palatable and minimises dosing frequency in

order to optimise adherence. Penicillin V and flucloxacillin suspensions are not well tolerated by children due to their taste.

- Although there has been great anxiety about prescribing amoxicillin in patients with tonsillitis due to the risk of adverse events associated with EBV, there is emerging data to suggest that the use of amoxicillin does not significantly increase the risk of rash in acute EBV – see <https://www.ncbi.nlm.nih.gov/pubmed/23589810> and <https://adc.bmj.com/content/101/5/500> . In addition, data suggest that EBV accounts for as little as 1% of tonsillitis presenting to doctors - see <https://www.ncbi.nlm.nih.gov/pubmed/17904463> and more importantly, EBV is extremely rare prior in children below 12 years of age. For this reason, the current recommendation is to use penicillin V bd tablets for children able to swallow tablets.
- For review of dosing frequency bd versus qds, see <https://www.ncbi.nlm.nih.gov/pubmed/10654979>

9) Need to challenge the bacterial versus viral paradigm:

It is extremely difficult for a clinician to confidently distinguish a mild/moderate bacterial infection from a viral illness. Yet we remain obsessed about making this distinction. This partly stems from our firmly held belief that if a bacterial infection is not treated with antibiotics, the patient is likely to come to harm.

There is also a very real risk that focusing on whether an infection is caused by a bacteria or virus (and then trying to justify why a patient does not need antibiotics in terms of “it’s just a virus”) negatively impacts on the effectiveness of the consultation. Parents seek the advice of a healthcare professional because are worried that their child might be seriously unwell. The role of the clinician is to establish whether or not this is the case, and if not, to effectively convey their professional opinion to the family. Examining the patient thoroughly and checking physiological parameters (heart rate, respiratory rate, capillary refill) can help reassure the parent. Explaining your findings in terms of objective markers of severity (red, amber, green criteria) and providing the family with clear information about what to watch out for (safety netting) is also extremely effective in allaying parental anxiety.

Clinicians should adopt a *severity of illness approach* when deciding whether to prescribe antibiotics rather than relying on their ability to distinguish bacterial from viral infections. Not only is this likely to significantly reduce antibiotic prescribing, but an effective consultation that effectively addresses the concerns of the parent is far more likely to reassure them and to empower them in the long-term. Perhaps they will feel confident enough to not seek your input the next time their child has a fever?

10) Most children labelled with a penicillin allergy are not allergic to penicillin – lifelong implications of attaching a label of penicillin allergy in childhood in terms of likelihood of adverse infective outcomes and colonisation with resistant organisms:

- Features suggestive of a true penicillin allergy (type 1 hypersensitivity):
 - Timing post Ab (within 60 mins of first dose)

- Symptoms: urticaria, angio-oedema, wheeze, anaphylaxis
- NOT genetic / not familial
- True penicillin allergy rare in childhood

Evidence base supporting the updated paediatric prescribing recommendations in the SCAN guidelines

Key messages:

- Focus on clearer advice on when to prescribe and when not to
- Pragmatism versus purism:
 - If children require Abs, use a drug that is palatable (Baguley D et al. <https://adc.bmj.com/content/97/3/293.long>)
 - Amoxicillin suspension instead of pen V
 - Cefalexin suspension versus flucloxacillin suspension –research study being planned
 - If children require Abs, avoid qds dosing due to reduced adherence with therapy Falagas ME et al. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283966/>)
 - Amoxicillin 40mg/kg bd (max 1g/dose) – WHO dosing recommendation
 - Pen V tablets bd for older children with tonsillitis
- Reduce duration of Ab course where possible
 - Tonsillitis treatment course 7 days, not 10 days
- Adequate dosing – BNFC commonly underdoses!

BD dosing of pen V and amox - clinical efficacy (tonsillitis)

- Meta-analysis comparing overall cure rates between BID or once-daily (QD) versus more frequent dosing schedules in the treatment of streptococcal tonsillopharyngitis (Lan AJ. The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: A meta-analysis. [Pediatrics](#). 2000 Feb;105(2)
- A study was eligible for inclusion if it was a randomized clinical trial that compared the efficacies of different dosing frequencies of 10-day penicillin or amoxicillin in the treatment of streptococcal tonsillopharyngitis (6 studies met eligibility criteria).
- Results: BID dosing of 10-day penicillin is as efficacious as TDS/QID dosing regimens in the treatment of streptococcal tonsillopharyngitis. This result also holds true in a subgroup analysis confined to pediatric cases. Similar findings with amoxicillin.

Amox versus penicillin V for tonsillitis– side-effects

- Mantra about avoiding ampicillin in tonsillitis due to risk of EBV rash: 80-100% risk of rash reported
 - Risk of rash in children with confirmed EBV 29% with amoxicillin (23% in untreated children) - Chovel-Senna A et al. Incidence of Rash After

Amoxicillin Treatment in Children With Infectious Mononucleosis.

[Pediatrics](#). 2013 May;131(5):e1424-7

- EBV rare in children <12 years of age - Worrall GJ. Acute sore throat. *Can Fam Physician*. 2007 Nov; 53(11): 1961–1962
- EBV accounts for as little as 1% of tonsillitis presenting to doctors - Hurt C et al. Diagnostic evaluation of mononucleosis-like illnesses. [Am J Med](#). 2007 Oct;120(10):911.e1-8

BD dosing of amox - clinical efficacy (pneumonia)

- 412 and 408 children 2-60 months of age with non-severe pneumonia received amoxicillin thrice or twice daily, respectively (Vilas-Boas AL et al; Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial. [J Antimicrob Chemother](#). 2014 Jul;69(7):1954-9)
- Treatment failure was detected in 94 (22.8%) and 94 (23.0%) patients in intention-to-treat analysis (risk difference 0.2%; 95% CI: -5.5%-6.0%) and in 80 (20.1%) and 85 (21.3%) patients in per-protocol analysis (risk difference 1.2%; 95% CI: -4.4%-6.8%).
- Pneumonia was radiologically confirmed in 277 (33.8%) cases, among whom treatment failure was registered in 25/133 (18.8%) and 27/144 (18.8%) participants from the thrice and twice daily doses subgroups, respectively (risk difference -0.05%; 95% CI: -9.3%-9.2%).

BD dosing of amox - clinical efficacy (acute otitis media)

- Study comparing the clinical efficacy and side-effects of amoxycillin in two groups of children at the age of ≤ 6 years randomised to amoxycillin 40 mg/kg/day either two (n=180) or three times daily (n=187) for the clinical diagnosis of acute respiratory tract infections (>80% of cases in both groups had acute OM) - Valtonen M et al. Comparison of amoxycillin given two and three times a day in acute respiratory tract infections in children. [Scand J Prim Health Care](#). 1986 Nov;4(4):201-4
- Results: 82% of the patients with otitis media were cured in bd group vs 86% in tds group. Equivalence in terms of disappearance of the symptoms/improvement of the signs. Rate of side-effects same in both groups, 6.4% and 6.7% respectively.

Dosing frequency of amoxicillin – PK data

- Thirty-four children with upper or lower respiratory tract infections were randomly allocated to receive either a twice daily or three times daily dose of amoxycillin 50 mg /kg/day - Fonseca W et al. Comparing Pharmacokinetics of Amoxicillin Given Twice or Three Times per Day to Children Older than 3 Months with Pneumonia. [Antimicrob Agents Chemother](#). 2003 Mar; 47(3): 997–1001
- On day 1, 16 of 27 children in the b.i.d. group and 11 of 26 children in the t.i.d. group had concentrations that were above 2.0 µg/ml for <50% of the dose interval

- On day 3, 18 of 31 children in the b.i.d. group and 8 of 31 children in the t.i.d. group had concentrations that were above 2.0 µg/ml for <50% of the dose interval.
- Data supports dosing of 30-40mg/kg bd

Duration of Abs for tonsillitis

- Three to six days of oral antibiotics has comparable efficacy compared to the standard duration 10-day course of oral penicillin in treating children with acute GABHS pharyngitis. These findings are not applicable to areas where the prevalence of rheumatic heart disease is still high - The effect of short duration versus standard duration antibiotic therapy for streptococcal throat infection in children, Cochrane Database of Systematic Reviews 2012

Duration of antibiotics for tonsillitis in children with a confirmed penicillin allergy

- Meta-analysis of randomized, controlled trials that involved bacteriological confirmation of GAS tonsillopharyngitis, random assignment to receive either azithromycin or a 10-day comparator antibiotic - Casey JR et al. Higher dosages of azithromycin are more effective in treatment of group A streptococcal tonsillopharyngitis. Clin Infect Dis 2005;40:1748-55
- In children, azithromycin administered at 60 mg/kg per course was superior to the 10-day courses of comparators ($P < .00001$), with bacterial failure occurring 5 times more often in patients receiving the 10-day courses of antibiotics.
- Azithromycin administered at 30 mg/kg per course was inferior to the 10-day courses of comparators ($P = .02$), with bacterial failure occurring 3 times more frequently in patients receiving azithromycin. Three-day regimens were inferior to 5-day regimens ($P = .002$).
- SCAN guidelines recommend 10mg/kg for 5 days in order to maintain consistency of dosing (10mg/kg versus 12mg/kg)

Azithromycin versus clarithromycin in children with a confirmed penicillin allergy

- Differential selection of macrolide resistance: randomised, double-blind, placebo-controlled study of the effect of azithromycin (500 mg once daily for 3 days) and clarithromycin (500 mg twice daily for 7 days), was measured against placebo in four groups of volunteers by use of oral streptococci as model organisms (Malhotra-Kumar S et al. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007 Feb 10;369(9560):482-90).
- Results: clearly defined effect on commensal pharyngeal streptococci was observed, with both drugs selecting for macrolide resistance. Although azithromycin quantitatively selected for more persistent resistance, clarithromycin qualitatively selected for the higher resistance-conferring erm(B) gene. The acquisition of erm(B) represents a more efficient resistance mechanism for the organism. Not only does it confer increased resistance to the macrolide group of antibiotics, but it also induces resistance to

clindamycin and tetracyclines. This poses a heightened risk to public health. (Dancer SJ. Attention prescribers: be careful with antibiotics. Lancet. 2007 Feb 10;369(9560):442-3).

- SCAN guideline recommends azithromycin rather than clarithromycin for children with confirmed penicillin allergy with tonsillitis, pneumonia, acute otitis media, rhinosinusitis and skin/soft tissue infections.

Cefalexin for treating skin/soft tissue infections

- RCT comparing cefalexin bd to dicloxacillin qds in adults with staph aureus skin infections (n=70) - Dillon HC Jr. Treatment of staphylococcal skin infections: a comparison of cephalixin and dicloxacillin. J Am Acad Dermatol. 1983 Feb;8(2):177-81
- Results – no difference in treatment failures pr recurrence. Conclude that twice-daily therapy with cephalixin for staphylococcal skin and skin structure infections can be recommended with confidence.

Dosing recommendations

- Concerns that current BNFc dosing recommendations risk underdoing in children - Bielicki JA et al. Not too little, not too much: problems of selecting oral antibiotic dose for children. BMJ. 2015 Nov 3;351:h5447.
 - Methods for selecting dose of oral antibiotics in childhood must balance simplicity with accuracy
 - Although using exact weight is most accurate, it requires a recent weight and may not fit with fixed dose formulations
 - Age bands result in a substantial proportion of children receiving doses outside the recommended range and are context specific
- National study currently ongoing looking at dosing of penicillins in children- Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study (NAPPA study)
 - Provision data (awaiting publication) demonstrates underdosing with current BNFc co-amoxiclav dosing recommendations.

	SCAN	BNFc
Amoxicillin	40mg/kg bd (max 1g/dose) OR 3-11 months 250mg bd 1 year-4 years 500mg bd 5-11 years 750mg bd >12 years 1 gram bd	Up to 30mg/kg tds OR 1-11 months 125mg tds 1-4 years 250mg tds 5-11 years 500mg tds 12-17 years 500md tds/1g tds
Penicillin V	Age 6-12 years 500mg bd Age >12 years 1 g bd	Age 6-11 years 250mg qds Age 12-17 years 500mg qds/1g qds
Cefalexin	12.5mg/kg 8 hourly (max 1g per dose). Double dose if severe infection OR 3-11 months 125mg tds 1 year-4 years 250mg tds 5-11 years 500mg tds >12 years 1 gram tds	12.5mg/kg bd 3-11 months 125mg bd 1 year-4 years 125mg tds 5-11 years 250mg tds >12 years 500mg tds (in severe infection up to 25mg/kg qds (age >12 year 1.5g qds) WHO dosing cefalexin 50 mg/kg/day PO divided in 2 or 4 doses