

## CURRENT TOPIC

## Antimicrobial prophylaxis

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If asked to list the greatest advances of modern medicine in order of priority, many—both medical and lay—would put antibiotics at the top of their list. It is surprising therefore that so much of our use of these drugs is based on inadequate evidence and clinical “hearsay”. Nowhere is this more true than their use in prophylaxis against infection. This is particularly unfortunate as such use is complicated by concerns about the promotion of microbial resistance and, in some instances, about the side effects of long term drug administration and about poor compliance. Bacterial resistance to antibiotics is becoming a major issue in both hospital and community practice and has implications not only for the individual patient but also for the community at large. Nevertheless, patterns of treatment have become established and because of the belief, often correct one suspects, that patients would be at risk without them, it has often become difficult to seek objective evidence through placebo controlled trials. This paper examines some of these patterns of use and the evidence, such as it is, to support them. It covers short course prophylaxis first, then long term use, but not the ever changing field of prophylaxis against malaria in travellers<sup>1</sup> or the complex field of prevention of infection in children with malignant disease or following bone marrow or organ transplantation.

**Short course prophylaxis****BACTERIAL ENDOCARDITIS**

The use of a brief course of antibiotic treatment in patients with cardiovascular pathology known or thought to be associated with an enhanced risk of bacterial endocarditis, at times when bacteraemia is thought likely to occur, is a practice which has grown up largely based on hypothetical considerations. There are several practical reasons for this. Only around half of diagnosed cases of endocarditis are known to have predisposing cardiac pathology beforehand. Of those that do, many occur in the absence of a known preceding event or medical procedure likely to have caused bacteraemia.<sup>2</sup> These facts not only render the majority of cases impossible to prevent by antibiotic prophylaxis, but also mean that in cases following such treatment<sup>3</sup> there is always a possibility that prophylaxis was effective and endocarditis resulted from a later (or earlier) “spontaneous” bacteraemia,<sup>2</sup> such as that produced by normal chewing or tooth brushing.<sup>4 5</sup>

Despite the confusion that surrounds the cause-effect relation between dental and surgical procedures and endocarditis, the disease does sometimes occur following such treatments in some susceptible patients.<sup>3</sup> Overall, subacute *Streptococcus viridans* infection of the prolapsed mitral valve or post rheumatic mitral valve following dental procedures is the most common scenario.<sup>3 6</sup> Congenital lesions such as aortic stenosis, bicuspid aortic valve, patent ductus arteriosus, tetralogy of Fallot, pulmonary atresia or stenosis, and ventricular septal defects<sup>3</sup> are most frequently associated with endocarditis in children. Paediatricians should also be alert to the risks in children who have prosthetic valves or patches following cardiac surgery. The incidence of endocarditis in young children has increased fourfold over recent decades,<sup>7</sup> probably as a result of the increase in successful surgery performed to correct previously fatal congenital defects, and, in this group, to the risks of severe acute staphylococcal endocarditis which may masquerade as septicaemia or meningitis.

Many remain sceptical about the effectiveness of correctly administered antibiotic prophylaxis at preventing these cases,<sup>3 8</sup> particularly in the imperfect setting of routine practice.<sup>9</sup> What is certain is that, if it is to be done at all, prophylaxis should be given strictly according to well defined and regularly reviewed guidelines<sup>10 11</sup> combined with advice about good dental hygiene.

**POSTOPERATIVE INFECTIONS**

Infections in patients following surgery are uncommon for the vast majority of procedures, provided that high standards of aseptic technique are maintained. However, when they do occur they can be disastrous for the outcome of the procedure—particularly when any form of prosthetic material is involved—and may cause other serious morbidity, costly intervention, prolonged hospital stay or even death. It is small wonder that surgical colleagues often strive to minimise these risks, and in particular the incidence of wound infections, through the use of antibiotic prophylaxis. A fairly well defined approach to categorising procedures as “clean”, “clean contaminated”, “contaminated”, and “dirty” or “infected” has been established and combined with other risk factors, such as the length of operation, to draw up guidelines based on several studies in adults.<sup>12–14</sup> Although there is little evidence in

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children, the pathogenesis of such infections is likely to be similar.

Some types of surgery for which evidence supports preoperative prophylaxis, such as orthopaedic surgery with prosthesis insertion and peripheral vascular surgery, are not very commonly performed in children. However, there is also evidence to support antibiotic use in other specialist areas such as cardiac surgery via median sternotomy, head and neck surgery involving entry into the oesophagus, and craniotomy including ventricular shunt insertion.<sup>14</sup> Antibiotics are widely used in neonatal surgery but here data are scanty. Anecdotal evidence supports the use of antibiotic prophylaxis following surgery for biliary atresia.<sup>15</sup> Abdominal surgery involving opening of a hollow viscus is perhaps the archetypal "dirty" surgery, and the most common such procedure in children is certainly appendectomy. A single dose of parenteral broad spectrum antibiotics (for example, a cephalosporin, metronidazole, or both) is advocated preoperatively<sup>16</sup> and treatment is continued only if a ruptured or gangrenous appendix is found. While this approach may reduce the number of postoperative infections,<sup>16</sup> it means that all patients are receiving antibiotics to benefit the few with such complications which are often not apparent preoperatively. Perhaps one way round this problem would be to use intraperitoneal antibiotics in selected cases.<sup>17</sup> In every situation the risk and costs of routine antibiotic use have to be weighed against those of preventable infections. As problems such as *Clostridium difficile* associated diarrhoea<sup>18 19</sup> and antimicrobial resistance become more prominent, the balance may shift against routine use.

#### PREVENTION OF OPHTHALMIA NEONATORUM

In some areas of high prevalence of gonorrhoea, newborns receive routine prophylactic antimicrobial eyedrops shortly after birth. One per cent silver nitrate, 1% tetracycline, or 0.5% erythromycin solutions are usually used, although 2.5% povidone iodine is also effective.<sup>20</sup> Silver nitrate can cause chemical conjunctivitis as a side effect but it is the only agent with documented efficacy against penicillinase producing *Neisseria gonorrhoeae*. Although effective, such prophylaxis will not always prevent ophthalmic or disseminated infection, so infants born to mothers with known active gonorrhoea are usually given parenteral antibiotics as well. Since topical prophylaxis is not reliably effective against chlamydial conjunctivitis<sup>21</sup> some experts advise that infants born to mothers with manifest untreated genital chlamydial infection are given a course of oral erythromycin starting on the second or third day of life. These two genital infections often coexist.

#### SKULL FRACTURES

Antibiotics are sometimes given following basal skull fractures in order to reduce the risk of meningitis. There are no studies of adequate size to permit a good assessment of whether this is worthwhile, although the evidence available suggests it has no significant effect. Meta-

analysis of studies published since 1970 revealed that, of 848 fracture victims, 4% of those receiving prophylaxis contracted meningitis versus 3% of controls.<sup>22</sup> It has also been shown that prophylaxis alters the nasopharyngeal flora in favour of resistant organisms.<sup>23</sup>

#### ANIMAL AND TICK BITES

Antibiotics (usually oral amoxycillin/clavulanic acid) are commonly given prophylactically to children with contaminated soft tissue wounds such as human and animal bites although, once again, this practice is based on limited evidence.<sup>24</sup> Antibiotic prophylaxis is also sometimes offered to children known to have had tick bites in areas endemic for Lyme disease but, again, the available evidence is inadequate to judge whether this is useful and the individual risk of infection is extremely low.<sup>25</sup>

#### Long term prophylaxis

##### RECURRENT URINARY TRACT INFECTION

Understanding of the pathophysiology<sup>26</sup> and approaches to the management of infections of the renal tract are also based on limited evidence. Recurrence is certainly a feature of urinary tract infection (UTI) in children<sup>27 28</sup> but the roles of microbial and host factors and to what extent the latter are anatomical, immunological, transient or developmental is uncertain. There is an association between UTI and vesicoureteric reflux (VUR)<sup>29</sup> and, like UTI, prevalence of VUR drops with age.<sup>30 31</sup> Despite this association, there is no obvious direct explanation why this dysfunction of the upper renal tract should promote entry of gut organisms into the urinary tract via the urethra or, perhaps, the bloodstream. Nevertheless, it is clear that the combination of recurrent UTI and VUR can result in renal scarring with long term consequences. For this reason children with UTI undergo renal tract investigations which are now becoming standard.<sup>32</sup>

Preschool children with troublesome recurrent UTI, mild to moderate reflux (international grade<sup>33</sup> I or II—reflux reaches kidney but does not dilate ureters/renal pelvis), or both, are usually managed with prophylactic trimethoprim (2 mg/kg/day) or nitrofurantoin (1–2 mg/kg/day),<sup>31 34</sup> although this approach does not completely guarantee that scarring will not occur.<sup>31</sup> Use of both drugs has been proposed for girls with persistent recurrences on one of these medicines.<sup>35</sup> Children with more severe VUR (international grades III–V—ureteric, calyceal and/or renal pelvic dilatation of increasing severity) more commonly have surgery to reimplant the ureters, which usually stops the reflux so that antibiotic prophylaxis is then stopped. However, trials comparing this approach with long term antibiotic prophylaxis alone suggest that the two approaches result in similar long term rates of scarring and UTI recurrence.<sup>34 36 37</sup> A recent proposal is to screen infants with a positive family history of reflux by cystography so that chemoprophylaxis can be commenced earlier,<sup>38</sup> although the effectiveness of this approach in preventing scarring has not yet been studied.

## ABSENT OR REDUCED SPLENIC FUNCTION

One function of the spleen is to act as a lymphoid filter for the bloodstream, promoting opsonisation and phagocytosis of bacteria and infected cells.<sup>39</sup> Individuals, and in particular young children, with reduced splenic function are prone to septicaemia, particularly from the more virulent polysaccharide encapsulated bacteria such as pneumococci, *Haemophilus influenzae* type b, and meningococci<sup>40-42</sup> as well as a number of more unusual infections.<sup>43-46</sup> This immunodeficiency is compounded in many cases by underlying disorders necessitating splenectomy (for example, malignancy) or inducing hypofunction (for example, sickle cell disease), or associated treatments (for example, steroids, chemotherapy, bone marrow transplantation). It is recommended that all children with hyposplenism should receive continuous daily oral antibiotic prophylaxis<sup>47</sup> with phenoxymethyl penicillin, amoxicillin or, in allergic patients, erythromycin.<sup>48</sup> However, evidence to support this is incomplete and some argue that it is inappropriate to institute life long prophylaxis in most cases,<sup>49</sup> since virtually all cases of severe infection occur where identifiable additional risk factors are present and because it is difficult to ensure compliance. Nevertheless, perhaps in part because of the poor antibody responses to polysaccharide capsular antigens in infants and toddlers and associated higher risks, most experts agree that antibiotic prophylaxis should be used in young children. It should also be borne in mind that such treatment does not guarantee protection against invasive infection, so patients and their parents need to understand the need to seek urgent medical advice when they are feverish or unwell so that appropriate intravenous antimicrobial therapy can be instituted if necessary.

Although detailed discussion of immunisation is outside the scope of this paper, the use of vaccines is important in this group. Affected children should receive all routine immunisations, and protection with non-routine vaccines (such as pneumococcal, influenza, and meningococcal vaccines and booster doses of Hib vaccine) is also important, although current guidelines are not always consistent.<sup>48, 50</sup> Practice in this area will change in the near future with the arrival of new conjugated pneumococcal and meningococcal vaccines.

## RESPIRATORY INFECTIONS AND THE IMMUNODEFICIENT CHILD

Some children appear to suffer unusually frequently or severely from common respiratory infectious diseases such as bacterial otitis media, sinusitis, and pneumonia. In such children the threshold to intervene with standard treatment or to augment treatment to parenteral or high dose administration becomes lowered. A few with serious immunodeficiencies carry a risk of treatable respiratory infections not normally seen in healthy children, such as *Pneumocystis carinii* pneumonia, and may require high dose specific intravenous therapy (usually trimethoprim/sulphamethoxazole (cotrimoxazole)) if they present with acute pneumonia. Low daily or alternate

day prophylactic doses of cotrimoxazole reduce the risk of *Pneumocystis carinii* pneumonia in adults with AIDS,<sup>51</sup> and are also used in children with severe primary or secondary cellular immunodeficiency<sup>52</sup> in whom they may also reduce the low risk of symptomatic toxoplasma infection. Systemic long term anti-fungal agents (for example, fluconazole, itraconazole) are given to some patients with chronic mucocutaneous candidiasis and chronic granulomatous disease, principally to prevent or suppress candida and aspergillus infections, respectively.

The most common clinical situation is the need to prevent chronic or recurrent bacterial upper respiratory infections including otitis media and lower respiratory tract infections in children with demonstrable humoral (such as Ig isotype or IgG subclass) or other opsonic immunodeficiency, or an apparent predisposition to recurrent respiratory infection without a defined underlying cause. This is done both in order to try and avoid the disruptive consequences of such illness, such as significant school absence, and, in more severe cases, to prevent the development of chronic lung or ear injury. In very severe cases, particularly when an IgG production defect is demonstrable, antibiotic prophylaxis is combined with antibody replacement therapy.<sup>53</sup>

A meta-analysis published in 1993 indicates that antibiotic prophylaxis does have an impact on occurrence of recurrent acute otitis media, although not on chronic otitis media with effusion or "glue ear".<sup>54</sup> Several small placebo controlled studies have shown that a single daily dose of sulphonamide antibiotic reduces the incidence of recurrence of otitis media over a period of a few months in otitis prone children,<sup>55, 56</sup> and that such drugs are as efficacious as amoxicillin,<sup>57, 58</sup> which costs more, and more frequently causes side effects and resistance which is a major concern. One small placebo controlled study showed that phenoxymethyl/penicillin given intermittently at the time of upper respiratory infections in otitis prone children reduced the incidence of acute otitis by 50%,<sup>59</sup> but did not make any comparison with continuous prophylaxis. However, larger studies over longer periods have not been done, nor have trials in children with diagnosed immunodeficiency, probably because placebo controls among such cases would be considered unethical. Neither are there controlled data, except from small studies,<sup>60</sup> on the efficacy of antibiotic prophylaxis in preventing other bacterial infections (including those of the lower respiratory tract) in such children, although it is widely assumed to be effective.

In the UK, none of the mainstream antibiotics is specifically licensed for prevention of respiratory infection. The majority of paediatric immunologists use cotrimoxazole (a combination of trimethoprim plus sulphamethoxazole) given once daily at approximately a third to a quarter the therapeutic dose (60-120 mg in infants and toddlers, 240 mg in children up to approximately 40 kg, then 480 mg). This drug combination has a relatively long half life, is

Table 1 Percentages of laboratory isolates of common respiratory pathogens sensitive to trimethoprim alone and trimethoprim-sulphamethoxazole (cotrimoxazole)

Organism	Trimethoprim sensitive	Cotrimoxazole sensitive
<i>Haemophilus</i> species	90 (n = 32892)	92.4 (n = 15558)
<i>Streptococcus pneumoniae</i>	46.4 (n = 7921)	88.1 (n = 5385)
Moraxella	5.3 (n = 3929)	78.6 (n = 2002)
Group A streptococcus	73 (n = 8515)	80.7 (n = 3276)

Data were collected from UK clinical laboratories between 1986 and 1997 (Dr T Winstanley, Department of Microbiology, Royal Hallamshire Hospital, Sheffield, UK—"Microbe Base", sponsored by GlaxoWellcome UK).

well absorbed orally, and has good penetration into all body fluids, cells and mucosal surfaces. It is not now widely used as a first line routine paediatric antibiotic so that there are fewer concerns regarding emergence of bacterial resistance in the individual patient and more generally. It seems to be remarkably well tolerated by almost all children who usually seem to like the taste of at least one of the currently available preparations and their parents who can usually remember to give it once a day at bedtime. The drug, once used widely in the prophylaxis of urinary tract infection in both adults and children, has fallen into disfavour in that setting as trimethoprim alone is equally effective and is less likely to cause the very rare cases of severe Stevens-Johnson syndrome associated with the combination (see below). Although some have advised against use of the combination for treatment of respiratory infection,<sup>61</sup> there is good microbiological evidence to support the use of the combination, as opposed to trimethoprim alone, against the main bacterial upper respiratory pathogens (table 1).

Occasionally children develop a rash early after starting cotrimoxazole, necessitating discontinuation of treatment, but this is unusual<sup>62</sup>; the drug does not often seem to cause the gastrointestinal symptoms commonly associated with  $\beta$  lactams and some macrolides. The main rare serious side effects of concern with cotrimoxazole are bone marrow suppression and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, or both). This can be a serious problem in patients with HIV requiring pneumocystis prophylaxis.<sup>63</sup> In the general population, some studies suggest the incidence is comparable to that seen with amoxicillin and other antibiotics,<sup>64, 65</sup> although others show a higher risk for sulphonamides.<sup>66</sup> All studies agree that these are extremely rare events and almost always resolve on discontinuation of the drug.<sup>67, 68</sup> Amoxicillin with or without clavulanic acid, an oral cephalosporin, or erythromycin or one of the newer macrolides given once or twice daily are all used as alternatives in this setting.

### Conclusion

Although there is general agreement that medical practice should be based on sound evidence, there are some areas where it is lacking. Prophylactic use of antibiotics is one such area. Effective studies of both short and long term prophylaxis would require multicentre collaboration and large numbers of patients, in the former because the incidence of infections after procedures is low, and in the latter

because the patients concerned are relatively rare. Studies of long term prophylaxis also require painstaking follow up over prolonged periods. Placebo controlled trials are often unethical in such patient groups so that the only feasible studies are comparisons between alternative agents. The candidate antibiotics are generally not new—indeed, they are usually older, cheaper agents out of patent—and the quantities used in these settings are small compared to overall prescriptions for treatment of infections. There is thus little incentive for pharmaceutical companies, upon whom we seem to depend increasingly to fund clinical trials, to invest in such studies. Nevertheless, we need to seek this evidence. The growth in size and importance of European clinical societies in paediatric subspecialties (cardiology, surgery, respiratory medicine, infectious diseases, and immunology), combined with improving electronic communication and data handling, and with them opportunities for collaboration, may permit such studies to be done.

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