CURRENT TOPIC

Antimicrobial prophylaxis

Jason Smith, Adam Finn

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[1] 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.[2] These facts not only render the majority of cases impossible to prevent by antibiotic prophylaxis, but also mean that in cases following such treatment[3] there is always a possibility that prophylaxis was effective and endocarditis resulted from a later (or earlier) "spontaneous" bacteraemia,[2] such as that produced by normal chewing or tooth brushing.[4 5]

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.[3] Overall, subacute *Streptococcus viridans* infection of the prolapsed mitral valve or post rheumatic mitral valve following dental procedures is the most common scenario.[3 6] Congenital lesions such as aortic stenosis, bicuspid aortic valve, patent ductus arteriosus, tetralogy of Fallot, pulmonary atresia or stenosis, and ventricular septal defects[3] 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,[7] 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,[3 8] particularly in the imperfect setting of routine practice.[9] 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[10 11] 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.[12–14] Although there is little evidence in

Sheffield Institute for Vaccine Studies, Division of Child Health, University of Sheffield, Children's Hospital, Sheffield S10 2TH, UK
J Smith
A Finn

Correspondence to:
Dr Finn.
email: A.Finn@sheffield.ac.uk

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.[14] 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.[15] Abdominal surgery involving opening of a hollow viscus is perhaps the archetypal "dirty" surgery, and the most common such procedure in children is certainly appendicectomy. A single dose of parenteral broad spectrum antibiotics (for example, a cephalosporin, metronidazole, or both) is advocated preoperatively[16] and treatment is continued only if a ruptured or gangrenous appendix is found. While this approach may reduce the number of postoperative infections,[16] 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.[17] 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[18 19] 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.[20] 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[21] 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.[22] It has also been shown that prophylaxis alters the nasopharyngeal flora in favour of resistant organisms.[23]

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.[24] 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.[25]

Long term prophylaxis

RECURRENT URINARY TRACT INFECTION

Understanding of the pathophysiology[26] 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[27 28] 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)[29] and, like UTI, prevalence of VUR drops with age.[30 31] 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.[32]

Preschool children with troublesome recurrent UTI, mild to moderate reflux (international grade[33] 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),[31 34] although this approach does not completely guarantee that scarring will not occur.[31] Use of both drugs has been proposed for girls with persistent recurrences on one of these medicines.[35] 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.[34 36 37] A recent proposal is to screen infants with a positive family history of reflux by cystography so that chemoprophylaxis can be commenced earlier,[38] 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.[39] 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[40–42] as well as a number of more unusual infections.[43–46] 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[47] with phenoxymethyl penicillin, amoxycillin or, in allergic patients, erythromycin.[48] However, evidence to support this is incomplete and some argue that it is inappropriate to institute life long prophylaxis in most cases,[49] 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.[48 50] 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,[51] and are also used in children with severe primary or secondary cellular immunodeficiency[52] in whom they may also reduce the low risk of symptomatic toxoplasma infection. Systemic long term antifungal 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.[53]

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".[54] 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,[55 56] and that such drugs are as efficacious as amoxycillin,[57 58] 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%,[59] 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,[60] 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*
Haemophilus species	90 (n = 32892)	92.4 (n = 15558)
Streptococcus pneumoniae	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,[61] 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[62]; the drug does not often seem to cause the gastrointestinal symptoms commonly associated with β 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.[63] In the general population, some studies suggest the incidence is comparable to that seen with amoxycillin and other antibiotics,[64 65] although others show a higher risk for sulphonamides.[66] All studies agree that these are extremely rare events and almost always resolve on discontinuation of the drug.[67 68] Amoxycillin 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 subspecialities (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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1 Protective measures against malaria. In: *International travel and health*. Geneva: World Health Organization; 1997. (http://jupiter.who.ch/yellow/protect.htm)
2 Oakley CM. Controversies in the prophylaxis of infective endocarditis: a cardiological view. *J Antimicrob Chemother* 1987;**20**(suppl A):99–104.
3 Durack DT, Kaplan EL, Bisno AL. Apparent failures of endocarditis prophylaxis: analysis of 52 cases submitted to a national registry. *JAMA* 1983;**250**:2318–22.
4 Longman LP, Martin MV. The prevention of infective endocarditis-paedodontic considerations. British Society for Antimicrobial Chemotherapy. *International Journal of Paediatric Dentistry* 1993;**3**:63–70.
5 Silver JG, Martin AW, McBride BC. Experimental transient bacteraemias in human subjects with varying degrees of plaque accumulation and gingival inflammation. *J Clin Periodontol* 1977;**4**:92–9.
6 Delaye J, Etienne J, Feruglio GA, *et al*. Prophylaxis of infective endocarditis for dental procedures: report of a working party of the European Society of Cardiology. *Eur Heart J* 1985;**6**:826–8.
7 Normand J, Bozio A, Etienne J, Sassolas F, Le Bris H. Changing patterns and prognosis of infective endocarditis in childhood. *Eur Heart J* 1995;**16**(suppl B):28–31.
8 Anon. Chemoprophylaxis for infective endocarditis: faith, hope, and charity challenged. *Lancet* 1992;**339**:525–6.
9 Van der Meer JT, Van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet* 1992;**339**:135–9.
10 Simmons NA. Recommendations for endocarditis prophylaxis: endocarditis working party for antimicrobial chemotherapy. *J Antimicrob Chemother* 1993;**31**:437–8.
11 Dajani AS, Taubert KA, Wilson W, *et al*. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;**277**:1794–801.
12 Page CP, Bohnen JM, Fletcher JR, McManus AT, Solomkin JS, Wittmann DH. Antimicrobial prophylaxis for surgical wounds: guidelines for clinical care. *Arch Surg* 1993;**128**: 79–88.
13 Antimicrobial prophylaxis in surgery. *Med Lett Drugs Ther* 1995;**37**:79–82.
14 Dellinger EP, Gross PA, Barrett TL, *et al*. Quality standard for antimicrobial prophylaxis in surgical procedures. Infectious Diseases Society of America. *Clin Infect Dis* 1994;**18**: 422–7.
15 Lally KP, Kanegaye J, Matsumura M, Rosenthal P, Sinatra F, Atkinson JB. Perioperative factors affecting the outcome following repair of biliary atresia. *Pediatrics* 1989;**83**:723–6.
16 Soderquist Elinder C, Hirsch K, Bergdahl S, Rutqvist J, Frenckner B. Prophylactic antibiotics in uncomplicated appendicitis during childhood: a prospective randomised study. *Eur J Pediatr Surg* 1995;**5**:282–5.
17 Thomson SR, Carle G, Reid TM, Davidson AI, Miller SS. Antibiotic prophylaxis in non-perforated appendicitis of childhood: tetracycline lavage compared with peroperative intravenous cefuroxime and metronidazole. *J Hosp Infect* 1987;**9**:158–61.
18 Jobe BA, Grasley A, Deveney KE, Deveney CW, Sheppard BC. Clostridium difficile colitis: an increasing hospital-acquired illness. *Am J Surg* 1995;**169**:480–3.
19 Andrejak M, Schmit JL, Tondriaux A. The clinical significance of antibiotic-associated pseudomembranous colitis in the 1990s. *Drug Saf* 1991;**6**:339–49.

20 Isenberg SJ, Apt L, Wood M. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *N Engl J Med* 1995;**332**:562–6.
21 Ratelle S, Keno D, Hardwood M, Etkind PH. Neonatal chlamydial infections in Massachusetts, 1992–1993. *Am J Prev Med* 1997;**13**:221–4.
22 Rathore MH. Do prophylactic antibiotics prevent meningitis after basilar skull fracture? *Pediatr Infect Dis J* 1991;**10**:87–8.
23 Ignelzi RJ, VanderArk GD. Analysis of the treatment of basilar skull fractures with and without antibiotics. *J Neurosurg* 1975;**43**:721–6.
24 Cummings P. Antibiotics to prevent infection in patients with dog bite wounds: a meta-analysis of randomized trials. *Ann Emerg Med* 1994;**23**:535–40.
25 Warshafsky S, Nowakowski J, Nadelman RB, Kamer RS, Peterson SJ, Wormser GP. Efficacy of antibiotic prophylaxis for prevention of Lyme disease. *J Gen Intern Med* 1996;**11**: 329–33.
26 Benson M, Jodal U, Agace W, *et al*. Interleukin (IL)-6 and IL-8 in children with febrile urinary tract infection and asymptomatic bacteriuria. *J Infect Dis* 1996;**174**:1080–4.
27 Bergstrom T, Larson H, Lincoln K, Winberg J. Studies of urinary tract infections in infancy and childhood. XII. Eighty consecutive patients with neonatal infection. *J Pediatr* 1972;**80**:858–66.
28 Gruneberg RN, Smellie JM, Leakey A, Atkin WS. Long-term low-dose cotrimoxazole in prophylaxis of childhood urinary tract infection: bacteriological aspects. *BMJ* 1976;ii:206–8.
29 Medical versus surgical treatment of primary vesicoureteral reflux: a prospective international reflux study in children. *J Urol* 1981;**125**:277–83.
30 Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. *BMJ* 1977;ii:285–8.
31 Arant BS. Medical management of mild and moderate vesicoureteral reflux: followup studies of infants and young children: a preliminary report of the southwest pediatric nephrology study group. *J Urol* 1992;**148**:1683–7.
32 Pilling D, Postlethwaite R. *Imaging in urinary tract infection*. London: British Paediatric Association Committee on Paediatric Practice Guidelines, 1996.
33 Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen MTE. International system of radiographic grading of vesicoureteric reflux. International reflux study in children. *Pediatr Radiol* 1985;**15**:105–9.
34 Jodal U, Koskimies O, Hanson E, *et al*. Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. International reflux study in children. *J Urol* 1992;**148**:1650–2.
35 Smith EM, Elder JS. Double antimicrobial prophylaxis in girls with breakthrough urinary tract infections. *Urology* 1994;**43**:708–12.
36 Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). International reflux study in children. *J Urol* 1992;**148**:1667–73.
37 Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham reflux study group. *BMJ Clin Res* 1987;**295**:237–41.
38 Scott JE, Swallow V, Coulthard MG, Lambert HJ, Lee RE. Screening of newborn babies for familial ureteric reflux. *Lancet* 1997;**350**:396–400.
39 Rosse WF. The spleen as a filter. *N Engl J Med* 1987;**317**:704–6.
40 Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late postsplenectomy infection. *Br J Surg* 1991;**78**:716–21.
41 Traub A, Giebink GS, Smith C, *et al*. Splenic reticuloendothelial function after splenectomy, spleen repair, and spleen autotransplantation. *N Engl J Med* 1987;**317**:1559–64.
42 Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg* 1991;**78**:1031–8.
43 Rosner F, Zarrabi MH, Benach JL, Habicht GS. Babesiosis in splenectomized adults: review of 22 reported cases. *Am J Med* 1984;**76**:696–701.
44 McCarthy M, Zumla A. DF-2 infection. *BMJ* 1988;**297**: 1355–6.
45 Edwards LD, Digioia R. Infections in splenectomized patients: a study of 131 patients. *Scand J Infect Dis* 1976;**8**: 255–61.
46 Oster CN, Koontz LC, Wyler DJ. Malaria in asplenic mice: effects of splenectomy, congenital asplenia, and splenic reconstitution on the course of infection. *Am J Trop Med Hyg* 1980;**29**:1138–42.
47 Scopes JW. Continued need for pneumococcal prophylaxis after splenectomy. *Arch Dis Child* 1991;**66**:750.
48 Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996;**312**:430–4.
49 Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg* 1991;**78**:1031–8.
50 Chief Medical Officer. Asplenic patients and immunisation. *CMO's update* 1994;**1**:3.
51 Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for Pneumocystis carinii pneumonia in AIDS. *JAMA* 1988; **259**:1185–9.
52 1995 Revised guidelines for prophylaxis against Pneumocystis carinii pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR Recommendations and Reports* 1995;**44**:1–11.
53 Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. Consensus panel for the diagnosis and management of primary antibody deficiencies. *BMJ* 1994;**308**:581–5.
54 Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: a meta-analytic attempt to resolve the brouhaha. *JAMA* 1993;**270**:1344–51.
55 Liston TE, Foshee WS, Pierson WD. Sulfisoxazole chemoprophylaxis for frequent otitis media. *Pediatrics* 1983;**71**: 524–30.
56 Varsano I, Volovitz B, Mimouni F. Sulfisoxazole prophylaxis of middle ear effusion and recurrent acute otitis media. *Am J Dis Child* 1985;**139**:632–5.
57 Principi N, Marchisio P, Massironi E, Grasso RM, Filiberti G. Prophylaxis of recurrent acute otitis media and middle-ear effusion: comparison of amoxicillin with sulfamethoxazole and trimethoprim. *Am J Dis Child* 1989;**143**:1414–8.
58 Sih T, Moura R, Caldas S, Schwartz B. Prophylaxis for recurrent acute otitis media: a Brazilian study. *Int J Pediatr Otorhinolaryngol* 1993;**25**:19–24.
59 Prellner K, Fogle Hansson M, Jorgensen F, Kalm O, Kamme C. Prevention of recurrent acute otitis media in otitis-prone children by intermittent prophylaxis with penicillin. *Acta Otolaryngol Stockh* 1994;**114**:182–7.
60 Nydahl Persson K, Petterson A, Fasth A. A prospective, double-blind, placebo-controlled trial of iv immunoglobulin and trimethoprim-sulfamethoxazole in children with recurrent respiratory tract infections. *Acta Paediatr* 1995; **84**:1007–9.
61 Howe RA, Spencer RC. Cotrimoxazole. Rationale for re-examining its indications for use. *Drug Saf* 1996;**14**: 213–18.
62 Gutman LT. The use of trimethoprim-sulfamethoxazole in children: a review of adverse reactions and indications. *Pediatr Infect Dis* 1984;**3**:349–57.
63 Anderson JA. Antibiotic drug allergy in children. *Curr Opin Pediatr* 1994;**6**:656–60.
64 Chan HL, Stern RS, Arndt KA, *et al*. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990;**126**:43–7.
65 Jick H, Derby LE. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy* 1995;**15**:428–32.
66 Roujeau JC, Kelly JP, Naldi L, *et al*. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;**333**:1600–7.
67 Myers MW, Jick H. Hospitalization for serious blood and skin disorders following cotrimoxazole. *Br J Clin Pharmacol* 1997;**43**:649–51.
68 Schopf E. Skin reactions to co-trimoxazole. *Infection* 1987;**15**(suppl 5):S254–8.