Adverse Effects, Treatment, and Precautions

As for Polymyxin B Sulfate, p.318.

Colistin sulfate is poorly absorbed from the gastrointestinal tract and adverse effects do not normally occur with usual oral doses. However, gastrointestinal absorption is limited and unpredictable in infants under 6 months of age and systemic adverse effects such as transient sensory disturbances may occur in this patient group.

Cough and bronchospasm may occur during inhalation; cases of sore throat or sore mouth, possibly due to hypersensitivity or superinfection with *Candida* spp., have also been reported. Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery. Pain and local irritation are reported to be less troublesome after intramuscular injection of colistimethate sodium than with colistin sulfate or polymyxin B. Overgrowth of nonsusceptible organisms, particularly *Proteus* spp., may occur after prolonged use.

Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/mL) are recommended.

Cystic fibrosis. Intravenous colistin sulfate was reported to be associated with a lower rate of severe nephrotoxicity among 19 patients with cystic fibrosis than has been previously reported in other patient populations.[1] However, fatal acute respiratory distress syndrome (ARDS) has been reported in a cystic fibrosis patient after inhalation of colistimethate sodium 75 mg twice daily.[2] The solution used had been compounded 5 weeks previously, and it was considered that ARDS was caused by the conversion of colistimethate sodium to the active form colistin which may cause airway or alveolar injury. The FDA subsequently warned that inhalation solutions should be used promptly after preparation (see Stability, above).

1. Bosso JA, *et al.* Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991; **25:** 1168–70.
2. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; **357:** 2310–1.

Effects on the cardiovascular system. Significant, but transient, hypotension occurred in a patient after starting aerosolised colistin inhalation.[1] Intravenous colistin, alone or with aerosolised amikacin, had no such effect on blood pressure.

1. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant Pseudomonas aeruginosa. *Ann Pharmacother* 2006; **40:** 1677–80.

Porphyria. Colistin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Polymyxin B Sulfate, p.318.

Antimicrobial Action

The antimicrobial spectrum and mode of action of colistin is similar to that of polymyxin B (p.318) but colistin sulfate is slightly, and colistimethate significantly, less active.

Pharmacokinetics

Colistin sulfate and colistimethate sodium are poorly absorbed from the gastrointestinal tract of adults and children; however, limited and unpredictable gastrointestinal absorption occurs in infants under 6 months of age. The drugs are not absorbed through mucous membranes, or intact or denuded skin. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistin is reported to be more than 50% but that of colistimethate sodium is low. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate. Some colistimethate sodium may be hydrolysed to colistin *in vivo*. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment; values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute. Half-life may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days.

Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults; it is reduced in patients with renal impairment. Colistin crosses the placenta but diffusion into the CSF is negligible. It is distributed into breast milk.

Cystic fibrosis. References.

1. Reed MD, *et al.* The pharmacokinetics of colistin in patients with cystic fibrosis. *J Clin Pharmacol* 2001; **41:** 645–54.
2. Li J, *et al.* Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. *J Antimicrob Chemother* 2003; **52:** 987–92.
3. Ratjen F, *et al.* Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006; **57:** 306–11.

Uses and Administration

Colistin is a polymyxin antibacterial that has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*, although other drugs are usually preferred. Colistimethate sodium is used by inhalation in the management of respiratory infections, especially in patients with cystic fibrosis (p.166). Colistin has been given orally as the sulfate for the treatment of gastrointestinal infections. Colistin sulfate is also given orally for bowel preparation before abdominal surgery, and with other drugs in regimens for selective digestive tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p.175).

The usual oral dose of colistin sulfate is 1.5 to 3 million units given 3 times daily. For bowel preparation, the same dose is given for 24 hours with the course being completed 12 hours before surgery.

Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units given 3 times daily (maximum dose 6 million units in 24 hours) for patients weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients (see Adverse Effects and Precautions, above).

Colistimethate sodium may also be given by inhalation in respiratory infections as an adjunct to systemic antibacterial therapy. The usual dose is 1 to 2 million units given 2 or 3 times daily. A 3-week course of 2 million units twice daily may be given initially, increased to a maximum of 2 million units given 3 times daily for up to 3 months in frequent recurrent infections; 1 to 2 million units twice daily may be given for long-term therapy. Solutions for inhalation should be freshly prepared (see Stability, above).

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

For details of doses in infants and children, see below.

Colistimethate sodium has also been given by subconjunctival injection and as a bladder instillation. Both colistin sulfate and colistimethate sodium have been applied topically, often with other antibacterials, in the management of ear, eye, and skin infections.

◊ Reviews.

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; **40:** 1333–41. Correction. *ibid.* 2006; **42:** 1819. [dose]
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; **4:** 138–46.
3. Li J, *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; **6:** 589–601.

Administration in children. The following doses of colistin sulfate may be given **orally** to children according to weight:

- up to 15 kg: 0.25 to 0.5 million units 3 times daily
- 15 to 30 kg: 0.75 to 1.5 million units 3 times daily
- over 30 kg: the usual adult dose (see above)

Parenteral doses of colistimethate sodium may vary between countries.

UK according to weight:

- up to 60 kg: 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 60 kg: the usual adult dose (see above)

USA:

- children may be given the usual adult dose, equivalent to colistin base, of 2.5 to 5 mg/kg daily in 2 to 4 divided doses

Monitoring of plasma concentrations is required in some patients (see Adverse Effects, Treatment, and Precautions, above).

For **inhalation** colistimethate sodium may be given in the following doses according to age:

- under 2 years: 0.5 to 1 million units twice daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 2 years: the usual adult dose (see above)

Doses and dosage intervals should be adjusted in patients with renal impairment (see below).

Administration in renal impairment. Dosage of parenteral and inhaled colistimethate sodium must be adjusted in renal impairment; both reduction in dose and decreased frequency of dosing may be required.

In the UK, the following **parenteral** doses of colistimethate sodium, based on creatinine clearance (CC), have been suggested for patients weighing more than 60 kg:

- CC 20 to 50 mL/minute: 1 to 2 million units every 8 hours
- CC 10 to 20 mL/minute: 1 million units every 12 to 18 hours
- CC less than 10 mL/minute: 1 million units every 18 to 24 hours

US licensed product information suggests the following modified doses (equivalent to colistin base) for adults with renal impairment in terms of plasma-creatinine concentrations:

- 1.3 to 1.5 mg/100 mL: 150 to 230 mg given daily in two divided doses
- 1.6 to 2.5 mg/100 mL: 133 to 150 mg given daily as a single dose or in 2 divided doses
- 2.6 to 4.0 mg/100 mL: 100 to 150 mg given every 36 hours

The following doses **by inhalation** have been suggested based on creatinine concentrations:

- 106 to 129 micromoles/litre: 1 to 1.5 million units every 12 hours
- 130 to 214 micromoles/litre: 1 million units every 12 or 24 hours
- 215 to 340 micromoles/litre: 1 to 1.5 million units every 36 hours

Preparations

BP 2008: Colistimethate Injection; Colistin Tablets;
USP 31: Colistimethate for Injection; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Colistin Sulfate for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Alfacolin; Alficetin; ***Austral.:*** Coly-Mycin M; ***Belg.:*** Colistineb; ***Canad.:*** Coly-Mycin M; ***Cz.:*** Colimycine†; Colomycin; ***Denm.:*** Colimycin; ***Fr.:*** Colimycine; ***Ger.:*** Diaront mono; ***Gr.:*** Tadim; ***India:*** Walamycin; ***Irl.:*** Colomycin; ***Israel:*** Coliracin; ***Ital.:*** Colimicina; ***Neth.:*** Belcomycine†; Colimycine†; ***Norw.:*** Colimycin; ***NZ:*** Coly-Mycin M†; ***Port.:*** Colixin; ***Spain:*** Colimicina; ***Thai.:*** Colistate; ***UK:*** Colomycin; Promixin; ***USA:*** Coly-Mycin M; ***Venez.:*** Colisil†.

Multi-ingredient: ***Arg.:*** Clarex Compuesto; Eristin; Eubetal Biotic†; ***Fr.:*** Bacicoline; ***Ger.:*** Ecolicin; ***Ital.:*** Colbiocin; Eubetal Antibiotico; ***Mex.:*** Colfur; ***Neth.:*** Bacicoline-B; ***NZ:*** Antibiotic Simplex; ***Philipp.:*** Elicocin; ***Rus.:*** Colbiocin (Колбиоцин); ***USA:*** Coly-Mycin S Otic; Cortisporin-TC.

Co-tetroxazine *(BAN)*

Tetroxoprima y sulfadiazina.
CAS — 73173-12-3.

Profile

Co-tetroxazine, a mixture of tetroxoprim and sulfadiazine in the proportion of 2:5, has properties similar to those of co-trimoxazole (below). It has been given orally, mainly in the treatment of infections of the urinary and respiratory tracts, including pneumocystis pneumonia.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Sterinor†; ***Venez.:*** Esterinor†.

Co-trifamole *(BAN)*

CN-3123; Cotrifamol.
ATC — J01EE04.

Profile

Co-trifamole, a mixture of 5 parts of sulfamoxole and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations

Proprietary Preparations (details are given in Part 3)
S.Afr.: Supristol†.

Co-trimazine *(BAN)*

Trimetoprima y sulfadiazina.
CAS — 39474-58-3.
ATC — J01EE02.

Profile

Co-trimazine, a mixture of 5 parts of sulfadiazine and 1 part of trimethoprim, has properties similar to those of co-trimoxazole (below) and has been used similarly.

Preparations are available in some countries which contain trimethoprim and sulfadiazine in proportions different to co-trimazine.

Co-trimoxazole *(BAN)*

Cotrimoxazol; Ko-trimoksazol.
CAS — 8064-90-2.
ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Stability. Diluted infusion solutions of co-trimoxazole have a limited stability and eventually form a precipitate: this happens more rapidly at higher concentrations. The manufacturers recommend a dilution of 480 mg in 130 mL, which is usually stable for up to 6 hours, but more concentrated solutions should be used within shorter periods of time, and a dilution of 480 mg in 80 mL should be used within 1 hour. The usual diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, have been stated to be compatible for adequate periods.

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components (see Sulfamethoxazole, p.340, and Trimethoprim, p.355). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, below).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] predominantly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the prescribing of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, below), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and remained predominantly in elderly patients.

1. Committee on Safety of Medicines. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al.* Co-trimoxazole toxicity. *BMJ* 1985; **291:** 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; **291**: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; **ii**: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; **ii**: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; **345:** 1118–19.
8. Committee on Safety of Medicines. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Precautions

As for Sulfamethoxazole, p.340 and Trimethoprim, p.355.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of skin rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al.* Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; **25:** 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; **1:** 687–91.

G6PD deficiency. It has been suggested that co-trimoxazole should be avoided by people with G6PD deficiency.[1]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; **67**: 601–11.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in **patients with AIDS** being treated for *Pneumocystis carinii* pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

The occurrence of high serum concentrations of trimethoprim and sulfamethoxazole in patients has been proposed as a contributing factor to the high incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the **dose** of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] demonstrated no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine **metabolites** of sulfamethoxazole which produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p.340.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92–106.
2. Gordin FM, *et al.* Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
3. Jaffe HS, *et al.* Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; **ii**: 1109–11.
4. Mitsuyasu R, *et al.* Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535.
5. Colebunders R, *et al.* Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **107**: 599–600.
6. Sattler FR, *et al.* Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **109**: 280–7.
7. Stevens RC, *et al.* Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; **35**: 1884–90.
8. Para MF, *et al.* Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; **24:** 337–43.
9. McLean I, *et al.* Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; **ii**: 857–8.
10. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
11. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47:** 571–3.
12. Gibbons RB, Lindauer JA. Successful treatment of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in hypersensitive AIDS patients. *JAMA* 1985; **253**: 1259–60.
13. Toma E, Fournier S. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338:** 954.
14. Kreuz W, *et al.* "Treating through" hypersensitivity to co-trimoxazole in children with HIV infection. *Lancet* 1990; **336**: 508–9.
15. Carr A, *et al.* Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7:** 65–71.
16. Absar N, *et al.* Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93:** 1001–5.
17. Cortese LM, *et al.* Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; **30:** 184–6.
18. Caumes E, *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133:** 465–9.
19. Demoly P, *et al.* Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; **102:** 1033–6.
20. Lin D, *et al.* Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/07/08).
21. Woods WG, *et al.* Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia. *J Pediatr* 1984; **105**: 639–44.
22. Drysdale HC, Jones LF. Co-trimoxazole prophylaxis in leukaemia. *Lancet* 1982; **i**: 448.
23. Dib EG, *et al.* Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 2004; **350:** 88–9.