It is given topically as the sulfate for the treatment of eye infections. It has also been given intramuscularly and orally. It is reported to be more toxic than kanamycin.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Kanacyl†.

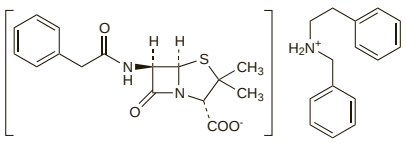
Multi-ingredient: ***Ital.:*** Visucloben Antibiotico; Visumetazone Antibiotico.

Benethamine Penicillin *(BAN, rINN)*

Bénéthamine Pénicilline; Benethaminum Penicillinum; Penicilinabenetamina. Benzyl(phenethyl)ammonium (6*R*)-6-(2-phenylacetamido)penicillanate.

Бенетамин Пенициллин

$C_{15}H_{17}N,C_{16}H_{18}N_2O_4S$ = 545.7.
CAS — 751-84-8.



Profile

Benethamine penicillin is a poorly soluble derivative of benzylpenicillin (p.213) with similar actions and uses, although it is not recommended for chronic, severe, or deep-seated infections. After deep intramuscular injection it forms a depot from which it is slowly absorbed and hydrolysed to benzylpenicillin. Benethamine penicillin is usually given with benzylpenicillin sodium and also sometimes procaine benzylpenicillin to produce both an immediate and a prolonged effect; overall, the effect lasts for 2 to 3 days.

Preparations

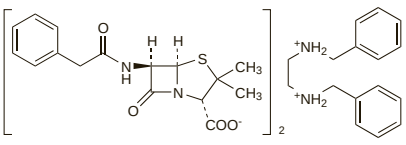
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Fr.:*** Biclinocilline; ***Port.:*** Atralmicina.

Benzathine Benzylpenicillin *(BAN, rINN)*

Bensylpenicillinbensatin; Bensylpenicillinbenzatin; Bentsyylipenisilliinibentsatiini; Benzathin-benzylpenicilin; Benzathine benzylpénicilline; Benzathine Penicillin; Benzathini Benzylpenicillinum; Benzatin Penisilin; Benzatina bencilpenicilina; Benzethacil; Benzilpenicilinas benzatinas; Benzilpenicillina Benzatinica; Benzilpenicillin-benzantin; Benzylopenicylina benzatynowa; Benzylpenicillinum Benzanthinum; Benzylpenicillinum benzathinum; Penicillin G Benzathine; Penisilin G Benzatin; Penzaethinum G. *NN′*-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenylacetamido)penicillanate].

Бензатина Бензилпенициллин

$C_{16}H_{20}N_2(C_{16}H_{18}N_2O_4S)_2$ = 909.1.
CAS — 1538-09-6 (anhydrous benzathine benzylpenicillin); 5928-83-6 (benzathine benzylpenicillin monohydrate); 41372-02-5 (benzathine benzylpenicillin tetrahydrate).
ATC — J01CE08.
ATC Vet — QJ01CE08.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Int.* *Jpn* and *US* include the tetrahydrate.
Ph. Eur. 6.2 (Benzylpenicillin, Benzathine). It contains a variable quantity of water. A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide and in formamide. Store in airtight containers.
USP 31 (Penicillin G Benzathine). The tetrahydrate is a white, odourless, crystalline powder. Soluble 1 in 5000 of water and 1 in 65 of alcohol. pH in a solution prepared by dissolving 50 mg in 50 mL of dehydrated alcohol, and adding 50 mL of water is between 4.0 and 6.5. Store in airtight containers.

Adverse Effects and Precautions

As for Benzylpenicillin, p.213.

Non-allergic (embolic-toxic) reactions similar to those associated with procaine benzylpenicillin, p.319, have been reported rarely with benzathine benzylpenicillin.

Benzathine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Interactions

As for Benzylpenicillin, p.214.

Pharmacokinetics

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see below).

Distribution into the CSF is reported to be poor.

Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.

Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gastrointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak concentrations are also produced less rapidly, but may persist for longer.

Plasma concentrations. Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks to ensure adequate plasma concentrations of benzylpenicillin. Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study[1] adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study,[2] in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900-mg dose of benzathine benzylpenicillin usually recommended might prolong the duration of protective plasma concentrations of benzylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against rheumatic fever.

1. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; **115:** 146–50.
2. Currie BJ, *et al.* Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrob Agents Chemother* 1994; **38:** 1203–4.

Pregnancy. The pharmacokinetics of benzathine benzylpenicillin appear to be altered in late pregnancy. Of 10 healthy pregnant women given benzathine benzylpenicillin 1.8 g intramuscularly before caesarean section, only 4 achieved adequate serum concentrations of benzylpenicillin (for syphilis, at least 18 nanograms/mL) for 7 days.[1]

1. Nathan L, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; **82**: 338–42.

Uses and Administration

Benzathine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p.214), to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations of benzylpenicillin produced, its use should be restricted to micro-organisms that are highly susceptible to benzylpenicillin. In acute infections, and when bacteraemia is present, the initial treatment should be with benzylpenicillin by injection.

Infections treated with benzathine benzylpenicillin include diphtheria (asymptomatic carriers), pharyngitis (*Streptococcus pyogenes; Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*)), and syphilis (including non-venereal treponematoses). It is also used for primary and secondary prophylaxis of rheumatic fever. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Benzathine benzylpenicillin is given by deep intramuscular injection, sometimes with procaine benzylpenicillin and benzylpenicillin itself. It has been given orally for mild infections, although phenoxymethylpenicillin is usually preferred. Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF. Infants up to 2 years of age may be given a single intramuscular dose of 37.5 mg/kg for the treatment of congenital syphilis, provided there is no evidence of infection in the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given; a dose of 450 mg may be used in children.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg; children under 30 kg may be given 225 to 675 mg. To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4 weeks to adults; a dose of 450 mg has been used for children under 30 kg.

Preparations

USP 31: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Benzathine Injectable Suspension; Penicillin G Benzathine Oral Suspension; Penicillin G Benzathine Tablets.

Proprietary Preparations (details are given in Part 3)

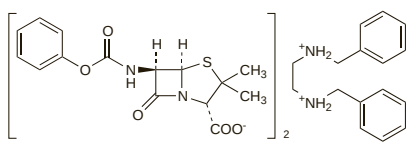
Arg.: Benzetacil; Galtamicina; Pen di Ben; Retarpen; ***Austral.:*** Bicillin L-A; ***Austria:*** Retarpen; ***Belg.:*** Penadur; ***Braz.:*** Bactopen; Benzatron; Benzetacil; Bepeben; Longacilin; Neo Benzil†; Pencil B; ***Cz.:*** Pendepon Compositum; Retarpen; ***Fr.:*** Extencilline; ***Ger.:*** Pendysin; ***Gr.:*** Penadur; ***Hung.:*** Retarpen†; ***India:*** Pencom; Penidure; ***Israel:*** Durabiotic; ***Ital.:*** Diaminocillina; Wycillina; ***Malaysia:*** Retarpen; ***Mex.:*** Benacilina; Bencelin; Benzafur; Benzanil Simple; Benzetacil; Ipenxin; Lentopenil; Unicil 6:3:3; Unicil L-A; ***Neth.:*** Penidural; ***NZ:*** Bicillin L-A; ***Philipp.:*** Penadur; Zalpen; ***Pol.:*** Debecylina; ***Port.:*** Lentocilin S; Penadur†; ***Rus.:*** Bicillin-1 (Бициллин-1); Extencilline (Экстенциллин); ***S.Afr.:*** Bicillin L-A; Penilente LA†; ***Singapore:*** Retarpen; ***Spain:*** Benzetacil; Cepacilina; ***Thai.:*** Penadur†; ***Turk.:*** Benzapen; Benzapen 6.3.3; Deposilin; Deposilin 6.3.3; Penadur; Penadur 6.3.3; ***USA:*** Bicillin L-A; Permapen; ***Venez.:*** Benzetacil L-A; Silcopen†.

Multi-ingredient: ***Austria:*** Retarpen compositum; ***Chile:*** Karbasalin†; ***Ger.:*** Retacillin compositum; Tardocillin; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Pecivax; Pendiben Compuesto; ***Neth.:*** Penidural D/F†; ***Port.:*** Lentocilin; Penadur 6.3.3†; ***Rus.:*** Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Benzetacil Compuesta; Cepacilina 633; Penilevel Retard; ***USA:*** Bicillin C-R; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Benzathine Phenoxymethylpenicillin

Benzatin Fenoksimetil Penisilin; Benzatina fenoximetilpenicilina; Penicillin V Benzathine *(USAN)*; Phenoxymethylpenicillini Dibenzylaethylendiaminum. *N,N′*-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenoxyacetamido)penicillanate].

$(C_{16}H_{18}N_2O_5S)_2,C_{16}H_{20}N_2$ = 941.1.
CAS — 5928-84-7 (anhydrous benzathine phenoxymethylpenicillin); 63690-57-3 (benzathine phenoxymethylpenicillin tetrahydrate).
ATC — J01CE10.
ATC Vet — QJ01CE10.



Pharmacopoeias. In *US.*
USP 31 (Penicillin V Benzathine). A practically white powder having a characteristic odour. Soluble 1 in 3200 of water, 1 in 330 of alcohol, 1 in 37 of acetone, 1 in 42 of chloroform, and 1 in 910 of ether. pH of a 3% suspension in water is between 4.0 and 6.5. Store in airtight containers.

Profile

Benzathine phenoxymethylpenicillin has actions and uses similar to those of phenoxymethylpenicillin (p.314) and is given orally in the treatment of susceptible mild to moderate infections. Doses are expressed in terms of phenoxymethylpenicillin.

Preparations

USP 31: Penicillin V Benzathine Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Abbocillin-V; Cilicaine V; ***Austria:*** Ospen; ***Canad.:*** Pen-Vee†; ***Cz.:*** Ospen; ***Fr.:*** Oracilline; ***Ger.:*** InfectoBicillin; ***Gr.:*** Ospen; ***Hung.:*** Ospen; Oxybion†; ***Pol.:*** Ospen; ***Rus.:*** Ospen (Оспен); ***Spain:*** Benoral; ***Switz.:*** Ospen; Phenocillin; ***Turk.:*** Pen-Os; ***Venez.:*** Ospen.

Benzylpenicillin *(BAN, rINN)*

Bencilpenicilina; Bensylpenicillin; Bentsyylipenisilliini; Benzil Penisiliin; Benzylpénicilline; Benzylpenicillinum; Crystalline Penicillin G; Penicillin; Penicillin G; Penisilin G. (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; (6*R*)-6-(2-Phenylacetamido)penicillanic acid.

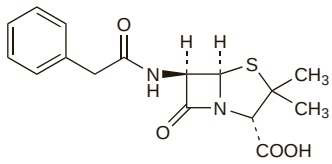
Бензилпенициллин

$C_{16}H_{18}N_2O_4S$ = 334.4.

CAS — 61-33-6.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QJ51CE01; QS01AA14.



Description. The name benzylpenicillin is commonly used to describe either benzylpenicillin potassium or benzylpenicillin sodium as these are the forms in which benzylpenicillin is used. In *Martindale*, benzylpenicillin means either the potassium or sodium salt.

Benzylpenicillin Potassium *(BANM, rINNM)*

Bencilpenicilina potásica; Bensylpenicillinkalium; Bentsyylipenisilliinikalium; Benzilpenicilino kalio druska; Benzilpenicillin-kálium; Benzylopenicylina potasowa; Benzylpenicilin draselná sůl; Benzylpénicilline potassique; Benzylpenicillinum kalicum; Kalii Benzylpenicillinum; Penicillin G Potassium; Penisilin G Potasyum.

Калия Бензилпенициллин

$C_{16}H_{17}KN_2O_4S$ = 372.5.

CAS — 113-98-4.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Potassium). The potassium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Potassium). Colourless or white crystals, or white crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Very soluble in water, in sodium chloride 0.9%, and in glucose solutions; sparingly soluble in alcohol. Its solutions retain substantially full potency for several days at temperatures below 15°, but are rapidly inactivated by acids, by alkali hydroxides, by glycerol, and by oxidising agents. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility and stability. As for Benzylpenicillin Sodium, below.

Benzylpenicillin Sodium *(BANM, rINNM)*

Bencilpenicilina sódica; Bensylpenicillinnatrium; Bentsyylipenisilliininatrium; Benzilpenicilino natrio druska; Benzilpenicillin-nátrium; Benzylopenicylina sodowa; Benzylpenicilin sodná sůl; Benzylpénicilline sodique; Benzylpenicillinum natricum; Natrii Benzylpenicillinum; Penicillin G Sodium; Sodyum Penisilin G.

Натрий Бензилпенициллин

$C_{16}H_{17}N_2NaO_4S$ = 356.4.

CAS — 69-57-8.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Sodium). The sodium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Sodium). Colourless or white crystals, or white to slightly yellow crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15°. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidising agents, and by penicillinase. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility. Benzylpenicillin has been reported to be incompatible with metal ions and some rubber products. Its stability may be affected by ionic and nonionic surfactants, oxidising and reducing agents, alcohols, glycerol, glycols, macrogols and other hydroxy compounds, some paraffins and bases, some preservatives such as chlorocresol or thiomersal, carbohydrate solutions in an alkaline pH, fat emulsions, blood and blood products, and viscosity modifiers. Benzylpenicillin is incompatible with a wide range of acidic and basic drugs (see Stability, below) and with a number of other antimicrobials, including amphotericin B, some cephalosporins, and vancomycin. Benzylpenicillin and aminoglycosides are mutually incompatible and injections should be given at separate sites.

Stability. Benzylpenicillin is hydrolysed in aqueous solutions by degradation of the beta-lactam ring and hydrolysis is accelerated by increased temperature or alkaline conditions; inactivation also occurs under acid conditions. Degradation products include penillic, penicillenic, and penicilloic acids which lower the pH and cause a progressive increase in the rate of deterioration; *N*-formylpenicillamine and very small amounts of penicillamine have also been detected. Degradation is minimal at about pH 6.8 and deterioration of benzylpenicillin in solution may be retarded by using a citrate buffer. Dilute solutions are more stable than concentrated ones.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2** (Mar): 22–39.
2. Bird AE, *et al.* N-Formylpenicillamine and penicillamine as degradation products of penicillins in solution. *J Pharm Pharmacol* 1986; **38:** 913–17.

Units

The second International Standard Preparation (1952) of benzylpenicillin sodium contained 1670 units of penicillin per mg but was withdrawn in 1968 since penicillin can now be characterised completely by chemical tests. Despite this, doses of benzylpenicillin are still expressed in units in some countries.

Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal.

Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; a sore mouth or tongue or a black hairy tongue have occasionally been reported. Pseudomembranous colitis has been associated with the use of most antibiotics; ampicillin or amoxicillin are the most frequently implicated penicillins (see Antibiotic-associated Colitis, p.171).

Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal dosage and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used.

Hepatitis and cholestatic jaundice have been reported rarely with some penicillins, notably penicillinase-resistant penicillins such as flucloxacillin and oxacillin, and also combinations of amoxicillin or ticarcillin with clavulanic acid.

Nephropathy and interstitial nephritis, which may have some immunological basis, have been especially associated with meticillin, but may be produced by other penicillins.

Some patients with syphilis and other spirochaete infections may experience a Jarisch-Herxheimer reaction shortly after starting treatment with penicillin, which is probably due to the release of endotoxins from the killed treponemes and should not be mistaken for a hypersensitivity reaction. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis, or where there is a serious risk of increased local damage, such as with optic atrophy.

Hypersensitivity. The overall incidence of allergic reactions to penicillin has been reported to vary from about 1 to 10% although some patients may have been incorrectly labelled 'allergic to penicillin'. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking oral penicillin.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia. Reactions are considered to be due mainly to breakdown products produced *in vitro* before use or to metabolites of penicillin, and possibly penicillin itself. These act as haptens which, when combined with proteins and other macromolecules, produce potential antigens. As the hypersensitivity is related to the basic penicillin structure, patients who are genuinely allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other beta-lactam antibiotics.

Tests for hypersensitivity may be used to determine those patients most likely to develop serious allergic reactions to penicillins. Skin tests are used to evaluate the current risk of immediate or accelerated IgE-mediated reactions, the most serious being anaphylaxis. Both the major and minor determinants of penicillin hypersensitivity should be used; the major determinant is available as penicilloyl-polylysine (p.2364) and a minor-determinant mixture consisting of benzylpenicillin and its derivatives, including penicilloic acid and benzylpenicilloylamine, can be used, although if this is not available a solution of benzylpenicillin may be substituted. Adrenaline should be available in case an anaphylactic reaction develops. The results of skin tests are unreliable if a significant time has elapsed before beginning therapy. A number of *in-vitro* tests including the radioallergosorbent test (RAST) have been developed.

Desensitisation may be attempted in patients allergic to penicillin when treatment with penicillin is considered essential. It involves very small doses of penicillin given at relatively short intervals of 15 minutes or more, and gradually increased to therapeutic concentrations. However, desensitisation may be hazardous and should only be carried out if the patient can be monitored continuously and adrenaline and resuscitation equipment are immediately available. Desensitisation should be regarded as temporary, and allergic reactions may recur during the next exposure to penicillin.

Neutropenia. Neutropenia has been widely reported in patients given high doses of beta lactams and an incidence of from 5 to more than 15% has been reported in patients treated for 10 days or more. Warning signs include fever, rash, and eosinophilia. Monitoring of the leucocyte count is recommended during long-term treatment with high doses. Some have proposed a direct toxic effect whereas others have postulated an immune mechanism.

Effects on the blood. References to neutropenia associated with penicillins.

1. Anonymous. Antibiotic-induced neutropenia. *Lancet* 1985; **ii:** 814.
2. Neftel KA, *et al.* Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. *J Infect Dis* 1985; **152:** 90–8.
3. Olaison L, Alestig K. A prospective study of neutropenia induced by high doses of β-lactam antibiotics. *J Antimicrob Chemother* 1990; **25:** 449–53.
4. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.