creases in liver enzymes and abnormalities in haematological parameters have been reported.

Loracarbef should not be given to patients known to be hypersensitive to it or to other beta lactams because of the possibility of cross-sensitivity. It should be given with caution, with appropriate dosage reduction, in patients with renal impairment.

Effects on the kidneys. References.

1. Thieme RE, *et al.* Acute interstitial nephritis associated with loracarbef therapy. *J Pediatr* 1995; **127:** 997–1000.

Interactions

Probenecid decreases the renal excretion of loracarbef thereby increasing its plasma concentrations.

Antimicrobial Action

Loracarbef is bactericidal with antibacterial activity similar to that of cefaclor (p.217).

Pharmacokinetics

Loracarbef is well absorbed from the gastrointestinal tract with a bioavailability of 90%. Peak plasma concentrations after 200- and 400-mg doses as capsules are about 8 and 14 micrograms/mL respectively at 1.2 hours. Peak concentrations are achieved more rapidly after an oral suspension and a paediatric dose of 15 mg/kg produces a concentration of about 19 micrograms/mL within 40 to 60 minutes. Absorption is delayed by the presence of food. A plasma half-life of about 1 hour has been reported which is prolonged in renal impairment. About 25% is bound to plasma proteins.

Loracarbef is excreted largely unchanged in the urine, and therapeutic concentrations are maintained in the urine for up to 12 hours. Probenecid delays excretion. Loracarbef is removed by haemodialysis.

Uses and Administration

Loracarbef is an oral carbacephem antibiotic. The carbacephems are closely related to the cephalosporins, but replacement of the sulfur atom in the 7-aminocephalosporanic acid nucleus by a methylene group is said to enhance stability. It is used similarly to cefaclor in the treatment of susceptible infections of the respiratory and urinary tracts and of skin and soft tissue. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Loracarbef should be given 1 hour before food or on an empty stomach. Loracarbef is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous loracarbef. The usual adult dose is 200 to 400 mg every 12 hours. In uncomplicated urinary-tract infections, a dose of 200 mg daily may be adequate. A dose for children is 7.5 mg/kg every 12 hours for uncomplicated infections or 15 mg/kg every 12 hours for acute otitis media or acute maxillary sinusitis.

For details of reduced doses of loracarbef in patients with renal impairment, see below.

◊ General references.

1. Moellering RC, Jacobs NF. Advances in outpatient antimicrobial therapy: loracarbef. *Am J Med* 1992; **92** (suppl 6A): 1S–103S.
2. Brogden RN, McTavish D. Loracarbef: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45:** 716–36.

Administration in renal impairment. Doses of loracarbef should be reduced in patients with renal impairment; patients with a creatinine clearance of 10 to 49 mL/minute may be given half the usual dose at the usual dosage interval or the full usual dose at twice the usual interval; patients with a creatinine clearance of less than 10 mL/minute may be treated with the usual dose given every 3 to 5 days. Patients on haemodialysis should receive another dose following dialysis.

Preparations

USP 31: Loracarbef Capsules; Loracarbef for Oral Suspension.

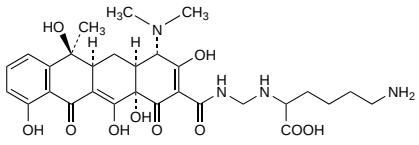
Proprietary Preparations (details are given in Part 3)
Ger.: Lorafem; ***Gr.:*** Lorbef; ***Mex.:*** Carbac†; Lorabid†; ***S.Afr.:*** Lorabid; ***Swed.:*** Lorabid; ***Turk.:*** Lorabid; ***USA:*** Lorabid†.

Lymecycline *(BAN, rINN)*

Limeciclina; Limesiklin; Lymécycline; Lymecyclinum; Lymecyklin; Lymecyklina; Lymesykliini; Tetracyclinemethylene lysine. (+)-*N*-(5-Amino-5-carboxypentylaminomethyl)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonapthacene-2-carboxamide; N^2-{[(+)-5-Amino-5-carboxypentylamino]methyl}tetracycline.

Лимециклин

$C_{29}H_{38}N_4O_{10}$ = 602.6.
CAS — 992-21-2.
ATC — J01AA04.
ATC Vet — QJ01AA04.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Lymecycline). A reaction product of formaldehyde, lysine, and tetracycline. A yellow, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.8 to 8.2. Store in airtight containers. Protect from light.

Profile

Lymecycline is a tetracycline derivative with general properties similar to those of tetracycline (p.347). Although its absorption is not significantly affected by moderate amounts of milk, it is still affected by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc.

Lymecycline is given orally and doses are expressed in terms of the equivalent amount of tetracycline base. Lymecycline 407 mg is equivalent to about 300 mg of tetracycline and to about 325 mg of tetracycline hydrochloride. The usual adult dose is the equivalent of 300 mg of tetracycline base twice daily. In severe infections total daily doses of up to the equivalent of 1.2 g may be given. In the treatment of acne, the equivalent of 300 mg is given daily for at least 8 weeks.

For details of use in children and adolescents, see below.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, lymecycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given by mouth. However, in some countries, it is licensed for use in those over 8 years old.

Skin disorders. For reference to the use of lymecycline in the treatment of acne, see under Tetracycline, p.350.

Preparations

BP 2008: Lymecycline Capsules.

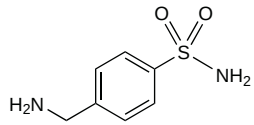
Proprietary Preparations (details are given in Part 3)
Arg.: Tetralysal; ***Austria:*** Tetralysal; ***Belg.:*** Tetralysal; ***Braz.:*** Tetralysal; ***Denm.:*** Tetralysal; ***Fin.:*** Tetralysal; ***Fr.:*** Tetralysal; ***Hong Kong:*** Tetralysal; ***Hung.:*** Tetralysal; ***Irl.:*** Tetralysal; ***Ital.:*** Tetralysal; ***Mex.:*** Tetralisal; ***Norw.:*** Tetralysal; ***NZ:*** Tetralysal; ***Philipp.:*** Tetralysal; ***S.Afr.:*** Tetralysal; ***Swed.:*** Tetralysal; ***Switz.:*** Tetralysal; ***UK:*** Tetralysal; ***Venez.:*** Tetralysal.

Mafenide *(BAN, USAN, rINN)*

Mafenid; Mafenida; Maféride; Mafenidi; Mafenidum; NSC-34632. α-Aminotoluene-*p*-sulphonamide.

Мафенид

CAS — 138-39-6.
ATC — D06BA03.
ATC Vet — QD06BA03.



Mafenide Acetate *(BANM, rINNM)*

Acetato de mafenida; Maféride, Acétate de; Mafenidi Acetas.

Мафенида Ацетат

$C_7H_{10}N_2O_2S,C_2H_4O_2$ = 246.3.
CAS — 13009-99-9.
ATC — D06BA03.
ATC Vet — QD06BA03.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Mafenide Acetate). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.4 and 6.8. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Mafenide is absorbed to some extent after topical application and may produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p.340). Fatal haemolytic anaemia with disseminated intravascular coagulation, related to G6PD deficiency, has been reported.

Mafenide cream may cause pain or a burning sensation on application to the burnt area, with occasional bleeding or excoriation. The separation of the eschar may be delayed and fungal invasion of the wound has been reported. By its action in inhibiting carbonic anhydrase, mafenide may cause metabolic acidosis and hyperventilation; acid–base balance should therefore be monitored, particularly in patients with extensive burns, or with pulmonary or renal impairment. If persistent acidosis occurs, mafenide treatment should be temporarily suspended and fluid therapy continued.

Pharmacokinetics

Mafenide is absorbed from wounds into the circulation and is metabolised to *p*-carboxybenzenesulfonamide, which is excreted in the urine. The metabolite has no antibacterial action but retains the ability to inhibit carbonic anhydrase.

Uses and Administration

Mafenide is a sulfonamide that is not inactivated by *p*-aminobenzoic acid or by pus and serum. The acetate is used as a cream, containing the equivalent of mafenide 8.5%, in conjunction with debridement, for the prevention and treatment of infection, including *Pseudomonas aeruginosa*, in second- and third-degree burns (p.1578). A solution containing mafenide acetate 5% is also available for use under moist dressings in burns. Mafenide hydrochloride and mafenide propionate have also been used.

Preparations

USP 31: Mafenide Acetate Cream; Mafenide Acetate for Topical Solution.

Proprietary Preparations (details are given in Part 3)
USA: Sulfamylon.

Multi-ingredient: ***Indon.:*** FG Ointment; ***Spain:*** Pental Forte†.

Magainins

Magaininas.

Магаинины

Profile

The magainins are a group of antibacterial peptides derived from amphibians. A number of semisynthetic derivatives including pexiganan acetate (MSI-78), MSI-93, and MSI-94 have been investigated as topical anti-infectives.

◊ References.

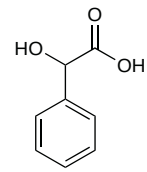
1. Lamb HM, Wiseman LR. Pexiganan acetate. *Drugs* 1998; **56:** 1047–52.
2. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; **67:** 195–214.

Mandelic Acid

Ácido fenilglicólico; Ácido mandélico racémico; Amygdalic Acid; Mandélico, ácido; Phenylglycolic Acid; Racemic Mandelic Acid. 2-Hydroxy-2-phenylacetic acid.

Миндальная Кислота

$C_8H_8O_3$ = 152.1.
CAS — 90-64-2; 17199-29-0 ((+)-mandelic acid); 611-71-2 ((–)-mandelic acid); 611-72-3 ((±)-mandelic acid).
ATC — B05CA06; J01XX06.
ATC Vet — QB05CA06; QJ01XX06.



Profile

Mandelic acid has bacteriostatic properties and is used as a 1% flushing solution for the maintenance of indwelling urinary catheters. Mandelic acid and acetyl mandelic acid are used topically in preparations for the treatment of acne. It was formerly given orally in the treatment of urinary-tract infections, usually as the ammonium or calcium salt.

Mandelic acid is a component of methenamine mandelate (p.298).

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Rolip†.

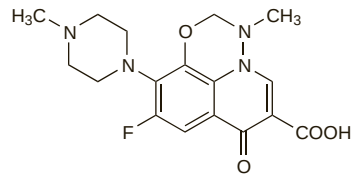
Multi-ingredient: ***Chile:*** Neostrata; ***Fr.:*** Sphingogel†; Zeniac LP Fort†; Zeniac LP†; Zeniac†; ***Ital.:*** Neoceuticals Clear Skin; Neoceuticals Spot Treatment; ***Port.:*** Mandelip†.

Marbofloxacin *(BAN, rINN)*

Marbofloksasiini; Marbofloxacine; Marbofloxacino; Marbofloxacinum. 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid.

Марбофлоксацин

$C_{17}H_{19}FN_4O_4$ = 362.4.
CAS — 115550-35-1.
ATC Vet — QJ01MA93.



Pharmacopoeias. In *Eur.* (see p.vii) for veterinary use only.

Ph. Eur. 6.2 (Marbofloxacin for Veterinary Use). A light yellow, crystalline powder. Slightly soluble in water; very slightly solu-

ble in alcohol; sparingly soluble or slightly soluble in dichloromethane. Protect from light.

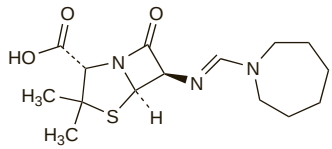
Profile
Marbofloxacin is a fluoroquinolone antibacterial used in veterinary medicine.

Mecillinam *(BAN, rINN)*

Amdinocillin *(USAN)*; FL-1060; Mecilinam; Mécillinam; Mecillinamum; Mesillinaami; Ro-10-9070. (6*R*)-6-(Perhydroazepin-1-ylmethyleneamino)penicillanic acid.

Мециллинам

$C_{15}H_{23}N_3O_3S$ = 325.4.
CAS — 32887-01-7.
ATC — J01CA11.
ATC Vet — QJ01CA11.



Adverse Effects and Precautions
As for Benzylpenicillin, p.213.

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

Interactions
As for Benzylpenicillin, p.214.

Antimicrobial Action
Mecillinam is a derivative of amidinopenicillanic acid. Unlike benzylpenicillin and related antibiotics, it is active against many Gram-negative bacteria, in particular Enterobacteriaceae including *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Salmonella*, and *Shigella* spp. The susceptibility of *Proteus* spp. varies; *Serratia marcescens* is generally resistant. It is less active against *Neisseria* spp. and *Haemophilus influenzae*. *Pseudomonas aeruginosa* and *Bacteroides* spp. are considered to be resistant. It is much less active against Gram-positive bacteria; enterococci including *Enterococcus faecalis* are resistant.

Mecillinam interferes with the synthesis of the bacterial cell wall by binding with a different penicillin-binding protein from benzylpenicillin. This difference in mode of action may explain the synergism against many Gram-negative organisms that has been reported *in vitro* between mecillinam and various penicillins or cephalosporins.

Mecillinam is inactivated by beta-lactamases, but is more stable than ampicillin.

Pharmacokinetics
Mecillinam is poorly absorbed from the gastrointestinal tract. Peak plasma concentrations of about 6 and 12 micrograms/mL have been achieved half an hour after intramuscular doses of 200 and 400 mg, respectively. The usual plasma half-life of about 1 hour has been reported to be prolonged to 3 to 5 hours or more in severe renal impairment. Between 5 and 10% of mecillinam is bound to plasma proteins. Mecillinam is widely distributed into body tissues and fluids; little passes into the CSF unless the meninges are inflamed. It crosses the placenta into the fetal circulation; little appears to be distributed into breast milk.

Mecillinam is metabolised to only a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular filtration and tubular secretion. Renal tubular secretion can be reduced by probenecid. Some mecillinam is excreted in bile where high concentrations are achieved.

Mecillinam is removed by haemodialysis.

Uses and Administration
Mecillinam is a semisynthetic penicillin with a substituted amidino group at the 6-position of the penicillanic acid nucleus. It is given by slow intravenous injection, by intravenous infusion, or intramuscularly, in the treatment of susceptible Gram-negative infections (see under Antimicrobial Action, above).

For urinary-tract infections a dose of 800 mg is given every 6 to 8 hours. A total dose of up to 60 mg/kg daily may be used in very severe infections.

Mecillinam has been used with other beta lactams to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

The pivaloyloxymethyl ester of mecillinam, pivmecillinam, is used orally (see p.317).

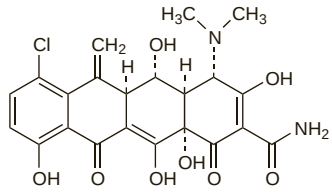
Preparations
Proprietary Preparations (details are given in Part 3)
Denm.: Selexid; ***Gr.:*** Selexid; ***Norw.:*** Selexid; ***Swed.:*** Selexid.

Meclocycline *(BAN, USAN, rINN)*

GS-2989; Meclociclina; Méclocycline; Meclocyclinum; Meklocyklin; Meklosykliini; NSC-78502. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

Меклоциклин

$C_{22}H_{21}ClN_2O_8$ = 476.9.
CAS — 2013-58-3.
ATC — D10AF04.
ATC Vet — QD10AF04.



Meclocycline Sulfosalicylate *(USAN)*

Meclociclina, sulfosalicilato de; Meclocycline Sulphosalicylate. Meclocycline 5-sulphosalicylate.

$C_{22}H_{21}ClN_2O_8,C_7H_6O_6S$ = 695.0.
CAS — 73816-42-9.
ATC — D10AF04.
ATC Vet — QD10AF04.

Pharmacopoeias. In *US*.
USP 31 (Meclocycline Sulfosalicylate). pH of a 1% solution in water is between 2.5 and 3.5. Store in airtight containers. Protect from light.

Profile
Meclocycline is a tetracycline antibacterial derived from oxytetracycline (p.312). It is applied topically as the sulfosalicylate for the treatment of acne vulgaris and superficial skin infections. Potency is expressed in terms of meclocycline. Preparations containing the equivalent of 1 or 2% are available. Meclocycline sulfosalicylate has also been given as a pessary in the treatment of vulvovaginal infections.

Preparations
USP 31: Meclocycline Sulfosalicylate Cream.

Proprietary Preparations (details are given in Part 3)
Ger.: Meclosorb; ***Ital.:*** Mecloderm; Mecloderm Antiacne; Mecloderm Ovuli; Mecloderm Polvere Aspersoria†; Meclutin Semplice†.

Multi-ingredient: ***Ital.:*** Anti-Acne; Mecloderm F; Meclutin†.

Meleumycin

Pharmacopoeias. In *Chin.*

Profile
Meleumycin, a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens*, consists of a mixture of midecamycin A_1 and kitasamycin A_6. It has actions and uses similar to those of erythromycin (p.269) and is given orally in the treatment of susceptible infections.

Meropenem *(BAN, USAN, rINN)*

ICI-194660; Meropeneemi; Méropénem; Meropenemum; SM-7338. (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylcarbamoylpyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Меропенем

$C_{17}H_{25}N_3O_5S,3H_2O$ = 437.5.
CAS — 96036-03-2 (meropenem); 119478-56-7 (meropenem trihydrate).
ATC — J01DH02.
ATC Vet — QJ01DH02.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.
USP 31 (Meropenem). Colourless to white crystals. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone and in ether; soluble in dimethylformamide and in 5% monobasic potassium phosphate solution. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Adverse Effects and Precautions
As for Imipenem, p.286.

Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem (see also below).

Effects on the nervous system. *Animal* studies have indicated that meropenem induces fewer seizures than imipenem-cilastatin and clinical data from the manufacturer have substantiated this.[1] Comparison of data[2] from 4872 patients with a variety of infections (including meningitis) treated with meropenem with that from 4752 patients who received other antibacterials, principally cephalosporin-based regimens or imipenem-cilastatin, showed that meropenem was not associated with any greater risk of seizures than the other antibacterials and was likely to have less neurotoxic potential than imipenem-cilastatin, making it a suitable drug to use in the treatment of meningitis.

1. Norrby SR, *et al.* Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995; **36** (suppl A): 207–23.
2. Norrby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand J Infect Dis* 1999; **31:** 3–10.

Interactions
Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to meropenem, see p.510.

Antimicrobial Action
As for Imipenem, p.287.

Meropenem is slightly more active than imipenem against Enterobacteriaceae and slightly less active against Gram-positive organisms.

Pharmacokinetics
After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.

Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Meropenem is removed by haemodialysis.

◊ References.

1. Chimata M, *et al.* Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. *Antimicrob Agents Chemother* 1993; **37:** 229–33.
2. Dagan R, *et al.* Penetration of meropenem into the cerebrospinal fluid of patients with inflamed meninges. *J Antimicrob Chemother* 1994; **34:** 175–9.
3. Mouton JW, Van den Anker JN. Meropenem clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 275–86.
4. Blumer JL, *et al.* Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children. *Antimicrob Agents Chemother* 1995; **39:** 1721–5.
5. Novelli A, *et al.* Clinical pharmacokinetics of meropenem after the first and tenth intramuscular administration. *J Antimicrob Chemother* 1996; **37:** 775–81.
6. Thalhammer F, *et al.* Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* 1999; **43:** 523–7.
7. Giles LJ, *et al.* Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. *Crit Care Med* 2000; **28:** 632–7.
8. Thalhammer F, Horl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. *Clin Pharmacokinet* 2000; **39:** 271–9.
9. Ververs TF, *et al.* Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous veno-venous hemofiltration. *Crit Care Med* 2000; **28:** 3412–16.
10. van Enk JG, *et al.* Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23:** 198–201.
11. Goldstein SL, *et al.* Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. *Pediatr Nephrol* 2001; **16:** 1015–18.
12. Ariano RE, *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39:** 32–8.