Clinical Pharmacology

Edited by
Ronald H. Girdwood

TWENTY-FIFTH EDITION

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President of the
Royal College of Physicians of Edinburgh

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Preface

Major alterations have been made in the text of this book which has now reached a hundred years of continuing publication. By chance, too, it appears exactly fifty years after the editor commenced his studies as a medical student, and it is during this latter period that most of the drugs in use today have been marketed for the first time. Each year about forty completely new products appear to which must be added many others that are fairly similar to those already available.

In this edition, the chapter on Antimicrobial Drugs has been completely rewritten by Dr J. A. Gray, an expert in this complex area of therapy. Three new authors, Drs A. D. Toft, I. W. Campbell and J. S. A. Sawers, have combined their specialist knowledge to rewrite the chapter on The Pharmacology of the Endocrine System. Dr J. A. J. H. Critchley, another new author, has written the section on Heavy Metals. Many readers have suggested that it is not necessary for a book of this nature to commence with an introductory chapter on such general subjects as pharmacodynamics (the mode of action of drugs), pharmacokinetics (the absorption, distribution, metabolism and elimination of drugs) or other matters with which they are already familiar. It is likely, however, that this view is not universally shared and that many readers welcome basic information. Accordingly, Dr A. Pottage's general chapter (now retitled General Aspects of Drug Action) has been included as Appendix 1. It is probable, too, that important though it is to know about adverse drug reactions, this section should not come before consideration of the individual therapeutic agents and hence the subject is dealt with towards the end of the volume.

Our knowledge of drug therapy changes rapidly and all the authors have found it necessary to discard information about substances no longer in common use and to add sections dealing with agents that have been recently introduced. Reference has also been made to new techniques such as the use of medical genetic engineering and the possible practical value of monoclonal antibodies. Few pages remain unchanged since the 24th Edition was produced, but some of the substances mentioned have been introduced so recently that their true place in therapeutics is, as yet, uncertain. This creates problems for the reader and on many occasions the editor has been asked to provide a much shorter list of preferred drugs. Unfortunately, there is no general agreement as to which medicinal agents should be included in such a list and preferences may depend on many factors such as the geographical area concerned, the teachings of local specialists, the age of the majority of patients being treated, the degree of persistence of the attentions of company

representatives, the amount of cost consciousness and the information provided by local hospital pharmacists. In Appendix 2 there is given a list of 200 medicinal agents, selected after much discussion amongst physicians and pharmacists in a large teching hospital in Scotland that deals with adult patients. Agreement was not unanimous and, although most of the substances required for specialized units have been omitted, a few remain, usually at the request of authors. The numbering employed is that of the *British National Formulary* No. 5 (1983). It may be of interest to note that of the 709 different medicinal agents listed in the index of the 1884 edition of this book, only six are included in Appendix 2, not necessarily in exactly the same form. These are digitalis, atropine, nitroglycerin, morphine, ferrous sulphate and calcium. (In AD 43 the Romans in Britain were using belladonna, opium and iron salts). By 1934 a further 17 substances still considered to be basic necessities today were included, namely adrenaline hydrochloride, aspirin, codeine phosphate, dextrose solution, diamorphine hydrochloride, glycerin suppositories, insulin, kaolin, parathyroid extract, phenobarbitone, sodium chloride, thyroxine, vitamins A, B, C, D and G (riboflavin). As a student, the editor heard with much interest about the introduction of the new substance sulphanilamide, which was said to be able to control certain infections. Some clinical teachers of the time were very doubtful about this claim. By the time of his graduation in 1939, there was not yet a suitable drug to arrest the progress of pulmonary tuberculosis. In the First Edition of this book the author, Dr J. Mitchell Bruce, wrote 'Phthisis is rarely benefited by iodides, unless there be a syphilitic taint present'. So far as drug therapy is concerned, there was no true progress until 1945.

In a hundred years we have passed from volatile oils and infusions to the products of complex industrial procedures and to substances prepared or extracted as a result of detailed knowledge of physiological and pathological processes in the body. Individuals may have ideas, but large teams are usually now required to give us the finished product. The initial cost in money terms may be enormous, but the benefits to mankind are great.

The medical student and practitioner of 1884 or 1934 had difficulty in remembering the names and doses of drugs used empirically and often chosen for no obvious reason. In 1984 the problems are of keeping up to date as new products appear, and appreciating sufficient of the detailed knowledge that is available about modes of action and side-effects of the various therapeutic agents to make understanding and learning possible. In the First Edition of this book Dr Bruce wrote in the Foreword 'In using the book the first year's student is recommended to confine his attention to the Materia Medica proper; and under the action and uses of the drugs to read only the words printed in thick type'. Thus, under the heading *Digitalis*, only forty words out of 1500 are marked in this way. It was reasonable to suggest that it was not necessary to read about the action of a drug when this was not understood, but things are very different now, and the student of today would find it tedious and difficult to adopt such an approach. It is hoped that this Centenary Edition will provide

the student with sufficient information to understand the action in man of the drugs now in common usage.

The editor has travelled widely abroad in recent years, particularly in eastern countries, and has obtained helpful advice from doctors, students, hospital pharmacists and medical librarians; hence the problems of the overseas reader have constantly been borne in mind, in addition to those of his or her counterpart in the British Isles.

The editor and contributors are again most grateful to Miss Elspeth R. Shields for typing the manuscript in her leisure hours, and to Dr M. E. Jones for helpful discussion relating to the use outside Britain of certain drugs mentioned in Chapter 1. They are also grateful to Messrs David Dickens and Peter Gill of Baillière Tindall, who have been most co-operative in ensuring that the Centenary Edition was produced with the minimum of delay, so that it would, indeed, appear at the correct time.

Ronald H. Girdwood

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1 Antimicrobial Drugs

J. A. Gray

ANTIBACTERIAL AGENTS

The dramatic decline in mortality from communicable diseases in the past 50 years has been variously attributed to improved nutrition, housing and sanitation, to immunization, international programmes for disease surveillance and control, and to the natural waning in virulence of certain micro-organisms. In addition, antimicrobial drugs have played a significant part. From the discovery of the antimalarial properties of Peruvian bark early in the 17th century to Ehrlich's magic antisyphilitic bullet, salvarsan, in 1909, little progress in antimicrobial therapy was made. Then the era of synthetic antibacterial drugs opened with the development of Prontosil by Domagk in the early 1930s; next, during the 1940s, penicillin was developed as the first of the naturally occurring antibacterial substances, following Fleming's discovery of the bactericidal property of the mould *Penicillium notatum* in 1929.

Subsequently a plethora of antibiotics has been discovered, many, like penicillin, initially derived from mould or fungi. Once the nucleus of the natural compound was identified, numerous semisynthetic substances were produced by manipulation of the side chains, so altering the antibacterial and pharmacokinetic properties of the parent drug. Alongside the development of antibacterial agents, the past 50 years have also seen the production of drugs effective against some fungi, protozoa, helminths and viruses.

Wisely applied, these antimicrobial drugs have an enormous potential for good in human and veterinary medicine and animal husbandry, but they are often misused with disastrous results. Many organisms against which these drugs are effective are shared by man and animals either as commensals or pathogens. Consequently, the use of an antimicrobial agent in a member of one species may have unpredictable results extending far beyond the initial site where it was first employed.

The prescriber of antimicrobial drugs rarely appreciates the enormous responsibility he assumes. Firstly, the drug may be toxic to the host's tissues as well as to the pathogen against which it has been directed. The host's commensals may be inhibited along with the target organism, leaving an ecological vacuum into which opportunists may be drawn. Alternatively, the commensals and pathogens may not be killed, but may acquire multiple

resistance both to the drug being used and to several others in addition. This sinister property can be transferred from the micro-organisms of the host to those of his fellows, to those of other species and then to the environment at large, leading to a microflora largely insensitive to many of the previously effective drugs.

The model described applies mainly to antibiotics and bacterial infections which have been extensively studied. The use of antibacterial substances to accelerate fattening of livestock for the market has rightly been condemned. Antibiotics should only be given to animals for therapy under the direction of a qualified veterinary surgeon. Otherwise a reservoir of resistant micro-organisms will grow up and the usefulness of the antibiotics will fast diminish. Similarly, in human medicine and dentistry, antibacterial drugs must be cherished and only prescribed by qualified doctors and dentists when genuinely indicated. The availability of antibacterial agents is all too easy in some countries and often leads to self-medication, widespread antibiotic abuse and high levels of multiple antibiotic resistance amongst dangerous bacterial pathogens. Prolonged or repeated therapy and low dose suppressive antibacterial prophylaxis are most likely to induce drug resistance amongst bacteria. Although less is known about the development of resistance amongst non-bacterial micro-organisms, it is likely that the same trends will occur. An example of protozoal resistance is the chloroquine insensitivity of malarial parasites already found in many different parts of the world. Similar problems may develop amongst viruses and fungi if proper control is not exercised in the use of antimicrobial agents.

Before any antibacterial drug is prescribed, it is important not only to be sure that an infection is present, i.e. that the tissues have been successfully invaded by the micro-organism, but also that the bacteria are doing harm or are likely to do harm if left untreated. Antibiotics are often wrongly given simply because some potentially pathogenic organisms have been isolated even though they are not making the patient ill or are sufficiently trivial for the patient's own defence mechanisms to deal with them unaided. Ideally, when an infection is to be treated, the organism should first be isolated and its sensitivity determined. Some bacteria, such as *Streptococcus pyogenes*, are always sensitive to penicillin, so assessment of sensitivity need not be routinely requested. Others may be variably resistant to antibiotics, in which case laboratory help is essential in determining the antibiogram, as it is now called.

Whenever possible, a bactericidal drug should be used, especially in the immunocompromised patient. The spectrum should be narrow to avoid interference with commensals. It is equally important to ensure that the chosen drug will penetrate to the site of the infection. Thus orally administered antibiotics must be well absorbed from the intestine if they are to provide adequate antibacterial concentrations in infected tissues. Pyogenic meningitis, for example, can only be successfully treated other than by direct intrathecal or intraventricular injection if the antibacterial drug crosses the

blood–brain barrier and enters the CSF in sufficient amounts.

The pharmacokinetics of the drug must therefore be understood and caution exercised in very ill or elderly patients who cannot metabolize or excrete these drugs efficiently because of hepatic or renal functional impairment. Special care must be observed during pregnancy and lactation and in the newborn, whose immature handling of certain drugs may be quite different from that in the older child or adult. In these circumstances, certain antimicrobial drugs should be avoided altogether or else their dosage modified.

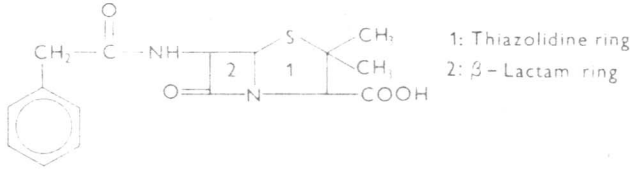
Sometimes it is important to monitor drug concentrations in body fluids to ensure that an adequate antibacterial concentration has been achieved. In the context of toxic antimicrobial drugs, monitoring is essential to prevent the drug level rising excessively, which could lead to tissue damage unless a reduction is made in the dose or the interval between doses is prolonged. It is occasionally difficult to find the right balance between the therapeutic and toxic doses in acutely ill patients whose pharmacological handling of the drug may fluctuate rapidly due to hypotension, reduced renal clearance or hepatic insufficiency.

Another reason for limiting the use of antimicrobial agents for genuine therapeutic indications is their ability sometimes to induce severe or fatal adverse reactions. A history of previous drug sensitivity must be sought and the same drug or a closely allied one should be avoided if a reaction has been recorded before. Certain drugs are more liable to be toxic when used in particular disease states. Ampicillin and amoxycillin skin eruptions are more common when lymphoid tissue is exuberant, as in lymphomas or glandular fever. Chloramphenicol is more likely to induce aplastic anaemia if long or repeated courses are given. Some drug combinations increase the risk of reactions, such as the nephrotoxicity associated with the combination of an aminoglycoside with certain cephalosporins, or the use of cephaloridine or cephalothin with frusemide or ethacrynic acid. Interference with the anticoagulant action of warfarin can be a dangerous side-effect of various antimicrobial drugs, notably the sulphonamides. The low oestrogen pill may lose its contraceptive effect if taken with rifampicin or other drugs that induce liver enzymes (pp. 37, 425).

In general, a single antimicrobial agent should be employed, depending on the known or expected sensitivity of the pathogen causing the infection. Antibacterial drug combinations are only justified in three circumstances: (i) for the blind treatment of the severely ill septicaemic patient whose infecting agent has not yet been identified and who urgently requires antibiotic cover for Gram-positive and -negative bacteria and also possibly anaerobes, (ii) to prevent the emergence of resistance, as in the management of tuberculosis, where three drugs may be initially used until the sensitivity of the tubercle bacilli is known, whereupon they should be replaced by two effective drugs, or in chloroquine-resistant malaria, where a combination of pyrimethamine with sulfadoxine or dapsone is advocated, and (iii) where the synergism occurs as

with co-trimoxazole, whose two components, sulphamethoxazole and trimethoprim, sequentially interfere with bacterial folinic acid synthesis. Disadvantages of combined therapy include the increased risk of toxicity by the use of more than one drug, the difficulty of assaying drug concentrations in tissue fluids, the greater chance of superinfection because of the broader overall spectrum of activity, and, not least, the cost.

Penicillins



BENZYLPENICILLIN

The number of penicillins continues to increase from Fleming's original crystalline, benzylpenicillin (penicillin G), which remains a very effective antibiotic, to the highly sophisticated broad- and narrow-spectrum penicillins now produced from the original fermentation product nucleus by semi-synthetic processes. The penicillins are a particularly valuable group of antibiotics, being relatively non-toxic and so therapeutically very useful.

Description and General Properties

The 6-aminopenicillanic acid (6-APA) nucleus, from which all penicillins are derived, is a thiazolidine ring fused to a β-lactam ring. Different and often lengthy side-chains added to this basic structure confer different antibacterial and pharmacokinetic properties. One disadvantage of penicillin G is its inability to resist gastric acid, making the drug effective only after parenteral administration. Adding phenoxyacetic acid instead of phenylacetic acid during the fermentation process results in the production of phenoxymethylpenicillin (penicillin V), which is acid stable, unlike the original penicillin G.

Organisms such as *Staphylococcus pyogenes* and certain coliforms produce β-lactamase (penicillinase), an enzyme which disrupts the β-lactam ring of the 6-APA nucleus and renders the drug pharmacologically inert. A heavy side-chain added to 6-APA, as shown originally with methicillin, confers β-lactamase stability. The isoxazolyl penicillins, like cloxacillin, flucloxacillin and oxacillin, also possess heavy β-lactamase resisting side-chains, but, unlike methicillin, they are also acid resistant and so can be given by mouth as well as by injection. The substitution of a single chlorine atom by fluorine on the side-chain confers on cloxacillin an enhanced degree of absorption from the gut as flucloxacillin.

Until the arrival of ampicillin, which is active against many of the

Enterobacteriaceae, the penicillins were mainly effective against Gram-positive cocci and bacilli and only a few Gram-negative species, like gonococci and meningococci, were sensitive to it. Various esters of ampicillin have been developed with enhanced absorption from the gastrointestinal tract, but the closely related compound, amoxycillin, which differs from ampicillin only by the addition of a hydroxyl radical on the side-chain, is particularly well absorbed and gives higher serum concentration than ampicillin after a similar oral dose.

The amidino-penicillins, injectable mecillinam (p. 8) and the orally acceptable pivmecillinam (p. 8) have a similar, but not identical, spectrum to ampicillin and this includes activity against salmonellae. The amidino-penicillins have a single attachment site to the bacterial cell wall at protein binding site 2, thus differing from other penicillins which can attach at various different sites. Although their action is different because of the formation of easily ruptured bacterial spheroplasts, the therapeutic value of the amidino-penicillins on their own is not superior to that of other penicillins; used in combination with other antibiotics, they may have more than an additive antibacterial effect.

Carbenicillin was the first penicillin active against *Pseudomonas aeruginosa*, but, being acid labile, it had to be given by injection and in very high i.v. doses in order to be effective. The orally administered carbenicillin derivatives, carindacillin and carfecillin, are therapeutically disappointing for use in serious pseudomonas infections. One new development from carbenicillin, ticarcillin, however, has a better spectrum of activity than carbenicillin against Gram-negative bacilli, including *Ps. aeruginosa*, and the recently introduced piperacillin is even more active in vitro. The ureido-penicillins, mezlocillin and azlocillin, are also particularly effective anti-pseudomonas drugs. These valuable agents with special properties must be safeguarded and only used when specifically indicated. Ticarcillin, piperacillin and the ureido-penicillins are acid labile like carbenicillin and must be given parenterally. They are all sensitive to β-lactamase to a variable degree.

One discovery running parallel with the development of the newer penicillins has been the production of two β-lactamase inhibitors, clavulanic acid and sulbactam. Although they only have weak antibacterial properties on their own, a small amount of these new agents will render β-lactamase sensitive drugs, like ampicillin, resistant to enzymatic degradation. The exact therapeutic place of these new preparations is still unclear, despite intense marketing pressure by the pharmaceutical companies.

Mode of Action

Penicillins interfere with bacterial cell wall synthesis and render the bacterium unable to withstand changes in osmotic pressure which cause it to swell up and rupture. Penicillins bind at one of several sites on the cell wall, except the amidino-penicillins, which only bind to protein binding site 2. Bacterial cell

walls consist of long glycopeptide and peptidoglycan chains. Penicillins prevent the formation of the cross linkages between these chains by interference with the enzymes transpeptidase and endopeptidase, but do so only when the bacteria are dividing. Long filamentous forms result if end-wall synthesis is disrupted, as with ampicillin, or spheroplasts result if side-wall synthesis is inactivated, as with amoxycillin and the amidino-penicillins. As peptidoglycan is common to all bacteria but is not found as such in human cells, the penicillins can be used almost with impunity, thanks to the exploitation of a basic biochemical difference between host and pathogen.

Pharmacokinetics

The acid stable penicillins, like penicillin V, ampicillin, amoxycillin, isoxazolyl penicillins (pp. 7, 9), carindacillin, carfecillin and pivmecillinam, are absorbed variably in the upper small intestine. Amoxycillin is better absorbed than ampicillin, so that higher blood levels are reached. Accordingly, 8-hourly rather than 6-hourly administration can be used. Amoxycillin penetrates into sputum better than ampicillin. Various ampicillin esters, like talampicillin, have been developed. They have no pharmacological action on the gut flora before absorption, but are rapidly hydrolysed to ampicillin and esters on crossing the gut wall. Higher serum ampicillin concentrations result on a weight for weight basis than with the non-esterified drug.

After injection i.v. or i.m., the acid labile penicillins are handled similarly to the orally administered acid stable compounds. Serum levels rise steeply and tissue diffusion is good, except to the cerebrospinal fluid, where therapeutic concentrations of penicillin are only achieved when the meninges are inflamed. Protein binding of some penicillins is high, especially the isoxazolyl penicillins. Some biliary excretion occurs with all the penicillins, but particularly with ampicillin, where bile levels of ampicillin may be 300 times greater than the serum concentration. Very little penicillin is metabolized. Most is excreted in the urine by renal tubular mechanisms within a few hours, necessitating repeated administration of any penicillin several times in 24 hours to maintain therapeutic concentrations. Probenecid interferes with the tubular excretion of penicillins and may be used to achieve very high tissue concentrations of the antibiotic.

Preparations

Benzylpenicillin (penicillin G; Crystapen). This drug remains the least toxic of the family and has been used safely in extremely high doses. It is usually prepared for i.m. injection in a concentration of 150 mg/ml in water and does not keep for longer than a day at room temperature. The usual dose range is from 300 to 600 mg 6-hourly, although an insensitive organism may only be eradicated with doses of 6 g or more given 6-hourly.

Procaine penicillin (Depocillin). A relatively insoluble preparation, procaine penicillin is slowly released from the injection site, and it therefore takes

longer for high blood levels to be achieved. It is less painful for the recipient than is benzylpenicillin. The dose is 600 mg and this is required only once a day. Procaine penicillin may be mixed with benzylpenicillin (Bicillin) to achieve fast mobilization to the tissues and less frequent dosage.

Benzathine penicillin (Penidural). This pink *suspension* is given in adult doses of 458 mg every 6–8 hours (229 mg in 5 ml) or as *paediatric drops* in lower doses according to body weight (115 mg in 1 ml).

Benethamine penicillin (Triplopen). This is available as a powder in a vial which contains 475 mg of benethamine penicillin, 250 mg of procaine penicillin and 300 mg of sodium penicillin. When water for injections is added, a suspension for i.m. use is formed. One vial is given every two or three days.

Phenoxymethylpenicillin (penicillin V) (Aspin VK, Crystapen V, Distaquaine V-K, Econocil VK, Icipen, Stabillin V-K, V-Cil-K). Tablets (usually 125 or 250 mg) of phenoxymethylpenicillin are stable in gastric acid and one is taken every 4–6 hours. Absorption is delayed by food, so doses should be given prior to meals.

Phenethicillin (Broxil) and *Propicillin*. These drugs are less active than phenoxymethylpenicillin, but are better absorbed. Propicillin is tightly bound to protein in the plasma and is therefore distributed less well in the tissues and is less active. Phenethicillin is similar in efficacy to phenoxymethylpenicillin and the dose is identical. The amount usually given is 250 mg 4–6 hourly on an empty stomach.

Methicillin (Celbenin). While being useful against penicillinase-producing bacteria, methicillin is unstable in gastric acid. It is best given by injection i.m. or i.v. in a dose of 1 g 4–6 hourly. It is approximately one-fiftieth less active against Gram-positive bacteria than benzylpenicillin, though higher concentrations are attainable free in plasma owing to lower binding to protein.

Cloxacillin (Orbenin) and *Flucloxacillin* (Floxapen). These penicillins combine the properties of penicillinase resistance and acid stability. Accordingly, they may be given orally, and flucloxacillin achieves particularly satisfactory plasma levels at a dose of 250 mg 6-hourly. The same dose may be used for the i.m. preparation. Cloxacillin may also be given orally or i.m., the dose being 500 mg 6-hourly. Both drugs surpass methicillin in antibacterial action, although neither gives results comparable with those obtained when benzylpenicillin is used against organisms that are sensitive to it.

Ampicillin (Amfipen, Penbritin, Vidopen). Ampicillin, a widely used drug, can be given orally, i.m. or i.v. in a dose of 250 mg 6-hourly. It has a broad range of activity, but many bacteria quickly form resistance to it. Like benzylpenicillin, it is not found in high concentration in brain tissue, though

bactericidal levels reach the CSF in purulent meningitis. Combinations of 250 mg of ampicillin with 250 mg of cloxacillin (Ampiclox) or of 250 mg ampicillin with 250 mg of flucloxacillin (Magnapen) are available for parenteral and oral use, respectively. These are combined in an effort to produce broad spectrum properties and at the same time have penicillinase resistance. Sulbactam, a β-lactamase inhibitor, combined with ampicillin renders the ampicillin resistant to enzyme destruction, but it is not yet available for general use.

Amoxycillin (Amoxil). This is twice as well absorbed as ampicillin and so can give therapeutic serum levels after 250 mg capsules are given at 8-hourly intervals. Although not a penicillin, clavulanic acid, a β-lactamase inhibitor, combined with amoxycillin, confers resistance to the enzyme. An adult dose of 125 mg of potassium clavulanate with 250 mg amoxycillin (Augmentin) is given 8-hourly or may be doubled in severe infections.

Talampicillin (Talpen). This is one of several ampicillin-ester preparations which has no pharmacological activity against gut flora, but which is rapidly de-esterified in the gut mucosa or liver to release ampicillin to the systemic circulation. Absorption is good and 250 mg 8-hourly (or 125 mg 8-hourly for children over 2 years) gives good serum concentrations.

Carbenicillin (Pyopen). This was the first penicillin to be effective against *Ps. aeruginosa*. For suspected or proven pseudomonas septicaemia up to 30 g daily was necessary in 4–6 hourly divided doses i.v. It has now been supplanted by ticarcillin, the ureido-penicillins, and piperacillin. It is acid labile and β-lactamase sensitive. Two oral derivatives can be used for pseudomonas urinary infection without systemic involvement. They are carindacillin (Geocillin — USA only), 500 mg to 1 g 6-hourly, or carfecillin (Uticillin in the UK), 500 mg 8-hourly. Note that in the USA, Uticillin VK is a proprietary name for phenoxymethylpenicillin (p. 7).

Ticarcillin (Ticar). Ticarcillin is chemically closely related to carbenicillin, but much more active against *Ps. aeruginosa*. It is acid labile and β-lactamase sensitive. For septicaemias, 5 g may be given intravenously every 6 hours.

Mezlocillin (Baypen) and *Azlocillin* (Securopen). These ureido-penicillins should be reserved for serious infections with Gram-negative species, especially *Ps. aeruginosa*. They are less active against Gram-positive organisms. They are acid labile and variably β-lactamase sensitive. In septicaemic adults 2–5 g may be required i.v. every 6–8 hours.

Piperacillin (Pipril). This is very active against *Pseudomonas* spp. and sufficiently broad-spectrum to include many Gram-positive and Gram-negative bacteria, except some staphylococci and klebsiella organisms. For seriously ill bacteraemic adults 3–4 g may be given i.v. 6-hourly.

Mecillinam (Selexidin) and *Pivmecillinam* (Selexid). These amidino-penicillins are β-lactamase sensitive. Mecillinam is acid labile and is given i.m.