Penicillin and Related Antibiotics: Gram-negative Infections: Urine

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PENICILLIN-LIKE SUBSTANCES AT PRESENT IN USE
In retrospect, it is perhaps surprising that after the introduction of benzylpenicillin, this substance was not used more widely for the treatment of urinary infections. Following intramuscular injection, high concentrations are obtained in the urine which greatly exceed the minimal inhibitory concentrations of common pathogens such as Escherichia coli and Proteus mirabilis.

Isolated reports can be found in the literature advocating its use in cystitis due to Bacillus proteus (Stewart, 1945) and subsequently Weinstein and his colleagues (1964) have shown that, even where there is tissue involvement with bacteraemia, intravenous benzylpenicillin in massive doses can be a highly effective form of treatment. However, it was not until the introduction of ampicillin (Rolinson and Stevens, 1961) that the effective use of a penicillin for urinary infection was demonstrated in substantial numbers of patients (Brumfitt et al., 1962) but subsequently its use became commonplace.

Ampicillin differs from benzylpenicillin but resembles phenoxyethyl penicillin in being acid stable, thus making it suitable for oral administration. It also differs from benzylpenicillin in its pattern of excretion and by having a peak level that is lower but better sustained. For example, following an oral dose of 500 mg ampicillin, a peak blood level of about 5 μg/ml can be expected after two hours and small quantities are detectable after six hours. This contrasts with benzylpenicillin where the peak level is higher, occurs earlier, and excretion is more rapid. Although probenecid delays the renal excretion of ampicillin it is less effective than with benzylpenicillin.

More recently, the newer penicillin, carbenicillin, was introduced; this must be given by the intramuscular or intravenous route. Intramuscular carbenicillin in doses of 1 g 6 hourly is useful against a number of ampicillin-resistant Proteus spp. (morganii, rettgeri and vulgaris), usually because it is resistant to the β-lactamase produced by these organisms. Similar success

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may be obtained when treating infections due to *Pseudomonas aeruginosa* if they are restricted to the urine (Brumfitt et al., 1967). However, where there is also parenchymal renal infection (with or without bacteraemia) the use of carbenicillin alone may require massive dosage by the intravenous route unless renal damage impairs excretion. Alternatively, if there is synergy with gentamicin (Brumfitt et al., 1967) carbenicillin can be used to supplement treatment with the former antibiotic. The mechanism of resistance of *Ps. aeruginosa* is not clear and many strains have an intrinsic resistance rather than resistance conferred by production of ‘carbenicillinase’.

The other group of antibiotics that may be classed with penicillins are the cephalosporins. Three are at present in use in this country: cephaloridine, cephalothin, and cephalexin. The spectrum of the cephalosporins differs from the penicillins described, particularly in their activity against the *Klebsiella* spp. (but not *Enterobacter* spp.). They are inactive against pseudomonads and *Streptococcus faecalis*, but against *Proteus* spp. the sensitivity is difficult to predict.

Cephalothin is not absorbed when given orally and is extremely painful when given intramuscularly so that intravenous administration is necessary. Cephaloridine is also not absorbed by the oral route, even though the compound is stable in the presence of acid but is remarkably well tolerated when given intramuscularly. Large doses (of the order of 2 g) can be given intramuscularly with little or no discomfort. This contrasts with ampicillin which causes pain when given intramuscularly in doses exceeding 0.5 g. The most recently introduced cephalosporin is cephalexin which, apart from being absorbed when given by mouth, has the important property of being very well excreted even in the presence of moderate degrees of impairment of renal function although in renal failure with substantial reduction in the glomerular filtration rate the dose needs to be adjusted.

**The Future Development of Penicillin-Like Compounds**

Over the years attempts have been made to synthesise penicillins with a higher co-efficient of activity against Gram-negative pathogens. The most obvious method is to produce compounds with a higher specific activity but another approach is to produce compounds that are better absorbed. Ampicillin given by mouth produces not only lower but much more variable blood levels than when the same dose is given by intramuscular injection (Brumfitt et al., 1964; Neumann, 1965). Some years ago, hetacillin, a condensation product of ampicillin and acetone, was claimed to be a compound that released greater amounts of ampicillin into the blood after an equivalent oral dose. However, these claims were not substantiated (Sutherland and Robinson, 1967).
More recently, two new compounds have been described, both of which appear to produce higher serum levels. The first of these is parahydroxy-ampicillin (Long et al., 1971) which is absorbed unchanged and whose excretion is delayed by probenecid. The other is pivampicillin, which is a pivaloyloxymethyl ester of ampicillin from which only ampicillin is absorbed (Daehne et al., 1970).

A number of workers have shown enhanced absorption with both compounds when tested in volunteers, but it remains to be seen whether the enhancement produces a better clinical response with oral dosage. Since conventional dosage of oral ampicillin gives very high urine levels, improved results must be looked for in those patients where there is also tissue involvement, when a higher blood level of ampicillin is needed to achieve penetration. In this connection, it must be pointed out that the reliability of absorption of ampicillin from the alimentary canal following the administration of the two ‘new’ ampicillin-like compounds given by mouth must be studied in sick patients since absorption is known to be less reliable than in volunteers. A formal trial to compare these compounds with both oral and intramuscular ampicillin will also be needed before their place can be defined.

Another recently introduced compound that is absorbed when given by mouth is the indanyl ester of carbenicillin (Wallace et al., 1970). In view of the large intramuscular doses needed to deal with parenchymal Ps. aeruginosa infections, its place here will probably be restricted but it may be useful if the infection is confined to the bladder. It may also have a special place in treating resistant proteus infections.

FUNDAMENTAL CONSIDERATIONS IN THERAPY

Toxicity Testing

With the development of new antibiotics, the initial assessment must first be made in the animal, and valuable information may emerge concerning the absorption, excretion, metabolism, teratogenicity and effectiveness of the substance. Nevertheless, very misleading results may occur. For example, a single intramuscular injection of penicillin in a guinea-pig leads to a hypersensitivity reaction that is usually fatal within a few days. Consequently, it has recently been suggested that, following a relatively small number of experiments on animals, a single very small dose of the antibiotic should be given to two or three human volunteers in order to observe the response, and by means of a number of laboratory tests find which animals handle the substance in the same way. Subsequent experiments are carried out on animals which simulate the human situation most closely. A method such as this may be especially important when the recently introduced esters of penicillin are
being tested, in order to see whether any of the ester is absorbed. If so, it is clearly vital to demonstrate suitable detoxification mechanisms.

Clinical Evaluation
Choice of a number of clinical illnesses is of great importance in assessing the value of an antimicrobial agent. Patients with the particular illness must be available in sufficient numbers to the investigator in order to complete the study in a reasonable period of time. Urinary infection is a useful disease for the evaluation of antimicrobial agents that are excreted in the urine. The presence or absence of infection can be diagnosed with great accuracy, and specimens obtained without discomfort or inconvenience to the patient. Furthermore, infection of the urinary tract can be localised in many sites and it will be shown that treatment demands the use of compounds with different properties. For example, trimethoprim penetrates prostatic tissues better than acidic sulphonamides or any of the penicillins so far available (Reeves and Ghilchik, 1970). This difference may be related to the pKa value and lipid solubility, both of which are believed to influence membrane penetration. Effective methods are now available for determining the site of the infection within the urinary tract. This information enables antimicrobial agents to be evaluated in various sites where the local conditions affect antibiotic penetration. Such studies also allow much to be learnt about these agents, including their pharmacokinetic properties.

**Important Factors Affecting the Results of Treatment of Urinary Infection with the Penicillins**
It is clearly impossible to discuss the correct antimicrobial agents for the treatment of urinary infection without appreciating that this condition is not a homogeneous disease.

Before attempting to define the place of the penicillin group of drugs in therapy, it is important to remember the very different response that may be expected in the various sub-groups and types of infection. Four main aspects of the condition need to be emphasised: the type of patient, the site of the infection, the infecting organism and the host response.

**Type of Patient**

**Infection Acquired Outside Hospital.** Many sub-groups could be listed but the most important varieties are: dysuria-frequency syndrome, asymptomatic bacteriuria, prostatitis, and acute or chronic active pyelonephritis (i.e. chronic, usually recurrent, infection of the urine with a focus of infection in one or both kidneys).
Hospital-acquired Infection. This has many causes, including some that are extremely difficult to cure, such as patients with bladder dysfunction or indwelling catheters.

In domiciliary practice the cure rate varies in the defined groups but in a predictable way. For example, using conventional treatment such as a seven-day course of sulphonamide or ampicillin, 85 to 90 per cent of the patients are cured. However, the situation is complicated by a spontaneous cure-rate of 50 per cent that occurs during the seven-day period. An identical course of treatment of bacteriuria in pregnancy results in a lower cure-rate (70–75 per cent) but the spontaneous cure-rate during the whole of the gestation period is only 7 per cent.

The spontaneous cure-rate in hospital patients varies according to the underlying complications and, therefore, precise knowledge of the type of patient being treated is essential in assessing the results of chemotherapy. For example, a paraplegic patient can be resistant to vigorous and repeated attempts to eradicate a chronic infection (Table 1).

### Table 1. Variations in the spontaneous cure-rate and the results of treatment. The patients treated were given a seven day course of conventional therapy

|                                | Expected Cure Rate (%) |
|--------------------------------|------------------------|
|                                | No treatment | Treated  |
| Frequency-dysuria syndrome     | 50+          | 80–95    |
| Bacteriuria in pregnancy       | 7            | 70–75    |
| Hospital-acquired infection    | Varies       | 0–75     |

Site of Infection
The site of infection will also affect the cure-rate. If infection is limited to the bladder, 75 to 90 per cent will be cured, but if there is also renal parenchymal involvement, this falls to about 60 per cent.

Recently there has been an interest in prostatitis, which can be divided into three varieties. First, that seen in the young adult which has an expected cure-rate in excess of 90 per cent; second, that seen in middle-aged men, which usually presents as a recurrent urinary infection; and finally, the fibrous type, usually seen in the older man, which is recalcitrant to treatment, with a cure-rate of about 20 per cent.

Infecting Organism
The organism responsible for urinary infection varies considerably, depending upon whether the infection is acquired in or outside hospital. Table 2 gives
our experience at Edgware Hospital where 1,000 consecutive organisms responsible for urinary infection were compared with the same number occurring in domiciliary patients in the surrounding population.

Patients infected with the same organism show other differences. During 1968–9, 15 per cent of the *Escherichia coli* isolated from hospital patients were resistant to 25 μg/ml or more of ampicillin, compared with only 2 per cent of resistant *Esch. coli* isolated from the surrounding general practice population. In other hospitals, where ampicillin is used more freely, the percentage of ampicillin resistant *Esch. coli* has exceeded 30 per cent.

In both hospital and domiciliary practice, resistance may be of a high order (MICs in excess of 500 μg/ml).

**Host Response**
Finding a significant bacteriuria (over 10⁵/ml) merely indicates that bacteria are multiplying in the bladder urine. However, infection is not necessarily confined to the bladder and the absence of symptoms is a poor guide to the absence of infection in the upper urinary tract.

It must also be remembered that urinary tract infection may disseminate into the blood stream. With a severe renal parenchymal infection (so called ‘classical acute pyelonephritis’) a positive blood culture can be obtained in 50 per cent of patients. Nevertheless, such infections, although dramatic, usually respond promptly to suitable antimicrobial treatment. Unfortunately, where similar infections are complicated by an altered host response, as, for example, in a post-kidney graft with a leaking ureter and the simultaneous administration of immunosuppressive agents, a cure-rate of only about 25 per cent was found (Brumfitt and Leigh, 1969).

Table 2. A comparison between the organisms causing urinary infection in hospital and in domiciliary practice

| Organism                  | Hospital | Domiciliary |
|---------------------------|----------|-------------|
| Total Studied             | 1,000    | 1,000       |
| *Escherichia coli*        | 59%      | 90%         |
| *Proteus* spp.            | 16%      | 5 (mirabilis) |
| Klebs: *Enterobacter*     | 9%       | 2           |
| Staphylococci             | 5%       | 3 (albus)   |
| *Pseudomonas aeruginosa*  | 3%       |             |
| *Streptococci*            | 7%       |             |
| Miscellaneous             | 1%       |             |
In summary, it is clear that for proper assessment more than just the isolation of an organism from the urine and determination of its sensitivity is needed. As a minimum the diagnosis must be made first by quantitative bacterial counts. Secondly, accurate determination of the sensitivity of the organism to the antimicrobial substance is necessary and this must be considered in the light of serum, tissue (predicted) and urine levels. Thirdly, in certain conditions the site of the infection may influence the nature of treatment and its dose. Finally, in the assessment of an antimicrobial regime, relapse must be distinguished from reinfection. An organism can be eradicated by an antibiotic but perhaps because of some organic abnormality, another organism may invade the urinary tract. This is reinfection, in contrast with relapse, where there has been failure to eradicate the original organism. Since the majority of infections are due to *Esch. coli* the second organism is also often *Esch. coli*. In these circumstances, serotyping is needed to distinguish between the two conditions. Only where the same organism re-appears after treatment can the chemotherapy be said to have failed.

**THE LENGTH OF A COURSE OF THERAPY**
Simple infections with symptoms confined to the lower urinary tract often become asymptomatic within 24 hours of starting treatment. Nevertheless, in the past, some workers have recommended three or six months' treatment and have even recommended changing the antibiotic at monthly intervals. All the evidence suggests that this is unnecessary. Indeed, the response is the same whether the patient is treated for one, two or six weeks, although, at least with oral ampicillin, reducing the duration below one week begins to produce inferior results. Furthermore, other advantages arise from a short course of therapy. Once treatment has been withdrawn, failures can be identified quickly and anybody who fails to respond to two courses of therapy with appropriate drugs requires investigation to see whether there is abnormality of the urinary tract. For example, our own usual regime for women with bacteriuria in pregnancy, who have sensitive organisms, is a sulphonamide first, followed by ampicillin.

Ultra-long-acting sulphonamide has been used successfully to treat infections associated with the frequency-dysuria syndrome and asymptomatic bacteriuria in pregnancy. Because cephaloridine is painless on injection and rarely gives rise to allergic reactions, it is possible to give a large dose by the intramuscular route. Following the injection of 2 g, extremely high blood and urine levels are found that are greatly in excess of the MIC of most urinary pathogens isolated from patients in domiciliary practice (Table 2)
However, the cure-rate using a single dose was found to be lower than that expected in the treatment of similar groups of patients with a 7 to 10 day course of conventional treatment (Brumfitt et al., 1970). A possible reason for the failures was that, although bactericidal, cephaloridine has a less rapid effect than other antibiotics, such as the aminoglycosides, so that under the circumstances of the treatment it is likely that complete eradication of the bacterial population did not occur and a few 'persisters' remained. After elimination of the infection, these bacteria multiplied to re-establish the infection. However, Williams and Smith (1970) have tried a single dose of streptomycin (which is rapidly bactericidal) with similar results to those found by us when using cephaloridine.

Cephalexin, which can be taken by mouth, produces higher blood levels than ampicillin but for most of the important pathogens has a correspondingly higher MIC. It was effective, but in our hands adverse effects occurred in 35 per cent of patients, which inevitably limited its value, although others did not encounter this problem (Postgraduate Medical Journal, 1970). However, with certain exceptions, such as infections due to Klebsiella spp. and some Proteus spp., experience to date indicates that neither cephaloridine nor cephalexin have a tangible advantage over ampicillin for the treatment of most urinary infections. The major difficulty in using ampicillin for treating patients with tissue infection is that it is relatively poorly absorbed from the alimentary tract. Intramuscular ampicillin in equivalent doses produces peak serum levels three to four times greater.

Finally, a study in hospital patients to compare ampicillin given by mouth with the trimethoprim-sulphamethoxazole combination indicated that the latter was superior although the results were not statistically significant (Reeves et al., 1969). Of course, being a newly introduced substance, trimethoprim was likely to be more successful, as judged by the MICs of the organisms isolated from the patients. It remains to be seen whether more resistant strains are found when the drug has been in use for a number of years. Nevertheless, trimethoprim-sulphamethoxazole is clearly a major advance in the treatment of urinary infections and will undoubtedly stimulate the search for better penicillins.

In conclusion, while one must pay a high tribute to the great advances in the management of urinary infection brought about by penicillin and its associated compounds, we still need to achieve uniformly good results in treatment. New penicillins are being introduced and will undoubtedly prove to be valuable. But it is at least equally important to insist on proper diagnosis and follow-up in order to bring about a still greater reduction in the morbidity and mortality that results from urinary infection.
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**Book Review**

*The Management of Mental Illness in General Practice*. By R. R. Tilleard-Cole, John Marks and N. H. Moynihan, London. No date. Pages VIII + 92. Issued on request by Roche Products Ltd.

The authors’ aim is to summarise the psychiatry of general practice in a short, readable, and practical way. In the main they succeed, through the co-operation of a psychiatrist, a clinical pathologist, and a general practitioner. The balance between the physical, psychological, and social approaches to mental illness is somewhat tilted towards the physical, but not to the point of imbalance.

A particularly commendable feature is the recurrent theme that mood swings, anxiety and even paranoid ideas are not necessarily pathological. Similarly, some sexual deviations are very close to what is normal.

A potentially good feature is a group of drawings of anxious, depressed, mentally defective, and alcoholic patients. But although the drawings have artistic merit, they do not make convincing impressions of essential characteristics.

The weaknesses of the book lie paradoxically in its strongest theme—the physical approach. The most important is the repeated mention of the drugs Chlordiazepoxide and Diazepam. These are useful drugs without doubt, but surely Roche Products Ltd. in sponsoring a book ‘as a service to the medical profession’ would have had vastly more prestige if no special mention of their own products had been made.

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