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Leading articles

Serratia marcescens infections—selection of an antibiotic

Serratia marcescens is commonly encountered in nosocomial infections in the U.S.A. but evidence of its presence as a pathogen in the U.K. has been lacking. Recent reports, however, have indicated that *S. marcescens* infections may be becoming significant in the U.K. (Black & Hodgson, 1971; Ball, McGhie & Geddes, 1976) and that its apparent infrequent isolation in the past has been due to difficulties in identification. The ability to produce pigment which was formerly used as a marker for this organism is now lacking in up to 90% of clinical isolates (Wilkowske, Washington, Martin & Ritts, 1970). Serratia infections occur almost exclusively in patients with compromised host defences and may be life-threatening, e.g. septicaemia (Dodson, 1968; Altemeier, Culbertson, Fuller & McDonough, 1969) and endocarditis (Alexander, Reichenbach & Merendino, 1969). *Serratia marcescens* shares with other opportunist pathogens such as *Pseudomonas aeruginosa* the problem of multiple antibiotic resistance. Broad spectrum antibiotic therapy often, in fact, predisposes to infection with this organism. Cooksey, Bannister & Farrar (1975) found over 50% of isolates to be resistant to five or more drugs while Medeiros & O'Brien (1969) demonstrated R factor mediated resistance in 21 of 22 equally resistant isolates. Hedges, Rodriguez-Lemoine & Datta (1975) studied transferrable resistance in 29 of 236 isolates from world-wide sources and demonstrated the presence of plasmids from groups S and L, which do not occur in other bacteria and which determine resistance to a variety of antimicrobial agents.

Clinical isolates of *S. marcescens* show a variable sensitivity pattern, with predictable sensitivity usually only to the aminoglycoside group and nalidixic acid. Cephalosporins are of little value, 100% of isolates being resistant to cephalothin (Koch & Rose, 1966; Cooksey *et al.*, 1975). Tsang, Sansang & Miller (1975) however, found over 70% of stains sensitive to cefoxitin, a cephamycin currently under clinical trial. Sensitivity to the penicillins is variable, in part due to β-lactamase production (Tsang *et al.*, 1975). Up to 90% of stains are resistant to ampicillin (Cooksey *et al.*, 1975), and sensitivity to carbenicillin varies between 60 and 80% (Hedges *et al.*, 1975; Cooksey *et al.*, 1975); a similar percentage applying to ticarcillin (Tsang *et al.*, 1975). *S. marcescens* appears to be naturally resistant to the polymixins (Traub & Kleber, 1975). Disc testing may indicate a degree of sensitivity, although Annear (1970) has drawn attention to an unusual target zone of apparent inhibition around colistin discs which may explain this finding. Cooksey *et al.* (1975) found that colistin failed to inhibit any of their isolates at achievable serum concentrations, using an agar incorporation technique, although conventional disc testing indicated that only 57% of these isolates were resistant. Traub & Kleber (1975) found that none of their isolates were inhibited by less than 1000 μg/ml of colistin, but demonstrated an interesting, if unexplained, synergy between colistin and rifampicin.

Aminoglycosides have been the sheet anchor of management of serious serratia infections. Kanamycin has been widely and effectively used and the high level of sensitivity (98% of strains) found by Cabrera (1969) has fallen only slightly recently to around 80% (Cooksey *et al.*, 1975; Hedges *et al.*, 1975). The introduction of gentamicin was soon followed by reports of its marked activity against *S. marcescens*. Thornton & Andriole (1969) found the MIC of gentamicin to vary between 0·0015 and 1·5 μg/ml and Wilkowske *et al.* (1970) reported 97% of strains sensitive at 1 μg/ml or less. The situation had not changed 3 years later when Waterworth (1972) found the MIC to lie between 0·25 and 0·5 μg/ml. These and other similar reports have lead to the adoption of gentamicin as the drug of choice in serratia infections. However, resistance has been increasing and recently Cooksey *et al.* (1975) found a 20% resistance rate and

Meyer, Lewis, Halter & White (1976) reported 50% resistance amongst serratia isolates from one major American general hospital. These reports cast grave doubts on the continuing value of gentamicin for serratia infections. Tobramycin does not appear to have any advantage over gentamicin in this respect. Waterworth (1972) reported an MIC for tobramycin of between 1 and 4 μg/ml and Dienstag & Neu (1972) found that most *S. marcescens* strains were resistant to serum concentrations of tobramycin safely attainable in man. However, the newer kanamycin-like aminoglycoside, amikacin does appear to show promise. Bodey & Stewart (1973) found that 48 of 50 isolates of *S. marcescens* were sensitive to concentrations of amikacin of 6·25 μg/ml or less. Traub & Kleber (1975) confirmed that the MIC of amikacin was between 1·6 and 6·3 μg/ml (attainable in the patient) and Meyer, Lewis, Carmalt & Finegold (1975) reported the successful treatment of 3 out of 5 patients with septicaemia. Meyer *et al.* (1976) suggest, on the basis of 100% sensitivity of isolates of *S. marcescens in vitro*, that amikacin may become the drug of choice in infections caused by this organism.

An alternative option may be suggested by the finding of Adenyi-Jones, Neilly, Roberts & Kaufmann (1973), who reported that *S. marcescens* was sensitive to between 0·1 and 1·0 μg/ml of trimethoprim, and demonstrated synergy between trimethoprim and sulphamethoxazole (TMP/SMZ). Grunberg, Beskid, DeLorenzo & Cleeland (1973) have confirmed the synergistic activity of TMP/SMZ (co-trimoxazole) and have shown the activity of SMZ against *S. marcescens* to be potentiated 2 to 12 fold *in vivo* (in mice) by TMP. In 4 cases SMZ resistant organisms were susceptible to the combination, but 4 strains *in vivo* and 3 strains *in vitro* were resistant. In a current study (Ball, McGhie, Gray & Geddes, unpublished data) 2 patients with pneumonia and 1 with a urinary tract infection have been successfully treated with co-trimoxazole but a septicaemic patient died despite therapy with the drug (Ball *et al.*, 1976). Thomas, Leonard & Alford (1976) have recently evaluated the effect of a combination of TMP/SMZ and colistin sulphmethate against multiply resistant isolates of *S. marcescens* from a hospital outbreak of infection. A synergistic effect was established *in vitro*. Four of 6 patients treated with this combination improved, but all were seriously ill with underlying disease from which they subsequently died. The results of treatment are, therefore, difficult to interpret.

In non-invasive lower urinary tract infection the sensitivity of *S. marcescens* to nalidixic acid is a useful loophole in this organism's resistance pattern. Cabrera (1969) found 91% of isolates sensitive to nalidixic acid and Wilkowske *et al.* (1970) demonstrated that 86% of isolates were sensitive to 10 μg/ml or less, which is easily exceeded in urine despite the fact that a large proportion of nalidixic acid is excreted as the inactive glucuronide.

The therapy of life-threatening infection caused by *S. marcescens* will normally be dictated by the sensitivity pattern of the infecting organism, but as a 'best guess' the current drug of choice is gentamicin. However, the emergence of significant resistance to this antibiotic indicates that its period of usefulness may be limited at least in the U.S.A. Amikacin may eventually be a satisfactory alternative. It is, however, imperative to continue to study the efficacy *in vivo* of alternative agents such as co-trimoxazole and cefoxitin and combinations of other drugs such as colistin and either rifampicin or co-trimoxazole.

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Epidemiology of anthrax

There is no more delightful chapter in the annals of infectious disease than Christie's account of anthrax and the 57 varieties of spread of anthrax spores by the discharges of animals and their carcasses. The hide becomes leather, the hair and wool are converted to clothing or brushes, the hooves and horn to fertilizer and the bones to glue or gelatine (Christie, 1974). Bone meal fertilizer was recently responsible for the abrupt onset and rapid progression of fatal pulmonary anthrax in an amateur gardener, who inhaled *Bacillus anthracis* from the bone meal which he had used liberally, while continuing to smoke (Severn, 1976). He presented with a fulminant bronchopneumonia with radiological evidence of a mediastinal mass and a pleural effusion. He had been treated with penicillin, but unfortunately this infection proved to be due to a rare penicillin-resistant organism. Just as fertilizer seemed innocent to an unsuspecting gardener, so are there suspect items of clothing, gifts and souvenirs brought home from overseas holidays by well-meaning friends. Beware of imported goatskin handicrafts from Haiti. The Center for Disease Control (C.D.C.), Atlanta, Georgia (*Morbidity Report*, 1976*a*), isolated *Bacillus anthracis* from 96 of 368 (26%) goatskin products examined, including rugs, bongo drums, voodoo dolls, mosaic pictures and purses. Rugs were the most prolific source for positive cultures occurred in 45 of 58 (78%) including one which was still infected 3 years after it had been bought. Attention had been focused on this source of infection because a young United States visitor to Haiti developed what was regarded as severe conjunctivitis with periorbital pain and oedema, eventually progressing to a blue-black upper eyelid. *Bacillus anthracis* was isolated from an aspirate of the eyelid and she recovered after large doses of penicillin and a short course of corticosteroids. She had contracted the infection from goathide bongo drums she had bought in Port-au-Prince, some of which, unwittingly, she had gift-wrapped and posted to her parents and friends (*Lancet*, 1976*a*).

Anthrax may also visit do-it-yourself enthusiasts using imported yarn. A 32-year old Californian doing home-weaving recently died from infection contracted from contaminated yarn which had originated in Pakistan. Like the gardener who inhaled the bone meal, the weaver developed pulmonary anthrax with a pleural effusion and mediastinal lymphadenopathy and complicating meningitis.

Products made from yarn at present under review by the C.D.C. include blankets, purses and wall hangings (*Morbidity Report*, 1976*b*).

Anthrax is probably underdiagnosed. Now that native home products from exotic corners of the earth have become highly fashionable, this is just about the right time to remind ourselves of the dangers of contaminated products and to reread Christie's travels to Carbonaria.

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Chemoprophylaxis in chronic bronchitis

About 30,000 people die each year from chronic bronchitis in England and Wales. Besides this death-toll the disease causes many workers to be unable to attend to their jobs because of illness, and it has been estimated that the order of 40 million man working days may be lost to British industry each year due to exacerbations of chronic bronchitis. The prevention of such exacerbations therefore has obvious importance. Patients with chronic bronchitis produce sputum throughout the year. During the winter months, however, this becomes purulent (often following an upper respiratory tract infection) and acute exacerbations occur. During these the commonest organisms that can be isolated from the sputum are *Haemophilus influenzae* and *Streptococcus pneumoniae*. The treatment of such acute exacerbations will obviously include the administration of an antibacterial agent and the role of such agents here is well established.

The use of prophylactic antibiotics is more controversial, however. Differences of opinion still exist about the values of chemoprophylaxis largely due to the apparently conflicting results obtained in previous trials. Full details of all such trials cannot be considered but two are worth discussing briefly. The Medical Research Council (M.R.C., 1966) reported the results of a collaborative trial in which 373 male bronchitics received prophylactic oxytetracycline or placebo from mid-September to mid-April during 5 successive winters. During the first 3 the dose was 0·5 g a day, but this was increased to 1 and 2 g a day respectively during the last 2 winters of the trial. Exacerbations occurring during the trial period were treated with chloramphenicol, sulphonamide, oral penicillin or placebo. During the 5-year period 1214 separate exacerbations occurred. The smallest number of exacerbations occurred in the group receiving oxytetracycline prophylaxis and active treatment of exacerbations. This reduction of the *total number* of exacerbations was statistically significant compared with the other groups. This decrease occurred mainly in a group of men who normally had frequent infective episodes with many exacerbations. The number of days off work amongst the group receiving prophylaxis was only significantly reduced if one particular statistic was used. The rate of decline of the FEV was not altered by treatment. This trial is often quoted as demonstrating that chemoprophylaxis in chronic bronchitis is ineffective. A truer interpretation might have been that the trial suggested some possible benefit, but was inconclusive. A 5-year prophylactic trial was also carried out by a Scottish group (Johnston *et al.*, 1969). They included 74 patients who each received one of the following regimes during the winter months:

(1) placebo for 5 years,
(2) tetracycline 500 mg b.d. for 2 years then placebo for 3,
(3) placebo for 2 years then tretacycline for 3,
(4) tetracycline for all 5 winters.

In addition all patients had exacerbations treated with tetracycline. The results were rather similar to the previous trial namely that chemoprophylaxis only produced a significant reduction in the number of exacerbations in those patients who had more frequent attacks (more than one each winter). There was no overall statistically significant reduction in the number of exacerbations, nor any effect on the number of days lost from work or rate of decline of FEV, nor did the sputum volume or purulence appear significantly reduced. In both these trials the tetracyclines were tolerated well and no significant resistance to tetracycline occurred in organisms cultured from the sputum of those receiving prophylaxis. These trials did not suggest that such

continuous prophylaxis was appropriate for *all* cases of chronic bronchitis, but rather that it might be valuable in the severe bronchitic who is especially susceptible to frequent winter exacerbations. Those patients who have regularly had 2 or more such exacerbations each winter should certainly be considered for such therapy, especially if their lung function is much impaired or if they are already in chronic respiratory failure. Oxytetracycline would still (*vide infra*) be the drug of choice from the point of view of safety, efficacy and cost, though in the last 2 years strains of both *Haemophilus influenzae* and *Streptococcus pneumoniae* resistant to this antibiotic have been reported with increasing frequency. The incidence of such resistance seems to vary from one part of the country to another and from one time of year to another and a range as wide as 5 to 33% has been reported. The choice of prophylactic drug may therefore depend on the *local* pattern of resistance in some cases. Co-trimoxazole may be a reasonable alternative though more expensive. In theory its prolonged administration might lead to an interference in folate metabolism in man but in clinical usage this has not been found to be the case (Hughes, Jenkins & Gurney, 1975). Ampicillin or cephalexin are unsuitable for *long-term* administration because of gastro-intestinal upsets, whilst sulphonamides and penicillin V are unlikely to prevent haemophilus infections.

Another approach is to supply the bronchitic patient with a supply of antibiotic at the beginning of the winter and advise him to take a *course* of antibiotic at the least sign of infection. This might be the presence of a 'head cold' or the appearance of even the least trace of pus in the sputum. At least one study provides good evidence for such an approach. Malone, Gould & Grant (1968) gave such instructions to a group of 32 patients with excellent results. When their patients began treatment within 24 h of the onset of infection all except *one* were cured by a week's course of antibiotic. These authors used ampicillin (1 g a day), tetracycline (1 g a day) and methacycline (600 mg or 1000 mg a day) and found no difference in the effectiveness of these drugs. Pus was eliminated from the sputum within 4 days in 29 cases and *Haemophilis influenzae* or/and *Streptococcus pneumoniae* was isolated from the sputum in the same number. This type of regimen has several points to recommend it. (1) A smaller amount of drug needs to be taken with a saving in cost, and at least theoretically, a reduction in possible toxicity. (2) A number of different antibacterial agents can be used. Either (a) a rotation of antibiotics each winter or (b) using the same antibiotic throughout any particular winter but varying the one used from one winter to the next. In either situation the following drugs are appropriate tetracyclines, ampicillin, erythromycin and co-trimoxazole (see below). (3) The use of *different* antibacterial agents should lessen the likelihood of any resistant organisms emerging though in practice few have been found even after continuous tetracycline. The main disadvantage is that it is the patient rather than the doctor who decides when to start therapy. With an intelligent patient this may work well, but there are many patients who are loath to take extra drugs or who keep postponing treatment 'just another day' so that the beneficial effect may be lost.

The choice of antibacterial agent may not be quite as simple as has been suggested so far and certain factors must be taken into consideration when treating chronic bronchitis (either the exacerbations or a longer term point of view). Purulent sputum may fail to yield a pathogenic organism and in such cases *Haemophilus influenzae* should be assumed to be the culprit (May, 1972). The interpretation of sensitivity tests may be difficult and need particular attention to detail. It is important to choose an agent which will achieve adequate blood, and more importantly sputum levels, after oral administration. In this respect the levels of ampicillin (May & Delves, 1965) and the newer amoxycillin (Ingold, 1975) in sputum and serum have been studied. Both achieve adequate levels to eradicate haemophilus. Amoxycillin may have advantages in that its sputum level does not seem to be affected by the presence of pus and also appears to rise as the oral dose (which is well absorbed) is increased. Levels of tetracycline (Campbell, 1970) and doxycycline (Hartnett & Marlin, 1976) in bronchial secretions have also been reported. Doxycycline has a long serum half-life so that a single daily administration is recommended which might be attractive for a prophylactic regime. Though mean serum concentrations of the drug in bronchitic patients throughout a week's treatment were above 1·0 μg/ml (the mean MIC of doxycycline against *Haemophilus influenzae*) virtually throughout the study the *maximum* mean sputum level at any one time was only 0·62 μg/ml with a mean throughout the period of only 0·34 μg/ml. Nevertheless the drug proved effective and there was no correlation

between the sputum doxycycline concentrations and the degree of purulence. Though minocycline has also been suggested as a useful agent in chronic bronchitis its long-term prophylactic use is probably contraindicated by its toxic side effects (Lambert, 1975). Co-trimoxazole contains trimethoprim and sulthamethoxazole both with relatively long serum half-lives so that a twice daily regime is possible. The two constituents do not enter the sputum of bronchitic patients to the same extent, however. It has been demonstrated (Hughes, Bye & Hodder, 1972) that the trimethoprim concentration in sputum is about double that in serum whilst that of the sulphonamide component is only about half. This combination is nevertheless effective. The final choice must always be for the individual patient, however, and besides a compound's antibacterial activity, its potential toxicity must also be considered. Furthermore the sensitivity of strains of haemophilus or *Streptococcus pneumoniae* may vary from one area to another and even from one year to another. In general terms, however, continuous chemoprophylaxis with a tetracycline or co-trimoxazole should be considered for the bronchitic subject with frequent winter exacerbations. If a scheme of rotating antibiotics on 'patient demand' therapy is to be employed, then ampicillin or amoxycillin is useful though their continued use for more than one month could lead to gastrointestinal side effects.

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Diabetes and infection

Diabetics are at risk of developing abscesses at the site of insulin injections, infected ulcers secondary to ischaemic and neuropathic changes in the feet, and candidiasis of the urogenital tract in the presence of uncontrolled glycosuria. It has also been widely considered that they are more prone to other infections than the non-diabetic though the evidence to support this assumption is not clear cut and the impression of a high infection rate may be partly due to the additional hazards of infection in diabetic patients. However, there are various abnormalities of cellular defence mechanisms which appear to increase the diabetic's susceptibility to infection. Migration of polymorphonuclear (PMN) leucocytes is delayed (Mowat & Baum, 1971) and PMN phagocytosis is impaired. Although the impairment is probably multifactorial (Robertson & Polk, 1974) it can be related to poor diabetic control and the evidence would suggest that hyperglycaemia itself is the most important single factor (Bagdade, Root & Bulger, 1974).

It has also been demonstrated that although T and B lymphocyte subpopulations are normal in the well and poorly controlled diabetic, lymphocyte activity as measured by response to the mitogen phytohemagglutinin is depressed in poorly controlled subjects (MacCuish, Urbaniak, Campbell, Duncan & Irvine, 1974). The impairment is reversible and can also be directly related to the degree of hyperglycaemia (MacCuish, 1976). These *in vitro* findings are in keeping with the clinical observation that, as distinct from keto-acidosis, the development of severe

hyperosmolar, hyperglycaemic non-ketotic coma is often multifactorial (Gerich, Martin & Recant, 1971). It might be argued that the infective component is as much effect as cause.

Thus a vicious circle situation appears to exist; not only can infection precipitate metabolic decompensation, but poorly controlled diabetics are rendered more susceptible not only to infection, but also to septicaemia.

Severe keto-acidosis is a life threatening condition. Its appropriate management demands not only an awareness of the underlying metabolic disturbance, but also of the initial precipitating cause. Recent studies have shown that bacterial infection is the single most common factor being present in up to 56% of episodes (Beigleman, 1971; Alberti, 1974). In one series significant bacterial infection occurred in 41% of 211 episodes (Campbell, Munro, MacCuish & Duncan, 1974), the incidence being particularly high in previously undiagnosed diabetics aged 45 years or more and previously diagnosed insulin dependent diabetics. Most infections arise from the urinary and respiratory tracts (including β haemolytic streptococcal sore throats) with skin sepsis and a mixture of other infections responsible for the remainder. As the vast majority of episodes develop outside hospital, in otherwise healthy diabetics, infection by resistant organisms or opportunists is unusual, but an 'epidemic' of keto-acidosis has been described during an influenzal outbreak (Watkins, Soler, Fitzgerald & Malins, 1970). The symptoms and signs of infection are often concealed by the severity of the metabolic upset and even septicaemia can occur in the absence of a leucocytosis or of elevation in temperature.

With increasing awareness of the appropriate management of the biochemical disturbances, there has been a major reduction in the mortality from keto-acidosis. Most deaths can now be attributed to the underlying cause, myocardial infarction carrying a particularly poor prognosis. Severe infection, in particular septicaemia, is a major contributing factor in 33 to 44% of deaths and is responsible for the majority of deaths in patients under the age of 45 (Beigleman & Warren, 1973; Campbell, Munro, MacCuish & Duncan, 1974). Although the presence of infection may only be detected by appropriate bacteriological sampling, the clinician cannot afford to wait for bacteriological confirmation before initiating therapy. It is the old story of the quick and the dead. If you are not quick, they are dead. In the most severely ill, whether there is clinical evidence of infection or not, chemotherapy should be commenced once bacteriological samples, including blood for culture, have been obtained.

Because vomiting is common and alimentary absorption is impaired, chemotherapy must be given parentally. Hypotension and peripheral circulatory collapse associated with the inevitable fluid and electrolyte depletion can markedly reduce the rate of intramuscular absorption. It follows that initially antibiotic therapy should be given by bolus intravenous injection. When the infecting organism can be identified an appropriate narrow spectrum agent is indicated. Often this is not possible and broad spectrum cover is necessary. There is evidence to suggest that the poorly controlled diabetic is especially prone to gram positive infections (Robson, 1970) and the selected regime should effectively cover staphylococcal and streptococcal organisms. One effective combination is that of gentamicin with soluble penicillin.

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