The tetracyclines in purulent exacerbations of chronic bronchitis

After 30 years the major questions to ask with regard to the use of tetracyclines in chronic bronchitis are:

1. was bacterial resistance to the common respiratory pathogens developed?
2. of the many derivatives of tetracyclines which is the best to use?
3. how do the tetracyclines compare with other antibiotics more recently introduced?

An increasing percentage of bacterial resistance has been noted with \( \beta \)-haemolytic streptococci (Robertson, 1965), pneumococci (Percival, Armstrong & Turner, 1969) and \textit{Haemophilus influenzae} (Williams & Andrews, 1974). In some areas up to 40% of pneumococci may be resistant to the tetracyclines. A recent nationwide survey found 3% of \textit{H. influenzae} resistant (Philpott-Howard, Hince & Williams, 1981). In my area the percentage resistance for both pathogens is only 3%-5%. With more doubtful respiratory pathogens such as \textit{Staphylococcus aureus} and \textit{Escherichia coli} more than 50% are resistant. \textit{Mycoplasma} spp are usually sensitive. Though resistance to tetracycline applies equally to all its derivatives, some strains may be inhibited \textit{in vitro} by minocycline (Wood et al., 1975) but the clinical significance of this is uncertain. Thus in some but not all areas of the U.K. the tetracyclines retain their usefulness for the treatment of infection caused by most strains of respiratory pathogens. Tetracycline resistance and its growing importance has been reviewed recently (Chopra et al., 1981).

Much experience in hospitals and outpatients has convinced me that for clinically mild illness 1 g daily of tetracycline may be sufficient and with this dose there are few side effects. For more severe illness, both at home and in hospital, 1.5 to 2 g daily is necessary and at this dose side effects become a problem. For optimal absorption the tetracyclines are best given on an empty stomach, which increases gastric intolerance. Most tetracyclines gives low intra-bronchial concentrations though these may be higher with doxycycline (Hartnett & Martin, 1976) and minocycline (Brogan et al., 1977; Bergogne-Berezin, 1981). Tetracycline hydrochloride 1000 mg daily is of moderate clinical efficacy and side effects are low. Equivalent dosages of derivatives are lymecycline (Tetralysal) 600 mg daily, demeclocycline 600 mg daily (Ledermycin), methacycline hydrochloride (Rondomycin) 600 mg daily, minocycline hydrochloride (Minocin) 200 mg daily, doxycycline (Vibramycin) 100 mg daily, clomocycline (Megaclor) and chlortetracycline, tetracycline and demecycline in a mixture (Deteclo). In these dosages there is probably no difference in clinical efficacy between all these compounds and all exhibit a low incidence of side effects (McGill & Bienenstock, 1965; Clarke, 1965: Bendowski, 1970; Geerts, 1971; Bohlau, British Thoracic Association, 1973; Store et al., 1973).

For very many infections tetracycline 1.5-2.0 g daily is necessary for optimal clinical effect. Gastro-intestinal side effects occur in 15-40% of patients (Pines et al., 1968a, 1972b). These side effects were present in 10-15% receiving lymecycline 1200 mg daily (Pines et al., 1964), in nearly 50% of patients given demeclocycline 1200 mg daily and well over 30% given methacycline in the same dose (Pines et al., 1968a), in 10% given minocycline 400 mg daily (Pines, Raafat, & Sreedharan, 1974), or receiving 1000 mg daily of tetracyline hydrochloride in a slow release preparation (Tetrabid), (Pines et al., 1972a). In all these personal studies the clinical effect was otherwise equal to tetracycline hydrochloride 2 g daily. I know of no controlled evidence comparing higher doses of doxycycline, clomocycline and ‘Deteclo’ against 2 g daily of tetracycline.

Ampicillin 2 g daily was no more effective than tetracycline 2 g daily (Hahn et al. 1972). Ampicillin 4 g and lymecycline 2440 mg both plus intramuscular supplements, were equal in effect and the incidence of side effects was similar at 20% (Pines et al., 1968). When
750 mg of amoxycillin daily were compared with 816 mg of lymecycline, amoxycillin was perhaps inferior (Murphy, Donald & Molla, 1976) though in another comparison with tetracycline 1 g daily was perhaps superior (Molla, 1974). In my own experience amoxycillin 1500 mg daily is equal in immediate clinical effect to tetracycline 2 g daily but superior in the long term, more patients given tetracycline relapsing. With trimethoprim-sulphamethoxazole (cotrimoxazole) comparisons have been made using a dose consisting of sulphamethoxazole (cotrimoxazole) compared with tetracycline relapsing. With trimethoprim-sulphamethoxazole 1600–2000 mg daily. One gram of tetracycline daily was less effective (Lal & Bhalla, 1969) but another investigation with 2 g of tetracycline daily showed no difference (British Thoracic Association, 1972). 480 mg of trimethoprim plus 2400 mg of sulphamethoxazole was superior to 2 g daily of tetracycline and resulted in fewer relapses during follow-up (Pines, 1973). However, the higher dose of cotrimoxazole gave more side effects, including serious blood and skin dyscrasias. A lower dose of cotrimoxazole was compared with 600 mg of democycline and gave equivalent results (Geerts, 1971). Erythromycin with inferior to tetracycline (lymecycline) in my experience (Pines et al., 1969).

The tetracyclines may retain their place in areas in Britain where the incidence of resistance to pneumococci and H. influenzae remain low. An additional reason for using them in mild cases of aspiration pneumonia is that many are due to mycoplasma, which are sensitive to them but not to ampicillin or demethylchlor-tetracycline, erythromycin is an alternative.

With a dose of 1 g of tetracycline hydrochloride daily, side effects are few and there is no evidence that other derivatives are superior while their cost is much higher. At home for convenience one can use those antibiotics that need only be given twice daily. 'Detecto' is perhaps the cheapest. For more severe infections tetracycline hydrochloride 2 g daily is essential. There is no evidence of clinical superiority for the derivatives of tetracyclines but if there is intolerance or should this be feared, then equivalent doses of lymecycline, minocycline or doxycycline could be employed. With more severe infections intramuscular supplements of tetracycline can be given but are more painful and less effective than ampicillin in very ill patients in whom a placebo was markedly inferior (Pines et al., 1972b). Patients with chronic bronchitis often relapse with purulent exacerbations. Long-term treatment with tetracycline is largely ineffective (Medical Research Council, 1966) and may lead to overgrowth with resistant organisms such as pseudomonas (Pines, 1973). Relapse seems to occur less frequent with ‘bactericidal’ antibiotics such as ampicillin, amoxycillin and cefuroxime. However, in acute bronchitis without underlying chronic disease tetracycline is adequate.

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Antibiotics in suspected neonatal meningitis

Meningitis in the first month of life is unique and should be considered as a separate clinical entity, because the offending pathogens, the clinical presentation and still the unacceptably high mortality are strikingly different from meningitis afflicting all other age groups. The incidence varied from 0.26/1000 live births (Goldacre, 1976) in a defined population in the North-west Metropolitan Region between the years 1969–73, to 0.46/1000 live births between 1959 and 1966 in the collaborative Perinatal Research Study Group in the United States (Overall, 1970). Moreover, for birth weights above and below 2500 g, it was 0.37/1000 and 1.36/1000 live births, respectively. Therefore, the incidence of neonatal meningitis may be comparatively higher in countries with a high low-birthweight rate. Escherichia coli and Group B streptococcus together account for the majority of cases, followed by other Gram-negative bacteria, e.g. Proteus, Klebsiella-Enterobacter-Serratia species, Pseudomonas