Antibiotic Treatment of Chronic Bronchitis

D. T. D. HUGHES, BM, FRCP
Physician, The London Hospital

The most common pathogenic organisms cultured from the sputum of patients with exacerbations of chronic bronchitis are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Sputum bacteriology is often unsatisfactory and, apparently, purulent sputum is often reported to contain no pathogens, and conversely, a pathogen may be cultured from apparently mucoid sputum. There are several reasons for this. First, *H. influenzae* (the commonest pathogen) is quite a delicate organism with rather fastidious requirements when grown in culture media, needing both Factor X and Factor V. If sputum is sent to the laboratory fresh, and cultured with care, a higher rate of positive cultures is obtained. This is illustrated in Table 1, which shows the proportion of pathogenic organisms cultured from sputum samples over a series of winters (Drew *et al.*, 1967; Hughes *et al.*, 1969; Hughes, 1969). Certain organisms such as Proteus and Pseudomonas may grow very readily on artificial culture media and swamp more sparse growth of *H. influenzae*. Such organisms may also be cultured from mucoid uninfected sputum. Table 2 shows the organisms cultured from 161 consecutive patients with exacerbations of chronic bronchitis studied during three winters. *H. influenzae* and *Strep. pneumoniae*, either singly or in combination, were by far the commonest organisms grown but some other organisms were isolated. It is often difficult to determine the role of such additional pathogens in exacerbations of chronic bronchitis.

A number of antibiotics are active against *H. influenzae* and *Strep. pneumoniae* (Table 3). The most effective are ampicillin and similar semi-synthetic penicillins, chloramphenicol, co-trimoxazole, erythromycin and tetracycline in its various forms. There is no evidence that combinations of nystatin and tetracycline are more effective, or less likely to cause Candida infections, and combining bromhexine with tetracycline, as in Bisolvomycin, has not been shown to improve the efficacy of tetracycline.

What factors should determine the choice of antibiotic for exacerbations of chronic bronchitis? First, the sensitivity of the organisms to the antibiotic should be considered. Secondly, relative toxicity and adverse effects of the drug are important; for example, chloramphenicol is highly effective against *H. influenzae* and *Strep. pneumoniae* but it should be reserved for special cases because of its known toxicity. Thirdly, individual idiosyncrasy to an antibiotic must be considered; for example, hypersensitivity to penicillins or to the sulphonamide component of co-trimoxazole are common. Co-trimoxazole is a poor name for this combination of trimethoprim and sulphamethoxazole, as it does not indicate that the

This article is based on a paper given at a Teach-in held at the Royal College of Physicians in April 1978.

Table 1. Isolation of pathogens, particularly *Haemophilus influenzae*, from the sputum of patients with exacerbations of chronic bronchitis.

Author	Date	No. of Patients	No. with pathogens (and %)	No. from whose sputum *H. influenzae* grown (and %)
Drew *et al*	1967	50	33 (66%)	17 (34%)
Hughes *et al*	1969	50	27 (54%)	13 (26%)
Hughes	1969	50	35 (70%)	15 (30%)
Hughes (unpublished)	1970	30	24 (80%)	18 (60%)

Table 2. Pathogenic organisms cultured from the sputum of 161 consecutive patients with exacerbations of chronic bronchitis (mostly treated as hospital in-patients).

1. *Haemophilus influenzae*	29
2. *Streptococcus pneumoniae*	17
3. *Haemophilus influenzae* plus *Streptococcus pneumoniae*	14
4. *Esch. coli*	17
5. *Proteus spp.*	13
6. *Staphylococcus pyogenes*	5
7. *Klebsiella pneumoniae*	4
8. *Pseudomonas spp.*	3
Total number of organisms	102
(less cases—other than (3) above—in which *two* organisms were isolated)	5
Total number of patients whose sputum grew pathogens	97
No. of patients growing no pathogens	64
TOTAL	161

Table 3. Antibacterial substances effective against *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Tetracycline and its derivatives
Chloramphenicol
Erythromycin
Ampicillin (and talampicillin)
Amoxycillin
Co-trimoxazole (trimethoprim plus sulpha-methoxazole)

combination contains a sulphonamide. Fourthly, the pattern of likely resistance of the organism in a particular area or individual patient and previous antibacterial treatment may be important. Fifthly, consideration of the pharmacokinetics of the antibiotic is relevant. *In vitro* effectiveness of an antibiotic is irrelevant if the drug fails to reach the site of infection in adequate concentrations to kill organisms. This point may be illustrated by some studies on co-trimoxazole. In one particular study (Hughes *et al.*, 1972), simultaneous levels of the two components of co-trimoxazole in serum and sputum were measured. It was found that the concentration of trimethoprim in the sputum was nearly twice that in the serum, while the sputum concentration of sulphamethoxazole was only about one quarter of that in the serum. In the treatment of chronic bronchitis the sputum level of the drug is likely to be most relevant, while in pneumonias and other infections the serum level may be more important.

An extensive study of the probable serum levels to be achieved after administration of various antibiotics, comparing them with the minimum inhibitory concentrations (MIC) required to be effective against 60 strains of *H. influenzae,* was carried out by Williams and Andrews (1974). The results may be summarised as follows. Ampicillin (particularly at a dose of 500 mg), co-trimoxazole, tetracycline and erythromycin estolate would all be expected to give minimum inhibitory concentrations in the serum greater than the minimum concentration needed to kill the majority of strains of *H. influenzae*. The same was true of chloramphenicol. Conversely, absorption of erythromycin base is more variable and it cannot be relied upon to give adequate serum levels. Similar results were obtained with clindamycin, lincomycin and cephalexin. Because of this, cephalexin and the lincomycin group of antibiotics are unlikely to be effective in exacerbations of chronic bronchitis. From studies of sputum and/or serum levels of ampicillin, amoxycillin, talampicillin, tetracycline and doxycycline it seems likely that adequate levels will be obtained by oral administration (Hughes, 1976). Although it has been suggested that doxycycline administered once daily would be effective in treating exacerbations of chronic bronchitis for longer term treatment, the serum concentrations during a week's administration were found to be above 1 μg/ml (the mean MIC needed against *H. influenzae*) while the sputum levels were very much lower. In spite of this, doxycycline was effective in eradicating *H. influenzae* from the sputum (Hartnett and Marlin, 1976). This again illustrates the point that laboratory studies of bacterial sensitivity, even if taken in conjunction with pharmacokinetic data, are not the only factors to be considered in the choice of an antibiotic for treatment of exacerbations of chronic bronchitis.

In Great Britain, tetracycline has been the main drug used for the treatment of exacerbations of chronic bronchitis, and it has proved a most useful drug over a number of years. However, a recent report suggests that tetracycline resistance is beginning to occur much more frequently in the case of *Strep. pneumoniae (British Medical Journal,* 1977). In 1,528 strains of pneumococci isolated from 21 different laboratories 13 per cent of these strains were tetracycline-resistant. Tetracycline resistance was defined as organisms requiring an MIC of greater than 8 μg/ml. The extent of the resistance varied between laboratories, ranging from 2 per cent in Ayr (in fact only one case out of 42) to some 32 per cent at The London Hospital. It is possible that the proportion of resistant organisms may vary from one time of the year to the next. Concern generated by this study has led to a further multicentre study for a three-month period in 1977 at some 20 centres in the United Kingdom. The results of this study have just been published (Howard *et al.*, 1978). They may be summarised as follows: 952 strains of *H. influenzae* were studied. The overall resistance to tetracycline among these was 2.7 per cent, the range being 0-8.8 per cent. A level of 2 μg/ml was taken as the level of MIC above which resistance occurred. With *Strep. pneumoniae* 866 strains were studied and the incidence of tetracycline resistance varied from 0 to 12 per cent with a mean of 6.8 per cent, which was lower than the 13 per cent reported the previous year. In addition, the sensitivity of *H. influenzae* to some of the other antibiotics was also studied. The overall resistance to ampicillin was 1.5 per cent with a range of 0 to 13.3 per cent, whereas there was virtually no resistance to either chloramphenicol or co-trimoxazole. From these studies it seems reasonable to conclude that tetracycline and its derivatives are becoming less suitable for the treatment of exacerbations of chronic bronchitis. At present, co-trimoxazole, ampicillin, or related drugs seem most suitable for treating acute exacerbations. It is often necessary to continue treatment for 10 to 14 days rather than the more conventional 5 or 7 days. As yet, amoxycillin or talampicillin have not been shown to possess important clinical advantages compared with ampicillin, although adverse effects may be less frequent with amoxycillin. The standard dosage of this drug is 250 mg three times daily. In severe exacerbations, particularly in elderly patients in whom these may be life-threatening, chloramphenicol should be considered for its marked effectiveness. There are no good grounds for choosing cephalexin, lincomycin, clindamycin, Mysteclin or Bisolvomycin in routine cases.

The prophylactic use of antibiotics in the treatment of chronic bronchitis remains controversial. Some of the arguments for and against their use have recently been reviewed (Hughes, 1976). Prophylactic antibiotic therapy may be of value in some patients with chronic bronchitis who suffer very frequent exacerbations, or in whom respiratory function is so compromised that any further deterioration could be fatal. Here tetracycline or co-trimoxazole are probably the best agents, since long-term use of ampicillin may well lead to gastrointestinal side effects. Rather surprisingly, studies of the use of long-term tetracycline showed it to be quite free of adverse effects and unlikely to cause bacterial resistance. In a study using co-trimoxazole in ten patients with chronic bronchitis or bronchiectasis, resistance did not develop during the course of treatment (Hughes *et al.*, 1975) lasting from 3 to 30 months, with a mean of 10.6 months. There were no significant haematological abnormalities.

Chemoprophylaxis may be given continuously, which is probably the simplest, or the patient may be given a large supply of tetracycline or co-trimoxazole and told to treat

UPDATE BOOKS ORDER FORM

Update Books are not normally available from bookshops. To order your book through the post, complete this form and send it to Book Sales Dept, Update Books Ltd, 33-34 Alfred Place, London WC1E 7DP. Allow up to 28 days for delivery. **Post and packing are free.**

☐	**Send me copy(ies) of Medical Aid at Accidents (£7.65)**
☐	**" " Rehabilitation Today (£6.20)**
☐	**" " Dermatology (£8.25)**
☐	**" " Neonatal Medicine (£6.20)**
☐	**" " Oral Disease (£6.20)**
☐	**" " Immunisation (£4.20)**
☐	**" " Preventive Dentistry (£5.95)**
☐	**" " Interpreting the Electrocardiogram (£5.50)**

NAME .....
(in block capitals)
ADDRESS .....
(in block capitals)
.....
.....
.....

Now select your payment method from the two possibilities (post and packing are free):

1. I enclose cheque/PO for £
made payable to Update Books Ltd.

2. Access VISA Please debit my Access/Barclaycard account for £

Access/Barclaycard No. .....

Signature.....

Please tick these boxes if you would like information about:
☐ all new Update books
☐ discount on purchases of more than 10 Update books

Money back guarantee. If you are in any way dissatisfied with an Update book and return it to us in perfect condition within 14 days your money will be refunded in full.

PO179

himself at the earliest sign of infection. This latter method, although theoretically preferable, does need a degree of intelligence and co-operation on the part of the patient. Lastly, it would be wrong to think antibiotics are the only important treatment in exacerbations of bronchitis. Nevertheless, in trials in which attempts have been made to include a placebo group, for one reason or another such patients have had to be withdrawn from the studies.

References

British Medical Journal (1977) *Ad hoc* study group on antibiotic resistance, **1**, 131.

Drew, C. D. M., Hughes, D. T. D., Fowle, A. S. E. and Cassell, M. (1967) *Proceedings of the Fifth International Congress of Chemotherapy*, Supplement A1-5/3, 293.

Hartnett, B. J. S. and Marlin, G. E. (1976) *Thorax*, **31**, 144.

Howard, A. J., Hince, C. J. and Williams, J. D. (1978) *British Medical Journal*, **1**, 1657.

Hughes, D. T. D. (1969) *British Medical Journal*, **4**, 470.

Hughes, D. T. D. (1976) *Journal of Antimicrobial Chemotherapy*, **2**, 320.

Hughes, D. T. D., Bye, A. and Hodder, P. (1972) *Advances in Antimicrobial and Anti-neoplastic Chemotherapy* (report on the Seventh International Congress of Chemotherapy), Vol. 1, p. 1105. Vienna: Urban and Schwarzenberg.

Hughes, D. T. D., Drew, C. D. M., Johnston, T. C. W. and Jarvis, J. D. (1969) *Chemotherapy*, **14**, 151.

Hughes, D. T. D., Jenkins, C. G. and Gurney, J. D. (1975) *Journal of Antimicrobial Chemotherapy*, **1**, 55.

Williams, J. D. and Andrews, J. (1974) *British Medical Journal*, **1**, 134.

Buy Update Books from our Central London Office

Update Books are now on display and for sale at the Update offices in central London. You can call into the 2nd floor reception, Update Publications, 33-34 Alfred Place, London WC1E 7DP, to inspect or purchase Update books any time between 9.30 a.m. and 5.30 p.m., Monday to Friday. This map shows how to find Alfred Place. The Update building is clearly recognisable by the display of books in the front window at street level.