Antibiotics in Acute Respiratory Disease

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Acute respiratory disease constitutes one of the largest groups of illnesses in which antimicrobial drugs are commonly administered. The frequency and importance of these infections are evident from everyday experience and many epidemiological studies. It is estimated that, in Western Europe, one-fifth of all time lost from work, and three-fifths of all time lost from school, is on account of respiratory infections. In the famous Newcastle family survey 80 per cent of illnesses in the first five years of life were infections, and 61 per cent of the infections were respiratory. Most respiratory infections are minor, but pneumonia and influenza remain important causes of death, and this group remains the only category of infectious disease among the ten leading causes of death in the USA.

The task of reviewing the role of penicillin and related drugs in this field of medicine can be tackled in two different ways. One is to study the effect of these agents on disease caused by each specific pathogen, classified in the manner of a textbook. In this way it is easy to see the highlights, for example, the dramatic success of antimicrobial drugs in pneumococcal and some other bacterial pneumonias, and the failures, such as the lack of specific treatment directed against the viruses that are dominant in severe respiratory infection of infancy. The alternative is to view acute respiratory disease as it actually presents to clinicians when tidy outlines disappear and the picture is full of confusion and contradiction.

The reason for this is clear. Aetiological diagnosis of respiratory infection is difficult and diagnosis often goes no further than a rough anatomical-pathological label. Table 1 shows some of the names used for the more common

| Table 1. Classification of acute respiratory diseases |
|-----------------------------------------------|
| **Upper respiratory syndromes** | **Lower respiratory syndromes** | **Other** |
| Cold | Influenza | Bronchitis |
| Influenza | Sore throat | Bronchiolitis |
| Sore throat | | Pneumonia |
| Otitis media | Sinusitis | Acute epiglottitis |
syndromes. It is evident that, although some of them, e.g. colds, are predominantly viral, bacterial and mycoplasmal causes cut across the various groups. So, in sore throat, we have to consider, as well as the viruses, one common bacterial cause, *Streptococcus pyogenes*, and the spectre of the now rare diphtheria. A child with group probably has viral laryngo-tracheobronchitis, but might have haemophilus epiglottitis; even here, and certainly in many other countries, he might have diphtheria. Passing to the infections of the lower respiratory tract, it is among the pneumonias that antimicrobial drugs have their most common and valuable use. But even here we find an astonishing diversity of aetiological agents, arising with an order of frequency that varies greatly according to the age of the patient and the setting in which the pneumonia occurs. The most dramatic differences are associated with the age of the patient.

**Table 2. Pneumonia in previously healthy children and adults**

| Common Viruses                          | Bacteria and Mycoplasma |
|-----------------------------------------|--------------------------|
| Influenza                              | *Streptococcus pneumoniae* |
| Influenza + bacteria                    | *Mycoplasma pneumoniae*  |
|                                        | Other                    |

**Table 3. Causes of adult pneumonia**

| Source       | Year | No. of cases | Pneumococcal % | Other bacteria % | Unknown % |
|--------------|------|--------------|----------------|------------------|-----------|
| MRC Humphrey et al. | 1951 | 267          | 73             | 5                | 21        |
| Fiala        | 1948 | 351          | 79             | 6                | 15        |
| Bath et al.  | 1969 | 193          | 55             | 11               | 34        |
|              | 1964 | 156          | 57             |                  | 38        |

In children and young adults (Table 2) *Strep. pneumoniae* and *Mycoplasma pneumoniae* take pride of place and to them must be added, at times when it is prevalent, the influenza virus. The table reminds us of the great variety of organisms that may cause pneumonia. Despite this diversity, the pneumococcus remains the dominant bacterial pathogen in pneumonias of this age group serious enough to require hospital care.

Until the 1950s the predominance of this organism emerged very clearly in all published series. Since then, the proportion of patients in whom no causal diagnosis is reached has increased and the proportion in which a pneumococcus is identified has decreased (Table 3). But antibacterial drugs
have often been given before admission to hospital, and optimal methods for the isolation of this organism are used less often. When a bacterial pathogen is identified, however, it is still most often the pneumococcus and for this reason benzyl penicillin is still the drug of choice for pneumonia arising outside hospital in a previously healthy adult. One exception to this general rule would be an outbreak of *M. pneumoniae* infection, best treated by a tetracycline or by erythromycin. Strains of pneumococci resistant to tetracycline, lincomycin, and erythromycin have been noted, and a modest increase in penicillin resistance has been reported from Australia and from New Guinea (Hansman et al., 1971). Whether this last tiny cloud is a herald of worse weather to come remains to be seen. It seems at first a remote matter related to special circumstances until one remembers that it was only a quarter of a century after the introduction of sulphonamides that sulphonamide-resistant meningococci emerged into clinical significance at the San Diego Naval Base. A very different picture emerges when considering severe lower respiratory tract infections in infancy (Table 4). Two virus groups so far not mentioned, the respiratory syncytial and para-influenza viruses, are front runners, together with measles, still not to be neglected as a cause of serious respiratory disease. Bacterial causes, which include *Staphylococcus pyogenes* and *Bacillus pertussis* as well as the pneumococcus, are still significant but are vastly less common than viral agents. A thorough study of acute lower respiratory tract disease in children, originating from the University of North Carolina (Glezen et al., 1971), virtually dismisses bacteria from consideration except for the association between acute epiglottitis and *Haemophilus influenzae* type B infection. In Newcastle, a careful study of 106 children with bronchiolitis and 45 with pneumonia revealed only two significant bacterial infections (Elderkin et al., 1965); these two were nevertheless important, since they were both deaths from staphyloccocal pneumonia. For this reason, if an infant with pneumonia is judged to need antibacterial drugs, they should include activity against penicillinase-forming staphylococci.

In older patients, two other factors greatly influence the list of potential pathogens to be considered. One is the presence of chronic lung disease,
Since here we have to reckon with *H. influenzae, Staph. pyogenes* and sometimes other less common bacterial as well as viral causes of exacerbation (Table 5).

| Table 5. Pneumonia with chronic chest disease                      |
|------------------------------------------------------------------|
| *Streptococcus pneumoniae*                                      |
| *Haemophilus influenzae*                                        |
| *Staphylococcus Pyogenes*                                       |
| Other bacteria                                                  |
| Viruses                                                          |

| Table 6. Pneumonia in low resistance states, or hospital setting |
|------------------------------------------------------------------|
| *Streptococcus pneumoniae*                                      |
| *Staphylococcus pyogenes*                                       |
| Gram-negative bacteria                                          |
| (Klebsiella, etc.)                                              |
| Other                                                            |

The other factor is the setting in which the pneumonia occurs. Although the pneumococcus is still found in pneumonia arising in hospital, the two great spectres are the hospital staphylococcus, and the increasingly important Gram-negative infections associated with low resistance states, the hospital environment, and the use of artificial ventilation (Table 6). This latter group may present intractable problems in treatment, partly because the organisms may show multiple antibiotic resistance, which may now include methicillin resistance in *Staph. pyogenes*, but mainly because of factors in the host which may render even appropriate antimicrobial treatment unsuccessful. It should be stressed that pneumonia caused by Gram-negative rods is very uncommon in previously healthy people. Tillotson and Lerner (1968) collected only 38 patients with Gram-negative infection in 1,032 patients with pneumonia drawn from the indigent population of Detroit, and 36 of the 38 had serious chronic illness, mostly alcoholism, heart disease, or diabetes.

Given this great diversity of causal agents in pneumonia, it is clear that a wide variety of treatments may be optimal for different causes; yet it is in the matter of precise aetiological diagnosis that our evidence is often weakest. Causal diagnosis of pneumonia, as of respiratory infections in general, is often difficult, and many of the best loved ways of attempting it, using pointers such as the distribution of consolidation, purulence of sputum, presence of pleural fluid, and so on, are of little or no value. A few clues such as a high leucocytosis in some bacterial pneumonias and a high ratio of general to chest symptoms in some non-bacterial pneumonias may help, but it is often impossible to sort out pneumonias at a clinical level, except for the good clinical diagnoses of measles and pertussis.

Laboratory evidence of bacterial infection is also often hard to achieve in the acute stage, and the reasons for this are well known. Children rarely produce sputum except in pertussis. Sputum bacteriology in adults may poorly
represent the bronchial flora, the flora grown may be affected by previous treatment, and most physicians are, quite reasonably, unwilling to consider tracheal aspiration or lung puncture in those seriously ill patients in whom the need for a precise diagnosis is greatest. Moreover, mere isolation of a bacterium from the upper respiratory tract has not the same significance as that of a virus, since most important viral pathogens of the respiratory tract are rarely found except in association with disease, whereas the common bacterial pathogens of the lung are also normal commensals of the upper respiratory tract.

These difficulties mean that antibiotics are, in practice, given for a variety of reasons, sometimes for a firm bacterial diagnosis, sometimes because of a general expectation of a bacterial cause or because the patient is so ill that it would be unreasonable not to act on this possibility, and sometimes because of an assumption that bacterial infection must have supervened on an originally viral illness. This assumption is so common a reason for antimicrobial drug administration that it is worth further examination. Since the common bacterial flora of the upper respiratory tract are also conditional pathogens in the lung, it is a reasonable hypothesis that pathogenicity may be induced by coincident viral infection. There is good evidence that this does happen; the most vivid example is that of influenza virus and *Staph. pyogenes* acting in concert. Moreover, notifications of adult pneumonia show a striking peak at times of high prevalence of influenza infection. In seeking a parallel with other viruses and other bacteria, the evidence becomes much more fragmentary. Mufson et al. (1967), commenting on the clear-cut group of pneumococcal pneumonias associated with a positive blood culture for this organism, could find no evidence of infection by any virus except herpes simplex. In a similar study from Cleveland, Lepow et al. (1968) were unable to correlate recovery of the pneumococcus with viral infection, although some statistical association was found between the recovery of viruses and that of *H. influenzae*; but the evidence of viral infection in this study was relatively poor, consisting mainly of antibody rises to adenovirus. Even more striking was the finding of Court and his group in Newcastle (Gardner et al., 1967), who made a careful study of 21 deaths from lower respiratory infection in childhood. Respiratory syncytial virus was grown from the lung at autopsy in 7 children, 4 of whom had had pneumonia; in none of them was bacterial infection demonstrated.

The idea of bacterial-on-viral infection is invoked especially commonly in exacerbation of chronic bronchitis; it is supported by the frequent isolation of potential pathogens from the sputum of these patients, and the modest success of some antibiotic trials. On the other hand, if one goes into the patient’s home, as we did in a family study of infection in the households of chesty subjects, an astonishing variety of agents is found associated with exacerbation.
of bronchitis or of asthma, often without any evidence of significant change in the bacterial flora (Table 7). The subject of bacterial-viral interactions is an

| Table 7. Agents associated with acute exacerbations of bronchitis or asthma |
|--------------------------------------------------------------------------------|
| Rhinovirus H and M. |
| Adenovirus |
| Respiratory syncytial virus |
| Para-influenza virus 1, 3 |
| Rickettsia burnetii |
| Mycoplasma pneumoniae |
| Streptococcus pneumoniae |
| Haemophilus influenzae |

old and perhaps a tired one, but we need to know much more about it to help us in making rational antibiotic policies for respiratory infection.

Two large paradoxes remain. Whereas in many fields of medicine diagnosis is highly efficient but treatment lacking, the reverse applies in many serious respiratory infections. Penicillins and other antimicrobial drugs give us powerful weapons to attack the majority of bacterial agents causing these syndromes. But deficiencies in diagnosis make it hard to use these weapons with precision. The other paradox is that virology has overtaken bacteriology in this field and it is often easier, for the reasons outlined, to define a viral than a bacterial cause of acute respiratory disease.

It is important that this diagnostic gap should be narrowed so that we can approach more nearly the aims of rational therapy so well set out by Garrod and O’Grady (1971): ‘Successful chemotherapy must be rational, and rational treatment demands a diagnosis. This may only be provisional, and it may later be proved wrong, but the treatment chosen should be based on some explicit assumption as to the nature of the disease process. This may or may not carry with it an implication that the cause is a particular micro-organism’. Moreover, it can be shown that efforts to base treatment on precise diagnosis do pay off in better patient care. A few years ago all children with acute bronchiolitis received antibiotics, but now many centres have given up their use entirely. This change has come about for three reasons. The respiratory syncytial virus has been identified as the dominant pathogen in the syndrome. Second, trials have shown no benefit from antimicrobial drugs; and third, advances in immunofluorescent technique have enabled an early and definitive virological diagnosis to be made.
Although new discoveries in antibacterial therapy will always be greeted with gratitude and delight, the main advances in this field of medicine seem to lie, first, in the prevention and control of viral disease of the respiratory tract, and second, in increased precision of diagnosis to match the precise tools of antibacterial treatment, and so to achieve the highest possible ratio of benefit to risk in the management of serious respiratory infection.

References
Bath, J. C. J. L., Boissard, G. P. B., Calder, M. A. and Moffat, M. A. J. (1964) British Journal of Diseases of the Chest, 54, 1.
Co-operative Controlled Trial (1966) British Medical Journal, 1, 1329.
Elderkin, F. M., Gardner, P. S., Turk, D. C. and White, A. C. (1965) British Medical Journal, 2, 722.
Fiala, M. (1969) American Journal of the Medical Sciences, 257, 44.
Gardner, P. S., Turk, D. C., Aherne, W. A., Bird, T., Holdaway, M. D. and Court, S. D. M. (1967) British Medical Journal, 4, 316.
Garrod, L. P. and O'Grady, F. (1971) Antibiotic and Chemotherapy, 3rd Ed., London: E. & S. Livingstone, p. 264.
Glezen, W. P., Loda, F. A., Clyde, W. A., Senior, R. J., Sheaffer, C. I., Conley, W. G. and Denny, F. W. (1971) Journal of Pediatrics, 78, 397.
Hansman, D., Glasgow, H., Sturt, J., Devitt, L. and Douglas, R. (1971) New England Journal of Medicine, 284, 175.
Humphrey, J. H., Joules, H. and Van der Walt, E. D. (1948) Thorax, 3, 112.
Lepow, M. I., Balassanian, N., Emmerich, J., Roberts, R. B., Rosental, M. S. and Wolinsky, E. (1968) American Review of Respiratory Diseases, 97, 533.
MRC (1951) British Medical Journal, 2, 1361.
Mulson, M. A., Chang, V., Gill, V., Wood, S. C., Romanski, M. J. and Chanock, R. M. (1967) American Journal of Epidemiology, 86, 525.
Tillotson, J. R. and Lerner, A. M. (1968) Medicine, 45, 65.

Smoking at Eton
Sir Walter Raleigh was much concerned by the arrow poisons of Guiana. ‘There was nothing whereof I was more curious then to finde out the true remedy of these poisoned arrows.’ Apparently he missed the Joyfull Newes out of the Nece Founde Worlde (1577) which announced that, ‘In Venom and venomous Woundes our Tabaco hath greate experience . . . ’ Perhaps he would have been surprised by the therapeutic properties claimed for tobacco a century after his death. For one who advocated garlic for the plague he would have been interested in the diary of Thomas Hearne for 1720. ‘I have been told that in the last great Plague at London, none that kept tobacconists’ shops had the plague. It is certain that smoking was looked upon as a most excellent preservative, insomuch that even children were obliged to smoke. And I remember that I heard formerly Tom Rogers, who was yeoman-beadle, say, that when he was that year, when the plague raged, a school boy at Eton, all the boys of that school were obliged to smoke in school every morning, and that he was never whipped so much in his life as he was one morning for not smoking.’