A new look at erythromycin

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Summary

This article reviews the current place of erythromycin in antibiotic therapy. Overall, erythromycin is thought to be underused because: (1) the fear of resistance has been exaggerated; (2) significant toxicity has been associated with only one derivative (the estolate); (3) newer antibiotics have very rarely been demonstrated to be superior to erythromycin. Erythromycin has an important place in treating acute upper and lower respiratory tract infections, acute otitis media, sinusitis, skin and soft tissue infections, osteomyelitis, prostatitis, infections due to *Mycoplasma* spp. and *Chlamydia* organisms, and infections due to anaerobes.

Introduction

It is nearly 25 years since erythromycin was introduced: why therefore a new look at erythromycin?

Firstly, many of the antibiotics introduced during the last decade have failed to fulfil their expected promise. With one or two exceptions no notable new antibiotic has been introduced since 1963. The next reason is that many of the fears of the development of bacterial resistance have not materialized. Lastly, the safety record of most compounds of erythromycin is remarkable. This review will attempt to assess new data on the antibiotic and indicate its current place in treating bacterial infections.

Safety

It is impossible to claim safety for any drug until it has been in use for a number of years. Thus, several years elapsed before the toxicity of chloramphenicol was apparent.

One of the derivatives of erythromycin used, i.e. erythromycin estolate, has itself been found to be hepato-toxic. Thus, some patients who received this drug for more than 2 weeks were found to suffer from liver damage and sometimes developed frank jaundice, although most recovered when the drug was stopped. This toxicity contrasts with the lack of toxicity of erythromycin base itself. Thus it has been stated recently 'no toxic effects of any consequence have ever been recorded from the administration of erythromycin base' and 'there is no doubt that erythromycin is one of the most inno-

cuous antibiotics in current use' (Garrod, Lambert and O'Grady, 1973).

Compounds of erythromycin currently available include erythromycin stearate and erythromycin ethyl succinate. Clinical use of these compounds indicates their safety to be comparable to that of the base alone and side effects associated with their use to be insignificant. The only side effect of note with these preparations is a relatively mild gastrointestinal disturbance.

In the 25 years of its use no teratogenic effects have been observed or reported and erythromycin is indicated in the treatment of young children and women of child-bearing age whether or not they may be pregnant. This contrasts with other drugs such as tetracycline and co-trimoxazole which should not be administered to pregnant women.

Development of bacterial resistance

Soon after erythromycin was introduced a number of reports showed an increase in resistance of staphylococci to erythromycin after it had been used extensively in a ward or hospital. Subsequent experience has shown this to be an incomplete aspect of a complicated story. The staphylococcus has acquired resistance to all antibiotics that have been widely used against it and it is now policy in most hospitals not to use a single drug intensively for a long period. Another aspect of antibiotic resistance that has only recently become apparent is that those bacteria that are resistant tend to have a disadvantage compared with those that are sensitive to the drug. Thus, when a drug is withdrawn, say for a few weeks or a few months, those bacteria that had acquired resistance from the use of the drug will soon become replaced by bacteria once more sensitive. Most antibiotic policies involve the use of effective antibiotics in rotation.

It does not follow, therefore, because one or two reports describe antibiotic resistance following the use of an antibiotic, that the drug becomes obsolete thereafter.

It is now established that because one bacterial species has acquired resistance to a drug, it does not follow that other bacteria are also prone to resistance, e.g. pneumococci and group A streptococci have virtually never become resistant to penicillin or

erythromycin. We know now the precise chemical mechanisms whereby staphylococci have acquired resistance to erythromycin and the conclusions of these experiments are as follows: an occasional bacterium possessing a freak mechanism that enables it to resist erythromycin is present initially in low numbers in a very few patients. When the drug is used on a very wide scale this bacterium will initially multiply in one or a few patients only, and then later spread in the hospital ward from patient to patient so that it gradually becomes the predominant organism. But in general practice most patients will harbour no bacteria that are erythromycin-resistant and it therefore follows that, in these, however long, or whatever dose, or whatever number of courses of erythromycin, there will be virtually no risk that strains of *Staphylococcus aureus* will acquire resistance during treatment (Lacey, 1973). The idea that bacteria mutate to erythromycin resistance and that mutation is encouraged by prolonged use of the drug is probably erroneous (Lacey, 1976).

Effect on normal bacterial flora

The ideal antibiotic is one that destroys the infecting organism and offers no toxicity to the host. We have discussed already the lack of side effects associated with the use of erythromycin when considering its direct effect upon the human body. Many antibiotics produce side effects indirectly—by eliminating some of the normal flora, particularly those in the gut. Well known examples of these include tetracycline, ampicillin and oral neomycin. Severe gastro-intestinal side effects have virtually never been reported following the use of erythromycin.

When considering the long term use of erythromycin, another important aspect is its effect on the gut flora. This is the unlikelihood of its use promoting the appearance of strains of *Escherichia coli* resistant to other antibiotics (Gould, 1975). It is now thought that there is a risk that antibiotic resistance will spread from the relatively harmless commensal *E. coli* to important pathogens such as *Salmonella typhi*. There is dispute about how frequently such transfer could occur, but a single transfer event which conveyed antibiotic resistance genes from commensal *E. coli* to *Salm. typhi* could be serious. It is therefore important to use antibacterial agents in such a way so as to discourage antibiotic-resistant *E. coli* to persist in the gut. The use of erythromycin would not be expected to select resistant *E. coli* strains because *E. coli* does not possess factors resistant to erythromycin.

This contrasts with the use of tetracycline and ampicillin, which are now well known to encourage the overgrowth of normal sensitive gut coliforms by

strains able to donate their resistance to *Salmonella*, etc.

Infections of the upper respiratory tract

Acute pharyngitis and tonsillitis

Tetracycline. This is undesirable on two counts. Firstly, many of the patients with acute bacterial pharyngitis are children, and the administration of tetracycline, particularly in prolonged or repeated courses, is known to cause its deposition in the bones and teeth with severe effects on bone growth and teeth formation. Secondly, tetracycline is undesirable because about 30–40% of strains of Group A streptococci isolated from all over the country are resistant to this antibiotic.

The next group of drugs that are undesirable comprise lincomycin and clindamycin on account of toxicity (Leading Article, 1975). Thus we are left with three drugs which merit further consideration—benzyl penicillin, erythromycin, and an oral cephalosporin. All three of these drugs are relatively non-toxic and there is virtually no resistance to them in group A streptococci. However, both penicillins and the cephalosporins have certain snags. Benzyl penicillin must be given by injection and the so-called oral penicillins such as penicillin V must still be viewed with suspicion because of their uncertain rates of absorption from the gastro-intestinal tract. The oral cephalosporins available today—cefalexin and cefradine—have rather low potency against the group A *Streptococcus*. The decision on the ideal antibiotic seems, therefore, to rest between the use of erythromycin orally for the majority of patients with bacterial pharyngitis or benzyl penicillin injections for those who have very severe forms of pharyngitis.

In the latter instance, a throat swab is mandatory. Another reason for not prescribing a penicillin routinely for trivial infections is that the widespread use of this antibiotic will select strains of many bacterial species that are resistant to penicillin and ampicillin (Manners *et al.*, 1976).

Acute otitis media

Because of uncertainty over the identity of the pathogen in otitis media, it is important to take a swab before starting antibacterial therapy. Benzyl penicillin by itself is undesirable because of the possibility of *Haemophilus influenzae*, and penicillinase-producing *Staph. aureus*. Ampicillin or one of its variants would be a reasonable choice against group A streptococci and *Str. pneumoniae*, but is inactive against most staphylococci and an increasing number of strains of *H. influenzae* (recently there has been an alarming increase in the number of strains of *H. influenzae* that are ampicillin-resistant). Therefore, erythromycin seems to be the drug of choice

for treating otitis media pending the result of bacteriology. One exception to this would be patients severely ill in whom there was thought to be a danger of meningeal spread. It might be advisable to give these a mixture of antibiotics, e.g. penicillin and gentamicin by injection, but this cannot be recommended routinely.

Laryngitis and tracheitis

As with acute pharyngitis the commonest bacterial cause in adults is streptococcal. In children however, an important cause is *H. influenzae* or *H. parainfluenzae*, often associated with acute epiglottitis that may result in respiratory obstruction. Many causes of laryngitis and tracheitis are in fact non-bacterial. The treatment of these conditions can be considered in two aspects.

(1) A desperately ill child with a presumed *H. influenzae* infection, this is a medical emergency and requires the most potent antibacterial therapy available and most people would prescribe chloramphenicol.

(2) In less ill children and adults with laryngitis and tracheitis who have an irritating cough and hoarseness, often following acute pharyngitis, the treatment can be less dramatic: the drugs can be benzyl penicillin, erythromycin and perhaps ampicillin. Of these, benzyl penicillin has the disadvantage that it must be injected and ampicillin is liable to cause substantial gastro-intestinal disturbances. Thus, for the treatment of acute bacterial infections of the larynx and trachea which are not immediately life-threatening, erythromycin seems an ideal choice.

Acute bronchitis

The incidence of acute bacterial bronchitis is uncertain; many patients with bronchitis may have had virus infections which caused over-production of mucus. Thus, many patients with acute bronchitis are inappropriately treated with antibiotics.

The common bacterial causes of acute bronchitis include the pneumococcus and *H. influenzae* which account for about 80–90% of the cases. It is often impossible to decide whether a bacterium isolated from the sputum of patients suffering from acute bronchitis is a pathogen or a commensal. The choice of antibiotic, here, is difficult and includes ampicillin, erythromycin, tetracycline, co-trimoxazole and a cephalosporin. The use of erythromycin will be directed mainly at those patients in whom the disease is chiefly due to the pneumococcus and those who are either allergic to penicillin or who are not sufficiently ill to merit injections.

Sinusitis

The concentration of erythromycin in sinus fluid is high (Kalm *et al.*, 1976), being substantially

greater than the amount needed to inhibit the growth of the two main pathogens found in sinusitis, i.e. *H. influenzae* and *Str. pneumoniae*. Thus, for a single drug to be used in the treatment of sinusitis the choice must be erythromycin. Ampicillin causes gastro-intestinal side effects and hypersensitivity to penicillin, and may become increasingly ineffective against *H. influenzae* because of the development of resistance.

Soft tissue infections

Boils, styes, paronychia, etc.

The skin infections for which antibiotics are most important are those which are liable to develop a dangerous spreading thrombophlebitis, e.g. those of the face and neck which can lead to a cavernous sinus thrombosis and other severe complications. It is, however, axiomatic that for the treatment of large collections of pus such as are found in boils, some styes and forms of paronychia, the treatment of choice is surgical incision with or without antibiotics. If an antibiotic is indicated in these conditions the first to be considered are benzyl penicillin and ampicillin. These are now redundant in the treatment of staphylococcal infections because more than two-thirds of staphylococci isolated from almost any source throughout Great Britain produce the enzyme penicillinase which destroys the antibiotic before it can destroy the organism. Even if the pathogen is reported sensitive to penicillin, there is a possibility that the commensal, *Staph. albus*, which is always present in the skin, may itself produce penicillinase and destroy the antibiotic. Another agent that has been recommended for the treatment of purulent lesions is co-trimoxazole. But it is now clear that certain components of pus (thymidine and thymine) inactivate co-trimoxazole before it can eliminate the organism. The origins of these components are uncertain, but they may be derived from necrotic polymorph DNA or from commensal or even pathogenic bacteria (Maskell, Okubadejo and Payne, 1976). The presence of these substances make bacteria no longer dependent on the process leading to the formation of folic acid so that they are in effect resistant to co-trimoxazole although if tested *in vitro*, they may appear to be sensitive.

The drugs available for treating boils, styes and paronychia include erythromycin, fusidic acid and a cephalosporin, e.g. cefradine. At present there is little evidence of controlled trials to indicate which of these drugs is most desirable. In any case the relevant drugs must be prescribed according to the local sensitivity patterns.

Cellulitis

The drugs available for treating dangerous streptococcal cellulitis are limited. The two drugs that merit

most attention are a penicillin and erythromycin. Virtually all group A streptococci are sensitive to both these drugs. The choice is therefore between either injections of benzyl penicillin at intervals followed by an oral form, or the use of oral erythromycin from the outset. There is little place for ampicillin or an oral form of penicillin in serious cellulitis because of their uncertain absorption.

Infected dermatoses

In this category are included infected eczema, infected psoriasis, infected dermatitis of industrial or other cause. One of the problems for the clinician is whether the bacteria isolated from these skin conditions are pathogenic rather than commensal. When an 'allergic' skin becomes infected, bacteria responsible are usually either *Staph. aureus* or the group A *Streptococcus*. Frequently these two bacteria are found in association. The treatment of the combined infection poses problems because few antibiotics are reliably active against both bacteria.

Thus, whilst benzyl penicillin is extremely potent against the group A *Streptococcus*, it will probably be hydrolysed by the penicillinase produced from the staphylococcus before the drug can eliminate the streptococcus.

As with other skin conditions, the choice of the antibiotic rests either with erythromycin, or a cephalosporin such as cefradine. It is difficult to recommend any other drug. However, it cannot be stressed too strongly that the isolation of these bacteria associated with psoriasis, for example, does not indicate the need for treatment in itself; antibiotics should only be prescribed where clinical manifestations of infections are present, preferably after bacterial swabs have been submitted to the laboratory.

Venereal and other genital infections

Prostatitis

The precise cause of prostatitis is rarely established but is often assumed to be microbial—either bacterial or due to agents such as *Chlamydia* or other less well recognized groups of micro-organisms. One of the factors in selecting a drug for prostatitis will be the degree of penetration of the antibiotic into the prostatic fluid. This is usually assessed by the presence of the antibiotic in seminal fluid in man (e.g. Malmberg, *et al.*, 1976) or in prostatic fluid from experimental animals.

Previously, tetracycline has been advocated as the drug of choice in treating prostatitis. Certainly penicillin or ampicillin are not generally recommended because the microbes that are thought to be a cause of prostatitis do not have conventional bacterial cell walls on which penicillin acts; in other words, the bacteria are resistant.

Alternative drugs include erythromycin and injectable antibiotics which act on protein synthesis rather than the cell wall. However, data showing whether tetracycline is superior to erythromycin are scanty and either drug would seem to be a very reasonable choice in the treatment of this condition.

Mycoplasma

Mycoplasma infections occur in two main sites in man:

- (1) Primary atypical pneumonia.
- (2) Genital infections.

There is a growing body of opinion that implicates *Mycoplasma* infection in abortion and/or sterility in the female, and non-specific (non-gonococcal) urethritis in the male.

However, it must be stated that some of the evidence on which this opinion is based is inconclusive. In the treatment of *Mycoplasma* infections, the antibiotic selected must not be one which acts on the cell wall because the *Mycoplasma* organisms do not possess a bacterial cell wall. Thus, penicillin, ampicillin and cephalosporins are quite ineffective in treating *Mycoplasma* infections. The antibiotics that may be considered, therefore, are those that act inside the cell, e.g. tetracycline, erythromycin, streptomycin, and co-trimoxazole. Tetracycline has been the traditional choice in treating *Mycoplasma* infections but the great majority of strains are also sensitive to the less toxic erythromycin which would be a very reasonable alternative drug. In practice this means that a patient with an apparently non-specific urethritis or one with a presumed gonorrhoea that had not responded to penicillin could be treated with erythromycin, tetracycline or co-trimoxazole.

Most strains of *Mycoplasma* are extremely difficult to grow, and very few laboratories can confidently isolate this organism.

Anaerobic infections

Peritonitis, pelvic sepsis and other anaerobic infections

The treatment of peritonitis and pelvic sepsis must be aimed primarily at eliminating *Bacteroides* spp. and other anaerobes and the appropriate antibiotic will be one of the following: clindamycin, erythromycin, metronidazole, tetracycline, ampicillin, cephalosporin, chloramphenicol.

Bacteroides spp. are invariably resistant to streptomycin, kanamycin and gentamicin, which have no activity against anaerobic bacteria. Recent antibiotic resistance surveys indicate that the drugs to which *Bacteroides* is most reliably sensitive are chloramphenicol, erythromycin and tetracycline (Peach, 1975). Many strains of *Bacteroides* spp. are resistant to ampicillin, lincomycin and clindamycin.

One of the difficulties of treating peritonitis is that one often has to give a combination of drugs (one appropriate for *Bacteroides*, the other for *E. coli* and other pathogens). Whilst tetracycline in combination with other drugs such as the penicillins, may be antagonistic, there is little reason to think that the use of erythromycin in a combination will produce antagonism, indeed, there may be synergism with ampicillin (May, 1973).

Chlamydial infections

Whilst there is much doubt as to whether *Mycoplasma* spp. are directly causative in non-specific urethritis, there are recent reports of a high incidence of chlamydial isolations in this condition (Oriel *et al.*, 1976). At present, therefore, the evidence is strong that *Chlamydia* organisms are the aetiological agents of some non-specific urethritis infections. What of the antibiotic sensitivity of this organism? Not much is known about the *in vitro* sensitivity of *Chlamydia* spp. because of their exacting growth requirements. However, Ridgeway, Owen and Oriel (1976) have recently described a cell culture system for demonstrating the determination of the minimal inhibitory concentration (MIC) of antibiotics to chlamydiae. In their preliminary results, the test strain of *C. trachomatis* was highly resistant to gentamicin (MIC > 256 µg/ml) and to trimethoprim (256 µg/ml), but sensitive to tetracycline (0.06 µg/ml) and erythromycin (0.03 µg/ml).

From these *in vitro* data, erythromycin would be expected to be effective in treating chlamydial infections clinically, and preliminary reports support this.

Uterine infections

The bacteria responsible for the most serious uterine sepsis are *Clostridium welchii* and β-haemolytic streptococci, usually group A, although other groups are sometimes implicated. The drug for both group A streptococci and *Clostridium* spp. in situations that are liable to be life-threatening is undoubtedly penicillin or one of its derivatives, such as ampicillin. Indeed, for a woman with a high post-abortion or post-delivery pyrexia, very high doses of benzyl penicillin are usually mandatory.

There are, however, some patients (about 3%) who are allergic to penicillin and for these the choice of an antibiotic presents problems. There is some doubt as to how confident one can be that a patient who is allergic to penicillin is not also allergic to cephalosporins and, in fact, whilst it is probably true that the allergies to the penicillins and cephalosporins are distinct, the person who develops an allergic reaction to one tends to develop an allergic reaction to the other more often than may be thought. For such individuals the available drugs include

erythromycin and tetracycline, either of which would be a reasonable alternative to penicillin.

Vincent's angina

For therapeutic success it is thought necessary to eliminate only one of the offending bacteria because this infection is a result of a symbiotic relationship between two (at least) causative organisms. There is no doubt that the drug of choice is a penicillin, e.g. benzyl penicillin, to which the spirochaete is hypersensitive. However, in patients allergic to penicillin, alternatives include erythromycin.

Osteomyelitis

Osteomyelitis is now sufficiently rare to make clinical trials of antibiotics difficult. There are little enough data on the ability of various antibiotics to penetrate normal bone, and even less is known about the ability of antibiotics to penetrate infected bone. As *Staph. aureus* is the commonest causative organism of osteomyelitis (accounting for 90% of cases), the antibiotic must not only penetrate infected bone but must also have an anti-staphylococcal activity. As already mentioned, most strains of staphylococci produce penicillinase that will destroy both benzyl penicillin and ampicillin and some of the cephalosporins.

Drugs that may be considered in the treatment of osteomyelitis include the penicillinase-resistant penicillins. However, these antibiotics are only relatively resistant to the action of staphylococcal penicillinase and compounds such as flucloxacillin can be destroyed to a considerable extent by staphylococcal penicillinase (Lacey and Lewis, 1976) and it would now seem unwise to rely on flucloxacillin alone in treating osteomyelitis. A similar argument applies to the cephalosporins where some, such as cephaloridine, are highly inactivated by the penicillinase and there is experimental and therapeutic evidence that supports this (Burgess and Evans, 1966). Other agents that have been used in the treatment of osteomyelitis include fusidic acid, erythromycin and lincomycin. There would seem to be no advantage of lincomycin over erythromycin and indeed there is good clinical evidence that combinations of erythromycin and fusidic acid produce good therapeutic effect in osteomyelitis (Blockey and McAllister, 1972).

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