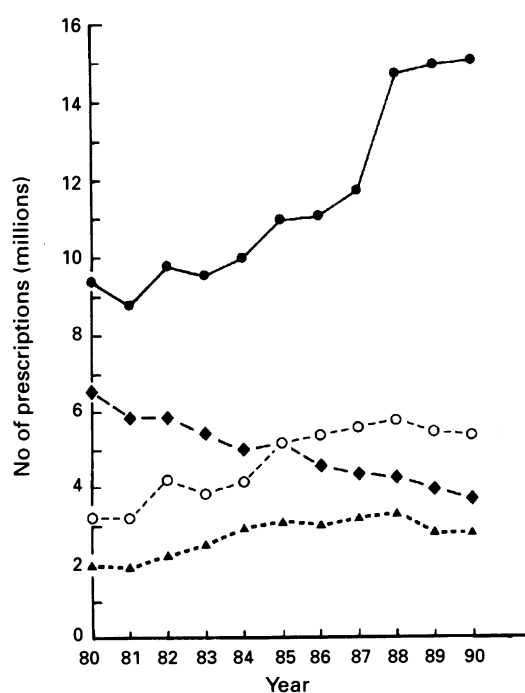


## Why use erythromycin?

Erythromycin is a macrolide antibiotic with a primarily bacteriostatic action against a broad range of bacteria. It is generally well tolerated and only rarely causes serious adverse effects. However, it has a stimulant activity on the gut, and gastrointestinal disturbances such as abdominal discomfort, nausea, vomiting, and diarrhoea tend to occur after both oral and parenteral administration. These gastrointestinal side effects are dose related and are more common in younger than in older subjects.<sup>1</sup> It was the first of the macrolide antibiotics to be used for the treatment of infections and there are now more than 40 years' experience of use with the drug.<sup>2</sup> Initially it was used primarily against Gram positive cocci such as pneumococci, streptococci, and staphylococci, and was of particular use in the treatment of these infections in patients allergic to penicillin. This remained the place of erythromycin for some years, but in the last 20 years or so, and particularly in the last 10 years, there has been a significant increase in the prescription of the drug.

Between 1980 and 1990 there was a 30% increase in total antibiotic prescriptions in England.<sup>3</sup> During this period the prescriptions for erythromycin increased by 72% (figure); there was also a significant increase in the prescription for broad spectrum penicillins (45%) and cephalosporin antibiotics (50%). Over the same period prescriptions for the sulphonamides and trimethoprim remained almost static, whereas tetracycline prescriptions fell by 43%. The methods for calculating antibiotic prescriptions have changed since 1990 so subsequent figures are not strictly comparable. Erythromycin was responsible for 14% of total antibiotic prescriptions in 1992, cephalosporins and tetracyclines accounted for about 10% each, with the broad



Prescription of some antibiotics in England 1980-90; ●—●, broad spectrum penicillin; ○—○, erythromycin; ▲—▲, cephalosporins; ◆—◆, tetracyclines. Compiled from data produced by permission of Statistics Division, Department of Health, UK.

spectrum penicillins accounting for over 60%. Data from other countries show a similar change in the pattern of prescriptions. In 1988 erythromycin accounted for 15% of total antibiotic prescriptions in Finland, with a threefold increase having taken place over the previous 10 years.<sup>4</sup> It is interesting to study the reasons for this increase in the use of erythromycin.

### Indications for erythromycin

Its main use is in the treatment of upper and lower respiratory tract infections and in various skin and soft tissue infections. It is also useful in pertussis, Lyme disease, toxoplasmosis, and in *Campylobacter* infections, and has a place in certain sexually transmitted diseases.<sup>5</sup> There are no data as to the type of infection for which prescriptions are issued, but it can be assumed that a large proportion are for respiratory infections. The increase is probably partly due to the recognition of its efficacy in the treatment of atypical infections caused by mycoplasmas and chlamydia, but interest was also stimulated by the recognition of its activity against Legionnaires' disease.<sup>6</sup> *Legionella pneumophila* was first isolated in 1976 and erythromycin is considered to be the drug of choice. Its effect on *Mycoplasma pneumoniae* was first reported in the late 1960s,<sup>7</sup> and it was later shown that erythromycin has about the same antichlamydial activity as tetracycline.

Studies of the aetiology of community acquired respiratory infections have shown the importance of the atypical organisms as causes of pneumonia and milder respiratory infection, and this has stimulated the use of erythromycin in community acquired infections. There has been some discrepancy in estimates of the frequency of mycoplasma, chlamydia, and legionella as causes of community acquired infection,<sup>8-12</sup> probably because some studies have looked at the incidence over one year while others have looked at the pattern over several years. The cyclical variation in the incidence of mycoplasma infections, with epidemics occurring every three or four years, is well known, but outbreaks of legionella infection have also appeared from time to time and this initially led to an overestimate of its importance as a pathogen. Taking into account these variations, it does appear that the atypical infections, for which erythromycin would be the drug of choice, occur in about 10% of community acquired infections. Tetracyclines remain the drug of choice in chlamydial and probably rickettsial infections, but the problems of tetracyclines in children and pregnant women have led to the more routine use of erythromycin.

Since the antimicrobial spectrum of erythromycin includes activity against pneumococci, and since these are the commonest cause of community acquired pneumonia, some physicians have advocated its routine use in community acquired infection. Used alone it may well be inadequate for some infections – for example, it will be less effective in bacteraemic illness because of the relatively poor serum levels and this would be of particular concern in severe pneumococcal infection with bacteraemia. There is also concern about increasing resistance of *Streptococcus pneumoniae* to erythromycin. The resistance varies from country to country and is thought to relate to the amount of use of the antibiotic. In France, where its use is extensive, the resistance averages 20-25%, whereas in Spain it is less than 10% and in the USA, where its use is lower, resistance is

uncommon.<sup>13</sup> It is not highly effective against *Haemophilus influenzae* which is an important pathogen in patients with pre-existing lung disease and one survey has shown that one in six isolates had a high level of resistance to the drug.<sup>14</sup> Its combination with other bacterial agents is recommended where there is a suspicion of one of the atypical organisms. Such suspicion may stem from a history of recent foreign travel for Legionnaires' disease, bird contact for psittacosis, or a known mycoplasma epidemic.

Clinically and radiologically there are no features that are particularly characteristic of these infections, but the production of mucoid sputum and lack of increased total white blood count in a patient with substantial consolidation may be an indication of atypical infection. The converse is not the case because a normal or low white cell count does not exclude pneumococcal or other bacterial infection. Suspicion of an atypical infection should also arise if there has been poor clinical response to treatment with antibiotics to which these organisms will not be sensitive.

Erythromycin or any other macrolide should also form part of the initial antibiotic regimen in all patients with severe or life threatening illness, and in these patients it should be given intravenously in the first instance.

Improved knowledge of the type of pathogens responsible for community acquired infections has been of help in producing guidelines on the antibiotic treatment of pneumonia.<sup>15</sup> The British Thoracic Society guidelines suggest the combination of erythromycin with a penicillin or a cephalosporin in severely ill patients and in those in whom atypical infection is suggested. Erythromycin has little place in the treatment of nosocomial infection because of the different spectrum of organisms in these patients. The frequency of Gram negative organisms in such patients makes it an unsuitable antibiotic unless a hospital acquired legionella outbreak is suspected.

### Dosage

The standard oral dose prescribed by physicians is 250–500 mg six hourly, but 1 g six hourly should be given intravenously in severe infections. Most studies of erythromycin, when used in comparison with other antibiotics, have used a six hourly regimen. This accords with the elimination half life of 1.5–2.5 hours. An alternative dose regimen of 500 mg or 1 g 12 hourly has been recommended,<sup>16</sup> but without more evidence of the efficacy of this regimen most physicians will probably feel more comfortable with the well tried six hourly regimen.

### New macrolide antibiotics

The introduction of the new macrolide antibiotics such as clarithromycin and azithromycin is likely to result in considerable changes in the use of erythromycin over the next few years. Although it has been shown to be a very safe antibiotic, it has the disadvantages of gastrointestinal intolerance, erratic blood concentrations after oral administration, and inconvenience of a six hourly regimen. Different oral preparations of erythromycin have been formulated to overcome the poor availability, but there is little convincing evidence to show that the modifications have resulted in improvement in efficacy.<sup>17</sup> The main microbiological drawback is the lack of good activity against *Haemophilus influenzae* and, since this is an important pathogen in both upper and lower respiratory tract infections, its use as a single agent is unreliable when this is the likely pathogen.

Experience with the new macrolides is increasing. They have longer half lives and therefore reduced frequency of dosage, so compliance with treatment will therefore be improved. They appear to be better tolerated with less gastrointestinal upset. As well as having good tissue levels, clarithromycin in particular has been shown to have good serum concentrations. Clarithromycin is active against *Legionella pneumophila*<sup>18</sup> and *Mycoplasma pneumoniae*,<sup>19</sup> and both clarithromycin and azithromycin have been shown to be efficacious in clinical studies of exacerbations of chronic bronchitis and pneumonia.<sup>20–22</sup> Early studies have shown clinical efficacy of clarithromycin in infections due to *H influenzae*,<sup>17</sup> but more information is awaited before it can be recommended as monotherapy for all community acquired respiratory infections.

The cost of the newer macrolides is considerably higher than that of erythromycin but more convenient dosage, better compliance, improved tolerance, and wider antimicrobial activity are likely to justify their increased use. Future studies of the comparative merits of these newer macrolides are awaited with interest.

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