Respiratory exacerbations

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Respiratory exacerbations are loosely defined in terms of more breathlessness, increased cough, change in sputum colour to more yellow or green, changes on chest x-ray and loss of appetite and weight. We have found an increased severity of two or more lower respiratory tract symptoms and a fall of 10% or more from baseline FEV<sub>1</sub> or FVC to best reflect a new respiratory exacerbation (Pond & Conway, 1996). We recommend that respiratory exacerbations are treated with two intravenous antibiotics to minimise the risk of antibiotic resistance developing (Cheng et al., 1996; Denton et al., 1996). Combined therapy may also have an additive or synergistic effect (synergy means that the antibiotics have an antibacterial effect when given together that is greater than would be expected by simply “adding” together their individual antibiotic potencies).

The details of hospital treatment for intravenous antibiotics and intensive treatment have changed little (Conway et al., 1985) except for our policy of “no mixing” between patients. The duration of a course of intravenous therapy varies but is usually about two weeks.

Antibiotics prescribed

Usually an aminoglycoside (tobramycin) is combined with a beta lactam (aztreonam, ceftazidime, meropenem or piperacillin-tazobactam). We try to keep colistin as a second line agent e.g. if there are concerns about allergy or bacterial aminoglycoside resistance (Conway et al., 1997). Colistin is used instead of an aminoglycoside and not in combination due to the risk of renal failure. The individual patient’s history of antibiotic hypersensitivity reactions is taken into account when deciding treatment.

The initial choice of antibiotics still depends on the bacterial sensitivity pattern, although there is dispute about whether the laboratory deduced sensitivities are of any relevance in-vivo. The reliability of susceptibility testing of P. aeruginosa isolates from chronic infections in CF is uncertain. Foweraker et al showed that standard laboratory protocols often under-represented the complexity of resistance patterns and this contributed to widespread inter-laboratory variability in determining susceptibility patterns (Foweraker et al., 2005). Further evidence also suggests that the susceptibility pattern in chronic P. aeruginosa infections is poorly predictive of clinical response. As a result we have reduced the number of routine sensitivity tests done in our clinic. Isolates of P. aeruginosa obtained from patients with CF and chronic infection are only routinely tested if they have not been checked in the previous three months, or if obtained from a sample taken at the commencement of intravenous antibiotics, or if the patient is failing on their current antibiotic regimen (Etherington et al., 2007). Clinical improvement may reflect the drugs’ anti-inflammatory and/or antioxidant effects, or activity against P. aeruginosa virulence factors such as exotoxin A, total protease, elastase, phopholipase C, lipase and lecithinase, rather than its bactericidal effect (Adeboyeku et al., 1999; Ledson et al., 1999; Davey et al., 2000).

It is established that once daily tobramycin is as effective and safe as thrice daily administration (Masters et al., 2001; Whitehead et al., 2002; Smyth et al., 2005; Smyth & Tan, 2006). Most patients find once daily dosing more convenient. Trough drug levels should be monitored before the second dose and on day eight and should be <1 mg/litre. In a small number of patients, toxicity may still occur despite a trough level of < 1mg/litre. Future monitoring may involve taking two blood samples at one and
eight hours post dose (Coulthard et al, 2007).

Studies indicate that ceftazidime is as effective when given as two rather than three doses each day - an added convenience particularly for patients on home treatment (Conway, 1996).

Improvement during a course of intravenous treatment can be demonstrated by performing regular respiratory function tests and carefully assessing other symptoms and signs including body weight.

**Routine three-monthly treatment for patients with chronic *P. aeruginosa* infection**

This regimen was recommended by the Copenhagen group in 1989 when they showed a significantly better five year survival when patients with chronic *P. aeruginosa* infection were treated with intravenous anti-pseudomonal antibiotics every three months irrespective of their clinical condition (Jensen et al, 1989; Frederiksen et al, 1996). We and others believe that the picture has changed and that only patients requiring this frequency of treatment to maintain clinical stability should be so treated. We believe that for other patients the risks of antibiotic induced toxic effects on renal function, hearing and balance outweigh the possible benefits of this treatment regimen (Al-Aloul et al, 2005; Etherington et al, 2007). The physical status of patients with CF in 2007 is totally different to that in 1989 and most patients will keep well without recourse to four intravenous antibiotic courses annually. Moreover, patients are living much longer and therefore the potential for serious adverse events from a lifetime of frequent antibiotic treatments is significantly increased. A greater frequency of antibiotic use also increases the risk of patients developing hypersensitivity reactions (allergies) to these medications (Koch et al, 1991; Burrows et al, 2007). Finally, there is the cost of treatment to the hospital and health service and the extra costs incurred by hospitalisation for the patient and relatives.

Whenever it is considered that a patient needs elective three monthly intravenous antibiotic courses all efforts should be made to minimise its intrusive effect on the patient's and family's life style. The family and/or patient should be offered teaching so they can administer treatment at home. Home intravenous treatment also reduces the risk of cross infection.

**Antibiotic treatment of multi-resistant organisms**

Increasingly we are faced with multi-resistant isolates of *P. aeruginosa*. Innately resistant organisms such as *Burkholderia cepacia complex* (Bcc), *Stenotrophomonas maltophilia* and *Acromobacter xylosoxidans* are becoming more prevalent. Methicillin *Staphylococcus aureus* (MRSA) is also a growing problem. These changing patterns probably result from greater patient longevity and increased antibiotic use for acute exacerbations and maintenance care. The optimal treatment for these resistant bacteria, or even if treatment is always necessary, is not known (Conway et al, 2003).

Multi-resistant *P. aeruginosa* infection may be treated successfully by using two antibiotics with different mechanisms of action. In practice antibiotic choices have usually been made on a best-guess basis. It had been hoped that better directed therapy could have been achieved through the application of multiple-combination bactericidal testing (MCBT), (Lang et al, 2000). This systematically tests isolates against different combinations of antibiotics to determine optimal sensitivity patterns. However a follow-up study showed that clinical outcomes were not significantly improved when using regimens selected on the basis of MCBT compared to standard susceptibility tests (Aaron et al, 2005).

The selection of antibiotics for pan-resistant bacteria is problematic. In practice they should be treated with the antibiotics that by experience have produced the best clinical response in that individual patient. Combination antibiotic therapy is recommended, usually tobramycin and high dose meropenem or ceftazidime, but the choice of treatment regimen should always be guided by the clinical response (Harris et al, 1999).

Aerosol delivery of Tobramycin for Inhalation Solution (TOBI ®) achieves high endobronchial concentrations that may overcome bacterial resistance as defined by standard laboratory protocols (Saiman et al, 1996; Lang et al, 2000). Resistance to colistin is rare and this antibiotic should be seen as a valuable second line intravenous drug to be reserved for multi-resistant *P. aeruginosa* (Goldman & Alcorn, 1993). Mechanisms of antibiotic delivery (timing, dosage, infusion rate), should be reviewed to achieve optimal bactericidal effect. The efficacy of new antibiotic groups such as the macrolides should be evaluated.
We recommend a combination of tobramycin with high dose meropenem and/or ceftazidime for patients infected with resistant Bcc as this combination appears to confer effective in-vitro bactericidal activity (Bonacorsi et al, 1999; Aaron et al, 2000). If there is intermediate or full sensitivity to ciprofloxacin, the use of this agent in combination with meropenem or piperacillin-tazobactam may increase bactericidal activity (Kumar et al, 1992). The antibiotic regimen should always be guided by clinical response and combinations altered where and when appropriate. However, when triple therapy is given, e.g. meropenem-tobramycin-ceftazidime, growth of other microorganisms is frequently found (Aaron et al, 2005).

The clinical significance of MRSA, *S. maltophilia* and *A. xylosoxidans* in CF lung disease remains uncertain. If patients show clinical decline and are chronically colonised/infected with either of the former two agents, treatment is recommended but efficacy data are lacking. There are defined microbiological reasons for attempting eradication of MRSA but no proven deleterious effects of this infection on lung function in CF. Various treatment protocols exist but none has been subject to a randomised control trial.

Studies examining the clinical efficacy of different agents and combinations for significant infections with *S. maltophilia* are lacking and data are extrapolated mainly from in-vitro studies. Co-trimoxazole (Septrin) has consistently been shown to be the most active agent in-vitro, with most isolates susceptible on initial testing. This is regarded as the treatment of choice for significant infections with *S. maltophilia* (Karpati et al, 1994). Because the activity of co-trimoxazole is only bacteriostatic, it has often been tried in combination with other agents such as ticarcillin-clavulanate or ceftazidime when treating significant infections in immunocompromised patients. There are no data available regarding the efficacy of co-trimoxazole, alone or in combination, for the treatment of chronic *S. maltophilia* colonisation in patients with CF.

There are no controlled trials investigating the treatment of patients chronically colonised with *Achromobacter* species. If the latter is the sole pathogen in a symptomatic patient showing a decline in respiratory function tests or worsening chest x-ray, *A. xylosoxidans* should be treated in a similar way to *P. aeruginosa* infection with antibiotic choice guided by bacterial sensitivity patterns.

Multi-resistant micro-organisms are an important and growing issue in CF care. Each patient infected with such strains should be assessed individually and antibiotic treatment planned according to any in-vitro sensitivity, patient drug tolerance, and in-vitro studies that may direct the physician to the antibiotic combinations most likely to succeed. Antibiotic choices in these difficult cases must always be guided by the patients’ clinical response.

We have treated a small number of patients with multi-resistant pathogens with tigecycline, a new injectable glycylcycline antibiotic related to minocycline (Denton et al, 2007). Tigecycline has in-vitro activity against non-fermentative Gram negative bacteria (excluding *P. aeruginosa*), *S. aureus* (including MRSA), *H. influenzae*, and rapid-growing non-tuberculous mycobacteria. We have so far treated seven patients with various pathogens including Bcc, *Pandoraea apista*, *S. maltophilia*, *M. abscessus* and *M. chelonae*. Two patients were unable to tolerate the drug due to nausea while five patients showed clinical response. Properly constructed trials are required to ascertain the effectiveness of tigecycline in CF.

**Key points**

• Prompt and effective antibiotic treatment of respiratory infection has played a major part in the improved prognosis for people with CF

• Viral infections should be “covered” with additional oral antibiotic administration and treated with intravenous antibiotics if symptoms do not settle

• Patients receiving routine three monthly treatments with intravenous antibiotics should be individually reviewed with regard to the risk: benefit ratio of this regimen

• The choice of antibiotics for the treatment of pan-resistant bacteria should always be guided by the clinical response
References


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