Intravenous antibiotics and *Pseudomonas aeruginosa*

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Introduction

We believe that prompt initiation of eradication protocols for new *Pseudomonas aeruginosa* infection and early, high dose intravenous antibiotic treatment of respiratory exacerbations have been the most important factors responsible for the improved outlook for people with CF (Conway *et al,* 1985; Smith *et al,* 1988; Regelmann *et al,* 1990; Bradley *et al,* 1999). All patients require regular respiratory cultures (throat/cough swabs or sputum) and appropriate antibiotic treatment to eradicate any pathogenic bacteria (Cystic Fibrosis Trust, 2002).

There are four main indications for intravenous antibiotic therapy.

To eradicate early *P. aeruginosa* infection

i) As an alternative to combined oral and nebulised antibiotic treatment e.g. when treating an infant or young child
ii) As a prelude to the standard oral and nebulised antibiotic regimen when a new *P. aeruginosa* culture is associated with new respiratory symptoms
iii) When a standard eradication regimen has failed

To treat a new cough that has not settled with the addition of an oral antibiotic

If new respiratory symptoms do not settle after two different oral antibiotics, or if there are significant continuing symptoms after a single oral antibiotic course, we recommend treatment with intravenous antibiotics. It is important to remember that significant new infection may be present even when careful listening with the stethoscope does not reveal any new added sounds in the chest, and in the absence of any new chest X-ray changes. There may be only a persistent or new cough.

Neglect of these early signs and symptoms may result in permanent damage to the respiratory tract and the onset of a slowly progressive deterioration in respiratory function.

It is our experience that the persistent cough "dries up" within a few days of starting intravenous antibiotic therapy. The antibiotics prescribed will depend on previous respiratory cultures for the patient.

To treat a respiratory exacerbation

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_1 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.

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). 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 < 1 mg/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.

As a 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 resistant 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 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,* 2000).

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 mutli-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 several 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.

Desensitisation to antibiotics

On occasions when there is a multi-resistant organism, it may be necessary to use an antibiotic to which the patient has had a previous allergic reaction. The patient can undergo a desensitisation regimen. The patient will need desensitising to the drug at the start of EVERY treatment course and during any course of therapy if more than one dose is omitted.

The regimen uses a logarithmic scale, giving a total of seven doses, starting with a minute dose and increasing by a factor of ten for each subsequent dose, until the therapeutic dose for the patient is achieved. Each dose is diluted to 45 mls, given over 20 minutes and the doses are given consecutively. The whole process takes two and a half to three hours.

Once successfully completed, the full treatment course of the antibiotic can commence as normal. If any of the escalating desensitisation doses are not tolerated the process is abandoned (Etherington *et al,* 1998). If the desensitisation is unsuccessful it may be repeated at a later date with steroid and/or antihistamine cover prior to and following the procedure.

Drug	Dose	Max dose/other	Levels/Notes
Amikacin	30 mg/kg once daily as infusion (once daily regimen usually used)	Maximum daily dose: 2000 mg	Levels required. Trough <1mg/L taken before 2nd dose.
	Child and adult 10 mg/kg tds Max Initial dose 500 mg tds	Max initial dose: 500 mg tds. Dose may be increased after evaluating levels	Take levels pre-dose and 1 hour post at the 4th dose and after each week. Trough: <10mg/L Peak: 25-30mg/L
Aztreonam	80mg/kg tds Max dose: 2.5g tds	Adult dose: 2.5g tds	
Ceftazidime	100mg/kg bd	Maximum dose: 6g bd	Use bd for convenience but tds if nausea and vomiting occur. Pregnancy dose: 2g tds
Ciprofloxacin	Under 5 years: 4-8mg/kg bd 5-17 years: 10mg/kg tds Adult: 400mg bd	Maximum dose 400mg tds	IV preparation only needed when oral preparation not tolerated.

Colistimethate sodium (colistin, Colomycin®)	Child: 25,000 units/kg tds. Max: 2 megaunits tds Over 40 kg: 2 megaunits tds	Adult dose: < 40 kg: 1 megaunit tds. > 40 kg: 2 megaunits tds Max: 2 megaunits tds	Caution when using with other nephrotoxic drugs.
Imipenem	22mg/kg tds/qds Max: 90 mg/kg/day, 1g qds	Max. 1g qds	
Meropenem	40mg/kg/tds Adult: 2g td	Max. 2g tds	Bolus or infusion
Piperacillin/ tazobactam (Tazocin®)	Under 12 years: 90mg/kg tds/qds Over 12 years: 2.25-4.5g tds/qds Max : 4.5g qds	Adult: 4.5g tds-qds	In acute severe infection the dose may be given four times a day. For home treatment three times a day dosing is appropriate.
Tobramycin (once daily regimen usually used)	10mg/kg od over 30-60 minutes. Maximum dose: 700mg daily	Once daily regimen	Preferably take level immediately before 2nd and 8th dose (i.e. 24hours after the 1st and 7th dose) and after each week thereafter. Ideal level: <1 mg/L Or: Take level 14 hours after the 2nd dose and after each week. Ideal level: <2mg/L
	4mg/kg tds as a bolus	Use dose that achieved therapeutic levels on last admission .	Peak taken at 1 hour, 8-12mg/L Trough <2 mg/L

Table 1. Examples of anti-pseudomonas antibiotics. 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). The individual patient's history of antibiotic hypersensitivity reactions is taken into account when deciding treatment.

Key points

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

Recommendations

• Prompt initiation of eradication protocols for new *Pseudomonas aeruginosa* infection and early, high dose intravenous antibiotic treatment of respiratory exacerbations should be undertaken

• 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

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