# CF Guidelines - Pseudomonas Aeruginosa

## Pseudomonas aeruginosa:

Pseudomonas aeruginosa remains the major pathogen of most patients with CF, with chronic infection occurring by the early teens. In the majority of patients the classical non-mucoid form infects the airways prior to the subsequent emergence of the mucoid alginate-producing variants. This latter form defends itself against ingestion and destruction by the white blood cells by producing large amounts of a protective film called alginate. Alginate also protects Pseudomonas aeruginosa against the activity of antibiotics. The presence of the non-mucoid form is frequently asymptomatic and may be intermittent.

- Chronic – Ps. aeruginosa isolated in more than 50% of months when spu tum, cough of throat swab taken in previous 12 month period.
- Intermittent – Ps. aeruginosa isolated in 50% or less months when sputum, cough or throat swab sample taken in previous 12 month period.
- Free of infection – Ps. aeruginosa isolated previously but not in past 12 months.
- Never – Ps. aeruginosa never isolated.

Eradication or major reduction of the bacteria in the early stages of colonisation is possible with appropriate antibiotic therapy thus reducing the microbial reservoir from which the alginate producing mutants later arise. Once the transition to the mucoid form has occurred, infection becomes chronic and is associated with intermittent exacerbations and progressive lung disease. Antibiotic treatment of mucoid Pseudomonas aeruginosa infection may reduce the bacterial population in the sputum and produce some clinical benefit but permanent eradication is seldom ever achieved. Early eradication treatment is only 80% successful; therefore avoidance of Pseudomonas aeruginosa infection is preferable, and economically advantageous.

Prevention of chronic Pseudomonas aeruginosa infection has important beneficial effects for people with CF and early eradication therapy is thought to be a major reason for the increased survival of patients with CF. Those chronically infected with Pseudomonas aeruginosa have more respiratory symptoms and significantly worse general health, a more rapid decline of their respiratory function, a more rapid deterioration in their CXR scores and significantly worse survival.

## Sources of Pseudomonas aeruginosa:

Cross-infection with Pseudomonas aeruginosa has been reported between individuals with CF, and from CF to non-CF (usually immunosuppressed or otherwise vulnerable) populations.

- General environmental:
  - Pseudomonas aeruginosa is found in many natural and domestic environments including plants, soils and surface water, especially warm and moist environments containing organic material or contaminated by human or animal waste. Hydrotherapy pools and Jacuzzis have been reported as a risk, but swimming pools are generally safe provided chlorination is maintained. Showers have not been reported as a source.

- Equipment:
  - Although not proved specifically, contaminated equipment may be a source of infection although the risks are low provided that appropriate

standards of hygiene are maintained. Home nebulisers have not been shown to harbour the infection despite other organisms being identified.

- Hospital:
  - Pseudomonas aeruginosa is frequently found in some hospital environments, particularly intensive care units. In a recent study from the Danish CF centre, where precautions are taken to avoid cross-infection, including segregation of patients according to their microbiological status and good hygienic practice, the mean age of acquisition of chronic Pseudomonas aeruginosa infection over the past decade has risen from 6 to 15 years.

- Other factors:
  - There has been some historical evidence that prophylactic anti-staphylococcal therapy with a broad spectrum antibiotic increased the incidence of new Pseudomonas aeruginosa infections but a recent systematic review shows the evidence is inconclusive.

## Identification of infection:

- A sputum specimen should be sought at each clinic visit and at the onset of an exacerbation of respiratory infection. Pseudomonas species can be cultured from samples stored at room temperature for several days after collection, but refrigeration is preferable and ideally samples should be processed within 2 or 3 hours to maximise the chances of isolating the full range of pathogens present.
- Cough swabs are less sensitive and are also non-specific in detecting lower respiratory infection with Pseudomonas aeruginosa.
- Bronchoalveolar lavage might be useful in the context of worsening respiratory complications in the presence of negative cultures results from the upper airways.
- There is good correlation between positive respiratory cultures and raised antibody levels to Pseudomonas aeruginosa. On the other hand a normal antibody level suggests that there has been no tissue invasion by the Pseudomonas aeruginosa and thus no immunological response. Usually antibody levels are normal when the first positive culture occurs. In such patients eradication with appropriate treatment is usually easily achieved. It is helpful to measure Pseudomonas aeruginosa antibody levels at each annual review and consider there use at times of early Pseudomonas aeruginosa infection and at the start of IV antibiotic treatment for pulmonary exacerbations in chronically infected patients.

## Treatment:

Pseudomonas aeruginosa is inherently very resistant to antimicrobials. In addition there is often poor correlation between in vitro and in vivo behaviour of the Pseudomonas aeruginosa, with respect to antibiotic susceptibility testing, which can result in poor therapeutic efficacy. An explanation for this is that as colonisation progresses considerable heterogeneity arises with different colonial morphotypes exhibiting a range of sensitivity. Thus in vitro susceptibility tests based on examination of a single colonial representative may not reflect the true populations of Pseudomonas aeruginosa within the lung.

Management after the first respiratory culture positive for Pseudomonas aeruginosa: Treatment of first isolates of Pseudomonas aeruginosa should be aggressive and prompt. Optimum treatment regimes have not been determined. Consider enrolling

patient in TORPEDO study (Bristol/Nottingham) which seeks to determine the value of initial treatment with IV antibiotics. Otherwise:

- Check the patient is not unwell and needing IV antibiotic treatment.
- Start nebulised Colistin (for 3 months) and oral Ciprofloxacin (for 6 weeks). If Ciprofloxacin is not tolerated consider nebulised Tobramycin alone or nebulised Colomycin in combination with a 2 week course of intravenous antibiotics.
- Repeat culture.
- If negative stop treatment and check sputum each month for recurrence.
- If sputum cultures remain positive, strongly advise a 2 weeks course of intravenous antibiotics and continue nebulised antibiotics for further 3 months, before reassessment. Check compliance, consider nebulised TOBI.

Some centres also prescribe azithromycin for the first month to try and increase the success rate by decreasing Pseudomonas aeruginosa adherence to the respiratory epithelium and biofilm growth.

Recommendations for patients chronically infected with Pseudomonas aeruginosa:

- All patients should be considered for regular nebulised anti-pseudomonal antibiotic treatment.
- Initially Colistin should be given. If not tolerated or clinical progress unsatisfactory consider alternative preparations.
- Consider oral azithromycin which has been demonstrated to reduce exacerbation frequency.

Treatment for chronically infected patients with increasing signs and symptoms or colds:

- 2 week course of Ciprofloxacin should be given to patients with CF at time of upper respiratory infections at the first sign of an increase in symptoms and signs of their chest infection. These patients should usually be taking a regular nebulised anti-pseudomonal antibiotic, which should be continued.

Intravenous antibiotics for respiratory exacerbations in patients chronically infected with Pseudomonas aeruginosa:

- There should be a low threshold of concern for starting intravenous antibiotic treatment. Two antibiotics should be used in combination and should have a different mechanism of action e.g. an aminoglycoside and a beta-lactam. The optimum frequency of antibiotic delivery is currently debated. Beta-lactams are usually given 3-4 times a day, as their killing of Pseudomonas aeruginosa is most effective when the antibiotic levels are maintained above the MIC for prolonged periods of time. Aminoglycosides are traditionally given 3 times a day but are increasingly given as a single daily dose, since their best effect is related to achieving intermittent high levels and their toxicity to failure to clear the drug adequately between doses. Two weeks treatment is usually given. Longer courses should be considered if clinical improvement is slow.

## Note:

An elective 3-monthly IV antibiotic regime (rather than ‘on demand’) has been adopted by a number of specialist CF centres. Although there are some data to

support this strategy in children, its value has not been established by a satisfactory controlled trial in adults.

## References:

1, Pseudomonas aeruginosa infection in people with cystic fibrosis. Suggestions for prevention and control. Cystic Fibrosis Trusts 2004.
2, Antibiotic Treatment for Cystic Fibrosis. Report of the UK Cysitic Fibrosis Trust Antibiotic Group. Cystic Fibrosis Trust 2002.

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