Segregation is good for patients with cystic fibrosis

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It is bewildering, in the face of so much evidence for the potential for cross-infection between patients – cross-infection that may have devastating consequences – that we continue to debate the advantages (numerous and important) and disadvantages (few and largely irrelevant) of keeping patients separated. Amazingly, to my mind, there has been no resolution of the conflicting points of view since Professor Geddes and I first argued this issue in a cystic fibrosis (CF) conference in 2001. Some CF centres have a strict patient segregation policy, some centres have no policy at all, and many centres follow management protocols that fall at varied points between these two extremes. In this paper I will provide evidence which I believe supports a strict segregation policy as practised in the Leeds CF centres.

An interesting and quizzical starting point might be to ask this question: Why does the international CF community readily accept separation of patients with *Burkholderia cepacia* complex (Bcc) infection from all other patients but does not universally accept separation of all patients from each other? It is instructive to consider this. We treat patients with Bcc infection separately because we know that Bcc is a potentially virulent pathogen, that it can cause an accelerated or catastrophic clinical deterioration, that it is difficult to treat and almost impossible to eradicate, that it may preclude acceptance onto a lung transplant programme, but most of all because Bcc infection is transmitted from patient to patient.

As a result of these and many other studies, every CF unit segregates patients with Bcc infection. Some units, correctly in my opinion, also segregate within the Bcc infected group, arranging clinics and inpatient protocols to minimize contact between these patients. So why do we not follow similar protocols to minimize the risk of infection with *Pseudomonas aeruginosa* and other pathogens?

To fulfil criteria which would support a segregation policy aimed at reducing the risk of infection, *P. aeruginosa* infection should be common, accelerate clinical decline and spread between patients. Cohorting of patients must be seen as effective and workable. We know that up to 73% of children acquire their first *P. aeruginosa* infection by three years of age, as shown by bronchoalveolar lavage and oropharyngeal cultures.6 We know that by late adolescence up to 80% of patients may have chronic infection.7 Patients with *P. aeruginosa* infection show lung function test results about 10% below levels achieved by patients free of infection.8 We know that almost 90% of CF deaths are because...
of respiratory failure,\(^7\) in many cases a direct result of \(P. \text{aeruginosa}\) infection and the damaging host inflammatory response. We have known for over two decades that patients with chronic \(P. \text{aeruginosa}\) infection die younger. In 1985, Wilmott et al. described 53\% and 84\% survival to 16 years in patients with chronic infection compared to patients with no infection.\(^9\) Data from the USA CF Foundation in the 1990s documented average survival to 28 years and 39 years for patients with and without chronic \(P. \text{aeruginosa}\) infection. We know that pathogens within respiratory droplets can live for hours on surfaces and that infection is spread from person to person by these droplets of infected secretions, either indirectly by contact with contaminated objects (e.g. toys, shared toothbrushes, eating utensils or respiratory equipment) or by direct body-to-body surface transfer (e.g. kissing, touching, patient care or shaking hands). Cultures from routine sputum samples in our own paediatric unit found six patients with colistin-resistant \(P. \text{aeruginosa}\). Four of these showed identical genotypes and had had overlapping admissions, suggesting patient-to-patient transfer in a nosocomial setting.\(^10\)

Holiday camps for people with CF have virtually disappeared because of the reported spread of \(P. \text{aeruginosa}\) infection within the camps. Tümmler et al. documented new \(P. \text{aeruginosa}\) infection in eight of ten patients after a four- to six-week stay. Two weeks of intravenous antibiotic treatment failed to eradicate the infection in seven of eight patients. Three of the seven had infection with a mucoid \(Pseudomonas\) strain characteristic of chronic infection and therefore strongly suggestive of person-to-person spread at the camp.\(^11\) Ojeniyi et al. documented 17 of 22 patients with chronic infection before a one-week winter camp. All 22 stayed at the same hotel and participated in the same activities. After the camp all 22 patients had \(P. \text{aeruginosa}\) infection. Pulsed Field Gel Electrophoresis (PFGE) showed the new acquisitions were identical to the strains from the other 17 patients, demonstrating a cross-colonization rate of 100\%.\(^12\) Those who ignore these reports continue to risk cross infection with \(P. \text{aeruginosa}\).\(^13\) Experience at the Liverpool Alder Hey Hospital paediatric unit provided the first unequivocal evidence of an epidemic in unrelated patients involving a \(\beta\)-lactam-resistant strain of \(P. \text{aeruginosa}\).\(^14\) Sixty-five children had ceftazidime-resistant strains, and 55 of these had the same epidemic strain.

Importantly, these data show how the pattern of \(P. \text{aeruginosa}\) infection can mimic that of Bcc infection. In our own experience in the late 1980s, when Bcc infection was beginning to decimate CF clinics, two of our patients attended American summer camp holidays. Two and six months later, respectively, Bcc was isolated for the first time from these patients. One patient progressed to an accelerated decline over two years. The other showed a precipitous deterioration and died 65 days later. Therefore, knowing that \(P. \text{aeruginosa}\) infection can spread in the same way as Bcc infection, and that it is also likely to result in greater morbidity and decreased life expectancy, the only logical response is to take all reasonable steps possible to minimize the chances of patients acquiring this infection.

We know that increased separation of patients from each other limits the spread of \(P. \text{aeruginosa}\) infection. When CF holiday camps are abandoned the cross infection rate falls markedly.\(^11\) A comparison of the proportion of patients free of infection over a five-year period showed a significantly lower prevalence of infection in a centre with a faster throughput of patients and no shared waiting room for those with and without \(P. \text{aeruginosa}\) infection, compared to a centre where all patients shared a single waiting area before their appointment with a single-handed doctor.\(^15\) The Copenhagen Unit reported a monthly prevalence of chronic \(P. \text{aeruginosa}\) infection increasing from \(<40\%\) in 1976 to \(>60\%\) in 1980. Over this five-year period, patients were treated according to a new protocol of three monthly elective courses of inpatient intravenous antibiotic therapy, with time spent in hospital increasing from two to eight weeks per year. Because the wards were near the outpatient clinics where all patients were seen, this new policy had increased the cross infection rate. As a response a protocol for cohort isolation was introduced in 1981, with the following results: the annual incidence of intermittent \(P. \text{aeruginosa}\) infection fell from 32\% to 17\% \((P<0.05)\); the incidence of chronic infection fell from 16\% to 9\%; and the time from the first infection to chronic \(P. \text{aeruginosa}\) infection increased from one to four years. This proved that cohort isolation alone can delay chronic \(P. \text{aeruginosa}\) infection.\(^16\) The Copenhagen data show that we can prevent cross infection by simple hygienic measures and reduce the new infection rate to the ‘natural background’ level of 1–3\%. Following similar protocols in Leeds, the average age of onset of chronic \(P. \text{aeruginosa}\) infection increased from just over nine years of age to just under 12 years of age between 1990 and 2000. One hundred and forty-five children presently have full care in our clinic. Only 12\% have chronic
P. aeruginosa infection, and only five children <11 years old (7%) have chronic P. aeruginosa infection.

The need for patient segregation has been recently highlighted by the emergence of highly transmissible strains of P. aeruginosa. The Liverpool adult centre has documented that these strains can infect patients who already have chronic P. aeruginosa. The epidemic transmissible strain may then achieve dominance or co-dominance with the patient’s previous strain. If patients are allowed to mix freely, cohort isolation alone does not provide sufficient protection. If patients are allowed to mix freely, epidemic strains will spread across the CF community. In Australia, a genetically identical clone of P. aeruginosa was identified in five clinics separated by 1,800 km along the Eastern Seaboard. The failure to find an environmental reservoir further supports the belief that the spread of infection is consequent on airborne spread between patients. Eighty percent of patients’ room air samples were positive for the epidemic strain. Yet another reason to separate patients from each other is because epidemic strains are multi-resistant and show enhanced virulence. Nine adult patients with the Liverpool epidemic strain were matched for age, lung function and BMI with nine patients with unique Pseudomonas strains. The mean annual changes in FEV1 (% predicted) and BMI were, respectively, −5 versus −0.7% (P<0.05) and −0.21 versus +0.31 (P<0.05). The treatment requirements over one year for the Manchester adult patients with chronic highly transmissible P. aeruginosa infection, compared to those with chronic infection with unique strains, were significantly greater in terms of inpatient episodes, inpatient days and intravenous antibiotic treatment days. They also suffered a greater number of exacerbations. In Australia in a study cohort of 92 infants, five unrelated children under five years old died from severe lung disease. Mucoid P. aeruginosa infection had been identified 0.5–16 months before death. PGFE showed an identical pattern in eight of 27 infected children, including all five who died. In the 18-month period following the study, children with the clonal strain were more likely to die from lung disease than those with other P. aeruginosa isolates (odds ratio 3.7). The clonal strain was significantly more resistant to ceftazidime, imipenem, gentamicin and tobramycin.

We must also remember the risk of infection with bacteria not commonly associated with respiratory infection in patients with CF, a risk enhanced by allowing patients to mix freely. Burkholderia dolosa, Burkholderia pseudomallei and Pandora apista have been associated with chronic infection, accelerated loss of lung function, and decreased survival. Pandorea species may, like Bcc, present with bacteraemia. MRSA has been isolated with increasing frequency from CF units with prevalence rates ranging from 0 to about 23%. Epidemiological studies suggest that nosocomial transmission during hospital admissions, rather than social contact outside of hospital, is the most significant route of transmission for MRSA. Some patients may show increased dyspnea, wheeze and sputum production concurrent with MRSA isolation, whilst others show no disease progression even when no specific treatment is given. However, although some studies suggest that MRSA infection has only a minimal effect in CF despite its undisputed pathogenic role in non-CF patients, these studies are of short duration, uncontrolled and conducted on only a small numbers of patients. Larger studies of longer duration might show deleterious effects of MRSA infection in CF. In Miall’s study, ten infected children were compared to controls from one year before to one year after the onset of MRSA infection. The MRSA group showed a non-significant trend towards decreased respiratory function, an increased requirement for intravenous antibiotic treatment in the year after the first isolate and a significantly worse height standard deviation score. Data from the Epidemiologic Study of CF show that, compared to patients with methicillin-sensitive Staphylococcus aureus only,
patients with MRSA only had significantly more airflow obstruction, significantly greater likelihood of hospital admission, and more treatment with oral, inhaled and intravenous antibiotics.35

CF multidisciplinary team members who argue against segregation often refer to the support that families and patients give each other. However, our experience and the literature tell us that patients and families appreciate the need for segregation, deal with it well, and are concerned if they perceive it to be breached on any occasion. The majority of parents and patients are positive about segregation measures.36 Children were most concerned with boredom and isolation, issues that can be successfully addressed in a number of ways by imaginative staff and family. Parents were aware of the positive and negative aspects but concluded that segregation was necessary.37

In conclusion, there is overwhelming evidence that cross infection with a number of respiratory pathogens occurs in CF units when patients are allowed to mix with each other. There is evidence that segregating patients from each other interrupts the spread of infection. Most patients and parents appreciate the need for strict adherence to segregation protocols. It is very difficult to understand why anyone would argue against a policy that is more likely than not to decrease patient morbidity and increase longevity.

References


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