Prospective Surveillance for *Pseudomonas aeruginosa* Cross-Infection at a Cystic Fibrosis Center

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We have performed a 4-year prospective surveillance for *Pseudomonas aeruginosa* cross-infection at a large regional adult cystic fibrosis center. Despite purpose-built facilities in a new building and the practice of strict hygiene, *P. aeruginosa* cross-infection has continued. In contrast, individuals segregated from the cohort of patients with chronic *P. aeruginosa* infection but who attend the same center have not acquired infection with transmissible *P. aeruginosa* strains. Simple infection control measures alone do not prevent the spread of transmissible *P. aeruginosa* strains between individuals with cystic fibrosis. However, in our clinic patient segregation effectively controlled spread of such strains.

Keywords: incidence; infection control; prevalence

Cystic fibrosis (CF) is the most common lethal inherited disease among whites (1). Morbidity and mortality is primarily from chronic suppurative lung disease (2). The major pathogen for this group of patients is *Pseudomonas aeruginosa* (3). The epidemiology and management of *P. aeruginosa* cross-infection in CF is controversial and has been highlighted in three recent editorial articles (4–6). Recent studies have reported evidence for *P. aeruginosa* cross-infection at CF centers in the United Kingdom and Australia (7–12), although Speert and colleagues did not find epidemiological evidence of *P. aeruginosa* cross-infection at a large Canadian CF center (13). To date, there are no published large prospective studies of cross-infection with *P. aeruginosa* in CF centers.

An initial cross-sectional study at the Manchester Adult CF Center discovered convincing evidence of *P. aeruginosa* cross-infection (7). The CF Center is located in a modern purpose-built dedicated facility. Close attention is paid to hygienic principles in keeping with the recommendations of the UK Cystic Fibrosis Trust Infection Control Subcommittee (14). In brief, all inpatients have their own bedroom, although only two of the eleven rooms have en-suite facilities. Rooms are cleaned between patients. Treatment including nebulization and airway clearance is performed in the patient's own room with the door closed. Compressor and nebulizer systems, airway clearance devices, and oxygen therapy delivery systems are not shared between patients. Staff are educated to practice hand washing or disinfection with alcohol rubs before and after physical contact with patients; false fingernails are prohibited. Covered sputum pots are provided for patients. Single use disposable mouthpieces with one-way valves are used with the spirometers. An extensive microbiological screening of the CF Center failed to show an environmental reservoir for or contamination with transmissible strains of *P. aeruginosa* (15). Similarly, the same study showed no evidence of carriage of *P. aeruginosa* on the hands of the health care workers. Spirometry was previously done in a small room on the ward. Since 2002, following our findings from air sampling study at the center (15), spirometry is performed in each patient's own room with the door closed. The patients did have access to a kitchen area and dayroom on the ward and were allowed to socialize outside their own rooms.

As our initial study had documented cases of new *P. aeruginosa* infection with a transmissible strain in patients previously free of *P. aeruginosa* infection, we instituted a policy of segregation for patients with CF with and without chronic *P. aeruginosa* infection. Patients without *P. aeruginosa* infection attended outpatient clinic appointments on a different day than other patients with CF. As inpatients they were housed on the same CF ward as patients with chronic *P. aeruginosa* infection, but in rooms with en-suite facilities, and were advised not to socialize with other patients on the ward. We have continued prospective microbiological surveillance for *P. aeruginosa* cross-infection and now report the incidence and prevalence of transmissible *P. aeruginosa* at our center for the past 4 years (2000–2003). Some of the results of these studies have been previously reported in the form of an abstract (16).

METHODS

Patients

Over a 4-year period (2000–2003) we have prospectively typed *P. aeruginosa* isolates from patients with CF who attend the Manchester Adult Center to assess clonality of strains. This has been part of clinical practice at the center, instituted after the finding from an initial study (7) that patients at the center shared the same clonal *P. aeruginosa* strain, indicative of cross-infection. We ensured that all patients with CF with chronic *P. aeruginosa* infection had an isolate(s) retyped since the original cross-sectional typing study (7). For the purpose of this study we have defined chronic *P. aeruginosa* infection as the regular culture of the organism from the sputum or respiratory secretions, on two or more occasions extending over 6 months (14). *P. aeruginosa* isolates from patients were retyped more frequently if they displayed unusual phenotypic features, including a change in antibiotic resistance pattern. In addition, patients with multiple inpatient admissions or patients found to have been exposed to potential risk of cross-infection, such as through social contact with other patients with CF, had isolates retyped more frequently. We also targeted all new acquisitions of *P. aeruginosa* infection in any previously "*Pseudomonas*-free" patients.

The group of patients with CF at this center infected with organisms of the *Burkholderia cepacia* complex have been segregated from all other patients with CF for over 10 years. Patients with *B. cepacia* complex infection share the same outpatient facilities but attend on different days or clinic times to other patients with CF; as inpatients they are treated on a different ward. In the original survey, no patients with *B. cepacia* complex infection were found to harbor a transmissible *P. aeruginosa* strain. *P. aeruginosa* isolates from patients with *B. cepacia* complex infection were again screened to identify if any were known transmissible strains.

Patient demographics, including inpatient admissions to the adult center, were recorded.

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Bacterial Isolates

All isolates were confirmed as *P. aeruginosa* using standard biochemical reactions and the API 20 NE system (BioMerieux, Basingstoke, UK). Different colonial morphotypes on the same culture plate were investigated individually. Isolates were initially screened for the unusual pyocin type characteristic of the Manchester transmissible strain typed using the pyocin typing method for *P. aeruginosa* (17) and genotyped by pulsed-field gel electrophoresis (PFGE: CHEF-DRII system; BioRad, Hemel Hempstead, UK) using the restriction enzyme *Xba1* (7). The criteria of Tenover and colleagues were used to describe relatedness (18). Strains were described as "transmissible" if there was previously published epidemiologic and molecular typing evidence for transmission among patients with CF. Strains shared between small numbers of patients without definitive epidemiologic evidence of spread were termed "clusters." Individual strains with unique typing profiles were described as "sporadic."

RESULTS

Currently, 243 patients attend the Manchester Adult CF Center; 176 have chronic *P. aeruginosa* infection (and a further 15 are co-infected with both *P. aeruginosa* and *B. cepacia* complex—*see below*). We have retyped isolates from all but three patients with chronic *P. aeruginosa* on at least one occasion during the study. After our initial cross-sectional study (7), we typed a further 311 sputa samples from patients with *P. aeruginosa* infection between 2000 and 2003. Between 1, 2, and 3 isolates were typed from each sputum sample in 54.2%, 40.2%, and 5.6% of samples, respectively. The incidence and prevalence figures for infection with the two major transmissible *P. aeruginosa* strains (7, 8) encountered at this CF center among patients with chronic *P. aeruginosa* infection are given in Table 1.

In addition, seven small clusters of patients sharing the same clonal *P. aeruginosa* strains were also found. These comprised one cluster of eight patients, two clusters of three patients, and four clusters of two patients each. There was no family relationship between patients in any of the clusters. The majority (6/8) of patients in the first cluster had received their care at the same pediatric CF center.

Among a total of 31 *P. aeruginosa*–negative patients, there were five cases of new *P. aeruginosa* infection by sporadic strains in the preceding year before segregated clinics were introduced and three cases due to transmissible *P. aeruginosa*. After the introduction of segregated clinics and strict inpatient isolation measures, 12 *P. aeruginosa*–negative patients have developed *P. aeruginosa* infection over a period of 3 years. Isolates from all but one patient were available for typing; none were found to be a transmissible strain (Table 2).

In the original survey, 25/30 with *B. cepacia* complex infection were co-infected with *P. aeruginosa*. None were found to harbor a transmissible *P. aeruginosa* strain. Ten patients have since died, two others no longer receive their care at this center, and four remain free of *P. aeruginosa* infection. *P. aeruginosa* isolates from 11 of the original patients co-infected with *B. cepacia* complex together with a further 4 additional patients who have since developed *B. cepacia* complex were typed in 2003. None are infected with transmissible *P. aeruginosa.*

DISCUSSION

There has been a continued increase in incidence and prevalence of transmissible *P. aeruginosa* at this adult CF center. This is despite adherence to strict hygienic practises in a modern purpose built dedicated CF facility with single bedrooms for all inpatients. Patients with CF who are segregated from those with transmissible *P. aeruginosa* have not acquired infection with a transmissible strain.

It has been suggested that *P. aeruginosa* cross-infection may result from a simple breakdown in infection control measures at CF centers rather than the increased transmissibility of particular strains (4). The cross-infection outbreak at this center has continued despite adherence to strict hygienic practices in a dedicated CF facility with single bedrooms for all inpatients. The center adheres to recommendations from the UK CF Trust in good hygienic practice at a CF center (14). The continued cross-infection outbreak at this center is primarily as a result of the spread of two particular transmissible strains (7, 9) between patients. The mechanism of *P. aeruginosa* cross-infection is not known, and establishing experimental proof of the mode(s) of spread is prevented by ethical limitations. We have previously reported results of extensive microbiological screening of the inpatient and outpatient environment of the center (15). This failed to find an environmental reservoir or environmental contamination for the transmissible strains of *P. aeruginosa*; however, airborne dissemination of transmissible *P. aeruginosa* was observed. Direct patient-to-patient transmission seems likely to be the main mode of spread in this particular cross-infection outbreak.

A disturbing feature of our initial study was several cases of new *P. aeruginosa* infection with transmissible strains in patients previously free of *P. aeruginosa* infection. Subsequently, we instituted an outpatient policy of segregation for patients with CF with and without chronic *P. aeruginosa* infection in 2000. Patients without *P. aeruginosa* infection attend outpatient clinic appointments on a different day; as inpatients they are housed on the same CF ward, but in rooms with en-suite facilities and advised

TABLE 1. INCIDENCE AND PREVALENCE OF TRANSMISSIBLE *Pseudomonas aeruginosa* INFECTIONS AT THE MANCHESTER ADULT CYSTIC FIBROSIS CENTRE OVER A 4-YEAR PERIOD AMONG PATIENTS WITH CHRONIC *P. aeruginosa* INFECTION

Year	1999	2000	2001	2002	2003
Total number of patients	216	221	228	250	243
Total number of patients with chronic *P. aeruginosa* infection	156	164	184	186	176
Patients chronically infected with transmissible strains	28	31	35	40	45
New cases of superinfection by transmissible *P. aeruginosa*	N/A	6	5	7	8
Deaths of patients with chronic infected by transmissible strains	N/A	2	0	2	5
Incidence of superinfection by transmissible strains among patients with chronic *P. aeruginosa* infection	N/A	4.4%	3.3%	4.6%	5.9%
Prevalence of transmissible strains for patients with chronic *P. aeruginosa* infection	17.9%	18.9%	19.0%	21.5%	25.6%
Prevalence of infection with transmissible *P. aeruginosa* strains for all patients with CF	13.0%	14.0%	15.4%	16.0%	18.5%

TABLE 2. CASES OF NEW *P. aeruginosa* INFECTION AMONG *P. aeruginosa*–NEGATIVE PATIENTS AT THE MANCHESTER ADULT CYSTIC FIBROSIS CENTRE

	2000	2001	2002	2003
Total number of *P. aeruginosa*–negative patients	31	30	37	45
New cases of *P. aeruginosa* infection with sporadic strains	5	3	4	4
New cases of *P. aeruginosa* infection with transmissible strains	3	0	0	0

One further case of transient *P. aeruginosa* infection 2003 but no isolate was available for strain typing.

not to socialize with other inpatients. Over the remainder of this study we typed isolates from all but one of 12 patients who developed new *P. aeruginosa* infection at the center. Since the above measures were introduced there has not been a fall in the number of cases of new infection due to sporadic strains of *P. aeruginosa*, but no *P. aeruginosa*–negative patient has developed infection with a transmissible *P. aeruginosa* strain.

The new cases of transmissible *P. aeruginosa* infection since 2000 are cases of super-infection (8), with transmissible strains infecting patients already chronically infected by sporadic strains of *P. aeruginosa*; this emphasizes the high colonizing potential of these strains. Although cohort segregation for patients infected with transmissible *P. aeruginosa* was introduced for outpatient clinics, the center has only one CF ward and there was still some social mixing between the patients on the ward. All patients who became infected with a transmissible strain since 2000 had a recent inpatient admission before or during the time when the superinfection was confirmed.

This CF center has operated strict segregation policy for patients with CF infected with *B. cepacia* complex infection for over 10 years. Interestingly, none have acquired infection with a transmissible strain of *P. aeruginosa*. Patient segregation, to prevent *B. cepacia* complex cross-infection, may have protected *B. cepacia* complex–infected individuals from acquiring transmissible *P. aeruginosa* through patient-to-patient spread. An alternative hypothesis that *B. cepacia* complex protects against transmissible *P. aeruginosa* is unlikely because the majority of patients who harbor *B. cepacia* complex are co-infected with sporadic strains of *P. aeruginosa*.

Individuals with CF who are segregated from the cohort of patients which include those with transmissible *P. aeruginosa* infection, but attend the same center, seem to have been protected from infection with transmissible *P. aeruginosa*. The implementation of cross-infection control measures to include strict inpatient and outpatient segregation for all patients who harbor transmissible *P. aeruginosa* will challenge the presently available resources of most large CF centers. Measures instituted at CF centers may also need to be extended to social contact outside hospital and at CF meetings and gatherings. Microbiological surveillance, involving genotyping of *P. aeruginosa* strains, is necessary to monitor the effectiveness of cross-infection control measures. Surveillance has significant resource implications but needs to be balanced with the high costs, increased morbidity, and intransigence of treating transmissible strains, some of which demonstrate multiresistance.

The Manchester Adult CF Center has a relatively stable clinic population. No patients infected with a transmissible strain have, as yet, transferred their care to another adult CF center. However one patient infected with a different transmissible *P. aeruginosa* strain recently transferred their care from another adult CF center to the Manchester Adult CF Center. This patient transferred in late 2003 and has not been included in the present study. It has recently been shown that transmissible strains are present in many of the CF centers in the United Kingdom (11) and clonal strains are found in geographically distinct CF clinics in Australia (12). There is now an evident need to include details about the *P. aeruginosa* strain type among the clinical information given by one center to another when a patient who has *P. aeruginosa* infection transfers their care between CF centers in countries where cross-infection has been found.

We also identified seven clusters each comprising between two and eight nonsibling patients who shared the same clonal strain. Recent studies by O'Carroll and coworkers (12) and Speert and colleagues also identified clusters of unrelated patients sharing clonal strains (13). Speert and colleagues found no epidemiologic evidence to support spread among the clusters of patients sharing clonal strains in Canada. One of the clusters of patients in the study by O'Carroll and colleagues, however, consisted of eight patients who harbored a strain previously identified at another Australian CF Center (10). In the present study, the majority of patients in the largest cluster had received their care at the same pediatric CF center. The finding of small clusters of patients who share common strains raises the dilemma as to whether this represents patient-to-patient spread or acquisition from a common environmental source. At present, no common transmissibility factor has been identified for *P. aeruginosa* strains associated with cross-infection and microbiological surveillance continues to rely on genotyping of isolates and epidemiologic analysis.

There is early evidence of adverse clinical effects associated with infection by both the major transmissible strains of *P. aeruginosa* found at the Manchester Adult CF Center. Recent studies have reported an increased treatment burden for infected patients in comparison to those who harbor their own sporadic strain (19) and increased morbidity among chronically infected patients with CF (20). Nixon and associates (21) have also reported an observed increase in patient mortality associated with a transmissible *P. aeruginosa* clone at an Australian pediatric CF center.

As a consequence of the results of this study we have now introduced a strict segregation policy for all ward patients at the Manchester Adult CF Center. We have closed the dayroom and kitchen area on the ward where patients could prepare snacks and drinks. All inpatients are now required to remain in their own rooms and not to mix at any time with any other patients on the ward, irrespective of their microbiological status. We plan to continue microbiological surveillance to assess the effectiveness of these measures.

In conclusion, in the absence of patient segregation close attention to hygienic principles did not prevent cross-infection with transmissible *P. aeruginosa* strains at our modern purpose-built CF facility. Transmissible *P. aeruginosa* strains continue to present cross-infection control problems at large CF centers in Europe and Australia (7–12). In addition to adherence with strict hygienic principles, patient segregation seems necessary to control spread of these strains.

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