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Epidemic of *Pseudomonas cepacia* in an Adult Cystic Fibrosis Unit: Evidence of Person-to-Person Transmission

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An epidemic of *Pseudomonas cepacia* occurred in an adult cystic fibrosis center in the United Kingdom, despite a policy of segregation of infected and noninfected patients within the hospital. Investigation of the outbreak by ribotyping and pulsed-field gel electrophoresis to characterize *P. cepacia* strain genomes together with inquiry into social contacts between patients revealed evidence of person-to-person transmission outside the hospital environment. Segregation policies aimed at reducing the spread of this infection in the cystic fibrosis community need to encompass patient contacts outside the hospital environment.

In recent years, *Pseudomonas cepacia* has emerged as an important respiratory pathogen in patients with cystic fibrosis (CF). Initial reports from Canada (9) of an adverse outcome for a proportion of those who acquire this organism have been confirmed in other centers in North America (22, 25) and the United Kingdom (5, 19), and the general consensus is that *P. cepacia* infection is best avoided if at all possible (11, 18).

The mode of acquisition of *P. cepacia* by patients with CF remains unclear. *P. cepacia* is apparently ubiquitous in the environment (6), and such sources may be responsible for a proportion of new *P. cepacia* infections in patients with CF. However, increasing evidence suggests that some individuals acquire the organism from other patients, either directly or via the immediate shared environment. Thus, the concordance rate for *P. cepacia* infection is high in sibling pairs with CF living in the same household (23).

Some CF centers which have reported an increase in new *P. cepacia* infections have separated patients with the organism from those without it and have subsequently shown a reduction in the rate of new *P. cepacia* infections (24). This suggests that contact within the hospital or group environment is a risk factor for the acquisition of *P. cepacia*. Genotyping of *P. cepacia* strains from three North American centers revealed that a single, center-specific strain accounted for more than half of the isolates within each center, supporting the contention of nosocomial acquisition (14). In addition, transmission of a strain between two patients attending a conference over a 6-day period was documented by genotyping (13).

In the United Kingdom, there is increasing evidence of the importance of person-to-person transmission, whether direct or indirect, in the acquisition of some new *P. cepacia* infections (15, 17, 20), although some studies remain inconclusive (4).

The Adult Cystic Fibrosis Unit at East Birmingham Hospital (EBH) provides inpatient and outpatient services for 120 patients, the majority of whom reside in the West Midlands. Despite a policy of separation of *P. cepacia*-positive and *P. cepacia*-negative patients within the hospital environment, during the latter half of 1991, the unit experienced an outbreak of new *P. cepacia* infections. We therefore investigated the genotypes of these isolates and inquired into the degree and nature of contacts between patients outside the hospital environment.

MATERIALS AND METHODS

Patient data. All patients attending the CF unit are under the care of a single physician and that physician's staff. Antibiotic therapy is given on an as required basis for pulmonary exacerbations. First-line therapy for those colonized with *Pseudomonas aeruginosa* consists of an aminoglycoside in combination with a beta-lactam guided by the antibiotic susceptibilities of sputum isolates. Such patients also receive chronic aerosolized colistin therapy when tolerated. Antibiotic treatment of *P. cepacia*-positive patients is guided by susceptibility testing, with the combination of ceftazidime and tobramycin being commonly used. Patients whose sputum persistently grows *Staphylococcus aureus* receive continuous oral antistaphylococcal agents. Sputum samples are obtained at every clinic visit and at least weekly during periods of hospitalization. All sputum samples are examined for the presence of *P. cepacia*. There had been no change in these management policies in the period preceding the outbreak. For the last 4 years we have been operating a policy of separating *P. cepacia*-positive from *P. cepacia*-negative patients in that *P. cepacia*-positive outpatients are seen in a different clinic location and on a different day than *P. cepacia*-negative patients. Hospital admission, when required for a *P. cepacia*-positive patient, is to a separate ward with its own nurses and physiotherapists.

Clinical details and dates of visits of all *P. cepacia*-positive patients to the center since 1988 were noted, including visits made before the first isolation of *P. cepacia* from each individual. Social contacts between patients attending the center and with other patients with CF were recorded.

Identification of *P. cepacia*. A selective medium for the isolation of *P. cepacia* (Mast Diagnostics Ltd.) was introduced for routine use on all sputum specimens from patients with CF in 1989. Polymyxin B and ticarcillin are used as selective agents in concentrations as described by Gilligan et al. (3). The medium selectively supports the growth of *P.*

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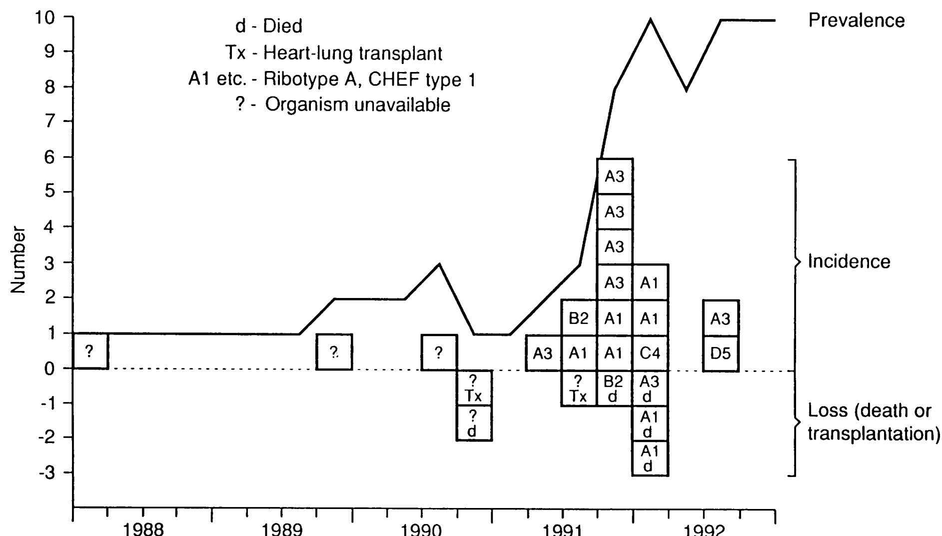

FIG. 1. Quarterly incidence and prevalence of *P. cepacia* infections in an adult CF clinic together with losses from death and transplantation.

cepacia and was superior to MacConkey agar, while it inhibited the growth of other respiratory pathogens except ticarcillin-resistant *P. aeruginosa*. All isolates on *P. cepacia* agar plates were identified by using the API 20 NE system (API bio Merieux, France). The identities of the initial isolates from patients were confirmed by the National Collection of Type Cultures, Central Public Health Laboratory, Colindale, London, United Kingdom. Before 1989, isolates were identified by the same system but had been cultured on nonselective medium. No attempt was made to quantify the growth of *P. cepacia*.

Genotyping of *P. cepacia* strains. Single isolates of *P. cepacia* from each of the 14 patients who had become *P. cepacia* positive from 1991 on were characterized by ribotyping (2). Pulsed-field gel electrophoresis by the clamped homogeneous electric field (CHEF) technique (21) was used as a secondary genotyping method to confirm the relatedness of strains within each ribotype. Isolates from the three remaining patients who were *P. cepacia* positive before the 1991 outbreak were not available for genotyping.

RESULTS

Incidence and prevalence of *P. cepacia* infection. The number of patients attending our center rose from 69 in 1988 to 120 in 1992. One new case of *P. cepacia* infection was seen each year from 1988 to 1990 (average annual incidence, 1%), but 9 (8.2%) were identified in 1991 and 5 (4.2%) were identified in 1992. *P. cepacia* was detected in the sputa of six patients at their first attendance at our center, and only two of these had been identified as *P. cepacia* positive by the referring hospital. Failure to detect *P. cepacia* in these patients may have been due to the microbiological techniques used by the hospitals. The maximum prevalence of *P. cepacia*-positive patients attending the CF unit in each year was 1 (1.4%) in 1988, 2 (2.1%) in 1989, 3 (2.8%) in 1990, 8 (7.2%) in 1991, and 10 (8.3%) in 1992 (Fig. 1).

Characteristics of patients with *P. cepacia* infection. Our 17 patients with *P. cepacia* infection included 10 males (mean ± standard deviation age, 23 ± 3.9 years; range, 16 to 28 years) and 7 females (mean age, 23.7 ± 3.4 years; range 19 to 28 years). Fifteen of the 17 patients (88%) had previously been chronically colonized with *P. aeruginosa*, often in combination with *S. aureus* (9 patients). Pseudomonads had not previously been isolated from the sputa of two patients. Sixteen of the 17 patients (94%) remained colonized with *P. cepacia* following the time their first sputum specimen was cultured, and they were always colonized in tandem with *P. aeruginosa*. Only one patient exhibited intermittent *P. cepacia* colonization. Fourteen of the 17 patients (82.4%) had received colistin as an inhalant prior to the first *P. cepacia*-positive culture, 5 had taken oral steroids (prednisolone; mean dose, 2.5 mg daily), and 7 had taken steroids as an inhalant. Four patients had insulin-dependent diabetes. Lung function measurements at the time of the first *P. cepacia*-positive culture revealed a group with moderate to severe lung disease except for one patient with well-maintained pulmonary function. Individual patient data are shown in Table 1.

Outcome of *P. cepacia* infection. Five (30%) of our 17 patients with *P. cepacia* infection have died, all within 6 months of the first *P. cepacia*-positive culture (mean time from first *P. cepacia*-positive culture to death, 2.8 ± 1.5 months; range, 1 to 5 months). In the patient with the shortest survival time (1 month), the first *P. cepacia*-positive culture preceded heart, lung, and liver transplantation by 2 weeks. Although initially successful, transplantation was followed by death 2 weeks later from widespread *P. cepacia* infection including septicemia and multiorgan failure. In the other four patients who died, acquisition of *P. cepacia* was followed by persistent progressive pulmonary infection which showed little response to antimicrobial therapy and culminated in death from respiratory failure. Persistent pyrexias and pleural involvement manifest as pleuritic chest pain accompanied by progressive weight loss were prominent features of these illnesses.

Two (12%) of our 17 patients had undergone successful heart and lung transplantations at 43 and 20 months, respectively, following the first *P. cepacia*-positive culture. Both remained well 24 and 15 months, respectively, following surgery. *P. cepacia* has not subsequently been isolated from these patients.

TABLE 1. Characteristics of 17 patients with CF and chronic *P. cepacia* infection at the time of the first *P. cepacia*-positive culture

Patient no.	Sex	Age (yr)	Prior microbiology[a]	% FEV1[b]	% FVC[c]	Concomitant microbiology[d]	Ribotype or CHEF type	Outcome
1	Female	21	PAm, SAm, HIm, PM1	24	59	PAm, SAm, HIm	A1	Survivor, deteriorated
2[e]	Male	25	PAm, SAm, HIm, ECm	15	13	PAm, PFm	A1	Died at 15 weeks
3	Female	21	PAm, SAm	34	47	PAm, CAm	A1	Died at 8 weeks
4	Female	26	PAm, SAm, CA1	18	34	PAm	A1	Survivor, stable
5	Female	19	PAm, SAm	82	95	PAm, SAm, CA1	A1	Survivor, stable
6[e]	Male	28	PAm	44	65	PAm	A3	Survivor, stable
7	Male	28	PAm	41	68	PAm, CAm	A3	Survivor, stable
8[e]	Female	25	PAm	19	32	PAm	A3	Survivor, deteriorated
9	Female	26	PAm, SAm, HIm	35	64	PAm	A3	Survivor, deteriorated
10	Male	21	PAm, PP1, PF1	31	61	PAm	A3	Died posttransplant
11	Male	21	PAm	45	78	PAm	A3	Survivor, <6 mo
12	Male	20	PAm, SAm	16	28	PAm, SAm	B2	Died at 12 wk
13[e]	Male	25	PAm	15	26	PAm	D4	Survivor, deteriorated
14	Male	25	SAm, HIm	25	49	PAm, SAm	C5	Survivor, <6 mo
15	Male	20	PAm, HIm	16	42	PAm, SAm, HIm	NA[f]	Died at 20 wk
16[g]	Female	28	SAm	24	44	PAm, SAm, PMm	NA	Transplanted
17	Male	16	PAm	42	68	PAm	NA	Transplanted
Mean		23		31	51			
SD		4		17	21			
Range		16–28		15–82	13–95			

[a] Sputum cultures in the year preceding the first *P. cepacia*-positive culture. PA, *P. aeruginosa*; PF, *Pseudomonas fluorescens*; PM, *Pseudomonas maltophilia*; PP, *Pseudomonas pickettii*; SA, *S. aureus*; HI, *Haemophilus influenzae*; EC, *Escherichia coli*; CA, *Candida albicans*; m, multiple cultures; 1, single culture.
[b] FEV1, forced expiratory volume in 1 s.
[c] FVC, forced vital capacity.
[d] Sputum cultures following the first *P. cepacia*-positive culture. See footnote *a* for definitions of abbreviations.
[e] Insulin-dependent diabetic.
[f] NA, not available.
[g] Intermittent *P. cepacia* isolation only.

Ten (59%) of our 17 patients have survived *P. cepacia* infection without transplantation to date. Two of these patients have been *P. cepacia* positive for less than 6 months, and the long-term outcome remains unclear. In four of the eight patients who have survived for 6 months or longer, acquisition of *P. cepacia* has produced a reduction in pulmonary function and body weight when compared with those in the 12-month period prior to the first *P. cepacia*-positive culture. For the remaining four long-term survivors, acquisition of *P. cepacia* has had no discernible effect on pulmonary function, body weight, or well-being.

Genotyping studies. Ribotyping and typing by the CHEF technique were used hierarchically to determine the genotypes of the *P. cepacia* isolates. Strains exhibiting distinct ribotypes also showed distinct CHEF profiles. Isolates from 11 patients shared ribotype A, but these 11 isolates were divided into two groups by CHEF typing, A1 (5 patients) and A3 (6 patients). Ribotypes B, C, and D were each found in a single patient only.

Patient contacts. The temporal relationship of acquisition of *P. cepacia* and periods of social contact between patients who had become *P. cepacia* positive since 1991 are shown in Fig. 2. The patients can be classified into the following three groups: group 1 (patients 1 to 5), patients who shared the A1 genotype; group 2 (patients 6 to 11), patients who shared the A3 genotype; and group 3 (patients 12 to 14), patients who had individually unique genotypes (B2, C4, and D5).

In group 1, all patients acquired *P. cepacia* infection within a 7-month period. The index case (patient 1) was the girlfriend of patient 2 prior to conversion to *P. cepacia* positivity. Intimate contact continued between this couple after the conversion of patient 1 to *P. cepacia* positivity, and patient 2 (the boyfriend) became *P. cepacia* positive 3 months later. Patient 4 was the sister of patient 2. Although living apart, she made frequent visits between her home and her parents' domicile, where patient 2 (her brother) still resided. Patients 2 and 1 were also frequent visitors to the home of patient 4. After the conversions of patients 1 and 2 to *P. cepacia* positivity, these contacts continued, but at a reduced rate; patient 4 became *P. cepacia* positive 15 weeks later. It seems likely that patients 4 and 2 acquired their infections through the social contacts outlined above. The remaining two patients in group 1 were neither related to nor close friends of patients 1, 2, and 4. However, both had been hospitalized concurrently with another member of this group (patient 3 with patient 2; patient 5 with patients 1 and 2) within a 2-week period of *P. cepacia* conversion of that contact. It seems possible that patients 3 and 5 acquired their infections from the hospital contacts outlined above. This suggests that *P. cepacia*-positive patients may be infectious before they are culture positive and segregated from *P. cepacia*-negative patients.

In group 2, the date of conversion to *P. cepacia* positivity could not be accurately assessed for two patients (patients 7 and 8). Patient 7 had a negative sputum culture 6 months prior to the first *P. cepacia*-positive culture, but no samples were taken between these times. Conversion to *P. cepacia* positivity may have occurred at any time between these dates. Patient 8 was found to be *P. cepacia* positive at the time of her first attendance in our laboratory, although she was diagnosed as *P. cepacia* negative by another center and therefore may have been *P. cepacia* positive for some time prior to attending our center. The index case in group 2 was patient 6, who was *P. cepacia* positive at the first referral to our center and had been diagnosed as *P. cepacia* positive by the referring hospital some 8 months earlier. There were no

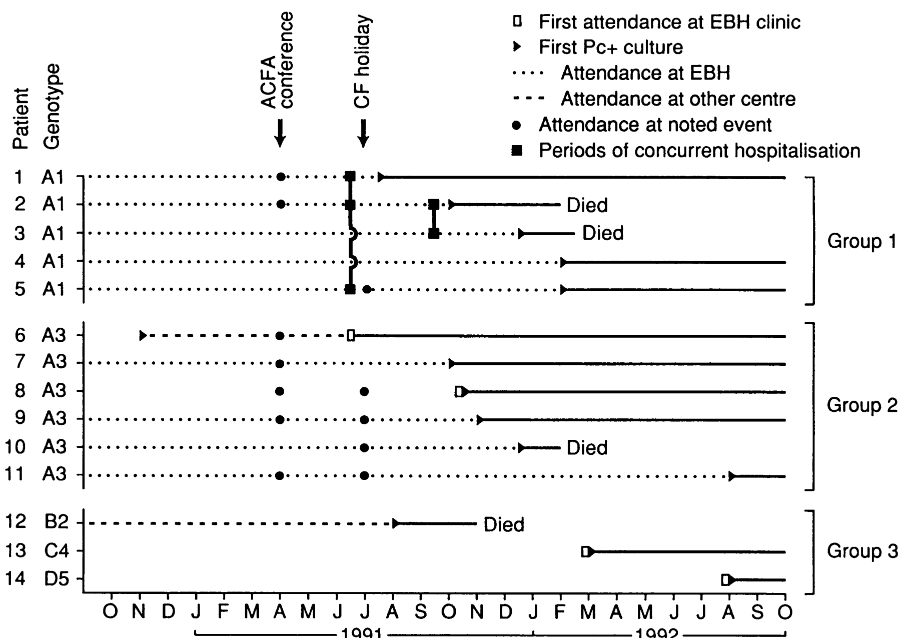

FIG. 2. Temporal relationship of acquisition of *P. cepacia* and periods of contact between patients.

shared periods of hospitalization or clinic visits prior to the first *P. cepacia*-positive culture, none of the patients were siblings, nor were there any long-standing boyfriend-girlfriend relationships in this group. However, five of the six members, including the index case, who was not at that time a patient at EBH (patients 6, 7 to 9, and 11), had attended a 3-day conference of the Association of Cystic Fibrosis Adults (ACFA) 6 months before the conversion of the majority of the patients in the group to *P. cepacia* positivity. The conference was attended by a total of 78 adults with CF, 11 of whom were patients at EBH (including four of the five group 2 members) known to be *P. cepacia* negative at that time. Five of the seven attendees from EBH remain *P. cepacia* negative at the time of this writing; the other two patients subsequently became *P. cepacia* positive but were infected with a strain of a different genotype and are included in group 1 (patients 1 and 2). Three months later, four of the six members of group 2 (patients 8 to 11), who at this time were still *P. cepacia* negative, had taken part in a week-long holiday with other individuals with CF, with some shared sleeping accommodations. It seems likely that acquisition of the infection from the index case and its subsequent spread throughout the group occurred in the context of the social interactions outlined above. The sources of *P. cepacia* infection in the index cases in groups 1 and 2 remain unknown, although both were active members of ACFA and had multiple contacts with other individuals with CF outside our own center.

The third group of patients (patients 12 to 14) harbored *P. cepacia* strains with genotypes that were unique to each individual. Patient 12, although well known to us, transferred to another center because of geographical relocation 1 year prior to becoming *P. cepacia* positive. He subsequently made a single visit to our clinic when *P. cepacia* infection was noted, but care was continued at the second center. There he had contacts with *P. cepacia*-positive patients both as an outpatient and during admissions for treatment, and it is possible that he may have contracted his infection under those circumstances. In the year prior to conversion to *P. cepacia* positivity, he had no contact with patients attending our own center. Patient 13 was found to be *P. cepacia* positive on first referral (because of recent clinical deterioration) from a peripheral hospital. Prior to his first attendance, he had had no contact in the hospital or socially with any of the patients with CF described above. Patient 14 was also *P. cepacia* positive at the time of his first attendance at our center. He was visiting the United Kingdom and had had little contact in hospital and no social contacts with other patients with CF prior to this.

Relationship of genotype to outcome. Of the five deaths that occurred in *P. cepacia*-positive patients in our center, two were patients colonized with a strain of the A1 genotype (patients 2 and 3), one was a patient colonized with a strain of the A3 genotype (patient 10), and one was a patient colonized with a strain of the B2 genotype (patient 12). The fifth patient's isolate was not available for genotype analysis (Fig. 3).

DISCUSSION

Our experience with the outcome of *P. cepacia* infections in adults with CF is in keeping with those seen in North America (12) and Canada (9). Clinical outcome is varied; almost a third of our 17 patients (30%) deteriorated rapidly and died within 6 months of acquisition of *P. cepacia*, 4 have exhibited a worsening rate of decline but have survived for longer than 6 months, and a similar number have experienced no adverse clinical effects from *P. cepacia* acquisition. Two (12%) of our *P. cepacia*-positive patients have undergone successful heart and lung transplantations without complications, remaining well and, to date, free of *P. cepacia* infection. In a third patient, triple-organ transplantation was followed by death from overwhelming *P. cepacia* sepsis 2 weeks later.

The marked increase in new *P. cepacia* infections in the latter half of 1991 occurred despite our hospital's segregation

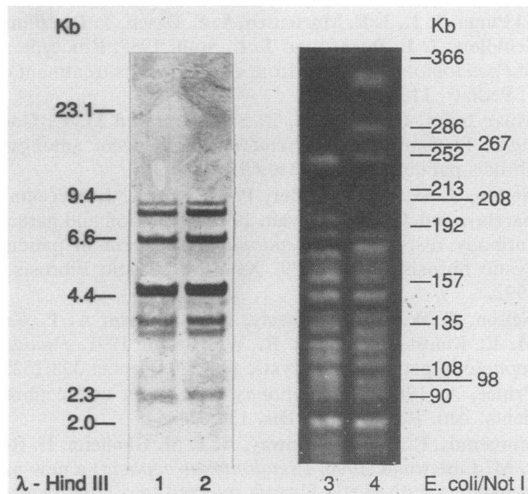

FIG. 3. Ribotyping and pulsed-field gel electrophoresis (clamped homogeneous electric field technique, CHEF) of *P. cepacia* DNAs from two isolates from patients. Lane 1, ribotype A (patient 1, group 1); lane 2, ribotype A (patient 6, group 2); lane 3, CHEF type 1 (patient 1, group 1); lane 4, CHEF type 3 (patient 6, group 2).

policy and the high degree of awareness of the potential for cross-infection among hospital staff. Our results suggest that a significant proportion of cases of infection may have been acquired by person-to-person transmission (whether direct or indirect) outside the hospital environment.

Early studies of the inanimate environment of patients with CF failed to find contamination by *P. cepacia* (7); however, more recent work has revealed the potential for transmission of this organism via the immediate patient environment (17). It seems likely that both direct transmission (e.g., by interpersonal contact or aerosol spread) and indirect transmission (e.g., via shared equipment and by third parties) play a role. Thus, measures aimed at limiting the spread of this infection need to address both of these issues.

Transmission of *P. cepacia* through social contact has been well documented in siblings (22) and summer educational camps (13). Our study shows that transmission of a strain (genotype A1) occurred over a 3-month period in the context of an intimate relationship and over a similar time period between other members of this group, in two patients (patients 3 and 5) through hospital contact. The time interval between transmission of strain A3 among group 2 patients is less certain, mainly because of multiple social contacts between members of this group. An interval of at least 10 months (time between last contact with other members of group 2 and last *P. cepacia*-negative sputum culture) was identified for patient 11, although for other episodes of transmission within the group, shorter time intervals were noted. The observation that two patients who subsequently acquired the A1 strain also attended the ACFA conference underlines the frequency of social interactions between some of our adults with CF.

There is evidence to suggest that some strains may be more transmissible than others. In the United Kingdom, a single ribotype (type A) of *P. cepacia* has been found in samples from five regional CF centers, including the clinic at EBH (10). In a study of *P. cepacia* ribotypes in three centers in North America (14), the majority of patients within each center harbored strains of the same ribotype, but different ribotypes predominated at each center. The explanation for the finding of a common ribotype across the United Kingdom, in contrast to the case in North America, may lie in the increasing levels of activity of associations such as the ACFA on a national basis in the United Kingdom. This association has been organizing national meetings for the last 8 years for an increasing number of adults with CF. However, in 1992 patients with *P. cepacia* infection were asked not to attend the International ACFA meeting in Dublin, Ireland, for fear of spread of this organism (8). In contrast, in North America, patients with CF and infected with *P. cepacia* have been segregated at summer camps and meetings of adults with CF for a number of years.

Our study suggests a picture of greater complexity, with the finding that the type A ribotype may be further distinguished into two strains by CHEF typing. Furthermore, each of these two strains appears to have been responsible for separate small outbreaks. Thus, the CHEF typing system provided greater resolution of genomic differences than ribotyping for the strain identification of *P. cepacia*; this has proved useful in understanding the spread of infection within our own unit.

Another issue raised by our study is that of recognition of *P. cepacia*-positive status. A number of patients referred to us arrived with *P. cepacia* infection not previously diagnosed by the referring center. This has necessitated the introduction of a screening policy for all new referrals who cannot now gain admission to our ward for *P. cepacia*-negative patients without *P. cepacia*-negative sputum cultures from our own laboratory. There is a need for all physicians who care for patients with CF to ensure that their hospital laboratory is able to identify this infection when it is present.

Also of concern is that patients may be infectious before they are recognized as *P. cepacia* positive by the laboratory. Although an increase in the frequency of microbiological surveillance will theoretically reduce this period, transmission may occur at levels of bacterial load in the sputum that are below the level of detection by culture techniques. In support of this there is evidence that a humoral response to *P. cepacia* predates positive sputum cultures (1, 16). Moreover, our own experience suggests that this may be the case, and therefore, a rigorous policy of segregation on the basis of sputum cultures may still prove lacking unless patients are all separated as individuals.

We believe that *P. cepacia* can be socially transmitted between patients, and therefore, segregation of *P. cepacia*-positive and -negative patients only within the hospital environment may not protect them against transmission. Indeed, for gregarious individuals, social rather than hospital contacts may represent the greater risk. Since for a proportion of those infected acquisition of *P. cepacia* results in early death, we advise against social contacts between *P. cepacia*-positive and -negative individuals in the hope of limiting the spread of the organism. There will always, however, be occasions when social necessities (e.g., family ties and preexisting relationships) outweigh the risks associated with such contacts for the individual. For those involved in such occasions, careful and sympathetic counseling is imperative. The implications of adopting such a policy are widespread and difficult for all concerned, but we are heartened by the positive attitudes and support of our patients in our approach to the management of this problem.

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