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Transmission of Bacteria during Cystic Fibrosis Educational Programs

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Abstract

CF is a progressive, lethal disease characterized by mucous build-up in the airways and a continuous annual deterioration of lung function. The host inflammatory response is considered a central pathological feature and constitutes an important target for non-steroidal anti-inflammatory drug therapy. Airway obstruction and bacterial colonization may cause inflammation, or it may be attributable to dysfunction of the cystic fibrosis transmembrane conductance regulator. Educational programs for this group of patients increase the compliance and quality-of-life, but cystic fibrosis patients have been recommended to abstain from attendance for concerns of microbial cross infection. When guidelines for optimal hand and respiratory hygiene and cough etiquette are observed in professionally supervised CF educational programs, an increased risk of bacterial transmission has not been documented. A recommendation to avoid indoor educational events with fellow CF patients must be weighed against the benefits of educational and rehabilitation programs. Further investigations are required to clarify the relative contribution of microbiological and genetic factors to the progression of CF lung disease.

Keywords: Inflammation; Cross-infection; CF educational programs

Introduction

The continuous destruction of lung tissue caused by inflammation and infection is the most serious threat to patients with cystic fibrosis (CF) [1,2]. The inflammatory response in the CF lung is complex and only partly understood. Neutrophils often undergo necrosis rather than clearance by normal apoptotic mechanisms, and the intense neutrophilic inflammation with release of proteases and reactive oxygen species damage normal host tissues [3-5]. Anti-inflammatory drug therapy is in clinical use with new compounds in various stages of development [6-9], but a major focus has been devoted to identification, typing and treatment of microorganisms cultured from airway secretions of CF patients [10-12].

Bacterial species or group	% per year [95% CI]
B. cepacia complex	-1.95 [-2.52, -1.39]
Achromobacter sp.	-1.55 [-2.21, -0.90]
P. aeruginosa	-0.95 [-1.24, -0.66]
S. maltophilia	-0.67 [-1.21, -0.13]

Table 1: Change in the rate of decline of lung function (% forced expiratory volume in 1 s) following onset of chronic infection [13].

Table 1 shows a recent assessment of the relation of accelerated decline in lung function with acquisition of chronic colonization with Gram-negative bacteria [13]. The dataset encompass more than 50 thousand lung function measurements on 432 patients during 30 years. The change in slope of lung function refers to the time point at which individuals transitioned to have more than 50% positive culture samples with a particular bacterium during 12 months. Commencement of chronic colonization was associated with a decline in lung function, with *Burkholderia cepacia* complex having the largest effect and *Stenotrophomonas maltophilia* the smallest. The relation of cause and effect is yet unproven, and the observation that chronic *Pseudomonas aeruginosa* colonization not necessarily influence the rate of decline in patients with ≥ 80% (maintained) forced expiratory volume in 1 s [14] suggest that both environmental and genetic factors modify CF lung function [15]. However, the association of chronic colonization with an accelerated decline in lung function [13,16] supports the use of early antimicrobial treatment that prevents or postpones chronic infection with *P. aeruginosa* [17,18] and Achromobacter [19].

Inhaled or aspirated microorganisms colonize the airways in a sequential order beginning with ordinary pathogens related to the commensal flora, such as *Haemophilus influenzae* and *Staphylococcus aureus*, often replaced later by *P. aeruginosa*. At later stages of the disease, environmental bacteria of limited significance to healthy individuals may ensue, such as *B. cepacia* complex and *Achromobacter* sp. [20-22]. Whereas bacteria intimately associated with the human host are acquired by contact with fellow human beings, environmental bacteria can be acquired from the natural environment such as soil, organic matter, moist and water. However, selected species, subspecies or clones of environmental bacteria possess a particular propensity to colonize the damaged airways of CF patients and may cross-infect patients. Examples include *Burkholderia cenocepacia*, which was the most commonly encountered species of genus *Burkholderia* in CF until patient-to-patient contact became limited and Burholderia-infected patients were segregated [23,24]; in contrast, *Burkholderia multivorans* is usually the most commonly reported *Burkholderia* species in clinics where bacteria are introduced by sporadic acquisition from the environment [25,26]. The Liverpool epidemic strain (LES) is a particular clone of *P. aeruginosa* that have spread among patients from

several clinics in the UK [27,28], while the Danish epidemic strain (DES) of *Achromobacter ruhlandii* has infected a substantial fraction of patients from both Danish CF centers [29,30].

In addition, patient-to-patient transmission of *P. aeruginosa* has occurred among CF patients attending summer camps [31,32], winter camps [33] and stay at a rehabilitation center [34]. Consequently, social contacts and coincidental encounters in outpatient CF clinics have been progressively restricted. Summer camps and common winter holydays are generally not supported, while segregation of outpatients has changed from focusing on particular bacterial species towards an all-inclusive strategy. The US CF Foundation now recommends that patients remain more than 6 feet (2 meters) apart from each other and wear masks in common areas of healthcare facilities [35]. A recent investigation found infrequent air contamination during clinical visits of CF patients, while the air of spirometry rooms was more likely to be contaminated with CF-respiratory pathogens [36]. The recommendation to wear masks in common areas must be weighed against several considerations, including the difficulty of children and people with respiratory distress of tolerating masks. Moreover, the US CF foundation suggest patients to avoid activities associated with transmission of CF pathogens, including social and physical contact between people with CF; only 1 person with CF should attend indoor events, while several people with CF can participate in outdoor events, providing they maintain a distance of at least 6 feet [35].

The unconditional separation of persons with CF who do not live in the same household, regardless of their respiratory tract culture results, is an obstacle to the practice of educational and rehabilitation programs for this group of patients. The intuitive solace of the awareness of fellow human beings coping with similar challenges receives scientific support from assessment of program attendees, where lung function and weight gain improved [37]. Additionally, a significant improvement of behavioral and emotional symptoms for children and adolescents were reported by parents [38]. At our center in Aarhus, Denmark, we have a long tradition of educational programs for young patients with CF. We recently assessed the putative risk of bacterial transmission by characterization and comparison of isolates cultured one year before to one year after attendance to CF educational programs [39].

Patients are grouped according to age (5-6 y, 10 y, 12-13 y, 14 y and 15-18 y old) and meet from 1 to 6 times for a period of up to 10 months. Sessions lasts 4-6 h and address theoretical lessons on health and disease, as well as physical activities and discussions of responsibility, living with CF, and dreams for the future. Physical examinations and collection of airway secretions for culture are carried out at each session. If *P. aeruginosa* has been cultured six months prior to attendance, patients receive treatment with oral ciprofloxacin and inhaled tobramycin the evening before and on the morning of educational program days. Compliance with guidelines for optimal hand and respiratory hygiene and cough etiquette is compulsory. Patients colonized with methicillin-resistant *S. aureus* or multiresistant *P. aeruginosa*, as well as certain Gram-negative non-fermenting bacteria, cannot participate in the programs. Forty-six patients aged 5–18 years attending six educational programs during 2009–2011 were analyzed. The routine visit on a monthly basis entails a high bacterial detection rate and an increased proportion of patients being positive for certain microorganisms. Notably, the regular use of laryngeal aspiration revealed an abundant presence of *H. influenzae* in young patients who rarely produce sputum (Figure 1). Thirty-two patients carried *H. influenzae* that was cultured from 201 airway secretions (1–16 samples per patient) during the study period. Pulsed-field gel electrophoresis of 201 *H. influenzae* isolates revealed that strain replacement was common. Coincidental sharing of *H. influenzae*-types was observed among five patients, who shared pulso-types with patients from programs they had not attended. However, three cases of shared pulso-types were observed among patients attending the same educational program, indicating putative transmissions of *H. influenzae*.

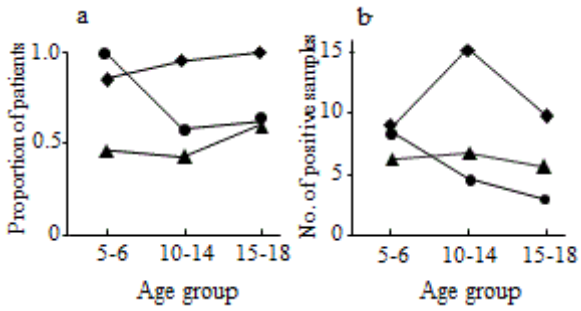

Figure 1: Culture of *H. influenzae* (circle), *S. aureus* (diamond) or *P. aeruginosa* (triangle) from 46 CF patients divided in three age groups during a period of one year before to one year after participation in an educational program. (a) Proportion of patients with one or more positive cultures, (b) average number of positive cultures among patients with one or more positive cultures.

As commonly observed, *S. aureus* was the most preponderant pathogen cultured from 613 airway secretions from 43 of 46 attendees (2–31 samples per patient). *spa*-typing of 613 isolates of *S. aureus* differentiated 78 *spa*-types. Coincidental sharing of *spa*-types was observed among 36 patients, who shared *spa*-types with patients from programs they had not attended. However, three cases of shared *spa*-types were observed among patients attending the same educational program, indicating putative transmissions of *S. aureus*.

Twenty-four patients carried *P. aeruginosa* that was cultured from 170 airway secretions (1–29 samples per patient). Pulsed-field gel electrophoresis of 170 *P. aeruginosa* isolates differentiated 28 pulso-types, but according to accepted criteria all patients carried unique types of *P. aeruginosa* not shared with any fellow attendee during the study period.

Thus, six patients experienced detection of a strain of *S. aureus* or *H. influenzae* shared with a fellow attendee. Because of limited capability for survival in the environment, acquisition of *S. aureus* or *H. influenzae* involves transfer from a fellow human or, in the case of certain strains of *S. aureus*, an animal host. Characterization of *S. aureus* isolates has revealed a clustering of clones that can be acquired in various geographic areas at various time points. The frequency of *spa*-types among educational program attendees was similar to the distribution among all patients at the center [40], and among Danish bacteremia cases (Annual Report on *S. aureus* Bacteremia Cases in Denmark, www.ssi.dk). Thus, CF patients acquire *S. aureus* types that are prevalent in the community at large, and statistical analysis is required for assessment of risk of cross-infections in relation to specific activities. This is also emphasized by the common sharing of *spa*-types among patients attending different programs. By use of a permutation

test to compare patients attending the same program with patients attending different programs and non-attendees, educational program attendance was not associated with an increased risk of sharing a strain of *S. aureus* or *H. influenzae* [39].

Four patients experienced a first-time detection of *P. aeruginosa* within 12 months after attendance. The possibility that one or more of these bacterial clones were cultured from a fellow attendee prior to the study period should be considered. However, a sequence of events involving transfer of a strain of *P. aeruginosa* that is undetectable during two years, including the sample investigated on the day of attendance, appear unsubstantiated.

The thorough characterization of strains prior to, during, and after attendance to professionally supervised CF educational programs did not document an increased risk of patient-to-patient transmission of *P. aeruginosa*, *S. aureus* and *H. influenzae*. A recommendation to avoid indoor educational events with fellow CF patients deserves careful consideration. Physical and psychological improvements after attendance are documented in the literature, and our program attendees are obviously satisfied with their participation. CF educational programs are continuously being developed at Aarhus University Hospital.

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