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Infection Control in Cystic Fibrosis

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INTRODUCTION

Over the past 20 years there has been a greater interest in infection control in cystic fibrosis (CF) as patient-to-patient transmission of pathogens has been increasingly demonstrated in this unique patient population. Furthermore, the epidemiology of pathogens in CF patients has become more complex. *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* remain the most common pathogens, but *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Aspergillus* species, nontuberculous mycobacteria (NTM), and respiratory viruses may also be pathogens in patients with CF. The delivery of health care for CF patients has shifted from inpatient to ambulatory and home settings. Patients receive repeated courses of antimicrobial agents administered orally, by aerosolization, and intravenously, which may lead to increasing antimicrobial resistance and the emergence of multidrug-resistant organisms. Screening of newborns for CF has been initiated in several states in the United States as well as in other countries, which has created a cohort of relatively healthy young infants intermingling with older CF patients in outpatient clinics. Life expectancy continues to increase; in 2001, the median survival of a CF patient increased to 33.4 years, and 37% of CF patients were adults 18 years of age or older (45–51). This has led to separate adult and pediatric CF clinics at most CF centers. These changes have had an enormous impact on infection control practices. In recognition of these changes, in May 2001 the U.S. CF Foundation sponsored a consensus conference to craft recommendations for infection control practices for CF care

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TABLE 1. The CDC and HICPAC infection control guidelines relevant to CF

Guidelines (reference)	Content
Guideline for Isolation Precautions in Hospitals (70)[a]	Standard precautions
	Transmission-based precautions
	Pathogen-specific recommendations
	Management of patients infected or colonized with multidrug-resistant organisms and other transmissible infectious agents
Guideline for Disinfection and Sterilization in Healthcare facilities (171)	Methods and indications for sterilization and disinfection of respiratory therapy equipment
Guideline for Hand Hygiene in Health-Care Settings, 2001 (23)	Use of alcohol-based antiseptic handrubs
	Use of antimicrobial-containing soap
	Educational programs to enhance adherence to recommended practices
Guideline for Environmental Infection Control in Healthcare Facilities (83)	Management of air, water, and surface to decrease the risk of transmission of infectious agents
Guidelines for Prevention of Healthcare-Associated Pneumonia (35)[a]	Transmission-based precautions for patients with pneumonia
	Care of respiratory therapy equipment
	Adjunctive measure to prevent acquisition of health-care-associated pneumonia
Guideline for Infection Control in Healthcare Personnel, 1998 (19)[b]	Recommendations for HCWs with preexisting or acquired medical conditions that could have implications for the transmission of potential pathogens
Guideline for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities (34)	Recommendations for management of patients with suspected or proven tuberculosis

[a] Under revision.
[b] Approximately 6% of patients with CF will choose health-care-related professions.

providers. The proceedings of this conference and evidence-based recommendations have been recently published (173, 174). This review provides a summary of the literature addressing infection control in CF.

INFECTION CONTROL GUIDELINES THAT APPLY TO CYSTIC FIBROSIS

A variety of infection control guidelines developed for general patient populations also have applicability to patients with CF. Before 1998, infection control guidelines were applicable to acute-care hospitals, but more recently, they include recommendations for non-acute-care settings such as ambulatory settings. This is particularly relevant to CF since care has shifted from the hospital to outpatient clinics and the home in efforts to provide chronic suppressive treatments and reduce days of hospitalization.

Guidelines with applicability for infection control in CF have been developed by the Centers for Disease Control and Prevention (CDC) with the Healthcare Infection Control Practices Advisory Committee (HICPAC), a committee of experts in infection control and health care epidemiology outside the CDC. These guidelines are listed in Table 1 and are available on the CDC website (www.cdc.gov/ncidod/hip).

GENERAL PRINCIPLES OF INFECTION CONTROL THAT ARE RELEVANT TO CYSTIC FIBROSIS

Standard precautions, transmission-based precautions, appropriate hand hygiene for health care workers (HCWs), patients, and their families, and care of respiratory tract equipment to prevent the transmission of infectious agents serve as the foundations of infection control and prevent the acquisition of potential pathogens by patients with CF.

Standard Precautious

The rationale for the practice of standard precautions is that blood, body fluids, secretions including respiratory tract secretions, nonintact skin, mucous membranes, and excretions (except sweat) can harbor potentially transmissible infectious agents. To prevent patient-to-patient or patient-to-HCW transmission of infectious agents, HCWs should observe an appropriate combination of practices (e.g., practicing hand hygiene and disinfection) and barrier precautions (e.g., wearing gloves, gown, and mask) based on the anticipated exposure when they care for a patient (Table 2). Because patient care equipment (e.g., ventilator) or items (e.g., bed rails) in the patient environment can become contaminated by infectious secretions, standard precautions extend to equipment and

TABLE 2. Standard precautions for all CF patients in all health care settings[a]

Practice and barrier precaution	Patient care activity
Hand hygiene	Before and after all patient contacts
	After touching blood, body fluids, secretions, excretions, and contaminated items
	Immediately after removing gloves
Gloves	For touching blood, body fluids, secretions, and excretions
	For touching mucous membranes and nonintact skin
	For touching contaminated equipment or patient care items
Gown, mask, eye protection, and face shield	During procedures and patient care activities likely to generate splashes or sprays of blood, body fluids, secretions, or excretions

[a] Data are from reference 70.

TABLE 3. Transmission-based precautions to prevent the spread of epidemiologically important pathogens in CF patients

Type of transmission-based precaution	Potential pathogens
Standard	Applicable to all CF patients including those infected with:
	NTM
	P. aeruginosa (not multidrug resistant)
	S. aureus (not MRSA)
Contact	Multidrug-resistant organisms
	MRSA
	B. cepacia complex
	Multidrug-resistant *P. aeruginosa*
	S. maltophilia
	Viruses
	RSV
	Parainfluenza virus
Droplet	Viruses
	Influenza virus
	Adenovirus
Airborne	*M. tuberculosis*
Protective environment	No data supporting the use of positive-pressure ventilation and >12 air exchanges for CF patients with lung transplantation; may consider in the setting of suspected transmission of *Aspergillus* spp. within a transplant center

other items in the patient's environment and apply to all patients, both with and without CF.

Transmission-Based Precautions

Transmission-based precautions are implemented for patients with documented or suspected infection with highly transmissible or epidemiologically important infectious agents that require additional precautions to prevent transmission. Categories of transmission-based precautions include contact, droplet, airborne infection isolation, and protective environment. Examples of pathogens requiring transmission-based precautions are given in Table 3.

The CF community must recognize that the respiratory secretions of all CF patients potentially harbor clinically and epidemiologically important microorganisms, even if they have not yet been detected in cultures from the respiratory tract. Such secretions can transmit infectious agents to other CF patients. Thus, HCWs must use appropriate precautions when caring for all CF patients to prevent patient-to-patient transmission of pathogens. CF patients should be educated to contain their secretions and maintain a distance of >3 ft from other CF patients to avoid the transmission of potential pathogens, even if culture results are unavailable or negative.

Hand Hygiene

Adherence to hand hygiene practices by HCWs, patients, and families is the most important practice to prevent the transmission of infectious agents. Hand hygiene must be implemented before and after all patient contacts and when respiratory secretions contaminate the hands following direct contact with patients or contact with contaminated patient equipment (Table 2). Alcohol-based hand rubs reduce bacterial contamination of hands more than handwashing with water and plain soap or antimicrobial-containing soap (e.g., chlorhexidine or triclosan) (23, 24). Therefore, alcohol-based hand rubs have become the recommended hand hygiene agents in both hospitals and outpatient settings (23). However, if hands are visibly dirty or soiled with blood or with body fluids, soap (preferably an antimicrobial-containing soap) and water should be used.

Additional components of hand hygiene include care of fingernails and the skin of hands (23). HCWs wearing artificial nails are more likely to harbor gram-negative pathogens than are HCWs with natural nails, even after washing (128). Artificial nails have been linked to outbreaks of infectious agents, including *P. aeruginosa*, in intensive care units (67, 134, 147, 148). Although studies have not documented that artificial nails play a role in the transmission of pathogens among CF patients, the experience in intensive care units can extend to CF settings. Therefore, only natural nails are recommended for HCWs in direct contact with CF patients. While there are no studies among non-HCWs, it may be prudent for CF patients and their immediate family members to avoid the use of artificial nails as well.

Care of Respiratory Therapy Equipment

Cleaning and sterilization or disinfection of reusable respiratory therapy equipment are essential to prevent infections of patients with CF. Devices used for respiratory therapy (e.g., nebulizers), diagnostic evaluation (e.g., bronchoscopes or spirometers), or treatment (e.g., medication vials) may be reservoirs or vehicles for the transmission of infectious organisms. Transmission may be due to a contaminated device itself or may from occur from patient to patient via a contaminated device or from one body site to the respiratory tract of the same patient. Aerosol-producing devices (e.g., nebulizers) may contain bacteria that can be aerosolized during use. In non-CF patients, health care-associated pneumonia has resulted from bacterial contamination of multidose medications vials due to aerosols generated by in-line and hand-held low-volume nebulizers (82, 130, 160, 176; A. Crespo, P. Axelrod, K. St. John, K. Micklow, S. Alexander, F. Austan, P. Samuel, J. Arentzen, and A. Truant, Proc. 12th Annu. Meet. Soc. Healthcare Epidemiol. Am., 267, 2002) or contamination of tap water used to rinse and fill the reservoir (35, 83). Thus, single-unit dose medication vials are always preferred, but if only multidose vials are available, the manufacturer's recommendations for handling, dispensing, and storing must be followed to avoid contamination of the vial. Sterile water is recommended because tap water may harbor NTM, fungi, *Pseudomonas* spp., or *Aeromonas* spp. (31, 35, 63, 88). Water processed through a 0.2-μm-pore-size filter to remove bacteria is acceptable, but such filtration systems are not readily available in the home and must be maintained as recommended by the manufacturer.

To date, there are no published reports of CF patients acquiring infections from respiratory therapy equipment during home use. However, several lines of circumstantial evidence suggest that contaminated respiratory therapy equipment used in the home may play a role in the acquisition of potential pathogens by patients with CF. First, contamination of home

TABLE 4. Effective methods to disinfect respiratory
equipment in the home[a]

Disinfection method	Recommended duration
Immerse in one of the following[b] (118, 170):	
1:50 dilution of 5.25–6.15% sodium hypochlorite (household bleach)	3 min
70–90% ethyl or isopropyl alcohol	5 min
3% hydrogen peroxide	30 min
or	
Boil in water (171)	5 min
or	
Use a standard-cycle dishwasher (32, 81, 169)	30 min at >158°F (70°C)
or	
Use a home microwave (2.45 Ghz) (165, 166, 175)	5 min

[a] Must be permissible by the manufacturer.
[b] These preparations lose activity with time, but the optimal storage time is unknown. For example, chlorine preparations have a 50% reduction in activity after 30 days (D. Weber and W. Rutala, personal communication).

nebulizers with bacterial pathogens (e.g., *P. aeruginosa*) has been documented, as have inadequate cleaning techniques (95, 97, 157, 168). Second, use of aerosolized medications was associated with earlier acquisition of *P. aeruginosa* in a newborn screening study (104). Third, as evidence of the importance of caring for equipment, cleaning and drying of home respiratory therapy equipment between uses decreased the risk of acquiring *B. cepacia* complex (199). Fourth, siblings should not share respiratory therapy equipment since this practice has been associated with acquisition of *B. cepacia* complex (187). Furthermore, potential pathogens from environmental sources (e.g., tap water) or colonizing flora in the oropharynx could contaminate a nebulizer and subsequently be aerosolized into the lower respiratory tract.

To prevent the acquisition of pathogens from respiratory therapy equipment used in the home, such equipment should be cleaned and disinfected by using the following steps. First, complete cleaning of the equipment prior to disinfection to remove all organic and inorganic debris is required. In experimental studies, hot water and soap removed most of the bacteria that had been experimentally inoculated into the nebulizers (168). Dried or baked debris is more difficult to remove from equipment, and disinfection or sterilization can become less effective or even ineffective (17, 129). After cleaning, reusable items that come in contact with mucous membranes (e.g., nebulizers and tracheostomy tubes) can be disinfected (if permissible as stated by the manufacturer) by one of several methods described in Table 4. Acetic acid (vinegar) has inadequate activity against some potential pathogens including gram-positive (e.g., *S. aureus*) and gram-negative (e.g., *Escherichia coli*) bacteria and is no longer recommended to disinfect nebulizers (102, 169). Of note, vinegar does kill *P. aeruginosa*. After disinfection, equipment should be rinsed with sterile or appropriately filtered water because tap water or distilled water may harbor pathogenic organisms. In the home, sterile

water can be prepared by bringing water to a rolling boil for 5 min. Distilled water should not be used because *B. cepacia* complex may contaminate the water during the manufacturing process, although the only manufacturing regulations for preparation of distilled water are to prevent contamination with coliform bacteria, (e.g., *E. coli* and *Klebsiella-Enterobacter* spp.) (124).

Thus, CF centers should promote the use of standardized protocols to clean, disinfect, and dry respiratory therapy equipment used in health care settings and should educate patients and families about the proper care of such equipment in the home.

EPIDEMIOLOGY AND TRANSMISSION OF PATHOGENS TO CYSTIC FIBROSIS PATIENTS

To date, the source of most pathogens in CF patients remains unknown. Potential reservoirs include the natural environment (e.g., soil and water), the environment in health care settings (e.g., sinks), contaminated equipment (e.g., nebulizers), other contaminated objects, and other CF patients. Patients without CF and family members without CF are not thought to transmit bacterial pathogens to CF patients. This section briefly reviews the epidemiology of common and emerging pathogens in CF and reviews the evidence for patient-to-patient transmission.

Most CF-patient-to-CF patient transmission has occurred via direct contact with infected secretions (e.g., during kissing), indirect contact with infected secretions (e.g., sharing a toothbrush, drinking from the same glass as another CF patient, or shaking hands with someone whose hands are contaminated with secretions), or via droplets (i.e., inspiration of large infectious particles that are spread by coughing, sneezing, or singing and that can be inspired within 3 ft of an infected patient). In contrast, airborne transmission of CF pathogens, i.e., inspiration of smaller infectious particles that remain suspended in shared air supplies that are transported over long distances via air currents, and that can be viable for minutes to hours, has not been documented.

While *P. aeruginosa* is the most clinically significant pathogen in patients with CF, more is known about the transmission of *B. cepacia* complex. Furthermore, assessment of risk factors for transmission and documentation of infection control strategies that work to curtail transmission have been studied for *Burkholderia*. Thus, *B. cepacia* complex serves as a prototype for infection control issues in patients with CF and is discussed first.

Burkholderia cepacia Complex

Epidemiology and clinical impact. Most of the patient-to-patient transmission studies performed to date have focused on *B. cepacia* complex. Therefore, the molecular epidemiology, routes of transmission and effective infection control interventions are somewhat better understood for this pathogen. However, some of the lessons learned from studies of *B. cepacia* complex may be applicable to other pathogens.

Two research centers in North America study the epidemiology of *B. cepacia* complex in CF patients (112, 113). The U.S. CFF *B. cepacia* Research Laboratory and Repository provides

an identification of specific species (genomovars) within the *B. cepacia* complex. In an analysis of *Burkholderia* strains from 606 CF patients from 105 cities, genomovar III, now called *B. cenocepacia* (195), and *B. multivorans* were most common and accounted for 50 and 38% of isolates, respectively (117). Molecular typing documented both intercity spread of a *B. cenocepacia* strain and persistence of this epidemic strain for 20 years in a large CF center (37). The Canadian *B. cepacia* complex Research and Referral Repository analyzed 905 isolates from 447 patients from eight Canadian provinces (183). In all, 80% of patients were infected with *B. cenocepacia* strains and 9% were infected with *B. multivorans*, but substantial regional differences were noted. Thus far, all nine species of the *B. cepacia* complex have been recovered from CF patients.

B. cepacia complex is found in soil and plants. Different species of the *B. cepacia* complex appear to occupy different niches in the natural environment, but more study of this point is needed. *B. cenocepacia* strains have been found in agricultural soil (10, 75), the maize rhizosphere (18), onion fields (116), and occasionally soil in urban settings (132). To date, *B. multivorans* has only rarely been recovered from soil samples. The risk posed by strains in the natural environment remains uncertain.

To identify a possible reservoir for *B. cepacia* complex, 916 sites within the homes of 14 CF patients and 13 controls were cultured (135). Three sites in the homes of CF patients and two sites in the homes of controls were found to harbor *B. cepacia* complex strains. *B. cepacia* complex is found in high concentrations in the sputum of CF patients and survives for prolonged periods on surfaces (57).

B. cepacia complex was first described as a pathogen in CF patients in the late 1970s and early 1980s. Initial descriptions documented the marked virulence of this multidrug-resistant pathogen, the so-called "cepacia syndrome," i.e., high fever, bacteremia, and rapid pulmonary deterioration that led to the death of 62 to nearly 100% of patients (96, 188). Thus, infection with *B. cepacia* complex can cause a decline in lung function and a shortened median survival (41, 111, 136, 167, 188, 201).

In contrast to the initial descriptions of the *cepacia* syndrome, many CF patients have chronic infection with *B. cepacia* complex and others appear to have transient or intermittent infection or colonization. At present, the proportion of CF patients with transient infection and the criteria to confirm eradication are unknown. Unidentified host and bacterial factors are possible determinants of different clinical presentations. *B. cenocepacia* may be more virulent and more likely to be transmitted from patient to patient, but further study is needed before this can be confirmed (7, 54, 123). Replacement of one strain by another has been documented (110), as has replacement of *B. multivorans* by *B. cenocepacia* with subsequent deterioration of the patient's condition (123). Among 347 patients chronically infected with *B. cepacia* complex, replacement of the infecting strain occurred in 6.6% (15).

Transmission. Patient-to-patient transmission of *B. cepacia* complex in both non-health-care and health care settings has occurred via direct and indirect contact with infected secretions and the droplet route. Numerous risk factors for transmission that reflect these routes of transmission have been described, as summarized in Table 5 (76, 112, 152, 153, 187,

TABLE 5. Factors associated with acquisition of *B. cepacia* complex

Risk factor in non-health-care settings
  Attendance at CF summer camp (114, 115, 152, 178)
    Sleeping in the same cabin
    Sharing a personal item (e.g., eating utensils)
    Dancing with or hugging a camper infected with *B. cepacia*
      complex
  Attendance at summer educational program
  Participation in a support group for adults with CF

  Social contact (55, 76, 137, 153, 178)
    Kissing
    Intimate contact
    Prolonged car rides
    Fitness class
    Sharing drinking utensils
    Handshaking

  Sibling with *B. cepacia* complex (188)

Risk factor in health care settings
  Inpatient exposures (153, 188)
    Recent hospitalization
    Use of specific shower
    Sharing hospital room with another patient infected with *B. cepacia* complex (153)
    Cared for by a medical student
  Use of respiratory therapy equipment (28, 76, 96)
    Sharing equipment
    Hospital nebulizers
    Spirometer
    Mouthpiece filters

188). Detection of patient-to-patient transmission may be delayed; a ribotype identified in CF patients cared for at different CF centers was the same as the one acquired at a CF summer educational program 2 years prior to detection (115). Similar studies from the United States, Scotland, England, and Canada demonstrated transmission associated with close contact in social settings and led to the disbanding of CF summer camps worldwide (33, 76, 114).

Transmission of *B. cepacia* complex in health care settings has been documented (153, 191). Acquisition of *B. cepacia* complex has been associated with recent hospitalization (153), poor adherence to handwashing (90, 153), contaminated respiratory therapy equipment (90, 162), and possibly contaminated hospital showers (137, 153). Dental care has not been linked to acquisition of *B. cepacia* complex (145). During a 3-month study period, 73 throat cultures from seven HCWs remained negative for *B. cepacia* complex (59).

While direct, indirect, and droplet spread are well-known routes of transmission for *B. cepacia* complex, true airborne transmission seems less likely. Air samples obtained in rooms before, during, and after chest physiotherapy were positive in 16, 47, and 44% of instances, but the air was sampled within the 3-ft range defined for droplet transmission (60). Other studies have detected *B. cepacia* complex in air samples under a variety of experimental conditions. Samples obtained 15 to 45 min after patients left the room were positive for *B. cepacia* complex, but those obtained at 60 min were negative (92). Very low counts (1 CFU/mm^3) of *B. cepacia* complex were detected in 2 of 29 air samples obtained 39 in. from patients' mouths

(93). In contrast, *B. cepacia* complex was not detected from the air samples from the rooms of patients infected with *B. cepacia* complex (28), within 39 in. of patients undergoing chest physiotherapy, or in a clinic waiting room (76, 153). To date, transmission of *B. cepacia* complex has not been documented among CF patients who used the same air supply but did not have contact within 3 ft of each other.

Virulence factors associated with transmission. There has been a great deal of interest in understanding the potential virulence factors linked to patient-to-patient transmission. The spread of *B. cenocepacia* strains has been linked to the cable pili (*cblA*) (186) or the *B. cepacia* complex epidemic strain marker (BCESM) (122). The *cblA*-encoded pili is expressed by the *B. cenocepacia* strain ET12 clone that caused outbreaks in Canada and the United Kingdom (186). The BCESM is expressed by other *B. cenocepacia* strains and has been linked to patient-to-patient spread in Canada (183). Thus far, only *B. cenocepacia* strains have been shown to express these transmissibility markers (123). However, the ET12 strain is rarely found in CF patients in the United States and patient-to-patient transmission of strains that do not express either the cable pili or BCESM has been documented, suggesting that other virulence factors may be responsible (37, 117). Chen et al. described an epidemic strain, PHDC, which has been linked to patients cared for in most CF centers in the mid-Atlantic region of the United States (37) and has been found in agricultural soil samples (116).

Potential clinical impact of different genomovars. Several studies have investigated potential differences in the clinical impact of different genomovars. As described above, *B. cenocepacia* appears more likely to be spread from patient to patient and to be associated with outbreaks than are other genomovars (40, 117). However, patient-to-patient transmission of *B. multivorans* has been described in a referral center for lung transplantation (84). *B. cenocepacia* is more likely to replace other members of *B. cepacia* complex (37, 110, 123) and to confer increased morbidity and mortality in CF patients following lung transplantation (7).

Successful infection control interventions. Numerous infection control interventions have been successful in preventing the transmission of *B. cepacia* complex. It is difficult to assess the relative impact of individual interventions since multiple interventions were usually used simultaneously. These interventions are described in Table 6. One of the most widely practiced and successful strategies is the practice of segregation of patients infected with *B. cepacia* complex, i.e., keeping such patients apart from other patients with CF, including those harboring *B. cepacia* complex. Patients with *B. cepacia* complex must avoid contact with each other because strains that are potentially more virulent may replace an initial infecting strain (15, 37, 110, 123). Ongoing transmission of epidemic clones has been documented in clinics that did not implement segregation (37, 69, 149).

To date, studies have not demonstrated that patient-to-patient transmission of potential pathogens has been prevented by routinely placing surgical masks on CF patients. The incidence of *B. cepacia* complex has been decreased without the use of masks (191), but the efficacy of mask use by CF patients has not been studied for other pathogens (e.g., *P. aeruginosa*). However, mask use by patients can prevent droplet transmis-

TABLE 6. Infection control interventions associated with decreased transmission of *B. cepacia* complex among CF patients

Category of intervention	Specific intervention
Education (37, 69, 149, 191, 204)	Emphasize hand hygiene for CF patients and HCWs
	Educate patients, families, and HCWs about risk factors for transmission of *B. cepacia* complex
Intervention in health care setting (37, 69, 76, 149, 152, 153, 185, 191, 201)	Use single-patient rooms with separate showers, for hospitalized patients with *B. cepacia* complex
	Eliminate socializing between CF patients infected with *B. cepacia* complex and other CF patients while in hospital
	Place hospitalized patients with *B. cepacia* complex on contact precautions
	No CF patients should share rooms
	Inpatients and outpatients should wear masks
	Inpatients should wear gloves
	Segregate outpatient clinics; i.e., *B. cepacia* complex patients attend a different clinic or on a different day
	Ban patients with *B. cepacia* complex from attending CF conferences
Environmental decontamination (37, 69, 149, 191, 204)	Decontaminate the environment, including respiratory equipment
	Monitor environmental decontamination (e.g., drains, showers, exercise equipment, and physiotherapy equipment)
Laboratory practices (69, 191)	Improve microbiological detection, including the use of selective media and prolonged incubation
Intervention in non-health-care setting (69, 76, 149, 191)	Reduce social contact between patients infected with *B. cepacia* complex and other CF patients in non-health-care facilities
	Provide separate summer camps for CF patients with *B. cepacia* complex[b]

a Thomassen et al. (191) admitted patients with *B. cepacia* complex to a different hospital ward.
b It is recommended that CF summer camps be discontinued.

sion of infectious agents such as influenza virus, *Bordetella pertussis*, and adenovirus (35, 70).

In summary, *Burkholderia* species can be transmitted from CF patient to CF patient in both non-health-care and health care settings. Prolonged close contact between CF patients, sharing of equipment, and intrinsic bacterial factors can facilitate transmission. Accurate identification and molecular typing can be provided by reference laboratories. Numerous interventions have successfully prevented transmission, but it is difficult to assess the relative contribution of an individual intervention. Thus, CF patients infected with *B. cepacia* complex must avoid close contact with other CF patients, including those harboring *B. cepacia* complex, to avoid acquiring potentially more virulent strains.

Pseudomonas aeruginosa

Epidemiology and clinical impact. *P. aeruginosa* is the most common and clinically important pathogen in patients with CF.

By adulthood, over 80% of patients are infected with this pathogen, which adversely affects lung function and survival (2, 91, 105, 138). Children infected with *P. aeruginosa* have poorer pulmonary function, worse chest X-ray scores, and reduced 10-year survival than do children who are not infected with *P. aeruginosa* (91). Similarly, infants identified by a screening program of newborns for CF who became infected with *P. aeruginosa* had a lower National Institute of Health clinical score, worse pulmonary function, and more hospital days (138). The mucoid phenotype has been associated with a deterioration in lung function (85, 146) and early death (138). Over time, *P. aeruginosa* strains become increasingly resistant to antimicrobial agents and effective therapy becomes progressively more difficult (172).

Most CF patients harbor the same clone of *P. aeruginosa* throughout their lives (121, 140, 163). However, an individual patient may harbor more than one clone (139). Patients who are treated with antimicrobial therapy to eradicate *P. aeruginosa* may have recurrent infection with the initial strain after transient suppression (203).

Transmission. Numerous studies have attempted to identify the initial source of *P. aeruginosa* in CF patients, but this remains unknown for most patients. *P. aeruginosa* can survive for prolonged periods; nonmucoid strains suspended in saline can survive on dry surfaces for 24 h, mucoid strains can survive 48 h or more (55, 204), and strains suspended in sputum of CF patients can survive on dry surfaces for as long as 8 days (55).

(i) Potential sources. *P. aeruginosa* has been recovered from environmental sources in both in- and outpatient health care settings, and possible transmission of these strains to patients has been studied (21, 55, 204). Numerous strains exhibiting great genetic variability have been isolated in and around water sources including sinks and tap water in a pediatric ward for CF patients (55, 164); toys, baths, and hand soaps (204); and pulmonary function test machines and hospital drains (181). On occasion, strains detected in the health care environment matched strains in patients, but it is unclear if patients were the initial source of environmental contamination or if the strains originated from the contaminated source (20, 55, 203). In contrast, a shared strain of *P. aeruginosa* demonstrated among adult patients could not be recovered from repeated cultures of sinks, drains, toilets, showers, and communal surfaces (126). *P. aeruginosa* can be cultured from the hands of HCWs and CF patients (55, 181, 204). Studies of experimental handwashing demonstrated that hands became contaminated with the *P. aeruginosa* strains that contaminated sink drains (55, 56).

The role of home nebulizers in transmitting potential pathogens has been studied. A significant proportion (25 to 55%) of home nebulizers were contaminated with *P. aeruginosa* (157, 168) or other potential pathogens, e.g., *Klebsiella* spp. and *B. cepacia* complex (95, 97).

Other potential sources of *P. aeruginosa* include whirlpools, hot tubs (16, 65), swimming pools, or dental equipment, but none of these sources have been linked conclusively to acquisition by patients with CF. In contrast, adequately chlorinated swimming pools do not harbor *P. aeruginosa* (65, 77). Dental equipment can be contaminated with *P. aeruginosa* (98), but standard cleaning and disinfection/sterilization procedures of dental equipment eliminate potential pathogens.

Other investigators have assessed the role of droplet and airborne transmission. Droplet transmission has been demonstrated by isolating *P. aeruginosa* from agar plates placed 1.25 to 3 ft from a coughing CF patient (55, 204). In contrast, true airborne transmission of *P. aeruginosa* has not been documented. Air samples from CF clinics and hospital rooms obtained by an air sampler have yielded contradictory results (181, 203, 204). It is unlikely that *P. aeruginosa* in the sputum of a CF patient could remain suspended in the air for long enough to be transmitted to other CF patients sharing the same air supply.

(ii) Patient-to-patient transmission. Evidence of patient-to-patient transmission of *P. aeruginosa* has been sought by investigators worldwide. The best documentation of shared strains of *P. aeruginosa* among CF patients has been noted between siblings with CF (79, 181, 191, 203). There have been several reports of shared strains of *P. aeruginosa* among CF patients linked to non-health-care settings, including recreational summer camps (66, 139, 203).

In addition, health-care-associated transmission of *P. aeruginosa* has been observed. In the 1980s, a Danish CF center reported an epidemic, multidrug-resistant strain of *P. aeruginosa*, as confirmed by serotyping and phage typing. In contrast, pulsed-field gel electrophoresis (PFGE) typing of this epidemic clone identified two strain clusters, highlighting the need for discriminatory typing techniques. Implementation of several infection control measures was associated with a decreased incidence and prevalence of *P. aeruginosa* infection (140, 151). The measures included a separate clinic for patients infected with *P. aeruginosa*, emphasis on good hand hygiene for patients and HCWs, and establishment of a larger clinic (68, 89, 150).

Patient-to-patient transmission has been documented in Germany (94) and the United Kingdom (38). In the United Kingdom, investigators became aware of patient-to-patient transmission when resistance to ceftazidime increased even among patients who had never received this agent. PFGE and a probe for the flagellin gene of *P. aeruginosa* demonstrated that 85% of children harboring strains of *P. aeruginosa* that were resistant to β-lactam agents had acquired a clone that had been present in this clinic population for at least 7 years. Transmission of *P. aeruginosa* among adults with CF has also been described (101, 126). In two different CF centers in the United Kingdom, a multidrug-resistant *P. aeruginosa* strain "superinfected" patients previously infected with other strains (101). While no social contact occurred between these patients outside of the clinic, nearly all had been inpatients during the previous 2 years. The epidemic strain was not isolated from patients coinfected with *B. cepacia* complex and *P. aeruginosa* (since they had been segregated for 8 years due to their infection with *B. cepacia* complex), from non-CF patients infected with *P. aeruginosa*; or from environmental cultures of the inpatient or outpatient units.

In Australia, early mortality was noted in four children infected with a mucoid, multidrug-resistant strain of *P. aeruginosa* acquired from older children attending the same CF clinic (138). In the United States, the time to acquisition of *P. aeruginosa* was shorter in infants diagnosed by neonatal screening for CF than in those diagnosed due to symptoms consistent with CF (62). Investigators attributed this to crowded clinic condi-

tions in one center; care in that center and aerosol use predicted the acquisition of *P. aeruginosa*, while higher levels of maternal education proved protective (104). In contrast, several investigators failed to detect patient-to-patient transmission of *P. aeruginosa* in non-health-care (184) or health care (121, 181, 202) settings.

To our knowledge, only one case report has described the transmission of *P. aeruginosa* from a patient with CF to her non-CF parents, both of whom carried a CF mutation but did not have CF (126). Both parents developed pneumonia and became chronically colonized with the epidemic strain (described above) circulating among adult patients in the United Kingdom (127). This suggests that this strain has unique virulence properties worthy of study.

In summary, it has been documented that CF patients can harbor the same strains of *P. aeruginosa*. No epidemiologic studies have confirmed the acquisition of *P. aeruginosa* from the environment. Patient-to-patient transmission generally results from prolonged social contact such as that between siblings or close friends (182). Most probably, there is strain variation in transmission potential, as has been noted for strains of *B. cepacia* complex. While the routes of transmission are not fully understood, infected respiratory secretions may contaminate the health care environment, which then serves as a potential reservoir for *P. aeruginosa*. Crowded physical conditions and the contaminated hands of HCWs may further facilitate transmission.

Staphylococcus aureus

Epidemiology and clinical impact. *S. aureus* is often the first pathogen to infect the respiratory tract of CF patients. In the preantibiotic era, *S. aureus* and *H. influenzae* caused substantial morbidity and mortality in infants with CF (6), but with the advent of antibiotic therapy effective against these pathogens, the life expectancy of infants with CF has increased (6).

Colonization of the anterior nares with *S. aureus* is an important risk factor for subsequent disease with the same genotype in CF and non-CF patients (74, 154, 155, 197). CF patients without recent treatment with antibiotics had a higher prevalence of nasal colonization with *S. aureus* than did CF patients receiving recent treatment or healthy controls (74). *S. aureus* strains spread within families, but loss or replacement of a strain was frequently observed in families with and without a family member with CF. In contrast, CF patients may be infected or colonized with the same strain of *S. aureus* for at least 1 to 2 years (25).

An increase in the prevalence of methicillin-resistant *S. aureus* (MRSA) has been noted in CF patients. In 2001, 7% (range, 0 to 23%) of CF patients reported to the U.S. CFF National Patient Registry had MRSA isolated from their respiratory tract (51). The proportion of CF patients with MRSA was substantially higher than among those who were hospitalized than among those who were not, probably reflecting differences in age, underlying severity of illness, antimicrobial exposure, and health-care-associated acquisition (14).

The clinical impact of MRSA in CF patients remains uncertain. Children with MRSA received more courses of intravenous antibiotics but had worse chest X-ray findings at baseline, suggesting an overall increased severity of illness. However,

MRSA did not affect growth or lung function (131). Adults with MRSA had poor lung function, but colonization was frequently brief (22, 190). In contrast, the same clone of MRSA can persist in an individual CF patient for years (73).

Transmission. Patient-to-patient transmission of *S. aureus* can occur. Methicillin-susceptible *S. aureus* was shared among CF patients attending a summer camp (177). Transmission of MRSA from patient without CF to CF patient and from CF patient to CF patient has been reported and was facilitated by hospitalizing CF patients on general medical wards (73). Therefore, policies to prevent patient-to-patient transmission of MRSA must be applied to CF patients who are colonized or infected with MRSA (70).

Emerging Pathogens: *S. maltophilia* and *A. xylosoxidans*

S. maltophilia and *A. xylosoxidans* may be emerging pathogens in CF patients, and it is critical to establish the transmissibility of these microorganisms.

The overall prevalence of *S. maltophilia* in American CF patients is 8.4% (51), but there are significant differences among CF care centers. In 2001, 11 (9%) of 117 CF centers reported that no patients harbored *S. maltophilia* while other CF centers reported that 25% of patients did so (52, 53). The CF patient registry may underestimate the prevalence of *S. maltophilia* colonization and infection due to variable use of selective media and incomplete identification of gram-negative bacilli (44). However, the prevalence of *S. maltophilia* in CF patients may be increasing (189). Chronic treatment with oral, aerosolized, and intravenous antimicrobial agents is a risk factor for acquisition of *S. maltophilia* (189). In 1997, the prevalence of *A. xylosoxidans* in U.S. CF patients was only 2.7%; in 2001, it was 4.4%.

The pathogenicity of *S. maltophilia* (178, 185, 196) and *A. xylosoxidans* in CF is not yet established, although an association of these microorganisms with pulmonary exacerbations has been reported (58, 61).

Potential transmissibility. Several studies have sought to define the transmissibility of *S. maltophilia* in patients with CF by using PFGE and PCR-based methods to examine isolates from a single CF center or hospital or sequential isolates from an individual patient (52, 53, 58, 133, 194, 198). In two studies, isolates from different patients were unique but the same genotype persisted in an individual patient (194, 198). The homes of both colonized (36% positive) and noncolonized (42% positive) CF patients, the hospital ward (32% positive), and the CF clinic (17% positive) were contaminated with *S. maltophilia*, and clinics may harbor the same clone for a year (54). At three of six U.S. centers, two patients at each were infected or colonized with the same clone of *S. maltophilia*, although two pairs did not have a known epidemiologic link (107). Similarly, in Spain, three patients with CF harbored the same strain of *S. maltophilia* (194).

The molecular epidemiology of *A. xylosoxidans* has not been well studied. Two studies failed to identify shared isolates among CF patients (58, 198), but a third study found that two of eight chronically infected patients did harbor the same strain genotype of *A. xylosoxidans* (133). Although an environmental source was not identified, the patients had been hospitalized at the same time. Similarly, five of seven U.S. centers

had patient pairs with the same isolate. Some epidemiologic links were found; two pairs were siblings, and one pair consisted of friends hospitalized at the same time.

Nontuberculous Mycobacteria

Over the past 15 years, there have been increasing reports that CF patients may become infected or colonized with mycobacterial species, most commonly NTM. In single-center studies, the prevalence has varied from 3 to 28% depending on the patient population studied and the culture technique used (3, 87, 103, 144, 179). A multicenter study of 986 American CF patients aged 10 years or older was conducted from 1992 to 1998 and the overall prevalence of NTM was 13%, but among these 21 sites, the prevalence ranged from 7 to 24% (143). *Mycobacterium avium* complex was the most common (70%) followed by *M. abscessus* (16%). Many patients appeared to have transient carriage since repeat cultures were negative (142). The clinical impact of these organisms in CF patients is uncertain since some investigators have reported no adverse clinical consequences in patients with positive sputum cultures for NTM (141). However, other reports indicated that patients with positive cultures and clinical lung disease have responded to antimycobcterial therapy and that caseating granulomas were demonstrated on biopsy or at autopsy in patients with clinical disease (43, 192). Olivier et al. studied 60 patients with newly detected NTM infections and compared their pulmonary function and chest computed tomography findings with those of 99 control subjects without NTM (142). Patients infected with NTM did not have an increased decline in lung function during the 15-month study period but did have at least two computed tomography findings that were consistent with NTM. Patients with *M. abscessus* (4 of 7; 57%) were more likely to meet the American Thoracic Society criteria (5) for disease than were patients with *M. avium* complex (14/45, 31%).

Risk factors for NTM colonization and infection in CF patients have included the use of intravenous and aerosolized antibiotics (193). Patients harboring NTM were found to be older and to have better lung function, a higher frequency of *S. aureus*, and a lower frequency of *P. aeruginosa* than patients who had negative cultures for mycobacteria (143).

Very few studies have used molecular typing of NTM isolates to examine the possibility of patient-to-patient transmission among CF patients; thus far, shared strains have not been consistently demonstrated in these studies (11, 143).

In summary, CF patients are at increased risk of colonization or infection with mycobacteria. The majority of these bacteria are NTM, but *M. tuberculosis* may also infect CF patients. To prevent patient-to-patient spread of *M. tuberculosis* and to direct appropriate treatment, acid-fast bacilli must be identified to the species level. Therefore, CF patients whose sputum smears contain acid-fast bacilli must be placed in airborne infection isolation rooms until *M. tuberculosis* has been excluded.

Fungi and Molds

Epidemiology and clinical impact in CF patients. The annual prevalence of *Aspergillus* as reported in 2001 was 10.6%.

However, in a multicenter study using a research laboratory, 24.5% of patients aged 6 years or older harbored *Aspergillus* spp. (29). Most isolates were *A. fumigatus*, although some CF patients harbored other *Aspergillus* spp. and, rarely, other molds. *Aspergillus* spp. can colonize the lungs of CF patients and, in some, can cause allergic bronchopulmonary aspergillosis (APBA). There have been rare case reports of aspergilloma and invasive aspergillosis in CF patients who were not lung transplant recipients (27, 120). The prevalence of ABPA in CF patients is poorly defined, in part due to the difficulties in making the diagnosis. However, the prevalence rates reported from large multicenter databases in North America and Europe were 2 and 7.8%, respectively (71, 125). Among adult patients with CF, prophylactic antibiotics (both oral and aerosolized agents) were risk factors for colonization with *Aspergillus* spp. but the lung function was not decreased in colonized patients (12). Similarly, more frequent acquisition of *Aspergillus* spp. occurred among patients receiving aerolized tobramycin (18%) than among the patients in the placebo group (8%), but ABPA and fungal pneumonia did not occur (30).

The prevalence and clinical impact of other molds are not well studied. Overall, 2.4% of patients participating in an aerosolized tobramycin trial were found to harbor saprophytic fungi other than *Aspergillus* spp. (29). A recent European study reported that the incidence of *Scedosporium apiospermum* was 8.6% over 5 years (39).

Transmission of *Aspergillus* spp. *Aspergillus* infections are acquired from environmental exposures, and exposure to *Aspergillus* spp. cannot be completely prevented because they are ubiquitous in nature. However, prolonged intense exposure can be limited. High concentrations of spores may become aerosolized during construction or renovation within health care facilities or during gardening and lawn cutting. Water leaks that are not completely dried within 72 h may be a source of *Aspergillus* spp. in the health care environment (83). Therefore, specific recommendations for dust containment during construction and renovation and drying of leaks must be implemented to minimize the exposure of vulnerable patients, including CF patients who have received solid-organ transplants, to *Aspergillus* spores (13, 83).

Respiratory Viruses

Respiratory viruses are important pathogens in patients with CF. Viruses such as respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, adenovirus, and rhinoviruses have relatively short incubation periods (less than 1 week), and transmission occurs primarily via direct contact with infected persons or indirect contact by touching items handled by infected persons. Droplet transmission of infectious respiratory secretions occurs with influenza virus and adenoviruses. As with non-CF patients, viral particles enter the mucous membranes of the eyes and nose of susceptible patients and multiply in the respiratory epithelium, subsequently decreasing ciliary movement and increasing mucus production (35, 70).

Children with CF are not more susceptible to viral respiratory tract infections than their siblings without CF or age-matched controls (86, 161). However, respiratory viral illnesses can be more severe in patients with CF. Infections of the lower respiratory tract, hospitalization (2, 86, 159, 200), and de-

creased pulmonary function may follow viral infections in infants with CF (2, 86). Viral respiratory infections may predispose CF patients to bacterial infection, although the pathophysiology of this observation is not well understood (8, 86, 180). The number of viral infections per year and the progression of pulmonary disease in CF patients are correlated (200).

Respiratory syncytial virus. RSV can cause severe acute illness, requiring prolonged hospitalization and mechanical ventilation and resulting in residual impairment in lung function in CF patients (1, 8, 86). Cost-effective infection control strategies that reduce the incidence of health-care-acquired RSV infection include rapid diagnostic testing, placement of patients in a single room or placement of RSV-infected patients together, adherence to standard precautions plus contact precautions, screening of visitors for signs and/or symptoms of respiratory tract infection, and active surveillance for RSV infection (119).

Prophylactic strategies are available for RSV infection, and some are being studied in patients with CF. These include RSV intravenous immune globulin and an RSV monoclonal antibody, palivizumab, administered intramuscularly monthly throughout the RSV season (4). Several investigators have suggested that infants with CF should be considered for RSV prevention by using RSV immune globulin or palivizumab. A safety trial of palivizumab has been conducted with 106 infants with CF, but these results are pending (8, 9, 86; P. Campbell, personal communication). Studies using an investigational RSV subunit vaccine in CF patients are also being performed (156).

Influenza virus. Influenza infection can cause deterioration in lung function and increased hospitalization among patients with CF (64, 159). Influenza vaccine is safe and effective in CF patients (78, 80) and is recommended for all CF patients 6 months of age or older and the close contacts of all CF patients (26).

Other respiratory viruses. Adenovirus, rhinovirus, and parainfluenza viruses can cause pulmonary disease in patients with CF (2, 86, 180). Adenovirus infection leads to worsening lung function and increased airway obstruction after the acute phase of illness (86). The impact of rhinoviruses on CF patients has not been studied, but rhinoviruses can cause exacerbations of asthma, including severe episodes requiring hospitalization (72).

ADHERENCE TO INFECTION CONTROL GUIDELINES

Crafting evidence-based infection control guidelines is only the first step in preventing health-care-associated infections. It is increasingly recognized that it is critical to measure the dissemination, implementation, and potential impact of guidelines to monitor changes in practice and reduction in infections. For example, HCW adherence to recommended hand hygiene practices occurs less than half the time despite the documented clinical effectiveness and cost savings of this practice (23, 24). Similarly, despite the efficacy and cost savings of contact precautions for controlling bacterial (e.g., MRSA [36, 99, 100]), or viral (e.g., RSV [109, 119]) infections, HCWs do not adhere to recommended barrier precautions.

Therefore, it is critical to implement measures to improve

TABLE 7. Barriers to HCW adherence to infection control guidelines for CF patients

Barriers[a]	Examples of reasons cited by HCWs for nonadherence
Knowledge	Lack of awareness of or familiarity with guideline
	Lack of time to review the guidelines
	Lack of understanding of the mode of transmission of pathogens and effective measures to interrupt transmission
Attitude	Lack of agreement with guidelines in general
	Lack of understanding or belief that the recommended practices are effective or applicable to every institution
Practice	
Patient factors	Adverse psychosocial impact on patients
	Concern that use of gloves, masks, and gowns:
	Impersonalize care
	Increase patient anxiety
	Decrease the frequency of HCW-patient contact
Guideline factor	Inconvenient to don appropriate barrier protection (e.g., gloves and gowns)
Environmental factors	Lack of time to implement the guideline
	Cost of supplies
	Lack of support from health care leaders and administrators

[a] Data are from references 23, 24, 106, and 158.

adherence to infection control practices (23, 24). Educational programs with the visible support of administrators have improved adherence to recommended hand hygiene practices and decreased MRSA and VRE infections (23, 24, 108, 158). To sustain new guidelines, it is essential to provide ongoing administrative support, monitor infection control practices, track the incidence of new infections with target pathogens, and provide feedback to workers. It is recognized that the members of the CF community are strongly motivated to embrace preventive programs, but barriers to adherence to infection control guidelines at CF centers must be identified and overcome. Examples of barriers to adherence to infection control guidelines are described in Table 7 (23, 24, 106, 158). Involvement of CF patients and their families in the implementation of measures in health care and non-health-care settings will be helpful as well.

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