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REVIEW

Infection prevention and control in cystic fibrosis: a systematic review of interventions

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ABSTRACT

Introduction: Cystic fibrosis is a life-limiting genetic condition characterized by recurrent pulmonary infection. Acquisition of infection can occur from environmental reservoirs, person-to-person transmission and from the healthcare environment. Primary prevention of infections through infection prevention and control measures is an important strategy in cystic fibrosis care.

Areas covered: Here we present a systematic review of the evidence base around infection prevention and control in cystic fibrosis. We found 36 studies and 7 guidelines that met our inclusion criteria. Strategies covered include cohort segregation, individual segregation, hand hygiene, facemasks, combination strategies, equipment strategies, and adherence. Quality of evidence overall was deemed low or very low. Most guideline recommendations have little or no evidence to support them.

Expert opinion: Although low quality, there is an abundance of evidence suggesting segregation is beneficial in reducing pathogen spread. Undertaking high-quality studies may, therefore, be ethically challenging. Large-scale registry studies may provide a better strategy for answering questions on the efficacy of infection control policy. With the rise of antibiotic resistance, effective eradication of cystic fibrosis pathogens is becoming more difficult so primary prevention through infection control will become increasingly important over the coming years.

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Cystic Fibrosis; infection prevention and control; systematic review

1. Introduction

Cystic fibrosis (CF) is the commonest autosomal recessive life-limiting condition in Caucasian populations, affecting between 70,000 [1] and 100,000 [2] people worldwide. Median age of death and median predicted survival have both increased significantly over recent decades [3]. The CF gene is located on chromosome 7 and mutations lead to absence or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein which forms a chloride channel in cell membranes in many body systems. In respiratory epithelial cells, lack of CFTR function leads to failure of the mucociliary escalator, stasis of respiratory secretions and opportunistic infection. CF is characterized by a cycle of recurrent pulmonary infection, inflammation and tissue damage which may ultimately lead to respiratory failure and death [4].

The prevalence of respiratory organisms affecting individuals with CF changes from infancy, through childhood and into adult life [2]. In preschool children, the commonest respiratory infections are *Staphylococcus aureus* and *Haemophilus influenzae*. In older children, intermittent infection with *Pseudomonas aeruginosa* (PA) becomes more prevalent and over half of the individuals with CF will have a chronic pulmonary infection with this organism by their early twenties [1,2]. Some strains of PA are antibiotic resistant and transmissible between patients [5]. Infection with PA is associated with a greater risk of death and a more rapid decline in lung function in people with CF [6]. Eradication of early infection with PA can delay the onset of chronic infection. Once the chronic infection has developed, eradication is impossible [7]. The prevalence of some organisms varies greatly between countries. Methicillin-resistant *S. aureus* (MRSA) is present in around 3% of adults with CF in the UK [2] but in the US [1] the prevalence reaches over 30%. Other organisms are less prevalent but are highly antibiotic resistant with evidence of transmission. This category includes *Burkholderia cepacia* complex (BCC) and non-tuberculous mycobacteria (NTM), particularly *Mycobacterium abscessus* complex. Finally, a number of gram-negative organisms are found in sputum samples from CF individuals whose status as a CF pathogen has not yet been fully established, including *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*.

Infection in the CF airways drives inflammation and leads to bronchiectasis. Effective treatment is limited by antibiotic resistance and the favorable niche provided by the CF lung. Primary prevention of these infections, through infection prevention and control, is, therefore, an important strategy. Prevention requires an understanding of how pulmonary infection is acquired in CF, and the evidence behind different modes of acquisition will be briefly considered here under the following headings:

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Supplementary data for this article can be accessed here

Article highlights

- Recurrent pulmonary infection in cystic fibrosis can lead to tissue damage and ultimately respiratory failure and death.
- Acquisition can occur through person-to-person transmission, from the healthcare environment and environmental reservoirs.
- There is an abundance of low-quality evidence to support cohort and individual segregation measures as methods to prevent transmission between patients.
- Face masks are effective at reducing the release of potential infective Pseudomonas aerosols and are tolerable to participants in studies of adults with cystic fibrosis.
- With the rise of antibiotic resistance, primary prevention through infection control will become increasingly important.

- Out of hospital acquisition through environmental reservoirs
- Person to person transmission
- Acquisition from the healthcare environment

1.1. Out of hospital acquisition through environmental reservoirs

Many CF pathogens, including PA, NTM, and BCC are found in soil and water. They may also contaminate similar environments in the home. PA has been found in the home environment, commonly in sinks and drains [8,9]. However, in only 9 out of 50 patients with acute PA infection was an identical strain isolated in both the patient and their home environment [9]. Outside the home, swimming pools [10] and paddling pools [11] may be contaminated with PA, though regular use of a swimming pool has been found to reduce the risk of PA acquisition in CF and use of hot tubs had no effect [12]. Living in a location with warmer temperatures, greater humidity, and increased rainfall also increases the risk of acquisition of PA, whilst living further from the equator reduces the risk [13]. Geography also plays a part in NTM infection. In the US, the prevalence of NTM in CF patients is greatest in states in the West or the South East of the country and prevalence increases with increasing humidity [14]. In the US [1], NTM infection in people with CF is mainly *Mycobacterium avium* complex whereas, in the UK [2], *M. abscessus* complex predominates. For BCC there is no phenotypic correlation between clinical and soil isolates [15], though a study of clinical and agricultural *B. cenocepacia* samples found strains from onion rhizospheres that were identical on multilocus sequence typing (MLST) to the PHDC clinical strain [16].

1.2. Person to person transmission

Transmission of an antibiotic-resistant strain of PA was first documented in the CF center in Copenhagen in 1986 [17]. Ten years later, genomic finger-printing techniques showed that a beta-lactam resistant clone of PA was responsible for an outbreak in a CF center in Liverpool [5]. This was subsequently named the Liverpool Epidemic Strain and carries a worse prognosis than infection with 'unique' strains of PA [18]. The pivotal study of newborn screening for CF found that an increase in PA infection, amongst infants diagnosed through screening, was attributable to one of two study centers allowing mixing of young children with older patients. The median time from diagnosis by newborn screening to PA acquisition was 289 weeks in the center which employed segregation versus 52 weeks in the center which did not [19]. More recently, whole genome sequencing has shown transmission of multidrug-resistant NTM between patients with CF at a center in Cambridge, despite infection control measures [20]. The route of transmission was uncertain, but epidemiological analysis suggests this may be indirect. There is also evidence for person to person transmission of BCC. Govan *et al.* [21] used pulsed-field gel electrophoresis to identify a *B. cenocepacia* clone, subsequently named ET12, as the source of an outbreak involving two UK CF Centres. Significant social contact both within and outside of the CF Centre was blamed for transmission [21].

Environmental contamination by the Liverpool Epidemic Strain of PA was detected on respiratory equipment in the immediate vicinity of infected CF patients and in air samples taken from the patient's room and the corridor outside [22]. Although this epidemic strain of PA could survive longer than other PA strains on dry surfaces, no environmental reservoir was found. The researchers concluded that airborne dissemination is an important mechanism of the patient to patient spread for this organism. The Liverpool Epidemic Strain of PA (which is highly antibiotic resistant) has the ability to cause superinfection in CF patients who already have chronic infection with another strain of PA (which may be less resistant) [22]. These observations demonstrate that cohort segregation of CF patients by organism may still allow patients to acquire a strain of the same organism which is more difficult to treat and carries a worse prognosis. More recent studies have investigated the potential for CF patients to generate infected aerosols and droplet nuclei, as well as looking at how far these infectious particles travel and how long they can persist. A droplet nucleus (originally described in tuberculosis) is the residue of a cough aerosol droplet which is left after evaporation and which contains any organisms present in the original aerosol. Droplet nuclei remain airborne in air currents found in any occupied room and are rapidly dispersed [23]. Wood and colleagues [24], used an Andersen impactor to study cough aerosols in CF. The majority of CF patients studied were found to produce aerosols containing PA during coughing, in contrast to talking which produced little viable organism. Aerosols produced by CF patients during coughing contained PA in droplet nuclei of respirable size (<4.7 μm). These investigators also studied the effect of patients wearing a mask, and we discuss this below in the results of our systematic review. The airborne transmission of other organisms has been investigated using the same approach. *S. aureus* (both sensitive strains and MRSA) and gram-negative bacteria (including *Burkholderia* species, *S. maltophilia* and *Achromobacter* species) are aerosolized during coughing, can travel up to 4 m and remain viable within droplet nuclei for up to 45 min [25] as can *M. abscessus* complex [26].

1.3. Acquisition from the healthcare environment

In an environmental study from a pediatric ward in Germany [27], the majority of sink drains were found to be contaminated with PA, whereas contamination with BCC was uncommon. Transmission of the PA was demonstrated from CF patients or the environment, to

other patients or to hospital staff. One episode of transmission of PA from the hospital environment to a CF patient was documented. The same study found that PA or BCC embedded in sputum can contaminate the hands of patients or health professionals and can be transmitted by shaking hands for up to 180 min. Bryant and colleagues [26] propose environmental fomite contamination as another mechanism of indirect transmission of *M. abscessus* complex. They identified identical clones in three patients with novel infection following an inpatient stay in a room previously occupied by a patient with known *M. abscessus* complex infection. Identical isolates were obtained from environmental sampling of the room.

S. maltophilia was found in the respiratory secretions of a quarter of patients in a pediatric CF center in Leeds [28]. Genotyping of environmental and patient samples led to the conclusion that person to person transmission was unlikely but that there may have been multiple, independent acquisitions of the organism from a variety of environmental sites both within and outside the hospital.

Potential CF pathogens have been found on nebulizers [29–33] but only in a few instances have these been consistent with pathogens identified from the patient's respiratory samples [34,35]. Increased use of aerosolized medications was found to be a risk factor for PA acquisition in a mathematical model of PA risk factors [36]. Epidemic PA was not found on spirometers [37] in the investigation of an outbreak, though contaminated nebulizers can transmit PA and BCC to clean hands [27]. Respiratory filters are effective at preventing the passage of pathogens into the machine [38].

1.4. Infection control strategies

A number of infection prevention and control guidelines have been produced for CF (see Table 1). Guideline recommendations include:

- Cohort segregation of CF patients (based on carrier status of organisms).
- Individual segregation of CF patients.
- Personal hygiene methods such as handwashing.
- Wearing personal protective equipment such as gloves, gowns, and masks by both patients and health-care workers.
- Cleaning and disinfection of areas and equipment.

Here we systematically review the evidence base for infection prevention and control strategies in CF. We intend to highlight what is known about strategies to prevent infection and identify where further research is needed. This will help the CF community understand what constitutes appropriate prevention strategies and reduce the burden of unnecessary measures.

2. Methods of systematic review

Our full protocol can be found on PROSPERO (CRD42018109999) [39]. Studies (of any type) and guidelines which included interventions or strategies for infection prevention and control in people of any age with a formal diagnosis of CF and in English were eligible for inclusion. We excluded epidemiological studies, non-patient studies, non-systematic review articles and studies relating to vaccination or eradication.

We undertook a search for studies of the following databases in October 2018: EMBASE, MEDLINE, CINAHL, Cochrane Library and PubMed [40–44]. Search strategies were devised iteratively and search terms kept broad to increase sensitivity (Supplementary file1).

Clinical guidelines published in the last 10 years were identified by searching the following guideline repositories: CF Trust; CF Foundation; European Cystic Fibrosis Society (ECFS); National Institute for Health and Care Excellence (NICE); National Guidelines Clearing House; Cystic Fibrosis Federation Australia. Search results were downloaded to Endnote (vX7) [45] and checked for duplicates. The online program Covidence [46] was used for screening by two reviewers with arbitration by a third in case of disagreement.

The resulting studies were recorded in Microsoft Excel [47] and organized into categories. Strength of evidence for each category was assessed using GRADE [48].

3. Results of systematic review

Our searches identified 3485 references after duplicates had been removed, 41 (36 studies) of these met the criteria for inclusion. We excluded 3070 on title and abstract alone and 374 from the full-text article with reasons described (Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart).

Within the included studies there were two randomized controlled trials, with the majority (n = 22) consisting of 'before-after' studies. There were five interventional studies, two prospective cohort studies, two comparative studies and one audit looking into adherence to infection control policies. Two systematic

Table 1. Evidence within guideline recommendations.

Guideline source	Guideline	Year	Total number of recommendations included	Level of evidence			
				High	Low	None	Expert opinion
NICE [37]	Cystic fibrosis: diagnosis and management	2017	6		5	1	
CF Trust [38]	Antibiotic treatment for cystic fibrosis. Third edition.	2009	9	4	5		2
CF Trust [39]	NTM guidelines	2018	34		34		
CF Foundation [40]	Infection prevention and control clinical care guidelines	2014	87	40	6	2	39
CF Foundation [41]	Eradication of initial *P.* aeruginosa clinical care guidelines	2013	3	1	1	1	
CF Foundation [42]	Nontuberculous Mycobacteria clinical care guidelines	2015	8				8
CF Federation of Australia [43]	Infection control guidelines	2012	21			21	

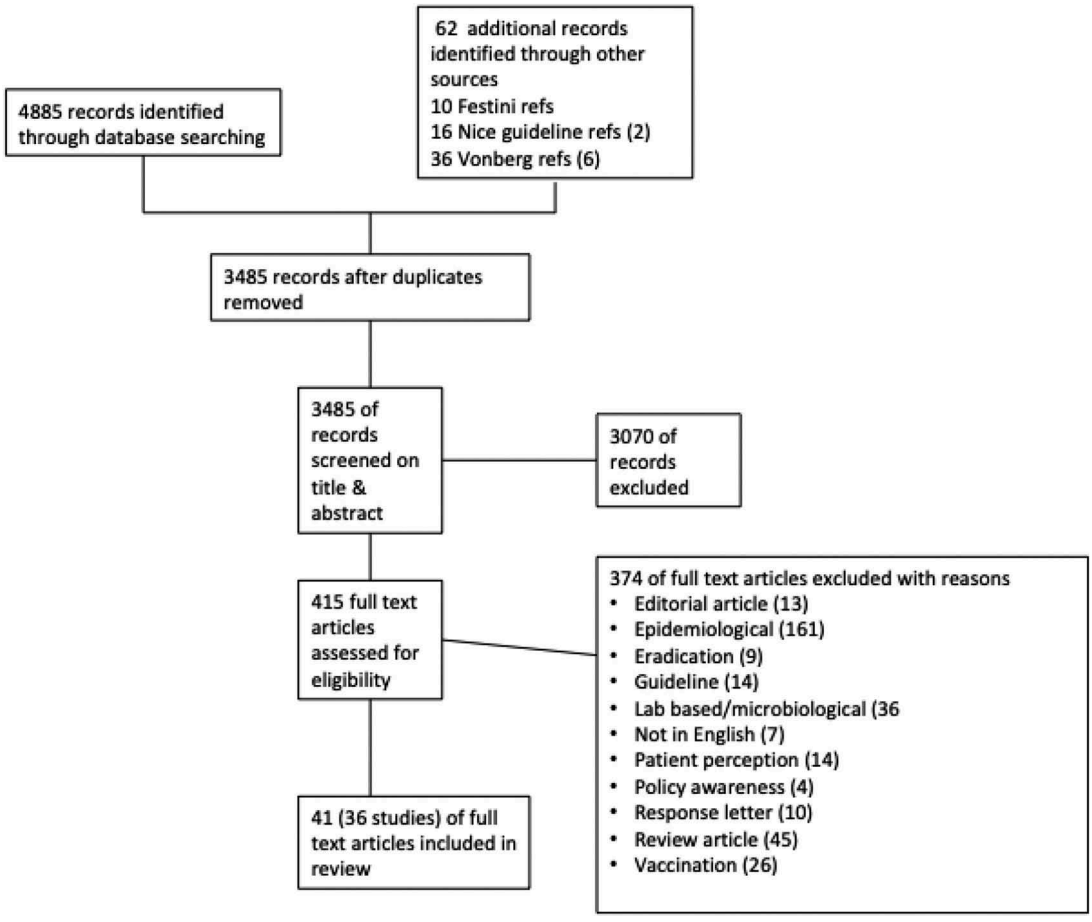

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) chart.

reviews for interventions of infection prevention and control in CF met our inclusion criteria so their included studies were double-checked for inclusion. Characteristics of the included studies are presented in Supplementary file 2.

We found seven guidelines [49–53] with reference to infection prevention and control policies. These are summarised in Table 1 which shows the guideline source, number of recommendations, and level of evidence for these. Most guideline recommendations had little or no evidence to support them.

4. Evidence for infection control and prevention strategies

Table 2 shows the strength of evidence for each category discussed below.

4.1. Cohort segregation

4.1.1. Inpatient cohort segregation

Three studies have reported on the effectiveness of cohort segregation in inpatients. Physical separation of inpatients colonized with BCC (then known as *Pseudomonas cepacia*) led to a sharp decline in incidence from 8.2% in 1983 to 1.7% in1984 in one North American CF center [54]. Paul *et al.* [55] showed that, when comparing Australian hospitals, a CF center that practiced cohort segregation of inpatients with BCC had no evidence of cross-infection between patients. In contrast, in a center where there was no cohort segregation, the same endemic strain was found in 19 of 20 patients [55]. Chen *et al.* [56] also showed that cohorting of inpatients based on BCC infection status led to a drop in incidence.

4.1.2. Outpatient cohort segregation

One RCT has looked into the effectiveness of cohort segregation of outpatients by PA status [57]. This showed no clinically significant difference in 10-year incidence of PA between CF children diagnosed by newborn screening and randomized to either segregated or mixed clinics. However, the authors noted that at the time of the study one clinic moved into a much newer building with more space and better provision of hygienic precautions. They speculated that reduced patient–patient interactions in the new building confounded the study, with the median time to initial PA acquisition increasing from 1.7 years in the old building to 5.0 years in the new. Furthermore, the study lacked statistical power.

There are two before–after studies which looked at outpatient segregation [58,59]. Lee *et al.* [58] showed a drop in the prevalence of chronic PA, in children under 11 years, from 23.8% to 4.3% over a 10-year period, following the introduction of cohort segregation. Similarly, McKay *et al.* [59] noted a drop in acquisition of mucoid PA following the introduction of 'color-coded' (by age and PA status) clinic segregation.

Table 2. Quality of evidence for infection prevention and control strategies.

Strategy/ recommendation	Number of studies	Study design	Direction of findings	GRADE	GRADE description
Cohort segregation					
Inpatient	3 [54–56]	2 before and after studies, 1 comparative epidemiological study	All three studies supported inpatient cohorting	Low	The quality of evidence is low based on the study design. However, all three studies support inpatient cohorting.
Outpatient	3 [57–59]	1 RCT, 2 before and after studies	The RCT and one of the before and after studies found no change in acquisition of PA after segregation in outpatient clinics. The third study supported segregation for mucoid PA but not non mucoid PA.	Very low	Although there is an RCT which contributes to the evidence for this strategy, there is heterogeneity amongst the results of the three studies. The before and after studies do not have a control group and so it is difficult to control for confounding variables.
Combined in and outpatient	7 [60–68]	7 Before and after studies	All seven studies found evidence to support cohort segregation in the inpatient/outpatient setting. Two of the studies showed only a decrease in epidemic strains.	Low	The quality of evidence is low based on the study design but there are seven studies which all support inpatient/outpatient cohorting.
Other	3 [69–71]	1 before and after study, 1 prospective cohort study and one comparative epidemiological study	All three studies supported cohort segregation	Very low	The three studies contributing evidence to this strategy are heterogeneous in their design and setting.
Individual segregation					
Combined in and outpatient	1 [72]	1 before and after study	Supported individual segregation measures	Very low	The study contributing evidence was a before and after study but there was no control group to compare the effect of segregation. The evidence was downgraded due to there only being one study.
Hand hygiene					
Outpatient	1 [73]	1 before and after study	Supported hand hygiene measures	Very low	The study contributing evidence was a before and after study but there was no control group to compare the effect of segregation. The evidence was downgraded due to there only being one study. The study authors highlight the fact that it was difficult to control for confounding factors, particularly transmission of PA outside the clinic.
Face masks					
Outpatient/lab based	3 [24,74–76]	3	The two interventional studies found face masks to be effective in reducing aerosol PA load. The RCT found no difference in exam room contamination rate.	Low	Although there is an RCT which contributes to the evidence for this strategy, the outcome is exam room contamination rate which is an indirect measure of evidence for the effectiveness of face masks in reducing spread of infection. The remaining two studies are not RCTs and therefore the quality of the evidence is deemed to be low.
Combination of strategies	7 [56,77–82]	6 before and after studies, 1 prospective cohort study	6/7 studies found combinations of infection control strategies to be effective in reducing infection rates. The remaining study showed no difference after the strategies were introduced.	Very low	The quality of the evidence has been downgraded to very low due to the heterogeneity in the strategies implemented and study designs.
Social events	1 [83]	1	The findings support the suggestion that transmission of P cepacia is through social contact.	Very low	With only one small study contributing to the evidence for reducing social contact to prevent spread of infection, the quality of evidence has been downgraded to very low.
Equipment strategies	3 [29,84,85]	3 intervention studies	The three studies looked at different interventions and outcomes. Not possible to combine results.	Very low	The evidence was downgraded to very low due to heterogeneity in study interventions and outcomes.
Adherence	2 [86,87]	1 audit, 1 before and after study	Both studies reported on compliance after the implementation of IP&C guidelines. The audit did not give a before comparison.	Very low	Downgraded due to there being only two studies with different designs but both looking at compliance.

4.1.3. Combined inpatient and outpatient cohort segregation

Many before–after studies have shown combined inpatient and outpatient cohort segregation to be effective in preventing the spread of infection. Segregation of patients without PA, with PA, and with a multi-resistant strain of PA, by wards (as inpatients) and by different days (outpatients) was shown to decrease incidence of both new PA acquisition in those previously uncolonized, and superinfection with a transmissible strain in patients with previous, unique, PA [60]. Cohort segregation was also shown to reduce PA incidence by Frederiksen *et al*. [61]. Cohort segregation of clinics and strict inpatient isolation measures controlled the spread of transmissible PA in adults in Manchester, UK [62] and the Australian epidemic strain of PA in children in Victoria, Australia [63,64]. Ashish *et al*. [65,66] showed that their cohort segregation policy in both outpatient clinics and for inpatients by cohorting on separate wards was effective in preventing the spread of the Liverpool epidemic strain of PA in their clinic population. Whiteford *et al*. [67] showed that following an outbreak of BCC, simple cross-infection measures involving inpatient and outpatient segregation of children colonized with BCC, with no additional environmental measures, effectively interrupted the progress of the outbreak. The introduction of complete cohort segregation of adult inpatient and outpatients at a UK center led to a reduction in incidence and prevalence of BCC [68].

4.1.4. Other supporting evidence for the role of cohort segregation

Agodi *et al*. [69] introduced new infection control measures, including cohort segregation, which arrested a BCC epidemic in several Italian CF centers. Festini *et al*. [70] noted that the prevalence of multi-resistant PA was lower in Italian centers with segregation policies. However, they did not state whether these were in inpatients, outpatients or both. Greenberg *et al*. [71] showed that through cohort segregation there was no direct spread during the summer camps by the dead-sea. However, only small numbers took part and follow up was limited to the three weeks duration of the camp.

4.2. Individual segregation

4.2.1. Inpatient individual segregation

Single patient rooms are recommended in infection control guidelines from the US, UK and Australia [49–53] (Table 2). We found no studies looking at individual segregation of inpatients as a stand-alone intervention.

4.2.2. Combined inpatient and outpatient individual segregation

The standard in the Netherlands is for strict individual isolation of CF patients as both inpatients and outpatients regardless of infection status. Van Mansfield *et al*. [72] looked at PA acquisition before and after implementation of individual isolation. They found that PA acquisition declined though this was not statistically significant. There were no new acquisitions with the epidemic ST406 strain (which is a strictly CF-related strain) among non-infected patients after segregation, indicating that segregation prevented the spread of epidemic clones.

4.3. Hand hygiene

Zuckerman *et al*. [73] looked at the effectiveness of hand hygiene in preventing bacterial contamination in CF clinics. They showed that use of alcohol-based hand hygiene products effectively reduced hand carriage of respiratory pathogens, but that acquisition of new organisms on hands can occur during clinic visits suggesting that repeated hand hygiene is needed to control the risk of recurrent contamination.

4.4. Face masks

In a laboratory cough rig Wood *et al*. [24] investigated the efficacy of various face masks and cough etiquette (covering mouth with the hand while coughing) in reducing cough aerosols of PA generated by people with CF. They found that both surgical and N95 face masks significantly reduced the amount of PA which can be recovered from aerosols, with surgical masks being favored by patients for comfort. Cough etiquette resulted in about half the reduction of that found with masks. Stockwell *et al*. [74] looked at the efficacy of wearing masks over different time periods (10, 20 and 40 min). They concluded that face masks worn for clinically relevant time periods are effective at reducing the release of potentially infectious aerosols during coughing in people with CF. Again surgical masks were found to be more comfortable than the N95 ones. However, Zuckerman *et al*. [75] compared room contamination rates between patients wearing surgical masks and those without and found similar contamination rates between the two groups. The Stockwell and Wood studies support the recommendation, made in US infection control guidelines for CF [50] which says that masks should be worn by CF patients while they are in a health-care facility. However, it has recently been suggested that masks need only be worn in communal areas and not, for example, in the patient's own side room [76].

4.5. Combination of strategies

Several studies looked at the efficacy of a combination of infection control strategies. After suspecting nosocomial acquisition of PA in 12 out of 40 of their patients over a 4-year period, Tummler *et al*. [77] looked into the effect cohort segregation of both inpatients and also physiotherapy outpatient classes had on PA acquisition. Following the introduction of these measures, there was only one case of nosocomial acquisition during the subsequent two years. Chen *et al*. [56] showed that multiple infection prevention measures including cohorting of inpatients, wearing of personal protective equipment when out of bedrooms, a hospital-wide education program on infection control and cohorting of outpatient clinics with mandatory face masks in waiting rooms decreased annual incidence of BCC from 8.8% at baseline to less than 1%. Savant *et al*. [78] compared respiratory organism culture rates in patients before and after the introduction of a new infection control process in children's outpatient clinics. Regardless of organism status, all patients underwent individual isolation during clinic appointments. Alongside this, strict hygiene measures were instigated and an education program for health-care providers, patients and families commenced. There were statistically significant drops in both PA and MRSA rates following these measures. Matt *et al*. [79] looked

at the genetic diversity of PA in their center following implementation of an infection control package comprising: strict individual isolation measures; wearing of masks by patients; wearing of masks, gowns and gloves by clinical staff; thorough disinfection of clinical areas and equipment; home hygiene advice; and discouraging CF patients from mixing. Genetic analysis showed heterogeneity of PA isolates in the majority of patients and no transmission of PA isolates between CF patients under their care, indicating the success of the intervention. Wiehlmann et al. [80] also showed that cohort segregation and hygiene measures prevented cross-infection of PA between patients in their Hanover center. After an outbreak of *M. abscessus* subsp *massiliense*, Kapnadak *et al*. [81] showed that no newly acquired cases were identified after strict infection control interventions were implemented, including source investigation, education, isolation, high priority culture alerts, clinic environment sterilization, treatment, and surveillance. Kim *et al*. [82] looked into incidence or prevalence of pathogenic bacteria in their center's first year after implementation of the new CF Foundation Infection Control Guidelines. They found no significant differences, however, the follow-up period was short.

4.6. Social events

Smyth *et al*. [83] noted that on cessation of Adult CF Association meetings in the local area, no new isolates of BCC occurred.

4.7. Equipment strategies

Jakobsson *et al*. [29] looked at bacterial contamination rates in home nebulizers of CF patients. They found that although contamination rates were generally low, those that were contaminated were those that had inadequately followed disinfection recommendations or drying. In this study, none of the patients were colonized with the contaminating organisms suggesting environmental acquisition rather than the device being infected from the patient. Fishman *et al*. [84] looked into how often nebulizer mask and tubing should be changed. On comparing two groups consisting of children and young adults, they found that changing equipment every 12 months led to similar clinical outcomes as changing every 6 months with no difference in PA growth after 2 years. Greenwood *et al*. [85] studied contamination of a dry-powder inhaler *vs*. a nebulizer and suggested that the dry powder device has a lower contamination rate. One patient in the Greenwood study had the same organism (*S.aureus*) isolated from both sputum and the device, however the other 11 patients with contaminated devices did not have the same organism isolated from their sputum. This study was sponsored by the pharmaceutical company which marketed the dry powder device.

4.8. Adherence to infection prevention strategies

Adherence at Irish CF centers to the 2013 CFF guidelines was evaluated by Breen *et al*. [86]. They found 100% adherence to inpatient guidelines but found that no center adhered to outpatient mask wearing or room ventilation guidelines. Overall adherence ranged from 64% to 77%.

4.8.1. Education of staff and inpatients

Re-education of all ward staff and inpatients through videos and introduction of 'safe-zone' decals on floors was shown to improve patient and staff adherence to infection control policy [87].

5. Conclusion

From the 36 studies included in this systematic review, the majority have focussed on segregation methods for infection control. Although deemed low or very low quality, the abundance of studies showing reduction in the spread of transmissible organisms after the introduction of segregation measures cannot be ignored. All the guidelines included here recommend single patient rooms for inpatients.

Recent studies have shown that facemasks are effective at reducing the release of potential infective *Pseudomonas* aerosols. These studies were carried out in adults who reported the wearing of facemasks to be tolerable. The tolerability to children and for greater lengths of time are yet to be determined.

As with all areas, policies and strategies are only effective if the relevant people adhere to them. Regular re-education of clinical and non-clinical staff as well as people with CF and their carers improve adherence.

Acquisition of pathogenic organisms can occur through person-to-person transmission, from the healthcare environment and environmental reservoirs. We have summarised the evidence supporting strategies to prevent spread from the first two sources but have not found any data for strategies to prevent acquisition from environmental sources.

6. Expert opinion

We have found no high-quality evidence supporting infection prevention and control measures in CF. Despite this, infection control guidelines are widely implemented in CF centers globally. We identified two previously published systematic reviews on the topic of infection prevention and control in CF. In 2004 Vonberg *et al*. [88] identified 102 studies which fitted their inclusion criteria and graded the quality of evidence using a 5-point scale. They presented results only for the papers which scored two or more points on this scale. They separated studies into those in which the authors supported segregation and those in which segregation was not supported, finding that 31/39 authors supported segregation. Festini *et al*. [89] also concentrated on the question of segregation. They identified 10 studies, none of which were RCTs. The authors concluded that whilst the studies were of generally low quality, in view of the ethical constraints of prospective, controlled studies sufficient evidence exists to recommend segregation.

The most recent guideline for infection control practices in CF is the UK National Institute for Health and Care Excellence (NICE) guideline published in late 2017 [49]. This identified 16 eligible studies examining infection prevention and control practices, including segregation (cohort and individual), use of personal protective equipment and any combination of these. Ultimately they recommend a combination of cohort segregation in the clinic setting and individual rooms with ensuite facilities for in-patients, whilst grading all the evidence (using the GRADE tool) as low or very low as shown in Table 2.

Undertaking RCTs into infection prevention and control strategies is ethically difficult. Acquisition of transmissible organisms is associated with worse clinical status. Evidence for segregation is of limited quality but is abundant and the consistent conclusion is that segregation is beneficial in reducing the spread of transmissible organisms. In this situation exposing patients to the risk of cross-infection, in the setting of an RCT, may be unethical. For those measures, such as negative pressure rooms, where there may be equipoise amongst clinicians, trials may be more ethically acceptable. However, such trials would be expensive and (given current acquisition rates of epidemic strains) would require long term follow up. Designing trials of the efficacy of individual elements of an infection control package would be challenging.

Large-scale epidemiological registry studies may provide a strategy to answer some of these questions. Most geographic areas that have a population with CF have their own registries: the UK CF Trust, the US CF Foundation, and the European CF Society all collect data on infection. Data showing year-on-year prevalence of organisms and infection control measures undertaken at each center may help provide more evidence to underpin infection control guidelines.

The benefits of infection prevention and control measures must be balanced against the degree to which they intrude upon the lives of people with CF. Health professionals may give parents of children with CF advice regarding measures to reduce infection in the home which results in a great deal of parental anxiety and yet there may be little robust evidence for such advice [90]. In both parents of children and adults with CF, fear of infection with PA may lead to great anxiety and inappropriate avoidance measures [91].

Antimicrobial resistance has always been a feature of the organisms causing pulmonary infection in people with CF. Initially, this was exemplified by PA which has intrinsic resistance to many antibiotics and which can acquire resistance through the expression of efflux pumps [92] and through the biofilm mode of growth [93]. More recently, other highly resistant organisms, which originate in the environment, such as BCC [21] and *M. abscessus* complex [20] have found a niche in the CF lung and may be transmitted between patients. Effective eradication of these organisms is difficult or impossible and so primary prevention through infection prevention and control will be critical over the next 5 years. The evidence around facemasks is a relatively recent area with more questions still to be answered. Most CF centers do not have communal waiting areas; however, facemasks may be effective in other areas where patient to patient contact may occur such as pharmacy or the X-ray department. There is currently no evidence to support the use of facemasks outside the CF center to prevent transmission from environmental sources. Wearing of facemasks may have considerable psychological effects on the person with CF. With increasing use of digital technology, face to face contact between the person with CF and the clinical team may be needed less frequently. Reducing the need to attend clinics in person, through the use of digital technology, would lessen the cross-infection risk. Regimens comprising multiple antibiotics are a significant burden for the person with CF and carry the risk of drug-related toxicity. Effective, evidence-based, infection prevention and control strategies may, therefore, allow CF clinicians to promote antimicrobial stewardship more effectively.

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