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Short Communication

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

Nicola J Rowbotham [a,*], Sherie Smith [a], Nikki Jahnke [a], Sarah Milczanowski [b], Zoe C Elliott [c], Andrew P Prayle [a,d], Alan R Smyth [a,d,e]

[a] Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK
[b] Person with CF, Bradford, UK
[c] Parent of children with CF, Nottingham, UK
[d] Nottingham Biomedical Research Centre and School of Medicine, University of Nottingham, Nottingham, UK
[e] School of Medicine, Dentistry and Biomedical Sciences, Queens University, Belfast, UK

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ABSTRACT

Preventing transmissible infection is a priority in cystic fibrosis (CF) care. This is an update of a systematic review of the evidence for infection prevention and control interventions in CF.

Our full protocol can be found on PROSPERO (CRD42018109999). We searched for studies and guidelines which included interventions for infection prevention and control in CF.

We included 39 studies and 7 guidelines. Strategies included: cohort or individual segregation, hand hygiene, facemasks, equipment, enhanced adherence or a combination of these. Many studies showed a reduction in transmission with segregation. However, the certainty of evidence (using GRADE) was low or very low. Most guideline recommendations have little evidence to support them, with no updates since our original review.

Undertaking RCTs in this area is ethically difficult. Large-scale registry-based studies may be the best pragmatic approach. Benefits of infection control must be balanced against the intrusion in the lives of people with CF.

1. Introduction

Cystic fibrosis (CF) is synonymous with recurrent pulmonary infection. The pattern of respiratory organisms changes through the life of a person with CF with *Staphylococcus aureus* and *Haemophilus influenzae* common in preschool children. With increasing age, intermittent infection with *Pseudomonas aeruginosa* becomes more prevalent and by their early twenties between 12 % and 22 % of individuals with CF will have chronic pulmonary *P. aeruginosa* infection [1,2]. Other bacteria such as Methicillin resistant *S. aureus* (MRSA) vary by location, with 1.9 % of adults with CF infected in the UK [2] but US prevalence reaching 20 % in younger age groups [1]. Other organisms are less prevalent but highly antibiotic-resistant, such as *Burkholderia cepacia* complex (BCC) and non-tuberculous mycobacteria (NTM), particularly *Mycobacterium abscessus* complex. Gram-negative organisms including *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* are also commonly found with unclear significance at present. It is unclear whether an apparent decline in the prevalence of many organisms in people with CF since the advent of CF transmembrane conductance regulator (CFTR) modulators is related to the absence of infection and/or the reduction in sputum density and subsequent difficulty in obtaining respiratory specimens [3].

Transmission between individuals occurs and infection drives inflammation leading to bronchiectasis [4]. Infection with *P. aeruginosa* is associated with a more rapid decline in lung function and greater risk of death. Therefore, prevention of these infections, through infection prevention and control, is of utmost importance.

Here we present an update of our previous systematic review of the evidence base around infection prevention and control in CF [5] to see if evidence has changed five years on, and with the increased use of CFTR modulators.

2. Methods of systematic review

Our full protocol for this update can be found on PROSPERO (CRD42018109999) [6]. Studies and guidelines which included interventions or

* Corresponding author.
E-mail address: nicola.rowbotham@nottingham.ac.uk (N.J. Rowbotham).

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strategies for infection prevention and control in people of any age with a formal diagnosis of CF and in English were eligible for inclusion. At review stage we agreed to exclude any studies that were descriptive epidemiological studies, non-patient studies, review articles which were not systematic reviews and studies relating to widespread vaccination strategies applicable to the general population, or those relating to eradication as it is thoroughly covered in existing Cochrane reviews.

We undertook an updated search for studies of the following databases in July 2023: EMBASE, MEDLINE, CINAHL, Cochrane Library and PubMed [7–11]. 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 (vX9) [12] and checked for duplicates. The online program Covidence [13] was used for screening by two reviewers with arbitration by a third reviewer in case of disagreement.

The resulting studies were recorded and organised into categories. The strength of evidence for each category was assessed using GRADE [14].

3. Results of systematic review

Our combined searches identified 4671 references after duplicates had been removed, 46 (39 studies) of these met the criteria for inclusion. We excluded 4206 on title and abstract alone and 419 from the full text article with reasons described (Fig. 1).

Within the included studies there were two randomized controlled trials, with the majority (n = 25) consisting of "before-after" studies (outcomes were reported before and after the intervention was implemented). There were five interventional studies, two prospective cohort studies, two comparative studies and one audit looking into adherence to infection control policies. Two systematic reviews for interventions of infection prevention and control in CF met our inclusion criteria so their

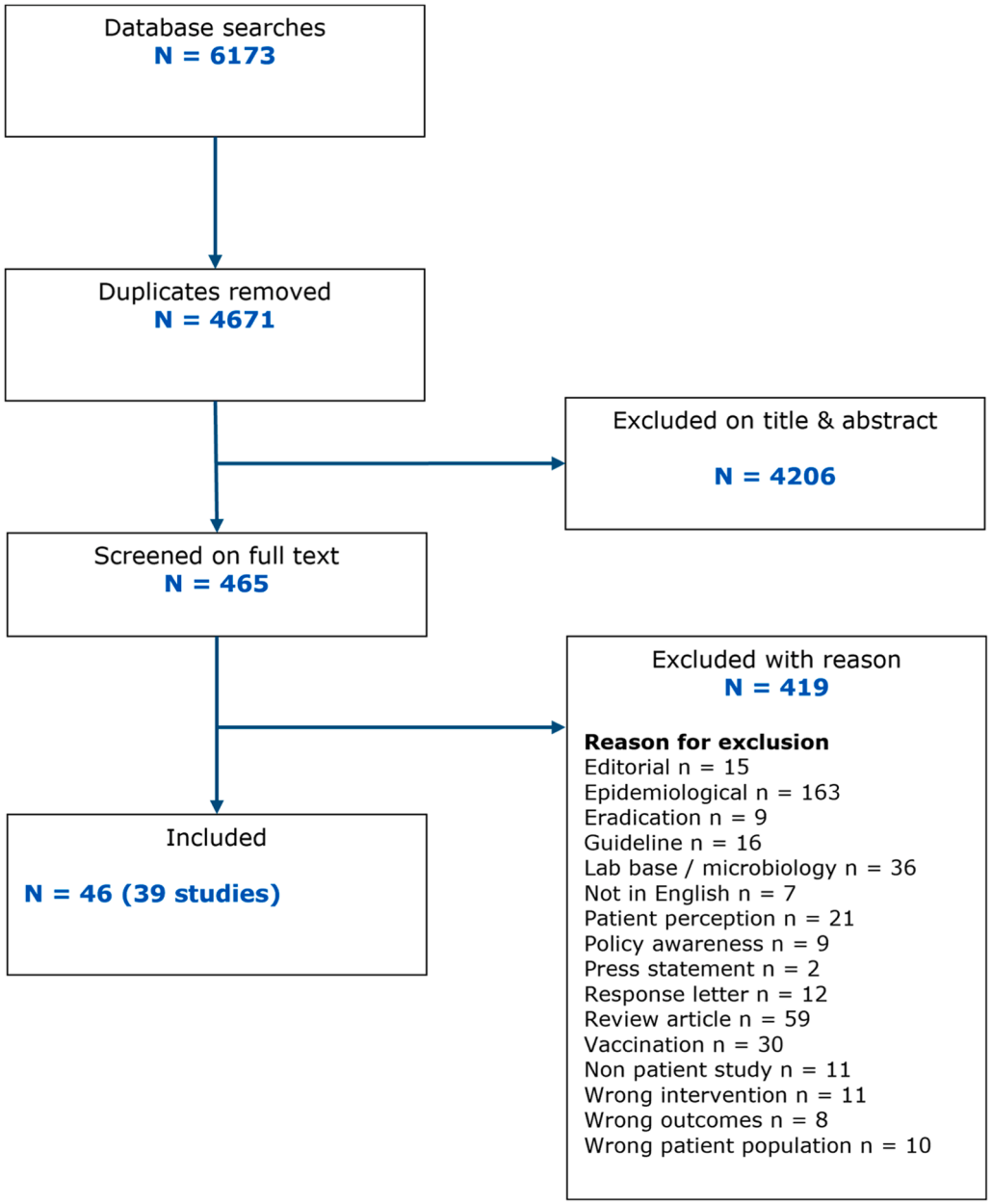

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

included studies were double-checked for inclusion. At this update only two studies were newly included [15,16]. A third was an extension to a study included in the original review [17]. Characteristics of the included studies are presented in Supplementary file 2.

We have grouped the included studies by intervention, graded the certainty of evidence for each intervention and presented our findings in Table 1. Cohort and individual segregation were the interventions most commonly implemented and, whilst the certainty of evidence was either low or very low, the results supported segregation in preventing infection. Eight studies implemented a combination of infection prevention

Table 1
Certainty 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	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	4	1 RCT, 3 before and after studies	The RCT and one of the before and after studies found no change in acquisition of *P. aeruginosa* after segregation in outpatient clinics. A third study supported segregation for mucoid *P. aeruginosa* but not non mucoid *P. aeruginosa*. The fourth study found that patients reported a reduction in anxiety and a feeling of empowerment but did not comment on new infection acquisition	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	6	6 Before and after studies	All six 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 six studies which all support inpatient/outpatient cohorting.
Other (included segregation during activities such summer camps)	3	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	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	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 *P. aeruginosa* outside the clinic.
Face masks					
Outpatient/lab-based	3	1 RCT, 2 interventional studies	The two interventional studies found face masks to be effective in reducing aerosol *P. aeruginosa* 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	8	7 before and after studies, 1 prospective cohort study	7/8 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	1 before and after study	The findings support the suggestion that transmission of *B. cepacia* sp. 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 (including decontamination, changing of devices)	3	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	1 audit, 1 before and after study	Both studies reported on adherence after the implementation of Infection Prevention & Control 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 adherence.

strategies, the majority of which were found to be effective although the certainty of evidence was very low. The remaining interventions included hand hygiene, use of face masks, social event planning and cleaning of equipment (very-low certainty evidence).

We found seven guidelines with reference to infection prevention and control policies. There were no new guidelines found with this update. These are summarized in Table 2 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. Discussion

Since we published our original review [5], much has changed across the CF landscape with the introduction of CFTR modulator therapy for the majority of people with CF. Alongside this, the global Covid-19 pandemic has brought infection prevention and control to the attention of the wider population, with the adoption of measures which were not in general use pre-pandemic.

The interventions that we identified in the review included: segregation (cohort segregation e.g. as an inpatient or an outpatient, individual segregation), hand hygiene, face masks, a combination of measures, equipment strategies and measures at social events.

The majority of the 39 studies included in this systematic review, focused on segregation methods for infection control, including the two new studies [15,16]. MacDuff and Crockett introduced The CRAFT System (Color Risk Assessment Folder and Treatment System) which involved people with CF visibly carrying color-coded wallets to show their microbial status and so aid segregation while in hospital. They found that people with CF reported a reduction in anxiety and a feeling of empowerment but did not comment on new infection acquisition (conference abstract only) [15]. The Kevat study also looked at cohort segregation in the inpatient and outpatient setting and found that cohort segregation was associated with a reduction in prevalence of *P. aeruginosa* but also reported confounding factors such as early eradication treatment [16].

Although we deemed the certainty of this evidence to be low or very low, the abundance of studies showing a reduction in the spread of transmissible organisms after introduction of segregation measures is an important finding. All the guidelines included here recommend individual rooms for inpatients.

Studies have shown that facemasks are effective at reducing the release of potential infective *Pseudomonas* aerosols [18]. Tolerability had previously been a concern but, following the COVID pandemic, there is a wider acceptance of the use of face masks in public places, especially in clinical environments.

With the improvements in health shown for those on CFTR modulators, infection prevention and control measures may be felt to be less pertinent. However, recent studies have shown that although airway microbiome diversifies, inflammation reduces and sputum rheology shifts towards a healthier picture, there is still significant infection and inflammation present suggesting the need for continued measures [19,20]. It is also unclear whether infection rates are lower for people on modulators or whether infection is still present but is more difficult to diagnose.

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

CRediT authorship contribution statement

Nicola J Rowbotham: Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Visualization. **Sherie Smith:** Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Visualization. **Nikki Jahnke:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing. **Sarah Milczanowski:** Writing – review & editing. **Zoe C Elliott:** Writing – review & editing. **Andrew P Prayle:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Alan R Smyth:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Table 2
Evidence from guidelines.

Guideline source	Guideline	Year	Total number of recommendations included	Level of evidence			
				High	Low	None	Expert opinion
CF Trust Cystic Fibrosis Trust, *Mycobacterium abscessus.* Recommendations for infection prevention and control. 2018: London	NTM guidelines	2018	34		34		
NICE NICE. Cystic Fibrosis: diagnosis and management. London: National Institute for Health and Care Excellence: Clinical Guidelines; 2017.	Cystic fibrosis: diagnosis and management	2017	6		5	1	
CF Foundation Floto, R.A., et al., US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax, 2016. 71(Supplement 1): p. i1-i22.	Nontuberculous Mycobacteria clinical care guidelines	2015	8				8
CF Foundation Saiman, L., et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. Infection Control & Hospital Epidemiology, 2014. 35 Suppl 1: p. S1-S67.	Infection prevention and control clinical care guidelines	2014	87	40	6	2	39
CF Foundation Mogayzel, P.J., Jr., et al., Cystic Fibrosis Foundation pulmonary guideline. pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. Ann Am Thorac Soc, 2014. **11** (10): p. 1640–50	Eradication of initial P. aeruginosa clinical care guidelines	2013	3	1	1	1	
CF Federation of Australia Cystic Fibrosis Australia, *Infection Control Guidelines for Cystic Fibrosis Patients and Carers*. 2012: Baulkham Hills NSW 2153	Infection control guidelines	2012	21			21	
CF Trust Cystic Fibrosis Trust, *Antibiotic Treatment for cystic fibrosis*. 2009: London	Antibiotic treatment for cystic fibrosis. Third edition.	2009	9	4	5		

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NR reports support for attending meetings and/or travel from the Cystic Fibrosis Trust, British Paediatric Respiratory Society and European Cystic Fibrosis Society, all outside the current work. AP reports grants or contracts from Vertex Pharmaceuticals, Cystic Fibrosis Trust, Action for AT, Nottingham University Hospitals Charity, SBRI and support for attending meetings and/or travel from Vertex Ltd and Quince Therapeutics, all outside the current work. AS has research grants (paid to the University of Nottingham) from Vertex Pharmaceuticals and payment for an advisory board (paid to the University of Nottingham) from Viatris Pharmaceuticals, all outside the current work. AS has patents issued (Camara M, Williams P, Barrett D, Halliday N, Knox A, Smyth A, Fogarty A, Barr H, Forrester D. Alkyl quinolones as biomarkers of Pseudomonas aeruginosa infection and uses thereof. US-2016131648-A1; https://pubchem.ncbi.nlm.nih.gov/patent/US-2016131648-A1 Outside the current work. AS reports participation on a Data Safety Monitoring Board for the North American Cystic Fibrosis Foundation Therapeutic Development Network, outside the current work. SS, NJ, ZE and SM have no competing interests

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2024.08.004.

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