

European Respiratory Journal 2018, 51(1), 1701937.

Copyright:

This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for publication in the European Respiratory Journal, prior to copy-editing, formatting and typesetting. This version of the manuscript may not be duplicated or reproduced without prior permission from the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication.

DOI link to article:

https://doi.org/10.1183/13993003.01937-2017

Date deposited:

16/03/2018

Embargo release date:

11 July 2019

James D Chalmers, Felix C Ringshausen, Bridget Harris, Stuart Elborn, Annette Posthumus, Charles S Haworth, Nicola Pilkington, Eva Polverino, Thomas Ruddy, Stefano Aliberti, Pieter C Goeminne, Craig Winstanley, Jeanette Boyd, Anthony De Soyza

1. Scottish Centre for Respiratory Research, University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland.
2. Department of Respiratory Medicine, Hannover Medical School, Member of the German Centre for Lung Research, Hannover, Germany
3. European Lung Foundation (ELF)/EMBARC bronchiectasis patient advisory group, Sheffield, UK
4. Host Defence Unit, Royal Brompton Hospital, Imperial College, London, UK
5. Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, UK
6. Servei de Pneumologia, Hospital Universitari Vall d'Hebron (HUVH), Institut de Recerca Vall d'Hebron (VHIR)
7. Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Center Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan, Italy
8. Department of Respiratory Medicine, AZ Nikolaas, Sint-Niklaas,
9. Institute of Infection and Global Health, University of Liverpool, UK
10. Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK

Corresponding Author: Dr James D Chalmers, Division of Molecular and Clinical Medicine, University of Dundee, Dundee, DD1 9SY. E-mail: jchalmers@dundee.ac.uk, phone: 01382 383642

Conflict of interest statement: all authors declare no conflicts of interest.

Acknowledgements: We acknowledge the EMBARC registry steering committee and the ERN-Lung bronchiectasis core network who approved this document. Bridget Harris, Annette Posthumus and Thomas Ruddy are representatives of the broader EMBARC/ELF bronchiectasis patient advisory group.

EMBARC is a European Respiratory Society Clinical Research Collaboration. This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking iABC grant agreement n° 115721
Twitter summary: There is a small risk of cross infection with *Pseudomonas aeruginosa* in bronchiectasis, but the benefit of specialised clinics, chest physiotherapy and pulmonary rehabilitation outweigh theoretical risks.
The risk of cross-infection with pathogens such as *Pseudomonas aeruginosa*, Methicillin Resistant Staphylococcus aureus (MRSA) and Burkholderia cepacia complex, and most recently Mycobacterium abscessus is a matter of considerable concern in patients with cystic fibrosis bronchiectasis (CF). (1-4) As a result of compelling evidence of transmission of these organisms between people with CF and, in the case of *P. aeruginosa*, the identification of transmissible “epidemic” strains, clear guidance and restrictions on contact between CF patients have been introduced. (5,6) CF clinics are segregated, with separate clinics for patients with *B. cepacia* complex infection, *P. aeruginosa* and other infections. Within clinics, any direct contact between individuals with CF is avoided. In hospital wards, patients in most countries will be kept in side rooms separated from other patients, or may be kept on separate wards if patients with different infections are hospitalised concurrently. (5,6) CF physicians are also advised to practice rigorous hand hygiene and other measures since microorganisms can survive on surfaces, hands or clothing for several hours. (4,7) For patient support events and conferences, participation by CF patients is heavily restricted. The CF Trust in the UK limits participation strictly to a single CF patient for indoor events and has strict regulations for outdoor events. Virtually all international guidelines for CF advocate similar measures to reduce the risk of cross-infection. (5,6)

*P. aeruginosa* transmission is also a potential concern in bronchiectasis not due to CF (henceforth referred to as bronchiectasis) because of evidence that *P. aeruginosa* infection is associated with an increased risk of death, exacerbation and worse quality of life. (8) The European Respiratory Society (ERS) guidelines for bronchiectasis, published in the European Respiratory Journal in September 2017, did not address the issue of cross-infection. (9) This reflects the lack of evidence, which prevents recommendations being made in a GRADE based guideline. Of note, the current Spanish Society of Pneumology and Thoracic Surgery (SEPAR), the British Thoracic Society and the guidelines from Australia and New Zealand also make no specific recommendations regarding the risk of cross-infection. (10-12)
The ERS guidelines do, however, emphasise the importance of specialised care for the management of bronchiectasis, which is best delivered within specialised centres seeing a large number of patients. The ERS guidelines recommend that patients with bronchiectasis and significant breathlessness attend pulmonary rehabilitation. Pulmonary rehabilitation and specialist outpatient clinics are two environments where patients with bronchiectasis will inevitably come into contact with other patients.

Bronchiectasis has been a neglected condition. This has led, in part, to the development of strong patient led advocacy groups. These groups have been a major benefit to the field, aiding in the development of clinical guidelines, priority setting, peer support and education. Nevertheless, meetings involving multiple patients with bronchiectasis represent a further occasion where patients will come into direct contact.

Consequently, as part of the ongoing development of the European Bronchiectasis Multicentre Audit and Research Collaboration (EMBARC) and European Lung Foundation (ELF) bronchiectasis patient advisory group, we were asked to consider what guidance should be provided to clinicians and patients about the risk of cross-infection with bacterial pathogens for patients in clinical practice, or attending patient support or academic meetings.

What is the evidence for the risk of cross-infection in bronchiectasis?

Bronchiectasis and CF are two quite distinct conditions, with a different spectrum of microbiology and a different pathophysiology. B. cepacia complex, the most feared transmissible pathogens in CF, is very rarely cultured in bronchiectasis. While P. aeruginosa is almost universal in CF over a patient’s lifetime, P. aeruginosa affects only 20% of patients with bronchiectasis in Europe. It may be speculated that only a proportion of patients with bronchiectasis are susceptible to persistent
*P. aeruginosa* infection which tends to be concentrated in patients with more severe and extensive bronchiectasis.\(^{(20)}\)

We conducted a systematic review using Pubmed (using search terms “cross-infection” OR “transmission” AND “bronchiectasis”, supplemented by searches of American Thoracic Society, ERS, BTS and World Bronchiectasis Conference abstracts 2014-2017. Searches were limited to articles in English only and no date limits were applied). The primary search identified 117 articles, and an additional 8 abstracts and 4 papers were identified as potentially relevant in supplementary searches. Review of the full manuscripts/abstracts excluded 123 articles/abstracts that did not report on cross-infection leaving 6 potentially relevant articles. These are discussed below.

Based on this literature review, reports of cross-infection in bronchiectasis to date are extremely rare. Acquisition of a multidrug resistant strain of *P. aeruginosa* in a fourteen-year old boy with bronchiectasis due to chronic aspiration was reported by Robinson *et al* in 2003.\(^{(21)}\) The patient had shared accommodation and physiotherapy facilities with a CF patient harbouring a genetically identical strain making transmission likely.\(^{(21)}\) In contrast, a study of 64 *P. aeruginosa* isolates from 16 patients with bronchiectasis in Spain found no evidence of cross-infection, based on the high degree of genetic dissimilarity between each isolate.\(^{(22)}\)

De Soyza and colleagues performed a single centre study of 56 isolates and 36 bronchiectasis patients.\(^{(23)}\) They identified that the vast majority of *P. aeruginosa* isolates appeared to be acquired from the environment but could not exclude cross-infection in two cases. Genetic similarity between strains does not prove cross-infection, since acquisition from a common environmental source is also possible.\(^{(23)}\) A lack of longitudinal “before and after” data also means we do not know if these strains represented a new infection by *P. aeruginosa*, or acquisition of a new strain among many in a patient already infected with *P. aeruginosa*. It is also not known whether any acquisition is associated with a clinical deterioration.\(^{(23)}\)
Most recently Hilliam et al performed a multi-centre study using whole genome sequencing of 189 isolates from 91 patients attending 16 UK bronchiectasis centres. (24) In this study there were 5 examples of strains from different patients that were genetically similar but again did not have the epidemiological or longitudinal data to prove transmission vs common source acquisition. The authors concluded that there was no evidence to suggest a widespread transmissible strain in the UK bronchiectasis community, and that the \textit{P. aeruginosa} lineages that are common in bronchiectasis are generally those that are also highly abundant in the environment. (24) In a study reported in abstract form only, variable number tandem repeat (VNTR) typing was used on 144 isolates from 84 patients with bronchiectasis. (25) This study identified 3 cases of bronchiectasis patients infected with 1 x Midlands and 2 x Liverpool epidemic strains apparently acquired from CF patients during inpatient stays in proximity to CF patients. (25) No evidence of transmission from bronchiectasis patients to other bronchiectasis patients was identified. A recently published cohort study from the UK identified 3 patients sharing strains likely to have been acquired through cross-infection. (26) All three patients were known to be chronically infected with \textit{P. aeruginosa} prior to the presumed acquisition event. (26) Based on the apparently infrequent nature of transmission, the authors of this study did not advocate a change in infection control policy. (26)

\textbf{Interpretation}

The above review identifies that cross-infection with \textit{P. aeruginosa} has occurred in bronchiectasis patients but that

1. Such events are rare, and there is so far insufficient evidence to establish if new acquisition of \textit{P. aeruginosa} infection (vs. acquisition of new strains in patients already infected with \textit{P. aeruginosa}) has occurred.
2- There is insufficient evidence to show that cross-infection is associated with clinical deterioration.

3- Epidemic and highly transmissible strains have not been identified in the bronchiectasis population, except in one study where these were shown to be likely acquired from CF patients.

4- The strongest evidence for transmission overall and transmission of multidrug resistant or highly virulent strains in particular appears to be from CF patients to bronchiectasis patients, rather than within the bronchiectasis population. EMBARC data suggests that 10% of bronchiectasis patients in Europe are managed in CF clinics, while 45% are managed in centres with shared facilities for CF patients. (27)

5- The current studies are inadequate in terms of numbers of patients and availability of clinical data and longitudinal follow-up. There are no studies addressing cross-infection with \textit{Staphylococcus aureus}, \textit{MRSA}, \textit{NTM} or less common organisms in bronchiectasis.

\textit{Patient perspective}

The EMBARC/ELF patient advisory group discussed this issue with a panel of clinicians at the \textit{2$^{\text{nd}}$ World Bronchiectasis Conference} in Milan, facilitated by the European Lung Foundation. The discussions revealed that patients have diverse views on the importance of cross-infection. Patients infected with organisms such as \textit{P. aeruginosa} or \textit{S. aureus} are concerned about the risk of transmitting this to other patients or indeed to immunosuppressed patients and would value guidance on how to reduce any such risk. The majority of patients regarded the risk of acquiring new organisms from other patients as small, and an acceptable risk if the alternative is a lack of availability of peer support, specialised clinics and services such as pulmonary rehabilitation which currently require patients to be together. The majority of patients thought they had a right to know about the risks so that they could make an informed decision about, for example, attending patient support group events. Many patients expressed concern
that their condition would be stigmatised if they are required to wear masks or are unable to be in contact with others. In general, patients expressed frustration that infection control measures are often neglected in terms of their general management. Exacerbations resulting from exposure to relatives, members of the public or other patients with viral infections is a more frequent and regular problem for patients, and measures to avoid acquiring such infections are rarely discussed with patients.

**Recommendations**

Where Bronchiectasis patients are managed within a CF service we suggest managing these patients according to the same strict infection control procedures as patients with CF. This includes cohorting patients according to their infection status and avoiding contact between patients in both outpatients and hospital wards. The same efforts should be made where CF and bronchiectasis patients share facilities but do not attend the physical space at the same time. Patients with bronchiectasis should avoid sharing outpatient waiting rooms, clinic rooms or hospital bays with patients with CF. For the purposes of patient support group meetings, congresses or other events, patients with bronchiectasis should not have direct contact with individuals with CF. Detailed guidelines on infection control in patients with CF are available from relevant national and international societies. (28)

Within bronchiectasis clinics, a balance must be found between the theoretical risk of cross-infection, and the risk of adversely impacting patient care. Patients with bronchiectasis benefit from specialist care in centres that see a large number of patients. Cohorting patients by organism is likely to be impractical in many hospitals in the absence of specific funding for this. Cohorting is also difficult to justify since our review did not identify a single confirmed case of new infection with *P. aeruginosa* acquired from a fellow patient with bronchiectasis. It is our judgement that there is currently not sufficient evidence to recommend separation of bronchiectasis patients with *P. aeruginosa* infection. Similarly, there are clear benefits of pulmonary rehabilitation with the evidence demonstrating improved exercise capacity,
improved quality of life and reduced exacerbations. These benefits outweigh the theoretical risk that attending a pulmonary rehabilitation class with other patients could expose the patient to the risk of transmission of a microorganism. Again, there is no evidence that pulmonary rehabilitation related transmission has occurred. Care for bronchiectasis in Europe is currently heterogeneous and predominantly inadequate with data suggesting most patients do not receive what may be regarded as the basic components of bronchiectasis care, such as access to chest physiotherapy, sputum culture, antibiotic therapy and self-management. In this context, precious resources should be directed at improving basic medical management.

Nevertheless, we suggest that patients with specific multi-drug and pan-drug resistant pathogens including *M. abscessus* and MRSA should be managed according to strict infection control procedures in the outpatient and inpatient setting. For all patients, care should be taken with aerosol generating procedures and we suggest that procedures such as sputum induction, chest physiotherapy or spirometry should be performed in separate and well ventilated rooms.

In the event of suspected transmission or a suspected outbreak we recommend seeking expert microbiological help. Facilities to investigate potential outbreaks using molecular methods should be made available.

We recommend that discussing the topic of infection control, including avoiding infections as well as the risk of transmission should be part of the bronchiectasis clinic consultation for all patients.

For patient support groups, research initiatives and social events, the balance of risks and benefits must be carefully weighed on a case-by-case basis. The value to patients of participation in such events is clear, and the need for advocacy and support in a disease like bronchiectasis is acute. Therefore, in the absence of evidence of harm, we do not currently advocate preventing patients from participating in such activities. We nevertheless make the following recommendations:
• Patients should be informed that contact with other patients may carry a risk of transmission of infection. This allows patients to make an informed decision about whether to participate in such events.

• All participants at such events should practice rigorous hand hygiene measures. Patients should aim to minimise aerosols e.g. conduct chest clearance at home prior to attending and at events and cover their mouth while coughing.

• Since shaking of hands is known to be a primary source of pathogen transmission in other areas, hand shaking at events is discouraged.

• Venues should have adequate space and ventilation.

• Basic infection control measures to reduce close contact between patients should be practiced e.g avoid sharing food/drinks/mobile phones and avoid activities promoting close physical contact.

• Patients should not attend events with other patients if they are unwell, or have a current exacerbation.

• We suggest that specific groups of patients are at higher risk from cross-infection e.g immunocompromised patients, or those with multidrug resistant organisms should discuss with their physician prior to attending events.

• Where electronic or virtual means of communication (teleconferences, webinars etc) can be used, they should be used.

Patients are also concerned to reduce their risk of exacerbation by reducing the acquisition of viral and other infections from patients. We identified no evidence that infection control measures can prevent exacerbations. We therefore suggest that patients are advised to practice standard hygiene measures, such as hand washing before meals and that patients should avoid contact where possible with children and adults with active viral infections. It was discussed that some patients in online forums recommend
face-masks to reduce infection risk in bronchiectasis. The panel recommended against the use of facemasks due to a lack of evidence for their effectiveness and the risk of stigmatising bronchiectasis patients.

Finally, the topic of cross-infection is a key research priority in bronchiectasis. Cross-infection was identified by both patients and physicians as one of the 55 key research questions in the field of bronchiectasis, in the EMBARC “roadmap” published in 2016.(17) We strongly recommend that large scale longitudinal studies are performed to ascertain the incidence and clinical implications of cross-infection in bronchiectasis.

References


5. Cross-infection guidance, cystic fibrosis trust, UK
   accessed 25th June 2017


   abscessus isolated from people with cystic fibrosis in artificially generated aerosols. Eur Respir J.

   impact of Pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am
   Thorac Soc ;1602-11.

   J 2017; in press

    [Internet] 2008; 44: 629–640


    children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand

13. Goeminne PC, De Soyza A. Bronchiectasis: how to be an orphan with many parents? Eur Respir J.


