

<b>Institution:</b> University of Dundee		
<b>Unit of Assessment:</b> UoA 1 Clinical Medicine		
<b>Title of case study:</b> Transforming the diagnosis and management of bronchiectasis		
<b>Period when the underpinning research was undertaken:</b> 2012-2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
James Chalmers	Lecturer / Consultant / Clinical Professor	May 2012 – to date
<b>Period when the claimed impact occurred:</b> 2014 - ongoing		
<b>Is this case study continued from a case study submitted in 2014?</b> N		

### 1. Summary of the impact

Bronchiectasis is a chronic respiratory disease characterised by bronchial dilation. Research by Professor **Chalmers** and his team has transformed the management of this debilitating condition resulting in greater awareness of the disease and its causes, leading to a shift away from reactive symptom control to proactive evidence-led management. **Chalmers** led the preparation of treatment guidelines, raised awareness, supported the development of a patient registry involving over 15,000 patients from >30 countries and championed a patient-focussed approach to research planning and guideline development. The development of a new drug therapy for the treatment of this previously neglected disease is currently in Phase 3 clinical trials led by **Chalmers**.

### 2. Underpinning research

Bronchiectasis is a chronic, debilitating respiratory disease characterised by permanent bronchial dilation and a constellation of symptoms including cough, sputum production and/or recurrent respiratory infections. Once thought rare, it is now among the three commonest chronic airway inflammatory diseases. Its prevalence in the UK was 125.7/100,000 in 2015 [cited in **R1**] and is increasing.

Recognising the challenge this set, **Chalmers** was key to the establishment of the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), the second phase of which runs to November 2021. Its objectives were to bring researchers together internationally to develop a European Bronchiectasis Registry and drive improvements in research, clinical care and education. Through EMBARC and the University of Dundee, **Chalmers** and colleagues established the European Bronchiectasis Registry to contribute to evidence-based guidelines and improve patient care [**R1**]. By 31-Dec-20 it had recruited >15,000 patients across 32 countries. The Registry database is held securely by the University of Dundee's Health Informatics Centre.

Clinical decision-making in bronchiectasis involves identifying patients at risk of mortality, hospital admissions and exacerbations (acute deterioration with increasing sputum volume and purulence and/or systemic upset). In 2014, **Chalmers** and colleagues published a risk stratification tool which uses routine, readily available clinical parameters to identify patients at risk and those who are most likely to benefit from new treatments [**R2**]. This "Bronchiectasis Severity Index" (BSI), the first clinical prediction tool for bronchiectasis, was derived from an international multicentre prospective study involving 1310 patients in five cohorts. An online BSI calculator is now freely available [**R2**].

**Chalmers** has also demonstrated that patients who experience frequent exacerbations represent a distinct clinical phenotype, with poorer quality of life and increased risks of hospitalisation and mortality over five years [R3]. This is important in targeting preventative therapies appropriately and facilitating the design of effective clinical trials.

*Pseudomonas aeruginosa* is particularly problematic in bronchiectasis patients because of its ability to form biofilms and tendency to develop antimicrobial resistance. In the largest single study to date, **Chalmers** and colleagues addressed the prevalence and burden of chronic infection with *P. aeruginosa* in 2596 bronchiectasis patients across 10 centres in Europe and Israel [R4]. The prevalence of chronic infection with *P. aeruginosa* was 15%. Infection was independently associated with exacerbation frequency, hospital admissions and poor quality of life; mortality was also increased in patients with *P. aeruginosa*, particularly in those experiencing frequent exacerbations.

Independent patient data meta-analysis conducted by **Chalmers** through EMBARC has shown that long-term low-dose macrolide antibiotic treatment reduces exacerbation frequency [R5]. Similar benefits were observed in all subgroups, including patients with *P. aeruginosa* infection and those experiencing <3 exacerbations per year.

An EMBARC-sponsored systematic review and meta-analysis led by **Chalmers** and colleagues demonstrated reduced exacerbations and consistent antimicrobial efficacy with the use of inhaled antibiotics in 2597 adult bronchiectasis patients [R6]. Inhaled antibiotics were well tolerated and reduced both bacterial load and exacerbation frequency, in patients with bronchiectasis and chronic respiratory tract infections [R6].

This underpinning research has contributed to the better understanding of bronchiectasis by providing a key tool, the BSI, which can be used to identify patients at highest risk of complications. It has highlighted the harmful effects of exacerbations and *P. aeruginosa* and demonstrated the value of treatments such as macrolides and inhaled antibiotics. These findings have contributed to the development of treatment guidelines in Europe and beyond.

### 3. References to the research

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[R1] Chalmers, J. D., Aliberti, S., Polverino, E., *et al.* (2016). The EMBARC European Bronchiectasis Registry: Protocol for an international observational study. *ERJ Open Research*, Vol. 2, no. 1, 00081-2015, pp1-9. DOI: [10.1183/23120541.00081-2015](https://doi.org/10.1183/23120541.00081-2015).

[R2] Chalmers, J. D., Goeminne, P., Aliberti, S., *et al.* (2014). The Bronchiectasis Severity Index. An international derivation and validation study. *American Journal of Respiratory and Critical Care Medicine*, Vol. 189, No. 5, pp. 576-85 DOI: [10.1164/rccm.201309-1575OC](https://doi.org/10.1164/rccm.201309-1575OC). A printout of the online tool is appended (<http://www.bronchiectasisseverity.com/15-2/>).

[R3] Chalmers, J. D., Aliberti, S., Filonenko, A., *et al.* (2018). Characterization of the "Frequent Exacerbator Phenotype" in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine*, Vol. 197, No. 11, pp. 1410-1420 DOI: [10.1164/rccm.201711-2202OC](https://doi.org/10.1164/rccm.201711-2202OC).

[R4] Araújo, D., Shteinberg, M., Aliberti, S., Goeminne, P. C., Hill, A. T., Fardon, T. C., Obradovic, D., Stone, G., Trautmann, M., Davis, A., Dimakou, K., Polverino, E., De Soyza, A., McDonnell, M. J. & Chalmers, J. D. (2018). The independent contribution of *Pseudomonas aeruginosa* infection to long-term clinical outcomes in bronchiectasis. *European Respiratory Journal*, Vol. 51, No. 2, 1701953 DOI: [10.1183/13993003.01953-2017](https://doi.org/10.1183/13993003.01953-2017).

[R5] Chalmers, J. D., Boersma, W., Lonergan, M., *et al.* (2019). Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: An individual participant data meta-analysis. *Lancet Respiratory Medicine*, Vol. 7, No. 10, pp. 845-854 DOI: [10.1016/s2213-2600\(19\)30191-2](https://doi.org/10.1016/s2213-2600(19)30191-2).

[R6] Laska, I. F., Crichton, M. L., Shoemark, A. & Chalmers, J. D. (2019). The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: A systematic review and meta-analysis. *Lancet Respiratory Medicine*, Vol. 7, No. 10, pp. 855-869 DOI: [10.1016/s2213-2600\(19\)30185-7](https://doi.org/10.1016/s2213-2600(19)30185-7).

#### 4. Details of the impact

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Bronchiectasis is described by the President of the European Respiratory Society (2018-19) as a “neglected disease with a high morbidity and mortality” [E1]. Historically, poor awareness of the condition and a lack of research meant there was uncertainty about the underlying causes of bronchiectasis and the effectiveness of treatments, further compounded by poorly developed services.

Chalmers’ work has provided much-needed evidence for the investigation and management of bronchiectasis, shifting the clinical approach from reactive symptom control to proactive management based on an understanding of disease aetiology. His work has informed the first international guidelines for the management of bronchiectasis, raised global awareness of the disease and supported the establishment of a patient registry and patient-focussed approaches.

##### Development of international guidelines

Prior to 2017 there were no international treatment guidelines for bronchiectasis; management of the condition focused primarily on alleviating symptoms. Chalmers (with co-chair Polverino) directed the development of the 2017 European Respiratory Society (ERS) guidelines [E2]. The guidelines draw on Chalmers’ work, prioritising the prevention of exacerbations using mucoactive medications and antibiotics [R2]. According to the President of the ERS, the guidelines:

have been instrumental, as the first international guidelines published for this condition, in driving improvements in care including increased use of diagnostic testing [E1].

Following publication of the ERS guidelines, adoption of evidence-based interventions has increased. A comparison of three-year periods immediately before and after September 2017 reveals, among patients in the registry, increases in appropriate diagnostic testing from 44.7% to 51.8% ( $p < 0.0001$ ), airway clearance use from 47.0% to 57.4% ( $p < 0.0001$ ) and use of prophylactic antibiotic treatment from 28.6% to 32.2% ( $p = 0.009$ ) [E3].

Chalmers was also part of the British Thoracic Society Bronchiectasis in Adults Guideline Development Group [E4]. The resulting (2019) guideline recommends use of the BSI [R2] at baseline/diagnosis in all patients for evaluation and to support treatment planning.

##### Improving disease management and raising awareness worldwide

The impact of the research is evident beyond Europe. EMBARC (co-chaired by Chalmers) has driven improvements to bronchiectasis services across Europe as well as in Israel and India [E5].

In 2014, EMBARC partnered with the Respiratory Research Network of India to establish the Indian Bronchiectasis Registry. The Registry operates across 31 centres in India; it was the first prospective multicentre bronchiectasis registry established in a lower middle-income country [E6] and according to the Chair of the Respiratory Research Network of India, “by far the largest study into this orphan disease in an Asian country” [E7].

The research identified key differences with European studies including a distinct aetiology (the commonest underlying cause was tuberculosis) and characterisation (typified by early onset, extensive lung damage and severe symptomatology). The findings enabled physicians to identify how management of the condition could be improved, leading to an increased use of diagnostic testing for bronchiectasis patients and improved guideline adherence [E7]. Additionally the registry provided evidence of the underutilisation of macrolide antibiotics for frequently

exacerbating patients, thus informing the development of evidence-based consensus recommendations aimed at increasing the use of macrolide antibiotics in bronchiectasis and other respiratory conditions (submitted January 2019, accepted September 2020; final publication March 2021 was delayed due to COVID) [E8].

The work of EMBARC is credited with raising awareness of the condition worldwide, leading to greater public and professional awareness of the disease and ensuring that the disease is now firmly established as a regular core topic at major international meetings [E1] [E7]:

Prior to 2015 there were no specific European meetings on bronchiectasis and the topic was rarely discussed at international society events... Bronchiectasis has now become a core topic, addressed at all international meetings such as the ERS and the American Thoracic Society annual meetings...[E1]

### **Promoting evidence-based interventions**

Until recently, no licensed therapies for bronchiectasis were available and clinical trial findings were inconsistent, possibly because specific treatment-responsive endotypes of bronchiectasis had not yet been identified [E5]. The BSI [R2] is now used to characterise patients for randomised clinical trials and has been used in 12 clinical trials between its publication in March 2014 and the end of 2020. It was, for example, used in a 24-week Phase 2 trial led by Chalmers which tested the effectiveness of Brensocatib, a selective, orally active inhibitor of dipeptidyl peptidase I. This enzyme activates elastase during neutrophil maturation [E9]. The overall risk of exacerbation during the treatment period was 40% less than with placebo, demonstrating the benefits of an evidence-based approach to treatment. Brensocatib entered Phase 3 trials in December 2020, led by Chalmers (NCT04594369).

### **Championing a patient-focussed approach**

Before the establishment of EMBARC, there was no formal patient organisation, charity or advocacy group for bronchiectasis. From the outset, EMBARC has been patient-focussed and, where appropriate, patient-led.

The EMBARC Roadmap Study Group including Chalmers and four “expert patients” set out to identify the challenges faced by bronchiectasis patients, their families and friends. A questionnaire asking what changes would most improve quality of life for people with bronchiectasis was published online in 12 languages, eliciting 1086 responses from 22 countries. The results were used to set priorities and develop an EMBARC consensus statement [E10].

Three members of the Patient Advisory Group established as a result of these efforts participated in the EMBARC steering group and were full members of the 2017 Guidelines Task Force [E11], the first-time patients had played such a role “...the patients’ perspective often differed from those of guideline panellists....[they]....made an important contribution in modifying the ultimate guideline recommendations” [E11].

Patients also led the development of the comprehensive “Patient Priorities: Bronchiectasis” online resources. The website holds a range of resources including factsheets in 21 languages, alongside videos and lay summaries of guidelines in multiple languages to support patients to understand and self-manage their bronchiectasis [E12]. In summary, according to the President of the European Respiratory Society 2018-19 [E1]:

There is no doubt that EMBARC and the collaborative European research that Professor Chalmers has led has been a major contributor....It is no exaggeration to say that this research has transformed this previously neglected disease and is improving the lives of patients worldwide.

## 5. Sources to corroborate the impact

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[E1] European Respiratory Society President 2018-19. To whom it may concern. *Letter of Support 25th March 2021*.

[E2] Polverino, E, Goeminne, PC, McDonnell, *et al* (2017), 'European Respiratory Society guidelines for the management of adult bronchiectasis', *European Respiratory Journal*, vol. 50, no. 3, 1700629, pp. 1-23 DOI: [10.1183/13993003.00629-2017](https://doi.org/10.1183/13993003.00629-2017). Chalmers is corresponding author. R1 is cited as Ref 12, R2 is cited as Ref 9; Chalmers is a co-author on 6 other papers cited.

[E3] Chalmers, J. D. 2020. *European bronchiectasis registry analysis and guideline adherence dataset (unpublished data)*.

[E4] Hill, AT, Sullivan, AL, Chalmers, JD, *et al* (2019), 'British Thoracic Society Guideline for bronchiectasis in adults', *Thorax*, vol. 74, no. Suppl 1, 74, pp. 1-69 DOI: [10.1136/thoraxjnl-2018-212463](https://doi.org/10.1136/thoraxjnl-2018-212463). R2 is cited as Ref 120; Chalmers is a co-author on 7 other papers cited.

[E5] EMBARC Clinical Research Collaboration, Aliberti, S, Polverino, E, Chalmers, JD *et al* (2018), 'The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) ERS Clinical Research Collaboration', *European Respiratory Journal*, vol. 52, no. 5, 1802074, pp. 1-5 DOI: [10.1183/13993003.02074-2018](https://doi.org/10.1183/13993003.02074-2018). For the latest information, see <https://www.bronchiectasis.eu/> [Accessed 31st December 2020].

[E6] Dhar, R, Singh, S, Talwar, D, *et al* (2019), 'Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry', *The Lancet Global Health*, vol. 7, no. 9, pp. e1269-e1279. DOI: [10.1016/s2214-109x\(19\)30327-4](https://doi.org/10.1016/s2214-109x(19)30327-4). Chalmers is corresponding author.

[E7] Chair of the Respiratory Research Network of India/EMBARC Bronchiectasis Registry. Re: REF2021 application entitled "Transforming the global management of bronchiectasis". *Letter of Support, 18th March 2021*.

[E8] Dhar, R., Talwar, D., Singh, V., Dumra, H., Rajan, S. & Jindal, S. K. (2021). Expert recommendations on the role of macrolides in chronic respiratory diseases. *Lung India*, Vol. 38, No. 2 pp.174-182 DOI: [10.4103/lungindia.lungindia\\_498\\_19](https://doi.org/10.4103/lungindia.lungindia_498_19). Chalmers is co-author on 3 papers cited.

[E9] Chalmers, JD, Haworth, CS, Metersky, ML, *et al* (2020), 'Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis', *New England Journal of Medicine*, vol. 383, no. 22, pp. 2127-2137. DOI: [10.1056/NEJMoa2021713](https://doi.org/10.1056/NEJMoa2021713). A list of other clinical trials which have used the Bronchiectasis Severity Index for patient characterisation is appended.

[E10] Aliberti, S, Masefield, S, Polverino, E, *et al* (2016), 'Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration', *European Respiratory Journal*, vol. 48, no. 3, pp. 632-647. DOI: [10.1183/13993003.01888-2015](https://doi.org/10.1183/13993003.01888-2015). Chalmers is senior author.

[E11] European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), European Lung Foundation (ELF), EMBARC/ELF patient advisory group, Chalmers, JD, Timothy, A, Polverino, E, Almagro, M, Ruddy, T, Powell, P & Boyd, J (2017), 'Patient participation in ERS guidelines and research projects: the EMBARC experience', *Breathe*, vol. 13, no. 3, pp. 194-207. DOI: [10.1183/20734735.009517](https://doi.org/10.1183/20734735.009517).

[E12] European Lung Foundation. 2020. *Patient priorities: Bronchiectasis* [Online]. Available: <https://www.europeanlunginfo.org/bronchiectasis> [Accessed 30th December 2020].