Conclusions and future developments

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This Monograph represents a “state-of-the-art” review of non-cystic fibrosis (CF) bronchiectasis and highlights many recent advances in our understanding of this condition and how best to manage it. However, it is clear, that many important unanswered questions remain about the patho-physiology, investigation and treatment of bronchiectasis. The management of these patients remains hampered by a paucity of clinical trial evidence which, through necessity, requires us to draw on potentially misleading data from CF or chronic obstructive pulmonary disease studies. Furthermore, inadequate education and training of physicians remain barriers to optimal delivery of care to patients with non-CF bronchiectasis, something which this Monograph may hopefully begin to address.

There are a number of potential future developments, discussed below, which may significantly contribute to our understanding of why non-CF bronchiectasis develops in particular individuals, how to best investigate possible aetiological factors and how to optimally manage these patients.

Why does bronchiectasis develop?

As described in the chapter by Bilton and Jones [1], a large number of conditions leading to impaired host immunity and/or defective muco-ciliary clearance have been implicated in the development of non-CF bronchiectasis. However, using established investigative approaches, outlined by Drain and Elborn [2], we are currently unable to define an obvious triggering cause in a large percentage of adults with bronchiectasis.

Immunity and inflammation

Developments in our understanding of the mechanisms controlling lung inflammatory and immune responses [3] and their resultant effects on lung tissue [4] may allow researchers to focus on specific critical host responses that may qualitatively or quantitatively vary within a population predisposing particular individuals to bronchiectatic lung damage. Future developments in immunological testing [2, 5] may focus on identifying aberrant responses in patients’ immune cells to inflammatory or infective stimuli. Furthermore, more detailed analysis of patients with bronchiectasis associated with inflammatory bowel disease [6] and systemic autoimmunity [7] may provide important insights into how aberrant immunological responses might lead to bronchiectasis.
Microbiology

A better understanding of the role of bacteria and how they interact with epithelial cells and viruses [8] is likely to permit more targeted treatments and more effective prophylaxis. Nonculture-based microbial detection methods [9] are likely to provide mechanistic insights into the possible protective role of commensal microbial flora, the role of anaerobic and intracellular organisms and the dynamic interplay between bacterial species in specific lung niches. For fungal diseases [10] and nontuberculous mycobacterial infection [11], future research into the basic mechanisms of disease may permit development of novel diagnostic tools and more effective treatment strategies.

Mucociliary clearance

Recent work has suggested that nonclassical or secondary ciliary dysfunction [12] and epithelial channel mutations [13] may be important determinants in compromising mucociliary clearance (MCC) and, thus, predisposing to bronchiectatic damage. Novel developments in lung imaging [14], including quantification of global and regional MCC, may permit more detailed investigation of bronchiectasis patients and assessment of the impact of specific physiotherapy techniques and mucolytic therapies.

Novel genetic approaches

There are potentially three ways in which new developments in genetics might be exploited to better understand the pathophysiology of non-CF bronchiectasis.

1) Genome-wide association scans (GWAS) may, as in other conditions [15], identify novel disease-associated, single-nucleotide polymorphisms and potentially uncover critical pathways involved in bronchiectasis in an unbiased, “hypothesis-free” way. Challenges in undertaking GWAS studies include the large number of patient DNA samples required (usually several thousand), as well as the problem of multiple initiators for the development of bronchiectasis leading to reduced signal discrimination.

2) Candidate gene approaches could also be used to identify disease-associated polymorphisms in more well defined subsets of patients. Obvious candidates would include known genetic modifiers of CF [16], genes involved in lung inflammation and those encoding proteins that are critical for epithelial cell function.

3) Whole exome analysis using massive parallel sequencing can now permit rapid sequencing of the entire expressed genome of individuals [17], potentially permitting detection of gene mutations in small cohorts of patients with familial disease.

Can we improve the treatment of patients with non-CF bronchiectasis?

It is reasonable to anticipate a number of future developments which may impact on the management of patients with non-CF bronchiectasis.

New antibiotic strategies

As highlighted in the chapter by Haworth [18], the development of new nebulised or inhaled formulations of single or combination antibiotics may significantly impact on our ability to provide adequate prophylaxis for patients. In addition, a number of novel approaches are being developed for the treatment of Pseudomonas aeruginosa which may prove useful, including novel β-lactamase inhibitors, blockers of bacterial efflux pumps (which normally remove otherwise toxic antibiotics), antimicrobial peptides and species-specific bacteriophage-based therapy [19].
**Novel anti inflammatory agents**

As discussed in the chapter by Smith et al. [20], anti-inflammatory therapy may be of considerable benefit in bronchiectasis. Novel agents that may have a future role include nonantibiotic macrolides, HMG-CoA inhibitors (statins) and peroxisome proliferator-activated receptor-γ agonists. The difficulty will be to balance control of inflammation with compromise of host defence.

**Mucolytic strategies**

The potential benefits of improved airway clearance [21] are likely to be vast. Future therapies that reduce mucus viscosity (by altering mucin production or blocking subsequent cross-linking), increase airway-surface liquid (through osmosis or altered epithelial channel activity) or improve ciliary function may all have potential benefit.

**Surgery and lung repair**

More research will be needed to define the precise role of surgery in the management of non-CF bronchiectasis [22]. Anticipated improvement in surgical techniques and reductions in perioperative morbidity will impact on when surgery is considered and in whom. Future developments in stem cell biology (including studies re-programming induced pluripotent stem cells and overcoming engraftment difficulties) may open the door for therapeutic lung repair and regeneration.

Over the next few years we can optimistically look forward to greater advances in our understanding of the patho-physiology and genetic determinants of non-CF bronchiectasis, the development of more sophisticated methods for investigation of patients and an increasing number of clinical trials focusing on improving evidence-based treatment of this challenging condition.

**Statement of interest**

None declared.

**References**