

interferon β should be designed with either a serum marker or clinical prediction instrument that will increase the number of susceptible patients with vascular leak or low concentrations of CD73.

Perhaps the most closely watched emerging therapy for ARDS is intravenous infusion of allogeneic bone marrow-derived human mesenchymal stem (stromal) cells.⁶ Pharmacological interventions might be failing in ARDS because the inflammatory cascade is too complex and redundant and the syndrome too heterogeneous to respond to single drugs. Human mesenchymal stem (stromal) cells are therefore appealing as they exert a broad range of anti-inflammatory and antifibrotic effects. Supporting a growing body of preclinical data and a currently enrolling phase 1 trial in humans (NCT02097641), Asmussen and colleagues⁷ randomly assigned 15 sheep to receive placebo, low dose, or high dose mesenchymal stem cells 1 h after a standard smoke inhalation and *Pseudomonas aeruginosa* lung injury. Mesenchymal stem (stromal) cells improved oxygenation and reduced lung oedema in a dose-dependent way without deleterious effects on pulmonary vascular pressures or resistance.

A study by Hernu and colleagues⁸ is representative of several similar studies critically assessing the recent Berlin ARDS Definition.⁹ The investigators noted that the Berlin categorisation based on $\text{PaO}_2:\text{FiO}_2$ ratio did not predict mortality.⁸ In addition to being fairly underpowered compared with the 4188 patients assessed in the derivation study of the Berlin Definition,⁹ this study missed the point of the empirical evaluation of the definition. The purpose of the validity assessment was not to predict mortality, but to test and reject a more complex severe definition of ARDS proposed purely by consensus. Despite demand from the research and clinical community, the available evidence does not support including any single biomarker in the generic

definition of ARDS.¹⁰ Nothing in the current definition of ARDS precludes researchers from including biomarkers, advanced imaging, or specific ventilator settings in the enrolment criteria for clinical trials in ARDS to enrich the study population with subsets of patients likely to benefit from the treatment. Although ARDS remains a challenge because of the heterogeneity of the patient population, recent studies suggest that important advances are being made to improve patient outcome and to provide insights into the pathogenesis of the syndrome.

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Asthma 2014: from monoclonals to the microbiome

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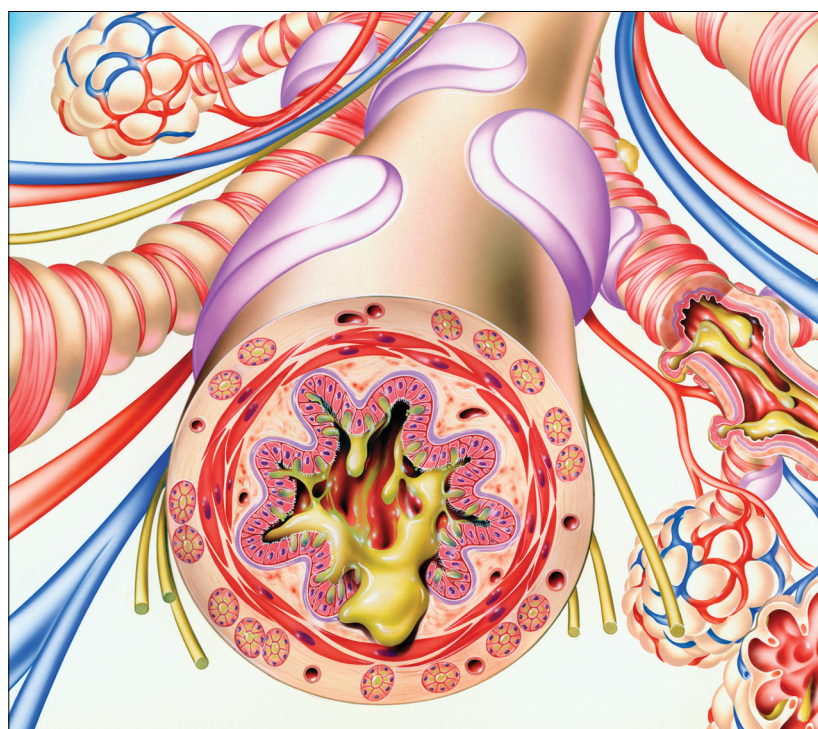
Asthma is a common disease that continues to plague us. Despite the peaks and troughs in mortality—we are currently in the nadir of a trough—the burden of this illness remains high. Ongoing challenges are prevention, better treatment, and cure. Present treatment for asthma relies on the same drug classes that have been used for decades,

namely β agonists and corticosteroids. Targeted therapy for asthma is a new paradigm that holds the promise of improved outcomes through delivery of the right drug to the right person at the right time. However, the feasibility of targeted therapy for asthma and whether it could move beyond refractory disease has been questioned.

The MENSA study answers some of these questions.¹ This randomised controlled trial enrolled 576 patients who remained symptomatic despite high-dose corticosteroids. Participants were identified through clinically accessible measurements of high blood eosinophil count and exacerbation history, and were randomly assigned to receive mepolizumab, a humanised monoclonal antibody against interleukin 5, either intravenously or subcutaneously, or placebo. The results, a massive 53% reduction in the rate of severe exacerbations in the subcutaneous mepolizumab group and a 47% reduction in the intravenous mepolizumab group, were statistically significant and in the same range noted with other targeted therapy approaches for asthma. Further confirmation of this concept was shown in a phase 2b trial of interleukin-5 receptor blockade by benralizumab.² By extending the patient group beyond oral steroid-dependent asthma, and using simple measures to direct the therapy to likely responders, these studies show that targeted therapy in asthma is both effective and feasible.

However, the prevention of asthma remains elusive. As we move beyond the underperformance of our interventions for allergic sensitisation, and the overpromise of asthma genetics, several new hypotheses have emerged. These relate to the role of the intestinal microbiome in modulating the immune response in asthma, and the specific innate immune defect that makes RNA viral infections, such as influenza and rhinovirus, a huge problem for people with asthma. In an elegant demonstration of the power of well-constructed population registries, Stokholm and colleagues³ showed that use of antibiotics by a mother is associated with a dose-related increase in the risk of asthma in her children. This effect was seen both during pregnancy and in the year before and after pregnancy. These data suggest that both the intestinal microbiome and maternal infection risk could be new targets for asthma prevention.

Both the nature and the metabolic output of the intestinal microbiome could be contributing factors to the regulation of immunity and inflammatory responses in asthma. In a ground-breaking study, Trompette and colleagues⁴ have shown that manipulation of host-microbe cross-talk influences inflammation in the gut and lung by modulating bone marrow haemopoiesis. Mice fed a high-fibre diet had increased concentrations of circulating microbial derived short-chain fatty acids



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(SCFAs) and were protected against allergic inflammation in the lung (asthma-like disease), whereas a low-fibre diet decreased concentrations of SCFAs and increased allergic airway disease.⁴ This study raises the intriguing possibility that, in some individuals, asthma could be managed by controlling diet, targeting specific subclasses of G-protein coupled receptors that bind SCFAs, or both. The potential role of impaired antiviral immunity in mediating the effects of the microbiome on immunity in asthma was identified by Semic-Jusufagic and colleagues⁵ who reported impaired cytokine responses to RNA viruses in children who received antibiotics in infancy. Explanations for these effects will need to focus on the mechanisms of impaired antiviral immunity, and how changes to the intestinal microbiome, perhaps induced by antibiotics, might affect this.

Continuing the theme of early-life asthma risk, preterm birth has now been established as both a consequence of maternal asthma⁶ and a risk factor for childhood asthma.⁷ Second-hand tobacco smoke also poses a major risk for preterm birth and childhood asthma, and public health measures have the potential to minimise these risks by reducing exposure. Governments have responded by enacting legislation to minimise second-hand smoke exposure. The very

significant benefits of these health policy initiatives were reported in a meta-analysis of the effect of local and national smoke-free legislation involving 2.5 million births in North America and Europe.⁸ The authors reported that smoke-free legislation was associated with a reduction in preterm birth and hospital attendances for asthma.

Another avenue for investigations is the respiratory epithelium, which is the first line of defence against inhaled pathogens such as RNA viruses. The respiratory epithelium is abnormal in asthma and may also play a central part in orchestrating allergic inflammation in some other respiratory conditions. Recently, Collison and colleagues⁹ have identified a novel pathway in the respiratory epithelium that has a critical role in predisposition to asthma-like disease in a mouse model. Exposure of the airways to either house dust mite or rhinovirus infection (which are both strongly linked to exacerbations in patients with asthma) resulted in the upregulation of the E3 ubiquitin ligase midline 1 (MID1) in the epithelium, which was dependent on Toll-like receptor 4 signalling. Activation of MID1 led to allergic inflammation and airway hyperreactivity; pharmacological inhibition with small RNA species profoundly attenuated these hallmark features of disease. Further understanding the links between infection, activation of the epithelium, and the immune response is likely to result in new therapeutic approaches for the treatment of specific cohorts of patients in whom pathogens drive aspects of the disease.

Asthma research is moving in new directions. Targeted therapy is now feasible using monoclonal

antibodies to control resistant disease, and novel disease mechanisms are under investigation, such as the gut-diet-microbiome axis and its relation to immune modulation. These approaches might better explain the origin and persistence of this perplexing disorder.

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Non-cystic fibrosis bronchiectasis: an evidence-base for new therapies

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In 2010, publication of the British Thoracic Society Guidelines¹ for non-cystic fibrosis bronchiectasis emphasised the need for research to establish evidence-based treatments for patients with this debilitating disease. Non-cystic fibrosis bronchiectasis is characterised by recurrent bronchial infection in association with CT evidence of dilated airways and bronchial wall thickening.¹ These guidelines¹

provided an opportunity for therapy to be based on characterisation of the disease causes, coupled with recognition that once bronchiectasis is present a treatment approach can be applied to tackle each step of the so-called vicious cycle—impaired mucociliary clearance encouraging airway bacterial infection with an inflammatory response that further damages clearance mechanisms.