Contemporary Concise Review 2020: Asthma

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SUMMARY OF KEY POINTS
- Bushfires and coronavirus 2019 (COVID-19) were dominate features of 2020.
- Patients with asthma were significantly affected by the 2019/2020 bushfire season with an increased burden compared to the general population.
- Patients with controlled asthma do not appear to be at higher risk of severe COVID-19 infection or death than the general population.
- Personalized medicine is proposed as the next era for asthma management, with treatable traits as a strategy to implement personalized medicine into practice.
- Patient engagement in personalized medicine strategies is important and needs to be further explored.
- Oral corticosteroid (OCS) use in asthma is common and contributes a major burden. OCS stewardship is recommended.
- Biologic therapies reduce exacerbations of severe asthma and biomarkers can be used to predict treatment responders.
- Epithelia at mucosal and cutaneous surfaces are components in asthma pathogenesis, through airway immunity and inflammation.
- Dysregulation of resident microbial communities in the lung, gut and skin microbiome is relevant to asthma pathogenesis, but there are still many unknowns in this field.

KEYWORDS
asthma, epithelial, microbiota, personalized medicine, treatable traits

INTRODUCTION

Asthma is a heterogeneous inflammatory disease, which is often triggered by environmental factors and viral infections, among other factors. As we consistently heard throughout 2020, the year was ‘unprecedented’ in many respects. It was a year of disaster for many individuals, including those with asthma. Australia welcomed 2020 amid a catastrophic climate emergency: the 2019/2020 Australian Bushfire Season. Australians were only barely emerging from this disaster when the world was hit by another international crisis: the COVID-19 pandemic. These significant events had major impacts on people with asthma, and studies rapidly emerged to characterize these impacts, mechanisms and identify treatments. Despite these catastrophic events, there were continued advances in asthma research and practice, with improved understanding of asthma heterogeneity, in personalized medicine approaches and in mechanisms.

In summarizing the important contributions for 2020, we have identified themes that we considered significant. Starting with the disaster theme, we highlight studies related to asthma and bushfire smoke, and asthma and COVID-19. We then take a look at advances that were made in personalized medicine strategies for asthma, specifically targeting treatable traits and oral corticosteroid (OCS) stewardship. Finally, we will delve into studies that addressed epithelial function in asthma, and the microbiota and asthma.

DISASTERS

Bushfires

The 2019/2020 Australian Bushfire Season wreaked havoc through Eastern Australia from October 2019 to February 2020. Using standard methods for assessing the health impacts of air pollution, Borchers-Arriagada et al. estimated that there were 417 (95% CI: 153–680) excess deaths, and 1305 (95% CI: 705–1908) hospitalizations for respiratory disease related to these fires. Millions of people were exposed to serious levels of air pollution and there was significant material and environmental loss.
The impact of these fires on people with asthma was significant. Responding to the emergency that unfolded, Asthma Australia conducted an online survey to capture the experience of Australians during the bushfire period. Of the 12,152 people who completed this survey 7285 (61%) reported a prior doctor diagnosis of asthma. Of those, the majority (93.6%) reported respiratory symptoms during the event compared to 70.2% of the population without asthma. Overall, people with asthma reported more symptoms, greater use of healthcare resources (hospitalization and emergency department visits), greater need for OCS and greater financial burden due to reduced work, more costs associated with doctor visits, medication needs and protective equipment (masks) than people without asthma.2

A review by Walter et al.3 evaluated Australian epidemiological studies reporting on the effects of pollution from landscape fire smoke (LFS) to emphasize the effects of fires on cardiorespiratory outcomes. Overall, nine studies were included, all of which reported significant associations between LFS and respiratory impacts. There were seven studies specifically reporting on the associations with asthma and LFS, all seven found strong associations between particulate matter (PM) or smoke event days and asthma hospitalizations or emergency department attendances. The impacts on asthma were greatest on the day of exposure.3 Further research is needed to determine approaches for people with asthma that can be enacted during future events.

COVID-19

On 11 March 2020, the World Health Organization declared a pandemic due to COVID-19. The health, personal, societal and economic costs from this disease have been disastrous. By 15 May 2021, there were 161,513,458 confirmed cases of COVID-19, as well as 3,352,109 reported deaths from the disease.4

It is well known that common coronaviruses trigger a worsening of asthma symptoms.5 Correspondingly, there were concerns that pre-existing asthma would pose a risk of COVID-19 susceptibility and indeed disease course.6 However, studies conducted during the pandemic indicate that this is not the case.7,8 A systematic review of 131 studies from around the world found asthma was not associated with COVID-19 disease severity or prognosis.8 Nor did asthma correlate with a higher risk of death among patients with COVID-19.8,9

While the data indicates that people with controlled asthma do not have a greater risk of severe infection than the general population, uncontrolled asthma is a risk for severe COVID-19.10 Wang et al. highlight the importance of optimizing asthma management through regular maintenance controller medication, including inhaled corticosteroid (ICS) to effectively mitigate exacerbations,6 ensuing adherence to treatment, effective self-management skills and avoidance of infections by shielding and good hand hygiene.11

PERSONALIZED MEDICINE IN SEVERE ASTHMA

In 2020, Respirology celebrated its 25th birthday. To commemorate, Professors Richard Beasley and Peter Gibson contributed a commentary piece exploring advances in asthma over those years. The authors reflected on the past quarter century as a ‘golden epoch’ for asthma management, highlighting ‘the inflammation era’, that is, the period of increase in the use of ICS for asthma, resulting in major improvements in asthma mortality. They also reminded the reader of the ‘dark bronchodilator era’ which saw increases in mortality as a result of poorly selected high-dose beta-agonist use. A new era in asthma management was introduced for the present, in which asthma heterogeneity is routinely recognized to allow personalized medicine with individualized treatments targeted to identifiable treatable traits.12 Treatable traits is an approach that addresses heterogeneity by ensuring patients are individually assessed for treatable characteristics or ‘traits’, and an individualized treatment programme is developed and implemented to target traits.13,14 Studies published throughout 2020 advanced this area.

Treatable traits

The first randomized controlled trial (RCT) of a multicomponent treatable traits intervention in a severe asthma population was published in 2020.15 Participants were randomized to receive either severe asthma usual care (n = 28) or a treatable traits intervention (n = 27) over a 16-week period. The core components of the intervention included a multidimensional assessment to identify pulmonary and extra-pulmonary traits and behavioural/risk factors, targeted therapies individualized to each trait and support from a respiratory nurse case-manager to facilitate implementation of the personalized plan (Figure 1).

Participants had a mean age of 52 years and were predominately female (65%). The intervention led to significant improvements in asthma-related quality of life and asthma control compared to the usual care control group. Improvements in inflammatory biomarkers and primary care visits for acute attacks were also shown.15

This study made a significant contribution to the treatable traits body of knowledge but also raised several important questions for future research. Specifically, the need to evaluate the cost-effectiveness of such an approach, and importantly what is the implementation potential to clinical practice of an intervention such as the one tested.

Heaney et al. conducted a single-blind, parallel-group RCT involving 301 adults with severe asthma to assess the effect of treating Type 2 inflammation guided by a composite biomarker (fractional exhaled nitric oxide, periostin and blood eosinophil) strategy, compared to a symptom and risk-based algorithm. Participants were randomly assigned (4:1) to the biomarker-adjusted treatment strategy or symptom and risk-based algorithm. The study’s primary outcome

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was the proportion of people with corticosteroid reduction at 48 weeks. In the intention-to-treat analysis, the primary outcome was not significant.\textsuperscript{16} It was evident that there were participants who did not follow treatment adjustment advice. In the per-protocol analysis ($n = 121$), which excluded these participants, there was a greater proportion of participants in the intervention using a lower corticosteroids dose (30.7\%) compared to control (5\%) ($p = 0.026$).\textsuperscript{16}

This study also raises a number of important questions about the design and implementation potential of treatable traits studies and the importance of engaging patients in the intervention, whether it be one trait targeted or many. In the study by McDonald et al.,\textsuperscript{15} the case-manager had an integral role in the provision of education, as well as in ensuring patients understood the rationale for the treatment and engaged in the treatment advice. Health literacy and patient engagement of the treatable traits strategies are important areas for further exploration and implementation.

**Asthma management**

Advances in the management of severe asthma over the last 10–15 years have been significant. Biological therapies targeted to airway inflammatory phenotypes have allowed greater precision in treatment choices; however, a residual disease burden remains and maintenance OCS use among people with asthma remains high, as reported by the International Severe Asthma Registry.\textsuperscript{17}

Hew et al.\textsuperscript{18} analysed a random 10\% sample of Australian Pharmaceutical Benefits Scheme dispensing data. The aims were to assess OCS dispensing pattens for the management of asthma, and to determine the cumulative dispensing of doses >1000 mg prednisolone equivalent; a dose shown to be associated with long-term adverse effects when given within a lifetime. Data were extracted for the period between 1 January 2014 and 31 December 2018. Within the sample, there were 124,011 people who met the definition of asthma and who were dispensed at least two prescriptions of ICS. Within this population, 51.4\% also had an OCS prescription dispensed, of which 27.9\% were cumulatively dispensed a dose >1000 mg. The group that was dispensed this level of treatment were also dispensed more medications for diabetes and osteoporosis. The authors also analysed the data relating to the proportion of people who during 2018 were cumulatively dispensed >1000 mg prednisone equivalent and stratified this by inhaler controller medicine dose and frequency of use. In those dispensed >1000 mg of prednisolone equivalent, controller inhaler use was considered infrequent in more than half of the people.\textsuperscript{19} These data suggest that OCS are being used in people with suboptimal asthma skills and adherence, highlighting an area for improved management.

Chung et al. summarized the significant reduction in asthma attacks with omalizumab, mepolizumab, benralizumab, reslizumab and dupilimab from RCTs conducted in severe asthma in an important review aiming to highlight the need to transform our approach to OCS in asthma, ensuring
minimization of use when safe and practical. The authors, in line with the recommendations from international experts, recommend the need for OCS stewardship. A summary of guiding principles for such an approach is presented in Figure 2.

This issue of OCS stewardship was certainly topical throughout 2020, with several publications addressing the use of OCS in asthma, the need to minimize their use and efficacious strategies to do so. Suehs et al. reported a modified Delphi survey which was conducted to develop expert consensus statements on the use of OCS, specifically relating to tapering of treatment, adverse effects, patient-physician shared decision-making and adrenal insufficiency. The panel of 131 international experts achieved consensus on appropriate use of OCS, on tapering of treatment, adverse effects and on shared decision-making. A schematic algorithm for tapering OCS was produced and is presented in Figure 3.

The European Respiratory Society/American Thoracic Society guideline on the management of severe asthma was also published. The guideline authors conducted systematic reviews of the evidence to provide recommendations on the efficacy of mAb therapies, macrolide antibiotics and long-acting muscarinic agents. They also made recommendations for the use of biomarkers to predict responders to IL-5 treatments and omalizumab.

**MECHANISMS**

**Epithelial function and asthma**

Rapid urbanization and industrialization have increased pollution-related respiratory diseases in the last decade. There is an observed link between air pollution, the prevalence of asthma and elevated risk of exacerbations, as well as air pollution and sensitization to house dust mites. Understanding the underlying mechanisms of these asthma triggers are challenges faced in managing adult asthma.

Epithelia at mucosal and cutaneous surfaces build a protective barrier against airborne substances, for example allergens, microbes, noxious particles and gases, which has been described as a major component in asthma pathogenesis, through the regulation of airway inflammation and immunity. Epithelial cells express pattern recognition receptors that monitor environmental stimuli and produce endogenous danger signals, which activate dendritic cells and bridge innate and adaptive immunity. For example, Alternaria, which is an allergen associated with allergic asthma and rhinitis, can induce inflammatory cytokine expression from epithelia independent of protease-activated receptors. Furthermore, elevated levels of cockroach-induced IL-9, IL-13 and IL-31 appear to be associated with the development of asthma and other allergic diseases. The increased epithelial release of alarmins including IL-33, thymic stromal lymphopoietin (TSLP) and IL-25 have a key role in activating Type 2 cytokine-producing T-helper 2 cells and innate lymphoid cells, which promote airway hyper-responsiveness (AHR), goblet cell hyperplasia and eosinophilia in asthma.

Airway epithelia damage is a pathological feature, observed in asthma irrespective of inflammatory phenotype. This may offer important insight into the pathogenesis of the foetal origins of asthma. Zazara et al. demonstrated that the foetal origin of asthma is related to a disrupted airway epithelium. In this study, the authors established bone marrow chimeric (BMC) mice harbouring either prenatally stress-exposed lungs...
or a prenatally stress-exposed immune (haematopoietic) system and induced asthma via ovalbumin (OVA). In the BMC mice with prenatally stress-exposed lungs, there was enhanced AHR, fibrosis and inflammation. All effects were sustained if both the lungs and the immune system were exposed to prenatal stress. However, the severity of these features of asthma was not increased by a prenatally stress exposed immune system alone. RNA sequencing analysis of lungs from prenatally stressed, non-BMC, OVA-sensitized females demonstrated a deregulated expression of genes related to asthma pathogenesis, tissue remodelling and tight junction formation.

A 2020 study published by Burgess et al.35 found that IL-13 as a Type 2 cytokine induces periostin expression in airway epithelia, which in turn results in epithelial changes in asthma. The secretion of periostin induced by IL-13 in airway epithelial cells contributes to mucus hypersecretion and perpetuates eosinophilic airway inflammation, leading to worsening of asthma symptoms. This suggests that periostin could be a potential treatment target in asthma.

An et al.36 examined the therapeutic potential that IL-25, IL-33 and TSLP were simultaneously blocked in a murine asthma model to monitor airway responses induced by OVA in St2−/− mice, in which the IL-33 receptor signalling is lacking. Airways reactivity, inflammatory cellular infiltration, expression of Th2 cytokines and fibrosis-related proteins in lung tissue and serum total IgE in response to OVA sensitization and challenge were significantly reduced by deletion of the St2−/− gene. Furthermore, anti-IL-25 and anti-TSLP blocking antibodies further reduced inflammation, expression of Th2 cytokines, airways fibrosis and IgE production in the St2−/− mice, while anti-TSLP alone

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**Figure 3** Schematic algorithm with consensus information on oral corticosteroid tapering. ACQ, asthma control questionnaire; ABPA, allergic bronchopulmonary aspergillosis; EGPA, eosinophilic granulomatosis with polyangiitis; OCS, oral corticosteroid. Reproduced from Suehs et al.,21 with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved.
reduced eosinophil infiltration and local IL-4 expression. These findings suggest that combined inhibition of epithelial cytokines may provide additional benefit in improving airway pathology in this murine model of asthma, and may have some implications for human asthma. In fact, clinical drug development of anti-IL-33 or ST2 monoclonal antibodies is currently underway, with some findings indicating that blocking IL-33 or ST2 could reduce ‘loss of asthma control’ events compared with placebo. In a recent review, Porsbjerg et al. propose that blocking alarmins (TSLP, IL-25 and IL-33) may be a promising approach in a broader asthma population, as these alarmins are triggered early in the inflammatory response which orchestrates broad T2 inflammatory effects.

**Microbiota and asthma**

Studies have consistently shown that the density of microbes that thrive in tissues is low, which seems to be essential for maintaining healthy lungs. Conversely, disorders in the gut, lung or skin microbiome have been linked to the pathogenesis of lung diseases, including asthma. Reviews published in 2020–2021 explored the relationship between dysbiosis of host microbiota and asthma. Lifestyle changes, including an increase of the rate of caesarean section, increased use of antibiotics in early life, westernized obesogenic diets and changes in physical activity patterns, directly and indirectly affect the formation of a diverse microbiota, which has a leading role in orchestrating (early) immune responses and increasing the occurrence of asthma. As there are still many unknowns about the role of microbiota in the pathogenesis of asthma, research in this area is increasing.

In the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC2010) cohort, delivery of babies by caesarean section was associated with significant changes in intestinal microbiota composition. In this study, the risk of developing asthma by the age of 6 was threefold for children who retained their caesarean section gut microbial profile at 1 year of age. Data obtained from a population-based and prospective cohort analyses from British Columbia reported a significant association between exposure to antibiotics in the first year of life and an increased risk of early childhood asthma. Six amplicon sequence variants of gut microbiota (including Rikenellaceae family, Faecalibacterium prausnitzii, Roseburia, Ruminococcus bromii and Clostridium perfringens) were found to mediate the association between antibiotics and asthma. Furthermore, Park et al. demonstrated that azithromycin altered the gut microbiota by reducing airway inflammation in allergic asthma.

In the PASTURE birth cohort, Depner et al. reported that the gut microbiome may be protective against asthma by metabolites. The authors found that there were inverse associations with asthma occurrence and faecal butyrate level, the relative abundance of bacterial taxa that produce butyrate and the level of gene of butyryl–coenzyme A (acetate–CoA-transferase, which is a major enzyme in the butyrate metabolism).

Outside the host microbiota, alterations in the indoor microbiome were also associated with clinical characteristics of severe asthma patients. In a cohort study, 55 individuals with severe asthma underwent an analysis of the indoor microbial flora using electrostatic dust collectors (EDCs). The amplicon-targeted metagenomics was used to compare the difference of microflora from EDC and sputum samples in patients with Type 2 high (T2-high)-asthma and Type 2 low (T2-low)-asthma. The indoor fungal community and microbial community of people with severe asthma were characterized by T2 endotype. Those with T2-high severe asthma had lower fungal diversity but higher bacterial diversity. The indoor environments of those with T2-high asthma was significantly enriched with disease causing fungi and bacteria, such as Aspergillus, Candida, Sphingomonas and Pseudomonas. These findings have rekindled interest in uncovering the interactions between the indoor environment, fungi and the host, thus facilitating the development of new treatments.

**SUMMARY**

Our selection of publications for this concise review of the 2020 asthma literature has highlighted advances, identified ongoing gaps in knowledge and has provided an opportunity to reflect on the year that was. We acknowledge that there are many areas of asthma research that we have not included but hope that this sample is of interest to a broad readership.

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