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Will the asthma revolution fostered by biologics also benefit adult ICU patients?

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Abstract

Purpose: Asthma exacerbations are inflammatory events that rarely result in full hospitalization following an ER visit. Unfortunately, certain patients require prolonged support, including occasional external lung support through ECMO or ECCOR (with subsequent further exposure to other life-threatening issues), and some die. In parallel, biologics are revolutionizing severe asthma management, mostly in T2 high patients.

Methods: We extensively reviewed the current unmet needs surrounding ICU-admitted asthma exacerbations, with a focus on currently available drugs and the underlying biological processes involved. We explored whether currently available T2-targeting drugs can reasonably be seen as potential players not only for relapse prevention but also as candidate drugs for a faster resolution of such episodes. The patient's perspective was also sought.

Results: About 30% of asthma exacerbations admitted to the ICU do not resolve within five days. Persistent severe airway obstruction despite massive doses of corticosteroids and maximal pharmacologically induced bronchodilation is the main cause of treatment failure. Previous ICU admission is the main risk factor for such episodes and may eventually be considered as a T2 surrogate marker. Fatal asthma cases are hallmarked by poorly steroid-sensitive T2-inflammation associated with severe mucus plugging. New, fast-acting T2-targeting biologics (already used for preventing asthma exacerbations) have the potential to circumvent steroid sensitivity pathways and decrease mucus plugging. This unmet need was confirmed by patients who reported highly negative, traumatizing experiences.

Conclusions: There is room for improvement in the management of ICU-admitted severe asthma episodes. Clinical trials assessing how biologics might improve ICU outcomes are direly needed.

KEYWORDS

asthma, IL4Ralpha, IL5, severe exacerbation, T2 airway inflammation

1 | INTRODUCTION

Decreasing asthma admissions and mortality are currently attributed primarily to increased disease awareness and improved inhaled corticosteroid (ICS) availability worldwide.^{1,2} The development of new anti-asthma drugs has focused on moderate to severe exacerbations, which represent a majority of the asthma disease burden due to their immediate and future associated-risks.³⁻⁵ Work impairment, presence and sick-leave, emergency room (ER) visits and admissions, intensive care unit (ICU) admissions, and death can all be directly related to an acute episode of airway obstruction. They can also be indirectly linked to the aggravation of severe episodes because of associated or treatment-induced comorbidities (such as diabetes mellitus, hypertension, tachycardia, and atrial fibrillation). Future risks are mostly related to oral corticosteroid (OCS)-related side effects.⁶⁻⁸

Regarding exacerbations, severe asthma attacks involving the ICU are presently attributed to poor ICS adherence resulting in beta-2 agonist overuse, and other known causes of poor corticosteroid response (such as, for example, obesity or cigarette and cannabis smoking or drug abuse).⁹⁻¹⁶ However, a tangible fraction of admissions and death remain insufficiently explained by these criteria.^{7,17-19} The extremities of the T2 airway inflammation spectrum are poorly steroid-sensitive²⁰ and have led to the development of new anti-asthma drugs. Severe and steroid-refractory T2-inflammation is currently well addressed by IL5 and IL4-IL13 targeting drugs, whereas T2-low asthmatics—also poorly steroid-sensitive—are currently waiting for an appropriately targeted intervention. FDA approvals for biologics mention in the “Limitations of use” that these drugs are “Not for relief of acute bronchospasm or status asthmaticus.”²¹⁻²⁵

Asthma patient trajectories leading to intensive care are unfortunately hallmarked by relapse. Beyond willingness to improve the awareness of intensivists concerning new medications demonstrated to prevent severe exacerbations,^{17-19,26-30} the present review aims to better characterize the burden of severe exacerbations resulting in ICU admission and the current unmet needs related to these episodes, including the patients’ point-of-view. Deciphering the underlying mechanisms involved in these episodes and juxtaposing this knowledge with the mechanisms of action known for standard and biological anti-asthma therapies may help elucidate useful ICU-concomitant indications.

2 | PATHOBIOLOGY OF FATAL AND NEAR-FATAL ASTHMA

Autopsy studies revolutionized the understanding of fatal asthma episodes.^{31,32} Luckily, they are rare. However, the relative paucity of cases often results in the imperfect characterization of the exact clinical circumstances associated with death. Nevertheless, such insight is invaluable for evaluating the relative contributions of the potential contributing factors involved in these tragic episodes. Dying from a fatal asthma episode undoubtedly denotes particularities either in the intensity or the nature of the airway obstruction.

Not all asthmatics exposed to toxic substances such as heroin or who are absolutely not adherent to their treatment will ever experience such an episode. Coupling metacholine-induced ventilatory mismatches with mathematical models emphasized the mandatory involvement of small airway obstruction in near-fatal asthma episodes, with certain such episodes eventually rescued thanks to regional disparities within the lung.³³ Accordingly, most efforts were then concentrated on assessing the contribution of small airways to overall airway obstruction. It was shown that although their relative contribution was smaller at steady state than the proximal airways, a fivefold to 10-fold increase in small airway resistance made them by far the main contributor to near-fatal asthma (NFA) episodes.³⁴⁻³⁷ Biological and histological insights were then sought at the structural and inflammatory levels to further understand this phenomenon.

2.1 | Structural changes characteristic of FA and NFA

Increased airway smooth muscle (SM) mass, thickening of the basement membrane, enlarged submucosal glands, and enlargement of the distal alveolar spaces have all been recurrently reported in association with FA/NFA³⁸⁻⁴² (Table 1). SM mass is clearly a major contributor to these episodes and could, via different indirect pathways, be seen as the process underlying AHR. Interestingly, airway SM cells were shown to be hyperplastic without being hyperproliferative, even in FA cases.^{40,43-45} SM hyperplasia might be specific to asthma, but not necessarily fatal episodes. Similarly, the SM layer is currently seen as a contributor to fatal episodes, but not as the ideal culprit.⁴³ When considering the course of an episode, fast onset likely relates to non- or poorly inflammatory mechanisms.^{46,47} Examples of the latter may include Zyxin, an actin regulator, which was found to be a SM potential stabilizer that accumulates in the airways of FA.⁴⁸ Additionally, the transcriptomic signature of the SM glucocorticoid receptor response in FA cases was shown to be different from that of non-asthmatics.⁴⁴

Extracellular matrix (ECM) deposition was demonstrated as increased in the airway wall, mostly affecting the outer ring, with higher levels of collagen I, III, fibronectin, proteoglycans (decorin, versican, and lumican), and matrix metalloproteinases (MMPs).⁴⁹ Conversely, observed decreases in elastic fibers were likely involved in loss of elastic recoil, “pseudoemphysematous” changes, and subsequent increases in small airway obstruction.^{42,50} Interestingly, these structural changes frequently reported as “remodeling” have been seen as a Janus paradigm. If the airway lumen is narrowed because the airway wall is thickened because of ECM deposition for example, or edema, a smaller increase in the smooth muscle tone would be sufficient to close the airway. On the other hand, some have suggested that a thickened airway should be stiffer, which may confer protection against excessive smooth muscle constriction—and this may eventually explain why fatal asthma can occur in mild asthmatics and why asthma duration is not a risk factor.^{51,52} Impaired

TABLE 1 Inflammatory and structural changes found in near-fatal or fatal asthma studies

Compartment	Frequently reported	Sparsely reported	Inflammatory cells	Remarks	Ref
Airway lumen	Mucus plugging	Bronchial casts	Eosinophils And Neutrophils		[53,55,68,85,91]
Airway epithelium	Thickened	Desquamated	Eosinophils	Increased TLR 2, 3, and 4 Increased TSLP	[108]
Submucosal glands	Enlarged; increase of myoepithelial cells	Goblet cell hyperplasia	Eosinophils and neutrophils Predominant in long courses	No difference in MUC5AC and MUC5B	[31,109]
Basement membrane	Thickened				
Submucosal vessels	Hypervascularity		mast cells, eosinophils, and neutrophils lymphoid aggregate		[53,74,110]
Airway smooth muscle	Hyperplastic	Hypertrophic	Mast Predominant in short course		[31,40]
Extracellular matrix	Altered elastic fibers Increased collagen, fibronectin, proteoglycans, and MMP deposition		Mast Eosinophils	Increased FcεR1 expression	[40,42,111]
Alveolar level	Enlargement of the distal airspaces	Disruption	DC Eosinophils Neutrophils		[42]
Lymph nodes			Eosinophils	HLA-DR+	[75]

perception of airflow obstruction is also one of the leading causes of delayed management and a risk for ICU admission and death. However, it was already known in the “before corticosteroid” era that only a fraction of asthmatics were subject to fatal or near-fatal episodes, and therefore, SM and ECM involvement are most often not in themselves sufficient to provoke NF/NFA. In this regard, the final contribution of mucus plugging may then be seen as the critical drop required to make the vase overflow.

Hence, the most striking change described in NFA/FA is the constant description of intense mucus plugging of both the small and large airways^{39,50,53-57} (Figure 1). A decreased density of club cells has also been shown,⁴⁹ supposedly in relation to goblet cell hyperplasia.⁵⁹ Ultimately, authentic and frightening airway casts are removed at autopsy.^{50,60} Additionally, the myoepithelial cells of the submucosal glands were found to be increased. A potential contribution of blood vessels, both bronchial and pulmonary arteries, has also been shown.⁶¹ A possible worsening of airway narrowing by interstitial emphysema is discussed via a few case reports.⁶²

2.2 | Inflammatory changes characteristic of FA and NFA

Intriguingly, few data recording airway inflammatory patterns at ICU admission exist, despite the availability of new non-invasive sampling techniques (eg, nasal washes) (Table 1). All inflammatory cell types have more-or-less been shown to be increased in FA episodes,



FIGURE 1 Mucus plug shaping a bronchial tree cast coughed by a patient. *With permission of Prof Klatt*

including B cells, T cells, eosinophils, neutrophils, mast cells, dendritic cells, and invariant natural killer T cells. Variations may be seen according to the onset of the episode: Most of the following findings were found in slow-onset episodes, in contrast with rapid onset (less than 3 h classically) where inflammatory signals were rarely present.^{46,47} Heterogeneities in the inflammatory patterns seen in asthma at steady state and during an exacerbation, outside the ICU context, are largely known and deciphered thanks to seminal papers.^{63,64} These patterns may change according to the trigger (viral, fungal, bacteria, airborne pollutants, and allergens for example) but

little is known regarding whether these patterns can change in a given patient (eg, having a T2 exaggerated response after an allergen challenge but T1 in response to a pollutant). Residual exacerbations in IL5-blocked patients may indicate that this scenario may explain why not all patients are super responders.⁶⁵ Asthma exacerbations, including the worst ICU situations requiring ECMO, are largely driven by viral infections, with rhinoviruses being the most commonly found.^{3,66,67}

Neutrophils are the predominant inflammatory cells in the airways of FA patients, but this might also be largely attributable to the high doses of corticosteroids these patients receive.⁶⁸ Interestingly, high blood eosinophil counts are associated with more frequent and more severe exacerbations.^{69,70} In this regard, a positive relationship between the blood and airway compartments has been established and clinically used in asthma for initiating biologics, even though many confounders—corticosteroids in first place—demonstrate the limits of this biomarker.^{71,72} Descriptions of relatively similar patterns of inflammation can be found for either the airways, the vessels, and the lymph nodes.^{32,43,53,69,73-75} Mast cell degranulation was found to be related to the time to death but also to mucus plugging.^{31,76} Many mast cell-derived mediators have been shown to be overexpressed in samples assessed at autopsy such as tryptase, chymase, eicosanoids, and others. Not specific to fatal asthma cases, the infiltration of mast cells within the airway smooth muscle bundle was found as a micro-anatomical demonstration of the relationship linking airway hyper-responsiveness (AHR) with inflammation.⁷⁷⁻⁸² The complement component receptors C3aR and C5aR were found increased in the epithelium and the vessels.⁸³ This followed a period where “airway anaphylaxis” was a supposed subphenotype of asthma in the ICU, even though it looks rather complex to address the eventual specificities of the clinical presentations.⁸⁴ Eosinophils are also widely found alongside the entire airway tree in asthma, in FA, and the nose.³² Eosinophils are critical contributors to mucus secretion⁸⁵ and rheology, and this can result in clinical consequences measurable at HRCT.⁵⁵ Extracellular eosinophil traps and Charcot-Leyden crystals might be the biological substrate underlying this process. Indeed, anti-galectin10 antibodies may neutralize most of the features classically found during an exacerbation of asthma.⁸⁶ But in the end, mast cells may be the most specific contributor to fatal and near-fatal episodes when compared to exacerbations that are managed in the ward or outside the hospital (but this needs validation). Accordingly, most T2 cytokines are likely involved in the process. Among them, IL4 and IL13 are likely more specific of near-fatal episodes given their contribution to mucus plugging

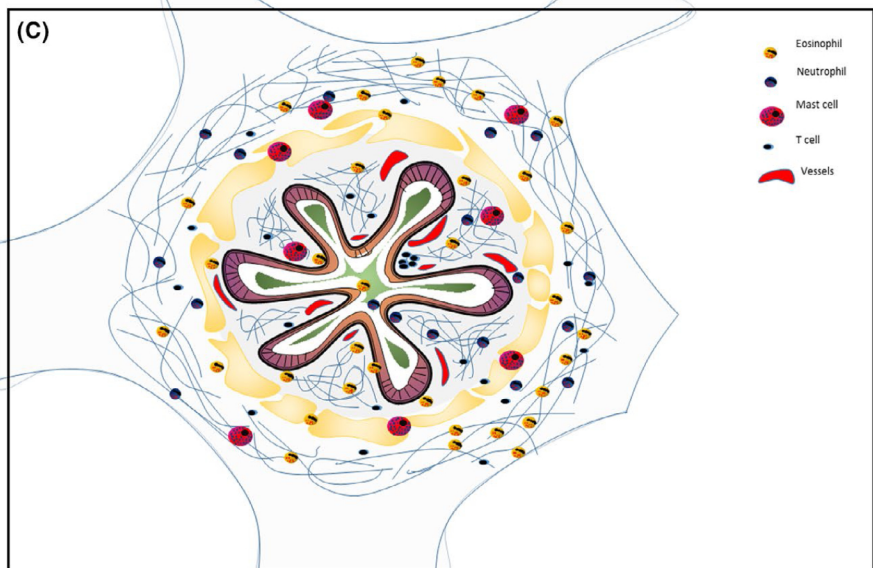
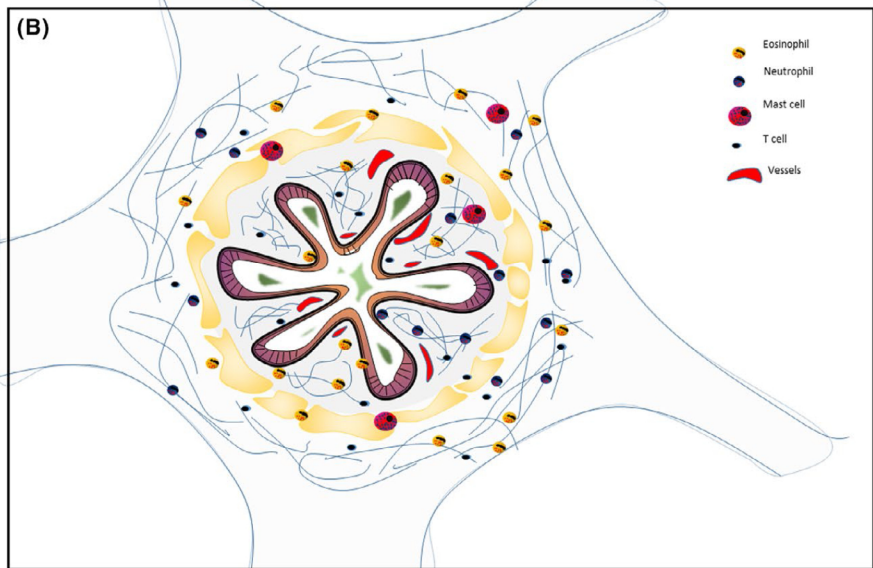
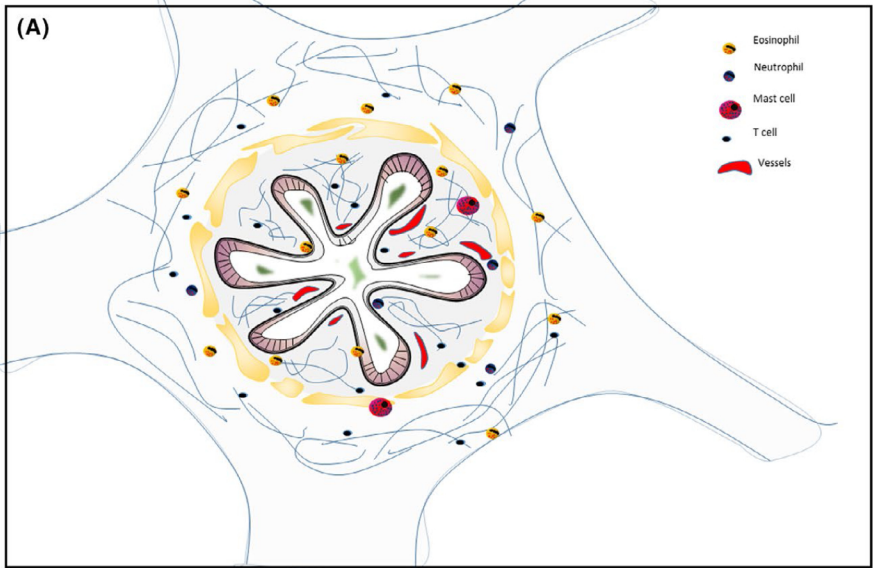
and airway casts, but also the acknowledged importance of mast cells. IL5 and IL8 should be important in granulocyte trafficking, but whether this is of importance at the acutest phase of near-fatal episodes is less clear. Alarmins have never been assessed in this setting. Intuitively, their upstream mechanism of action might be relevant at the earliest phase of these dramatic episodes, as well as their ability to affect both the smooth muscle layer and the submucosal glands. The timing of the T2 cascade is unknown in near-fatal and fatal asthma episodes, and the ideal target can only be suggested by deduction of what is known in other asthma events where immunopathological data are available. At a glance, although heterogeneous inflammatory patterns are characteristic of severe asthma, the most common features found in NFA and FA episodes are evocative of a T2-driven patterns or a mixed T1 and T2 pattern—finally similar to that seen in the ward.^{87,88}

Figures 2 and 3 summarize all these findings at the small airway level, highlighting the specificities related to near-fatal asthma.

3 | EPIDEMIOLOGY, NATURAL HISTORY, AND TRAJECTORIES LEADING TO ICU ADMISSION

Achieving a definite diagnosis of asthma in the ICU is complex, and this may explain why epidemiological data are not as robust as they might be. This is moreover true when patients are old, comorbid, unable to talk, and frequently exhibit overlapping features with COPD in their past history and/or non-CF bronchiectasis (if seen by the angle of HRCT). Epidemiological data are also sparse and heterogeneous among countries. Thanks to the Global Burden of Disease study group, it is known that around 0.40 million people (0.36 to 0.44 million) died from asthma in 2015, a decrease of 26.7% (–7.2 to 43.7) from 1990.⁸⁹ Once in the emergency department, around one half of patients are admitted whereas only 26% of asthma attacks present “life threatening” features. It is also worth recalling at this time that not all episodes pass through an ED and that some asthma deaths occur outside the hospital (eg, in the street, in jail, and at home).⁹⁰⁻⁹³ The average length of stay is around 6 days, with huge discrepancies and large ranges depending on the healthcare system, age, and comorbidities.^{91,94,95} Prognosis is dominated by age and comorbidities.^{93,96} The risk of developing ICU-related adverse events such as diabetes, ventilator-associated pneumonia, neuro-mopathy, and ventilator-associated barotrauma ultimately leading to hazardous pneumothorax and/or pneumomediastinum are

FIGURE 2 Representative illustrations of a small airway. (A) in mild asthma, important findings are as follows: Eosinophil, Limited mast cell myositis, Activated airway epithelium, No mucus plugging, and Efficient elastic fiber network. (B) during an exacerbation of asthma, consistent findings are as follows: Eosinophils and neutrophils, T cells, Smooth muscle hyperplasia, Hyper-activated airway epithelium and Thickened basement membrane. (C) in a near-fatal or fatal episodes, specific findings are: mucus plug—airway casts, intense mast cell myositis, aggregated T cells, intense outer-wall ECM deposition, disrupted elastic fiber network, intense inner-wall ECM, hypervascularity, perivascular inflammation, and loss of alveolar attachments



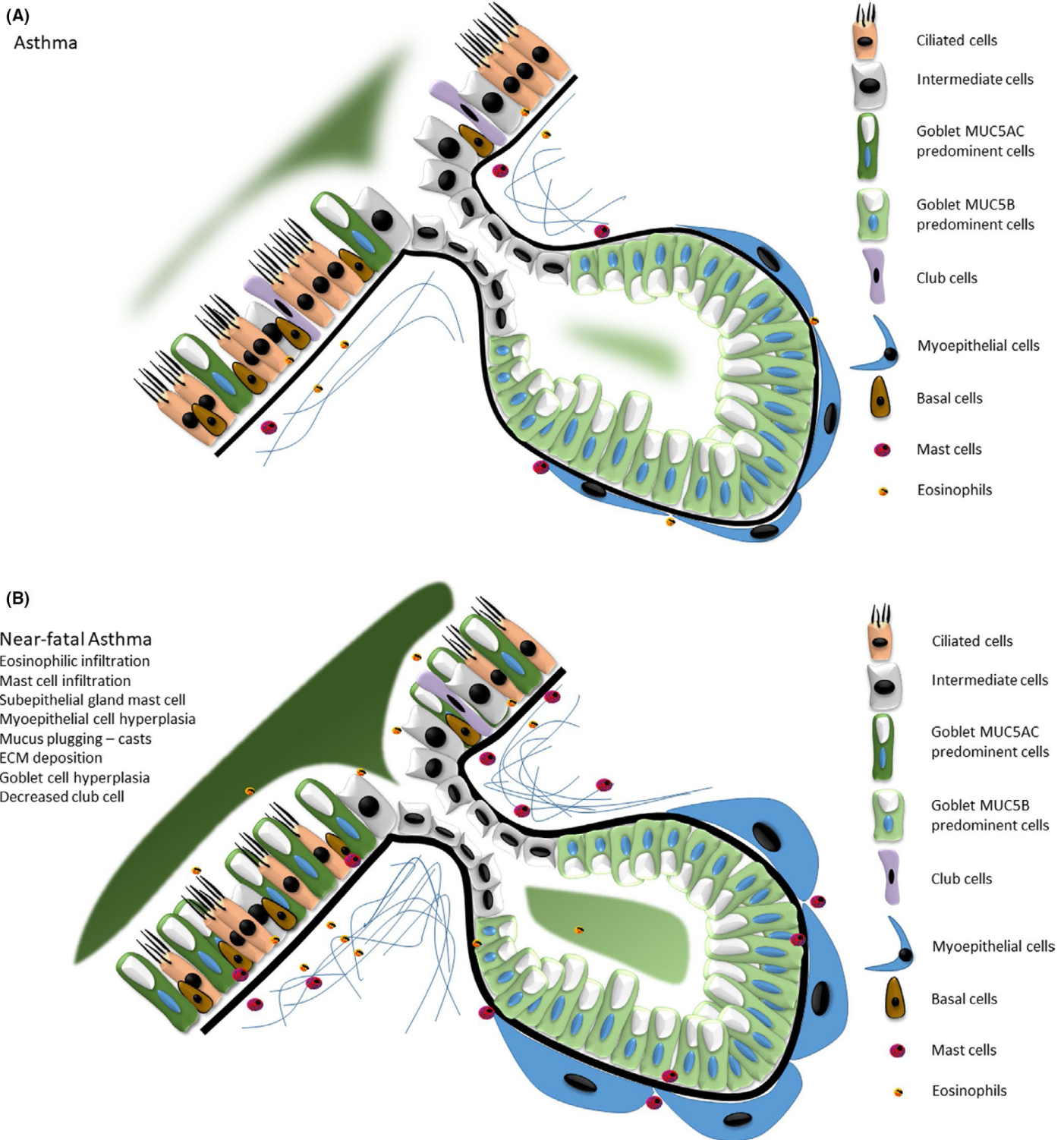


FIGURE 3 Representative illustrations of the small airway epithelium and submucosal glands in (A) mild asthma and (B) near-fatal or fatal asthma with eosinophilic infiltration, mast cell infiltration, subepithelial gland mast cell, myoepithelial cell hyperplasia, mucus plugging—casts, ECM deposition, goblet cell hyperplasia, and decreased club cell density

classic, but relevant rates are poorly reported.^{92,97-99} In-hospital mortality rates range between 1% and 1.45% in various studies in the ward, but can reach nearly 10% in patients intubated in the ICU,^{96,100,101} stressing the importance of developing new therapeutic approaches. In a twenty-year follow-up study of patients with severe asthma, 10 among 52 finally died of a fatal asthma episode despite being optimally managed.⁷

4 | THE CURRENT UNMET NEEDS OF INTENSIVE CARE FOR ASTHMA AND THE OPPORTUNITY TO USE T2 TARGETING BIOLOGICS

In ICU-admitting asthma, mucus plugging eventually leading to airway casts appears as the most striking barrier to punch through,

BOX 1 Patient perspectives

“Better understanding the mechanisms that lead to near fatal and fatal exacerbations in asthma is important. Creating insights that could lead to more effective treatment resulting in fewer fatal attacks would be beneficial to patients. “Better understanding the mechanisms that lead to near fatal and fatal exacerbations in asthma is important. Creating insights that could lead to more effective treatment resulting in fewer fatal attacks would be beneficial to patients.

Survival is important from a patient perspective, but not only survival. Recuperation after a severe, near fatal asthma attack that requires admittance to an ICU is important. Does the treatment used in the ICU to increase survival support recovery? What is the impact of the treatment chosen on the co-morbidities that are an integral part of the patients’ burden of disease?

I realize that very often survival is seen as the most important, the one and only goal, and that is understandable. It would however be great if survival could be combined with a positive outcome on recuperation and quality of life for the patient. The impact on the patient’s lungs, asthma, comorbidities and other bodily functions of a very severe asthma attack should be included in the considerations of what treatments are preferred for that patient. If we can combine survival with as little harm as possible, that would be the best outcome.

What is also often lacking from a patient perspective after an ICU stay is tailor-made counselling and support for the patient and his or her carers during the recuperation in hospital and at home. This might also decrease the feelings of uncertainty and fear in both patients and carers and facilitate recovery.”

BOX 2 Main needs in ICU-admitted asthma

Mechanistic

How can airway mucus plugging be prevented?

Does a NFA episode indicate T2 inflammation per se?

Clinical

Prevent intubation

Determine optimal ventilator settings when required

Identify when ECMO and/or ECCOR are indicated

Decrease in-hospital mortality

Reduce massive OCS and SABA exposure and subsequent side effects

Should steroid-naïve patients be initiated with a biological?

Reduce length of stay

Reduce ICU-related adverse events (neuromyopathy, ventilator-acquired pneumonia, etc)

Prevent readmission

Reduce overall psychological distress related to ICU admission—fear of readmission

drug before intubation was required in order to prevent ICU-related complications.

Given the high dose of systemic steroids administered, side effects (and in particular the risk of ventilator-acquired pneumonia) are important with potentially poor outcomes. Neuromuscular blockades associated with sedation and steroids can lead to ICU-associated neuromyopathy, a great cause of concern given the subsequent massive burden.

Psychological distress and anxiety related to ICU admissions, asphyxia, and relapse have gained in awareness, but are not always well taken into account clinically. Finally, it is worth remembering that most patients who have been admitted to an ICU are excluded from most clinical trials and are thus under-represented in research. A synthesis of the main clinical needs is proposed BOX 2.

5 | AVAILABLE T2-TARGETING BIOLOGICS IN SEVERE ASTHMA AND THEIR POTENTIAL USEFULNESS IN THE ICU

Table 2 summarizes available pharmacological and clinical data. Only one study was performed in an emergency department, but with the aim of preventing readmission successfully reached.¹⁰² Intuitively, and because IL5 targeted-treated patients present less frequent but also less severe exacerbations than those receiving placebo, both mepolizumab and benralizumab have been successfully used in some cases.^{65,103-106} Conversely, given their respective T2 targets, there is a strong rationale for testing other biologics such as reslizumab obviously, but also dupilumab, in the

literally as well as figuratively. The complexity of finding effective mechanical ventilation settings is consistently reported, given the high regimen of pressure aiming at preventing barotrauma and subsequent complications. Onset of action of currently available drugs (such as bronchodilators and systemic steroids) is clearly a current limitation, especially in very rapidly progressing episodes. The current use of helium-oxygen, magnesium sulfate, and others suggest that more potent bronchodilators are required. Indeed, this may indicate the need for blocking mucus production, which at least depends on eosinophilic inflammation, mast cell degranulation, and IL13. Accordingly, all the currently available biologics, if they act fast enough, are likely to provide benefits to NFA management. The main aim would be to reduce the rates of ICU admission and intubation, and accelerate recovery from episodes that may have progressed with such rapidity as to preclude starting the

TABLE 2 Currently available biologics in severe asthma. Pharmacological characteristics, established benefits, and possible benefits in the ICU

	Route	Pharmacokinetic	Bio-disponibility	Half life	Elimination	Current posology	Mechanism of action	OCS sparing
Omalizumab	SC	IgE binding: Peak at day 3 (urticaria), detectable after 1h	68%	6-8 days	IgG and IgE complexes (reticulo-endothelial system—liver)	Q2 - Q4	Anti IgE	?
Mepolizumab	SC	Peak 4-8 d	64%-80%	16-22 days	Proteolytic enzymes	Q4	Anti IL5	-50%
Benralizumab	SC	Eosinophilic depletion at 24h	59%	15.5 days	Proteolytic enzymes	Q8	Anti IL5R	-75%
Reslizumab	IV	Immediate	100%	24 days	Proteolytic enzymes	Q4	Anti IL5	?
Dupilumab	SC	Tmax 3-7 days	61%-64%	Non-linear 9-11 weeks	Proteolytic enzymes	Q2	Anti IL4 IL13	-70%

Abbreviations: NP, nasal polyps; HES, hypereosinophilic syndrome; EEo, eosinophilic oesophagitis; EGPA, eosinophilic granulomatosis with polyangiitis; AD, atopic dermatitis; AHR, airway hyper-responsiveness.

ICU. Which of the available mAbs would most likely be efficient in the ICU? This question must be carefully considered not only in terms of mechanisms, but also pharmacokinetics (PK). The usual criteria used for assessing small molecules are not transposable to mAbs. This is because the mechanisms of binding, internalization, and diffusion are complex, and the resulting plethora of variables can preclude efficient PK models. According to available data (summarized in Table 2), the immediate availability conferred by intravenous Reslizumab makes it one likely candidate. However, the superiority of the latter over a subcutaneous administration is not obvious and should not be assumed based on this unique characteristic. As concerns benralizumab, eosinophil depletion starts as early as 24hr after the first administration, making this drug a second likely candidate—and available case reports support this point. These examples demonstrate how different aspects of pharmacological assessment may come into play. Current data describing mechanisms of action and immediate clinical and biomarker responses are limited and a crucial area of research. For example, very rapid improvements were reported with dupilumab in the SINUS studies¹⁰⁷ (around 48 h for smell recovery in some patients) whereas the currently available data do not necessarily support such rapid improvement given the need for 3–7 days to reach the Tmax. Finally, little is known about the immediate kinetics of IL4 versus IL13 blockades, which both target the alpha subunit of the IL4-receptor. However, that PK difference may considerably affect efficiency in the ICU.

6 | CONCLUSION

There is substantial room for improvement in managing asthma in the ICU. Despite recent improvements in managing severe asthma, asthma in the ICU is still a cause for concern. Targeting T2-related features characteristic of near-fatal pathology, such as mucus plugging, smooth muscle constriction, and mast cell degranulation, may help address this issue.

CONFLICT OF INTEREST

None of the authors report interests related to the present work.

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Exacerbation rate	FEV1 improvement	Comorbidities covered	Known effect in ICU	Likelihood of acute effect in ICU	Side effects	Ref
-50%	Likely	Urticaria, NP	None	IgE binding is present in NFA. Rapid IgE neutralization. May target mast cells.	Very rare anaphylaxis	[24]
-60%	100 ml	NP, HES, EEO, EGPA	None	Eosinophils are highly present and may participate in both mucus and AHR	Post-marketing indicates possible very rare anaphylaxis	[21]
-60%	100 ml	NP, HES, EGPA	Prevention of readmission One case report	Eosinophils are highly present and may participate in both mucus and AHR	-	[22,105]
-60%	100 ml		None	Eosinophils are highly present and may participate in both mucus and AHR	Very rare anaphylaxis	[25]
-70%	200 ml	AD, NP	None	Mast cells, mucus, and smooth muscles are potentially targeted by IL4 and IL13.	Possible transient blood eosinophilia	[23]

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