Review Article

Targeting Inflammatory Responses to *Streptococcus pneumoniae*

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**Abstract**

*Streptococcus pneumoniae* is a common cause of infectious morbidity and mortality, causing otitis media, pneumonia, septicemia, and meningitis. The host inflammatory response is required for clearance of bacteria, but excessive inflammation can mediate bystander tissue damage. The host response is complex; involving initial recognition by pattern recognition receptors, clearance by tissue macrophages and the institution of an inflammatory response. This is orchestrated by the synthesis of a range of cytokines and chemokines that mediate both local and distant inflammatory effects. This causes neutrophil recruitment, upregulation of mucosal immunity, an acute phase response, and eventually the generation of antibodies. Currently, apart from antibiotic initiation, the use of adjuncts is limited to steroids in meningitis, with less evidence for their use in pneumonia. Some antibiotics used in recommended treatment regimens have immunomodulatory effects which may explain their beneficial effects above and beyond their antibacterial functions. By understanding the role of inflammation in pathogenesis better, more targeted approaches are being developed to limit excessive inflammation. Pathways being evaluated include inhibition of chemokines, inhibition of coagulation pathways that crosstalk with inflammatory signalling, and possibly the repurposing of statins to take advantage of their immunomodulatory effects. All these approaches much strike the balance of reducing excessive inflammation while allowing enough phagocyte recruitment to enable effective bacterial clearance.

**Focal Points:**

- **Bedside:** Targeted inhibition of inflammatory pathways may be a useful adjuvant to antibiotic therapy of *S. pneumoniae* pneumonia and meningitis, to ameliorate host induced tissue damage. Nuance approaches may yield more benefit than broad brush immunosuppression, such as with corticosteroids.
- **Benchside:** The dissection of the complex interaction of pathways downstream of *S. pneumoniae* recognition will allow targeting of specific components of the inflammatory response. This will allow enough inflammation to control bacterial replication, but limit bystander tissue damage.
- **Industry:** Several drugs have been trialled for use in sepsis and pneumonia trials to control excessive inflammation that may be effective against *S. pneumoniae* induced disease. By identifying more effective targets, and identifying the cause of infection early, there is the potential to develop drugs that have therapeutic benefit.

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1. Importance of *Streptococcus pneumoniae* and the role of inflammation

*Streptococcus pneumoniae* (also known as pneumococcus) is one of the leading global causes of pathogen associated morbidity and mortality. For severe disease the mortality rate remains high at 10–35% [63] even if the patient receives effective antibiotics, emphasising the importance of inflammation-induced physiological disturbance for disease pathogenesis. As well as causing over half of pneumonia cases, *S. pneumoniae* is a common cause of otitis media, septicemia, and meningitis [65,53]. However, in most people *S. pneumoniae* is only found as a relatively common asymptomatic nasopharyngeal commensal controlled by the host immune response with little local tissue damage. If the bacteria stray into other parts of the body, a brisk inflammatory response is organised to limit bacterial outgrowth. While this is necessary to contain infection, the sequelae of an exuberant inflammatory response can cause significant bystander tissue damage – leading to disease manifestations. In pneumonia this inflammatory response to infection usually clears after bacterial clearance with resolution of the cellular infiltrate. Occasionally the inflammatory response to pneumonia can be severe enough to cause acute respiratory distress syndrome (ARDS), and in other organ compartments inflammation can be detrimental to the host and contributes to the high mortality rates associated with septic shock and meningitis. For these reasons there is considerable interest in the potential therapeutic role of anti-inflammatory agents. However therapies targeting the complex pathogenesis of host tissue damage due to acute inflammation will need to be effective without compromising host defence.

2. Mechanisms of inflammatory response

The initial host immune response during lung invasion by *S. pneumoniae* involves mucociliary clearance, antibacterial peptides in epithelial fluid, phagocytosis and killing by resident macrophages, and epithelial cells acting as a barrier to further invasion. Alveolar macrophage independent clearance mechanisms are important for the clearance of *S. pneumoniae*, particularly in the presence of encapsulated *S. pneumoniae* [13]. Virulent forms of *S. pneumoniae* express a polysaccharide capsule that inhibits opsonisation by complement and antibody, so inhibiting effective phagocytosis [38,39]. If bacterial replication is not contained, an inflammatory response induces leucocyte recruitment; initially of neutrophils, then monocytes and lymphocytes. Neutrophils increase the capacity to phagocytose *S. pneumoniae*, and monocytes amplify the inflammatory response and regulate interferon (IFN) γ and interleukin (IL) 17 production [66]. T helper (Th) 17 cells increase mucosal immunity by increasing antibacterial peptide secretion and epithelial barrier functions as well as promoting neutrophil recruitment, whereas Th1 cells activate macrophages and may increase bacterial killing. An adaptive response develops after nasopharyngeal colonisation and after infection, including anti-capsular antibodies generated largely by splenic macrophages presenting capsular polysaccharide to neighbouring B lymphocytes [17,28], anti-protein antibody and cellular responses. These adaptive responses can prevent subsequent infection; for example, nasopharyngeal colonisation of mice with *S. pneumoniae* induces an antibody and Th17 cellular response to protein antigens that in combination reduces bacterial load during subsequent pneumonia [98].

Lytic antibiotics such as penicillin may cause the release of bacterial pathogen associated molecular patterns (PAMPs) such as cell wall lipopolysaccharides and peptidoglycans that exacerbate inflammatory tissue damage analogous to the Jarisch–Herxheimer reaction. Different tissues vary in their ability to tolerate inflammatory damage. For example, the delicate meninges and brain often have residual damage after successful treatment of meningitis with consequent neurological defects, whereas the lungs are usually left with minimal or no tissue damage after a severe *S. pneumoniae* pneumonia, but. However, recent studies suggest *S. pneumoniae* infections may exacerbate underlying pulmonary fibrosis [46], and are a common cause of exacerbations of chronic obstructive pulmonary disease [27] probably due to the effects of the inflammatory stimulus of infection on the underlying disease-associated inflammation.

Although critical to initiating an effective inflammatory response alveolar macrophages also play an important role in limiting excessive inflammation. In the resting state alveolar macrophages are relatively anti-inflammatory, and this is regulated by neighbouring cells such as alveolar epithelium. Damage to epithelial cells results in loss of negative regulators of alveolar macrophages such as Triggering Receptor Expressed On Myeloid Cells 2 (TREM2) and Cluster of differentiation (CD) 200, skewing them towards a pro-inflammatory phenotype [33,33]. As well as phagocytic killing of pathogens, apoptotic cell death of macrophages can also limit *S. pneumoniae* numbers without generating excessive inflammation [22]. In addition macrophages are important for effective effectorcytosis of cellular infiltrate, again limiting neutrophil mediated tissue damage. The alveolar macrophage population is rapidly depleted with the onset of *S. pneumoniae* pneumonia, and recruited monocytes are probably able to fill a similar role and could be important in limiting inflammation [81].

While recruited neutrophils increase the phagocytic capacity at the site of infection, release of neutrophil granular proteases and reactive oxygen species, and possibly neutrophil extracellular traps production are likely contributors to the associated bystander tissue damage and breakdown of the epithelial barrier. This may be promoted by unregulated necrotic cell death, caused by both neutrophil granular proteins and the action of the *S. pneumoniae* toxin pneumolysin (Ply) [108,57]. Lymphocytes also play a role in the inflammatory response to pneumococcus. The dominant response is Th17 cells which upregulate mucosal immunity and potentiate inflammation [106,55]; however regulatory T cells downregulate inflammation, ameliorate tissue damage and appear to be important in survival in mouse models of pneumonia [64].

2.1. Recognition of *S. pneumoniae*

Humans express a broad range of pattern recognition receptors (PRR) that recognise specific motifs that are conserved among a broad range of pathogens, including *S. pneumoniae* (see Table 1). These comprise of cell membrane bound receptors expressed at the cell surface or within endosomes, and cytosolic receptors. Several families of PRR are directly involved in generating the
inflammatory response to *S. pneumoniae*, including Toll like receptors (TLRs), nucleotide binding oligomerisation domain (NOD) 2, and components of the inflammasome.

TLRs are a family of single, membrane-spanning non-catalytic proteins with 10 members in humans. Several are expressed on the cell surface; TLR1, 2, 4, 5, 6. The rest are expressed on intracellular endosomal membranes. They form homo- or heterodimers and on recognition of PAMPs, recruit adaptor proteins to elicit intracellular signalling cascades that initiate inflammation. TLR2 recognises lipoproteins expressed on the cell surface of *S. pneumoniae* [84], and TLR4 may be recognised by Ply [54], although this is controversial [100,205,58,8]. When either TLR2 or 4 bind their ligands, the cytosolic adaptor protein myeloid differentiation primary response gene 88 (MyD88) is recruited to the cell membrane, and initiates a signalling cascade, involving the interleukin-1 receptor-associated kinase (IRAK) proteins, that culminates in the translocation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) to the nucleus. NFκB induces transcription of many genes, including inflammatory cytokines such as tumour necrosis factor (TNF), IL1β, and IL6 which are the chemical signalling molecules that sentinel immune cells use to communicate with surrounding tissues (discussed in more detail in the next section). TLR9 is expressed on the phagolysosomal membrane and recognises bacterial DNA [1], and acts via the same signalling pathway, as well as separately inducing interferon genes. There is some redundancy within the TLR system for recognising components of bacteria, but deficiency in the common adaptor protein MyD88 has more profound effects in *in vivo* models than defects of single TLR proteins [2,47]. Humans with defects in innate immune signalling such as IRAK4 and MyD88 have a very high incidence of severe *S. pneumoniae* infections [92], demonstrating that the recruitment of leucocytes and institution of the acute phase response are essential for preventing invasive disease.

NOD2 is a cytosolic PRR that recognises muramyl dipeptide, the breakdown product of cell wall peptidoglycan (PG) from *S. pneumoniae*, and also acts via nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) via activation of receptor-interacting serine/threonine-protein kinase 2 (RIPK2) to induce inflammation [67]. NOD2 deficient mice have a less inflammatory phenotype in a mouse meningitis model [52]. Although *S. pneumoniae* is resistant to lysozyme-mediated lysis [91], activation of NOD2 in mice remains dependent on a specific isoform of lysozyme (LysM) for release of NOD2 ligands without pneumococcal lysis [18]. In addition, the bacteria must possess Ply for the PG to enter the cytosol [18].

NOD Like Receptor family pyrin containing domain 3 (NLRP3), and absent in melanoma 2 (AIM2) form cytosolic protein complexes called inflammasomes that promote inflammation by activating post-translational changes to activate cytokines by cleaving zymogenic proforms, IL1β and IL18 in particular. These proteins contain the adaptor molecule apoptosis-associated speck-like protein containing a caspase activation recruitment domain (ASC) and caspase-1. NLRP3 is expressed minimally in macrophages, but is inducible by inflammatory stimuli such as cytokines [23]. NLRP3 is known to be activated by pore-forming toxins like Ply as well as damage associated molecular patterns such as uric acid, ATP, and silica [37]. *S. pneumoniae* interaction with NLRP3 is dependent on Ply, with human and mouse macrophages showing reduced IL1β release if stimulated by Ply deficient mutants despite IL1β mRNA expression remaining unaffected [58]. NLRP3 appears to be activated by ion shifts due to Ply mediated pore formation, and deficient mice have greater mortality and albumin leak into bronchoalveolar fluid in a mouse pneumonia model [100,58], whereas AIM2 is activated by bacterial DNA, which enters the cytosol through pores created by Ply. However, deficiency of ASC has a less redundant role than NLRP3 [26]. In a *S. pneumoniae* meningitis model NLRP3 deficient mice have better survival [35], though the opposite was found in a study using a different *S. pneumoniae* serotype [29,30]. Caspase activation recruitment domain (CARD8) forms part of the NLRP3 inflammasome and is implicated in negative regulation of IL1β secretion; a polymorphism that causes a truncated form of the protein is associated with worse outcomes in human meningitis. In addition, higher levels of IL1β and IL18 in cerebrospinal fluid (CSF) during meningitis are associated with systemic and neurological complications [29,30]. These studies support the concept that inflammation in response to *S. pneumoniae* has deleterious effects within the central nervous system.

### 2.2. Cytokines and chemokines

After cellular recognition of *S. pneumoniae* by PRRs, generation of the inflammatory response requires cellular production of cytokines and chemokines (chemical signalling molecules that induce influx of leucocytes to the site of infection) (see Tables 2 and 3). In mouse models of intranasal *S. pneumoniae* infection, levels of the pro-inflammatory cytokine TNF are elevated in bronchoalveolar lavage fluid within an hour of infection followed by IL1β, particularly in lung homogenates, and IL6. IL6 is also rapidly elevated in serum. These cytokines responses are associated with neutrophil infiltrate starting from 2 hours onwards, with a later influx of inflammatory monocytes [12]. In meningitis models there is a similar time course of inflammatory cytokine levels in CSF: TNF followed by IL1β, then IL6. Mice deficient in any of these cytokines have increased mortality rates...
Table 2

Cytokines known to play a role in inflammatory response to *S. pneumoniae* and their functions.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function during <em>S. pneumoniae</em> infection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN α/β</td>
<td>Uregulate tight junctions and downregulate Platelet Activating Factor receptor in murine pneumonia models</td>
<td>[50,69]</td>
</tr>
<tr>
<td>IFNy</td>
<td>Induces inflammatory monocyte infiltrate in murine meningitis model. Induces neutrophil infiltrate by stimulating chemokines in a murine pneumonia model</td>
<td>[60,79]</td>
</tr>
<tr>
<td>IL1β</td>
<td>Endogenous pyrogen, potentiates inflammatory responses in murine pneumonia models</td>
<td>[107,40,56]</td>
</tr>
<tr>
<td>IL6</td>
<td>Induces acute phase response and potentiates inflammatory responses in murine pneumonia model</td>
<td>[73,88–90]</td>
</tr>
<tr>
<td>IL10</td>
<td>Inhibits inflammatory responses and inhibits neutrophil recruitment by affecting chemokine expression</td>
<td>[97]</td>
</tr>
<tr>
<td>IL12</td>
<td>Induces IFNγ secretion in murine pneumonia models</td>
<td>[79,105]</td>
</tr>
<tr>
<td>IL17</td>
<td>Potentiates inflammatory responses including neutrophil recruitment, and increases mucosal immunity in murine pneumonia and human colonisation models</td>
<td>[102,106,51]</td>
</tr>
<tr>
<td>IL23</td>
<td>Stimulates T cells, increases IFNγ and IL17 in murine pneumonia models</td>
<td>[45]</td>
</tr>
<tr>
<td>IL27</td>
<td>Inhibits IL17 production, so increasing susceptibility in a murine pneumonia model</td>
<td>[14]</td>
</tr>
<tr>
<td>TNF</td>
<td>Endogenous pyrogen, and potentiates inflammatory responses in murine pneumonia sand meningitis models</td>
<td>[31,40,80,88–90]</td>
</tr>
</tbody>
</table>

Table 3

Cytokines known to play a role in inflammatory response to *S. pneumoniae* and their functions.

<table>
<thead>
<tr>
<th>Chemokine</th>
<th>Function during <em>S. pneumoniae</em> infection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL2 (MCP-1)</td>
<td>Monocyte chemoattractant in a murine pneumonia model</td>
<td>[99]</td>
</tr>
<tr>
<td>CCL5 (RANTES)</td>
<td>Th1 cell chemoattractant</td>
<td>[68]</td>
</tr>
<tr>
<td>CCL7</td>
<td>Neutrophil chemoattractant in a murine pneumonia model</td>
<td>[42]</td>
</tr>
<tr>
<td>CXCL1 (GRO-1)</td>
<td>Neutrophil chemoattractant in a murine pneumonia model</td>
<td>[42]</td>
</tr>
<tr>
<td>CXCL8 (IL8)</td>
<td>Neutrophil chemoattractant in an in vitro macrophage/epithelial cell co-culture mouse pneumonia model (IC)</td>
<td>[56]</td>
</tr>
<tr>
<td>CXCR3 receptor for CXCL9/CXCL10 (IP-10)/CXCL11</td>
<td>Neutrophil recruitment and lung inflammation in a murine pneumonia model</td>
<td>[77]</td>
</tr>
</tbody>
</table>

These proinflammatory cytokines also induce the acute phase response, upregulate adhesion molecules to facilitate transmigration of leucocytes from the blood, and act in a paracrine fashion to induce more inflammation required for control of bacterial replication. However, they may also lead to down-regulation of the tight junctions between epithelial cells, facilitating *S. pneumoniae* invasion across epithelial layers [16].

The cytokine IL17 is involved in maintaining mucosal immunity against *S. pneumoniae* [106], and is secreted by γδT cells and Th17 lymphocytes as part of the innate response and adaptive immune responses respectively. Polymorphisms in IL17A are associated with increased colonisation and lung infection [62]. Functions include increasing neutrophil recruitment, β defensin production, and expression of polymeric Ig receptor expression on alveolar epithelial cells (required for transport of antibodies into epithelial lining fluid) [102]. IL17 neutralisation reduced neutrophil recruitment and decreased survival in a murine pneumonia model [14]. IFNy, secreted by Natural Killer cells and Th1 cells after intracellular PRR activation [66], activates macrophages and improves phagocytosis and intracellular killing. IFNy is largely protective in pneumonia models [95]; however neutralisation of IFNy was protective in a meningitis model in terms of survival and bacterial clearance due to reduced inflammatory monocyte infiltrate [60].

The pro-inflammatory cytokines act in concert with chemokines such as C–X–C motif chemokine (CXCL) 1, 2, and 8 to recruit leucocytes to the site of infection. Chemokine relationships to their receptors are variable with some redundancy; several chemokines bind to the same receptor, and many receptors binding several chemokines. In particular, inhibition of C–X–C chemokine receptor (CXCR) 2 (activated by CXCL1-3, CXCL5-8), which is expressed on neutrophils and macrophages, appears to be protective in non-infective acute lung injury and chronic inflammation [83], but the absence of CXCR2 compromises host defence [34]. In contrast, targeting individual chemokines may prove to be beneficial at attenuating neutrophilic inflammation without compromising host defence [42], although further studies are required to assess this possibility further.

The largely anti-inflammatory cytokine, IL10, also plays an important role in regulating infection by *S. pneumoniae*. Deficiency of IL10 in murine models results in increased inflammation that is associated with improved bacterial clearance [71,88–90]. In murine models, IL10 levels are reduced in the lungs of infected aged mice, suggesting that immune dysregulation and enhanced inflammation in these mice is partly due to loss of this anti-inflammatory cytokine resulting in increased levels of chemokines, particularly chemokine (C–C motif) ligand (CCL) 3 and CCL5 [97]. Furthermore the administration of IL10 in combination with antibiotics improves survival of mice infected with *S. pneumoniae* compared to infected mice treated with antibiotics alone [94].

C5a, the complement component and anaphylatoxin is a powerful inflammatory mediator and effective chemoattractant for monocytes and neutrophils. A polymorphism in C5 is associated with worse outcome in *S. pneumoniae* meningitis in humans and mice [101]. Neutralising C5a antibodies, in conjunction with dexamethasone and antibiotics, have an additional mortality benefit above that of each individual treatment in a murine meningitis model [44].

3. Targeting inflammatory responses

Various approaches have been investigated to limit the inflammatory damage caused by *S. pneumoniae* (Fig. 1). Effective adjunctive treatment of pneumococcal disease includes the use of dexamethasone in meningitis, where the inflammatory response causes much of the damage leading to mortality and residual neurological deficit [19,9]. Whether adjuvant corticosteroids improve the outcomes of pneumonia has been less clear. In a murine model of severe *S. pneumoniae* pneumonia associated with increased neutrophil infiltrates and protein in bronchoalveolar lavage fluid, adjunctive dexamethasone with antibiotic therapy improved survival from 40% to 70%. Interestingly, if the dexamethasone was administered prior to bacterial infection the outcome was adversely affected [32]. In humans, there have been several recent large controlled trials of adjuvant corticosteroid treatment of pneumonia (not restricted to those caused by *S. pneumoniae*). One trial showed no benefit, with oral prednisolone commenced on day of admission with community acquired pneumonia (CAP) showed faster defervescence and decline in C reactive protein (CRP), there was no difference in clinical cure rates, and a slight increase in late treatment failure in the prednisolone arm [78]. Others have suggested some evidence of a
positive benefit [59,7,85]. Dexamethasone commenced on the day of admission due to CAP reduced length of stay by one day [59]. Methylprednisolone treatment of patients with severe CAP and high inflammatory response (CRP > 150 mg/L) demonstrated fewer treatment failures in the intervention group [85], and one week of oral steroids commenced within 24 h of hospital admission decreased time to clinical stability [7]. However, although the recent trials show some benefits for adjunct corticosteroids for treatment of pneumonia, these effects don't appear to impact mortality or morbidity and may not achieve sufficient clinical benefit to be incorporated into current treatment algorithms.

Pulmonary infections initiate a pro-coagulant state by activating coagulation pathways, and inhibiting anti-coagulant and fibrinolysis pathways. The tissue factor pathway is the main initiator of inflammation-induced activation of coagulation and the abundance of coagulation proteases (e.g., Thrombin and factor X) can further induce inflammation by activating proteinase-activated receptor (PAR) signalling, in particular PAR-1 [41]. Targeting the coagulation pathway has therefore been of interest as an indirect way of controlling exaggerated inflammatory responses. In rodent studies of S. pneumoniae pneumonia the use of natural and recombinant anti-coagulants (anti-thrombin, activated protein C, tissue factor pathway inhibitor) is beneficial at attenuating inflammation [15,36,7,86], however in human disease these agents have not resulted in improved outcomes [103] and are associated with an increased risk of bleeding. The focus has now shifted to delivery of these anti-coagulants locally in the lungs to limit systemic effects; current results from rodent and human studies are promising [21,87]. Targeting PAR-1 may also be a useful therapeutic strategy; a recently Food & Drug Administration approved PAR-1 antagonist (SCH530348) attenuated neutrophilic inflammation and alveolar leak in a murine model of S. pneumoniae pneumonia [42]. This was associated with reduced levels of IL1β, CXCL1, CCL2, and CCL7. In addition, the neutralisation of CXCL1 systemically and CCL7 in the lungs reduced neutrophil recruitment to the lungs without compromising host defence, suggesting that these may also be future therapeutic targets. Furthermore, subgroup analysis of the PROWESS study showed that activated protein C improved outcome in patients with sepsis secondary to community acquired pneumonia, particularly if caused by S. pneumoniae [25,49]. Taken together these studies suggest that the pathways involved in coagulation-inflammation crosstalk may be amenable to intervention to reduce the lung damage from the effects of an excessive inflammatory response without compromising host defence.

In bacterial pneumonia, treatment with cell wall active antibiotics such as β-lactams may release bacterial PAMPs that exacerbate inflammatory responses. For example, mice infected with S. pneumoniae after prior influenza infection had better survival with bacteriostatic antibiotics such as clindamycin or azithromycin than with ampicillin (100% v 40% survival) despite complete bacterial clearance with any of the antibiotics or infection with a strain resistant to azithromycin. Survival from secondary pneumonia was also improved in TLR2 deficient mice, suggesting that cell wall constituents activating TLR2 contribute to immunopathology in the context of secondary bacterial pneumonia [43]. The potential beneficial immunomodulatory effects of macrolides are one reason why observational studies show improved outcomes in CAP for dual therapy with β-lactams and macrolides versus β-lactams alone [10,5,75]. Macrolides seemed to be more beneficial in more severe CAP, though not when patients required inotropic support [74,82]. However, a recent randomised controlled trial (RCT) suggested non-inferiority of β lactams alone in 90 day mortality [72], and while a meta-analysis suggested a mortality benefit of macrolide-based regimens over non-macrolides, this benefit was lost when the analysis was restricted to RCTs or when compared in terms of β-lactam/macrolide versus respiratory quinolones [4].

The fluoroquinolone moxifloxacin, a topoisomerase inhibitor, is also thought to have immunomodulatory effects over and above its antibacterial effects, perhaps through inhibition of mitogen-activated protein kinase and NFkB signalling [96]. In a mouse model of S. pneumoniae pneumonia pre-treatment with moxifloxacin reduced IL1β and keratinocyte chemoattractant (KC) levels and inflammatory cell infiltrate into lavage fluid [6]. Whether these effects of moxifloxacin could improve outcomes in human disease is not known.

Statins, widely used cholesterol lowering drugs, also have anti-inflammatory effects. One of their effects is to inhibit isoprenoid synthesis, which affects the membrane localisation and function of intracellular signalling molecules such as small GTPases. They decrease NFkB activation and subsequent IL8 and CCL2 expression, and so reduce cellular recruitment in atherogenesis models [11]. Epidemiological studies suggest that patients already taking statins have lower sepsis mortality rates [24,53]. However, acute cardiac ischaemia is a major cause of mortality in patients with pneumonia, and any positive effects of statins may be due to their effect on associated coronary events rather than inflammation [61]. The antiplatelet agents aspirin and clopidogrel also reduce mortality from CAP in observational studies, again possibly by decreasing the incidence of myocardial infarction in patients with CAP [104].

### 4. Conclusion

In conclusion, the mechanisms by which the inflammatory responses to S. pneumoniae are elicited and potentiated are complex and incompletely understood. The inflammatory response is critical to bacterial clearance, but persistent or excessive inflammation due to large numbers of bacteria and antibiotic-mediated release of PAMPs can result in local tissue damage. The marked inflammatory response associated with S. pneumoniae infection is a target for therapeutic strategies, which will probably need to be more nuanced than immunosuppression with corticosteroids. Further work is required to understand both bacterial factors and the host response so that these targeted approaches can be achieved.
5. Executive summary

*Streptococcus pneumoniae* is an important cause of community acquired pneumonia and meningitis, and excessive inflammation plays a key role in pathogenesis of morbidity and mortality.

Tissue resident macrophages and epithelial cells play an important role in recognising components of *S. pneumoniae*, and so instituting an inflammatory response. Cell membrane receptors and cytosolic receptors induce transcription of cytokines and chemokines. Inflammation results in a leucocyte infiltrate that can cause bystander tissue damage.

Currently steroid treatment is recommended as an adjunct for meningitis treatment, but their role in pneumonia treatment is less defined.

The induction of coagulation pathways by *S. pneumoniae*, and their crosstalk with inflammatory pathways may prove an effective avenue of targeting inflammation without impacting on bacterial clearance. The inhibition of individual chemokines may be an important role in recognizing components of *S. pneumoniae*.

In so instituting an inflammatory response associated with this publication and there has been no conflict of interest associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

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Ethical statement

No ethical permission was required to undertake this review.

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