

# Therapy in pneumonia: What is beyond antibiotics?

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## ABSTRACT

Community-acquired pneumonia (CAP) is a common and serious disease with significant mortality, morbidity and associated healthcare costs. Severity of pneumonia is related to the extent of the inflammatory response. Primary goal in the treatment of pneumonia is starting adequate antibiotic therapy as soon as possible. However, antimicrobial resistance among the most common bacteria causing pneumonia is increasing. For those two reasons, extended inflammatory response and increasing antibiotic resistance, it is interesting to look at adjunctive non-antibiotic therapeutic strategies aimed at modulation of the inflammatory response or at the micro-organism itself. In this review, we discuss the current knowledge regarding these therapies and their possible role in the future.

## KEYWORDS

Pneumonia, therapy, corticosteroids, immunomodulation

## INTRODUCTION

Community-acquired pneumonia (CAP) is the most common infectious disease that necessitates hospitalisation.<sup>1</sup> Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are serious complications of hospital stay and mechanical ventilation, respectively.<sup>2,3</sup> Despite advances in prevention by vaccination, microbiological diagnostics and antibiotic therapy, pneumonia is still characterised by a high mortality and morbidity and is associated with significant healthcare costs.<sup>4,5</sup> The mainstay of CAP therapy is early diagnosis and initiation of appropriate antibiotic therapy

within four hours to minimise the door-to-needle time.<sup>6</sup> Antibiotic therapy for HAP and VAP is even more challenging due to the increase in antibiotic resistance of Gram-negative bacteria.<sup>7</sup> Unfortunately, there is also a trend of increasing antibiotic resistance in the most common bacteria that cause CAP, *Streptococcus pneumoniae* and *Haemophilus influenzae*.<sup>8,9</sup> Despite adequate antibiotic therapy, a substantial number of patients at high risk of deterioration require additional therapies for pneumonia. These therapies are aimed either at the micro-organism or at the host. Therapeutic targets are improvement of recognition of microbial antigens (with complement or toll-like receptors), improvement of effector mechanisms of the immune response (with immunoglobulins) and limiting immunopathology caused by the cytokine storm (with corticosteroids, statins or activated protein C (APC)). Certain antibiotics, such as macrolides, can also limit the damage caused by an overactive immune system. We will limit this review to treatment options for an immunocompetent hospitalised patient receiving appropriate antibiotics.

## THERAPY TARGETED AT IMPROVEMENT OF BACTERIAL OPSONISATION

### Complement cascade

The complement system can be activated in three ways: classical pathway activation after antibodies have been bound to the micro-organisms, alternative pathway activation, and activation by mannose residues (mannose-binding lectin (MBL) route). Complement activation via either route ultimately results via a cascade of steps in the formation of a membrane-attack complex, which results

in lysis of the pathogen. Other complement split products are deposited on the surface of the micro-organism which promote its phagocytosis. MBL binds to several respiratory pathogens including *Haemophilus influenzae*,<sup>10,11</sup> *Mycoplasma pneumoniae*<sup>12</sup> and *Legionella pneumophila*,<sup>13</sup> and to a lesser degree *Streptococcus pneumoniae*.<sup>14</sup>

Polymorphisms in the structural and promoter sequences of the *MBL2* gene lead to a deficiency in MBL production, with a frequency of approximately 10 to 15% in the normal healthy population.<sup>15</sup>

Susceptibility to lower respiratory tract infections does not seem to be affected by MBL deficiency.<sup>16-18</sup> However, MBL deficiency is associated with a more severe clinical course of pneumonia and the development of more severe forms of sepsis, ICU admission and fatal outcome in lower respiratory tract infections.<sup>18,19</sup> Also in invasive pneumococcal disease, several studies found an increased frequency of MBL deficiency.<sup>20-22</sup>

Thus far, MBL substitution therapy has only been tested in phase I and II trials, and to date no negative clinical effects are reported.<sup>23,24</sup> However, over-substitution should be avoided because high MBL genotypes are associated with nephropathy in patients with diabetes mellitus type I and vascular tissue damage in myocardial ischaemia-reperfusion injury.<sup>25,26</sup> To date, MBL replacement has not been used in pneumonia patients. MBL substitution might be of value as adjunctive therapy for MBL-deficient patients.

### Toll-like receptors

Toll-like receptors (TLRs) are a family of receptors that activate the inflammatory response after recognition of molecular patterns that are present on different pneumonia-associated micro-organisms.<sup>27,28</sup> The role of TLRs in sepsis has been recently reviewed.<sup>29,30</sup> Polymorphisms in the genes coding for TLRs are associated with increased susceptibility to (severe) sepsis, including pneumonia or sepsis caused by *S. pneumoniae*.<sup>31,32</sup> Because they are a major trigger for the inflammatory response, TLRs are regarded as a promising target for anti-inflammatory therapy.

In an animal model for pneumococcal pneumonia, triggering of TLR5 with its ligand, flagellin, leads to substantially better survival.<sup>33</sup> This shows the importance of the immediate activation of the innate response in clearance of a pulmonary infection.

As indicated above, over-activation of the inflammatory response can cause substantial damage and should therefore be avoided. TAK-242 is an agonist of another TLR, TLR4, and inhibits intracellular signalling, thereby preventing up-regulation of the inflammatory response. TLR4 is a lipopolysaccharide (LPS) binding receptor, and Gram-negative LPS containing bacteria are a major cause of severe sepsis in critically ill patients. TLR4 is the

only receptor in which blocking seems an interesting additive therapy.<sup>34,35</sup> The first recently published double-blind randomised trial comparing TAK-242 to placebo in patients with severe sepsis and septic shock did not show a difference in mortality. Furthermore, treatment with TAK-242 did not succeed in decreasing cytokine levels, which suggests that other inflammatory pathways are involved.<sup>36</sup> These studies have been performed in critically ill patients, and subgroup analyses of patients with pneumonia are lacking. Furthermore, TLR4 is mainly involved in the inflammatory response to LPS-containing bacteria, and these bacteria are uncommon in community-acquired pneumonia.

Currently, there is no role for TLR antagonists in the treatment of pneumonia, or severe sepsis or septic shock.

## THERAPY TARGETED AT IMPROVEMENT OF EFFECTOR MECHANISMS OF THE IMMUNE RESPONSE

### Immunoglobulins

In the period before antibiotics were available (up to 1940) treatment of pneumococcal pneumonia consisted of the passive administration of serotype specific antibodies.<sup>37</sup> Nowadays, substitution therapy with immunoglobulins is used for long-term treatment of patients with humoral immunodeficiency diseases.<sup>38,39</sup> By replacing or increasing the levels of immunoglobulins, especially Immunoglobulin G (IgG), the inflammatory response to the bacteria could be improved by trapping endotoxins and facilitating phagocytosis. Clinical studies on the use of intravenous immunoglobulins IgG (IVIG) in infectious disease are limited and mainly focused on patients with streptococcal toxic shock syndrome and severe sepsis and septic shock.<sup>40</sup> Although consecutive reviews showed improved outcome of patients treated with IVIG, the use of immunoglobulins in critically ill patients is still controversial.<sup>41,44</sup> It is unclear whether the benefit of IVIG therapy was due to the antibody concentration or to volume resuscitation with proteins, or to an anti-inflammatory effect.<sup>45</sup> All studies contained numerous patients with severe sepsis or septic shock due to pneumonia, but there were no subgroup analyses investigating the effect of IVIG in patients with pneumonia. Therefore, the use of immunoglobulins for pneumonia in general remains unclear and remains restricted to patients with severe sepsis or septic shock.

## THERAPY TARGETED AT LIMITING IMMUNOPATHOLOGY

### Corticosteroids

The inflammatory cytokine response in the lung is characterised by a short intense elevation in TNF- $\alpha$

followed by increases in IL-1 $\beta$  and IL-6. A subsequent increase in IL-10, which is an anti-inflammatory cytokine that inhibits macrophage and neutrophil production, is the beginning of the anti-inflammatory response that prevents an uncontrolled inflammatory response.<sup>46-48</sup> In pneumonia patients, this hierarchy of cytokine response is not observed, because the inflammatory response is already ongoing upon admission to the hospital.<sup>49</sup> In most patients these cytokines control and eliminate the primary infection; however, in some patients, the cytokine activation becomes widespread. This indicates the need for a delicate balance between a sufficient and excessive cytokine response. The extended systemic inflammatory response is presumed to play a role in the organ dysfunction that is characteristic of severe sepsis and septic shock.<sup>50</sup> Among patients with pneumonia, non-survivors of CAP exhibit persistent elevation in inflammatory cytokine levels over time, compared with survivors.<sup>49,51</sup> Modulation of this inflammatory response during infection is an attractive concept.

Corticosteroids are the most important physiological inhibitors of inflammation. They can switch off genes that encode pro-inflammatory cytokines and switch on those that encode anti-inflammatory cytokines.<sup>53</sup> Prolonged (>5 days) treatment with low-dose corticosteroids can down-regulate inflammatory cytokine transcription and accelerate the resolution of critical illness.<sup>53</sup> In addition to this direct effect on gene transcription, recent observations have shown that corticosteroids might be effective in patients with severe sepsis due to relative adrenal insufficiency associated with critical illness and systemic inflammation-induced glucocorticoid receptor resistance. Not only in severe sepsis and septic shock, but also in pneumonia there are different reasons in support of a beneficial effect of corticosteroids.<sup>54,55</sup> Corticosteroids might be effective in reducing excessive pulmonary inflammation and thereby reducing lung injury.<sup>56</sup> Furthermore, in some cases of pneumonia, bronchospasm can play a significant role (e.g., in patients with COPD/asthma or viral-induced pneumonia), which can be counteracted by corticosteroids.<sup>57,58</sup>

Over the last several decades, corticosteroids have been used as adjunctive therapy in patients with sepsis and septic shock. Initial trials investigating short courses of high doses found no beneficial effect on mortality, whereas more recent trials showed that a low dose (< 300 mg/d) of hydrocortisone for a longer duration (>5 days) may improve survival.<sup>59-62</sup>

In contrast to this large number of studies on sepsis and septic shock, randomised controlled trials (RCT) using corticosteroids as an adjunctive treatment to antibiotics in pneumonia are limited and have variable results. The

use of corticosteroid treatment in CAP dates back to 1956, when favourable effects of hydrocortisone in patients with pneumococcal pneumonia were reported.<sup>63</sup> Two more recent studies found a significant reduction in hospital mortality and length of hospital stay in patients with severe CAP who were treated with adjunctive corticosteroids. Confalonieri *et al.* found a marked improvement in the ratio of the partial pressure of oxygen in arterial blood (Pa<sub>O<sub>2</sub></sub>) to the fraction of inspired oxygen (Fi<sub>O<sub>2</sub></sub>) as well as a survival advantage in patients with severe CAP treated with hydrocortisone for seven days. A retrospective study showed that patients with severe CAP who were treated with systemic corticosteroids had a reduced risk of mortality compared with patients without adjunctive corticosteroids.<sup>64</sup> A smaller randomised controlled trial (RCT) compared prednisolone for three days with a placebo in patients with CAP of any severity and found no effect on hospital stay; however, in patients with moderate or severe CAP, corticosteroids promoted resolution of clinical symptoms and reduced the duration of intravenous antibiotic treatment.<sup>65</sup> To date, a recent study by Snijders *et al.* is the largest to evaluate the role of prednisolone in patients with CAP of any severity.<sup>66</sup> In that RCT no beneficial effects of adjunctive corticosteroids on CAP were found.

There may be some potential adverse effects of the use of corticosteroids for CAP. From a theoretical point of view, the risk of gastrointestinal bleeding, muscle weakness and metabolic disorders is increased. In addition, down-regulation of the host response to infection might increase the risk of nosocomial infections and reactivation of viral infections. In a systematic review of 20 RCTs that involved adjunctive corticosteroid therapy in sepsis, these serious adverse events did not occur more often than in placebo-treated patients. However, hyperglycaemia and hypernatraemia were observed more frequently in the corticosteroid-treated patients.<sup>67</sup>

### Statins

In addition to modulation of the inflammatory response by corticosteroids, in experimental studies statins have shown to have significant anti-inflammatory properties.<sup>68</sup> These benefits are not ascribed to their cholesterol-lowering activity but rather to a pleiotropic effect on isoprenoid synthesis that results in the down-regulation of intracellular inflammatory signalling; this leads to modulation of the immune response, which results in a reduction in cytokine levels.<sup>68</sup> Moreover, statins improve endothelial function and may modify the balance of coagulation towards a less prothrombotic state, as seen in sepsis. Large retrospective observational studies have shown a potential positive effect on mortality in patients with severe infections or sepsis.<sup>69,70</sup> However, in a prospective cohort study, statins were not associated with

reduced mortality or less ICU admissions.<sup>71</sup> Large RCTs are needed to evaluate the effect of an intervention with statin therapy during CAP.

### Activated protein C

An exaggerated inflammatory response can result in a decline in protein C, which is a soluble anticoagulant and profibrinolytic enzyme. Reduced levels of activated protein C (APC), which leads to a procoagulant state, are associated with an increased risk of death in septic patients.<sup>72</sup> In patients with severe sepsis, APC has been shown to reduce mortality (PROWESS trial).<sup>73</sup> This may be due to its anticoagulant activity, but there is also evidence that APC is an inhibitor of the systemic inflammatory response.<sup>74</sup> In a subanalysis of the PROWESS trial, a survival benefit was seen in patients with CAP-associated sepsis and a high mortality risk (APACHE >25) who were treated with APC compared with placebo.<sup>75</sup> However, administration of APC increases the risk of serious bleeding, with reported rates of up to 10%.<sup>76</sup> Therefore, recent guidelines recommend that APC should only be considered in patients with severe sepsis and a high risk of death but not in the overall CAP population.<sup>77</sup>

### Macrolide antibiotics

Several antibiotics that are used in the therapy of CAP appear to have actions beyond direct antibacterial activities. Macrolides are known to also possess immunomodulatory effects.<sup>78</sup> Macrolides accumulate in inflammatory cells and modulate their actions, which results in modification of leukocyte function, cytokine expression and mucus production. Macrolides infer a biphasic effect on the host. First, they have direct antimicrobial activity by stimulating the host defence against bacteria via stimulation of leukocyte degranulation, phagocytosis and oxidative burst. Second, after the acute infection, neutrophils that are primed by cytokines or lipopolysaccharide (LPS, is an endotoxin) are inhibited by macrolides, which leads to resolution of the inflammatory response. Moreover, macrolides may also improve macrophage function, which results in the increased removal of apoptotic debris.<sup>79</sup> Another potential explanation for the beneficial effects of macrolides is reduction in bacterial load with less cell wall lysis than beta-lactam antibiotics; this results in a more gradual reduction in bacterial load and, therefore, a more gradual release of immunologically reactive components, which may prevent an extended systemic inflammatory response.

The beneficial effect of macrolides has been recognised in chronic pulmonary diseases, probably through inhibition of quorum-sensing in bio films, but some studies found improved outcomes in CAP patients who were treated with macrolide-containing antibiotic regimes.<sup>80,81</sup> The outcome in pneumococcal pneumonia was improved when

a macrolide was added to standard treatment, even when the bacteria was sensitive to standard treatment.<sup>82,83</sup> This effect appears to be most prominent in severe bacteraemic pneumococcal pneumonia.<sup>84</sup> However, other studies were unable to show a beneficial effect of macrolides in CAP.<sup>85,86</sup>

## CONCLUSION

At this moment, timely administration of appropriate antibiotics is still the most important therapy in pneumonia.<sup>87</sup> Beyond antibiotics, there are other targets for adjunctive therapy. For immunoglobulins, APC and TLR4 antagonists, the majority of evidence is extrapolated from studies on severe sepsis and septic shock. Many patients in these studies suffered from pneumonia, but reliable subgroup analysis was only performed in some of these studies. Furthermore, results from these studies are conflicting and most meta-analyses do not provide firm conclusions. The only conclusion that can be drawn is that immunoglobulins are a promising therapy in patients with pneumonia and severe sepsis or septic shock. APC might be used in patients with pneumonia and severe sepsis or septic shock with an APACHE score >25. To date, for the patient with CAP there is no role for therapy with TLR4 antagonists or MBL. Adding macrolides to the antibiotic regimen is an interesting and promising strategy, but prospective RCTs are necessary. Currently, there is consensus on the use of corticosteroids in septic shock. Nevertheless, the use of corticosteroids in patients with pneumonia without severe sepsis or septic shock is still unclear, but the results of new studies will be reported in the near future.

In conclusion, in this review we have discussed the various options for supportive therapy of patients who are treated with otherwise effective antibiotics. In view of increasing resistance, these supportive therapies might become the only option left. However, probably neither corticosteroids, nor APC, immunoglobulins or any of the others can be used as monotherapy. As adjunctive therapy so far, corticosteroids, APC, and immunoglobulins are available and can be used in patients with CAP complicated by severe sepsis or septic shock. Complement, including MBL and TLR agonists and antagonists, are attractive options but warrant additional studies because insufficient evidence is available to date.

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