Streptococcus pneumoniae and lytic antibiotic therapy: are we adding insult to injury during invasive pneumococcal disease and sepsis?

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Abstract

Streptococcus pneumoniae (S. pneumoniae), otherwise known as ‘the pneumococcus’, is a fascinating microbe that continues to pose a significant problem to public health. Currently there are no specific National Institute for Clinical Excellence (NICE) or British Thoracic Society (BTS) clinical guidelines referring to the treatment of invasive pneumococcal infection. NICE clinical guidelines suggest the use of lytic β-lactam antibiotic regimens for the management of community-acquired pneumonia and bacterial meningitis; infections for which S. pneumoniae is a likely causative organism. Lytic antibiotics have been shown to increase the release of pneumolysin (the highly inflammatory and damaging toxin of the pneumococcus), thus theoretically increasing host damage, which may lead to a decline of clinical outcomes in vulnerable patients. In light of this information, should the use of non-lytic antibiotics, such as quinolones, rifamycins and macrolides, be considered for the treatment of invasive pneumococcal disease?

THE PNEUMOCOCCUS AND ITS DISEASE BURDEN

Streptococcus pneumoniae (S. pneumoniae), otherwise known as ‘the pneumococcus’, was initially isolated in 1880 by Louis Pasteur [1], and is a fascinating microbe that continues to pose a significant problem to public health. It colonises the nasopharynx, forming part of the diverse flora of the upper respiratory tract. However upon the host environment becoming compromised, S. pneumoniae has a tendency to cause invasive disease, such as pneumonia, meningitis and bacteraemia [2]. These diseases may result in the development of sepsis [3]; a clinical syndrome defined as the presence of infection in patients, coupled with evidence of a systemic inflammatory response (SIR) such as tachycardia and pyrexia [4], causing multiple organ failure and ultimately death [5].

To this day, pneumococcal infection continues to be a significant cause of death worldwide with an estimated 1.6 million deaths annually [2], with the most at risk groups being adults over 65 years old, and those with pre-existing comorbidities, and children under 5 years old [6]. Respiratory infections in particular remain the third highest cause of death in the UK [7], with S. pneumoniae being the causative microbiological agent in the majority of cases of adult community-acquired pneumonia [8]. Therefore, it is clear that S. pneumoniae is an important pathogen, responsible for a great burden of disease both globally and in the UK.

PNEUMOLYSIN - THE TOXIN OF THE PNEUMOCOCCUS

Pneumolysin is the haemolysin of the pneumococcus. Present in the majority of strains and as part of a larger family of pore-forming cholesterol-dependent cytolysin (CDC) proteins, pneumolysin constitutes an integral virulence factor for S. pneumoniae [9]. Importantly, there is controversy about the release of pneumolysin from the pneumococcus. The toxin has classically been observed to be released during the stationary phase of bacterial growth, adding weight to the long-standing idea that pneumolysin is released upon lysis of the bacteria [10]. The characteristic rings seen upon blood agar culture of the pneumococcus are not due to the release of hydrogen peroxide; which then in turn causes the reduction of haemoglobin, producing the green oxidized derivative methaemoglobin, characteristic of viridans streptococci grown on blood agar plates [11]. However, new evidence has recently emerged suggesting that pneumolysin...
may also be released from the bacterium by a non-autolysis secretory mechanism, due to one strain having been found to non-characteristically release pneumolysin in the early-log phase of growth [12]. Regardless, for the context of this discussion, the fact remains that lysis of *S. pneumoniae* bacteria causes stored pneumolysin release.

Structurally, pneumolysin is composed of four domains that are released from *S. pneumoniae* as monomers (Fig. 1a), which then bind via domain 4 to host-membrane cholesterol and oligomerize to form a ring-like pre-pore arrangement (Fig. 1b). Conformational changes then occur, permitting membrane permeation and pore formation (Fig. 1c, d) [13].

In addition to its pore forming effects, pneumolysin possesses the ability to induce a multitude of supplementary inflammatory effects. Pneumolysin can activate the classical complement pathway and therefore induce inflammation [14]. Furthermore, pneumolysin has also been found to play a role in amplifying the host inflammatory response by interfering with interleukin signalling [15, 16].

This is relevant as it is acknowledged that damage caused by *S. pneumoniae* infection is more prominently inflammatory in nature, as there is excessive activation of the host immune system and immune cell recruitment to tissues, in response to the infection [17], and thus these actions of pneumolysin bear clinical importance.

**CURRENT MANAGEMENT OF PNEUMOCOCCAL DISEASE: A FOCUS ON LYTIC ANTIBIOTIC THERAPY**

There are no clinical guidelines surrounding the treatment of pneumococcal disease specifically that have been released by large reputable organisations in the UK such as the British Thoracic Society (BTS) or the National Institute for Clinical Excellence (NICE); instead there are disease-based guidelines published by these bodies. In particular guidelines by these organisations are commonly followed in clinical practice within the UK, especially for rapid reference with regard to first line care in an emergency, non-infectious disease-specific setting, such as accident and emergency departments and acute medical services.

There are two reputable clinical guidelines for the management of community-acquired pneumonia in the UK, produced by NICE and the BTS. Both come to a consensus that oral amoxicillin is to be used as a first line antimicrobial agent; the course can vary from five to seven days depending on the severity of illness [18, 19]. It must be noted however that it is notoriously difficult to determine the true causative agent in pneumonia [20]; therefore tailoring specific antimicrobial treatment can be challenging.

In addition to this guidance, for patients presenting with suspected pneumococcal or bacterial meningitis, NICE guidelines recommend that empirical intravenous cefotaxime plus either amoxicillin or ampicillin are indicated. Upon microbiological confirmation of the causative microbiological agent after a cerebrospinal fluid (CSF) culture, antimicrobial treatment should be further tailored; if *S. pneumoniae* is isolated, intravenous ceftriaxone is indicated for 14 days [21].

Other societies which have released guidelines regarding the treatment of community-acquired pneumonia and invasive pneumococcal disease are the infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS). The most recent guidelines published jointly by these bodies regarding the management of community-acquired pneumonia was in 2007; there is an update pending though not yet released. In these guidelines it is recommended that for the outpatient treatment of community-acquired pneumonia in adults, without any risk of drug-resistant *S. pneumoniae* infection, macrolide therapy is recommended as first line, with the alternate of doxycycline. In drug-resistant *S. pneumoniae* (DRSP) patients or patients receiving inpatient, non-intensive care unit (ICU) treatment, fluoroquinolone therapy is recommended along with the alternative regimen of a macrolide plus a β-lactam. However as first line in ICU management, a β-lactam plus a fluoroquinolone or macrolide is recommended [22]. These guidelines often recommend newer antibiotic regimens in North America than in the UK, however in general, most doctors in the UK should be seen to be adhering to BTS or NICE guidelines [23].

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**Fig. 1.** The structural basis of pore formation by pneumolysin. Figure adapted from Gilbert et al. [13]. (a) Pneumolysin monomer attachment to the cell surface membrane. (b) Oligomerization of monomers to form the pre-pore complex. (c) Membrane insertion and pore formation. (d) Transmission electron micrograph of pneumolysin pores on red blood cells (magnification ×25,000), used with the permission of T. J. Mitchell.
Guidelines released by Randle et al. regarding the treatment of adult lower respiratory tract infection, recognised by the British Infection Association (BIA), still recommend penicillin-based agents and cephalosporins in the treatment of community-acquired pneumonia. However, in cases of highly resistant S. pneumoniae, alternatives have been recognised for use, such as ofloxacin and vancomycin [23].

In suspected sepsis and bacteraemia, patients should be treated empirically for the most likely source of infection [5].

Antibiotics can be broadly split into two categories based on their mechanism of action: lytic or non-lytic. Lytic antibiotics inhibit cell-wall synthesis such as β-lactam antibiotics. Non-lytic antibiotics have a more diverse range of antibacterial activity including inhibition of DNA replication, inhibition of RNA synthesis and inhibition of protein synthesis by quinolones, rifamycins and macrolides, respectively [24]. All of the antibiotics mentioned in current recommendations for use in commonly occurring pneumococcal infection by the BTS and NICE are lytic in mechanism. Non-lytic regimens are recommended by the ATS and the IDSA, although occasionally these are used in combination with a lytic antibiotic therapy, such as the use of a macrolide with a β-lactam [22].

The role of macrolide antibiotics has been highlighted as an interesting area for debate with regards to the treatment of community-acquired pneumonia in particular, and is an area suggested as a point for guideline re-evaluation in the future [25].

**LYTIC ANTIBiotic USE MAY BE HARMFUL IN S. PNEUMONIAE INFECTION**

The use of lytic antibiotics is controversial in S. pneumoniae infection. The theory behind this revolves around the fact that S. pneumoniae, as previously detailed, does not actively secrete pneumolysin, instead it is released upon bacterial cell lysis; meaning that when lytic antibiotics cause bacterial death, there is a huge release of the highly damaging and inflammatory toxin. This has been demonstrated in work where ceftriaxone was found to cause an increased release of pneumolysin in CSF during bacterial meningitis [26]. Based on this principle and evidence, should we be moving from lytic to non-lytic antibiotic therapy in pneumococcal disease?

In contrast, the non-lytic antibiotic clindamycin was found to be neuro-protective during S. pneumoniae infection as compared with ceftriaxone in rabbits, reducing neurological damage [27]. Furthermore, protein-synthesis-inhibiting antimicrobials, such as macrolides, have been claimed to reduce bacterial cell lysis and reduce the enhancement of inflammatory responses by bacterial endotoxins when compared with penicillin [28]. It has also been demonstrated that rifampicin, a RNA synthesis inhibitor, inhibits the increased release of pneumolysin by ceftriaxone [28].

In addition to this direct lysis mechanism, the β-lactam antibiotic penicillin has been shown to increase autolysis of S. pneumoniae via activation of autolysins, thereby potentially causing increased release of pneumolysin from the bacteria [29]. However non-lytic antibiotics have been found to have opposite effects to lytic antibiotics on autolysins, with selected DNA- and protein-synthesis-inhibiting antimicrobials decreasing the lytic activity of pneumococcal autolysins; in particular some quinolones have been shown to specifically decrease the lytic activity of lytA [30], though other studies dispute this in more potent quinolones [31].

There is very little evidence available regarding clinical outcomes in lytic versus non-lytic antibiotic use in pneumococcal infection. The only evidence available compares β-lactam use to a dual therapy including a non-lytic antibiotic [32], which simply should not be relied upon for a fair comparison, as logic dictates that dual antibiotic therapy is likely to produce better clinical outcomes in more severe cases than monotherapy. Regardless of this, one study reports that the combination of a lytic and non-lytic antibiotic produced a synergistic lytic effect and thus created an enhanced destruction of pneumococcal cells, which would in theory mean enhanced pneumolysin release accompanying this effect hand-in-hand [33]; unfortunately this was not assessed in this case, though if proven to be true could be even more detrimental than simply lytic antibiotic use alone.

Moving forwards, there is a need for more studies to accurately compare effects on patient parameters including acute lung injury, morbidity and mortality, ensuring that there is no detrimental effect to using non-lytic as opposed to lytic antibiotic monotherapy. In addition, there is no evidence at present to postulate the effects of non-lytic versus lytic antibiotic use and the release of pneumolysin in quiescent versus actively replicating bacterial S. pneumoniae cells. This would be an interesting caveat of research to undertake, as for the mechanism of action of most antibiotics to work effectively against bacterial cells, there is a requirement for active growth. For example, in order to achieve cell-wall synthesis disruption as with lytic antibiotics, or protein- and DNA-synthesis disruption with most non-lytic antibiotics, actively dividing bacterial cells are required, therefore further clarification of this point may be both academically and clinically useful information.

**CONCLUSIONS**

S. pneumoniae infection remains an important cause of mortality. Current management strategies revolve around lytic antibiotic use, which has been shown to increase pneumolysin release. This in theory worsens host cell damage, over-activation of systemic inflammatory responses and clinical outcomes, effects that may be improved with the use of non-lytic antibiotics. However, although non-lytic antibiotic use has been shown to be protective of these effects *in vitro* and *in vivo*, it is recognised that more studies comparing the effects of lytic and non-lytic antibiotic use on clinical outcomes is required. Although there remains a diagnostic
issue for causative microbiological agents in cases of pneumonia, not applying to meningitis, a different approach to antibiotic prescribing could be considered, based on the principles presented, so long as patient outcomes are shown not to be compromised.

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