

## TITLE PAGE

### Acute bacterial meningitis in adults.

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## Community acquired bacterial meningitis in adults – mobile summary

Bacterial meningitis in adults carries a significant morbidity and mortality. In many parts of the world the most common pathogen is *Streptococcus pneumoniae*, which tends to occur at an older age whereas *Neisseria meningitidis* generally occurs in younger adults. *Staphylococcus aureus*, the Enterobacteriaceae, *Streptococcus suis* and *Listeria monocytogenes* are also prominent pathogens in different parts of the world or specific populations. Widespread use of conjugate vaccines against *Haemophilus influenzae* type B, certain serotypes of *Streptococcus pneumoniae* and *Neisseria meningitidis* has reduced the incidence of bacterial meningitis although mostly in children. Herd immunity has provided some benefits for adults but serotype replacement may undermine any benefits seen in older populations. In meningococcal disease, different serogroups are also emerging in areas where they had been previously unrecorded.

The mortality from bacterial meningitis is high and significant for pneumococcal disease, in part due to the uncontrolled host inflammatory response. Although much is still unknown, new discoveries in pathogenesis give an improved understanding of colonisation and invasion into the blood stream and central nervous system, as well as factors responsible for immune system evasion. This in turn allows new targets for vaccines and therapeutics to be developed.

Clinical diagnosis, based on symptoms and signs, is difficult and cerebrospinal fluid analysis is essential both to confirm the aetiology and to perform antimicrobial susceptibility testing of any organism isolated. Newer molecular techniques are useful for diagnosis if culture is negative. The role of neuroimaging before lumbar puncture is controversial, and is only recommended in cases where clinical features suggest there may be brain shift.

Early antibiotic treatment saves lives and empirical antibiotics should be tailored to local resistance patterns. In general, beta-lactams should be a component of empirical therapy where possible. Adjunctive corticosteroids should be given in some circumstances. Further research should focus on epidemiological surveillance, developing new vaccines and new adjunctive therapies.

## Abstract

Over the last several decades, there has been a reduction in the incidence of bacterial meningitis in children but there remains a significant burden of disease in adults, carrying a mortality of up to 30%. Although the pathogenesis of bacterial meningitis is not completely understood, our knowledge of bacterial invasion and entry into the central nervous system is improving. Clinical features alone cannot determine whether meningitis is present and cerebrospinal fluid analysis is essential for diagnosis. Newer technologies, such as multiplex polymerase chain reaction, and novel diagnostic platforms that incorporate proteomics and genetic sequencing, may help provide a quicker and more accurate diagnosis. Even with appropriate antimicrobial therapy, mortality is high and so attention has focused on adjunctive therapies; adjunctive corticosteroids are beneficial in certain circumstances. Any further improvements in outcome are likely to come from either modulation of the host response or novel approaches to therapy, rather than new antibiotics. Ultimately the best hope to reduce the disease burden is with broadly protective vaccines.

## Search Strategy

We searched SCOPUS with the terms “Meningitis”, “meningo\*”, “neurological infection” together with “Aetiology”, “epidemiology”, “treatment”, “management”, “antibiotic”, “antimicrobial”, “investigation”, “therapy”, “prevention”, “vaccin\*”, “lumbar puncture” for articles published between 1<sup>st</sup> January 2010 and 31<sup>st</sup> Dec 2015. We also included any studies referenced within these articles if deemed relevant. In addition, any older references known to the authors were also included, as were abstracts of articles not written in English. Review articles are included to guide the reader to a more extensive reference list.

## Burden of disease and epidemiology

The incidence of bacterial meningitis varies throughout the world. In Western settings, the incidence is 1-2 cases per 100,000, whereas it can reach 1,000 cases per 100,000 in the Sahel region of Africa (Figure 1)<sup>1-3</sup>. A huge reduction in incidence has been seen over the last few decades, largely secondary to the introduction and widespread use of conjugate vaccines<sup>1,3-6</sup>. Conjugate vaccines have a protein attached to purified bacterial capsular polysaccharide. This elicits a more robust and sustained immune response, especially in young children. Table 1 gives an overview of vaccines currently available to prevent bacterial meningitis. Much of the reduction in incidence has been in children under one year<sup>1,5</sup>. Similarly the largest reductions in meningitis-associated mortality, globally, have been seen in children under five years of age, with a 43% decrease in neonates and a 54% reduction in children aged between one and 59 months<sup>7</sup>. For those over five years, the reported number of deaths globally only reduced by 2.7%, from 165,900 to 161,500 between 1990 and 2013<sup>7</sup>.

### *Streptococcus pneumoniae*

Pneumococcus is the commonest cause of bacterial meningitis in adults in much of the world<sup>1,5,8,9</sup>. There are over 90 antigenically different serotypes of *S. pneumoniae* as determined by the polysaccharide capsule - the target for all currently licensed vaccines.

Pneumococcal conjugate vaccines (PCV) have been used for the last 15 years. PCV7 targeted seven pneumococcal serotypes and more recently PCV10 and PCV13 (covering ten and thirteen serotypes respectively) were licensed in the US and Europe. The polysaccharide vaccine, PPV23, covers 23 serotypes. Until recently, conjugate vaccines were largely used only in children but a recent placebo-controlled trial in people 65 years of age and older has shown good efficacy of PCV13 in preventing vaccine-type pneumococcal pneumonia, non-bacteraemic pneumonia and invasive pneumococcal disease, with vaccine efficacies of 45.6%, 45%, and 75% respectively<sup>10</sup>. Although the

majority of studies on the immunogenicity of pneumococcal vaccines are non-comparative, there is some evidence that PCV is more immunogenic<sup>11</sup>. The conjugate vaccines also produce substantial herd immunity, when vaccination of part of the population provides protection for non-vaccinated individuals. . Recent large studies have shown dramatic reductions of disease caused by vaccine serotypes in both vaccinated and unvaccinated populations<sup>12-15</sup>.

Since conjugate vaccines were first introduced serotype replacement has been observed. This is an increase in the incidence of disease and/or asymptomatic carriage caused by non-vaccine serotypes.<sup>16-19</sup> Despite this the overall incidence of invasive pneumococcal disease has dropped. A meta-analysis from Europe, the Americas and Australia confirmed a sustained reduction in the incidence of pneumococcal meningitis in children seven years post-vaccination (risk ratio for meningitis was 0.40, (95% CI 0.25-0.64). There was a similar, but smaller, reduction in adults with a relative risk of meningitis in 18-49 year olds of 0.61, (95% CI 0.4-0.95) seven years after vaccination. For older adults aged 50-64 years, there was a decrease in meningitis caused by the vaccine serotypes but this was offset by a significant increase in non-vaccine serotype disease (RR 2.83 95% CI 1.46-5.47)<sup>20</sup>. Mathematical models have predicted a substantial reduction in disease following the introduction of PCV13, even taking serotype replacement into account<sup>21,22</sup>. Recent observational studies confirm this with a 32% reduction in invasive pneumococcal disease following the introduction of PCV13, but a 25% increase in non-PCV13 serotypes<sup>23</sup>.

### **Neisseria meningitidis**

Meningococci are categorised into 13 serogroups; five (A, B, C, W135, and Y) are responsible for most cases of invasive disease. Serogroup B is the commonest strain across Europe, including England and Wales where it is responsible for the majority of cases<sup>24,25</sup>. Serogroup Y is predominant in the USA<sup>26</sup> and the second most common in parts of Europe<sup>27</sup>. Recently there has been a rise in serogroup W135 in the UK, which has been shown to be linked with a South American clone.

Disease caused by this clone is associated with a higher mortality as they are part of the more deadly

ST11 clonal complex (or cc11)<sup>28</sup>. The same clonal complex is responsible for recent outbreaks of meningococcal C disease amongst gay men<sup>29,30</sup>.

Serogroup C was previously responsible for most meningococcal disease in Western countries, but incidence has markedly declined following the introduction of the meningococcal C conjugate vaccine. In the Netherlands, incidence has declined from 4.5/100,000 in 2001 to 0.6/100,000 in 2012<sup>27</sup>. Similar results have been seen in other countries<sup>5,14</sup>. In 2015, serogroup C disease appeared for the first time in the Sahel region of Africa<sup>31</sup>. Serogroup A has been responsible for large outbreaks in the meningitis belt of Africa; however, massive reductions have been seen in recent years following widespread vaccination<sup>32,33</sup>. The Meningitis Vaccine Project – a collaboration between the World Health Organisation and PATH (the Programme for Applied Technology in Health) - set out to vaccinate 250 million people in Africa with the new serogroup A conjugate vaccine. This has been a massive public health triumph. In Burkina Faso there was a risk reduction of 99.8% and similar dramatic results were seen in Niger where serogroup A disease had virtually disappeared by 2011<sup>33,34</sup>. Meningococcal A is also responsible for epidemics in parts of Asia including India, Indonesia, Nepal, Mongolia, and Pakistan<sup>35</sup>.

## Other bacteria

*Haemophilus influenzae* type B was a significant cause of meningitis, especially in infants and young children, prior to widespread use of conjugate vaccines<sup>6</sup>. As with meningococcal disease, *H. influenzae* type B has virtually disappeared in areas where immunisation has been implemented, but remains a problem where vaccination is not commonplace<sup>36</sup>. The incidence of invasive *haemophilus* disease due to non-type B strains has, however, increased in recent years. The majority of these cases are due to non-typeable organisms but a number are due to other encapsulated forms of *H. influenzae*, in particular types e and f<sup>37-39</sup>.

*Streptococcus suis* is a major cause of meningitis in some parts of Asia, especially Thailand and Vietnam. It is a pathogen of pigs, and close contact with pigs or pork is a significant risk factor for

disease. Although the case fatality rate is only 4%, some degree of hearing loss occurred in more than 50% of survivors<sup>40</sup>. It has also been reported from many other parts of the world<sup>41-43</sup>. Other causes of meningitis include the Enterobacteriaceae, *Staphylococcus aureus*<sup>1,5</sup>, and *Listeria monocytogenes* which is normally seen in those with risk factors such as older adults, alcoholics, diabetics, patients with malignancies, and those on immunosuppressive drugs<sup>4,44-47</sup>.

## Pathogenesis

Many aspects of the pathogenesis of bacterial meningitis have yet to be understood; however, there are four main processes: colonisation, invasion into the blood stream, survival in the bloodstream and, entry into the subarachnoid space. The subsequent inflammation and neurological damage is caused by a combination of bacterial and host factors. Figure 2 schematically shows the pathogenesis of *S. pneumoniae* and *N. meningitidis* meningitis.

## Colonisation

Many bacteria that cause meningitis initially colonise the mucous membranes of the upper respiratory tract. Colonisation involves a combination of the bacteria adhering to the cell surfaces and avoidance of the host's defence mechanisms. Many organisms have fimbriae (a fringe) or pili (hair-like appendages) which assist in their attachment to the epithelium. The main requirement for meningococcal adhesion is the type IV pili (tfp). Tfp adhere via various receptors including the platelet activating factor receptor (PAFR), beta 2 adrenoceptor receptors and CD147<sup>64, 65</sup>. The meningococcal outer membrane proteins including lipopolysaccharide and the opacity proteins (OpC and OpA) have also been proposed to contribute to the maintenance of adhesion<sup>48,49</sup>. Three main receptors have been proposed for pneumococcal adhesion to epithelial surfaces – PAFR, laminin receptors and the polyimmunoglobulin receptor (PIgR).

## Invasion

Invasion into the blood stream occurs either transcellularly (passing through the cells) or pericellularly (between cells)<sup>85</sup>. Pneumococci utilise both of these methods via receptors such as the PAFR or the pneumococcal choline binding receptor<sup>50</sup>. Meningococci are transported across the epithelial cells in phagocytic vacuoles<sup>51</sup>. Survival in the bloodstream requires evasion of the immune system. Meningococci utilise factor H binding protein (fHbp), a lipoprotein responsible for dysregulation of the complement pathway and Por A, an outer membrane protein, to evade complement<sup>52,53</sup>.

Most cases of meningitis probably occur following bacteraemia but the high incidence of pneumococcal meningitis in patients with sinusitis and otitis media suggest direct spread to the central nervous system may also occur<sup>8</sup>. This possibility is supported by mouse models showing pneumococcal meningitis after respiratory infection without blood stream involvement<sup>54</sup>. Direct entry from the nose through dural defects is also possible.

### **Entry into the central nervous system and inflammation**

Due to a lack of host defences in the subarachnoid space, bacteria multiply relatively unhindered. Bacterial components are recognised by pattern recognition receptors, present on microglia and other brain cells. A cascade of events is then triggered that ultimately leads to the release of pro-inflammatory mediators such as  $\text{TNF}\alpha$ , IL-6 and IL-1 $\beta$ . Many of these are released in greater quantity in pneumococcal disease compared with other organisms and may account for the worse prognosis associated with pneumococcal meningitis<sup>55</sup>. Following the release of the cytokines granulocytes cross the blood-brain barrier and it becomes more permeable. Bacterial lysis occurs in response to antibiotics or, in the case of pneumococci, when the bacteria reach the stationary growth phase (autolysis). Lysis leads to the release of pro-inflammatory agents, such as lipopolysaccharide, lipotechoic acid and peptidoglycans, from the cell wall of the bacterium and augments the inflammatory process<sup>56</sup>.



Neutrophils have been implicated in much of the neurological damage found in meningitis and MRP-14, a protein expressed in myeloid cells, has been found in the CSF of patients with pneumococcal meningitis; inhibition of MRP-14 led to reduced sequelae in a mouse model<sup>57</sup>. Matrix metalloproteinases (MMPs) are released by white cells in the CSF. They are seen very early in infection and aid the release and activation of pro-inflammatory cytokines, the degradation of extracellular matrix components, and the recruitment of further leukocytes into the subarachnoid space. As with other inflammatory mediators, the levels of MMP-9 are especially high in pneumococcal meningitis<sup>55</sup>.

### **Genetic predisposition**

Several studies have suggested a genetic predisposition to bacterial meningitis, with most related to deficiencies that affect the complement system. In particular, C2 deficiency was found in 58% of patients with pneumococcal meningitis, factor D deficiency predisposed to meningococcal disease, and susceptibility to meningococcal serogroups W135 and Y arose in those with properdin deficiency. Case-control studies revealed that polymorphisms in mannose binding lectin and complement factor h (cfh) were associated with susceptibility to pneumococcal and meningococcal disease, respectively. Approximately one fifth of patients with meningococcal disease were defined as having meningitis. Due to variations in definitions no analysis could be performed excluding patients who did not have meningitis<sup>58</sup>. More recently genome wide association studies have confirmed that a polymorphism in cfh predisposes to meningococcal disease, just over one third had meningitis, and a polymorphism in the C3 gene predisposes to pneumococcal meningitis<sup>59,60</sup>.

## **Diagnosis**

### **Clinical diagnosis**

Diagnosing bacterial meningitis clinically can be difficult as many illnesses present with similar symptoms. The classical triad of neck stiffness, fever and altered consciousness is seen in less than 50% of patients with acute bacterial meningitis<sup>8</sup>. However, any two of headache, fever, neck

stiffness and altered consciousness are seen much more commonly, in up to 95%<sup>8</sup>. Kernig's and Brudzinski's signs have been used in the clinical assessment of meningitis for many years, but their usefulness is doubtful. They have been reported to have high specificity (up to 95%), although this is very clinician dependent, but the sensitivity can be as low as 5%<sup>61</sup>. They should not be relied upon to exclude, or establish, a diagnosis of bacterial meningitis. Differential diagnoses include viral meningitis and other forms of infective meningitis, non-infectious causes of meningitis such as autoimmune conditions, medications such as trimethoprim and non-steroidal anti-inflammatories and malignancy, as well as non-meningitic illnesses such as sub-arachnoid haemorrhage, migraine and other 'simple' viral illnesses.

### Laboratory diagnosis

The gold standard for diagnosing meningitis is examination of the cerebrospinal fluid (CSF); typical findings are shown in table 2. Measuring the opening pressure at the time of lumbar puncture (LP) is very useful and is often high in bacterial meningitis. A raised white blood count in the CSF is taken as an indication of inflammation of the meninges, although some patients may have bacteria in their CSF without an elevated white blood count. These patients have a poor prognosis.

CSF protein and glucose should also be measured. Patients with bacterial meningitis typically have a raised protein and low glucose. CSF glucose is influenced by the serum glucose concentration and, therefore, a concurrent serum sample must also be taken. CSF lactate may have advantages over CSF glucose in that it is unaffected by the serum concentration. CSF lactate, if taken prior to antibiotics, has a sensitivity of 0.93 (95% CI 0.89-0.96) and specificity of 0.96 (CI 0.93-0.98) in differentiating bacterial from viral meningitis<sup>62</sup>. Serum and CSF procalcitonin concentrations have also been suggested as useful tests to indicate a likely bacterial cause but well-designed diagnostic accuracy studies, including cost-effectiveness analyses, are required before recommending the routine use of procalcitonin in the diagnostic workup of bacterial meningitis.

Gram stain and culture of the CSF allow both the identification of the causative pathogen and assessment of antimicrobial susceptibilities. If the LP is delayed until after antibiotics have been given, the likelihood of identifying an organism may be reduced by up to 44%<sup>63,64</sup>. Molecular methods are, therefore, becoming increasingly important for diagnosis. The most common of these is the polymerase chain reaction (PCR) which can detect organisms in blood or CSF for several days after antibiotics have been given<sup>65,66</sup>. It has high sensitivity (87-100%) and specificity (98-100%)<sup>67-70</sup>. Dried spot CSF PCR tests, which could be useful in the absence of a laboratory, have shown a 90% sensitivity in diagnosing bacterial meningitis caused by *S. pneumoniae*, *S. suis*, and *N. meningitidis*<sup>71</sup>. In addition to CSF analysis, blood cultures may identify the cause and should be taken before antibiotics are given.

There has been recent interest in the ability to detect multiple pathogens with one platform such as multiplex PCR, 16S PCR, MALDI-TOF (matrix associated laser dissociation and ionisation-time of flight), and whole genome sequencing<sup>72,73</sup>. The 16S rRNA gene is present in almost all bacteria; one meta-analysis showed 16S rRNA PCR to be both sensitive and specific for the diagnosis of bacterial meningitis compared with standard culture (pooled sensitivity of 92% and specificity of 94%)<sup>74</sup>. The commonest method for species identification was sequencing. MALDI-TOF is now commonplace in many clinical laboratories. It utilises the protein mass of the organism to identify the bacteria. This has revolutionised clinical microbiology by reducing the time to identification of an organism; it normally requires a cultured organism but there are reports of success direct from CSF<sup>75</sup>. Whole genome sequencing has been used in the investigation of outbreaks, but as it becomes faster and cheaper, it may be incorporated into routine surveillance and diagnosis<sup>76,77</sup>.

Loop-mediated isothermal amplification (LAMP) is another method of DNA amplification and detection. The LAMP method is quick, with results in less than 2 hours, and a positive result can be seen with the naked eye. This technique has recently shown good sensitivity for detection of *N. meningitidis*, *S. pneumoniae*, *H. influenzae* and *Mycobacterium tuberculosis*<sup>78-81</sup>. It has also recently

been evaluated as a bedside test in the UK where it had a PPV of 100% and a NPV of 97%<sup>82</sup>. The speed and ease of diagnosis makes this a very attractive diagnostic tool, especially within resource poor settings.

### **The role of neuroimaging**

The use of neuroimaging before LP has generated considerable debate with some recommending cerebral imaging is performed before LP for all patients. However this has been associated with delays in antibiotic administration, reduced likelihood of identifying a pathogen and an increase in mortality<sup>64,83-85</sup>. The reason for neuroimaging is to detect cerebral herniation syndromes, or shift of brain compartments. If these are present and an LP is performed, there is the theoretical concern that a reduction in pressure caused by the LP can precipitate a further brain shift which may lead to fatal herniation. Neuroimaging should therefore be performed on patients who have clinical signs which may suggest brain shift and, if shift of brain compartments or herniation is found, LP should be delayed. Indications that brain shift might be present include focal neurological signs and reduced level of consciousness. The exact level of consciousness at which an LP is safe is debated and different authorities recommend different cut-off points ranging between 8 and 13 on the Glasgow coma scale<sup>86-88</sup>.

No study has identified features associated with an increased risk of herniation post-LP. One study found certain features (age over 60 years, immunocompromise, history of neurological disease, recent seizure, and certain abnormal neurological examination findings) were associated with abnormalities on imaging, but the risk of herniation or brain shift was not assessed<sup>84</sup>. A recent retrospective study found that removing impaired mental status as a contraindication for LP was associated with significantly earlier treatment and a favourable outcome however there are several limitations to this study and cause and effect cannot be attributed<sup>89</sup>. Every patient with suspected bacterial meningitis must be carefully assessed to ascertain whether they have signs or symptoms consistent with brain shift. If they do not, LP should be carried out as soon as possible without prior

neuroimaging The supplementary table outlines the situations when neuroimaging should be performed before LP.

## Treatment

Antibiotics should be given as soon as possible to patients with suspected bacterial meningitis, ideally after both blood and CSF have been obtained for culture. Early antibiotic treatment is associated with a lower mortality<sup>83</sup>. If there are delays in sampling, the priority is for treatment to be given. Many antibiotic regimens are based on data from animal models or clinical experience rather than randomised trials. The choice of antibiotic depends on the likely pathogen, local patterns of antibiotic resistance and the CSF penetration of the drug. Penicillin and other beta-lactams are effective against the commonest pathogens and the CSF concentration (even with uninflamed meninges) tends to be close to the minimum inhibitory concentrations for moderately susceptible bacteria<sup>90</sup>. The worldwide emergence of antimicrobial resistance, especially against *S. pneumoniae*, affects the choice of empirical treatment in many countries. This is especially important in the poorer regions of the world where newer antibiotics may not be available or affordable. Table 3 gives recommendations for empirical antibiotics.

## Antimicrobial resistance

Penicillin-resistant pneumococci have been reported from all parts of the world<sup>91</sup> and have been associated with an increase in mortality<sup>92</sup>. Vancomycin is widely recommended when penicillin-resistant pneumococci are possible, but due to the fact that it crosses the blood brain barrier poorly it should be used in conjunction with another antimicrobial, often a cephalosporin. .

Fluoroquinolones may be good alternatives in the era of penicillin-resistant pneumococci. Experimental mouse models have shown moxifloxacin to be equivalent to cephalosporins<sup>93</sup>. Caution should be exercised in using fluoroquinolones as single agents as organisms may rapidly develop resistance and clinical data are lacking. There are several case reports and case series showing the

efficacy of other antibiotics in meningitis, such as ceftaroline<sup>94</sup>, linezolid<sup>95,96</sup>, daptomycin<sup>97-99</sup>, and doripenem<sup>100</sup>. Without evidence from comparative therapeutic trials, these agents should be used with caution and only when other better tested agents cannot be used either because of resistance, patient intolerance or allergy.

Efforts should be made to identify local patterns of antibiotic resistance to determine the optimal empirical treatment for each geographic area. In the UK, where there is a low prevalence of penicillin-resistance, third-generation cephalosporins (cefotaxime or ceftriaxone) remain the empirical choice. However, many parts of the world have penicillin-resistant pneumococci (MIC  $\geq 0.12\mu\text{g/ml}$ ) with rates of approximately 25% in the United States and parts of Europe (e.g. Spain, Croatia, Romania) and over 50% in Asia; 100% of isolates were found to be penicillin resistant in Vietnam and Thailand but numbers were small (n=6 and 1 respectively)<sup>101-103</sup>. In these areas vancomycin (with or without rifampicin) should be given in addition to a third-generation cephalosporin<sup>104</sup>. Alternatives are listed in table 3.

Antibiotic resistance in meningococci is rare<sup>27</sup> although decreased susceptibility to penicillin has been particularly associated with some serogroups, especially C and W135<sup>105-108</sup>.

### **Duration of therapy**

There is limited trial evidence to guide how long to treat adults with bacterial meningitis. Using shorter courses of antibiotics can reduce hospital stay and costs and may also reduce the risk of adverse events such as nosocomial infections. Paediatric studies have shown that shorter courses are safe and effective<sup>109,110</sup>. A meta-analysis, looking at all causes of bacterial meningitis in children, found a short (4-7 days) course to be as efficacious as a long (7-14 days) course of antibiotics; unfortunately, no adult studies could be identified for inclusion<sup>111</sup>. Three days of intravenous benzylpenicillin has been shown to be sufficient for adults with meningococcal disease<sup>112</sup>; there was no control group in this study, but the mortality of 9% is in keeping with other studies<sup>8,25,113</sup>. During meningococcal epidemics, a single dose of ceftriaxone or chloramphenicol is effective<sup>109</sup>.

Although there are no randomised trials, current guidance in many richer nations is to give relatively short courses of antibiotics for meningococcal disease ( 5 to 7 days ), and a slightly longer duration in pneumococcal meningitis (10-14 days)<sup>114 115</sup>. *Listeria* meningitis should be treated for a minimum of 21 days.

### Adjunctive therapies

Even in the presence of a susceptible organism and appropriate antibiotics, mortality in bacterial meningitis is high, around 10-30% in industrialised nations<sup>4,8,113,116-119</sup> and nearer 50% in many poorer nations<sup>120-122</sup>. The high number of deaths, despite apparently appropriate treatment, is thought to be due to the inflammatory processes described earlier. Efforts have, therefore, focused on identifying useful adjunctive therapies which might reduce inflammation and brain oedema.

### Corticosteroids

Following several paediatric studies<sup>123</sup>, a large multi-centre European randomised controlled trial in adults showed a significant reduction of both an unfavourable outcome and death in patients who were treated with dexamethasone compared to placebo (RR 0.59 and 0.48 for unfavourable outcome and death respectively), most striking for the subgroup of patients with pneumococcal meningitis<sup>124</sup>. Subsequent studies carried out in adults in Malawi and Vietnam failed to reproduce the European findings<sup>122,125</sup>, although there was a better outcome (significant reduction in the risk of death at 1 month and risk for death or disability at 6 months) for patients in Vietnam with confirmed bacterial meningitis. A meta-analysis of individual patient data (n=2029) suggested the differences were not due to the high rates of HIV and tuberculosis in these countries<sup>126</sup>. This meta-analysis concluded that there were no subgroups that might benefit from adjunctive dexamethasone, although post-hoc analyses did suggest there might be some benefit in HIV negative adults and a lower rate of hearing loss amongst all survivors.

Another meta-analysis of 25 studies, in both adults and children, showed a small reduction in hearing loss in adults treated with corticosteroids compared with placebo (16% versus 22% RR 0.74, 95%CI 0.56-0.98) but no difference in mortality<sup>152</sup>. A subgroup analysis demonstrated a slight decline in mortality in all patients with pneumococcal meningitis (RR 0.84 95% CI 0.72-0.98) with no effect on *H. influenzae* or meningococcal meningitis (although numbers in these groups were very small). It should be noted that this benefit did not remain when a random-effects model was used (which may have been more appropriate given the heterogeneity of the studies ( $I^2$  47%))<sup>123</sup>.

Both these meta-analyses compared very diverse studies and populations including children and adults, high and low socio-economic status and differences in co-morbidities. This is reflected in the heterogeneity of the analyses and possibly accounts for the conflicting conclusions. However, there needs to be a balance between the risks and potential benefits of corticosteroid use. Overall, it seems that corticosteroids may offer a small benefit in adults with regard to reducing hearing loss and may have a slightly lower mortality in pneumococcal meningitis. In most studies there is no increase in side-effects when corticosteroids were given in comparison to placebo. It is, therefore, recommended to give steroids to all adults with suspected bacterial meningitis in resource rich countries. Although the meta-analyses did not demonstrate a difference between countries of high and low income, there was considerable heterogeneity and in lower income countries the benefits are probably less pronounced; therefore, corticosteroids are not recommended in this group.

The dose of corticosteroids differs between trials, but the one that was used in the large Dutch trial is 10 mg of dexamethasone given four times a day<sup>124</sup>. The Cochrane review and expert guidelines recommend administration with or just prior to the first antimicrobial dose<sup>150</sup>. Sub-group analyses in both meta-analyses showed no statistical differences in terms of mortality when corticosteroids were given before or with antibiotics compared with when they were given afterwards<sup>123,126</sup>. There were differences when hearing loss was the outcome of interest and indeed the effect size was bigger in the group who received corticosteroids *after* antibiotics compared with the group who



received corticosteroids before or concurrently (RR 0.62 (95% CI 0.43-0.89) versus RR 0.8 (95% CI 0.7-0.92))<sup>123</sup>.

### ***Other adjunctive therapies***

Glycerol and hypothermia have been trialled as potential adjunctive therapies in bacterial meningitis. Theoretically osmotic substances such as glycerol can draw extravascular fluid from the brain into the vascular space and reduce intracranial pressure. One clinical study in adults, conducted in a resource limited setting with a high HIV prevalence, failed to show any benefit<sup>120</sup>. Induced hypothermia is used as a treatment for cerebral hypoxaemia following cardiac arrest and animal models have shown it to reduce intracranial hypertension in meningitis. Observational clinical studies also suggested it might be beneficial<sup>127,128</sup>. However, a recent randomised controlled trial was stopped early due to an increased risk of death in patients in the intervention arm<sup>129</sup>. It is unlikely that hypothermia or glycerol will be widely implemented without adaptation and further controlled trials.

### **Prognosis and sequelae**

Features associated with a poor prognosis include older age, reduced conscious level, tachycardia, a CSF leukocyte count of less than  $1000 \times 10^9$  cells/ml, reduced platelet count<sup>8</sup>. Prognosis may be improved by instigating both antibiotic and steroid treatment early<sup>3</sup>. Sequelae are more common in pneumococcal meningitis than meningococcal meningitis. Hearing loss is a one of the most common problems after meningitis, particularly pneumococcal meningitis, and a prompt hearing assessment with cochlear implants can be incredibly beneficial for the patient. Other sequelae include limb loss, especially if meningococcal sepsis is present, subdural empyema, hydrocephalus and seizures. Other less life threatening sequelae include neurocognitive dysfunction including sleep disorders.

### **The Future**

## *New vaccines*

Many of the pneumococcal vaccines in development are focussing on protein-based strategies (rather than being based on the capsular polysaccharide), to be given either in addition or as a replacement to conjugate vaccines. This may allow pan-serotype protection and eliminate the problem of serotype replacement. Several early phase studies have been conducted, one of which (combining pneumolysin toxoid and histidine triad protein D, a pneumococcal surface protein thought to be involved in complement inhibition) has recently reported good evidence of immunogenicity with an acceptable safety profile in both younger and older adult cohorts<sup>130-132</sup>.

The search for a widely effective vaccine against meningococcal serogroup B has been difficult because of the poorly immunogenic capsule. Vaccines were developed that targeted sub-capsular proteins (see figure 3) and were used with some success in epidemics in Norway, Cuba, Brazil, New Zealand, and France<sup>133-135</sup>. However, they were poorly immunogenic in young children and strain specific, and so could not be rolled out on a larger scale. Using a novel genome sequencing method, a multicomponent serogroup B meningococcal vaccine has been produced. It contains four immunogenic components: 3 proteins – neisserial adhesion A (NadA) which is involved in the adhesion of *Neisseria* to the nasal epithelium, neisserial heparin binding antigen (NHBA) thought to be involved in serum resistance, and fHbp - in combination with outer membrane vesicles from the New Zealand vaccine strain. The vaccine has been shown to be immunogenic in young infants<sup>136,137</sup> and older children<sup>138</sup>. It may also reduce carriage rates of other meningococcal serogroups (as some of the sub-capsular antigens in the vaccine are also present in non-B serogroups)<sup>139</sup>, indicating that it could affect transmission once fully implemented and have a significant impact on disease in adults as well as children. The vaccine has been estimated to provide coverage against 88% of circulating serogroup B strains in England and Wales<sup>140</sup>, and was permitted for investigational use in the US in late 2013 and early 2014 in two outbreaks. In September 2015 the UK Department of Health incorporated it into their childhood immunisation schedule. The US Food and Drugs Administration

have also recently approved another serogroup B vaccine for adolescents and young adults. This vaccine is a bivalent vaccine that utilises two families of fHbp.

### *Other research priorities for the future*

New treatments to improve outcome are needed. Research is focussed on adjunctive therapy targeting the host inflammatory response. Some areas of interest include matrix metalloproteinase (MMP) inhibitors and MRP-14 inhibitors such as paquinimod which has anti-inflammatory effects without affecting bacterial killing<sup>57</sup>. Inhibitors of complement and other neurotoxic mediators are also being investigated as well as compounds that can modulate the leukocyte response (e.g. G-CSF)<sup>141</sup>.

Finally, surveillance around the world remains important. The global epidemiology of bacterial meningitis is continually changing, especially with the introduction of new vaccines, and surveillance is needed to determine the breadth of coverage, monitor for serotype replacement and follow the emergence of new meningococcal serogroups. Robust epidemiological studies must document clearly the causative agents in lower-resourced settings, especially Asia, to determine what vaccination strategies are necessary. Surveillance for antimicrobial resistance is also of utmost importance. Epidemiological research into risk factors for disease in adults and preventative strategies will also be important.

Ultimately we are still some way off from the effective control of bacterial meningitis and the combination of a rare and deadly disease requires vigilance of the clinician, to identify and treat it in a timely manner, and the continued support of research partners to develop new vaccines and treatments.

## **Author Contributions**

FM performed the initial literature search and drafted the first version. All authors then contributed to further drafts and approved the final submitted version. SP gave specific input to the pathogenesis section and designed figure 2 and 3.

## **Conflicts of Interest**

All authors disclose no conflicts of interest.







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