An audit of acute bacterial meningitis in a large teaching hospital 2005–10

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Summary

Background: Acute bacterial meningitis (ABM) is a rare disease associated with severe neurological sequelae and death. Clinical features on admission may be subtle and thus delay recognition. Previous studies have shown association between early administration of antibiotics and favourable outcomes.

Aim: To examine the presenting clinical features of patients aged >15 years with ABM admitted to a University teaching hospital. To audit investigations and treatment including lumbar puncture (LP), computed tomography (CT) and antibiotics against British Infection Association guidelines.

Design: Retrospective observational audit.

Methods: Hospital records were reviewed for presenting clinical features and timing of CT scan, LP and antibiotics.

Results: Records of 39 patients with ABM were reviewed. The classical triad of fever, neck stiffness and altered mental state was present on admission in only 21% of cases. LP was contraindicated in 69% of cases. Immediate LP was carried out in only 17% of those who had no contraindication. Antibiotics were administered after a median of 79 min (interquartile range 24–213 min); 65% were given within 3 h after arrival. Eighty-five percent of patients had antibiotics in accordance with local guidelines.

Conclusions: In patients with ABM, the classical clinical features are uncommon on arrival to hospital and frequently evolve following admission. The majority of patients have contraindications to immediate LP. Efforts should be made to facilitate immediate LP performed in the Emergency Department when there are no contraindications. Earlier administration of antibiotics in cases of suspected ABM and close review following admission is recommended.

Introduction

Acute bacterial meningitis (ABM) is a rare disease in the UK associated with serious neurological sequelae and death. In 2009, there were 162 deaths from bacterial meningitis in people aged over 15 in England and Wales and 352 notified cases of confirmed meningococcal disease.\textsuperscript{1,2} In 2005, there were 145 notified cases of confirmed pneumococcal meningitis in this group.\textsuperscript{3} This is equivalent to an annual incidence of 0.79 and 0.34 cases per 100,000, respectively.\textsuperscript{2–4}

On this basis a university teaching hospital serving a population of 500,000 patients could expect to see around six cases of confirmed bacterial meningitis in adults per year. This is likely to underestimate the true incidence given the possibility of
under-reporting, the presence of causative organisms other than *Neisseria meningitidis* or *Streptococcus pneumoniae* and the possibility that an organism may not be identified.

The diagnosis of meningitis is complicated by the variability of presenting features and this may delay recognition and thus early and effective treatment. Several observational studies have shown that early antibiotic administration is associated with favourable outcomes.5–9

We aimed to determine the presenting clinical features of patients with bacterial meningitis. Secondly, we aimed to audit local practices against British Infection Association (BIA) guidelines10 with regard to timing of administration of antibiotics and use of computed tomography (CT) head scanning and lumbar puncture (LP).

**Methods**

**Setting**

Addenbrooke’s Hospital is a 1100-bed tertiary referral University hospital in East England serving a population of approximately 500,000 people.

**Search strategy**

All patients admitted between 1 January 2005 and 31 October 2010 with a final diagnosis of ABM were identified by

1. A search of computerized microbiology records for (number of samples identified)
   - All cerebrospinal fluid (CSF) samples culture positive for any organism (922).
   - All polymerase chain reaction (PCR) tests from blood or CSF positive for *N. meningitidis* or *S. pneumoniae* (79).
   - All blood cultures positive for *N. meningitidis* (17) or *S. pneumoniae* (188).

2. A search of hospital discharge coding records for patients with a primary diagnosis of International Classification of Diseases-10 code G00 (bacterial meningitis) (number of patients identified = 69)

Patients were included if they had both:

1. onset of symptoms in the community and within 7 days prior to admission; and
2. compatible clinical picture of bacterial meningitis (two or more of: fever, headache, neck stiffness, altered mental state or reduced conscious level, photophobia and vomiting).

And one of the following:

1. positive CSF bacterial culture;
2. positive CSF PCR for *N. meningitidis* or *S. pneumoniae*;
3. CSF microscopy with white cells >1000 cells per microlitre and neutrophil predominance;
4. positive blood culture for *N. meningitidis* or *S. pneumoniae*; and
5. PCR of blood for *N. meningitidis* or *S. pneumoniae*.

Identification of organisms based on CSF Gram stain was not an inclusion criterion.

Patients were excluded if they were: under the age of 16 years; under the care of the neurosurgery team with congenital hydrocephalus, a ventriculoperitoneal shunt or previous neurosurgery; and admitted for elective LP or known to be immunocompromised.

The full medical records of all included patients were reviewed and data extracted using Microsoft Excel. Statistics were calculated using SPSS version 17. Variables were tested for normal distribution and independent samples *t*-test, or Mann–Whitney *U*-test, as appropriate, were used to determine the effect of various factors on time to delivery of antibiotics.

**Audit guidelines**

Standards from the BIA 2004 guidelines for adults presenting with suspected meningitis or meningococcal septicaemia were used to audit practice.10 Target timing of antibiotics from arrival is not specified in the guidelines and for this reason based on prospective observational evidence5 and European Federation of Neurological Societies guidelines11 an audit standard of 180 min was used. Audited standards were:

1. LP was performed prior to administering antibiotics unless there were signs of raised intra-cranial pressure, shock or respiratory failure (as defined in BIA guidelines shown in Box 1).
2. LP was appropriately deferred until stabilization and/or CT head scan if signs of raised intra-cranial pressure, shock or respiratory failure were present (see Box 1).
3. Blood cultures were taken prior to the administration of antibiotics.
4. Intravenous antibiotics were administered within 180 min of arrival.
5. The choice and dose of antibiotic was appropriate and complied with Trust antibiotic guidelines (initial dose of intravenous ceftriaxone or cefotaxime 2 g, then continued at standard doses).

**Approval**

Permission to carry out this audit was granted by the Audit Department of Addenbrooke’s Hospital.
Results

Of the 1258 samples identified from computerized medical records, 50 patients fulfilled the above criteria. Eleven further patients were excluded: six cases were transfers from another hospital and initial management took place prior to transfer; in four cases it was not possible to locate the medical records; and in one case the patient had disseminated pneumococcal sepsicaemia with pneumonia and delayed development of meningitis.

Presenting clinical features and investigations of the 39 included patients, stratified by identified organism, are shown in Table 1.

Clinical features

*Neisseria meningitidis* was the commonest causative organism in this series and occurred in a younger age group [median 22 years, interquartile range (IQR) 19–56] than the second commonest organism, *S. pneumoniae* (median 54 years, IQR 35–67), $U = 101.5$, $Z = -2.093$, $P = 0.036$.

The classical triad of meningitis, namely fever, neck stiffness and altered mental state, was present at admission in only 21% of all cases; in 15% of cases caused by *N. meningitides*; and 29% of cases due to *S. pneumoniae* while at least one of the three clinical features were seen in 90 and 100% of cases, respectively. Fever, headache and altered mental state were the commonest presenting symptoms while photophobia and neck stiffness were uncommon.

Timing of antibiotics, CT and LP

Patients were seen by a doctor after a median of 5 min (IQR 0–56) after arrival. The median time to administration of antibiotics was 79 min (IQR 24–213).

Thirty-six of 39 patients (92%) had a CT scan of the head and this was ordered after a median time from admission of 70 min (IQR 33–253) and a verbal report was received after a median of 129 min (IQR 66–435).

In 9 of 39 cases (23%), a CT of the head was performed before giving antibiotics resulting in a significantly greater delay from arrival to antibiotic administration [median 194 min (IQR 122–302)] compared to those who did not have a prior CT [median 50 min (IQR 17–182)], $U = 55$, $Z = -2.95$, $P = 0.01$.

Thirty of 39 patients (77%) had a LP and this was performed after a median of 354 min (IQR 250–808). Twelve patients had no documented contraindication to immediate LP, yet the majority had a prior CT scan of the head (10/12, 83%).

In twenty-seven patients (69%) there were contraindications to performing an immediate LP, most commonly due to reduced or falling conscious level (see reasons in Table 2). An immediate LP

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Box 1  Comparison of International/National Guidelines of ABM: listed contraindications to LP

<table>
<thead>
<tr>
<th>British Infection Society/ Meningitis Research Foundation 2003</th>
<th>European Federation of Neurological Societies 2008</th>
<th>Infectious Diseases Society of America 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
<td><strong>Absolute contraindications</strong></td>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td>Marked depressed conscious level (GCS &lt;12) or fluctuating level (fall in GCS &lt;2)</td>
<td>Signs of raised ICP (papilloedema, decerebrate posturing)</td>
<td>Immunocompromise</td>
</tr>
<tr>
<td>Focal neurology</td>
<td>Local skin infection in needle track</td>
<td>History of central nervous system disease</td>
</tr>
<tr>
<td>Persistent seizures</td>
<td>Evidence of obstructive hydrocephalus, cerebral oedema or herniation on CT/Magnetic resonance imaging</td>
<td>New onset seizure</td>
</tr>
<tr>
<td>Bradycardia and hypertension</td>
<td></td>
<td>Papilloedema</td>
</tr>
<tr>
<td>Papilloedema</td>
<td></td>
<td>Altered consciousness</td>
</tr>
<tr>
<td><strong>Reason to delay</strong></td>
<td><strong>Relative (therapeutic measures indicated first)</strong></td>
<td>Focal neurological deficit</td>
</tr>
<tr>
<td>Rapidly progressive rash</td>
<td>Sepsis/hypotension BP &lt;100/60</td>
<td></td>
</tr>
<tr>
<td>Poor peripheral perfusion (capillary refill time &gt;4 s, oliguria, systolic blood pressure &lt;90)</td>
<td>Coagulation disorder (disseminated intravascular coagulation, platelet &lt;50, use of warfarin)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate &lt;8 or &gt;30</td>
<td>Presence of focal neurological deficit, especially when posterior fossa lesion is suspected</td>
<td></td>
</tr>
<tr>
<td>Pulse &lt;40 or &gt;140</td>
<td>GCS eight or less</td>
<td></td>
</tr>
<tr>
<td>Acidosis pH &lt;7.3 or base excess &lt;-5</td>
<td>Epileptic seizures</td>
<td></td>
</tr>
</tbody>
</table>

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was still carried out in one case despite the presence of a contraindication (reduced conscious level). A LP was performed prior to administration of antibiotics in only one case (1/39, 3%).

The limited sample size restricted analysis for clinical factors responsible for delay in antibiotics. There was no significant association seen between number of compatible presenting symptoms or signs (grouped into \( \leq 3 \) or \( >3 \) of the six listed above) and timing of antibiotics (\( U = 138, Z = -1.05, P = 0.30 \)) or mortality and timing of antibiotics (\( U = 71, Z = -1.00, P = 0.32 \)). The timing of investigations and treatment from arrival is shown in Figure 1.

**Microbiology**

In 69% of cases, blood cultures were taken prior to administering antibiotics (27/39); in the remaining 12 cases they were taken afterwards. In 51% of cases (20/39), a microbiological diagnosis was made from blood cultures.

A blood sample was tested by PCR for *N. meningitidis* or *S. pneumoniae* in 11 of 39 patients (28%) and was positive in 8 of 39 (21%), including seven (18%) where blood cultures were negative and four (10%) where this test was the only method that identified an organism.

Organisms were seen on microscopy in 9 of the 30 patients (30%) who had an LP and CSF cultures were positive in 7 of 30 (23%). In 4 of 30 cases (13%), microscopy showed organisms but culture was negative. An organism was identified by PCR of CSF in 12 of 23 CSF-culture negative cases (52%) and in 7 of the 39 patients (18%) this was the only method that identified an organism.

*Neisseria meningitidis* was identified in 20 patients. Seventeen of 20 (85%) were serogroup B.
while three were serogroup Y. Susceptibility testing based on British Society of Antimicrobial Chemotherapy guidelines was carried out in 8 of 10 cases where a culture isolate was obtained (80%). This showed that one of eight isolates was resistant to penicillin (13%).

Streptococcus pneumoniae was identified in 17 patients. The serogroup was characterized in 13 patients and 8 of these patients (62%) had strains that are included in the 13-valent pneumococcal conjugate vaccine used in the UK Infant vaccination schedule (Prevenar 13®). In 8 of 12 cases (67%) where a culture isolate was obtained, susceptibility testing was carried out. All isolates were sensitive to ceftriaxone, one of eight was intermediate to penicillin (13%) and the remaining seven were susceptible.

### Table 2 Audit standards and outcomes

| Standard 1: LP was performed prior to antibiotics unless there were signs of raised ICP, shock or respiratory failure |
| No. with no contraindications to immediate LP | 12/39 (31) |
| No. with no contraindications who had immediate LP | 2/12 (17) |
| Standard 2: LP was appropriately deferred until stabilization and/or CT scan of the head if there were signs of raised intracranial pressure, shock or respiratory failure |
| No. with contraindications to immediate LP | 27/39 (69) |
| No. who had CT then subsequent LP | 17/27 (63) |
| No. who never had LP | 9/27 (33) |
| In those with contraindication(s), n who had immediate LP | 1/27 (4) |
| Standard 3: Blood cultures were taken prior to administration of antibiotics |
| Blood cultures performed prior to antibiotics | 27/39 (69) |
| Standard 4: Intravenous antibiotics were administered within 180 min of arrival to the Emergency Department |
| Antibiotics given within 180 min of arrivala | 26/38 (68) |
| Standard 5: The choice and dose of initial antibiotic was appropriate and complied with Trust antibiotic guidelines |
| Antibiotics given in accordance with Trust guidelines | 33/39 (85) |

| Documented contraindications to immediate LPb |
| Reduced Glasgow Coma Scale | 13 (48.1) |
| Reduced GCS and septicaemia predominating | 3 (11.1) |
| Septicaemia predominating | 3 (11.1) |
| Acidosis and reduced GCS | 2 (7.5) |
| Acidosis | 1 (3.7) |
| Acidosis and seizures | 1 (3.7) |
| Acidosis and shock | 1 (3.7) |
| Focal neurological signs | 1 (3.7) |
| Reduced GCS and respiratory failure and shock | 1 (3.7) |
| Seizures and shock and acidosis | 1 (3.7) |
| Total | 27 (100) |

| Mortality | 7/39 (18) |

aIn one patient, the time of antibiotic administration was not recorded. bFor more specific definitions of the listed contraindications see Box 1 (British Infection Society guidelines), shock refers to poor peripheral perfusion in Box 1.

### Treatment

In 33 of 39 patients (85%) antibiotics followed the hospital policy of an initial dose of 2 g intravenous ceftriaxone or cefotaxime, continued at standard doses (2 g twice daily or 2 g four times daily, respectively). Alternative antibiotics were used in three cases and were benzylpenicillin with ciprofloxacin (rationale not given), piperacillin/tazobactam (for presumed abdominal sepsis) and meropenem with vancomycin (for severe sepsis of undetermined origin in a patient admitted to intensive care). In two cases, the initial dose was too low (ceftriaxone 1 g and cefotaxime 750 mg) and in one, higher than recommended (ceftriaxone 4 g).

Full details of outcomes measured by the five audit standards are shown in Table 2.
Discussion

In this audit, patients with ABM frequently presented without classical features, making diagnosis difficult. Only a small minority had neck stiffness or photophobia on admission. This is likely to be a major contributory factor to delays in antibiotic treatment. While the rarity of neck stiffness could be due to the admitting junior clinician not documenting or missing the sign, this is unlikely as neck stiffness is generally not difficult to elicit. Furthermore, our relatively small sample size may have led to insufficient sampling bias, although the lack of classical features concurs with findings from larger observational studies.\textsuperscript{12–14}

Substantial delays in initiating antibiotic treatment were seen with a median delay of 79 min (IQR 24–213) following arrival. Early antibiotic treatment has been associated with reduced mortality. A multivariate analysis of 156 patients admitted to 56 French intensive care units (ICUs) with pneumococcal meningitis showed that a delay of >3 h between admission and antibiotic treatment was associated with an odds ratio for death at 3 months of 14.1 (95% CI 3.93–50.9).\textsuperscript{5} A retrospective Canadian single centre study of 123 cases of ABM showed that door-to-antibiotic time of >6 h was associated with an adjusted odds ratio of death of 8.4 (95% CI 1.7–40.9, \(P<0.01\)).\textsuperscript{6} A multicentre retrospective study of 269 patients from the USA showed that treatment with antibiotics before progression of clinical severity occurred, judged by a staging system, was associated with significantly improved outcomes.\textsuperscript{7} A multivariate analysis of retrospective data of 187 patients from Denmark predicted an odds ratio of an unfavourable outcome of 1.09 (95% CI 1.01–1.19) per hour of antibiotic delay following admission.\textsuperscript{8} Further studies have demonstrated similar outcomes.\textsuperscript{9} Finally, two observational studies from Japan\textsuperscript{15} and Taiwan\textsuperscript{16} have shown that the level of consciousness at initiation of antibiotics but not symptom duration until antibiotic treatment are significantly associated with mortality.

There are difficulties with the use of observational evidence to derive recommendations for timing of antibiotics and it would be unethical to test this question in a randomized study.\textsuperscript{17–19} Association between early antibiotics and survival may represent bias or confounding. For example, typical cases are likely to be treated earlier and recognition may reflect differences in host immune function which offer survival advantage rather than effect of early treatment.\textsuperscript{17}

In this audit, antibiotics were given after the CT scan was performed and reported in a quarter of

![Graph](image.png)

**Figure 1.** Time from arrival at emergency department until...
cases. This may be due to clinicians considering other differential diagnoses, particularly where there was reduced conscious level. The difficulty in recommending empirical early antibiotics in all cases of suspected meningitis is that it will result in overtreatment of the majority who do not have bacterial meningitis.

In six cases, the diagnosis was particularly delayed and the clinical abstracts are presented in Table 3. This series demonstrates the need for maintaining a high level of suspicion for the possibility of meningitis, even in the absence of classical signs. Clinical features frequently evolved following admission, highlighting the need for planned review following an admission. Overall mortality was 18%, a reminder of the seriousness of this condition.

It was observed that patients frequently have a contraindication or reason to defer LP, this case is seen in 69% of cases. The contraindication was most commonly reduced or falling conscious level. In those with no contraindications, very few had an LP prior to CT, which may reflect concern with occult raised intra-cranial pressure potentially leading to brain herniation. A prospective observational study from the USA followed 301 adults with suspected meningitis of whom 78% underwent CT prior to LP. Patients with abnormal CT scans were reliably predicted by: age >60 years, immunosuppression, history of CNS disease, a seizure within 1 week prior to presentation, abnormal level of consciousness and focal neurological signs. While 56 patients (24%) had an abnormal result, only four patients (2%) had findings that caused the clinician to avoid LP and all of these cases had one of the features listed above. The remaining 52 patients with abnormal scans underwent LP and none had brain herniation at 1 week later. A second prospective trial has corroborated these results. Case series have shown that even when cerebral herniation occurs, CT can be normal. A recent systematic review concluded that CT cannot reliably detect the risk of herniation in ABM and that clinical signs are most accurate in detecting patients who are at risk. Contraindications to LP in the British, European and US guidelines are shown in Box 1.10,11,24

LP was delayed for a median of 5.9 h in this audit. Delays were caused by: waiting for a prior CT scan, failure to consider the diagnosis and waiting for the patient to be stabilized first. In most cases the LP was carried out after the patient had been transferred to the ICU. A recent retrospective UK audit showed that patients who had an LP >4 h after antibiotics had a positive CSF culture in 11% compared to 73% taken within 4 h (P<0.001). They concluded that too many patients were waiting for unnecessary

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Time from arrival to antibiotics (h)</th>
<th>Clinical abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>M</td>
<td>27</td>
<td>Discharged the previous evening from the Emergency Department with a diagnosis of viral upper respiratory tract infection and represented with worsening symptoms</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>2.9</td>
<td>Complained of abdominal pain and fever and was triaged under the surgical team. The diagnosis of meningitis was considered after conscious level fell to Glasgow Coma Scale 9/15</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>12.9</td>
<td>Presented with fever, headache and otalgia and was diagnosed with otitis media and admitted under ENT surgery. Six hours following admission became acutely confused</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>4.2</td>
<td>Admitted with headache, vomiting and reduced conscious level. LP was initially unsuccessful. A history of possible overdose was given from a third party and she was treated as presumed overdose. Two days following admission with no clinical improvement a repeat LP confirmed the correct diagnosis</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>4.6</td>
<td>Presented with fever, headache and vomiting with a complex medical history including liver cirrhosis. Initially treated for sepsis of presumed abdominal source. Three days following admission her conscious level fell and at this point the diagnosis of meningitis was considered</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>17.6</td>
<td>Presented with fever, back pain and noted to have fast atrial fibrillation. Treated for presumed pyelonephritis. The morning following admission on the post take ward round, was noted to have reduced conscious level and was transferred to the intensive care unit. Three days following admission a LP confirmed meningitis due to S. pneumoniae</td>
</tr>
</tbody>
</table>

Audit of ABM
CT head scans and delaying LP. In our series, the microbiological diagnosis was most commonly made from blood culture followed by PCR of CSF, while diagnosis by CSF culture was uncommon. This may reflect delay in LP. It also confirms the clinical utility of PCR in the diagnosis of culture negative meningitis.

The audit findings were presented to the relevant clinical departments in our hospital. The recommendations made include prioritizing early antibiotic treatment in suspected ABM, facilitating early LP in the Emergency Department where appropriate and close review of patients admitted with symptoms or signs that might be compatible with meningitis.

Conclusions

Bacterial meningitis is rare, can be difficult to accurately diagnose, and results in a high level of morbidity and mortality. It may present with a range of clinical symptoms and signs and a high level of clinical suspicion is warranted. The classical triad may be uncommon and symptoms commonly progress following admission. Future guidelines should acknowledge this level of uncertainty and spectrum of clinical presentation.

Contraindications to immediate LP are common but routine use of CT head scan prior to LP is widespread and may reflect undue concern with adverse outcomes such as brain herniation despite evidence of its safety in the absence of adverse clinical features.

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References


