Third-generation cephalosporin resistance among Gram-negative bacilli causing meningitis in neurosurgical patients: significant challenges in ensuring effective antibiotic therapy

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Received 4 October 2005; returned 18 October 2005; revised and accepted 29 November 2005

Objectives: The treatment of meningitis caused by Gram-negative bacilli in neurosurgical patients is a major challenge because of the complexity of these patients, the emergence of antibiotic resistance in many of the causative organisms and the restricted choice of antibiotics suitable for use, owing to a failure to achieve high enough concentrations in the CSF. We reviewed the incidence, aetiology, treatment and outcome of all patients with Gram-negative bacillary meningitis (GNBM) in our centre over a 7 year period.

Methods: Beaumont Hospital, Dublin is a 720 bed tertiary referral hospital and contains the national neurosurgical centre for the Republic of Ireland. The case notes and microbiological records of all patients with GNBM between 1998 and 2004 inclusive were reviewed retrospectively. Only patients with positive CSF culture and clinical features compatible with meningitis were included.

Results: Forty separate episodes of GNBM involving 34 different patients occurred during the study period. The most common causative organisms were Enterobacter spp. (35%), Escherichia coli (22.5%) and Pseudomonas aeruginosa (15%). Twenty-five per cent of isolates were resistant to third-generation cephalosporins. The median duration of treatment was 19.2 days and a combination of intravenous and intraventricular antibiotics was the most common treatment regimen used. Mortality directly related to GNBM was 2.5%.

Conclusions: Although the mortality directly related to GNBM was low, the emergence of strains resistant to third-generation cephalosporins represents a therapeutic challenge. Treatment with combined intravenous and intraventricular antibiotics is recommended for 2–3 weeks, but more studies are required to determine the optimal management of this difficult condition.

Keywords: nosocomial meningitis, neurosurgery, cephalosporin-resistant, CSF

Introduction

Gram-negative bacilli are an unusual cause of meningitis in adults. However, the incidence of Gram-negative bacillary meningitis (GNBM) appears to be increasing and now accounts for 15–20% of cases of meningitis in adults.1 GNBM has become increasingly important in patients after neurosurgical intervention.2 Patients with GNBM are difficult to treat successfully owing to existing co-morbidities and challenges in diagnosis and treatment. Appropriate antimicrobial therapy for the treatment of GNBM is essential to minimize morbidity and mortality.3 However, antibiotic selection is complicated by the poor penetration of many antimicrobial agents into the CSF. Although parenteral third-generation cephalosporins were a major therapeutic advance in the treatment of GNBM when first introduced,4 the increasing resistance of many Gram-negative bacilli to these agents in the intervening period is of concern.5 In this study, we retrospectively reviewed all neurosurgical patients with GNBM diagnosed in our centre during a 7 year period, and we assessed the incidence of third-generation cephalosporin resistance in this cohort of patients, and its implications for the future.

Patients and methods

Beaumont Hospital, Dublin is a 720 bed tertiary referral centre and contains the national neurosurgical centre for the Republic of Ireland.

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Cephalosporin resistance and meningitis

GNBM was defined on the basis of isolation of Gram-negative bacilli in one or more CSF cultures and clinical features of acute meningitis that required treatment with antimicrobial agents. All patients included were reviewed by a medically qualified microbiologist to confirm the diagnosis. Contamination was defined as growth of a Gram-negative bacillus from a CSF specimen in a patient without clinical features of meningitis, who did not deteriorate in the absence of 3 days or more of appropriate antibiotic treatment and repeated CSF sampling did not result in isolation of a Gram-negative bacillus. Appropriate antibiotic treatment was defined as the administration of one or more antimicrobial agents shown to be active against the Gram-negative bacillus isolated on culture by susceptibility testing and capable of passing through the blood–brain barrier in adequate concentrations. A second episode of meningitis in the same patient was considered a recurrence if it was due to a different organism from the first. A relapse of meningitis was defined as being due to the same organism after completion of therapy for the initial episode.

Data were collected on patient demographics including predisposing conditions, organisms isolated and their susceptibilities, antibiotic treatment administered and the outcome. Gram-negative bacilli were identified by conventional microbiological methods, antibiotic susceptibility was tested by the comparative disc diffusion method and MICs were determined by Etest (AB Biodisk, Solna, Sweden) where necessary and the results were interpreted using NCCLS breakpoints. Information on the antimicrobial agents used, duration of treatment and route of administration were recorded. Combination therapy was defined as the administration of ≥2 antimicrobial drugs appropriate for the causative bacterium. Outcome measurements included recurrent or relapsing GNBM, and hospital mortality. The day of collection of the first CSF specimen that grew Gram-negative bacilli was defined as day 0. Mortality was classified as meningitis-attributable, if death was due to meningitis or its complications, but was considered meningitis non-attributable if it was due to a pre-existing serious illness after bacteriological cure and clinical recovery from meningitis. Cure was defined as complete resolution of signs and symptoms of meningitis. Failure of treatment was defined as meningitis-related death or a relapse of GNBM.

Results

During the 7 year period of the study, i.e. from 1998 to 2004 inclusive, when full laboratory and patients records were available, Gram-negative bacilli were isolated from the CSF of 42 different neurosurgical patients admitted to our hospital. Eight patients were excluded from the study as they did not fit the case definition for GNBM. There were 40 episodes of GNBM in the 34 patients during the 7 year period. Twenty-eight patients had a single episode of GNBM, three patients had a recurrent episode of GNBM and three patients relapsed. Of the 34 patients included in the study, 17 were male and 17 were female, with a mean age of 43 years.

The underlying predisposing conditions of the 34 patients included in the study are shown in Table 1. Thirty-three of the 34 (97%) had undergone recent neurosurgical interventions; the remaining patient had a traumatic head injury. Of the 40 episodes of GNBM, the initial positive CSF specimen was taken from an existing external ventricular drain (EVD) in 23, at removal or revision of ventricular peritoneal (V-P) shunt in ten, from a V-P reservoir in four, at the time of insertion of an EVD or V-P shunt in two, and from a lumbar puncture in one patient.

The Gram-negative bacilli isolated from CSF culture are listed in Table 1; there were no episodes of polymicrobial meningitis. Among the 40 episodes of GNBM, 8 (20%) were due to organisms resistant to the third-generation cephalosporins on initial positive CSF sampling, i.e. cefotaxime or ceftazidime resistant. Two other organisms, initially susceptible, became resistant to third-generation cephalosporins during treatment. Three (7.5%) episodes of GNBM were due to organisms (two Enterobacter cloacae and one Klebsiella pneumoniae) that were resistant to gentamicin, but susceptible to amikacin. All organisms were susceptible to meropenem. Details of the ten episodes of GNBM with documented third-generation cephalosporin resistance occurring in a total of nine patients are outlined in Table 2. All patients in our series with GNBM caused by bacteria resistant to third-generation cephalosporins were treated with a carbapenem either at the beginning or at some stage during the course of the treatment regimen. One patient was initially treated with high-dose ciprofloxacin for 9 days and subsequently changed to a carbapenem owing to concerns regarding adequate penetration into the CSF.

Antimicrobial therapy for GNBM included intravenous monotherapy, combination intravenous therapy and a combination of intravenous and intraventricular therapy. Excluding one patient who died while on treatment for GNBM, the median duration of treatment was 19.2 days (range 7–72 days). Intravenous monotherapy was used in 10 episodes for a median duration of 14.8 days (range 7–23 days). Such episodes were treated with either a third-generation cephalosporin (n = 9) or meropenem (n = 1). Two episodes were treated with combination intravenous therapy for a median duration of 19 days (range 8–20 days); in both episodes this consisted of a third-generation cephalosporin and gentamicin (administered for 5 days in each case). A combination of intravenous and intraventricular antimicrobials was used in

### Table 1. Predisposing neurosurgical conditions and causative organisms in 34 patients with Gram-negative bacillary meningitis

<table>
<thead>
<tr>
<th>Major predisposing neurosurgical condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral tumour; post-craniotomy and EVD in situ</td>
<td>13</td>
</tr>
<tr>
<td>Intracerebral haemorrhage; post-craniotomy and EVD in situ</td>
<td>10</td>
</tr>
<tr>
<td>Congenital abnormality and V-P shunt in situ</td>
<td>3</td>
</tr>
<tr>
<td>Previous meningitis and V-P shunt in situ</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral infarct and V-P shunt in situ</td>
<td>2</td>
</tr>
<tr>
<td>Traumatic head injury; post-craniotomy and EVD in situ</td>
<td>1</td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td>1</td>
</tr>
<tr>
<td>Aqueduct stenosis and V-P shunt in situ</td>
<td>1</td>
</tr>
</tbody>
</table>

GNBM caused by bacteria resistant to third-generation cephalosporins on initial positive CSF sampling, i.e. cefotaxime or ceftazidime resistant. Two other organisms, initially susceptible, became resistant to third-generation cephalosporins during treatment. Three (7.5%) episodes of GNBM were due to organisms (two Enterobacter cloacae and one Klebsiella pneumoniae) that were resistant to gentamicin, but susceptible to amikacin. All organisms were susceptible to meropenem. Details of the ten episodes of GNBM with documented third-generation cephalosporin resistance occurring in a total of nine patients are outlined in Table 2. All patients in our series with GNBM caused by bacteria resistant to third-generation cephalosporins were treated with a carbapenem either at the beginning or at some stage during the course of the treatment regimen. One patient was initially treated with high-dose ciprofloxacin for 9 days and subsequently changed to a carbapenem owing to concerns regarding adequate penetration into the CSF.

Antimicrobial therapy for GNBM included intravenous monotherapy, combination intravenous therapy and a combination of intravenous and intraventricular therapy. Excluding one patient who died while on treatment for GNBM, the median duration of treatment was 19.2 days (range 7–72 days). Intravenous monotherapy was used in 10 episodes for a median duration of 14.8 days (range 7–23 days). Such episodes were treated with either a third-generation cephalosporin (n = 9) or meropenem (n = 1). Two episodes were treated with combination intravenous therapy for a median duration of 19 days (range 8–20 days); in both episodes this consisted of a third-generation cephalosporin and gentamicin (administered for 5 days in each case). A combination of intravenous and intraventricular antimicrobials was used in

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Episode cephalosporin-resistant Gram-negative bacillary meningitis outcome in nine patients (10 episodes) with third-generation morbidity and mortality.1 Patients at high risk include the elderly, Although uncommon, GNBM has been associated with significant relapsing GNBM was therefore 10%. failure rate over the 7 year period, including the three episodes of another five (12.5%) death was due to the underlying neurosurgical episode patient death was directly attributable to meningitis, but in therefore treated for a total of 72 days.

Six patients died in our centre during follow-up. In one (2.5%) meningitis developed a relapse. Prosthetic devices facilitate colonization by bacteria and provide a potential portal of entry into the CSF causing meningitis. Prosthetic devices such as ventriculostomies have been associated with a risk of infection of 4–11%.8 Although the majority of these infections are caused by staphylococci, the risk of colonization of prosthetic devices by Gram-negative bacilli is increased in hospitalized patients post-surgical intervention. In our study, 39 (97.5%) episodes occurred in patients with pre-existing EVDs or V-P shunts in situ, which strongly suggests that prosthetic devices were the probable route of infection. However, in this retrospective study, as in the report by Parodi et al.,8 we could not assess other factors that might have contributed to the potential risk of infection, e.g. compliance with full aseptic technique during surgery or the post-operative care of external CSF drains, such as EVDs and V-P shunts.

Treatment of GNBM is based on the same general principles guiding management of other more common causes of meningitis, i.e. the prompt diagnosis of the infection, and early effective antimicrobial therapy. Third-generation cephalosporins have been widely used in the treatment of patients with GNBM over the past 20 years because these antibiotics penetrate well into the CSF after intravenous administration and this has resulted in dramatic decreases in meningitis-related mortality.9 However, the treatment of patients with GNBM with third-generation cephalosporins is threatened by the emergence of Gram-negative bacilli with plasmid-encoded or inducible chromosomal β-lactamases that hydrolyse extended-spectrum cephalosporins. Resistance to third-generation cephalosporins occurring among patients with GNBM have been reported in the past.5,10 One large series by Lu et al.5 identified 93 patients with GNBM over a 12 year period, of which 9% were caused by isolates resistant to third-generation cephalosporins. In our study, 10 (25%) episodes were due to organisms that were resistant to third-generation cephalosporins before the start of treatment or organisms that became resistant during the course of treatment for GNBM. This is of concern; even though patients with third-generation cephalosporin-resistant GNBM in our series were treated with carbapenems either initially or at some stage during the treatment regimen, as all isolates were carbapenem susceptible. Three (7.5%) episodes were due to organisms resistant to gentamicin, which necessitated the use of intraventricular amikacin in these patients.

The use of intraventricular antibiotics in combination with intravenous antibiotics should be considered at the earliest opportunity as this is a condition with significant morbidity and mortality. Intraventricular antibiotics ensure a high concentration of antibiotic at the site of infection. Vancomycin, gentamicin and colistin are the most commonly used intraventricular agents. We

Table 2. Details of the aetiology, treatment regimen and outcome in nine patients (10 episodes) with third-generation cephalosporin-resistant Gram-negative bacillary meningitis

<table>
<thead>
<tr>
<th>Episode</th>
<th>Organism isolated</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K. pneumoniae</td>
<td>MEM d1 to d15</td>
<td>cure</td>
</tr>
<tr>
<td>2</td>
<td>P. aeruginosa</td>
<td>CAZ d1 to d3</td>
<td>cure</td>
</tr>
<tr>
<td>3</td>
<td>E. cloacae</td>
<td>CTX d1 to d2</td>
<td>failure, relapse</td>
</tr>
<tr>
<td>4</td>
<td>E. cloacae</td>
<td>MEM d0 to d15</td>
<td>cure</td>
</tr>
<tr>
<td>5</td>
<td>E. cloacae</td>
<td>CAZ d1 to d3</td>
<td>cure</td>
</tr>
<tr>
<td>6</td>
<td>E. cloacae</td>
<td>CAZ d0 to d2</td>
<td>cure</td>
</tr>
<tr>
<td>7</td>
<td>E. cloacae</td>
<td>MEM d1 to d15</td>
<td>cure</td>
</tr>
<tr>
<td>8</td>
<td>E. cloacae</td>
<td>CTX d1 to d8</td>
<td>cure</td>
</tr>
<tr>
<td>9</td>
<td>Enterobacter aerogenes</td>
<td>MEM d1 to d1</td>
<td>cure</td>
</tr>
<tr>
<td>10</td>
<td>E. cloacae</td>
<td>CIP d1 to d9</td>
<td>cure</td>
</tr>
</tbody>
</table>

CTX, cefotaxime; CAZ, ceftazidime; MEM, meropenem; CIP, ciprofloxacin; IV GEN = intraventricular gentamicin; IV AMK, intraventricular amikacin; d, day (e.g. d0 = day of collection of first CSF specimen that grew Gram-negative bacilli; d1 = 1 day post-collection of first positive CSF specimen).

28 episodes of GNBM. The median duration of treatment, excluding one patient who died while on treatment, was 20 days (range 12–72 days). One patient with E. cloacae meningitis developed a brain abscess due to the same organism while on treatment and was therefore treated for a total of 72 days.

Discussion

Although uncommon, GNBM has been associated with significant morbidity and mortality.1 Patients at high risk include the elderly, immunsuppressed and neurosurgical patients. Post-operative GNBM typically occurs among patients without previous co-morbidities.2 In our study, which was carried out at the national neurosurgical centre for the Republic of Ireland, there were 40 episodes of GNBM occurring in neurosurgical patients over the 7 year period, of which all but one occurred in patients with prior neurosurgical intervention. In the one remaining patient, meningitis occurred after a traumatic head injury. In comparison with many other reported studies, we report an apparently larger number of episodes of GNBM during a relatively short period, i.e. 7 years,1–3,6 but this may be explained by the presence on site of the national neurosurgical centre, to which the most complex patients would have been referred from the rest of the country.

Prophylactic antibiotics should be considered in patients at high risk for GNBM; however, the use of prophylactic antibiotics has not been routinely employed in our centre, as the decision to use these agents is dependent on the risk of infection, the presence of risk factors and the potential for surgical prophylaxis. The use of intraventricular antibiotics in combination with intravenous antibiotics should be considered at the earliest opportunity as this is a condition with significant morbidity and mortality. Intraventricular antibiotics ensure a high concentration of antibiotic at the site of infection. Vancomycin, gentamicin and colistin are the most commonly used intraventricular agents. We

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used intraventricular amikacin in some patients to treat infection caused by multiresistant Gram-negative bacilli as we had no alternative treatment option. Prosthetic devices such as an EVD should also be removed if the patient fails to respond to antimicrobial treatment. The median duration of antimicrobial treatment for all episodes (excluding one patient who died while on treatment) of GNBM in our series was 19.2 days. The treatment failure rate was 10%; including one death owing to GNBM and three episodes of relapsing GNBM. This compares favourably with mortality ranging from 12 to 70% in other published studies. In view of our low treatment failure rate, between 2 and 3 weeks of therapy appears appropriate for an uncomplicated case of GNBM and is in keeping with the findings or recommendations of other authors. However, the patient’s CSF should be monitored at regular intervals to ensure that it is being sterilized and that the pathogens have not become resistant to the antimicrobial agents being used.

Our study, although carried out retrospectively, highlights a number of important points. The prevalence of resistance to third-generation cephalosporins is a significant development. Although the mortality and treatment failure rates were low in our centre, the future occurrence of GNBM owing to organisms resistant to both cephalosporins and carbapenems is a cause of worry as there are few options for therapy. New antimicrobials effective against these organisms and capable of penetrating into the CSF in high concentrations are required. Detailed surveillance of local pathogens and resistance patterns are also essential to guide empirical therapy.

Acknowledgements

We are grateful to our consultant neurosurgical colleagues, Mr S. Young, Mr C. Pidgeon, Mr D. Alcutt, Mr D. Rawluk and Professor C. Bolger for permission to review the data and the medical records department of Beaumont Hospital for facilitating the patient chart review.

Transparency declarations

None to declare.

References


