Pseudomonas aeruginosa meningitis/ventriculitis in a UK tertiary referral hospital


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Summary

Background: Pseudomonas aeruginosa is a rare cause of meningitis and ventriculitis but is generally associated with significant morbidity and mortality.

Aim: We sought to determine the epidemiology, risk factors and outcome of meningitis and ventriculitis due to P. aeruginosa at our institution in order to inform preventive strategies and treatment guidelines.

Methods: Retrospective study of all patients with a positive cerebrospinal fluid (CSF) culture admitted to a tertiary care hospital over 18 years. Clinical details, demographic, microbiological and antibiotic data were obtained from laboratory and medical records.

Results: Twenty-four episodes occurred in 21 patients over 18 years. Pyrexia (75%), fluctuating mental status (50%) and headache (41%) were the most frequent presenting symptoms. Nineteen of the 21 patients had previously undergone a neurosurgical procedure and seven had extra-ventricular devices in situ. Twelve (57%) patients had P. aeruginosa isolated from another site prior to their episode. Most (89%) CSF samples demonstrated a neutrophilia; the CSF protein, when measured, was raised in all cases. Gram-negative bacilli were visible on CSF microscopy in only three isolates. There were relatively low rates of resistance to most antimicrobials tested and combination treatment of intravenous with intrathecal antibiotics was often used. No patients died within 28 days.

Conclusion: Pseudomonas aeruginosa meningitis and ventriculitis are predominantly nosocomial and related to prior neurosurgery. It can be difficult to diagnose as CSF Gram-film and meningism are insensitive markers. Appropriate empirical treatment, neurosurgical prophylaxis and surveillance can aid in managing this infection.

Introduction

Infections of the central nervous system, including meningitis and ventriculitis due to Pseudomonas aeruginosa, are uncommon. They are commonly hospital-onset and typically related to neurosurgery, with or without extra-ventricular drain (EVD) or shunt insertion. Previous studies have shown P. aeruginosa to be responsible for 1–18% of nosocomial meningitis cases. Additional reported risk factors include prolonged hospital stay and the use of broad spectrum antibiotics.

Due to the resistance profile of P. aeruginosa, treatment options can be limited and are typically restricted to intravenous (IV) drugs such as ceftazidime, carbapenems (meropenem and...
imipenem), aminoglycosides (gentamicin, amikacin or tobramycin) and ciprofloxacin, often in combination with intrathecal (IT) agents such as aminoglycosides or colistin. Recommended duration of therapy is prolonged and ranges from 14 to 28 days. Despite this, both treatment failure and relapses are known to occur, and the recorded mortality is often high, approaching 80% in some studies.

We sought to determine the epidemiology, risk factors and outcome of both meningitis and ventriculitis due to P. aeruginosa at our institution to help inform preventive strategies and possible revision of guidelines for managing this infection.

**Methods**

**Setting**

Cambridge University Hospitals (CUH) NHS Foundation Trust is a tertiary referral hospital with ~1200 beds and ~70,000 inpatient episodes per year. It offers a number of specialist services including organ transplantation (liver, kidney, small bowel and pancreas), haematology/oncology (including stem cell transplantation), infectious diseases, neurosurgery and intensive care (including neonatal, paediatric and neuro-critical care and general adult) facilities.

**Study design and patients**

A retrospective study of all patients with a positive cerebrospinal fluid (CSF) culture growing P. aeruginosa admitted to our institution between November 1995 and August 2013 and who had notes available to review. The study was considered to be a service evaluation so ethical approval was not required. All patient data were anonymized and patient management was not affected.

**Definitions**

Pseudomonas meningitis/ventriculitis was defined as P. aeruginosa cultured from CSF AND at least one of the following signs and symptoms: fever (>38°C), headache, neck stiffness, meningism, cranial nerve signs or irritability. Clinical cure was defined as full resolution of signs and symptoms at completion of therapy. A positive CSF culture was regarded as part of a single episode if it occurred within 14 days of a previous positive CSF culture. Subsequent positive CSF cultures that occurred after this time were considered to be recurrences.

**Variables**

Demographic, clinical details and the antibiotic history were obtained from laboratory and microbiology records and medical, nursing and pharmacy notes as well as the patient administration system. Data obtained included age, gender, temperature at the time of sampling, presenting symptoms, microbiology results, inflammatory markers, radiology findings, renal function (defined as chronic kidney disease stage ≥2 or raised serum creatinine >120 μmol/l), neurological disorder, diabetes, liver disease, immunosuppression [receipt of cytotoxic chemotherapy, immunosuppressant therapy or prednisolone (≥3 0 mg/day or equivalent)], American Society of Anaesthesiology (ASA) score, antibiotic history (in the preceding 3 months and post-diagnosis), IV line usage (central and peripheral), urinary catheter usage, presence of EVD, previous neurosurgical procedure, previous microbiology results, primary outcome data (death at 28 days) and secondary outcome data [requirement for intensive care (ITU), requirement for ventilation, requirement for surgery and recurrence].

**Microbiology**

Microbiology data were obtained from the laboratory information system. Samples were processed using standard methodology. P. aeruginosa was identified to species level by API20NE (Biomerieux UK Ltd., Basingstoke, UK) and MALDI-ToF technology (Bruker UK Ltd., Coventry, UK) for samples received after 2012. Susceptibility testing was performed by BSAC disc diffusion methodology.

**Statistical analysis**

Descriptive analyses were performed on all variables, with median, range, interquartile range and percentages reported.

**Results**

**Demographics**

Twenty-four episodes occurred in 21 patients (three recurrences) over the 18-year period. Four episodes occurred in 2008, three each in 2006 and 2011 and none for 6 years (Figure 1). Nine patients (42.9%) were male and the median age was 33 (range 0.6–72; IQR = 21–58).

**Clinical characteristics**

Pyrexia (>38.0°C (15/20; 75%), fluctuating mental status (10/20; 50%) and headache (7/17; 41.2%) were the most frequent presenting symptoms. Meningism (3/20; 15%) and photophobia (2/18; 11.1%) were rarely reported. Eleven patients (52.4%) needed admission to ITU. ITU length of stay ranged from 2 to 64 days (median 25 days). Nine of these patients required mechanical ventilation (range 1–19 days).

Serum C-reactive protein (CRP) was measured in 19 patients. Four patients (21%) had a CRP within the normal range; (<10 mg/l), while the median CRP was 101 mg/l (range 1–250, IQR 33–121). Nineteen patients had a serum white cell count (WCC) tested; seven had a level within the normal range (between 4 and 11 × 10⁹/l). The median WCC was 12.4 (range 2–43.9, IQR = 10.2–15.8).

Fifteen (of 20; 75%) had CT/MRI findings; four had multiple changes. These included hydrocephalus (four), dilated ventricles (four) and collections (four).

**Underlying conditions**

Nineteen of 21 patients (90.5%) had previously undergone a neurosurgical procedure and 12 (57.1%) had a history of a CSF leak. Eleven (52%) had undergone one procedure, four (19%) had two procedures, one (5%) had three procedures and three (14%) had undergone more than five procedures. Procedures included drain insertion, with seven EVDs (33%; two with craniotomy; one with lumbar drain); four (19%) ventriculo-peritoneal (VP) shunt insertions or revisions; two ventriculo-atrial (VA) shunt insertions or revisions and one insertion of an Ommaya reservoir (Table 1). Three (14.3%) had undergone craniotomies for tumour excision. The reasons for the above neurosurgical procedures were vascular (seven patients), functional (hydrocephalus, meningocoele, benign intracranial hypertension) (six), tumour resection (five) and infection (cryptococcal meningitis; one). The EVDs and drains had been in situ for between 1
and 31 days (median 10.6, IQR 1.75–11) prior to infection with *P. aeruginosa*. Both patients who had not undergone a neurosurgical procedure were neutropenic due to an underlying haematological malignancy (non-Hodgkins lymphoma and acute myeloid leukaemia). Both responded to ceftazidime.

Time from neurosurgical procedure to drain ventriculitis ranged from 1 to 250 days (IQR 33–121). Specifically for EVD insertion the time from insertion to ventriculitis ranged from 1 to 31 days (median 10; IQR 3.25–12.5).

Additional co-morbidities included hypertension (four patients, 18.2%), chronic lung disease (four patients, 18.2%), high-dose steroids in the preceding week (four patients, 18.2%), chemotherapy in the preceding week (three patients, 13.6%), haematological malignancy (two patients, 9.1%) and gastrointestinal pathology (two patients; 9.1%) (Table 1). The median ASA grade at the time of diagnosis was 3 (range 1–4, IQR 2–3).

*Pseudomonas aeruginosa* was previously isolated from 12 (57.1%) patients. Sites included skin swab (five patients), line tip (two patients), catheter specimen urine (two patients), respiratory tract (two patients) and blood culture (one patient).

### CSF findings

CSF WCCs ranged from 0 to 12 800 in the 19 patients; it was performed on (median 340; IQR 86–1218), with three patients having cell counts of ≤ 2. These were predominantly neutrophils (> 90%) in 17 of these 19 (89.4%) patients. The CSF WCC:RCC ratio had a median value of 0.2 (range 0–126.6, IQR 0.27–0.88). CSF protein was only measured in six patients and was always elevated (> 0.4 g/l). CSF glucose levels ranged from 0.7 to 5.3 (mean 2.9). Data for comparative serum glucose levels are not available.

Gram-negative bacilli were seen on microscopy from three (14.2%) isolates. Gram-positive cocci were seen once (with *Staphylococcus aureus* subsequently grown) and Gram-positive bacilli were seen once (coryneforms were additionally subsequently grown). Five (24%) patients had another organism identified from the CSF sample. These included *S. aureus* (two patients), *Enterobacter cloacae*, *Klebsiella pneumoniae* and coryneforms (one each).

All *P. aeruginosa* isolates were susceptible to ceftazidime, gentamicin, colistin and piperacillin-tazobactam. Two isolates (9.5%) demonstrated reduced susceptibility to meropenem and one isolate was resistant to ciprofloxacin.

### Treatment

Treatment data were available from 20 patients. Nineteen (95%) received therapy; meropenem was used to treat 16 patients.

### Figure 1. Episodes of meningitis/ventriculitis due to *P. aeruginosa.*

Twelve of these had concomitant IT gentamicin and three had IV gentamicin. Ten patients received ceftazidime (six of whom also received IT gentamicin and one received IV gentamicin). Eight patients received meropenem and ceftazidime. Two patients received ciprofloxacin.

In terms of treatment duration, meropenem was given for 1–29 days (median = 16; IQR = 3.5–20), ceftazidime was given for 3–74 days (median = 19; IQR = 16–24), IT gentamicin was given for 2–25 days (median = 11; IQR = 7–16), IV gentamicin for 1–6 days (median = 3; IQR = 1.7–4.5) and ciprofloxacin was given for 14 and 30 days. Nine patients (42.9%) received IV therapy for ≥ 21 days. Eleven of the 13 patients (84.6%) who received IT gentamicin received ≥ 5 days of therapy.

### Outcome

Clinical cure was achieved in 16 patients (89%). In hospital and 28-day mortality was 0%; three (16.7%) patients died at 50, 202 and 285 days after diagnosis. Nine patients (50%) were

### Table 1. Summary of results

<table>
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<tr>
<th>Co-morbidities/risk factors</th>
<th>Number</th>
<th>%</th>
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<tr>
<td>Clinical characteristics at diagnosis</td>
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<tr>
<td>Pyrexia</td>
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<tr>
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<tr>
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<tr>
<td>affecting central nervous system</td>
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<tr>
<td>Relapse following treatment</td>
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EVD, extraventricular drain; ITU, intensive care unit; LD, lumbar drain; VA, ventriculo-atrial; VP, ventriculo-peritoneal.
discharged home, eight patients (44%) to the referring hospital and one patient to a hospice. Three patients had a recurrence (Table 1).

Total hospital stay within this centre ranged from 14 to 125 days (median 42; IQR 23–58). Hospital stay post-diagnosis ranged from 7 to 99 days (median 29 days; IQR = 23–58 days).

Discussion

We provide data from over an 18-year period from a large regional neurosurgical centre. The number of meningitis/ventriculitis episodes due to *P. aeruginosa* appears to be increasing over recent years. The majority (90%) were neurosurgical patients from a diverse population with a median age of 33 years. We highlight previously recognized risk factors such as recent neurosurgery and presence of drains.7–9,18

The time from neurosurgical procedure (e.g. insertion of EVD or VP shunt) to isolation of *P. aeruginosa* from CSF ranged from 1.75 to 11 days (median 10 days). This is similar to other studies that have reported a median of 11.6 days.7

We found that isolation of *P. aeruginosa* from the patient prior to the meningitis episode only occurred in 57% (12 of 21) of episodes. Presentation is typically non-specific, and may simply be fever or confusion. This is similar to other studies. Fever was present in studies by Chang et al. (73.3%)4 and Erdem et al. (92%).6 Fluctuating consciousness was described in 20 and 56% of these patient groups respectively. Chang et al. also described respiratory failure being the presenting complaint in 27% of patients. Several studies also described seizures and cranial nerve palsies.5,7

Significant immunosuppression was present in nine of 21 patients (42.9%); this has not been described previously, but probably reflects the underlying conditions of our patient group; the median ASA grade at the time of diagnosis was 3.

We found that a raised CRP can be helpful (perhaps more so than WCC) but both can be normal. We also found that CSF cell count and Gram stain is insensitive and can be misleading; three of 19 patients had normal CSF WCCs, whilst Gram-negative bacilli were only seen in three episodes. This contrasts to other published studies, when all CSF samples had raised WCCs and Gram film had a much higher sensitivity.1,4,16,19 A raised CSF protein (only performed six times) was the only consistent finding and mixed cultures were seen in a similar proportion of cases in a study from India.7

We had relatively low rates of resistance to most antimicrobials tested and this compares favourably to other studies.7,20 The numbers were too small to determine if there was increasing resistance over time, but no trend was obvious (data not shown).

There are a wide range of treatment options in the literature, in terms of route (IV vs. intravenous combined with IT) and duration. We had a relatively low recurrence rate (3/20; 15%) and low mortality rate, suggesting our treatment was appropriate. This typically involved >2 weeks of IV therapy (meropenem or ceftazidime) and IT therapy for >5 days for patients with EVDs in situ. Relapse was seen less often in those given combination (IV plus IT) therapy compared with IV therapy alone in one study.17

With a high rate of mortality and morbidity recorded in other studies, it’s not surprising that a number of studies have discussed preventive measures to try to combat post-surgical meningitis/ventriculitis. One outbreak of *P. aeruginosa* occurring in patients with EVDs was ascribed to a healthcare worker.21 Changes in infection control practices, including more frequent placement of sterile EVD insertion-site dressings and a protocol to reduce contamination at the EVD insertion site, ended the outbreak and resulted in a significant decrease in the rate of CSF infection. Educational interventions with involvement of all healthcare workers were the cornerstone of reducing infection in an interventional study from Brazil.22 The use of antibiotic prophylaxis during EVD insertion is a matter of debate.23–25 Lack of prophylactic antibiotics was not a risk factor for ventriculitis in one study by Korinek et al.22 and in another study by Schade et al.23 prophylaxis failed to achieve a reduction in the rate of infection.

There are several limitations to this study. These include the retrospective single centre nature of the study, prolonged time frame (18 years), during which clinical practice may have changed, time to therapy and a number of patient notes being unavailable for review. However, we believe this is an important area of clinical practice and adds to the available literature.

Should be considered a potential pathogen in post-neurosurgical patients with features consistent with meningitis, especially in those with prior *P. aeruginosa* infection and/or colonization; treatment with a broad-spectrum anti-pseudomonal agent is recommended at least until culture results are available. Our results have shown a recent, albeit small, increase in the number of cases of *Pseudomonas* ventriculitis/ meningitis. This has led to a review in our practices along with heightened surveillance to ensure the appropriate empirical and prophylactic treatment is administered where required, including EVD insertion.

In summary, *P. aeruginosa* is a rare form of meningitis that is predominantly nosocomial and related to prior neurosurgery. It can be difficult to diagnose in that meningism, prior colonization or infection with *P. aeruginosa* and even headache are insensitive markers, as is CSF Gram film and CRP.

Conflict of interest: None declared.

References


