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MAJOR ARTICLE

Comparison of Suspected and Confirmed Internal External Ventricular Drain-Related Infections: A Prospective Multicenter United Kingdom Observational Study

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Background. Diagnosis of internal external ventricular drain (EVD)-related infections (iERI) is an area of diagnostic difficulty. Empiric treatment is often initiated on clinical suspicion. There is limited guidance around antimicrobial management of confirmed versus suspected iERI.

Methods. Data on patients requiring EVD insertion were collected from 21 neurosurgical units in the United Kingdom from 2014 to 2015. Confirmed iERI was defined as clinical suspicion of infection with positive cerebrospinal fluid (CSF) culture and/or Gram stain. Cerebrospinal fluid, blood, and clinical parameters and antimicrobial management were compared between the 2 groups. Mortality and Modified Rankin Scores were compared at 30 days post-EVD insertion.

Results. Internal EVD-related infection was suspected after 46 of 495 EVD insertions (9.3%), more common after an emergency insertion. Twenty-six of 46 were confirmed iERIs, mostly due to Staphylococci (16 of 26). When confirmed and suspected infections were compared, there were no differences in CSF white cell counts or glucose concentrations, nor peripheral blood white cell counts or C-reactive protein concentrations. The incidence of fever, meningism, and seizures was also similar, although altered consciousness was more common in people with confirmed iERI. Broad-spectrum antimicrobial usage was prevalent in both groups with no difference in median duration of therapy (10 days [interquartile range {IQR}, 7–24.5] for confirmed cases and 9.5 days [IQR, 5.75–14] for suspected, $P = 0.3$). Despite comparable baseline characteristics, suspected iERI was associated with lower mortality and better neurological outcomes.

Conclusions. Suspected iERI could represent sterile inflammation or lower bacterial load leading to false-negative cultures. There is a need for improved microbiology diagnostics and biomarkers of bacterial infection to permit accurate discrimination and improve antimicrobial stewardship.

Keywords. antimicrobial treatment; aseptic meningitis; external ventricular drain; intraventricular antimicrobials; post-neurosurgical meningitis.

External ventricular drain (EVD) insertion is a common neurosurgical procedure for cerebrospinal fluid (CSF) diversion to manage raised intracranial pressure due to CSF obstruction. In addition to external skin and soft tissue infection, a major complication is internal EVD-related infection (iERI), resulting in meningitis or ventriculitis. This is associated with increased length of stay, healthcare costs, morbidity, and mortality [1, 2]. In our recent prospective multicenter United Kingdom (UK) cohort study, including 495 EVD insertions, we reported an iERI incidence of 9.3%, consistent with the 5%–10% reported in the literature [3–5]. Incidence is associated with catheter type, dwell time, and sampling frequency [5]. Practices to prevent iERI include the use of antimicrobial-impregnated catheters [6] and standardized protocols regarding insertion procedure and catheter maintenance [7, 8].

Staphylococci, especially coagulase-negative staphylococci (CoNS), are the most common aetiologic agents of iERI, but infection can also be due to Gram-negative bacilli [4, 9–11]. When iERI is suspected, empiric systemic antimicrobial therapy is initiated before CSF microbiology results, and it usually includes intravenous vancomycin and a carbapenem or anti-pseudomonal cephalosporin. Management involves device replacement to achieve source control combined with 7–14

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days of antimicrobial therapy based on microbiology results. For suspected iERI with negative microbiological investigations, there is no clearly defined consensus regarding the duration of therapy. The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy suggest initial empirical treatment, which should be discontinued if culture is negative after 3 days [12]. In cases in which a patient's CSF sample is culture negative, diagnosis relies largely on clinical assessment, such as the presence of a fever or altered consciousness, and on CSF studies, including lymphocytosis and hypoglycorrhachia. However, this method of diagnosis is complicated by systemic and local inflammation due to the primary disease; for example, subarachnoid blood can lead to features of fever, meningism, and CSF pleocytosis [13]. A recent meta-analysis has found that no single CSF, serum, or clinical feature can be used on its own to distinguish bacterial meningitis associated with EVDs from sterile inflammation [14].

To add to the clinical characterization of suspected and confirmed iERI, we analyzed data from a previously reported UK multicenter cohort of patients treated for iERI to compare diagnostic parameters and antimicrobial practices.

METHODS

Data Collection

Data were collected across 21 neurosurgical units in the UK and Ireland from November 2014 to May 2015 as part of the British Neurosurgical Trainee Research Collaborative (BNTRC). Patients of any age with any tunneled EVD catheter, without evidence of pre-existing infection, were included in the study [5]. Internal EVD-related infection was classified as confirmed or suspected (Table 1) [15]. Data including demographic information (age, sex), neurological status at baseline and at 30 days, details of EVD insertion and maintenance, laboratory parameters, antimicrobial prophylaxis, and treatment received including type, route, and duration, and mortality at 30 days were collected. Neurological status was assessed using the Glasgow Coma Score (GCS) and Modified Rankin Score (mRS), a measure of neurological disability [16].

Table 1. Definitions of Confirmed and Suspected iERI Used in This Study

Classification	Definition
Confirmed	1. Clinical suspicion of iERI 2. Microbiologic confirmation (1 of the following): 2.1. Positive CSF culture 2.2. Positive CSF Gram stain
Suspected	1. Clinical suspicion of iERI 2. Negative CSF culture and Gram stain

Abbreviations: CSF, cerebrospinal fluid; iERI, internal external ventricular drain-related infection.

Statistical Analysis

GraphPad Prism (Version 9.3.1) and IBM SPSS Statistics (Version 28) were used for statistical analysis and plotting graphs. Categorical variables were compared by χ^2 tests and continuous variables were compared by Mann-Whitney *U* tests (Shapiro-Wilk test demonstrated nonnormal data distribution). A $P < .05$ indicated statistical significance.

Patient Consent Statement

Approval for the study was previously granted by the audit and clinical governance committees of participating hospitals, as described in Jamjoom et al [5]. Patient consent was not required as this was an audit of routine data.

RESULTS

Included Patients

A total of 495 EVD insertions were included in the study and an iERI was confirmed or suspected in 46 of these (9.3%) (Figure 1). In 26 of 46 (56.5%) cases, 1 or more organisms were identified by either culture or Gram stain of CSF, meeting our definition of confirmed infection. At baseline, there were no significant differences between people with confirmed/suspected iERI considering baseline mRS, preoperative ASA grade, preoperative GCS, indication for EVD insertion, or time to infection (Table 2). People with confirmed iERI were more likely to have undergone an emergency EVD insertion (73% vs 35%; $P = .02$). The majority of cases received antimicrobial prophylaxis peri-insertion (84.8%), and all but 1 case received antimicrobials within 24 hours of EVD insertion. This is in line with recommendations from the Neurocritical Care Society Consensus Statement for EVD management [17]. The median duration of EVD placement was 13 days in suspected infections (IQR, 10–16) and 14 days in confirmed infections (IQR, 9–18; $P = .95$), compared to 8 days (IQR, 4–13) in the overall cohort.

Microbiologic Findings

Of confirmed cases, 21 cases had Gram-positive pathogens identified, mostly CoNS (n = 10) or *Staphylococcus aureus* (n = 6) (Supplementary Table 1). Gram-negative pathogens were infrequently identified (n = 8). In 4 cases, coinfection was identified: 1 CoNS and *Enterobacter* spp coinfection, 1 CoNS and *Streptococcus* spp, 1 *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and 1 *S aureus* and *Enterococcus* spp.

Diagnostic and Clinical Parameters

We compared CSF parameters, blood inflammatory markers, and clinical features between cases of suspected and confirmed iERI (Figure 2). Despite the microbiologic differences between the 2 groups, no differences in measured CSF or blood parameters were identified. People with confirmed iERI were more likely to have altered consciousness at the time of diagnosis (46% vs 10%), but clinical findings of fever, meningism, and

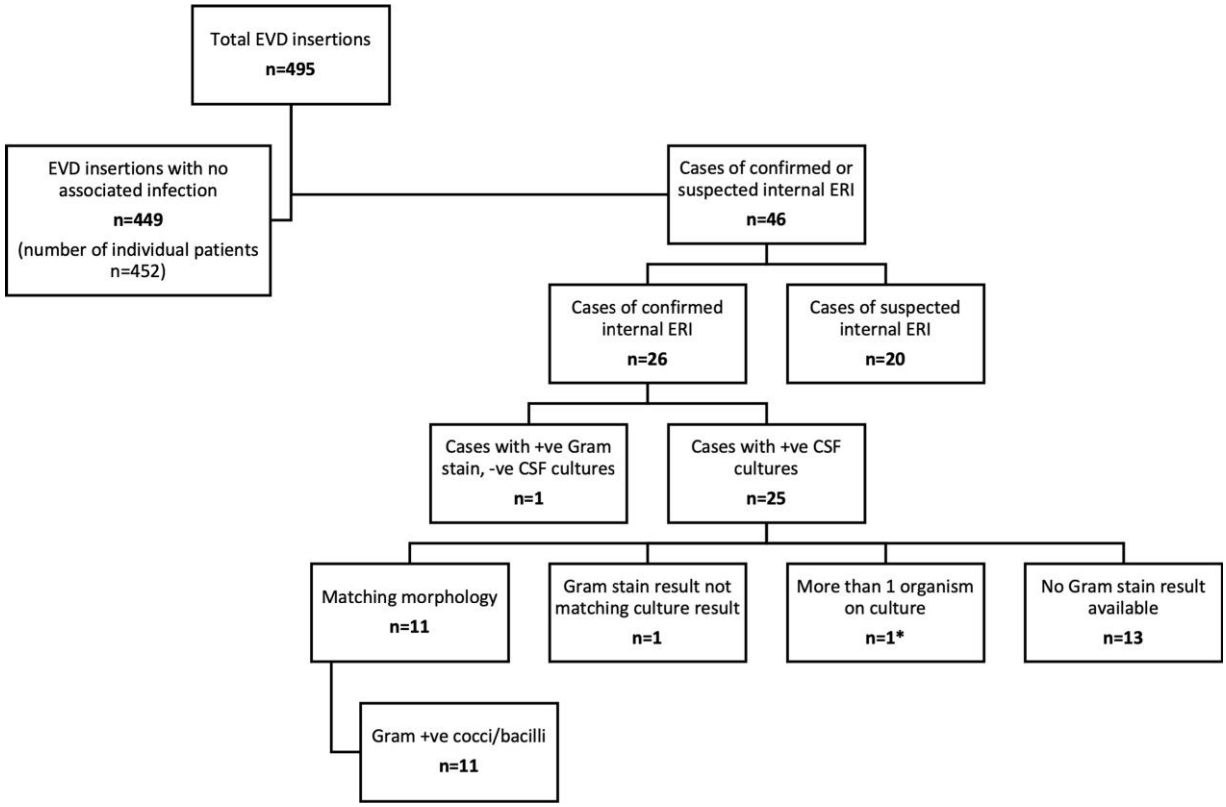

Figure 1. Study cohort overview. *, Two organisms found in culture, matching morphology for 1 organism on Gram stain. EVD, external ventricular drain; ERI, EVD-related infection;

seizures were not different between the 2 groups. There was no significant difference in time to infection between confirmed and suspected ERIs (confirmed median 9 days [IQR, 2–16]; suspected median 7 days [IQR, 6–11]; $P = .7$).

Despite comparable baseline mRS, GCS, and ASA (Table 2), suspected iERI was associated with lower 30-day mortality (suspected 0% vs confirmed 23.1%, $P = .03$) and 30-day mRS (suspected median 2.5 [IQR, 1–4] vs confirmed 4.5 [IQR, 3–5]; $P = .03$).

Antimicrobial Treatment

The majority (24 of 46) of patients received a combination of intravenous and intrathecal antimicrobials (Figure 3). Intravenous meropenem (43.4%, n = 20) and intravenous vancomycin (37.0%, n = 17) were the most commonly used individual antimicrobials across all ERIs (Table 3). Vancomycin monotherapy was the most common intrathecal treatment (n = 24). The median length of antimicrobial treatment for the entire cohort was 10 days (IQR, 6.75–14.0). The median length of treatment was 10 days (IQR, 7–24.5) for confirmed cases and 9.5 days (IQR, 5.75–14) for suspected cases ($P = .3$).

Consistent with the primarily Gram-positive microbiologic findings, intravenous vancomycin was the most commonly used antimicrobial in confirmed iERI (46%). Suspected iERIs were predominantly treated with intravenous meropenem (43%). Intrathecal antimicrobials were more commonly used in confirmed cases (81%) than in suspected cases (55%). Vancomycin was the most common intrathecal antimicrobial therapy for both groups. For confirmed cases, intrathecal therapy was largely guided by microbiology (Supplementary Table 2). For Gram-positive bacteria, the majority of cases were treated with intrathecal vancomycin monotherapy (n = 13); 1 case with *Pseudomonas aeruginosa* was treated with intrathecal gentamicin, whereas 1 case of CoNS was treated with combined intrathecal gentamicin and vancomycin. Intrathecal gentamicin monotherapy was used for cases with Gram-negative bacteria.

Two confirmed cases were treated with adjunctive rifampicin in conjunction with intravenous and intrathecal antimicrobials. One case of *S aureus* iERI received rifampicin with intravenous cefotaxime, meropenem, gentamicin, and vancomycin, and intrathecal vancomycin; 1 case of *Staphylococcus epidermis* iERI received rifampicin with intravenous meropenem and intrathecal vancomycin.

DISCUSSION

This study found no significant differences in CSF or blood results between suspected and confirmed IERI. Altered

Table 2. Characteristics of Patients With Confirmed and Suspected iERI[a]

Characteristics	All (n = 46)	Suspected (n = 20)	Confirmed (n = 26)	*P* Value[b]
Demographics				
Age, years, mean (SD)	48.8 (±18.1)	52.7 (±17.3)	45.8 (±18.5)	.20
Female sex	25 (54.3)	12 (60)	13 (50)	.56
Reason for EVD insertion				.13
Congenital, IIH, and NPH	2 (4.3)	1 (5.0)	1 (3.8)	
Infectious blockage	1 (2.2)	1 (5.0)	0 (0.0)	
Neurovascular	33 (71.7)	15 (75.0)	18 (69.2)	
Other	1 (2.2)	0 (0.0)	1 (3.8)	
Trauma	3 (6.5)	1 (5.0)	2 (7.7)	
Tumour	6 (13.0)	2 (10.0)	4 (15.4)	
Urgency of Insertion				.02
Emergency	26 (56.5)	7 (35.0)	19 (73.1)	
Urgent	20 (43.5)	13 (65.0)	7 (26.9)	
Preoperative ASA Grade				.62
1	10 (21.7)	3 (15.0)	7 (26.9)	
2	11 (23.9)	7 (35.0)	4 (15.4)	
3	11 (23.9)	5 (25.0)	6 (23.1)	
4	11 (23.9)	4 (20.0)	7 (26.9)	
5	3 (6.5)	1 (5.0)	2 (7.7)	
Preoperative GCS, median (IQR)	9 (4–12)	9 (7–11)	9 (3–12.5)	.96
Catheter Type				.01
Plain	12 (26.1)	1 (5.0)	11 (42.3)	
Silver-bearing	20 (43.5)	12 (60.0)	8 (30.8)	
Antibiotic-impregnated	14 (30.4)	7 (35.0)	7 (26.9)	
Antimicrobial prophylaxis				.65
At induction[c]	39 (84.8)	16 (80)	23 (88.5)	
<24 hours of insertion	3 (6.5)	2 (1.0)	1 (3.8)	
Already receiving	3 (6.5)	2 (1.0)	1 (3.8)	
None	1 (2.2)	0	1 (3.8)	
Time from insertion to iERI, days, median (IQR)	8.5 (5.1–15.0)	7.08 (5.6–11.1)	8.91 (2.4–15.5)	.71

Abbreviations: ASA, American Society of Anesthesiologists; EVD, external ventricular drain; GCS, Glasgow Coma Score; iERI, internal EVD-related infection; IIH, idiopathic intracranial hypertension; IQR, interquartile range; NPH, normal pressure hydrocephalus; SD, standard deviation.

[a]n (%) unless otherwise stated. χ^2 tests used for categorical variables, Mann-Whitney *U* tests for continuous/ordinal variables.

[b]Suspected versus confirmed.

[c]Induction of anesthesia for EVD insertion.

consciousness was more common in the confirmed cases and no other clinical features were markedly different between the 2 groups. Modified Rankin Score and mortality at 30 days were higher in confirmed cases, supporting differences in pathology between the 2 groups. Intravenous antimicrobial therapy was widely used for both groups, with no significant differences in duration. Intravenous vancomycin was more commonly used in confirmed cases, whereas intravenous meropenem was used widely in both groups. Intrathecal antimicrobial therapy was used more commonly in confirmed cases, with choices largely reflecting microbiologic findings.

Culture-negative cases with a high suspicion for iERI remain an area of diagnostic and treatment difficulty due to confounding factors such as previous antimicrobial therapy and sterile inflammation from the original pathology or procedure [18]. The results of this study found no significant differences in biochemical tests between confirmed and suspected ERIs, which has been mirrored in the rest of the field. In a recent meta-analysis, researchers found that there is no CSF, blood, or microbiological measure that can on its own differentiate between bacterial and aseptic iERI [14]. On the other hand, positive cultures alone, without other correlating features, may represent contamination or colonization, rather than infection, with a false-positive rate of up to 20% [4, 14]. This suggests a more comprehensive diagnostic approach is needed, as presented by Hussein et al [11], whose institution has implemented an algorithm incorporating consideration of several diagnostic markers for diagnosis of IERI.

Overall, the majority of iERIs received intravenous antimicrobial treatment. The majority of suspected iERIs were treated with intravenous antimicrobials, and a large proportion received intravenous meropenem as part of empiric treatment, indicating that culture-negative iERIs are likely to be treated with broad-spectrum antimicrobials in UK neurosurgical units.

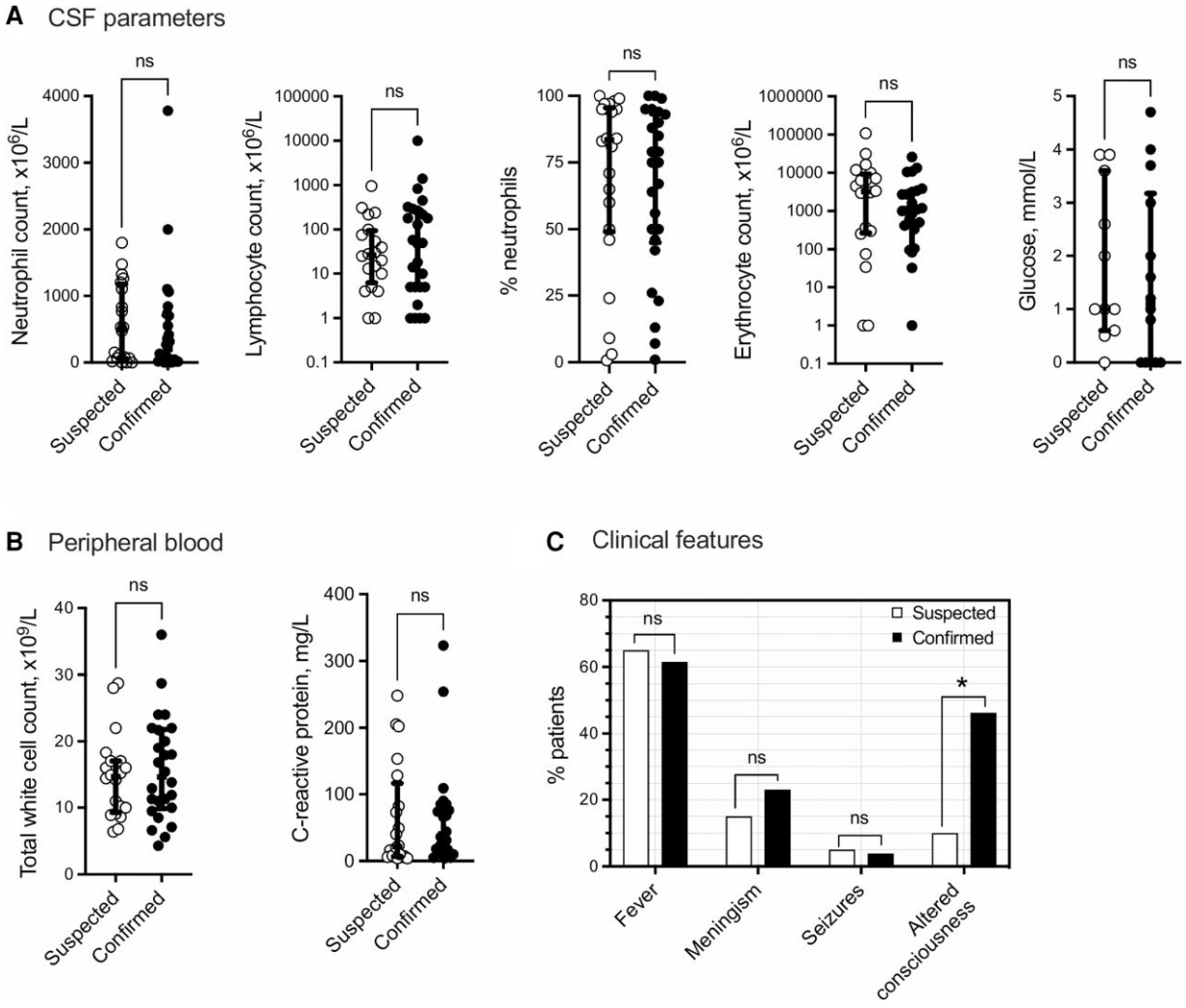

Figure 2. Cerebrospinal fluid (CSF), blood, and clinical parameters. The CSF glucose results were recorded for 11 cases of suspected internal external ventricular drain-related infection (iERI) and 14 cases of confirmed iERI. Data points represent patients. Bars on dot plots show median and interquartile range. A: CSF parameters; B: Peripheral blood parameters; C: Clinical features. *, $P < .05$, ns: not significant.

This corresponds to consensus in the field to treat suspected iERIs empirically before confirmation with microbiological tests [12, 19], with most authors recommending intravenous vancomycin and an antipseudomonal cephalosporin or carbapenem [3, 11, 19, 20]. Without culture results available in these cases to guide antimicrobial treatment options, it is difficult to step down antimicrobial treatment, leading to protracted use of broad-spectrum antimicrobials [21]. In contrast, a greater proportion of confirmed iERIs included intravenous vancomycin as part of the antimicrobial regime than in suspected iERIs, likely reflecting targeted treatment for CoNS, which was the most common cultured organism. This further highlights the need for more sensitive identification of true bacterial infection, to be able to appropriately target antimicrobial treatment. However, meropenem was still used in a significant minority of confirmed iERIs, demonstrating a possible area for improvement in optimization of antimicrobials.

More than two thirds of iERIs overall received intrathecal antimicrobials, in which a smaller proportion of suspected iERIs received intrathecal treatment compared with confirmed iERIs. Intrathecal antimicrobials are generally recommended in cases with poor response to intravenous antimicrobials, although there is weak evidence at present for their efficacy versus safety for intrathecal administration [11, 17, 19]. However, intrathecal vancomycin, for iERI secondary to CoNS, is recommended for first line use by the Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy [12]. In favor of intrathecal administration, several studies have found that there is decreased mortality and earlier stabilization of CSF parameters when intrathecal and intravenous antimicrobials are used in

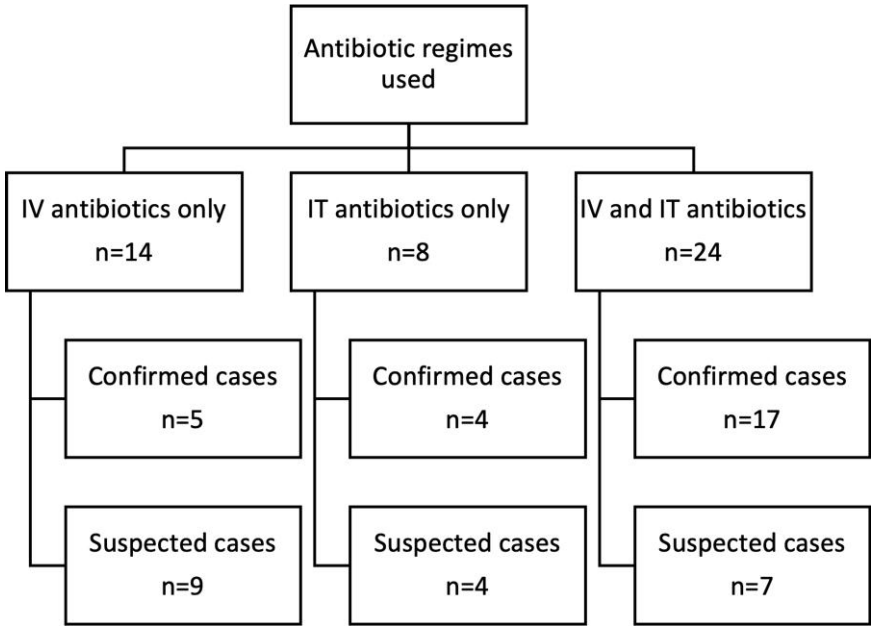

Figure 3. Flowchart of antimicrobials received.

conjunction compared with intravenous therapy alone [11, 22, 23]. Furthermore, intraventricular vancomycin and gentamicin have been found to be safe and effective in terms of sterile CSF cultures and clinical outcome [22, 24, 25]. Our results show that the majority of culture-positive iERIs are treated with intrathecal antimicrobials in the UK, which is predominantly pathogen-directed. We also find that suspected iERIs are still likely to receive intrathecal antimicrobials, possibly due to lack of response from the patient with systemic antimicrobials. Finally, the average length of antimicrobial treatment found in this study was 10 days overall, with no significant difference between the suspected and confirmed groups. This possibly reflects adherence to a standard duration of treatment of 10 days as per recommendations [11, 19].

Patients with suspected and confirmed iERIs had comparable median durations of EVD placement, which were longer than the overall median. We had previously reported from this cohort that those with either suspected or confirmed iERIs were significantly more likely to have a median duration of EVD placement above 8 days [5]. This, along with finding a similar duration of antibiotic treatment between the 2 groups, could contribute to a longer inpatient stay and increased associated healthcare costs in suspected iERIs. However, it would be useful for future studies to more explicitly evaluate the effects of antimicrobial use in suspected iERI on costs and length of stay.

This study had several important limitations. Because data collection was across multiple neurosurgical units in the UK, there will be intersite differences in practice and selection bias of cases recorded at different sites. Follow-up CSF results, clinical evidence of external iERI, antibiograms of organisms, paired plasma glucose, and blood culture results were not collected in the case report form. Furthermore, the small sample remains relatively small.

Table 3. Antimicrobial Usage in Confirmed and Suspected iERI[a]

Antimicrobial used	All (n = 46)	Suspected (n = 20)	Confirmed (n = 26)
Intravenous			
Meropenem	20 (43.4)	11 (55.0)	9 (34.6)
Linezolid	4 (8.7)	2 (10.0)	2 (7.7)
Vancomycin	17 (37.0)	5 (25.0)	12 (46.2)
Ceftriaxone	4 (8.7)	2 (10.0)	2 (7.7)
Gentamicin	3 (6.5)	1 (5.0)	2 (7.7)
Flucloxacillin	2 (4.3)	0 (0.0)	2 (7.7)
Cefotaxime	6 (13.0)	2 (10.0)	4 (15.4)
Cefuroxime	1 (2.2)	1 (5.0)	0 (0.0)
Piperacillin-tazobactam	4 (8.7)	2 (10.0)	2 (7.7)
Other[b]	4 (8.7)	2 (10.0)	2 (7.7)
Not known	8 (17.4)	4 (20.0)	4 (15.4)
Intrathecal			
Vancomycin	27 (58.7)	11 (55.0)	16 (61.5)
Gentamicin	6 (13.0)	1 (5.0)	5 (19.2)
Other[b]	2 (4.3)	0 (0.0)	2 (7.7)
None	14 (30.4)	9 (45.0)	5 (19.2)

Abbreviations: iERI, internal external ventricular drain-related infection.

[a]Table shows n (%).

[b]Other antibiotic—not specified.

CONCLUSIONS

Overall, this study finds wide use of intravenous broad-spectrum antimicrobials in both culture-positive and culture-

negative iERIs, with no significant differences in biochemical markers, clinical features, or duration of antimicrobial use. Despite this, suspected iERIs seem to have better outcomes in terms of neurological disability and mortality at 30 days. This could indicate that suspected iERIs may be due to a different pathology, such as sterile inflammation post-neurosurgical procedure, or may indicate that suspected iERIs represent infections that have a lower bacterial load so are less severe, leading to false-negative cultures.

Our results highlight iERIs as an area for optimization of diagnostic practice to promote antimicrobial stewardship. In this respect, future work should focus on identifying infection-specific non-microbiological biomarkers. Some possible candidates include nucleic acid amplification assays, CSF cytokines (interleukin-6), CSF lactate, or CSF procalcitonin, which have had variable results in the literature so far [26–30]. 16S rRNA has had a number of studies evaluating its diagnostic value, and it may be of use for culture-negative suspected iERIs [31, 32]. Future research could also include work on developing and validating scoring systems, diagnostic trees [11], or predictive algorithms, which have previously been found to have high accuracy in differentiating between bacterial and viral meningitides [33]. This would be significant not only from a diagnostic standpoint, but for promotion of antimicrobial stewardship, to reduce unnecessary use of broad-spectrum antimicrobials, especially meropenem.

It would be worthwhile for future audits to include an assessment of the impact of antimicrobial use in suspected iERIs. This could include adverse drug reactions, *Clostridioides difficile* infection, and subsequent infection or colonization with antimicrobial-resistant organisms [34], as well as healthcare costs and duration of stay. Furthermore, there is presently a paucity of high-quality evidence for the efficacy and safety of intrathecal vancomycin and gentamicin, despite their frequent use in our study, other institutions [11], and recommendation by the Neurosurgery Working Party [12]. Future work should evaluate their effectiveness, pharmacokinetics, and safety further to work towards licensing their intrathecal use.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Authorship Supplement

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