Journal of Clinical Neuroscience 42 (2017) 54–58

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Commentary

Clinical characteristics, microbiology and outcomes of external ventricular drainage-associated infections: The importance of active treatment

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ARTICLE INFO

Article history:
Received 24 December 2016
Accepted 6 March 2017

Keywords:
External ventricular drainage
Neurosurgical infections
Gram-negative
Multidrug resistance
Treatment

ABSTRACT

Data concerning clinical characteristics, microbiology, treatment and outcomes of external ventricular drainage-associated infections (EVDAI) are limited. All hospitalized patients with EVDAI in a University Hospital between January 2009 and December 2015 were retrospective recorded. Only the first episode per patient was included. An antibiotic was considered "active" when its pharmacokinetic properties were appropriate for EVDAI and the implicated microorganism was in vitro susceptible. During the 7-year study period, 36 EVDAI were identified. Median patient age was 53 years and 23 (63.9%) were male. Catheter types were intraventricular (70.6%) and lumbar (29.4%). Median catheterization duration before infection was 14 days. Gram-negative bacteria (GNB) predominated (57.9%), followed by gram-positives (36.8%) and fungi (5.3%). Administered antibiotics were considered "active" in 69.4% of empirical and in 86.1% of definitive treatment regimens. In 10 infections, intraventricular/intrathecal (IVT) antibiotics were administered. Eleven patients died (30.6%) during hospitalization. Patients who died had higher rates of EVDAI by GNB ($p = 0.011$) and higher rates of treatment with intravenous colistin ($p = 0.019$ for empirical and $p = 0.006$ for definitive colistin). Compared to EVDAI by other pathogens, patients with EVDAI by GNB had longer catheter-days before infection ($p < 0.001$) and higher mortality ($p = 0.011$). In our study, GNB were a frequent cause of EVDAI, and were related with high rates of inactive treatment and mortality. Intravenous colistin alone is not effective and treatment should include IVT antibiotics and intravenous antibiotics that achieve adequate CSF levels.

1. Background

Placement of an external ventricular drainage (EVD) catheter is common practice in neurosurgical patients, as it helps monitor intracranial pressure (ICP), control elevated ICP and drain intraventricular blood [1,2]. Infections, such as ventriculitis, meningitis, brain abscess, or sepsis, are serious complications of EVD catheterization, with significant impact on patient outcome [1].

Reported rates of EVD-associated infection (EVDAI) vary between 1 and 45% in different series [2]. Traditionally, gram-positive bacteria of the skin flora are responsible for the majority of EVDAI, but gram-negative bacteria (GNB) account for a significant percentage [2] and even predominate in some series [3–6]. Furthermore, recent studies report infections caused by resistant strains of GNB [7–15], with important implications on patient outcomes and on required antimicrobial treatment. Although the majority of published guidelines focus on the management of infections by susceptible strains, nowadays, antibiotic-resistant bacteria are an important consideration in postneurosurgical and EVD-associated infections [16–18].

The aims of this study are to describe the clinical characteristics, microbiology, treatment and outcomes of patients with EVDAI.

2. Methods

2.1. Setting

A retrospective observational study of all hospitalized patients with EVDAI was conducted from January 2009 through December

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http://dx.doi.org/10.1016/j.jocn.2017.03.023
0967-5868/

2015 at the University Hospital of Heraklion. This is a 750-bed tertiary care institution and a referral center for Southern Greece, with approximately 55,000 admissions annually. The study protocol was approved by the hospital's Ethics Committee.

2.2. Definitions

The study cohort included all adult patients with an EVD in place for at least 48 h who developed EVDAI. Only the first EVDAI per patient was recorded. An EVDAI was defined as positive cerebrospinal fluid (CSF) culture plus abnormal CSF findings (reduced glucose and/or increased protein) plus relevant clinical signs (fever and/or reduced level of consciousness). According to published definitions, a multidrug resistant (MDR) pathogen was resistant to at least 3 antibiotic classes, whereas an extensively drug resistant (XDR) pathogen was resistant to all except one or two antibiotic classes [19].

Antimicrobial therapy was selected at the discretion of the attending physicians. Before EVD placement, all patients received antibiotic prophylaxis with intravenous (IV) second generation cephalosporin. Treatment given before obtaining culture results was defined as "empirical". Treatment given after the culture results became available was defined as "definitive". An antibiotic was defined as "active" when two criteria were met: the implicated microorganism was in vitro susceptible and the antibiotic's pharmacokinetic properties and mode of administration were considered appropriate for treatment of central nervous system infections [17,20].

2.3. Data collection

Clinical, microbiological and treatment data were obtained retrospectively from the patients' medical charts and electronic records. Data collected for each patient included demographic characteristics; disease severity, determined by the use of the Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission [21]; comorbidity, determined by the use of the weighted Charlson comorbidity index at the time of admission [22]; department and conditions (emergency or not) of EVD placement; catheter-days prior to EVDAI diagnosis; Intensive Care Unit (ICU) stay; antibiotics used for the management of the infection; and clinical outcome.

2.4. Microbiology

Species identification and antibiotic susceptibility testing were performed by the Vitek 2 system (bioMérieux SA, Marcy L'Etoile, France) in accordance with the Clinical and Laboratory Standards Institute standards for all antibiotics except for tigecycline [23]. Susceptibility to tigecycline was performed by the Etest (AB Biodisk, Solna, Sweden). According to the susceptibility breakpoints of Enterobacteriaceae used by the U.S. Food and Drug Administration, an AB organism with an MIC $\leq$ 2 μg/mL to tigecycline was considered susceptible [24].

2.5. Statistical analysis

Data are presented as number (%) for categorical variables and median (interquartile range, IQR) for continuous variables. Pearson's Chi-square test or Fisher's exact test were used to compare categorical variables. Continuous variables were compared using Student's t-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. All tests were two-tailed and *p*-values <0.05 were considered to be significant. EpiInfo version 7.1.2.0 (CDC, Atlanta, GA) was used to carry out required calculations.

3. Results

3.1. Patient characteristics

During the 7-year study period, a total of 36 episodes of EVDAI were recorded in 36 patients. Twenty-three patients (63.9%) were male and median patient age was 53 years (range, 21–79 years). Median Charlson comorbidity index was 2 (IQR, 0–3) and median APACHE II score on admission (recorded in 12 patients) was 16 (IQR, 14–22). Diagnoses on admission were central nervous system malignancy (33.3%), cerebral hemorrhage (25.0%), head trauma (25.0%), hydrocephalus (8.3%), peripheral neuropathy (5.6%) and postoperative observation (2.8%). Placement of EVD was performed in the Neurosurgery department (44.1%), the operating room (35.3%) and the ICU (20.6%), while the majority (87.1%) were placed as an emergency. Catheter types, recorded in 34/36 cases, were ventricular (70.6%) and lumbar (29.4%).

3.2. Infections and microbiology

Infection occurred on a median 20.5 days (IQR, 13–33) after admission and 14 days (IQR, 7–22) after EVD placement. Twenty-two infections (61.1%) were diagnosed in the Neurosurgery department and the remaining (38.9%) were diagnosed in the ICU.

Among 38 isolated microorganisms (2 EVDAI were polymicrobial), 22 were gram-negative (57.9%), 14 were gram-positive (36.8%) and 2 (5.3%) were fungi. Isolated pathogens were coagulase-negative staphylococci (CoNS, 11/38, 28.9%), *Klebsiella pneumoniae* (6/38, 15.8%), *Pseudomonas aeruginosa* (6/38, 15.8%), *Acinetobacter baumannii* (5/38, 13.2%), *Proteus mirabilis* (2/38, 5.3%), *Candida albicans* (1/38, 2.6%), *Candida parapsilosis* (1/38, 2.6%), *Citrobacter sedlakii* (1/38, 2.6%), *Enterococcus durans* (1/38, 2.6%), *Enterococcus faecium* (1/38, 2.6%), *Escherichia coli* (1/38, 2.6%), *Pseudomonas stutzeri* (1/38, 2.6%), and *Streptococcus oralis* (1/38, 2.6%).

Regarding the resistance profile of isolated microorganisms, the following were observed: 14/22 (63.6%) GNB isolates were resistant to third generation cephalosporins (5 *A. baumannii*, 4 *K. pneumoniae*, 3 *P. aeruginosa*, 1 *P. mirabilis*, 1 *C. sedlakii*); 12/22 (54.5%) GNB isolates were resistant to carbapenems (5 *A. baumannii*, 4 *P. aeruginosa*, 3 *K. pneumoniae*); 9/22 (40.9%) GNB isolates were XDR (4 *A. baumannii*, 3, *K. pneumoniae*, 2 *P. aeruginosa*); 1 *A. baumannii* strain was resistant to all tested antibiotics; and 8/11 (72.7%) CoNS were methicillin-resistant.

3.3. Treatment of EVDAI

Empirical IV treatment was considered "active" in 25 (69.4%) infections (Table 1). After culture results were available, the EVD catheter was removed in 23 cases (63.9%) and in 14/23 cases a new EVD was placed. Definitive antibiotic treatment was considered "active" in 31 (86.1%) infections. Among them, intraventricular/intrathecal (IVT) antibiotics were administered in 10 infections (27.8%). IVT regimens comprised of colistin (5 infections), gentamicin (3 infections), and colistin plus amikacin (2 infections, 20%). The dosage of IVT antibiotics was as follows: colistimethate sodium (colistin; Norma, Athens, Greece) at 125,000 IU (10 mg) every 12 h or 250,000 IU (20 mg) every 24 h; gentamicin at 10 mg every 12 h; amikacin at 10 mg every 24 h.

3.4. Outcomes

Two infections due to *K. pneumoniae* were complicated with abscess formation. Overall, 11 patients (30.6%) died during hospitalization. The causative microorganisms in patients who died