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ORIGINAL WORK

Early Intraventricular Antibiotic Therapy Improved In-Hospital-Mortality in Neurocritical Patients with Multidrug-Resistant Bacterial Nosocomial Meningitis and Ventriculitis

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Abstract

Background: Hospital-acquired multidrug-resistant (MDR) bacterial meningitis and/or ventriculitis (MEN) is a severe condition associated with high mortality. The risk factors related to in-hospital mortality of patients with MDR bacterial MEN are unknown. We aimed to examine factors related to in-hospital mortality and evaluate their prognostic value in patients with MDR bacterial MEN treated in the neurointensive care unit.

Methods: This was a single-center retrospective cohort study of critically ill neurosurgical patients with MDR bacterial MEN admitted to our hospital between January 2003 and March 2021. Data on demographics, admission variables, treatment, time to start of intraventricular (IVT) therapy, and in-hospital mortality were analyzed. Both univariate and multivariable analyses were performed to identify determinants of in-hospital mortality.

Results: All 142 included patients received systemic antibiotic therapy, and 102 of them received concomitant IVT treatment. The median time to start of IVT treatment was 2 days (interquartile range 1–5 days). The time to start of IVT treatment had an effect on in-hospital mortality (hazard ratio 1.17; 95% confidence interval 1.02–1.34; adjusted $p = 0.030$). The cutoff time to initiate IVT treatment was identified at 3 days: patients treated within 3 days had a higher cerebrospinal fluid (CSF) sterilization rate (81.5%) and a shorter median time to CSF sterilization (7 days) compared with patients who received delayed IVT treatment (> 3 days) (48.6% and 11.5 days, respectively) and those who received intravenous antibiotics alone (42.5% and 10 days, respectively).

Conclusions: Early IVT antibiotics were associated with superior outcomes in terms of the in-hospital mortality rate, time to CSF sterilization, and CSF sterilization rate compared with delayed IVT antibiotics and intravenous antibiotics alone.

Keywords: Antibiotic therapy, Intraventricular, Meningitis, Ventriculitis, Neurointensive care

Introduction

Hospital-acquired meningitis and/or ventriculitis (MEN) is associated with high mortality and negatively affects the prognosis of critically ill neurosurgical patients. Moreover, it impairs neurological function when the responsible pathogens are multidrug-resistant (MDR) bacteria, which are associated with a higher mortality

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rate of 39–70% [1–4]. MDR bacteria may also lead to prolonged hospital stay and are associated with high cost and a high morbidity rate. Factors associated with a decreased risk of in-hospital mortality in patients with MDR bacterial MEN have not been fully investigated. Antibiotic therapy in these patients is problematic.

Although intraventricular (IVT) administration of antibiotics is often used in addition to intravenous therapy to treat hospital-acquired MDR bacterial MEN, whether other factors, such as the timing of IVT treatment initiation, affect the prognosis of these patients in the neurointensive care unit (neuro-ICU) remains unclear. Previous studies usually considered IVT antibiotics as the last resort in cases of severe neuroinfections that did not respond to intravenous administration [1, 4, 5]. It is not known whether starting IVT treatment earlier could improve the prognosis of patients with MDR bacterial MEN. Therefore, it is necessary to investigate the reasonable timing for starting IVT treatment to establish a standard for the treatment of MDR nosocomial MEN. In this study, we aimed to identify the risk factors of in-hospital mortality and to determine whether the timing of initiation of IVT treatment affects the outcome of patients with MDR bacterial MEN in the neuro-ICU.

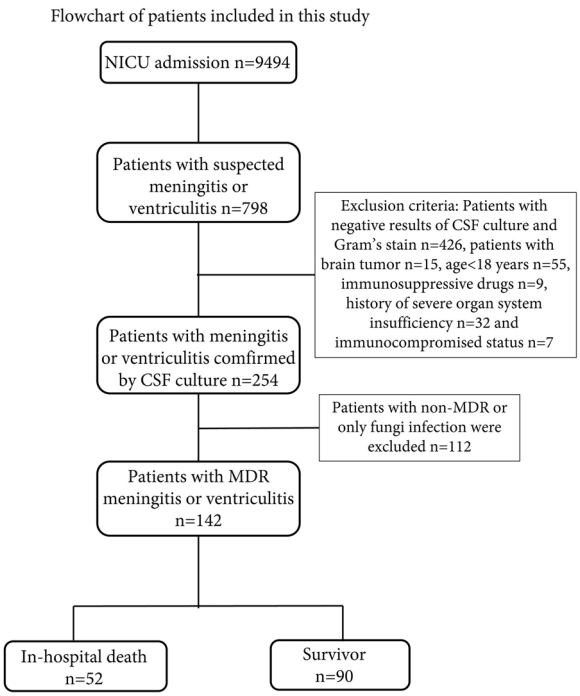

Fig. 1 Flowchart of the study. *CSF* cerebrospinal fluid, *MDR* multidrug-resistant, *NICU* neurointensive care unit

Methods

Patients and Inclusion Criteria

All patients admitted to the neuro-ICU of the level I Neurotrauma Center of Huashan Hospital from January 2003 to March 2021 were evaluated retrospectively. Figure 1 shows a flowchart of the study. The clinical and microbiological databases were screened to identify all cases of nosocomial MEN that met the diagnostic criteria defined by the Centers for Disease Control and Prevention [6]: (1) MEN developing more than 48 h after hospital admission; (2) definitive microbial culture from cerebrospinal fluid (CSF); (3) at least one of the following signs or symptoms (with no other recognized cause): fever > 38 °C, headache, stiff neck, meningeal signs, cranial nerve signs, and/or irritability; and (4) at least one of the following laboratory abnormalities: an increased white cell count, an elevated protein level, and a decreased glucose level in the CSF; microbes evident on gram staining of the CSF; microbial culture from blood; a positive laboratory CSF, blood, or urine test; a diagnostic single antibody titer (immunoglobulin M); and/or a fourfold increase in the paired serum pathogen-specific immunoglobulin G level.

For patients who were suspected of central nervous system (CNS) infection, CSF samples were collected from the external ventricular drainage (EVD) site or by sustainable lumbar drainage when EVD was not available. Patients were excluded if the results of three CSF cultures or gram stain smears were negative during a 6-day period. Other exclusion criteria included an age of < 18 years, presence of brain tumors, the offending organisms not MDR, currently taking immunosuppressive drugs, history of severe organ system insufficiency, and an immunocompromised status. The procedures followed were in accordance with the ethical standards of the Ethics Committee for the Evaluation of Biomedical Research Projects of Huashan Hospital and with the Helsinki Declaration of the World Medical Association. Informed consent was obtained from the patients' next of kin.

Data Collection

The patient's state of consciousness was determined by the Glasgow Coma Scale (scores ranging from 3 [deep coma or death] to 15 [fully awake]). Other data collected included age, sex, diagnosis, Simplified Acute Physiology Score II (SAPS II) at the time of admission, open compound cranial fractures (including basilar skull fractures and CSF leakage), surgical procedure performed (includes decompressive craniectomy and/or craniotomy with hematoma evacuation), intracranial implantable device that includes intracranial pressure (ICP) monitoring procedure performed (all ICP monitors were placed in the ventricle and can be used for CSF drainage if necessary), EVD procedure performed, Ommaya reservoir procedure performed and ventricular–peritoneal shunt

performed, incidence of pneumonia and/or sepsis, days of the period at risk for nosocomial MEN, time to start of IVT treatment, the time required for CSF sterilization, IVT treatment time, pathogenic organisms identified in the CSF, empirical and definitive intravenous antimicrobial regimens used, results of antibiotic susceptibility testing, length of hospital stay, and in-hospital mortality.

Definitions

In this study, pathogenic organisms were considered to be resistant to a certain class of antibiotics if they were reported as intermediate or resistant to at least one of the agents within a class. Pathogens were defined as MDR if they were resistant to at least one representative drug in three or more of the seven categories of antimicrobial agents: cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, extended-spectrum penicillin, macrolides, and β-lactam/β-lactamase inhibitors [7].

The date of the first CSF culture yielding the pathogen was considered being the date of nosocomial MEN onset. Patients who were diagnosed with nosocomial MEN by another hospital and transferred to our hospital were also reviewed and analyzed. The period during which the patient was at risk for MEN was defined as the period between hospital admission and MEN onset. We also recorded the total hospital stay. Critically ill patients who required surgery were given prophylactic antibiotics using our institutional protocol [8]: 2 g of ceftriaxone sodium or 1.5 g of cefuroxime sodium (or 1 g of vancomycin if a patient was allergic to penicillin) was administered intravenously within 60 min prior to surgical incision and discontinued within 24 h after surgery.

Any intravenous antimicrobial agents used before the in vitro susceptibility data of the CSF isolate were available were included in the final analysis of the empirical antimicrobial regimens. Each empirical antimicrobial regimen was then determined to be adequate or inadequate according to whether the regimen contained any antimicrobial agents with activity against the pathogens isolated in vitro. Definitive intravenous therapy was considered to be a treatment that was continued or started on the day that the antibiogram results became available. Time to CSF sterilization was defined as the number of days between the index culture and the first negative CSF culture. Time to start of IVT treatment was calculated (in days) from MEN onset to the administration of the first dose of IVT therapy. Antibiotic treatment was considered successful if three consecutive CSF cultures obtained on separate days produced negative results.

Treatment

All patients were empirically treated intravenously with high blood–brain barrier permeable extended-spectrum antibiotics within a few hours of being diagnosed with nosocomial MEN following the first CSF culture collection. The antimicrobials were administered intravenously to all patients throughout the treatment course. If the initial systemic intravenous antibiotics were considered as inadequate, it would be altered to appropriately target the isolated pathogen when susceptibility data were available. The decision to start the IVT treatment and its timing were determined by treating physicians based on their judgment of the patients' clinical status and the effect of intravenous antibiotics therapy. No patients died before the CSF culture results were available. The doses for intravenous and IVT administration conformed to the current recommendations for the treatment of nosocomial MEN [5, 9, 10], and the IVT regimens were as follows (antimicrobial agents were directly infused into the ventricles through a drainage catheter, and the catheter was usually closed for 1 h to maintain an effective CSF concentration): vancomycin, 10 mg every 24 h; gentamicin, 4 mg daily; amikacin, 30 mg every 24 h; tigecycline, 5 mg every 24 or 12 h; or colistin, 50,000 IU every 24 or 12 h.

For intracranial implant-related MEN, the therapeutic strategies included not only antibiotic treatment but also changing the ventricular catheter or removal of the original implant and continuous CSF drainage via a lumbar subarachnoid catheter. All patients underwent EVD through a long-tunnel catheter inserted into the ventricle and/or by inserting an Ommaya reservoir into the contralateral ventricle. In our hospital, if CSF appears purulent, we perform a thorough ventricular lavage with a gentamicin or amikacin solution (selected based on the pathogen epidemiology in our neuro-ICU) in an operating room immediately after EVD placement until the output becomes clear.

Statistical Analysis

Categorical variables are reported as percentages and were assessed with the χ^2 test or two-tailed Fisher's exact test as appropriate. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Continuous variables are expressed as means ± standard error of mean or medians and interquartile range. Normally and nonnormally distributed continuous variables were compared using Student's *t*-test and the Mann–Whitney *U*-test, whereas the Kruskal–Wallis test was used for comparing more than two variables. Cox regression analysis was performed to identify risk factors for in-hospital mortality of patients with MDR bacterial MEN. The results of Cox regression are reported as hazard ratios with 95% CIs. All variables that had a p value less than 0.05 by univariate analysis were used for multivariate regression. All p values

were two-tailed, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using Stata software (version 12.0; StataCorp, College Station, TX). The ability of the time to initiate IVT therapy to predict in-hospital mortality was assessed through receiver operating characteristic (ROC) curves. The sensitivity and specificity of different cutoff levels were calculated using ROC regression to determine the cutoff points.

Results

Patient Characteristics and Distribution of Pathogens

A total of 254 critically ill neurosurgical patients (194 male patients and 60 female patients; mean age 46.1 years; range 18–80 years) were diagnosed with nosocomial MEN in the neuro-ICU of Huashan Hospital during the study period based on positive CSF cultures and the inclusion/exclusion criteria. Among these cases, 142 were caused by at least one MDR pathogen and were included in the final analysis (Table 1). The diagnosis

Table 1 Predictive factors of in-hospital death in critically ill neurosurgical patients with nosocomial MEN caused by multidrug-resistant bacteria

Variable	Death ($n = 52$)	Survivor ($n = 90$)	Odds ratio (95% CI)	p value
Sex			0.83 (0.38–1.93)	0.665
Male	40 (77%)	72 (80%)		
Female	12 (23%)	18 (20%)		
Age (years)[a]	48.8 ± 2.3	44.9 ± 1.6	$t = 1.40$	0.165
GCS at admission[b]	6 (4–9)	7 (6–10)	$U = 1890$	0.055
GN bacterial infection	**52 (100%)**	**79 (88%)**	**–**	**0.009**
Acinetobacter baumannii	**33 (63%)**	**40 (44%)**	**2.17 (1.10–4.23)**	**0.029**
Klebsiella pneumonia	16 (31%)	22 (24%)	1.37 (0.62–2.89)	0.412
Pseudomonas aeruginosa	3 (6%)	5 (6%)	1.04 (0.27–4.19)	0.958
Multi-bacterial infection	9 (17%)	13 (14%)	1.24 (0.52–2.98)	0.649
Hospital stay (days)[a]	45.7 ± 5.1	53.0 ± 3.7	$t = 1.19$	0.235
Intracranial implants	39 (75%)	54 (60%)	2.00 (0.93–4.18)	0.070
Time interval between implant surgery and nosocomial MEN[b] ($n = 93$)	15 (11–21)	12 (10–16)	$U = 816.5$	0.065
Surgical procedure	33 (63%)	47 (52%)	1.59 (0.80–3.09)	0.193
Pneumonia	**49 (94%)**	**74 (82%)**	**3.53 (0.99–11.84)**	**0.043**
Mechanical ventilation	**46 (88%)**	**57 (63%)**	**4.44 (1.69–11.06)**	**0.001**
Sepsis	**34 (65%)**	**34 (38%)**	**3.11 (1.55–6.25)**	**0.002**
Open compound cranial fractures	19 (37%)	24 (27%)	1.58 (0.77–3.18)	0.217
SAPS II at admission[a]	**40.1 ± 1.7**	**31.6 ± 1.2**	***t* = 4.16**	**< 0.001**
Inadequate initial antibiotics therapy	**45 (87%)**	**62 (69%)**	**2.90 (1.15–7.36)**	**0.019**
Period at risk (days)[a]	14.2 ± 1.3	17.1 ± 1.3	$t = 1.49$	0.138
Ventricular lavage	28 (54%)	50 (56%)	0.93 (0.48–1.85)	0.844
Empirical combination antibiotics therapy	**25 (48%)**	**63 (70%)**	**0.40 (0.20–0.80)**	**0.010**
Time to IVT treatment (days) ($n = 102$)[c]	5 (2–5)	2 (1–3)	$U = 662$	**< 0.001**
Day 0–1	7 (21%)	30 (43%)	0.35 (0.14–0.91)	**0.029**
Day 2–3	5 (15%)	23 (33%)	0.36 (0.14–0.98)	0.054
Day 4 or later	21 (64%)	16 (24%)	5.80 (2.35–14.53)	**< 0.001**
Intravenous antibiotics alone ($n = 40$)	19 (37%)	21 (23%)	1.89 (0.91–3.93)	0.092
Total IVT treatment time (days)[b] ($n = 102$)	14 (9–30)	17 (8.5–26)	$U = 1095$	0.758
Time to CSF sterilization (days)[b] ($n = 88$)	10 (6–11.5)	9 (4–14)	$U = 303.5$	0.817

CI confidence interval, *CSF* cerebrospinal fluid, *GCS* Glasgow Coma Scale, *GN* gram-negative, *IVT* intraventricular, *MEN* meningitis and/or ventriculitis, *SAPS II* Simplified Acute Physiology Score II

Bold font indicates the significant differences ($p < 0.05$)

[a] Data are compared by Student's *t*-test, and results are showed as mean ± standard error of mean

[b] Data are compared by Mann–Whitney *U*-test, and results are showed as medians and interquartile ranges

[c] A total of 102 patients received IVT treatment, of whom 33 died in the hospital and 69 survived

on admission was traumatic brain injury (TBI) in 74 patients, primary intracerebral/intraventricular hemorrhage in 64 patients, hydrocephalus in two patients, primary subarachnoid hemorrhage in one patient, and ischemic stroke in one patient. A total of 170 strains were confirmed by CSF cultures and gram staining (Table 2).

Early IVT Treatment Reduced In-Hospital Mortality in Patients with MDR Bacterial Nosocomial MEN

Based on the univariate analysis (Table 1), the following six factors were associated with a high risk of in-hospital death among neuro-ICU patients complicated by MDR bacterial MEN: gram-negative bacterial infection ($p=0.009$), higher SAPS II (40.1 ± 1.7 vs. 31.6 ± 1.2; $p<0.001$) on admission, pneumonia (OR 3.53; 95% CI 0.99–11.84; $p=0.043$), mechanical ventilation (OR 4.44; 95% CI 1.69–11.06; $p=0.001$), sepsis (OR 3.11; 95% CI 1.55–6.25; $p=0.002$), and inadequate initial antibiotic therapy (OR 2.90; 95% CI 1.15–7.36; $p=0.019$). Empirical combination antibiotic therapy (OR 0.40; 95% CI 0.20–0.80; $p=0.010$) was associated with a lower risk of in-hospital death. We also found that the time to start of IVT treatment had an effect estimate on in-hospital mortality in a time dependent manner; patients were more likely to survive if the IVT treatment was initiated earlier ($p<0.001$). In the final Cox regression analysis, only time to start of IVT treatment (hazard ratio 1.17; 95% CI 1.02–1.34; $p=0.030$) had an independent effect estimate on in-hospital mortality for neuro-ICU patients with MDR bacterial MEN (Table 3).

When to Initiate IVT Treatment for Patients with MDR Bacterial MEN

The ROC regression analysis was used to determine the threshold for the time to initiate IVT treatment in patients with MDR bacterial MEN. We found that the time to start IVT therapy was associated with in-hospital mortality (area under the curve 0.71; 95% CI 0.61–0.80) (Fig. 2). The reasonable time to initiate IVT therapy was day 3; this cutoff had 64% sensitivity and 77% specificity. This suggests that IVT antibiotic therapy should be initiated no more than 3 days after MEN onset to decrease in-hospital mortality for patients with MDR bacterial MEN. Moreover, patients who received early IVT treatment (≤ 3 days after MEN onset) had a higher CSF sterilization rate (53 of 65, 81.5%) compared with those who started IVT treatment > 3 days after MEN onset (18 of 37, 48.6%) and those who received intravenous therapy alone (17 of 40, 42.5%) (Fig. 3). Patients who received early IVT treatment needed less time for CSF culture sterilization compared with patients with delayed IVT treatment and those who received intravenous therapy alone (7 [interquartile range 3–12], 11.5 [interquartile range 9.75–17.25], and 10 [interquartile range 5.5–14.5] days, respectively; $p=0.008$, Kruskal–Wallis test) (Fig. 4).

Table 2 The list of all offending organisms

Pathogens	The number of all strains	The number of MDR/XDR strains
Gram-negative bacteria		
Acinetobacter baumannii	73	73
Klebsiella pneumoniae	38	38
Pseudomonas aeruginosa	8	7
Acinetobacter lwoffii	7	5
Stenotrophomonas maltophilia	2	1
Chryseobacterium meningosepticum	2	2
Brevundimonas diminuta	2	0
Serratia marcescens	1	1
Enterobacter cloacae	1	1
Bacillus proteus mirabilis	1	0
Pseudomonas mendocina	1	0
Shewanella alga	1	0
Citrobacter freundii	1	1
Klebsiella oxytoca	1	0
Enterobacter aerogenes	1	0
Delftia acidovorans	1	1
Aeromonas hydrophila	1	0
Acinetobacter junii	1	0
Gram-positive bacteria		
Staphylococcus aureus	5	5
Staphylococcus capitis	4	3
Epidermidis staphylococcus	3	2
Staphylococcus haemolyticus	3	3
Enterococcus faecium	3	0
Staptococcus hominis	1	1
Streptococcus sanguis	1	0
Streptococcus acidominimus	1	1
Streptococcus viridans	1	0
Corynebacterium	1	0
Microbacterium oxydans	1	1
Fungi[a]		
Candida albicans	2	–
Candida glabrata	1	–
Total	170	146

MDR multi-drug resistant, *XDR* extensive-drug resistant

[a] The fungal drug resistance was not tested because susceptibility testing of fungi is not recommended on a routine basis in our hospital

Discussion

Treatment of nosocomial MEN is a major challenge in the neuro-ICU setting because of its complexity and the increasing prevalence of MDR organisms [11].

Table 3 Independent predictive factors of in-hospital death in critically ill neurological patients with nosocomial meningitis and/or ventriculitis caused by multidrug-resistant bacteria

Variable	Hazard ratio (95% CI)	Adjusted *p* value
Pneumonia	1.74 (0.21–14.79)	0.608
Mechanical ventilation	2.67 (0.66–10.84)	0.171
Sepsis	1.39 (0.96–2.01)	0.079
SAPS II on admission	1.02 (0.98–1.06)	0.279
Inadequate initial antibiotic therapy	1.24 (0.37–4.13)	0.729
Empirical combination antibiotic therapy	0.94 (0.44–2.04)	0.883
Time to IVT treatment	**1.17 (1.02–1.34)**	**0.030**

CI confidence interval, *SAPS II* Simplified Acute Physiology Score II, *IVT* intraventricular

Bold font indicates the significant differences ($p < 0.05$)

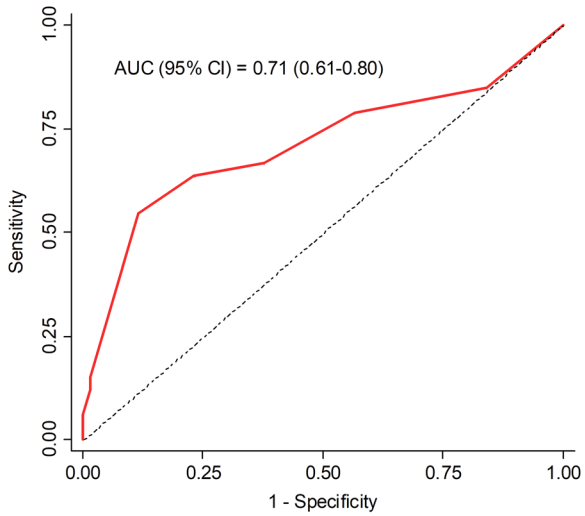

Fig. 2 Receiver operating characteristic curve of time to initiate IVT therapy for prediction of in-hospital mortality. *AUC* area under the curve, *CI* confidence interval, *IVT* intraventricular

IVT antibiotic administration is considered effective for hospital-acquired MEN and is becoming an indispensable part of MDR bacterial MEN treatment. Intravenous antibiotics alone may not achieve sufficiently high concentrations in the CSF because of poor blood–brain barrier penetration. The CSF penetration of β-lactams, aminoglycosides, and vancomycin is 1.5–21%, 0–30%, and 7–14%, respectively [12]. A cerebral microdialysis study of patients with TBI found that the concentration of intravenously administered vancomycin in edematous brains never exceeded the minimum inhibitory concentration (MIC) [13]. Similar results were also found for colistin, which is especially useful for gram-negative infections resistant to other antibiotics, suggesting inadequate levels of intravenous colistin in the CSF [14]. Moreover, the ventricular system is not a contiguous fluid compartment when pyogenic ventriculitis develops, and there is a nonuniform distribution of antibacterial agents in different CNS compartments. Often, the lowest concentration is in ventricular CSF, which partly explains why ventriculitis is so difficult to eradicate [4, 15]. Under these circumstances, the IVT route provides direct access and could potentially overcome these problems. The Infectious Diseases Society of America meningitis and ventriculitis guidelines also recommend IVT administration for difficult-to-eradicate organisms in nosocomial infections [2]. However, the optimal timing for initiation of IVT antibiotics has not been defined, and its effect on outcomes in patients with MDR nosocomial MEN in the neuro-ICU setting has not been investigated.

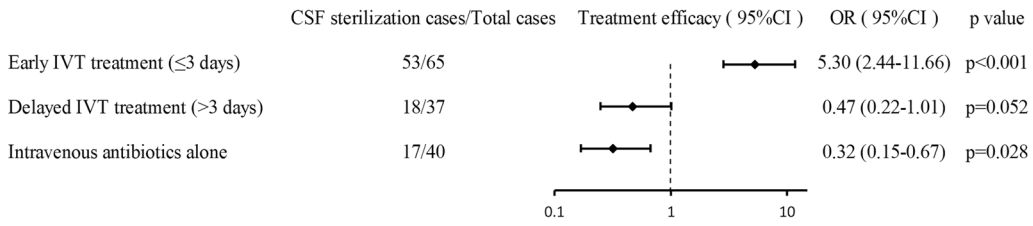

Fig. 3 Patients who received early IVT treatment (≤ 3 days after MEN onset) had a higher treatment efficacy compared with those who started IVT treatment > 3 days after MEN onset and those who received intravenous antibiotics alone. *CI* confidence interval, *CSF* cerebrospinal fluid, *IVT* intraventricular, *MEN* meningitis and/or ventriculitis, *OR* odds ratio

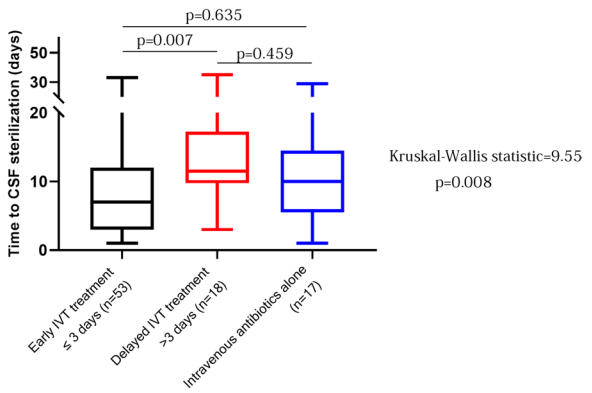

Fig. 4 Boxplots are shown as median (middle bar), 25th and 75th percentiles (upper and lower limits of the box), and min to max range (whiskers). Indicated *p* values were calculated using the Kruskal–Wallis test with Dunn's modification. *CSF* cerebrospinal fluid, *IVT* intraventricular

In previous studies, IVT antibiotic administration was usually the last therapeutic resort for the treatment of refractory MEN, and the optimal initiation time for IVT antibiotics has not been reported [3, 16–18]. In the few studies that have reported the initiation time for IVT treatment, the results were conflicting. Remes et al. reported the use of IVT antibiotics only in cases in which intravenous antibiotics were ineffective and laboratory and clinical signs of MEN persisted for 5–8 days despite intravenous treatment [15]. Khan et al. used IVT antibiotics only in cases in which antibiotics were ineffective despite 5 days of intravenous therapy [11], whereas De Bonis et al. reported a median time of 3 days (range 0–9 days) from diagnosis to initiation of IVT treatment [19].

In this study, when in-hospital mortality was examined based on the number of days from MEN onset to IVT therapy initiation, there was a significant relationship in both univariate and multivariate analyses (Tables 1 and 3). The rate of in-hospital mortality increased with the delay in IVT therapy, whereas patients who received IVT antibiotics earlier were more likely to survive. Our results demonstrated that the threshold for early IVT treatment was 3 days after MEN onset. It usually takes 8–12 and 48–72 h to report CSF gram staining and antibiotic sensitivity results, respectively, from our clinical microbiology laboratory. Therefore, it was reasonable to initiate IVT treatment with appropriate antibiotics based on the susceptibility of the microorganisms within 3 days. In this study, we did not find any particular patterns on which pathogens received early IVT treatment. However, local pathogen prevalence and individual patient factors should also be considered in the context of empirical therapy if microorganism susceptibility reports are not available within 3 days.

Previous studies on MDR bacterial MEN reported CSF sterilization rates of 33–89% and a mean time to CSF sterilization of 8.9–21 days [1, 3, 10, 15, 19–24]. In a recent multicenter retrospective study on IVT treatment for MEN, Lewin et al. reviewed 105 critically ill adult patients with CNS infections who received at least one dose of IVT antimicrobials along with systemic antimicrobials [3]. The authors reported a high CSF sterilization rate of 88.4%, possibly because they did not include patients with severe underlying conditions, TBI, and intracerebral hemorrhage, who are more vulnerable to systemic immunosuppression [25, 26]; moreover, the responsible pathogen was not MDR in most cases. In one of the largest reviews of IVT colistin for MDR MEN, Karaiskos et al. reviewed 81 cases of MDR *Acinetobacter baumannii* MEN and reported a successful outcome rate of 89% [1]. However, they included patients with only *A. baumannii* infections, and their results may not be applicable to other pathogens. Compared to previous studies, not only are our results more comprehensive (including 17 MDR bacterial species), but we also achieved a high treatment success rate (81.5%) and a shorter median time to CSF sterilization (7 [3–12] days) for the IVT treatment of MDR nosocomial MEN.

Early IVT treatment had significantly higher efficacy for MDR nosocomial MEN and a shorter time to CSF sterilization compared to delayed IVT treatment and intravenous treatment alone. This may be because MDR bacteria, such as MDR *A. baumannii* and *Klebsiella pneumonia*, usually have high pathogenicity and virulence and are resistant to multiple antibiotics. It is difficult to achieve the MIC in the CSF using intravenous antibiotics alone. Early IVT antibiotic therapy may quickly reduce the bacterial load to prevent irreversible damage to the CNS, alleviate symptoms, prevent malignant brain edema, and avoid sepsis and systemic inflammatory response syndrome caused by transfer of bacteria from the CNS to the blood. Timely limitation of MEN progression is crucial for the treatment and recovery of neuro-ICU patients with acute brain injury.

Although most studies did not report the IVT initiation time, the importance of early IVT treatment should not be underestimated. The advantages of early antibiotic administration have been confirmed in some other hospital-acquired infections. Zasowski et al. reported that early antibiotic therapy reduced the 30-day mortality rate in hospital-acquired enterococcal bloodstream infections [27]. Similar results were reported by Lodise et al., who found that the risk of mortality increased if antibiotic therapy was delayed by approximately 48 h in *Staphylococcus aureus* and

Pseudomonas aeruginosa bloodstream infections [28, 29]. Cabellos et al. analyzed 527 cases of invasive meningococcal disease and found that early antibiotic therapy was a protective factor in the multivariate analysis of mortality [30].

In addition to IVT treatment, we also performed thorough ventricular lavage for patients with purulent or thick viscous CSF. This could help prevent purulent compartment formation within the ventricle, reduce the amount of pus in the CSF, accelerate CSF circulation, and increase antibiotic perfusion [10]. The selection of antibiotics should be based on the pathogen epidemiology in the local neuro-ICU or the susceptibility data of the isolated pathogen. We found that inadequate initial antibiotic therapy was correlated with in-hospital mortality, but this association was not confirmed in the multivariate analysis. This may be because the patients included in this study all had MDR bacterial MEN, and most of the gram-negative pathogens were resistant to almost all commonly used antibiotics, except polymyxin and tigecycline, which makes it more difficult for the initial treatment to cover the pathogens. However, we will timely replace initial treatment with appropriate antibiotics with activity against the isolated pathogens as soon as the susceptibility data are available. This may possibly minimize the influence of inadequate initial therapy on in-hospital mortality. To date, few studies have focused on the effect of inadequate initial therapy on in-hospital mortality of patients with MDR MEN in the neuro-CCU. Further studies on this topic are still needed.

Limitations

There are several considerations to note when interpreting our results. First, the retrospective design of the study has some caveats, such as missing data due to incomplete documentation in the medical record. To address this, we selected objective, easily measurable outcomes, such as all-cause mortality. Second, the safety profile of IVT cannot be adequately addressed in this retrospective study. However, according to previous studies, adverse events related to IVT antimicrobial therapy, such as seizures or chemical meningitis or ventriculitis, may occur commonly as a result of the primary insult or inappropriate dosing and are reversible [5, 10]. Third, this was a single-center analysis restricted to nonimmunocompromised adult neuro-ICU patients in an attempt to maximize internal validity for addressing the study question. It is uncertain whether these results are directly applicable to other settings and populations, such as pediatric patients, and further studies are required to confirm these findings.

Conclusions

This was, to our knowledge, the first clinical study to investigate the effect of the time to initiate IVT treatment on the outcomes of neuro-ICU patients with MDR bacterial MEN. Our results suggested that early concomitant IVT antibiotic therapy was independently associated with decreased in-hospital mortality. The reasonable time to initiate IVT treatment for MDR bacterial MEN was ≤ 3 days after MEN onset. IVT treatment within 3 days was superior to IVT treatment > 3 days after MEN onset or intravenous antibiotics alone in terms of the time required for CSF sterilization and the CSF sterilization rate.

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Author Contributions
The study was designed by ZL and JH, and data collection was performed by ZL, WY, and XY. Results were analyzed by ZL, WY, XY, QY, JZ, and ZD. JY, YS, XW, and JH coordinated the project. ZL, WY, and JH wrote the article. JH supervised the study and made critical revision of the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest
All authors have disclosed that they do not have a potential conflict of interest.

Ethical Approval/Informed Consent
The procedures followed were in accordance with the ethical standards of the Ethics Committee for the Evaluation of Biomedical Research Projects of Huashan Hospital and with the Helsinki Declaration of the World Medical Association. Informed consent was obtained from the patients' next of kin.

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