An updated approach to healthcare-associated meningitis

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Among hospital-associated infections, healthcare-associated central nervous system infections are quite important because of high morbidity and mortality rates. The causative agents of healthcare-associated meningitis differ according to the status of immune systems and underlying diseases. The most frequent agents are Gram-negative bacilli (*Pseudomonas* spp., *Acinetobacter* spp., *Escherichia coli* and *Klebsiella pneumoniae*) and Gram-positive cocci (*Staphylococcus aureus* and *coagulase-negative staphylococci*). There are currently several problems in the treatment strategies of healthcare-associated meningitis due to a globally increasing resistance problem. Strategies targeting multidrug-resistant pathogens are especially limited. This review focuses on healthcare-associated meningitis and the current treatment strategies with a particular focus on methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis.

In spite of considerable developments in antibiotics, science and medicine, infectious diseases and infectious complications related to multidrug-resistant (MDR) bacteria such as staphylococci, enterococci, Enterobacteriaceae, *Pseudomonas aeruginosa* or *Acinetobacter baumannii* remain important causes of human morbidity and mortality. While necessitating more expensive and broad-spectrum antibiotics, the treatment of such resistant nosocomial pathogens, including meningitis, is challenging [1–4].

Bacterial meningitis may develop in the community or may be associated with a variety of invasive procedures or trauma [5]. The latter group has often been classified as nosocomial meningitis because a different spectrum of microorganisms may be the etiology of the meningitis, and different pathogenetic mechanisms (e.g., following neurosurgery or lumbar puncture (LP) or in association with placement of ventricular catheters) are associated with development of this disease [5]. According to the very recently revised CDC/National Healthcare Safety Network (CDC/NHSN) definitions dated January 2014 [6], not the terms 'nosocomial' or 'hospital-acquired meningitis' but 'healthcare-associated meningitis/ventriculitis' is used. These definitions standardized the classification of an infection as present on admission (POA) or a healthcare-associated infection (HAI). If all of the elements used to meet a CDC/NHSN site-specific infection criterion are present during the two calendar days before the day of admission, the first day of admission (day 1) and/or the day after admission (day 2) are documented in the medical record, and the infection is considered as POA. A HAI is defined as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not POA to the acute care facility. An infection is considered as a HAI if all elements of a CDC/NHSN site-specific infection criterion were not present during the POA time period but were all present on or after the third calendar day of admission to the facility (the day of hospital admission is calendar day 1). Healthcare-associated meningitis/ventriculitis is grouped among CNS infections. A healthcare-associated meningitis/ventriculitis must meet at least one of the following criteria [6]:

• Patient has organisms cultured from cerebrospinal fluid (CSF);
• Patient has at least one of the following signs or symptoms: fever (>38°C), headache,

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stiff neck, meningeal signs, cranial nerve signs or irritability with no other recognized cause and at least one of the following:

– Increased white cells, elevated protein and decreased glucose in CSF;
– Organisms seen on Gram's stain of CSF;
– Organisms cultured from blood;
– Positive laboratory test of CSF, blood or urine;
– Diagnostic single antibody titer (IgM) or fourfold increase in paired sera (IgG) for pathogen and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

• Patient ≤1 year of age has at least one of the following signs or symptoms: fever (>38°C core), hypothermia (<37°C core), apnea, bradycardia, stiff neck, meningeal signs, cranial nerve signs or irritability with no other recognized cause and at least one of the following:

– Increased white cells, elevated protein and decreased glucose in CSF;
– Organisms seen on Gram's stain of CSF;
– Organisms cultured from blood;
– Positive laboratory test of CSF, blood or urine;
– Diagnostic single antibody titer (IgM) or fourfold increase in paired sera (IgG) for pathogen and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy. These recent definitions [6] recommend to report CSF shunt infection as surgical site infection meningitis/ventriculitis, if it occurs within 90 days of placement; if later or after manipulation/access, it is considered as CNS infection meningitis/ventriculitis.

Although many of these nosocomial meningitis cases present clinical symptoms during hospitalization, bacterial meningitis may develop long after hospital discharge [5]. Hence, in this review, we used the term 'healthcare-associated bacterial meningitis/ventriculitis (HA-MEN).'

HA-MEN are relatively rare infections (0.34% in 51,133 hospitalized cases in neurosurgery clinic between 1993 and 2002) [7]. However, these are considered among the most serious infections because of the associated morbidity and mortality [7–12]. Durand *et al.* [9] reported that HA-MEN comprised 40% of 495 acute bacterial meningitis episodes in a 27-year period. This rate may increase in centers with a higher number of invasive hospital practices and the introduction of new technologies [2]. This review focuses on HA-MEN and current treatment strategies with particular concern regarding methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis.

Etiology

In contrast to the community-acquired acute-purulent meningitis where pneumococci and meningococci are the dominating pathogens [3,9], the major causative agents in HA-MEN are Gram-negative bacilli including *Escherichia coli*, *Pseudomonas*

aeruginosa, *Acinetobacter* spp. or *Enterobacter* spp. and Gram-positive cocci such as staphylococci or enterococci [2,11–14].

Durand *et al.* [9] analyzed 493 meningitis cases followed up in a 27-year period. HA-MEN comprised 40% (n = 197) of all cases. In the same study, Gram-negative bacteria were reported to be responsible for 33% of the HA-MEN, whereas 9% were *S. aureus* meningitis. Sacar *et al.* [12] reviewed 22 CNS shunt infections developed between 2000 and 2004 at the Pamukkale University–Faculty of Medicine in Turkey. The study showed that congenital hydrocephalus and meningitis were the most common causes of hydrocephalus in shunt-infected patients, and the most prevalent causative agents were *S. aureus* (N = 6, 30%), *Acinetobacter* spp. (N = 4, 20%) and *Staphylococcus epidermidis* (N = 3, 15%). Finally, MRSA was responsible for 14 cases (15.7%) of 89 HA-MEN followed up between 2006 and 2010 at the Neurosurgery Clinic of Ege University [Sipahi OR, UNPUBLISHED DATA; 2010].

TABLE 1 summarizes the distribution of major etiological agents in eight series from eight different countries including Brazil, France Germany, Holland, Korea, Taiwan, Turkey and the USA. Accordingly, coagulase-negative staphylococci were the most common etiological agents (20.6%). *S. aureus* comprised 93 (18.3%) of 508 cases. Out of 93 cases, 65 were detailed about methicillin resistance and 50.7% were methicillin resistant. Among Gram negatives, *Acinetobacter* spp. was the most common and comprised 11.6% of 508 cases. Carbapenem resistance (CR) rates in the series, depicted in TABLE 1, were not mentioned specifically. Recently, Bayramoglu *et al.* reported 19.9% CR in 21 *A. baumannii* meningitis cases followed up between 2007 and 2010 [15]. Moon *et al.* from South Korea [16] reported that 55% of 40 *A. baumannii* meningitis cases followed up between 2007 and 2011 were CR. Wang *et al.* from Taiwan [17] reported CR of 50% (10 of 20 cases) in *A. baumannii* and 3% (1/33 cases) in *P. aeruginosa* meningitis. Nagaveni *et al.* from India [18] analyzed antimicrobial susceptibility of 53 *P. aeruginosa* strains isolated from CSF and reported 32% imipenem resistance.

Risk factors

The most common underlying factors for HA-MEN include previous neurosurgery operation and the presence of foreign materials such as shunt and/or lumbar drain [2,7]. Concomitant infections increase the risk for meningitis by approximately six times [2,14]. The risk also varies according to the type of neurosurgery; the incidence is 0.8–1.5% after craniotomy, 4–17% after intraventricular catheterization, 5% after lumbar drainage and 1 in 10,000–50,000 cases after LP. The risk of developing meningitis following head trauma is 1.4% [14]. Most of the patients in whom meningitis develops as a complication of closed head trauma have a basilar skull fracture, which causes the subarachnoid space to be connected to the sinus cavity [14]. CSF leakage after neurosurgery, external lumbar or ventricular catheterization or cranial fractures increase the meningitis risk [2,10,14]. Other risk factors for infection of external

Table 1. Distribution of major etiological agents in eight series from eight different countries including Turkey, Germany, Holland, USA, Taiwan, Brazil, France and Korea.

Etiology	Ref. [11]	Ref. [7]	Ref. [75]	Ref. [9]	Ref. [19]	Ref. [76]	Ref. [77]	Ref. [78]	Total
Coagulase-negative staphylococci	3	7	7	13	4	3	34	34	105
Staphylococcus aureus (methicillin resistance unmentioned)	12			13		3			28
MSSA		7	2		1		2	20	32
MRSA		6	11		3		8	5	33
Acinetobacter spp.		15	4	6	1	4	27	2	59
Escherichia coli	3	9	5	17		1			35
Klebsiella pneumoniae	2	9	3	13		1			28
Pseudomonas spp.	2	3	5	6	1	1	1	7	26
Pneumococci	13		3	8					24
Enterococci	1	2	1	4	1	1	5		15
Haemophilus influenzae	4		1	6					11
Other	10	9	11	33	1	4	6	38	112
Total	50	67	53	119	12	18	83	106	508

MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*.

ventricular catheters are the routine sampling of CSF, blockage of the drain and intraventricular hemorrhage [14].

Even though neurosurgery is the leading cause of staphylococcal meningitis, it can also develop secondarily to another infected focus. Almost 60% of MRSA meningitis occur after head trauma and neurosurgical operations (including shunt insertion) [22]. Additionally, staphylococcal meningitis may arise as a result of hematogenous spread of the causative agent from a focus of infection such as infective endocarditis, osteomyelitis or pneumonia [2,22]. Other underlying conditions that are also associated with community-acquired meningitis include diabetes mellitus, alcoholism, chronic renal failure requiring hemodialysis, intravenous illicit drug abuse injections and malignancies [21].

Pintado *et al.* [22] reported that among 44 cases of *S. aureus* meningitis, 28 were postoperative and 16 were spontaneous meningitis. The most common underlying reasons for postoperative meningitis were CSF leakage, intracranial foreign material and head trauma. The authors also reported the presence of concurrent staphylococcal wound infections in seven cases.

In a previous study held in our setting, shunt infection, neurosurgery for malignancies and fracture in cervical vertebrae were reported to be the underlying causes for four, three and two cases of MRSA meningitis, respectively [23]. In another study, we had reported 17 cases of staphylococcal meningitis, 10 of which had ventriculoperitoneal or atrial shunt insertion in the history. The remaining cases were operated because of intracerebral hemorrhage (two cases), meningioma (two cases), lumbar degenerative stenosis (one case), spondylolisthesis (one case) and posterior fossa tumor (one case) [24].

Aguilar *et al.* detected *S. aureus* in 4.9% (33/668) of CSF cultures from bacterial meningitis cases followed up between 1999 and 2008. In the same study, methicillin-sensitive *S. aureus* (MSSA) was detected in 17 cases. Among 16 MRSA cases, 6 were postoperative meningitis, while 10 were hematogenous meningitis [25].

Clinical presentation

The classical meningitis triad (fever, disturbances in the consciousness and neck stiffness) is not as common as in the community-acquired meningitis in HA-MEN, especially in cases with CSF leakage probably due to the nonincreased CSF pressure [26]. According to a study, among 50 meningitis cases, 70% were associated with classical symptoms fever, headache and neck stiffness, whereas only 41% had disturbances in the consciousness [11]. Meningeal irritation symptoms may be evident in less than 50% of shunt-associated infections, symptoms like sub febrile body temperature (defined as of, relating to, or constituting a body temperature very slightly above normal but not febrile) [37] and fatigue are more common [2,14]. Symptoms often arise due to the failure of shunt function and are often accompanied by headache, nausea and vomiting.

S. aureus meningitis is mostly health care-associated [23–25]. As HA-MEN, its clinical progress is slower than that of the community-acquired type. In a study evaluating 37 meningitis episodes, fever (73%) and altered consciousness (48.6%) were the most common symptoms reported [29]. According to Pintado *et al.* [22], disturbances in the consciousness, neck stiffness, patechial rashes, bacteremia and septic shock were observed less often in postoperative than in spontaneous *S. aureus* meningitis. Disturbances in the consciousness and fever were reported in 66–81% and 50–77% of postoperative MRSA meningitis [24,25].

Treatment

Early diagnosis with lumbar or shunt or extraventricular/lumbar drainage puncture and starting antimicrobial therapy is crucial in the management of HA-MEN. Empirical antibacterial treatment should be initiated according to the underlying status and the age of the patient, following blood cultures, in cases cranial imaging is indicated before LP or LP is contraindicated [30].

In contrast to numerous infectious diseases, such as pneumonia or urinary tract infections, antibiotic treatment strategies for bacterial meningitis are based on case series or animal meningitis models [2,31], rather than prospective, double-blinded controlled studies.

The antimicrobial agent must have a high CSF penetration capacity to be effective in meningitis therapy. Low molecular weight and lipid-soluble antibiotics can cross blood–brain barrier more, whereas the high rate of protein binding has a negative effect. Besides the pharmacological properties of antibiotics, the presence of inflammation can also influence CSF penetration. Relatively, high penetration will decrease as inflammation reduces; hence, antibiotics must be administered at a high dosage by way of intravenous (i.v.) route in order to achieve optimum drug level. It is also important for the antimicrobial agent to be stable and to have a bactericidal effect in the purulent CSF [2,21]. The penetration rate of some antimicrobial agents into inflamed CSF are: 20–40% for ceftazidime, 10% for ceftriaxone, 20% for cefepime, 30% for meropenem, 70% for linezolid, 40% for ciprofloxacin, 80% for moxifloxacin and levofloxacin, 50% for tigecycline, 30% for rifampin, 20% for vancomycin, 10% for teicoplanin and 5% for daptomycin [32].

According to the Infectious Diseases Society of America (IDSA) guidelines, empirical vancomycin is the recommended antibiotic against infections with Gram-positive bacteria such as *S. aureus* and coagulase-negative staphylococci (especially *S. epidermidis*) that are abundant in postneurosurgical and CSF shunt infections. Empirical cefepime or ceftazidime or meropenem are recommended for empirical therapy of Gram-negative bacterial meningitis such as *P. aeruginosa*, *E. coli* and *Klebsiella pneumoniae*. This combination therapy may be de-escalated according to the sensitivity pattern of the isolated bacteria [30,33].

Staphylococci & enterococci

Today, in many references, the first treatment option considered for MRSA meningitis is vancomycin. Vancomycin cannot penetrate CSF at a high level. Hence, when it is used together with rifampicin in susceptible strains, its effect can be enhanced further while theoretically vancomycin can also prevent the development of resistance to rifampin. Vancomycin can also be administered intrathecally [21,30,31,33,34]. Other alternative agents can be linezolid, trimethoprimsulfamethoxazole [26,33] as well as teicoplanin and daptomycin. Arda *et al.* [23] reported the successful treatment of six MRSA meningitis cases by teicoplanin including regimens. Furthermore, Sipahi *et al.* [35] showed that teicoplanin had similar antibacterial activity as vancomycin in the MRSA meningitis model in rabbits. In contrast to IDSA guidelines [30,33], the European Federation of Neurological

Societies guidelines on the management of community-acquired bacterial meningitis recommends the use of linezolid for MRSA meningitis [26]. Recently, Calik *et al.* [36] compared linezolid 10 and 20 mg/kg q12 h with 20 mg/kg vancomycin q12 h for 24 h in a rabbit MRSA meningitis model. At the end of treatment, the decrease in bacterial counts in the vancomycin group was approximately two logs higher than the linezolid-20 group (p > 0.05) and approximately four logs higher than in the linezolid-10 group (p = 0.037) (Vancomycin group: -2.860 ± 4.495 vs Linezolid-20: -0.724 ± 4.360, vs Linezolid-10: 1.39 ± 3.37). Full or partial bacteriological response was higher in vancomycin versus linezolid-10 (p = 0.01), but not vancomycin versus linezolid-20 or linezolid-10 versus linezolid-20 groups. We reviewed nine MRCoNS, seven MRSA and one MRCoNS and MRSA mixed HA-MEN cases treated with linezolid. Seven out of eight MRSA (including one with mixed infection) meningitis cases and eight out of nine MRCoNS cases had microbiological clearance on day 5 [24]. Additionally, Ntziora *et al.* [37] reviewed four MRCoNS and three MRSA patients treated with linezolid. Finally, we compared linezolid and vancomycin in a retrospective cohort study. Seven out of nine linezolid administered and two out of eight vancomycin admninistered. MRSA meningitis cases had microbiological success on day 5 of treatment (p = 0.044). On the other hand, among six MRSA meningitis cases with vancomycin minimum inhibitory concentration (MIC) of 2 mg/l, only one case had microbiological success with vancomycin on day 5 [38].

Nafcillin, oxacillin and flucloxacillin are the recommended agents for MSSA meningitis [30,33].

Another relatively new agent used to cure infections with resistant Gram-positive bacteria is daptomycin. Daptomycin was also tested with vancomycin by using experimental meningitis models. In a study conducted by Gerber *et al.* [39], daptomycin (15 mg/kg) was reported to be more effective than vancomycin (20 mg/kg administered twice 2 h apart) at the end of the 8-h treatment in rabbit meningitis model with MSSA. Recently, Bardak-Ozcem *et al.* [40] compared daptomycin with vancomycin by using the same dosages as Gerber *et al.* [39] in MRSA meningitis model in rabbits. After an 8-h period of treatment, bacterial counts decreased significantly in both treatment groups compared with the control group (p < 0.05). However, there was no statistically significant difference between treatment groups. There are case reports that suggest daptomycin as an alternative salvage therapy agent for meningitis treatment. Among them, Riser *et al.* [41] reported successful treatment of MSSA bacteremia and MSSA meningitis by using high doses of daptomycin (9 mg/kg) and reported daptomycin CSF penetration rate as 5%. Lee *et al.* [42] reported the treatment of a MRSA meningitis case, which was allergic to vancomycin and had septic brain emboli with daptomycin. Another case with MRSA meningitis and MRSA bacteremia was reported to be cured when daptomycin was used together with linezolid and rifampin [43].

Finally for enterococcal meningitis treatment, guidelines recommend ampicillin/gentamicin and vancomycin/gentamicin for

ampicillin sensitive and ampicillin resistant, vancomycin-sensitive strains, respectively [30]. There are anecdotal data including case reports suggesting linezolid and daptomycin for vancomycin-resistant enterococcal (VRE) meningitis treatments. For instance, Ntziora et al. [37] systematically reviewed six linezolid-treated enterococcal meningitis cases. Two cases received linezolid monotherapy for 21 and 28 days. One case received 28 days of linezolid in combination with quinupristin/dalfopristin, the fourth case was given 5 days of gentamicin + linezolid followed by 16 days of linezolid. The fifth patient received 7 days of linezolid + gentamicin followed by 35 days of linezolid and the last case was treated with 4 days of linezolid + chloramphenicol followed by 24 days of linezolid. Jaspan et al. [44] cured a pediatric case by intrathecal daptomycin and i.v. tigecycline combination. Additionally, Le et al. [45] reported daptomycin (6–12 mg/kg) and gentamicin or linezolid combinations for the treatment of three VRE meningitis cases. There are also additional case reports related to the successful therapy of enterococcal CNS infections with daptomycin [46].

Gram-negative bacillary meningitis

The continuous increase in MDR (being resistant to at least three different antibiotic groups) Acinetobacter spp. challenges the current treatment strategies [1,2,47]. If the strain is sensitive to cefepime or ceftazidime, then each can be used. If the strain is sensitive only to meropenem, then meropenem may be recommended. In case of CR Gram-negative bacterial meningitis, treatment must be directed according to the sensitivity pattern of the bacteria.

If the infecting pathogen is CR Acinetobacter spp. that is a spreading global problem, then there are case reports or case series that suggest the use of sulbactam, intrathecal aminoglycosides, i.v./intrathecal colistin or i.v. tigecycline for salvage therapy.

Sulbactam is a β-lactam β-lactamase inhibitor. Stahl et al. reported that they detected up to 12 µg/ml sulbactam after 1–4 h in CSF of patients with bacterial meningitis after 4 g/day sulbactam [48]. Sulbactam has antibacterial activity against Acinetobacter spp. and appears to be effective in high dosages. Levin et al. [20] reported two cases of A. baumannii meningitis in which sulbactam resulted in failure. Kendirli et al. [49] reported the successful treatment of an A. baumannii (sensitive to netilmicin and imipenem) meningitis patient by using high doses of ampicillin/sulbactam (300 mg/kg/day) after failure with imipenem. However, the authors did not give any information regarding meropenem sensitivity. Sipahi et al. [50] used ampicillin/sulbactam (12 g/day) to cure an A. baumannii meningitis case who was unresponsive to meropenem. Sayin Kutlu et al. [51], reported a CR A. baumannii meningitis case treated by 12 g ampicillin/6 g sulbactam.

Today, colistin, administered as its prodrug colistin methanesulfonate, is one of the few antibiotics available for the treatment of infections by MDR Gram-negative organisms [52]. However, its penetration to CSF is not high. In the first data related to the CSF penetration of colistin into CSF for MDR A. baumannii meningitis treatment, 5 mg/kg/day of colistin resulted in 25% CSF/serum rate [53]. In another recent study, Ziaka et al. [52] analyzed colistin pharmacokinetics prospectively after i.v. administration of colistin methanesulfonate in critically ill patients without CNS infection (controls, n = 5) and in patients with external ventricular drain-associated ventriculitis after i.v. administration (EVDVi.v., n = 3) or combined i.v./intraventricular administration (EVDVcomb, n = 4). CSF/serum colistin concentration ratios were higher in EVDVi.v. than in control patients (11 vs 7%, p ≤ 0.05) and in EVDVcomb compared with all other patients (40–45%, p < 0.0001). CSF colistin concentrations above the MIC of 0.5 µg/ml were achieved only in EVDVcomb patients.

The data related to the use of colistin A. baumannii meningitis are mainly acquired from case reports [53–55]. In a systematic review related to the use of polymyxin for Gram-negative bacterial meningitis by Falagas et al. [55], i.v. and/or intrathecal/intraventricular polymyxin was found to be able to cure 51 (80%) out of 64 published Gram-negative bacterial meningitis cases. In the same study, 10 (91%) out of 11 Acinetobacter spp.-infected cases were reported to be treated by colistin (4 i.v. + intrathecal/intraventricular, seven intrathecal or intraventricular). In addition to these case reports, Pachón-Ibáñez et al. [56] analyzed the efficacy of rifampin and its combinations with imipenem, sulbactam and colistin in rabbit meningitis model induced by imipenem-resistant A. baumannii. Colistin alone showed less antibacterial activity than colistin and rifampin combination and they concluded that rifampin in monotherapy or with imipenem, sulbactam or colistin showed efficacy. It is also worth noting that recently published pharmacokinetic data [57] suggest that the colistin dosage (to even two million units per 8 h) should not be decreased in critically ill patients receiving continuous venovenous hemodiafiltration and should rather be kept equal to or even higher than the daily dose in patients with normal renal function.

Another therapy option for CR A. baumannii infections is tigecycline. In the literature, there are a few case reports related to the successful treatment of A. baumannii meningitis with tigecycline [58,59]. There are also a limited number of animal studies regarding tigecycline. Fang et al. [60] analyzed the effects of tigecycline at different doses with or without vancomycin on penicillin-resistant S. pneumoniae-induced meningitis model. In this study, when used at concentrations above 20 mg/kg, tigecycline was reported to be bactericidal and was at concentration above 1 µg/ml in CSF after 3 h of treatment.

For carbapenem-sensitive Pseudomonas spp., if the strain is also sensitive to cefepime or ceftazidime, then each may be used. In case of ceftazidime and cefepime resistant but meropenem-sensitive Pseudomonas spp., meropenem is recommended. Treatment options for CR Pseudomonas spp. meningitis are restricted to i.v./intrathecal aminoglycosides and colistin [14,30]. Corpus et al. [61] treated a case of P. aeruginosa meningitis with meropenem + i.v. and intrathecal amikacin. Bray and Calcaterra [62] reported three cases of P. aeruginosa meningitis treated successfully with carbenicillin + i.v. and intrathecal

gentamicin. Recently, Wang et al. [17] reported three cases treated with ceftazidime + 10 mg intrathecal amikacin, cefepime + 30 mg intrathecal amikacin and ceftazidime/meropenem + 4 mg intrathecal gentamicin. As in the Acinetobacter meningitis, there are several successful treatment reports of *P. aeruginosa* meningitis cases via i.v. and intrtahecal colistin or intrathecal colistin alone [55,63,64]. In the systematic review of 30 published *P. aeruginosa* meningitis cases [55], i.v. and/or intrathecal polymixins resulted in 87% cure in 30 reported cases.

When compared with many other antibiotics, quinolones have a relatively high CSF penetration rate. However, quinolones also have the possibility of inducing seizures [65]. Furthermore, the probability of a cephalosporin/carbapenem-resistant *P. aeruginosa* strain to be susceptible to quinolones is generally low [1]. In addition to aminoglycosides and colistin, ciprofloxacin has also been used for the salvage therapy of *P. aeruginosa*, *Acinetobacter* spp., both coagulase positive and negative staphylococci, *Salmonella* spp. and *Enterococcus faecalis* meningitis in anecdotal case reports [66,67].

In Enterobacteriaceae meningitis ceftriaxone, cefotaxime or meropenem may be used in sensitive strains [26,30,68]. While carbapenem-resistant Enterobacteriaceae meningitis is not yet seen as a problem, colistin and/or tigecycline may theoretically be effective in such a case.

Repeated CSF culture

Repeated CSF culture may be necessary during the course of meningitis in certain situations: partially treated cases, uncertain diagnosis, poor clinical response in the absence of other causes, vancomycin-treated patients receiving dexamethasone, Gram-negative bacillary meningitis, meningitis complicating CSF shunt in whom reshunting is planned and for intrathecal antibiotic therapy [26].

Duration of therapy

The optimum duration of therapy in HA-MEN is not known [9,11,28,75,76,79]. European Federation of Neurological Societies guidelines [26] suggest 21–28 days of therapy in Gram-negative bacillary or Pseudomonas meningitis. IDSA meningitis guidelines [30] suggest 21 days of therapy for aerobic Gram-negative bacilli meningitis. There is no recommendation for the treatment of staphylococcal or enterococcal meningitis in either guidelines as well as in IDSA guidelines related to *S. aureus* [26,30,33].

Treatment of shunt infections

Numerous methods for the treatment of CSF shunt infections have been reported; however, randomized, prospective studies have not been performed. Factors to be considered in the therapy of an infected CSF shunt are the selection of antimicrobial therapy, the timing of hardware removal, the timing of shunt replacement and the duration of antimicrobial therapy. The principles of antimicrobial therapy for CSF shunt infections are generally the same as those for acute bacterial meningitis [69].

If bacterial meningitis develops in a patient who has an external ventricular catheter, then the catheter should be removed to increase the likelihood that the infection can be cured [14]. In the case of internal ventricular catheters or shunts, antimicrobial therapy, the removal of all components of the infected catheter and the placement of an external drain appear to be the most effective treatment methods, with success in more than 85% of patients. The optimal timing for the reinsertion of the shunt is not clearly defined although general guidelines can be suggested. For patients with shunt infections that are caused by a coagulase-negative staphylococcus or *Propionibacterium acnes* in association with abnormalities of the CSF (e.g., pleocytosis), antimicrobial therapy for 7 days is commonly recommended before the placement of a new shunt; if repeat cultures are positive, antimicrobial therapy should generally be continued until CSF cultures have been negative for 10 consecutive days before a new shunt is implemented [14,69]. In the case of shunt infections caused by *S. aureus* or Gram-negative bacilli, 10 days of antimicrobial therapy after repeated negative cultures are recommended before placement of a new shunt, although some authorities recommend an even longer duration of therapy when Gram-negative bacilli are isolated. Some experts have recommended a 3-day observation period after the completion of antimicrobial therapy before a new shunt is placed to confirm that the infection has been cleared, although this is not uniformly recommended [14,69].

Combination antimicrobial therapy

Although international guidelines [26,30] suggest combination empirical therapy in the management of HA-MEN, there is no controlled clinical trial that proves the efficacy of the combination therapy over monotherapy. Another unknown issue is the cutoff for methicillin-resistant rate in which empirical vancomycin should be added.

Moreover, while vancomycin is the primarily recommended option in MRSA meningitis under IDSA guidelines [30,33] and adding rifampin is considered as an alternative, there are no controlled data regarding this issue except one animal model study [8].

Combination therapy as ampicillin + gentamicin or vancomycin + gentamicin is also the recommended regimen in the treatment of enterococcal meningitis [30] while there is a lack of controlled data regarding this issue. In fact, a large uncontrolled series consisting 39 enterococcal meningitis cases demonstrated 22% mortality in combination therapy versus 16% in monotharapy [70].

For carbapenem-resistant Gram-negative meningitis in the case of tigecycline usage, a combination therapy with another available option may be rational, since tigecycline monotherapy may be associated with higher mortality [71].

Intrathecal treatment

Toxicity makes dose escalation difficult for the aminoglycosides, glycopeptides and polymyxins; therefore, intrathecal or intraventricular administration of these agents might be needed

Table 2. Treatment recommendations in multidrug-resistant organism related healthcare-associated meningitis.

Etiological agent	Recommended therapy	Alternative/salvage therapy
Methicillin resistant staphylococci	Linezolid if vancomycin MIC > 1 mg/l Vancomycin if vancomycin MIC ≤ 1 mg/l	Linezolid, teicoplanin, daptomycin
Vancomycin-resistant enterococci	Linezolid	Daptomycin, tigecycline
Cefepime-ceftazidime-carbapenem resistant Gram negatives	Colistin	Tigecycline (except *Pseudomonas* spp.), sulbactam (for *Acinetobacter* spp.), intrathecal aminoglycosides

MIC: Minimum inhibitory concentration.
Derived from [2,23,24,26,30,33,38].

to reach effective CSF concentrations. However, data to support the safety and efficacy of this approach are scarce [17,32]. *Acinetobacter* spp., *Pseudomonas* spp., *E. coli* and *K. pneumoniae* meningitis cases that are unresponsive/resistant to intravenous treatment can potentially be cured by intrathecal administration of colistin (5–10 mg or 75,000–150,000 units [17,52,55]. Published data suggest that the combination of intravenous and intrathecal colistin may give a pharmacokinetic/pharmacodynamic advantage over intrathecal colistin or intravenous colistin [52]. Since penetration of aminoglycosides into CSF is negligible [34], they can be used intrathecally such as gentamicin (4–10 mg), netilmicin (up to 150 mg) and amikacin (5–50 mg) [2,14,17,62,72]. For Gram-positive bacterial meningitis cases in which primary treatment was not successful, vancomycin (5–20 mg) or teicoplanin (5–40 mg) can be administred intrathecally [2,14]. While deciding the course of action for intrathecal admnistration, it must be kept in mind that the data related to this practice are confined to case reports. There is no US FDA-approved indication for intrathecal practice of any antibiotics. The practice may be associated with side effects such as epileptic attacks. The amount of antibiotics to be admninistered intrathecally must be calculated so that its concentration in 150 ml CSF would be almost 20-times more than its MIC value [14]. Since there is no evidence to support the superiority of intrathecal treatment over intravenous treatment and intrathecal therapy with gentamicin may even be associated with higher mortality [73], it seems rational to keep the intrathecal therapy as a salvage therapy option until the publication of further evidence.

Mortality

Mortality of HA-MEN ranges between 16 and 40.8% [9,11,75,76,28,32,79]. Dizbay *et al.* [79] reported 33% mortality in 48 nosocomial CNS infections followed up between 2003 and 2009. In the same study, the mortality rate was found to be associated with the presence of extraventricular drainage, invasive procedures, meningitis due to resistant Gram-negative pathogens and young age. On the other hand, Erdem *et al.* [28] reviewed 62 postneurosurgical meningitis episodes (2.7%) in 49 cases (2.1%) after 2265 neurosurgery operations. They reported 40.8% mortality. The authors also showed that low CSF glucose levels, presence of a concommitant infection and having a Glasgow Coma score <10 were associated with mortality. Similar to the acute bacterial meningitis [72], logistic regression analysis showed that mortality was significantly associated

with GCS score <10 (OR: 19.419; 95% CI: 1.637–230.41; p = 0.001), the CSF glucose level ≤30 mg/dl (OR: 10.272; 95% CI: 1.273–82.854; p =0.002) and the presence of a concurrent HAI (OR: 28.744; 95 % CI: 1.647–501.73; p = 0.001).

While crude mortality for *S. aureus* meningitis ranges between 14 and 77%, the mortality rate of spontaneous meningitis is higher (19–71%) than postoperative meningitis (11–28%) [80–86]. Spontaneous *S. aureus* meningitis is mostly observed in elderly patients. *S. aureus* can lead to bacteremia and develop as a result of hematogenous spread of the staphylococci from a distant focus of infection to CNS especially [82,83,85,86]. Crude mortality of MRSA meningitis ranges between 10 and 37.5% [23–25,38,86].

Expert commentary

Antibacterial resistance exists and will continue to exist. Antibacterial resistance is not always but usually associated with higher morbidity, mortality and excess costs. MDR bacteria associated infections including meningitis are increasing problems in most parts of the world [1].

With few exceptions, such as linezolid, chloramphenicol and some of the quinolones [33,34], almost all antibacterial agents used for the treatment of HA-MEN display poor CSF penetration. If the most commonly recommended drug vancomycin fails in treating MRSA meningitis, then linezolid, teicoplanin or daptomycin are the main alternative agents. Linozolid is a more rational choice in the subgroup with MIC values >1 mg/l due to low vancomycin success rate in these cases. Today, linezolid, daptomycin or tigecycline combinations are the available treatment options for VRE meningitis.

Ceftriaxone or cefotaxime may be used for susceptible *E. coli* or *K. pneumoniae* strains. Ceftazidime or cefepime may be used in susceptible *Pseudomonas* spp. or *Acinetobacter* spp. strains. Meropenem can be chosen in cephalosporin-resistant bacterial meningitis. In case of MDR Gram-negative bacterial meningitis, treatment must be directed according to the sensitivity pattern of the bacteria. Colistin may be preferred in carbapenem-resistant Gram negatives, while tigecycline, sulbactam intrathecal or intravenous aminoglycosides can be used as alternative therapy options depending on the susceptibility pattern of the infecting strain. Treatment recommendations in methicillin-resistant staphylococci, vancomycin-resistant enterococci and cefepime–ceftazidime–meropenem-resistant Gram negatives are summarized in TABLE 2.

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Five-year view

Microorganisms will keep on developing and disseminating resistance and therefore patients will continue to die due to antibiotic-resistant microorganisms. Although there are promising agents such as linezolid, tigecycline, quinupristin/dalfopristin, daptomycin and possibly ceftobiprole for MDR Gram-positive organisms, the situation is not the same for Gram negatives [1]. Drugs such as tigecycline, colistin and fosfomycin (for which there are a few case reports) [87,88] are likely to prompt further research in their possible use in MDR Gram negatives. Data related to adjuvant therapy in HA-MEN as well as treatment-oriented randomized controlled studies are lacking in meningitis. This situation needs support by either multicenter retrospective or prospective cohort studies [89,90] or funding by independent research investors (NI H, EU, governments, etc.). Investments on infection control measures will increase in countries where human life is of higher value or the fact that infection control is more cost-effective than treating them gets generalized acceptance.

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Key issues

- In the case of methicillin-resistant *Staphylococcus aureus* meningitis, vancomycin is the mainstay therapy. Linezolid or teicoplanin or daptomycin may also be used as alternatives. In cases when vancomycin minimum inhibitory concentration values are >1 mg/l, linezolid can be especially preferred due to low vancomycin success rate.
- Linezolid, daptomycin or tigecycline combinations are the treatment options for vancomycin-resistant enterococcal meningitis.
- Ceftriaxone or cefotaxime may be used for susceptible *Escherichia coli* or *Klebsiella pneumoniae* strains.
- Ceftazidime or cefepime may be used in susceptible *Pseudomonas* spp. or *Acinetobacter* spp. strains. Meropenem can be chosen in cephalosporin-resistant bacterial meningitis. Finally, colistin may be preferred in cabapenem-resistant bacteria, while tigecycline, sulbactam intrathecal or intravenous aminoglycosides can also be used in carbapenem-resistant Acinetobacter depending on the susceptibility pattern of the infecting strain.

References

1. Sipahi OR. Economics of antibiotic resistance. Expert Rev Anti Infect Ther 2008;6(4):523-39

2. Bardak-Ozcem S, Sipahi OR. Approach To Hospital-acquired and Methicillin-resistant Staphylococcus Aureus Meningitis. Mediter J Infect Microb Antimicrob 2012;1:13

3. Arda B, Sipahi OR, Atalay S, Ulusoy S. Pooled analysis of 2,408 cases of acute adult purulent meningitis from Turkey. Med Princ Pract 2008;17(1):76-9

4. Nau R, Djukic M, Spreer A, Eiffert H. Bacterial meningitis: new therapeutic approaches. Expert Rev Anti Infect Ther 2013;11(10):1079-95

5. Laxmi S, Tunkel AR. Healthcare-associated bacterial meningitis. Curr Infect Dis Rep 2011;13(4):367-73

6. CDC/NHSN surveillance definitions for specific types of infections. Available from: www.cdc.gov/nhsn/pdfs/pscmanual/ 17pscnosinfdef_current.pdf [Last accessed on 25 January 2014]

7. Palabiyikoglu I, Tekeli E, Cokca F, et al. Nosocomial meningitis in a university hospital between 1993 and 2002. J Hosp Infect 2006;62(1):94-7

8. Sato K, Lin TY, Weintrub L, et al. Bacteriological efficacy of nafcillin and vancomycin alone or combined with rifampicin or amikacin in experimental meningitis due to methicillin-susceptible or –resistant Staphylococcus aureus. Jpn J Antibiot 1985;38(8):2155-62

9. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993;328:21-8

10. Beer R, Lackner P, Pfausler B, Schmutzhard E. Nosocomial ventriculitis and meningitis in neurocritical care patients. J Neurol 2008;255(11):1617-24

11. Weisfelt M, Van de Beek D, Spanjaard L, de Gans J. Nosocomial bacterial meningitis in adults. A prospective series of 50 cases. J Hosp Infect 2007;66(1): 71-8

12. Sacar S, Turgut H, Toprak S, et al. A retrospective study of central nervous system shunt infections diagnosed in a university hospital during a 4-year period. BMC Infect Dis 2006;6:43

13. Forster DH, Daschner FD. Acinetobacter species as nosocomial pathogens. Eur J Clin Microbiol Infect Dis 1998;17: 73-7

14. Van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. N Engl J Med 2010;362:146-54

15. Bayramoglu G, Kaya S, Besli Y, et al. Molecular epidemiology and the clinical significance of Acinetobacter baumannii complex isolated from cerebrospinal fluid in neurosurgical intensive care unit patients. Infection 2012;40(2):163-72

16. Moon C, Kwak YG, Kim BN, et al. Implications of postneurosurgical meningitis caused by carbapenem-resistant Acinetobacter baumannii. J Infect Chemother 2013;19(5):916-19

17. Wang JH, Lin PC, Chou CH, et al. Intraventricular antimicrobial therapy in postneurosurgical gram-negative bacillary meningitis or ventriculitis: a hospital-based retrospective study. J Microbiol Immunol Infect 2012. [Epub ahead of print]

18. Nagaveni S, Rajeshwari H, Oli AK, et al. Widespread Emergence of Multidrug Resistant Pseudomonas aeruginosa Isolated from CSF Samples. Indian J Microbiol 2011;51(1):2-7

19. Scheithauer S, Bürgel U, Ryang YM, et al. Prospective surveillance of drain associated meningitis/ventriculitis in a neurosurgery and neurological intensive care unit. J Neurol Neurosurg Psychiatry 2009;80(12):1381-5

20. Levin AS, Levy CE, Manrique AE, et al. Severe nosocomial infections with imipenem-resistant Acinetobacter baumannii treated with ampicillin/sulbactam. Int J Antimicrob Agents 2003;21(1):58-62

21. Tunkel AR, Scheld WM. Acute meningitis. In: Bennett JE, Dolin R, Mandell GL, editors. Principles and practice of infectious diseases. 7th edition. Churchill Livingstone, NY, USA; 2010;p. 1189-230

22. Pintado V, Meseguer MA, Fortún J, et al. Clinical study of 44 cases of Staphylococcus aureus meningitis. Eur J Clin Microbiol Infect Dis 2002;21:864-8

23. Arda B, Yamazhan T, Sipahi OR, et al. Ulusoy S, meningitis due to methicillin-resistant Staphylococcus aureus (MRSA): review of 10 cases. Int J Antimicrob Agents 2005;25:414-18

24. Sipahi OR, Bardak S, Turhan T, et al. Linezolid in the treatment of methicillin-resistant staphylococcal post-neurosurgical meningitis: a series of 17 cases. Scand J Infect Dis 2011;43:757-64

25. Aguilar J, Urday-Cornejo V, Donabedian S, et al. Staphylococcus aureus meningitis: case series and literature review. Medicine (Baltimore) 2010;89(2):117-25

26. Chaudhuri P, Martinez-Martin P, Kennedy PG, et al. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. Eur J Neurol 2008;15(7):649-59

27. Subfebrile. Available from: www.merriam-webster.com/medical/subfebrile [[Last accessed on 20 January 2014]

28. Erdem I, Hakan T, Metin F, et al. Clinical features, laboratory data management and the risk factors that affect the mortality in patients with postoperative meningitis. Neurol India 2008;56(4):433-7

29. Huang WC, Lee CH, Liu JW. Clinical characteristics and risk factors for mortality in patients with meningitis caused by Staphylococcus aureus and vancomycin minimal inhibitory concentrations against these isolates. J Microbiol Immunol Infect 2010;43(6):470-7

30. Tunkel AR, Hartman BR. Practice guidelines for the management of bacterial meningitis. IDSA guidelines. Clin Infect Dis 2004;39:1267-84

31. Greenlee JE, Carroll KC. Cerebrospinal fluid in central nervous system infections. In: Scheld WM, Whitley RJ, Marra CM, editors. Infections of the central nervous system. 3rd edition. Lippincott Williams and Wilkins; Philadelphia, PA, USA: 2004. p. 5-30

32. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. Lancet 2012;380(9854):1693-702

33. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52(3):e18-55

34. The Sanford guide to antimicrobial therapy 2011, 41st edition; 2011;p. 79-84

35. Sipahi OR, Arda B, Yurtseven T, et al. Vancomycin versus teicoplanin in the therapy of experimental methicillin-resistant Staphylococcus aureus (MRSA) meningitis. Int J Antimicrob Agents 2005;26:412-15

36. Calik S, Turhan T, Yurtseven T, et al. Vancomycin versus linezolid in the treatment of methicillin-resistant Staphylococcus aureus meningitis in an experimental rabbit model. Med Sci Monit 2012;18(11):SC5-8

37. Ntziora F, Falagas ME. Linezolid for the treatment of patients with central nervous system infection. Ann Pharmacother 2007;41(2):296-308

38. Sipahi OR, Bardak-Ozcem S, Turhan T, et al. Vancomycin versus Linezolid in the Treatment of Methicillin-Resistant Staphylococcus aureus Meningitis. Surg Infect (Larchmt) 2013;14:357-62

39. Gerber P, Stucki A, Acosta F, et al. Daptomycin is more efficacious than vancomycin against a methicillin-susceptible Staphylococcus aureus in experimental meningitis. J Antimicrob Chemother 2006;57:720-3

40. Bardak-Ozcem S, Turhan T, Sipahi OR, et al. Daptomycin versus vancomycin in treatment of Methicillin-Resistant Staphylococcus aureus Meningitis in an experimental rabbit model. Antimicrob Agents Chemother 2013;57(3):1556-8

41. Riser MS, Bland CM, Rudisill CN, Bookstaver PB. Cerebrospinal Fluid Penetration of High-Dose Daptomycin in Suspected Staphylococcus aureus Meningitis. Ann Pharmacother 2010;44:1832-4

42. Lee DH, Palermo B, Chowdhury M. Successful treatment of methicillin-resistant Staphylococcus aureus meningitis with daptomycin. Clin Infect Dis 2008;47(4):588-90

43. Kelesidis T, Humphries R, Ward K, et al. Combination therapy with daptomycin, linezolid, and rifampin as treatment option for MRSA meningitis and bacteremia. Diagn Microbiol Infect Dis 2011;71(3):286-90

44. Jaspan HB, Brothers AW, Campbell AJ, et al. Multidrug-resistant Enterococcus faecium meningitis in a toddler: characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. Pediatr Infect Dis J 2010;29(4):379-81

45. Le J, Bookstaver PB, Rudisill CN, et al. Treatment of meningitis caused by vancomycin-resistant Enterococcus faecium: high-dose and combination daptomycin therapy. Ann Pharmacother 2010;44(12):2001-6

46. Elvy J, Porter D, Brown E. Treatment of external ventricular drain-associated ventriculitis caused by Enterococcus faecalis with intraventricular daptomycin. J Antimicrob Chemother 2008;61(2):461-2

47. Kim BN, Peleg AY, Lodise TP, et al. Management of meningitis due to antibiotic-resistant Acinetobacter species. Lancet Infect Dis 2009;9:245-55

48. Stahl JP, Bru JP, Fredj G, et al. Penetration of sulbactam into the cerebrospinal fluid of patients with bacterial meningitis receiving ampicillin therapy. Rev Infect Dis 1986;8(Suppl 5):S612-16

49. Kendirli T, Aydín HI, Hacíhamdioğlu D, et al. Meningitis with multidrugresistant Acinetobacter baumannii treated with ampicillin/sulbactam. J Hosp Infect 2004;56(4):328

50. Sipahi OR, Pullukçu H, Taşbakan M, et al. A case of Acinetobacter baumannii meningitis successfully treated with high dose ampicillin/sulbactam after failure with meropenem. Ankem Dergisi 2006;20:236-8

51. Sayin Kutlu S, Saçar S, Süzer T, et al. Successful treatment of a patient with multidrug resistant Acinetobacter baumannii meningitis with high dose ampicillin-sulbactam. Mikrobiyol Bul 2008;42(2):353-8

52. Ziaka M, Markantonis SL, Fousteri M, et al. Combined intravenous and intraventricular administration of colistin methanesulfonate in critically ill patients with central nervous system infection. Antimicrob Agents Chemother 2013;57(4):1938-40

53. Jiménez-Mejías ME, Pichardo-Guerrero C, Marquez-Rivas FJ, et al. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant Acinetobacter baumannii meningitis. Eur J Clin Microbiol Infect Dis 2002;21:212-14

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54. Ho YH, Wang LS, Chao HJ, et al. Successful treatment of meningitis caused by multidrugresistant Acinetobacter baumannii with intravenous and intrathecal colistin. J Microbiol Immunol Infect 2007;40:537-40

55. Falagas ME, Bliziotis IA, Tam VH. Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence. Int J Antimicrob Agents 2007;29:9-25

56. Pachón-Ibáñez ME, Docobo-Pérez F, López-Rojas R, et al. Efficacy of rifampin and its combinations with imipenem, sulbactam, and colistin in experimental models of infection caused by imipenem-resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2010;54(3):1165-72

57. Karvanen M, Plachouras D, Friberg LE, et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. Antimicrob Agents Chemother 2013;57(1):668-71

58. Wadi JA, Rub MA. Multidrug resistant Acinetobacter nosocomial meningitis treated successfully with parenteral tigecycline. Ann Saudi Med 2007;27(6):456-8

59. Sipahi OR, Bardak S, Ozgiray E, et al. Multidrug resistant (MDR) Acinetobacter baumannii meningitis treated with tigecycline. In: Third Eurasia Congress of Infectious Diseases. Baku, Azerbaijan; 2009

60. Fang G, Weiss W. Comparative efficacy of GAR-936 (GAR), a novel glycylcycline, alone and in combinatiun wirh vancomycin against penicillin-resistant S.pneumoniae (PRPS) experimental memigitis in rabbits. In: Fortieth İnterscience Conference on Antimicrobial Agents and Chemoteraphy. Toronto, Canada; 2000

61. Corpus KA, Weber KB, Zimmerman CR. Intrathecal amikacin for the treatment of pseudomonal meningitis. Ann Pharmacother 2004;38(6):992-5

62. Bray DA, Calcaterra TC. Pseudomonas meningitis complicating head and neck surgery. Laryngoscope 1976;86(9):1386-90

63. Schina M, Spyridi E, Daoudakis M, et al. Successful treatment of multidrug-resistant Pseudomonas aeruginosa meningitis with intravenous and intrathecal colistin. Int J Infect Dis 2006;10(2):178-9

64. Quinn AL, Parada JP, Belmares J, O'Keefe JP. Intrathecal colistin and sterilization of resistant Pseudomonas aeruginosa shunt infection. Ann Pharmacother 2005;39(5):949-52

65. Hooper DC, Strahilevits J. Quinolones. In: Bennett JE, Dolin R, Mandell GL, editors. Principles and practice of infectious diseases. 7th edition. Churchill Livingstone; NY, USA: 2010. p. 487-510

66. Lipman J, Allworth A, Wallis SC. Cerebrospinal fluid penetration of high doses of intravenous ciprofloxacin in meningitis. Clin Infect Dis 2000;31(5):1131-3

67. Krcméry V Jr, Filka J, Uher J, et al. Ciprofloxacin in treatment of nosocomial meningitis in neonates and in infants: report of 12 cases and review. Diagn Microbiol Infect Dis 1999;35(1):75-80

68. Arda B, Zeka AN, Bardak-Ozcem S, et al. Two Cases of Escherichia coli meningitis developing after transrectal prostate biopsy. Mediter J Infect Microb Antimicrob 2012;1:3

69. Tunkel AR, Drake JM. Cerebrospinal fluid shunt infections. In: Bennett JE, Dolin R, Mandell GL, editors. Principles and practice of infectious diseases. 7th edition. Churchill Livingstone; NY, USA: 2010. p. 1231-6

70. Pintado V, Cabellos C, Moreno S, et al. Enterococcal meningitis: a clinical study of 39 cases and review of the literature. Medicine (Baltimore) 2003;82(5):346-64

71. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66(9):1963-71

72. van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351(18):1849-59

73. McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in Gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. Lancet 1980;315:787-91

74. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 2010;23(3):467-92

75. Wang KW, Chang WN, Huang CR, et al. Post-neurosurgical nosocomial bacterial meningitis in adults: microbiology, clinical features, and outcomes. J Clin Neurosci 2005;12(6):647-50

76. Reichert MC, Medeiros EA, Ferraz FA. Hospital-acquired meningitis in patients undergoing craniotomy: incidence, evolution, and risk factors. Am J Infect Control 2002;30(3):158-64

77. Kim HI, Kim SW, Park GY, et al. The causes and treatment outcomes of 91 patients with adult nosocomial meningitis. Korean J Intern Med 2012; 27(2):171-9

78. De Bels D, Korinek AM, Bismuth R, et al. Empirical treatment of adult postsurgical nosocomial meningitis. Acta Neurochir (Wien) 2002;144(10):989-95

79. Dizbay M, Güzel-Tunçcan Ö, Arman D, et al. Factors associated with mortality in nosocomial central nervous system infections. ANKEM Derg 2011;25(1):6-11

80. Fong IW, Ranalli P. Staphylococcus aureus meningitis. QJM 1985;53:289-99

81. Schlesinger LS, Ross SC, Schaberg DR. Staphylococcus aureus meningitis: a broad-based epidemiologic study. Medicine (Baltimore) 1987;66:148-56

82. Jensen AG, Espersen F, Skinhoj P, et al. Staphylococcus aureus meningitis. A review bof 104 nationwide, consecutive cases. Arch Intern Med 1993;153:1902-8

83. Kim JH, Van der Horst C, Mulrow CD, Corey GR. Staphylococcus aureus meningitis: review of 28 cases. Rev Infect Dis 1989;11:698-706

84. Gordon JJ, Harter DH, Phair JP. Meningitis due to Staphylococcus aureus. Am J Med 1985;78:965-9

85. Falco V, Almirante B, Pahissa A, et al. Meningitis caused by Staphylococcus aureus. Analysis of 16 cases. Med Clin (Barc) 1990;94:208-11

86. Pintado V, Pazos R, Jiménez-Mejías ME, et al. Methicillin-resistant Staphylococcus aureus meningitis in adults: a multicenter study of 86 cases. Medicine (Baltimore) 2012;91(1):10-17

87. Seto C, Ikeda A, Ohkawa M. [A case report of urinary tract infection and meningitis caused by methicillin-resistant Staphylococcus aureus (MRSA) after transurethral resection of the prostate]. Nihon Hinyokika Gakkai Zasshi 1999;90(3):466-9

88. Mellon G, Clec'h C, Picard B, et al. Postsurgical meningitis due to multiresistant Acinetobacter baumannii successfully treated with high doses of ampicillin/sulbactam combined with rifampicin and fosfomycin. J Infect Chemother 2012;18(6):958-60

89. Erdem H, Ulu-Kilic A, Kilic S, et al. Efficacy and tolerability of antibiotic combinations in neurobrucellosis: results of the Istanbul study. Antimicrob Agents Chemother 2012;56(3):1523-8

90. Mourvillier B, Tubach F, van de Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. JAMA 2013;310:2174-83

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