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REVIEW

Pragmatic overview on acute bacterial and fungal infections of the central nervous system: a holistic update from diagnosis to treatment

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SUMMARY

Although progress has led to a drop in infections, meningitis still represents a threat worldwide, affecting some areas more than others. As a medical emergency, it requires prompt recognition and treatment. Moreover, diagnosis relies on invasive methods, while representing a tug-of-war with timely therapeutic interventions, since delays are burdened by mortality and life-long sequalae. While counterbalancing the overuse of antimicrobials, it is imperative to assess correct interventions in order to optimize treatments and reduce negative outcomes. Because the drop in mortality and consequences has been consistent, although not as impactful as with other vaccine-preventable diseases, the WHO has traced a roadmap detailing actions to reduce the meningitis burden by 2030. There are currently no updated guidelines, whereas novel diagnostic methods as well as pharmacological interventions are increasing, along with the shifting epidemiology.
In light of the above, this paper wishes to summarize existing data and evidences and suggest potential novel solutions to a complex problem.

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INTRODUCTION

Central nervous system (CNS) infections are considered medical emergencies requiring prompt recognition and treatment, as delays are associated with substantial morbidity, mortality, or long-term sequelae and considerable life-long impact.
Acute CNS infections may be further subdivided into 3 categories, namely meningitis, encephalitis, and abscesses, and may be ascribable to a wide range of pathogens which may penetrate the subarachnoid space via intrinsic (e.g., bloodborne or contiguous spread) or extrinsic (e.g., intraoperative or via devices/malformations causing contamination) pathways and breaches in the blood brain barrier (BBB) (e.g., microhemorrhage or necrosis of surrounding tissue) (Archibald LK, Quisling, 2013; Giovane, Lavender, 2018).

Key words:
Bacterial infection, central nervous system, fungal infections, meningitis.

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Encephalitis is caused mainly by viruses such as herpes simplex virus or varicella zoster virus, which can infect the CNS via intraneural pathways, while enterovirus and arboviruses penetrate the CNS by blood, whereby the infection is localized in the brain parenchyma (a topic beyond the scope of this review).
Meningitis, on the other hand, occurs when pathogens penetrate the subarachnoid space, leading to local inflammation and damage, increased permeability, and eventual disruption and leakage of the BBB due to the elicited immune response and consequential release of inflammatory mediators such as cytokines (Giovane, Lavender, 2018). Meningitis may also arise as a result of non-infectious factors, including certain medications, cancer, and autoimmune diseases (a topic beyond the scope of this review) (WHO, 2021).
Abscesses involve smaller portions of the CNS and may arise from septic emboli deriving from other loci such as endocarditis or lung abscesses, eased by breaches in the BBB. Meningitis may also occur via contiguous spread from adjacent CNS abscesses (Archibald, Quisling, 2013).

Although current advances and vaccination strategies have been beneficial, mortality (especially in developing countries) remains high, with elevated burden worldwide, an opposite trend compared to other vaccine-preventable diseases. For this reason, the WHO recently called to action by elaborating a roadmap to reduce meningitis-related morbidity and mortality by improving awareness, diagnosis, and management (WHO, 2021).
The present review will primarily address bacterial and fungal central nervous system infections, and is aimed at providing an updated, pragmatic overview on currently available data concerning epidemiology and risk factors as well as novel diagnostic tools and advances in treatment options.

Bacterial Meningitis

Bacterial meningitis occurs upon invasion of cerebrospinal fluid (CSF) and surrounding meninges by a variety of bacteria, concurring to local inflammation and release of inflammatory factors. Bacterial infection may arise via the upper airways or by hematogenous or contiguous spread, through breaches in the BBB.
Meningitis may be subdivided further into community-acquired meningitis and nosocomial or healthcare-acquired meningitis, according to the underlying etiological agent and acquisition setting (Tunkel *et al.*, 2017). Despite changes in the epidemiology, bacterial meningitis is still burdened by high morbidity and mortality (WHO, 2021; Ramgopal *et al.*, 2019; Lien *et al.*, 2019; Fuentes-Antrás *et al.*, 2019).

Community-acquired meningitis

Epidemiology and burden. Trends in incidence of bacterial community-acquired meningitis have changed over time, whereby the introduction of vaccines and HIV targeting therapies have concurred to a localized decline in vaccine-targeted bacterial infections, especially in well-resourced countries (Zunt *et al.*, 2018, van de Beek *et al.*, 2021). However, incidence was reported to be globally on the rise with elevated burden and mortality despite an overall 21% decrease in mortality (Zunt *et al.*, 2018). This is far behind other vaccine-preventable decreases, estimated around 57% to over 90% (Zunt *et al.*, 2018). For this reason, WHO has elaborated a roadmap to defeat meningitis by 2030 in order to tackle the 4 leading causes of bacterial meningitis (WHO, 2021).
Indeed, current epidemiology has undergone a shift as a result of vaccination coverage of specific serotypes, whereby the introduction of pneumococcal and meningococcal conjugate vaccines has substantially reduced the burden of bacterial meningitis. In line with this, rates of *Haemophilus influenzae* type B, a leading cause of pediatric meningitis in the pre-Hib vaccination era (Hib), have shown a substantial decrease (McIntyre *et al.*, 2012).
Incidence varies according to season and age. *Streptococcus agalactiae* (Group B streptococci) and *Escherichia coli* affect newborns and are subsequently replaced by *Streptococcus pneumoniae* and *Neisseria meningitidi*s by the sixth week of life (Van de Beek *et al.*, 2016).
S. pneumoniae remains the most common bacterial agent, followed by N*eisseria meningitidi*s and *Listeria monocytogenes* (van de Beek, 2016; Mylonakis *et al.*, 1998).
However, increases in infections and meningitis due to serotypes that have not been included in vaccine products, such as those occurring in the cases of HiB and *Streptococcus pneumoniae*, have recently been reported in some countries, as well as increases in serotypes of meningococcal diseases (van Kessel *et al.,* 2019; Parikh *et al.,* 2020; Koelman *et al.,* 2020; van de Beek *et al.*, 2021; Li *et al.*, 2022; Taha S *et al.,* 2022). Increases in *Streptococcus agalactiae* have also been reported in some parts of the world (van Samkar *et al.*, 2016). An overview of the main bacteria responsible for infections along with risk factors and vaccines are reported in *Table 1*.

Serotyping. Anti-pneumococcus vaccination strategies have drastically reduced vaccine serotype related meningitis in Europe and North America. This said, replacement of other non-vaccine serotype infections has been reported, following the introduction of the 7-, 10- and 13-valent pneumococcal conjugate vaccines, along with changes in antimicrobial susceptibilities of strains (Li *et al.*, 2022; Koelman *et al.*, 2020). Indeed, multidrug resistant strains in some regions deserve particular attention, and higher levels of prevention and attention are required in order to detect serotype shifts and changes in antibiotic resistance. Novel approaches and vaccine strategies (vaccine with more serotypes included and different target population) are thus required in order to target the WHO road map goals.
The introduction of meningococcal vaccination back in 2000 led to a drop in Meningococcal C disease. However, the serogroup was substituted by other Non-C serogroups. In particular, the recent emergence of ST 11 hyper-virulent meningococcal group W clone has driven many countries to shift from monovalent meningococcal C to quadrivalent ACWY conjugate vaccines as national immunization programmers were updated (Parikh *et al.*, 2020).
Knowledge of local epidemiology and shifts are therefore crucial in order to target appropriate interventions in a timely manner (Taha *et al.*, 2022) as novel vaccination interventions will become available (https://www.pfizer.com/news/press-release/press-release-detail/us-fda-accepts-review-biologics-license-application-pfizers).

Risk factors. Common risk factors for the acquisition of community-acquired meningitis include immuno-

Table 1 - *Overview of the main responsible and risk factor for bacterial meningitis along with vaccines and emerging resistance.*

Pathogen	*Transmission*	*Population affected*	*Risk factors (Van de Beek et al.)*	*Available licensed vaccines*	*Emerging resistance*
S. agalactiae	Vertical transmission mother to child, Horizontal transmission through nosocomial sources, nonmaternal caregiver, possibly infected human milk (Tavares *et al.*, 2022)	– Neonates/ infants	Maternal colonization with Group B Streptococci, HIV infected mothers, preterm/ low weight birth, preterm labor, prolonged rupture of membranes; intrapartum fever (Tavares *et al.*, 2022)		A singular capsulated serotype III GBS clone, (hypervirulent clonal complex 17 (CC17), Serotype III type 283, Asia, foodborne (Tan *et al.*, Neurology 2016, van Samkar *et al.* Neurology 2016)
E. coli		– Neonates/ infants	Diabetes mellitus, alcoholism, cirrhosis, HIV infection, Chronic Obstructive Pulmonary Disease (COPD), chronic organ dysfunction, rarely with human T-lymphotropic virus 1 (HTLV-1), Marfan syndrome, hemochromatosis, myelodysplasia, and B-cell lymphoma (Bichon A, *et al.*, 2018; Kohlmann R, *et al.*, 2015)		
N. meningitidis		– Neonates/ infants, – Infants – Adults	Complement system / properdin deficiencies, CSF leak, nasopharingeal colonization	Men ACWY 4C Men B	Emerging resistance to penicillin, RIFA, FQ. Emerging ST11 hypervirulent clones
S. pneumoniae		– Adults – Infants >1month (Adriani et al., 2015)	Splenectomy/hyposplenic state, chronic kidney/ liver disease, HIV infection, alcoholism, hypogammaglobulinaemia, diabetes mellitus, immunosuppressive drugs, Mannose-binding lectin deficiency (MBL2) - low MBL2 blood levels (Chen *et al.*, 2019), organ transplants, CSF leak, nasopharingeal colonization	Polysaccharide PPV 23 Conjugate PCV 10-13 valent	Non-PCV-13 serotypes
H. influenzae		– Children (2-18 yrs)	Diabetes mellitus, alcoholism, splenectomy or asplenic states, multiple myeloma and immune deficiency/ hypogammaglobulinaemia, CSF leak	Type B monovalent	Non-typeable and antibiotic resistant
L. monocytogenes		– Neonates – Elderly	elderly patients (>60 years), acquired immunodeficiencies, diabetes, cancer immunosuppressive drugs, organ transplant		
Salmonella		– Children – Adults	HIV (low CD4 count)		

suppression (iatrogenic, pathogen-induced or host-related) along with other predisposing factors related to comorbidities. Immune system impairment, either of iatrogenic origin (e.g., use of immunosuppressive medication or splenectomy), disease-induced (e.g., cancer, diabetes mellitus, alcoholism, human immunodeficiency virus – HIV – infection) or hereditary (e.g., hypogammaglobulinemia, properdin or late complement component deficiency, common variable immunodeficiency), increase the risk of bacterial meningitis. Functional asplenia (e.g., during leishmaniosis and so on) might be a risk factor for acquiring community-acquired bacterial meningitis (van de Beek *et al.*, 2016; Block *et al.*, 2022; Adriani *et al.*, 2015).
Further factors include age extremities or host-related conditions such as structural defects leading to increased permeability of the brain barrier, along with colonization (Adriani *et al.*, 2015). As a result, the underlying causative pathogens may vary according to age or to the underlying medical condition predisposing to infection. Associations of risk factors are collectively reported in *Table 1*.

Clinical Presentation. Clinical signs and symptoms have been ascribed to the classical triad, namely fever, neck stiffness and headache/altered mental status. However, approximately 40-50% of adults and children present with a combination of the three (van de Beek *et al.*, 2004). Moreover, symptoms often overlap with other conditions, such as autoimmune diseases or subarachnoid hemorrhage (van de Beek *et al.*, 2021).
Since meningitis is a medical emergency requiring immediate treatment, clinical recognition is crucial for prompt appropriate management. In this sense, a crucial role is also played by awareness and experience, and centers having managed more than 4 complex cases present with a reduced mortality (Contou *et al.*, 2021; Menichetti *et al.*, 2018). Supporting the importance of awareness, some specific clinical features may provide clues concerning the causative pathogen. Meningococcal disease, for instance, may present with non-blanching petechial or purpuric rash (*Figure 1*) though the finding may be absent in 37% of cases (Attia *et al.*, 1999).
Initial presentation with influenza-like illness, fever, muscle aches and vomiting may be indicative of meningococcal infection before meningitis becomes clinically apparent, along with rapid evolution and progression towards severity within hours (Young *et al.*, 2018). Sepsis may also precede by 12-24 hours. Hence, specific manifestations of meningitis may be less evident as sepsis signs may be predominant. Underlying conditions and predisposing factors may also limit recognition (Young *et al.*, 2018), as well as age, whereby signs may be less evident among the elderly (Gorse *et al.*, 1984).

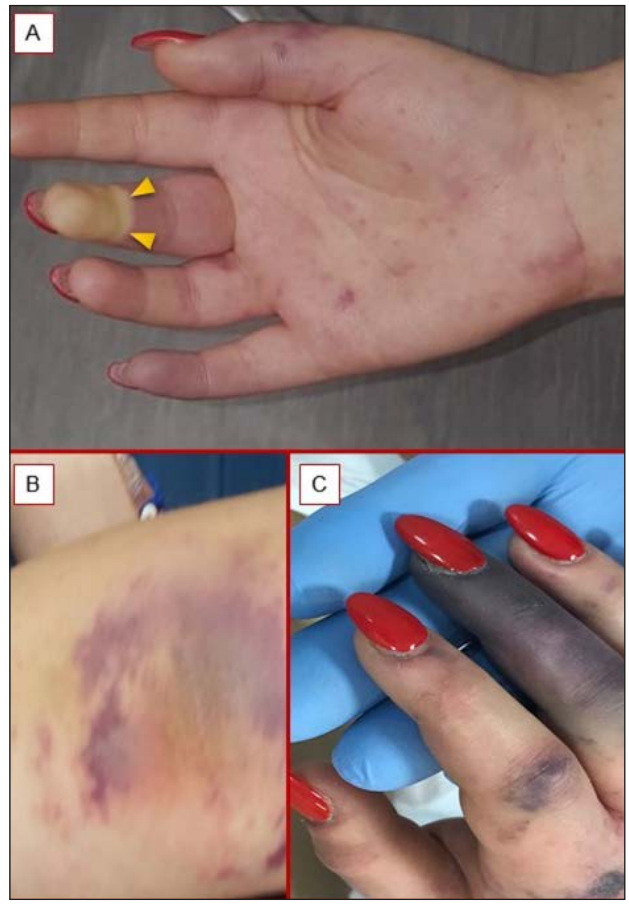

Figure 1 - *Cutaneous lesion during meningococcal disease. Panel A - hand petechiae with skin hypoperfusion area (arrowheads). Panel B - Purpura fulminans on the arm. Panel C - Pre-necrotic evolution of skin lesions.*

Predisposing conditions suggestive of pneumococcal meningitis include extra-meningeal foci of infection (otitis, mastoiditis, sinusitis, cochlear implants, pneumonia, endocarditis) along with other conditions (cerebrospinal fluid leak, asplenia, immunosuppression). Rash can also be observed in patients with meningitis caused by *S. pneumoniae* infection. Moreover, since pulmonary involvement along with bloodstream infections may have preceded meningitis in the case of pneumococcus, it is likely that patients present with symptoms related to such infections, including chills and signs and symptoms ascribable to respiratory tract infections. Other more specific symptoms may appear gradually in time (Young *et al.*, 2018; Carpenter *et al.*, 1962).
Travel may be associated to *Listeria* spp. infections along with other host-related features (age ≥50 years-old, an immunocompromised state, diabetes, alcoholism, cirrhosis, end-stage renal failure, malignancy, etc.) (Young *et al.*, 2018; van de Beek *et al.*, 2021). Seizures or focal neurological deficits, such as aphasia and hemiparesis, or with cranial nerve palsies

may also be present. Kernig and Brudzinski signs may also be present, though they were shown to have poor sensitivity (5-30%) in the diagnosis bacterial meningitis (Brouwer *et al.*, 2012).
Clinical signs of shock, including tachycardia, poor peripheral perfusion, tachypnoea, oliguria, confusion, and hypotension may be present. Rarely, invasive disease may take the form of focal infection, such as arthritis, pneumonia, conjunctivitis, pericarditis, or endophthalmitis (Nadel *et al.*, 2007).

Diagnostic workup. Initial diagnostic assessments are crucial in order to ensure the correct management of patients. A consistent proportion of cases remain without a microbiological diagnosis despite it being considered a medical urgency (Saha *et al.*, 2020). There are currently no biochemical parameters enabling to diagnose meningitis, and scores and predictive models offer low additional value (Viallon *et al.*, 2016; Van de Beek *et al.*, 2016). As diagnosis is postulated based on clinical presentation, cerebrospinal fluid analysis provides the basis for microbiological assessments (Viallon *et al.*, 2016).
Though the procedure is considered riskless in most cases, safety of lumbar puncture (LP) should be assessed, especially upon risk of complications due to the procedure.
Contraindications to LP include the following circumstances:
– The presence of a mass lesion with a shift of the brain median line.
– Bleeding disorders: coagulopathies due to anticoagulant use, severe thrombocytopenia or an uncorrected bleeding diathesis (Young *et al.*, 2018; Archibald, Quisling, 2013; van de Beek, 2016, 2021).

Tendency to bleed. Platelet count below 50,000/µL, a quick test below 50%, an INR of >1.8, and a clearly pathologically activated partial thromboplastin time (aPTT) are considered contraindications for LP. Platelet aggregation time or bleeding time are suggested surrogates by recently published German guidelines on LP (Tumani *et al.*, 2020). In the case of a patient with fewer than 50,000 platelets, if LP is mandatory, the clinician may proceed to the transfusion of platelets prior to LP, whereby thrombopenia below 10,000/µL is an absolute contraindication.
Caution is advised in patients taking anticoagulants; INR values below 1.5 according to European Society of Anesthesiology Guidelines (Gogarten *et al.*, 2010) are indicated.
In case of emergency LP procedure, administration of intravenous vitamin K, 5 mg, at least 6-8 hours prior to puncture is indicated to reverse the effects of warfarin. If greater urgency is necessary, additional treatment with prothrombin complex concentrates can rapidly return the value of INR below 1.5 (Dodd *et al.*, 2018).
There is a paucity of available evidence concerning NOACs (new oral/or non-vitamin K-dependent anticoagulants) antidotes. For this reason, in patients undergoing NOAC therapy, and if there is a strong suspicion of meningitis, it is mandatory to begin antibiotic therapy, while LP should be postponed for 48 hours. Case reports concerning administration of anticoagulant antidotes are available (Agosti *et al.*, 2018), but consultation with a hematologist is also advised (Dodd *et al.*, 2018).

Imaging. Patients presenting with increased ICP or suspicion (includes fluctuating or deteriorating levels of consciousness; unequal, dilated or poorly reacting pupils; focal neurological signs or abnormal posturing; seizures; and papilla-edema) and risk of cerebral herniation and complications may be considered for imaging.
Imaging by means of computed tomography (CT) scan may provide support in such cases, though neuroimaging has been identified as risk factor for a delayed appropriate treatment and poor disease outcome (Glimåker *et al.*, 2015; Glimåker *et al.*, 2018). Hence, CT scan should not delay treatment, and antimicrobial treatment and adjunctive dexamethasone therapy should be initiated before sending the patient for a CT scan as a delay in appropriate antibiotic administration may lead to negative outcome.
A recent revision by van De Beek suggests the following criteria in order to guide selection of patients for CT scan prior to LP (van de Beek *et al.*, 2021):
– new-onset seizures, focal neurological deficits;
– immunocompromised state (e.g., HIV/AIDS infection or immunosuppressive medication after organ transplantation);
– moderate-to-severe impairment of consciousness.
Guidelines lack alignment concerning imaging prior to LP and no clear indication is available concerning signs leading to imminent brain herniation. However, studies referring to guidelines operating a more stringent selection of patients undergoing CT scan prior to LP have shown shorter time to therapy and improved outcome (Glimaker *et al.*, 2018; Young *et al.*, 2018).
Blood cultures should be drawn and may be especially helpful if LP is not feasible. Positivity is observed in 75% of cases (van de Beek *et al.*, 2016) presenting from the community.
Treatment with dexamethasone and antibiotics (preferably also bactericidal non bacteriolytic) should be administered without delay also in case of CT scanning (Young *et al.*, 2018). Efficiency of pathogen recovery drops in case of prior administration of antibiotics.

Laboratory assessments

Cerebrospinal fluid testing. CSF analysis is a key step in the management of CNS infections. Assessments

include microbiology and clinical biochemistry testing enabling to define the underlying cause of CNS disorder and etiology. As of today, culturing of CSF it is still considered the "gold standard" for the diagnosis of bacterial meningitis, with 85% positivity rate, while allowing antimicrobial sensitivity testing of the identified pathogen (Brouwer *et al.*, 2010; van de Beek *et al.*, 2021).
The need for speed is counterbalanced by the invasiveness of the test and lack of alignment from available guidelines as to contraindications for puncture, though generally it should be performed within 1 hour of suspected diagnosis of meningitis without awaiting further investigations (Young *et al.*, 2018; Tumani *et al.*, 2020; Laible *et al.*, 2016).

CSF parameters. Normal CSF presents as a clear, colorless liquid, with normal parameters defined as number of cells not exceeding 5 cells/μL, glucose/blood ratio =50-75%, proteins =15-45 g/L.
An overview of parameters and their changes in different etiologies is depicted in *Figure 2*. Generally, CSF examination, if accurately performed, will yield typical abnormalities represented by increased white blood cell count (pleocytosis), decreased CSF glucose/blood glucose ratio, and increased protein levels in most cases (van de Beek *et al.*, 2021). Derangements were used to differentiate between different etiological causes.

Cell count. CSF cell count should be carried out within 1-2 hours of collection as further delays may result in a false low cell assessment because of cell lysis or adherence of cells to the walls of the specimen tube or coagulation. Collection tube type is also crucial.
However, a consistent body of evidence is indicative of absence of abnormal cell counts, as bacterial infection may occur also in the absence of pleocytosis and is associated with higher morbidity and mortality (Troendle *et al.*, 2019). Indeed, 2%-10% of bacterial meningitis do not present with pleocytosis (van Soest *et al.*, 2022; Durand *et al.*, 1993; van de Beek *et al.*, 2016) and reaches 15% in pediatric cases (Viallon *et al.*, 2011). The absence of cells may be due to an immunocompromised state along with previous antibiotic treatment. Hence, lack of cells should not lead to underestimate suspicion of meningitis or encephalitis upon clinical suspicion.
In particular, other clues related to the clinical presentation or abnormalities in CSF analyses should be carefully considered as a whole, and microbiological information pointing to a CNS infection should be pursued when necessary (Erdem *et al.*, 2017).

Appearance. CSF appearance may also be indicative of an infective process, though this may not always be sufficient to enable a differential diagnosis. Normal CSF is clear and colorless, whereas a purulent, turbid appearance may indicate infection.
A yellow/orange/pink tinge, termed xanthochromia, may occur due to red blood cells (RBC) lysis or CSF protein concentrations above 150 mg/dL. The presence of red blood cells may be due to subarachnoid hemorrhage or through a traumatic tap, and the evaluation of CSF appearance is important once sequential specimen tubes of CSF are obtained. Sometimes red blood cells in the CSF might be due to necrotizing encephalitis such as herpes simplex-1 encephalitis.
Traumatic lumbar punctures are usually defined as CSF specimens with ≥500 red blood cells/mm^3. WBC and RBC CSF contamination may be resolved by "subtracting" the contribution of peripheral blood introduced during puncture by calculation (see *Box 1*). A tinge may disappear from successive tubes, indicating contamination.

RBC count performed successively. In case of few cells in the CSF and presence of RBC, a differential count should be performed. RBC to WBC peripheral blood

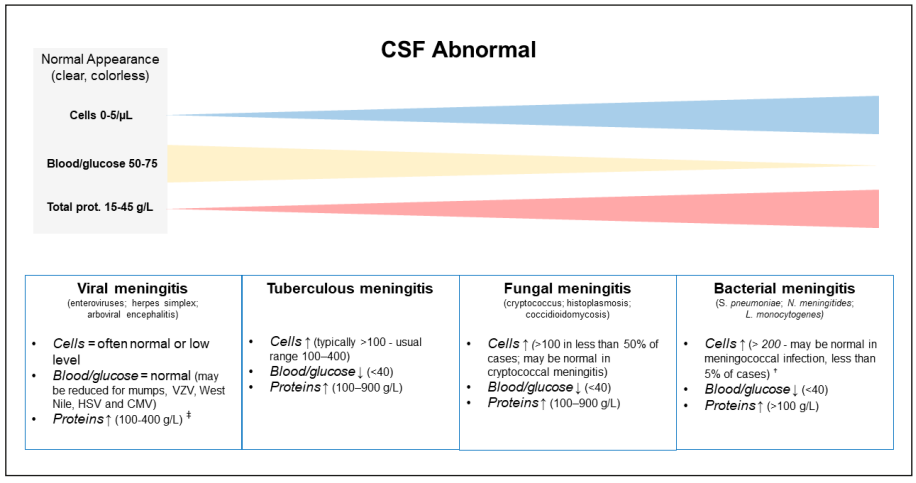

Figure 2 - *CSF parameters in viral, tuberculous, fungal and bacterial meningitis.*

Legend: †: Excluding Listeria meningitis, where CSF leukocytes are often <1000 cells/μL and CSF may be lymphocytic; ‡: Excluding HSV and VZV meningitis, where protein may be ≥1.0 g/L; CSF: cerebrospinal fluid; CMV - cytomegalovirus; HSV: herpes simplex virus - VZV: varicella zoster virus (Young N et al., 2018; Troendle M, 2019; Archibald LK, Quisling RG, 2013).

Box 1 - *Example of RBC count normalization.*

Corrected WBC = Reported CSF WBC [(WBC in peripheral blood x RBC in CSF) / (RBC in peripheral blood)]

Example:

CSF count yields 15 WBC /mmc and 10.400 RBC / mmc

Peripheral blood WBC/RBC is 1:800, hence the WBC due to traumatic tap are 10.400/800 : 13 → the real WBC in CSF are 15-13: 2 cells.

Legend: CSF: cerebrospinal fluid; RBC: red blood cells; WBC: white blood cells.

ratio is then used to "normalize" the CSF WBC to RBC ratio expected to be contaminated, since peripheral blood contains more cells compared to uncontaminated CSF (Greenberg *et al.*, 2008). Online tools are available for correcting.

Glucose. CSF glucose levels are the result of transport through the blood-brain-barrier (BBB) and rate of consumption within the CNS. Normal CNS glucose/blood values are considered to be on average 60-75% of blood glucose levels (Rand *et al.*, 2004; Archibald, Quisling, 2013) and 0.6 considered a cut-off value for abnormality (Hegen *et al.*, 2004). A drop suggests abnormal consumption and the presence of pathogens, though this may not always be the case. Moreover, CSF/serum glucose ratio retains accuracy when serum glucose values are within 89 and 115 mg/dL (Skipper, Davis, 1997), whereby the ratio drops with increasing glucose values. Upon blood glucose exceeding 5.5 mmol/L (100 mg/dL), CSF glucose levels begin to plateau. Consequently, CSF/serum ratio may be less accurate in hyperglycemic states such as in the case of diabetes and sepsis patients, as in the case of meningitis cohorts (Hegen *et al.*, 2004).

Proteins. Due to passage impedance of the BBB, CSF protein levels are usually below 40 mg/dL, though derangements and increased permeability due to inflammation and infections tend to raise CSF protein levels (Archibald, Quisling, 2013). Pathological levels are considered as protein values above 100 mg/dL (Hasbun, 2022). Like glucose levels, CSF protein levels due to contamination from traumatic tap should also be corrected (Seehusen *et al.*, 2003).

Opening pressure. The physiologic value of CSF opening pressure is 6-20 cmH_2O. In most central nervous system infections there is evidence of incremented CSF pressure.

The pressure should be measured with the patient in lateral decubitus. The most used device for the measurement of CSF opening pressure is the water column manometer, even if the use of a digital manometer has recently been proposed, which could ensure the same accuracy with less time required than the classic manometer (Sekhri *et al.*, 2019; Heider *et al.*, 2022).

Normal opening pressure ranges from 1 to 10 cm H_2O in young children, 6-20 cm H_2O after 8 years of age, and up to 25 cm H_2O in obese patients. The level should fluctuate with respiration and can be elevated by the Valsalva maneuver.

There are some evidences about the importance of CSF opening pressure measurement in cryptococcal meningitis. In this case, CSF pressure is often above 25 cmH_2O and it has been demonstrated that CSF pressure correlates with the fungal burden and with the occlusion of Pacchioni's foramina (Bicanic *et al.*, 2009).

Increased CSF pressure in cryptococcal meningitis may lead to sudden visual loss due to ischemic lesion of optical nerves and death; for this reason, it could be useful, during the treatment of the Cryptococcal meningitis, to do serial lumbar punctures to evaluate fungal clearance and reduce CNS pressure.

Microbiology assessments. Upon clinical suspicion of meningitis, microbiological assessments should be performed immediately, ideally prior to antimicrobial therapy. CSF samples, where possible, should be accompanied by adequate blood culture sets for testing. Blood cultures are positive in up to 75% of patients with community-acquired bacterial meningitis, depending on causative pathogen and time of presentation. Gram staining and culture of skin lesions can identify the pathogen in patients with suspected meningococcal disease, particularly useful when a lumbar puncture is contraindicated because of coagulation disorders (van de Beek *et al.*, 2021).

Initial CSF assessments include immediate Gram staining and plating of CSF specimens in order to identify the underlying causative pathogen and assess susceptibility to antimicrobial therapy.

Gram staining is positive in approximately 75% of patients with acute bacterial meningitis, though the yield varies according to the underlying pathogen. Recovery percentages may range from 87-90% of untreated patients with pneumococcal meningitis, 86-96% in case of *H. influenzae*, approximately 75-82% in cases due to *N. meningitidis* (Herndon, Brumback, 1989; Nigrovic, 2008), and 67% positivity in children. Positive gram staining for *L. monocytogenes* is fairly rare (less than 25% of cases). Ideally, samples should be drawn before antimicrobial treatment, as recovery efficiency drops dramatically to 50% in pre-treated patients.

Syndromic panels are available for multiple target testing, including the most commonly encountered pathogens in community-acquired meningitis and encephalitis. They rely on molecular biology techniques, implying greater sensitivity driven by the presence of nucleic acid. Increased yield is observed even in the case of previous pre-treatment, and there-

fore may represent a valid tool for improved detection without culturing.
These novel molecular techniques may ensure early detection, avoiding unnecessary antibacterial coverage (Nabower *et al.*, 2019; Moffa *et al.*, 2020; Tansarli, Chapin, 2020). Sample to result molecular methods are available for specific syndromes, including community-acquired meningitis (Feagins *et al.*, 2020). Other syndromic panels on different samples detect a wider array of pathogens from positive blood cultures (Peri *et al.*, 2022; Bassetti *et al.*, 2022). Direct detection from whole blood is limited to a few methods (Paggi *et al.*, 2021).
A growing body of evidence supports the benefits of syndromic testing both for decreased time to result and length of hospital stay as well as better management (Cailleaux *et al.*, 2019; Nabower *et al.*, 2019; Moffa *et al.*, 2020; O'Brien *et al.*, 2018; DiDiodato, Bradbury, 2019).
Recent meta-analyses point toward elevated sensitivity and specificity, indicating the usefulness of tests as adjunctive tools in the management of patients (Tansarli, Chapin, 2019). However, most commercially available panels lack nosocomial etiological targets.
This said, given the incidence, along with the burden of sequelae and mortality, it is both convenient and efficient to put in place the most stringent testing strategy (Duff *et al.*, 2018).

Table 2 - *Specific culture media for the most common meningitis bacterial pathogen agents.*

Pathogen	*Specific culture media*
S. pneumoniae	Blood agar
H. influenzae	Chocolate agar
N. meningitis	Thayer-Martin agar
L. monocytogenes	Blood agar
S. aureus	Salt-mannitol agar

The WHO roadmap for defeating meningitis by 2030 has set out goals aimed at improving the diagnosis of meningitis at all levels of care through the development of and access to diagnostic assays. For this aim, it required that all important causes of meningitis such as tuberculosis, cryptococcosis, enteric bacteria and viruses such as Enterovirus, should be targeted by available diagnostic tests, along with the four priority bacterial pathogens (meningococcus, pneumococcus, *Haemophilus influenzae* and group B streptococcus) (Defeating meningitis by 2030: a global road map. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO).
The confirmatory test for identification of the causative microorganism is growth in specific culture media. *Table 2* lists the specific culture media for the most common meningitis bacterial pathogen agents. *Figure 3* shows a pragmatic flow chart of initial testing workup in suspected community-acquired meningitis. The next future for the molecular diagnosis of community-acquired meningitidis will be comprehensive molecular testing to identify all microorganisms causing this disease, such as amplificon and sequencing 16srRNA (Welinder-Olsson *et al.*, 2007), and/or next generation sequences (NGS) methodologies (Morsli *et al.*, 2022).

Antigen testing. Bacterial antigen testing in cerebrospinal fluid can provide a rapid diagnosis but was previously found to have little additional value compared with cerebrospinal fluid culture and Gram stain, with sensitivities as low as 50% (Parlakay *et al.*, 2013; Picazo *et al.*, 2013; Samra *et al.*, 2003). More recent studies have reported higher performances with newer tests in meningococcal diagnosis (Haddar *et al.*, 2020) offering a valuable tool in low-income countries.

Latex agglutination. Latex agglutination can be used to rapidly determine the causative microorganism. Com-

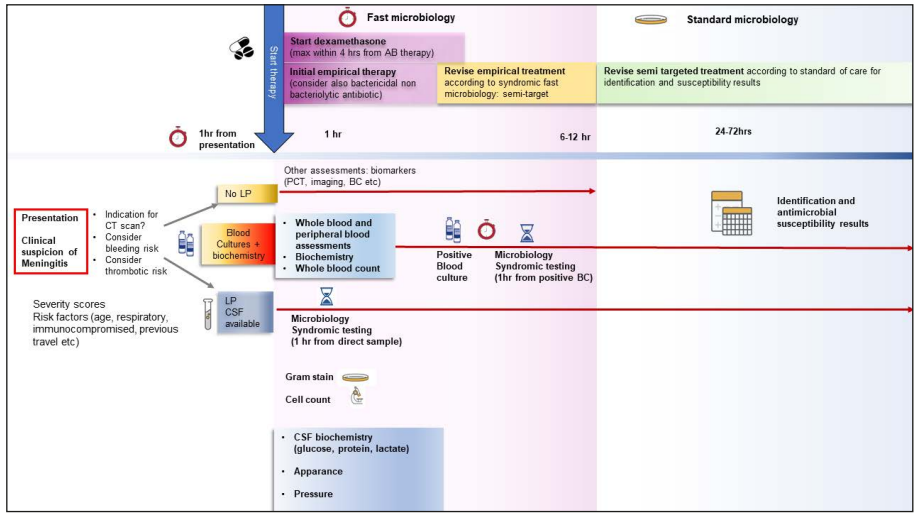

Figure 3 - *Pragmatic flow chart of initial testing work-up in suspected community acquired meningitis*

mercially available kits for detection of *H. influenzae*, *S. pneumoniae*, and 5 serotypes of *N. meningitidis* as well as other species, such as *E coli K1*, are available with different reported sensitivities in CSF according to the causative microorganism: *H. influenzae* 78-100%, *S. pneumoniae* 59-100%, and *N. meningitidis* 22-93% (Brouwer *et al.*, 2010; Hayden, Frenkel, 2000; Mein, Lum, 1999; Archibald, Quisling, 2013).
Sensitivity of latex agglutination tests decreased from 60% to 9% in patients in whom antibiotic treatment was started before the lumbar puncture was performed. Due to the limited impact of latex agglutination on management and the low performance (below 85% of WHO-advised range) (WHO, 2021), guidelines do not advise carrying out these tests for the diagnosis of bacterial meningitis when other methods such as Gram staining are available (Brouwer *et al.*, 2010; van de Beek *et al.*, 2016). Moreover, the limited range of pathogens implies limited use in many contexts, especially when nosocomial off-panel pathogens may be the underlying cause (Feagins *et al.*, 2020).

Other biochemistry assessments

CSF Lactate. CSF lactate may help discriminate bacterial from aseptic meningitis, although values are susceptible to antibiotic treatment: as a result, sensitivity drops in pre-treated patients have been reported and are highlighted in guidelines (van De Beek *et al.*, 2016, 2021). Elevated CSF lactate concentration >3.5 to 4.2 mmol/L is often reported in bacterial rather than in aseptic meningitis, and two large meta-analyses have concluded that elevated CSF lactate concentration is better than the CSF white blood cell count, glucose, or protein in differentiating bacterial meningitis from aseptic meningitis (sensitivity of 93% and 97% and specificity of 96% and 94%, respectively) (Huy *et al.*, 2010; Sakushima *et al.*, 2011). This said, its additional value is still uncertain, although recently published retrospective studies suggest increased performance in association with other parameters (de Almeida SM *et al.*, 2019). Lactate values are susceptible to decay at room temperature and should be analyzed promptly (within 1 hour). An interesting trial recently assessed the use of blood gas analyzers on neurosurgical patients with comforting results, by using cut-offs of 4.2 mmol/L (Stephani *et al.*, 2021).
The following cut-off values may help the clinician in distinguishing bacterial versus viral infections:

- Adults: values >6 mmol/L discriminate bacterial meningitis from partially treated meningitis (4-6 mmol/L) and aseptic meningitis (<2 mmol/L) (Dashti *et al.*, 2017).
- Danish prospective cohort study: 3.5 mmol/L cut-off yields a sensitivity of 96% and specificity of 85% (Buch *et al.*, 2018).

Lastly, an interesting performance was observed in a study assessing combined data from CSF lactate and PCT for the diagnosis of bacterial meningitis (Li *et al.*, 2015).

CSF Procalcitonin (PCT). Procalcitonin levels increase during bacterial infections, while lower levels are correlated to the presence of viral infections.
Elevated CSF procalcitonin levels have been found in central nervous system infections, possibly as a result of both blood brain barrier disruption, leading to increased leakage of serum PCT along with increased serum PCT levels during bacterial infections and sepsis (Halvorson *et al.*, 2017).
Assessment of PCT levels may therefore provide further support in the discrimination between viral and bacterial infections of the central nervous system (Velissaris *et al.*, 2018).
Both serum and CSF PCT values were reported to have optimal performance in the discrimination of bacterial from aseptic meningitis, as opposed to Gram stain and culture (Makoo *et al.*, 2010). A review analyzing data on PCT serum and CSF data, however, concluded on the usefulness of only serum PCT assessment (Vellisaris *et al.*, 2018). No further conclusions could be drawn concerning CSF PCT, as data report variable performance of CSF PCT using different thresholds (0.057 ng/mL -0.15 ng/mL). At CNS level, however, brain tissue PCT secretion mechanisms are still uncertain and the role of PCT itself in the diagnosis of intracranial infection is yet to be clarified. Conversely, cranial infections are localized, hence serum PCT may be less specific (Wang H, 2020). Consequently, both serum and CSF PCT may be useful markers, although CSF PCT may supposedly yield better results (Samsudin, Vasikaran, 2017; Zhu *et al.*, 2019; Zhang *et al.*, 2019). Conflicting data from studies indicate there is still space for further validation, as other findings suggest serum PCT may provide superior value (Shen *et al.*, 2015).
PCT assessments relative to meningitis hence show limitations due to lack of specificity related to bacterial meningitis, as elevated levels are also found in other bacterial infections, such as pneumonia, acute otitis media, and sepsis. Moreover, PCT levels are susceptible to previous antibiotic use, leading to poorer performance in patients undergoing pre-treatment with antibiotics (Kim *et al.*, 2021).

Cytokines. Dysregulated immune response is typically associated with severe infections, whereby imbalances of pro- and anti-inflammatory cytokines concur to severity. As a result, several studies have attempted to determine the role of cytokine assessment in both serum or CSF in order to achieve differential diagnosis of bacterial and viral meningitis while elaborating prognostic values for outcome (Krebs *et al.*, 2005; Pinto Junior *et al.*, 2011; Takahashi *et al.*, 2014; García-Hernández *et al.*, 2016; Vázquez *et al.*, 2012; Grandgirard *et al.*, 2013; Kępa *et al.*, 2014). El-

evated CSF pro-inflammatory cytokines, namely IL-1β, tumor necrosis factor (TNF)-α, and IL-6 were found in patients with bacterial meningitis undergoing neurosurgery (Liu *et al.*, 2015). A meta-analysis found potential discriminatory power of CSF TNF-a and IL-1b for bacterial meningitis from aseptic meningitis (Panato *et al.*, 2014). IL-6 CSF levels may also be indicative of different etiologies. Cut-off levels of 64.4 pg/dL can distinguish bacterial meningitis according to Takahashi *et al.* (Takahashi *et al.*, 2014) while CSF IL-6 concentrations >90 pg/dL can diagnose bacterial meningitis, with reported sensitivities and specificities of 100% and 95%, respectively, in adults, whereas concentrations of 1000 pg/dL or above may help discern bacterial meningitis from aseptic meningitis in children, with sensitivity of 96% and specificity of 51% (Vázquez *et al.*, 2012; Hsieh *et al.*, 2009) when tested by enzyme-linked immunosorbent assay technique upon suspicion of meningitis. Discrepancies in cut-off values may be due to the use of different measurement devices for each study (Takahashi *et al.*, 2014). However, a recent report found elevated CSF cytokine levels in both viral and bacterial meningitis, while serum cytokine levels elevations could be seen in bacterial but not in viral infection in children, concluding on the lack of discriminatory power of CSF cytokine levels (Xu *et al.*, 2020).

Treatment and management

As a medical emergency, meningitis requires prompt treatment, advised and endorsed by guidelines (van de Beek *et al.*, 2016). As a result, European guidelines support administration of antimicrobials within 1 hour from hospital presentation, even if a diagnosis is still ongoing and LP is delayed (e.g., due to CT ascertainments) (van de Beek *et al.*, 2016). This said, there is a paucity of information concerning indications of early and immediate administration of antibiotics, especially in the pre-hospital setting (Young *et al.*, 2018), as the impact of antimicrobial treatment still lacks study data. In this setting, fast microbiology could offer guidance when patient conditions may allow withholding antibiotics until result, or guide treatment in the fastest possible way (Trujillo-Gómez *et al.*, 2022). All these aspects will be discussed in this section.

Dexamethasone. The use of glucocorticoids is advised in order to reduce neurological sequelae and death in bacterial meningitis. Corticosteroid treatment (dexamethasone) acts by reducing the inflammatory response and tissue damage. A consistent body of evidence suggesting improved outcomes was included in a Cochrane review assessing the impact on sequelae and mortality upon adjunctive treatment (Brouwer *et al.*, 2015). A significant reduction in mortality was observed when early dexamethasone is administered as adjunctive treatment in *S. pneumoniae*-sustained meningitis in adults. While adjunctive treatment was significant only in reducing hearing loss and other neurological sequelae, with no impact on mortality in children with *H. influenzae* meningitis, no significant effect was seen for *N. meningitidis* sustained infections. This was recently debated by Van De Beek *et al.* (van de Beek *et al.*, 2022) as the latter studies were not powered to assess and impact per pathogen. As a result, albeit not demonstrating a significance on impact, adjunctive treatment did, however, have beneficial effects on neurological and hearing outcomes in meningococcal meningitis (de Gans, van de Beek, 2002).

Dexamethasone treatment is therefore advised in the event of *S. pneumoniae* meningitis, although the benefits can be extended to non-pneumococcal pathogens such as *H. influenzae* and *N. meningitidis*. (van de Beek *et al.*, 2022). Currently available guidelines suggest starting all adult patients on 10 mg of intravenously administered dexamethasone treatment every 6 hours, before or at the same time as antibiotic administration. Treatment should be continued for at least 4 days, regardless of microbial cause, except *L. monocytogenes* (Tunkel *et al.*, 2004; van de Beek *et al.*, 2016; McGill *et al.*, 2016; Pappas *et al.*, 2001).

In case of previously administered antibiotics, adjunctive dexamethasone treatment is considered safe and efficacious within 4 hours from the first antimicrobial dose (van de Beek *et al.*, 2016).

Corticosteroids other than dexamethasone are not advised due to suboptimal penetration of the BBB (Tunkel *et al.*, 2004).

Antimicrobial treatment. Immediate and appropriate treatment is crucial to ensure favorable outcome and should not be delayed. A study conducted on a Swedish cohort assessing the impact of CT scan prior to LP highlighted the negative impact of delayed antibiotic therapy (Glimåker *et al.*, 2015). The study found that patients could be treated 1.2 hours earlier if altered mental status was not among criteria for LP delay and therapy. Similarly, a recently published meta-analysis demonstrated that risk of death increased with treatment beyond 2 hours from emergency department access, and time to antibiotics of beyond 3 hours was associated with an increase in the occurrence of neurological impairment (Eisen *et al.*, 2022). Possible confounding factors relative to early administration of antibiotics may also concur to unclear results (Hahné *et al.*, 2006; Alam *et al.*, 2018), such that beneficial effects of early administration of antibiotics may not be captured.

While it is clear that early appropriate treatment impacts mortality in severe bacterial infections (Bassetti *et al.*, 2020), appropriate treatment should be administered in order to target the underlying causing pathogen and avoid events related to bacterial lysis.

Table 3 - *Empirical treatment for community acquired meningitis (adults, normal kidney function) - 10 mg dexamethasone IV every 6h (4 days except L. monocytogenes) + antibiotics (Adapted from: Van de Beek 2016, 2021; Hasbun et al. 2022).*

Pathogen	*First line*	*Resistance (epidemiology)*	*Other options (penicillin allergy)*	*Dosage*	*Other considerations*
S. pneumoniae *N. meningitidis*	Ceftriaxone or cefotaxime + rifampicin (non bacteriolytic choice)	+ vancomycin or linezolid	Moxifloxacin	– ceftriaxone 2 g q12 h or 4 g q24h; – cefotaxime 2 g q4-6 h; – vancomycin 10-20 mg/kg q8-12 h to achieve serum trough concentrations of 15-20 µg/mL; – rifampicin 300 mg q12 h or 600-900 mg q24 h – moxifloxacin dosed at 400 mg IV q24 hr – linezolid: 600 mg q12 h	
L. monocytogenes	ampicillin or penicillin G	+ vancomycin or trimethoprim/ sulfamethoxazole, meropenem	trimethoprim/ sulfamethoxazole	– ampicillin 2 g q4 h – vancomycin 10-20 mg/kg q8-12 h to achieve serum trough concentrations of 15-20 µg/mL; – rifampicin 300 mg q12 h – trimethoprim/ sulfamethoxazole dosed at 160/800 mg IV q6 hr. – meropenem 2 g every 8 hours continuous infusion	

Hence, early and appropriate diagnostics also impact outcomes in such settings (Bassetti *et al.*, 2022), whereby guidance is provided on the underlying etiological agent. Treatment should consider the most possible causative pathogen as well as susceptibility patterns. While empirical therapy should be administered as soon as a diagnosis of meningitis is formulated, rapid diagnostic techniques may provide faster identification in order to drive empirical therapy toward a semi-targeted approach. This is also true in the case of meningitis.

Bactericidal, non-bacteriolytic antibiotics have been demonstrated to provide protection against neurological damage, as toxin and inflammatory bacterial contents are not released, as opposed to cephalosporin treatment (Bretonnière *et al.*, 2015; Gerber *et al.*, 2003; Grandgirard *et al.*, 2012; Maldiney *et al.*, 2021). Hence, additional therapy with non-bacteriolytic antibiotics may provide further benefits against mortality and sequelae, especially when administered in the first 24 hours from symptoms onset. *Table 3* reports the empirical antibiotic therapy in case of community-acquired bacterial meningitis. Targeted treatments are reported in *Table 4*, providing optimal treatment according to the identified pathogens.

Definitive conventional microbiology results providing identification and susceptibility to antimicrobials in days should always be considered for final targeted therapy. As previously reported, a proposed implementation is depicted in *Figure 2*.

HEALTHCARE-RELATED BACTERIAL MENINGITIS

Meningitis or ventriculitis acquired in the healthcare setting or following device insertions or surgical management are referred to as healthcare-acquired meningitis or ventriculitis. Underlying etiologies are due mainly to local epidemiology, implying different pathogens and resistance patterns (Tunkel *et al.*, 2004). As such, they require a different approach and attention (Martin *et al.*, 2018). The major risk factor for nosocomial meningitis is represented by neurosurgery (Durand *et al.*, 1993). However, the relative risk varies significantly with the type and location of the neurosurgical procedure, as well as with other factors, with greatest risk upon disruption of the dura mater. Factors include duration of surgical intervention, device access and entry in sinuses, postoperative CSF leak, infected wounds, and presence of implanted CNS device (Blomstedt GC, 1985; Kourbeti *et al.*, 2015). Conditions leading to increased risk of infections are summarized in *Box 2*.

Symptoms. Post-neurosurgical meningitis presents with a more elusive symptomatology, and clinical

Table 4 - *Targeted treatment for community acquired meningitis (adults, normal kidney function) – 10 mg dexamethasone IV every 6h (4 days except L. monocytogenes) + antibiotics (Adapted from Van de Beek 2016, 2021; Hasbun 2022; Tunkel 2017).*

Pathogen	*First line*	*Resistance (antiibiotic susceptibility test)*		*Alternative (allergy)*	*Dosage*	*Other considerations*
S. pneumoniae	Ampicillin Ceftriaxone or cefotaxime (consider additional rifampicin-non-bacteriolytic, bactericidal antibiotic as first line therapy)	Penicillin MIC ≥0.12 mg/L	Ceftriaxone or cefotaxime Alternative: meropenem or cefepime	Vancomycin + FQ (moxifloxacin or levofloxacin)	– ceftriaxone 2 g q12 h or 4 g q24 h; – cefotaxime 2 g q4-6 h; – vancomycin 10-20 mg/kg q8-12 h to achieve serum trough concentrations of 15-20 µg/mL; – rifampicin 300 mg q12 h or 600-900 mg q24 h – moxifloxacin dosed at 400 mg IV q24 hr – linezolid: 600 mg q12 h	5% risk of recurrence of pneumococcal Meningitis: pneumococcal vaccination is recommended in predisposing immuno-deficiency or CSF leak
		Cephalosporin resistant (MIC ≥1 mg/L)	Vancomycin + rifampicin, or Vancomycin*poor pk + ceftriaxone or cefotaxime + rifampicin			
H. influenzae	Ampicillin Alternative: Ceftriaxone, cefotaxime or chloramphenicol	β-lactamase positive	Ceftriaxone or Cefotaxime Aletrnative: cefepime	FQ (levofloxacin, ciprofloxacin, or moxifloxacin)		
		β-lactamase neg, ampicillin resistant	Ceftriaxone or cefotaxime			
N. meningitidis	Penicillin or ampicillin Alternative: Ceftriaxone, cefotaxime, chloramphenicol (consider additional rifampicin-non-bacteriolytic, bactericidal antibiotic as first line therapy)	Penicillin MIC ≥0.12 mg/L Ceftriaxone or cefotaxime Alternative: Cefepime, meropenem, or chloramphenicol		FQ (levofloxacin, moxifloxacin, or ciprofloxacin)	– ceftriaxone 2 g q12 h or 4 g q24 h; – cefepime: 2 g q8h or 6 g q24 h – meropenem 2 g q8 h – rifampicin 300 mg q12 h or 600-900 mg q24 h – moxifloxacin dosed at 400 mg IV q24 hr – levofloxacin 750 mg q24 h – ciprofloxacin 400 mg q 8-12 h	Droplet precaution, Prophylaxis for close contacts Serotyping: Vigilance for emergence of a penicillin-resistant clade of N. meningitidis serogroup W and B,
L. monocytogenes	Ampicillin or penicillin G + Gentamicin Alternative: meropenem	Ampicillin Resistance ≥0.12 mg/L: trimethoprim-sulfamethoxazole		trimethoprim-sulfamethoxazole, FQ moxifloxacin, Linezolid	– ampicillin 2 g q4 h – gentamicin: 2 mg/kg as loading dose, then 1.7 mg/kg q8 h – trimethoprim-sulfamethoxazole: 20 mg/kg q6-12 h	Suspend dexamethasone, no RCT for dexamethasone in L. meningitidis
Enterobacterales	Ceftriaxone or Cefotaxime Alternative: Aztreonam, meropenem, or Ampicillin		For Carbapenamase producing strain see table 5	FQ: (ciprofloxacin, levofloxacin, moxifloxacin), Trimethoprim-sulfamethoxazole,	– ceftriaxone 2 g q12 h or 4 g q24 h; – cefotaxime 2 g q4-6 h; – meropenem 2 g q8 h	
S. aureus	Flucloxacillin, nafcillin, oxacillin	Methicillin Resistant Vancomycin, linezolid, daptomycin	Vancomycin hetero-resistant MIC ≥1 mg/L linezolid, daptomycin, ceftaroline/ ceftobiprole	Trimethoprim/ sulfamethoxazole, Combination therapy wiith: rifampicin, fosfomycin, daptomycin,	– flucloxacillin: 2 g q4-6 h – vancomycin 10-20 mg/kg q8-12 h to achieve serum trough concentrations of 15-20 µg/mL; – linezolid: 600 mg q12 h	

Antibiotic dosage: Ampicillin 2 g q24h; Aztreonam 6-8 g q6-8 hr; Cefepime 6g q8 hr; Cefotaxime 2 g q4-6 h; Ceftaroline 600 mg q8h; Ceftazidime 6g q8hr; Ceftobiprole 500 mg q8 h; Ceftriaxone 2 g q12h or 4 g q24h; Chloramphenicol 1g q4-6hr; Ciprofloxacin 800-1200 mg 8-12hr; Daptomycin 10mg/Kg q24; Fosfomycin 200 mg/kg q12, or q8 hr; Gentamycin 5 mg/kg q8hr; Meropenem 2 g every 8 hours continuous infusion; Moxifloxacin dosed at 400 mg IV q4hr; Linezolid: 600mg q12h; Nafcillin12g q4; Oxacillin 12g q4; Penicillin 24 million units q4; Rifampicin 300 mg q12h or 600-900 mg q24h; Trimethoprim/ sulfamethoxazole dosed at 160/800 mg IV q6hr; Vancomycin 10-20 mg/kg q8-12h to achieve serum trough concentrations of 15-20 µg/mL.

signs may not always be sensitive and specific, as opposed to community-acquired meningitis, whereby the classic meningitis triad of fever, neck stiffness, and altered mental status or headache has a sensitivity of only 40% to 50% for healthcare-associated CNS infections. (Viallon *et al.*, 2016).
All meningitis-specific symptoms may be confused with the underlying condition, including level of consciousness and CSF pleocytosis, residing in both the etiology and status. Indeed, such infections may be sustained by organisms inducing subacute symptom processes, such as coagulase negative staphylococci (CoNS) and *P. acnes*. In addition, neurosurgery patients already present with baseline compromission and fever (Martin *et al.*, 2018). Pleocytosis and hypoglycorrhachia may overlap and be confounded by other conditions such as hemorrhage, especially subarachnoid hemorrhage, malignancies and specific tumors, such as dermoid and epidermoid cysts (Cherian *et al.*, 2012). In the CNS drainage, the inflammation in the CSF taken from spinal tap might be absent and therefore CSF from the drainage should be analyzed.
This holds especially true in patients with infected shunts and may be misleading, as these often include nonspecific complaints such as malaise, lethargy, or headache without meningeal signs as the only indication of infection (van de Beek *et al.*, 2010; Tunkel *et al.*, 2017). In these instances: typical clinical signs of meningitis may be absent while nausea, lethargy, and change in mental status (65% of cases) may be most frequently reported as symptoms (Tunkel *et al.*, 2017). Pain, often related to infection at the peritoneal or pleural endings of the shunt, may be absent in as many as 60% of infections (Bryant *et al.*, 1988).
Neurosurgical meningeal infection often presents with fever and altered mental status (Chen *et al.*, 2005). Other signs, including meningeal irritation and nuchal rigidity, may be seen in only 20%-30% of patients, as symptoms may be confused by hemorrhage and insults from procedures. (Wiberg *et al.*, 2008; Oostenbrink R *et al.*, 2001).
Cerebrospinal fluid drain-related infections present with symptoms including changes in mental status, although they may be difficult to discern due to the level of impairment due to the underlying condition. Confounding underlying conditions such as subarachnoid hemorrhage or tumor may overlap, along with unresponsiveness. Although fever may also be due to other underlying infections, findings such as increasing CSF pleocytosis and fever were found to be the most reliable indicators of infection (Walti *et al.*, 2013).

Pumps. There is a paucity of data concerning infections in patients with indwelling pumps, although clinical features reported included fever and drainage from the surgical site (Wunderlich, Krach, 2006). Other symptoms include signs of local wound infection and those indicative of meningitis. In a study by Motta et al, up to one third of patients presented with meningitis symptoms, whereas half of them showed no symptoms (Motta, Antonello, 2014).

Diagnosis. As specific symptoms may be missing while overlapping with the complexity of the patient, diagnosing healthcare-associated CNS infections may pose a challenge. Along with this, the paucity of guidance may add to the complexity of the problem. The Infectious Diseases Society of America (IDSA) has attempted to simplify the process by elaborating guidance and definitions (Tunkel *et al.*, 2004), although many aspects, including negative CSF cultures or classifying colonization and managing the presence of potentially infecting pathogens, are still a matter of debate (Martin *et al.*, 2018).
CSF analysis may not yield classical abnormalities seen in community-acquired meningitis. Neverthe-

Box 2 - *Conditions leading to increased risk of meningitis or ventriculitis acquired in the healthcare setting.*

Neurosurgery or trauma: craniectomy or craniotomy

Craniotomy: Meningitis may occur in 0.3% and 8.6% of all patients (Korinek AM, *et al.*, 2006; McClelland S 3rd, Hall WA, 2007; Chen C, *et al.*, 2014). Consistently, with nosocomial infections, rates depend on a variety of factors, including the presence of devices and local epidemiological patterns as well as implementation of infection control strategies (van de Beek D, *et al.*, 2010; Chatzi M, *et al.*, 2014; Lwin S, *et al.*, 2012; Kubilay Z, *et al.*, 2013).

External devices

Cerebrospinal fluid shunts: Infection develops in 5% to 41% of all CSF shunts, although the incidence is usually in the range of 4%-17% (Renier D, *et al.*, 1984; Younger JJ, *et al.*, 1987; Quigley MR, *et al.*, 1989; Kontny U, *et al.*, 1993; Piatt JH Jr, Carlson CV, 1993; McGirt MJ, *et al.*, 2002; Vinchon M, Dhellemmes P, 2006).

Cerebrospinal fluid drains. Infection of drains has been reported to occur between 4% and 17% (internal ventricular catheters), 0% and 22% (external ventricular drains) and 0.8% and 7% (external lumbar catheter) of cases (Chen C, et al., 2014; Conen A, *et al.*, 2008; Vinchon M, Dhellemmes P, 2006; Lozier AP, *et al.*, 2008; Schade RP, *et al.*, 2005).

Intrathecal infusion pumps. Infection rates according to the placement: from 3.6% (subfascial pump placement) to 20% (subcutaneous pump placement) (Motta F, Antonello CE, 2014).

Deep brain stimulation hardware. Implantation of deep brain stimulation hardware may cause infections with rates ranging from 0.62% to 14.3%. Infections of devices may affect all 3 components of the device. (Stenehjem E, Armstrong WS, 2012; Bergey GK, *et al.*, 2015).

less, when infection is suspected, CSF and blood tests should be performed to evaluate the underlying cause of infections and CSF (and device) and blood should be cultured. CSF has to be taken from the device and sometimes eosinophils are the cells demonstrated in the inflamed CSF.

Laboratory assessments. Laboratory and imaging assessments provide crucial guidance when clinical signs are confounding. The main assessments are enlisted below:

• CSF testing is indicated upon clinical suspicion of infection. Criteria include new or worsening signs and symptoms or imaging findings such as appearance of new headache, persistent or recurrent fever, new or worsening leukocytosis, nausea, lethargy, or change in mental status/neurological deterioration. Patients with devices should be considered for further assessments, while the presence of shunts, new or worsening seizures along with abdominal pain should be considered as an indication of CNS infection.

• CSF cultures in such cases should include an anaerobic culture component in specific bottles/broth and should be incubated for extended times, ranging from 10 to 14 days, in order to enable detection of slow-growing bacteria such as *C. acnes*. Candida or fungi should also be accounted for according to epidemiology features or risk factors (e.g., immunocompromised patients or outbreaks). Beta-D-Glucan and galactomannan testing from CSF may also provide support provided the laboratories have validated the test.

• IDSA guidelines also recommend culturing explanted shunt or drain components (i.e., hardware) in patients with a suspected device infection but not as a routine practice when devices are removed for other reasons (Tunkel *et al.*, 2017). Tests results should be interpreted in accordance with clinical features of the patients. Serial assessments are generally not advised due to risk of infection, although guidelines suggest repeating assessments in patients presenting with an unclear or unstable clinical picture, and unclear test results (e.g., negative cultures).

Shifting biochemical parameters such as down-trending glucose or increases in pleocytosis support a diagnosis of CNS infection in such cases. Discrepant results such as slow-growing non-fastidious organism (e.g., *Staphylococcus epidermidis*) from cultures or detection of multiple organisms may suggest contamination or colonization, especially in the latter case if the clinical picture is not consistent with polymicrobial infection. Positive CSF cultures from permanent hardware should be confirmed by repeating testing, although they are generally considered as indicative of a true infection. Positive or abnormal CSF tests and cultures are often repeated in infected patients in order to confirm treatment effectiveness (i.e., test of cure), especially in case of doubt (Tunkel *et al.*, 2017).

Other tests. The IDSA guidelines suggest that elevated CSF lactate or an elevated CSF PCT, or the combination of both, could support the diagnosis of healthcare-associated bacterial ventriculitis and meningitis. PCT may help differentiate bacterial from surgical events (Wang, 2020; Yu, Li, 2017). Inflammatory markers such as cytokine levels, in association with lactate, may provide support in discerning meningitis from non-infective forms (Goktas *et al.*, 2021).

Molecular testing may help provide fast identification of pathogens in the CSF, as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to make a specific diagnosis, although commercially available panels for syndromic testing are generally comprehensive of community-acquired targets (Markovich *et al.*, 2022). Syndromic testing on positive blood cultures may provide further support in the detection of nosocomial meningitis (López-Amor *et al.*, 2020).

Metagenomics and next generation sequencing have recently been applied in the field, and a consistent body of evidence is demonstrating value in supporting and aiding diagnosis (Wilson MR *et al.*, 2019), including in resource-limited settings with reduced time to result (Pallerla *et al.*, 2022).

Imaging. Since clinical signs and symptoms are usually vague and nonspecific, imaging of the brain or spine may also provide further support for diagnosing infections, particularly when a CNS device is present. Nevertheless, imaging may be confused by the underlying trauma or insult induced by surgery and infection may not always be easily discriminated, with high rates of false-negative and false-positive findings due to previous surgical manipulation of tissue (Xu, *et al.*, 2014; Tamaki *et al.*, 2004; Farrell *et al.*, 2008). This said, both CT scan and Magnetic Resonance Imaging (MRI) with gadolinium may support assessment of abnormalities and focal infection (i.e., subdural empyema or brain abscess).

CSF may also accumulate rarely in the peritoneal space in the case of shunts, and CSF may be recovered in the peritoneum. The finding is rare, although it may occur in case of infection (Li *et al.*, 2019).

Treatment. Initial empirical treatment suggested by IDSA guidelines includes gram-positive coverage offered by vancomycin or using linezolid as well as an antipseudomonal beta lactam (Tunkel *et al.*, 2017). Other anti-pseudomonal drugs are suggested in case of allergy (meropenem, aztreonam or ciprofloxacin). However, with the increasing resistance rates and the availability of novel molecules, some considerations concerning other treatments should be made despite the paucity of data.

Beta lactam-beta lactamase inhibitor combinations may provide an interesting option, although there is little data supporting their use (McCreary *et al.*, 2020; Winans *et al.*, 2021; Kerz *et al.*, 2018; Roujansky *et al.*, 2020; Chen *et al.*, 2020). Other novel antibiotics are also available with expanded indications despite the scarcity of data concerning this application and context (Meschiari *et al.*, 2021).
A schematic overview of both empirical and targeted therapy is reported in *Table 5* and in *Table 6*. *Table 6* also provides specific indications according to pathogen and resistance mechanisms and CNS penetration.

Gram-positive Bacteria. Beyond the addition of vancomycin as indicated by guidelines (Tunkel *et al.*, 2017), other molecules may be considered for the management of Gram-positive cocci. Rifampicin or fosfomycin may be recommended as companion molecules for the treatment of methicillin-sensitive *S. aureus* and coagulase-negative staphylococci. Monotherapy is not recommended due to emergence of resistance (Tsegka *et al.*, 2020; Van de Beek *et al.*, 2016).
Fosfomycin offers both an expanded spectrum as well as acceptable penetration, while rifampicin is of particular interest in device-associated infections due to its biofilm activity (Conen *et al.*, 2020). Other options may include linezolid, aminoglycosides, and daptomycin, although its use should be decided by considering its limited penetration sustained by its activity (Riser *et al.*, 2010).
Though included as first-line regimen, vancomycin has poor pharmacokinetics, and with novel molecules other considerations should be made despite the paucity of data thereof (Beach *et al.*, 2017). Beta lactams offer a non-toxic option, and their PK may offer more flexible administration (Nau *et al.*, 2010). Moreover, novel 5th - generation cephalosporins have demonstrated potent anti-Gram-positive activity, beyond their poor penetration in non-inflamed meninges (Cies *et al.*, 2020; Kuriakose *et al.*, 2015; Stucki et al., 2012). This, along with the narrow therapeutic window offered by vancomycin, should be accounted for when considering the value of vancomycin treatment in this setting (Mounier *et al.*, 2017).

Gram-Negative Bacteria. Given the rise in antimicrobial resistance (ECDC) and the availability of novel molecules, it is of utmost importance to consider alternative strategies when faced with difficult-to-treat infections (Karvouniaris *et al.*, 2022). Guidelines suggest older beta lactams and fluoroquinolone therapy. Other options for these pathogens may include older antimicrobials such as aminoglycosides, polymyxins, and tigecycline (Karvouniaris *et al.*, 2022). However, novel molecules may offer a less toxic profile with a broader therapeutic window, such as new-generation beta lactam-beta lactamase inhibitor combi-

Table 5 - *Empirical treatment for nosocomial meningitis (adult, normal kidney function) (Adapted from Van de Beek 2016, 2021; Hasbun 2022; Tunkel 2017).*

Pathogen	*First line*	*Resistance*	*Alternative (penicillin allergy)*	*Resistance New molecules (MIC 50,90 mg/L)*	*CNS penetration*	*Dosage*	*Other considerations*
Gram positive	– Vancomycin – Linezolid			Ceftobiprole (0.5, 2 for MRSA 1, 2) Ceftaroline (0.25, 1 for MRSA 1, 2) Daptomycin (0.25, 0.5 for MRSA 0.5, 0.5) Companion drug: Fosfomycin	see the table below	– Vancomycin 10-20 mg/kg q8-12 h to achieve serum trough concentrations of 15-20 µg/mL; – Linezolid: 600mg q12 h – Ceftobiprole 500 mg q8 h – Ceftaroline 600 mg q8 h – Daptomycin 10 mg/Kg q24 – Fosfomycin 200 mg/kg q12, or q8 hr	cosider the local epidemiology of your institution
Gram negative	Anti-pseudomonal beta-lactam (such as cefepime, ceftazidime, or meropenem)		Aztreonam, ciprofloxacin		see the table below	– Cefepime 6g q8 hr – Ceftazidime 6g q8 hr – Meropenem 6g q8 hr – Aztreonam 6-8 g q6-8 hr – Ciprofloxacin 800-1200 mg 8-12 hr	– cosider the local epidemiology of your institution

Table 6 - *Targeted treatment for nosocomial meningitis.*

Pathogen	*First line*	*Resistance*		*Alternative (allergy)*	*New molecules (resistant strains) MIC 50, 90, mg/L*	*CNS penetration*	*Dosage*	*Other considerations*
S. aureus	Flucloxacillin, nafcillin, oxacillin	Methicillin Resistant:	Vancomycin, linezolid, daptomycin Rifampicin	Trimethoprim/ sulfamethoxazole, Combination therapy wiith: rifampicin, fosfomycin, daptomycin,	Ceftobiprole (0.5, 2) for MRSA (1, 2) Ceftaroline (0.25, 1 for MRSA 1, 2) Daptomycin (0.25, 0.5 for MRSA 0.5, 0.5) Companion drug: Fosfomycin (not monotherapy)	Ceftobiprole (16% inflamed meninges animal models) Ceftaroline (15% animall model, between 3 and 40% case report) Daptomycin 5%-11% Fosfomycin = 3X fold increase in meningies (from 18%)	See the table above	
		Vancomycin reduced susceptibility (MIC >1.0 µg/mL):	linezolid, daptomycin, ceftaroline/ ceftobiprole					
C. acnes	penicillin G	3° gen cefalosporin+ Vancomycin, linezolid, daptomycin						
Enterobacterales (no ESBL, no CRE)	Ceftriaxone or Cefotaxime Alternative: Aztreonam, meropenem	ESBL	Meropenem	FQ: (ciprofloxacin), trimethoprim/ sulfamethoxazole, Fosfomycin	Ceftazidime avibactam Meropenem-vaborbactam Imipenem relebactam	ceftazidime avibactam = 38% anim model	– Ceftazidime/ avibactam: 2.5 mg q8 h – Meropenem/ vaborbactam: 4 g q8 h	Ceftazidime avibactam = Not indicated for intrathecal use
		AmpC	Cefepime	Intrathecal Colistin	Cefiderocol (companion?)	Meropenem vaborbactam = 8% Imipenem relebactam = 11% Cefiderocol = 12.4%	– Aztreonam: 2 g q 6-8 h – Cefiderocol: 2 g q 8 h	IT colistin
		KPC	ceftazidime avibactam, meropenem vaborbactam					
		NDM	ceftazidime avibactam + aztreonam					
		VIM, IMP	Cefiderocol					
P. aeruginosa	Cefepime, ceftazidime, meropenem Alternative: aztreonam	AmpC = cefepime	VIM, IMP: cefiderocol	FQ (ciprofloxacin)	Ceftazidime avibactam Ceftolozane tazobactam Imipenem relebactam	ceftazidime avibactam = 38% anim model Ceftolozane tazobactam = 0.2, 0.2? Imipenem relebactam = 11% Cefiderocol = 12.4%		
A. baumannii	Meropenem	Colistin or polymixin B		Intrathecal colistin	PBP active: Cefiderocol + sulbactam	Cefiderocol = 12.4%		

Antibiotic dosage: Ampicillin 2 g q24h; Aztreonam 6-8 g q6-8 hr; Cefiderocol 6g q8 (extended infusion)*; Cefepime 6g q8 hr; Cefotaxime 2 g q4-6 h; Ceftaroline 600 mg q8h; Ceftazidime/avibactam 7.5g q8*; Ceftazidime 6g q8hr; Ceftobiprole 500 mg q8 h; Ceftolozane/tazobactam 9g q8 or CI (pneumonia dosage)*; Ceftriaxone 2 g q12h or 4 g q24h; Chloramphenicol 1g q4-6hr; Ciprofloxacin 800-1200 mg 8-12hr; Daptomycin 10mg/Kg q24; Fosfomycin 200 mg/kg q12, or q8 hr; Gentamycin 5 mg/kg q8hr; Imipenem/relebactam 1,250g q6*; Meropenem 2 g every 8 hours continuous infusion; Meropenem/vaborbactam2g/2g q 8*; Moxifloxacin dosed at 400 mg IV q4hr; Linezolid: 600mg q12h; Nafcillin12g q4; Oxacillin 12g q4; Penicillin24 million units q4; Rifampicin 300 mg q12h or 600-900 mg q24h; Trimethoprim/sulfamethoxazole dosed at 160/800 mg IV q6hr; Vancomycin 10-20 mg/kg q8-12h to achieve serum trough concentrations of 15-20 µg/mL; * - Indication according to standard EmA dosage in SMPC.

nations, despite the paucity of available data in the literature (Tamma *et al.*, 2022a; Tamma *et al.*, 2022b). Ceftolozane/tazobactam has demonstrated potent activity on *P. aeruginosa* strains, although results from a recent study fail to support its use in CNS infections (Sime *et al.*, 2020). On the other hand, comforting real-life data is available concerning the use of other molecules such as cefiderocol and its penetration (Meschiari *et al.*, 2021).
Most likely, these molecules will require a companion drug in order to enhance their antimicrobial activity and preserve their activity from overwhelming resistance.

Intraventricular/Intrathecal Therapy. Intraventricular or intrathecal (IT) administration can be considered, especially for some molecules that do not penetrate the BBB, and should be accompanied by systemic treatment. The most commonly employed molecules for IT therapy are vancomycin, polymyxin B, colistin, aminoglycosides, and, more recently, daptomycin and tigecycline (Nau *et al.*, 2020). Intraventricular administration, unlike intra-lumbar therapy, reaches therapeutic concentrations in all CSF compartments.
IT beta-lactams have an increased risk of epilepsy as opposed to intravenous administration. Relative risk of seizure normalized to penicillin (considered as risk equal to 1) of other beta-lactams is reported in *Table 7*.
As of today, Colistin is the only approved drug for IT administration, demonstrating sterilization of infection at the CNS level (Tunkel *et al.*, 2017; Karvouniaris *et al.*, 2018).
In a retrospective study, adjunct IT to IV polymyxin B was compared to IV drug for DTR *A baumannii* and resulted in a 91.3% to 18.4% eradication rate and improved mortality (8.7% *vs* 55.3%) (Pan *et al.*, 2018). Tigecycline has recently been introduced as an adjunct IT to IV tigecycline therapy; in a case series the antimicrobial combined with IVT colistin often sterilized the CSF 9-45-day treatment regimen (Tsolaki *et al.*, 2018). Further data and randomized trails are desirable in order to assess the best treatments in these settings. The recommended doses for IT therapy are reported in *Table 8*.
Therapeutic drug monitoring is advised only in cases that do not improve and trough concentration should be assessed.

Table 7 - *Relative risk of seizure normalized to penicillin (considered as risk equal to 1) of other beta-lactams (Guilhaumou R, et al., 2019; Tunkel AR, et al., 2017).*

Drug	*Relative risk of epileptic seizures*
	High
Penicillin	1
Cefazolin	2,94
Cefepime	1,6
Imipenem	0,71
	Low
Ampicillin	0,21
Ceftazidime	0,17
Meropenem	0,16
Ceftriaxone	0,12
Piperacillin	0,11

FUNGAL INFECTIONS

CNS infections sustained by fungi species are considered rare. As opportunistic pathogens, they usually affect immunocompromised hosts, such as HIV infected individuals or subjects affected by diabetes mellitus or renal failure (Godkhindi *et al.*, 2022). This said, an increase in incidence has been observed, possibly due to increased use of immunosuppressive therapies and advances in HSCT and transplants (Nathan *et al.*, 2021; Sharma *et al.*, 2010). CNS infections may be caused by three main categories of fungal pathogens: yeasts, dimorphic fungi, and molds (Sharma *et al.*, 2010). Manifestations generally depend on the morphology of the infecting fungus, al-

Table 8 - *Antibiotics dose recommended for intrathecal therapy.*

Drug	*Dosage*	*Adverse events (references)*
Gentamicin	4-10 mg every 24 hours	Hearing loss, seizures, aseptic meningitis, and CSF eosinophilia (Ziai WC, *et al.*, 2009)
Amikacin	30 mg every 24 hours	Hearing loss, seizures, aseptic meningitis, and CSF eosinophilia (Ziai WC, *et al.*, 2009)
Colistin	10 mg every 24 hours	Meningeal inflammation, seizures, CSF eosinophilia, intra-ventricular haemorrhages (Falagas ME, *et al.*, 2007)
Polimyxin B	5 mg every 24 hours	Meningeal inflammation, seizures, CSF eosinophilia, intra-ventricular haemorrhages (Falagas ME, *et al.*, 2007)
Daptomycin	5-10 mg every 24 hours	Fever (Mueller SW, *et al.*, 2012)
Vancomycin	10-20 mg every 24 hours	Headache, red men syndrome, hearing loss (Ng K, *et al.*, 2014)
Tigecycline	1-10 mg every 24 hours	Well tolerated (Lauretti L, *et al.*, 2017)
Amphotericin B	0,5 mg every 24 hours Liposomal 1 mg every 24 hours	Tinnitus, fever, photophobia, arachnoiditis (Nau R, *et al.*, 2020)

though syndromes may appear with overlapping symptoms. Yeasts (cryptococcus, blastomycosis, histoplasmosis, coccidiomycosis, and sporotrichosis) generally cause meningitis or leptomeningitis. Abscesses are usually ascribable to fungi growing as pseudomycetes (candida species) while hyphae growing fungi such as *Aspergillus* and zygomycoetes preferably invade blood vessels, causing stroke as well as invasion of orbits, sinuses, and cranial bone. Fungal infections are initiated by seeding via airway access and subsequent installation in the lungs and/or lymph nodes, less frequently in paranasal sinuses. Hematogenous spread from lungs precedes systemic infection and CNS involvement. The CNS may also be involved by direct spread from paranasal sinuses, orbits or other facial sites (Nathan *et al.*, 2021).

Incidence and burden. Table 9 reports percentages of overall CNS fungal infections as reported in the literature. Cryptococcal meningitis accounts for the vast majority, while differences may be seen in the distributions of other fungi. Risk factors generally include immunosuppressed states, including HIV mediated or induced by immunosuppressants, age, geographical distribution or exposure, along with specific therapies such as anti-tumor necrosis factor (TNF). Therapies such as methotrexate and infliximab for treatment of neuro-sarcoidosis have been associated with fungal infections. Such infections include histoplasmosis, coccidiomycosis, candidiasis, cryptococcosis, and aspergillosis (Ali *et al.*, 2013). Increased susceptibility to fungal infections may be due to TNF-α, involved in the formation/maintenance of granulomas as well as macrophage activation. Eculizimab, approved for treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremia syndrome, can increase risk of fungal infections such as aspergillosis and candidiasis due to its inhibition of terminal complement activation (Socié *et al.*, 2019; Nathan *et al.*, 2021; Góralska *et al.*, 2018).

Epidemiology, diagnosis and management

Cryptococcus. Cryptococcus is the most common cause of fungal meningitis. Two species in particular, *C. neoformans* (three serotypes: A, D, and AD) and *C. gattii* (two serotypes: B and C), are considered dangerous to humans. *Cryptococcus gattii* tends to be found more often in the non- immunocompromised host. Clinical symptoms include headache (87%), fever (60%), nausea/vomiting (53%), altered mental status (52%), meningismus (50%), visual disturbances (33%), cranial nerve palsies (32%), papilledema (28%), ataxia (26%), seizures (15%), and aphasia (10%), convulsions and strokes. Increased CSF pressure due to drainage block of the Pacchioni foramina caused by the presence of polysaccharide antigen and sudden visual loss might also occur. This may lead to ischemic damage of optic nerves (Menichetti,

Table 9 - *Epidemiology, risks factor and treatment for CNS fungal infections (Adapted from Nathan 2021; Tunkel 2017).*

Species (% cause fungal meningitis worldwide)	*Risk factors*	*Diagnosis laboratory/ imaging (sensitivity, specificity)*	*Treatment*
Cryptococcus (67-84%)	HIV, chronic steroids, inherited immunodeficiency chronic kidney, liver or lung disease, sarcoidosis, diabetes, malignancy (such as lymphoma or leukemia), and solid-organ transplants, fingolimod, an S1P receptor modulator	– CSF culturea 82.4%-94.2% 100% – CSF India Ink stain 42%-86% 97.3% – CSF Ag LFA 99.3% 99.1% – Serum Ag LFA 99.6% 92% – CSF Ag latex agglutination >99% >99% – Serum Ag latex agglutination 83–97% 98-100% – MRI with and without contrast is much more sensitive	Amphotericin B 5 mg/kg q24 hr + flucytosine 25 mg/kg q 6 h. Intrathecal amphotericin B can also be used in those with poor response or intolerance to IV therapy (side effects)
Candida (3-64%)	Trauma, surgery, prematurity, inherited immunodeficiency, chronic steroids, intravenous drug users, neutropenia, diabetes, AIDS or extensive wounds (burns and operations) are particularly susceptible to candidiasis, as well as premature infants, those recovering from transplantation, or patients who have undergone catheterisation, prolonged antibiotic use, total parental nutrition, parental lipids, endotracheal intubation, surgery, and prolonged hospitalization	Fungal CSF culture MRI not sensitive	Amphotericin B 5 mg/kg q24 hr + flucytosine 25 mg/kg q 6 h Removal of CNS hardware if applicable or fluconazole or voriconazole

Tascini, 1992; De Socio *et al.*, 2011). Additional skin lesions may be present in 5% of patients and secondary cerebral infarction in 4% (Searls *et al.*, 2009).
More rarely, cerebral cryptococcosis may appear as intracranial mass lesions, defined as cryptococcoma. Such features are characterized by the presence of a ring-shaped enhancement of mass lesions, where cystic changes may be visible by MRI, located in basal ganglia (reach of melanin), cerebellum or parietal lobe (Nosanchuk *et al.*, 2015).
Diagnosis and treatment. The diagnostic pathway includes imaging and CSF testing. Non-contrast CT scan of the head lacks sensitivity and may reveal nonspecific atrophy or no clear abnormalities, whereas MRI with and without contrast is much more sensitive. CSF culture sensitivity is also variable and depends upon disease burden. Moreover, testing may require up to 10 days. As a result, Cryptococcus capsular polysaccharide antigen (CrAg) detection in CSF is a more useful and sensitive test with positive detection rates in over 90% of cases. CrAg serum testing has similar performance and can even be picked up 3 weeks prior to symptoms of meningitis. The WHO recommends screening those with CD4 <100 for cryptococcal antigen (Nathan *et al.*, 2021). Early CrAg titers were shown to be associated with an increased risk of concurrent cryptococcal meningitis in HIV-positive patients (Wake *et al*., 2018), and CSF CrAg titers ≥1:1024 were associated with significantly higher mortality (Saag *et al*., 1992).
Other parameters, such as cytokine levels, may provide diagnostic support. CSF cytokine levels (IL-6, IL-8, IL-10, and TNF-α) were found to be higher in HIV-negative cryptococcal meningitis subjects than in HIV-positive subjects (Lortholary *et al.*, 2001). IL-10 was found to increase with increasing burden of disease in *C. gattii* meningitis (Tascini *et al.*, 2002). IL-12 increases as disease burden decreases following therapy, counteracting the effect of IL-10 and stimulating an immune response. CSF IL-10 levels could therefore be assessed providing prognostic value in C. neoformans var. gatti meningitis, as IL-10 is stimulated by the yeast and suppresses the inflammatory response limited only in the CSF (Tascini *et al.*, 2002).
The severity of cryptococcal meningitis correlates with CSF Cryptococcal antigen titers. Titer ratios above 1:1024 displaying negative prognostic value are indicative of increased disease burden with elevated levels of Cryptococcus leading to higher probability of negative outcome. Such cases require higher fungicidal activity. For this reason, combination therapy based on amphotericin B (liposomal amphotericin B) and 5-flucytosine is recommended, in order to reduce fungal burden.
The guidelines for treatment of cryptococcal meningitis have recently been updated in light of the results of the AMBITION Trial (WHO 2022). The AMBITION Trial, whose results were published in March 2022, demonstrated the non-inferiority of induction therapy with a single dose of liposomal amphotericin B (10 mg/kg) associated with 14 days of flucytosine (100 mg/kg) and fluconazole (1200 mg) to the standard regimen with 7 days of amphotericin B deoxycholate (1 mg/kg) plus flucytosine, followed by 7 days of fluconazole.
For maintenance treatment of cryptococcal meningitis, the WHO suggests using fluconazole (800 mg) for 8 weeks, while the last EACS guidelines, published in 2022, recommend a single dose of fluconazole 800 mg and continuation of therapy with fluconazole 400 mg/day for at least 12 months until the CD4 count is above 100 cells/μL or the HIV-viral load is undetectable for over 3 months. In case of increased pressure, frequent spinal taps are suggested, in conjunction with acetazolamide (Patel *et al.*, 2003).
Cryptococcal meningitis is one of the most common causes of immune reconstitution inflammatory syndrome (IRIS) in the HIV antiretroviral therapy (ART) - naïve patient. For this reason, EACS and WHO guidelines recommend delaying the ART for 4-6 weeks (EACS, WHO 2022).

Candida. Meningitis sustained by Candida species usually affects immunocompromised hosts or subjects who have undergone neurosurgical interventions. Infections are initiated as disseminated candidiasis whereby approximately half of patients show CNS involvement. Infections are mainly sustained by *C. albicans*, although other Candida species display pathogenicity in humans, including *C. tropicalis*, *C. lusitaniae*, and *C. parapsilosis*. An increasing frequency of non-*C. albicans* species has also been reported (Kirkland TN, Fierer, 2018). The overall incidence of CNS infections sustained by *Candida* spp. in the CNS has increased from 6% to 17% in neurosurgical patients (Grebenciucova *et al.*, 2016). In patients with underlying malignant diseases or Hemopoietic Stem Cell Transplant recipients (HSCT), *C. albicans* was responsible for 33% of neuroinfections, with non-*Candida* species accounting for 77%; *C. parapsilosis* was most frequently observed, while *C. krusei, C. glabrata, C. tropicalis*, and *C. guilliermondii* were also isolated in individual cases. Mortality, even with adequate treatment, ranges between 10 and 30%, with neurologic sequelae reaching rates of 18-29% in survivors (Rauchway *et al.*, 2010). Candida meningitis-related symptoms are very similar to bacterial meningitis, including fever, headache, neck stiffness, and altered mental status, presenting initially with subacute onset. Vascular invasion occurs in up to 23% of patients with CNS infection, and basal ganglia are particularly involved (Sánchez-Portocarrero *et al.*, 2000). Other clinical presentations include endophthalmitis, multiple cerebral abscesses with ring enhancement or nodular enhancing le-

sions, vasculitis, intraventricular fungus balls, hydrocephalus, calcifications, and cranial neuropathies, with rare cases demonstrating stroke syndromes (Góralska *et al.*, 2018).

Diagnosis and treatment. Diagnosis relies on CSF testing, which may be indicative of fungal infection in 80% of cases. Imaging techniques are of limited use, although they may provide information concerning the presence of abscesses such as ischemic and hemorrhagic lesions and annular ring enhancement by MRI (Godkhindi *et al.*, 2022; Nathan *et al.*, 2021).

Treatment choices include Amphotericin B and flucytosine or other active azoles (voriconazole or isavuconazole) according to activity. Epidemiological aspects and resistance patterns should be accounted for, as increasing resistance rates to azoles are being reported worldwide (Pristov, Ghannoum, 2019; Roilides, Iosifidis, 2019) with increasing resistance particularly in *C. auris* species (Murphy, Bicanic, 2021). Further information concerning other potential causes of invasive fungal infections of the CNS and treatments thereof are detailed in *Table 9*.

Authors' contribution

SG, SF, GML: review design and manuscript preparation; AZF, ML, DP: literature review and manuscript preparation; FS: editing and manuscript preparation; VA, CT: review design, literature review and manuscript preparation.

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References

Adriani K.S., Brouwer M.C., van de Beek D. (2015). Risk factors for community-acquired bacterial meningitis in adults. *Neth J Med.* **73** (2): 53-60.

Agosti S., Casalino L., Daffonchio A., Arena L., Celli L., Rota E. (2018). Emergency lumbar puncture for suspected meningitis after dabigatran reversal with idarucizumab: a case report. *J Clin Case Rep*, **8** (1103), 2.

Alam N., Oskam E., Stassen P.M., Exter P.V., van de Ven P.M., et al. (2018). Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. *Lancet Respir Med.* **6** (1): 40-50.

Ali T., Kaitha S., Mahmood S., Ftesi A., Stone J., et al. (2013). Clinical use of anti- TNF therapy and increased risk of infections. *Drug Healthc Patient Saf.* **5**, 79-99.

Archibald L.K., Quisling R.G. (2013). Central nervous system infections. In *Textbook of neurointensive care* (pp. 427-517). Springer, London.

Attia J., Hatala R., Cook D.J., Wong J.G. (1999). The rational clinical examination. Does this adult patient have acute meningitis? *JAMA.* **282** (2): 175-81.

Bassetti M., Kanj S.S., Kiratisin P., Rodrigues C., Van Duin D., et al. (2022). Early appropriate diagnostics and treatment of MDR Gram-negative infections. *JAC Antimicrob Resist.* **4** (5): dlac089.

Bassetti M., Rello J., Blasi F, Goossens H., Sotgiu G., et al. (2020). Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections. *Int J Antimicrob Agents.* **56** (6): 106184.

Beach J.E., Perrott J., Turgeon R.D., Ensom M.H.H. (2017). Penetration of Vancomycin into the Cerebrospinal Fluid: a Systematic Review. *Clin Pharmacokinet.* **56** (12): 1479–90.

Bergey G.K., Morrell M.J., Mizrahi E.M., et al. (2015). Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology.* **84**: 810-7.

Bicanic T., Brouwer A.E., Meintjes G., Rebe K., Limmathurotsakul D., et al. (2009). Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS.* **23** (6): 701-6.

Bichon A., Aubry C., Dubourg G., Drouet H., Lagier J.C., et al. (2018). Escherichia coli spontaneous community-acquired meningitis in adults: A case report and literature review. *Int J Infect Dis.* **67**, 70-4.

Block N., Naucler P., Wagner P., Morfeldt E., Henriques-Normark B. (2022). Bacterial meningitis: Aetiology, risk factors, disease trends and severe sequelae during 50 years in Sweden. *J Intern Med.* **292** (2): 350-64.

Blomstedt G.C. (1985). Infections in neurosurgery: a retrospective study of 1143 patients and 1517 operations. *Acta Neurochir* (Wien). **78** (3-4): 81-90.

Bretonnière C., Jozwiak M., Girault C., Beuret P., Trouillet J.L., et al. (2015) Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study. *Crit Care.* **19** (1): 303.

Brouwer M.C., McIntyre P., Prasad K., van de Beek D. (2015). Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev.* **2015** (9): CD004405.

Brouwer M.C., Thwaites G.E., Tunkel A.R., van de Beek D. (2012). Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet.* **380** (9854): 1684-92.

Brouwer M.C., Tunkel A.R., van de Beek D. (2010). Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev.* **23** (3): 467-92.

Bryant M.S., Bremer A.M., Tepas J.J. 3rd, Mollitt D.L., Nquyen T.Q., et al., (1988). Abdominal complications of ventriculoperitoneal shunts. Case reports and review of the literature. *Am Surg.* **54**, 50-5.

Buch K., Bodilsen J., Knudsen A., Larsen L., Helweg-Larsen J., et al. (2018). Cerebrospinal fluid lactate as a marker to differentiate between community-acquired acute bacterial meningitis and aseptic meningitis/encephalitis in adults: a Danish prospective observational cohort study. *Infect Dis* (Lond). **50** (7): 514-21.

Cailleaux M., Pilmis B., Mizrahi A., Lourtet-Hascoet J., Nguyen Van J.C., Alix L., et al. (2020) Impact of a multiplex PCR assay (FilmArray®) on the management of patients with suspected central nervous system infections. *Eur J Clin Microbiol Infect Dis.* **39** (2): 293-7.

Carpenter R.R., Petersdorf R.G. (1962). The clinical spectrum of bacterial meningitis. *Am J Med.* **33**: 262-75.

Chatzi M., Karvouniaris M., Makris D., Tsimitrea E., Gatos C. (2014). Bundle of measures for external cerebral ventricular drainage-associated ventriculitis. *Crit Care Med.* **42** (1): 66-73.

Chen C., Zhang B., Yu S., Sun F., Ruan Q., et al. (2014). The incidence and risk factors of meningitis after major craniotomy in China: a retrospective cohort study. *PLoS One.* **9** (7): e101961.

Chen H.A., Yang C.J., Tsai M.S., Liao C.H., Lee C.H. (2020). Linezolid as salvage therapy for central nervous system infections due

to methicillin-resistant Staphylococcus aureus at two medical centers in Taiwan. *J Microbiol Immunol Infect.* **53** (6): 909-15.
Chen H.P., Lai C.H., Chan Y.J., Chen T.L., Liu C.Y., *et al.* (2005). Clinical significance of Acinetobacter species isolated from cerebrospinal fluid. *Scand J Infect Dis.* **37** (9): 669-75.
Chen N., Zhang X., Zheng K., Zhu L., Zhang N., et al. (2019). Increased risk of group B Streptococcus causing meningitis in infants with mannose-binding lectin deficiency. *Clinical Microbiology and Infection*. **25** (3): 384.e1-384.e3.
Cherian A., Baheti N.N., Easwar H.V., Nair D.S., Iype T. (2012). Recurrent meningitis due to epidermoid. *J Pediatr Neurosci.* **7** (1): 47-8.
Cies J.J., Moore W.S. 2nd, Enache A., Chopra A. (2020). Ceftaroline Cerebrospinal Fluid Penetration in the Treatment of a Ventriculopleural Shunt Infection: A Case Report. *J Pediatr Pharmacol Ther.* **25** (4): 336-9.
Conen A., Raabe A., Schaller K., Fux C.A., Vajkoczy P., et al. (2020) Management of neurosurgical implant-associated infections. *Swiss Med Wkly.* **150**, w20208.
Conen A., Walti L.N., Merlo A., Fluckiger U., Battegay M., et al. (2008). Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. *Clin Infect Dis*. **47**, 73e82.
Contou D., de Prost N., HOPEFUL Study group (2021). Clinical phenotype and outcomes of pneumococcal versus meningococcal purpura fulminans: a multicenter retrospective cohort study. *Crit Care*. **25** (1): 386.
Dashti A.S., Alizadeh S., Karimi A., Khalifeh M., Shoja S.A. (2017). Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: a cross-sectional study. *Medicine*. **96** (35): e7637.
De Almeida S.M., Furlan S.M.P., Cretella A.M.M., Lapinski B., Nogueira K., et al. (2020) Comparison of Cerebrospinal Fluid Biomarkers for Differential Diagnosis of Acute Bacterial and Viral Meningitis with Atypical Cerebrospinal Fluid Characteristics. *Med Princ Pract*. **29** (3): 244-54.
De Gans J., van de Beek D., European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators (2002). Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. **347** (20): 1549-56.
De Socio G.V., Bernini L., Menduno P., Pitzurra L., et al. (2011). Monolateral visual loss due to cryptococcal meningitis. *J Int Assoc Physicians AIDS Care* (Chic). **10** (2): 76-8.
Di Diodato G., Bradbury N. (2019). Cerebrospinal Fluid Analysis With the BioFire FilmArray Meningitis/Encephalitis Molecular Panel Reduces Length of Hospital Stay in Patients With Suspected Central Nervous System Infections. *Open Forum Infect Dis*. **6** (4): ofz119.
Dodd K.C., Emsley H.C.A., Desborough M.J.R., Chhetri S.K. (2018). Periprocedural antithrombotic management for lumbar puncture: Association of British Neurologists clinical guideline. *Pract Neurol.* **18** (6): 436-46.
Duff S., Hasbun R., Ginocchio C.C., Balada-Llasat J.M., Zimmer L., et al. (2018). Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients. *Future Microbiol.* **13**: 617-29.
Durand M.L., Calderwood S.B., Weber D.J., Miller S.I., Southwick F.S., et al. (1993). Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med.* **328** (1): 21-8.
Eisen D.P., Hamilton E., Bodilsen J., Køster-Rasmussen R., Stockdale A.J., et al. (2022). Longer than 2 hours to antibiotics is associated with doubling of mortality in a multinational community-acquired bacterial meningitis cohort. *Sci Rep.* **12** (1): 672.
Erdem H., Ozturk-Engin D., Cag Y., Senbayrak S., Inan A., et al. (2017) Central nervous system infections in the absence of cerebrospinal fluid pleocytosis. *Int J Infect Dis.* **65**, 107-9.
Falagas M.E., Bliziotis I.A., Tam V.H. (2007). Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence. *Int J Antimicrob Agents*. **29**, 9-25.
Farrell C.J., Hoh B.L., Pisculli M.L., Henson J.W., Barker F.G., II, et al. (2008). Limitations of diffusion-weighted imaging in the diagnosis of postoperative infections. *Neurosurgery.* **62**, 577-83.
Feagins A.R., Ronveaux O., Taha M.K., Caugant D.A, Smith V., et al. (2020). Next generation rapid diagnostic tests for meningitis diagnosis. *J Infect*. **81** (5): 712-718.
Fuentes-Antrás J., Ramírez-Torres M., Osorio-Martínez E., Lorente M., Lorenzo-Almorós., et al. (2019). Acute Community-Acquired Bacterial Meningitis: Update on Clinical Presentation and Prognostic factors. *New Microbiol.* **41** (4): 81-7.
García-Hernández P., Prieto B., Martínez-Morillo E., Rodríguez V., Álvarez F.V. (2016). Interleukin-6 in cerebrospinal fluid as a biomarker of acute meningitis. *Ann Clin Biochem*. **53** (Pt 1): 155-63.
Gerber J., Pohl K., Sander V., Bunkowski S., Nau R. (2003). Rifampin followed by ceftriaxone for experimental meningitis decreases lipoteichoic acid concentrations in cerebrospinal fluid and reduces neuronal damage in comparison to ceftriaxone alone. *Antimicrob Agents Chemother.* **47** (4): 1313-7.
Giovane R.A., Lavender P.D. (2018). Central Nervous System Infections. *Prim Care.* **45** (3): 505-18.
Glimåker M., Johansson B., Grindborg Ö., Bottai M., Lindquist L., et al. (2015). Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture. *Clin Infect Dis.* **60** (8): 1162-9.
Glimåker M., Sjölin J., Åkesson S., Naucler P. (2018). Lumbar Puncture Performed Promptly or After Neuroimaging in Acute Bacterial Meningitis in Adults: A Prospective National Cohort Study Evaluating Different Guidelines. *Clin Infect Dis*. **66** (3): 321-8.
Godkhindi V.M., Monappa V., Kairanna N.V., Sharma S., Vasudevan G., et al. (2022). Brain infections that mimic malignancy. *Diagnostic Histopathology.* 28 (10): 456-66, ISSN 1756-2317.
Gogarten W., Vandermeulen E., Van Aken H., et al. (2010). Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol.* **27** (12): 999-1015.
Goktas S.Y., Oral A.Y., Yılmaz E., Akalın E.H., Guvenc F., et al. (2021). Diagnostic value of the CSF levels of D-Lactate and pro-inflammatory cytokines (TNF-alpha, IL-6, IL-8 and IL-17) in the patients with suspected nosocomial meningitis. Singapore Med J. Góralska K, Blaszkowska J, Dzikowiec M (2018). Neuroinfections caused by fungi. *Infection*. **46** (4): 443-59.
Gorse G.J., Thrupp L.D., Nudleman K.L., Wyle F.A., Hawkins B., et al. (1984). Bacterial meningitis in the elderly. *Arch Intern Med.* **144** (8): 1603-7.
Grandgirard D., Burri M., Agyeman P., Leib S.L. (2012). Adjunctive daptomycin attenuates brain damage and hearing loss more efficiently than rifampin in infant rat pneumococcal meningitis. *Antimicrob Agents Chemother.* **56** (8): 4289-95.
Grandgirard D., Gäumann R., Coulibaly B., Dangy J.P., Sie A., et al. (2013). The causative pathogen determines the inflammatory profile in cerebrospinal fluid and outcome in patients with bacterial meningitis. *Mediators Inflamm.* **2013**, 312476.
Grebenciucova E., Reder A.T., Bernard J.T. (2016). Immunologic mechanisms of fingolimod and the role of immunosenescence in the risk of cryptococcal infection: A case report and review of literature. *Mult Scler Relat Disord.* **9**, 158-62. Epub 2016 Aug 4. Erratum in: *Mult Scler Relat Disord.* **10**, 213.
Greenberg R.G., Smith P.B., Cotten C.M., Moody M.A., Clark R.H. et al. (2008). Traumatic lumbar punctures in neonates: test performance of the cerebrospinal fluid white blood cell count. *Pediatr Infect Dis J.* **27** (12): 1047-51.
Guilhaumou R., Benaboud S., Bennis Y., Dahyot-Fizelier C., Dailly E., et al. (2019). Optimization of the treatment with betalactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Soci.t. Fran.aise de Pharmacologie et Th.rapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Soci.t. Fran. aise d'Anesth.sie etR.animation-SFAR). *Crit Care.* **23**, 104.
Haddar C.H., Terrade A., Verhoeven P., Njanpop-Lafourcade B.M., Dosso M., et al. (2020). Validation of a New Rapid Detection Test for Detection of Neisseria meningitidis A/C/W/X/Y Antigens in Cerebrospinal Fluid. *J Clin Microbiol.* **58** (3): e01699-19.
Hahné S.J., Charlett A., Purcell B., Samuelsson S., Camaroni I., et al. (2006). Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ*. **332** (7553): 1299-303.
Halvorson K., Shah S., Fehnel C. (2017). Procalcitonin is a Poor Predictor of Non-Infectious Fever in the Neurocritical Care Unit. *Neurocrit Care.* **27**, 237-41.
Hasbun R. (2022). Progress and Challenges in Bacterial Meningitis: A Review. *JAMA.* **328** (21): 2147-54.

Hayden R.T., Frenkel L.D. (2000). More laboratory testing: greater cost but not necessarily better. *Pediatr Infect Dis J.* **19** (4): 290-2.

Hegen H., Auer M., Deisenhammer F. (2014). Serum glucose adjusted cut-off values for normal cerebrospinal fluid/serum glucose ratio: implications for clinical practice. *Clin Chem Lab Med.* **52** (9): 1335-40.

Heider R., Kranz P.G., Weant E.H., Gray L., Amrhein T.J. (2022). Digital manometry to measure cerebrospinal fluid pressure during lumbar puncture. *The Neuroradiology Journal.* **35** (4): 486-9.

Herndon R.M., Brumback R.A. (1989). The cerebrospinal spinal fluid. Boston: Kluwer Academic Publishers.

Hsieh C.C., Lu J.H., Chen S.J., Lan C.C., Chow W.C., et al. (2009). Cerebrospinal fluid levels of interleukin-6 and interleukin-12 in children with meningitis. *Childs Nerv Syst.* **25** (4): 461-5.

Huy N.T., Thao N.T., Diep D.T., Kikuchi M., Zamora J., et al. (2010). Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systemic review and meta-analysis. *Crit Care.* **14** (6): R240.

Jarvis J.N., Lawrence D.S., Meya D.B., Kagimu E., Kasibante J., et al. (2022). Ambition Study Group. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. *N Engl J Med.* **386**, 1109-20.

Kabanda T., Siedner M.J., Klausner J.D., Muzoora C., Boulware D.R. (2014). Point-of-care diagnosis and prognostication of cryptococcal meningitis with the cryptococcal antigen lateral flow assay on cerebrospinal fluid. *Clin Infect Dis.* **58**, 113-6.

Karvouniaris M., Brotis A., Tsiakos K., Palli E., Koulenti D. (2022). Current Perspectives on the Diagnosis and Management of Healthcare-Associated Ventriculitis and Meningitis. *Infect Drug Resist.* **15**, 697-721.

Karvouniaris M., Brotis A.G., Tsiamalou P., et al. (2018). The role of intraventricular antibiotics in the treatment of nosocomial ventriculitis/meningitis from gram-negative pathogens: a systematic review and meta-analysis. *World Neurosurg.* **120**, 637-50.

Kępa L., Oczko-Grzesik B., Boroń-Kaczmarska A. (2014). Cerebrospinal fluid interleukin-6 concentration in patients with purulent, bacterial meningitis - own observations. *Przegl Epidemiol.* **68** (4), 645-9.

Kerz T., Von loewenich F.D., Roberts J., Neulen A., Ringel F. (2018). Cerebrospinal fluid penetration of very high dose meropenem: a case report. *Ann Clin Microbiol Antimicrob.* **17** (1): 47.

Kim H., Roh Y.H., Yoon S.H. (2021). Blood Procalcitonin Level as a Diagnostic Marker of Pediatric Bacterial Meningitis: A Systematic Review and Meta-Analysis. *Diagnostics* (Basel). **11**(5): 846.

Kirkland T.N., Fierer F. (2018). Coccidioides immitis and posadasii; a review of their biology, genomics, pathogenesis, and host immunity. Virulence. **9** (1): 1426-35.

Koelman D.L.H., Brouwer M.C., van de Beek D. (2020). Resurgence of pneumococcal meningitis in Europe and Northern America. *Clin Microbiol Infect.* **26** (2): 199-204.

Kohlmann R., Nefedev A., Kaase M., Gatermann S.G. (2015). Community-acquired adult Escherichia coli meningitis leading to diagnosis of unrecognized retropharyngeal abscess and cervical spondylodiscitis: a case report. *BMC Infect Dis.* **15**, 567.

Kontny U., Höfling B., Gutjahr P., Voth D., Schwarz M., et al. (1993). CSF shunt infections in children. *Infection.* **21** (2): 89-92.

Korinek A.M., Baugnon T., Golmard J.L., van Effenterre R., Coriat P., et al- (2006). Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. *Neurosurgery.* **59** (1): 126-33; discussion 126-33.

Kourbeti I.S., Vakis A.F., Ziakas P., Karabetsos D., Potolidis E., et al. (2015). Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis. *J Neurosurg.* **122** (5): 1113-9.

Krebs V.L., Okay T.S., Okay Y., Vaz F.A. (2005). Tumor necrosis factor-alpha, interleukin-1beta and interleukin-6 in the cerebrospinal fluid of newborn with meningitis. *Arq Neuropsiquiatr.* **63** (1): 7-13.

Kubilay Z., Amini S., Fauerbach L.L., Archibald L., Friedman W.A., *et al.* (2013) Decreasing ventricular infections through the use of a ventriculostomy placement bundle: experience at a single institution. *J Neurosurg.* **118** (3): 514-20.

Kuriakose S.S., Rabbat M., Gallagher J.C. (2015). Ceftaroline CSF concentrations in a patient with ventriculoperitoneal shunt-related meningitis. *Journal of Antimicrobial chemotherapy.* **70** (3): 953-4.

Laible M., Beynon C., Sander P., Purrucker J., Müller O.J., et al. (2016). Treatment With Prothrombin Complex Concentrate to Enable Emergency Lumbar Puncture in Patients Receiving Vitamin K Antagonists. *Ann Emerg Med.* **68** (3): 340-4.

Lauretti L., D'Alessandris Q.G., Fantoni M., D'Inzeo T., Fernandez E., Pallini R., Scoppettuolo G. (2017). First reported case of intraventricular tigecycline for meningitis from extremely drug-resistant Acinetobacter baumannii J Neurosurg. **127**, 370-3.

Li D.K., Platt J.M., Shay J.E.S., Yarze J.C. (2019). Sterile cerebrospinal fluid ascites presenting as high SAAG ascites: a case report. *BMC Gastroenterol.* **19** (200): 8-11.

Li L., Ma J., Yu Z., Li M., Zhang W., et al. (2023). Epidemiological characteristics and antibiotic resistance mechanisms of Streptococcus pneumoniae: An updated review. *Microbiol Res.* **266**, 127221.

Li Y., Zhang G., Ma R., Du Y., Zhang L., et al. (2015). The diagnostic value of cerebrospinal fluids procalcitonin and lactate for the differential diagnosis of post-neurosurgical bacterial meningitis and aseptic meningitis. *Clin Biochem.* **48** (1-2): 50-4.

Lien C.Y., Lee J.J., Tsai W.C., Chen S.Y., Huang C.R., et al. (2019). The clinical characteristics of spontaneous Gram-negative bacterial meningitis in adults: A hospital-based study. *J Clin Neurosci.* **64**, 101-5.

Liu Z.H., Tu P.H., Chen N.Y., Yip P.K., Bowes A.L., et al. (2015). Raised Proinflammatory Cytokine Production Within Cerebrospinal Fluid Precedes Fever Onset in Patients With Neurosurgery-Associated Bacterial Meningitis. *Crit Care Med.* **43** (11): 2416-28.

López-Amor L., García-Prieto E., Fernández-Suárez J., Escudero D., Vázquez F., et al. (2020). Evaluation of a commercial multiplex PCR for diagnosis of central nervous system (CNS) nosocomial infections. *J Microbiol Methods.* **171**, 105865.

Lortholary O., Dromer F., Mathoulin-Pélissier S., Fitting C., Improvisi L., et al. (2001). Immune mediators in cerebrospinal fluid during cryptococcosis are influenced by meningeal involvement and human immunodeficiency virus serostatus. *J Infect Dis.* **183** (2): 294-302.

Lozier A.P., Sciacca R.R., Romagnoli M.F., Connolly E.S. Jr (2008). Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery.* **62** (Suppl. 2): 688-700.

Lukšić I., Mulić R., Falconer R., Orban M, Sidhu S., et al. (2013). Estimating global and regional morbidity from acute bacterial meningitis in children: assessment of the evidence. *Croat Med J.* **54** (6): 510-8.

Lwin S., Low S.W., Choy D.K., Yeo T.T., Chou N. (2012). External ventricular drain infections: successful implementation of strategies to reduce infection rate. *Singapore Med J.* **53** (4): 255-9.

Makoo Z.B., Soltani H.R., Hasani A., Makoo R.B., Mashrabi O. (2010). Diagnostic Value of Serum and Cerebrospinal Fluid Procalcitonin in Differentiation Bacterial from Aseptic Meningitis. *American Journal of Infectious Diseases*. **6** (4): 93-7.

Maldiney T., Bonnot D., Anzala N., Albac S., Labrousse D., et al. (2021). In vitro antimicrobial activity of daptomycin alone and in adjunction with either amoxicillin, cefotaxime or rifampicin against the main pathogens responsible for bacterial meningitis in adults. *J Glob Antimicrob Resist.* **25**, 193-8.

Markovich K., Wingler M.J.B., Stover K.R., Barber K.E., Wagner J.L., et al. (2022). Analysis of the Clinical Impact of the BioFire FilmArray Meningitis Encephalitis Panel on Antimicrobial Use and Duration of Therapy at an Academic Medical Center. *Diseases.* **20**; 10 (4): 110.

Martin R.M., Zimmermann L.L., Huynh M., Polage C.R. (2018). Diagnostic Approach to Health Care- and Device-Associated Central Nervous System Infections. *J Clin Microbiol.* **56** (11): e00861-18.

McClelland S. 3rd, Hall W.A. (2007). Postoperative central nervous system infection: incidence and associated factors in 2111 neurosurgical procedures. *Clin Infect Dis.* 45 (1): 55-9.

McCreary E.K., Byers K.E., Fernandes C., et al. (2020). Plasma and cerebrospinal fluid therapeutic drug monitoring of ceftolozane and tazobactam during treatment of multidrug-resistant Pseudomonas aeruginosa meningitis. *Open Forum Infect Dis.* **7** (12): ofaa549.

McGill F., Heyderman R.S., Michael B.D., Defres S., Beeching N.J., et al. (2016). The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect*. **72** (4): 405-38.

McGirt M.J., Leveque J.C., Wellons J.C. 3rd, Villavicencio A.T., Hopkins J.S., et al. (2002). Cerebrospinal fluid shunt survival and etiology of failures: a seven-year institutional experience. *Pediatr Neurosurg*. **36** (5): 248-55.

McIntyre P.B., OBrien K.L., Greenwood B., van de Beek D. (2012). Effect of vaccines on bacterial meningitis worldwide. *Lancet*. **380** (9854): 1703-11.

Mein J., Lum G. (1999). CSF bacterial antigen detection tests offer no advantage over Gram's stain in the diagnosis of bacterial meningitis. *Pathology*. **31** (1): 67-9.

Menichetti F., Fortunato S., Ricci A., Salani F., Ripoli A., et al. (2018) Invasive Meningococcal Disease due to group C N. meningitidis ST11 (cc11): The Tuscany cluster 2015-2016. *Vaccine*. **36** (40): 5962-5966.

Menichetti F., Tascini C. (1992). Amphotericin versus fluconazole in cryptococcal meningitis. *N Engl J Med*. **326** (23): 1568; author reply 1568-9.

Meschiari M., Volpi S., Faltoni M., Dolci G., Orlando G., et al. (2021). Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant Pseudomonas aeruginosa (DTR-P) infections. *JAC Antimicrob Resist*. **3**(4): dlab188.

Moffa M.A., Bremmer D.N., Carr D, Buchanan C., Shively N.R., et al. (2020) Impact of a Multiplex Polymerase Chain Reaction Assay on the Clinical Management of Adults Undergoing a Lumbar Puncture for Suspected Community-Onset Central Nervous System Infections. *Antibiotics* (Basel). **26**; 9 (6): 282.

Morsli M., Lavigne J.P., Drancourt M. (2022) Direct Metagenomic Diagnosis of Community-Acquired Meningitis: State of the Art. *Front Microbiol*. **13**: 926240.

Motta F., Antonello C.E. (2014). Analysis of complications in 430 consecutive pediatric patients treated with intrathecal baclofen therapy: 14-year experience. *J Neurosurg Pediatr*. **13**, 301-6.

Mounier R., Lobo D., Hulin A., Nebbad B., Cook F., et al. (2017). Is first line vancomycin still the best option to treat Staphylococcus healthcare-associated meningitis? *World Neurosurg*. **9**, 812. e1–812.e5.

Mueller S.W., Kiser T.H., Anderson T.A., Neumann R.T. (2012). Intraventricular daptomycin and intravenous linezolid for the treatment of external ventricular-drain-associated ventriculitis due to vancomycin-resistant Enterococcus faecium. *Ann Pharmacother*. **46**, e35.

Murphy S.E., Bicanic T. (2021). Drug Resistance and Novel Therapeutic Approaches in Invasive Candidiasis. *Front Cell Infect Microbiol*. **11**, 759408.

Mylonakis E., Hohmann E.L., Calderwood S.B. (1998). Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine* (Baltimore). **77** (5): 313-36.

Nabower A.M., Miller S., Biewen B., Lyden E., Goodrich N., et al. (2019) Association of the FilmArray Meningitis/Encephalitis Panel With Clinical Management. *Hosp Pediatr*. **9** (10), 763-769.

Nadel S., Kroll J.S. (2007). Diagnosis and management of meningococcal disease: the need for centralized care. *FEMS Microbiol Rev*. **31** (1): 71-83.

Nathan C.L., Emmert B.E., Nelson E., Berger J.R. (2021). CNS fungal infections: A review. *J Neurol Sci*. **422**, 117325.

Nau R., Blei C., Eiffert H. (2020). Intrathecal antibacterial and antifungal therapies. *Clin Microbiol Rev*. **33** (3): e00190–19.

Nau R., Sörgel F., Eiffert H. (2010). Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. **23** (4): 858-83.

Ng K., Mabasa V.H., Chow I., Ensom M.H. (2014). Systematic review of efficacy, pharmacokinetics, and administration of intraventricular vancomycin in adults. *Neurocrit Care*. **20** (1): 158-71.

Nigrovic L.E., Kuppermann N., Malley R. (2008). Bacterial Meningitis Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Children with bacterial meningitis presenting to the emergency department during the pneumococcal conjugate vaccine era. *Acad Emerg Med*. **15** (6): 522-8.

Nosanchuk J.D., Stark R.E., Casadevall A. (2015). Fungal Melanin: What do We Know About Structure? *Front Microbiol*. **6**, 1463.

O'Brien M.P., Francis J.R., Marr I.M., Baird R.W. (2018). Impact of Cerebrospinal Fluid Multiplex Assay on Diagnosis and Outcomes of Central Nervous System Infections in Children: A Before and After Cohort Study. *Pediatr Infect Dis J*. **37** (9): 868-71.

Oostenbrink R., Moons K.G., Theunissen C.C., Derksen-Lubsen G., Grobbee D.E., et al. (2001). Signs of meningeal irritation at the emergency department: how often bacterial meningitis? *Pediatr Emerg Care*. **17**, 161-4.

Paggi R., Cenci E., De Socio G.V., Belati A., Marini D., et al. (2021) Accuracy and Impact on Patient Management of New Tools for Diagnosis of Sepsis: Experience with the T2 Magnetic Resonance Bacteria Panel. *Pathogens*. **10** (9), 1132.

Pallerla S.R., Van Dong D., Linh L.T.K., Van Son T., Quyen D.T., et al. (2022). Diagnosis of pathogens causing bacterial meningitis using Nanopore sequencing in a resource-limited setting. *Ann Clin Microbiol Antimicrob*. **21** (1): 39.

Pan S., Huang X., Wang Y., Li L., Zhao C., et al. (2018). Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of polymyxin B for post-neurosurgical intracranial infections due to MDR/XDR *Acinectobacter baumannii*: a retrospective cohort study. *Antimicrob Resist Infect Control*. **7**, 8.

Panato A.P., Tomasi L.T., Simon C.S., Madeira K., Simoes L.R., et al. (2014). Meta-analysis identifies tumor necrosis factor-alpha and interleukin-1 beta as diagnostic biomarkers for bacterial and aseptic meningitis. *Curr Neurovasc Res*. **11** (4): 340-8.

Pappas P.G., Perfect J.R., Cloud G.A., Larsen R.A., Pankey G.A., et al. (2001). Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis*. **33** (5): 690-9.

Parikh S.R., Campbell H., Bettinger J.A., Harrison L.H., Marshall H.S., et al. (2020). The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination. *J Infect*. **81** (4): 483-98.

Parikh S.R., Campbell H., Bettinger J.A., Harrison L.H., Marshall H.S., et al. (2020) The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination. *J Infect*. **81** (4): 483-98.

Parlakay A.O., Ceyhan M., Celik M., Ozsürekci Y., Karadać Oncel E., et al. (2013). Evaluation of pneumococcal PCR and urinary antigen detection in children. *Clin Lab*. **59** (11-12): 1409-11.

Patel S., Lederman E., Wallace M. (2003). Acetazolamide therapy and intracranial pressure. *Clin Infect Dis*. **36** (4), 538.

Perfect J.R., Dismukes W.E., Dromer F., Goldman D.L., Graybill J.R. et al. (2010). Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. **50** (3): 291-322.

Peri A.M., Ling W., Furuya-Kanamori L., et al. (2022). Performance of BioFire Blood Culture Identification 2 Panel (BCID2) for the detection of bloodstream pathogens and their associated resistance markers: a systematic review and meta-analysis of diagnostic test accuracy studies. *BMC Infect Dis*. **22**, 794.

Piatt J.H. Jr, Carlson C.V. (1993). A search for determinants of cerebrospinal fluid shunt survival: retrospective analysis of a 14-year institutional experience. *Pediatr Neurosurg*. **19** (5): 233-41; discussion 242.

Picazo J.J., Contreras J.R., Ríos E., Culebras E., Rodríguez-Avial I., et al. (2013). Rapid diagnosis of invasive pneumococcal disease in pediatric population. *J Microbiol Methods*. **93** (2): 116-20.

Pinto Junior V.L., Rebelo M.C., Gomes R.N., Assis E.F., Castro-Faria-Neto H.C., et al. (2011). IL-6 and IL-8 in cerebrospinal fluid from patients with aseptic meningitis and bacterial meningitis: their potential role as a marker for differential diagnosis. *Braz J Infect Dis*. **15** (2): 156-8.

Pristov K.E., Ghannoum M.A. (2019). Resistance of Candida to azoles and echinocandins worldwide. *Clin Microbiol Infect*. **25** (7): 792-8.

Quigley M.R., Reigel D.H., Kortyna R. (1989). Cerebrospinal fluid shunt infections. Report of 41 cases and a critical review of the literature. *Pediatr Neurosci*. **15** (3): 111-20.

Ramgopal S., Walker L.W., Vitale M.A., Nowalk A.J. (2019). Factors associated with serious bacterial infections in infants ≤60 days with hypothermia in the emergency department. *Am J Emerg Med*. **37** (6): 1139-43.

Rand K.H., Ulm A.J., Pincus D.W. (2004). Central nervous system

infections. In: Layon AJ, Gabrielli A, Friedman WA, editors. Textbook of neurointensive care. Philadelphia: WB Saunders.
Rauchway A.C., Husain S., Selhorst J.B. (2010). Neurologic presentations of fungal infections. *Neurol Clin.* **28** (1): 293-309.
Renier D., Lacombe J., Pierre-Kahn A., Sainte-Rose C., Hirsch J.F. (1984). Factors causing acute shunt infection. Computer analysis of 1174 operations. *J Neurosurg.* **61** (6): 1072-8.
Riser M.S., Bland C.M., Rudisill C.N., Bookstaver P.B. (2010). Cerebrospinal fluid penetration of high-dose daptomycin in suspected Staphylococcus aureus meningitis. *Ann Pharmacother.* **44** (11): 1832-5.
Roilides E., Iosifidis E. (2019). Acquired resistance in fungi: how large is the problem? *Clin Microbiol Infect.* **25** (7): 790-1.
Roujansky A., Martin M., Gomart C., Hulin A., Mounier R. (2020). Multidrug-resistant Staphylococcus epidermidis ventriculostomy-related infection successfully treated by intravenous ceftaroline after failure of daptomycin treatment. *World Neurosurg.* **136**: 221-5.
Saag M.S., Powderly W.G., Cloud G.A., Robinson P., Grieco M.H., et al. (1992). Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. *N Engl J Med.* **326** (2): 83-9.
Saha S. (2020). Unearthing the Unknown Causes of Meningitis. *Am J Trop Med Hyg.* **103** (2): 544-5.
Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S (2011). Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. J Infect. **62**(4):255-62.
Samra Z., Shmuely H., Nahum E., Paghis D., Ben-Ari J. (2003). Use of the NOW Streptococcus pneumoniae urinary antigen test in cerebrospinal fluid for rapid diagnosis of pneumococcal meningitis. *Diagn Microbiol Infect Dis.* **45** (4): 237-40.
Samsudin I., Vasikaran S.D. (2017). Clinical Utility and Measurement of Procalcitonin. *Clin Biochem Rev.* **38** (2): 59-68.
Sánchez-Portocarrero J., Pérez-Cecilia E., Corral O., Romero-Vivas J., Picazo J.J. (2000). The central nervous system and infection by Candida species. *Diagn Microbiol Infect Dis.* **37** (3): 169-79.
Schade R.P., Schinkel J., Visser L.G., Van Dijk J.M., Voormolen J.H., et al. (2005). Bacterial meningitis caused by the use of ventricular or lumbar cerebrospinal fluid catheters. *J Neurosurg.* **102** (2): 229-34.
Searls D.E., Sico J.J., Omay S.B., Bannykh S., Kuohung V., et al. (2009). Unusual presentations of nervous system infection by *Cryptococcus neoformans*. *Clin Neurol Neurosurg.* **111**, 638-42.
Seehusen D., Reeves M., Fomin D. (2003). Cerebrospinal fluid analysis. *Am Fam Physician.* **68** (6): 1103-8.
Sekhri N.K., Parikh S., Weber G.M. (2019). Comparison Of Digital Manometer And Water Column Manometer Pressures Measurements During Lumbar Puncture. *Med Devices* (Auckl). **12**, 451-8.
Sharma R. Raman (2010). Fungal infections of the nervous system: current perspective and controversies in management. *Int. J. Surg.* **8** (8) 591-601.
Shen H.Y., Gao W., Cheng J.J., Zhao S.D., Sun Y., et al. (2015). Direct comparison of the diagnostic accuracy between blood and cerebrospinal fluid procalcitonin levels in patients with meningitis. *Clin Biochem.* **48** (16-17): 1079-82.
Sime F.B., Lassig-Smith M., Starr T., Stuart J., Pandey S., et al. (2020). Cerebrospinal Fluid Penetration of Ceftolozane-Tazobactam in Critically Ill Patients with an Indwelling External Ventricular Drain. *Antimicrob Agents Chemother.* **65** (1): e01698-20.
Skipper B.J., Davis L.E. (1997). Ascertaining hypoglycorrhachia in an acute patient. *Am J Emerg Med.* **15** (4): 378-80.
Socié G., Caby-Tosi M.P., Marantz J.L., Cole A., Bedrosian C.L., et al. (2019). Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. *Br J Haematol.* **185** (2): 297-310.
Stenehjem E., Armstrong W.S. (2012). Central nervous system device infections. *Infect Dis Clin North Am.* **26**, 89-110. 31.
Stephani C., Choi A.H.K., Moerer O. (2021). Point-of-care detection of lactate in cerebrospinal fluid. *Intensive Care Med Exp.* **9** (1):18.
Stucki A., Cottagnoud M., Acosta F., Egerman U., Läuffer J., et al. (2012). Evaluation of ceftobiprole activity against a variety of gram-negative pathogens, including Escherichia coli, Haemophilus influenzae (β-lactamase positive and β-lactamase negative), and Klebsiella pneumoniae, in a rabbit meningitis model. *Antimicrob Agents Chemother.* **56** (2): 921-5.
Taha S., Taha M.K., Deghmane A.E. (2022). Impact of mandatory vaccination against serogroup C meningococci in targeted and non-targeted populations in France. *NPJ Vaccines* **7**, 73.
Takahashi W., Nakada T.A., Abe R., Tanaka K., Matsumura Y., et al. (2014). Usefulness of interleukin 6 levels in the cerebrospinal fluid for the diagnosis of bacterial meningitis. *J Crit Care.* **29** (4): 693.e1-6.
Tamaki T., Eguchi T., Sakamoto M., Teramoto A. (2004). Use of diffusion weighted magnetic resonance imaging in empyema after cranioplasty. *Br J Neurosurg.* **18**, 40-4.
Tamma P.D., Aitken S.L., Bonomo R.A., Mathers A.J., van Duin D., et al. (2022). Infectious Diseases Society of America Guidance on the Treatment of AmpC ć-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. *Infectious Diseases Society of America.* 2022; Version 2.0.
Tamma P.D., Aitken S.L., Bonomo R.A., Mathers A.J., van Duin D., et al. (2022). Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2022; Version 1.1.
Tansarli G.S., Chapin K.C. (2020). Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. *Clin Microbiol Infect.* **26** (3): 281-90.
Tascini C., Ferranti S., Gemignani G., Messina F., Menichetti F. (2002). Clinical microbiological case: fever and headache in a heavy consumer of eucalyptus extract. *Clin Microbiol Infect.* **8** (7): 437, 445-6.
Tavares T., Pinho L., Bonifácio Andrade E. (2022). Group B Streptococcal Neonatal Meningitis. *Clin Microbiol Rev.* **35** (2): e0007921.
Troendle M., Pettigrew A. (2019). A systematic review of cases of meningitis in the absence of cerebrospinal fluid pleocytosis on lumbar puncture. *BMC Infect Dis.* **5**, 19 (1): 692.
Trujillo-Gómez J., Tsokani S., Arango-Ferreira C., Atehortúa-Muñoz S., Jimenez-Villegas M.J., et al. (2022). Biofire FilmArray Meningitis/Encephalitis panel for the aetiological diagnosis of central nervous system infections: A systematic review and diagnostic test accuracy meta-analysis. E Clinical Medicine. **44**, 101275
Tsegka K.G., Voulgaris G.L., Kyriakidou M., Falagas M.E. (2020). Intravenous fosfomycin for the treatment of patients with central nervous system infections: evaluation of the published evidence. *Expert Rev Anti Infect Ther.* **18** (7): 657-68.
Tsolaki V., Karvouniaris M., Manoulakas E., et al. (2018). Intraventricular CNS treatment with Colistin-Tigecycline combination: a case series. *J Crit Care*. **47**: 338-41.
Tumani H., Petereit H.F., Gerritzen A., Gross C.C., Huss A., et al. (2020) S1 guidelines "lumbar puncture and cerebrospinal fluid analysis" (abridged and translated version). *Neurol Res Pract.* **16**, 2: 8.
Tunkel A.R., Hartman B.J., Kaplan S.L., Kaufman B.A., Roos K.L., et al. (2004). Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* **39** (9): 1267-84.
Tunkel A.R., Hasbun R., Bhimraj A., Byers K., Kaplan S.L., et al. (2017). Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis.* **64** (6): e34-e65.
van de Beek D., Brouwer M.C., Koedel U., Wall E.C. (2021). Community-acquired bacterial meningitis. *Lancet.* **398** (10306): 1171-83.
van de Beek D., Brouwer M.C., Koedel U., Wall E.C. (2022). Steroid use in non-pneumococcal and non-Haemophilus bacterial meningitis - Authors' reply. *Lancet.* **399** (10326): 718.
van de Beek D., Cabellos C., Dzupova O., Esposito S., Klein M., et al. (2016). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect.* **22** (Suppl. 3): S37-62.
van de Beek D., de Gans J., Spanjaard L., Weisfelt M., Reitsma J.B., et al. (2004). Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med.* **351** (18): 1849-59.
van de Beek D., Drake J.M., Tunkel A.R. (2010). Nosocomial bacterial meningitis. *N Engl J Med.* **362** (2): 146-54.

van Kessel F., van den Ende C., Oordt-Speets A.M., Kyaw M.H. (2019) Outbreaks of meningococcal meningitis in non-African countries over the last 50 years: a systematic review. *J Glob Health*. **9**(1):010411.

van Samkar A., Brouwer M.C., van der Ende A., van de Beek D. (2016). Zoonotic bacterial meningitis in human adults. *Neurology*. **87** (11): 1171-9.

van Soest T.M., Chekrouni N., van Sorge N.M., Brouwer M.C., van de Beek D. (2022). Bacterial meningitis presenting with a normal cerebrospinal fluid leukocyte count. *J Infect*. **84** (5): 615-20.

Vázquez J.A., Adducci Mdel C., Coll C., Godoy Monzón D., Iserson K.V. (2012). Acute meningitis prognosis using cerebrospinal fluid interleukin-6 levels. *J Emerg Med*. **43** (2): 322-7.

Velissaris D., Pintea M., Pantzaris N., Spatha E., Karamouzos V., et al. (2018). The Role of Procalcitonin in the Diagnosis of Meningitis: A Literature Review. *J Clin Med*. **11**; 7 (6): 148.

Viallon A., Botelho-Nevers E., Zeni F. (2016). Clinical decision rules for acute bacterial meningitis: current insights. *Open Access Emerg Med*. **8**, 7-16.

Viallon A., Desseigne N., Marjollet O., Birynczyk A., Belin M., et al. (2011). Meningitis in adult patients with a negative direct cerebrospinal fluid examination: value of cytochemical markers for differential diagnosis. *Crit Care*. **15** (3): R136.

Vinchon M., Dhellemmes P. (2006). Cerebrospinal fluid shunt infection: risk factors and long-term follow-up. *Childs Nerv Syst*. **22** (7): 692-7.

Wake R.M., Britz E., Sriruttan C., Rukasha I., Omar T., et al. (2018) High cryptococcal antigen titers in blood are predictive of subclinical cryptococcal meningitis among human immunodeficiency virus-infected patients. *Clin Infect Dis*. **66**, 686-92.

Walti L.N., Conen A., Coward J., Jost G.F., Trampuz A. (2013). Characteristics of infections associated with external ventricular drains of cerebrospinal fluid. *J Infect*. **66**, 424-31.

Wang H. (2020). Higher Procalcitonin Level in Cerebrospinal Fluid than in Serum Is a Feasible Indicator for Diagnosis of Intracranial Infection. *Surg Infect* (Larchmt). **21** (8): 704-8.

Welinder-Olsson C., Dotevall L., Hogevik H., Jungnelius R., Trollfors B., Wahl M., et al. (2007) Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. *Clin Microbiol Infect*. **13**, 879-86.

WHO (2021). Defeating meningitis by 2030: a global road map. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO

Wiberg K., Birnbaum A., Gradon J. (2008). Causes and presentation of meningitis in a Baltimore community hospital 1997-2006. *South Med J*. **101** (10): 1012-6.

Wilson M.R., Sample H.A., Zorn K.C., Arevalo S., Yu G., et al. (2019). Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. *N Engl J Med*. **380** (24): 2327-40.

Winans S.A., Guerrero-Wooley R.L., Park S.H., et al. (2021). Continuous infusion of ceftolozane-tazobactam resulted in high cerebrospinal fluid concentrations of ceftolozane in a patient with multidrug-resistant Pseudomonas aeruginosa meningitis. *Infection*. **49** (2): 355-9.

Wunderlich C.A., Krach L.E. (2006). Gram-negative meningitis and infections in individuals treated with intrathecal baclofen for spasticity: a retrospective study. *Dev Med Child Neurol*. **48**, 450-5.

Xu J., Jiang J., Zhang Y., Li W. (2020). Cytokine characteristic of cerebrospinal fluid from children with enteroviral meningitis compared to bacterial meningitis. *J Clin Lab Anal*. **34** (5): e23198.

Xu X.X., Li B., Yang H.F., Du Y., Li Y., et al. (2014). Can diffusion-weighted imaging be used to differentiate brain abscess from other ring-enhancing brain lesions? A meta-analysis. *Clin Radiol*. **69**, 909-15.

Young N., Thomas M. (2018). Meningitis in adults: diagnosis and management. *Intern Med J*. **48** (11): 1294-307.

Younger J.J., Simmons J.C., Barrett F.F. (1987). Operative related infection rates for ventriculoperitoneal shunt procedures in a children's hospital. *Infect Control*. **8** (2): 67-70.

Yu Y., Li H.J. (2017) Diagnostic and prognostic value of procalcitonin for early intracranial infection after craniotomy. *Braz J Med Biol Res*. **50** (5): e6021.

Zhang L., Ma L., Zhou X., Meng J., Wen J., et al. (2019) Diagnostic Value of Procalcitonin for Bacterial Meningitis in Children: A Comparison Analysis Between Serum and Cerebrospinal Fluid Procalcitonin Levels. *Clin Pediatr* (Phila). **58** (2): 159-65.

Zhu L., Dong L., Li Y., Lu G., Zhang H., et al. (2019). The Diagnostic and Antibiotic Reference Values of Procalcitonin for Intracranial Infection After Craniotomy. *World Neurosurg*. **126**, e1-e7.

Ziai W.C., Lewin J.J., III. (2009). Improving the role of intraventricular antimicrobial agents in the management of meningitis. *Curr Opin Neurol*. **22**, 277-82.

Zunt J.R., Kassebaum N.J., Blake N., Glennie L., Wright C., Nichols E., et al. (2018) Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. **17** (12): 1061-82.