Community-acquired bacterial meningitis in adults: emergency department management protocol

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Abstract

Acute bacterial meningitis (ABM) is a rare but disabling infectious condition that requires a performant multidisciplinary management approach. Between 70 and 90 adult patients are diagnosed with community-acquired ABM in Belgium annually, and reported case fatality rates range from 17 to 40%. The currently available guidelines provide evidence-based guidance on how to manage this disease. However, these guidelines do not translate the evidence to the daily practice at the emergency department in a Belgian healthcare context. We created a taskforce in University Hospitals Leuven consisting of experts with complementary expertise in managing this disease: neurology, neurosurgery, intensive care medicine, microbiology and infectious diseases. The taskforce agreed upon a flowchart containing seven management steps encompassing all relevant phases in emergency ABM management. In addition to the focus on timely and adequate initiation of antimicrobial treatment, the flowchart and protocol also provide guidance on practical hurdles such as how to assess the safety of performing a lumbar puncture and when to refer patients to the intensive care department. This protocol was implemented in University Hospitals Leuven and fosters inter-disciplinary coordination of ABM care.

Abbreviations

ABM	Acute bacterial meningitis
aPTT	Activated partial thromboplastin time
CRP	C-reactive protein
CT	Computed tomography
CSF	Cerebrospinal fluid
DIC	Diffuse intravascular coagulation
EFNS	European Federation of Neurological Societies
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
ICU	Intensive care unit INR International normalized ratio
ISDA	Infectious Diseases Society of America
IM	Intramuscular
LP	Lumbar puncture
PCR	Polymerase chain reaction
PT	Prothrombin time
WBC	White blood cell

Introduction

Despite the advent of vaccinations against key causative pathogens, acute bacterial meningitis (ABM) remains one of the most disabling infectious diseases worldwide. Based on the reported incidence in the Western World, between 70 and 90 adult patients are diagnosed with community acquired ABM in Belgium annually [1], and reported case fatality rates range from 17 to 40% [2]. These numbers emphasize the need for a comprehensive protocol that optimizes medical management. Efforts to standardize meningitis care have been successfully implemented abroad. The introduction of the Dutch bacterial meningitis guideline in 2013 was associated with a trend towards more early initiation of treatment and with increased adherence to antibiotic policy [3]. Similarly, Sweden observed a reduction of 1.2 h to initiate adequate antibiotic therapy after protocol implementation [4]. Given the current lack of practical clinical guidance on ABM that can be applied in a Belgian healthcare context, a local taskforce was created. The goal was to translate existing guidelines on community acquired ABM management into a practical flowchart for registrars at the emergency department.

Methodology

Within the University Hospitals Leuven, there was an apparent need for a multidisciplinary management plan for community-acquired ABM. In this context, a local taskforce on ABM was composed. Members were recruited based on their complementary expertise in ABM management: neuroinflammation (B.D., I.S.), microbiology (K.L.), infectious diseases (E.V.W.), intensive care medicine (G.M.; A.W.) and neurosurgery (J.V.L.). The ABM guidelines that were used as evidence-based input for the taskforce were issued by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [2], European Federation of Neurological Societies (EFNS) [5] and the Infectious Diseases Society of America (IDSA) [6]. A draft clinical algorithm was created which was further developed and discussed through electronic correspondence among the experts. This resulted in a consensus clinical protocol encompassing seven ABM management steps that was implemented at the emergency department of University Hospitals Leuven.

Results

The discussions in the ABM taskforce resulted in a seven-step ABM management protocol (Fig. 1, Table 1). The rationale for each step in this protocol is outlined in the following headings covering initial evaluation, antibiotic treatment, and intensive care management.

Initial evaluation (STEP 1–5)

Clinical evaluation (STEP 1)

A meta-analysis including 845 patients over a 30-year period showed a poor sensitivity and specificity for individual symptoms such as headache, nausea and vomiting to diagnose meningitis [7]. The classic triad of fever, stiff neck and alterations in mental status was present in maximum two-thirds of adult patients when looking at retrospective cohorts [8, 9] and in 27% of a prospective cohort [10]. Fever was the most common symptom with frequencies ranging from 84 to 95%. However, it was only observed in 70% of elderly patients [11]. As there is considerable clinical heterogeneity in ABM presentation, we outlined in our protocol that any clinical suspicion of ABM should always warrant semi-urgent neurological evaluation. Importantly, a neurological evaluation needs to be complemented by a general evaluation. A rash was present in 176 of 696 patients of a large Dutch meningitis cohort [12] and might be suggestive for diffuse intravascular coagulation (DIC), a clinical and laboratory based diagnosis involving findings of coagulopathy and/or fibrinolysis, associated with an inflammatory insult such as sepsis [13]. Findings such as thrombocytopenia ($< 100 \times 10^9$/L or a rapid decline), low fibrinogen and elevated D-dimers are considered to be relatively sensitive but not specific. For patients without bleeding or thrombosis, the platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT) provide sufficient information. Peripheral blood smear, fibrinogen and D-dimers are required in patients with prolonged PT and aPTT and/ or bleeding or thrombosis. We emphasized that the clinical suspicion of DIC is a contraindication to perform a lumbar puncture (LP) [2, 13]. Furthermore, DIC contributes highly to morbidity and the risk of mortality and urges immediate transfer to an intensive care unit [13].

Blood markers of inflammation and blood cultures (STEP 1)

Blood markers such as white blood cell (WBC) count and C-reactive protein (CRP) need to be determined to monitor baseline inflammation and its evolution (Table 2). They are not useful in the differential diagnosis of ABM as other bacterial infections can also induce an increase in these parameters. Blood cultures are extremely valuable for detection of the causative organism and to establish susceptibility patterns. The rate of positive blood cultures is dependent on the causative organism, namely 75% for Streptococcus pneumoniae, 50–90% for Haemophilus influenzae and 40–60% for N. meningitidis [14]. The yield of blood cultures decreases with 20% if patients are pre-treated with antibiotics [15].

Brain CT (STEP 2)

The most important reason to perform a brain computed tomography (CT) is excluding non-infectious pathology (e.g., subarachnoid haemorrhage and cerebral sinus thrombosis). In addition, brain CT can be used to evaluate cerebral oedema and (impending) brain shift. Apart from the detection of obstructive hydrocephalus or space-occupying masses (e.g., subdural empyema, brain abscess or intracerebral haemorrhages), clinicians should evaluate CT images to detect early, less obvious signs

of diffuse brain swelling, such as: (1) loss of differentiation between grey and white matter in cases with diffuse cytotoxic oedema, (2) compression of the ventricles, giving the frontal horns a slit-like appearance, (3) loss of sulcal markings and (4) lack of visualization of the peri-mesencephalic, suprasellar or quadrigeminal cisterns [16]. Importantly, no technical examination is infallible. Cranial CT has been reported to be normal in some patients with an aggressive disease course and rapidly evolving brain oedema [16, 17] and the interrater reliability is only moderate [18].

Lumbar puncture (STEP 3–5)

Evaluating safety to perform a lumbar puncture (STEP 3)

Lumbar puncture is crucial to diagnose ABM and to determine the causative pathogen. As obtaining a brain CT before LP can introduce delays in administering antibiotics, the guidelines urge to perform a LP without previous brain imaging [2, 5, 6]. However, in patients with a space occupying lesion, withdrawal of cerebrospinal fluid (CSF) at the lumbar point can cause a cranial–caudal pressure gradient with the potential to increase existing brain shift [19]. Adults with papilledema, focal neurological deficits, new-onset seizures, moderate-to-severe impairment of consciousness (GCS ≤ 10) and/or a severe immune deficiency should, therefore, always have brain imaging before LP is performed [2, 17]. Notably, the presence of an isolated Babinski sign is not considered as a focal neurological deficit in this setting [16]. However, putting the recommendation of 'LP before brain CT' into practice has proven difficult. In three teaching hospitals in the United States, only 9% of the patients with suspected ABM underwent a LP before CT [20]. A prospective cohort in the Netherlands could equally not demonstrate differences in the timing of imaging relative to LP after guideline implementation (LP performed after brain CT: 67% pre-guideline; 66% post-guideline) [3]. These numbers illustrate the difficulty of narrowing down the differential diagnosis based on clinical presentation. In addition, brain CT is an easily accessible examination in many first-world hospital settings that often can be obtained while waiting for the coagulation analysis. Although our taskforce agreed that brain CT before LP is unnecessary in many cases and incorporated this recommendation in the flowchart, we realize that the majority of the patients will have a brain CT before LP in practice. Furthermore, coagulation disorders such as DIC, use of anticoagulant drugs or significant thrombocytopenia (platelets ≤ 50×109 /L) are absolute contraindications for LP.

Opening pressure (STEP 4)

In a large prospective cohort, LP opening pressures were normal in only 18% of the ABM cases and 39% had a pressure of ≥40 cmH20 [12]. Patients with opening pressures of more than 40 cmH20 were more likely to be admitted in a coma than those with lower pressures. However, the percentage of patients with an unfavourable outcome was similar in the two groups. Even in the high-pressure group, only a quarter of the patients developed coma. Notably, not every patient that presents with decreased consciousness manifests with increased intracranial pressure (ICP) which illustrates the confounding effect of systemic pathology or sepsis [21]. As CSF opening pressures can be relatively easily obtained when performing a LP, we recommended in our flowchart to measure this variable.

Laboratory tests on CSF (STEP 4)

Classic CSF laboratory investigations are leukocyte count, glucose, total protein and lactate level (Table 2). CSF culture is the gold standard for the diagnosis of ABM and is positive in 50–90% of patients depending on the causative organism [2]. The yield of CSF culture is lower when CSF is collected once antibiotic treatment has started. Danish and American cohort studies found a decrease in lumbar culture positivity from 66 to 62% and from 88 to 70%, respectively, when there was pre-treatment with antibiotics before LP [15, 22]. CSF gram stain is a relatively simple and quick method to assess the

presence of bacterial species with a high sensitivity (40–90%) for common causative organisms [2]. However, the yield is infrastructure and operator dependent. Therefore, the possibility of an erroneous result should be taken into account when requesting the test after office hours [23]. The gram stain yield may decrease slightly if there was pre-treatment with antibiotics though studies are not consistent [2]. There is no benefit of routinely performing bacterial polymerase chain reaction (PCR) as it can only identify the pathogen and does not allow susceptibility testing [2]. Moreover, there are issues with false positive rates when using multiplex panels [24]. However, our taskforce decided in line with the ESCMID guidelines that in patients pre-treated with antibiotics for ≥8 h and a negative CSF gram stain, PCR can be useful to confirm the diagnosis and cost saving (e.g., duration antibiotics treatment). PCR on CSF resulted in sensitivities of 79–100% for S. pneumoniae, 91–100% for N. meningitidis and 67–100% for H. influenzae [19]. Reported specificity was around 95–100% for all microorganisms. A prospective study from Sweden evaluated PCR in repeat LP's in 25 ABM cases: PCR was positive in 89% of samples taken on days 1–3, in 70% from days 4–6 and in 33% from days 7–10, whereas all CSF cultures of repeat LP's were negative [25]. The incremental value of PCR in Listeria meningitis is currently unclear [2].

CSF alterations in bacterial meningitis (STEP 5)

CSF measurements that reliably predict ABM are more than 2000 leukocytes/µL or more than 1180 polymorphonuclear leukocytes/µL; a protein level over 2.2 g/L; a glucose level lower than 35 mg/dL and a ratio of CSF glucose to blood glucose of less than 0.23 [26]. In practice, the majority of ABM patients will not present with such well-distinguished CSF alterations (Table 3). Three retrospective studies found a WBC count less than 100 cells/µL in 10–19% of confirmed ABM patients [9, 27, 28]. In a prospective study of 258 cases of meningococcal meningitis, 5% of the patients had less than 100 cells/µL and 1.7% had a completely normal CSF composition [10]. Low cell counts can be expected in neutropenic patients, patients with active cancer, concomitant septic shock and listeria meningitis [14, 29]. Glucose and protein levels are equally not always reliable. Their concentrations are strongly influenced by antibiotic pre-treatment [15]. Patients with ≥12 h pre-treatment had significantly higher median CSF glucose levels (48 vs. 29 mg/dL) and lower median CSF protein levels (0.12 vs. 0.18 G/L), compared with patients with shorter pre-treatment duration. Furthermore, lactate is frequently used to distinguish bacterial from aseptic meningitis. Two meta-analyses concluded that the diagnostic accuracy of CSF lactate to diagnose ABM is higher than that of CSF WBC count. However, when patients are pre-treated with antibiotics sensitivity dropped considerably (from 96 to 49%) [30, 31]. Moreover, CSF lactate concentration cannot reliably differentiate from other central nervous system diseases such as herpes encephalitis or seizures [32]. As laboratory values have to be interpreted in their respective clinical contexts, we emphasized in our flowchart that it is always necessary to critically review the microbiological results.

Treatment of acute bacterial meningitis (STEP 1, 5–7)

Empiric therapy for community-acquired bacterial meningitis (STEP 1, 5, 6)

The choice of empirical antibiotic treatment is conditional on age, comorbidities and the regional susceptibility patterns of S. pneumoniae (Table 4). In Belgium, epidemiological data did not demonstrate true resistance of S. pneumoniae against third-generation cephalosporins [33]. Therefore, ceftriaxone or cefotaxime are the first-line choice. When the patient's history reveals a recent stay abroad (≤ 2 weeks), in particular in Southern and Eastern Europe as well as other endemic regions worldwide, the addition of vancomycin needs to be considered [2, 6, 34]. When risk factors for L. monocytogenes infection are present (e.g., older age > 50 years, diabetes mellitus, use of immune suppressive drugs, cancer) empirical antibiotic treatment should include amoxicillin or ampicillin [2, 5, 6]. In a retrospective cohort, four cases of L. monocytogenes occurred over a period of 6 years in adults under the age of 50 without an immunocompromised state [35]. In patients with a known allergy to β-lactam antibiotics, the therapy should be adapted [2, 5, 6]. In this situation, meropenem or vancomycin in combination with aztreonam may replace cephalosporins as a first-line treatment (Table 3). As there is some similarity in the chemical structure between penicillins and carbapenems, cross-reactivity might exist. Prospective studies have however demonstrated that carbapenems are a safe alternative in more than 99% of patients with either IgE- (Gell-Coombs Type I) or T-cell-mediated (Gell-Coombs Type IV) reactions to penicillins or cephalosporins [36, 37]. Furthermore, it is recommended to involve the infectious disease service when beta-lactam allergy is suspected or confirmed as not all types of allergy require a change in antibiotic management [38]. We stressed in the protocol that empiric antibiotic treatment does not change when ABM is caused by contiguous otitis or mastoiditis [39, 40].

Targeted antibiotic therapy for community-acquired bacterial meningitis (STEP 5, 7)

After identification of the pathogen through culture, the antibiotic treatment needs to be optimized in consultation with the infectiology and/or microbiology department [2]. Shorter courses of narrow-spectrum antibiotics can reduce hospital stay, costs and the risk of adverse events such as nosocomial infections with resistant strains.

Routes of antibiotic administration (STEP 1, 5, 6)

Antibiotics can be administered by continuous infusion or bolus administration. As β-lactam's pharmacokinetic/ dynamic profile is time dependent, it has been hypothesized that penicillin might be more efficient when given continuously compared to the currently used bolus injections. However, a randomized trial did not show significant differences between continuous and bolus administration of cefotaxime in children with ABM [41] and, therefore, no recommendation regarding continuous antibiotic administration can be given [2].

Timing of antibiotics (STEP 1–6)

Failure of timely antibiotic administration negatively influences outcome. Delays of more than 6 h were associated with adverse outcomes in a Canadian study [42, 43]. There was a relative increase in mortality of 12.6% per hour of delay of antibiotics administration in a Swedish study [43]. Hence, the ESCMID advised a time-to-antibiotic-administration interval of maximally one hour [2]. This implies that antibiotics have to be administered in every case with ABM in the differential diagnosis before laboratory results are known. A Swiss medical centre advocates a more focused approach where antibiotics are administered before LP in cases with high clinical suspicion, blood pressure < 90/60 mmHg, petechiae, GCS ≤ 9, focal neurological deficits and/or papillary oedema [23]. We decided in our protocol to start antibiotics promptly, especially in those cases with high clinical suspicion or with the

presence of negative prognostic factors at presentation. Importantly, also when antibiotics are administered early clinicians need to think about obtaining blood cultures.

Duration of antibiotic treatment (STEP 7)

The time interval to eradicate all pathogenic ABM bacteria varies widely and depends on the causative strain, disease severity and the antimicrobial agent. Available data suggest that the currently accepted treatment intervals are probably too extended for the majority of the patients. In a meta-analysis of five controlled trials investigating shorter (4–7 days) versus longer (7–14 days) antibiotic treatments for ABM, investigators noted no difference in outcome between both regimens [44]. Similar results were obtained in trials conducted in Africa and Asia [45, 46]. Although the results are promising, these studies did not have the power to assess the efficacy of the shorter regimens in individual strains, in patients with severe disease or in patients with potentially resistant pathogens. Hence, guidelines aimed at high-income countries recommend cautiously 7 days of treatment for Haemophilus and meningococcal meningitis and 10–14 days of treatment for pneumococcal meningitis [2, 5, 6].

Administration of adjunctive dexamethasone (STEP 1, 5, 6)

Experimental animal models have shown that ABM outcome is related to the severity of inflammation in the subarachnoid space. For adults with community-acquired ABM, the results of a European controlled trial showed that adjunctive dexamethasone was associated with a reduced risk of an unfavourable outcome (15% vs. 25%) and mortality (7% vs. 15%) [47]. In a Cochrane meta-analysis, corticosteroids decreased overall hearing loss and neurologic sequelae but did not reduce mortality [48]. A subgroup analysis showed that corticosteroids reduced mortality in pneumococcal meningitis and severe hearing loss in H. influenzae meningitis. No excess of relevant dexamethasone-related adverse effects was observed compared to placebo. Although the duration of corticosteroid administration varied in different ABM trials, the most commonly applied regimen is currently 10 mg dexamethasone for 4 days intravenously every 6 h [2, 5, 49]. Dexamethasone needs to be stopped when the causative organism is not S. pneumoniae or H. influenzae [2]. There was no beneficial effect of corticosteroids in low-income countries potentially due to the often delayed presentation and high rate of concomitant malnutrition and human immunodeficiency virus infection [48, 49]. Ideally, dexamethasone is administered before or together with the first dose of antibiotics. It is unclear at what time point after the initiation of antibiotics adjunctive dexamethasone ceases to be beneficial. The ESCMID guideline committee advises arbitrarily to associate dexamethasone up to 4 h after the initiation of parenteral antibiotics [2]. Of note, also in patients presenting with ABM and septic shock the survival benefit of adjunctive dexamethasone probably outweighs corticosteroid-associated risks [34].

Prophylaxis (STEP 5)

Prophylactic treatment of household contacts of meningococcal meningitis patients is necessary as the risk of meningococcal disease is increased 400–800-fold in these individuals (Table 5) [2]. Close contacts are defined as household members and anyone directly exposed to oral secretions (e.g., tracheal intubation).

Intensive care management (STEP 6)

Outcome in patients with decreased consciousness at presentation (STEP 6)

A decreased level of consciousness at admission is a major predictor of bad outcome [8, 12, 50]. Nonetheless, an American cohort of 39 patients with GCS ≤ 8 at or within 24 h of admission reported 23 patients surviving and 8 with no or a slight disability [51]. A Dutch nation-wide study detected 30 patients with a score of three on GCS on admission of whom seven had a good functional outcome and 12 survived with remaining disabilities [52]. Some anecdotal case reports about patients with a refractory increase in ICP treated with craniotomy observed a good outcome [53–55]. Practice guidelines state that in patients with impending cerebral herniation ICP monitoring, use of osmotic diuretics and craniotomy may be considered but that the outcome is reserved [2, 5]. The taskforce agreed that patients with decreased consciousness cannot be excluded a priori from more aggressive management strategies. Nonetheless, these measures need to be used cautiously and judged on a case-by-case basis.

Evidence for neuro-intensive care management (STEP 6)

When patients are referred to the ICU department, it is obviously important to rule out systemic causes of decreased consciousness. Radiological abnormalities such as space occupying lesions or hydrocephalus require neurosurgical management and follow-up. However, the evidence regarding the modalities of intensive care unit (ICU) management and especially how to manage brain oedema in ABM patients is scarce [2, 56, 57]. An open-label randomized trial in France evaluating the effect of induced hypothermia in severe ABM was stopped preliminarily after inclusion of 98 patients because of a higher mortality in the intervention group (51 versus 31%) [58]. A double-blind randomized trial comparing glycerol therapy versus placebo in 265 adults with ABM in Africa was halted for the same reason [59]. A Cochrane review concluded that glycerol has no effect on mortality, whereas there appeared to be marginal protection against deafness and neurological disability [60]. Mannitol can be administered but no conclusive evidence regarding its benefit exists [2, 56]. For more invasive ICP management, there is even more limited and only non-randomized evidence available. A Swedish intervention–control study on early ICP-targeted treatment in ABM patients found a significant difference in mortality after 2 months: 5 of 52 patients (10%) in the intervention group died and 16 of 53 (30%) in the control group [21]. Full recovery was also more frequent in the per protocol group. A retrospective Canadian cohort study on the effect of lumbar drainage as adjunctive therapy in patients with ABM and altered mental status showed a significantly decreased mortality in the lumbar drainage group [61]. However, a retrospective nation-wide United States cohort did not show any benefit of ICP monitoring in children [62]. As no fixed protocols are available, the taskforce decided that the specifics of the ICU management protocols can be left at the discretion of the intensivists.

Conclusions

Treatment algorithms for the management of community acquired ABM should follow a ‘time is brain’ philosophy. Previous reports have demonstrated that the translation of the ABM guidelines into a locally applicable protocol leads to a more optimal standardized medical management [3, 4, 63]. Importantly, the University Hospitals Leuven protocol goes beyond the medical treatment of ABM, and provides guidance on every decision that needs to be taken along the ABM care path. Finally, we hope the protocol could be useful for other first-world hospitals aiming to optimize ABM care.

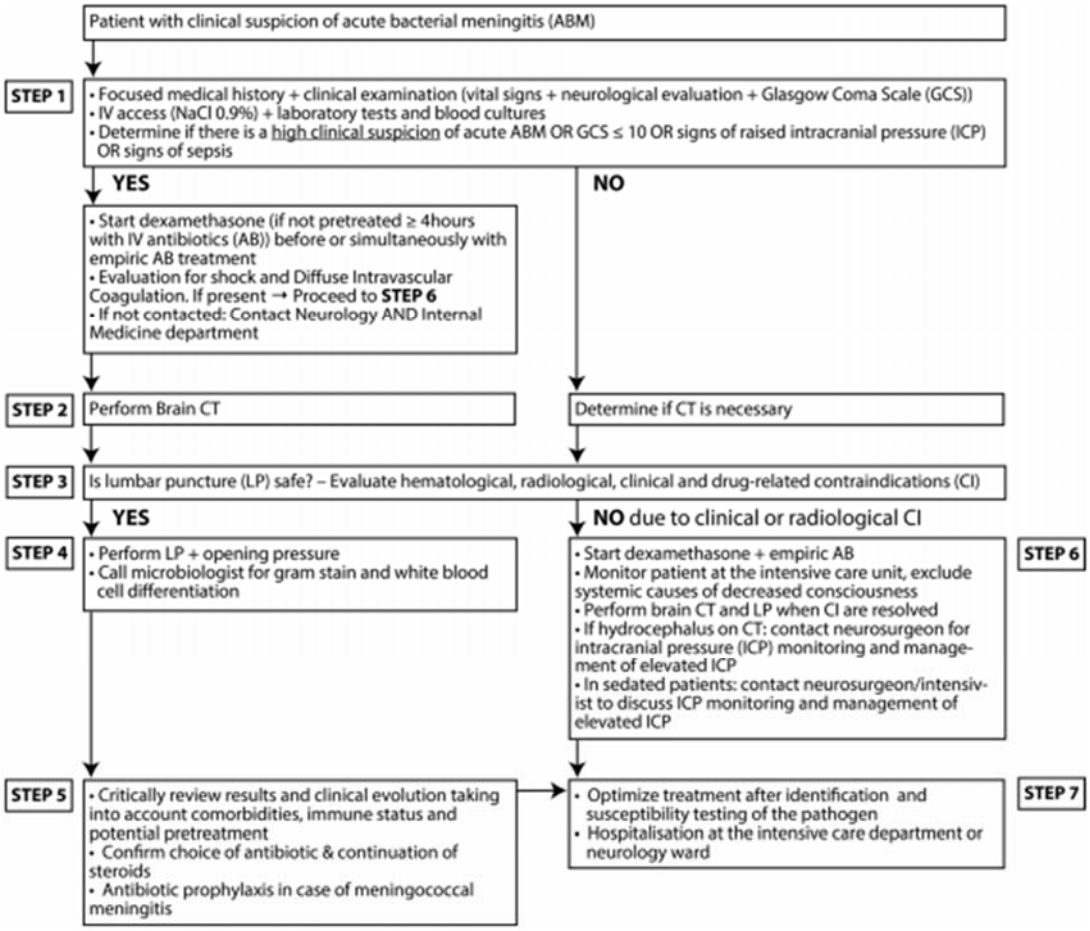

Fig. 1 Consensus flowchart for treatment of community-acquired acute bacterial meningitis in adults

Table 1 Consensus protocol for treatment of community-acquired acute bacterial meningitis in adults

In every adult (≥ 16 years) patient with a clinical suspicion of acute bacterial meningitis (ABM):

STEP 1: Initial evaluation

– Focused medical history documenting conditions predisposing to an immunocompromised state, recent intake of antibiotics or anticoagulant drugs and recent (≤ 2 weeks) travels abroad
– Neurological examination documenting signs of raised intracranial pressure (ICP), Glasgow Coma Scale (GCS), vital signs
– Ascertain IV access (NaCl 0.9%), order laboratory tests (Table 2) including blood culture
– In case of GCS ≤ 10 OR signs of raised ICP OR when there is a high clinical suspicion of ABM (e.g. pronounced nuchal rigidity and fever) OR signs of sepsis:
* Initiate dexamethasone (10 mg, every 6 h, IV) before or simultaneously with empiric AB treatment (Table 3) unless the patient was pre-treated with intravenous antibiotics for ≥ 4 h. Signs of sepsis or septic shock are no contraindication for corticosteroids
* Evaluate signs of shock or diffuse intravascular coagulation (DIC) (e.g., petechiae, platelet count < $100*10^9$/L). If present, immediately proceed to **STEP 6** If not contacted before: contact the department of neurology AND internal medicine

STEP 2: Perform brain CT

– Evaluate non-infectious pathology, especially subarachnoid haemorrhage or venous sinus thrombosis
– Evaluate the presence of space-occupying lesions and/or hydrocephalus
– Evaluate any indication of (impending) brain herniation:
(1) loss of differentiation between grey matter and white matter,
(2) compression of the ventricles, giving the frontal horns a slit-like appearance,
(3) loss of sulcal markings and
(4) lack of visualization of the peri-mesencephalic, suprasellar or quadrigeminal cisterns

STEP 3: Assess safety of lumbar puncture

– Exclude haematological (e.g., DIC, INR > 1.7, platelets < 50×10^9/L) and drug-related contraindications
– Exclude radiological contraindications as outlined in **STEP 2**
– Exclude presence of clinical signs indicative of raised ICP
– Exclude rapid clinical deterioration, especially when GCS decreased ≥ 2 in the preceding hour
If none of the above-mentioned contraindications are present: proceed to **STEP 4**
If one or more contraindications are present: proceed immediately to **STEP 6**

STEP 4: Perform lumbar puncture

– Document opening pressure
– Contact the microbiology department to perform a gram stain and WBC differentiation
– Determine CSF parameters mentioned in Table 2

STEP 5: Critically review results

– Critically review the microbiological results (Table 4), clinical presentation and evolution, always taking into account the comorbidities and immune status of the patient as well as the level of antibiotic pre-treatment. If ABM cannot be ruled out, start empiric treatment (Table 3) if this was not initiated before
– When the patient appears to be HIV positive OR when the Gram stain is positive and does not demonstrate Gram-positive diplococci (S. *pneumoniae*) or Gram-negative rods (H. *influenza*) dexamethasone can be stopped
– In patients with a suspected or confirmed beta-lactam allergy, consult the Infectious Disease department on the most optimal antimicrobial therapy
– When meningococcal meningitis is confirmed, assess the necessity for ABM prophylaxis in close contacts (Table 5). Close contacts are defined as household members and anyone directly exposed to oral secretions. Prophylaxis needs to be initiated within 24 h after N. *meningitidis* identification
– If concomitant acute otitis or mastoiditis: contact the otorhinolaryngology department to optimize the local infectious management

STEP 6: Neuro-intensive care

– Start dexamethasone simultaneously with empiric AB treatment if this was not started before
– Monitor patient at the intensive care unit when clinical or radiological CI for LP are present and exclude systemic causes of decreased consciousness
If not performed before: perform brain CT (**STEP2**) and LP when safe (**STEP 3**)**.** Interpret results as outlined in **STEP 5**
If hydrocephalus is present on CT: contact neurosurgeon for ICP monitoring and management of elevated ICP
If the patient is sedated: contact neurosurgeon/intensivist to discuss ICP monitoring and management of elevated ICP

STEP 7: Hospitalization

– Daily neurological examination. Consider repeat brain CT and LP when clinical deterioration.
– Optimize antibiotic treatment immediately after identification of the pathogen and antibiotic susceptibility testing becomes available.
– Stop dexamethasone when the identified pathogen is not S. *pneumoniae* or H. *influenzae*. If not: continue dexamethasone for 4 days (10 mg, every 6 h, IV)
– Duration antibiotic therapy: N. *meningitidis* and H. *influenzae*: 7 days. S. *pneumoniae*: 10–14 days
If no etiological error can be made and/or when the patient was pre-treated with antibiotics in combination with a high clinical suspicion of ABM: treat patient with empiric antibiotics during 10 days

Table 2 Blood and CSF work-up in patients with suspected community-acquired acute bacterial meningitis

Sample	Tests
Blood	- CRP, WBC count and differentiation - INR, PT, aPTT, platelet count - Glucose - Renal and hepatic function tests - Culture - In case of petechiae: fibrinogen, D-dimer, peripheral blood smear
Cerebrospinal Fluid	- Cytology and differentiation - Glucose, ratio blood glucose/CSF - Protein and lactate - Culture - Gram stain - PCR enterovirus, herpes simplex virus 1/2, and potentially varicella zoster virus - When pre-treated with antibiotics OR culture negative and high clinical suspicion: multiplex PCR

CRP C-reactive protein, *WBC* white blood cell count, *INR* international normalized ratio, *PT* prothrombin time, *aPTT* activated partial prothromboplastin time, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction

Table 3 Empirical treatment of community-acquired bacterial meningitis

Patient group	Antibiotic	Intravenous dose
Age ≥ 16 and ≤ 50 years In case of β-lactam anaphylaxis	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h, Cefotaxime 2 g q4h
	Meropenem	Meropenem 2 g q8h
	Vancomycin[b] + aztreonam	Vancomycin 25–30 mg/kg loading dose, followed by 15 mg/kg q12h (or per continuous infusion protocol) Aztreonam 2 g q8h
Age > 50 years, or age ≥ 16 and ≤ 50 years plus risk factors for listeria monocytogenes[a] In case of β-lactam anaphylaxis	Cefotaxime or ceftriaxone + amoxicillin	Ceftriaxone 2 g q12h, Cefotaxime 2 g q4h, Amoxicillin 2 g q4h
	Meropenem + co-trimoxazole	Meropenem 2 g q8h, Co-trimoxazole 160/800 mg q6h
	Vancomycin[b] + aztreonam + co-trimoxazole	Vancomycin 25–30 mg/kg loading dose, followed by 15 mg/kg q12h (or per continuous infusion protocol) Aztreonam 2 g q8h

Doses are suitable for patients with normal renal and hepatic function

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing an immunocompromised state

[b]Requires therapeutic drug monitoring

Table 4 Typical CSF alterations in bacterial, viral and tuberculous meningitis

	Acute bacterial meningitis	Viral meningitis/meningo-encephalitis	Tuberculous meningitis	Normal CSF
Characteristics	Turbid, cloudy, purulent	Clear	Clear, cloudy	Clear
Opening pressure (cmH_20)	> 18	> 18	> 18	10–20
WBC count (cells/μL)	Raised (normally > 1000)	Raised (normally < 1000)	Raised, (normally < 500)	0–5
Predominant cell type	Neutrophils	Lymphocytes	Lymphocytes	NA
Protein (G/L)	Raised	Mildly raised	Highly raised	0.15–0.5
Glucose (mg/dL)	Low	Normal or slightly decreased	Low	60% of glycaemia
CSF/blood glucose ratio	Very low	Normal or slightly decreased	Very low	0.6

A traumatic lumbar puncture or pre-treatment with antibiotics will affect the results. In case of a traumatic lumbar puncture, a correction factor should be applied: adjusted white blood cells in *CSF* measured white blood cells in *CSF* [(white blood cells in blood × red blood cells in CSF)/ red blood cells in blood × 1 000 000] (*CSF* cerebrospinal fluid)

Table 5 Antibiotic prophylaxis in case of meningococcal disease

Antibiotic	Dose	Duration
Ciprofloxacin	Adult ≥ 16 years: 500 mg oral	Once
Levofloxacin	Adult ≥ 16 years: 250 mg oral Pregnancy: do not use	
Ceftriaxone	Child < 16 years: 125 mg IM Adult ≥ 16 years: 250 mg IM Pregnancy: 250 mg IM (first choice during pregnancy)	Once

IM intramuscular

Funding

None.

Compliance with ethical standards

Conflicts of interests

The authors declared that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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