

Review Article : Treatment of Bacterial Meningitis at Educational Al Hussein Hospital and Review of Antibiotics from Global Sources¹

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ABSTRACT

The outcome of bacterial meningitis critically depends on the rapid initiation of bactericidal antibiotic therapy and adequate management of septic shock. In the main laboratory at Educational Al Hussein Hospital. antibiotics have been used to have bacteriocidal effect on bacteria and the review of empirical and specialized antibiotics for meningitis from global sources.

In bacterial meningitis, the choice of an optimum initial empirical antibiotic depends on the resistance patterns. who demonstrate the use of cephalosporin groups, penicillins with amoxicillin, according to the age groups and the amount of dose , also treatment (specific antibiotic) according to the bacterial species that causes meningitis and explains the duration. If you do not respond to this treatment, there is an alternative, this method is specialized in the elimination of meningitis.

Keyword : *bacterial meningitis , Empirical therapy and Antibiotics*

1. Introduction

Bacterial meningitis is a life threatening disease that results from infection of the meninges. It is commonly caused by a bacterium or a virus. Bacterial types will depend on age, history of vaccination, and past medical illnesses. Some factors can increase the risk of developing bacterial meningitis, including contact with bacterial meningitis, recent infection (ear or sinus infection), travelling to places where bacterial meningitis is common, serious head injury, and low immunity. Often, differentiating bacterial meningitis from viral and tuberculous meningitis is not easy and it is vital to diagnose viral meningitis, which does not require antibiotic therapy from conditions that can be treated. Acute bacterial meningitis is serious with a

high rate of fatality. (Muller, 2016 ; Bijlsma, *et al.*, 2016 ; Hasbun R and Bronze, 2016 ; Simon, 2016).

Bacterial meningitis is a potentially infectious disease associated with substantial mortality and a risk of permanent disability in survivors.(Tunkel ,*et al.*,2015) Despite ongoing advances in diagnostic methods and treatment strategies, mortality remains as high as 30% in pneumococcal meningitis and 5–10% in meningococcal meningitis. (Brouwer, *et al.*,2015; Strelow and Vidal ,2013). However, outcomes are improved by prompt therapy.(Glimaker, *et al.*,2015; Grindborg, *et al.*,2015).

For this reason bacterial meningitis needs empiric treatment with appropriate potent antibiotics to avoid fatality. The empirical antibiotic regimens should be updated periodically to overcome the development of

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antimicrobial resistance. The combination of vancomycin with either ceftriaxone for adults or cefotaxime for pediatric ages is given empirically for those with suspected bacterial meningitis, based upon susceptibilities of isolated pathogens..(Muller ,2016 ; Bijlsma , *et al.*,2016). This therapy is to combat against most penicillin-resistant pneumococci and β lactamase resistant Haemophilus influenzae. (Muller,2016 ; Bijlsma, *et al.*,2016 ; Verma, *et al.*,2013) Both ceftriaxone and cefotaxime achieve good cerebrospinal fluid (CSF) levels.

At present, therapy of bacterial meningitis relies on β -lactam antibiotics. In countries with a low incidence of third-generation cephalosporin resistance among *Str. Pneumonia* ($\leq 1\%$), ceftriaxone and cefotaxime remain the antibacterials of choice. In Germany, according to the 2009–2014 European Committee on Antimicrobial Susceptibility Testing breakpoints, cases (6.6% in 2010–2011 and 11.9% in 2012–2013), (Imohl , *et al.*,2014) . This underlines the necessity of thorough search of the causative organism by culture of blood, CSF and local infection sites, followed by the adjustment of the antibiotic therapy according to the susceptibility determination. Polymicrobial infections are rare in meningitis. They are encountered particularly in nosocomial meningitis and in the immunocompromised host, and often include uncommon strains with a high rate of antimicrobial

resistance (Pintado, *et al.*,2012) .including mycobacteria and fungi (Conde-Pereira, *et al.*,2015). This must be considered in the case of failure of the initial empirical therapy or of relapse (Wang, *et al.*,2005). The aim of the study was to determine the optimal antibiotic treatment for bacterial meningitis in Educational Al Hussein Hospital and compare it with its empirical and specialized treatment from global sources

2. Method

Time and Place

The information was taken from the main laboratory unit at Educational Al -Hussein Hospital in Nasiriyah for patients on the fifth floor subject to spinal cord fluid examination(CSF),For the period from November 2020 to March 2021 .

The results of the antibiotic susceptibility test for bacterial growth were taken from (CSF) samples and a review of anti-meningitis drugs used by global sources

Result:

Table (1) represents antibiotics used against bacteria isolated from (CSF) samples. For bacterial meningitis patients in Teaching Al Hussein Hospital, most antibiotics are bacteriostatic because of their mechanism of action.

Table 1:Anti-Meningitis drugs currently used in AL-Nassiriyha

| NO | Drugs | Effect | Comments |
|----|------------------------------|---------------|---|
| 1 | Ceftazidime | bacteriocidal | activation of bacterical cell autolysins which may contribute to bacterial cell lysis. (Specific antibiotic) |
| 2 | Gentamycin | bacteriocidal | binding the 30S subunit of the bacterial ribosome, negatively impacting protein synthesis. (effective concentrations within the CNS) |
| 3 | Co-Trimethoxazole | bacteriocidal | sequential blockade of folic acid enzymes in the synthesis pathway. |
| 4 | penicillin | bacteriocidal | inhibiting the transpeptidase that catalyzes the final step in cell wall biosynthesis, the cross-linking of peptidoglycan. (Standard treatment) |
| 5 | Ticarcilline/clavulanic acid | bacteriocidal | prevent cross-linking of peptidoglycan during cell wall synthesis |
| 6 | Ciprofloxacin | bacteriocidal | inhibiting DNA gyrase, and a type II topoisomerase, topoisomerase IV, necessary to separate bacterial DNA, |
| 7 | ceftriaxone | bacteriocidal | inhibits bacterial cell wall synthesis by binding to transpeptidases (Specific antibiotic) |
| 8 | Rifampin | bacteriocidal | inhibits bacterial RNA polymerase |
| 9 | Amikacin | bacteriocidal | effective concentrations within the CNS |
| 10 | Nitrofurantion | bacteriocidal | inactivate or alter bacterial ribosomal proteins and other macromolecules. |

Experimental treatment of bacterial meningococcal patients who demonstrate the use of cephalosporin groups, penicillins with amoxicillin , according to the age groups and the amount of dose, especially against the *Streptococcus pneumonia* which is one of the causes of bacterial meningitis. **As in a table (2)**

Table 2: Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis (van de Beek, et al., 2012)

| Patient group | Standard treatment | | Intravenous dose |
|---|---|--|---|
| | Intravenous dose a Reduced <i>Streptococcus pneumoniae</i> antimicrobial sensitivity to penicillin | <i>S. pneumoniae</i> susceptible to penicillin | |
| Neonates <1 month old | Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside | | Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h |
| Age 1 month to 18 years | Cefotaxime or ceftriaxone plus vancomycin or rifampicin | Cefotaxime or ceftriaxone | Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h) |
| Age >18 and <50 years | Cefotaxime or ceftriaxone plus vancomycin or rifampicin | Cefotaxime or ceftriaxone | Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h |
| Age >50 years, or Age >18 and <50 years plus risk | Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G | Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/penicillin G | Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h |

Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions associated with causing immunocompromise. The **table(3)** shows the treatment according to the bacterial species that causes meningitis and explains the duration. If you do not respond to this treatment, there is an alternative. this method is specialized in the elimination of meningitis

Table (3): Specific antibiotic in-hospital treatment for community-acquired bacterial meningitis

| Microorganism | Standard treatment | Alternatives | Duration |
|--|--|---|------------|
| <i>Streptococcus pneumoniae</i> 1-Penicillin susceptible (MIC <0.1 µg/mL) | Penicillin or amoxicillin/ampicillin | Ceftriaxone, cefotaxime, chloramphenicol | 10–14 days |
| 2-Penicillin resistant (MIC >0.1 µg/mL), third-generation cephalosporin susceptible (MIC <2 µg/mL) | Ceftriaxone or cefotaxime | Cefepime, meropenem, moxifloxacinb | 10–14 days |
| 3-Cephalosporin resistant (MIC ≥ 2 µg/mL) Vancomycin plus rifampicin, or | vancomycin plus ceftriaxone or cefotaxime, or rifampicin plus ceftriaxone or cefotaximec | Vancomycin plus moxifloxacin, b linezolid | 10–14 days |
| <i>Neisseria meningitidis</i> 1-Penicillin susceptible (MIC <0.1 µg/mL) | Penicillin or amoxicillin /ampicillin | Ceftriaxone, cefotaxime, chloramphenicol | 7 days |

| | | | |
|---|---|---|------------------|
| 2-Penicillin resistant (MIC \geq 0.1 $\mu\text{g/mL}$) | Ceftriaxone or cefotaxime |) Cefipime, meropenem, ciprofloxacin or chloramphenicol | 7 days |
| <i>Listeria monocytogenes</i> | Amoxicillin or ampicillin, penicillin Gd | trimethoprim-sulfamethoxazole, moxifloxacin, b meropenem, linezolid | At least 21 days |
| <i>Haemophilus influenzae</i> | Amoxicillin or ampicillin | Ceftriaxone, cefotaxime or chloramphenicol | 7–10 days |
| β -Lactamase negative | Ceftriaxone or cefotaxim | Cefepime, ciprofloxacin, chloramphenicol | 7–10 days |
| β -Lactamase positive | ampicillin resistant Ceftriaxone or cefotaxime plus meropenem | Ciprofloxacin | 7–10 days |
| <i>Staphylococcus aureus</i> Methicillin sensitive | Flucloxacillin, nafcillin, oxacillin | Vancomycin, linezolid, rifampicin, e fosfomycin, e daptomycinb | At least 14 days |
| Vancomycin resistant (MIC $>$ 2.0 $\mu\text{g/mL}$) | Linezolidf | Rifampicin, e fosfomycin, e daptomycinb | At least 14 days |

Table (4) shows recommended experimental treatment by age group. Which is characterized by cephalosporin group and Vancomycin

Table(4): Recommended Empirical therapy of bacterial meningitis.

| Community acquired age group | Recommended antibiotic therapy |
|------------------------------|--|
| Newborns | Cefotaxime plus ampicillin |
| Infants and children | Third-generation cephalosporin |
| Previously healthy adults | Third-generation cephalosporin plus ampicillin |
| Elderly patients | Third-generation cephalosporin plus ampicillin |
| Nosocomial | Vancomycin plus meropenem or vancomycin plus ceftazidime# (plus metronidazole after surgery with access through mucus membranes) |
| Shunt infection | Vancomycin plus meropenem or vancomycin plus ceftazidime |

Use of high-impact antibiotics on the central nervous system (CNS) and the appropriate dose with the side effect of these antibiotics on the patient most of which are temporary. Antibiotics appear here Streptomycin, Colistin and Daptomycin and its effective role in the treatment of bacterial meningitis as show in table (5)

Table(5) Intraventricular application of antibiotics to reach effective concentrations within the CNS (Nau R, et al., 2010).

| Antibiotic | Dose in adults Severe reported | side effects |
|--|--------------------------------|---|
| Gentamicin | 5 mg every 24 h | (Temporary)hearing loss, epileptic seizures, aseptic meningitis, eosinophilic CSF pleocytosis |
| Tobramycin | 5 mg every 24 h | Similar as gentamicin |
| Amikacin | 30 mg every 24 h | (Temporary) hearing loss |
| Streptomycin 1 mg/kg | every 24–48 h | (Temporary) hearing loss, epileptic seizures, radiculitis, transverse myelitis, arachnoiditis, paraplegia |
| Vancomycin | 10–20 mg every 24 h | (Temporary) hearing loss |
| Colistin (polymyxin E) methanesulfonate (12,500 IU = 1 mg) | 10 (1.6–20) mg every 24 h | Meningeal inflammation, with high doses epileptic seizures, loss of appetite, agitation, eosinophilia, edema, pain, albuminuria |
| Daptomycin | 5–10 mg every 24–72 h | Fever |

CONCLUSION

1. Antibiotics used in the laboratory for bacteria that cause meningitis are mostly bacteriocidal.

2. There is no evidence of superiority of continuous administration of antibiotics in bacterial meningitis patients (BMP).

2. The empiric antibiotic treatment in (BMP) is expert opinion based on and differentiated for demographic/epidemiologic factors (age and rate of reduced antibiotic susceptibility).

3. The specific antibiotic treatment in (BMP) is based on antimicrobial susceptibility testing.

RECOMMENDATIONS

1. In patients with suspected bacterial meningitis (BM), it is strongly recommended to perform blood cultures before the first dose of antibiotics is administered.

2. In patients with negative CSF cultures, the causative microorganisms can be identified by PCR

3. The recommended empiric treatment for (BMP) is based on age and local resistance rates, as displayed in Table (2).

4. The recommended specific treatment for (BMP) should be determined by the antibiotic susceptibility pattern, as displayed in Table (3).

DISCUSSION

In the current study, bacteriocidal antibiotic were used, including cephalosporin and penicillin, also gentamicin, which has a specialized effect on the central nervous system (CNS). The reason for the choice of this antibiotic indicates that the distribution of treatment (Special compartment) entry of drug into the cerebrospinal fluid (CSF) and central nervous system (CNS). Drug also has relatively poor access too thus making the treatment of infections in these regions difficult.

When comparing the antibiotic used against the bacteria resulting from the cultured of spinal fluid samples. We found most of them are similar but did not specify any bacterial species and its effect is broad spectrum and not narrow spectrum. It was not determined by age groups and no accompanying diseases with meningitis. It was determined by the sensitivity of the bacteria to this antibiotic

The international distribution of antibiotics for bacterial meningococcal patients was divided by age, accompanying disease cases and initial, specialist and standard treatment. But at Al Hussein Educational

Hospital. Just select the antibacterial (bacteriocidal).this encourages many deaths due to antibiotic selection and non-identification of bacterial species. Studies should be conducted on how best to use the treatment For this serious illness.

Empiric antibiotic treatment. The choice of empiric antibiotic treatment is conditional on the age of the patient and the regional rate of decreased susceptibility to penicillin and third-generation cephalosporins of *S. pneumoniae*. The spectrum of pathogens in neonates is considerably different to that of children

beyond the neonatal age and adults, which is reflected by the empiric antibiotic treatment for this age group. When there is a risk of decreased susceptibility of *S. pneumoniae*, empiric treatment should include vancomycin or rifampicin. However, some experts advise the use of ceftriaxone or cefotaxime as empiric

treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporin. When risk factors for an infection with *L. monocytogenes* are present in adults under the age of 50 years (e.g. diabetes, use of immunosuppressive drugs, cancer) or in adults over the age of 50 years, empiric antibiotic treatment should include amoxicillin or ampicillin (Koopmans, *et al.*, 2013), for all adults with bacterial meningitis.

Specific antibiotic treatment after identification of causative microorganism.

After identification of the pathogen through culture and antibiotic susceptibility testing, the antibiotic treatment can be optimized. *S. pneumoniae* is currently the most common causative microorganism in adults and the second most common in children beyond the neonatal age. Reduced susceptibility to penicillin and third-generation cephalosporins of *S. pneumoniae* is a growing problem in Europe, although resistance rates vary considerably between countries (van de Beek, *et al.*, 2012).

There is uncertainty regarding the benefit of adding vancomycin or rifampicin to a third-generation cephalosporin in pneumococcal meningitis patients in the setting of decreased susceptibility rates of pneumococci. We systematically evaluated the literature for studies of the efficacy of vancomycin and rifampicin in infections caused by pneumococci resistant to third-generation cephalosporins, (Suntur, *et al.*, 2005). These showed that ceftriaxone combined with either vancomycin or rifampicin resulted in a higher rate of CSF sterilization after 24 hours compared to monotherapy with ceftriaxone.

Another study showed the superiority of ceftriaxone combined with either rifampicin or rifampicin and vancomycin compared to ceftriaxone combined with vancomycin. Although there is no clinical evidence for adding vancomycin or rifampicin in the setting of lower pneumococcal susceptibility rates, the committee advises addition of vancomycin or rifampicin to third-generation cephalosporins based on *in vitro* susceptibility patterns (Erdem, *et al.*, 2014). The advised duration of treatment is 10–14 days (van de Beek, *et al.*, 2012).

This underlines the necessity of thorough search of the causative organism by culture of blood, CSF and local infection sites, followed by the adjustment of the antibiotic therapy according to the susceptibility determination. Polymicrobial infections are rare in meningitis. They are encountered particularly in nosocomial meningitis and in the immunocompromised host, and often include uncommon

strains with a high rate of antimicrobial resistance (Pintado, *et al.*, 2012), including mycobacteria and fungi (Conde-Pereira, *et al.*, 2015). This must be considered in the case of failure of the initial empirical therapy or of relapse (Wang, *et al.*, 2005).

The introduction of linezolid and daptomycin into therapeutic has increased the options to treat CNS infections by multiresistant *St. aureus*, coagulase-negative staphylococci, vancomycin-resistant enterococci and multiresistant *S. pneumoniae*. Severe problems in finding an adequate antibacterial can arise in rare cases of meningitis caused by vancomycin-resistant enterococci (Knoll, *et al.*, 2013). Whether the bacteriostatic agent linezolid because of its favorable pharmacokinetics is more effective than vancomycin (in particular, in combination with another agent such as rifampicin or gentamicin and when administered intravenously and intrathecally) is still a matter of debate

Bacterial cure of meningitis due to vancomycin-resistant *En. faecium* has been achieved with various antimicrobial drugs used as monotherapy or in combination and with or without intrathecal in addition to intravenous therapy: linezolid, rifampicin, daptomycin, quinupristin-dalfopristin, chloramphenicol, ampicillin, gentamicin. the choice of the antibiotic (or antibiotic combination).

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الخلاصة

تعتمد نتيجة التهاب السحايا البكتيري بشكل حاسم على البدء السريع في العلاج بالمضادات الحيوية للجراثيم والاعداد الجيد للصدمة الإنتانية. في وحدة المختبر الرئيسي في مستشفى الحسين التعليمي تم استخدام المضادات الحيوية ذات التأثير القاتل للبكتيريا مع استعراض المضادات الحيوية التجريبية والمتخصصة لالتهاب السحايا من مصادر عالمية.

في التهاب السحايا البكتيري ، يعتمد اختيار نظام العلاج المبدئي و التجريبي على أنماط المقاومة للمضادات فاستخدام مجموعات السيفالوسبورين والبنسلين مع الأموكسيسيلين ، تبعا للفئات العمرية وكمية الجرعة. وايضا العلاج المتخصص يكون وفقاً لأنواع البكتيرية التي تسبب التهاب السحايا وتشرح مدة اخذ المضاد و إذا لم يستجب لهذا العلاج ، فهناك بديل ، فهذه الطريقة متخصصة في القضاء على التهاب السحايا البكتيري