Advanced therapeutic methods for the treatment of meningococcal septic shock — case report

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Abstract

Background. Meningitis caused by Neisseria meningitidis is primarily a disease of children and young adults. If septic shock complicates the course of meningitis, it must be treated in the intensive care unit.

Case report. A 18-years old man with symptoms of meningococcal meningitis and clinical features of septic shock was admitted to the ICU. A patient with tachycardia (heart rate 140 min⁻¹) required vasopressor to maintain blood pressure (noradrenalin 1 µg kg⁻¹ min⁻¹) on admission. Respiratory failure developed (respiratory rate of 40 min⁻¹, \( \text{SaO}_2 \) 79%, \( \text{PaO}_2/\text{FiO}_2 \) ratio = 55) and mechanical ventilatory support was used. The presence of Neisseria meningitidis was confirmed with the rapid latex agglutination test. Cefotaxime with vancomycin was administered on day one and vancomycin was replaced with meropenem on day two. Additionally to the standard treatment of septic shock and multiorgan failure, hemoperfusion with LPS adsorber was performed to eliminate endotoxins from the bloodstream, and drotrecogine alfa was administered. Hemoperfusion was performed twice for 2 hours session and blood endotoxin activity decreased from 0.75 EAU do 0.4 EAU after 48 hours. Patient was admitted with signs of acute kidney injury and required continuous renal replacement therapy (Ca-Ca CVVHD, CVVHDF).

Conclusions. Rapid pathogen identification, adequate antimicrobial therapy and endotoxin elimination from the bloodstream improved hemodynamic and respiratory parameters of the patient. Application of routine plus non-standard methods of treatment of septic shock prevented the progression of the biological cascade in sepsis and improved patient’s clinical condition.

Key words: septic shock, meningococcal meningitis, endotoxin elimination, LPS Adsorber

Cerebrospinal meningitis (CSM) caused by Neisseria meningitidis affects mainly children and young people. Its estimated annual incidence in Europe is 0.5/100 000 individuals. The lowest incidence rates are reported in Poland, Hungary and Italy, while the highest ones in Ireland, Iceland and Malta [1, 2, 3]. Group B Neisseria meningitidis accounts for 40–95% of CSM cases whereas group C meningococci cause 3–55% of infections, however their course is generally more severe [3]. The mortality in these infections increases with age; this increasing tendency is visible since the age of 20 reaching the highest mortality (20%) in patients over 65 years of age [1]. Patients with cerebrospinal meningitis accompanied by septic shock have to be promptly admitted to the ICU and the guidelines of the Surviving Sepsis Campaign should be considered [4]. Such a form of disease is characterized by rapid clinical course and high mortality (> 50%). Half of deaths occur within the first 12 hours after admission to hospital [5].

The present report is the first Polish description of the treatment of septic shock in the course of Neisseria meningitidis-induced meningitis using the Alteco LPS Adsorber, continuous citrate haemodialysis and infusion of recombinant activated protein C (rAPC).

CASE REPORT

An 18-year-old male patient without medical history was admitted to the ICU from the department of infectious diseases due to septic shock in the course of meningococcal meningitis. The acute physiology and chronic health evaluation II (APACHE II) score was 29 and sequential organ failure
assessments (SOFA) score 15. The disease started the same day and manifested with headache, fever to 40°C, vomiting and rapidly increasing hemorrhagic skin lesions over the entire body. During the several-hour stay in the department of infectious diseases (11.40 pm – 2.00 am), the patient was conscious; massive hemorrhagic lesions on the skin and oral mucosa and meningeval symptoms were observed. The laboratory abnormalities are presented in Table 1. The head CT scan did not reveal any pathologic changes. The blood was sampled for microbiological testing (at minute 40 after hospital admission) and the patient received cefotaxime (2.0 g), crystalline penicillin (6 mln units), amikacin (1.0 g), and dexamethasone (8 mg). The lumbar puncture and CSF collection for the diagnosis of cerebrospinal meningitis were abandoned due to clotting disorders. Arterial pressure was found to be decreasing; therefore, the central vein catheter was placed, the noradrenaline infusion initiated and the patient was transferred to ICU for further treatment.

On admission to ICU, the patient presented the features of shock; circulation was unstable. Tachycardia was observed — 140 min⁻¹; arterial pressure was 140/80 mm Hg at the continuous infusion of noradrenaline in a dose of 1 µg kg⁻¹ min⁻¹. Due to respiratory failure (number of respirations 40 min⁻¹, SaO₂ 79%, PaO₂/FiO₂ 55), the patient was intubated immediately after admission and mechanical ventilation was started. Before intubation, the patient was in verbal contact albeit confused. The skin of the entire body, particularly of limbs, was covered with merged hemorrhagic lesions. Numerous bilateral rales were heard over the entire lung fields. The chest X-ray showed massive, patchy and infiltrative changes as well as blurring of both lung fields characteristic of acute respiratory distress syndrome.

Within an hour after ICU admission, blood was re-sampled for microbiological testing (pharyngeal swab and bronchial tree secretion were also collected); the patient received vancomycin 1.0 g and amikacin was discontinued. Cefotaxime in a dose of 2 mg every 12 h (tailored for continuous renal replacement therapy) was continued. Eight hours after admission, the presence of C Neisseria meningitidis antigen was confirmed using the Wellcogen Bacterial Antigen Kit Rapid latex agglutination test. The test is designed for identification of antigens of group B Streptococcus, type B H. influenzae, S. pneumoniae; group A, C, Y, W135 N. meningitides, group B N. meningitidis in body fluids. Since the latex test results excluded pneumococcal infection, vancomycin was withdrawn.

On treatment day 1, the patient’s circulation was unstable and he required noradrenaline in the incremental doses to 1.0 µg kg⁻¹ min⁻¹ (5 mg h⁻¹) and adrenaline in intravenous infusion in a dose of 0.83 µg kg⁻¹ min⁻¹ (4 mg h⁻¹). On the following day, the infusion of adrenaline was discontinued and the dose of noradrenaline increased to 2 µg kg⁻¹ min⁻¹ (10 mg h⁻¹).

During treatment day 1, extracorporeal endotoxin elimination with Alteco LPS adsorber column (Alteco Medical AB, Lund, Sweden) was used. Adsorber consisted of polyethylene discs coated with the antibody specifically binding endotoxins. The blood flow through the adsorber was 150 mL min⁻¹ and was maintained using the renal replacement therapy machine (Fresenius Medical Care, Hamburg, Germany). The efficacy of therapy was monitored by measurements of endotoxin activity in blood. The hemiluminescence method (Endotoxin Activity Assay — EAA, SPECTRAL Diagnostics, Canada) was employed, in which the value < 0.4 EAU (endotoxin activity units) is considered low, 0.4–0.59 EAU indicates endotoxaemia whereas > 0.6 confirms endotoxaemia and septic shock. The baseline activity of endotoxins in our patient was 0.75 EAU; 24 h after the first haemoperfusion procedure, the activity decreased to 0.68 EAU, and 24 h after the second procedure to 0.4 EAU. The circulatory efficiency significantly improved after the second procedure of haemoperfusion (Table 2).

The patient’s lungs were mechanically ventilated, initially using the PCV mode with FiO₂ 1.0, reaching PaO₂ = 87 mm Hg. Short-term, several-minute high-frequency oscillatory ventilation (HFOV) with FiO₂ 1.0 did not improve arterial blood oxygenation (PaO₂/FiO₂ = 66), and during the procedure abundant amounts of foamy-bloody secretions flown out of the endotracheal tube. The return to pressure-controlled ventilation enabled to obtain satisfactory PaO₂ values on day 1.

At hour 3 after ICU admission, the intravenous infusion of drotrecogin-a was started in a dose of 24 µg kg⁻¹ day⁻¹ and continued for 96 h.

| Table 1. Assessment of patient’s clinical status on ICU admission and discharge |
|-------------------------------------|----------------|----------------|
| **Parameter**                      | ICU admission | ICU discharge |
| Body temperature (°C)              | 38.1          | 37.8          |
| WBC (G L⁻¹)                        | 28.41         | 15.06         |
| CRP (mg L⁻¹)                       | 111.4         | 41.45         |
| Procalcitonin (ng mL⁻¹)             | > 200.0       | 1.06          |
| Platelets (G L⁻¹)                  | 35.0          | 148.0         |
| AST (U L⁻¹)                        | 470           | 5             |
| ALT (U L⁻¹)                        | 1616          | 20            |
| Serum creatinine (mg dL⁻¹)         | 2.41*         | 3.13*         |
| Total bilirubin (mg dL⁻¹)          | 2.6           | 0.5           |
| Prothrombin ratio (%)              | 40.4          | 80.2          |
| aPTT (sec)                         | 169           | 40.4          |
| D-dimers (µg mL⁻¹)                 | 27.4          | 16.8          |
| Lactates (mmol L⁻¹)                | 7.58          | 0.7           |

*anuria, continuous renal replacement therapy; *oliguria, dialysis therapy
At hour 4 after ICU admission, continuous veno-venous haemodialysis was initiated with regional anticoagulation using citrates — Ci-Ca CVVHD (multiFiltrate KIT CI-CA, Fresenius Medical Care, Hamburg, Germany), continued for 3 days. Since septic shock persisted and features of multiple organ failure increased, on day 2, meropenem was additionally included into empiric treatment, 2 mg every 8 h. The microbiological results of blood collected on admission to the department of infectious diseases received on ICU treatment day 3 confirmed the presence of N. meningitidis. MIC for penicillins was 0.25 µg mL\(^{-1}\), which, according to the EUCAST recommendations, did not allow de-escalation. However, within the range of MIC values, the strain showed susceptibility to cefotaxime and meropenem, which were used in combined therapy since the clinical response to monotherapy was poor. Cefotaxime was administered for 20 successive days whereas meropenem for 13 days.

The features of acute renal injury persisted; therefore, once CI-CA CVVHD was completed, continuous veno-venous haemodiafiltration (CVV HDF) was initiated with systemic anticoagulation with heparin. The therapy was continued until day 9; between day 10 and 25, haemodialysis procedures were performed on a daily basis and since day 26 every other day. On treatment day 20, the volume of diuresis was 400 mL day\(^{-1}\). Oliguria was observed until the discharge from the unit.

The clinical condition of our patient gradually improved. On day 7, the supply of catecholamines and hydrocortisone was stopped. On day 8, sedatives were discontinued; the patient was extubated, yet required passive oxygen therapy until discharge.

On hospitalization day 24, hospital pneumonia was diagnosed, which was treated empirically with levofloxacin and amoxicillin with clavulanic acid according to the antibiogram for methicillin-sensitive Staphylococcus aureus (MSSA) isolated from the throat and sputum.

The changes in inflammation parameters (leucocytes, CRP, PCT) are presented in Figure 1. Due to persistent leukocopenia, on hospitalization day 22, the patient received a single dose of filgrastim 30 µg and leukocytes counts increased to 24.76 G L\(^{-1}\).

The gas exchange markedly improved on day 25 after drainage of the right pleural cavity and evacuation of 2500 mL of transudate.

The earliest possible, appropriate antibiotic therapy in severe sepsis is an essential factor improving survival [8, 9, 10]. When acute cerebrospinal meningitis is suspected, prior to the identification of pathogens, the empiric antibiotic therapy should be instituted against the most commonly identified pathogens, according to the recommendations of IDSA and the European Federation of Neurological Societies (EFNS) [6, 7]. In patients under 50 years of age, the most common pathogens of acute cerebrospinal meningitis include Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae. In patients over the age of 50 years, antibiotics active against Listeria monocytogenes should be considered for empiric antibiotic therapy, i.e. ampicillin or amoxicillin [7].

In our case, the use of cefotaxime was in accordance with the accepted standards. The increasing resistance of Streptococcus pneumoniae to penicillin limits its use for empirical therapy. According to the recommendations of the European Commit-

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**Table 2. Changes in LPS concentrations and haemodynamic parameters after LPS elimination procedures using the Alteco LPS adsorber**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before the first endotoxin elimination</th>
<th>24 h after the first procedure</th>
<th>24 h after the second procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS (EAU)</td>
<td>0.76</td>
<td>0.68</td>
<td>0.4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>60</td>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td>PaO(_2)/FiO(_2)</td>
<td>60</td>
<td>166</td>
<td>291</td>
</tr>
<tr>
<td>Noradrenalin</td>
<td>1 µg kg(^{-1}) min(^{-1})</td>
<td>0.8 µg kg(^{-1}) min(^{-1})</td>
<td>0.25 µg kg(^{-1}) min(^{-1})</td>
</tr>
</tbody>
</table>

EAU — endotoxin activity units; MAP — mean arterial pressure
tee on Antimicrobial Susceptibility Testing (EUCAST), benzyl penicillin can be used for the treatment of neuroinfections caused by *Neisseria meningitidis* and *Streptococcus pneumoniae* when MIC for penicillin is ≤ 0.064 µg mL⁻¹ [11]. The European Antimicrobial Resistance Surveillance System (EARSS) study conducted in 2008 demonstrated that 30% of *Streptococcus pneumoniae* strains in Poland were resistant to penicillin [12]. The available literature reports did not contain the current data on penicillin resistance of *Neisseria meningitidis* species in Poland. In developed countries, empiric treatment of patients with cerebrospinal meningitis has mainly involved cefotaxime or ceftriaxone, often with vancomycin (until microbiological confirmation has been available) [5, 13]. Once the presence of type C *Neisseria meningitidis* antigen was confirmed in the rapid latex agglutination test, the spectrum of empiric antibiotic therapy was narrowed and vancomycin was abandoned. *Neisseria meningitidis* cultured in blood showed reduced sensitivity to penicillin (confirmed by E-tests), thus only cefotaxime and meropenem could be used. In the initial stage of disease, the combined therapy was decided due to the patient's severe condition; the doses of antibiotics were adjusted to the continuous renal replacement therapy applied [14]. The beneficial effects of combined antibiotic therapy on survival of patients with severe infections of various aetiologies were demonstrated by Kumar [8]. Prior to this report, such beneficial effects were only demonstrated in *Pseudomonas aeruginosa*-induced infections [15]. During the initial stage of septic shock, the concentrations of antibiotics may be difficult to determine and often too low doses are used. The pharmacokinetic parameters of antibiotics in patients with sepsis change markedly and poor clinical responses may result from their improper dosage. In the case presented, combined antibiotic therapy with cephalosporin with carbapenem was used, which resulted in good clinical response and eradication of pathogens. Nevertheless, it should be admitted that the combination of cephalosporin (a potent beta-lactamase inhibitor) and carbapenem is disputable. Additionally, the patient received dexamethasone as the pneumococcal infection was suspected. The literature data indicate that this glucocorticoid shows beneficial effects on survival only in pneumococcal infections of the central nervous system [6, 7]. Severe respiratory failure observed in our patient required aggressive mechanical ventilation while acute renal injury was the indication for early use of CVVHDF. According to epidemiological studies, CVVHDF techniques are the treatment of choice in sepsis cases complicated with acute renal injury [16]. The use of citrate anticoagulation was dictated by the presence of severe haemorrhagic diathesis. Citrate anticoagulation substantially prolongs the lifespan of a filter and reduces the risk of bleeding; however, it does not affect mortality [17]. During citrate haemodialysis and CVVHDF with systemic low-molecular-weight heparin anticoagulation, no life-threatening haemorrhagic complications were observed. The head CT scan revealed small haemorrhagic foci in the brain, which evolved on day 12 and did not affect the patient's neurological condition after the completion of therapy.

Considering the extremely severe condition of our patient (APACHE II score 29) and multiple organ failure, which developed within 24 hours, activated protein C (drotrecogin-α) was used according to the recommendations included in the therapeutic product characteristics. Analysis of 1064 cases of patients with severe sepsis conducted in Poland demonstrated the mortality reduced by 20.4% in the group of patients treated with activated protein C (56.4 vs. 36.0%) [18]. The drug was withdrawn from the market on October 25, 2011.
Severe meningitis of Neisseria meningitidis aetiology and rapid course are characterised by high blood concentrations of bacteria (10^8–10^9 mL^-1) and of endotoxins (10^{-1}–10^{-2} mL^-1) [5]. High (> 250 EU mL^-1) endotoxin concentrations are associated with 100% mortality whereas the concentrations of 50–250 EU mL^-1 and 10–50 EU mL^-1 with 75% and 15% mortality, respectively [5]. Intravenous administration of an appropriate antibiotic dose was found to eradicate meningococci from the cerebrospinal fluid after 3–4 h and to reduce the endotoxin concentration in serum by 50% after 2 hours [5].

In our case, an extremely high activity of endotoxins in blood correlated with increased symptoms and pathological changes characteristic of septic shock. Elimination of endotoxins from circulation is to support the standard therapy of sepsis caused by Gram-negative bacteria [19]. Moreover, it contributes to the improvement of haemodynamic parameters and reduced mortality [20].

The available literature contains only a few descriptions of cases, in which the Alteco filter was used to eliminate endotoxins in patients with septic shock. The filter was applied during cardiac surgeries with extracorporeal circulation [21, 22]. Since endotoxins were not detected in the patients studied and they did not have symptoms of septic shock, no significant effects of endotoxin elimination on the level of cytokines or improved clinical conditions were demonstrated. Effective elimination of endotoxins using the Alteco filter was described in a patient with severe sepsis induced by Gram-negative bacteria complicating peritonitis [23]. Reduced levels of endotoxins in plasma correlated with increased efficiency of the cardiovascular system. Likewise, in our case, after two 2-hour procedures with the Alteco filter, concentrations of endotoxins were found markedly lower and patient’s clinical condition improved.

CONCLUSIONS
The instant decision to transfer the patient to ICU and early identification of the type C Neisseria meningitidis antigen using the latex test enabled the institution of suitable antibiotic therapy. Thanks to the use of basic and advanced therapeutic methods, i.e. infusion of activated protein C, continuous renal replacement therapy and elimination of endotoxins, the patient recovered from multiple organ failure in the course of meningococcal shock.

References:

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