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Case Report

Successful Treatment of Septic Shock with the Use of IgM Enriched Immunoglobulin Solution and Antibiotic Policy

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Abstract

Introduction: In case of severe infections and sepsis the universal scheme of treatment is still under discussion. Those, which have a proven effectiveness, are included into Surviving Sepsis Campaign treatment guidelines. In cases where standard therapy provided according to the guidelines proves unsuccessful, other options, like administration of IgM enriched immunoglobulin infusions may be justified. The IgM represents a different class of antibodies than IgG, and possesses many unique properties like effective endotoxin inactivation, high level of complement system supported direct bacteriolysis, low concentration phagocytosis stimulation and activation pathways for immune system. But the evidence is still insufficient to support a robust conclusion of benefit for such therapy.

Case Report: A 21 years old woman with history of abdominal pain, nausea, vomiting and diarrhea after swimming in lake with dirty water 2 days earlier, was aggressively treated according to the guidelines because of septic shock. The therapy resulted in no visible improvement up to the moment of administration IgM enriched immunoglobulin solution (Pentaglobin – Biotest, Dreieich, Germany) with typical speed of infusion 5 ml/kg b.w./24 h through 72 hours. After 3 weeks of intensive care treatment and significant improvement she was transferred in stable condition, with full sufficiency of base vital systems and partially improved organ functions to the regional hospital. Follow up observation showed progressive improvement of patient's health condition during hospitalization and ambulatory rehabilitation program.

Results: After adjuvant administration IgM enriched immunoglobulin infusion the significant improvement in laboratory test results occurred: procalcitonin serum concentration (PCT) decreased from 21.27 to 1.89 ng/ml, C reactive protein (CRP) serum concentration decreased from 19.71 to 10.72 mg/L, and Platelet (PLT) countgrow from minimal value 9 G/L to normal 249 G/L.

Conclusion: In case of ineffective standard therapy of septic shock, the early IgM enriched immunoglobulin solution infusion according to the SPC dosage (5 ml/kg b.w./24 h through 72 hours) may improve patient's status and increase survival rate. A further properly managed multicenter randomized clinical trial (RCT) on large group of patients with septic shock is necessary for evaluation of this therapy.

Keywords: Severe sepsis; Antibiotic therapy; Adjuvant therapy; Survival; Effectiveness

Abbreviations

AMR: Antimicrobial Resistance; AMS: Antimicrobial Stewardship; ARDS: Acute Respiratory Distress Syndrome; ASP: Antimicrobial Stewardship Program; CRP: C Reactive Protein; DNR: Don't Resuscitate Order; HFJV: High Frequency Jet Ventilation; ICU: Intensive Care Unit; IgM: Class M immunoglobulin; IgG: Class G Immunoglobulin; IVIG: Intravenous IgG; MODS: Multiple Organ Dysfunction Syndrome; N: Neutrophils; PCT: Procalcitonin; PLT: Platelet Count; RCT: Randomized Clinical Trial; SIRS: Systemic Inflammatory Response Syndrome; SLED: Slow Low Efficacy Dialysis; SPC: Summary of Product Characteristic; VC-AC: Volume Control – Assist Control Ventilation (Continuous Mandatory Ventilation); WBC: White Blood Cells count

Introduction

In case of severe infections and sepsis the universal scheme of treatment is still under discussion, because many theoretically important elements of the therapy failed to be effective in clinical practice, according to the achieved results from the randomized clinical trials (RCT). Those, which have proven effectiveness, are included into Surviving Sepsis Campaign treatment guidelines [1]. Among many therapies involved into this discussion, implementation of the antibiotic policy and possible benefits from the use of adjuvant therapies are probably the most commonly studied ones. Current data available for analysis may indicate that many of these therapies need much more specific circumstance prescribed for improvement in results [2].

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Antibiotic policy is a worldwide necessity because of growing bacterial strains resistance and a drop in effectiveness of therapy. Recently it has been increasingly recognized that antimicrobial stewardship (AMS) may be a key component of international efforts to limit global tendency of growing antimicrobial resistance (AMR) [3]. Appropriate antibiotic stewardship in intensive care unit (ICU) includes not only rapid identification and optimal treatment of bacterial infections, but as well avoidance of unnecessary wide spectrum antibiotic administration [4]. However, antimicrobial stewardship program (ASP) adaptation for ICU may face certain challenges, e.g. infrastructure and personnel issues, information network software issues, patient specific factors and problems with doze optimization [5]. In case of severe sepsis and septic shock there is a widespread consensus, that the blood cultures should be collected before antibiotic administration, and wide spectrum antibiotics should be administered within 1 hour after diagnosis [1]. This is an empiric antibiotic therapy, and designed choice of antimicrobial agents should be prepared for such situation by Antibiotic Management Teams or Therapeutic Committee [6]. The involved patient need frequent reevaluation, for diagnosis confirmation and therapy effectiveness control. Additionally it may prevent unnecessary continuation of antibiotic treatment [7].

According to published results from many studies there is still a controversy about possible usefulness of IgM enriched immunoglobulin infusions in severe sepsis and septic shock therapy [8]. Thus this kind of treatment is still classified as a therapy out of guidelines, because the evidence is still insufficient to support a robust conclusion of benefit. But in clinical practice probably the most important question in case of life-threatening septic shock is: can we do anything else for our patient? If traditional treatment is successful, or at least effective we may avoid necessity to answer such as a question, but what if the administered therapy is ineffective? In some cases we may conclude, that additional limitations may cut off survival possibility, like history of chronic diseases or insufficiencies - but what with the patients who don't have such as ones? And, what is much more important, do we have a right to take such as decision without at least trying another options and approach? In our opinion we should offer a therapeutic alternative in case of ineffective standard therapy, especially if there is existing data indicating possible benefits from disputed elements of therapy in the literature.

Such as therapy should be always carefully asses with the use of all available knowledge. But if there are some chances for possible improvement in case of unsuccessful standard therapy provided according to the guidelines - it may justify another option, like administration of IgM enriched immunoglobulin infusions. We present our case to the discussion as a one of many possible indications for further improvement in the effectiveness and successful rate of severe sepsis treatment.

Case Presentation

A 21 years old woman was admitted into the local hospital with history of abdominal pain, nausea, vomiting and diarrhea after swimming in lake with dirty water 2 days earlier. She presented the signs of severe sepsis with high body temperature (up to 41°C), increased level of the inflammatory markers in blood, growing multiple organ dysfunction syndrome (MODS) and coagulation disturbances, progressive deterioration of neurological status and seizures. She was intubated, treated with the use of antibiotics, fluid resuscitation and ventilator therapy without any improvement. Because even with intensified therapy a progressive deterioration of patient's status, with signs of septic shock were observed, she was transferred into our University Clinical Intensive Care Unit. On admission she was in critical status, deeply unconscious and artificially ventilated, with hemodynamic decompensation even with fluid resuscitation and continuous catecholamine infusions. The ventilator therapy was continued with protective strategy dedicated for Acute Respiratory Distress Syndrome (ARDS), with the use of classical mode of VC-AC ventilation (Volume Control – Assist Control Ventilation) and High Frequency Jet Ventilation (HFJV) for active recruitment of alveoli, fluid resuscitation was intensified as well as catecholamine infusion. After collecting blood samples for microbiological examination and incubation the new scheme of antibiotic therapy dedicated for septic shock treatment according to hospital antibiotic policy was introduced into treatment, with the use of meropenem, linezolid (Zyvoxid) and colistin intravenously. Additionally electrolyte and acid-base balance disturbances were corrected. Strict observation show growing decrease in urine output after achieving hemodynamic stabilization. The Continuous Renal Supportive Therapy with the use of Slow Low Efficacy Dialysis technique (SLED) was initiated after central venous dialysis catheter implantation. These elements of the therapy created some kind of physiological functions stabilization, without visible improvement. She suffered because of growing liver functions disturbances and jaundice. Additionally she has had a need for blood product transfusions. The next element of therapy created for the patient during the first 24 hours period after admission was IgM enriched immunoglobulin administration (Pentaglobin – Biotest, Dreieich, Germany) with typical speed of infusion 5 ml/kg b.w./24 h through 72 hours. Severe thrombocytopenia was treated with the use of Platelet (PLT) Blood Cell transfusion. We observed regression of the signs of severe sepsis as well as decrease in measured laboratory equivalent parameters for Systemic Inflammatory Response Syndrome (SIRS). It created possibility for decrease in aggressiveness of ventilator treatment, and next slow progression of weaning from the ventilator program as well as reduction in catecholamine infusion. After 2 weeks of treatment, visible improvement occurred: patient was successfully disconnected from the ventilator and spontaneous kidney urine output increased above 1000 ml/24 h, with slow restitution of other necessary physiological functions. After next 5 days of monitored improvement and infectious diseases consultation she was transferred in stable condition, with full sufficiency of base vital systems and partially improved function of kidneys and liver to the regional hospital for further treatment and observation. Follow-up observation showed progressive improvement of patient's health condition. After 2 weeks of treatment and observation in internal unit, she was transferred into ambulatory rehabilitation program, continued successfully trough next 3 months.

Results

Initial blood samples show no signs of bacterial growth. The tests for viral infection were negative. The laboratory test results and some monitored parameters are presented in Table 1. Clinical observation show progressive improvement of patient's status with slow regression of organs insufficiency after administration as an adjuvant

Table 1: Observed disturbances, therapeutic interventions and the laboratory test's results.

Time (h)	MAP (mm Hg)	HR (/min)	PaO_2 (mm Hg)	PCT (ng/ml)	CRP (mg/L)	WBC (G/L)	Neutrophils (%)	PLT (G/L)	Lactate (mg/dL)	Creatinine (mg/dL)	Bilirubin (mg/dL)
0-1.5	42→52	148→122	57	21.27	19.71	14,570	73.6	21	118.9	3.09	2.35
+0.5-2.0	**Deteriorated patient – early fluid resuscitation, new antibiotic administration, CRRT (SLED) initiation**										
+11	56	118	51	12.99	12.9	10,910	91.0	16	68.9	1.64	3.61
+20	**Unstable patient with growing signs of DIC and MODS – start of Pentaglobin continuous infusion**										
+25	90	116	58	3.09	11.52	20,340	94.2	9	48.2	1.13	6.36
+37	100	72	84	-	-	19,22	93.1	7	40,2	-	-
+49	95	68	92	4.72	11.01	17,840	93.4	15	31.9	1.14	7.26
	No signs of DIC – Platelet cells transfusion										
+62	96	78	111	-	-	16,660	92.5	55	21.5	-	-
+73	98	72	155	3.43	10.70	14,710	90.7	60	15.6	1.26	7.57
+77	**Stable patient, end of Pentaglobin continuous infusion**										
+97	93	89	135	2.84	14.14	12,010	87.5	31	12.6	1.55	7.3
+120	98	86	96	1.92	17.83	13,760	87.1	35	13.2	1.59	7.14
+144	86	96	120	2.31	15.73	12,710	81.1	45	9.9	1.48	7.63
Last Value	90	76	98	1.89	10.72	10,870	81.7	249	10.8	2.12 without RRT	6.09

therapy of IgM enriched immunoglobulin solution. The procalcitonin (PCT) serum concentration measured every day decreased from21.27 to1.89 ng/ml and the C reactive protein (CRP) serum concentration decreased from 19.71 to 10.72 mg/L.

Discussion

The IgM enriched immunoglobulin infusions were introduced into clinical practice in 1985 (Pentaglobin - Biotest, Frankfurt, Germany). The first RCT was performed in 1991 on homogenic population of general medical patients with septic shock and high concentrations of blood endotoxin. The study showed a dramatic decrease of mortality in study group (4% vs. 32%), and was an indication for wide spread use of this preparation [9]. But further studies involving different and much more heterogenic groups of patients showed mixed results. In another RCT study on mixed population of surgical and general medical patients with moderate sepsis the only significant finding was decrease in PCT concentrations in blood [10]. On the other hand if study population involved septic shock patients the results of other RCT showed significant decrease in mortality (22% vs. 40%) [11]. A very interesting analysis was published in 2005 by A. Rodriguez et al., showing interaction between the results of the study and another most important element of therapy – appropriate antibiotic therapy. The study involved 56 surgical patients with severe sepsis and primary reduction in mortality was insignificant (27.5% vs. 48.1%, p=0.06), probably because of limited number of patients. But the authors performed secondary analysis with exclusion of cases, in which inappropriate antibiotic therapy were administered. Although the patients population was decreased, the reduction in mortality among the patients with appropriate antibiotic therapy and IgM enriched immunoglobulin infusions was significant (8.7% vs. 33.3%, p=0.04) [12].

The main problems with IgM enriched immunoglobulin infusions studies are use of a heterogenic population and limited number of study patients. The heterogeneity of sepsis patient's population even creates the questions about real value of clinical trials without significant results [13]. It is visible in many aspects of patient's clinical situation, e.g. diagnostic criteria for sepsis recognition in laboratory tests [14]. It may also explain trouble in case of sepsis with achieving significant results during many RCT studies. For IgM enriched immunoglobulin infusions now there is lack of valuable multicenter RCT study on large number of patients – which can show a real impact of this therapy on achieved results [15]. Additionally there are common misunderstandings, because there is a big difference in properties and activity between immunoglobulin solution with or without IgM. The IgM represents a different class of antibodies than IgG, and presents many unique properties like effective endotoxin inactivation, high level of complement system supported direct bacteriolysis, low concentration phagocytosis stimulation and activation pathways for immune system. Thus the results achieved in RCT trials with intravenous IgG (IVIG) can't be identified as for IgM enriched immunoglobulin solutions [16-18].

For IgM enriched immunoglobulin infusions the expert's panel established a strict list of confirmed indications, in which the beneficial effect of the therapy may occur. It consist of persistence of septic shock or severe sepsis with more than 2 organ dysfunctions after initial resuscitation and treatment, for patients with abdominal infections after surgery, meningococcal sepsis, toxic shock syndrome, overwhelming post splenectomy infection, necrotizing fasciitis. According to the same panel of experts exclusion criteria for this therapy should consist of standing do not resuscitate (DNR) order, or adequate to the prognosis limitation of therapy, incurable metastatic malignant disease, neutropenia due to hematological malignancies and according to the contraindications in the summary of product characteristic (SPC). Additionally they focused on the timing of the therapy – it should be started as early as possible. Best effects were observed and are expected if the treatment is initiated within first 8 hours of sepsis. On the other hand late start of treatment (above 48 hours) is not recommended [19].

Sepsis and septic shock may have many possible origins, and

different clinical course. The primary objective of the treatment is early resuscitation and stabilization [20]. In many cases it may improve patient's status significantly, but sometimes the improvement is slow or absent [21]. In such as cases the primary concern is possible presence of undiagnosed pathology or pathogens missed by administered antibiotic therapy. Another possible reason for lack of administered therapy effects is variability of host immune response to the pathogen antigens and toxins as well as varies according to the genetic predisposition, immune status and comorbidity of the host [22]. In our case initial blood samples were sterile, probably to the previously administered antibiotics. What was much more confusing, the initial aggressive resuscitation and treatment for previously health young woman with the use of advanced intensive therapy methods and commonly effective antibiotic therapy scheme, reserved for septic shock didn't resulted in patients improvement. The observed breakpoint in patient's clinical course was intravenous administration of IgM enriched immunoglobulin solution.

Such as clinical observation have had of course many limitations, because there is no possibility for real assessment of objective impact each of different elements from polipragmatic treatment on patients status. On the other hand after administration of the IgM enriched immunoglobulin solution patient's status improved, with regression the signs of severe sepsis as well as decrease in measured laboratory equivalent parameters for SIRS. During further period of treatment there were no signs of sepsis or life threatening infection.

Conclusion

According to our observation, in case of ineffective standard therapy of septic shock, the early IgM enriched immunoglobulin solution infusion according to the SPC dosage (5 ml/kg b.w./24 h through 72 hours) may improve patient's status and increase survival rate. Further properly managed multicenter RCT trial on large group of patients with septic shock is necessary for objective evaluation of real benefits from this kind of therapy.

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