Observational Study

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Outcomes of patients with sepsis due extensively drug-resistant bacterial infections with and without polyspecific intravenous immunoglobulin therapy

A retrospective study

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Abstract

Sepsis caused by extensively drug-resistant (XDR) pathogens is characterized by high mortality rates. Polyspecific intravenous immunoglobulin (IVIG) has been used as an adjunctive therapy in sepsis for a long time, but it is not routinely recommended due inconclusive results. This retrospective study investigates the effect of IVIG therapy on 30-day mortality in 50 patients with sepsis caused by XDR pathogens, according to Sepsis-3 criteria. Fifty patients were included, with 28 receiving IVIG alongside standard treatment. Mortality was 74%, with no significant difference in 30-day mortality (71.4% for IVIG-treated vs 77.3% for non-IVIG-treated, $P = .886$) or intensive care unit (ICU) stay duration (median of 9.0 days for both groups, $P = .883$) between the groups. The study concludes that adding polyspecific IVIG to conventional sepsis treatment does not reduce 30-day mortality or ICU stay in XDR pathogen-induced sepsis.

Abbreviations: ICU = intensive care unit, IVIG = intravenous immunoglobulin, MDR = multidrug-resistant, PDR = pandrup resistant, SOFA = sequential organ failure assessment, XDR = extensively drug-resistant.

Keywords: drug resistance mortality, IVIG, septic shock, XDR pathogen

1. Introduction

Sepsis is an organ dysfunction that develops because of the host's uncontrolled immune response to infection.[1] Following early diagnosis, resuscitation and broad-spectrum antibiotic therapy constitute the cornerstone of treatment.[2] However, despite advances in supportive therapies, mortality due to septic shock remains around 40%.[3] Standardized definitions for multidrug-resistant (MDR), extensive drug-resistant (XDR), and pandrug-resistant (PDR) were proposed in 2012. XDR pathogens are those that exhibit in vitro resistance to at least 1 agent in all but 2 or fewer antibiotic categories.[4] These pathogens are causative agents of hospital-associated infections and are more frequently observed in patients with immune paralysis.[5] The prevalence of XDR Pseudomonas aeruginosa among nosocomial pathogens ranges between 9% and 11.2%, according to the INFORM database.[6] In sepsis patients infected with these pathogens, mortality rates are higher. The mortality rate in patients with infections caused by XDR Acinetobacter has been identified as 70%, whereas in the same study, the mortality rate for infections with susceptible Acinetobacter was found to be 25%.[7,8] Advanced age, immunosuppressive treatment, diabetes, end-stage liver disease, steroid use, organ transplantation, and recent antibiotic use are host-associated risk factors for XDR infections.[9] The positive effect of early targeted antibiotic therapy in sepsis on survival is well known.[10] Because of high initial antibitoic inappropriateness and underlying immune dysfunction, treatment becomes more challenging in infections caused by XDR pathogens. Therefore, additional treatments are required for sepsis caused by XDR pathogens.[11]

Intravenous immunoglobulin (IVIG) therapy, due to its antibacterial and immunomodulatory effects, has long been tested

All patients or their relatives provided written informed consent.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The Institutional Ethical Review Board of the study center (Ege University, Faculty of Medicine), approved the study (21-6.1T/54). The study was conducted in accordance with Good Clinical Practice guidelines and adhered to the principles of the Declaration of Helsinki.

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as an adjunct therapy in sepsis.[12,13] Although recent meta-analyses suggest its effectiveness in sepsis, it is not routinely recommended by international guidelines due to heterogeneous results.[2] This study aimed to evaluate the contribution of polyspecific IVIG therapy on 30-day mortality in patients with XDR bacterial infections.

2. Materials and methods

2.1. Patient selection and study design

This retrospective study was conducted in a single-center internal medicine (non-surgical) intensive care unit (ICU) between September 2013 and February 2021. The Institutional Ethical Review Board of Ege University Hospital approved the study (21-6.1T/54). The study was conducted in accordance with good clinical practice guidelines and adhered to the principles of the Declaration of Helsinki. Patients or their relatives provided written informed consent. We included all adult patients (≥18 years old) diagnosed with sepsis due to XDR bacterial infection.

2.2. Data collection

Following data were retrieved using electronic medical records: age, sex, length of ICU stay, comorbidities, site of infection, isolated pathogens and inflammatory markers among laboratory parameters. The sequential organ failure assessment score (SOFA) on admission were calculated. During ICU stay; presence of organ dysfunction, vasopressor support (norepinephrine), need for renal replacement therapy, glasgow coma score change, appropriateness of empiric antimicrobials on the first day and 30-day mortality were recorded. Source of infection was hospital-acquired in all patients. Isolated pathogens were also recorded.

The diagnosis of sepsis and septic shock were made according to the Sepsis-3 criteria.[1] The definition of XDR pathogen was defined, according to the international guideline recommendation, as non-susceptible to ≥ 1 agent in all but ≤ 2 antibiotic categories.[4] Empirical antibiotic therapy was considered inappropriate if the isolate did not display in vitro susceptibility to any systemic antibiotic administered on the day of culture sampling. Standard sepsis treatment was administered to all patients (initiation or modification of broad-spectrum antibiotic therapy, IV fluid resuscitation, vasopressors, hemodialysis and ventilator support as needed). Glucocorticoid therapy was not used for sepsis treatment. The standard dose for polyspecific IVIG therapy was 1 g/kg over 2 days and initiated within the first 48 hours after sepsis diagnosis. IVIG treatment was administered based on its availability in the hospital during the period of treatment. The clinical conditions of the patients did not influence the decision for treatment.

Patients under 18 years of age, those who died before completing IVIG treatment, and patients with incomplete data for the evaluation of sepsis-3 criteria were excluded. Figure 1 shows the patient inclusion. Primary outcome was 30-day mortality and the secondary outcome was ICU length of stay among patients who received polyspecific IVIG therapy and those who did not.

2.3. Statistical analysis

Descriptive statistics were used to summarize the data obtained from the study. Continuous (numerical) variables are presented in tables as mean ± standard deviation or median, minimum, and maximum, depending on the distribution. Categorical variables are summarized as counts and percentages. The normality of the numerical variables was checked using Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. In statistical analyses, a significance level of $P < .05$ was used and considered 2-sided to evaluate differences in both directions.

For comparisons between 2 independent groups, the Independent Samples *t*-test was used when numerical variables were normally distributed, whereas the Mann–Whitney *U* test was used when they were not normally distributed. Pearson chi-square test was used for comparisons of differences between categorical variables in groups in 2 × 2 tables where expected counts were 5 or more, Fisher exact test was used for tables where expected counts were <5, and Fisher Freeman Halton test was used for R C tables where expected counts were <5. Additionally, a multivariate regression analysis was performed to evaluate the impact of IVIG on 30-day mortality. Missing values were not addressed or imputed and were thus excluded from analyses. Statistical analyses were conducted using "Jamovi project (2020), Jamovi (Version 1.8.4.0) [Computer Software]"

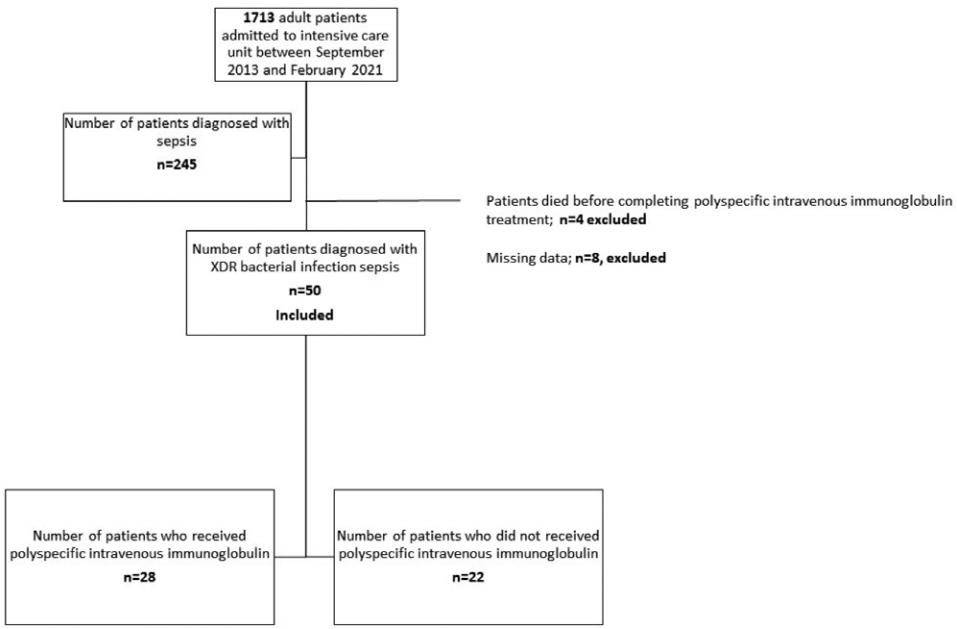

Figure 1. Flowchart of patient inclusion.

(retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (retrieved from https://jasp-stats.org) programs, and a significance level of .05 (*P*-value) was considered for statistical analyses.

3. Results

During the study period, 245 patients diagnosed with sepsis were followed up in the ICU. Among them; in 50 patients (20.4%), XDR pathogens were identified as the causative agents of sepsis. Demographic information, comorbid conditions, presence of organ failure, and infection site of these patients, along with the differences between the 2 groups, are presented in Table 1. The median age of the group receiving IVIG therapy was 55 years, whereas it was 63 years those who did not received IVIG ($P = .024$). No significant difference was found between the 2 groups in terms of gender and comorbid conditions ($P > .05$ for each). In the assessment of the severity of sepsis between the 2 groups, the median SOFA score was 9.5 [3–11] in the group not receiving IVIG and 9 [3–15] among the patients who received IVIG ($P = .478$). There was no difference between the 2 groups in the SOFA scores and organ failure assessments ($P > .05$ for each). Additionally, there was no difference in the sources of infection causing sepsis and the rates of appropriate initial antibiotic therapy use (40.9% vs 42.9%, respectively, $P = .999$). In the 30-day mortality analysis, mortality was found to be 71.4% in the group receiving IVIG therapy and 77.3% in the group not receiving IVIG therapy ($P = .886$). The impact of IVIG use on 30-day mortality was evaluated after adjusting for age, SOFA score, appropriate antibiotic use, infection site, and vasopressor need. In this multivariate regression analysis, the adjusted odds ratio for IVIG use was 0.867 (95% CI: 0.126–5.968, $P = .885$). The length of ICU stay (days) in the group receiving IVIG therapy was a median of 9.0 [3.0–58.0] days, and in the group not receiving IVIG therapy, it was a median of 9.0 [2.0–48.0] days ($P = .883$).

The laboratory results at the time of sepsis diagnosis and isolated pathogens are shown in Table 2. No difference was found between the 2 groups in terms of inflammatory markers and lactate levels. Upon examining the culture results, it was observed that in a total of 49/50 patients, gram-negative XDR pathogens were isolated, and in only 1 patient in the group not receiving IVIG, a gram-positive XDR bacteria was

Table 1

Demographic and clinical characteristics of patients.

	IVIG		
	No (n = 22)	**Yes (n = 28)**	***P***
Age*	63.0 [20.0–86.0]	55.0 [18.0–76.0]	.024
Gender†			
Male	9 (40.9)	18 (64.3)	.174
Female	13 (59.1)	10 (35.7)	
Length of ICU stay, d*	9.0 [2.0–48.0]	9.0 [3.0–58.0]	.883
Mortality, present†	17 (77.3)	20 (71.4)	.886
Comorbidity†	16 (72.7)	17 (60.7)	.556
Diabetes mellitus	9 (40.9)	7 (25.0)	.373
Cardiovascular disease	5 (22.7)	7 (25.0)	.999
Chronic heart failure	2 (9.1)	4 (14.3)	.683
COPD/asthma	5 (22.7)	1 (3.6)	.075
Chronic renal disease	2 (9.1)	4 (14.3)	.683
Vasculitis	1 (4.5)	3 (10.7)	.621
Connective tissue disease	1 (4.5)	2 (7.1)	.999
Hematological malignancy	6 (27.3)	12 (42.9)	.399
Solid organ malignancy	0 (0.0)	1 (3.6)	.999
Site of infection†			
Pneumonia	10 (45.5)	13 (46.4)	.999
Urinary tract	6 (27.3)	4 (14.3)	.302
Catheter and blood stream	4 (18.2)	5 (17.9)	.999
Abdomen (other than biliary system)	1 (4.5)	3 (10.7)	.621
Biliary system	1 (4.5)	1 (3.6)	.999
Skin and soft tissue	2 (9.1)	2 (7.1)	.999
Meningitis	0 (0.0)	1 (3.6)	.999
Septic arthritis	1 (4.5)	0 (0.0)	.440
Primary bacteremia (source can't find)	0 (0.0)	1 (3.6)	.999
Organ dysfunction			
Heart rate*	114.0 [95.0–145.0]	117.0 [79.0–160.0]	.971
Hypotension, yes†	20 (90.9)	22 (78.6)	.439
Vasopressor support, yes†	18 (81.8)	17 (60.7)	.106
Acute kidney injury, yes†	15 (68.2)	14 (50.0)	.315
Renal replacement therapy, yes†	7 (31.8)	9 (32.1)	.999
Hepatobiliary dysfunction, yes†	3 (13.6)	8 (28.6)	.306
Disseminated intravascular coagulation, yes†	4 (18.2)	7 (25.0)	.734
Thrombocytopenia (<150,000 µL), yes†	15 (68.2)	23 (82.1)	.416
Acute respiratory failure, yes†	11 (50.0)	14 (50.0)	.999
Glasgow coma score change, *yes*†	6 (27.3)	9 (32.1)	.950
SOFA score*	9.5 [3–11]	9 [3–15]	.478
Appropriateness of empiric antimicrobials on day 1†	9 (40.9)	12 (42.9)	.999

Abbreviations: COPD = chronic obstructive pulmonary disease, ICU = intensive care unit, IVIG = intravenous immunoglobulin, SOFA = sequential organ failure assessment.

* Median [Min. to Max.].

† n (%).

Table 2

Hematological, biochemical parameters and microbiological findings of patients.

	IVIG		
	No (n = 22)	**Yes (n = 28)**	***p***
Neutrophil count, /μL*	4085.0 [0.0–19700.0]	1500.0 [0.0–57930.0]	.310*
Lymphocyte count, /μL*	450.0 [0.0–5840.0]	240.0 [0.0–3660.0]	.100*
Albumin, g/dL*	2.8 [1.8–4.3]	2.5 [1.8–3.5]	.429*
Lactate dehydrogenase, U/L*	288.0 [155.0–1409.0]	295.0 [99.0–927.0]	.615*
Lactate, mmol/L*	2.8 [0.6–9.4]	3.1 [1.3–7.2]	.463*
C-reactive protein, (mg/L)*	225.5 [53.0–329.0]	235.0 [32.0–366.0]	.333*
Procalcitonin, μg/L*	3.0 [0.3–50.0]	7.3 [2.2–100.0]	.064*
Isolated pathogens†			
ESBL producing Enterobacteriaceae	1 (4.5)	2 (7.1)	.999
Carbapenem-resistant Enterobacteriaceae	6 (27.3)	14 (50.0)	.181
Methicillin-resistant *Staphylococcus Aureus*	1 (4.5)	0 (0.0)	.440
Pseudomonas spp.	9 (40.9)	4 (14.3)	.071
Acinetobacter baumannii	10 (45.5)	12 (42.9)	.999
Methicillin-resistant CoNS	2 (9.1)	1 (3.6)	.576
Candida spp.	1 (4.5)	1 (3.6)	.999
Cytomegalovirus infection	0 (0.0)	2 (7.1)	.497
Aspergillus spp.	0 (0.0)	1 (3.6)	.999
Enterococcus faecalis	4 (18.2)	2 (7.1)	.385
ESBL negative enterobacteriaceae	1 (4.5)	0 (0.0)	.440
Methicillin-sensitive *Staphylococcus Aureus*	1 (4.5)	0 (0.0)	.440
Other	1 (4.5)	1 (3.6)	.999
Gram-negative bacteria isolation†	21 (95.5)	28 (100.0)	.440
Gram-positive bacteria isolation†	7 (31.8)	3 (10.7)	.084
Bacteremia†	16 (72.7)	19 (67.9)	.950

Abbreviations: CoNS = coagulase-negative staphylococci, ESBL = extended-spectrum beta-lactamase, IVIG = intravenous immunoglobulin.

* Median [Min. to Max.].

† n (%).

the causative agent of sepsis. The other culture isolates are listed in Table 2. There was no statistically significant difference between those who received and did not receive IVIG in terms of the proportions of pathogens identified in the cultures ($P > .05$ for each).

4. Discussion

Recent studies have shown that during sepsis, pro-inflammatory and anti-inflammatory processes are activated simultaneously. Following the recognition of Pathogen-associated molecular patterns and Damage-associated molecular pattern molecules by the immune system, the release of cytokines and mediators occurs, leading to a cytokine storm. In addition, T-cell exhaustion and apoptosis in immune cells result in immunosuppression, which increases the risk of nosocomial infections, prolongs hospital stays, and can lead to death. This double-edged inflammatory process in sepsis poses challenges in the application of immunomodulatory treatments.[14]

Patients with sepsis caused by XDR pathogens tend to have higher mortality rates than those caused by other pathogens.[15] The high mortality rate in these patients is generally due to the prevalent immune dysfunction and ineffectiveness of empirical antibiotics.[16] Studies to enhance the effectiveness of antibiotic therapy using new antibiotics and combined regimens are ongoing.[17,18] However, failure or delay in pathogen isolation results in patients being deprived of effective antibiotic therapy during this period.[11] During this time, when they are not receiving effective antibiotics, XDR pathogens can induce a higher inflammatory response than susceptible pathogens, leading to septic shock.[19] To suppress this inflammatory response, methods such as extracorporeal blood purification techniques and IVIG therapy can be used in patients with sepsis caused by XDR pathogens.[20,21]

IVIG contains a broad spectrum of antibodies obtained from live donors.[22] These antibodies have antibacterial effectiveness against microorganisms.[23] In vitro studies have shown that adding IVIG along with antimicrobial agents to *Acinetobacter baumannii* isolates can increase bacterial cell damage.[24] In addition to its antibacterial efficacy, it has an immunomodulatory effect on the excessive inflammatory response developed against the pathogen.[25] It can also contribute to the prevention of secondary infections that may arise due to potential immune paralysis during sepsis.[26] Due to its antibacterial, immunomodulatory effects and potential to replenish decreased Ig levels in sepsis, IVIG can reduce both early mortality related to the high inflammatory condition in the initial phase of sepsis and long-term hospitalization-related mortality due to the late phase low-grade inflammatory, immunosuppressed phenotype. Therefore, IVIG therapy is an attractive treatment option, especially in patients with sepsis and resistant microorganisms.

Studies indicate that the timing of administration (early or late), type of IVIG preparation (IgM-enriched or standard IVIG), and the dose of IVIG can influence its effectiveness. Evidence suggests that use within the first 24 hours, high-dose IVIG therapy (>1 g/kg), and IgM-enriched preparations may be more effective.[27,28] However, due to the heterogeneous results in studies, it is not routinely recommended in the current guidelines.[2]

There are limited data in the literature regarding the effectiveness of IVIG therapy in MDR and XDR pathogens. In a previous study evaluating IVIG therapy in sepsis patients with MDR and XDR pathogens, the positive effect of IgM-enriched IVIG therapy on survival was demonstrated. However, there are no direct data on the effectiveness of standard IVIG therapy in this patient group.[29]

In our retrospective study evaluating the effectiveness of IVIG therapy in 50 patients with sepsis caused by XDR bacteria, there was no difference between the group that received IVIG therapy and the group that did not in terms of sepsis severity and inflammatory markers. Additionally, both groups were equal in terms of using effective antibiotic therapy initially. In the 2 groups with similar baseline characteristics, no difference was observed in 30-day mortality and ICU stay durations with IVIG treatment. Based on

these results, it has been concluded that standard IVIG therapy is not effective in patients with sepsis caused by XDR bacteria.

Recent meta-analyses have suggested that IgM-enriched IVIG therapy in sepsis treatment may be more effective than standard IVIG therapy.[30] The pentameric structure of IgM enhances its antimicrobial and opsonization activities. Therefore, it may strengthen standard treatment, especially in patients with gram-negative infections who are not receiving effective antibiotic therapy.[12] The IVIG preparations used in our patients were all IgM poor, which might be the reason for the inability to demonstrate a difference in survival.

We presented a highly selected patients group, however, the study's retrospective, single-center nature and the inclusion of a small number of patients (n = 50) are limitations and have limited generalizability. However, despite its retrospective nature, there was no significant difference in SOFA scores among the included patients, indicating 2 comparable groups of patients in terms of sepsis severity, is the major strength of our study. All patients used the same IVIG preparation, and the study did not include heterogeneity in terms of administration dose (1 g/kg over 2 days) and the initiation time (within the first 48 hours).

5. Conclusion

Mortality rates are high in XDR pathogen related sepsis and septic shock. We noted that in the similar severity illness populations, contribution of polyspecific IVIG on standard therapy does not appear have effect on 30-day mortality and ICU length of stay. There is limited research on the effectiveness of polyspecific IVIG therapy in patients with sepsis caused by resistant pathogens. IVIG therapy with IgM-enriched preparations might be more appropriate particularly in hospital-acquired sepsis, where there is a risk of resistant pathogens and doubts about the adequacy of empirical antibiotic treatment.

Author contributions

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References

[1] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10.
[2] Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–247.
[3] Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019–results from a systematic review and meta-analysis. Crit Care. 2020;24.
[4] Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81.
[5] Mira JC, Gentile LF, Mathias BJ, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45:253–62.
[6] Tabak YP, Merchant S, Ye G, et al. Incremental clinical and economic burden of suspected respiratory infections due to multi-drug-resistant Pseudomonas aeruginosa in the United States. J Hosp Infect. 2019;103:134–41.
[7] Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and pathophysiological overview of Acinetobacter infections: a century of challenges. Clin Microbiol Rev. 2017;30:409–47.
[8] Lee HY, Chen CL, Wu SR, Huang CW, Chiu CH. Risk factors and outcome analysis of acinetobacter baumannii complex bacteremia in critical patients. Crit Care Med. 2014;42:1081–8.
[9] Bassetti M, Carnelutti A, Peghin M. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. Expert Rev Anti Infect Ther. 2017;15:55–65.
[10] Baltas I, Stockdale T, Tausan M, et al. Impact of antibiotic timing on mortality from Gram-negative bacteraemia in an English district general hospital: the importance of getting it right every time. J Antimicrob Chemother. 2021;76:813–9.
[11] Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18:596.
[12] Rossmann FS, Kropec A, Laverde D, Saaverda FR, Wobser D, Huebner J. In vitro and in vivo activity of hyperimmune globulin preparations against multiresistant nosocomial pathogens. Infection. 2015;43:169–75.
[13] Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol. 2013;13:176–89.
[14] Liu D, Huang SY, Sun JH, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. Mil Med Res. 2022;9:1–19.
[15] Martin A, Fahrbach K, Zhao Q, Lodise T. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to enterobacteriaceae: results of a systematic literature review and meta-analysis. Open Forum Infect Dis. 2018;5:ofy150.
[16] Kumar A, Ellis P, Arabi Y, et al; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009;136:1237–48.
[17] Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant enterobacteriaceae infections: the TANGO II randomized clinical trial. Infect Dis Ther. 2018;7:439–55.
[18] Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents. 2018;51:62–4.
[19] Giamarellos-Bourboulis EJ, Plachouras D, Tzivra A, et al. Stimulation of innate immunity by susceptible and multidrug-resistant Pseudomonas aeruginosa: an in vitro and in vivo study. Clin Exp Immunol. 2004;135:240–6.
[20] Payen DM, Guilhot J, Launey Y, et al.; ABDOMIX Group. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med. 2015;41:975–84.
[21] Jarczak D, Kluge S, Nierhaus A. Use of intravenous immunoglobulins in sepsis therapy – a clinical view. Int J Mol Sci. 2020;21:5543–17.
[22] Durandy A, Kaveri SV, Kuijpers TW, et al. Intravenous immunoglobulins – understanding properties and mechanisms. Clin Exp Immunol. 2009;158(Suppl 1):2–13.
[23] Matsuo H, Itoh H, Kitamura N, et al. Intravenous immunoglobulin enhances the killing activity and autophagy of neutrophils isolated from immunocompromised patients against multidrug-resistant bacteria. Biochem Biophys Res Commun. 2015;464:94–9.
[24] de Lima FCG, de Araújo AR, do Nascimento AV, et al. In vitro evaluation of human intravenous immunoglobulin in combination with antimicrobials and human serum against multidrug-resistant isolates of Acinetobacter baumannii. Braz J Microbiol. 2023;54:2845–56.
[25] Chaigne B, Mouthon L. Mechanisms of action of intravenous immunoglobulin. Transfus Apher Sci. 2017;56:45–9.
[26] Benbrahim O, Viallard JF, Choquet S, et al. The use of octagam and gammanorm in immunodeficiency associated with hematological malignancies: a prospective study from 21 French hematology departments. Hematology. 2019;24:173–82.
[27] Berlot G, Vassallo MC, Busetto N, et al. Effects of the timing of administration of IgM- and IgA-enriched intravenous polyclonal immunoglobulins on the outcome of septic shock patients. Ann Intensive Care. 2018;8:122.
[28] Iizuka Y, Sanui M, Sasabuchi Y, et al. Low-dose immunoglobulin G is not associated with mortality in patients with sepsis and septic shock. Crit Care. 2017;21:181.
[29] Giamarellos-Bourboulis EJ, Tziolos N, Routsi C, et al; Hellenic Sepsis Study Group. Improving outcomes of severe infections by multidrug-resistant pathogens with polyclonal IgM-enriched immunoglobulins. Clin Microbiol Infect. 2016;22:499–506.
[30] Pan B, Sun P, Pei R, Lin F, Cao H. Efficacy of IVIG therapy for patients with sepsis: a systematic review and meta-analysis. J Transl Med. 2023;21:765.