Official journal of the Spanish Society of Chemotherapy

Original

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Clindamycin but not Intravenous Immunoglobulins reduces mortality in a retrospective cohort of critically ill patients with bacteremic Group A Streptococcal infections

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ABSTRACT

Objectives. Mortality of patients requiring Intensive Care Unit (ICU) admission for an invasive group A streptococcal (GAS) infection continues being high. In critically ill patients with bacteremic GAS infection we aimed at determining risk factors for mortality.

Patients and methods. Retrospective multicentre study carried out in nine ICU in Southern Spain. All adult patients admitted to the participant ICUs from January 2014 to June 2019 with one positive blood culture for *S. pyogenes* were included in this study. Patient characteristics, infection-related variables, therapeutic interventions, failure of organs, and outcomes were registered. Risk factors independently associated with ICU and in-hospital mortalities were determined by multivariate regression analyses.

Results. Fifty-seven patients were included: median age was 63 (45-73) years, median SOFA score at admission was 11 (7-13). The most frequent source was skin and soft tissue infection (n=32) followed by unknown origin of bacteremia (n=12). In the multivariate analysis, age (OR 1.079; 95% CI 1.016-1.145), SOFA score (OR 2.129; 95% CI 1.339-3.383) were the risk factors for ICU mortality and the use of clindamycin was identified as a protective factor (OR 0.049; 95% CI 0.003-0.737). Age and SOFA were the independent factors associated with hospital mortality however the use of clindamycin showed a strong trend but without reaching statistical significance (OR 0.085; 95% CI 0.007-1.095).

Conclusion. In this cohort of critically ill patients the use of intravenous immunoglobulin was not identified as a protective factor for ICU or hospital mortality treatment with clindamycin significantly reduced mortality after controlling for confounders.

Keywords: Clindamycin; Intravenous Immunoglobulins; Bacteriemia; Critically ill patients; Group A Streptococcal infections.

Tratamiento con clindamicina, y no con inmunoglobulinas intravenosas, disminuye la mortalidad en una cohorte retrospectiva de pacientes críticos con bacteriemia por *Streptococcus* del Grupo A

RESUMEN

Objetivo. La mortalidad de los pacientes que requieren ingreso en la Unidad de Cuidados Intensivos (UCI) por una infección invasiva por estreptococos del grupo A (GAS) continúa siendo inaceptablemente alta. El objetivo del estudio fue determinar los factores de riesgo de mortalidad en pacientes críticos con infección estreptocócica bacterémica del grupo A.

Pacientes y métodos. Estudio retrospectivo multicéntrico realizado en nueve UCI del sur de España. Se incluyeron pacientes consecutivos ingresados en las UCI participantes desde enero de 2014 hasta junio de 2019 con un hemocultivo positivo para *S. pyogenes*. Se registraron las características de los pacientes, las variables relacionadas con la infección, las intervenciones terapéuticas, el fracaso de los órganos y el pronóstico. Se determinaron mediante análisis de regresión multivariante los factores de riesgo asociados de forma independiente con la mortalidad en UCI y hospitalaria.

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Resultados. Se incluyeron cincuenta y siete pacientes: la mediana de edad fue de 63 (45-73) años, la mediana de la puntuación SOFA al ingreso fue de 11 (7-13). El foco más frecuente fue la infección de la piel y los tejidos blandos (n=32) seguida de la bacteriemia de origen desconocido (n=12). En el análisis multivariante, la edad (OR 1,079; IC del 95%: 1,016-1,145), y la puntuación SOFA (OR 2,129; IC del 95%: 1,339-3,383) se identificaron como factores de riesgo para la mortalidad en UCI. El uso de clindamicina se identificó como un factor protector (OR 0,049; IC del 95%: 0,003-0,737). La edad y la SOFA se asociaron de forma independiente con la mortalidad hospitalaria, mientras que el tratamiento con clindamicina mostró una tendencia fuerte pero sin alcanzar significación estadística (OR 0,085; IC del 95%: 0,007-1,095).

Conclusión. En esta cohorte de pacientes críticos, el uso de inmunoglobulina intravenosa no se identificó como un factor protector para la mortalidad en UCI u hospitalaria, el tratamiento con clindamicina redujo significativamente la mortalidad después de controlar los factores de confusión

Palabras clave: Clindamicina; inmunoglobulinas intravenosas; Bacteriemia; pacientes críticos; infecciones estreptococos grupo A

INTRODUCTION

In spite of the advances in modern medicine, invasive group A streptococcal (GAS) infections cause a significant morbidity and mortality. Even though the resistance rates of GAS (*Streptococcus pyogenes*) to several antibiotics vary considerably worldwide, GAS remains universally susceptible to β-lactams antibiotics including penicillin [1], the lethality of severe invasive GAS infections requiring ICU admission remains high, about 50% in different series [2]. In these severe forms, *S. pyogenes* exotoxins act as superantigens to trigger polyclonal T-cell activation, cytokine cascade, shock, and death [3].

The low incidence of the invasive GAS disease explains the difficulties of randomized controlled trials evaluating management strategies. Likewise, observational cohort studies have been carried out using the majority of them administrative databases [4-6]. Moreover, conflicting results have been reported about the impact on mortality of different therapeutical strategies, specifically with the use of clindamycin or immunoglobulins [5,6].

In order to contribute to our knowledge about risk factors associated with mortality of severe invasive GAS infections, we performed this multicenter study including only patients admitted to the ICU. Our purposes were to stablish predictors of death carefully examining the clinical impact of antimicrobial strategies and the use of immunoglobulins on mortality after controlling for confounding variables.

METHODS

This is a retrospective multicenter study carried out in nine Spanish Intensive Care Units in Andalusia. The study was approved by the Spanish Agency of Medicinal Products and Medical Devices and by the local institutional review boards; written

patient consent was not required because of the retrospective nature of this study.

All adult patients (≥18 years) admitted to the participant ICUs from January 2014 to June 2019 with one positive blood culture for *S. pyogenes* were included in this study. Patient baseline characteristics, infection-related variables and subsequent evolution were obtained from the automated hospital medical record and microbiology database of the participating centers. All patients were followed up for 90 days after the admission to the ICU for invasive GAS.

The following data were collected: age, gender, source of infection (skin and soft tissue, lung, unknow origin, and others) and underlying diseases: diabetes mellitus, liver cirrhosis, chronic renal disease, chronic heart failure, chronic obstructive pulmonary disease, and cancer. Severity of illness at ICU admission was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and by the Sequential Organ Failure Assessment (SOFA) scale considering the worst data point of the first 24 h in the ICU [7,8]. Clinical presentation was classified as sepsis or septic shock following Sepsis-3 definitions. The presence of a SOFA score of each organ >3 points at admission or during the ICU stay was considered as failure of this organ [9].

Data regarding management of these patients were also gathered: empirical antimicrobial regimen, use of clindamycin or linezolid, use of penicillin G as the β-lactam in directed therapy, administration of intravenous immunoglobulins (IVIG), mechanical ventilation and need of renal replacement therapy. In patients with skin and soft tissue infection (SSTI), date of the first surgical debridement and the total number of surgical interventions were also noted.

Standard microbiological methods were used by all the participating centers. This included the use of an automated continuous monitoring blood culture system, the performance of standard identification biochemical test, Lancenfield antigen immunoassay detection or, automated rapid test such as matrix-assisted laser desorption ionization-time of flight mass spectrometry (Maldi-tof). Susceptibility testing was performed using accepted methods at each hospital and results were interpreted according to the Clinical Laboratory Standard Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

Statistical analysis. Qualitative variables are presented as the absolute numbers and frequency, quantitative variables as mean ($\pm$ SD) if their distribution was normally distributed or as median (percentile 25 – percentile 75) if the distributions were skewed. Student's t test was used to compare continuous variables with normal distribution, U Mann-Whitney tests for skewed distributed variables. Chi-2 and Fisher's exact tests were used for comparisons of categorical variables. Logistic regression models using variables with a *p* value <0.2 in the univariate analysis and those considered potentially relevant were used to determine the factors independently associated with ICU and in-hospital mortalities. All comparisons were two-tailed and signification was set at p<0.05.

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SPSS 15.0 software (IBM SPSS, Chicago, IL, USA) was used for statistical analysis.

This analysis is reported following the STROBE recommendations [10].

RESULTS

During the study period, 57 patients were diagnosed of invasive GAS in the participant ICUs. The median age was 63 (45-73) years and 70.2 % were male. Median SOFA score at admission was 11 (7-13). The median time from hospital admission to positive blood culture was 0 (0, 1) days and the time elapsed from positive blood culture to ICU admission was 0 days (-1, 0). Twenty-eight patients (49.1%) died in the ICU, 30 patients (52.6%) during hospitalization, and mortality rate at 90 days was 64.9% (37 patients).

All patients had received empirical antibiotic treatment with a β-lactam antibiotic active against *S. pyogenes*. Bivariate analyses for ICU and hospital mortality are shown in Table 1. At baseline, there were no significant differences in sex, comorbid illnesses (except liver cirrhosis), or site of infection between survivors and non-survivors. All isolates were susceptible to penicillin although only 23 patients received penicillin G in the directed therapy. Eleven patients received IVIG and all of them were treated with clindamycin as well. All patients treated with clindamycin received this antibiotic during the first 48 hours after blood culture collection. In the multivariate analysis, two variables were identified as risk factors for ICU death meanwhile treatment of clindamycin was a protective factor (Table 2). Results of the multivariate analysis for hospital mortality is also depicted in the Table 2. Notably, use of IVIG was not identified as a protective factor for ICU or hospital mortality.

The comparison of clindamycin-treated patients and those who did not receive clindamycin is shown in table 3. Median duration of therapy with clindamycin was 7 days. Of note, clindamycin was more frequently used in patients with SSTI as source of bacteremia.

In the present study, the most frequent organ failure was cardiovascular, followed by respiratory (n=29) and renal failure (n=29). The incidence of other failure of organs was lower: coagulation (23.2%), central nervous system (22.8%), and hepatic failure (12.3%). The median number of organs failing in a patient was 2 (1-4). In our series, 41/57 (71.9%) required invasive mechanical ventilation and 28/57 (49.1%) needed continous renal replacement therapy (CRRT). Table 4 depicts the association between failure of the different organs and mortality.

DISCUSSION

Our multicenter study including severely ill patients with high-grade of organ dysfunction secondary to bacteremic invasive GAS confirms that this infection has a significant morbidity and a high mortality rate. Importantly, clindamycin as part of the antimicrobial therapy significantly reduced mortality after controlling for confounders while we could not demonstrate a beneficial effect of IVIG and survival was similar in patients who did or did not receive IVIG.

To the best of our knowledge, there is a paucity of studies carried out in patients with GAS requiring ICU admission. In our series, mortality rate is very high dying in the hospital 50% of the patients admitted to the ICU with this infection. These high figures have been reported previously by other authors. As an exception, an observational study reported an ICU mortality rate as low as 5.7% and even lower than the mortality of a heterogeneous group of septic patients. Importantly, only 60% of these 53 patients with invasive GAS presented septic shock and the rate of bloodstream infection is not reported by the authors [11].

Because the mortality rate with invasive GAS remains high, the therapeutical approach must be prompt and aggressive. In the present study, clinical and demographic characteristics were similar between patients treated and not treated with clindamycin, with the exception that severity of illness assessed by APACHE II score was significantly higher in the non-clindamycin group. Nevertheless, although severity of illness at admission to the ICU is a strong predictor of death in critically ill septic patients [12], treatment with clindamycin was a protective factor after controlling for confounding variables. Two observational studies have concluded that clindamycin improves survival in patients with invasive GAS [5,6]. A large observational study of patients with GAS infection has recently confirmed the reduction of mortality with the administration of clindamycin and this beneficial effect was present also present if the patient was not in septic shock or in another source of infection different to SSTI [13]. Conversely, a retrospective study evaluating patients with invasive GAS admitted to the ICU, the use of clindamycin was not associated with a better survival [14]. Linezolid is another theoretical alternative with a mechanism of action similar to that of clindamycin [15]. The experience with this oxazolidinone in invasive GAS is scarce but our findings do not support its use in invasive GAS for toxin synthesis inhibition.

The current surviving sepsis guidelines for adults recommends against the use of IVIg in patients with sepsis and septic shock [16]. However, the role of IVIG in patients with streptococcal septic shock has been a moot point during the last years. The largest observational study using propensity score matching and involving 4,127 patients with necrotizing fasciitis and streptococcal toxic shock concluded that IVIG had no effect on mortality or length of hospital stay [17]. The aforementioned studies about the beneficial effect of clindamycin also concluded that the use of IVIG was associated with higher survival [5,6]. A multicenter, randomized, double-blinded, placebo-controlled trial of IVIG in SSTI was prematurely stopped due to the lack of recruitment after enrolling only 21 patients [18].

SSTI and pneumonia were the most common sites of infection at presentation. In our series, source of infection does not have a prognostic value. Nevertheless, bacteremia without an identified focus was independently associated with an increased risk of a fatal outcome in a heterogenous group of

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Table 1	Bivariate Analysis for ICU Mortality and Hospital Mortality.					

	ICU mortality			In-hospital mortality		
Variables	Non-survivors (n=28)	Survivors (n=29)	p value	Non-survivors (n=30)	Survivors (n=27)	p value
Age (years)	68 (61-75)	52 (44-70)	0.006	69 (61-75)	52 (43-67)	0.002
Sex (man)	16 (57.1%)	24 (82.8%)	0.035	18 (60%)	22 (81.5%)	0.077
Underlying diseases						
Diabetes	10 (35.7%)	9 (31%)	0.708	11 (36.7%)	8 (29,6%)	0.574
Cirrhosis	4 (14.3%)	0 (0%)	0.035	4 (13.3%)	0 (0%)	0.049
Immunosuppression	4 (14.3)	5 (17.2%)	0.760	5 (16.7%)	4 (14,8%)	0.484
Chronic Heart Failure	3 (10.7%)	6 (20.7%)	0.302	4 (13.3%)	5 (18,5%)	0.592
Chronic Kidney Disease	5 (17.9%)	3 (10.3%)	0.414	5 (16.7%)	3 (11,1%)	0.547
Cancer	7 (25%)	5 (17.2%)	0.473	8 (26.7)	4 (14,8%)	0.273
COPD	6 (21.4%)	4 (13.8%)	0.449	5 (16.7%)	5 (18,5%)	0.854
Source of iGAS						
Skin and soft tissue	14 (50.0%)	18 (62.1%)	0.515	16 (53.3%)	16 (59.3%)	0.622
Unknown	8 (28.6%)	4 (13.8%)		8 (26.7%)	4 (14.8%)	
Lung	4 (14.3%)	5 (17.2%)		4 (13.3%)	5 (18.5%)	
Other	2 (7.2%)	0 (0%)		4 (13.3%)	2 (7.4%)	
APACHE II score at ICU admission	29 (22-32)	21 (16-25)	0.000	29 (22-32)	21 (16-25)	0.001
SOFA score at ICU admission	13 (11-15)	8 (6-10)	0.000	13 (11-15)	8 (6-10)	0.000
Respiratory	3 (2-3)	1 (1-2)	0.006	3 (2-3)	2 (1-2)	0.094
Cardiovascular	4 (3-4)	3 (1-4)	0.020	4 (3-4)	3 (1-4)	0.039
Renal	3 (2-4)	2 (1-2)	0.009	2 (2-4)	2 (1-3)	0.039
Coagulation	1 (0-2)	1 (0-2)	0.565	1 (0-2)	1 (0-2)	0.126
Liver	1 (0-2)	1 (0-2)	0.328	1 (0-2)	1 (0-2)	0.151
Central Nervous System	1 (1-3)	0 (0-0)	0.000	2 (1-2)	0 (0-0)	0.000
Worst SOFA score in the ICU	15 (12-17)	10 (6-11)	0.000	15 (12-16)	10 (6-12)	0.000
Respiratory	4 (3-4)	2 (1-2)	0.000	3 (2-4)	2 (1-3)	0.053
Cardiovascular	4 (4-4)	4 (3-4)	0.016	4 (4-4)	4 (3-4)	0.058
Renal	4 (2-4)	2 (1-4)	0.003	4 (2-4)	2 (1-4)	0.039
Coagulation	2 (0-3)	2 (0-2)	0.667	2 (0-3)	2 (0-2)	0.346
Liver	2 (0-2)	1 (0-2)	0.362	2 (0-2)	1 (0-2)	0.224
Central Nervous System	2 (1-4)	0 (0-1)	0.000	2 (1-4)	0 (0-1)	0.000
Therapeutic approach						
Clindamycin	14 (50%)	25 (86.2%)	0.003	16 (53.3%)	23 (85.2%)	0.010
Linezolid	7 (25%)	8 (27.6%)	1	8 (26.7%)	7 (25.9%)	1
Penicillin G in directed therapy	9 (32.1%)	14 (48.3%)	0.215	10 (33.3%)	13 (48.1%)	0.255
Immunoglobulin	6 (21.4%)	5 (17.2%)	0.689	6 (20%)	5 (18.5%)	0.887
Mechanical ventilation	28 (100%)	13 (44.8%)	0.000	28 (93.3%)	13 (48.1%)	0.000
Renal Replacement Therapy	18 (64.3%)	10 (34.5%)	0.024	17 (56.7%)	11 (40.7%)	0.230

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; iGAS: invasive group A *Streptococcus.*

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Table 2	Factor independently associated with ICU and Hospital Mortality in the multivariate analysis		
ICU MORTALITY	OR	CI 95%	p
Age	1.079	1.016-1.145	0.013
Use of clindamycin	0.049	0.003-0.737	0.029
SOFA	2.129	1.339-3.383	0.001
HOSPITAL MORTALITY			
Age	1.092	1.026-1.162	0.005
Use of clindamycin	0.085	0.007-1.095	0.085
SOFA	2.089	1.345-3.246	0.001

Table 3	Comparison of clindamycin-treated patients and those who did not receive this antibiotic		
Variables	Clindamycin (n=39)	No clindamycin (n=18)	p value
Age (years)	61 (44-73)	68 (61-75)	0.091
Sex (man)	28 (71.8%)	12 (66.7%)	0.694
Underlying diseases			
Diabetes	12 (30.8%)	7 (38.9%)	0.546
Cirrhosis	0	4 (22.2%)	0.002
Immunosuppression	6 (15.4%)	3 (16.7%)	0.902
Chronic Heart Failure	5 (12.8%)	4 (22.2%)	0.366
Chronic Kidney Disease	6 (15.4%)	2 (11.1%)	0.666
Cancer	8 (20.5%)	4 (22.2%)	0.883
COPD	4 (10.3%)	6 (33.3%)	0.033
Source of iGAS			
Skin and soft tissue	26 (66,7%)	6 (33.3%)	0.031
Unknown	7 (17.9%)	5 (27,8%)	
Lung	5 (12,8%)	4 (22.2%)	
Others	1 (2.6%)	3 (16,7%)	
APACHE II score at ICU admission	29 (22-32)	21 (16-25)	0.000
SOFA score at ICU admission	13 (11-15)	8 (6-10)	0.000
Respiratory	3 (2-3)	1 (1-2)	0.006
Cardiovascular	4 (3-4)	3 (1-4)	0.020
Renal	3 (2-4)	2 (1-2)	0.009
Coagulation	1 (0-2)	1 (0-2)	0.565
Liver	1 (0-2)	1 (0-2)	0.328
Central Nervous System	1 (1-3)	0 (0-0)	0.000
Worst SOFA score in the ICU	10 (7-12)	13 (7-15)	0.130
Respiratory	2 (1-3)	2 (1-3)	0.180
Cardiovascular	4 (3-4)	3 (1-4)	0.360
Renal	2 (1-3)	2 (2-3)	0.785
Coagulation	1 (0-2)	1 (0-2)	0.413
Liver	1 (0-2)	1 (0-2)	0.221
Central Nervous System	0 (0-1)	1 (0-3)	0.026
Therapeutic approach			
Linezolid	15 (38.5%)	8 (44.4%)	0.669
Penicillin G in directed therapy	21 (53.8%)	2 (11.1%)	0.002
Immunoglobulin	11 (28.2%)	0	0.012
Mechanical ventilation	26 (66.7%)	15 (83.3%)	0.193
Renal Replacement Therapy	19 (48.7%)	9 (50%)	0.928
ICU mortality	14 (35.9%)	14 (77.8%)	0.003
Hospital mortality	16 (41%)	14 (77.8%)	0.010
90-day mortality	23 (60.5%)	14 (77.8%)	0.203

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit; iGAS: invasive group A *Streptococcus*.

non-critically ill patients with a mortality rate much lower than ours (14%) [19].

Our data also highlight that the high incidence and the severity of organ failures in patients with invasive GAS requiring ICU admission explaining the high mortality and the burden of care associated with this disease. In our series, degree of organ disfunction assessed by SOFA score is an independent predictor of ICU and hospital mortality. Similarly, the number of dysfunctional organs correlated with mortality being coagulopathy and liver failure factors independently associated with mortality [14]. Invasive mechanical ventilation was used in two-thirds of our patients and 50% of them fulfilled criteria of severe respiratory failure. Likewise, half of the patients developed acute renal failure requiring CRRT. Information regarding failure of organs is lacking in previous studies that have observed the beneficial effect of clindamycin in invasive GAS [5,6,13]. The SOFA score as a mortality estimation tool presents a high discriminatory capacity to predict ICU mortality [20].

We acknowledge several limitations of this study. First, this is a retrospective study and as our sample size was relatively small for some comparisons, a type II error is possible. Second, the gold standard for demonstrating that a therapeutic intervention impacts on the outcome is a randomized, controlled, blinded trial. Nevertheless, observational studies can provide valuable information about treatment effectiveness especially in infections with low frequency of presentation. Third, although we could not demonstrate a beneficial impact of immunoglobulins on survival both the quantity and quality of neutralizing antitoxin antibodies vary from batch to batch of IVIG what may have influence our negative findings [21]. Fourth, sequencing of the variable M serotype–specific region of the *emm* gene has not been carried out in our study. This is important since certain GAS *emm* sequence types have been associated with mortality [22,23].

To sum up, our findings are of the utmost importance since, in this cohort of critically ill patients with multiple organ dysfunction secondary to bacteremic GAS, we have demonstrated the beneficial effect in terms of mortality of adding clindamycin as part of the antimicrobial management. In these

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Table 4	Association between failure of the different organs and ICU and Hospital mortalities.					
	ICU mortality			In-hospital mortality		
Organ Failure	Non-survivors (n=28)	Survivors (n=29)	p value	Non-survivors (n=30)	Survivors (n=27)	p value
Respiratory failure	22 (78.6%)	7 (24.1%)	<0.001	21 (70%)	8 (29.6%)	0.002
Renal failure	19 (67.9%)	10 (34,5%)	0.012	18 (60%)	11 (40,7%)	0.146
Cardiovascular failure	27 (96.4%)	22 (75.9%)	0.025	28 (93.3%)	21 (77.8%)	0.091
Liver failure	5 (17.9%)	2 (6.9%)	0.208	6 (20%)	(3.7%)	0.061
Coagulation failure	9 (32.1%)	4 (13.8%)	0.099	10 (33.3%)	3 (11.1%)	0.046
Central Nervous System failure	12 (42.9%)	1 (3.4%)	<0.001	13 (43.3%)	0	<0.001

ICU: Intensive care unit

patients, we were unable to determine that IVIG has a beneficial effect. Due to the significant morbidity and mortality of invasive GAS infections, further studies are warranted to define the role new therapeutic strategies to improve the somber prognosis of bacteremic invasive GAS.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

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