Intravenous immunoglobulin therapy could have efficacy in severe sepsis

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P37

Stratifying septic patients using lactate: severe sepsis and cryptic, vasoplegic and dysoxic shock profile

Otavio T Ranzani[1,2*], Mariana B Monteiro[1], Elaine M Ferreira[3], Fernando Leibel[1], Sergio Ricardo Santos[1], Flavia R Machado[3,4], Danilo T Noritomi[1]
[1]Hospital Paulistano, São Paulo, Brazil; [2]Disciplina de Emergências Clínicas, Hospital das Clínicas, Universidade de São Paulo, Brazil; [3]Latin America Sepsis Institute, São Paulo, Brazil; [4]Disciplina de Anestesiologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil
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Background: The current consensus definition of severe sepsis and septic shock includes a heterogeneous profile of patients under the same definition. Although the prognostic value of hyperlactatemia in sepsis is well established, hyperlactatemia can be found both in severe sepsis and septic shock patients. We sought to compare features and outcomes of septic patients stratified by two factors: the presence of hyperlactemia and persistent hypotension.
Materials and methods: This was a secondary analysis of a multicenter observational study from 10 private hospitals in Brazil (Rede Amil-SP) aiming to evaluate the impact of a multifaceted program to implement the Surviving Sepsis Campaign bundles. We retrieved 1,948 septic patients with an initial lactate level collected within the first 6 hours of diagnosis. Based on previous literature, we stratified them into four groups according to the presence of hypoperfusion (lactate >4 mmol/l) and/or persistent hypotension despite adequate fluids: 1, severe sepsis (without both criteria); 2, cryptic shock (hypoperfusion without persistent hypotension) [1]; 3, vasoplegic shock (persistent hypotension without hypoperfusion); and 4, dysoxic shock (with both criteria) [2].
Results: Severe sepsis was found in 1,018 (52%), cryptic shock in 162 (8%), vasoplegic shock in 549 (28%) and dysoxic shock in 219 (12%) patients. Mean age was 60 years, 47% were male and the majority was admitted form the emergency department (47%). The lung was the principal source of infection, followed by the urinary tract and abdominal. Overall, the four groups presented significant differences in APACHE II and SOFA scores ($P < 0.001$ for both), dysoxic shock being the most severe group. In *post-hoc* analysis, patients in the severe sepsis group presented similar SOFA score to patients in the cryptic shock group ($P = 0.20$). Overall, 28-day crude survival was different between groups ($P < 0.001$), being higher for the severe sepsis group (69%, $P < 0.001$ vs. other), similar between cryptic and vasoplegic shock (53%, $P = 0.39$) and lower for dysoxic shock (38%, $P < 0.001$ vs. other). In an adjusted analysis considering age, APACHE II and SOFA, the 28-day survival remained different between groups ($P < 0.001$) and the hazard ratio for the dysoxic shock group was the highest: HR 2.99 (95% CI 2.21 to 4.05).
Conclusions: Current definitions for severe sepsis and septic shock include four different phenotypes, which should be considered for epidemiology purposes, customizing treatment goals and inclusion criteria for future studies. Although previous studies showed similar outcomes between cryptic shock and overt septic shock (vasoplegic and dysoxic profile), we demonstrated that cryptic shock is similar only to vasoplegic shock.
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P38

Antithrombin III concentrate may contribute to sepsis in nonovert disseminated intravascular coagulation

Noriko Saito*, Mari Yokota, Ahmin Kim, Tomoyuki Harada, Munekazu Takeda, Mizuho Namiki, Arino Yaguchi
Department of Critical Care and Emergency Medicine, Tokyo Women's Medical University, Tokyo, Japan
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Background: Antithrombin III (AT III) has been known to contribute to anti-inflammatory response as well as its anticoagulation. Our previous study showed AT III deficiency happened in the early stage of sepsis with no relation to disseminated intravascular coagulation (DIC) status. Whether AT III concentrate is a beneficial therapy or not for septic patients is still a controversial issue. Our hypothesis is that AT III concentrate may have efficacy as an anti-inflammatory for sepsis.
Materials and methods: From January 2009 to June 2013, adult septic patients with nonovert DIC whom were given AT III concentrate in our medico-surgical ICU were included in this study. DIC scoring was used with the definition of the International Society on Thrombosis and Haemostasis (ISTH). AT III concentrate was administered 30 to 60 U/kg intravenously every 24 hours for 3 days in the patients. Between before and after the AT III concentrate therapy, WBC (/mm^3), CRP (mg/dl), platelet (×10^4/μl), PT (seconds), fibrinogen (mg/dl), FDP (μg/ml), SOFA score and DIC score by ISTH were compared. Values are expressed as mean ± SD. Data were analyzed by Wilcoxon signed-rank test. $P < 0.05$ was considered significant.
Results: There were 157 patients (100 men, 57 women; age range 19 to 96 years (mean 70.0 ± 16.0)), and the 28-day mortality rate was 25.5% and APACHE II score was 17.2 ± 8.3. WBC, CRP, PT, and SOFA score were significantly improved after AT III concentrate therapy (13,411 ± 8,794 vs. 11,798 ± 6,562, $P = 0.0007$, 17.1 ± 11.5 vs. 13.9 ± 7.0, $P = 0.0001$, 16.5 ± 10.9 vs. 15.2 ± 5.3, $P = 0.002$, and 8.6 ± 3.6 vs. 7.7 ± 4.5, $P = 0.005$, respectively), although platelet was significantly decreased (15.8 ± 11.3 vs. 13.7 ± 11.3, $P < 0.00013$). There were no significant differences in fibrinogen, FDP and DIC score (464.7 ± 235 vs. 437.6 ± 185.4, $P = 0.10$, 25.1 ± 36.9 vs. 25.6 ± 36.2, $P = 0.85$, 2.0 ± 1.5 versus 2.3 ± 1.7, $P = 0.06$, respectively). One week after the therapy, SOFA score was significantly improved, while the DIC score did not change compared with before the therapy (6.1 ± 4.7, $P < 0.0001$ and 2.3 ± 1.7, $P = 0.98$).
Conclusions: In the patients with septic nonovert DIC, WBC, CRP and SOFA score were immediately improved after the AT III concentrate therapy, while fibrinogen, FDP and DIC score did not change. AT III concentrate may also contribute to anti-inflammatory without DIC status.

P39

Intravenous immunoglobulin therapy could have efficacy in severe sepsis

Ahmin Kim*, Mari Yokota, Noriko Saito, Munekazu Takeda, Tomoyuki Harada, Mizuho Namiki, Arino Yaguchi
Department of Critical Care and Emergency Medicine, Tokyo Women's Medical University, Tokyo, Japan
Critical Care 2013, **17(Suppl 4):**P39; doi:10.1186/cc12939

Background: Intravenous immunoglobulin (IVIG) administration has been approved to use for severe sepsis with antibiotics by the Ministry of Health, Labour and Welfare since 1980 in Japan. IVIGs are commonly used for severe sepsis and septic shock in Japan, while the international guidelines for management of severe sepsis and septic shock in 2012 suggest not using IVIG in adult patients. Our hypothesis is that IVIG administration has an efficacy for severe sepsis and septic shock.
Materials and methods: This retrospective observational study included all adult patients in our ICU who were administered IVIG for severe sepsis and septic shock from January 2011 to June 2013. IVIG was used at 5,000 mg/day every 24 hours for 3 days. We compared body temperature (℃), WBC (/mm^3), CRP (mg/dl), procalcitonin (ng/ml) and serum immunoglobulin G (IgG) (mg/dl; normal >870) between before and after IVIG treatment. Values are expressed as the median. The Wilcoxon signed-rank test was used for the statistical analysis. $P < 0.05$ was considered significant.

Results: One hundred and fifty-one patients (85 men, 66 women; age range 23 to 96 (median 67.8)) were included in this study. The 28-day mortality after IVIG treatment was 13.9%. The SOFA score before IVIG treatment was 5.0. Values of WBC, CRP and procalcitonin were significantly decreased after IVIG treatment (10,905 vs. 9,805, $P < 0.0001$, 12.3 vs. 7.7, $P < 0.0001$, 2.4 vs. 1.7, $P = 0.0003$, respectively). Body temperature did not significantly change (37.4 vs. 37.2, $P = 0.07$). Serum IgG was significantly increased after the treatment (1,046 vs. 1,563, $P = 0.003$).
Conclusions: The present study has some limitations because of being a retrospective observational study. However, the mortality was quite low in the group of patients included in this study. Moreover, after IVIG treatment values of WBC, CRP and procalcitonin were improved. The median value of serum IgG before treatment was within the normal range, but after treatment was also significantly improved. There is a possibility that severe septic patients require additional IgG regardless of its normal concentrations in their blood.

P40

Polymyxin B-direct hemoperfusion therapy improves mean arterial pressure in septic shock

Mari Yokota*, Ahmin Kim, Taijiro Goto, Tomoyuki Harada, Munekazu Takeda, Mizuho Namiki, Arino Yaguchi
Department of Critical Care and Emergency Medicine, Toyo Women's Medical University, Tokyo, Japan
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Background: In our previous study, we reported that polymyxin B-direct hemoperfusion (PMX-DHP) (Toraymyxin®; Toray Medical Co., Tokyo, Japan) therapy could contribute to oxygen delivery due to improved hemodynamic status, while decreasing inotropic agents in septic patients immediately after that treatment. The randomized controlled studies are ongoing in other countries, because its efficacy and indication are still controversial issues. The purpose of this study is to evaluate whether PMX-DHP therapy sustains to improve hemodynamic status after the treatment.
Materials and methods: All adult patients treated with PMX-DHP and receiving a pulmonary arterial catheter (PAC) in our ICU from July 1994 to June 2010 were included in this retrospective observational study. Patients' clinical, microbiological and PAC data were collected from medical archives. PAC variables were compared between immediately before and after 24 hours of PMX-DHP therapy. Values were expressed as mean ± SD. Data were analyzed by Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant.
Results: There were 63 patients (36 men, 27 women; age mean 63.4 ± 14.8) studied. The mortality rate was 30.2% 28 days after PMX-DHP. APACHE II score and SOFA score on the day of PMX-DHP therapy were 20.2 ± 14.8 and 7.3 ± 3.8, respectively. Mean arterial pressure (MAP) (mmHg) was significantly increased after PMX-DHP therapy (77.5 ± 22.5 vs. 87.2 ± 15.9, $P = 0.02$). The inotropic score decreased 24 hours after PMX-DHP, but did not reach statistical change (10.0 ± 16.1 vs. 6.3 ± 11.6, $P = 0.08$). The cardiac index (CI) (l/minute/m^2), systemic venous resistance index (SVRI) (dyn·second·m^2/cm^5), mixed venous oxygen saturation (SvO_2) (%), oxygen delivery and consumption (DO_2 and VO_2) (ml/minute) and P/F ratio were not statistically different before and after PMX-DHP therapy.
Conclusions: Only the increasing of MAP was sustained after 24 hours of PMX-DHP therapy, while the inotropic agents were decreased. Although the CI, DO_2, VO_2, and P/F ratio were improved immediately after PMX-DHP therapy in our previous study, these were not significantly changed between before and after 24 hours. PMX-DHP could improve MAP with decreasing inotropic agents, while alterations of other PAC variables were not sustained in 24 hours of PMX-DHP.

P41

Fungal disease in AIDS patients in intensive care

Edwiges Santos*, Andre Japiassu, Marcia Lazera, Fernando Bozza
Instituto Evandro Chagas, Fiocruz, Brazil
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Background: Information about the prevalence of fungal diseases in critically ill AIDS patients is sparse. Our goal is to describe the prevalence of fungal diseases in this population, when they are admitted to the ICU.
Materials and methods: Prospective, observational study. Blood and urine samples were collected from 65 AIDS patients at a specialized ICU in infectious diseases, from August 2011 to June 2013. When indicated by clinical suspicion, samples of respiratory, bone marrow and/or tissue were collected. Cultures, cytopathology and serologic tests were performed to evaluate fungal colonization or infection. Clinical data were collected from medical records. Values are expressed as the median and percentage.
Results: Table 1 presents general characteristics of the HIV/AIDS patients. Patients with fungal disease did not differ from patients without fungal infection: age 35 versus 38 years ($P = 0.43$), male gender 76% versus 70% ($P = 0.29$); nadir CD4 cell count 27 versus 57 cell/mm^3 ($P = 0.15$). Most patients were exposed to HAART previously, while there were 47% naïve patients in the fungal group versus 31% in the no fungal group. The ICU mortality of patients without fungal disease was 31% versus 64.7% with fungal disease ($P = 0.02$); hospital mortality was not different between groups (52% vs. 64.7%, $P = 0.4$). Figure 1 presents 17 diagnoses of disseminated fungal diseases (prevalence 26%). All histoplasmosis diagnoses were made from marrow bone culture (11%). Disseminated cryptococcosis was diagnosed from serum serologic latex, direct examination and positive culture in LCR. Three patients (4.6%) were diagnosed with candidiasis in blood cultures. Pneumocystosis was diagnosed from immunofluorescence and Grogot positive in sputum. One patient had disseminated esporotricosis with positive cultures in LCR, blood, tissue, urine and sputum. The only case of aspergilosis is a previous tuberculosis-treated patient that developed a disseminated disease (galactomanana-positive) from a fungal ball.
Conclusions: One in four HIV/AIDS critically ill patients presents with fungal disease when they are admitted to the ICU. Surveillance of fungal pathogens shall be necessary in the first screening of medical HIV/AIDS patients in the ICU.

Table 1(abstract P41) Population characteristics

	No fungal ($n = 48$)	Fungal ($n = 17$)	*P* value
Age (years)	38 (31 to 43)	35 (33 to 46)	0.43
Gender (male)	34 (71%)	13 (76%)	0.29
$CD4^+$ lymphocyte count (cell/mm^3)	69 (32 to 204)	28 (14 to 115)	0.15
Nadir $CD4^+$ (cell/mm^3)	57 (27 to 153)	27 (14 to 122)	0.40
Time since HIV diagnosis (months)	31 (1 to 123)	13 (1 to 77)	0.53
HAART näive	15 (31%)	8 (47%)	0.56
Mortality	15 (31%)	11 (64.7%)	0.02

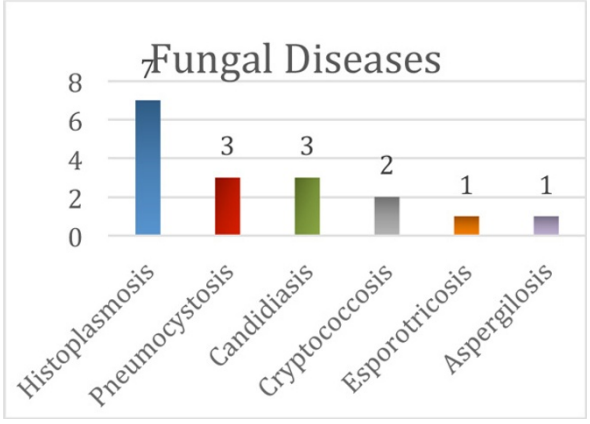

Figure 1(abstract P41) Fungal diseases.