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Features and Outcomes of Secondary Sepsis and Urinary Tract Infections in COVID-19 Patients Treated with Stem Cell Jet-Nebulization

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Abstract

Introduction: COVID-19 is the defining global crisis of our time. Secondary complications such as urinary tract infections and sepsis worsen the already established health and social problems.

Methods: We characterized the features and outcomes of COVID-19 patients suffering from secondary sepsis and urinary tract infection. An observational and analytical study was conducted within the SENTAD-COVID Study clinical trial framework at the Abu Dhabi Stem Cells Center. COVID-19 patients in group A received a jet-nebulization therapy with autologous stem cells cocktail as an add-on to the standard care. In contrast, group B as controls only received the COVID-19 standard treatment. We analyzed the culture samples, antimicrobial agents, and the therapy's efficacy on patient outcomes.

Results: A significant difference between the groups was found in the urinary infection incidence (p=0.020). Patients in group A showed a lower tendency to sepsis than group B (7% vs. 21%), hazard ratio=0.35 (95% confidence interval: 0.13-0.91), p=0.0175. The number needed to treat=7.3 was calculated and *Candida albicans* was the most frequent agent causing sepsis and urinary infections. The massive use of broad-spectrum antimicrobials was striking.

Conclusion: We found a protective factor of stem cells against secondary infection in COVID-19 cases in terms of sepsis and urinary infections. The suggested immunomodulatory effect of stem cells offers a therapeutic strategy to manage the disease and avoid several complications. However, antimicrobial agents can lead to increased opportunistic infections, so a rational use of these treatments must be considered.

Keywords: COVID-19 • Urinary tract infection • Sepsis • Stem cell therapies

Abbreviations

ADSCC: Abu Dhabi Stem Cells Center; AIDS: Acquired Immunodeficiency Syndrome; BMI: Body Mass Index; CI: Confidence interval; COVID-19: Coronavirus Diseases 2019; CRP: C-Reactive Protein; CT: Computerized Tomography Scans; DOH: Abu Dhabi Department of Health; HR: Hazard Ratio; ICU: Intensive Care Unit; MRSA: Methicillin-resistant *Staphylococcus aureus*; NNT: Number Needed to Treat; PB-NHESC-C: Peripheral Blood Non-hematopoietic Enriched Stem Cells Cocktail; RT-PCR: Real-time Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; UTI: Urinary Tract Infection.

Introduction

COVID-19 is the most significant global crisis of our time, and worldwide precautionary measures are taken to control the spread [1]. Sepsis and septic shock contribute to the cytokine storm syndrome causing a high mortality rate (60-90%) [2] and immune-mediated kidney damage [2,3], crucial to prevent this occurrence. Studies showed a sharp increase in Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas*, and *Candida* species infectious rates among the Intensive Care Unit (ICU) COVID-19 patients, indicating that secondary infections may affect the prognosis and subsequent treatment of these patients [4].

Strategies have been proposed to apply stem cells therapy to regulate inflammation and prevent or mitigate cytokine storms, taking into consideration their immunomodulatory potential by paracrine stimulation in sepsis and chronic conditions [5].

The Abu Dhabi Stem Cell Centre (ADSCC) developed a treatment for COVID-19 ("SENTAD COVID Study" clinical trial) using an autologous Peripheral Blood Non-hematopoietic Enriched Stem Cell Cocktail (PB-NHESC-C) [6].

This article analyzes the incidence of sepsis and Urinary Tract Infection (UTI) and related pathogens compared to the rest of the germs causing sepsis in the two study groups after receiving treatment or being recruited as controls.

Materials and Methods

Within the framework of the SENTAD-COVID Study clinical trial [7] we performed a multicenter, prospective, and analytical study to determine the sepsis and UTI incidence among patients during the intervention in April of 2020. Four different public hospitals from the Emirate of Abu Dhabi participated: Sheikh Khalifa Medical City, Al Rahba Hospital, Al Mafraq Hospital, and Al Ain Hospital, all administered by the Abu Dhabi Health Services Company.

In the main study, a total of 139 patients were divided into two groups:

1. Group A (Experimental) COVID-19 standard care plus nebulization with PBNHESC (n=69)

2. Group B (No intervention) COVID-19 standard care (n=70).

The same inclusion and exclusion criteria of the SENTAD-COVID Study,

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a clinical trial retrospectively registered July 16, 2020 (ClinicalTrials.gov Identifier: NCT04473170), were applied for recruitment and aleatorization, so adults (≥ 18 years old) of both sexes were included [7].

To define the clinical severity, the ordinal scale created by the WHO committee for COVID-19 was used [8] (Table 1).

Table 1. SENTAD-COVID Study: 8 category-ordinal scale for clinical involvement.

Category	Score
No limitation of activities, discharged from hospital	1
Limitation of activities	2
Hospitalized, no oxygen therapy	3
Oxygen by mask or nasal prongs	4
Non-invasive ventilation or high-flow oxygen	5
Intubation and mechanical ventilation	6
Mechanical Ventilation+additional organ support: ECMO, CRRT, vasopressors	7
Death	8

A registration of gender, age, body mass index (BMI), comorbidities, vital signs, and biochemical studies performed within 24 hours of inclusion in the trial was done. Both groups received COVID-19 standard treatment defined as "UAE National Guidelines for Clinical Management and Treatment of COVID-19, v.2.0" as per the Department of Health (DOH) [2]. After 300 cc of whole blood was withdrawn and processed at the stem cells laboratory, cells were characterized by flow cytometry and inverted automated fluorescent microscopy. A stem cell jet-nebulization with PB-NHESC-C was given in two doses of 10 cc during two consecutive days for patients in group A. Both groups were followed for 28 days or until discharge. Patients were diagnosed with a secondary infection if clinical symptoms were present and confirmed with a positive culture (blood, sputum, others) and UTI with a positive urine culture, following the trial's protocols. Consequently, reports of sputum, blood, specific requesting of MRSA strains, skin/wound, and urine cultures were collected, as well as the antimicrobial treatment.

Statistical analysis

A no normal distribution of the variables was found, so nonparametric stastical methods were used. Proportions comparison test (Chi-Square) for BMI category [9] and comorbidities, and U-Mann-Whitney for date intervals and laboratory test. The Hazard Ratio (HR), 95% Confidence Interval (CI), Number Needed to Treat (NNT), was calculated for the sepsis complication. A significance level of $p<0.05$ was prefixed.

Ethics and consent to participate and publishing

The Emirates Institutional Review Board for COVID-19 Research approved the SENTAD-COVID study (Ref. ID: DOH/CVDC/2020/1172). Study participants provided written informed consent per the Helsinki Declaration [16]. This manuscript has the approval of the ethical committee concerning publishing data derived from the main clinical trial.

Results

Of the 139 patients, 129 were males (93%) and ten females (7%) between 26 to 73 years old. BMI distribution was between 17.06 to 45.44 (mean 27.61) in group A, and between 16.95 to 47.75 for the group B (mean 27.93), with a statistical difference between groups in the normal and overweight categories favoring group B, because there was more overweight cases in group A. *Diabetes mellitus* and hypertension were the most common comorbidities. No significant differences were found in these parameters. Likewise, there were no differences in the clinical scores between the groups. However, more chronic smokers were in group A (8.69% vs. 1.42%, p=0.05). Neutrophil and lymphocytes absolute counts, neutrophil/lymphocyte ratio, creatinine, C-Reactive Protein (CRP), and D-Dimer test did not show significant differences; all tested the day before the intervention (Table 2).

Table 2. Clinical characteristics of the patients at recruitment.

Patients	**Group A**		**Group B**		**P**
Gender	**n**	**%**	**n**	**%**	
Males	65	94	64	91	0.503
Females	4	7	6	9	0.665
Age, years					
Mean ± SD	45.93 ± 9.75		44.38 ± 11.09		0.383
Body mass index	**n**	**%**	**n**	**%**	
Unknown	3	4.35	2	2.86	0.680
Normal (healthy weight)	17	24.64	29	41.43	0.047*
Overweight	35	50.74	19	27.14	0.005**
Obese Class I (moderately obese)	11	15.94	13	18.57	0.823
Obese Class II (severely obese)	0	0	3	4.29	0.244
Obese Class III (very severely obese)	3	4.35	4	5.71	1.000
Comorbidities					
Arterial hypertension	18	26.09	19	27.14	1.000
Diabetes mellitus	18	26.09	13	18.57	0.314
Cardiovascular disease and dyslipidemia	7	6.25	6	8.57	0.779
Chronic smokers	6	8.69	1	1.42	0.050*
Asthma/Chronic obstructive pulmonary disease	4	5.79	3	4.28	0.684
Severity score					
3	37	53.62	40	57.14	0.734
4	12	17.39	6	8.57	0.137
5	3	4.34	7	10	0.325
6	2	2.89	1	1.42	0.619
7	15	21.74	16	22.86	1.000
Initial laboratory results	Median (95% CI)				
C-Reactive protein (mg/L)	34 (0.6, 381.8)		21.79 (0.4, 335.3)		0.150
D-Dimer (µg FEU/mL)	0.4 (0.2, 8.1)		0.57 (0.21, 4.84)		0.158
Neutrophils count 10e9/L	4.4 (1.6, 17.75)		4.49 (1.812, 12)		0.776
Lymphocyte count 10e9/L	1.305 (0.58, 3.82)		1.305 (0.52, 3.46)		0.882
Creatinine (mg/dL)	0.92 (0.50-3.82)		0.89 (0.61-3.81)		0.844
NLR (Ud)	3.0 (0.86-15.66)		2.6 (0.85-15.71)		0.906

NLR: Neutrophils/Lymphocyte Ratio; p: Statistical Probability; *: significant difference; **: highly significant difference.

The length of hospital stay was shorter in group A after receiving the treatment (1 to 43 days), compared with group B after being included (2 to 125 days). Still, the median did not show statical differences (p=0.23). Apropos UTI incidence, a significant difference between the groups was found (p=0.02). Patients in group A were less propensity to sepsis in comparison with group B (7% vs. 21%), HR=0.35 (95% Confidence Interval: 0.13-0.91), p=0.01, with an NNT=7.3. In group B, there were six deaths, while in group A there were only 4 (Table 3).

Table 3. Clinical outcome characterizations.

Event	Group A		Group B		P
	n	%	n	%	
UTI	1	1%	7	10%	0.0206*
Sepsis	5	7%	15	21%	0.0175*
Mortality	4	6%	6	8%	0.6434
p: statistical probability; *: significant difference; UTI: Urinary Tract Infection					

A total of 43 critically ill patients admitted to the ICU were tested with cultures according to the trial's criteria, 20 from group A and 23 from group B (Figure 1). 17% of samples were positive in group A and 38% samples from group B (Table 4).

Table 4. Culture samples during the follow-up.

Sample	Group A		Group B	
	N	Positive	N	Positive
Blood	18	5	23	9
Urine	1	1	22	8
MRSA	9	0	22	1
Sputum	14	6	15	6
Wound/skin	0	0	3	3
Total cultures	42	12	85	27
MRSA: Methicillin-Resistant *Staphylococcus aureus* samples request tested				

The leading cause of sepsis in both groups was *Candida albicans* (21%), followed by *Staphylococcus aureus* 19%, *Pseudomonas aeruginosa* 16%, *Streptococcus pneumonia* 5%, *Klebsiella pneumoniae* 9%, *Escherichia coli* 9%, and *Enterobacter aerogenes* 2%. The patient from group A who had UTI suffered sepsis from *Candida albicans* and *Staphylococcus epidermidis*. In group B, six patients with UTI were found to have other positive cultures: 3 from blood, two from sputum, and 1 had MRSA. Of the deceased patients, only one from group B had a UTI (14%) caused by Klebsiella pneumoniae, none from group A (Figure 1).

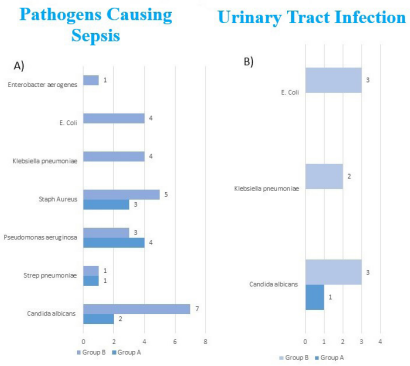

Figure 1. Cultures reports. A. Number and pathogen of positive cultures among sepsis cases; B. Number and pathogens found in urine cultures.

In 11 cases, more than one pathogen grew, nine from group B and two from group A, where *Candida albicans* was the most frequently found concomitant pathogen along with other germs (5 *vs.* 2), followed by *Staphylococcus aureus* (3 *vs.* 1), *Klebsiella pneumonia* (3 *vs.* 0) and *Pseudomonas aeruginosa* (2 *vs.* 1).

In total, 60 patients received antibiotics, 30 from each group. Piperacillin/Tazobactam was the most commonly used in both groups, followed by Meropenem, Vancomycin, and Linezolid. It was marked use of several antimicrobial agents in 42 patients (30%), 17 from group A (25%) and 25 patients from group B (35%), from those, 11 received 2 combination of antibiotics (8%, 9 from group A and 7 from group B), 15 received 3 (11%, 11 *vs.* 4), 6 received 4 (4%, 4 *vs.* 2), 3 received 5 (2%, 3 *vs.* 0) and 2 received 6 (1%, 2 *vs.* 0). Regarding the antifungal treatment, two patients from group A and seven from group B received therapy. One patient in group B received two antifungals (also received treatment with linezolid and meropenem). The most frequently used in group B was Anidalafungin, and Caspofungin was in group A (Figure 2).

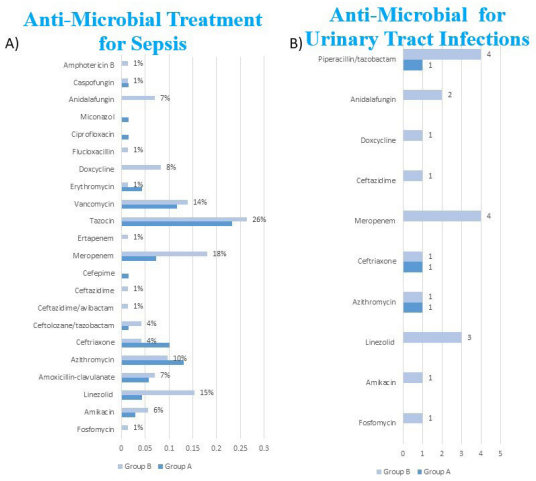

Figure 2. Antimicrobial treatment. A. Treatment from both groups; B. Treatment for patients with UTI.

Discussion

This study showed a higher incidence of COVID-19 among men, especially among critically ill patients (no women with high scores were found during the study period), correspondingly with other authors, as well as the fact that patients with diabetes, hypertension, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and kidney disease exhibit worse clinical outcomes [10,11] increasing the sepsis risk factors [12]. Despite the smoking rate and overweight cases among the treated patients, infectious complications were lower than those of the control group.

There is a lack of data on the bacterial and fungal secondary infection rate among hospitalized adults with COVID-19, associated with admission to the ICU and the use of invasive procedures, [4] leading to severe disease and mortality. Our study showed an elevated culture sampling rate among critically ill patients in both arms, with a high incidence of *Candida albicans* causing sepsis (21% of cultures) and associated with other bacterial infections. Treated patients were less likely to have multiple microorganisms in culture than controls with a statically significant difference, finding that around seven patients are required to be treated with PB-NHESC-C nebulization to have this protective effect against sepsis (NNT=7.3). Surprisingly, even though all septic patients had a urinary catheter, the rate of UTI was not strikingly high. Attenuation of bacterial sepsis stem cell-mediated has been described *via* several mechanisms such as improving the phagocytic ability, secreting antimicrobial peptides [5,13]. And increasing bacterial clearance [5,14].

COVID-19 sepsis causes an immunosuppressive effect and infection by opportunistic pathogens like *Candida albicans* and *Pseudomonas*. The reason for the fungal sepsis could be associated with the massive use of one or more broadspectrum antibacterials at the time of culture, in some cases up to 6 antibiotics. The increase in opportunistic infection among SARS-CoV-2 ICU patients due to MRSA, *Pseudomonas*, and *Candida* species

[4,15]. Could be related to the biofilm formation, especially in those with MRSA positive culture, which is a survival mechanism, being a reservoir of multi-resistance bacterias [16,17].

Antibacterial therapy, if indicated, should be prescribed in line with local guidelines and reviewed with the clinical response at 48 to 72 hours. If no evidence of bacterial coinfection is found, then stopping antibacterial therapy should be considered [18]. It is well known that the prolonged use of antimicrobials could contribute to the development of significant consequences, and we are facing a lack of data about antimicrobial use through this pandemic worldwide, then the emergence of new resistance to this treatment should be expected, without counting other adverse effects of therapies for kidney and liver function for example, with unimaginable implications for human and animal health and the environment [19].

Lymphopenic status among critically ill COVID-19 patients is another key point already reported [20]. There is a sustained and substantial reduction of peripheral lymphocyte counts, especially CD4 T and CD8 T cells, representing the immune suppression stage after the cytokine storm activation phase increasing the risk of developing secondary infection [4,21].

The use of multidrug antimicrobials was more common in the control group than in the group A patients, so our results perhaps mean a protective effect of the stem cells cocktail treatment regarding non only the frequency of secondary infections but also in need of multiple applications of antibiotics. Furthermore, it is imperative in the COVID-19 pandemic, where the intense hospital use of antibiotics has been described at the early pandemic, increasing the perception of its influence in the level of bacterial resistance [22]. Impacting the burden of disease well into the future [23].

Even though the median hospital stay after the intervention was not statistically significant comparing both groups, the range was shorter in group A than in group B, given the intervention group's homogeneity due to the therapy. The statistical dispersion of the control group's data opens another hypothesis of the lower incidence of sepsis and UTI in group A since shorter hospital stays are protective against nosocomial infections [24].

Our responsibility is to implement and develop actions to control or stop the disease and change dangerous practices through appropriate and consensual use of antimicrobials.

The loss of patients during the follow-up was the main limitation for collecting data. Many of the first and second tertiles patients recovered and were released from hospitals, rendering statistical limitations and bias in this study. However, a proper quantitative meta-analysis with a larger sample could be designed to validate the research and better assess the effect of treatment. Furthermore, it is well known that the patients had received several antimicrobial agents that can lead to increased fungal and opportunistic infections, so we recommend a rational approach to these treatments.

Conclusion

This study found a protective factor of stem cells against sepsis and UTI in COVID-19 cases. Furthermore, the treated group patients showed a lower tendency to develop these events than the control group. Thus, the proposed immunomodulatory effect of stem cells offers a therapeutic strategy to manage the disease and avoid several complications, becoming a crucial adjuvant tool for healing and achieving early recovery in severe COVID-19 infections.

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Conflict of Interest

We declare that all authors were members of the ADSCC researcher's staff. Nevertheless, there is no conflict of interest because the authors did not receive any grant or particular funding from any commercial, pharmaceutical, or other kind of organization.

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