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Co-Infection as a Risk Factor in COVID-19 Mortality Rate

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A B S T R A C T

The Antibiotics are not used to treat infectious disease caused by viruses, but it can also be prescribed for treating the infections caused by bacteria. The patient on ventilation is at risk for nosocomial pathogen and they need an urgent antibiotic intervention. In this study we aimed to find out the etiologies of secondary bacterial infection and the clinical outcome of COVID-19 patients admitted to isolation department, Sebha Medical Center (SMC). Eight patients (8/50) showed increased the inflammatory markers after 48hrs of admission. The antibiotic culture sensitivity profile showed that the gram-negative bacteria (Pseudomonas spp., Acinetobacter bumannii, Stenotrophomonas maltophil) were the predominant. 2/8 of the critically ill patient were improved and home discharged. The remaining (6/8) was deteriorated due to multidrug resistant bacteria infection and they did not receive the appropriate antibiotics.

العدوى المشتركة كعامل خطر في معدل وفيات COVID-19

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الملخص

لا تستخدم المضادات الحيوية لعلاج الالتهابات التي تسببها الفيروسات مثل COVID-19 ، ولكنها موصوفة بشكل أساسي لعلاج الالتهابات التي تسببها البكتيريا. المريض الذي يخضع للتنفس الصناعي معرض للغاية لعدوى بكتيرية من المستشفيات ويحتاج إلى تدخل مضاد حيوي عاجل. هدفت هذه الدراسة إلى معرفة مسببات العدوى البكتيرية الثانوية والتطورات السريرية لمرضى COVID-19 الذين تم إدخالهم إلى قسم العزل بمركز سبها الطبي. تم جمع عينات سريرية مختلفة من مرضى COVID-19 الذين تم إدخالهم إلى قسم العزل، وتم دراسة خصائص المضادات الحيوية الخاصة بهم بعد 48 ساعة من زمن الايواء، كانت البكتيريا سالبة الجرام (.Pseudomonas spp، Acinetobacter bumannii، Stenotrophomonas maltophil) أكثر شيوعًا في مرضى COVID-19 من البكتيريا الموجبة. والجدير بالذكر أن الغالبية كانت مقاومة لجميع المضادات الحيوية المطبقة (كاربابينيم ، سيفالوسبورين ، أمينوغليكوزيدات ، كينولون ، تتراسيكلين ، وكلورامفينيكول). في هذه الدراسة ، أبلغنا عن 6 حالات من COVID-19 معقدة بسبب عدوى بكتيرية ثانوية ومقاومة لمعظم المضادات الحيوية التطبيقية.

Introduction

The secondary infections which define as an infection that occurs during or after treatment for another infection ,It may be caused by the first treatment or by changes in the immune system, the most common secondary infection is the bacterial infections , which are

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serious complications in many respiratory diseases and are associated with high mortality rate [1-5]. In all age groups, the risk of secondary bacterial infection in hospitalized ventilated patient even without underling disease is high [6]. In critically COVID-19 patient, the ventilator-associated pneumonia has been reported as a frequent complication and is associated with high mortality rate [7], [8]. Moreover, It has previously been reported that bacterial co‐infection (coinciding infection of an organism by multiple bacterial species) can influence the mortality rate of patients with viral infections [9-11]. A nosocomial infection or health care-associated infection (HAI) is defined by the World Health Organization (WHO) as an infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. However, the prevalence of opportunistic pathogens in the health care facilities has deeply been studied; Staphylococcus spp., Klebsiella pneumoniae, spp., Escherichia coli, Acinetobacter bumannii, and Pseudomonas spp. are the most frequently isolated nosocomial pathogens [6], and [12-13]. It has been noticed that during influenza pandemic, the secondary bacterial infections was common and the risk of death has increased [14]. Fort that reason, several guidelines supporting the use of empirical antibiotics was applied to prevent secondary bacterial infection. On the other hand, co-infection with nosocomial pathogen in COVID-19 patients has also been reported and even higher in its prevalence compared to influenza patients [3], [4] and [15]. However, the overuse of antibiotic in this pandemic has lead to development of antimicrobial resistance. The regular microbiological surveillance of COVID-19 patients with secondary bacterial infection is crucial and it will ensure the prober antibiotic use and will prevent the negative consequence overuse.

Material and methods

This study is a consecutive case series study conducted during July-August 2021. 300 patients suspected COVID-50 cases were admitted at first to the triage department as showing in figure (1). Nasopharyngeal swabs were taken from all suspected patients and followed by clinician. Laboratory investigations, therapeutic, and outcome data were collected using a patient report form provided by National center for disease control, Libya. The COVID-19 patients were then transferred to isolation department at Sebha medical center after confirmation by RT-QPCR test; the COVID-19 patients were transferred to isolation department SMC.
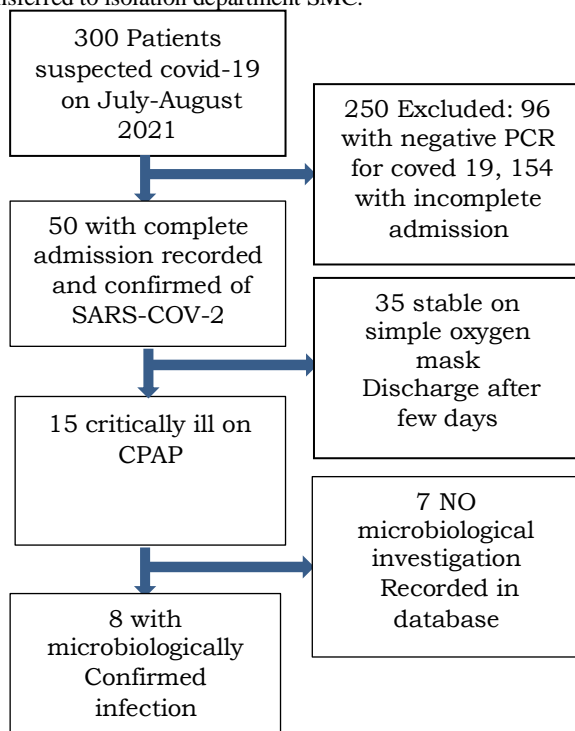
Fig. 1: proposed study flowchart

Antimicrobial profile study

Sputum cultures were taken from COVID-19 patient who clinically deteriorated after admission to isolation department. The samples were transferred to the local microbiology laboratory at Sebha medical center for microbiological study.

Results

Characterization of COVID-19 patients

A total of 50 admitted patients were confirmed as COVID-19 and all recorded negative COVID-19 patients were excluded from this study. As showing in Table (1).

Table 1. Patient's demographic and clinical characteristics

BASELINE VARIABLE	All patients (N=50)	ICU -NON N=35)(70%)(	ICU N=15 (30%)(	P-Values
Demographics Age Median	18-\+44	18-\+45	14-\+50	
Gender Men Women	(%76) 38 (%24) 12	(%80) 28 (%20)7	10 (%17) (%15)5	P=0.85*
Characteristics Co-infection Co-infection No co-infection	(%16)8 ---	------ ------	(%53) 8 -----	
Case fatality	(%28)14	----	14 (%93)	
Comorbidities Cardiovascular diseases	(%6) 3	(%0) 0	(%20) 3	P= 0.22*
Diabetics	(%60) 30	(%42) 15	15	P=0.64*
Chronic kidney diseases	(%4) 2	(%2) 1	(%100)	P=0.36*
others	(%22) 11	(%28) 10	(%9)1 (%6) 1	P= 0.02**
Inflammatory markers median)(d-dimer (0–0.5)	2.6	2.7	3.8	P=0.27*
c-reactive protein (CRP)(	55	30	75	P=0.22*
Less than 10 mg/L) Ferritin (24 to 336 micrograms per liter).	338	442	662	P=0.13*

Patients had a median age of 62 years (IQR 40–84) for COVID-19 males were more common among COVID-19 patients (80% vs 67%). The most common presenting symptoms were cough (80%) and fever (65%) and dyspnea in 95%. Regarding vital signs in covid-19 patients, they usually came with high systolic blood pressure of 140 mmHg (IQR 125–150 mmHg).

Laboratory findings

COVID-19 patients had elevated liver function enzymes lactate dehydrogenase (LDH), gamma-glutumine transferase, and aspartate transaminase (AST). The C-reactive protein (CRP) elevated in most COVID-19 patients. In this study we also observed elevated white blood cell count and low lymphocytes level. In the serious patients, The Ferritin level, D-dimer level, Fasting Blood sugar (FBS) all were above the normal values.

Antimicrobial profile study among COVID-19 patient Out of 50 patients, fifteen were critically ill and they were on the mechanical ventilation (CPAP). Eight patients (8/15) have worsened after 48h, the temperature has raised and the inflammatory markers were also increased. In order to find the cause behind their deterioration, Sputum samples were taken and in some cases urine specimens sent to the microbiology department. The most isolated organisms were A. baumannii (6/8), the rest were pseudomonas spp., S. maltophil, and K. pneumonia. Our data showed that A. baumannii was resistant to all available antibiotics but sensitive to Polymixin B and

Tigecycline. Pseudomonas Spp. was resistant to all applied antibiotic except Azetreonam and Polymixin B. We also observed that S. maltophil was resistant to the majority of antibiotic except Tigecycline and ciprofloxacin.

Clinical outcome of the COVID-19 patients

Based on the clinical picture of the patient and according to the antibiotic profile received from microbiology. Unfortunately, Due to shortage of antibiotics in the hospital and the difficulty of obtaining them from other areas due to the high prices compared to other antibiotics. Only two patients have received Tigecycline. Notably, A very significant improvement was noted from the next day, where vital signs, and inflammatory markers returned to normal values when the proper antibiotic was used. Moreover, the white blood cells (WBC) and neutrophil ratio became within normal range as showing in the table (2).

Table 2. Neutrophil-to-lymphocyte ratio (NLR) for eight covid-19 patients, patient NO 1 and 2 improved and discharge from hospital, the rest was died.

Patient NO	Total leucocytes in thousand cells/µl	Neutrophils	Lymphocytes	Neutrophil-to-lymphocyte ratio normal ratio (1 to 2)
1	6.2	3.4	2.7	**1.3**
2	6.8	3.9	2.2	**1.7**
3	8.1	5.8	1.7	**3.4**
4	7.5	4.6	2.1	**2.2**
5	11.4	5.7	1.5	**3.8**
6	15.2	7.3	1.8	**4.1**
7	12.6	6.2	2.3	**3**
8	14.4	8.1	1.9	**4.3**

We have also observed that CRP value also decreased to less than 50 on the third day. Out of 8 patients, two patients with A. baumannii were discharged home. As for the other, he was transferred to a special center for lung rehabilitation. Unfortunately, the remaining six (25%) patients went to rapid deterioration and death, because they have not received the appropriate doses of antibiotics. Their investigation showed rapid rise in white blood cells > 12, elevated CRP > 100, and some of them having complications of sepsis, such as multiple organs failure, and septic shock, The immediate cause of death for the eight patients is sudden cardiac and respiratory arrest as a result from refractory ARDS. In this study, we noticed that some of patients have been recorded as having multiple infections (e.g. urinary tract infection and respiratory infection) where different sample types at different times were taken during their stay at hospital.

Discussion

Nowadays, Antibiotic Resistance (AMR) is considered as a serious public problem with constantly increases the life threat of the patients [16]. Implementation of infection prevention and control such as hand hygiene, use of proper disinfectants and other measures are significantly important to decrease the microbial transmission.

The incidence of Nosocomial pathogen has increased during the last few decades in Libya generally and Sebha particularly. The Prevalence of nosocomial pathogens has got attention by several researchers during the last decades. In Libya many scientists have documented spread of nosocomial pathogen among hospitalized patients. Khadija and her group document that the gram positive and negative nosocomial pathogens have frequently been isolated from patients admitted to Sebha medical center [17-20]. Recently, the secondary bacterial infection (SBI) among viral infected patients has been documented world widely and several studies addressed this issue [21-23]. However, an early vs. late infections, differences in treatment protocols, the proper antibiotic use, and time of sample collection all is important in order to study the secondary bacterial infection and the clinical outcome in COVID-19 patients.

Our data showed that the most detected organisms in COVID-19 patients are gram-negative bacteria and the most common isolated strains were A. baumannii followed by Pseudomonas Spp. This finding is similar to that reported by Karataş and his group [24]. However, these species are commonly isolated as nosocomial pathogens, especially ventilator-associated infections [13]. Unfortunately, The complications following nosocomial infection among COVID-19 patient is usually associated with high mortality rate [25-27]. Turkey has recently reported that the overall mortality rate in COVID-19 patients is 4.5% [28], [29]. Our data also recorded a high mortality rate 25% and this result is in consistent with many other reports [30], [31]. In Wuhan where the Corona virus has first been detected, a High incidence of bacterial infections among dead COVID-19 patients have been reported [32, 33]. For clinicians, Pneumonia caused by superbugs is one of challenging complications in COVID-19 and it is possible that some patient died due to bacterial co-infection rather than virus itself. For that reason, secondary bacterial infection is considered critical risk factors for the severity of COVID-19. Unfortunately, The number of nosocomial infection in hospitalized patients rose during the last years and the reason behind that in not well understood. The multidrug resistant bacteria might be behind this prevalence of infection as some authors have suggested it [22], and [34-35]. In addition, the viral infection renders the immune system weak which influence the viral bacterial coinfection [36], [37]. This in agreement with our data where we showed that most of the patient had MDR bacteria. In risk group for instance in immunodeficiency, the secondary bacterial infection with viral disease have irreversible consequences [38].

Conclusion

The prevalence of nosocomial pathogens among COVID-19 patients and its resistance to mostly applied antimicrobial agents is an alarming finding. Therefore, Routine microbiological surveillance and implementation of infection prevention and control measures are mandated.

Acknowledgment

ETHICAL APPROVAL AND INFORMED CONSENT

This study includes data from patients attended triage department in which the suspected cases of COVID-19 were admitted and routine investigations are requested. This study does not require consent from patients since it was mainly focusing on outcome of COVID-19 with secondary bacterial infection. No sample was exclusively obtained for this study and all respiratory samples were collected for antibiotic profile. In addition, all patients' identifiers and the data were confidentially processed with. Scientific committee of Sebha medical center, where the study was conducted, has approved this project.

Conflicts of Interest:

The authors declare no conflict of interest.

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