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Original Research Article

Is empirical antibiotic treatment required in COVID-19 patients? What lessons have we learnt over the past 1 year?

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ABSTRACT

Background: Secondary bacterial infections manifest during or after a viral infection(s) and can lead to negative outcomes and sometimes fatal clinical complications. The choice for an empiric antibiotic therapy requires a broad spectrum of activity against pathogens including beta-lactamase producing pathogens. Ceftriaxone+sulbactam+disodium EDTA is one of the antibiotic combinations used to prevent secondary infections. The objective was to evaluate rate of secondary bacterial infections in patients receiving empirical antibiotic therapy through retrospective analysis of data from a tertiary care center.
Methods: A single center, retrospective analysis of data from hospital of COVID-19 patients treated in the ICU or wards was conducted. Patients who received empirical antibiotic therapy including ceftriaxone+sulbactam+disodium EDTA were included in the study.
Results: 99 patients (mena age 75±9.89 years) were included in the retrospective analysis. Diabetes and hypertension were the most common comorbidities in the patients. The total WBC count was raised (12.36±9.01). All the biological markers were raised. 45% patients had abnormalities in chest X-ray. The mean CT severity index was 13.81±5.64. Bacterial superinfection was observed only in 1 patient.
Conclusions: Bacterial co infections and secondary bacterial infections are a major risk factor for adverse COVID-19 outcomes. The use of appropriate prophylactic antibiotics such as ceftriaxone+sulbactam+disodium EDTA has significantly reduced the prevalence of secondary bacterial infections in patients with severe COVID.

Keywords: COVID-19, Ceftriaxone+sulbactam+disodium EDTA

INTRODUCTION

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a formidable challenge to clinicians. Decisions have been made based on limited clinical experience and scientific evidence of past pandemics. Insights from past pandemics of influenza viruses have been looked upon as a learning curve especially when treating patients hospitalized with coronavirus disease 2019 (COVID-19). One clinical dilemma is the administration of antibiotics to patients with COVID-19. Bacterial, especially *Streptococcus pneumoniae* and *Staphylococcus aureus* and viral or fungal co-infections have been commonly described in other pandemics caused by influenza viruses. But, data regarding the incidence of such co-infections in patients with COVID-19 has been scant. Secondly, another challenging question is whether bacterial superinfections occur in these patients which could justify the initiation of empiric antibiotic therapy.

Secondary bacterial infections manifest during or after a viral infection(s) and can lead to negative outcomes and sometimes fatal clinical complications. Research and development of clinical interventions is largely focused on the primary pathogen, with research on any secondary infection(s) being neglected. Secondary bacterial pneumonia in a patient on invasive mechanical ventilation has a similar presentation to that of hospital-acquired pneumonia but warrants the aggressive use of empiric broad-spectrum antibiotics with coverage for methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa* and possibly other multi-drug resistant organisms in accordance with the Infectious Diseases Society of America/American Thoracic Society guidelines. Drugs such as tocilizumab, investigational antivirals and anti-inflammatory therapies such as anti-IL-6 therapy have the potential to impair viral clearance, predispose to secondary infection and cause harm.[1]

In the era of antibiotic resistance, the choice for an empiric antibiotic therapy needs to be made prudently with a rationale of offering a broad spectrum of activity against pathogens including beta-lactamase producing pathogens. Any surge in antibiotic use during the COVID-19 pandemic will have a detrimental effect on antibiotic resistance rates for nosocomial bacterial pathogens, fuelling global growth of antibiotic resistant bacterial pathogens.[1] It is important to consider the side effects of antibiotics and institutional antibiograms. As the numbers of antibiotic-resistant bacterial strains continue to grow, there is an increased the risk of superinfection in severely ill patients, especially in intensive care units (ICUs).[1]

Salts of ethylenediamine tetraactic acid (EDTA) have long been used as antimicrobial agents, particularly against bacteria. They have also been used as enhancer of other agents, such as lysozyme, antibiotics and irradiation, by increasing permeability of bacterial membrane or by removal or destruction of covalently bound lipid component.[2]

Ceftriaxone+sulbactam+disodium EDTA was one of the antibiotics used to prevent secondary infections.

Objective

The objective was to evaluate rate of secondary bacterial infections in patients receiving empirical antibiotic therapy through retrospective analysis of data from a tertiary care center.

METHODS

The study was a single center, retrospective analysis of data from a tertiary care hospital (SL Raheja Hospital, Mumbai) of COVID-19 patients treated in the ICU or wards. Patients admitted in ICU with diagnosis of COVID-19 and received empirical antibiotic therapy including ceftriaxone+sulbactam+disodium EDTA during the time period from June 2020 to December 2020 were included in the study. An audit of data from the hospital of COVID 19 patients treated in the ICU or wards was conducted. The exclusion criteria included patients coming from other hospitals and with documented pre-existing infections.

The assessment parameters included patient demographics, comorbid diseases, treatment given and outcomes in terms of discharge or death. Ethics committee approval was taken prior to initiation of study.

Statistical analysis was conducted using the Wilcoxon-Mann-Whitney U test for nonparametric data and the unpaired t test for parametric data.

RESULTS

A total 99 patients (66 males and 33 females) were discharged or dead were included in the retrospective analysis (Figure 1). The mean age of the patients was 75±9.89 years. Diabetes and hypertension were the most common comorbidities in the patients (Figure 2). The total WBC count was raised (12.36±9.01). All the biological markers were raised 45% patients had abnormalities in chest X-ray. The mean CT severity index was 13.81±5.64. The mean oxygen saturation (SpO_2) 93.88±3.84.

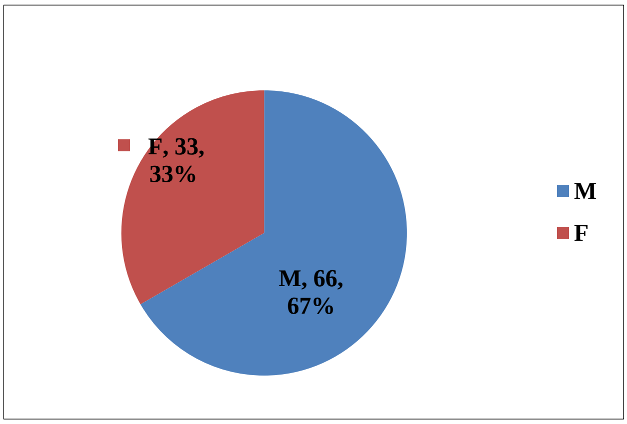

Figure 1: Gender distribution.

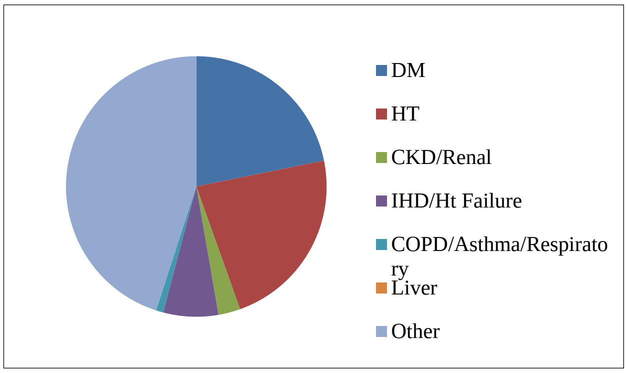

Figure 2: Comorbidities.

DM: diabetes mellitus; HT: hypertension; CKD: chronic kidney disease; IHD: ischemic heart disease; Ht failure: heart failure; COPD: chronic obstructive pulmonary disease.

Table 1: Outcomes of treatment.

Outcomes	TC	LC	CRP	LDH	Ferritin
Died	14.20±12.29	15.03±38.35	95.78±102.05	739.01±1,001.58	1,305.9±2,191.25
Discharged	11.31±5.87	11.52±6.87	79.47±76.43	433.95±238.33	1,077.64±1,286.70
P value	<0.01	<0.01	<0.01	<0.01	<0.01

TC: total WBC count; LC: leukocyte count; CRP: C-reactive protein; LDH: lactate dehydrogenase.

Bacterial superinfection was observed only in 1 patient. Co-infection with bacteria was presumed to have been present at the time of admission of the patient to the hospital. It may be possible that the delay in presentation of the patient to the hospital may have been responsible for the concomitant bacterial infection.

Treatment

Patients were treated with repurposed drugs as per the prevailing guidelines from Indian Council of Medical Research (ICMR). All patients were given empirical treatment with ceftriaxone+sulbactam+disodium EDTA.

Outcomes of treatment

62% patients were discharged while 38% patients died. The patients who died had higher markers of inflammation than the patients who were discharged. One patient had secondary bacterial infection. His recovery was uneventful and he was discharged (Table 1).

DISCUSSION

Respiratory infection caused by more than one viral pathogen (viral co-infection) or by both viral and bacterial pathogens (combined viral and bacterial pneumonia) may occur in patients with COVID-19. Secondary bacterial pneumonia can follow the initial phase of viral respiratory infection or can occur during the recovery phase. Data on SARS-CoV-2 are limited, but thus far, the overall incidence of viral co-infection has varied widely from 0% to 19% in different case series. In the previous influenza pandemic 25% patients had bacterial co-infection. Bacterial co-infection and secondary bacterial infection are considered critical risk factors for the severity and mortality rates of COVID-19.[3]

Recognizing combined viral and bacterial pneumonia or secondary bacterial pneumonia with COVID-19 requires a high index of suspicion. Some characteristics of bacterial infection may still be identifiable despite a significant overlap of viral and bacterial symptomatology. Neutrophilic leukocytosis is the hallmark of bacterial pneumonia, whereas COVID-19 patients typically present with a normal white blood cell count with lymphopenia.

While COVID-19 by itself can cause acute respiratory decompensation, data regarding secondary bacterial pneumonia playing a role in such decompensation are limited. Therefore, guideline-driven empiric antibiotic use may be reasonable until this secondary infection is ruled out. Supportive evidence for secondary bacterial pneumonia includes one or more of the following: new or recrudescent fever; new onset or change in the character of sputum; new leukocytosis or new neutrophilia (or both); new relevant imaging findings; and new or increasing oxygen requirements. It is also important to consider all other sources of hospital-acquired infections in these patients such as indwelling central venous catheters or urinary tract catheters and treat them accordingly.[3]

Secondary infections would lead to lower discharge rate and higher mortality rate. 52 critically ill patients with SARS-CoV-2 pneumonia in Wuhan were studied. Hospital-acquired infection occurred in seven (13.5%) patients and finally four of them died. Zhou et al reported a 50% secondary infection rate in non-survivors (27/54) and ventilator-associated pneumonia occurred in 31% (10/32) patients requiring invasive respiratory support.[4,5] Zhou et al showed that in the current coronavirus disease 2019 (COVID-19) pandemic, 50% of patients with COVID-19 who had died had secondary bacterial infections and Chen et al had recorded both bacterial and fungal co-infections.[6]

In the current study, the use of prophylactic antibiotics such as ceftriaxone+sulbactam+disodium EDTA had significantly reduced the prevalence of secondary bacterial infections. Only one patient had a secondary bacterial infection in our patient population but he had an uneventful complete recovery.

Salts of EDTA had long been used as antimicrobial agents, particularly against bacteria. They had also been used as enhancer of other agents such as lysozyme, antibiotics and irradiation, by increasing permeability of bacterial membrane or by removal or destruction of covalently bound lipid component.[2] Two modes of action of EDTA had been recognized, first EDTA potentiated the effect of antibiotics by binding to the metal ions which competed with aminoglycosides for cell wall receptor that allowed them into bacteria, second EDTA disrupted the lipopolysaccharides structure in the outer membrane of gram negative bacteria, through this disruption the membrane became more permeable to other agents such as antibiotic.[2] Ceftriaxone+sulbactam+ disodium EDTA was the most stable amongst tested antibiotics which were commonly used in ICU for treatment of carbapenem resistant *Enterobacteriaceae*

(CRE) infections and was effective against ESBL secreting pathogens.

Several Indian studies assessing the efficacy and safety of ceftriaxone+sulbactam+disodium EDTA had been published. Ceftriaxone+sulbactam+disodium EDTA had been reported in a post marketing surveillance study to be an effective and safe option for the management of patients with multi-drug resistant (MDR) bacterial infections in hospitalized patients.[7] Ceftriaxone+ sulbactam+disodium EDTA had been studied in patients with MDR septicaemia and was found to retain efficacy against SBL producing strains of pathogens.[8] Another Indian study by Sathe et al demonstrated efficacy of the ceftriaxone+sulbactam+disodium EDTA combination as an empiric treatment of *A. baumannii* infected VAP cases who were already being treated with meropenem and colistin.[9]

There were no studies of ceftriaxone+sulbactam+ disodium EDTA in prevention secondary infections in COVID-19 patients. The findings of the current study indicated that the combination of ceftriaxone+sulbactam +disodium EDTA can be an effective prophylactic treatment option in moderate to severe COVID-19 patients at risk of secondary bacterial infections. These findings were particularly important against the emerging backdrop of carbapenem resistance in *P. aeruginosa* and *A. baumannii* infections emerging in Indian ICUs and presence of *K. pneumoniae* strains resistant to commonly used antibiotics such as piperacillin tazobactam.[10-12]

Limitations

The study was a retrospective study and some data points could not be captured for some patients. A prospective double blind randomized study was required to corroborate the findings of this study.

CONCLUSION

Bacterial co-infections and secondary bacterial infections are a major risk factor for adverse COVID-19 outcomes. The use of appropriate prophylactic antibiotics such as ceftriaxone+sulbactam+disodium EDTA has significantly reduced the prevalence of secondary bacterial infections in patients with severe COVID.

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