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Original Articles

Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave

Takwa E. Meawed[a,1], Sherweet M. Ahmed[b,1], Sherif M.S. Mowafy[c,1], Ghada M. Samir[d,1], Reham H. Anis[a,*,1]

[a] Department of Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[b] Department of Tropical Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[c] Anesthesia and Surgical Intensive Care Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[d] Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt

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ABSTRACT

Background: The pandemic of coronavirus disease (COVID-19) has caused huge number of patients admitted to intensive care units (ICUs) in a critical need to mechanical ventilation. Ventilator associated pneumonia (VAP) has been noticed as a common complication in these patients with unfavorable outcomes. The current study aimed to assess bacterial and fungal VAP in COVID-19 patients admitted to ICUs during the second wave and to identify the possible risk factors.

Methods: Respiratory samples were collected from 197 critically ill COVID-19 patients under mechanical ventilation. Bacterial and fungal superinfections were diagnosed by microbiological cultures with subsequent antimicrobial susceptibility testing of the isolates using available kits.

Results: All specimens 197/197 (100%) were positive for bacterial infections, while fungal elements were detected in 134/197 (68%) of specimens. The most frequently isolated bacteria were pan drug resistant (PDR) *Klebsiella pneumoniae* (41.1%), followed by multi drug resistant (MDR) *Acinetobacter baumannii* (27.4%). On the other hand, *Candida* species represented the most frequently isolated fungi (75.4%) followed by molds including *Aspergillus* (16.4%) and *Mucor* (8.2%) species.

Possible risk factors for fungal VAP included underlying diabetes mellitus (95% confidence interval [CI] 1.09−3.31; p = 0.02), chest disease (95% CI 1.01−3.32; p = 0.05), hypothyroidism (95% CI 1.01−4.78; p = 0.05), and longer duration of mechanical ventilation (p < 0.001). Furthermore, all patients 134/134 (100%) who developed fungal VAP, were already under treatment with corticosteroids and Tocilizumab.

Conclusion: Bacterial and fungal VAP in critically ill COVID-19 patients is a serious problem in the current pandemic. Urgent and strategic steps to keep it under control are compulsory.

Introduction

Since the end of 2019, the world has been in the grip of coronavirus disease (COVID-19) caused by the infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). The pandemic is associated with a large number of patients who spend extended periods of time in intensive care units (ICUs). Most of these patients require invasive mechanical ventilation [1].

Viral pneumonia intensifies patients' susceptibility to both bacterial and fungal superinfections [2]. Moreover, during the hospital stay, COVID-19 patients have an increased risk of invasive fungal infections associated with intubation and corticosteroid therapy [3]. Therefore, a warning has been issued by early reports demonstrating the high prevalence of ventilator associated pneumonia (VAP) in critically ill COVID-19 patients [4].

Antimicrobial therapy plays a central role in the management of confirmed or suspected bacterial or fungal respiratory infections. However, a serious observation was reported that approximately 50% of the deceased COVID-19 patients had bacterial and fungal coinfections which were highly resistant to several antimicrobials [5].

During the second wave of COVID-19 pandemic, an unexpected high rate of VAP in mechanically ventilated COVID-19 cases was noticed in the ICUs of our hospital with subsequent high mortality

* Corresponding author.
E-mail address: anisreham@yahoo.com (R.H. Anis).
[1] All authors contributed equally.

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rate in these patients. Therefore, the authors found it necessary to investigate the local situation.

To our knowledge, this is the first report from Egypt to assess bacterial and fungal superinfection in mechanically ventilated COVID-19 patients admitted to intensive care units (ICUs) during the second wave.

Material and methods

Study design and setting

This cross-sectional study was carried out over a period of 6 months, from October 2020 to April 2021 in Zagazig University Isolation Hospitals, a tertiary care hospital in Egypt. The current study included 197 mechanically ventilated COVID-19 patients admitted to the intensive care units (ICUs). The online tool Open epi version 3.1 was used to calculate the sample size [6].

This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Zagazig University (IRB reference number: ZU-IRB# 6942/2020). It was conducted in accordance with the revised Declaration of Helsinki. Informed consents were obtained from all study participants or the legal guardians of the unconscious ones.

Study subjects

The present study included 197 critically ill COVID-19 adults (≥18 years old) under mechanical ventilation. Enrolled participants were reviewed on the day of admission by an ICU consultant and on daily basis for the development of VAP that was suspected by new or changing chest X-ray infiltrates appearing more than 48 h after the start of invasive mechanical ventilation. In addition to new onset of fever (body temperature ≥38 °C) or hypothermia (body temperature ≤35 °C), leukocytosis (total peripheral white blood cell count (WBC) of ≥10,000 cells/μL) or leukopenia (total WBC count of ≤4000 cells/μL), as well as new onset of suctioned respiratory secretions and/or the need to ventilator support system to improve oxygenation [7].

All participants underwent detailed history taking as well as clinical examination focusing on associated risk factors as underlying comorbidities. All patients were investigated by complete blood count, liver function tests, kidney function tests, coagulation profile, D-dimer, ferritin level, and serum inflammatory markers including C-reactive proteins (CRP), Interleukin-6 (IL6), and procalcitonin (PCT).

Diagnostic criteria and all investigations as well as treatment were performed for all registered patients following the relevant local guidelines, protocols, and regulations [8]. Steroids (Methyl prednisolone 2 mg/kg or its equivalent) were administrated. When steroids failed to control the case for 24 h, Tocilizumab was indicated to early block the storm (indicated by high serum level of IL-6) provided that PCT was negative. The ICU team on charge took the decisions related to the patients' management with no intervention from the investigators.

Our ICUs were dedicated only for COVID-19 patients with strict implementation of recommended COVID-19 infection control measures to limit the spread of infection including the appropriate personal protective equipment and environmental disinfection measures. Additionally, for ventilated patients implemented ventilator bundle with daily regular audit including head of bed elevation, the sub-glottic suction endo-tracheal tube, oral hygiene at least twice daily, and daily sedation vacation was also maintained. Moreover, the tight seals of ventilator circuits, the use of heat moisture exchange (HME) filters and in-line closed suction were maintained for each patient. Also, 70% alcohol was used at least twice daily for ventilator surface disinfection and to wipe the external surfaces around the patient including the monitors. With increasing the ICU capacity above normal, one to two nursing to patients' ratio was maintained, although the included nurses may be with limited ICU training, but they were working under supervision from critical care nurse.

Detection of SARS-CoV2 using reverse transcription real-time polymerase chain reaction (RT-PCR)

From each patient, a nasopharyngeal and an oropharyngeal swab were obtained under complete aseptic conditions. The two swabs obtained from one patient were placed in three ml of viral transport medium in a collection tube (VTM, Ismailia free zone, Egypt) and immediately sent to the Scientific & Medical Research Centre, Faculty of Medicine, Zagazig University.

Viral RNA was extracted using a commercial Kit, QIAamp® Viral RNA mini kit (Qiagen, Japan, cat. no. 52906) according to the manufacturer's protocol. Then, the RNA-dependent RNA polymerase gene of SARS-CoV2 was targeted with a one-step RT-qPCR utilizing a real-time PCR kit (Primerdesign Ltd, UK) in a Stratagene Mx3000P qPCR System (Agilent, USA).

The 20 μL reaction mix contained 2X RT-qPCR Master Mix (10 μL), Primer & Probe (2 μL), and RNA extract (8 μL). Positive and negative controls were included in each run.

The reverse transcription was carried out by heating the samples at 55 °C for 10 min. Following initial denaturation (heating at 95 °C for 2 min), 45 cycles of denaturation (at 95 °C for 10 s), annealing, and extension (at 60 °C for 1 min) were performed.

The cycle threshold (Ct) value was recorded for each sample. If the Ct value was less than 40 or the Ct value was not recorded, the sample was considered negative for SARS-CoV2 [9].

Detection of bacterial and fungal superinfection

Sputum and endotracheal aspirate (ETA) specimens were collected in appropriate containers according to the standard protocol, in a 3–4 days interval schedule [10]. Strict adherence to recommendations of Centers for Disease Control and Prevention (CDC) was applied during specimen collection, transportation, and processing [11].

The collected specimens were rapidly transferred to the microbiological laboratory where culture and identification were carried out following the standard laboratory procedures [12].

For detection isolation, direct microscopic examination of Gram-stained smears was carried out followed by inoculation on Blood Agar, Chocolate Agar and MacConkey. All media were purchased from (Oxoid, Basingstoke, UK).

After overnight incubation at 37 °C under standard conditions, any bacterial growth was identified by Gram-stained smears, classical biochemical tests, and VITEK® 2 compact system (Bio-Mérieux, France).

For fungal isolation, immediate KOH wet mount followed by lactophenol-cotton blue direct smears were examined under microscope. Then culture on Sabouraud dextrose agar with chloramphenicol and with/without cycloheximide each in duplicate culture plates incubated at 37 °C and room temperature.

Infection with *Candida* was highly suspected if direct smears revealed Gram positive pseudohyphae formation. Culture on blood, chocolate and MacConkey clarified the recovery of *Candida*. Subsequently, *Candida* species were differentiated using Brilliance chrome agar.

Filamentous fungi were identified based on their macroscopic and microscopic characteristics. *Aspergillus niger* is characterized by rapid growth of slightly brown, smooth walled colonies with grey reverse. Microscopically, hyaline septate hyphae with biseri-

ate radiate conidial heads. Conidia are in chains or detached and dispersed.

Mucor is identified by its rapid growth, cottony to fluffy colonies, varying in color from white to dark grey with aging with pale or yellow reverse. Microscopically, it shows broad, non-septate hyphae branching at wide angles (>90°) with terminal, spherical, multi-spored sporangia, supported and elevated by well-developed subtending columellae.

The diagnosis of bacterial or fungal superinfection was based on positive cultures 48 h or more after mechanical ventilation in clinically suspected cases, while earlier specimens from the same patients yielded negative cultures.

Antimicrobial susceptibility testing (AST)

The susceptibility of the isolated bacteria to different antimicrobials was tested by the standard disc diffusion method (Modified Kirby-Bauer) using Muller Hinton agar according to guidelines of the Clinical and Laboratory Standards Institute [11].

The following commercial antimicrobial discs were used; piperacillin (10 μg), amoxicillin–clavulanic acid (20, 10 μg); gentamicin (10 μg), amikacin (30 μg), imipenem (10 μg), meropenem (10 μg), cephalosporins: cefoxitin (30 μg), cefoperazone (75 μg), ceftriaxone (30 μg), cefotaxime (30 μg), ceftazdime (30 μg), cefipeme (30 μg), levofloxacin (5 μg), erythromycin (15 μg), azithromycin (15 μg), tetracycline (30 μg), and trimethoprim/sulfamethoxazole (1.25/23.75 μg), tigecycline (Tig 15 μg) (Oxoid, Basingstoke, UK).

Regarding vancomycin and colistin, the minimum inhibitory concentration (MIC) was determined according to CLSI guidelines.

As quality control strains, *Pseudomonas aeruginosa* ATCC® 27853™ and *Escherichia coli* ATCC® 25922™ were used (American Type Culture Collection Global Bioresource Center, USA).

Multidrug-resistant (MDR) and pan drug-resistant (PDR) bacterial isolates were identified based on susceptibility patterns to different classes of antimicrobials. Multidrug-resistant strains exhibited resistance to three or more antimicrobial drug classes, while pan drug-resistant strains showed resistance to all drug classes [13].

Statistical analysis

All results were analyzed using IBM SPSS 23.0 (SPSS Inc., Chicago, USA). Categorical data were presented as frequency and percentage, whereas continuous data were presented as mean ± standard deviation (SD). Odds ratios (ORs) with 95% confidence intervals (95%CI) were calculated for each significant variable based on univariate logistic regression. Significance was indicated by probability (*P*-value) ≤0.05.

Results

The participants in the current study included 118/197 (59.9%) male patients and 79/197 (40.1%) female patients, ranging in age from 40 to 83 years.

Of all participants, 168 cases (85.3%) had underlying medical problems including hypertension, obesity, hypothyroidism, diabetes, or underlying chest, heart or kidney diseases. All included patients (100%) died during their hospital stay.

Table 1 shows the demographic and clinical characteristics of the patients under study.

The mean time elapsed from mechanical ventilation to clinical suspicion of VAP development was (10 ± 2.5) days with a range from 9 to 14 days.

On microbiological investigation, all included specimens (197/197, 100%) yielded significant bacterial growth with single isolate each.

Table 1
Demographic and clinical characteristics of studied patients (critically ill COVID-19 patients who developed VAP).

Characteristics		Participants (n = 197)
Age (years)	Mean ± SD	65 ± 14.3
Sex		
Male	Number (%)	118 (59.9)
Female		79 (40.1)
Underlying comorbidities	Number (%)	
Obesity		37 (18.8)
Diabetes Mellitus		111 (56.3)
Hypertension		123 (62.4)
Hypothyroidism		51 (25.9)
Chest disease		88 (44.7)
Heart disease		34 (17.3)
Kidney Disease		43 (21.9)
Empiric antibiotic on admission	Number (%)	197 (100)
Immunomodulatory treatment	Number (%)	
Steroids		197 (100)
Tocilizumab		178 (90.4)
Days of invasive ventilation before VAP	Mean ± SD	10 ± 2.5
In-hospital mortality	Number (%)	197 (100)

COVID-19: Coronavirus Disease 2019; VAP: Ventilator-Associated Pneumonia; SD: Standard Deviation.

Table 2
Types and frequencies of isolated bacterial and fungal pathogens.

Variable	Number (%) (n = 197)
Results of bacterial cultures	
Positive	197 (100)
Negative	0 (0)
Organisms	
PDR *K. pneumoniae*	81(41.1)
MDR *A. baumannii*	54 (27.4)
ESBL *P. aueroginosa*	41 (20.8)
ESBL *E. coli*	3 (1.5)
MRSA	18 (9.1)
Results of Fungal cultures	
Positive	134 (68)
Negative	63 (32)
Organisms	
C. Albicans	57/134 (42.6)
C. non-Albicans	
C. Krusii	26/134 (19.4)
C. Auris	18/134 (13.4)
Aspergillus	22/134 (16.4)
Mucor	11/134 (8.2)

PDR: Pan Drug-Resistant; MDR: Multi-Drug Resistant; ESBL: Extended Spectrum β-Lactamase, MRSA: Methicillin Resistant *Staphylococcus aureus*.

The bacterial isolates were recovered after 11–14 days of mechanical ventilation. Unfortunately, most isolates were difficult to treat bacterial pathogens. The most frequently isolated one was PDR *Klebsiella pneumoniae* (41.1%), followed by MDR *Acinetobacter baumannii* (27.4%).

Fungal elements were detected in 134/197 specimens (68%). *Candida* species represented the most frequently isolated fungi followed by molds that included *Aspergillus* and *Mucor* species. The types and frequencies of isolated bacterial and fungal pathogens are illustrated in Table 2.

The fungal elements recovered in this work were due to superinfection, as they were recovered few days after bacterial isolates. Earlier specimens from the same patients tested free of these fungi both on direct film and culture levels.

Univariate analysis was done to detect possible risk factors associated with fungal superinfection among the studied group. Statistical significance was detected in cases of diabetes mellitus (95% confidence interval [CI] 1.09−3.31; p = 0.02), chest disease (95% CI 1.01−3.32; p = 0.05), and hypothyroidism (95% CI 1.01−4.78; p = 0.05). Furthermore, the longer duration of mechan-

Table 3
Univariate analysis of factors associated with fungal superinfection.

Variable	Fungal Superinfection (n = 134)	No fungal superinfection (n = 63)	OR (95%CI)	P
Age (years)	66 ± 13.7	65 ± 14.1		0.64
Sex				
Male	80	36	1.04 (0.64–1.71)	0.86
Female	54	27	0.94 (0.54–1.63)	0.83
Underlying comorbidities				
Obesity	24	13	0.87 (0.41–1.82)	0.7
Diabetes Mellitus	89	22	1.9 (1.09–3.31)	**0.02***
Hypertension	84	39	1.01(0.62–1.64)	0.95
Hypothyroidism	42	9	2.19 (1.01–4.78)	**0.05***
Chest disease	70	18	1.8 (1.01–3.32)	**0.05***
Heart disease	27	7	1.8 (0.75–4.39)	0.19
Kidney Disease	28	15	0.88 (0.44–1.76)	0.71
Days of invasive ventilation before VAP	10 ± 2.5	8 ± 2.1		**P <0.001***

VAP: Ventilator-Associated Pneumonia; OR: Odds Ratio; CI: Confidence Interval; *: Statistical Significance

ical ventilation was shown to be a highly significant risk factor ($p < 0.001$). The results are displayed in Table 3.

An important observation in our study that all COVID-19 patients (100%) who developed fungal superinfection under mechanical ventilation, were already under treatment with corticosteroids and Tocilizumab.

Discussion

Coronavirus disease-2019 (COVID-19) has emerged as a new public health problem that has significantly changed the world map epidemiologically, demographically, and clinically.

Previous research found a correlation between bacterial and fungal coinfection with SARS-CoV2 and disease severity [14]. Furthermore, cases of bacterial and fungal coinfection showed a more than two-fold increased risk of death [15], confirming the interaction between bacteria or fungi and SARS-CoV2.

Many COVID-19 patients need ICU admission and mechanical ventilation with unfavorable outcomes. Some studies investigated hospital acquired infections, especially VAP as a cause of patient deterioration. To our knowledge, this is the first Egyptian study assessing both bacterial and fungal VAP in critically ill COVID-19 patients.

An unexpected finding in the current study is the unprecedentedly high mortality rate. All the study participants deteriorated and died during their hospital stay under mechanical ventilation. Therefore, we need to further investigate the situation in our ICUs.

Surprisingly, all collected specimens tested positive for bacterial infection in microbiological examination (197/197, 100%). This finding strongly demonstrates an association between VAP, and the higher mortality rate recorded in our patients.

In the same context, a previous study conducted in Iran on nineteen mechanically ventilated COVID-19 patients reported that all had secondary bacterial pneumonia and died during their hospital stay except for one patient who survived [16].

In contrast, studies carried out in China and UK reported that only 13.9% and 6.1% of COVID-19 patients in the ICU had secondary bacterial infections [17,18].

The differences between various studies can be attributed to factors influencing the quality of care provided and the incidence of ICU acquired infections such as ICU type, admission/discharge criteria, used equipment rate, workload/nurse ratio.

Unfortunately, all bacterial isolates in the current study showed high antimicrobial resistance that can be attributed to the scheduled antibiotic administration of COVID-19 protocol that controlled other most susceptible pathogens leaving the resistant survivors that could escape this condensed management protocol.

The most frequently isolated organism was PDR *Klebsiella pneumoniae*, followed by MDR *Acinetobacter baumannii*. In the past years, many studies reported the existence of hypervirulent strains of both microorganisms with resistance to different antibiotic families [19,20].

Extended spectrum β-lactamase (ESBL) producing *Pseudomonas auerginosa* and *E. coli* in addition to Methicillin resistant *staphylococcus aureus* (MRSA) were the other identified causative organisms of VAP in study participants. These findings raise a serious warning that hospital-acquired superbugs causing a real problem in our ICUs.

These superbugs were previously isolated from other non-COVID-19 patients admitted to our ICUs [21]. Moreover, both *K. pneumoniae* and *A. baumannii* have been reported as the most common isolated pathogens even from non-COVID-19 ICU patients in Egypt [22], and other countries, including Iran, China, and India [23–25].

Consistent with the scenario in the present study, VAP was clinically suspected from approximately day 9–14 days following mechanical ventilation. This duration allowed bacterial superinfection and multiplication.

It should be noted that bacterial elements are not the only cause of VAP. Evidence of secondary fungal infection in critically ill COVID-19 patients was first noticed in China, in addition to becoming a clear manifestation as indicated by European case studies [26].

In the current study, the frequency of fungal superinfection in mechanically ventilated COVID-19 patients was unpredictable and challenging. Fungal elements were detected in 134/197 specimens (68%).

In Zhang's study, critically ill patients showed a significantly lower rate of coinfection with fungi (10.9%). Regarding the isolated fungi species, that study reported similar results to ours that *Candida* species represented the most frequently isolated fungi, followed by *Aspergillus* and *mucor* species [27].

Another study stated that among the COVID-19 cases in Wuhan, the most coinfecting fungi were *Candida albicans*, *Candida Glabrata*, and *Aspergillus flavus* [28]. The study carried out by Salehi et al. (2020) reported that *C. albicans* was the most common coinfecting fungus (70.7%), followed by other *Candida* species; *C. glabrata* (10.7%), *C. dubliniensis* (9.2%), *C. parapsilosis* (4.6%), *C. tropicalis* (3%), and *C. krusei* (1.5%) [29].

Viral pneumonia intensifies patients' susceptibility to both bacterial and fungal superinfections. SARS-CoV2 infection causes direct epithelial damage and delays ciliary clearance facilitating coinfection. Moreover, the ability of the virus to damage lymphocytes, particularly B cells, T cells, and Natural killer cells, results in immune system dysfunction along the course of the disease that could be the main cause of the coinfection [30].

The specific pathophysiology of COVID-19 is plausible for the unusual comorbidity with fungal infection. The catastrophic

changes caused by SARS-CoV2 virus to lung parenchyma and large bilateral alveolo-interstitial lesions raise the possibility of fungal infection, particularly those with an airborne route of infection such as *aspergillus* and *Mucor* [31].

Although previous studies reported *Candida* and *Aspergillus* as the main causes of fungal superinfection in critically ill COVID-19 patients, mucormycosis has gained special attention recently as a serious complication among these patients.

Mucormycosis is known as an uncommon but fatal opportunistic fungal infection, mainly reported in patients with immunocompromised conditions, such as uncontrolled diabetes mellitus and leukemias [32]. Recently, mucormycosis has been reported in several cases of critically ill COVID-19 patients in India that has raised a great alarm. Surprisingly, similar cases were reported in different countries all over the world [33].

Strong evidence demonstrated that mucormycosis is not simply caused by the immunological effects induced by the virus itself. Rather, it is more probably precipitated by the medications used for critically ill patients.

Surprisingly in the current work, all COVID-19 patients (100%) who developed fungal superinfection under mechanical ventilation, were already under treatment with corticosteroids and Tocilizumab.

While long term use of corticosteroids has been correlated with a variety of opportunistic fungal infections, even the short course of corticosteroids has recently been linked to mucormycosis, particularly in people with diabetes mellitus [34].

These findings strongly recommended a modification of the steroid administration protocol in such patients.

Tocilizumab is another drug that is strongly incriminated to predispose this severe complication. Tocilizumab is a recombinant humanized monoclonal antibody used against the interleukin-6 (IL-6) receptor. It is given to quickly reduce the IL-6 levels (cytokine storm) in COVID-19 patients. If not controlled, the inflammatory effects of IL-6 may lead to lung damage and eventual COVID-19 associated multiorgan failure [35,36].

Tocilizumab was considered as a promising drug for blocking IL-6 and control cytokine storm, but IL-6 inhibition can have also adverse consequences due to its central role in innate immunity and microbial clearance [37]. This has been proved by other studies that patients treated with Tocilizumab had a higher risk of serious secondary bacterial and fungal infections with subsequent higher mortality [38].

In the current study, about 90% of included patients were on treatment with Tocilizumab. This elucidates the high rate of secondary bacterial and fungal infections in COVID-19 patients with high mortality. In addition, it raises the importance of risk versus benefit assessment before using this drug.

A study that was conducted in Brazil reported an overall mortality rate of 28.8% among ICU patients, while the coinfected patients showed a mortality rate of 34.7% [39]. According to another study, the death rate of VAP in ICU patients ranges from 20 to 50% and may be even higher when caused by microorganisms that are highly resistant to antibiotics [40].

The current study reports unexpected high rate of bacterial and fungal VAP with subsequent high mortality in our ICUs. These challenging results could be attributed to inappropriate use of antibiotics and immunomodulatory drugs mainly the high doses of steroids that are not truly indicated. Moreover, the strict application of infection control measures during the second wave was adversely affected due to shortage of the supplies and shortage of human resources including physicians, nurses, and workers that magnified the workloads and leaded to staff burnout and collapse.

Generally, the current situation is fulminant and needs to be modified according to CDC guidelines and recommendations. Adequate staffing is required to achieve better infection control as well as to prevent burnout among exhausted staff. Redesigning most ICUs is essential to ensure the safety of patients and health care workers.

There should be separate entrance and exit for the ICU of COVID-19 patients, in addition to access via a dedicated lift and/or stairs with 24/7 safekeeping to control ICU entry. Furthermore, a separate donning and doffing area should be provided.

Medical equipment should be disinfected before removing from the patient's room. Personal items such as keys, phones, and bags should be thoroughly disinfected. Hand washing and hygiene conveniences are required in the COVID ICU, preferably with touchless sensors for hand washing [41].

Unfortunately, due to the death of all patients included in the current study, it was not possible to compare mortality rates in those with bacterial infection only versus bacterial and fungal coinfection.

With the currently observed challenge to healthcare systems during the SARS-CoV2 pandemic, more attention must be paid to maintaining proper infection control and accurate surveillance for healthcare associated infections.

Furthermore, the inappropriate and widespread use of antibiotics, especially during the second wave of COVID pandemic, is expected to lead to more antibiotic resistance. Therefore, to stop this dangerous misuse of antibiotics, it is recommended to start an empirical treatment of COVID patients based on clinical findings using the most appropriate antimicrobial agents according to the local guidelines. However, this empirical treatment should be modified as early as possible according to microbiological results.

Conclusion

Bacterial and fungal VAP in critically ill COVID-19 patients is a serious problem in the current pandemic second wave that requires immediate and strategic intervention to keep it under control.

Limitations

A significant limitation of the study is that no control patients were examined. Moreover, the death of all study participants during their stay in ICU made it impossible to investigate the effects of various factors on various outcomes. Therefore, further studies are strongly recommended including a control group such as 1) patients who survived and did not develop bacterial/fungal superinfection, 2) patients who developed bacterial/fungal superinfection but survived, or 3) patients who died, but due to direct COVID-19 infection (without superinfection).

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Conflicts of interest

Authors have no conflicts of interest to declare.

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