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Original Article

Pattern of Secondary Bacterial Infections and Antibiotic Susceptibility among Confirmed COVID-19 Patients at a Tertiary Care Hospital

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of pneumonia cases in Wuhan, China, at the end of 2019[1]. Secondary bacterial infection (SBI) is one of the lethal complications in hospitalized patients with COVID-19.

Objective: To determine the pattern of SBIs and antimicrobial susceptibility among confirmed COVID-19 patients.

Methodology: This cross sectional study was conducted at department of Pathology Combined Military Hospital Lahore from March-September 2020. Confirmed COVID-19 patients (n=1584) developing bacterial culture confirmed secondary bacterial infections (SBIs) were included. Antimicrobial susceptibility testing was performed by Modified Kirby Bauer disc diffusion method. Drug zones and mechanism of resistance among isolated bacteria was detected using CLSI guidelines.

Results: SBIs were detected in 73 (4.6%) patients. Among 73 patients 47 (64%) developed ventilator associated pneumonia (VAP), 11(15%) had catheter related blood stream infections (CRBSI), 8 (11%) developed catheter associated urinary tract infection (CAUTI) and 7 (9%) had surgical site infections (SSIs).All bacterial isolates were multidrug resistant and 48(66%) were extensively drug resistant. Among isolated bacteria, *Acinetobacter baumannii* exhibited the highest resistance. The isolation rates of extended-spectrum beta-lactamases (ESBLs) producing Gram-negative rods, carbapenem-resistant *A. baumannii* (CRAB) and carbapenem-resistant *Klebsiella pneumoniae* were 100%, 91% and 61%, respectively. About 100% of isolated *Staphylococci* were methicillin-resistant Staphylococcus aureus (MRSA), and 33% of isolated *Enterococci* were vancomycin-resistant (VRE).

Conclusion: Incidence of secondary bacterial infections in COVID-19 patients was 4.6%. VAP was the most common SBI followed by CRBSI, CAUTI and SSI respectively. High antimicrobial resistance was observed among isolated bacteria.

Key words: Antimicrobial resistance, Catheter associated urinary tract infection (CAUTI), Catheter related blood stream infections (CRBSI), Secondary bacterial infections (SBIs), Surgical site infections (SSIs) and Ventilator associated pneumonia (VAP)

Introduction

A novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, China, at the end of 2019[1]. Under its high contagious attribution, this novel coronavirus has spread rapidly across the globe resulting in a global pandemic[2]. The first two confirmed cases were reported in Pakistan on 26th February 2020 among religious pilgrims visiting Iran[3].

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The SARS-CoV-2 infection has a broad spectrum of clinical symptoms, ranging from asymptomatic infection to severe viral pneumonia-causing respiratory failure and even death[4].

Secondary bacterial infection (SBI) is one of the lethal complications in hospitalized patients with COVID-19. The approximate incidence of SBI reported in previous studies is 10-15%5. According to existing reports, approximately 50% of COVID-19 deaths suffered from SBIs[5]. A retrospective monocentric case-control study reported 91 events of SBIs, including 31% primary and 25% catheter-related bloodstream infections, 23% pneumonia, 10% tracheobronchitis and 8% urinary tract infection[6]. High antimicrobial resistance was observed in bacteria isolated from patients with SBIs[7].

Currently, a lot of research has been published regarding the epidemiological and clinical features of COVID-19; studies about SBIs are scarce, especially in our region. The rationale of our study was to determine the pattern of SBIs and antimicrobial susceptibility among confirmed COVID-19 patients for more accurate antimicrobial use. This study will not only help in deciding when to give empirical antibiotic therapy but will also guide which antibiotic to be given in order to treat such dreadful infections.
Multicentric studies from across country are needed to elaborate on the impact of SBIs on the morbidity and mortality of patients suffering from COVID-19.

Materials and Methods

It was a cross-sectional study using nonprobability convenience sampling technique conducted in the Department of Pathology Combined Military Hospital Lahore from March-September 2020 during COVID-19 outbreak crises in Pakistan. All confirmed COVID-19 patients, irrespective of age and gender, who developed bacterial culture-confirmed SBIs during hospital stay were included in the study. Bacterial cultures from COVID-19 confirmed cases that yielded more than one pathogen were excluded from the study to rule out any contamination. Patient demographics, clinical features, co-morbid conditions, patient hospital settings, duration of hospitalization after which SBI symptoms developed, type of microbiological culture, bacterial pathogen isolated and antibiotic susceptibility pattern of isolated bacteria were recorded in the especially designed Proforma after taking informed consent from confirmed COVID-19 patients. Approval of this study was taken by Institutional Ethical Committee (IRB NO. 187/2020). The definition of verified COVID-19 patient was in accordance with the WHO interim guidelines[8]. COVID-19 diagnosis was confirmed by the positive result of real-time RT-PCR from respiratory specimens (oropharyngeal swab, sputum or bronchoalveolar lavage). Secondary bacterial infections (SBIs) were defined as any culture-positive bacterial infection accompanied by related symptoms during or after treatment for COVID-19 infection in hospitalized patients[2].

WHO sample size calculator was used to calculate the sample size of this study taking 95% confidence level, 0.05[9] population proportion and 0.05 an absolute precision. The estimated sample size was 73. SBI was diagnosed through identification of bacterial pathogen causing any subsequent infections in CoVID-19 patients: ventilator-associated pneumonias (VAP), catheter-related bloodstream infections (CRBSIs), catheter-associated urinary tract infection (CAUTI), surgical site infections (SSIs). VAP was defined and diagnosed by using criteria used by Luyt *et al*[10]. CRBSI was defined and interpreted by using criteria explained by Khanna V *et al* [11]. Moreover, CAUTI was defined and diagnosed using criteria used by Sabir N *et* al [12] and SSI was defined and diagnosed using criteria by Losurdu P *et al*[13].

All microbiological specimens like NBL, paired blood cultures, urine and pure pus/ tissue from symptomatic patients fulfilling the clinical criteria of VAP, CRBSI, CAUTI and SSIs were collected by a trained specimen collector with an aseptic technique. Standard microbiological protocols were used to process bacterial cultures. Identification of bacterial isolates was made based on colony morphology, Gram staining, biochemical tests, API 20E and API 20NE (BioMerieux, France). A modified Kirby Bauer disc diffusion method was used to determine antimicrobial susceptibility testing of isolated bacteria. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853. The bacterial isolates were considered sensitive or resistant to the drug based on the zone of inhibition around the antibiotic discs as per Clinical and Laboratory Standard Institute (CLSI) guidelines[14]. International standardized definitions devised by European Centre for Disease Control (ECDC) and the Centre for Disease Control and Prevention (CDC) were used to define multidrug-resistant (MDR)and extensively drug-resistant (XDR) bacterial isolates[15]. Mechanism of resistance among Gram-negative and Gram-positive bacteria were detected using CLSI guidelines[14].

SPSS version 23 was used to analyze data. Descriptive statistics were calculated for both qualitative and quantitative variables. Mean ±SD was computed for quantitative variables like age. For qualitative variables like gender, co-morbid conditions, clinical characteristics, hospital settings, type of microbiological culture, bacterial pathogens isolated, drug susceptibility, our study utilized the frequency and percentages.

Results

Among 1584 confirmed COVID-19 positive patients admitted to Combined Military Hospital Lahore, SBIs were detected in 73 (4.6%) patients. The mean age of patients with SBI was 50.7 ±21.82 years. Out of 73 patients, 59 (81%) were males, and 14 (4.9%) were females. The clinical attributes of COVID-19 patients with SBIs are shown in Table 1.

Table 1: The Clinical Attributes of COVID-19 Patients with Secondary Bacterial Infections

Clinical Characteristics	N (%)
Comorbid Conditions	
Diabetes mellitus	40(55%)
Ischemic heart disease	23(31%)
Hypertension	19(26%)
COPD	11(15%)
Asthma	8(11%)
Recent surgery	7(9.6%)
Pulmonary T.B	7(9.6%)
Cancer	6(8%)
Recent traumatic history	3(4%)
Patient Hospital Settings	
Corona ward	4(5.5%)
Corona Intensive Care Unit	69(94%)
Clinical Features at Presentation	
Fever	73(100%)
Dry Cough	63(90%)
Sore throat	55(75%)
Myalgias	51(70%)
Difficulty in breathing	46(63%)
Loss of smell	36(49%)
Loss of taste	35(48%)
Shortness of breath	9(12%)
Chest tightness	6(8.2%)
Others	6(8.2%)
Duration of Hospitalization before SBI	
3-6 days	62(85%)
7-10 days	7(9.6%)
11-13 days	1(1.3%)
14-16 days	1(1.3%)
17-19 days	1(1.3%)

Among 73 patients 47 (64%) developed VAP, 11(15%) had CRBSI, 8 (11%) developed CAUTI and 7 (9%) had SSIs.

73 bacterial isolates were yielded from bacterial cultures of COVID-19 patients suffering from SBIs. Among the isolated bacteria, Gram-negative bacteria were predominant, accounting for 63(86.3%). *Acinetobacter baumannii* was the most common etiological agent of VAP, accounting for about 32 (48%). *Klebsiella pneumonia*4/11(36%), *E. coli* 6/8(75%) and *Staphylococci* 5/7(71%) were the leading pathogen of CRBSIs, CAUTI and SSI, respectively. The etiological distribution of SBI in patients hospitalized with COVID-19 is depicted in Table 2.

Alarmingly high antimicrobial resistance was observed in bacteria isolated from COVID-19 patients with SBIs. Out of 73 bacterial isolates, 73(100%) were MDR and 48(66%) were XDR. Among isolated bacteria, *Acinetobacter baumannii* exhibited the highest resistance. The isolation rates of extended-spectrum beta-lactamases (ESBLs)producing Gram-negative rods, carbapenem-resistant *A. baumannii* (CRAB) and carbapenem-resistant *Klebsiella pneumoniae* were 100%, 91% and 61%, respectively. About 100% of isolated *Staphylococci* were methicillin-resistant Staphylococcus aureus (MRSA), and 33% of isolated *Enterococci* were vancomycin-resistant (VRE). The antimicrobial resistance pattern for major Gram-negative and Gram-positive bacteria are shown in Table 3(a & b respectively).

Table 2: Etiological distribution of SBIs in COVID-19 patients N (%) in Different Sites

Etiological Agents					
Gram Negative	**NBL**	**Paired Blood Cultures**	**Urine**	**Pus/Tissue**	**Total**
Acinetobacter baumannii	32(48%)	0	0	0	32(44%)
Klebsiella pneumoniae	8(17%)	4(36%)	1(12%)	0	13(18%)
Pseudomonas aeruginosa	5(11%)	2(18%)	0	2(28%)	9(12%)
E. coli	2(4%)	1(9%)	6(75%)	0	9(12%)
Gram Positive Cocci	**NBL**	**Paired Blood Cultures**	**Urine**	**Pus/Tissue**	**Total**
Staphylococcus aureus	0	2(18%)	0	5(71%)	7(9%)
Enterococcus spp	0	2(18%)	1(12%)	0	3(4%)
Total	**47(64%)**	**11(15%)**	**8(11%)**	**7(9%)**	**73**

Table 3: Antimicrobial Resistance Pattern of Isolated Bacteria

3a. Antimicrobial Resistance Pattern of Gram-Negative Bacteria

Gram-Negative Bacteria N (%) Resistance				
Antibiotics	***Acinetobacter baumannii* (n=32)**	***Klebsiella pneumoniae* (n=13)**	***Pseudomonas aeruginosa* (n= 9)**	***E.Coli (n=9)***
Ampicillin	IR	IR	IR	9(100%)
Co-trimoxazole	32(100%)	13(100%)	IR	9(100%)
Amoxicillin-clavulunate	1R	13(100%)	IR	9(100%)
Tazobactam-piperacillin	32(100%)	13(100%)	7(78%)	9(100%)
Cefazolin	IR	13(100%)	IR	9(100%)
Ceftriaxone	32(100%)	13(100%)	IR	9(100%)
Ceftazidime	32(100%)	13(100%)	9(100%)	9(100%)
Cefepime	32(100%)	13(100%)	9(100%)	9(100%)
Aztreonam	IR	13(100%)	9(100%)	9(100%)
Imipenem	32(100%)	8(61%)	5(55%)	2(22%)
Meropenem	32(100%)	7(53%)	6(67%)	2(22%)
Amikacin	32(100%)	13(100%)	9(100%)	1(11%)
Gentamicin	32(100%)	13(100%)	9(100%)	8(88%)
Colistin	0(0%)	0(0%)	0(0%)	0(0%)
Doxycycline	32(72%)	13(100%)	IR	9(100%)
Minocycline	24(75%)	13(100%)	1R	NT
Tigecycline	20(62%)	5(38%)	IR	5(55%)
Ciprofloxacin	32(100%)	13(100%)	9(100%)	9(100%)
Levofloxacin	30(94%)	9(69%)	8((88%)	8(88%)
Resistance Mechanism Extended Spectrum Beta-lactamases Carbapenemase Resistance	32(100%) 29(91%)	13(100%) 8(61%)	9(100%) 6(67%)	9(100%) 2(33%)
MDR XDR	32(100%) 30(94%)	13(100%) 8(61%)	9(100%) 5(55%)	9(100%) 2(22%)

**IR indicates intrinsic resistance, NT indicates not tested and NA indicates not applicable.*

3b. Antimicrobial Resistance Pattern of Gram-Positive Bacteria

Gram- Positive Bacteria N (%) Resistance		
Antibiotics	***Staphylococcus aureus*(n=7)**	***Enterococcus spp* (n=3)**
Penicillin	7(100%)	3(100%)
Cloxacillin	7100%)	NT
Ampicillin	NT	3(100%)
Erythromycin	7(100%)	NT
Clindamycin	7(100%)	IR
Co-trimoxazole	7(100%)	IR
Ciprofloxacin	7(100%)	NT
Gentamicin	1(14%)	NT
Vancomycin	0(0%)	1(33%)
Doxycycline	7(100%)	2(66%)
Linezolid	0(0%)	0(0%)
Fusidic acid	7(100%)	IR
Cefoxitin	7(100%)	NA
Resistance Mechanism MRSA VRE	 7(100%) NA	 NA 1(33%)
MDR XDR	7(100%) 1(14%)	3(100%) 2(66%)

**IR indicates intrinsic resistance, NT indicates not tested and NA indicates not applicable.*

Discussion

The SBI tends to deteriorate clinical condition and increase mortality, morbidity, hospital stay, and costs of hospitalization in COVID-19 patients. The primary cause of mortality in COVID-19 patients is respiratory failure or multi-organ failure and SBIs have a vital role in this process. The incidence of SBIs (4.6%) was comparative low in our study compared to other studies conducted by Li *et al.* in Wuhan Union Hospital[2] and Huang C *et al.* in Jin Yin-tan Hospital Wuhan[4] in which reported incidence of SBIs was around 6.3% and 10%, respectively. Good infection control practices may be the reason for a lower incidence of SBI in our study.

COVID-19 pandemic has overburdened healthcare-associated system, especially ICUs. Mechanical ventilation is required in many COVID-19 patients due to severe pneumonia and acute respiratory distress syndrome. Low incidence of VAP was reported in our study 47(64%) than 80% reported by Luyt *et al.* [10]. Lower incidence of VAP in our study may be attributed to strict adherence to the VAP control bundle as described by Lim KP *et al.* [16] with particular emphasis on stringent hand hygiene, regular suctioning, maintaining good oral hygiene, prophylaxis of peptic ulcer and deep vein thrombosis. *Acinetobacter baumannii* was the most common etiological agent of VAP, accounting for about 32 (48%). Our findings were in contrast to the Luyt *et al.* study in which the leading pathogen of VAP were Enterobacteriaceae [10].

There is an increased risk of CRBSI in COVID-19 patients due to many reasons like escalated hospitalization, prolonged catheterization to administer treatment, and managed complications [17]. The incidence of CRBSI observed in our study was 15%, much lower than 25% observed in Bardi T *et al.* [6]. Strict implementation of CRBSI prevention bundle as described by O Grady N *et al.* [18] with particular emphasis on aseptic insertion, regular maintenance, and close observation of insertion site using transparent sponge dressings a measure to prevent infection may be the reason for lower incidence. *Klebsiella pneumoniae* accounting for 36%, was the leading pathogen of CRBSI in our study, which was in contrast to Bardi T *et al.*, which reported *Enterococcus faecium* as the leading pathogen accounting for about 43% [6].

CAUTI is a significant SBI in COVID-19 patients due to increased indwelling urinary catheter utilization and increased catheter days. Moreover, staff tend to minimize contact time with COVID-19 patients' further enhancing tendency to get device-related infections like CAUTI and CLABSI [19]. Our study's incidence of CAUTI was 11%, far less than 38.55% reported by Soriano MC *et al.* [20]. Strict adherence to CAUTI bundle [21] with a particular focus on appropriate use, aseptic insertion and maintenance, early removal, and hand hygiene were crucial factors that led to decreased CAUTI rates in our set up. *E. coli* (75%) was the leading pathogen of CAUTI in our study compared to *Enterococcus faecalis* (44%) reported by Bardi T *et al.* [6].

CDC reported that surgical site infections (SSIs) are the most common healthcare-associated infections comprising 46.4% of all infections[22]. SSI incidence rate in our study was 9% which was comparatively high than the 3.3% reported by Losurdo P *et al.* 13. The reason for this may be that our study population included COVID-19 positive patients who underwent emergency surgeries. This study generates an alarm, and strict implementation of SSI infection control bundle 23was implemented. *Staphylococcus aureus* accounting for 71%, was the leading pathogen of SSIs in our research, which was in contrast to a study conducted by Lubega A *et al*. in which *Klebsiella pneumoniae* was the leading pathogen accounting for 50%[23].

Currently, antimicrobial resistance is the greatest menace that has adverse effects on global health and the economy. The emergence of the COVID-19 pandemic is predicted to alarmingly accelerate AMR rates across the globe. During this global disaster, preventive measures against AMR should not be ignored[24]. High antimicrobial resistance was observed in our study. About 100% of isolated bacteria were MDR, and 66% were XDR. In line with our research, another study conducted by Ramadan HKA *et al.* also reported the MDR pattern of most isolated strains [30]. Our study showed that 91% of isolated *Acinetobacter baumannii* were CRAB, and 100% of isolated *Staphylococci* were MRSA. These findings were consistent with another study conducted by Li *et al.* [2]. Vancomycin resistance was elicited by 33% of isolated *Enterococci* in our research, which is in contrast to a study conducted by Ramadan HKA *et al*. in which all isolated Gram-positive cocci were sensitive to vancomycin [25].

Conclusion

Burden of secondary bacterial infections in COVID-19 patients was low in our set up accounting for about 4.6%. VAP was the most common SBI, followed by CRBSIs, CAUTI and SSIs, respectively. *Acinetobacter baumannii* was the most common etiological agent. High antimicrobial resistance was observed among isolated bacteria. Implementation of infection control bundles, robust leadership, training and accountability of health care workers will help in reducing the menace of SBIs. Diagnostic and antimicrobial stewardship principles should remain a hallmark in our clinical practice as antimicrobial resistance is the hidden threat behind the COVID-19 crises.

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Conflict of Interest:

None to be declared by any author.

References

26. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-513.
27. Li Jie, Wang J, Yang Y, Cai P, Cao J, Cai X et.al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrobial Res and Inf Con 2020; 9:153.
28. Noreen N, Siddiqui SW, Niazi SU, Khudaidad F, Khan NU, Dil Set.al. CoVID-19 outbreak in Pakistan; a situational analysis. J Emerg Dis and Virol.2020;2:1846-1853.
29. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Yi et.al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506
30. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
31. Bardi T, Pintado V, Roio MG, Sanchez RE, Lopez AA, Remesal YD. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis. 2021;3: 1-8.
32. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et.al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020;48(6): e440–69.
33. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: Interim guidance. 27-May-2020.

https://www.who.int/publications-detail/clinical-management-of-severe-acute- respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed May 27, 2020).
34. Fu Y, Yang Q, Xu M, Kong H, Chen H, Fu Y et.al. Secondary Bacterial Infections in Critical Ill PatientsWith Coronavirus Disease 2019. Open Forum Infect Dis.2020;7(6):ofaa 220.
35. Luyt CE, Sahnoun T, Gautier M, Vidal P, Burrel S, Chambrun MP, et.al. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann. Intensive Care. 2020; 10: 158. 11. Khanna V, Mukhopadhayay C, K.E V, Verma M, Dabke P. Evaluation of Central Venous Catheter Associated Blood Stream Infections: A Microbiological Observational Study. J of Path. 2013;https://doi.org/10.1155/2013/936864.
36. Sabir N, Ikram A, Zaman G, Satti L, Gardezi A et.al. Bacterial biofilm-based catheter-associated urinary tract infections: Causative pathogens and antibiotic resistance. AJIC. 2017;45(10):1101-1105.
37. Losurdo P, Paiano L, Samardzic N, Germani P, Borelli LB, Pozzetto B. Impact of lockdown for SARS-CoV-2 (COVID-19) on surgical site infection rates: a monocentric observational cohort study. Updates Surg. 2020; 14:1-9.
38. Clinical and Laboratory Standard Institute. Performance standards for antimicrobial susceptibility testing: twenty-ninth informational supplement (M100-S29). Wayne: Clinical and Laboratory Standard Institute; 2019.
39. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske LG, et al. Multi drug-resistant, extensively drug-resistant and pan drug resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(1): 268-81.
40. Lim KP, Kuo SW, Jeko W, Sheng WH, Chang YY, Hong MC, et.al. Efficacy of ventilator-associated pneumonia care bundle for prevention of ventilator-associated pneumonia in the surgical intensive care units of a medical center. J of Micro, Immun and Inf. 2015;48 (3): 316-321.
41. McMullen KM, Smith BA, Rehmann T. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: Predictions and early results. Am J Infect Control. 2020;48(11): 1409-1411.
42. Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et.al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9): e 162-e 193.
43. Knepper BC, Wallace K, Young H. CAUTI and CLABSI in hospitalized COVID-19 patients. Open Forum Infect Dis. 2020; 7(Suppl 1): S 178.
44. Soriano MC, Vaquero C, Fernandez AO, Caballero A, Ortiz AB. Low incidence of co-infection, but high incidence of ICU- acquired infections in critically ill patients with COVID-19. J of Infect. 2020:https://doi.org/10.1016/j.jinf.2020.09.010.
45. Davies PE, Daley MJ, Hobbs A, Burger C, Watkins L, Murray T, et.al. Effectiveness of a bundled approach to reduce urinary catheters and infection rates in trauma patients. AJIC.2018;46(7):758-763.
46. Hedenstierna G, Meyhoff CS, Perchiazzi G, Larsson A, Wetterslev J, Rasmussen LS. Modification of the World Health Organization global guidelines for prevention of surgical site infection is needed. Anesthesiology. 2019.131(4):765–768.
47. Lubega A, Joel B, Lucy NJ. Incidence and Etiology of Surgical site infections among emergency post-operative patients in Mbarara regional referral hospital, South west Ugenda. Surgery Res and Practice. 2017; 6365572: http://doi.org/10.1155/2017/6365172.
48. Murray A. K. The novel coronavirus covid-19 outbreak: global implications for antimicrobial resistance. Front. Microbiol. 2020; 11:1020. 10.3389/fmicb.2020.01020.
49. Ramadan HKA, Mahmoud MA, Aburahma MZ, Elkhawaga AA, El-Mokhtar MA, Sayed IM. Predictors of Severity and Co-Infection Resistance Profile in COVID-19 Patients: First Report from Upper Egypt. Infect and Drug Resistance. 2020; 13:3409-3422.

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