Original Article

Secondary bacterial infection in Adult Patients with COVID-19 in Iraq

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Abstract

Background Secondary bacterial and fungal infections were the leading causes of patient mortality and morbidity in Iraqi patients infected with COVID-19. Damage to the respiratory system was caused by a viral infection that occurred later.

Aim of the study: This research set out to identify the specific bacteria that tend to infect people who have contracted the COVID-19 virus.

Patients and methods: Adult male and female patients with a secondary bacterial infection were included in this study from isolation hospitals in Baghdad and Anbar province. Patients had sputum samples and blood drawn to check for Coronavirus infections; sputum samples were sent to VITEK2 for a bacteriological investigation, which included the cultivation and identification of secondary bacterial infections. Sputum RT-PCR for the detection of *Mycoplasma pneumonia*. concentrations of procalcitonin (PCT) in blood samples.

Results: The symptoms of lymphopenia and neutrophilia with other parameters were present in seventy-four (74) patients, both male and female. It was found that 51.60 % of the bacteria were Gram-positive and 23.15 % were Gram-negative. It was found that (15.78%) of the isolates were from fungi. One patient (1.05%) had a negative isolation result for mycoplasma pneumonia out of eight patients (8.42%) who tested positive.

Conclusion: *Staphylococcus aureus* was the most common bacteria found in our research, while *Enterobacter aerogenes* was the least. Our research showed that neutrophils and lymphocytes are inversely related.

Keywords: COVID-19,Age, sputum, bacterial infections, lymphopenia.

INTRODUCTION

In Iraq, COVID-19 has had a devastating impact on both morbidity and mortality rates. One of the leading causes of death in covid-19 is a bacterial infection of the lower respiratory tract, which leads to further damage to the respiratory system, a decline in pulmonary function, and a worsening of hypoxia, all of which has a domino effect on the rest of the body. This was especially challenging to control in Iraq, where multiple factors, such as the prevalence of hospital-acquired pneumonia, compounded the problem. Patients lead to secondary bacterial and or fungal infection. So the bacterial infection usually in these cases may be complicated by sepsis and multi-organ failure that may contribute directly to death. The type of bacterial infection may be typical or Atypical bacterial infection and sometimes mixed bacterial infection, or fungal infection may contribute to its cause. Some evidence suggests that the emergence of certain infections could be related to the spread of multidrug-resistant bacteria (1-3). Antimicrobial resistance in intensive care units (ICUs) is a worldwide issue, despite the success of infection control programs in many nations. Twenty-five to thirty percent of patients in ICUs have a lower respiratory tract (LRT) bacterial infection, with a correspondingly high rate of mortality (22-71%), morbidity, and mortality (4-7). Even in countries with strong infection control efforts, antimicrobial resistance is a global concern in intensive care units (ICUs). Twenty-five to thirty percent of intensive care unit (ICU) patients contract a lower respiratory tract (LRT) infection caused by resistant bacteria, resulting in high rates of mortality (22-71%), morbidity, and death (8). There was a higher incidence of deaths attributable to

COVID 19 among patients who had two or more chronic diseases compared to those who had no such diseases (9). Due to the effect of antibiotic use, the pattern of antibiotic resistance varies from one region to the next (10). Use of broad-spectrum antibiotics should be restricted to slow the rise of bacteria resistant to their effects (11). It is becoming more challenging to initiate appropriate empirical antibiotics prior to obtaining microbiological results due to the rise of ESBL-producing microbes, multidrug-resistant infections, MRSA, and other types of gram-negative bacilli (GNB). The Infectious Disease Society of America reports that *Escherichia coli*, *Klebsiella*, multidrug-resistant Pseudomonas, and carbapenem-resistant *Acinetobacter* species are the leading causes of death from infection in intensive care units (12). Elevated levels of infection biomarkers and inflammatory cytokines were found in patients with severe SARS-CoV-2 disease, suggesting that bacterial co-infection is the result of immune regulation (13). COVID-19 can cause carrier status, acute respiratory infection, severe pneumonia, and death in people who lack a functional immune system. Evidence of rapid transmission between people, most likely through nosocomial infection, is provided by clusters of cases in families and among healthcare workers (14). Patients with COVID-19 typically contract ventilator-associated pneumonia (VAP), which can be caused by a wide variety of bacteria and fungi (15-17). Patients in the intensive care unit have a co-infection rate between 13.5 and 44.5%. Superinfections in COVID-19 patients can be particularly challenging to manage in countries like India, where the high prevalence of multidrug-resistant organisms in intensive care unit (ICU) settings is well-established. If we're serious about lowering the number of times antibiotics are used when they aren't necessary, then we need to implement antibiotic stewardship programs that work. Elderly hospitalized patients with underlying systemic disorders are at a higher risk. An increased risk of infection is associated with immunosuppression, corticosteroid use, mechanical ventilation, and extended hospital and intensive care unit stay (18).

Patients and Methods:

Out of these thirty-six (36), seventy-four (74) covid-19 adult patients were enrolled in this study at two hospitals in the Baghdad Governorate. A total of 38 additional patients were being treated at the two hospitals in AL-Anbar Governorate (AL-Shifaa17 and Heet General Hospital). Patients' ages ran the gamut from (20-95) Everyone who has developed a respiratory infection or complication after COVID-19. Every patient had a sputum sample taken from them using a sterile cup and the WHO's protocol (2003). Patients with tracheostomies had sputum suctioned into a sterile container before being sent to the lab for bacterial analysis. The sputum was cultured on media by the streaking method. Bacteria growth was monitored on blood agar, MacConkey agar, and chocolate agar plates in an aerobic 37°C incubator at regular intervals for 48 hours. The sputum RT-PCR test is used to diagnose *Mycoplasma pneumonia*. We took one colony and used its unique physical traits to tell it apart from the rest. Gram stain and Vitek2 system bacteriological analysis was performed. The data was analyzed, and charts were made using (SPSS) version 26.0.

Result

The most common bacteria isolated were *Staphylococcus aureus* (24), followed by *Klebsiella pneumonia* (15), S*treptococcus pneumonia* (14), *Candida albicans* (15), and *Mycoplasma pneumonia* (8). The sum of the other organisms was negligible; it ranged from (1-4). Figure (1) .

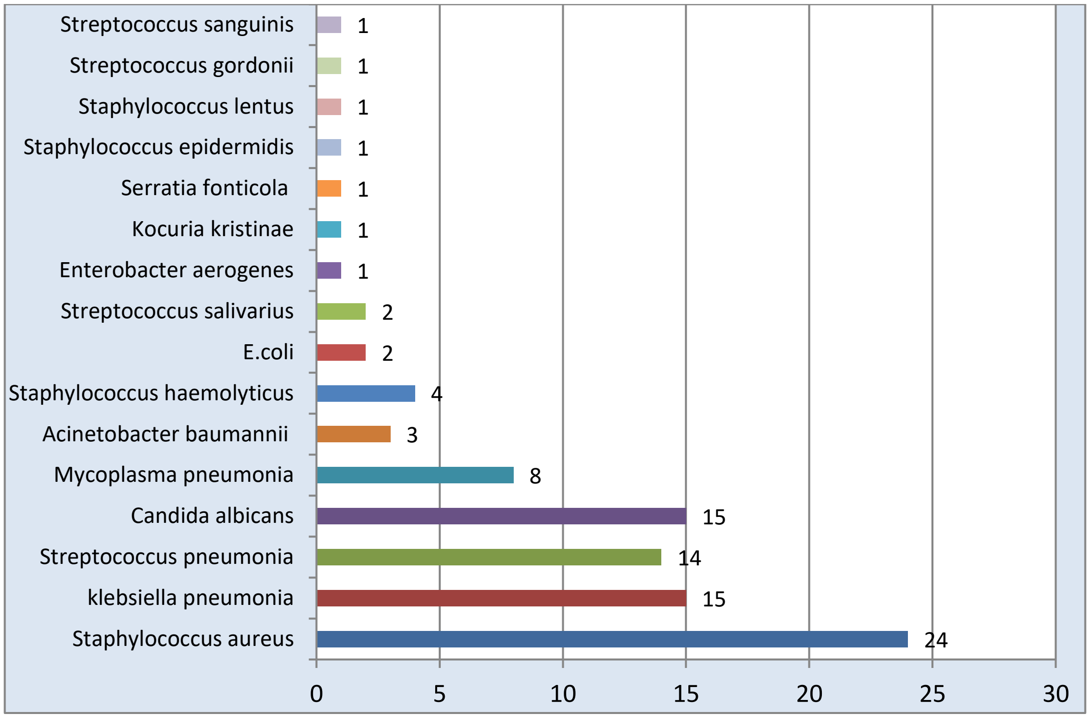

Figure (1): Microorganisms type isolates from patient with covid -19

NUT and LYM are negatively correlated at a significant level (0.01), whereas the other variables are not significantly correlated at this level (0.01). Table(1).

Table(1) : Analyzing the Correlations Between White Blood Cell, Lymphocyte, Neutrophil, C-Reactive Protein, Procalcitonin, and D-Dimer Levels and Age

		WBC	LYM %	NUT %	CRP/mg/L	PCT/ng/L	D dimer ng/mL	AGE
WBC	Pearson Correlation	1	-.112	.191	-.160	.120	.108	-.142
	Sig. (2-tailed)		.332	.092	.170	.302	.352	.214
	N	74	74	74	74	74	74	74
LYM %	Pearson Correlation	-.112	1	**-.710-** **	-.070	-.043	-.120	.005
	Sig. (2-tailed)	.331		**.000**	.541	.710	.302	.960
	N	74	74	74	74	74	74	74
NUT %	Pearson Correlation	.194	**-.720-** **	1	.098	-.063	.052	-.009
	Sig. (2-tailed)	.092	**.000**		.402	.591	.660	.931
	N	74	74	74	74	74	74	74
CRP/mg/L	Pearson Correlation	-.161	-.071	.098	1	-.084	.048	-.006
	Sig. (2-tailed)	.170	.548	.405		.479	.683	.957
	N	74	74	74	74	74	74	74
PCT/ng/L	Pearson Correlation	.120	-.044	-.063	-.084	1	-.124	-.057
	Sig. (2-	.308	.712	.596	.479		.294	.631

	tailed)							
	N	74	74	74	74	74	74	74
D dimer ng/mL	Pearson Correlation	.109	-.121	.052	.048	-.124	1	.136
	Sig. (2-tailed)	.357	.306	.661	.683	.294		.247
	N	74	74	74	74	74	74	74
AGE	Pearson Correlation	-.146	.005	-.009	-.006	-.057	.136	1
	Sig. (2-tailed)	.216	.968	.939	.957	.631	.247	
	N	74	74	74	74	74	74	74

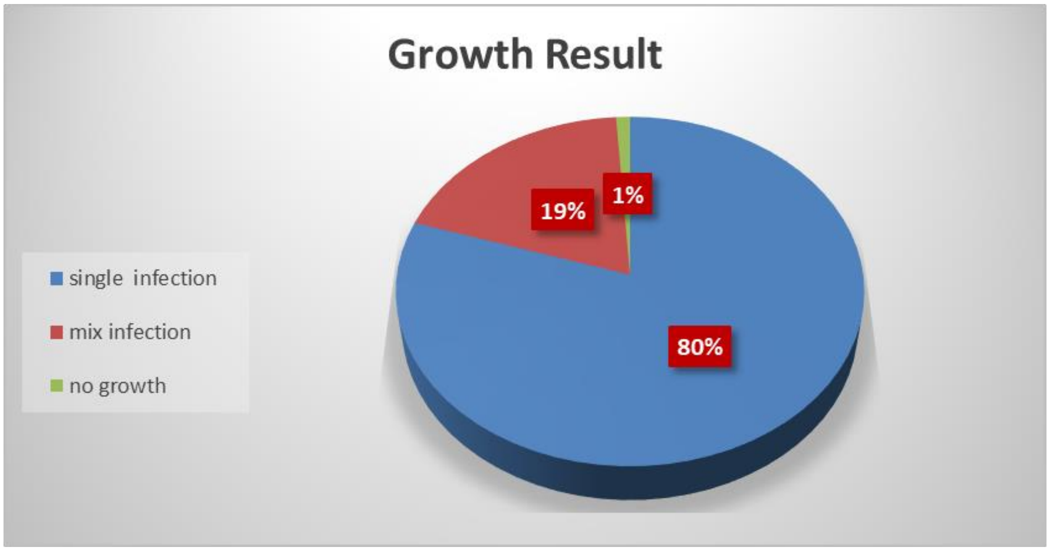

Figure 2 – Growth results representing the number of bacterial isolates

In terms of infections, out of a total of (95) bacterial isolates, 80% were from single bacterial types, 19% were from a combination of two or more bacterial isolates, and 1% showed no growth.

Discussion

This study found that patients between the ages of 46 and 70 had a significantly higher prevalence of infection (39.52%) than those younger or older than this age range. This finding may be explained by the fact that patients in this age range are more likely to have other predisposing diseases, such as diabetes mellitus, hypertension, liver dysfunction, or kidney failure. The research was conducted in the United States (Liu HH et al., 2021) (19). People between the ages of 56 and 80 had the highest infection rate (43%). In contrast to the findings of a study conducted in Italy, this one found the opposite (20). Patients older than 70 were more likely to contract infections and die overall. Although a previous study in Spain (21) found that most infections occurred in people younger than 50, the current study finds the opposite to be true. Patients younger than 50 years old had a significantly higher infection rate. *Staphylococcus aureus* was the most commonly isolated bacterium (52%), while Gram-positive bacteria accounted for 77%, similar to the findings of an earlier study (Ameen et al 2021). (22). Results from a study conducted on COVID-19 patients in Kirkuk showed that 31.3% of sputum samples tested positive for bacteria, with *Staphylococcus aureus* being the most isolated species. This is due to the fact that the bacteria's inherent pathogenicity factors gave it an upper hand in its battle against the host tissues (23). A study found that multidrug-resistant ESKAPE bacterial pathogens were primarily responsible for the initial co-infection of hospitalized COVID-19 patients (Cataldo MA et al,2020). The widespread presence of COVID-19 bacterial co-infections has been demonstrated by numerous studies in Iraq and elsewhere. *Staphylococcus aureus* was found to be the most common bacterium isolated in Diwaniyha (85%), followed by *Pseudomonas aeruginosa* (78%), *Streptococcus pneumonia* (60%), *Acinetobacter baumannii* (64%), and *Legionella pneumophilia* (60%), and a few types of fungi. Outcomes of (Zhu et al 2020). Among a group of 25 patients, *Klebsiella* *pneumonia* was the second most common bacterium isolated (after *Streptococcus pneumonia*). When compared to the results of another study, our rate of *Candida albicans* isolation of 16% is lower (Arestehfar et al., 2019). (26). According to a study conducted in Izmir, Turkey, 28% of patients were able to successfully isolate *Candida albicans*. Another point of contention is that the findings contradict those of (Retaini et al., 2020). (27). The most common COVID-19 isolate in Georgia was found in 54% of patients, followed by *Klebsiella pneumonia* (15%) and *Escherichia coli* (8%). Mycotic co-infections during the COVID-19 disease course can be explained by immune-comptonization of patients due to corticosteroid therapy, in addition to other predisposing factors like diabetes mellitus and extended hospital stays as a quarantine measure. A high rate of Staphylococcus aureus isolation in this study can be attributed to the pathogenicity factors possessed by this organism, such as Protein A and coagulase enzyme, as well as the antibiotic resistance factors in some strains, especially resistance to beta-lactams and Methicillin in the MIRSA group of *Staphylococcus aureus*. 15–20% of the population routinely carries *Staphylococcus aureus*, making co-infection with this bacterium extremely common in COVID-19 patients (Stefan et al 2019). Because the bacteria's inherent pathogenicity factors gave it an advantage over the host tissues, this occurred (23). Nevertheless, in Georgia, E. *Escherichia coli* (8%) and other bacteria (54% combined) were discovered to be the most prevalent pathogens. *Klebsiella pneumonia* was the most prevalent pathogen among COVID-19 patients, according to our research. Mycotic co-infections can be explained by the immune-comptonization of patients through corticosteroid therapy during the COVID-19 disease course, in addition to other predisposing factors such as diabetes mellitus and lengthy hospital stays as a quarantine measure. Due to the presence of pathogenicity factors such as Protein A and coagulase enzyme, some strains of *Staphylococcus aureus* are resistant to antibiotics, and the MIRSA group of *Staphylococcus aureus* is resistant to beta-lactams and Methicillin. Considering that 15–20% of the general population is chronically infected with *Staphylococcus aureus*, it is not surprising that people with COVID-19 frequently experience co-infection with this bacterium (23). Infections acquired in hospitals were the most common type treated via telemedicine's 716 patient caseload. Researchers in Anbar province found that patients with mild to moderate cases of covid-19 who utilized telemedicine health services had a lower risk of dying. (28). The mortality rate of patients treated outside the traditional healthcare system has been shown to be lower (29). Results showed that *Mycoplasma pneumonia* was present in 8% of sputum samples from COVID-19 patients, making it the most common cause of pneumonia in the general population. The immune complexification seen in COVID-19 patients treated with corticosteroids may be the result of patient stress during infection. Eighteen percent to twenty-four percent of 74 COVID-19 patients had mixed bacterial infection, as evidenced by the isolation of two or more microorganisms from their specimens. To the contrary, Tang (2021) found that only about 6% of bacterial infections were caused by a single organism (30). Results from sputum cultures showed a mixed infection type in 8.7% of 165 patients in one study (Liu HH et al, 2021). (19). We hypothesize that the lung tissue damage caused by COVID-19 infection makes the host more vulnerable to secondary infections brought on by opportunistic bacteria, a weakened immune system, and other factors. Procalcitonin appears to be a useful diagnostic marker for identifying COVID-19 patients at risk of severe disease at the time of ER presentation (31). Clinically, PCT is often used to diagnose systemic bacterial infections, and it has been hypothesized that PCT is a biomarker of secondary bacterial infection in COVID-19 (32). Thyroid C-cells and other cells (like monocytes) produce the precursor polypeptide calcitonin (PCT). Enhanced production occurs in the presence of bacterial infection, lipopolysaccharides, and cytokines (LPS). Diseases caused by viruses did not see an uptick (33). Antibiotic treatment for patients with VAP who take the procalcitonin test can be shortened (34). The onset of respiratory symptoms and the visibility of interstitial lung infiltrates on chest imaging mark the progression from the viremic to the hyperinflammatory stage of COVID-19, also known as a "cytokine storm" (35). Results from a study by Li et al. (2020) suggest that a rise in PCT may be a marker of the "viral sepsis" condition or the COVID-19 cytokine storm (36) Multiple meta-analyses have reached the same conclusion: an elevated PCT is a biomarker associated with mortality, the need for mechanical ventilation, and the development of COVID-19 from mild to severe and critical (37, 38). The upregulation of IL-1, IL-6, and TNF- in response to bacterial infection all aid in keeping the PCT elevated. Viral infection causes an increase in interferon (IFN) levels, which in turn blocks PCT production (39). Patients with COVID-19 admitted to the hospital have an absolute CRP concentration and a trajectory during the first week of admission that are both significant factors in predicting microbiology culture positivity and prognosis. Results showed that fluctuating CRP levels predicted microbiological and survival outcomes for COVID-19 in the patient population studied. It is possible that a standardized approach to optimizing COVID-19 antimicrobial management could be established by combining these results with stewardship input and rapid diagnostics (40). This study showed that procalcitonin was not a reliable indicator of positive microbiological investigations in COVID-19 patients hospitalized with a suspected bacterial coinfection. Extreme viral diseases are often accompanied by elevated levels of IL-6, which may make procalcitonin an unreliable indicator of bacterial infection. For doctors to know whether or not to give a patient an antibiotic, and for patients to know whether or not they have a bacterial infection, microbiological test results are still required (41). Rebounding PCT and CRP levels after dexamethasone withdrawal in critically ill COVID-19 patients are unrelated to the development of new bacterial infections. Furthermore, PCT and CRP may be significantly less useful for detecting secondary infections in COVID-19 patients who are treated with immunomodulatory drugs like dexamethasone and tocilizumab (42). Research shows that secondary bacterial infection is present in 50% of COVID-19 patients with elevated procalcitonin levels, while the other 50% have normal results. This suggests that the absence of sepsis in the control group may have resulted in a procalcitonin level close to that seen in healthy individuals. Sputum culture is still the best method for diagnosing bacterial co-infection in the lower respiratory tract, despite improvements in antibiotic and dexamethasone treatment that decreases the level of interleukin IL-6 that can induce PCT.

Conclusions:

The majority of the Gram-positive bacteria found in the study were Staphylococcus, with 26 out of 52 isolates being of this species. *Staphylococcus aureus* made up twenty-four of the isolates, while *Staphylococcus epidermidis* and *Staphylococcus lentus* each contributed one. Of the 23 Gram-negative bacteria isolated, 14 were *Klebsiella pneumonia*. Sputum samples from the COVID-19 patients studied yielded an isolation rate of (16%) for the mycotoxin *Candida albicans*. The prediction of secondary pyogenic or fungal infection in patients with significant lymphopenia despite aggressive COVID-19 management is not feasible. According to these criteria. Leukocytosis, neutrophilia, and elevated CRP titer and procalcitonin (PCT) were observed in both Gram-positive and -negative bacteria, but no significant differences were found between the two bacterial types. Results showed that PCT was elevated in 50% of patients, suggesting that procalcitonin may be linked to cytokine storm in COVID-19. Twenty-four percent of our patients had a commingled infection.

Ethical issues: Final approval to conduct the study was granted by the Research and Ethics Committee at Anbar University/Iraq, Scientific Research. dated 3-15-2022 per reference number 13.

Limitations: Bacterial subtypes associated with COVID-19 pneumonia are characterized in this study. For this reason, we did not investigate anaerobic bacteria in lung infection. For anaerobic bacterial infection, we suggest conducting additional research.

Declaration of Conflicting Interests: The authors declared no potential conflicts of interest.

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REFERENCES

1. Bengoechea JA, Bamford CG. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO molecular medicine. 2020;12(7):e12560.
2. Hendaus MA, Jomha FA. Covid-19 induced superimposed bacterial infection. Journal of Biomolecular Structure and Dynamics. 2021;39(11):4185-91.
3. Rawson TM, Moore LS, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clinical Infectious Diseases. 2020;71(9):2459-68.
4. Vincent J-L, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin M-H, et al. The Prevalence of Nosocomial Infection in Intensive Care Units in Europe: Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA. 1995;274(8):639-44.
5. Chastre J, Fagon J-Y. Ventilator-associated pneumonia. American journal of respiratory and critical care medicine. 2002;165(7):867-903.
6. Radji M, Fauziah S, Aribinuko N. Antibiotic sensitivity pattern of bacterial pathogens in the intensive care unit of Fatmawati Hospital, Indonesia. Asian Pacific journal of tropical biomedicine. 2011;1(1):39-42.
7. Patel Bhaumik V, Patel Purav G, Raval Payal N, Patel Mitesh H, Patel Piyush H, Vegad Mahendra M. Bacteriological profile and antibiogram of gram negative organisms isolated from medical and neurology intensive care unit with special reference to multi-drug resistant organisms. Nat J Med Res. 2012;2(3):335-38.
8. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. Critical care medicine. 2001;29(4):N64-N8.
9. Al-Ani A, Ghazzay HI, Al Shawi AF, Al-koubaisy HNE, Al-Ani F, Aldouri M. Association of chronic diseases with mortality among hospitalized patients with COVID-19 treated with convalescent plasma: Evidence from a single center–Iraq. Journal of Emergency Medicine, Trauma and Acute Care. 2022;2022(2):13.
10. Shehabi AA, Baadran L. Microbial infection and antibiotic resistance patterns among Jordanian intensive care patients. EMHJ-Eastern Mediterranean Health Journal, 2 (3), 515-520, 1996. 1996.
11. Tullu M, Deshmukh C, Baveja S. Bacterial profile and antimicrobial susceptibility pattern in catheter related nosocomial infections. Journal of Postgraduate Medicine. 1998;44(1):7.
12. Talbot GH, Bradley J, Edwards JE, Gilbert D, Scheld M, Bartlett JG. Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clinical Infectious Diseases. 2006;42(5):657-68.
13. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest. 2020;158(1):e9-e13.
14. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The lancet. 2020;395(10223):514-23.
15. Jose M, Desai K. Fatal superimposed bacterial sepsis in a healthy coronavirus (COVID-19) patient. Cureus. 2020;12(5).
16. Savannah F, Pedersen S, Ho Y. SARS-CoV-2: A storm is raging. J Clin Invest. 2020;130:2202.
17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.

18. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. bmj. 2020;368.
19. Liu HH, Yaron D, Piraino AS, Kapelusznik L. Bacterial and fungal growth in sputum cultures from 165 COVID-19 pneumonia patients requiring intubation: evidence for antimicrobial resistance development and analysis of risk factors. Annals of Clinical Microbiology and Antimicrobials. 2021;20(1):1-13.
20. Jalil AT. COVID-19 most affected age groups and lethality in Europe. Global Journal of Public Health Medicine (GJPHM). 2020;2(Special Issue):179-84.
21. Ouassou H, Kharchoufa L, Bouhrim M, Daoudi NE, Imtara H, Bencheikh N, et al. The pathogenesis of coronavirus disease 2019 (COVID-19): evaluation and prevention. Journal of immunology research. 2020;2020.
22. Ameen HM, Mahdi NB, Eldin AMK. Investigation of secondary Bacterial lung Infections associated with Corona virus COVID-19, and the extent of their Resistance to some types of Antibiotics in the city of Kirkuk. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO. 2021:9153-61.
23. Riedel S, Morse SA, Mietzner TA, Miller S. Jawetz Melnick & Adelbergs Medical Microbiology 28 E: McGraw Hill Professional; 2019.
24. Mahdi Jabir D. Bacterial Infections associated with COVID-19 and the effect of using many common antibiotics in the treatment these infections. Iranian Journal of Medical Microbiology. 2022;16(4):11-.
25. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus research. 2020;285:198005.
26. Arastehfar A, Ünal N, Hoşbul T, Alper Özarslan M, Sultan Karakoyun A, Polat F, et al., editors. Candidemia among Coronavirus Disease 2019 patients in Turkey admitted to intensive care units: a retrospective multicenter study. Open forum infectious diseases; 2022: Oxford University Press US.
27. Ratiani L, Machavariani K, Didbaridze T, Maziashvili G. Microbiological examination of lower respiratory tract specimens in COVID-19 patients. 2020.
28. Jasim MA, Ghazzay H, Noaman H, Khalil M, Johna S. The outcome of telemedicine services for COVID-19 patients in “Al-Anbar” province west of Iraq. Journal of Emergency Medicine, Trauma and Acute Care. 2021;2021(3):16.
29. Noaman H, Ghazzay H, Ali M, Maseer K, Faeq A, Ibrahim H, et al. Electronic Clinic in COVID-19: Benefit to Reduce Mortality in the Community. Frontiers. 2022;2(3):113-5.
30. Tang H, Zhao Z, Zhang X, Pan L, Wu Q, Wang M, et al. Analysis of pathogens and risk factors of secondary pulmonary infection in patients with COVID-19. Microbial Pathogenesis. 2021;156:104903.
31. Kaal A, Snel L, Dane M, van Burgel N, Ottens T, Broekman W, et al. Diagnostic yield of bacteriological tests and predictors of severe outcome in adult patients with COVID-19 presenting to the emergency department. Emergency Medicine Journal. 2021;38(9):685-91.
32. Vazzana N, Dipaola F, Ognibene S. Procalcitonin and secondary bacterial infections in COVID-19: association with disease severity and outcomes. Acta Clinica Belgica. 2022;77(2):268-72.
33. Anand D, Das S, Ray S, Bhargava S, Srivastava LM. Interrelationship between procalcitonin and organ failure in sepsis. Indian Journal of Clinical Biochemistry. 2014;29(1):93-6.
34. Mazlan MZ, Ismail MA, Ali S, Salmuna ZN, Shukeri WFWM, Omar M. Efficacy and safety of the point-of-care procalcitonin test for determining the antibiotic treatment duration in patients with ventilator-associated pneumonia in the intensive care unit: a randomised controlled trial. Anaesthesiology Intensive Therapy. 2021;53(3):207-14.
35. Fajgenbaum DC, June CH. Cytokine Storm. Reply. N Engl J Med. 2021:e59-e.
36. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;395(10235):1517-20.
37. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19 patients: a review of multiple biomarkers. Archives of pathology & laboratory medicine. 2020;144(12):1465-74.
38. Xu L, Mao Y, Chen G. Risk factors for 2019 novel coronavirus disease (COVID-19) patients progressing to critical illness: a systematic review and meta-analysis. Aging (Albany NY). 2020;12(12):12410.
39. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Clinica chimica acta; international journal of clinical chemistry. 2020;505:190.
40. Ming DK, Myall AC, Hernandez B, Weiße AY, Peach RL, Barahona M, et al. Informing antimicrobial management in the context of COVID-19: understanding the longitudinal dynamics of C-reactive protein and procalcitonin. BMC infectious diseases. 2021;21(1):1-7.
41. Relph KA, Russell CD, Fairfield CJ, Turtle L, de Silva TI, Siggins MK, et al., editors. Procalcitonin is not a reliable biomarker of bacterial coinfection in people with coronavirus disease 2019 undergoing microbiological investigation at the time of hospital admission. Open forum infectious diseases; 2022: Oxford University Press US.
42. Kooistra EJ, van Berkel M, van Kempen NF, van Latum CR, Bruse N, Frenzel T, et al. Dexamethasone and tocilizumab treatment considerably reduces the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. Critical Care. 2021;25(1):1-12.