Masterthesis

Assessing Candida species respiratory colonization in ventilated COVID-19 patients: a retrospective cohort study with a focus on corticosteroid impact

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Abstract

Background: **Managing mechanically ventilated patients in intensive care units (ICU) during the Coronavirus Disease 2019 (COVID-19) pandemic poses several multidimensional challenges. Among these, the occurrence of fungal and bacterial co-infections is detrimental to patient outcomes and creates significant diagnostic and therapeutic challenges. As insights grew, dexamethasone (DXM) administration became a standard part of the treatment strategy. Given the immunosuppressive effects of corticosteroids administered to an already vulnerable population, questions have arisen regarding the their possible impact of corticosteroids on the incidence of colonization of the respiratory tract by Candida species fungal co-infections.**

Objective: The current study aimed to assess the differences in morbidity and mortality between patients with and without evidence of respiratory tract Candida species colonization This study aimed to assess whether respiratory tract colonization by Candida species influences morbidity and mortality in ventilated COVID-19 ICU patients. Furthermore, as a secondary objective, we attempted to determine whether the addition of DXM was associated with an increased incidence of Candida species colonization and whether DXM treatment contributed to differences in outcome. had any detrimental effect on the incidence of complications, considering that patients were often colonized with Candida species, possibly selected under antimicrobial pressure.

Methods: **This single-center retrospective cohort study analyzed data from Polymerase Chain Reaction (PCR) confirmed COVID-19 patients receiving who required invasive ventilatory support in our ICU from March 2020 to January 2022. Patients were grouped based on the presence or absence of respiratory Candida species colonization. Clinical outcomes such as mortality, ICU length of stay (LOS) and ICU length of ventilation (LOV) were compared. In a secondary analysis, patients were grouped according to DXM exposure to explore the potential association between colonization and clinical parameters. were divided into DXM and non-DXM groups to compare the occurrence of respiratory colonization by Candida species (diagnosed through tracheal aspirates and bronchoalveolar lavage (BAL) fluid samples). In addition to DXM use, we investigated other possible confounding factors in the development of respiratory colonization by Candida species by creating two additional groups: patients displaying Candida species respiratory colonization and those without. The study was approved by the Institutional Ethics Committee of AZ Sint Blasius, Dendermonde.**

Results: **We included 59 patients: 38 received DXM treatment and 21 did not. Forty-three patients (73%) had positive respiratory Candida species culture results. No statistically significant difference reduction in mortality rate was observed between colonized and non-colonized ventilated COVID-19 patients. outcome in ventilated COVID-19 patients with respiratory tract Candida species colonization was revealed compared to those without. However, Candida species-colonized patients had a significantly longer ICU LOS and LOV. Respiratory Candida colonization was more frequent in the DXM group (83%) than in the non-DXM group (74%); however, this difference was not statistically significant. An increase in colonization did not translate into worse outcomes. Once DXM became the standard treatment, we only noted a non-significant increase in patients displaying signs of respiratory tract colonization. However, this did not translate into worse outcomes.**

Conclusion: In this retrospective cohort study of ventilated COVID-19 patients, respiratory Candida species colonization was not associated with increased mortality but was linked to prolonged ICU stay and mechanical ventilation. DXM treatment did not exacerbate the pathogenic behavior of Candida species or negatively impact the outcomes. in a niche field of medicine lacks sufficient power to reveal pronounced correlations. We demonstrated little difference in outcomes for patients who showed signs of Candida species respiratory tract colonization compared to those without. Notably, we did not register a single event where respiratory tract colonization led to invasive infection, indicating that this phenomenon remains benign in COVID-19. Moreover, the addition of DXM to the treatment did not intensify the pathogenic behavior of these Candida species. Further research on fungal co-infections is recommended.

Keywords: **COVID-19, Dexamethasone, Candida, Respiratory Tract Infections, Mechanical Ventilation.**

Introduction

The Coronavirus Disease 2019 (COVID-19) global pandemic has proven to be costly in terms of resources, lives lost, and physical and mental strain on healthcare professionals. In response, extensive research has been conducted to provide optimal treatment for COVID-19 patients at home, in hospitals, or intensive care units (ICU). Numerous studies have provided information on both bacterial and fungal co-infections in severely ill COVID-19 patients[1–10], as these contribute to increased mortality rates[6]. An impaired immune response to Candida species has been described in COVID-19 patients[5], and a possible link to corticosteroid treatment has already been proposed[11]. However, autopsy data[8,9] show that Candida pneumonia is considered a rare affliction in non-COVID ICU patients.

Studies have shown that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) dysregulates the immune system[12,13]. It affects innate and adaptive immune responses and triggers what is commonly called a "cytokine storm." This ongoing activation of the innate pathways may lead to hyperinflammation, which in turn damages the lung epithelium[1,14–16]. Moser et al. provided evidence of a disturbed immune response to Candida albicans owing to COVID-19[5]. To suppress this dysregulated immune system, the use of immunosuppressive drugs, such as corticosteroids, calcineurin inhibitors, anti tumor necrosing factor-α agents, and interleukin-6 inhibitors like tocilizumab, increased during the COVID-19 pandemic[17].

Corticosteroids are powerful anti-inflammatory drugs18 that were widely used in different doses during the COVID-19 pandemic[19]. They may limit the risk of respiratory complications, such as acute lung injury and acute respiratory distress syndrome, in viral pneumonia and may be associated with better outcomes in COVID-19 patients[20–25]. In contrast, several studies have demonstrated that corticosteroid use in COVID-19 ICU patients may negatively impact outcomes[26,27] by altering the respiratory tract's bacterial and fungal microbiome owing to immunosuppressive effects. Therefore, the risk-benefit relationship of using corticosteroids in COVID-19 patients should be thoroughly assessed.

This single-center retrospective study investigated the occurrence of Candida species-positive respiratory tract cultures in a cohort of invasively ventilated COVID-19 patients in the ICU. The primary outcome was whether respiratory tract colonization by Candida species influenced patient outcomes including mortality, length of ICU stay (LOS), and length of artificial ventilation (LOV). Second, because dexamethasone (DXM) was introduced as a standard treatment during our study period, we aimed to explore whether its administration might act as a confounding factor in the development of respiratory tract colonization by Candida species and whether these patients would experience worse outcomes. To address these objectives, we first compared patients with proven respiratory Candida species colonization to those without, to evaluate outcome differences and explore potential associations. We then compared two main patient cohorts (those who received DXM and those who did not) to assess whether DXM use influenced the risk of colonization and to identify other relevant clinical differences.

We predicted that a positive correlation might exist between DXM use and respiratory colonization by Candida species, owing to the immunosuppressive properties of DXM combined with impaired immune system functioning caused by COVID-19.

Methods

Study design and population

This retrospective single-center study includes data from all confirmed COVID-19 patients who required mechanical ventilation and were admitted to the ICU of a teaching hospital in Dendermonde, Belgium. The study inclusion period was from March 2020 to January 2022. The study is reported

based on the STROBE guidelines, as indicated by von Elm et al.[28] (shown in the supplement file (STROBE checklist)).

Inclusion and exclusion criteria

Patients were included upon confirmation of the diagnosis of COVID-19 through polymerase chain reaction (PCR) testing on either a tracheal aspirate or nasopharyngeal swab coupled with thoracic radiological imaging (X-ray or computed tomography (CT)) and a requirement for mechanical ventilation. Due to the absence of a pediatric ICU, only adult patients were included. Patients with COVID-19 who required ICU care without mechanical ventilation were excluded. Patients with incomplete or missing data, those lost to follow-up (e.g., due to transfer to another hospital), and those (or represented by their relatives) who opted out of participation were also excluded.

Ethical approval and informed consent

The study protocol was approved by the institutional ethics committee of az Sint Blasius, Dendermonde (chairperson: Dr. S. Serry) in May 2021 with study number 502479 and Belgian national registration number B0122021000003. As per the committee's request, a notation was made to the electronic medical records of each study participant. Patients or, when applicable, their relatives were allowed to opt out of the study through informed consent.

Data collection

To determine whether respiratory colonization by Candida species constituted additional morbidity and mortality in these vulnerable ventilated patients, two groups were compared to search for differing outcome patterns. We plotted invasively ventilated COVID-19 patients with confirmed Candida species-positive respiratory samples (Candida group) against those whose respiratory tract samples did not show Candida species-positive cultures during routine screening (No-Candida group). Additionally, classic risk factors for pulmonary fungal superinfections were considered[29], as we compared age, sex, Simplified Acute Physiology Score (SAPS II), length of artificial ventilation (LOV), length of stay (LOS), prevalence of Chronic Obstructive Pulmonary Disease (COPD)/asthma, prevalence of Diabetes Mellitus (DM), differences in Body Mass Index (BMI), chronic corticosteroid use and ICU-mortality (Tables I and II). Respiratory colonization by Candida species was determined using respiratory samples, including tracheal aspirates and bronchoalveolar lavage fluid (BAL) samples. The cultures of these samples were processed using COPAN WASP® (Walk-away Specimen Processor) on Chocolate Agar, ANC agar, MSA, MacConkey, and Sabouraud medium. Moreover, two more groups of patients were defined based on DXM treatment. Patients admitted before October 2020, who did not receive standardized DXM treatment, were classified into the non-DXM group. Patients admitted after October 2020 who received standardized DXM treatment consisting of an equivalent of 6 mg of enteral DXM formed the DXM group.

Study outcomes

The primary outcome was the effect of respiratory Candida species colonization in ventilated COVID-19 patients on mortality and other outcome parameters, namely, ICU LOS and LOV. The secondary outcome was to explore whether the administration of DXM might act as a confounding factor in the development of respiratory tract colonization by Candida species and whether these patients would experience a worse outcome. Moreover, differences and other potential confounding factors between the no-DXM and DXM groups and between the Candida and No-Candida groups were also examined.

Statistical analysis

Normality of the data was assessed using the Shapiro-Wilk test. For normally distributed data, Student's t-test was used. The Mann-Whitney U test was used for non-normally distributed data. Where appropriate, the median and interquartile range (IQR) were reported.

Binary data were compared using the chi-squared test.

Statistical tests were performed using free online software (Excel; Statistics Kingdom, https://www.statskingdom.com; Calculator Soup, https://www.calculatorsoup.com; Open Source Statistics for Public Health, https://www.openepi.com/TwobyTwo/TwobyTwo.htm). Statistical significance was set at $P < 0.05$.

Results

Study population

From March 2020 to January 2022, 59 patients were included (Figure 1, Table I), with a median age of 70 years (interquartile range (IQR 62-76), of which 68% were male. Twenty-one patients did not receive standardized DXM treatment (non-DXM group, 36%), and 38 patients were treated using standardized DXM (DXM group, 64%). Five patients in the early group received another form of corticosteroid (methylprednisolone) during their hospitalization in the ICU, usually in the

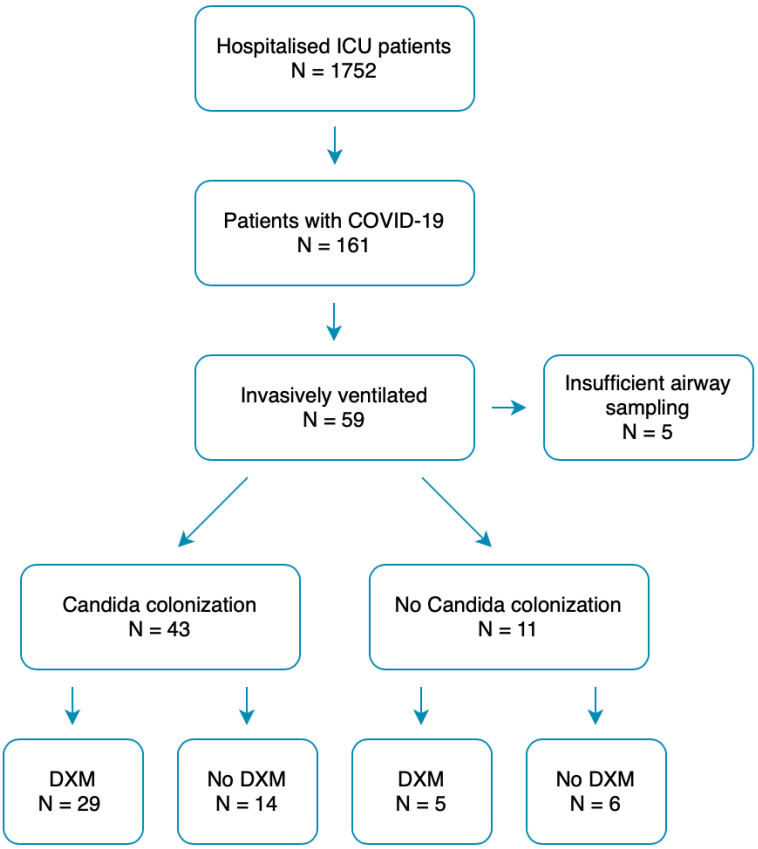

Fig. 1 — Flowchart of patient selection.

Table I. — Clinical data of overall patient population.
y = years, d = days, IQR = interquartile range.

Variable	Study population (n=59)
Age – y (IQR)	70 (62–76)
Male Sex (%)	40 (68)
SAPS II (IQR)	30 (24–38)
ICU Length of Ventilation – d (IQR)	10 (6–19)
ICU Length of Stay – d (IQR)	13 (8–26)
COPD / Asthma (%)	8 (13.6)
Diabetes Mellitus (%)	13 (22)
Body Mass Index (IQR) *	21.5 (5–29)
Corticoid use (%)	1 (1.7)
Dexamethasone treatment (%)	38 (64)
Candida species-positive samples (%) **	43 (73)
Mortality (%)	33 (56)

* No precise body weight could be determined from 8 patients at admission.
** No Candida sampling was performed in 5 patients.
BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; ICU = Intensive Care Unit; IQR = Interquartile Range; SAPS II = Simplified Acute Physiology Score II; y = years; d = days.

very late stages of ARDS. Of all the participants, forty-three patients (73%) had positive Candida cultures, whereas 11 (19%) had negative cultures. Three patients in the DXM group and two patients in the non-DXM group did not receive Candida sampling (8%). We included these patients in the overall cohort (Table I) for demographic context and to provide a more comprehensive overview of our ICU patient population, but excluded them from the subgroup analyses (DXM vs. Non-DXM and Candida vs. No Candida).

Of the 51 positive Candida cultures, 65% were C. albicans, 15% C. tropicalis, 14% C. glabrata, 4% C. dubliensis, and 2% were C. parapsilosis.

Table II. — Clinical data of patients who were diagnosed with Candida species respiratory tract colonization (Candida) and those who were not (No Candida). Statistical significance: P < 0.05. y = years, d = days, IQR = interquartile range.

Variable	Candida (n=43)	No Candida (n=11)	P-value
Age – y (IQR)	70 (63–77)	64 (42–76)	0.10
Male Sex (%)	27 (63)	9 (82)	0.23
SAPS II (IQR)	30 (23–40)	32 (25–37)	0.64
ICU Length of Ventilation – d (IQR)	14 (7–21)	6 (4–11)	0.01
ICU Length of Stay – d (IQR)	18 (12–30)	8 (7–11)	0.001
COPD / Asthma (%)	7 (16)	1 (9)	0.55
Diabetes Mellitus (%)	10 (23)	1 (9)	0.30
Body Mass Index (IQR) *	27.8 (25.9–32.2)	32.4 (26.7–35.5)	0.32
Corticoid use (%)	0 (0)	0 (0)	NA
Mortality (%)	25 (59)	6 (55)	0.83

* No precise body weight could be determined from 8 patients at admission. 6 in the Candida group and 2 in non-Candida group.
BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; ICU = Intensive Care Unit; IQR = Interquartile Range; NA = Not Applicable; SAPS II = Simplified Acute Physiology Score II; d = days; y = years. Statistically significance: P < 0.05.

Primary outcome

No significant difference was found regarding mortality between patients with and without proven respiratory Candida species colonization (59% and 55% respectively, P=0.83). Patients with colonization did experience a significant longer ICU LOV (14 days (IQR 7-21) for the Candida group vs. 6 days (IQR 4-11) for the No-Candida group, P=0.01) and a significant longer ICU LOS (18 days (IQR 12-30) for the Candida group vs. 8 days (IQR7-11) for the No-Candida group, P=0.001) (Table II).

Secondary outcomes

The prevalence of respiratory Candida species colonization was lower in the Non-DXM group than in the DXM group (74% and 83%, respectively), although the difference was not statistically significant (P=0.42). The Odds Ratio for Candida species colonization was 1.73 (95% CI 0.45-6.64). No significant difference was found between the DXM and the Non-DXM group regarding mortality (66% vs. 42%, respectively, P=0.09).

Several statistically significant differences were observed between the non-DXM and DXM groups (Table I). Specifically, the age difference (Non-DXM group: 62 years vs. DXM group: 70 years, P=0.03), SAPS II score (37 (IQR 29-42) for the Non-DXM group vs. 26 (IQR 21-37) for the DXM group, P=0.01), and LOS (10 days (IQR 8-18) for the Non-DXM vs. 18 (IQR 11-30) days for the DXM group, P=0.02) were statistically significant. No statistically significant differences were found between the two groups in terms of mortality, sex, LOV, COPD/asthma, DM, BMI, and corticosteroid use (other than DXM) (Table III). Additionally, no patients appear to have developed proven candidemia during their ICU stay, as all blood cultures were negative for Candida species growth.

Discussion

This retrospective study evaluated the impact of respiratory Candida colonization in mechanically ventilated COVID-19 patients and found that it was not associated with increased mortality. Silva et al. demonstrated increased mortality from fungal co-infections in COVID-19 patients with comorbidities such as DM, cardiovascular disease, or obesity[8]. These findings could indicate that our sample size was too small to achieve significant differences. Our results did however show a significant correlation between Candida colonization and a prolonged ICU stay and a longer mechanical ventilation time. The LOV being significantly longer in the Candida group is no surprise, as mechanical ventilation is known to be a risk factor for acquiring pulmonary infections[10] and this connection therefore seems to be a rather logic one. LOS was also significantly longer in the Candida group. This could be explained by the fact that the Candida group had a longer duration of mechanical ventilation, and therefore, extended hospitalization in the ICU. Remarkably, no significant differences in the SAPS II scores were found between the Candida and No-Candida groups, further complicating the interpretation of the extended LOV and LOS in the ICU in these patients. However, this score has not been validated in the COVID-19 pandemic setting.

When looking at the effect of DXM on acquiring respiratory tract colonization with

Table III. — Clinical data of patients who did not receive dexamethasone treatment (non-DXM group) and those who received dexamethasone treatment (DXM group). Statistical significance: P < 0.05.DXM = dexamethasone, y = years, d = days, IQR = interquartile range, SD = standard deviation.

Variable	Non-DXM (n=19)	DXM (n=35)	P-value
Age – y ± SD	62 ± 13.6	70 ± 8.6	0.03
Male Sex (%)	15 (71)	21 (60)	0.16
SAPS II (IQR)	37 (29–42)	26 (21–37)	0.01
ICU Length of Ventilation – d (IQR)	9 (6–16)	14 (6–21)	0.25
ICU Length of Stay – d (IQR)	10 (8–18)	18 (11–30)	0.02
COPD / Asthma (%)	3 (16)	5 (14)	0.88
Diabetes Mellitus (%)	3 (16)	8 (23)	0.54
Body Mass Index ± SD *	30.1 ± 4.6	30.4 ± 6.5	0.86
Corticoid use (%)	0 (0)	0 (0)	NA
Candida species-positive samples (%)	14 (74)	29 (83)	0.42
Mortality (%)	8 (42)	23 (66)	0.09

* No precise body weight could be determined from 8 patients at admission, all of them in the DXM group. BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; DXM = Dexamethasone; ICU = Intensive Care Unit; IQR = Interquartile Range; NA = Not Applicable; SAPS II = Simplified Acute Physiology Score II; SD = Standard Deviation; d = days; y = years.

Candida species, no statistically significant link could be found, which leads us to believe that the immunosuppressive effects of DXM did not induce a lower threshold for these vulnerable patients to develop invasive Candida species colonizations that could lead to infections. However, other studies did discover an association between corticosteroid use and secondary pulmonary Candida species colonization[30,31], emphasizing the limited patient population of this study with the associated lack in power.

A higher mortality rate was observed in the DXM group compared to the non-DXM group, although the difference was not statistically significant. Nonetheless, despite our non-significant findings regarding mortality, the effects of DXM on mortality remain controversial. Previous studies have demonstrated the beneficial effects of DXM on mortality in COVID-19 patients[32,33]. The RECOVERY trial suggests a reduction in mortality secondary to DXM use in COVID-19 patients requiring mechanical ventilation or with an oxygen requirement, but also a potentially associated harm or increased mortality in patients not requiring oxygen[32]. The EPICOVIDEHA study group also discovered that DXM use in COVID-19 patients with haematological malignancies resulted in higher mortality[34].

Significant differences in age, SAPS II score, and ICU LOS were observed were observed between the DXM and non-DXM groups. The observed significant difference in age can be attributed to the limited availability of ICU beds during the initial waves of the COVID-19 pandemic. This constraint necessitated stricter admission criteria, resulting in a higher rate of refusal for older patients. In later waves, the expansion of ICU capacity allowed for the admission of a broader range of patients, including older patients.

Of note, the similarity between invasive pulmonary aspergillosis (IPA) in patients with Influenza pneumonia[35,36] and COVID-19 patients[37,38], raises concern about the broader vulnerability of ventilated COVID-19 patients to fungal infections. As reported by Van Arkel et al., the incidence rates for IPA in COVID-19 patients mirror that observed in severely ill Influenza patients[38], underscoring shared risks.

As seen in this study and already previously demonstrated in multiple publications[2,3,39], prolonged invasive ventilation significantly increases the risk of respiratory candida species colonization. Tang et al. identified several invasive procedures, including tracheal intubation, central venous line placement, and mechanical ventilation, as key risk factors for pulmonary superinfections in COVID-19 patients[10]. Additional factors such as the use of multiple antibiotics, ECMO (Extracorporeal Membrane Oxygenation), and CRRT (Continuous Renal Replacement Therapy) also contribute to this risk.

Our study had several limitations. The sample sizes were small, with only 19 and 35 patients in the non-DXM and DXM groups, respectively. This was partly due to the single-center study design of a hospital with only 12 intensive care beds and a limited study period. We were also confronted with patients who were lost to follow-up and transferred to other hospitals. Moreover, owing to the retrospective design, data collection was restricted to previously documented information, leading to missing data (e.g., missing cultures in some patients). A formal power analysis to evaluate

the statistical power our study, was not performed due to the retrospective character of the study. This also limits the interpretation of our results. Also a regression analysis has not been carried out for the significant longer LOV and LOS in the Candida group, as we interpreted these findings to be largely driven by the longer ICU stay itself, which likely increased the opportunity for Candida detection.

Conclusion

In conclusion, this retrospective cohort study showed no significant association between respiratory colonization by Candida species and poor patient outcome. Colonization never resulted in an invasive infection, suggesting that it remains harmless in COVID-19. Also, no link was found between DXM treatment and respiratory tract colonization by Candida species, suggesting DXM treatment did not exacerbate pathogenic behavior of these Candida species. Further research into the prevention and treatment of respiratory fungal infections is essential, given the high comorbidity and poorer outcomes associated with such infections, particularly in high-risk patient populations.

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References

1. Arastehfar A, Carvalho A, Hong Nguyen M, Hedayati MT, Netea MG, Perlin DS, et al. Covid-19-associated candidiasis (Cac): An underestimated complication in the absence of immunological predispositions? J Fungi. 2020; 6(4):211
2. Cultrera R, Barozzi A, Libanore M, Marangoni E, Pora R, Quarta B, et al. Co-infections in critically ill patients with or without covid-19: A comparison of clinical microbial culture findings. Int J Environ Res Public Health. 2021; 18(8):4358
3. Ezeokoli OT, Pohl CH. Opportunistic pathogenic fungal co-infections are prevalent in critically ill COVID-19 patients: Are they risk factors for disease severity? South African Medical Journal. 2020; 110(11):1081-5.
4. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect. 2020; 26(10):1395–9.
5. Moser D, Biere K, Han B, Hoerl M, Schelling G, Choukér A, et al. COVID-19 Impairs Immune Response to Candida albicans. Front Immunol. 2021; 12:640644
6. Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses. 2021; 64(2):152-6
7. Pemán J, Ruiz-Gaitán A, García-Vidal C, Salavert M, Ramírez P, Puchades F, et al. Fungal co-infection in COVID-19 patients: Should we be concerned? Rev Iberoam Micol. 2020; 37(2):41–6.
8. Silva DL, Lima CM, Magalhães VCR, Baltazar LM, Peres NTA, Caligiorne RB, et al. Fungal and bacterial coinfections increase mortality of severely ill COVID-19 patients. J Hosp Infect. 2021; 113:145–54.
9. Song G, Liang G, Liu W. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. Vol. 185, Mycopathologia. 2020; 185(4):599–606.
10. 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. Microb Pathog. 2021; 156:104903
11. Segrelles-Calvo G, de S Araújo GR, Llopis-Pastor E, Carrillo J, Hernández-Hernández M, Rey L, et al. Candida spp. co-infection in COVID-19 patients with severe pneumonia: Prevalence study and associated risk factors. Respir Med. 2021; 188:106619
12. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. J Heart Lung Transplant. 2020; 39(5):405–7.
13. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033–4.
14. Cunha C, Carvalho A, Esposito A, Bistoni F, Romani L. DAMP signaling in fungal infections and diseases. Front Immunol. 2012 ;3:286.
15. Hoenigl M. Invasive Fungal Disease Complicating Coronavirus Disease 2019: When It Rains, It Spores. Clin Infect Dis. 2021; 73(7):E1645–8.
16. Tolle LB, Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. J Pathol. 2013; 229(2):145–6.
17. Schoot TS, Kerckhoffs APM, Hilbrands LB, van Marum RJ. Immunosuppressive Drugs and COVID-19: A Review. Front Pharmacol. 2020; 11:1333.
18. Williams DM. Clinical pharmacology of corticosteroids. Respir Care. 2018; 63(6):06314.
19. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020; 24(1):696.
20. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early Short-Course Corticosteroids in Hospitalized Patients with COVID-19. Clin Infect Dis. 2020; 71(16):2114–20.
21. Fernández-Cruz A, Ruiz-Antorán B, Muñoz-Gómez A, Sancho-López A, Mills-Sánchez P, Centeno-Soto GA, et al. A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. Antimicrob Agents Chemother. 2020; 64(9):e01169-20.
22. Lu X, Chen T, Wang Y, Wang J, Yan F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. Vol. 24, Critical Care. 2020.
23. Sanz Herrero F, Puchades Gimeno F, Ortega García P, Ferrer Gómez C, Ocete Mochón MD, García Deltoro M. Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study. J Intern Med. 2021; 289(2):259–63.
24. Ye Z, Wang Y, Colunga-Lozano LE, Prasad M, Tangamornsuksan W, Rochwerg B, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ. 2020; 192(27) :E756–67.
25. Cheng W, Li Y, Cui L, Chen Y, Shan S, Xiao D, et al. Efficacy and Safety of Corticosteroid Treatment in Patients With COVID-19: A Systematic Review and Meta-Analysis. Front Pharmacol. 2020; 11:571156.

26. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, et al. Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest. 2020; 50(10):e13319.
27. Patel C, Parmar K, Patel D, Patel S, Sheth D, Beladiya J V. Effect of corticosteroid therapy on mortality in COVID-19 patients—A systematic review and meta-analysis. Rev Med Virol. 2022; 32(5):e2386.
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61(4):344–49.
29. Koukaki E, Rovina N, Tzannis K, Sotiropoulou Z, Loverdos K, Koutsoukou A, et al. Fungal Infections in the ICU during the COVID-19 Era: Descriptive and Comparative Analysis of 178 Patients. J Fungi. 2022; 8(8):881.
30. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2017;12(12):CD007720.
31. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: A systematic review and meta-analysis. Crit Care. 2019; 23(1):99.
32. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021; 384(8):693–704.
33. Zhao J, Jiang HH, Wan HH, Liu D, Zhao Y, Chen YQ, et al. The impact of dexamethasone on short- and long-term mortality in hospitalized COVID-19 patients: a retrospective study. BMC Infect Dis. 2024; 24(1):1343.
34. Aiello TF, Salmanton-Garcia J, Marchesi F, Weinbergerova B, Glenthoj A, Van Praet J, et al. Dexamethasone treatment for COVID-19 is related to increased mortality in hematologic malignancy patients: results from the EPICOVIDEHA registry. Haematologica. 2024 Aug 1;109(8):2693–700.
35. Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med. 2020; 46(8):1524–35.
36. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med. 2018; 6(10):782–92.
37. Van Biesen S, Kwa D, Bosman RJ, Juffermans NP. Detection of invasive pulmonary aspergillosis in COVID-19 with Nondirected BAL. American J Respir Crit Care Med. 2020; 208:1171–1173.
38. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated pulmonary aspergillosis. American J Respir Crit Care Med. 2020; 202(1):132–5.
39. Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR, et al. Candida Colonization of the Respiratory Tract and Subsequent Pseudomonas Ventilator-Associated Pneumonia. Chest. 2006; 129(1):110–7.

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