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Research

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Superinfections in critically ill COVID-19 patients

– an association with dexamethasone?

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List of abbreviations:

ARDS: Acute respiratory distress syndrome

ICU: intensive care unit

VAP: ventilator associated pneumonia

BMI: body mass index

OR: Odds ratio

EARS-Net: European Antimicrobial Resistance Surveillance Network

PCR: polymerase chain reaction

ECMO: extra-corporal membrane oxygenation

Candida spp.: Candida subspecies

CRP: C-reactive protein

Abstract

Background: Super-infections in COVID-19 patients with acute respiratory distress syndrome (ARDS) on mechanical ventilation were initially reported to be rare. Little is known of their incidence after dexamethasone was introduced as standard care. We aimed to determine the incidence and characteristics of superinfections in mechanically ventilated COVID-19 patients during the course of the COVID-19 pandemic, and explore the possible impact of the introduction of dexamethasone as standard therapy.

Methods: In this national, multi-center, observational, retrospective study we included patients ≥ 18 years admitted from March 1st 2020 to January 31st 2021 with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection treated with invasive mechanical ventilation. Data was collected from electronic health records. Patient characteristics, clinical findings, microbiology, length of stay and 90-day survival were examined with backwards stepwise multiple regression.

Results: 155 patients (115 men, mean age 62 years, range 26-84 years) were included. 73 patients (47%) had a total of 101 superinfections where pneumonia dominated (70%). Superinfections were more commonly observed in patients receiving dexamethasone (67% vs 30%, $p<0.0001$), and in patients with pre-existing autoimmune disease (18% vs 5%, $p<0.01$). Invasive fungal infections were reported exclusively in dexamethasone-treated patients [9/72 (13%) vs 0/83 (0%), $p<0.0001$]. There was no difference in 90-day survival between patients with and patients without superinfections (64% versus 73%, $p=0.238$). In multiple regression analysis, superinfection was associated with dexamethasone use [OR 5.35 (2.62–11.35), $p<0.001$], pre-existing autoimmune disease [OR

4.90 (1.50–19.4), $p=0.008$] and higher lymphocyte count at the time of admission [OR 2.31 (1.23–4.86), $p=0.009$].

Conclusion: In critically ill COVID-19 patients receiving invasive ventilation, introduction of dexamethasone as standard of care was strongly and independently associated with superinfections. A focus on this complication is warranted when studying alternative anti-inflammatory therapy.

Keywords: COVID-19, ARDS, superinfections, dexamethasone, mechanical ventilation

Take home message: Dexamethasone therapy has increased survival in COVID-19 ARDS. We demonstrate in a national multi-center retrospective study that it also is strongly associated with superinfections in patients receiving invasive mechanical ventilation.

Declarations

Code availability: Not applicable

Ethics approval: The study was approved by the Regional Committee for Health and Research Ethics for South-East Norway (REK: 219370).

Consent to participate: All living patients included gave their informed consent to participate in the study through distribution of an opt-out participant information sheet. For deceased patients, implied consent was assumed.

Consent to publish: All authors have given their consent to publish this work.

Availability of data and material: Data supporting the findings of this study was used under license, and due to Norwegian legislation restrictions apply to their availability. Data are however available from the authors upon reasonable request, provided that permissions are obtained from the South-East Norway Regional Committee for Medical and Health Research Ethics and the Hospitals' Privacy Ombudsmen for Research.

Conflicts of interest/Competing interests: The authors declare no conflict of interest.

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Introduction

Bacterial or fungal superinfections following viral infections are well known from seasonal influenza epidemics, mostly in hospitalized patients and in particular in those needing treatment in an intensive care unit (ICU) [1]. At the onset of the SARS-CoV-2 pandemic, similar complications were anticipated. However, in early reports, the incidence of superinfections in hospitalized COVID-19 patients was remarkably low, with estimates not exceeding 16%, although in some studies, these infections had a negative impact on outcome [2-7]. Later publications suggested that COVID-19 patients did not show the same propensity for superinfections as patients with *Influenza virus*, and concluded that use of empiric antimicrobial therapy was not warranted [8, 9]. Still, in critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) on mechanical ventilation, a markedly higher rate of superinfections was reported [4, 10-13].

During the summer of 2020, it was demonstrated in randomized trials that dexamethasone improved survival in hospitalized patients with severe COVID-19 [14, 15]. Dexamethasone was rapidly implemented as standard of care in most countries. After the introduction of this therapy in Norway, the impression was that more Covid-19 patients acquired super-infections. In particular, we observed numerous cases of Enterobacteriaceae and fungus in patients with suspected pneumonia receiving mechanical ventilation. At present, data on the impact of dexamethasone therapy on the incidence of superinfections in hospitalized severely ill COVID-19 patients is limited. A multi-center retrospective study was therefore established in the south-eastern region of Norway to examine if superinfections in hospitalized COVID-19 patients on mechanical ventilation have increased during the COVID-19 pandemic, and whether the incidence of such complications was impacted by the introduction of dexamethasone as standard care.

Patients and Methods

Study characteristics and data collection

This was a multi-center, observational, retrospective study with seven participating hospitals in the south-eastern region of Norway. The protocol was approved by the Regional Committee for Health and Research Ethics for South-East Norway (REK: 219370). The study population included all patients at or above 18 years of age admitted from March 1st 2020 until January 31st 2021 who fulfilled the following inclusion criteria: (1) SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR), (2) ARDS, and (3) treatment during hospitalization included invasive mechanical ventilation and/or extra-corporal membrane oxygenation (ECMO).

Exclusion criteria were withdrawal of consent following distribution of a written summary of the study protocol to living eligible patients. In deceased patients, implied consent was assumed.

Data were manually collected from electronic medical records and charts and plotted into an electronic database (Ledidi.com, Oslo, Norway). Variables included gender, age, co-morbidities, blood values and clinical characteristics (on admission and during ICU stay), incidents of superinfections, putative causative organisms, use of dexamethasone and other immune-modulating drugs, targeted and/or empirical use of antimicrobial agents, length of stay in ICU and hospital, and 90-day survival (obtained from hospital records automatically updated from the Norwegian National Population Registry).

Definition of superinfections

A superinfection was defined as an incident when the following occurred: 1) clinical deterioration, 2) findings of pathogenic microorganisms (bacterial, fungal or viral) by cultures (bacteria and fungus), Galactomannan antigen assay (GM-EIA) (BioRad, Hemel, Hempstead, UK) or PCR (inhouse methods for fungus and virus) in clinical specimens and 3) the introduction of targeted antimicrobial therapy or the continuation of empiric antimicrobial therapy in agreement with the findings. Findings of coagulase-negative staphylococci in a single blood-culture and *Candida spp.* in airways were considered culture contaminants or commensal flora and were therefore not counted as superinfections.

Definition of pulmonary infections

The definition of ventilator associated pneumonia (VAP) includes radiographic infiltrates. However, the radiological presentation of COVID-19 ARDS precluded use of new pulmonary findings as an indication of VAP. Pulmonary infection was therefore in our dataset based on 1) respiratory deterioration and/or an increase in inflammatory biochemical markers and 2) microbiological findings and 3) the introduction of targeted antimicrobial therapy or the continuation of empiric antimicrobial therapy in agreement with the findings.

Statistical analysis

Reported values represent counts (%) and medians (25th-75th centiles) unless otherwise noted. Chi square test and Wilcoxon rank sum test were used to compare demographic and clinical characteristics among patients with and without superinfection, and to compare infections, microbiological findings and outcome with and without dexamethasone therapy. Factors associated with presence of infection were analyzed using backwards stepwise multiple logistic regression with p-value thresholds 0.20 to enter and 0.10 to leave the model (Fit Model

platform, Personality Stepwise, SAS-JMP 13.2.0 software for Mac, SAS Institute, Cary, NC, USA). Potential dichotomous (yes/no) predictors of superinfection explored included gender, hypertension, diabetes, chronic heart disease, chronic lung disease, chronic kidney disease, autoimmune disease, malignancy, ongoing immunosuppression prior to COVID-19 infection, dexamethasone administered related to COVID-19, and other immune-modulating drugs administered. Potential continuous predictors of superinfection included age by decile, body mass index (BMI), C-reactive protein (CRP), and neutrophil and lymphocyte counts. Results are reported as odds ratio (OR) with 95% confidence levels (95% CI) for having an infection versus no infection. The statistical significance level was set at $p < 0.05$.

Results

Patient characteristics

156 patients fulfilled inclusion criteria, of which one opted out. A total of 155 patients (115 men, mean age 62 years, range 26-84 years) were included from seven participating hospitals, with median 36 patients (range 5-50) per center (Table 1). Time from symptom start to hospital admission was 8 days (IQR 6-11). Time from hospital admission to administration of dexamethasone was 1 day (IQR 1-5). Time from hospital admission to ICU admission was 2 days (IQR 1-4). All patients had received mechanical ventilation; seven received ECMO therapy. Lowest value of $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio during the ICU stay was 14 kPa (105 mmHg; IQR 9-20). Overall 90-day survival rate was 69%. Patients' risk factors for severe COVID-19, clinical characteristics, use of dexamethasone and other immunomodulating drugs, length of stay in the ICU and hospital, and outcome are shown in Table 1.

Empiric antibiotic therapy was administered to 147 (95%) patients at some time point, median 3 (2-5) times during the course of hospitalization.

Occurrence of superinfections

A total of 101 superinfections were detected in 73/155 (47%) of patients. First occurrences included 64 monomicrobial and 9 polymicrobial infections. Fifty-five patients (75%) had only one superinfection (50 monomicrobial and 5 polymicrobial). Eighteen patients (25%) developed a second infection (14 with monomicrobial and 4 with polymicrobial). Eight of these (11% of total) experienced a third infection (7 monomicrobial and 1 polymicrobial), and two patients had a fourth incident while in the

ICU. Respiratory infections were found in 70% of the infections, followed by 8% urinary infections, 7% bloodstream infections and 3% combined respiratory and bloodstream infection.

The timing of superinfections in relation to hospital admission is presented in Figure 1. Table 2 summarizes all significant microbial findings and specimens of origin. In many patients, findings of the same microbe in more than one specimen occurred. Gram-negative rods were the dominant pathogens identified, while *Staphylococcus aureus* was the most common organism detected. Fungal infection was diagnosed in 9 patients, five fulfilling the recently redefined criteria for possible invasive aspergillosis in research and four with *Pneumocystis jirovecii* pneumonia (16).

Comparing the patient groups with and without superinfections, we found that patients with superinfections more often had received dexamethasone or an equivalent dose of methylprednisolone (Table 1). Patients with superinfections also more often had pre-existing autoimmune diseases, and had higher maximum neutrophil count, lower minimum PaO₂/FiO₂ ratio and longer hospital stay, ICU-stay and time on ventilator support. However, 90-day survival rates for patients with superinfections were not significantly lower than for those without superinfections (64% versus 73%, p=0.238). Moreover, high CRP levels or low number of lymphocytes, other co-morbidities than autoimmune disorders, or use of immunosuppressive drugs at the time of hospital admission were not significantly associated with the occurrence of superinfections. Use of hydroxychloroquine was statistically associated with a lower number of superinfections, but importantly, in our patient cohort, hydroxychloroquine use stopped abruptly at the same time as dexamethasone was introduced as standard therapy.

Use of dexamethasone was independently associated with the occurrence of superinfection in COVID-19 patients on mechanical ventilation

Superinfections were observed in 48/72 (67%) patients who did receive dexamethasone, while in patients who did not receive dexamethasone 25/83 (30%) had superinfections (p<0.0001). All invasive fungal infections were found in dexamethasone-treated patients (9/72 (13%) vs 0/84 (0%), p<0.001).

Backwards stepwise multiple logistic regression adjusting for demographics, comorbidities and admission lab values showed that detected superinfection was independently associated with having received dexamethasone (OR 5.35 (2.62–11.35), p<0.001) and having autoimmune disease (OR 4.90 (1.50–19.4), p=0.008). Higher

lymphocyte count on admission also increased the risk (OR 2.31 (1.23–4.86), $p=0.009$). The combined predictive value of the full regression model was moderate (AUROC 0.767).

Discussion

In this study of 155 consecutively treated COVID-19 patients requiring mechanical ventilation, we demonstrate that 47% experienced 1-3 superinfections according to our definition throughout their ICU stay. Significantly more superinfections occurred after the introduction of dexamethasone as standard treatment. The use of dexamethasone in these critically ill COVID-19 patients was independently associated with occurrence of superinfections, with an odds ratio of 5.4. As expected, COVID-19 patients with superinfections had longer hospital stays and time on ventilatory support. However, in this small study we could not demonstrate a statistically significant effect of superinfections on 90-day survival. Our findings suggest that whereas dexamethasone has been shown to increase survival in critically ill COVID-19 patients, it also appears to increase the risk of clinically relevant superinfections.

While it is not surprising that use of corticosteroids increases the risk of infections in COVID-19 patients, available data on the incidence of superinfections in COVID-19 patients in the dexamethasone era is scarce. In initial studies on its use in COVID-19, superinfections were not included as secondary outcome [14-15]. A later meta-analysis suggested a possible increase in secondary infections following corticosteroid therapy, but occurrence of secondary infection was not a pre-defined endpoint in the majority of the studies included, so the results should be interpreted with caution [17]. In a single-center study on severely ill patients, Saade et al. reported that dexamethasone was associated with increased risk of superinfection, but importantly, this population had a high prevalence of underlying immune defects (due to malignancies and organ transplantation (34%)) [12]. A recent study of ICU patients from three French ICUs reported a higher incidence of superinfections than that of the present study, but they found no association between the occurrence of VAP and the use of dexamethasone [18]. One possible contributor to discrepancies between our studies is differences in the utilization of broad-spectrum antibiotics, previously demonstrated to be independently associated with superinfections in COVID-19 [11]. Although 95% of our patients received empiric antibiotics, this to a large extent involved the use of relatively narrow-spectrum agents, due to moderate levels of antimicrobial resistance in the Scandinavian countries as demonstrated in EARS-Net [19]. Furthermore, in the French study the *non*-dexamethasone treated “first wave” patients were almost twice as likely to be on a ventilator at ICU admission and had 50% longer ventilator and ICU time than the dexamethasone treated “second wave” COVID-19 patients,

potentially influencing the results. Of note, the definition of pneumonia in mechanically ventilated patients was quite similar to ours.

In the present study, we found an independent association between the use of dexamethasone and the occurrence of superinfections in mechanically ventilated COVID-19 patients. Importantly, no such association was found between the use of immunosuppression prior to hospital admission or for other pre-existing co-morbidities including malignancies. Of note, an association was found between the occurrence of superinfection and pre-existing autoimmunity, although the number of patients with autoimmunity was relatively low. The association with dexamethasone was strongly present also after adjusting for occurrence of autoimmune disease.

Pneumonia was the most frequent form of infection observed, and nine patients (6%) had probable invasive fungal infection. Early in the pandemic, COVID-19-associated pulmonary aspergillosis (CAPA) was reported with varying incidence, with a median of 13.5%, ranging from 2.5% to 35% in a review [20]. In three prospective trials, the incidence was somewhat higher (14% to 38%) [21-23]. In ICU patients receiving mechanical ventilation, Marr et al. suggested an incidence of 20-30% [24]. However, few reports on the impact of corticosteroids used in COVID-19 have so far been published, with the exception of its association with the development of mucormycosis in Indian patients with diabetes mellitus [25, 26]. Although of low incidence, in our study invasive fungal infections in COVID-19 patients receiving invasive ventilation was strongly associated with dexamethasone therapy.

A clear limitation of this study is its observational, retrospective design. However, it was a multicenter study and included most Norwegian hospitals where COVID-19 patients were treated before dexamethasone was implemented as standard therapy in patients with ARDS. Due to the limited value of radiological diagnostics in assessing VAP in COVID-19 ARDS, the diagnosis was based solely on perceived clinical deterioration and microbiological findings, possibly leading to overestimation of true superinfections. Finally, patient numbers were relatively low possibly influencing some sub-analyses such as the occurrence of fungal infection.

Conclusion

We report that critically ill, invasively ventilated COVID-19 patients receiving dexamethasone had an almost five times higher odds ratio for contracting superinfections while in the ICU. These superinfections were associated with prolonged mechanical ventilation and ICU and hospital stay. Other anti-inflammatory and

immunosuppressive agents are now being tested in COVID-19 patients, often in combination with dexamethasone. Based on the present findings, a particular focus on superinfections is warranted.

Figure Captions

Fig. 1 Time from admission until superinfection in 155 COVID-19 patients on invasive mechanical ventilation Total count was 118 positive specimens. Red dots indicate findings in patients receiving or having received dexamethasone or an equipotent dose of prednisolone as COVID-19 treatment (72 of 155 patients).

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Table 1 Demographics, clinical characteristics, use of immunomodulatory drugs and outcome in 155 COVID-19 patients treated with invasive mechanical ventilation

	Full cohort N = 155	Superinfection N = 73	No superinfection N = 82	P value*
Male gender	115 (74)	55 (75)	60 (73)	0.758
Age (years)	62 (54–70)	62 (58–71)	61 (52–69)	0.197
BMI	27.8 (24.5–31.1)	27.8 (24.4–31.9)	27.8 (25.1–30.9)	0.824
Hypertension	69 (45)	37 (51)	32 (39)	0.174
Diabetes	38 (25)	19 (26)	19 (23)	0.680
Chronic heart disease	23 (15)	10 (14)	13 (16)	0.875
Chronic lung disease	36 (23)	19 (26)	17 (21)	0.456
Chronic kidney disease	12 (7.7)	7 (9.6)	5 (6.1)	0.417
Malignancy	7 (4.5)	4 (5.6)	3 (3.7)	0.560
Autoimmune disease	17 (11)	13 (18)	4 (4.9)	0.010
Primary Immunodeficiency	0	0	0	NA
Prior immunosuppressive therapy	17 (11)	11 (15)	6 (7.3)	0.123
Dexamethasone**	72 (46)	48 (64)	24 (29)	<0.0001
Duration (days)	11 (8–16)	11 (8–16)	12 (7–16)	0.761
Hydroxychloroquine [#]	43 (28)	11 (15)	32 (40)	<0.001
Anakinra	29 (19)	11 (16)	18 (22)	0.311
CRP Admission	129 (70–217)	130 (64–197)	129 (80–231)	0.475
Highest	280 (200–358)	271 (192–344)	281 (204–368)	0.335
Neutrophils Admission	5.8 (3.8–8.8)	4.9 (3.7–8.5)	6.2 (4.0–9.3)	0.399
Highest	12.8 (9.2–18.1)	14.6 (10.5–20)	11.9 (8.4–16)	0.010
Lymphocytes Admission	0.8 (0.6–1.2)	0.8 (0.6–1.3)	0.8 (0.6–1.1)	0.527
Lowest	0.7 (0.5–0.9)	0.7 (0.5–1.0)	0.7 (0.5–0.9)	0.409
PaO ₂ /FiO ₂ ratio (Worst)	14 (9–20)	11.5 (8.0–19)	15 (10–22)	0.045
Noradrenaline ≥0.1 µg/kg/min	77 (50)	37 (51)	40 (49)	0.813
Haemodialysis in ICU	27 (17)	10 (14)	17 (21)	0.249
Hospital LOS (days)	27 (20–42)	33 (24–53)	23 (18–32)	<0.0001
ICU LOS (days)	19 (14–31)	26 (17–42)	17 (12–21)	<0.0001
Time on ventilator (days)	16 (10–26)	21 (12–33)	13 (9–19)	0.0002
90-day survival***	107 (69)	47 (64)	60 (73)	0.238

Values are N (%) and medians (25th–75th centile). *Chi square tests or Wilcoxon test; **Dexamethasone 6 mg x 1 or equivalent dose methylprednisolone; ***All-cause out-of-hospital survival; BMI: Body mass index (kg/m²); ICU: intensive care unit; CRP: C-reactive protein (mg/L); Neutrophils and lymphocytes: x10⁹/L; LOS: length of stay. [#]Hydroxychloroquine was utilized solely during the time-period before dexamethasone treatment was adopted as standard care.

Table 2 Microbes and specimens in 73 critically ill Covid-19 patients with superinfections

Pathogen type	Species (numbers)	Specimens (numbers)
Gram-positive bacteria (N=44)	<i>Staphylococcus aureus</i> (22) <i>Streptococcus</i> spp. (6) <i>S. pneumoniae</i> (1) <i>S. anginosus</i> (2) <i>S. viridans</i> (2) <i>Streptococcus</i> sp. (1) <i>Enterococcus</i> spp. (16) <i>E. faecalis</i> (14) <i>E. faecium</i> (2)	BAL ¹ (13), Trach ² (5), Nasoph ³ (1), Blood (3) Nasoph (1) Trach (2) BAL (2) BAL (1) BAL (1), Trach (4), Blood (5), CVC ⁴ (3), Ur ⁵ (1) Trach (1), Ur (1)
Gram-negative bacteria (N=61)		
a) Enterobacteriaceae (N=35)	<i>Klebsiella</i> spp. (8) <i>Enterobacter</i> spp. (11) <i>Escherichia coli</i> (11) <i>Serratia marcescens</i> (2) <i>Citrobacter</i> sp. (1) <i>Pantoea</i> (2)	BAL (3), Trach (3), Blood (1), Ur (1) BAL (4), Trach (6), Ur (1) BAL (3), Trach (2), Blood (1), Ur (5) Trach (2) Trach (1) Trach (2)
b) Non-fermenters (N=22)	<i>Pseudomonas aeruginosa</i> (8) <i>Stenotrophomonas maltophilia</i> (7) <i>Acinetobacter</i> spp. (5) <i>Burkholderia</i> sp. (1) <i>Chryseobacterium</i> sp. (1)	BAL (4), Trach (1), Blood (2), Ur (1) BAL (2), Trach (4), Sput ⁶ (1) BAL (3), Trach (2) BAL (1) BAL (1)
c) Others (N=4)	<i>Moraxella catarrhalis</i> (1) <i>Hemophilus influenzae</i> (3)	Trach (1) BAL (2), Trach (1)
Anaerobe bacteria (N=2)	<i>Clostridium difficile</i> (2)	Faeces (2)
Fungal species (N=9)	<i>Aspergillus</i> spp. (5) <i>Pneumocystis jirovecii</i> (4)	Trach (5) BAL (2), Trach (1), Sput (1)
Viral species (N=2)	<i>Cytomegalovirus</i> (1) <i>Herpes simplex virus</i> (1)	Blood Blood

¹BAL: bronchioalveolar lavage; ²Trach: tracheal secretion; ³Nasoph: nasopharyngeal secretion; ⁴CVC: central venous catheter; ⁵Ur: urine; ⁶Sput: Induced sputum

Figures

Figure 1

Time from admission until superinfection in 155 COVID-19 patients on invasive mechanical ventilation. Total count was 118 positive specimens. Red dots indicate findings in patients receiving or having received dexamethasone or an equipotent dose of prednisolone as COVID-19 treatment (72 of 155 patients).