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Corticosteroids and superinfections in COVID-19 patients on invasive mechanical ventilation

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SUMMARY

Objectives: To determine the incidence and characteristics of superinfections in mechanically ventilated COVID-19 patients, and the impact of dexamethasone as standard therapy.

Methods: This multicentre, observational, retrospective study included patients ≥ 18 years admitted from March 1st 2020 to January 31st 2021 with COVID-19 infection who received mechanical ventilation. Patient characteristics, clinical characteristics, therapy and survival were examined.

Results: 155/156 patients (115 men, mean age 62 years, range 26–84 years) were included. 67 patients (43%) had 90 superinfections, pneumonia dominated (78%). Superinfections were associated with receiving dexamethasone (66% vs 32%, $p < 0.0001$), autoimmune disease (18% vs 5.7%, $p < 0.016$) and with longer ICU stays (26 vs 17 days, $p < 0.001$). Invasive fungal infections were reported exclusively in dexamethasone-treated patients [8/67 (12%) vs 0/88 (0%), $p < 0.0001$]. Unadjusted 90-day survival did not differ between patients with or without superinfections (64% vs 73%, $p = 0.25$), but was lower in patients receiving dexamethasone versus not (58% vs 78%, $p = 0.007$). In multiple regression analysis, superinfection was associated with dexamethasone use [OR 3.7 (1.80–7.61), $p < 0.001$], pre-existing autoimmune disease [OR 3.82 (1.13–12.9), $p = 0.031$] and length of ICU stay [OR 1.05 $p < 0.001$].

Conclusions: In critically ill COVID-19 patients, dexamethasone as standard of care was strongly and independently associated with superinfections.

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Abbreviations: ARDS, Acute Respiratory Distress Syndrome.

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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 secondary infections or 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.^{2,3,4,5,6,7} Later publications suggested that COVID-19 patients did not show the same propensity for superinfections as patients with influenza infection, and concluded that use of empiric antimicrobial therapy was not warranted.^{8,9} Still, in COVID-19 patients with acute respiratory distress syndrome (ARDS) on invasive mechanical ventilation, a markedly higher rate of superinfections was reported.^{4,10,11,12,13,14}

During the summer of 2020, randomized trials demonstrated that dexamethasone improved survival in hospitalized patients with severe COVID-19.^{15,16,17} The drug was rapidly implemented as standard of care in most countries.¹⁸ After the introduction of this therapy in Norway, the impression was that more COVID-19 patients acquired superinfections. In particular, we observed more cases of suspected pneumonia with findings of enterobacteriaceae and fungus in patients 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 multicentre retrospective study was therefore performed in the south-eastern region of Norway to examine if superinfections in hospitalized COVID-19 patients on mechanical ventilation had increased during the COVID-19 pandemic, and whether the incidence of such complications was influenced by the introduction of dexamethasone as standard care.

Patients and Methods

Study characteristics and data collection

This was a national, multicentre, 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) clinically diagnosed ARDS, and (3) treatment during hospitalization included invasive mechanical ventilation and/or extra-corporeal 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, consent was waived. The main objective was to examine whether the incidence of superinfections remained stable during the pandemic. Secondary aims were the characterisation of these infections, their relation to dexamethasone use, length of ICU and hospital stay and outcome.

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, date of ICU admission, date of intubation and invasive mechanical ventilation, duration of invasive mechanical ventilation, need for extra-corporeal mechanical ventilation (ECMO), superinfections with microbiological documentation and recurrences, use of dexamethasone and other immune-modulating drugs, tar-

geted and/or empirical use of antimicrobial agents, length of stay (LOS) in the ICU and hospital, and 90-day survival (obtained from hospital records automatically updated from the Norwegian National Population Registry). In Norway, the pandemic's first wave ended late in May 2020 coinciding with dexamethasone being implemented as standard of care.

Definition of superinfections

A superinfection, synonymous with secondary infection, was defined as an incident when the following occurred: 1) Clinical deterioration, 2) A positive specimen obtained >3 days after hospital admission, 3) Findings of pathogenic microorganisms other than SARS-Cov-2 (bacterial, fungal or viral) by cultures (bacteria and fungus), Galactomannan antigen assay (GM-EIA) (BioRad, Hemel, Hempstead, UK) or PCR (in-house methods for fungus and virus) in clinical specimens and, 4) The introduction of targeted antimicrobial therapy or the continuation of empiric antimicrobial therapy in agreement with the findings while the patients was admitted to the ICU. Findings of coagulase-negative staphylococci in a single blood-culture and *Candida spp.* in airways were considered contaminants or commensal flora and not superinfections. Co-infections, i.e. clinical signs of infection with findings of microbial agents diagnosed on Day 0-2 after admission, were excluded from this study.

Definition of pulmonary infection

The definition of ventilator-associated pneumonia (VAP) includes new radiographic infiltrates \geq 48 hours after intubation.¹⁷ 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 > 3 days after ICU entry and 2) Microbiological findings in airway secretion 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 superinfection were analysed 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), neutrophil and lymphocyte counts on hospital admission and ICU length of stay (LOS). 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 $p < 0.05$.

Table 1

Demographics, clinical characteristics, use of immunomodulatory drugs and outcome in 155 COVID-19 ARDS patients with or without superinfection

	Full cohort N = 155	Superinfection N = 67	No superinfection N = 88	P value*
Male gender	115 (74)	50 (75)	65 (74)	0.914
Age (years)	62 (54–70)	62 (57–71)	61 (52–70)	0.257
BMI	27.8 (24.5–31.1)	27.7 (24.4–31.9)	28.1 (25.1–30.9)	0.987
Hypertension	69 (45)	32 (48)	37 (43)	0.517
Diabetes	38 (25)	15 (22)	23 (26)	0.591
Chronic heart disease	23 (15)	9 (13)	14 (16)	0.609
Chronic lung disease	36 (23)	17 (25)	19 (22)	0.581
Chronic kidney disease	12 (7.7)	7 (10)	5 (5.9)	0.271
Malignancy	7 (4.5)	3 (4.5)	4 (4.6)	0.560
Autoimmune disease	17 (11)	12 (18)	5 (5.7)	0.016
Primary Immunodeficiency	0	0	0	NA
Prior immunosuppressive therapy	17 (11)	9 (13)	8 (9.0)	0.392
Dexamethasone given**	72 (46)	44 (66)	28 (32)	<0.0001
Duration (days)	11 (8–16)	11 (8–16)	12 (8–16)	0.705
Time from Admission (days)	0 (0–4)	0 (0–4)	0 (0–4)	0.811
Hydroxychloroquine	43 (28)	11 (16)	32 (36)	0.005
Anakinra	29 (19)	11 (16)	18 (20)	0.589
CRP Admission Highest	129 (70–217)	128 (60–191)	129 (80–244)	0.297
	280 (200–358)	273 (188–343)	280 (205–373)	0.261
Neutrophils Admission Highest	5.8 (3.8–8.8)	5.0 (3.8–8.5)	6.1 (3.8–8.8)	0.758
	12.8 (9.2–18.1)	14 (10–19)	12 (8.3–17)	0.027
Lymphocytes Admission Lowest	0.8 (0.6–1.2)	0.9 (0.6–1.3)	0.8 (0.6–1.1)	0.358
	0.7 (0.5–0.9)	0.7 (0.5–1.0)	0.7 (0.5–0.9)	0.585
PaO ₂ /FiO ₂ ratio (Worst)	14 (9–20)	12 (8.0–19)	15 (9.8–22)	0.070
Noradrenaline \geq 0.1 μ g/kg/min	77 (50)	33 (49)	44 (50)	0.927
Haemodialysis in ICU	27 (17)	8 (12)	19 (22)	0.117
Symptoms–Admission (days)	7 (5–10)	7 (6–10)	8 (5–11)	0.731
Symptoms–Intubation (days)	12 (9–15)	12 (9–16)	12 (9–15)	0.509
Hospital LOS (days)	27 (20–42)	32 (25–54)	23 (18–33)	<0.0001
ICU LOS (days)	19 (14–31)	26 (16–42)	17 (12–22)	<0.0001
Time on ventilator (days)	16 (10–26)	21 (12–34)	13 (9–19)	<0.0001
90-day survival***	107 (69)	43 (64)	64 (73)	0.254

Values are N (%) and medians (25th–75th centile). *Chi square tests or Wilcoxon test; **Dexamethasone 6 mg x 1 or equivalent dose methylprednisolone (nine patients); ***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: $\times 10^9/L$; LOS: length of stay.

Results

Patient characteristics

156 patients fulfilled inclusion criteria, of which one declined to participate. A total of 155 patients were included from seven participating hospitals, with median 36 patients (range 5–50) per centre (Table 1). Time from symptom start to hospital admission was median 7 days (IQR 5–10). Time from hospital admission to administration of dexamethasone was median 0 day (IQR 0–4). Time from hospital admission to ICU admission was median 2 days (IQR 1–4). All patients received invasive mechanical ventilation; seven received ECMO therapy. Risk factors for COVID-19, clinical data at admission and peak or lowest point, use of immune-modulating drugs, LOS in the ICU and hospital, and outcome are shown in Table 1. Seventy-two patients received Dexamethasone i.v. 6 mg x 1 or equivalent dose of methylprednisolone (nine patients) for a median of 11 d (8–16) (Table 1). Seven of the 72 patients who received dexamethasone were admitted during the first pandemic wave and 65 patients during the second wave, i.e. after the implementation of dexamethasone as standard care for COVID-19.

Occurrence of superinfections

In 67/155 (43%) of patients a total of 90 superinfections were detected. The first superinfections occurred 11 (range 7–17) days after admission and included 57 monomicrobial and 10 polymicrobial infections. Sixteen patients (24%) developed a second superinfection (11 with monomicrobial and 5 with polymicrobial findings) 10 (range 3–42) days after the first infection, of which four were

recurrences. Six patients (9% of total) experienced a third superinfection (5 monomicrobial and 1 polymicrobial) 16 (6–26) days after the second infection and four were recurrences. One patient had a fourth new infection while in the ICU. The predominant location for superinfections was the lower respiratory tract (78% of infections), followed by 10% bloodstream infections, 8.4% urinary tract infections, and 2% each of positive cultures of faeces and intravascular lines.

Microbes, specimens and the relation to dexamethasone treatment are presented in Figure 1. In some 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 subspecies detected. Fungal infection was diagnosed in 8 patients, five fulfilling the defined criteria for possible or probable COVID-19 associated pulmonary aspergillosis (CAPA) at a median of 14 days (9–27) from admittance, and three with *Pneumocystis jirovecii* pneumonia at 27 days (3–33) after admittance.¹⁹ Two patients had reactivation of HSV and CMV and were treated with antiviral drugs.

Comparing the patient groups with and without superinfections, we found that patients with superinfections more often had received corticosteroids (Table 1). Patients with superinfections also more often had pre-existing autoimmune diseases, and had higher maximum neutrophil count, a trend towards 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=0.25). Moreover, high CRP levels or low number of lymphocytes, other co-morbidities than autoimmune disorders, or use of immunosuppressive drugs

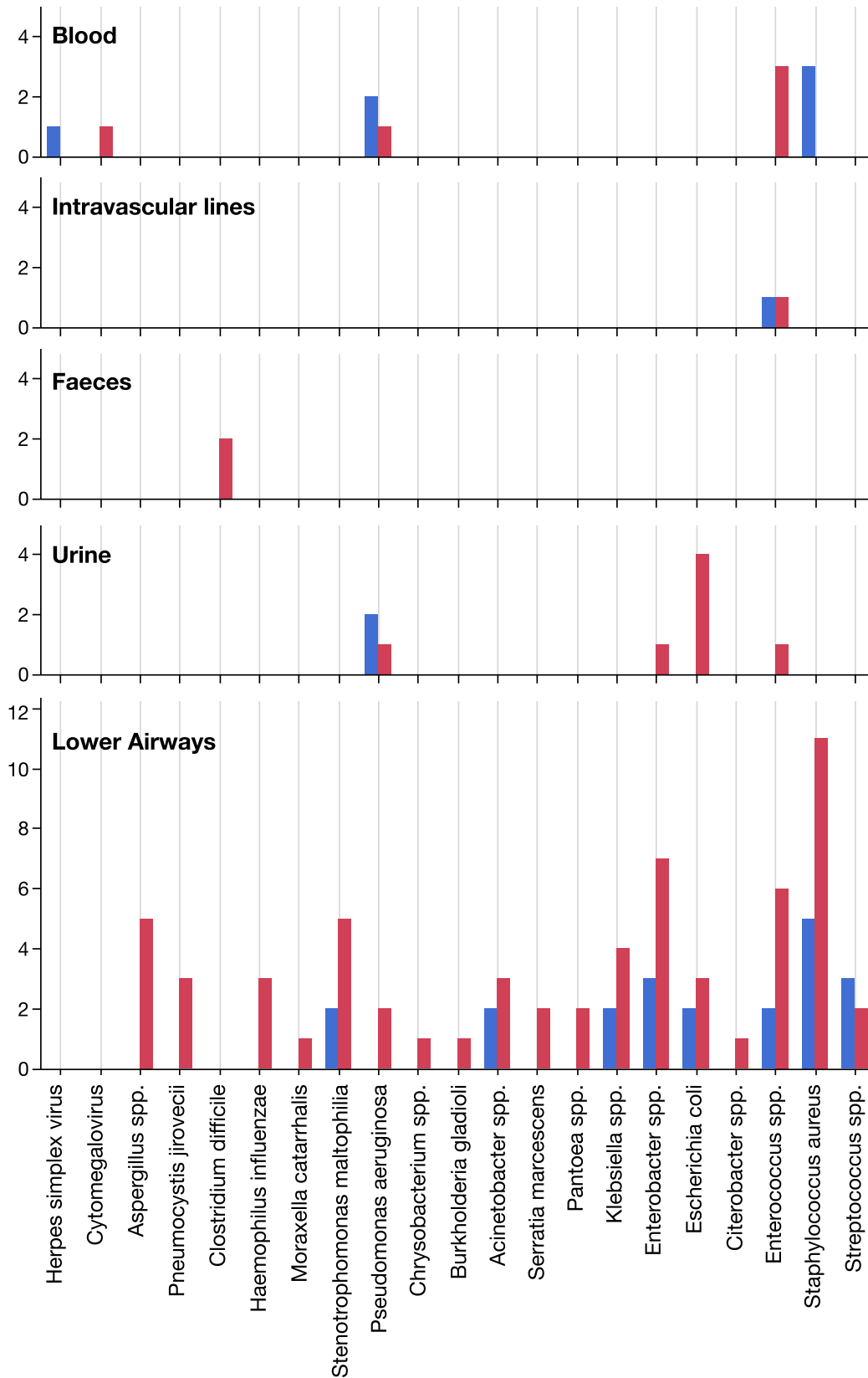


Figure 1. Superinfections in COVID-19 patients: Microbial agents and specimens Data from 155 COVID-19 patients on invasive mechanical ventilation. The definition of superinfection (N=90) included a positive specimen obtained >3 days after hospital admission. Red columns show findings in patients having received dexamethasone or an equipotent dose of methylprednisolone as COVID-19 treatment (72 of 155 patients); blue columns are findings in non-corticosteroid treated patients.

Table 2
Demographics, clinical characteristics, use of immunomodulatory drugs and outcome in 155 COVID-19 patients treated with or without dexamethasone

	Full cohort N = 155	DEXA yes N = 72	DEXA no N = 83	P value*
Male gender	115 (74)	53 (74)	62 (75)	0.877
Age (years)	62 (54–70)	62 (54–71)	62 (53–70)	0.711
BMI	27.8 (24.5–31.1)	28.5 (25.0–32.1)	27.2 (24.2–30.5)	0.104
Hypertension	69 (45)	36 (50)	33 (40)	0.225
Diabetes	38 (25)	20 (28)	18 (22)	0.379
Chronic heart disease	23 (15)	8 (11)	15 (18)	0.214
Chronic lung disease	36 (23)	20 (28)	16 (19)	0.211
Chronic kidney disease	12 (7.7)	7 (9.7)	5 (6.0)	0.390
Malignancy	7 (4.5)	7 (10)	0 (0)	0.003
Autoimmune disease	17 (11)	10 (14)	7 (8.4)	0.278
Primary Immunodeficiency	0	0	0	NA
Immunosuppression pre-admission	17 (11)	13 (18)	4 (4.8)	0.009
Dexamethasone given**	72 (46)	72 (100)	0	NA
Duration (days)		11 (8–16)		NA
Time from Admission (days)		0 (0–4)		NA
Hydroxychloroquine	43 (28)	1 (1.4)	42 (51)	<0.001
Anakinra	29 (19)	5 (7.0)	24 (30)	<0.001
Superinfection after 72 h	67 (43)	44 (61)	23 (28)	<0.001
CRP Admission Highest	129 (70–217)	126 (65–184)	130 (80–225)	0.398
	280 (200–358)	265 (187–326)	293 (235–380)	0.019
Neutrophils Admission Highest	5.8 (3.8–8.8)	5.1 (3.5–8.7)	6.1 (4.0–8.8)	0.613
	12.8 (9.2–18.1)	15 (10.4–20)	11.3 (8.3–16.6)	0.002
Lymphocytes Admission Lowest	0.8 (0.6–1.2)	0.8 (0.6–1.1)	0.8 (0.6–1.2)	0.220
	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.7 (0.5–0.9)	0.055
PaO ₂ /FiO ₂ ratio (Worst)	14 (9–20)	11 (8.0–20)	15 (10–23)	0.015
Noradrenaline ≥0.1 ug/kg/min	77 (50)	36 (50)	41 (49)	0.940
Haemodialysis in ICU	27 (17)	13 (18)	14 (17)	0.846
Symptoms–Admission (days)	7 (5–10)	7 (5–10)	8 (6–11)	0.086
Symptoms–Intubation (days)	12 (9–15)	13 (10–16)	11 (9–15)	0.013
Hospital LOS (days)	27 (20–42)	30 (22–49)	25 (18–36)	0.017
ICU LOS (days)	19 (14–31)	21 (15–37)	18 (13–26)	0.044
Intubation time (days)	16 (10–26)	16 (10–31)	15 (10–21)	0.256
90-day survival***	107 (69)	42 (58)	65 (78)	0.007

Values are N (%) and medians (25th–75th centile). *Chi square tests or Wilcoxon test. BMI: Body mass index (kg/m²); ICU: intensive care unit; **Dexamethasone 6 mg x 1 or equivalent dose methylprednisolone (nine patients); CRP: C-reactive protein (mg/L); Neutrophils and lymphocytes: x10⁹/L; LOS: length of stay; ***All-cause out-of-hospital survival. **NOTE:** In this cohort, 98% of patients *not* receiving dexamethasone arrived during the first wave of the pandemic, when early intubation was recommended and hydroxychloroquine was still in use.

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 superinfections in COVID-19 patients on invasive mechanical ventilation. Superinfections were observed in 44/72 (61%) patients who did receive dexamethasone, while in patients who did not receive dexamethasone 23/83 (28%) had superinfections ($p < 0.0001$). All invasive fungal infections were found in dexamethasone-treated patients [8/72 (11%) vs 0/83 (0%), $p < 0.001$] (Table 3). Survival rates were lower in patients receiving dexamethasone (58% vs 78%).

Backwards stepwise multiple logistic regression adjusting for demographics, comorbidities, admission lab values and ICU LOS showed that detected superinfection was independently associated with having received dexamethasone (OR 3.7 (1.80–7.61), $p < 0.001$) and having autoimmune disease (OR 3.82 (1.13–12.9), $p = 0.031$). Longer ICU LOS increased the occurrence of superinfections (OR 1.05 per day LOS, $p < 0.001$). The combined predictive value of the full regression model was moderate (AUROC 0.786).

Empiric antimicrobial therapy

Empiric antimicrobial therapy was administered to 147 (95%) patients at some time point, a median of 3 (2–5) courses dur-

ing the ICU stay. The proportion of patients starting such therapy on hospital admission was higher during the first pandemic wave than later in the study period (98% vs. 81%, $p = 0.004$). Predominant empiric antibiotics started on hospital days 0, 1 and 2 were penicillins (15%), cephalosporins (50%), fluorokinolones (25%), meropenem and gentamicin (3% each).

Discussion

In this study of 155 consecutively treated COVID-19 patients requiring invasive mechanical ventilation, we demonstrate that 43% experienced 1–4 superinfections according to our definition throughout their ICU stay. Use of dexamethasone in these patients was strongly and independently associated with the occurrence of superinfections, with an adjusted odds ratio of 3.7. Having an autoimmune disease and a long ICU stay also demonstrated a similar independent association. However, the association of superinfections with dexamethasone was strongly present also after adjusting for these two factors. In this small study we could not demonstrate a statistically significant effect of superinfections on 90-day survival. Examining the patients receiving dexamethasone vs. not, the same association with infections, in particular invasive fungal infections, and longer ICU stay persisted. Furthermore, the use of dexamethasone demonstrated a significant association with mortality. 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. In

Table 3
Possible invasive fungal infections in eight critically ill Covid-19 patients on invasive mechanical ventilation

Patients No	Sex and Age	Risk Factors for COVID-19 or IFI	DEXA	Pathogens	Specimens	Diagnostics	Therapy	Outcome
1	F 54	Autoimmune disease, Immunosuppressive drugs IMV 3 d	Yes	<i>P. jirovecii</i> *	BAL	PCR+	TMP/SMX 21 d	Alive
2	M 58	IMV 9 d	Yes	<i>Aspergillus</i> sp.	TRACH	Culture+, GM: nd, PCR: nd	Voriconazole 13 d	Alive
3	M 61	Autoimmune disease, Immunosuppressive drugs IMV 19 d	Yes	<i>A. fumigatus</i>	TRACH	Culture+, GM: nd, PCR: nd	Micafungin 1 d	Deceased
4	M 76	Autoimmune disease, COPD, Hypertension IMV 14 d	Yes	<i>A. fumigatus</i>	TRACH	Culture+, GM: nd PCR+	Anidulafungin 15 d	Deceased
5	M 82	MDS? Hypertension, IMV 11 d	Yes	<i>A. fumigatus</i>	TRACH	Culture+, PCR+, GM+	Anidulafungin 17 d	Deceased
6	M 60	BMI 30 IMV 27 d	Yes	<i>P. jirovecii</i> *	TRACH	PCR+	TMP/SMX 38 d + Anidulafungin 6 d	Deceased
7	F 62	Autoimmune disease, Hypertension, ECMO 33 d	Yes	<i>P. jirovecii</i> *	BAL	PCR+	TMP/SMX 5 d	Deceased
8	M 58	ECMO 27 d	Yes	<i>A. fumigatus</i>	TRACH	Culture+, PCR+, GM+	Isavuconazole 18 d	Deceased

IFI: invasive fungal infection; DEXA: Dexamethasone; F: female; M: male; IMV: invasive mechanical ventilations; d: days; COPD: chronic obstructive pulmonary disease; MDS: myelodysplastic syndrome; BAL: bronchioalveolar lavage; SPUT: induced sputum; TRACH: tracheal secretion; TMP/SMX: Trimethoprim/Sulfamethoxazole; PCR: polymerase chain reaction; GM: galactomannan; neg: negative; nd: not done.

*HIV-negative

this Norwegian study, although observational, its use also have an impact on outcome.

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 dexamethasone use in COVID-19, superinfections were not included as secondary outcome.^{15,16} 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.²⁰ In a single-centre 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.²¹ One possible contributor to the discrepancies between our findings and these 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 involved to a large extent the use of relatively narrow-spectrum agents due to moderate levels of antimicrobial resistance in Norway, as demonstrated in *EARS-Net*.²² 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 their results. Our findings of length of stay having an independent association with superinfections could support this.

Pneumonia was the most frequent form of infection observed, and eight patients (5%), increasing to 11% in the dexamethasone treated population, had possible or probable invasive fungal infection with a 75% mortality rate. Early in the pandemic, CAPA was reported with varying incidence, with a median of 13.5%, ranging from 2.5% to 35% in a review.²³ In three prospective trials, the incidence was somewhat higher, 14% to 38%.^{24,25,26} In ICU patients receiving mechanical ventilation, Marr et al. suggested an incidence of 20–30%.²⁷ Two recent studies from ICU populations with COVID-

19 reported 15% and 9% incidence of CAPA and both demonstrated an independent association to dexamethasone.^{28, 29} A recent multicentre study by Perner et al. using differing doses of dexamethasone in critically ill COVID-19 patients demonstrated only 3–4% of invasive fungal infections depending on dexamethasone dose.³⁰ These findings support the fact that CAPA is a real threat in COVID-19 ARDS, particularly when anti-inflammatory regimens are used.

We demonstrated a frequent use of empirical antimicrobial agents and its use diminished over time possibly making a positive contribution to the microbial yield in the dexamethasone era. However, the differences of empiric use at admission was small, 98% vs 81%, and 95% of all our patients received empiric therapy at some point during the ICU stay, making this a less plausible explanation for increased superinfection rate by time.

Having demonstrated a strong association with superinfections and dexamethasone without affecting survival rates, we examined the impact of dexamethasone on the same parameters and demonstrated a significant impact on unadjusted survival rates. As this is a small study, the findings should be interpreted carefully. Furthermore, survival rates might have been even lower at this time of the pandemic without dexamethasone.

A clear limitation of this study is its observational, retrospective design. However, it was a multicentre study and included most Norwegian hospitals where COVID-19 patients were treated both before and after 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 an overestimation of true superinfections. Finally, patient numbers were relatively low; this might have influenced some sub-analyses such as the occurrence of fungal infection.

Conclusion

We report that mechanically ventilated COVID-19 patients receiving dexamethasone had an over three times higher odds ratio for contracting superinfections while in the ICU. These superinfections were associated with autoimmune disease and longer ICU and hospital stays. Other anti-inflammatory and immunosuppressive agents are being tested in COVID-19 patients, often in combi-

nation with dexamethasone. Based on the present findings, a particular focus on superinfections is warranted.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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