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CLINICAL INVESTIGATION

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COVID-19 versus influenza A/B supeRInfectionS in the IntenSive care unit (CRISIS): Protocol for a Danish nationwide cohort study

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Background: Superinfection following viral infection is a known complication, which may lead to longer hospitalisation and worse outcome. Empirical antibiotic therapy may prevent bacterial superinfections, but may also lead to overuse, adverse effects and development of resistant pathogens. Knowledge about the incidence of superinfections in intensive care unit (ICU) patients with severe Coronavirus Disease 2019 (COVID-19) is limited.

Methods: We will conduct a nationwide cohort study comparing the incidence of superinfections in patients with severe COVID-19 admitted to the ICU compared with ICU patients with influenza A/B in Denmark. We will include approximately 1000 patients in each group from the time period of 1 October 2014 to 30 April 2019 and from 10 March 2020 to 1 March 2021 for patients with influenza and COVID-19, respectively. The primary outcome is any superinfection within 90 days of admission to the ICU. We will use logistic regression analysis comparing COVID-19 with influenza A/B after adjustment for relevant predefined confounders. Secondarily, we will use unadjusted and adjusted logistic regression analyses to assess six potential risk factors (sex, age, cancer [including haematological], immunosuppression and use of life support on day 1 in the ICU) for superinfections and compare outcomes in patients with COVID-19 with/without superinfections, and present descriptive data regarding the superinfections.

Conclusion: This study will provide important knowledge about superinfections in ICU patients with severe COVID-19.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded, enveloped RNA-coronavirus, which causes Coronavirus Disease 2019 (COVID-19). Symptoms in patients with COVID-19 range from mild upper airway symptoms to severe respiratory failure.[1,2] Other coronaviruses cause infections in humans and animals in the respiratory tract including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[3]

A study of COVID-19 patients admitted to the intensive care unit (ICU) found that 71% received mechanical ventilation, and 12% were put on extracorporeal membrane oxygenation (ECMO).[4] Ninety-four percent received antibiotics, and in 14%, a secondary hospital-acquired infection with bacteria or fungus was diagnosed.[4]

Bacterial superinfection is a known complication to influenza infections.[5,6] Studies have found an occurrence of bacterial superinfections following influenza ranging from 4% to 47%.[6-9] Amongst the most common pathogens in bacterial superinfections are *S pneumoniae*, *S aureus* and *H influenzae*.[10]

Invasive pulmonary aspergillosis (IPA) is known to follow severe influenza especially in immunocompromised patients, but recent studies have shown that otherwise healthy patients are also at risk of invasive pulmonary aspergillosis infection.[11-13]

The course of these infections tend to be very severe with up to 90% of the patients requiring invasive mechanical ventilation and mortality ranging from 45% to 57% in ICU patients with influenza and IPA-superinfection versus 33% in those without.[11,12]

For the above-mentioned reasons, empirical antibiotic administration is used widely in ICU patients with COVID-19, and the first choice is often broad-spectrum antibiotics. The use of these antibiotics[14] carries the risk of increasing antimicrobial resistance (AMR), that is, bacteria's ability to withstand the effects of administered antibiotics. AMR may develop even with the use of low dose and short duration antibiotics.[15]

In a review of the studies conducted in the beginning of the COVID-19 pandemic, it was found that 14%-57% of ICU patients acquired a superinfection.[4,14,16-18] A recent systematic review on bacterial secondary infections found the rate to be 16% in patients with COVID-19,[19] and antibiotics were administered in 71% of all patients in the studies.

In general, knowledge on COVID-19 and superinfections are lacking, as are data on the associations between use of empiric antibiotics and superinfections in ICU patients with COVID-19. Consequently, we aim to describe the incidence of superinfections in Danish ICU patients with COVID-19 and compare it with that in ICU patients with influenza A/B. Further, we will assess potential risk factors for superinfection in ICU patients with COVID-19 and describe pathogenic, antimicrobial therapy and resistance patterns.

2 | METHODS

2.1 | Setting

This is a protocol and statistical analysis plan for a nationwide cohort study using historical data, including all ICU patients registered in the Danish nationwide COVID-19 ICU database,[20] as well as all ICU patients with influenza A/B. We will identify ICU patients with influenza by coupling data from the Danish Intensive Care Database[21] with MiBa, a Danish database containing all microbiological sample results.

2.2 | Participants

The COVID-19 ICU database includes all ICU patients admitted to any Danish ICU with COVID-19 from the ICU-admission of the index patient on 10 March 2020, and the collection of data is ongoing. In this study, we will use data from the start of the pandemic and until 10 March 2021. The patients in the influenza group will be identified among patients hospitalised between 1 October 2014 through 1 April 2019 as there were very few cases of influenza during the COVID-19 pandemic. For the purpose of comparing waves of the pandemic, the COVID-19 patients will be divided into cohort 1 (1 March 2020 to 30 June 2020) and cohort 2 (from 1 July 2020 to 1 March 2021). For pragmatic reasons, wave 2 includes a rather long down-time in cases to not exclude any patients during the downtime in cases.

2.3 | Data sources

The Danish nationwide COVID-19 ICU cohort database[20] holds demographic, baseline and outcome data for all ICU patients with COVID-19 in Denmark. The Danish Intensive Care Database (DID)[21] holds demographic, baseline and outcome data for all ICU patients in Denmark. In Electronic Health Records, by permission, all data as mentioned in the supplements that is unavailable in the databases will be collected from the electronic health records. The Danish Microbiology Database, MiBa, holds data on microbiological testing on individuals in Denmark. A diagnostic and epidemiological tool. The Research Machine is a Danish research tool developed by Danish Health Data Authority, which aids researchers in extracting data from the well-developed national databases.[22]

2.4 | Data collection

See the supplements for list of variables.

All data will be obtained including historical data from electronic health records, the Danish Intensive Care database and MiBa and will be collected in the COVID-19 ICU REDCap-database merged with the database of the Danish Health Data Authority, the Research Machine, where data will be extracted from for analysis.

2.5 | Data access

As per the obtained permissions, all data will be extracted from secure databases where personal identification numbers are stated. The linkage between the databases and MiBa will be through social security numbers. Data will then be combined in one file pseudo-anonymized.

2.6 | Study objectives

The primary objectives are as follows:

- To estimate the incidence of patients with superinfections admitted to the ICU with COVID-19 and to compare this with the incidence in ICU patients with influenza A/B.

Secondary objectives are as follows:

- To identify potential risk factors of superinfections in ICU patients with COVID-19
- To compare the incidence of superinfections between the first and second waves of COVID-19
- To describe outcomes in ICU patients with COVID-19 with superinfections versus no superinfection
- To describe the pattern of pathogens causing the documented superinfection in ICU patients with COVID-19
- To describe the incidence of bacterial infections or colonization with resistant bacteria or fungi in ICU patients with COVID-19
- To estimate the use of antibiotics in ICU patients with COVID-19

2.7 | Outcomes

The primary outcome will be the incidence of superinfections in ICU patients with COVID-19 and ICU patients with influenza A/B, respectively, within 90 days follow-up.

Secondary outcomes will be mortality, length of stay in hospital, length of stay in ICU and type of pathogen, use of antibiotics and antibiotic resistance amongst pathogens during ICU admission up to 90 days follow up.

2.8 | Definitions

Microbiological findings: all positive blood cultures will be considered clinically significant except in cases where natural skin flora is identified. If typical skin commensals are identified, specialists in infectious diseases and clinical microbiology will review each case, if infection is corroborated by clinical symptoms and/or other microbiological findings, or if the blood culture finding is likely to be a contaminant. All other positive findings from microbiological test whether from cultures or from molecular (polymerase chain reaction; PCR) tests will be reviewed by specialists in clinical microbiology and infectious diseases to evaluate if infection or colonization is present. Infection is the microbiological identification of a relevant microorganism in the presence of clinical symptoms or radiological findings of active infection; absence of clinical symptoms and radiological findings indicate colonization. COVID-associated pulmonary aspergillosis is defined by the Defining and managing COVID-10-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance-definitions on proven, probable and possible COVID-19-associated pulmonary aspergillosis (CAPA).[23]

Any superinfection as assessed by specialists in infectious diseases and clinical microbiology in this time period will be registered. We will not distinguish between one or more superinfections in the analyses. It is expected that there may be several pathogens to one patient, resulting in more superinfections than number of patients. For the purpose of distinguishing between superinfection and co-infection, we will utilize the following definitions:

Superinfection case definition: a microbiologically diagnosed bacterial or fungal infection *following* COVID-19 infection or influenza A or B, respectively, in combination with clinically significant symptoms of infection. We will define *following* as a minimum of 48 h after diagnosis of COVID-19 or Influenza A/B.

Co-infection case definition: a microbiologically diagnosed bacterial or fungal infection *before or simultaneously* with a COVID-19 infection in combination with clinically significant symptoms of infection. We will define *before or simultaneously* as either positive culture within 48 h of the other.

Immunosuppression will be considered as any treatment with immunosuppressive drugs (TNF-inhibitors, calcineurin-inhibitors, mTOR-inhibitors, anti-thymocyteglobulin, IL2-inhibitors, mycophenolate, azathioprine and belimumab), including steroids such as dexamethasone over 12mg/d (as steroids now is standard of care to patients in respiratory distress because of COVID-19 and many trials regarding COVID-19 include the use of steroids[24]), methotrexate, cyclophosphamide, CD20-antibodies and alemtuzumab, or underlying diseases that causes immunodeficiency such as haematological malignancy or primary immunodeficiency on day 1 of the ICU stay.

Comorbidity will be defined by the Charlson Comorbidity Index[25] score registered in the DID.

Type of antibiotic therapy will be categorized into: carbapenems, flourquinolones, macrolides, cephalosporins, penicillins, and combination therapies (amoxicillin and clavulanic acid, piperacillin and tazobactam), glycopeptides, oxazolidinone and others.

2.9 | Ethics

The study is a registry-based study and in accordance with Danish legislation, no approval from ethical committees are needed.

Permission to obtain data from the national registries was applied for at the Danish Regions and permitted with journal-number R-20072621.

Permission to obtain data from the Danish Intensive Care Database and the nationwide COVID-19 database in association with the Research Machine have been applied for. The study will not start until all approvals have been obtained.

2.10 | Data analysis

2.10.1 | Statistical methods

Baseline, clinical and outcome characteristics as shown in the supplements will be presented using descriptive statistics. For numerical and categorial data, we will report medians with interquartile

ranges (IQR) and numbers (with percentages), respectively. These data will be presented separately for COVID-19 patients with/without superinfections and for influenza patients with/without superinfections.

The primary outcome will be assessed using a binary logistic regression model with any superinfections as the outcome, and disease (COVID-19 or influenza A/B, with the latter being the reference) as the primary independent variable of interest, with adjustment for the following potential confounders: sex (m/f), age (<50, 50-59, 60-69, 70-79, 80-89 and ≥90), cancer (including haematological malignancy) (y/n), immunosuppression (y/n), comorbidity (defined as the Charlson Comorbidity Index [0-37 points],[25,26] to be categorized), use of mechanical ventilation at baseline (non-invasive or invasive), use of renal replacement therapy (RRT) at baseline and COVID-19 wave 1 or 2. The results will be presented as an adjusted odds ratio (OR) for the effect of disease with 95% confidence intervals (CIs). As we expect few patients to have more than one superinfection, the outcome will be analysed as "any superinfection" and not the number of superinfections. In addition, the raw percentages of superinfections in each disease group will be presented using descriptive statistics, as outlined above. As most patients admitted to the ICU with COVID-19 are treated with broad spectrum antibiotics, which is expected to lower the incidence of bacterial pathogens, the primary outcome will additionally be presented descriptively as any superinfection registered on antibiotic-free days within the 90-day follow-up.

2.10.2 | Risk factors

We will assess the following variables as potential risk factors for acquiring a superinfection in patients with COVID-19:

- Sex (m/f)
- Age (<50, 50-59, 60-69,70-79, 80-89 and ≥90)
- Cancer (including haematological malignancy) (y/n)
- Immunosuppression on day 1 (y/n)
- Comorbidity (defined as the Charlson Comorbidity Index [0-37 points][25,26])
- Use of mechanical ventilation (MV) on day 1 of ICU admission (non-invasive or invasive) (y/n)
- Use of renal replacement therapy (RRT) on day 1 of ICU admission (y/n)
- COVID-19 wave 1 or 2
- Any antibiotic use on day 1 of ICU admission (y/n)

For the analysis of risk factors, we will assess the association between each potential predictor and superinfections for patients with COVID-19 using binary logistic regression models, with results presented as ORs with 95% CIs. We will present results from both unadjusted and adjusted (for all other potential predictors assessed) models.

Additional secondary outcomes, including 90-day mortality, will be presented descriptively for all patients and stratified by any superinfection (yes/no). The patterns of pathogens causing documented superinfections for both groups as well as use of antibiotic therapy (including types of antibiotics) for the COVID-19 group will be described using descriptive statistics (as described above). The incidence of bacterial or fungal infections or colonisation will also be presented descriptively.

2.11 | Study size considerations

The sample size will depend on the number of patients available in the databases. Assuming a 15% rate of superinfection in ICU patients with COVID-19 and 25% in ICU patients with influenza A/B [6,9,19] approximately 334 patients in each group are necessary to detect a difference using an alpha of 5% and a power of 90%.[27]

We expect inclusion of approximately 1000 patients in the COVID-19 group, and with an expected 15% rate of superinfections corresponding to approximately 150 events, we have decided to assess 13 model terms (nine risk factors, as some use multiple model terms) in the model assessing all predictors simultaneously.[28] We thus expect to have sufficient power for the analysis of potential predictors.

2.12 | Missing data

The amount of missing data for the included variables will be presented. Missing data in demographics and comorbidities will be handled using multiple imputation with chained Equation [29] We will use the predictive mean matching method for missing continuous variables and logistic regression for missing categorical variables.[30,31] We will impute 25 datasets for the COVID-19 group and include the following variables in the imputation model: sex, cancer (including haematological malignancy), immunosuppression (y/n), Charlson Comorbidity Index score, and use of MV on day 1 or use of RRT on day 1 and all outcomes (superinfection y/n, mortality, length of stay in hospital, length of stay In ICU, type of pathogen, type of antibiotic and resistance pattern). We will multiply impute 25 datasets in the influenza A/B group and include the following variables in the imputation model: sex, Charlson Comorbidity Index score and use of MV on day 1 or use of RRT on day 1 and all outcomes (superinfection y/n, mortality, length of stay in hospital, length of stay In ICU, type of pathogen, type of antibiotic and resistance pattern).

2.13 | Subject privacy and data confidentiality

Data will be stored in the respective databases only available to individuals by relevant application, as well as the combined file with extracted data available to the primary investigator and statistical aids. Data are pseudo-anonymized.

2.14 | Plan for record retention and disposal

Data will be stored in our database for 10 years and disposed of hereafter.

2.15 | Plans for dissemination of findings

We will aim to publish the results in an international, peer reviewed medical journal regardless of findings. Results will be reported in concordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement[33] and the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement.[34] This protocol has similarly been prepared according to the STROBE and RECORD checklists (completed checklists included in the supplements).

3 | DISCUSSION

The outlined cohort study will provide knowledge on superinfections in adult ICU patients with COVID-19 and influenza A/B. It is unknown whether ICU patients with COVID-19 are at increased risk of superinfections, as compared to ICU patients with influenza. In addition, the outlined study will provide knowledge on potential risk factors that may aid in future assessment of the risk of superinfection in patients with COVID-19.

Empirical antibiotics are widely used during the COVID-19 pandemic, however, the evidence supporting the need for this is lacking. We therefore also wish to describe the use of antibiotic therapy and resistant pathogen colonisations.

Strengths of the outlined study include use of existing nationwide databases (including all Danish patients with detected COVID-19 or influenza A/B admitted to an ICU during the period) with high data completeness and validity.[32]

Limitations include the historical dataset and use of routinely registered data from the electronic health records which may result in missing data and selection bias. Also, the necessity of utilizing two different time periods for the COVID-19 and influenza A/B patients increases the risk of confounding or differences due to temporal changes in case-mix or standards of care. When assessing risk factors, we have chosen to analyse life support (MV and RRT) on day 1 exclusively, as we expect analyses for more complex data over time periods will make for results too difficult to interpret.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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