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The diagnosis of superinfections in mechanically ventilated Covid-19 patients

Prospective, observational multicentre study

The inclusion criteria are as follows:

- Age > 18 years
- SARS-CoV-2 PCR positivity in the last 21 days
- Mechanical ventilation for Covid-19 pneumonia
- Presence of lung infiltrations on the chest X-ray or ground glass opacity, crazy paving or lung infiltrations on the chest CT
- Oxygenation disorder according to ARDS definition: PaO2 / FiO2 <300 mmHg with PEEP at least 5 cmH2O

The exclusion criteria are as follows:

- Disagreement with the inclusion in the trial

Outcomes

- Primary outcome is incidence and characteristics of superinfections in patients with COVID-19
- Secondary outcome:
    - Markers of infection / inflammation diagnostic values for the diagnosis of a specific type of superinfection
    - comparison of the incidence of bacterial and opportunistic superinfections with a historical cohort, where the extension of diagnostics with bronchoalveolar lavage was performed only in patients who did not respond to antibacterial therapy

Informed consent

Considering mechanical ventilation as the inclusion criteria, patients enrolled in this study will not be able to give informed consent. This will be replaced by consent obtained from a doctor independent of the study (at the University Hospital in Brno) or a close relative (at the University Hospital at St. Anne's in Brno), who will assess the risks and benefits of the study for the patient. Patients enrolled in the study are transported from the entire South Moravian region. In terms of their quick enrollment (within 36 hours of admission) and the inability of a close relative to appear in person to sign informed consent, consent to enter the study can be obtained as follows: The doctor will contact the close relative by telephone with two witnesses and the call will be with a loud speaker. After the consent of the close person to enroll the patient in the study, the signature clause will contain the names of the close relative / legal representative and the doctor who enrolled the patient in the study and communicated with the close relative. The telephone number, including the time of the call, as well as the names of both witnesses, including their signatures, will also be recorded. After regaining consciousness, patients will be asked for additional informed consent. If they refuse to participate in the study, the data obtained will not be used for analysis.

Size of the group of patients

The number of patients enrolled in the study depends on the epidemiological situation and the number of admitted patients with severe COVID-19 disease. We expect that the University Hospital at St. Anne's enrolls 75 patients and the University Hospital Brno also enrolls 75 patients. The size of the group is not relevant due to character of the study.

Monitored parameters

Bronchoalveolar lavage (BAL) is the only procedure that differs from standard care. It is usually performed in patients with a suspected lung infection that does not respond to antibiotic therapy. In the study, BAL will be performed early after admission and then in 7-day intervals (± 1 day).This interval can be shortened to a minimum of 3 days if there are signs of a new lung infection.

Basic characteristics of patients in trial

- age, gender
- COVID-19 vaccination and recovery from Covid-19 disease
- severe comorbidities – especially hypertension, diabetes (on PAD / insulin), chronic renal insufficiency, COPD, asthma, chronic heart failure, liver cirrhosis, immunosuppression or chemotherapy, immunodeficiency, cancer
- medication before admission to the ICU:
    - COVID-19 treatment: antiviral therapy (remdesivir,…), SARS-CoV-2 monoclonal antibodies, corticosteroids (type and total dose in dexamethasone equivalent), immunomodulatory monoclonal antibodies (eg tocilizumab), other drugs used to treat COVID-19
    - chronically used steroids and other immunosuppressive drugs
    - antibiotics
- first symptoms of respiratory disease, date of first positive PCR test
- length of UPV, NIV or HFNO before enrollment in the study
- APACHE II and SOFA scores at the day of enrollment in the study
- ClinicalFrailtyScale

Daily monitoring:

- laboratory: arterial blood gases, blood count + differential blood count+ reticulocytes, CRP, PCT, IL-6, urea, creatinine, bilirubin
- UPV parameters (RR, Vt, PEEP, FiO2, Pplateau, MV)
- need for vasopressors (Y / N)
- renal replacement therapy(Y / N)
- prone position (Y / N)
- ECMO (Y / N)
- medication: antibiotics, antifungal drugs, antiviral drugs; anti-SARS-CoV-2 monoclonal antibodies; immunomodulatory therapy (steroids, immunomodulatory monoclonal antibodies - eg tocilizumab, immunosuppressants); other medicines used to treat COVID-19

Extended monitoring

- indication:
  - within 36 hours of enrollment in the study
  - repeated when superinfection is suspected – especially when:
  - worsening or development of new lung infiltrations
  - worsening of oxygenation
  - new purulent secretion from the lower respiratory tract
  - increase of the level of CRP or PCT, leukocytosis or leukopenia
  - vasopressors administration or increasing the need for vasopressors
  - new fever
- repeated examination will be performed no earlier than 3 days from the previous BAL
- the examination will be routinely repeated at 7-day intervals (± 1 day) from the previous BAL
- for re-examination, paO2 / FiO2 must be<300 mmHg; if the condition is not met, repeated examination will be performed only if the condition worsens with a decrease in paO2 / FiO2 <300 mmHg

Bronchoscopy and BAL:

- standardized procedure according to the protocol
- bronchoscopic finding
- laboratory diagnostics of BAL fluid:
  - PCR: pneumonia panel, viral panel, sepsis panel – see below, quantitative monitoring of SARS-CoV
  - galactomannan (OKMI FN Brno)
  - cultivation - bacteria and fungi (local microbiology FNUSA / FNB)
  - albumin, total protein
  - part of the sample will be frozen for possible further analysis
- Blood:
  - OKMI FN Brno: galactomannan, beta-D-glucan
  - biochemistry: ALT, AST, ALP, GMT, LD, CK, ferritin
  - hematology: D-dimers

Clinical results:

- incidence of bacterial, fungal and viral superinfections
- comparison of PCR diagnostics and pathogens detected in cultivation and antigens
- days without UPV until day 28, days without organ support until day 28
- ICU length of stay
- length of stay in hospital
- mortality (in ICU, hospital, 28-day, 90-day)

End of the monitoring:

- daily and extended monitoring will end after disconnection from mechanical ventilation (CPAP or NIV are not considered as mechanical ventilation)
- participation in the study ends 90 days after enrollment