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Critical Rounds

MICRO LABS LIMITED

Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring "CRITICONNECT" containing latest information in the field of Critical care medicine.

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Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Ltd

The potential of Neutrophil Elastase Inhibitors prophylaxis in SARSCoV-2-induced respiratory complications

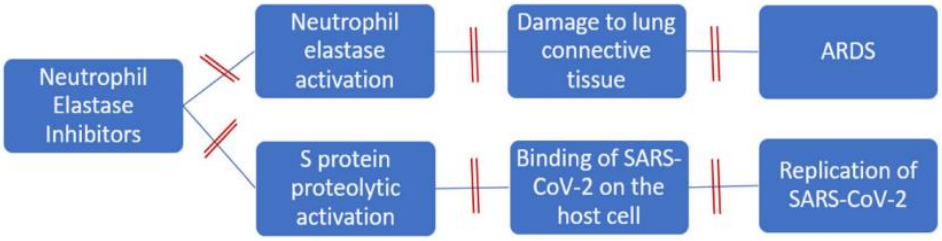
COVID-19 pandemic caused by SARS-CoV-2 continues to rise globally, scientists, health care agencies, and pharmaceutical companies are struggling to find a "cure" and to devise mortality reduction treatment strategies. "Repurposing" proven medications to counter COVID-19 appears to be a promising technique.

As respiratory failure remains one of the leading causes of death in COVID-19 patients, the potential benefit of neutrophil elastase inhibitors (NEIs) in patients hospitalized with severe COVID-19 was discussed critically in this commentary. Around one in three COVID-19 patients admitted to a hospital experience chronic inflammatory disorders such as cytokine release syndrome (CRS) and acute respiratory distress syndrome (ARDS) for example.

Since lymphocytopenia is sometimes recorded in serious COVID-19 patients, it indicates that leukocytes other than T cells are likely to mediate systemic inflammatory problems correlated with disease severity and mortality. The decline in lymphocyte count is attributed to an increase in neutrophil count and a decrease in monocytes, eosinophils, and basophils, indicating that increased neutrophil count and neutrophil-to-lymphocyte ratio together with lymphocytopenia can be important predictors of severity of disease in COVID-19 patients. A recent case study backed that hypothesis. The worsening of the individual on day 12 of illness was followed by an increase in his count of neutrophils on day 11, whilst the lymphocytes and monocytes stayed small. As there is always a brief period between hospital entry and the initiation of ARDS in serious situations, immediate prophylactic treatment is required to avoid infection and mortality in an appropriate manner.

Neutrophils play a crucial role in ARDS production by developing toxic mediators such reactive oxygen species and proteases, in particular elastase. In addition, in reaction to viral infections, neutrophils that generate interleukin 6 (IL-6), especially single-stranded RNA viruses such as SARS-CoV-2 through a Toll-like receptor 8 (TLR8)-mediated mechanism.

Such cells are also essential reservoirs of lung soluble IL6 receptors (IL-6R) and may lead to chronic respiratory disease pathogenic IL-6R trans-signaling. In patients diagnosed with chimeric antigen receptor T cell (CART) lymphoma the significance of this form of signaling for the production of CRS has been demonstrated. These studies suggest that increased neutrophil counts in patients with ARDS can contribute to CRS and lung damage. Additionally, the elastase secreted by these cells is one of the key proteolytic enzymes shown to activate the corona virus spike (S) protein and shift the viral entry to an independent low pH route. It is advocated that the use of NEIs such as sivelestat in high-risk COVID-19 patients to alleviate the neutrophil-induced damage. Sivelestat initiation will serve two strategic purposes; first, it will mitigate the damaging effect of neutrophil elastase on the lung connective tissue, and second, it will limit the ability of the virus to spread by preventing proteolytic activation of the protein S.



Mechanism of action of neutrophil elastase inhibitors in COVID-19

Sivelestat is approved for the treatment of acute lung injury and ARDS in Japan and the Republic of Korea. While current clinical findings are quite contradictory, the extent of lung damage in these patients remains a significant indicator for the medical outcomes. Clinical studies that recorded promising effects of sivelestat therapy of ARDS and ALI patients had enrolled participants mainly with a lung injury level (LIS) < 2.5. At the other side, studies documenting adverse effects including the STRIVE study had enrolled patients predominantly with LIS > 2.5 stressing the crucial value of an early intervention with sivelestat. Notably, participants involved in the STRIVE trial were more heterogeneous than the other studies which contained more events with non-pulmonary organ defects, disorders that are not applicable to COVID-19 participants. In addition, post-hoc analyzes of patient subgroups from the STRIVE study with mean LIS < 2.5 and those with systemic inflammatory response syndrome revealed a positive sivelestat result on mortality rates and ventilator-free days. More specifically, the STRIVE report declined to find any signs of drug-related toxicity and gave no reasonable reason for the elevated long-term mortality in groups treated with sivelestat.

Although current evidence to support the use of NEIs in ARDS induced by COVID-19 is lacking, it was hypothesized that early administration of these drugs to patients with lymphocytopenia and LIS < 2.5 may be of significant value to prevent disease progression. Future clinical trials should be designed to assess the efficacy of sivelestat in patients admitted to hospital with high risk of respiratory failure in COVID-19.

Source: Mohamed et al. Neutrophil Elastase Inhibitors: A potential prophylactic treatment option for SARSCoV-2-induced respiratory complications? Critical Care 2020; 24:311

Relation between Noninvasive Oxygenation Strategies with All-Cause Mortality in cases with Acute Hypoxemic Respiratory Failure

INTRODUCTION

Acute hypoxemic respiratory failure is one of the leading causes of admission in adult patients to an intensive care unit, often resulting in endotracheal intubation and invasive mechanical ventilation. The current pandemic of coronavirus disease in 2019 (COVID-19) further stressed the importance of understanding the best approach for providing respiratory support to patients with respiratory failure.

Severe adverse events are associated with invasive mechanical ventilation, and avoiding unnecessary endotracheal intubation remains a major goal in managing patients with acute hypoxemic respiratory failure. Multiple non-invasive oxygenation strategies have been developed to support oxygenation and ventilation that may result in reduced risk of intubation and mortality in the endotracheal. Which of these is the most effective, remains unclear. Normal oxygen therapy was the traditional method for supplying supplementary oxygen to patients with severe hypoxemic respiratory failure, usually at flow levels of less than 15 L / min. Alternatively, non-invasive ventilation was promoted using either a face mask or helmet interface to reduce the risk of intubation with the endotracheal. Oxygen delivery through the nasal cannula at high flow has been gaining acceptance due to the ability to more closely match the inspiring demand of a patient in setting hypoxemia. Conflicting results have been generated by randomized clinical trials (RCTs) comparing the efficacy of non-invasive ventilation or high-flow nasal oxygen with standard oxygen treatment. Patients in control groups received standard oxygen therapy in most of these trials, and there were few head-to - head comparisons of the other different non-invasive modalities of oxygenation. In addition, most metaanalyzes were limited to traditional pairwise comparisons and therefore did not combine direct and indirect evidence for any possible comparisons.

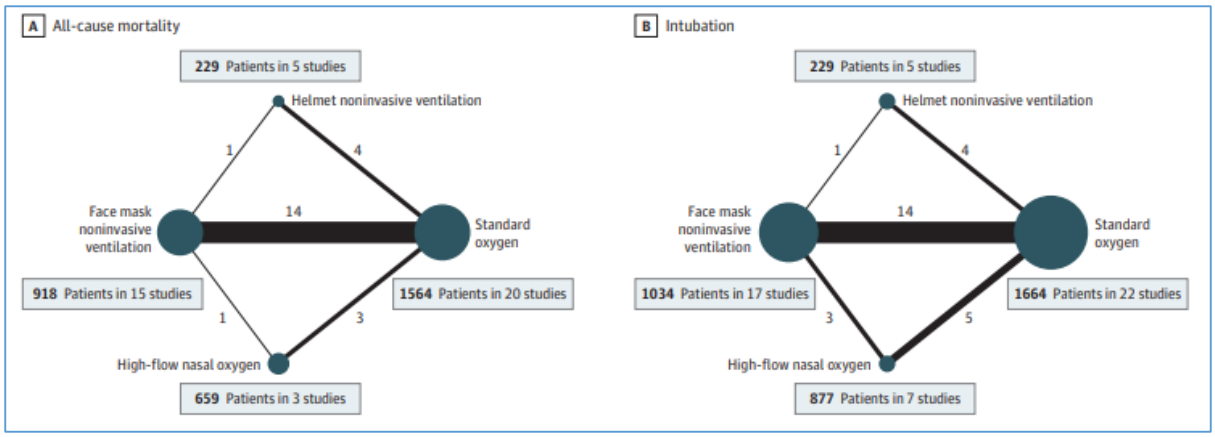
METHODS

Randomized clinical trials enrolling adult participants with acute hypoxemic respiratory failure comparing high-flow nasal oxygen, face mask noninvasive ventilation, helmet noninvasive ventilation, or standard oxygen therapy.

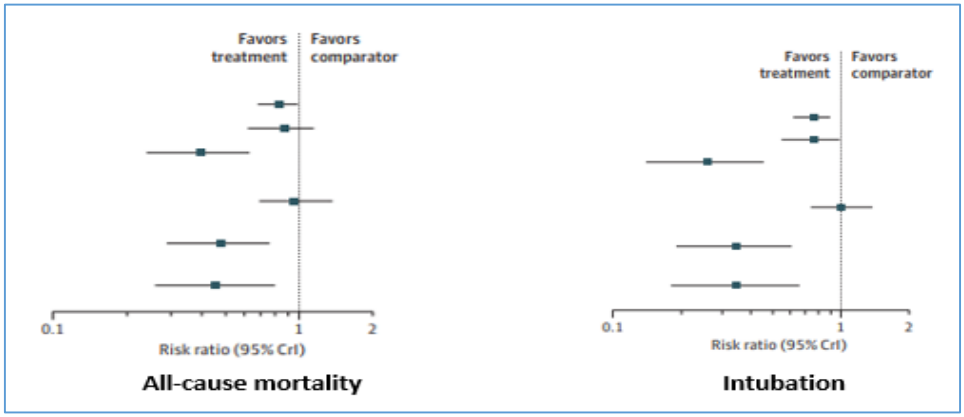
Two reviewers independently extracted individual study data and evaluated studies for risk of bias using the Cochrane Risk of Bias tool. Network meta-analyses using a bayesian framework to derive risk ratios (RRs) and risk differences along with 95%credible intervals (CrIs) were conducted. GRADE methodology was used to rate the certainty in findings. The primary outcomewas all-cause mortality up to 90 days. A secondary outcome was endotracheal intubation up to 30 days.

RESULTS

Twenty-five randomized clinical trials (3804 participants) were included. Compared with standard oxygen, treatment with helmet noninvasive ventilation (RR, 0.40 [95%CrI, 0.24-0.63]; absolute risk difference, −0.19 [95%CrI, −0.37 to −0.09]; low certainty) and face mask noninvasive ventilation RR, 0.83 [95%CrI, 0.68-0.99]; absolute risk difference, −0.06 [95%CrI, −0.15 to −0.01]; moderate certainty) were associated with a lower risk of mortality (21 studies [3370 patients]). Helmet noninvasive ventilation (RR, 0.26 [95%CrI, 0.14-0.46]; absolute risk difference, −0.32 [95%CrI, −0.60 to −0.16]; low certainty), face mask noninvasive ventilation (RR, 0.76 [95%CrI, 0.62-0.90]; absolute risk difference, −0.12 [95% CrI, −0.25 to −0.05]; moderate certainty) and high-flow nasal oxygen (RR, 0.76 [95%CrI, 0.55-0.99]; absolute risk difference, −0.11 [95%CrI, −0.27 to −0.01]; moderate certainty) were associated with lower risk of endotracheal intubation (25 studies [3804 patients]). The risk of bias due to lack of blinding for intubation was deemed high.



Network Plots for the Association of Noninvasive Oxygenation Strategies with All-Cause Mortality and Intubation



Forest Plots for the Association of Noninvasive Oxygenation Strategies With Study Outcomes

Noninvasive oxygenation strategies compared with standard oxygen therapy were significantly associated with lower risk of death.

CONCLUSIONS

In this network meta-analysis of trials of adults with acute hypoxemic respiratory failure, treatment with non-invasive oxygenation Strategies compared with standard oxygen therapy was associated with lower risk of death. Further research is needed to better understand the relative benefits of each strategy.

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Effect of C-Reactive Protein Guided Antibiotic Treatment in Uncomplicated Gram-Negative Bacteremia

INTRODUCTION

Long-term antibiotic exposure drives resistance emergence and increases adverse effects such as clostridioides difficult infection and other microbiotic disruptions; longer antibiotic courses are also associated with longer hospitalizations and higher costs. Gram-negative bacteremia, due in particular to Escherichia coli, is a common infection acquired by the community, and associated with health care. Clinicians' choice of antibiotic duration for this infection shows marked heterogeneity. Most patients with bacterial bloodstream infections still receive between 10 and 14 days of antibiotics, although those durations are largely based on expert opinion, and recent evidence from retrospective analyzes and a randomized trial indicates clinical non-inferiority between 7-day and 14-day courses. Set antibiotic durations offer clear instructions but do not take into consideration the characteristics of the infection or the reaction to the medication. Given the high variability of pathogens and their hosts, a different approach should be to individualize durations via guidance offered by biomarkers. This biomarker is not always available, affordable, or antibiotic-sparing, although procalcitonin provides guidance. C-reactive protein (CRP), an acute-phase protein produced by hepatocytes to coactivate the complement system in reaction to antigenic and other stimuli, is an inflammatory state marker which is readily available, inexpensive and highly responsive. The objective of this clinical trial was to compare the effects of individualized CRP-guided antibiotic durations and fixed 7-day durations on clinical failure by day 30 in patients with gram-negative bacteremia, with 14-day durations

METHODS

Multicenter, noninferiority, point-of-care randomized clinical trial including adults hospitalized with gram-negative bacteremia conducted in 3 Swiss tertiary care hospitals between April 2017 and May 2019, with follow-up until August 2019. Patients and physicians were blinded between randomization and antibiotic discontinuation. Adults (aged 18 years) were eligible for randomization on day 5 (±1 d) of microbiologically efficacious therapy for fermenting, gram-negative bacteria in blood culture(s) if they were afebrile for 24 hours without evidence for complicated infection (eg, abscess) or severe immunosuppression.

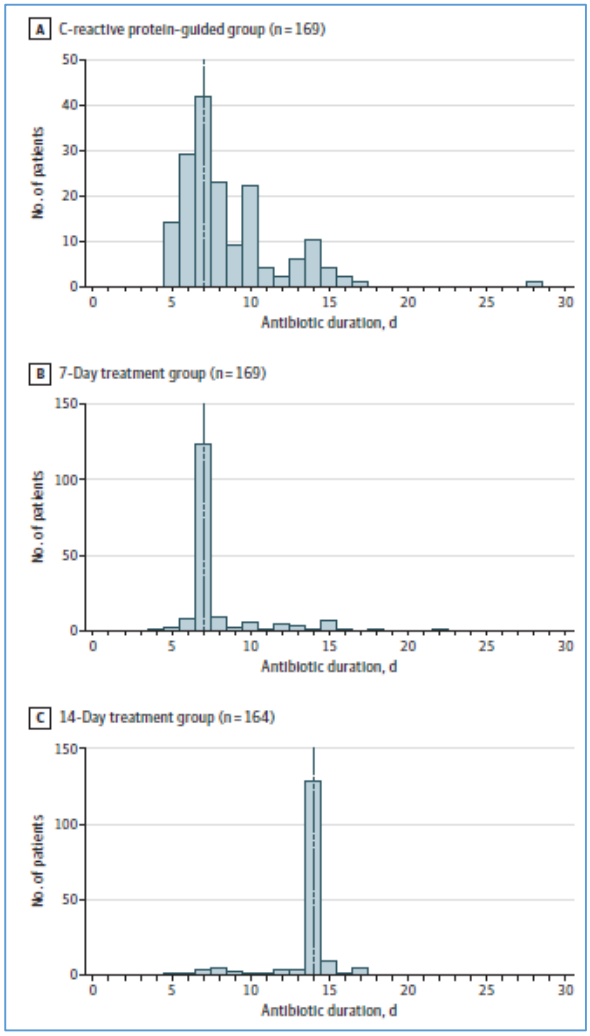
Intervention Randomization in a 1:1:1 ratio to an individualized CRP-guided antibiotic treatment duration (discontinuation once CRP declined by 75% from peak; n = 170), fixed 7-day treatment duration (n = 169), or fixed 14-day treatment duration (n = 165).

Main outcomes and measures The primary outcome was the clinical failure rate at day 30, defined as the presence of at least 1 of the following, with a non-inferiority margin of 10%: recurrent bacteremia, local suppurative complication, distant complication (growth of the same organism causing the initial bacteremia), restarting gram-negative–directed antibiotic therapy due to clinical worsening suspected

to be due to the initial organism, or death due to any cause. Secondary outcomes included the clinical failure rate on day 90 of follow-up.

RESULTS

Among 504 patients randomized (median [interquartile range] age, 79 [68-86] years; 306 of 503 [61%] were women), 493 (98%) completed 30-day follow-up and 448 (89%) completed 90-day follow-up. Median antibiotic duration in the CRP group was 7 (interquartile range, 6-10; range, 5-28) days; 34 of the 164 patients (21%) who completed the 30-day follow-up had protocol violations related to treatment assignment. The primary outcome occurred in 4 of 164 (2.4%) patients in the CRP group, 11 of 166 (6.6%) in the 7-day group, and 9 of 163 (5.5%) in the 14-day group (difference in CRP vs 14-day group, −3.1% [1-sided 97.5% CI, − to 1.1]; P < .001; difference in 7-day vs 14-day group, 1.1% [1-sided 97.5% CI, − to 6.3]; P < .001). By day 90, clinical failure occurred in 10 of 143 patients (7.0%) in the CRP group, 16 of 151 (10.6%) in the 7-day group, and 16 of 153 (10.5%) in the 14-day group.



Durations of Antibiotic Therapy in the Primary Analysis Set in a Study of the Effect of C-Reactive Protein (CRP)–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on Clinical Failure in Patients with Uncomplicated Gram-Negative Bacteremia

CRP-guided treatment and 7-day treatment were noninferior to 14-day treatment in patients with uncomplicated gram-negative bacteremia, but interpretation is limited by the large noninferiority margin compared with the low observed event rate and lower adherence in the CRP-guided group.

CONCLUSIONS

In adults with uncomplicated gram-negative bacteremia, clinical failure levels of 30 days for CRP-guided treatment period and fixed 7-day care is non-inferior to the defined 14-day care term. However, understanding is constrained by the broad non-inferiority gap relative to the low observed case incidence, as well as poor adherence and wide variety of treatment durations in the CRP-guided population.

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