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# Critical Rounds

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## Inside This Issue



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## Are Ventilators being overused in COVID-19: A feedback from world-renowned critical care specialists

As emergency and intensive care physicians across the globe operate frenzied to save people's lives of COVID-19 critically sick, one of the world's leading critical care specialists advises of what he terms the abuse and overuse of artificial ventilators.

A world-renowned Italian intensive care physician, Luciano Gattinoni, said the normal procedure cannot be extended to an unstandard illness. He referred to the current protocol for the machines used to push oxygen into the lungs of patients with COVID-19 seriously ill, the disease caused by the novel coronavirus.

At the onset of the coronavirus pandemic in Italy, several emergency departments quickly put COVID-19 patients with alarmingly low oxygen rates on mechanical ventilators, a common procedure for an acute respiratory disease syndrome (ARDS) diagnosis.

But in a paper published this week in the journal Intensive Care Medicine, Gattinoni and colleagues reported that COVID-19 tends to diverge from regular ARDS in key respects, and that the typical prescribed usage of high pressure ventilators that function with standard cases of respiratory failure can potentially damage certain COVID-19 patients.

COVID-19 patients, including those suffering from ARDS, have below-normal amounts of oxygen in their blood, which contributes to respiratory difficulties. For ARDS situations, the lungs surrender their elasticity. Yet in certain COVID-19 situations, the lungs stay resilient, so with the poor oxygen rates, people are able to continue breathing for some time.

He notes that this rare mixture is almost never found in extreme ARDS, and that patients with normal-looking lungs but insufficient oxygen are at risk of pulmonary failure from ventilators, where air pressure destroys the fragile air sacs that share oxygen with blood.

In the research by Gattinoni, just 20 to 30 per cent of patients completely matched the criteria for severe ARDS. CT scans are often used to distinguish various categories of patients needing specific forms of care, says Gattinoni. But if CT scans are not available, doctors can implicitly gage the needs of a patient dependent, for example, on "surrogate" lung stiffness measurements and other variables.

Gattinoni explains that, in the regular ARDS care, patients are often placed on a ventilator too late, or too early, with the strain generated by the ventilator becoming too high, causing harm. Marco Garrone, an emergency doctor at the Mauriziano Hospital in Turin, Italy, calls Gattinoni's paper "a game changer." He said it explicitly explains what he and his colleagues witnessed in the emergency room after the pandemic erupted in northern Italy late February.

Garrone said they started with a one-size-fits-all mentality that didn't pay off. And they're already seeking to postpone as long intubation as necessary. Factors such as the individual's general wellbeing before getting COVID-19, or how sick they are by the time they arrive at the facility, can often influence how much a person is paying.

**Oxygen without force**

Garrone claims his emergency room now continues with non-invasive ventilation — various methods to deliver oxygen into the lungs of patients without coercion, such as a mask or a nasal cannula. It allows patients to inhale adequate oxygen in the early phases of the illness, without destroying their lungs.

Physicians in the state of New York and elsewhere have raised common fears over placing people on the ventilators too early and exerting too much energy. Others have begun to postpone their use, after New York city recorded an 80 per cent mortality rate for those who go on ventilators.

Nonetheless, the Toronto University Health Network and Mount Sinai Hospital's director of critical care is cautioning against making any strong assumptions from Gattinoni's study.

Niall Ferguson, who is also the site chief at Toronto General Hospital, also claims that the 80% figure in New York is hypothetical and tends to be "serious" without evidence to back it up.

With several near-capacity ICUs, he states, doctors do not have the time to randomize patients to one care regimen or another to test the effectiveness of each.

Earlier this month JAMA released one report on the death rate of COVID-19 patients on ventilators in Lombardy's hardest-hit Italian area. This also found a fairly small death rate on ventilators, 26 per cent, although both Ferguson and Garrone discounted the findings as several people were already on ventilators while the statistics were gathered and might have died afterwards.

Garrone said it is when ICU units become overloaded where the possibility of the ventilators getting misused is greatest.

**'It's been a constant flood'**

Everybody is thinking of COVID as a tsunami because a tsunami is a moving wave. It was a relentless storm abroad, in Sicily. Throughout Italy ICU physicians are well versed throughout ventilation. Yet the figures of these patients were so daunting that they trickled into the emergency room from the ICU. So this is when we began to ventilate them.

Ferguson admits that the usage of ventilators is a concern for physicians who are drawn into a medical scenario, less familiar with the machines. Yet he said the IC group of physicians he's in contact with was fully informed of the need to individualize care of COVID-19 cases, which was the key argument of Gattinoni. Ferguson also said that there is a compromise to be found in seeking something that is straightforward and universally available and attempting to tailor something for and individual now.

Laura Duggan, an anesthesiologist at the Ottawa Hospital, told the Emcrit podcast for emergency and critical care doctors that she wanted to intubate patients with low oxygen instantly, as other ICU physicians, but that she was "happy to see the pendulum swing back a little" and find out what more might be accomplished.

# Acute kidney injury in COVID-19 infected patients

**AKI** in chronically compromised patients indicates a life-threatening condition, which also contributes to elevated likelihood of death. As Wilson et al. recently reported, the initiation of moderate-to-severe AKI identified a higher-risk group of ARDS patients, with a substantial mortality risk.

Considering the potential pathogenic pathways of AKI-associated ARDS, AKI can be ascribed to different causes such as gas exchange deficiency, hemodynamic alterations like right heart failure, fluid overload and systemic obstruction, injurious mechanical ventilation techniques, and secondary infection / sepsis growth.

Several studies have demonstrated the importance of the inflammatory / immune-mediated response to the release of high rates of circulating harmful mediators capable of interfering with kidney-resident cells that induce endothelial impairment, microcirculatory derangement and tubular injury.

According to previous research, the SARS-CoV beta coronaviruses and the most recent SARS-CoV-2 use angiotensin converting enzyme 2 (ACE-2) as a receptor to promote viral entry into target cells; ACE-2 is also located on the surface of tubular kidney cells, and their infection can intensify the local inflammatory reaction and thereby the frequency and length of AKI episodes.

**Key points of acute kidney injury in SARS-CoV-2 infected patients**

- AKI is frequently observed in ARDS patients affected by different comorbidities: similar findings were observed in Wuhan COVID-19 infected patients.
- ARDS-associated AKI may be ascribed to several causes including an inflammatory/immune reaction characterized by an enhanced release of circulating mediators able to interact and damage kidney-resident cells.
- Kidney epithelial cell viral infection may worsen local inflammatory response and consequently the incidence and the duration of AKI episodes.
- These comorbidities may be associated with a pre-existing chronic decline of kidney function (concept of renal functional reserve) and with a tendency to develop AKI episodes.
- Identification of patients with AKI may lead to a better allocation of hospital resources: early biomarkers of AKI may favor this process.
- The use of extracorporeal blood purification techniques and anti-viral therapies may theoretically limit the systemic and local inflammatory response at least in part responsible for multiple organ failures including AKI.

As defined, AKI formed along with secondary infections and acute cardiac injury, on average, 9 days after admission. Age, extent of illness, and prevalence of diabetes are risk factors for AKI in ARDS patients; however, the extent of AKI is correlated with BMI and heart failure history is often known as cardio-renal syndrome.

Similar observations, including the presence of diabetes, have been reported for COVID-19-associated ARDS. Both of these potential factors coupled to the elevated prevalence of AKI in elderly people contribute to the theory that renal injuries predominate in patients with pre-existing severe kidney function dysfunction that is impossible to determine dependent solely on plasma creatinine rates, thereby proposing to use modern biomarkers for early kidney injury.

Determining the likelihood of developing AKI in patients diagnosed with SARS-CoV-2 or escalating to extreme AKI involving renal replacement therapies is also a significant phase in the patient's prognosis and in the early adoption of prevention and protective steps.

Classical assessment of AKI is still based on serum creatinine and urine output, but they represent only indicators of established kidney damage. In this scenario, much attention has focused on novel biomarkers in the last years, particularly on markers of acute tubular stress/damage such as TIMP-2 (tissue inhibitor of metalloproteinase 2) and IGFBP7 (insulin-like growth factor binding protein 7) and their product [TIMP- 2] identified using the NephroCheck Test.

The method was designed for the estimation of mild to extreme AKI within 12 h of ICU entry, which is the only one approved in this environment by the Food and Drug Administration. Many evidence indicates that NephroCheck application can help physicians recognise patients with tubular stress prior to manifestation of kidney dysfunction.

In this environment, critically ill patients are currently subjected to many possible kidney insults (SARS-CoV-2 infection, medication nephrotoxicity, contrast media) during ICU stay; serial measurements of such biomarkers can be a valuable resource for predicting AKI within the first 7 days of ICU stay.

A positive result that indicates a high risk of developing AKI may include early nephrology assessment, close monitoring of creatinine and urine production, volume and hemodynamic state optimisation, avoidance of iodinated comparison procedures when appropriate, and use of nephrotoxic drugs (e.g. aminoglycosides, ACE inhibitors, NSAIDs), or close monitoring of medication rates (vancomycin)

ARDS patients that experience AKI show a greater likelihood of serious consequences and death. It is convincing to develop a predictive model to stratify patients diagnosed with SARS-CoV-2 according to AKI severity; this method may contribute to an creative interventional technique focused on biomarkers in this evolving clinical contest leading to a better distribution of hospital resources.

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# Empirical high-dose Meropenem: Clinical outcomes in critically ill patients with sepsis and septic shock

## INTRODUCTION

Sepsis is characterized as a severe disruption of the organ that results from the dysregulated host's reaction to the infection. This condition is a big health-care problem causing substantial morbidity and mortality. Effective sepsis detection and effective first hour treatment are the cornerstones for enhancing medical care. Initial pause in an effective antimicrobial treatment was associated with an rise in mortality. However, owing to altered pharmacokinetics (PK), and elevated multidrug-resistant (MDR) pathogens in critically ill patients, sufficient antimicrobial dosing is difficult.

Meropenem, a part of the carbapenem family, is commonly used as medical treatment for managing sepsis and septic shock with respect to its broad-spectrum efficacy and low toxicity profile. The meropenem PD, comparable to other beta-lactam antibiotics, is a time-dependent process. To achieve their bactericidal function, carbapenems need at least 40 per cent fT > MIC. Nonetheless, to obtain beneficial microbiological and clinical results for critically ill patients with serious infections, 100 per cent fT > MIC achievement is needed, and extended meropenem infusion is advised.

This study aimed to evaluate the effects of an empirical therapy of high-dose versus standard-dose meropenem in sepsis and septic shock patients.

## METHODS

This was a prospective randomized open-label study to compare the changes of modified sequential organ failure assessment (mSOFA) score and other clinical outcomes of the high-dose meropenem (2-g infusion over 3 h every 8 h) versus the standard-dose meropenem (1-g infusion over 3 h every 8 h) in sepsis and septic shock patients. Patients' characteristics, clinical and microbiological outcomes, 14 and 28-day mortality, vasopressor- and ventilator-free days, intensive care unit (ICU) and hospital-free days, percent of the time of antibiotic concentrations above the minimum inhibitory concentration (%T>MIC), and safety were assessed.

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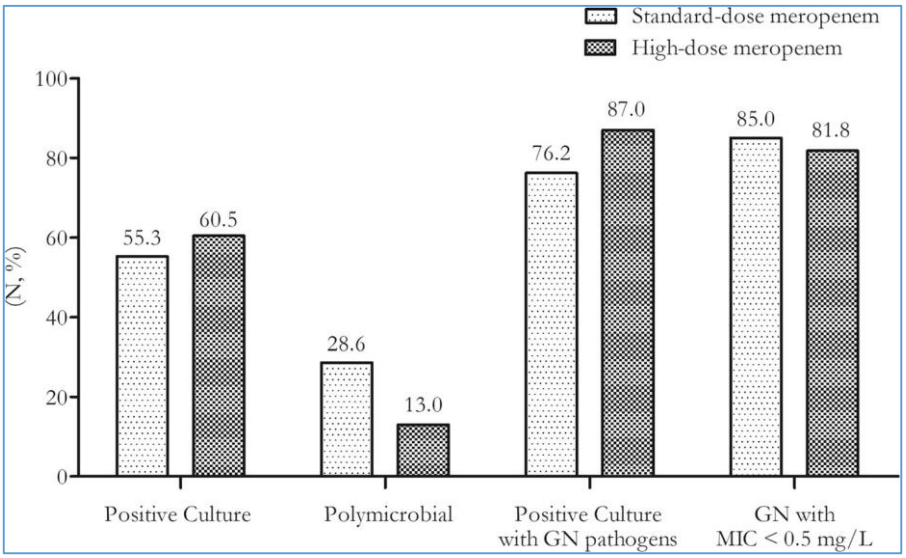
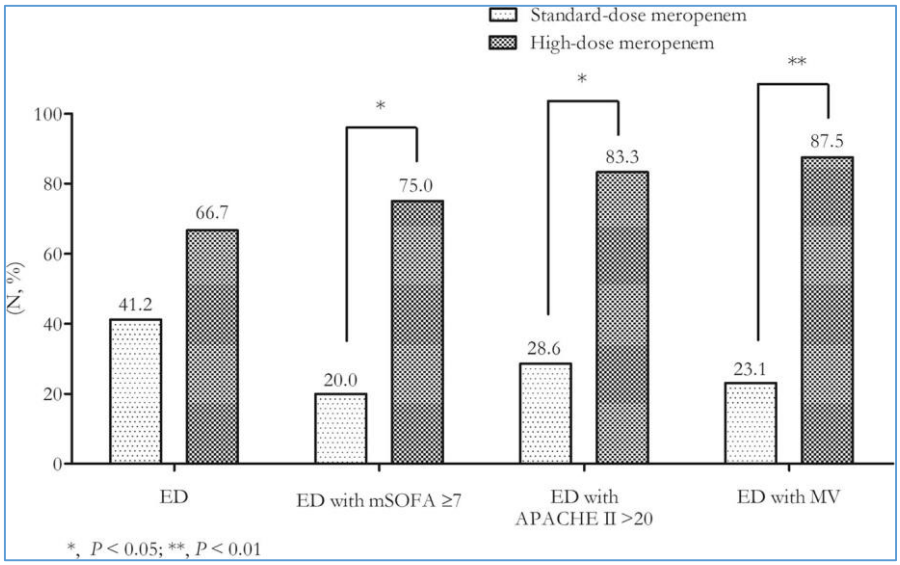
## RESULTS

Seventy-eight patients were enrolled. Median delta mSOFA was comparable between two groups (– 1 in the high-dose group vs. – 1 in the standard-dose group; P value = 0.75). There was no difference between the two groups regarding clinical and microbiological cure, 14- and 28-day mortality, vasopressor- and ventilator-free days, and ICU- and hospital-free days. In patients admitted from the emergency department (ED) with a mSOFA score ≥ 7, the high-dose group demonstrated significantly

better microbiological cure compared with the standard-dose group (75% (9/12 patients) vs. 20% (2/10 patients); P value = 0.03). Likewise, the high-dose group presented higher microbiological cure rate in patients admitted from ED who had either APACHE II score > 20 (83.3% (10/12) vs. 28.6% (2/7); P value = 0.045) or on mechanical ventilator (87.5% (7/8) vs. 23.1% (3/13); P value = 0.008) than the standard-dose group. Adverse events were comparable between the two groups.




**Bacterial isolates. GN, gram-negative bacteria; MIC, minimum inhibitory concentration**




**Comparison of microbiological cure rate in patients who admitted from the emergency department.** ED, emergency department; mSOFA, modified sequential organ failure assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; MV, mechanical ventilation

## CONCLUSIONS

Empirical treatment with a large dose of meropenem in chronically sick patients found little significant improvement in the health effects of the patient when opposed to a normal meropenem dosage.

Subgroup study, however, found that in sepsis or septic shock patients admitted from ED, patients who were admitted from ED and had mSOFA score some 7 or APACHE II score > 20 or who had been on mechanical ventilator displayed superior microbiological cure efficiency.

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