

Oxygen therapy and respiratory care in patients with covid-19 ARDS and AKI





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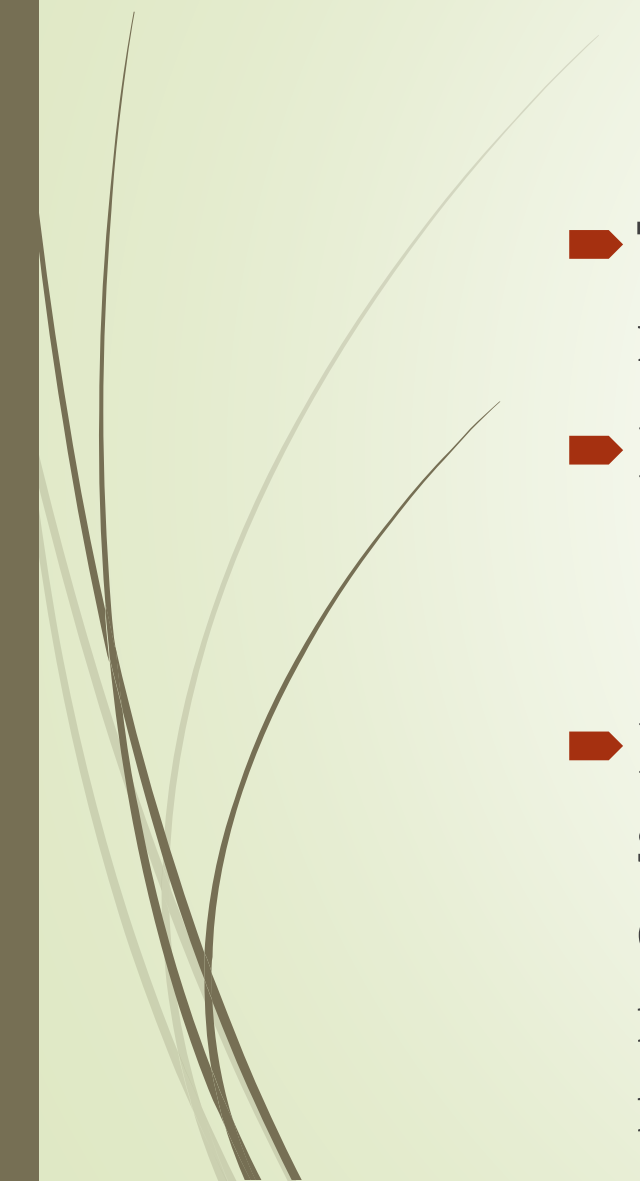

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- The SARS-CoV-2 has been identified as the agent of the pandemic known as Coronavirus disease 2019 (COVID-19). The first cases were noted towards the end of 2019 in Wuhan, China. COVID-19 infection is spontaneously resolute in most cases. The clinical presentation can vary from mild respiratory symptoms to severe pneumonia progressing to fulminant acute respiratory failure (ARF). COVID-2019 pneumonia is characterized by bilateral infiltrates which can progress to diffuse alveolar condensations.





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- The estimated prevalence of COVID19-related acute respiratory failure (ARF) is 15-20%.
 - In different published series, 41% had received O₂, 4-13% of patients non-invasive ventilation (NIV) and 2-12% needed intubation and mechanical ventilation.
 - In addition to MV some other techniques of respiratory support such as non-invasive ventilation (NIV) , continuous positive airway pressure (CPAP) or high flow oxygen therapy (HFOT) could be used in some forms of ARF.
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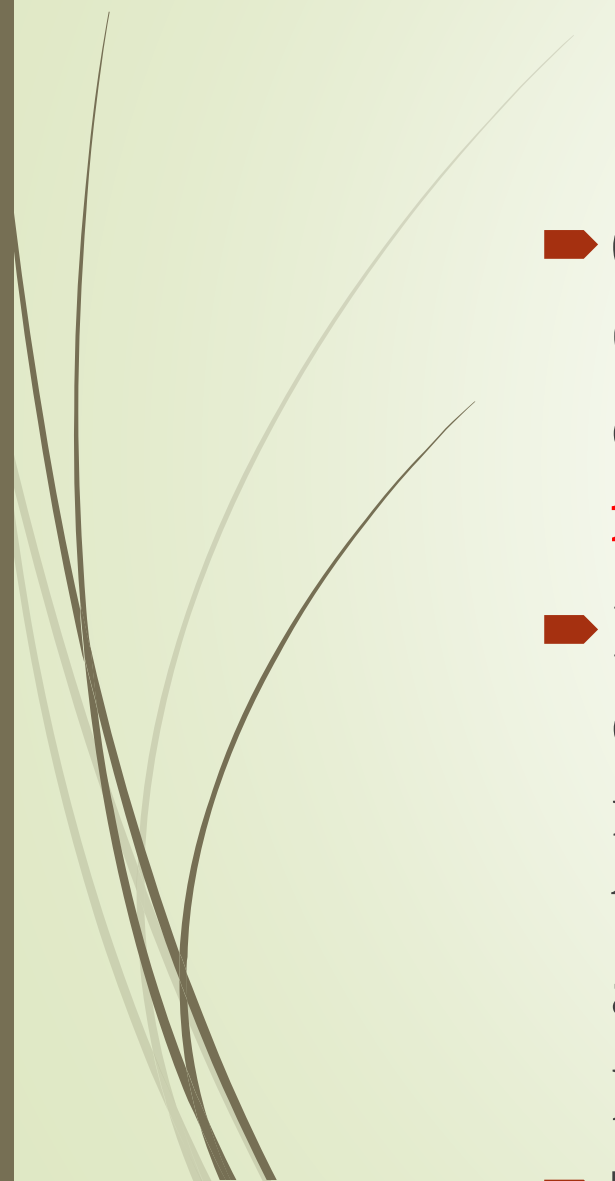
Oxygen therapy

Oxygen should be used in case of severe CoVID19 pneumonia probably as soon as SpO₂ <92% with a SpO₂ target between 92 and 96%.




- A meta-analysis of 25 randomized controlled studies has shown that a strategy with no upper limit on O₂ flow (“liberal” approach) increases the risk of in-hospital death compared to a conservative (“targeted” approach). This contrast with the results of a recent randomized controlled trial (RCT) comparing a “liberal” O₂ therapy strategy (target SpO₂ > 96%) to a conservative one (target SpO₂ >88% < 92%;). This study showed no difference in 28-days survival but an over mortality at 90 days in the conservative group. Thus, based on those data, a target of >92 < 96%


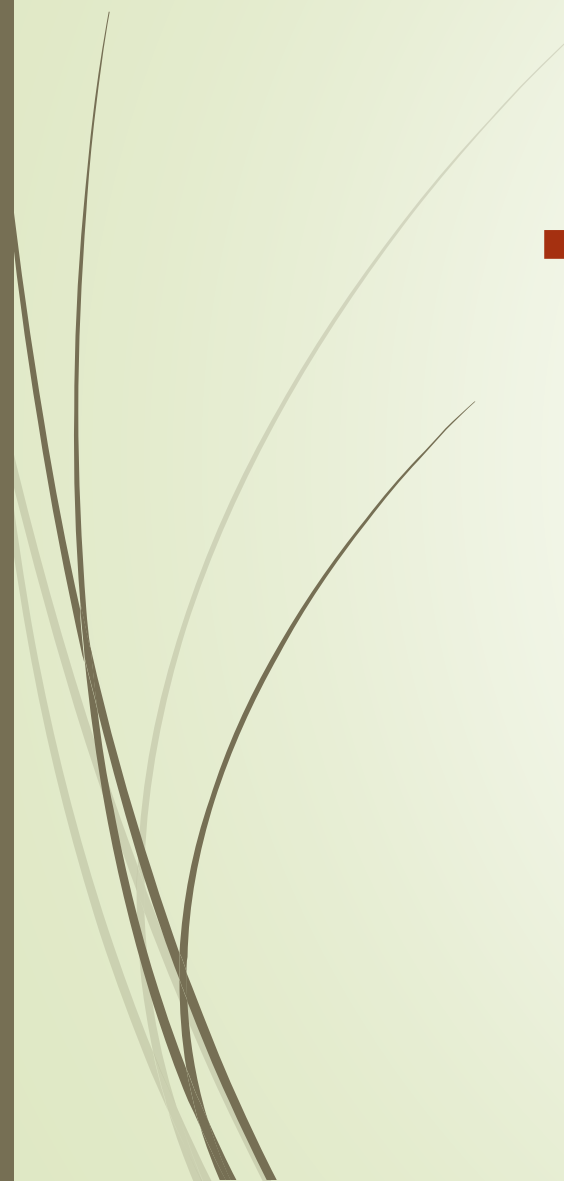
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- Based on clinical recommendations, a nasal cannula should be used for mild hypoxia and, if an oxygen flow >6 L/min is needed, a switch for a simple face mask set to deliver 5 to 10 L/min should be proposed. A non-rebreather mask with reservoir bag between 10 and 15 l/min should be used in patients remaining hypoxemic despite using a simple mask. These latter interfaces can ensure FiO_2 of 35–55% and 80–95% respectively FiO_2 depending on flow and breathing pattern.



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- CPAP (continuous positive airway pressure) with added O₂ could be used to improve oxygenation, if conventional O₂ failed and **there is no urgent indication for intubation.**
 - In hypoxemic ARF, applying an extrinsic positive end expiratory pressure (PEEP) increases alveolar recruitment and improves oxygenation. Furthermore, there is high level of evidence about the efficacy of adding PEEP during invasive ventilation in ARDS patients.



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- **NIV (non invasive ventilation)** with added O₂ could be used to improve oxygenation and/ for providing ventilatory support, if conventional O₂ failed and **there is no urgent indication for intubation.**
 - NIV could be harmful in those patients as it could worsen lung damage due to high pressures and high VT and could delay intubation. Moreover, NIV as CPAP is at high risk spreading of viral particles. In this field, WHO guidelines for the management of ARF in COVID-19 advocate the use of CPAP or NIV, provided that appropriate personal protective equipment is worn.
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- ▶ HFOT(high flow oxygen therapy) could be used to improve oxygenation, if conventional O₂ failed and **there is no urgent indication for intubation**. As HFOT is at high risk spreading of viral particles, protective measures must be applied to reduce caregiver's exposition. HFOT delivers a high-flow gas mixture (up to 70 l/min) with variable FiO₂ (up to 100%) administered by a nasal cannula. Compared to conventional oxygen, HFOT can ensure a constant and known FiO₂. Other advantages are dead space reduction and generation of a low PEEP level allowing

Suggested Criteria for Tracheal Intubation in Patients With COVID-19–related SARI Undergoing Oxygen Therapy or Noninvasive Ventilatory Support

Prompt tracheal intubation should be performed in the presence of one of the following conditions:	The following criteria probably do not justify by themselves tracheal intubation:
Alteration of consciousness	Low PaO ₂ /FiO ₂ ratio
Risk of airway inhalation	Prevention of clinical worsening
Severe decompensated acidosis (pH < 7.2-7.25)	Severity of chest CT findings
Severe hypoxemia (PaO ₂ < 50 mmHg or SaO ₂ < 90%)* despite maximal noninvasive support	Logistical, organizational, or medicolegal considerations
Signs or symptoms of significant respiratory distress or tissue hypoxia (eg, respiratory rate above 25-30 per minute, use of accessory respiratory muscles, sweating, dyspnea, tachycardia, increased blood lactate levels, etc.)	
Decision to implant VA ECMO	

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; F_IO₂, inspiratory oxygen fraction; PaO₂, partial pressure of oxygen; SaO₂, arterial oxygen saturation; SARI, severe acute respiratory infection; VA ECMO, venoarterial extracorporeal membrane oxygenation.



ARDS definition

Diagnostic Criteria for Diagnosis of ARDS (Adapted From the Berlin Definition [5])

Timing: Respiratory symptoms must have an onset within 1 week of known primary insult.

Chest imaging: Includes bilateral opacities not fully explained by effusions, lobar collapse, lung collapse, or nodules on chest X-ray or computed tomographic scan.

Cause of edema: Not fully explained by cardiac cause or fluid overload states with evidence from objective assessment and diagnostic tools required (i.e., echocardiography).

Severity assessment of hypoxemia using ratio of arterial oxygen tension to fraction of inspired oxygen:

Mild: $\text{PaO}_2/\text{FiO}_2 > 200 \text{ mm Hg}$ but $\leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}$

Moderate: $\text{PaO}_2/\text{FiO}_2 > 100 \text{ mm Hg}$ but $\leq 200 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}$

Severe: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$





ARDS AND AKI

- As seen in the ARDSNet trial, patients with AKI and ARDS had close to 2 times the mortality of that seen with ARDS alone (58% among subjects with AKI compared to 28% without AKI ($P < 0.001$))
- Adult studies in patients with ARDS have found that 35% of patients end up developing AKI.



What are the potential physiological and/ or pathophysiological mechanisms of AKI in patients with ARF/ARDS?




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- There have been some studies that attempt to explain the pathophysiology of AKI in ARDS. The three main possible mechanisms are :

1.mechanical ventilation

2.Hypoxemia

3.systemic inflammation


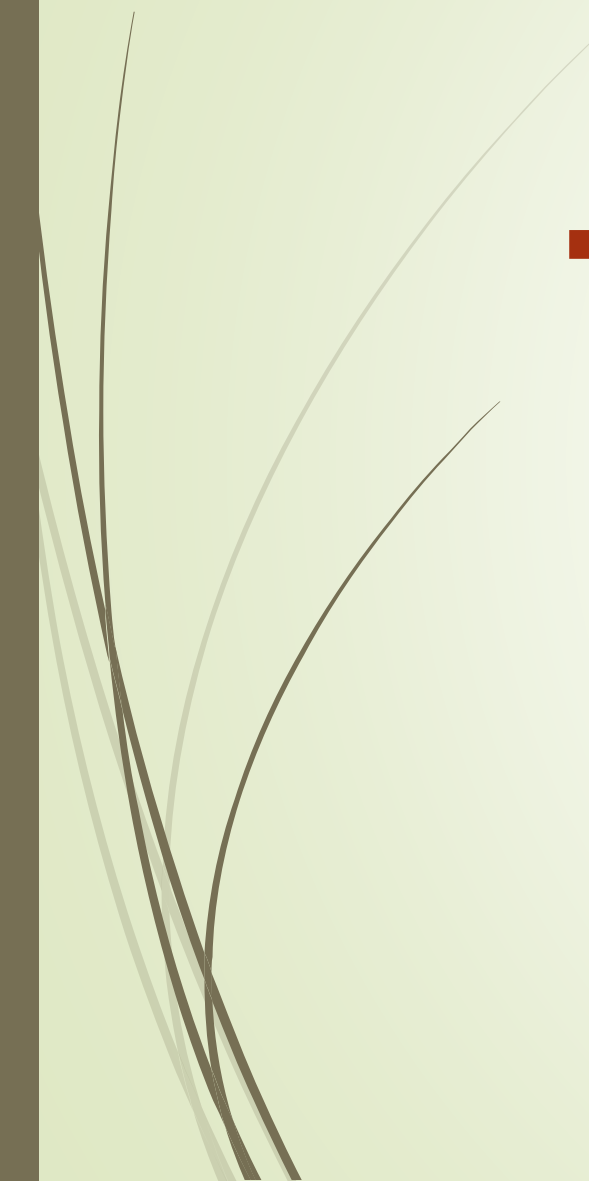
- However, among these three factors, mechanical ventilation appears to be the most significant event. Mechanical ventilation leads to a cascade of events in multiple organs, including kidney, which eventually leads to AKI thus increasing mortality. There have also been multiple studies that showed that mechanical ventilation can independently cause AKI.
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1. mechanical ventilation

- In an experimental lung model, Imai and his team found that high alveolar pressures, which occur in the setting of high PEEP, increase incidence of programmed cell death in renal tubules, which might lead to AKI. The consequence of these elevated pressure alter the hemodynamic of the heart, which in turn affects the homeostasis of the kidney.



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- ▶ Positive pressure ventilation decreases venous return to the heart, which alters the cardiac preload, pulmonary vascular resistance and afterload to the right side of the heart. All these hemodynamic changes eventually lead to decreased perfusion to all the organs in the body, especially kidneys, leading to reduced glomerular filtration rate (GFR) and AKI.



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- Elevation of central venous pressure, due to either right heart failure
 - high intrathoracic pressures (e.g. occult PEEP resulting from dynamic hyperinflation)
 - volume overload

may result in increased interstitial and tubular hydrostatic pressure within the encapsulated kidney, which decreases net glomerular filtration rate (GFR) and oxygen delivery.

2.hypoxemia


- ▶ Concomitant hypoxemia (SaO₂ 83–87%) and hypercapnia may reduce renal blood flow in a dose-dependent manner; correspondingly. In ARDS patients, short-term hypoxemia (SaO₂ 88–90%) is associated with altered renal function.



3.systemic inflammation

- Evidence indicated that barotrauma caused by high pressure ventilation, not only has potential to injure the lung, but also causes systemic inflammation and organ dysfunction due to release of inflammatory cytokines. Several cytokines such as tumor necrosis factor- α (TNF- α), transforming growth factor- β 1 (TGF- β 1), interleukin-1B (IL-1B), IL-6, and IL-8 have been identified with higher rates of AKI.




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- Systemic release of pro-inflammatory mediators from the injured lungs has been associated with the development of AKI. Increased levels of plasminogen activator inhibitor-1, IL-6 and soluble TNF receptors-I and II in ARF/ARDS are associated with AKI.
 - heparin binding protein (HBP) increased in sepsis may also have a detrimental effect on the kidneys by increasing endothelial permeability.



What are the interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS not requiring mechanical ventilation?



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- Current recommendations for the care of patients with, or at risk of AKI are suggesting several interventions based around mitigating risk of further renal injury, including
 - regular monitoring of urinary output
 - careful evaluation of fluid balance
 - optimization of hemodynamic status
 - review of potentially nephrotoxic medications
 - early recognition of systemic or pulmonary infection followed by timely treatment with antibiotics
 - adequate fluid status.



What are the interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS requiring mechanical ventilation?






► 1. low TV ventilation

- Breakthrough studies have shown the benefits of low TV ventilation strategies in the treatment of ARDS. Low TV ventilation, described as 6 mL/kg TV based on ideal body weight, decreased mortality, duration of intensive care unit (ICU) days, duration of ventilation, and incidence of non-pulmonary organ injury. Onset of renal failure took longer in low TV ventilation strategy when compared to traditional TV ventilation ($P = 0.005$).



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- In the ARDSNet study, patients allocated to low tidal volume ventilation had fewer days of AKI, defined as $sCr > 177 \mu\text{mol/L}$ (20 vs. 18 days; $p < 0.005$).
 - Studies have demonstrated that higher TVs were associated with increased levels of TNF- α , IL-1B, IL-6, and IL-8, with higher rates of AKI or higher number of days with AKI.





➤ 2. lowest PEEP

- High PEEP well documented to be beneficial in ARDS management, can also alter hemodynamic changes as it relates to venous return, cardiac afterload, thus decreasing cardiac output along with renal blood flow.
- Cardiorenal interactions studied by Annat et al has shown that increasing PEEP (PEEP of greater than 10 cm H₂O) leads to significant reductions in urinary output, renal blood flow, sodium excretion, and potassium excretion. These changes were reversed when PEEP was withdrawn.






➤ 3. Neuromuscular blockade



- applied to facilitate lung protective ventilation was associated with more ventilator free days and more days without renal failure (20.5 ± 10.1 vs. 18.1 ± 11.6 days; $p = 0.05$) in the ACURASYS trial.





► 4. conservative fluid management

- Often patients with ARDS are given liberal amounts of fluids for management of the underlying cause of systemic injury (e.g. sepsis, trauma, other organ pathology). Initial phases of these conditions necessitate large volume resuscitation in order to achieve and maintain hemodynamic stability. After the return of hemodynamic stability, administration of additional volume has been shown to be detrimental.
 - Inability to preserve lower fluid balance after hemodynamic stability was found to be an independent mortality risk factor in patients who
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- Compared to the use of liberal fluid strategies, conservative use of normal saline by achieving a negative fluid balance improved oxygenation index, lung injury as well as decreased length of stay in the ICU.
 - There was also less reported use of dialysis in the first 60 days with the conservative fluid strategies. This trial, also known as Fluid and Catheter Treatment Trial (FACTT) study, also showed that administration of intravenous (IV) fluids to shock-free patients did not lead to improvement of kidney function, but only lead to delay in the resolution of lung injury. Overall, the results of this study favored the use of a conservative fluid strategy for critically ill patients with

Overview of the recommendations for practice

Statement	Grade
What are interventions or modifiable risk factors which may mitigate respiratory dysfunction among patients with AKI?	
1. We recommend adherence to KDIGO guidelines for AKI management, as it may translate into improved pulmonary outcomes	1D
2. We suggest conservative fluid management and selected use of diuretics or ultrafiltration (RRT) in patients with AKI on IMV to improve respiratory function and decrease duration of IMV in patients with ARF/ARDS	2C
3. We recommend delivery of RRT to mitigate the metabolic consequences of AKI particularly where acid–base derangement may affect ventilation	1D
What are interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS not requiring mechanical ventilation?	
1. We recommend treating patients with ARF/ARDS according to the KDIGO guidelines who are at risk of or with AKI	1C
2. We suggest at least daily measurement of serum creatinine and regular monitoring of urine output in patients with severe ARF/ARDS to detect development of AKI	1B
3. We recommend the implementation of adequate screening measures for early reorganization of pulmonary infections, followed by early initiation of appropriate antibiotic therapy, which is associated with lower risk of AKI	1C
What are the interventions or modifiable risk factors to mitigate AKI among patients with ARF/ARDS requiring mechanical ventilation?	
1. We recommend monitoring of tidal volumes and ventilation pressures and application of lung protective ventilation strategies in patients receiving IMV to reduce the risk of new or worsening AKI	1C
2. We recommend monitoring and treatment of mechanically ventilated patients for hypotension, venous congestion, right heart failure, and intraabdominal hypertension, which can contribute to renal dysfunction	1B
3. We suggest avoiding—if possible—specific ancillary interventions known to be associated with AKI, including fluid overload, nephrotoxin exposure, and high doses of iNO	2B

