The following information resources have been selected by the National Health Library and Knowledge Service Evidence Virtual Team in response to your question. The resources are listed in our estimated order of relevance to practicing healthcare professionals confronted with this scenario in an Irish context. In respect of the evolving global situation and rapidly changing evidence base, it is advised to use hyperlinked sources in this document to ensure that the information you are disseminating to the public or applying in clinical practice is the most current, valid and accurate.

YOUR QUESTION

What is the current evidence-based treatment for COVID-19 patients with hypoxaemia?

IN A NUTSHELL

There is much research evidence for the treatment of hypoxaemia but not in the context of COVID-19 patients.

According to Murthy et al. (2020)[12]: "The principal feature of patients with severe disease is the development of ARDS, a syndrome characterized by acute onset of hypoxemic respiratory failure with bilateral infiltrates. Evidence-based treatment guidelines for ARDS should be followed, including conservative fluid strategies for patients without shock following initial resuscitation, empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extra corporeal membrane oxygenation for refractory hypoxemia."

Gattinoni et al. (2020)[9], reporting from Northern Italy, state that "patients with COVID-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristics we are observing, confirmed by colleagues in other hospitals, is the dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia."

An American Thoracic Society led international task force[4] agreed that patients with refractory hypoxemia due to progressive COVID-19 pneumonia [ie ARDS] should undergo prone ventilation. This was based on the assumption that ARDS due to COVID-19 behaves similarly to ARDS due to other causes for which the benefits of prone ventilation are well established. Agreement was not universal, however, as several task force members argued that ARDS in COVID-19 is unique because lung compliance is

maintained and the effects of prone ventilation are more modest than in typical ARDS. Nevertheless, the task force concluded that prone ventilation is worth a trial since it is low risk and low cost. However, they warned that placing the patient in the prone position must be done with caution since there is a risk of transmitting infection to healthcare staff due to aerosolized secretions.

Prone positioning is also supported by the Australian and New Zealand Intensive Care Society (ANZICS) COVID-19 Guidelines[3].

Reporting from Italy, La Regina et al. (2020)[8] recommend that "high-flow nasal oxygen (HFNO) or non-invasive ventilation [NIV, mainly c-PAP] should only be used in selected patients with hypoxemia, respiratory failure [P/F next to 300 for HFNO and 250-300 for NIV], but with alerts and with preserved ventilator dynamics."

Further strategies for managing severe hypoxaemia are high PEEP, recruitment manoeuvers and neuromuscular blocking agents (NMBAs)[6].

IRISH AND INTERNATIONAL GUIDANCE

What does the HSE say?

Health Service Executive (2020). HSE Operational Pathway of Care [COVID-19][1]
The HSE Operational Pathway of Care advises to give supplemental oxygen at a rate of 10-15L/minute to patients with severe acute respiratory infection and respiratory distress, hypoxaemia or shock. Titrate flow rates to reach a target SpO2 ≥90%.

What does the World Health Organization say?

World Health Organization (2020). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance 13 March 2020 [2]
See section 8. Management of critical COVID-19: acute respiratory distress syndrome (ARDS).
Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy and prepare to provide advanced oxygen/ventilatory support.

What do other international organizations say?

Australian and New Zealand Intensive Care Society (2020). Australian and New Zealand Intensive Care Society (ANZICS) COVID-19 Guidelines [3]
See Section 3. Identification and Treatment of Patients with COVID-19 Infection: Fundamental Principles (pages 26-30).
5. Prone positioning: Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19.
13. Rescue Therapies: Inhaled nitric oxide and prostacyclin: There is no evidence for routine use of inhaled nitric oxide, prostacyclin or other selective pulmonary vasodilators in acute respiratory failure. However, during emerging infectious disease outbreaks when resources are exhausted, inhaled nitric oxide and prostacyclin may be considered as a temporising measure when patients develop refractory hypoxemia despite prone ventilation, or in the presence of contraindications to prone ventilation or ECMO.

American Thoracic Society (2020). COVID19: Interim Guidance on Management Pending Empirical Evidence. From an American Thoracic Society- led International Task Force [4]
See pages 6–7.
The task force agreed that patients with refractory hypoxemia due to progressive COVID-19 pneumonia [ie ARDS] should undergo prone ventilation. This was based on the assumption that ARDS due to COVID-19 behaves similarly to ARDS due to other causes for which the benefits of prone ventilation are well established. Agreement was not universal, however, as several task force members argued that ARDS in COVID-19 is unique because lung compliance is maintained and the effects of prone ventilation are more modest than in typical ARDS. Nevertheless, the task force concluded that prone ventilation is worth a trial since it is low risk and low cost. However, they warned that placing the patient in the prone position must be done with caution since there is a risk of transmitting infection to healthcare staff due to aerosolized secretions.

Zhejiang University [China] (2020). Handbook of COVID-19 Prevention and Treatment [5]
See Section VII page 24ff: Anti-Shock and Anti-Hypoxemia Treatment.

POINT-OF-CARE TOOLS

What does UpToDate say?

UpToDate (2020). Coronavirus disease 2019 (COVID-19) patients: Airway management, anesthesia machine ventilation, and anesthetic care [6]
See section: Strategies for managing severe hypoxemia.
PRONE POSITIONING: For patients with COVID-19 ARDS that fail standard low tidal volume ventilation, prone ventilation is the preferred next step. Prone positioning is optimal for patients with severe ARDS because it decreases ventral alveolar distention and dorsal alveolar collapse. See [UpToDate] CORONAVIRUS DISEASE 2019 (COVID-19): CRITICAL CARE ISSUES, SECTION ON 'PRONE VENTILATION' and [UpToDate] PRONE VENTILATION FOR ADULT PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME and [UpToDate] VENTILATOR MANAGEMENT STRATEGIES FOR ADULTS WITH

ACUTE RESPIRATORY DISTRESS SYNDROME, SECTION ON 'REFRACTORY PATIENTS'.

It is critically important to adhere to appropriate precautions for prone positioning to avoid soft tissue injury: eg nerve damage, pressure-induced injury or ulceration, or compartment syndrome. See [UpToDate] PATIENT POSITIONING FOR SURGERY AND ANESTHESIA IN ADULTS", SECTION ON 'PRONE'.

OTHER STRATEGIES: If prone positioning is inadequate for maintenance of adequate oxygenation, other ventilation strategies include:

- High PEEP: Maintain tidal volumes at 6 cc per kg or down to 4 cc per kg with permissive hypercapnia and use higher levels of PEEP [eg 15 to 20 cm H20] as needed. See [UpToDate] CORONAVIRUS DISEASE 2019 (COVID-19): CRITICAL CARE ISSUES, SECTION ON 'VENTILATOR MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME' and [UpToDate] VENTILATOR MANAGEMENT STRATEGIES FOR ADULTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME, SECTION ON 'FURTHER TITRATION/INCREASE IN PEEP (HIGH PEEP)'.
- Recruitment Maneuvers: Recruitment maneuvers may be performed; data supporting their use to address severe hypoxemia in non COVID-related ARDS are described separately. See [UpToDate] VENTILATOR MANAGEMENT STRATEGIES FOR ADULTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME, SECTION ON 'VENTILATOR STRATEGIES TO MAXIMIZE ALVEOLAR RECRUITMENT'.
- Neuromuscular blocking agents (NMBAs)**:** NMBAs may be reserved for patients with refractory hypoxemia or ventilator dyssynchrony. We do not favor their routine use in any patient with ARDS since data on outcomes are conflicting. See [UpToDate] ACUTE RESPIRATORY DISTRESS SYNDROME: SUPPORTIVE CARE AND OXYGENATION IN ADULTS, SECTION ON 'PARALYSIS (NEUROMUSCULAR BLOCKADE)' and [UpToDate] NEUROMUSCULAR BLOCKING AGENTS IN CRITICALLY ILL PATIENTS: USE, AGENT SELECTION, ADMINISTRATION, AND ADVERSE EFFECTS.

INTERNATIONAL LITERATURE

What does the international literature say?

Cochrane Library [Special Collections] (2020). Coronavirus (COVID-19): evidence relevant to critical care [7]

See section: Managing Hypoxaemia.

Acute or chronic hypoxaemia is a common reason for admission to intensive care and for provision of mechanical ventilation. Various refinements of mechanical ventilation or adjuncts are employed to improve patient outcomes.

La Regina et al. (2020). Patient Safety Recommendations for COVID-19 Epidemic Outbreak: Lessons from the Italian Experience [8]

Author: Micaela La Regina et al.

See Part 3. RECOMMENDATIONS FOR HOSPITAL TREATMENT.

6. High-flow nasal oxygen (HFNO) or non-invasive ventilation [NIV, mainly c-PAP] should only be used in selected patients with hypoxemia, respiratory failure [P/F next to 300 for HFNO and 250-300 for NIV], but with alerts and with preserved ventilator dynamics. Monitor closely for clinical deterioration.

7. Do not prolong HFNO or NIV for over 2 hours in the case of failure to improve [HFNO: respiratory rate ≥24/min, NIV: respiratory rate ≥28/min and/or worsening P/F for both].

High flow nasal cannulas and non-invasive ventilation are not recommended in viral pandemics, based on studies conducted in influenza and MERS.

Gattinoni et al. (2020). COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome[9]

The clinical approach to these patients is the one typically applied to severe ARDS, namely high Positive End Expiratory Pressure (PEEP) and prone positioning. However, the patients with COVID-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristics we are observing, confirmed by colleagues in other hospitals, is the dissociation between their relatively well preserved lung mechanics and the severity of hypoxemia.

A possible explanation for such severe hypoxemia occurring in compliant lungs is the loss of lung perfusion regulation and hypoxic vasoconstriction.

Actually, in ARDS, the ratio between the shunt fraction to the fraction of gasless tissue is highly variable, with mean 1.25 ± 0.80. In eight of our patients with CT scan, however, we measured a ratio of 3.0 ± 2.1, suggesting remarkable hyperperfusion of gasless tissue. If so, the oxygenation increases with high PEEP and/or prone position are not primarily due to recruitment, the usual mechanism in ARDS, but instead, in these patients with a poorly recruitable pneumonia, to the redistribution of perfusion in response to pressure and/or gravitational forces. We should consider that: 1. Patients treated with Continuous Positive Airway Pressure or Non Invasive Ventilation, presenting with clinical signs of excessive inspiratory efforts, intubation should be prioritized to avoid excessive intrathoracic negative pressures and self-inflicted lung injury; 2. High PEEP in a poorly recruitable lung tends to result in severe hemodynamic impairment and fluid retention; 3. Prone positioning of patients with relatively high compliance results in a modest benefit at the price of a high demand for stressed human resources. After considering that, all we can do ventilating these patients is "buying time" with minimum additional damage: the lowest possible PEEP and gentle ventilation. We need to be patient.

Flower et al. (2020). Management of hypoxaemia in the critically ill patient[10]

Hypoxaemia is a common presentation in critically ill patients, with the potential for severe harm if not addressed appropriately. This review provides a framework to guide the management of any hypoxaemic patient, regardless of the clinical setting. Key steps in managing such patients include ascertaining the severity of hypoxaemia, the underlying diagnosis and implementing the most appropriate treatment. Oxygen therapy can be delivered by variable or fixed rate devices, and non-invasive ventilation; if patients deteriorate they may require tracheal intubation and mechanical ventilation. Early critical care team involvement is a key part of this pathway. Specialist treatments for severe hypoxaemia can only be undertaken on an intensive care unit and this field is developing rapidly as trial results become available. It is important that each new scenario is approached in a structured manner with an open diagnostic mind and a clear escalation plan.

Alhazzani et al. (2020). Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) [11]

See especially: B Ventilatory Support.

… We formed a panel of 36 experts from 12 countries. …We searched the literature for direct and indirect evidence on the management of COVID-19 in critically ill patients in the ICU. We identified relevant and recent systematic reviews on most questions relating to supportive care. We assessed the certainty in the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, then generated recommendations based on the balance between benefit and harm, resource and cost implications, equity, and feasibility. Recommendations were either strong or weak, or in the form of best practice recommendations. …

The Surviving Sepsis Campaign COVID-19 panel issued several recommendations to help support healthcare workers caring for critically ill ICU patients with COVID-19.

Murthy et al. (2020). Care for Critically Ill Patients With COVID-19 [12]

Management of severe COVID-19 is not different from management of most viral pneumonia causing respiratory failure [figure]. The principal feature of patients with severe disease is the development of ARDS: a syndrome characterized by acute onset of hypoxemic respiratory failure with bilateral infiltrates. Evidence-based treatment guidelines for ARDS should be followed, including conservative fluid strategies for patients without shock following initial resuscitation, empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extra corporeal membrane oxygenation for refractory hypoxemia.

Leeies et al. (2020). High-flow oxygen via nasal cannulae in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. [13]

A systematic review and meta-analysis to evaluate the efficacy and safety of high-flow oxygen via nasal cannulae (HFNC) compared to non-invasive ventilation (NIV) and/or standard oxygen in patients with acute, hypoxemic respiratory failure … CONCLUSIONS: In patients with acute hypoxemic respiratory failure HFNC was not associated with a difference in mortality

compared to NIV or standard oxygen. Secondary outcomes including dyspnea, tolerance, and safety were not systematically reported. Residual heterogeneity and variable reporting of secondary outcomes limit the conclusions that can be made in this review. Prospective trials designed to evaluate the efficacy and safety of HFNC in patients with acute hypoxemic respiratory failure are required.

OTHER

Rezaie (31 March 2020) [Blog]. "COVID-19 Hypoxemia: A Better and Still Safe Way" [14]

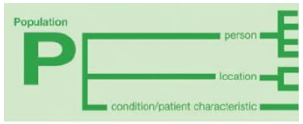
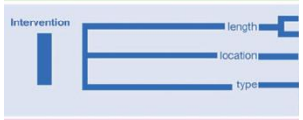
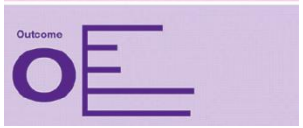
The reality is [that COVID-19] is not ARDS. Lung compliance is often normal in these patients, and many patients are not in respiratory distress despite low O2 saturations. Patients can have a bizarre hypoxemia that does not correlate with their symptoms.

Approaches to oxygen supplementation have stressed minimizing aerosolization of viral particles by avoiding HFNC and NIV. This appears to be a fear-based statement as opposed to an evidence based one. If we go straight from nasal cannula to intubation, we will simply run out of ventilators.

…I have yet to find a study that shows a mortality rate <50% once a patient is intubated. Maybe a better way to deal with these patients is an intermediary step using HFNC or CPAP while proning patients while they are awake, before considering intubation.

Produced by the members of the National Health Library and Knowledge Service Evidence Team.† Current as at 10 April 2020.This evidence summary collates the best available evidence at the time of writing and **does not replace clinical judgement or guidance**. Emerging literature or subsequent developments in respect of COVID-19 may require amendment to the information or sources listed in the document. Although all reasonable care has been taken in the compilation of content, the National Health Library and Knowledge Service Evidence Team makes no representations or warranties expressed or implied as to the accuracy or suitability of the information or sources listed in the document. This evidence summary is the property of the National Health Library and Knowledge Service and subsequent re-use or distribution in whole or in part should include acknowledgement of the service.

The following PICO(T) was used as a basis for the evidence summary:

	COVID-19 PATIENTS WITH HYPOXAEMIA/HYPOXEMIA
	EVIDENCE-BASED TREATMENTS
	
	

The following search strategy was used:

[ABBREVIATED] COVID-19 OR coronavirus or "corona virus" or (Wuhan N3 virus) or (("2019-nCoV" or "2019 ncov")) or "severe respiratory syndrome coronavirus2" or (("2019" and (new or novel) and coronavirus)) (HCoV-19) AND (Hypoxaemia OR Hypoxemia OR Hypoxia)

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Cochrane Clinical Answers

[1] Health Service Executive (2020). HSE Operational Pathway of Care [COVID-19]. https://hse.drsteevenslibrary.ie/c.php?g=679077&p=4841241. [Accessed 14 April 2020].
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