COVID-19 Scientific Advisory Group Rapid Response Report

Key Research Question: Are there clinical features that reliably indicate need for intubation and mechanical ventilation? Among patients requiring intubation and mechanical ventilation, are there clinical features that predict probability of survival or mortality?

Context

- The question originated with the clinical community, and the target of this review is clinicians working in acute care settings
- The rapid review was based upon limited literature and existing published guideline documents
- The review is limited to adult, non-pregnant patients with confirmed/suspected COVID-19

Key Messages from the Evidence Summary

- Several guidelines provide consensus based indications for intubation for patients with COVID-19, however there is no empirically-derived evidence to guide best practice to intubation/MV for patients with COVID-19.
- Published mortality rates for intubated/MV patients with COVID-19 is estimated to be 40-70%.
- Older patients and those with co-morbid conditions (cardiovascular disease, chronic respiratory disease, hypertension & diabetes) have higher mortality risk due to COVID-19, particularly after intubation and mechanical ventilation, however research continues to evolve.
- Based on the high mortality rate for intubated/MV patients it is recommended clinicians consider early goals of care discussions with patients and families.

Recommendations

1. Endotracheal intubation should be performed for patients with R1/R2 goals of care who are failing to maintain adequate oxygenation or ventilation in spite of high delivered FiO2. Consideration should be given to early intubation of deteriorating patients (ie.intubating deteriorating patients requiring lower FiO2), particularly those with underlying cardiopulmonary disease or altered mental status, to reduce the risk of severe hypoxemia and/or the need for bag-valve-mask ventilation during the intubation process.
2. Clinicians should engage hospitalized patients with COVID-19 in goals of care discussions that include data on low survivability of mechanical ventilation, particularly for older and/or multimorbid patients.

Committee Discussion

The committee reached consensus on the key messages and recommendations. While some clinical pathways with criteria for intubation of patients with COVID-19 disease have been disseminated by various sources, these reflect local practice patterns and are not based on empirically derived data. The primary indications for intubation of COVID-19 patients (as in other disease states) remain hypoxemic or hypercapneic respiratory failure or respiratory fatigue. The decision on when to intubate a patient will remain a patient-specific decision, but factors in this decision include variables such as FiO2, oxygen flow rate, respiratory rate, ventilatory status, and mental status. There was agreement among the committee that early intubation had important merits, including avoiding the risk of hypoxemia and bag-valve-mask ventilation during the induction sequence. There may be a subset of patients who can tolerate prolonged periods of hypoxemia with high supplemental oxygen administration without the need for mechanical ventilation, but identifying these patients remains a challenge. Committee members reinforced the value of clinical judgment in decisions around which patients require intubation and when, and emphasized the value of early involvement of critical care specialists in patients who may be at risk of respiratory failure. The high mortality rate observed in patients requiring mechanical ventilation, and factors associated with poor outcomes, should be discussed with patients during goals of care discussions.

Summary of Evidence

Credible information sources were identified through a rapid online search. A total of 23 articles were included in the final review including eight published guidelines or consensus documents that use a range of research sources and likely expertise consensus within these organizations. In addition, 3 meta-analysis papers, 10 retrospective cohort, observational or case reports, three prediction models, one commentary and one letter to the editor.

Key limitations of this review:

Rapid turnaround time resulted in a limited time to conduct a thorough search of the research and grey literature. Given the rapidly changing information and literature related to COVID-19, the literature available is limited primarily to reviews, guideline documents, published letters, and descriptive papers. This review will be updated as new information is published.

Research Question 1

Are there clinical features that reliably indicate need for intubation and mechanical ventilation?

Evidence from existing policies and guidelines

There is a paucity of primary research that identifies clinical features to predict the need for intubation and mechanical ventilation (MV).

This rapid review identified 7 guidelines that provide indication for intubation and MV. There is agreement that proactive intubation prior to the onset of profound hypoxemia is preferred (Alhazzani (2020); Department of EM, 2020; Cook, 2020; Meng (2020) & Brewster (2020)) to reduce aerosolization from bag-valve-mask oxygenation, and to minimize the risk of severe hypoxemia during the intubation procedure. Additionally, patients may present as relatively asymptomatic despite having significant hypoxemia (“silent hypoxemia”) (Meng, 2020). This silent hypoxemia may contribute to rapid decline.

The WHO (2020) suggest considering intubation for patients with increased breathing effort or hypoxemia despite oxygen via a face mask with reservoir bag (flow rates of 10–15 LPM; (FiO2 0.60–0.95). Similarly, the Department of EM at the University of Ottawa (2020) advocate to consider intubation/MV when FiO2 requirement > 50%, there are clinical signs of respiratory fatigue with supplemental oxygen, or hemodynamic instability.

The Chinese Society of Anesthesiology Task Force on Airway Management (2020) suggest intubation/MV should be considered for patients with severe disease, with no symptom relief (ongoing respiratory distress and / or hypoxemia) despite conventional oxygen therapy; or symptoms (respiratory distress, respiratory rate > 30 / min, oxygenation index <150 mmHg) persist or worsen after high-flow nasal oxygenation (HFNO) or non-invasive ventilation for 2 hours.

Others advocate following indications for intubation/MV that are applied in non-COVID patients, with an early intervention strategy (Brewster, 2020).

Research Question 2

Among patients requiring intubation and mechanical ventilation, are there clinical features that predict probability of survival or mortality.

There is little published research specifically about the outcomes of 2.3-12% of patients that require intubation/MV due to complications of COVID-19 (Alhazzani, 2020 & Meng, 2020). However, there are potential proxy measures that could be used to better understand this population, such as those that have severe disease, or require an ICU stay.

Evidence from the primary literature

ICU/Non-ICU

A case report of 41 patients with COVID-19 in Wuhan, China compared patients requiring ICU stays and those that did not (Huang, 2020). Prothrombin time and D-dimer level on admission were higher in ICU patients (median prothrombin time 12·2 s [IQR 11·2–13·4]; median D-dimer level 2·4 mg/L [0·6–14·4]) than non-ICU patients (median prothrombin time 10·7 s [9·8–12·1], p=0·012; median D-dimer level 0·5 mg/L [0·3–0·8], p=0·0042) (Huang, 2020). .Reported mortality rates of ICU patients in Jin Yin-Tan Hospital were 38–62%, and up to a third of critically ill patients developed nosocomial or secondary bacterial infections (Goh, 2020).

Severe Disease vs Less Severe

Guan and colleagues (2020) conducted a retrospective observational study of 1099 patients with COVID-19. Those with severe disease (173 patients) were older than those with less severe disease (926 patients) by a median of 7 years. Co-morbidities were more common among patients with severe disease and they had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia). Patients with severe disease had a higher incidence of physician- diagnosed pneumonia than those with less severe disease (99.4% vs. 89.5%). ICU stays occurred for 5% of the study population, with 2.3% MV and 1.4% mortality (Guan, 2020).

Mo (2020 conducted a multivariate analysis that suggested male sex (P=0.047; OR: 2.206, 95% CI: 1.012-4.809) and anorexia on admission (P=0.030; OR: 3.921, 95% CI: 1.144-13.443) were risk factors disease refractoriness, and fever on admission as the protective factor (P=0.039; OR: 0.331, 95% CI: 0.116-0.945). Refractory patients were more likely to receive oxygen (P=0.020; OR: 3.065, 95% CI: 1.189-7.897), expectorant (P=0.016; OR: 2.688, 95% CI: 1.204-6.003), corticosteroid (P=0.042; OR: 2.232, 95% CI: 1.030-4.838), lopinavir and ritonavir (P<0.001; OR: 13.975, 95% CI: 3.274-59.655), and immune enhancer (P=0.009; OR: 8.959, 95% CI: 1.724-46.564) (Mo, 2020).

Survivors vs. Non-Survivors

Zhao and colleagues (2020) conducted a meta-analysis (pre-print) of 30 studies including 53000 COVID-19 patients (1375 were identified as severe-definition not provided). Older age (≥ 60 yrs, RR =

9.45; 95% CI, 8.09-11.04), cardiovascular disease (RR = 6.75; 95% CI, 5.40-8.43) hypertension (RR = 4.48; 95% CI, 3.69-5.45) and diabetes (RR = 4.43; 95% CI, 3.49-5.61) were found to be independent factors of mortality.

Yang (2020) conducted a retrospective observational study of 710 patients with COVID-19 (52 critically ill and 32 died) and determined, non-survivors were older (64·6 years [11·2] vs 51·9 years [12·9]), more likely to develop ARDS (26 [81%] patients vs 9 [45%] patients), and more likely to receive mechanical ventilation (30 [94%] patients vs 7 [35%] than survivors. The survival time of the non-survivors is likely to be within 1–2 weeks after ICU admission. The 28-day mortality rate was 62% in patients who required ICU care; among patients who developed ARDS, 74% (Yang, 2020).

A study of over 72,000 cases of COVID-10 determine a case fatality rate of 49.0% among critical cases (Wu, 2020). It was elevated among those with preexisting comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer (Wu, 2020).

Similar to previously described findings (Wu(2), 2020) found mortality associated with older age (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17), and organ and coagulation dysfunction (eg, higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52] and D-dimer [HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04]).

Chen's (2020) descriptive study of 99 patients with COVID-19 also states older age, obesity, and presence of comorbidity may be associated with mortality. Bhatraju (2020) also identified a higher age in patients that died due to COVID-19 in Seattle, Washington, however data was preliminary, and case fatality rate was 37% in those under 65 years at the time of publication. Further research is needed to explore the duration of mechanical ventilation or ECMO in survivors compared to non-survivors (Goh, 2020).An Italian retrospective case series (Grasselli, 2020) of 1591 ICU admitted patients found 68% had comorbid conditions; 99% required respiratory support; 88% required MV. Older patients were found to have higher mortality (n = 795; age 63 years) (36% vs 15%; difference, 21% [95%CI, 17%-26%]; P < .001), however like much of this research, many of the patients remain in hospital/ICU and outcomes are incomplete.

Ruan (2020) wrote a letter to the editor of the Intensive Care Medicine Journal to demonstrate the clinical predictors of mortality for 150 COVID-19 patients in China. In the cohort, 68 patients died. Those that died were significantly older (p<0.001), had underlying diseases (p = 0.0069), and those with cardiovascular diseases have a significantly increased risk of death. 16% of those that died had secondary infections compared to 1% of the survivors (p = 0.0018). Laboratory results showed that there were significant differences in white blood cell counts, absolute values of lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, blood creatinine, myoglobin, cardiac troponin, C-reactive protein (CRP) and interleukin-6 (IL-6) between the two groups (Ruan, 2020).

While this research offers some preliminary information, there are many limitations. All but one of the studies are based in China. The health care delivery differs widely by country and clinical decision making such as the use of specific therapies (NIV, HHHFO, traditional therapies) and when to admit to ICU may be vastly different. Additionally, other jurisdictions may have experienced significant burden, creating an overwhelmed health care system which changes the therapeutic decision making process, and options available. Currently in Alberta we have not experienced the same challenges. Therefore, the research presented offers insight into the experiences and opinions of others, it has limited utility in the Alberta context.

Clinical Predication Models

Although not directly included in the question for this rapid review, it is noteworthy that there are increasing efforts to develop prediction models for COVID-19 prognosis. Wyants and colleagues (2002) conducted a meta-analysis that included 10 studies that provided prediction models for COVID-19 prognosis, including progression from severe to critical disease and mortality. While the prediction models offered some suggestions for common factors associated with poor outcomes (such as age, CT scoring, C reactive protein, lactic dehydrogenase, and lymphocyte count) there was a high risk of bias and the reported performance of the models is likely ambitious (Wyants, 2002). Three examples of these prediction models are presented below. Of note, they are non-peer reviewed and in pre-print publication.

1. Xie and team (2002 pre-print) developed a multivariable logistic regression model to predict mortality in COVID-19 positive patients. The final model included age, lymphocyte count, lactate dehydrogenase and SpO2 as independent predictors of mortality.
2. Bai and colleagues (2002 pre-print) used AI technology to develop a multivariate logistic regression to identify factors that may indicate mild patients with COVID-19 may deteriorate. The variables include: age >55years (OR 5.334, 95%CI 1.8-15.803), comorbid with hypertension (OR 5.093, 95%CI 1.236-20.986), a decrease of albumin (OR 4.01, 95%CI 1.216-13.223), a decrease of lymphocyte (OR 3.459, 95%CI 1.067-11.209), the progressive consolidation from CT1 to CT severe (OR 1.235, 95%CI 1.018-1.498), and elevated HCRP (OR 1.015, 95%CI 1.002-1.029); and a protective factor: the presence of fibrosis at CT1 (OR 0.656, 95%CI 0.473-0.91) (Bai, 2020).
3. Carmelo and colleagues (2002) state age presents higher risk of COVID-19 mortality, where 60 or older patients have an OR = 18.8161 (CI95% [7.1997; 41.5517]). Cardiovascular disease appears to be the most important co-morbidity (OR= 12.8328 CI95% [10.2736; 15.8643], and with chronic respiratory disease (OR=7.7925 CI95% [5.5446; 10.4319]). Men experience higher mortality than women (OR=1.8518 (CI95% [1.5996; 2.1270]).

Evidence from existing policies and guidelines

Alhazzani (2020) suggests that older age (>60 years), male gender, and the presence of underlying comorbidities such as diabetes, malignancy, and immunocompromised state are risk factors for critical illness/ICU stay. D-dimer of patients with severe disease was significantly increased, with frequent clotting disorders and microthrombotic formation in peripheral blood vessels (Jin, 2020). In critically ill patients, the case fatality rate was 49.0% and it was higher than 50% in those who received invasive mechanical ventilation. Pre-existing conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer; and older age were associated with higher risk of mortality (Alhazzani, 2020; Jin, 2020).

A commentary by Zhang (2020) states older, male patients with comorbidities have been identified as having more severe or fatal disease. Laboratory evaluation has found lymphopenia in 63% of patients and a cytokine storm profile in those who are critically ill (Zhang, 2020). As this data was presented in commentary article, it has limited applicability.

Evolving Evidence (if applicable)

The evidence is continuing to evolve as we better understand the patient with COVID-19 with severe, life-threatening disease. In addition, we have little information to understand the patient requiring intubation/MV within the Alberta context at this time. Future research to inform this topic should include all patients, better describe the care received and specific patient outcomes, and identify unique aspects of the health care system to provide context and generalizability to other settings.

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Authorship & Committee Members

This review was written by Heather Sharpe and scientifically reviewed by Andrew McRae, Kerri Johansson (external reviewer), Evan Minty (external reviewer), Chris Fung (external reviewer), Finlay McAlister (external reviewer), and Dan Zuege (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Lynora Saxinger (co-chair), Braden Manns (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

Appendix

List of Abbreviations

Literature Search Details

Search Strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 03, 2020

Key Terms

exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp.

exp Intubation/

exp Respiration, Artificial/

Airway Management/

(intubation* or laryngeal mask* artificial respirat* or ventilat* or positive end expiratory pressure* or positive end-expiratory pressure* or positive pressure respiration* or continuous positive airway pressure* airway management).mp.

TI (intubation* or laryngeal mask* artificial respirat* or ventilat* or positive end expiratory pressure* or positive end-expiratory pressure* or positive pressure respiration* or continuous positive airway pressure* or airway management) OR AB (intubation* or laryngeal mask* artificial respirat* or ventilat* or positive end

expiratory pressure* or positive end-expiratory pressure* or positive pressure respiration* or continuous positive airway pressure* or airway management)

(MH "Respiration, Artificial+")

(MH "Airway Management") OR (MH "Intubation+")

Screening

Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- Guidelines and credible academic writing on intubation/MV for COVID-19 patients. - Systematic reviews of Covid-19 clinical characteristics, imaging and outcomes. - Individual studies reporting outcomes for patients with COVID-19 and intubation/MV. -	- News articles. - Opinion pieces. - Cast studies or series. - Studies of unique populations (e.g. patients with cancer diagnoses, populations with high HIV rates, asymptomatic patients, seniors, low income settings). - Sources focused on children and pregnant persons. - Animal studies. - Studies proposing criteria for resource allocation when health system overwhelmed.

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