Respiratory CLIFF Peer Review

1. *Strength of evidence presented in CLIFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment?*

   Score: 2

   Grading Scale:

   4 - Confident

   3 - Somewhat confident

   2 – Neutral

   1 – Somewhat unconfident

   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2* *Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC* *Loss of Crew and probability*	*Table 4 - Clinical Phase 1, 2 durations* *Table 5 – CP 2 Loss of Crew*	*Table 4 – RTDC %* *Table 6 – RTDC Loss of Crew*	*Table 4 – Loss of Crew Life %* *Table 7 – Loss of Crew Life, Loss of Crew*	*Table 8 – TI*
Score	*2*	*1*	*3*	*3*	*2*	*3*

Comments and limitations:

1. **General comments.** This CLiFF characterizes acute respiratory failure (ARF) that occurs during spaceflight. The definition has changed over the years but for documentation purposes, ARF requires two of three criteria: a pO2 less than 60 mm Hg (or room air O2 saturation less than 91%), pCO2 greater than 50 mm Hg with pH less than 7.35, and signs/symptoms of respiratory distress. The most likely etiologies are hypoxia, from causes such as pneumonia, or hypercapnia from failure to remove CO2 (ventilatory failure). Given the equipment that is likely to be carried onboard, the diagnosis of ARF will probably be made by signs/symptoms of respiratory distress and low oxygen saturation. Capnography may be available to demonstrate hypercapnia. Although medical conditions that are covered in other CLiFFs such as toxic inhalation, lower respiratory tract infection, or inhalation of combustion products specifically state that they do not include respiratory failure, it is difficult to find literature that excludes those conditions when calculating the incidence of ARF. For purposes of this CLIFF the best case scenario is defined as respiratory failure requiring low flow oxygen such as nasal cannula, facemask, or non-rebreather at a flow rate of less than 10 LPM to maintain oxygen saturation. The worst case scenario is respiratory failure requiring high flow oxygen at >10 LPM or ventilatory support with non-invasive ventilation, or invasive ventilation. Since

astronauts are quarantined prior to flight, are in excellent general health, and are living in a sanitary environment in the spacecraft, it would be expected that this would be a very uncommon occurrence. It is also unlikely that astronauts will under-report this condition because of its potential seriousness.

2. **Incidence.** There have been no reported cases of ARF during spaceflight. The best epidemiologic data comes from a paper by Stefan et al. in 2013 which studied the epidemiology of respiratory failure in the United States. This paper categorized the incidence by age group and was preferred over other large studies, such as one by Kempker, et al. from which incidence could not be calculated. The incidence from the age group 18-44 years in the Stefan study was chosen as the closest to most astronauts. The average age in this group is lower than most astronauts and thus could represent an underestimation of the incidence. However, the paper reports the entire US population, many of whom have underlying medical conditions, and could therefore overestimate the expected incidence during spaceflight. The two factors somewhat negate each other. The probability distribution curve shows an extremely narrow distribution reflecting the large sample size of the study. This most likely overstates the precision of the data as it applies to spaceflight. The best case/worst case probabilities were derived from the Kempker paper which showed that 35% of all admissions for respiratory failure required invasive or non-invasive ventilatory support. This may represent an overestimation of the worst case since many mild cases that fit the definition of best case may not even present to the hospital. For example, most infections causing ARF only need to be treated with low flow nasal cannula, and it might be expected that this would be the major cause of ARF during spaceflight. Clinical phase durations, RTDC and LOCL probabilities are supported by terrestrial evidence, as well as the case definitions, and I am in agreement with their calculation. Hospitalization is considered a surrogate for RTDC.

3. **Clinical phase data**. I am in agreement with the clinical phase durations entered in this CLIFF. This data was compiled by a team of expert clinicians, and I was involved in the discussions leading to the calculation of the clinical phase durations.

4. **Task impairment**. The analysis was performed and reviewed by a separate team of expert clinicians. I am aware of the methods that were used but did not directly participate in the discussions.

5. **Dependence on mission phase or duration of mission**. This medical condition should not be dependent on mission phase. However, it should be noted that if someone develops acute respiratory failure once, the subsequent incidence rate may increase, depending on the insult.

6. **Limitations**

- There are no reports of ARF during spaceflight; therefore, terrestrial studies were used which do not approximate the spaceflight environment well.
- The probability distribution curve shows an extremely narrow distribution reflecting the large sample size of the study. This most likely overstates the precision of the data as it applies to spaceflight.
- Although other medical conditions that are covered such as toxic inhalation, lower respiratory tract infection, or inhalation of combustion products specifically state that they do not include respiratory failure, it is difficult to find literature that excludes those conditions when calculating the incidence of ARF. Thus, there is a large amount of overlap with this CLiFF. This may lead to “double counting” in which a single case could be given two diagnoses (pneumonia and ARF, for example).

- Acute respiratory failure can have some ambiguity as to its definition. We have chosen to define it as a patient unable to maintain oxygen saturation above 90% without support or meet ventilatory needs. This includes oxygen supplementation such as nasal cannula, face mask, or high flow nasal cannula, and ventilatory support such as non-invasive and invasive mechanical ventilation.
- The etiology of respiratory failure is varied and may be due to an acute insult, infection, or chronic disease. Each cause has different complication rates and a wide variety of outcomes. This CLiFF aims to address all causes as a whole but this may not accurately represent the duration, RTDC, or LOCL depending on the underlying pathophysiology.
- Outpatient treatment of mild respiratory failure requiring low volume, low flow nasal cannula support is limited but gaining momentum during the COVID 19 pandemic. Emerging data may change the estimated RTDC or LOCL, or may recommend against outpatient treatment altogether.
- High flow NC, Non-invasive ventilation, and mechanical ventilation all meet criteria for the WC scenario however each modality has very different complication and mortality rates. They are grouped to represent a higher level of resources required for treatment but may not have accurate LOCL or RTDC given the homogeneity of this group. This is similar in the BC scenario with includes low flow nasal cannula and non-rebreather.
- The incidence from the age group 18-44 years in the Stefan study was chosen as the closest to most astronauts. The average age in this group is lower than most astronauts and thus could represent an underestimation of the incidence. However, the paper reports the entire US population, many of whom have underlying medical conditions, and could therefore overestimate the expected incidence during spaceflight. The two factors somewhat negate each other.
- The best case/worst case probabilities were derived from the Kempker paper which showed that 35% of all admissions for respiratory failure required invasive or non-invasive ventilatory support. This may represent an overestimation of the worst case since many mild cases that fit the definition of best case may not even present to the hospital.

Reviewed by:

David C. Hilmers