

Sepsis 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	2	3	3	2	3

Comments and limitations:

1. General comments. This CLIFF characterizes the risk of sepsis during spaceflight. Sepsis is defined as organ dysfunction (lungs, kidneys, heart, etc) due to a dysregulated host response to infection. There is a wide spectrum of sepsis ranging from mild perturbation in vital signs (SIRS or systemic inflammatory response syndrome) to hypotension and severe end organ damage. There have been at least two episodes of infections during the history of manned spaceflight that could possibly be classified as sepsis, but there is not enough data to verify this and calculate an incidence. Outcomes depend on the early initiation of intravenous fluids and antibiotics. Large, well-controlled studies have looked at the incidence of sepsis terrestrially. Many have been done in general populations. While astronauts are generally healthier than the general population and are not afflicted with chronic conditions that predispose to sepsis, it is thought that immune dysregulation and increased virulence of microorganisms may occur during long-duration spaceflight. This would partially overcome the advantage that overall better baseline health confers. Since the definition of a number of CLIFFs that deal with infections such as lower respiratory tract infection, prostatitis, or pancreatitis that may also meet the definition of SIRS or sepsis, there is the possibility of overlap and overestimation of incidence for a single infection. For purposes of this CLIFF the best case scenario is

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defined as meeting SIRS criteria but responsive to intervention. The worst case scenario is septic shock (e.g. requiring vasopressors, end organ failure).

2. Incidence. There is little spaceflight data that can be utilized to calculate the incidence as it is not clear whether reported infections during spaceflight meet the definition of sepsis. A large analog study of US Armed Forces members diagnosed with sepsis or “septicemia” between 2000 and 2012 was used to estimate the incidence. The population studied is more applicable to astronauts since the cohort includes screened young men and women in good health. During the years of the study, however, the generally accepted definition of sepsis was changing. It is also unclear whether the spaceflight environment is more conducive to infection than the analog setting. The sample size of the Armed Forces’ study is large and shows a narrow distribution with a tight variance centered near the incidence reported. This most likely overstates the precision of the incidence as it applies to the spaceflight environment. The best case/worst case probability split is based on retrospective chart reviews that reported the percentage of sepsis admissions that experienced septic shock which is the worst case definition. The midpoint of these studies was 18% and was chosen as the WC probability. This could be an overestimate given the healthier astronaut population. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence. RTDC used the need for hospitalization as a surrogate. There is a paucity of data in the untreated cases, and expert opinion was relied upon to estimate the Loss of crew life in these instances.

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 a crewmember develops an infection leading to sepsis, it is likely that the incidence for that individual will increase in the future.

6. Limitations

- Spaceflight incidence data for serious infections are based on only a few cases and the diagnostic criteria may not be reliable. Thus, the spaceflight data was not deemed to be highly informative and was not used.
- The overall confidence in the mean incidence value is probably overstated because of the large sample size of the Armed Forces study which results in a very narrow probability distribution.
- Collecting appropriate data for the untreated scenarios was very difficult since few, if any, studies address not providing treatment for medical conditions.
- Once an episode of sepsis occurs, the incidence in the affected individual will likely increase significantly.
- The incidence of sepsis in US and global populations is on the rise over the last 20 years, in large part due to changes in data acquisition. Sepsis definitions have changed to be as sensitive as possible in order to reduce the rate of death associated with delay in diagnosis and treatment of sepsis. Many billing and hospital accreditation requirements are dependent on sepsis metrics which also incentivizes over-diagnosis when compared

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to prior years. Together these factors likely overestimate the true incidence of sepsis in a population.

- The US Armed Forces Data used for incidence was a chart review study that included years in which the definition of sepsis was changing. The authors included as many terms as possible (septicemia, sepsis, severe sepsis, etc...), but this may change the accuracy of the data.
- Population data on sepsis is often driven by the extremes of age and patients with severe comorbidities which is not representative of the astronaut population.
- The BC definition includes patients meeting SIRS criteria but responsive to treatment and the WC scenario includes septic shock. However, these definitions exclude moderate sepsis that requires prolonged treatment or ICU stay but does not meet criteria for septic shock. This moderate disease course is common and likely represents a large proportion of sepsis admissions.
- Sepsis is related to many other conditions on the condition list, both as a cause and effect. The specific estimates of duration, mortality, and need for RTDC are going to be heavily dependent on the source of the infection and the available antibiotics in flight.
- It is very likely that there is overlap between conditions characterized in various CLIFFs as some conditions such as lower respiratory tract infections or pancreatitis may also meet the criteria for SIRS or sepsis.

Reviewed by:

David C. Hilmers