

Venous Thromboembolism 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: 1

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	1	3	3	3	2	3

Comments and limitations:

1. General comments. This CLIFF characterizes venous thromboembolism (VTE) that might occur during spaceflight. This medical condition was added after a study done on the ISS using 11 astronauts as subjects noted one and possibly two internal jugular (IJ) deep vein thromboses (DVT) on examination with ultrasound. This is a much higher incidence than would be expected in a healthy population without risk factors. The mechanism of VTE in space is still undetermined, but it is theorized that VTE occurs secondary to increased venous stasis due to microgravity and its effects on the fluid dynamics of blood flow. There are many risk factors for VTE including the use of hormonal pharmaceuticals, obesity, immobility, age, trauma, genetic conditions such as factor V Leiden, acquired conditions such as lupus anticoagulant, and many others. The most dangerous VTE's are ones that develop in the pulmonary vasculature, called pulmonary embolism (PE). These are often caused by clots that form in the deep veins and migrate to the lungs. Treatment for DVT or PE is anticoagulation; the most commonly used currently medications are direct oral anticoagulants (DOAC). These can be taken without the need for frequent monitoring of coagulation times. There could be some overlap with this condition and the respiratory failure CLIFF since PE may be

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associated with respiratory compromise. The best case is considered to be a thrombus in situ (DVT). The worst case is pulmonary embolism.

2. Incidence. There have been 1 or possibly 2 reports of DVT during spaceflight. These were observed during a study looking at blood flow through the IJ. Since the sample size was so small (11 astronauts), it is difficult to draw conclusions about the overall incidence from this survey. Until final analysis is completed on these events and further studies are performed, it was decided to take another approach rather than to use the spaceflight data from a very small dataset. In our approach, the baseline rate of VTE in healthy adults of the average age of astronauts was first determined. Next, an approximation of a hazard ratio for VTE was applied for immobilized patients from a study that provided odds ratios for VTE given underlying conditions. It is felt that immobilization (e.g. bedrest) best approximates the additional risk that astronauts have for VTE in microgravity. This estimate can be further refined as more data becomes available. The best case/worst case probabilities used data from terrestrial studies that investigated the rates of DVT vs PE. The BC/WC split of 60/40% may overestimate the worst case given that both DVT's seen during spaceflight were asymptomatic and did not appear to have caused a PE. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence and the case definitions, and I am in agreement with their calculation. The CP2 times assume that anticoagulation will be needed the entire time that the risk factor (spaceflight) exists, i.e., end of mission. RTDC used hospitalization as a surrogate and is therefore non-zero for BC and 100% for worst case. This is in line with current terrestrial practices. Loss of crew life is small, but greater than zero for the treated cases and higher for the untreated cases. The probability density curve that was derived appears to be a reasonable representation of the data presented.

3. Clinical phase data. I am in agreement with the clinical phase 1 duration 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 duration. CP2 was supported by terrestrial evidence.

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 is not dependent on mission phase as VTE may occur during any time during the mission. However, the incidence is likely to be proportional to the length of time in microgravity as this increases the exposure to the postulated risk factor (immobilization) and the development of a VTE.

6. Limitations

- This medical condition is not dependent on mission phase as VTE may occur during any time during the mission. However, the incidence is likely to be proportional to the length of time in microgravity as this increases the exposure to the postulated risk factor (immobilization) and the development of a VTE.
- It is unknown whether there is some mitigation, or none at all, in partial g environments such as lunar or Martian gravity. It is assumed that the risk would be smaller than in microgravity, but there is no data to support that conclusion.
- There could be overlap with this condition and the respiratory failure CLIFF since PE may be associated with respiratory compromise.

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- The incidence estimation assumes that the risk factor of “immobilization” or “bedrest” simulates the additional risk of VTE in microgravity. This is a reasonable assumption but may not accurately describe the additional risk of VTE in microgravity.
- Other factors such as gender, hormonal contraceptive use, relative age, and trauma were not considered when calculating the baseline incidence of VTE. These can be considered for future iterations of this CLIFF using an “electronic calculator” that personalizes the individual risks for each astronaut.
- The BC/WC split of 60/40% used terrestrial data and may overestimate the worst case given that both DVT’s seen during spaceflight were asymptomatic and did not appear to have caused a PE.
- Many DVT’s are subclinical and may not be detected. This may affect the incidence and BC/WC calculations.

Reviewed by:

David C. Hilmer