

Headache 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: 3

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	3	3	3	3	3

Comments and limitations:

1. **General comments.** Headaches are a common complaint in astronauts during spaceflight just as they are on earth. During the first 5 days after insertion into orbit, many headaches are a result of increased intracranial pressure from microgravity-associated fluid shifts. Once a new equilibrium has been established, it is felt that most headaches are tension-type although cephalad fluid shift may still play some role. It is likely that astronauts under-report headaches as many are mild and resolve quickly. Headaches that occur during the first five days of flight are considered to be SAS-related and are covered in a separate CLIFF. Most headaches that have been reported after the initial acclimation to microgravity resolved within a couple of hours and were readily treatable with available medication. Headaches that are thought to be caused by elevated CO₂ concentrations during spaceflight are the subject of a separate CLIFF. The best case is an uncomplicated headache (unrelated to space adaptation), which resolves spontaneously or with first line medications or non-pharmacologic treatment. The worst case is a headache refractory to second line medications and non-pharmacologic treatments, requiring additional interventions.

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2. Incidence. There is spaceflight data that informs this CLIFF. Headaches associated with launch and during the space adaptation period (first 5 mission days) and those thought to be secondary to high CO₂ levels are not considered as they are covered in separate CLIFFs. The use of spaceflight data here is consistent with the team's intent to use robust spaceflight data as the source of incidence calculations whenever such data is available. The major source that informed the incidence was a paper by Vein, et al that cites data from astronaut reports to calculate an incidence of headaches. An additional paper that was a bedrest head-down tilt study was examined but excluded as it was considered to be an analog investigation. It is unclear whether the duration and mechanism of the headaches that result from being in a head-down position adequately reflect what occurs in microgravity. Fluid shifts that may play a role in spaceflight-related headaches in microgravity tend to equilibrate after some acclimation while this may not be true in head-down tilt studies where the fluid shift results from positive g. Some headaches in the head-down position may be mechanical in nature from maintaining this posture. Table 1 of Antonsen, et al (2017) lists a headache incidence of 2.27 which is remarkably close to the 2.56 incidence in Vein. The Antonsen figure could not be used by itself because it doesn't break down the number of headaches by mission phase (launch, landing, SAS or EVA-related). However, it should represent an UPPER bound on the non-SAS headache incidence for the missions that it covers. The bedrest study is not only suspect from a physiologic perspective, but the resulting incidence was quite different (15x higher) than the spaceflight experience as reported from two independent sources. The best case/worst case probabilities, clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. Of note, the Loss of crew life probability is considered to be zero. 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 dependent on mission phase. It does not cover SAS-related headache. Headaches also may be more common during transitions from gravity well operations or during the stress of EVA's.

6. Limitations

- There was little data to support the worst case untreated clinical phase durations or RTDC probabilities.
- Under-reporting for this condition could have been significant during past space missions due to mild cases that were treated symptomatically without being reported.
- It is unclear whether successive headaches were reported as separate events or a single, continuing event.
- Some spaceflight data is not clearly delineated into mission phase and makes interpretation difficult.
- The main paper used to compute incidence was based on astronaut recall.

Reviewed by:

David C. Hilmers

