

Nephrolithiasis 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	3	3	2	3	3	3

Comments and limitations:

1. General comments. Nephrolithiasis (kidney stones) is a condition that results from super saturation of the urine or from chronic urinary infections. Nephrolithiasis can result in severe, debilitating pain. Astronauts are at greater risk of stones in microgravity because of calcium wasting from bone loss leading to hypercalciuria as well as increased urine acidity and low urine citrate levels. Relative dehydration that occurs from cephalad fluid shifts leads to more concentrated urine and a propensity to form stones. Despite the higher risks of stone formation in microgravity there have been no reported cases during US spaceflights although there is one anecdotal case in a Russian cosmonaut that supposedly spontaneously passed. Preventive measures include keeping well hydrated and pharmacologic interventions such as potassium citrate. Subtype-selective alpha (1A) blockers such as tamsulosin can be used to aid in stone passage. Treatment options being investigated include moving an obstructing stone or shattering it with ultrasound. This CLIFF does not consider these as therapeutic options at this time and are not considered in the calculations. The best case for this CLIFF is formation of a stone that responds to conservative management while in the worst case, there is not resolution after conservative measures.

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2. Incidence. As there is no spaceflight data on the formation of kidney stones and as the spaceflight environment has several factors that favor the formation of stones, a predictive model that was previously constructed was used for the composite incidence. This model was developed using data from LSAH and the CDC. Information from these sources was combined using a Bayesian update approach to estimate the average rate of stone formation. From the output of this model an incidence calculation was made. The best case/worst case percentage is based on a terrestrial study indicating that 26% of kidney stone cases require surgical treatment. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. Both TWC and UTWC RTDC probabilities were considered to be 100% based on the definition. If ultrasound interventions become available which will allow dissolution of stones on-board, the RTDC probabilities may need to be changed. Loss of crew life is considered to be zero as the stone itself, which can cause severe pain, is not fatal. However, hydronephrosis leading to renal failure or infection that eventually causes sepsis can lead to death. Since sepsis is a separate condition, this possibility is not considered. 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. It is recommended that treated worst case scenario CP3 task impairment (TI) of 0% should be reconsidered since lithotripsy and surgery are not likely to be available on early exploration missions.

5. Dependence on mission phase or duration of mission. This medical condition is not dependent on mission phase. However, since hypocitraturia is more pronounced early in spaceflight, this might result in an increased incidence during the first phase of flight. Once an astronaut forms a stone, the likelihood of having a subsequent event increases.

6. Limitations

- Treatment options being investigated include moving an obstructing stone or shattering it with ultrasound. This CLIFF does not consider these as therapeutic options at this time and are not considered in the calculations. If such treatment becomes available on-board the space vehicle, this calculation will need to be reconsidered.
- There are no instances of symptomatic kidney stone formation during spaceflight among U.S. astronauts. Therefore, terrestrial general population studies and astronaut terrestrial data are used for incidence and outcomes.
- It is unknown to what extent spaceflight environmental and physiological factors increase the likelihood of the development of symptomatic kidney stones inflight.
- There is limited information regarding untreated kidney stones.
- Once an astronaut develops a kidney stone, it is likely that his/her risk for future stones increases. Thus, this would increase the conditional probability of a stone and the composite incidence.
- Future work may include updating the estimate of incidence of symptomatic inflight kidney stones based on the inclusion of more recent data and the use of inflight renal stone modeling currently under development at GRC which accounts for the biochemical alterations and environmental factors of spaceflight.

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- Additional future work may include accounting for future medical technologies that allow for the non-invasive treatment of kidney stones.
- It is recommended that treated worst case scenario CP3 task impairment (TI) of 0% should be reconsidered since lithotripsy and surgery are not likely to be available on early exploration missions.

Reviewed by:

David C. Hilmers