Renal Stone Flight and DMA NxPCM Assessment

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Study Title: Renal Stone Risk During Spaceflight: Assessment and Countermeasure Validation

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AND

Study Title: Data Mining Activity: Flight Data for Renal Stone Risk

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Research Gaps

- Gaps associated with this study:
  - **B5:** What is the current state of knowledge regarding renal stone formation?
  - **B6:** What are the contributing factors other than loss of bone mineral density?
  - **B8:** Do pharmaceuticals work effectively in spaceflight to prevent renal stones?
  - **B9:** What is the frequency of post-flight stone formation, the incidences and types of stone types, and the time course of formation? How does stone formation correlate with food intake and hydration status?
  - **B16:** Can inhibitors of stone formation be sufficiently provided through dietary sources?
  - **N13:** Can renal stone risk be decreased using nutritional countermeasures?
- Gap analysis and recommended future studies:
  - Based on the data provided by the flight study and the data mining effort, the NxPCM project recommends the closure of **Gap B5**. These reports in addition to the evidence book detail the state of knowledge regarding renal stone formation and efforts should focus towards countermeasure refinement and further development.
  - Additional research may need to be done to identify the links between renal stone formation, personal/family history, and genetic predisposition to completely close **Gap B6**.
  - These studies show that potassium citrate does decrease the risk of renal stone formation and the researchers recommended the addition of magnesium to the potassium citrated to the Human

Systems Risk Board to further decrease potential stone formation. **Gap B8** may potentially close after the evaluation of the addition of magnesium and the completion of the Bisphosphonate SMO.

- Based on data from these activities, the NxPCM project recommends the closure of **Gap B9**. These studies along with the evidence book detail the frequency of post-flight stone formation, the incidences, types of stones, and the time course of formation as well as the correlation of stone formation with food intake and hydration status.
- The NxPCM project will re-assess **Gaps B16** and **N13** upon completion of the Nutrition SMO to determine possible gap closure.
- The NxPCM project does not recommend any future Gaps at this time based on the available data, but will re-asses once current studies are completed.
- The IRP has a modified ground-based countermeasure study planned that could be used to evaluate the recommendations made by the PIs to the Human Systems Risk Board:
  - Increased Hydration
  - Use of Potassium Magnesium Citrate (addition of Magnesium from previous flight study). **This countermeasure now being implemented as a medical intervention under the transition from research to operations process**
  - Dietary Recommendations
  - Perform Risk Assessment and Educational Program

These studies also contribute to **Gap B7** (Does increased fluid intake mitigate stone formation?), although it is not an NxPCM assigned gap. The project would recommend the closure of this gap as well, since these investigations evaluated fluid intake and the PIs recommend increase fluid intake to aid in renal stone mitigation.

NxPCM Summary:

Renal Stone Flight Investigation: (Conclusion excerpts from submitted report)
"The objectives of the current study were to investigate the efficacy of potassium citrate to minimize the potential for calcium stone formation, to evaluate the effects of diet and microgravity on the risk for stone development and examine any potential effect of potassium citrate on the bone loss observed in humans exposed to a microgravity environment. Results from this investigation suggest that supplementation with potassium citrate decreases the risk of renal stone formation during and immediately after spaceflight."

"The risk of stone formation can be reduced by preventative dietary measures. High fluid intake resulting in increased urine volumes has been positively shown to reduce the recurrence rate among stone formers. Data from this study indicate that these crewmembers did not ingest adequate fluids to maintain 24-hr urine volumes at the recommended minimum output of 2L per day. In addition to water, ingestion of fruit juice, specifically orange juice and possibly other potassium-rich citrus juices, have been shown to produce an increase in urinary pH and citrate levels while producing a small decrease in urinary calcium excretion."

"In summary, dietary factors can contribute to the risk of stone formation. Results from this study showed inadequate hydration of the subjects and high sodium and protein intake along with inadequate calcium intake. Strategies for preventing stones include increasing the urine output and dietary modification, particularly reduction in animal protein and salt content. Studies to evaluate each of these on the ISS are underway."

"Crewmembers exhibiting an increased risk prior to spaceflight, then exposed to the microgravity environment and the resultant bone loss, hypercalciuria, increased urinary sodium and decreased urinary output, may further exaggerate their risk of renal stone formation. Components of an effective mitigation plan would include a personal and family medical history of nephrolithiasis and a history of chronic/recurrent urinary tract infections. Risk assessment would include a twenty-four urine collection for identification of metabolic, environmental or physiochemical alterations. Education of individual crewmembers on the benefits of increased hydration and dietary counseling should be advised to reduce the risk of stone formation. A significant limitation to increased hydration is the constraint on the quantity of water that is available on the International Space Station and on any future exploration class missions potentially resulting in additional mitigation strategies."

"Pharmacologic treatment to reduce the risk is available in the form of potassium citrate and has been effective in minimizing stone formation. An additional medication is now available, potassium magnesium citrate, enhancing the citrate available per dose and adding magnesium to the formulation. Magnesium has been shown to bind directly with urinary oxalate further lowering the supersaturation of calcium oxalate and producing a urinary environment that is less conducive to stone formation. A recent ground-based study by Zerwekh demonstrated the efficacy of potassium magnesium citrate to reduce the risk of stone formation in subjects undergoing 5 weeks of bed rest. The investigation on the use of bisphosphonates is currently is in progress on the International Space Station and if successful in preventing bone loss may lead to a decrease in urinary calcium excretion and a further reduction in the stone-forming risk."

Renal Stone Data Mining Activity Conclusions (from submitted final repot)

"Because of the reduced level of care, the formation of renal stones could cause acute illness resulting in loss of human performance during the mission and possible evacuation/mission termination. Therefore it is a critical requirement to have a validated countermeasure to prevent renal stone formation. Data mining activities for the renal stone risk were facilitated because of the spaceflight mission data base, much of which are reported in the literature. The multiple risk factors associated with renal stone formation are highlighted in these reports, but are further compounded by constraints of mission operations and the unique conditions of space and planetary habitability (e.g., dietary restrictions, food stability issues, and water availability). And while the primary risk factor for the formation of calcium renal stones in space is the increased calcium excretion resulting from bone atrophy, the risk is exacerbated by low urinary output and supersaturation of the stone-forming salts. Simply increasing urine volume alone would not address the underlying physiological adaptations to spaceflight. Furthermore, research priorities related to understanding the time course of bone loss (a contributor to urinary calcium), and the influence of mechanical loading (a mitigator of bone atrophy) are relevant to the risk for renal stone formation during prolonged missions.

In conclusion, based upon this DMA it seems likely that the most optimal countermeasure for the renal stone risk would be a combination of countermeasure approaches: bone anti-resorptives, hydration, diet counseling and prevention of skeletal adaptations by exercise loading. The countermeasure should be customized for each crewmember as dictated by the mission architecture and following a personal risk assessment to identify metabolic, environmental and physicochemical alterations. The effectiveness of pharmaceutical countermeasures may be improved by combined approaches."