Evidence Report:

Risk of Renal Stone Formation

Human Research Program

Exploration Medical Capabilities Element
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I. PROGRAM REQUIREMENTS DOCUMENT (PRD) RISK TITLE: RISK OF RENAL STONE FORMATION

II. STATUS

Active: Work/research is currently being done toward this risk.

Disclaimer: Further work is needed for this Renal Stone Evidence Report. The NASA Renal Stone Risk Custodians have reviewed the report but believe that it does not currently provide sufficient insight to buy down the risk for the development of renal stones for a prolonged Mars Exploratory or Planetary mission. This is also a function of such things as a lack of definition for exercise capabilities, hydration, pharmaceutical shelf-life/efficacy, mass/volume constraints, crew composition, or medical capabilities on those missions. More work is yet to be done regarding the causes of, countermeasures, and treatment for renal stones in Mars missions.

III. EXECUTIVE SUMMARY

Description: Kidney stone formation and passage has the potential to greatly impact mission success and crewmember health, especially for long-duration missions. Alterations in hydration state (relative dehydration), spaceflight-induced changes in urine biochemistry (urine super-saturation), and bone metabolism (increased calcium excretion) during exposure to microgravity may increase the risk of kidney stone formation. There are possible countermeasures and treatments available that are used terrestrially that may then be applied to spaceflight.

Directed Acyclic Graphs (DAGs) are used throughout this document to communicate spaceflight conditions that may lead to renal stone formation, the countermeasures that may be used to prevent their formation, and possible treatment modalities. The DAGs are sorted by strength of evidence, according to Table 6. Additionally, for the full Renal Stone Evidence Report Content: Directed Acyclic Graphs and Evidence Report, please see Appendix A, Expanded Directed Acyclic Graphs (DAGs) and Evidence.

Additionally, a proposed Concept of Operations for the Prevention, Diagnosis, and Treatment of Renal Stones for a Mars Mission was created in conjunction with and to complement this Evidence Report update. Please see Appendix B, Proposed Expanded Concept of Operations for the Prevention, Diagnosis and Treatment of Renal Stones for Mars Missions, for the full report. Areas in the following Evidence Report will be cross-linked to scenarios from the Concept of Operations.

IV. INTRODUCTION TO RENAL STONES IN SPACEFLIGHT

Nephrolithiasis is the condition marked by the development of renal stones. Renal stones are a common condition seen in terrestrial healthcare. In fact, from 2015-2018, it was estimated that the 12-month incidence of symptomatic kidney stones was 2.1%, calculated from 10,521 participants older than age 20 in the United States (Hill et al. 2022). Renal stones are aggregates of crystals that are formed in urine that is supersaturated in terms of its salt components and are particularly problematic if they form in the kidney or urinary tract, leading to obstruction of urine flow. Supersaturation can be thought of as a state where a solution is saturated with how much solute is being dissolved into the solution, leading to precipitation of solute.

First, elevated calcium levels in the urine, or hypercalciuria, a characteristic of the skeletal adaptation to space, contributes to the increased supersaturation of urine, with elevations of calcium phosphate or calcium oxalate. However, whether a renal stone forms in supersaturated urine depends upon other risk factors, as described below. The presence of these aggregates in the renal collection or excretion system can potentially result in stone formation, renal colic or severe flank pain, hematuria, infection or sepsis and can obstruct urine flow causing hydronephrosis, or a swelling of the kidney due to excess, backed-up urine.

There are many types of renal stones seen terrestrially, including calcium oxalate, uric acid, struvite, cysteine, and brushite (calcium phosphate) stones. The formation of a specific stone type depends upon the presence of particular risk factors. The most common renal stone is calcium-containing, whether calcium oxalate or calcium phosphate. This stone type is commonly caused by treatable metabolic disorders of hypercalciuria (Wang et al. 2021).

Additionally, oxalate, which is mostly dietary in origin, is a component of calcium oxalate renal stones. It has been found that individuals who secrete high levels of oxalate in urine, mainly due to nutritional intake vegetables or nuts, may be indexed to a higher renal stone risk and promote stone growth (Mitchell et al. 2019). When discussing elevated calcium, oxalate, or uric acid levels in urine, the terms hypercalciuria, hyperoxaluria, or hyperuricosuria, are used.

Uric acid stones are less common than calcium-containing renal stones and are translucent and, unlike the other stones, cannot be distinguished by radiographic imaging. Struvite stones are generated by infections of urease-containing microorganisms that are capable of hydrolyzing the urea in urine to carbon dioxide and ammonia. When urine pH exceeds 7.2, struvite stones may form, and the resulting obstruction can fill the renal collection system and erode into the renal tissue. Unlike other renal stones, cystine stones have a single etiology, hereditary cystinuria; with this condition, stone formation begins in childhood, and stones may grow large enough to fill the renal collection system. Just as on Earth, it is more cost effective to prevent stone formation during a spaceflight mission than it is to treat a crewmember (Parks and Coe 1996). Thus, understanding the etiology for the formation of specific stone types and identifying which stones are more likely to be formed during spaceflight missions will direct the application of appropriate countermeasures for nephrolithiasis.

It is possible that the astronaut selection process at NASA catches heritable renal stone disease through questions on family history; however, at the time of this writing, NASA cannot use genetic information to select out astronaut candidates or potential mission candidates who are already in the astronaut pool due to the Genetic Information Non-Discrimination Act (Reed and Antonsen 2018). It is clear, nonetheless, that a personal history of symptomatic stones could be a disqualifying condition given the potential increased risk of renal stones in spaceflight (Office of the Chief Health and Medical Officer 2021). Additionally, NASA uses a Clinical Practice Guideline (CPG), which is currently under revision, for screening and monitoring of renal stones in U.S. astronauts to standardize care and reduce overall mission risk. The CPG describes when waivers for flight duties should be instituted and also mentions preventative measures, as described below in this Evidence Report, for high-risk astronauts, including those with a urinary metabolic profile concerning for kidney stone development (Reyes et al. 2014).

However, given the severity of the consequences of renal stone formation, it is important to further characterize the spaceflight conditions that promote nephrolithiasis to take appropriate steps to mitigate this risk. In particular, altered gravity causes increased bone resorption/bone loss and reductions in bone mineral density with increased excretion of calcium (hypercalciuria) (Sibonga et al. 2017a, b), which can precipitate in urine, leading to calcium salt supersaturation with precipitation. Additionally, changes in nutrient intake/high sodium/high animal proteins may increase the risk for nephrolithiasis as well as change in hydration and relative dehydration. As individuals become more dehydrated, their urine becomes more concentrated, increasing the risk of stone formation. Changes in urinary solute concentrations and osmolality have been shown to affect urine chemistry in spaceflight (Nicogossian et al. 1982; Smith et al. 1997; Whitson et al. 2001b; Smith et al. 2012; Smith and Zwart 2015). These spaceflight conditions that may lead to renal stone formation are discussed further in the DAG Report in Appendix A.

Additionally, if conditions that favor increased urine saturation and stone formation are detected, countermeasure approaches, specific for stone type, can be implemented. For example, treating hypercalciuria (>300mg/day in males, >250mg/day in females) requires identifying and addressing the cause of increased urinary calcium. Foods high in oxalate (nuts, pepper, chocolate, rhubarb, spinach, dark green vegetables, fruits) and diets high in fat will reduce hyperoxaluria (>75-150g/ day). Less than 45mg/day of urine oxalate is considered in the range of decreased risk, and anything over 45mg/day prompts consideration of increased risk (Ennis and Asplin 2016). Reducing the ingestion of purine-containing foods, such as most meats, will suppress hyperuricosuria. Additionally, increasing fluid intake (as first-line renal stone prevention for all renal stones) to increase urine volume can dilute these factors under the upper limit of metastability for solubility of the stone-forming salts (Whitson et al. 2001b). Specific countermeasures besides those focusing on nutrition are discussed further as below. Unfortunately, given the constraints of mission operations, mass/volume concerns, and pharmaceutical expiration dates, the indiscriminate application of all these countermeasures would not be an effective approach to risk management. Instead, a full understanding of the risk factors incurred during spaceflight missions and directed implementation of countermeasures will be key to addressing this medical risk.

A. DAGs

Directed Acyclic Graphs (DAGs) are used in this document to evaluate exacerbating conditions, countermeasures, and treatment modalities for renal stones in spaceflight. Dr. Erik Antonsen has worked closely with the Human Research Program (HRP) and the Human System Review Board (HSRB) in the creation of DAGs related to the risk of renal stone formation in spaceflight. This graphical work can demonstrate relationships between nodes (as described below) with potential end-states based on strength of evidence and risk. For the full Renal Stone Evidence Report Content: Directed Acyclic Graphs and Evidence report, please see Appendix A. The HSRB approved the narrative Renal Stone DAG and published it publicly in 2022 (Antonsen et al. 2022a). This version of the DAG Report is used to step through each of the connections in the DAG and assess the Level of Evidence (LoE) scoring as described in the Human System Risk Management Plan (Antonsen 2020).

Figure 1 shows the legend for nodes, edges, and LoE scores used in the Narrative DAGs shown in this report. The color scheme was chosen to be interpretable by those with colorblindness: Hazards (orange), Contributing Factors (blue), Risks (grey), Countermeasures (purple), and Mission Level Outcomes (black).

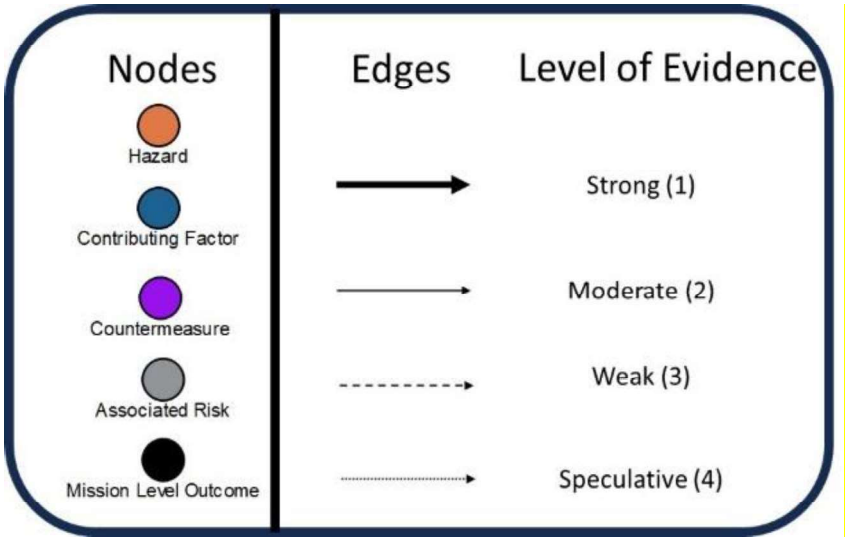

Figure 1 Legend for DAG visualizations for colorblindness with 508 compliance used

The connections between nodes are called edges and are a representation of the current understanding of causal flow within Human System Risks. Each edge is a falsifiable hypothesis, meaning that a review of the evidence can determine if the assertion shown by that edge is consistent with evidence or not.

By scoring the LoE according to procedures outlined in NASA processes, it is possible to visualize the level of uncertainty in the evidence base regarding the causal claim implied. These processes are used by NASA's HSRB and specify guidelines for creating and using DAGs as well as evaluating and assigning LoE (Antonsen 2020; Antonsen et al. 2023b, a; Ward et al. 2024). See **Error! Reference source not found.** for methods and assumptions by definition, design, standards (astronaut selection and recertification), and risk (how it relates to other known/tracked risks).

LoEs will sometimes be mentioned throughout this document, but they are not the primary focus of this Evidence Report. Please see Table 6 for full LoE results.

B. Concept of Operations for the Prevention, Diagnosis, and Treatment of Renal Stones for Mars Missions

As mentioned above, a Concept of Operations (ConOps) for the Prevention, Diagnosis, and Treatment of Renal Stones for Mars Missions was created in conjunction with and to complement this Evidence Report update. Please see Appendix B for the full report. Areas in the following Evidence Report will be cross-linked with scenarios from the Concept of Operations as above for ease of review. The purpose of this ConOps is to describe scenarios focusing on the prevention, mitigation, and management of kidney stones in a Martian mission scenario. The ConOps includes a set of scenarios that incorporate recent terrestrial and space-based medical data regarding kidney stones.

In this ConOps, there are 6 scenarios created to complement the Evidence Report in the following areas: pre-flight monitoring/prevention, in-flight prevention and training for renal stone detection, treatment of a symptomatic renal stone, and post-flight renal stone monitoring. These scenarios exemplify how the countermeasures and treatments listed in this Evidence Report update could be utilized successfully in a Mars mission.

In summary, the objective of this Evidence Report is to evaluate the current evidence regarding renal stones in spaceflight by evaluating their risk factors, countermeasures, diagnosis, and treatment, which may be applied to spaceflight missions, especially those of longer duration.

V. EVIDENCE

A. Spaceflight Evidence

The results from specimens obtained from crewmembers who have flown in space detail the biochemical and environmental risk factors associated with the risk for renal stone formation during and after spaceflight. Data sources are described below.

1. Historical Data from Skylab

Specific assessments in some Skylab crewmembers indicated that calcium excretion increased early in flight, notably by day 10 of flight, and almost exceeded the upper threshold for normal excretion (300mg/day in males) in some crewmembers during Skylab missions. This resulted in a urinary loss of approximately 50mg/day of calcium to 300mg/day at the end of 12 weeks (Rambaut and Johnston 1979). This is demonstrated through the changes in calcium balance shown in Figure 2, which is the difference between the amount of calcium the astronauts ingested every day and how much they lost.

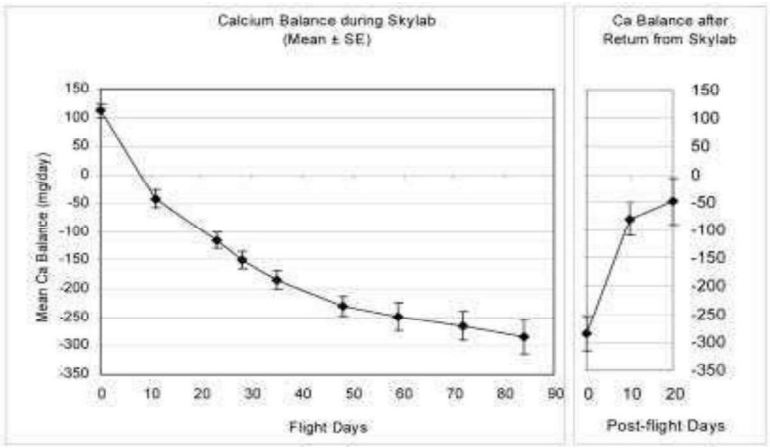

Figure 2 Calcium balance during and after Skylab missions. Adapted from (Rambaut and Johnston 1979)

2. Short-duration Spaceflight Missions on the Space Shuttle

In a series of investigations led by Peggy Whitson, Ph.D., environmental and biochemical risk factors for renal stone formation were extensively characterized for both short- and long-duration Space Shuttle missions. It was first reported that an increased risk of calcium oxalate and uric acid stone formation was evident immediately after spaceflight, concurrent with the hypercalciuria and hypocitraturia quantified after return (Whitson et al. 1993). Twenty-four-hour urine samples were obtained from 86 astronauts on a short-duration Space Shuttle mission. These were analyzed 10 days before launch and on landing day for missions both less than 6 days and those 6-10 days (Whitson et al. 1993); see Table 1 for a tabular description of data. It was found that urinary calcium levels did not change after missions less than 6 days in duration but did increase after 6-10-day missions (Whitson et al. 1993). Results were suggestive that for missions lasting longer than 6 days, crewmembers experienced hypercalciuria, hypocitraturia, and decreased urinary pH and volume (Whitson et al. 1993).

Table 1 Table showing renal stone risk factors after space flight, from (Whitson et al. 1993)

Variable	Launch −10 Days	SEM	Day of Landing	SEM	No.	P Value
Calcium (mg./day)	190	9.50	213	11.8	86	0.0159
Oxalate (mg./day)	33.7	1.87	34.6	2.30	85	0.6092
Uric acid (mg./day)	630	22.0	558	24.7	86	0.0047
Citrate (mg./day)	707	32.6	575	30.9	86	0.0002
pH	5.98	0.04	5.58	0.04	86	<0.0001
Total vol. (l./day)	1.94	0.13	1.63	0.09	86	0.0018
Sodium (mEq./day)	148	6.3	103	5.7	86	<0.0001
Sulfate (mmol./day)	21.3	0.73	26.1	1.05	86	<0.0001
Phosphorus (mg./day)	1,016	66.9	953	37.1	86	0.4084
Magnesium (mg./day)	112	4.0	92	4.1	86	<0.0001
Creatinine (mg./day)	1,667	39.7	1,791	60.0	86	0.0271
Potassium (mEq./day)	65	2.34	52.6	2.39	86	<0.0001
Relative supersaturation:						
Calcium oxalate	1.68	0.13	2.51	0.18	85	<0.0001
Brushite	1.43	0.15	1.00	0.11	86	0.0029
Sodium urate	2.98	0.31	1.61	0.14	86	<0.0001
Struvite	1.93	0.56	0.36	0.07	86	0.0061
Uric acid	2.09	0.20	3.35	0.20	86	<0.0001

The values listed represent the mean and standard error of the mean obtained from 24-hour urine samples collected 10 days before launch and on the day of landing. Data were analyzed using paired t tests, with each subject serving as his or her own control.

Further investigation, which included analysis of urine collected during flight, revealed that many of the contributing factors to renal stone formation associated with spaceflight were related to nutrition, urinary pH, and volume output (Whitson et al. 1997), as mentioned previously. In addition, biochemical analysis of urine specimens obtained during longer Space Shuttle missions provided a temporal reflection of the risk, indicating that the increased risk for renal stone formation occurs rapidly during spaceflight, continues throughout the mission, and persists following landing (Whitson et al. 1999). In-flight evidence from Space Shuttle missions shows urinary supersaturation; however, increasing the volume of urine output effectively reduced the urine supersaturation risk (Whitson et al. 2001b), a countermeasure and treatment to be discussed later in this document. Additionally, as can be seen in Table 2, urinary changes in Space Shuttle astronauts postflight evaluated over a time span of 10 years consisted of more acidic urine with elevated levels of calcium and a relatively decreased amount of other electrolytes in the urine. These results are consistent with the known electrolyte changes in the urine of astronauts returning from space, as described above.

Table 2 Table showing urinary biochemistry of astronauts pre- and post-flight from 1988-1998, from (Whitson et al. 2001b)

	1988–1993		1994–1998	
	Preflight	Postflight	Preflight	Postflight
Urine Vol ($L \cdot d^{-1}$)	1.99 (0.09)	1.79 (0.07)*	2.17 (0.07)	2.15 (0.08)
pH	5.98 (0.03)	5.66 (0.03)*	6.09 (0.03)	5.79 (0.04)*
Calcium ($mg \cdot d^{-1}$)	202.9 (7.5)	245.4 (8.9)*	168.4 (6.7)	221.5 (8.3)*
Phosphate ($mg \cdot d^{-1}$)	1051.9 (37.4)	915.1 (26.2)*	1008.2 (27.2)	800.0 (24.1)*
Oxalate ($mg \cdot d^{-1}$)	35.1 (1.1)	35.4 (1.3)	38.5 (1.4)	36.9 (1.0)
Sodium ($meq \cdot d^{-1}$)	156.5 (4.7)	111.4 (4.7)*	166.0 (4.8)	123.7 (5.0)*
Potassium ($meq \cdot d^{-1}$)	65.6 (1.6)	52.6 (1.5)*	68.2 (1.8)	53.1 (1.5)*
Magnesium ($mg \cdot d^{-1}$)	112.4 (2.9)	101.3 (3.1)	115.7 (3.4)	97.8 (2.8)*
Citrate ($mg \cdot d^{-1}$)	721.6 (22.1)	612.2 (25.1)*	685.3 (21.9)	632.7 (22.9)*
Sulfate ($mmol \cdot d^{-1}$)	22.1 (0.5)	25.6 (0.7)*	21.9 (0.6)	23.6 (0.6)*
Uric Acid ($mg \cdot d^{-1}$)	655.9 (15.3)	602.7 (20.2)*	632.5 (16.4)	535.7 (15.5)*
Creatinine ($mg \cdot d^{-1}$)	1709.7 (28.5)	1810.0 (40.2)*	1739.9 (34.3)	1712.0 (39.2)
Relative Urinary Supersaturation				
Calcium Oxalate	1.73 (0.09)	2.50 (0.11)*	1.35 (0.07)	1.98 (0.09)*
Brushite	1.48 (0.10)	1.11 (0.08)*	1.13 (0.08)	0.87 (0.07)*
Sodium Urate	2.92 (0.19)	1.67 (0.11)*	2.27 (0.14)	1.27 (0.09)*
Struvite	1.83 (0.32)	0.58 (0.10)*	2.89 (0.86)	0.66 (0.12)*
Uric Acid Saturation	2.08 (0.13)	3.03 (0.15)*	1.54 (0.10)	1.95 (0.10)*

* $p < 0.05$ vs respective preflight value. 1988–1993; n = 179, n = 178 for oxalate and CaOx. 1994–1998; n = 177. Data represent the mean and SEM.

3. Long-duration Shuttle-Mir Missions

The results from an investigation of eleven astronauts and cosmonauts who flew on the Mir space station provided evidence of the risk for stone formation during long-duration missions (Whitson et al. 2001a). Data from missions ranging from 129-208 days suggested spaceflight and the return to Earth have acute effects on the urinary biochemistry that may favor increased crystallization in the urine. Changes previously observed during short-duration Space Shuttle flights included a rapid increase in the supersaturation of the stone forming salts in the urine early during the flight that continued through landing day.

However, the stone-forming potential in the urine was different during and after long-duration spaceflight. During flight, an increased risk occurred for both calcium oxalate and calcium phosphate stones. Immediately after flight, however, the risk was greater for calcium oxalate and uric acid stone development, which could be attributed to low urine volumes and decreased urinary pH (see Table 3 for more information). In these long-duration crewmembers, there was a 47% decrease in urine volume early during the missions (before flight day 30) and a 39% lower urine output late in the mission (after mission day 60). Urinary calcium levels ranged from 159mg/day to 316mg/day during the pre-flight period and 129mg/day to 435mg/day during flight. During flight, 7 of the 11 crewmembers demonstrated higher in-flight urinary calcium values compared with their respective pre-flight levels, and 5 of these 11 crewmembers exhibited calcium excretion greater than 250mg/day (Whitson et al. 2001a). Data from these long-duration missions suggested a similar trend, as with short-duration missions, showing an increased risk for calcium phosphate stone formation occurring early in flight; however, this is just a portion of the entire data obtained during these flights. For example, in another study assessing bone markers and calcium kinetics of crew members on 4-6-month missions, Smith et al. found significant increases in urinary calcium post- compared with pre-flight, indicating an increase in bone resorption. Furthermore, their calcium kinetics data clearly demonstrated that intestinal calcium absorption was significantly lower during flight compared with preflight (Smith et al. 2004).

Table 3 Urinary biochemistry of Mir crewmembers before, during, and following long-duration space flight, from (Whitson et al. 2001a)

	Preflight	Early in-flight (< flight day 30)	Late in-flight (< flight day 60)	R+0–3 days	R+5–10 days	R+12+ days
Urine vol, l/day	1.344 (0.13)	0.914 (0.12)*	0.967 (0.08)*	1.083 (0.14)	1.34 (0.19)	1.158 (0.13)
pH	5.92 (0.10)	6.14 (0.10)	5.91 (0.11)	6.03 (0.12)	6.21 (0.15)	5.95 (0.12)
Calcium, mg/day	232.9 (19.6)	239.3 (29.3)	239.9 (30.9)	232.1 (25.5)	204.1 (16.5)	154.0 (14.2)*
Phosphate, mg/day	976.3 (54.7)	873.4 (102.9)	916.6 (109.6)	646.2 (78.7)*	830.7 (45.9)	771.4 (84.0)
Oxalate, mg/day	38.5 (2.9)	29.2 (10.1)	23.8 (2.9)*	32.2 (3.2)	41.2 (3.0)	32.9 (3.2)
Sodium, mg/day	4,140.3 (357.6)	2,839.3 (491.5)	3,112.0 (332.0)	2,876.9 (291.5)	4,385.3 (498.7)	3,252.0 (328.9)
Potassium, mg/day	2,945.1 (182.4)	2,515.6 (251.4)	2,916.7 (196.3)	2,427.9 (341.0)	3,484.2 (527.9)	2,610.4 (341.5)
Magnesium, mg/day	108.0 (7.8)	112.6 (15.2)	103.2 (11.4)	67.7 (7.7)*	86.0 (10.5)	75.9 (15.4)*
Citrate, mg/day	607.4 (59.4)	710.8 (88.1)	575.0 (59.5)	612.8 (65.0)	771.1 (85.5)	700.2 (113.4)
Sulfate, mmol/day	22.5 (1.15)	19.4 (3.32)	21.8 (1.9)	20.5 (2.3)	17.6 (1.3)	14.0 (2.1)*
Uric acid, mg/day	550.7 (52.1)	361.7 (67.6)	421.5 (52.0)	530.3 (38.2)	689.7 (59.4)	462.5 (44.7)
Creatinine, mg/day	1,658.7 (66.2)	1,569.9 (154.9)	1,592.6 (92.0)	1,668.2 (86.2)	1,688.9 (86.2)	1,517.3 (164.0)
Calculated relative supersaturation						
Calcium oxalate	2.66 (0.22)	3.57 (1.29)	2.59 (0.38)	3.67 (0.33)	2.76 (0.38)	2.26 (0.31)
Brushite	2.16 (0.24)	4.63 (0.75)*	3.29 (0.41)	2.62 (0.47)	2.17 (0.31)	1.54 (0.28)
Sodium urate	4.06 (0.55)	3.59 (0.62)	3.83 (0.53)	4.93 (0.96)	6.57 (1.02)	3.56 (0.72)
Struvite	1.50 (0.25)	5.54 (1.51)	3.31 (1.23)	2.90 (1.20)	4.10 (2.52)	1.49 (0.70)
Uric acid saturation	2.39 (0.37)	1.32 (0.26)	2.12 (0.40)	2.96 (0.52)	2.38 (0.64)	2.03 (0.37)

Data represent the means (±SEM) before, during and after space flight. n = 11; * $p < 0.05$. R+ = days from landing.

These data suggested that the early phase (<30 days) of spaceflight may generate conditions in which the risk of stone formation was greater than that during the later phases of the mission. These data are consistent with the short-duration Space Shuttle data in which both calcium oxalate and calcium phosphate risk increased.

4. International Space Station

Expanding upon the above findings, according to the Nutritional Biochemistry Laboratory at NASA Johnson Space Center, there is an ongoing increased urinary excretion of metabolites and electrolytes that are considered risk factors for nephrolithiasis during flight (Smith et al. 2015; Siew et al. 2024), even considering long-duration

missions to the International Space Station (ISS). Urinary excretion of calcium is expressed as fractional excretion (FECa). In the absence of plasma calcium abnormalities, FECa should be < 1%; however, in astronauts, FECa increases early during flight. A smaller increase was seen in oxalate (23%), phosphate (21%), and uric acid (8%) urinary excretion during spaceflight, all rapidly decreasing at return with some parameters transiently overcorrecting (Siew et al. 2024). There was also a decrease in urinary volume during spaceflight and an increase in urinary osmolality. As expected, the calculated supersaturation risk was also elevated during flight (brushite and calcium oxalate supersaturation risk increased by 150% and 115% during flight, respectively) (Pak et al. 1985b; Smith et al. 2015), with urine volume being a key factor in risk and risk mitigation. Ongoing information from the International Space Station regarding changes in urine chemistry will be further explored in an additional manuscript pending formal publication at this time.

However, according to the previous 2016 HSRB update from LSAH data, 19 of 36 stone events were found post-career in short-duration flyers (Pietrzyk 2016). Given potential confounders, including age, this evidence suggests that most stones are occurring after long periods post-flight and in short-duration flyers. This challenges our understanding of the mechanisms and timeframes involved in whether the spaceflight environment actually causes an increase in symptomatic stone formation in space missions at a rate that is different than would be expected terrestrially. These data underscore a lack of coherence between the urinary chemistry data interpreted from a terrestrial viewpoint and clinical symptomatic disease in the spaceflight domain.

Additionally, updated incidence rates for actual renal stone events detected by CT (versus mineralized renal material seen by ultrasound during routine screenings) in the astronaut corps as of mid-2024 were estimated, with analyses including astronauts who had spent time on the ISS. Data on urinary tract stone events detected by CT in the astronaut corps as of mid-2024 were obtained from LSAH and used to estimate incidence rates by career intervals. Data included all US NASA Astronauts (n = 360) followed for person years (PY) (PY = 11366.45). An astronaut's career was divided into the following categories: from selection through launch of first flight (Early NASA Career - no previous flight experience), In-flight (during each mission), 0 to 360 days post-flight (Post-flight), greater than 360 days post-flight, active astronauts (R > 360 days (Active)), and post-NASA astronaut career. An alternative model was also considered with post-flight, R > 360 days, and post NASA astronaut career further broken down by mission length (less than or greater than 30 days). Similarly, Post-flight, R > 360 (Active), and post-NASA astronaut career categories were broken down by the same mission length categories. These categories were broken down based on whether they had flown any mission over 30 days (or not). Mixed-effects models were used to address potential biases resulting from differing follow-up times, and repeated subjects was assumed across categories. Number of stones was modeled as a Poisson count with a fixed effect for career status. Subject-specific random effects addressed the repeated measures across follow-up status categories (individual susceptibility measures), and offset terms addressed the differences in follow-up time (time at risk) among astronauts. Table X shows person-years, number of events, rates per 100 person-years with 95% confidence intervals calculated using mixed effects Poisson modeling by NASA career status. As shown in **Error! Reference source not found.**, there have been no symptomatic kidney stones in-flight to date in US crewmembers on the ISS (In-flight). However, it should be noted that there was one previously reported potential episode of nephrolithiasis during spaceflight, whereby a cosmonaut experienced severe lower abdominal pain that spontaneously resolved, later attributed to renal colic (Lebedev 1990). In looking at Table 4, there were more events among crewmembers in the <30-day missions; however, there were more person-years (80% of total person-years) included in Missions<30 days, which should also be considered when reviewing these rates.

Table 4 ***Person time, number of events, and incidence rates of stones. Data are based on all U.S. astronauts (n=360) with person-years of follow-up (PY=11366.45) (Lifetime Surveillance of Astronaut Health team, NASA Johnson Space Center).***

All U.S Astronauts (n=360) with total person-years of follow-up (PY=11366.45)

	Observed values			Mixed effects Poisson model results		
	Person-years	# of Events	Crude rate per 100 PY	Rate per 100 PY	[95% CI]	
Total	11366.45	43	0.378	0.796	0.450	1.142
Time						
Early NASA Career	2165.728	4	0.185	0.391	0.011	0.771
In-flight*	70.071	0	0			
Post-flight: R < 360 days	770.465	8	1.038	2.131	0.505	3.757
Mission < 30 days	672.344	5	0.744	1.500	0.183	2.817
Mission > 30 days	97.375	2	2.054	4.959	0.000	11.883
R > 360 days (Active)	1746.871	8	0.458	0.971	0.180	1.762
Mission < 30 days	1391.197	7	0.503	1.056	0.141	1.970
Mission > 30 days	355.674	1	0.281	0.583	0.000	1.714
Post NASA Career	6613.316	23	0.348	0.735	0.341	1.129
Mission < 30 days	5814.846	20	0.344	0.697	0.297	1.097
Mission > 30 days	798.470	3	0.376	0.976	0.000	2.366

*In-flight rates with confidence intervals are inestimable until an observed event occurs. Additionally, person-years are an aggregate of shorter missions & do not adequately represent the true risk of renal stone that may increase over time during an actual one-year spaceflight mission.

Additionally, over the past 9 years, NASA's Flight Medicine Clinic at JSC has been using ultrasound to look for mineralized renal material (MRM) in asymptomatic astronauts. MRM can be precursors to or actual renal stones depending on their location and characteristics. The term "MRM" was created because calcifications in the kidneys of an asymptomatic person are of unknown clinical significance because they have never been studied before.

Surveillance has been performed on every active astronaut, annually and both pre- and post-flight, to look for mineralized material which may be precursors to the development of renal stones. Criteria used to identify MRMs include echogenic foci, posterior shadowing, presence in multiple imaging plains, and a "twinkle" pattern on Color Doppler.

Per their extensive review that is pending formal publication, as of April 2023, there were 282 studies performed on 73 astronauts with 30 paired pre- to postflight on short- and long-duration missions, which showed no observed increase in MRM burden between pre- and post-flight scans. The upcoming publication of this data will help us better understand the relative risk for development of renal stones in spaceflight (Reyes et al. 2024).

B. COMPUTER-BASED SIMULATION INFORMATION

A Population Balance Equation model was developed at NASA Glenn Research Center to predict a steady-state distribution of renal calculi size (calcium oxalate crystals) through stages of nucleation, growth and agglomeration as it moves in the kidney while in microgravity (Kassemi and Thompson 2016a). Data from the biochemical profile of astronauts were used to predict the efficacy and influence of dietary countermeasures, such as pyrophosphate, citrate supplementation, and hydration, on renal stone formation (Kassemi and Thompson 2016b) in this model. The model predictions suggested that some mitigation benefit is achieved by increasing citrate levels from average Earth-based levels, but maintaining normal urine citrate levels during spaceflight is as effective, if not more of a critical mitigation strategy. In addition, pyrophosphate has the potential of shifting the maximum crystal aggregate to a much smaller sized stone, presumably one that is safer, less symptomatic and easier to pass (Kassemi and Thompson 2016b). Finally, the risk for renal stone development increases when urinary volume drops below 1.5 liters/day; therefore, an effective hydration countermeasure should be sufficient to produce 2.5-3 liters/day of urine volume (Kassemi and Thompson 2016b). These countermeasures will be discussed in further detail below. Currently, according to NASA-STD-3001, Volume 2, a minimum of 2.5L of water is recommended per day on the ISS but is not always achievable in that amount due to various reasons.

NASA-STD-3001 Volume 2, Rev C Table 4 – Water Quantities and Temperatures
Technical Requirements in **bold boxes** are the focus of this technical brief

Technical Requirement	Quantity (quantities are mutually independent)	Temperature		
		Hot	Nominal	Cold
Potable Water for Hydration	Minimum 2.5 L (84.5 fl oz) per crewmember per day *(allocation to include 600 mL per meal per crewmember to be available as Hot Water)*	between 68 ºC (155 ºF) and 79 ºC (175 ºF) **	between 18 ºC (64 ºF) and 27 ºC (80.6 ºF)	maximum temperature of 16 ºC (60 ºF)

Figure 3 NASA-STD-3001, V2, Rev C, Requirement for potable water for hydration (NASA 2022, 2023a).

More recently and building upon this, Goodenow-Messman et al. produced a computational probabilistic biochemistry model of CaOx crystal precipitation, growth, and agglomeration (Goodenow-Messman et al. 2022). This model was trained on data from 1517 astronauts' 24-hour urine samples. Model development like this demonstrates a strong understanding of the *mechanism* of formation. The model was able to calculate incidence rate ratios for the increase in water intake that would be needed to reduce the Calcium Oxalate Incidence Rate Ratio (CaOxIRR) to the same level as pre-flight values. Their simulations predict that in-flight fluid intake alone would need to increase to ~3.2 L/day to approach the CaOx IRR of the pre-flight population. Bone protective interventions would reduce CaOx risk to pre-flight levels if Ca excretion alone is reduced to <150 mg/day or if current levels are diminished to 190 mg/day in combination with increasing fluid intake to 2.5–2.7 L/day.

VI. RISK IN CONTEXT OF EXPLORATION MISSION SCENARIOS

Because of the limitations of in-flight medical capabilities, nephrolithiasis during spaceflight could cause an acute illness with severe functional impairment, negative mission impact, or even significant morbidity or mortality for the afflicted crewmember. Therefore, it is a critical requirement to have validated countermeasures to prevent renal stone formation in spaceflight prior to exploration missions. Countermeasures related to space and planetary habitability are important; with respect to nephrolithiasis, this may include dietary restrictions to reduce risk factors, improved food science, and sufficient hydration. Increasing fluid intake and thereby increasing urine volume can provide favorable changes in the urinary supersaturation of the stone-forming salts. However, increased urine volume alone does not address the underlying physiological processes that may exacerbate the in-flight stone risk including hypercalciuria, hypocitraturia, and decreased urinary pH. Operational constraints, including supplies of onboard water and the busy crew workloads, may limit the benefits of hydration to minimize the risk of stone formation.

Optimal countermeasures for the risk could mitigate multiple risk factors ranging from bone atrophy to the supersaturation of urine. Ideally, a countermeasure for bone atrophy could also mitigate the risk for renal stone formation. Research priorities related to understanding the time course of bone loss and the influence of mechanical loading, from post-landing activities as well as fractional gravity, on planetary surfaces are relevant to the risk for renal stone formation during exploration missions (Sibonga 2008).

Specific scenarios for exploration missions are defined according to the Human Exploration and Operations Systems Engineering and Integration Decision Memorandum for Mars Mission Guidance (Robinson 2020) and differ by the duration of time in space; given mission duration, location, and time in transit, each mission profile may dictate significant differences in the relative risk of renal stone formation as well as the need for varied mitigation strategies to address such risk (Table 5). Total mission length will be expected to be around 771 days for a short Mars mission and 1094 days for a long Mars mission, so evaluating the risk of nephrolithiasis in long-duration spaceflight missions beyond LEO will be of upmost priority.

Table 5 Definition of Exploration Mission Durations (Robinson 2020).

Duration Length	Mission Location	Transit time to Location (days)	Length of Stay (days)	Transit time back to Earth-Orbit and Return (days)
Short	Moon	3	8	3
Long	Moon	5	170	5
Short	Mars	305	30	425
Long	Mars	429	300	365

The study mentioned previously by Goodenow-Messman et al. (Goodenow-Messman et al. 2022), using Bayesian analysis with a review of the literature comparing various groups (overall population, astronauts as of 2004, NASA Integrated Medical Model (IMM)/probabilistic risk assessment tool's estimated rate, non-stone former aviator rate assumption, astronaut 1-year post-flight incidence, and recurrent stone formers) revealed that there was wide uncertainty regarding the occurrence rate in events per 1000 person-years in the latter two groups. This review suggests that 1-year post-flight, astronauts experience incidence rates approaching 2-7 times that of pre-flight initial incidence rate estimates. However, terrestrially, individuals who are recurrent stone formers have recurrence rates 10-45 times the astronaut pre-flight estimated initial incidence rates, which does seem to highlight the risk for the development of kidney stones in spaceflight (Goodenow-Messman et al. 2022).

To better evaluate the risk of renal stones in spaceflight and the probability that a renal stone may result in such metrics as Task Impairment (TI), Return to Definitive Care (RTDC), or cause Loss of Crew Life (LOCL), a probabilistic risk assessment (PRA) tool was developed. NASA's Exploration Medical Capability (ExMC) Element has created such a PRA tool, which expanded upon its predecessor, the Integrated Medical Model (IMM), that focused more on conditions found in LEO. Informing Mission Planning via Analysis of Complex Tradespaces (IMPACT), scoped for beyond LEO, uses incidence information from the Medical Extensible Dynamic Probabilistic Risk Assessment Tool Evidence Library database (MEDPRAT). Evidence was obtained through terrestrial (including incidence values from the Center for Disease Control), analog, and spaceflight (including Lifetime Surveillance of Astronaut Health or LSAH) data (Lake et al. 2023).

From the CDC as of 2004 (Litwin et al. 2005), which was used in IMPACT, the incidence of renal stones per 1000 person-years varied; for males, the range was one to three incidents, while the female range was 0.6 to 1 incidents per 1000 persons per year. For this analysis, gender differences were not considered, and the average incidence rate of renal stones was 0.0018 (Gilkey et al. 2012). Within this analysis, for LSAH ground controls used in this analysis, out of 927 participants, there were 74 events over 17740.8 person-years. Crude IR: 4.171E-3 (95%CI: 3.299E-3, 5.207E-3). For the 332 included astronauts, there were 14 events over 5434.5 person-years (crude IR: 2.576E-3; 95%CI: 1.466E-3, 4.22E-3) (Gilkey et al. 2012).

Due to the low occurrence, in this model, Bayesian methods were used to combine the CDC terrestrial, LSAH ground control, and astronaut data sources to estimate incidence rates of nephrolithiasis. For nephrolithiasis, the resulting lognormal incidence distribution used in IMPACT has a mean incidence value of 0.00396 events/person year with a standard deviation of 0.00046 (as evidenced in the CLIFF, or Clinical Finding Form, excerpt as below; see Table 6 along with the Key).

Nephrolithiasis, in its most severe/worst case, which includes the need for surgical treatment or procedures, comes with a possible RTDC of 100% (see worst case condition end states as below). Although RTDC will be unlikely for a mission to Mars, for example, some form of procedural treatment for kidney stones, which will be discussed later in this document, may be available in lieu of an RTDC component. For nephrolithiasis, the LOCL was 0%, but this does not take into account conditions that may develop and cause LOCL, including sepsis or renal failure. TI% was up to 26.7606% in the untreated condition, which does make sense as a renal stone may cause intense pain in a crewmember, decreasing the ability to function at normal capacity.

Table 6 CLIFF Treatment and Outcome Table by Clinical Phase (with key) [Boley, Unpublished data]

			CP1: Diagnosis		CP2: Treatment			CP3: Condition End State				
			TI%	Duration	TI%	Duration		TI%	RTDC		LOCL	
Case Scenario	Composite Incidence	Condition Probability %	Preset	Preset	Preset	Min	Max	Preset	Min%	Max%	Min%	Max%
Treated Best Case (TBC)	mean 0.00396 and SD 0.00046	74 - 74	100	1.848	15.3069	197	293	0	0	0	0	0
Treated Worst Case (TWC)		26 - 26	100	1.848	15.3069	936	960	0	100	100	0	0
Untreated Best Case (UTBC)	N/A	N/A	100	1.848	63.3138	197	293	26.7606	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	100	1.848	63.3138	936	960	26.7606	100	100	0	0

Table 5 Key

Composite Incidence: The same composite incidence will be used for both TBC and TWC. For EVA conditions: events per EVA (events/EVA). For space adaptation conditions: events per person (events/person). For non-spaceflight conditions: events per person year (events/py).

Condition Probability: The probability that CLiFF condition progresses to a worst case scenario. Best case scenario: 100%-Worst Case.

Clinical Phase General Comments:

- TI% = Task Impairment %. Task Impairment is the % of tasks that the crewmember is incapable of performing without impairment secondary to the medical condition.
- Durations are defined in hours.
- Removal to Definitive Care (RTDC): The probability the entire crew aborts the mission and returns to earth. This is considered as a condition end state result if any of the following criteria are met: 1) the potential for LOCL, 2) potential for significant permanent task impairment, or 3) potential for intractable pain.
- Loss of Crew Life (LOCL): The probability of death of affected crewmember due to medical condition.

Clinical Phase 1: Initial Assessment and Diagnosis:

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%.

Clinical Phase 2: Stabilization, Treatment, and Convalescence:

- The affected crewmember is receiving any appropriate initial or follow-on treatment for his or her medical condition to allow the crewmember to recover as much as he or she is able to recover in the spaceflight environment. Clinical phase 2 also encompasses relapses or recurrences of the same original medical condition in Clinical Phase 1. The duration of Clinical Phase 2 is expressed as minimum and maximum hours.

Clinical Phase 3: Condition End State:

- Reached once the affected crewmember has recovered from the medical condition as much as he or she is able to recover in the spaceflight environment amongst treated and untreated best and worst case scenarios. This may or may not be recovery from the given medical condition to the full extent possible. If this "recovered" state results in Removal to Definitive Care (RTDC) or Loss of Crew Life (LOCL) this will be noted in the condition end state results.

Although the composite incidence of renal stone is quite low, it still has a risk of occurring. Additionally, the inclusion of repeated occurrences could influence the predicted rate of incidences, as it is known that the occurrence of one stone increases the likelihood of subsequent stones. However, it is likely a reasonable representation of the rate of stone formation in spaceflight given the occurrence data available and assumptions made during construction of the estimate.

A. MINIMIZING THE RISK OF STONE FORMATION

1. Countermeasures

There are various countermeasures proposed for the prevention of renal stones in spaceflight. Dietary modification with increased fluid intake, as described by the Goodenow-Messman et al. computational work mentioned above (Goodenow-Messman et al. 2022), and promising pharmacologic treatments may be used to reduce the potential risk of renal stone formation. Diets low in oxalate content and animal proteins may be advised. Some countermeasures are being considered for higher risk spaceflight crewmembers. In particular, taking oral fluids in amounts sufficient to maintain adequate hydration is encouraged. If an astronaut is suffering from severe space motion sickness early in flight, intravenous fluids may be considered to guard against dehydration. In addition to hydration, sodium consumption should be limited during flight. As discussed below, potassium citrate or potassium-magnesium citrate may be useful countermeasures to stone formation in certain high-risk individuals; however, water intake may be one of the most important (and perhaps easiest) countermeasure and treatment for renal stones in spaceflight.

Water Intake → Urine Flow (Scenario #2, p.14 AND 5, Part 2, p.16)

The relationship between water intake, hydration status, and renal stone development is well understood mechanistically and matches clinically observed data. Water intake is primarily used for the prevention of renal stones, but also shows promise in the treatment of them as well. Focused literature review showed a significant amount of data that supports the link between Water Intake and Nephrolithiasis directly from clinical studies. **Error! Reference source not found.** Figure 8 shows two equivalent DAGs highlighted by red lines.

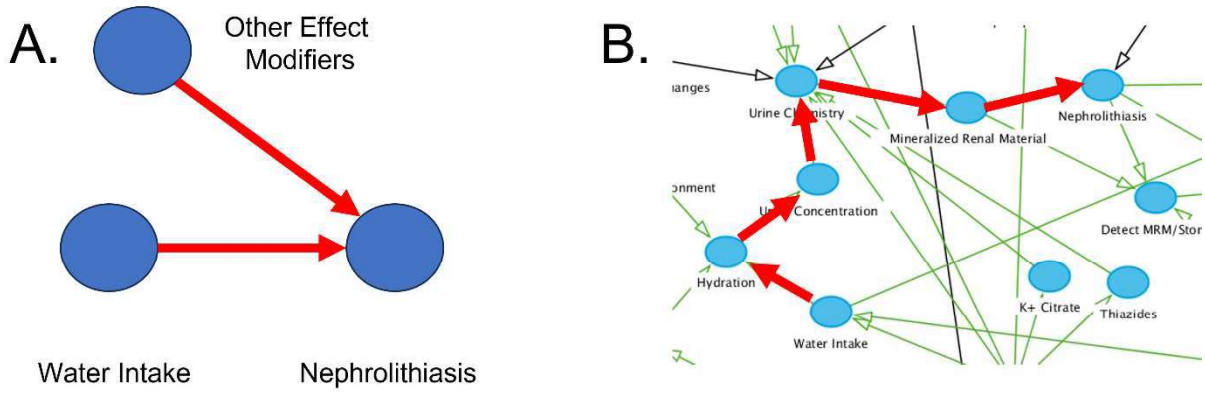

Figure 8 Comparison between DAG visualizations for the Water Intake effect on Nephrolithiasis. The image on the right is from the Renal Stone DAG and shows a higher level of mechanistic detail than the image on the left, but they are functionally the same.

The pathway from Water Intake to Nephrolithiasis is functionally the same between the two images, but the image on the right has additional nodes that show a different level of detail. The advantage of additional detail is that different countermeasures that work at different points along the mechanistic pathway can be differentiated from each other.

In a secondary analysis of 78,293 women from the prospective Women's Health Initiative Observational Study, 1,952 non-stone forming women were found to have kidney stones in follow up. This analysis found that the risk of kidney stone was decreased 13% to 31% ($p = 0.002$) with higher water intake after adjusting for nephrolithiasis risk factors (Sorensen et al. 2012).

Xu et al. reviewed 15 relevant studies (10 cohort and 5 case-control studies) in a meta-analysis with 9601 cases and 351,081 total participants. In the dose-response meta-analysis, they found that each 500 mL increase in water intake was associated with a significantly reduced risk of kidney stone formation (RR: 0.93; 95% CI: 0.87, 0.98; P<0.01) (Xu et al. 2015).

Therefore, water intake remains an important, conservative measure that can be used in the prevention of kidney stones in spaceflight.

K+ Citrate → Urine Chemistry (Scenario #2, p.14)

Potassium citrate, as described above, is used clinically to minimize the development of crystals and the growth of renal stones. Most orally administered citrate is metabolized to produce an alkali load. Administration of oral citrate increases both the urinary citrate and pH levels. The citrate complexes with calcium, decreasing ion activity, and, thus, the urinary supersaturation and crystallization of calcium oxalate and brushite. The increase in urinary pH decreases calcium ion activity by increasing calcium complexation to dissociated anions; it simultaneously increases the ionization of uric acid to the more soluble urate ion, leading to fewer uric acid stones.

Possible side effects of potassium citrate supplementation, although uncommon, include minor gastrointestinal (GI) complaints (for example, abdominal discomfort, vomiting, diarrhea, or nausea) and hyperkalemia, which may occur in subjects with renal disease, potassium-sparing diuretic ingestion, or acute dehydration. Upper GI mucosal lesions, including erosions and ulcerations, have been reported in association with oral potassium supplementation; however, studies including placebo controls have reported mixed results with no demonstrated correlation between such lesions and symptomatic complaints or occult bleeding. The risk of severe complications, such as small bowel ulceration, stenosis, or GI perforation, is estimated at less than 1 per 100,000 patient-years based on spontaneous adverse reaction reports (Gonzalez et al. 1998). These risks may be minimized by providing slow-release wax matrix tablets, ingesting the dose with meals, ingesting the tablet whole without chewing, crushing, or sucking, limiting additional salt intake, and encouraging high fluid intake. According to a previous version of this Evidence Report, potassium citrate has been used prophylactically during spaceflight in known stone-forming astronauts who have received a medical waiver for short-duration missions; the efficacy of potassium citrate supplementation has been demonstrated successfully in Space Shuttle crews. Additionally, no adverse side effects were associated with potassium citrate use during these missions (Whitson et al. 2009).

Therefore, potassium citrate and its effects on urine chemistry have been extensively evaluated both terrestrially and in spaceflight (Pak et al. 1983; Pak and Fuller 1986, 1991; Barcelo et al. 1993; Whalley et al. 1996; Ettinger et al. 1997; Whitson et al. 2001b, 2009; Sellmeyer et al. 2002; Pietrzyk et al. 2007; Robinson et al. 2009; Unno et al. 2017; Jones et al. 2019b; Zerwekh). The causal link between changes in urine chemistry and the use of potassium citrate is well understood mechanistically, has been explored in the spaceflight environment, and has had multiple studies confirming the effects of potassium citrate on urinary chemistry. Terrestrial data demonstrate that potassium citrate as a treatment does result in decreased renal stone incidence. Figure 4 shows two equivalent DAGs for visual clarity that illustrate the causal pathway to nephrolithiasis.

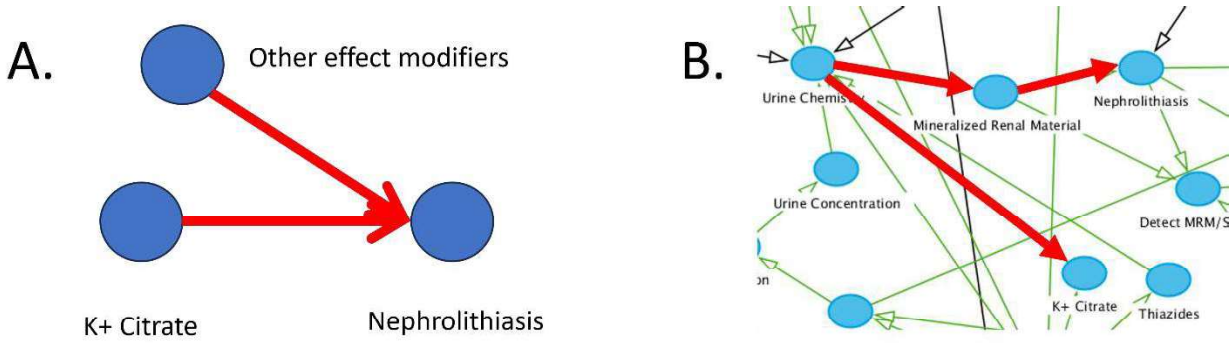

Figure 4 ***The effect of potassium citrate on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.***

There are several terrestrial studies worth discussing that demonstrate the equivalence of these pathways and enable a quantitative estimate of effect size for potassium citrate on nephrolithiasis probability of occurrence.

Pak et al. studied 89 participants and found that with potassium citrate therapy, the stone passage rate decreased from 5.14-7.41 stones/patient year before potassium citrate treatment to 0.66-1.33 stones/patient year during treatment, and 75.0-91.7% of patients were in remission (Pak et al. 1985a). They had a subgroup of 37 patients (Subgroup 2) who were similar to the astronaut population in that they did not have significant co-morbidities to consider. That subgroup demonstrated a decrease from pretreatment 1.17 +- 2.03 stones/year (duration 3 years) to 0.37+-1.53 stones/year (duration 1.8 years), showing a remission rate of 82% and a reduced stone formation rate of 93% (Pak et al. 1985a).

A review of 11 studies by Preminger et al. in 1985 showed that new stone formation was virtually eliminated by potassium citrate therapy (a decrease from 0.52 to 0.02 stones per patient per year, a remission rate of 96%, $p < 0.001$) (Preminger et al. 1985). New stone formation continued in 39% of the patients during conservative or placebo trials. In patients participating in conservative or placebo trials, new stone formation decreased by only 54% (from 0.54 to 0.25 stones per patient per year). Conservative therapy here is defined as diet modifications and increased water intake without other therapy.

In 1997, Ettinger et al. performed a prospective double blinded study of 64 patients randomized to either placebo or potassium-magnesium-citrate therapy (Ettinger et al. 1997). They found that when compared with placebo, the relative risk of treatment failure for potassium-magnesium citrate was 0.16 (95% confidence interval 0.05 to 0.46). Treatment failure here is defined as stone recurrence. Potassium-magnesium citrate had a statistically significant effect (relative risk 0.10; 95% CI 0.03, 0.36) even after adjustment for possible confounders, including age, pretreatment calculous event rate and urinary biochemical abnormalities (Ettinger et al. 1997).

Robinson et al. retrospectively evaluated 1480 patients at the Comprehensive Kidney Stone Center between 2000 and 2006 (Robinson et al. 2009). A total of 503 met the study inclusion criteria based on 24-hour urinary profiles. The mean potassium citrate therapy duration was 41 months (range 6 to 168). They found a significant change in urinary metabolic profiles as soon as 6 months after the onset of therapy, including increased urinary pH (5.90 to 6.46, $p < 0.0001$) and increased urinary citrate (470 to 700 mg a day, $p < 0.0001$). The stone formation rate decreased after the initiation of potassium citrate from 1.89 to 0.46 stones per year ($p < 0.0001$) (Robinson et al. 2009).

Importantly, the American Urologic Society guidelines in 2014 suggest that patients with renal stones should be offered potassium citrate as a treatment option and grade their level of evidence as level B (Pearle et al. 2014).

From this available evidence, the mechanism of changes in urine chemistry as it relates to renal stone formation is well understood and has been reproduced in multiple studies.

A flight experiment (96-E057) performed during long-duration missions ("Renal stone risk during spaceflight: Assessment and Countermeasure Evaluation," Primary Investigator P. Whitson) collected data from crewmembers of ISS missions (Whitson et al. 2009). The aim of the experiment was to evaluate the in-flight efficacy of potassium citrate as a mitigator of nephrolithiasis (particularly of stones composed of calcium salts) during long-duration spaceflight. In this double-blind study, crewmember subjects on Expeditions 3-6, 8, and 11-14 consumed two tablets, either placebo or 20mEq potassium citrate, with their last daily meal from L-3 to R+14 days (3 days pre-launch to 14 days after return). Twenty-four-hour urine specimens were collected three times during flight: early (<35 days into flight), middle (between 36-120 days of flight), and late mission (within 30 days of undocking for return). The urinary biochemistry was analyzed, and the urinary supersaturation levels were calculated after return. All diet, fluid, exercise and medications were logged for 48h before and during the urine collection time to assess any potential impact from environmental factors. In addition to evaluating the efficacy of potassium citrate to minimize the risk of stone formation, the results of this experiment described the renal stone forming potential in crewmembers as a function of time in space as well as the stone forming potential during the post-flight period.

The evidence base for this link reaches the level of coherence, and the LoE score is Strong that potassium citrate will modify urine chemistry in a favorable profile (proxy outcome) and by clinical demonstration in multiple studies it probably will decrease the likelihood of renal stone occurrence in spaceflight (target outcome).

Similar to potassium citrate, potassium-magnesium citrate is also under clinical study and may soon be approved as an additional supplement for inhibition of stone formation (Pak and Fuller 1986; Pak 1994; Whalley et al. 1996). Potassium-magnesium citrate was evaluated as a countermeasure for renal stones in a flight analog experiment (Zerwekh et al. 2007). A double-blind, placebo-controlled study was conducted in normocalciuric human test subjects skeletally unloaded by five weeks of prolonged bed rest as an analog for spaceflight. Two 24-hr urine collections were obtained to evaluate renal stone risk parameters and the relative saturation of calcium oxalate, brushite, and undissociated uric acid. Circulating parathyroid hormone and vitamin D metabolites were measured in serum samples. As expected, bed rest immediately induced hypercalciuria by an increase of 50mg/day in both groups. Subjects treated with potassium-magnesium citrate displayed reductions in the relative saturation of calcium oxalate and in the concentration of undissociated uric acid compared with placebo. Parathyroid hormone and vitamin D metabolites were reduced in both groups, with no significant difference between groups in the decrements. The study authors concluded that potassium magnesium citrate is an effective inhibitor of renal stone formation, as indicated by the reduced urine saturation of calcium oxalate and concentration of undissociated uric acid by the citrate chelation of calcium and the alkalization of pH, respectively (Zerwekh et al. 2007).

Thiazides → Urine Chemistry (Scenario #2, p.14)

Thiazide diuretics are a commonly used medication for control of hypertension. The mechanism of action is well understood as they inhibit the Na+/Cl- cotransporter in the renal Distal Convoluted Tubule (DCT) (Duarte and Cooper-DeHoff 2010; Reilly et al. 2010). Changes in urine chemistry occur with the sodium retention and transport of chloride ions into the urine. The blockage of the Na+/Cl- channel causes an increase in sodium and water retention in the lumen and a decrease in Na in the DCT. At the same time, blockage of the Na+/Cl- channel increases the flow of ions through the Na+/Ca++ channel, resulting in increased calcium reabsorption into the interstitium in exchange for Na return to the DCT (Akbari and Khorasani-Zadeh 2023). This results in decreased urinary calcium and has been the basis for the use of Thiazide diuretics for renal stone treatment (Akbari and Khorasani-Zadeh 2023).

A 2009 Cochrane Review of 5 prospective randomized double blind controlled studies examined the effect of thiazide use on urine chemistries (Escribano et al. 2009). These were in concert with dietary modifications (4 studies) and with a neutral potassium salt (1 study). The conclusions indicated there was a significant decrease in the number of new stone recurrences in those treated with thiazides (RR 1.61, 95% CI 1.33 to 1.96). The stone formation rate also showed a statistically significant decrease in the patients treated with thiazides (MD -0.18, 95% CI -0.30 to -0.06). Thiazides plus potassium salts significantly decreased calciuria and vitamin D levels. There is little doubt that thiazides affect urine chemistry. The question of specificity for useful application for risk reduction in spaceflight missions requires more insight into quantitative effects of stone reduction.

Quantitative estimates of the effects of thiazides on stone reduction are available, but there is disagreement among experts in the field of the magnitude of benefit (Knoedler and Krambeck 2014). In 1981, Brocks et al. published a randomized double-blinded study of 62 patients that showed no difference in the clinical course of idiopathic renal calcium stone formation between a thiazide group and a placebo group (Brocks et al. 1981). Similarly, Sholtz et al. performed another randomized double blinded study with 51 patients over a year and found the expected calcium decrease without a difference in stone formation or passage between thiazide and placebo groups (Scholz et al. 1982). A later meta-analysis in 1999 found thiazides to be effective in the prevention of recurrent stones (Pearle et al. 1999).

A separate double-blind randomized Norwegian study of 50 recurrent stone formers did find a clinically significant difference between thiazide and placebo groups. The median number of new stones decreased by 78% in the thiazide group and 59% in the placebo group. Additionally, the number of patients forming new stones in the placebo group was more than twice the number in the thiazide group, and, if a new stone was formed, thiazides had the effect of prolonging the stone-free interval by 52%. Additionally, the effect of thiazides was independent of whether the patient had hyper or normocalciuria with regard to stone formation. The Quality of Evidence (QoE) of this study was unable to be assessed (Laerum and Larsen 1984).

A 2022 systemic review by Ferre et al. reviewed 5 prospective randomized, double blinded studies using thiazides in 441 patients from 1987 – 2009 (Ferre et al. 2022). Four of the studies were performed in individuals with pre-existing renal stones, and one was in post-menopausal women with osteopenia. This review assigned QoE scores. The meta-analysis suggested that thiazide diuretics were likely to increase the number of stone-free patients (RR

1.61, 95% CI 1.33-1.96, moderate QoE). Notably, this only produced a slight decrease in stone formation rate (mean difference -0.18, 95% CI -0.30 - -0.06, Low QoE) (Ferre et al. 2022). Importantly, the American Urologic Society guidelines in 2014 suggest that patients with renal stones should be offered thiazides as a treatment option and grade their level of evidence as level B (Pearle et al. 2014).

Figure shows two equivalent DAGs for visual clarity that illustrate the causal pathway to nephrolithiasis.

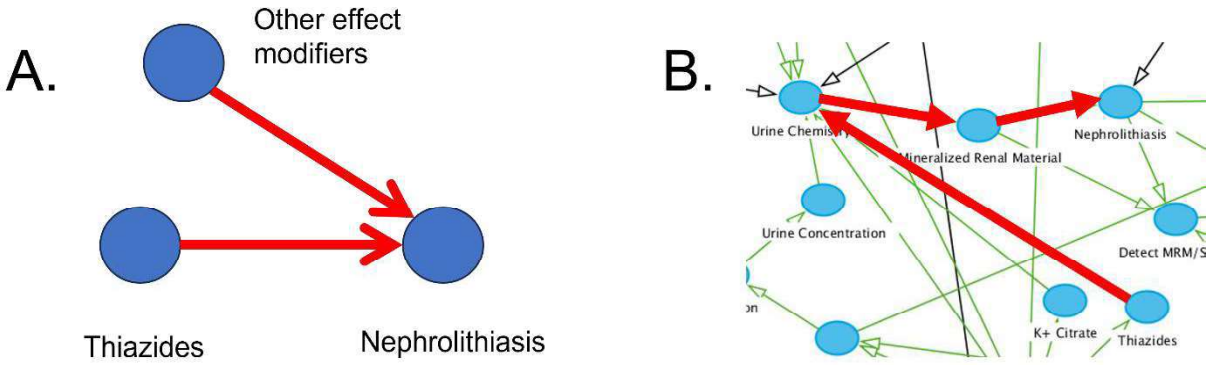

Figure 5 ***The effect of thiazide diuretics on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.***

There is some lack of coherence in the overall literature on the effectiveness of thiazides for renal stone treatment, and more importantly the generalizability of this information to an astronaut population in the spaceflight environment for the mission durations of interest. Additionally, thiazide use is not without concern in a spaceflight environment. For example, in a confined, time-sensitive mission, operationally, use of a toilet may not always be possible or easily accessible. Additionally, as noted above, given that an astronaut's urine may become super-saturated in space due to the above mechanisms, alongside dehydration, which was noted even in short-term spaceflight (Reynolds et al. 2024), increasing a crewmember's frequency of urination, may further dehydrate the individual, possibly causing deleterious consequences. However, despite these concerns, thiazides may be an upcoming pharmaceutical to be studied as a countermeasure for the development of renal stones in spaceflight.

Bisphosphonates → Bone Remodeling (Scenario #2, p.14)

Bisphosphonates are a class of drugs with demonstrated efficacy in treating elderly patients with osteoporosis by inhibiting the loss of bone. These agents could potentially prevent the bone loss observed in astronauts and thereby mitigate or avert stone formation, promoting resorptive hypercalciuria. They inhibit osteoclastic resorption of bone and have been used in spaceflight as a countermeasure for bone resorption (Sibonga et al. 2017a, b; Shackelford 2019). Additionally, Zoledronic Acid, a type of bisphosphonate, could be especially desirable given that a single injection is currently approved for fracture risk reduction in patients with high fracture risk every 12 months and every 24 months for those without high fracture risk (UpToDate 2024).

One extended (90-day) terrestrial bed-rest study demonstrated decreased urinary calcium excretion, alongside decreased supersaturation of calcium oxalate and calcium phosphate, in subjects receiving pamidronate (a bisphosphonate) as compared to controls; there was a concomitant trend towards decreased stone formation in the pamidronate group (Okada et al. 2008). Additionally, a joint study conducted by NASA and the Japanese Aerospace Exploration Agency (JAXA) evaluated the use of alendronate, in combination with resistive exercises, for its ability to decrease bone resorption and urinary calcium excretion in 18 astronauts, who used the interim resistance exercise device and 11 astronauts who used the advanced resistance exercise device (ARED). The group that used both a combination of ARED and bisphosphonate did show a trend toward a decline in altered bone physiology during spaceflight, including DXA-determined bone mineral density loss and Quantitative Computed Tomography (QCT)-determined loss in trabecular and cortical bone mass. However, compared with preflight, there were no significant in-flight changes in urinary calcium excretion in those with bisphosphonate use, thereby warranting a further investigation into this pharmaceutical and its effect on hypercalciuria (LeBlanc et al. 2013). Upon initial

evaluation, it seemed that the crewmembers who took bisphosphonates had a higher baseline calcium excretion. Additionally, this could have led to a greater change in urinary calcium excretion with the bisphosphonate use, as seen in the study. Also, crewmembers taking bisphosphonates excreted the same amount of calcium per day by Flight Day 60 as those who did not take bisphosphonates (LeBlanc et al. 2013; Smith et al. 2014), making these findings less straightforward with regard to the use of bisphosphonates in spaceflight.

Whether Bisphosphonates are likely to reduce nephrolithiasis because of these changes in the context of spaceflight is a broader question. Figure shows the path tracing (Panel B.) from Bisphosphonates and Resistive Exercise through Urine Chemistry, MRM, to Nephrolithiasis. Panel A shows the simplified equivalent for Bisphosphonates alone with all other effect modifiers shown in a single node.

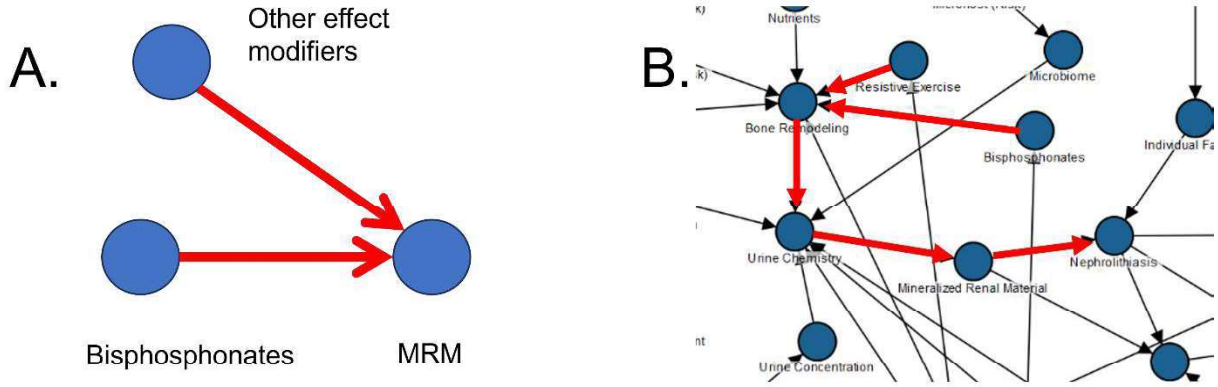

Figure 6 ***The effect of bisphosphonates and resistive exercise on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.***

Whether bisphosphonates clinically demonstrate a meaningful reduction in renal stone formation or symptoms is a separate question. In 2020, Kovacevic et al. showed ex vivo that bisphosphonates inhibited calcium salt formation in the urine (Kovacevic et al. 2020). Prochaska et al. performed a cross-sectional analysis of 2294 participants in the Nurses' Health Study II and concluded that among participants with low bone density, bisphosphonate use was associated with lower risk of incident kidney stone but was not independently associated with 24-hour urine calcium excretion. The multivariate adjusted relative risk for no bisphosphonate use was 1.39 (95% confidence interval [95% CI], 1.20 to 1.62) and with bisphosphonate use it was 0.68 (95% CI, 0.48 to 0.98) (Prochaska 2021). Another study showed decreases in calciuria and bone markers favorable to renal stone formation using bisphosphonates with and without thiazides (Arrabal-Polo et al. 2013), but these studies were limited as they are terrestrial.

The combination of bisphosphonates and a resistive exercise regimen appears to improve bone health and decrease urinary calcium excretion, and thus may reduce the risk of stone formation during and possibly after long-duration spaceflight.

Tamsulosin → Urine Flow (Scenario #5, Part 2, p.16)

Tamsulosin is a smooth-muscle inhibitor (alpha-blocker) that has been used clinically to improve the passage of renal stones. The mechanism of action is well-understood.

Wang et al. performed a systematic review in 2018 of eight randomized controlled trials totaling 1,384 patients (Wang et al. 2017). The pooled risk of stone passage in the tamsulosin arm was 85% versus 66% in the placebo arm, but substantial heterogeneity existed across trials. After stratifying the studies by stone size, the meta-analysis of the large stone subgroup (5 to 10 mm; N=514) showed a benefit of tamsulosin (risk difference = 22%; 95% confidence interval 12% to 33%; number needed to treat=5). The meta-analysis of the small stone subgroup (<4 to 5 mm; N=533) indicated no benefit (risk difference = –0.3%; 95% confidence interval –4% to 3%). This suggests that for small stones there is likely to be less benefit from Tamsulosin administration.

In 2019, Cui et al. also performed a large meta-analysis that included 56 randomized controlled trials for a total of 9,395 patients (Cui et al. 2019). Tamsulosin treatment was associated with a higher stone expulsion rate (RR 1.44,

95% CI 1.35-1.55, p <0.01), a shorter stone expulsion time (weighted mean difference -0.73, 95% CI -1.0—0.45, p <0.01), a lower incidence of ureteral colic (weighted mean difference -0.81, 95% CI -1.2—0.39, p <0.01) and fewer incidences of requiring subsequent treatment interventions (RR 0.68, 95% CI 0.50-0.93, p = 0.017). There was not a significant difference between the Tamsulosin group and the control group in the overall incidence of side effects (RR 1.14, 95% CI 0.86-1.51, p = 0.36). They also found a stronger benefit in the stone expulsion rate for tamsulosin among patients with stones greater than 5 mm (RR 1.44, 95% CI 1.22-1.68, p <0.01) and a diminished effect for stones 5 mm or less (RR 1.08, 95% CI 0.99-1.68, p <0.01).

Terrestrial clinical evidence suggests that tamsulosin is beneficial for relieving obstruction by larger stones (>5mm) through helping them pass more quickly. Larger stones are less common than small stones. Tamsulosin is also present on the ISS.

B. Renal Stone Risk Assessment

U.S. crewmembers are assessed with the renal stone risk profile (Mission Pharmacal, University of Texas Southwest Laboratories (Morgan and Pearle 2016), graphically plotted for each individual. Although the urinary risk profile does not directly predict the formation of renal stones, it illustrates to the flight surgeon and crewmember the current urine chemistry environment (Ryall and Marshall 1983; Pak et al. 1985b; Pak 1997; Grases et al. 1997). In our retrospective review of cases and the post-flight Renal Stone Risk Index (RSRI) assessment, we found a strong correlation (0.93) between known stone-formers and a high RSRI. All but one case was found to have significant urinary biochemical abnormalities in the stone risk profile; the one outlying case had minor abnormalities. There were some false positives in prospective cases, confounded by urine collection biases, but there were no false negatives.

The risk profile, considered in conjunction with the lifestyle and dietary habits of the individual, can be a valuable monitoring and education tool (Rivers et al. 2000). Individuals who are at an increased risk or have previously formed renal stones can be followed, patient compliance can be assessed, and the effectiveness of medical treatment can be determined with this profile. The renal stone risk profile has proven value in the clinical setting as a tool for classifying patients according to the etiology of the formation of their renal stones (Pak et al. 1985b; Yagisawa et al. 1998; Lifshitz et al. 1999). Further, the relatively low cost of the renal stone risk profile makes this a cost-effective methodology and may mitigate both the risk of developing a stone in-flight and the potential mission impact if nephrolithiasis occurs. Clinical and research experience has shown that monitoring the urinary environment and estimating the risk for renal stone development can lead to significantly improved control of stone disease when this information is used to guide medical therapy (Morgan and Pearle 2016), and the need for surgical intervention and stone removal can be dramatically reduced by an effective prophylactic program.

Studies have concluded that, for terrestrial stone-formers, the reproducibility of urinary stone risk factor analyses is satisfactory in repeat urine samples and a single stone risk analysis is sufficient for a simplified medical evaluation of urolithiasis (Pak et al. 2001). The accuracy of measuring urinary stone promoter- and inhibitor-substances is improved by including matrix components, uroproteins, uromucoid, and glycosaminoglycans in the analysis (Batinić et al. 2000). Other laboratory analyses for urinary stones include blood urea nitrogen, serum electrolytes, creatinine, calcium, uric acid, and phosphorous.

As applied to the U.S. space program, this health care monitoring program may provide several distinct advantages. Crewmembers with an increased baseline risk prior to spaceflight may further increase their risk of stone formation when exposed to the microgravity environment and the resultant bone loss, hypercalciuria, increased urinary sodium, and decreased urinary output. The RSRI evaluation may identify an increased risk prior to flight, help to identify appropriate medical intervention, and reduce the potential risk before, during, and after spaceflight. In implementing the schedule of RSRI measurement with 24h urine collection, it was determined that all astronauts should have an annual assessment dedicated to stone risk factor identification. Space Shuttle crewmembers with significant risk factors or history of previous calculi also had pre-flight evaluations for stones. Currently, this assessment is performed annually as well as post-flight, during the comprehensive medical examination, performed twice at 3 and 30 days after return in all crews.

Additionally, as mentioned previously, NASA's Flight Medicine Clinic at JSC uses ultrasound to look for mineralized renal material regularly in astronauts both pre- and post-flight annually. This material may represent precursors to the development of frank renal stones to better characterize risk and to determine if prophylactic treatments are necessary.

1. In-flight Diagnosis and Monitoring

Lab and Urine Studies → (Scenario 5, p.16-17)

Obstructing renal stones may present in various ways but usually are associated with a sudden onset of flank pain and/or back pain. If the stone leads to secondary urinary tract or renal infection, the individual may experience burning with urination (dysuria), decreased ability to urinate, fever, nausea, or vomiting. In severe situations, the kidney may become injured, leading to kidney failure. There are various other differential diagnoses that may present with similar symptoms to a renal stone. These include back/muscle strain, gastroenteritis, acute abdomen caused by appendicitis or cholecystitis, or, even kidney or bladder infection without stone.

Diagnosing nephrolithiasis is not as difficult as distinguishing the type of renal stone. It may be possible to delineate stones by physical features. Oxalate, cystine and struvite stones have distinctive appearances (mimicking stars, wax-like eggs, and tree roots, respectively), but final diagnosis requires recovery of the stone itself, which is not always possible. Laboratory evaluations can be used to determine risk factors for stone formation based upon saturation levels of calcium, oxalate, and uric acid measured in 24-hour urine specimens. However, assessment of pH, urine volumes, urine citrate levels (an inhibitor of stone formation) and oxalate levels, creatinine levels (a marker of optimal renal function), and serum calcium levels can provide evidence of whether conditions are conducive to stone formation. If hypercalcemia is detected, then assay of parathyroid hormone can be used to diagnose the existence of a metabolic disorder that may be at fault.

As touched on previously, urinary oxalate levels are currently obtained to evaluate risk of developing renal stones, however, there have been studies looking at a spot, rather than 24-hour urinary calcium measurement device using a fluorometric reader, based on Calcein as a reagent (Yeasmin et al. 2022). The benefits of this device are that it is portable and compact, which may give feedback to the effectiveness of renal stone countermeasures in real-time. In the future, this device may be tested in a spaceflight environment and could be used in a pre, in, and post-flight scenario.

Gold standards of testing associated with possible renal stones emergently on Earth include renal ultrasound (which will be discussed later in this document) or computed tomographic (CT) imaging, which is a modality that is not yet readily available in spaceflight but may be possible in the distant future (a lightweight, portable, stationary CT is currently being developed at the Massachusetts General Hospital for possible use in spaceflight (Cramer et al. 2018)). Additionally, laboratory studies including an elevated White Blood Count (WBC), which may be indicative of an infection, and, more importantly, blood chemistries to include evaluation of Creatinine level, which, if elevated, can be a sign of kidney injury or impending kidney failure, and Blood urea nitrogen (BUN), also evaluating for kidney function, are usually obtained. Additionally, urine studies are used to evaluate for urine infection or possibly impending kidney failure.

Currently, blood and urine testing are available on the International Space Station in a very simplistic fashion (basic electrolyte profile and urine dipstick testing). Otherwise, it may be assumed that for missions beyond LEO, there may be even more comprehensive evaluations possible.

Ultrasound → Detect MRM/Stone (Scenario #3 and #4 p.14-15)

Ultrasound imaging technology is available to the crews on the ISS. If symptoms suggesting nephrolithiasis occur in flight, spaceflight crews can take specific steps to respond and mitigate further risk, including the use of sonographic imaging. The onboard crew medical officer, with guidance from ground medical specialists, is able to monitor an affected crewmember's vital signs, hydration status, and clinical appearance, and may perform an ultrasound exam with real-time guidance from ground controllers. In the case of an acute renal stone event, image characterization would allow for stone localization and estimation of size, information that could prove critical to medical decision-making. Guided ultrasound examinations have been performed many times for investigational purposes and shown to provide adequate diagnostic imagery (Sargsyan et al. 2005; Jones et al. 2009). However, this may not be the case in missions beyond Low Earth Orbit (LEO), especially considering a mission to Mars, where

pre-flight and in-flight practice and training may prepare Crew Medical Officers to perform ultrasound evaluations without direct ground support.

For missions that lack a real-time support capability, the evidence is less clear regarding whether astronauts will be able to perform diagnostic, monitoring, and possibly interventions using ultrasound given the level of training that is required. In 2015 Hurst et al. performed an evaluation of image quality and time to image capture for remote guided and computer guided operators (Hurst et al. 2015). This initial data suggests that image quality was acceptable in both modalities. An on-orbit assessment was conducted in April 2020 and June 2022 with Autonomous Medical Officer Support (AMOS) software developed by the ExMC at NASA. The crewmembers involved did not receive any prior training and had no support. They were able to obtain 25 high-quality images of bladder and kidneys using the software alone (Ebert et al. 2023). However, no MRM or stone was identified, which was to be expected.

For the condition of renal stones, ultrasound may be used to show visible calculi in the ureteropelvic junction or renal pelvis and can further identify unilateral distension of the collecting system from either hydronephrosis or hydroureter if adequate time has passed to allow for distention to occur. Ultrasound may also show loss of the ureteral jet in the bladder ipsilateral to the side of pain, further supporting a clinical diagnosis of nephrolithiasis.

However, there is evidence at the level of animal studies that suggests that the spaceflight environment may make it more difficult to detect the twinkle/spectral artifact. In one animal study using pigs, the twinkle artifact decreased in visibility as the CO2 atmospheric levels increased to a threshold around 0.8% CO2 which is approximately 5.3 mmHg ppCO2. In this experiment 4 pigs were implanted with stones and imaged. The twinkle artifact faded after 9-25 minutes of exposure to 0.8% CO2 driven by an increase in the carrier gas and returned after the O2 levels were restored (Simon et al. 2017). ISS has reached this level of CO2 in the past in ambient conditions, but other issues drove re-evaluation of the standards (Law et al. 2014). Current NASA-STD-3001, Volume 2, Rev C [V2 6004] limits the average 1-hour CO2 partial pressure (ppCO2) in the habitable volume to no more than 3 mmHg (2022). Given this data comes from animal studies in a different environment, this particular study sheds light on possible mechanisms, but there has not been reproducibility or specificity observed in humans or the spaceflight environment.

However, evidence as above demonstrates that renal and bladder ultrasounds can be performed in space, and, therefore, could be used to detect the presence (or signs of) kidney stones, and may be utilized as a clinical trigger for in-mission preventive interventions to keep the stone from becoming symptomatic.

C. TREATMENT

Medications (Scenario 5, Part 2, p.16)

Pharmaceuticals are a mainstay of treatment for renal stones. These are defined as medications for control of pain and nausea, fluid hydration, and, in some cases, antibiotics, as needed for developing urinary tract or renal infection. These types of medications control nausea (Ondansetron, Promethazine), act as an analgesic (Ketorolac, Ibuprofen, Hydromorphone), aide in the expulsion of kidney stones (Tamsulosin), or, in the case of a urinary tract infection secondary to urine stasis caused by an obstructing renal stone, include antibiotics such as Sulfamethoxazole/Trimethoprim and Nitrofurantoin. These medications are available on the ISS and are listed in the publicly available sources of information (Stingl et al. 2015; Jones et al. 2019a). They are also confirmed with subject-matter experts (SMEs) in medical operations.

There is some question as to whether these medications will remain effective throughout the duration of a Mars mission (Blue et al. 2019), given length of mission and exposure to spaceflight environment, but is an area for future research.

Ultrasound Manipulation → Ureterolithiasis (Scenario #3 and #4, p.14-15)

Additionally, there is the development of technologies to manipulate renal stones, especially those that are in a favorable location in the kidneys or ureter. Hand-held ultrasound technology designed to push or break apart a renal stone with focused ultrasound beams has been advancing through clinical trials for applications in terrestrial medicine (Sorensen et al. 2013). The utility of this technology in a spaceflight mission assumes that a beam focuser for the ultrasound has been provided in the medical treatment capability. As this is a small, low power device that typically fits over the probe of an ultrasound machine, it is reasonable to assume this may be IDed if evidence of risk reduction can be demonstrated. Applications include repositioning a stone to an area less likely to progress to the ureter [i.e., inferior pole of the kidney (Dropkin et al. 2015)], pushing a stone out of the proximal or distal ureter, or possibly breaking a stone into smaller pieces that are able to pass with minimal symptoms (Sorensen et al. 2013).

In 2016, Harper et al. attempted to use this technology to reposition stones in the kidney in a first in human trial. They reported successful repositioning of stones in 14 of 15 subjects. "Of the 43 targets, 28 (65%) showed some level of movement while 13 (30%) were displaced > 3 mm to a new location. Discomfort during the procedure was rare, mild, brief, and self-limited. Stones were moved in a controlled direction with over 30 fragments being passed by 4 of 6 subjects who previously had a lithotripsy procedure. The largest stone moved was 10 mm. One patient experienced pain relief during treatment of a large stone at the UPJ. In 4 subjects a seemingly large stone was determined to be a cluster of small passable stones once moved" (Harper et al. 2016).

In 2022, a prospective unblinded study was performed in 29 subjects who received either ultrasonic propulsion alone (n = 16) or with burst wave lithotripsy bursts (n = 13) (Hall et al. 2022). They report observable stone motion in 19 (66%). Stone passage occurred in 18 (86%) of the 21 distal ureteral stone cases with at least 2 weeks follow-up in an average of 3.9±4.9 days post-procedure. Fragmentation was observed in 7 of the burst wave lithotripsy cases. Average pain scores (0–10) dropped from 2.1±2.3 to 1.6±2.0 (P = .03). Side effects were minimal including hematuria on initial urination post-procedure and mild pain. In total, 7 subjects had associated discomfort with only 2.2% (18 of 820) propulsion bursts.

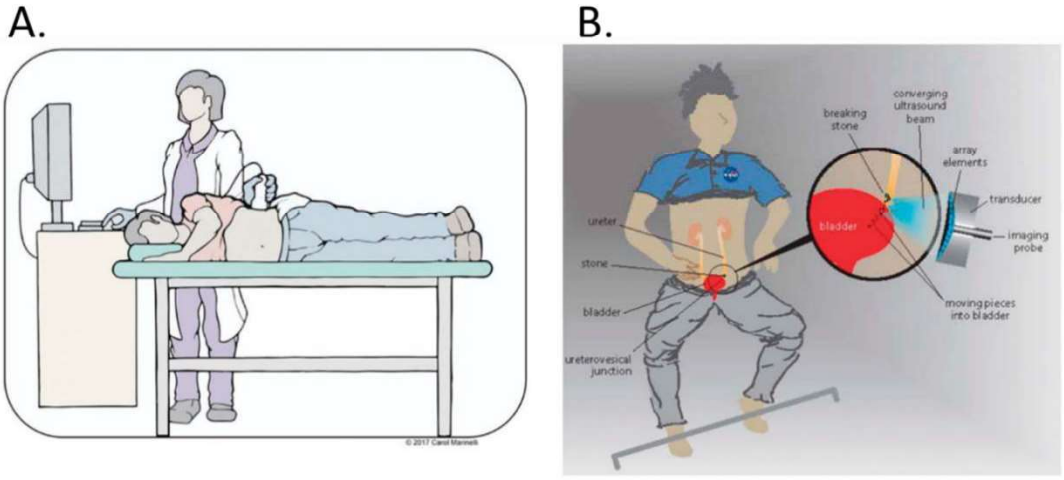

Figure 7 ***Figure modified from Hall et al. 2022 showing clinical positioning and use of ultrasonic stone propulsion and transcutaneous burst wave lithotripsy in A. terrestrial setting and B. spaceflight setting.***

Given the recency of this technology, the Technology Readiness Level is 5-6 given the demonstrations discussed here (2023b). The technology is expected to advance in the future. Mechanism is understood, but reproducibility and specificity are lacking at this time, but are promising for future use in spaceflight.

Additionally, it should be noted that dynamic phases of flight may affect where and how long a stone is lodged within the kidney or ureter, such as has been seen in the possible movement of kidney stones during rollercoaster rides in a small number of individuals. However, further work into the movement of kidney stones during dynamic phases of flight should still be considered.

Percutaneous Nephrostomy → Medical Illness (Scenario #5, Part 3, p.16-17)

In keeping with the prior discussion on autonomous ultrasound imaging, the evidence regarding the effectiveness of Percutaneous Nephrostomy (PCN) for risk reduction when autonomous performance is required is thin. PCN is a medical procedure where a clinician uses imaging guidance to place a catheter through the back into the renal pelvis and allow urine to pass from the body without passage through the ureters or bladder (Efesoy et al. 2018; de Sousa Morais et al. 2019). This is not required in all cases of renal stones but could be indicated in rare situations where a renal stone becomes stuck and obstructs the passage of urine. This can lead to hydronephrosis and the likelihood for infection increases.

Terrestrially these types of stones are treated with a variety of approaches including extracorporeal shock wave lithotripsy, flexible ureteroscopy, and PCN. PCN relieves hydronephrosis and decreases the likelihood of infections and is used to treat patients who are either in or at risk of sepsis with an obstructing stone (Khan et al. 2016; Jones et al. 2019b; Hsu et al. 2022). The purpose of this intervention is then to reduce the likelihood of progression to sepsis and renal failure, two events that would be exceedingly difficult to treat with the mass, volume, loss of real-time communications, and training restrictions that are a reality of an eventual Mars mission (Antonsen et al. 2022b). For Low Earth Orbit Design Reference Missions (DRMs), occurrence of the medical conditions that lead to consideration of PCN would likely result in an evacuation for definitive care on Earth. In a Mars mission where evacuation is not feasible, the provision of PCN as a medical capability may be lifesaving.

In 1998 Pearle et al. randomized 42 patients with obstructing calculi and clinical signs of infection including fever and elevated white blood cell count to PCN vs. retrograde ureteral catheterization to assess differences between the techniques (Pearle et al. 1998). For the PCN group, average time to normal temperature was 2.3 days and time to normal white blood count was 2. Those PCN patients stayed an average of 4.5 days.

Placing a PCN is not without risk. Efesoy et al. retrospectively evaluated four hundred and fifteen percutaneous nephrostomy tube placements performed in 354 patients (165 men and 159 women) suffering from obstructive uropathy over a 10-year period in Turkey. They found that overall technical success and minor and major complication rates were 96.1%, 11.1%, and 7.7%, respectively, for their experienced operators (Efesoy et al. 2018). Major complications included 10 cases where the tube needed to be replaced because of blood clots, 7 cases of macroscopic hematuria requiring blood transfusion (a medical capability which is unlikely to be available in a Mars mission (Nowak et al. 2019), 6 cases that needed tube replacement due to mechanical displacement, 5 cases of urosepsis, 2 cases of retroperitoneal hematoma that required blood transfusion, and 1 case of injury to a neighboring organ or vessels (Efesoy et al. 2018). Minor complications included temporary hematuria, fever, colicky pain, vasovagal symptoms and urinary extravasation that did not require additional intervention.

Sousa Morais et al. prospectively evaluated PCN (18 patients) against retrograde ureteral stent (RUS) placement (36 patients) and found that PCN was associated with a higher rate of spontaneous stone passage when adjusted for stone size and location and it was better tolerated and associated with fewer urinary symptoms when compared with RUS. Patients in RUS group experienced more urinary symptoms, mostly hematuria (68.7% vs 16.7% in PCN group < .001) and dysuria (78.3% vs 16.7% in PCN group, $p < .001$).

Determining if the evidence supports the use of PCN as a meaningful form of risk reduction in a Mars mission is a challenge. This procedure is under consideration because it requires a small kit and ultrasound, minimizing the mass and volume taken for a low likelihood, high consequence event. Lerner et al. performed initial studies into the differences between experienced operators and naïve operators for percutaneous placement of a drain by video training and remote guidance (Lerner et al. 2022). The techniques used are like PCN but were performed on gels with simulated abscesses and not on humans. Of 27 naïve subjects, all were able to complete the simulated procedure with time to completion different between experienced operators (2 mins) and naïve operators (~5.8 mins). This was designed as a proof-of-concept study only.

Moeen et al. performed a review of the literature recently that suggests that achieving competence for safe percutaneous renal access requires approximately 50 cases and pelvicalyceal system dilatation, which can be assessed by ultrasound prior to considering PCN (Moeen et al. 2023). Whether that level of training can be provided to non-astronauts in a meaningful fashion is unclear. PCN is more likely to be a procedure that is restricted to a physician astronaut on a mission and given the low likelihood that an obstructing stone will occur in one of these missions it may not be worth the mass, volume, and training investments for overall risk reduction.

D. LoE Scored DAG

From the discussions above, the resulting LoE scores are compiled in Table 7**Error! Reference source not found.**.

Table 7 LoE scores for all other edges with scoring 4-Speculative, 3-Weak, 2-Moderate, 1-Strong.

Starting Node	Ending LNode	LoE Score
Altered Gravity	Bone Remodeling	1
Bisphosphonates	Bone Remodeling	3
Bone Remodeling	Urine Chemistry	1
CO2 (Risk)	Urine Chemistry	4
Detect MRM/Stone	Ultrasound Manipulation	3
Hostile Closed Environment	Hydration	2
Humidity	Hydration	4
Hydration	Urine Concentration	2
Individual Factors	Nephrolithiasis	2
K+ Citrate	Urine Chemistry	1
Medical Illness	Individual Readiness	3
Medical Illness	Evacuation	3
Medical Illness	Loss of Crew Life	4
Medical Illness	Long Term Health Outcomes	4
Medical Prevention Capability	Water Intake	1
Medications	Medical Illness	1
Medications	Individual Readiness	3
Medications	Evacuation	4
Medications	Loss of Crew Life	4
Medications	Long Term Health Outcomes	4
Microbiome	Urine Chemistry	4
Mineralized Renal Material	Nephrolithiasis	2
Mineralized Renal Material	Detect MRM/Stone	2
Nephrolithiasis	Detect MRM/Stone	2
Nephrolithiasis	Ureterolithiasis	3
Nutrients	Bone Remodeling	1
Percutaneous Nephrostomy	Medical Illness	4
Resistive Exercise	Bone Remodeling	1
Tamsulosin	Urine Flow	3
Thiazides	Urine Chemistry	3
Ultrasound	Detect MRM/Stone	3
Ultrasound	Percutaneous Nephrostomy	4
Ultrasound Manipulation	Ureterolithiasis	3
Ureterolithiasis	Urine Flow	3
Urine Chemistry	Mineralized Renal Material	1
Urine Concentration	Urine Chemistry	2
Urine Flow	Medical Illness	3
Water Intake	Hydration	1

Starting Node	Ending LNode	LoE Score
Water Intake	Urine Flow	2

The results of scoring based on assumptions from Tables 1-5 and the focused literature review in Table 6 are shown in a combined visualization in Figure 9.

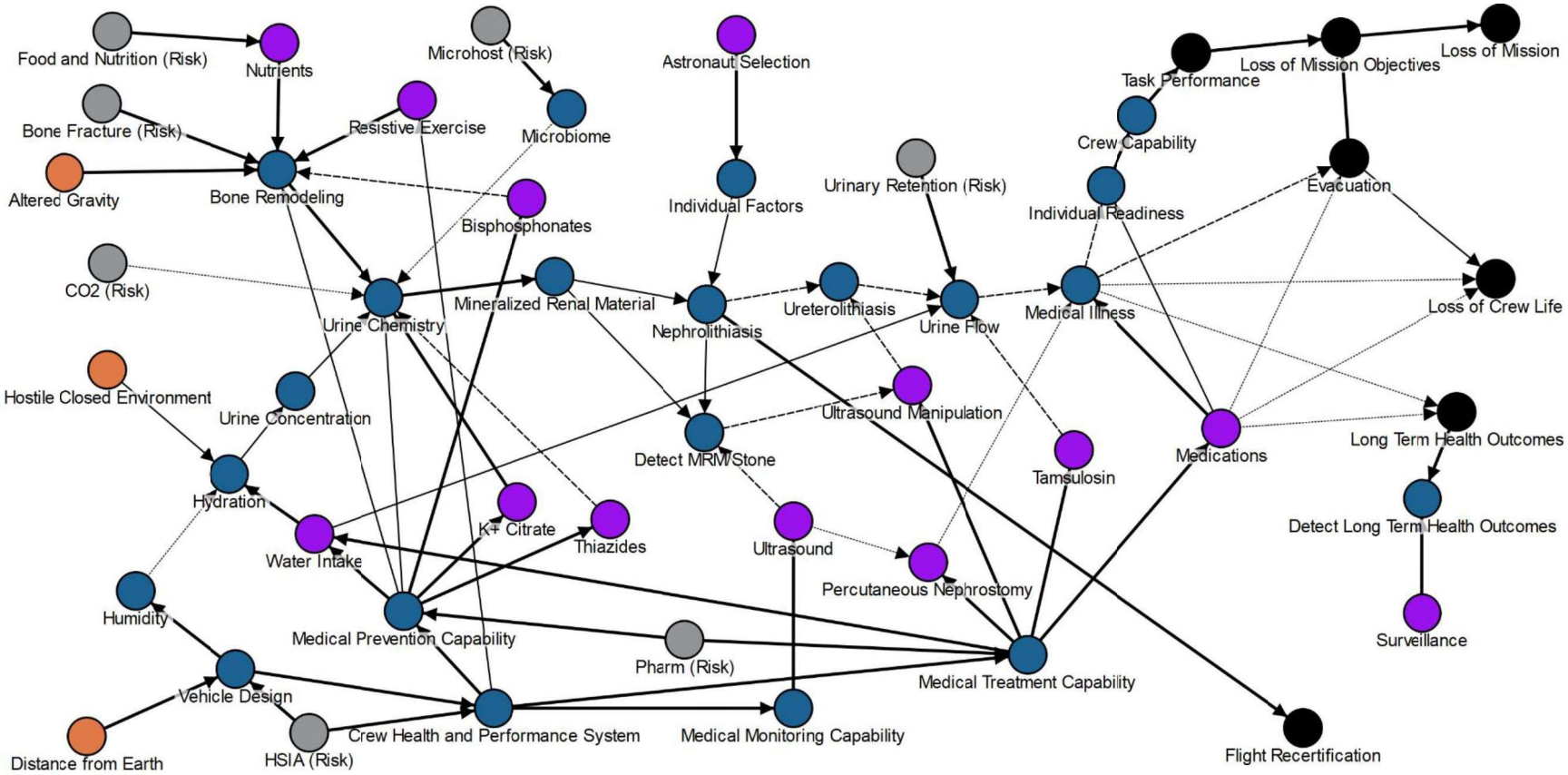

Figure 9 ***Visualization of the LoE Scoring on the Renal Stone DAG. Edge thickness corresponds to strength of evidence, and node color corresponds to node type (orange = hazard; teal = contributing factor; magenta = countermeasure; grey = associated risk; black = mission-level outcome.***

VII. KNOWLEDGE BASE

The following section raises relevant implementation issues and knowledge gaps associated with mitigating renal stone formation in the context of the current exploration mission scenarios and the operational constraints of power, mass, volume, time, and expense. At the time of writing, 1 research knowledge gap remains related to the Risk of Renal Stone Formation.

Gaps in knowledge

- **Renal-101 – We do not have the capability to mitigate renal stones in spaceflight.**
    - Renal stone mitigation may present unique challenges due to the spaceflight environment, resource limitations, or mission operational concepts. This gap provides a pathway for the incorporation of information and technology relevant to reducing the likelihood and/or consequence of renal stones in spaceflight.

State of Knowledge/Future Work:

One area of ongoing work includes the studies already being performed at NASA's Flight Medicine Clinic at JSC where ultrasound is used to evaluate for Mineralized Renal Material (MRM) pre-, in-, and post-flight and yearly in active astronauts. This ongoing work will be key to evaluating the effects of the spaceflight environment on the development of renal stones.

Additionally, there will be further research into medical risk and the development of medical systems for space exploration beyond LEO, ensuring that medical kits incorporate knowledge with respect to the risk of renal stones in spaceflight. In the same way, procedures for the treatment of renal stones (such as propulsive ultrasound and PCN), performed by both relative novices and in spaceflight, will be an area of future work.

Finally, an ongoing area of research and one that is separately listed in the NASA Human Research Roadmap, is that of pharmaceuticals (Risk of Ineffective or Toxic Medications During Long-Duration Exploration Spaceflight (Reichard et al. 2023)). As can be seen in this Evidence Report, pharmaceuticals are often listed as both countermeasures and treatments for kidney stones, so represent a critical area of future work to better understand prevention and treatment of renal stones in spaceflight, especially for Long-Duration missions. Additionally, constraints including shelf-life of pharmaceuticals, both in regard to re-packaging for long-duration missions, radiation/environmental shielding, and extensions beyond expiration dates will be key areas for future studies. In the same way, mass and volume constraints in carrying pharmaceuticals, both for prophylaxis and treatment of conditions such as renal stones, will need to be evaluated against the risk of their development, especially in missions beyond Low Earth Orbit. These areas of future study are beyond the scope of this current Evidence Report.

VIII. CONCLUSIONS

NASA's strategic goals are for a human presence for exploration-class missions, which include the goals of returning to the moon and landing on Mars. With these objectives, exploration crewmembers will experience extended exposure to the unique environments of space and the adaptive effects of human physiology to microgravity, partial gravity, and to the operational constraints and limitations of space habitation. It is known that spaceflight causes physiological changes that may increase the risk for the development of renal stones. Relative dehydration could lead to renal stone precipitation, as well as urine supersaturation and increased calcium excretion due to bone metabolism. There are possible terrestrial countermeasures, which include pharmaceuticals and hydration status, that could help to prevent and treat renal stones in spaceflight. Additionally, there are more invasive procedures including propulsive ultrasound and percutaneous nephrostomy, which could also be applied to the treatment of renal stones in spaceflight. DAGs are used in this document to better describe the pathway to renal stone development in spaceflight and can be used to evaluate risk, countermeasures that may be used to prevent stone formation, and treatment modalities that may be used in spaceflight, sorted by strength of evidence. Additionally, a Concept of Operations, exemplifying the above measures, in discrete scenarios is cross-linked throughout this document to better describe the monitoring, prevention, and treatment of renal stones in a Mars mission.

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I.

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XI. ACRONYMS AND ABBREVIATIONS

Acronym/Abbreviation	Definition
°C	degrees Celsius
°F	degrees Fahrenheit
AI	Artificial Intelligence
AMOS	Autonomous Medical Officer Support
ARED	Advanced Resistive Exercise Device
Ca3(PO4)2	calcium phosphate
CaOx	calcium oxalate
CaOxIRR	Calcium Oxalate Incidence Rate Ratio
CDC	Center for Disease Control
CDSS	Clinical Decision Support System
ChatGPT	Artificial intelligence chatbot application
CHMO	Chief Health and Medical Officer
CHS	Crew Health and Safety Program
Cl	chloride
CLiFF	Clinical Information Findings Form
cm	centimeter
CMO	Crew Medical Officer
CO2	carbon dioxide
ConOps	Concept of Operations
CT	Computed Tomography
DAG	Directed Acyclic Graph
DCT	Distal Convoluted Tubule
DRM	Design Reference Mission
EVA	Extravehicular Activity
EVAC	Evacuation
ExMC	Exploration Medical Capability
FDA	Food and Drug Administration
FI	Flight Integration or Focused Inspection
GI	gastrointestinal
H+	hydrogen ion
HRP	Human Research Program
HSIA	Human System Integration Architecture
HSRB	Human Systems Risk Board
iMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT	Informing Mission Planning via Analysis of Complex Tradespaces
ISS	International Space Station
JAXA	Japanese Aerospace Exploration Agency
JIT	Just-in-Time
JSC	[Lyndon B.] Johnson Space Center

Acronym/Abbreviation	Definition
LEO	Low Earth Orbit
LOCL	Loss of Crew Life
LoE	Level of Evidence
LSAH	Lifetime Surveillance of Astronaut Health
LSS	Life Support System
MEDPRAT	Medical Extensible Dynamic Probabilistic Risk Assessment Tool
mEq	milliequivalent
mg	milligram
mm	millimeter
mmHg	milliliters of Mercury
MPH	Master of Public Health
MRM	Mineralized Renal Material
Na	sodium
NASA	National Aeronautics and Space Administration
OCHMO	Office of the Chief Health and Medical Officer
ONJ	Osteonecrosis of the jaw
PCN	Percutaneous Nephrostomy
Pharm	Pharmacy
PK/PD	Pharmacokinetics/pharmacodynamics
pp	partial pressure
PRA	Probabilistic Risk Assessment
PRD	Program Requirements Document
R+	Return plus [day]
RSRI	Renal Stone Risk Index
RTDC	Return to Definitive Care
RUS	retrograde ureteral stent
SE&I	Systems Engineering and Integration
SEM	Standard Error of the Mean
SME	Subject Matter Expert
SPEAR	Simplified Pneumothorax Emergency Air Release
STD	Standard
TBC	Treated Best Case
TI	Task Impairment
TWC	Treated Worst Case
UTBC	Untreated Best Case
UTWC	Untreated Worst Case

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Renal Stone Evidence Report Content

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Appendix A: Directed Acyclic Graphs and Evidence

The HSRB approved the narrative Renal Stone DAG and published it publicly in 2022 (1). This version of the DAG is used to step through each of the connections in the DAG and assess the Level of Evidence (LOE) scoring as described in JSC-66705 Rev. A (2). The last evidence book for the risk of Renal Stone Formation was published in 2017 by the Human Research Program and is available online at: https://humanresearchroadmap.nasa.gov/Evidence/reports/Renal.pdf

Figure 1 shows the legend for nodes, edges, and Levels of Evidence (LoE) scores used in the Narrative DAGs shown in this report. The color scheme was chosen to be interpretable by those with color-blindness. Hazards (orange), Contributing Factors (blue), Risks (grey), Countermeasures (purple), and Mission Level Outcomes (black).

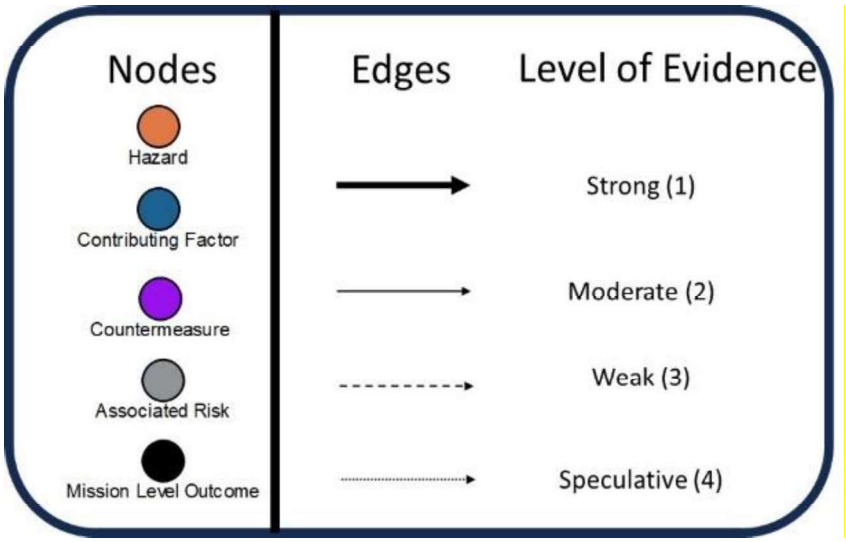

Figure 1: Legend for DAG visualizations using 508 compliance for colorblindness.

The connections between nodes are called Edges and are a representation of the current understanding of causal flow within Human System Risks. Each edge is a falsifiable hypothesis – meaning that a review of the evidence can determine if the assertion shown by that edge is consistent with evidence or not.

By scoring the Level of Evidence (LoE) according to procedures outlined in NASA processes, it is possible to visualize the level of uncertainty in the evidence base regarding the causal claim implied. These processes are used by NASA's Human Systems Risk Board (HSRB) and specify guidelines for creation and use of DAGs as well as evaluating and assigning Levels of Evidence (LoE) (2–5).

Figure 2 shows the Narrative Renal Stone DAG that has been officially accepted by the HSRB at NASA (1).

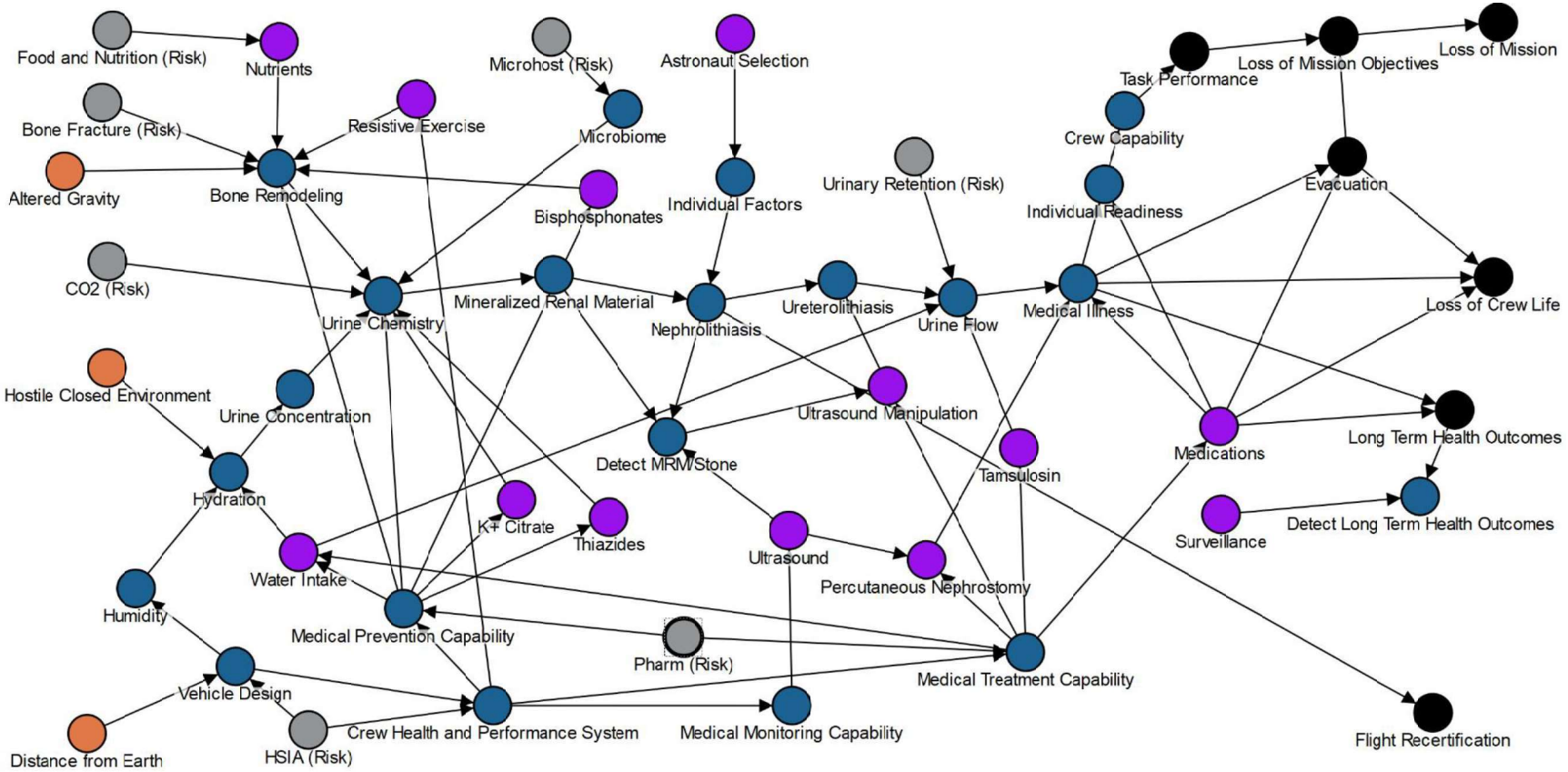

Figure 2: Official renal stone DAG without edge scoring. Colors have been modified to be 508 compliant. Orange = hazards, blue = contributing factors, grey = risks, purple = countermeasures, black = mission level outcomes.

Methods

A focused review of the literature was performed to assess the Edges within the DAG shown in Figure 2. This review was conducted using multiple tools including prior evidence reports, HSRB risk update packages, traditional internet search modalities such as PubMed and Google Scholar, and AI-assisted search modalities such as Elicit (6), Evidence Hunt (7), Research Rabbit (8), and LitMaps (9). These tools are specifically designed to search large databases and relationships between authors, citations, and other tools to enable rapid review of the literature. AI tools such as ChatGPT were not used for this process due to susceptibility to hallucination and evidence that they create citations that do not exist. Decisions on inclusion or exclusion of specific studies were based on SME assessment of Quality of Evidence (QoE) as defined in JSC-66705 Rev. A (2) and the unpublished work recently accepted at NPJ Microgravity (3).

This evidence document is also intended to be partnered with the Renal Stone Concept of Operations documentation from the Exploration Medical Capabilities Element [Ref]. Figure 3 shows the evolution of the scenarios in which different countermeasures are used.

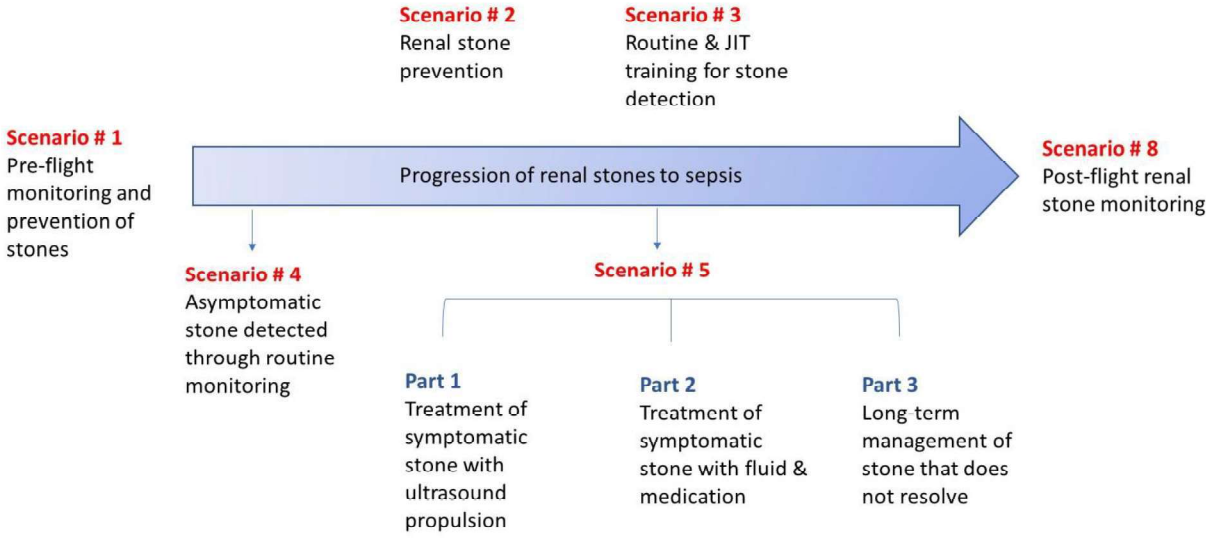

Figure 3: The Renal Stone Concept of Operations document specifies specific scenarios where different types of countermeasures are used.

Where appropriate the scenarios are referenced for various countermeasures for clarity.

Assumptions

When considering the edges within the Renal Stone DAG, several of them are not amenable to a meaningful evidence evaluation. What is meant by this is that there are some causal connections present that either have been defined to be causal elsewhere or perhaps are design decisions that will determine a binary outcome (yes/no) on whether a tool will be available to use as a countermeasure within a spaceflight mission. From that perspective, these are listed as assumptions and are given an LoE score of 1 (Strong). By setting these scores as strong, this visually preferences the LoE version of the DAG to highlight areas where there is less evidence available to support a claim of causation. This helps

identify knowledge or capability gaps relevant to forward research considerations. These assumptions are discussed below.

By Definition

The assumption of By Definition asserts that some of the edges within the DAG are assumed to represent a causal influence that is known. Table 1 shows the edges with pre-defined LoE based on starting and ending nodes in the DAG.

Table 1: Edges with LoE score 1 based on By Definition Assumption.

Starting Node	Ending Node	Assumption	LoE Score	Added Rationale
Individual Readiness	Crew Capability	By Definition	1	
Crew Capability	Task Performance	By Definition	1	
Task Performance	Loss of Mission Objectives	By Definition	1	
Loss of Mission Objectives	Loss of Mission	By Definition	1	
Evacuation	Loss of Mission Objectives	By Definition	1	
Long Term Health Outcomes	Detect Long Term Health Outcomes	By Definition	1	Necessary precondition

For example, the assertion that Loss of Mission Objectives can lead to Loss of Mission is defined by the agency. Attempting to assess evidence regarding this assertion is meaningless in this context. Similarly, assessing strength of evidence for the claim that Long Term Health Outcomes affects the ability to Detect Long Term Health Outcomes is meaningless when having Long Term Health Outcomes actually occur is a necessary pre-condition to being able to measure them. For this reason, these nodes were not assessed for Level of Evidence and were assigned LoE Strong.

By Design

Edges within the DAG that depend on design decisions not yet made by the agency are similarly meaningless to evaluate from a Level of Evidence perspective. The systems engineering processes include trade space analysis that ultimately determines whether specific items are included or excluded in a given vehicle, habitat, or space suit. Many of the nodes within the Renal Stone DAG are dependent on this process. Table 2 shows those nodes that have a pre-defined LoE based on engineering considerations.

Table 2: Edges with LoE score 1 based on By Design assumption. SE&I = Systems Engineering and Integration; CHS = Crew Health and Safety Program.

Starting Node	Ending Node	Assumption	LoE Score	Added Rationale
Distance from Earth	Vehicle Design	By Design	1	
Vehicle Design	Humidity	By Design	1	SE&I Trade Decisions
Vehicle Design	Crew Health and Performance System	By Design	1	SE&I Trade Decisions
Crew Health and Performance System	Medical Prevention Capability	By Design	1	SE&I Trade Decisions
Medical Prevention Capability	Urine Chemistry	By Design	1	SE&I Trade Decisions

Medical Prevention Capability	Bone Remodeling	By Design	1	SE&I Trade Decisions
Medical Prevention Capability	Bisphosphonates	By Design	1	SE&I Trade Decisions
Medical Prevention Capability	K+ Citrate	By Design	1	SE&I Trade Decisions
Medical Prevention Capability	Thiazides	By Design	1	SE&I Trade Decisions
Crew Health and Performance System	Medical Monitoring Capability	By Design	1	SE&I Trade Decisions
Medical Monitoring Capability	Ultrasound	By Design	1	SE&I Trade Decisions
Medical Treatment Capability	Percutaneous Nephrostomy	By Design	1	SE&I Trade Decisions
Medical Treatment Capability	Ultrasound Manipulation	By Design	1	SE&I Trade Decisions
Medical Treatment Capability	Tamsulosin	By Design	1	SE&I Trade Decisions
Medical Treatment Capability	Medications	By Design	1	SE&I Trade Decisions
Surveillance	Detect Long Term Health Outcomes	By Design	1	**Scenario #1 and #8** (See Figure 3)
Crew Health and Performance System	Medical Treatment Capability	By Design	1	SE&I Trade Decisions

As an example, the decision to include an Ultrasound as part of the Medical Monitoring Capability in the Crew Health and Performance System is dependent on a set of decisions that will be made by the agency throughout the SE&I process (10–12). First, the level 2 requirement that a CHP System is included must be set. Then the decomposition of that system must include Medical Monitoring Capabilities, Medical Prevention Capabilities, and Medical Treatment Capabilities. Historically these have all been included in system designs in one form or another. However, the decisions to include specific countermeasures within those subsystem capabilities for a given mission will be the result of discussions between multiple stakeholders during the trade space analysis for a given program. Additionally, the decision by NASA to fund Surveillance activities after spaceflight missions and post career for astronauts is the responsibility of the Agency, specifically the Crew Health and Safety Program at Johnson Space Center (13). Each of the Ending Nodes are fully dependent on decisions by NASA personnel. In this sense, the evidence that the Starting Node 'causes' the Ending Node is assumed to be Strong. Also, it is important to remember that just because the evidence is strong that one influences the other, this in no way implies that those countermeasures or capabilities will be supplied by the agency when needed.

By Standards

Two of the edges within the Renal Stone DAG are dependent on the implementation of standards that are held by the agency. At the time of this writing the Health and Medical Standards are held by the Office of the Chief Health and Medical Officer at NASA (14). Table 3 shows two edges that are assumed to have a Level of Evidence score determined by the application of standards.

Table 3: Edges with LoE score 1 based on By Standards assumption.

Starting Node	Ending Node	Assumption	LoE Score	Added Rationale
Astronaut Selection	Individual Factors	By Standards	1	STD 3001, Med A Requirements
Nephrolithiasis	Flight Recertification	By Standards	1	Med A Requirements

In these cases, OCHMO-STD-100.1A provides the publicly available governing document that includes medical requirements regarding astronaut selection and flight recertification in the context of kidney stone disease (15). These standards are intended to reduce the medical risk for spaceflight by selecting out potential astronauts or candidates who will bring an unacceptable level of risk to a mission. In this sense these standards are countermeasures against the renal stone risk. The LoE score for these edges is set at Strong.

In Risk

Several edges within the Narrative Renal Stone DAG represent connections with other officially tracked risks. The standard visual representation in NASA DAGs is to only show edges that are incoming from other risks and to not show edges that would be outgoing from the risk in question to other risks (16). Table 4 shows the edges that fall under the 'In Risk' assumption. These edges show connections from the Grey nodes that represent the entirety of the other risk to a Blue node within the Renal Stone DAG that is also shared by the other risk (See Figure 2).

Table 4: Edges with LoE score 1 based on In Risk assumption.

Starting Node	Ending Node	Assumption	LoE Score	Added Rationale
Bone Fracture (Risk)	Bone Remodeling	In Risk	1	
Food and Nutrition (Risk)	Nutrients	In Risk	1	
HSIA (Risk)	Vehicle Design	In Risk	1	Standards and Requirements, HSI Processes
HSIA (Risk)	Crew Health and Performance System	In Risk	1	Standards and Requirements, HSI Processes
Microhost (Risk)	Microbiome	In Risk	1	
Pharm (Risk)	Medical Prevention Capability	In Risk	1	SE&I Trade Decisions
Pharm (Risk)	Medical Treatment Capability	In Risk	1	SE&I Trade Decisions
Urinary Retention (Risk)	Urine Flow	In Risk	1	

As an example for the In Risk assumption, the Food and Nutrition (Risk) node (Grey in Figure 2) is shown influencing the Nutrients node (Blue in Figure 2). The Nutrients node exists in both the Food and Nutrition Node and the Renal Stone node. Therefore, the edge between the risk and the node is simply a visualization of the relationship between the risks. In these cases, the LoE is set to Strong. Note that for the HSIA (Risk) edges, the terms 'Standards and Requirements' and 'HSI Processes' are listed in rationale. These are specific precursor nodes present in the HSIA Risk DAG. For the Pharm (Risk) node, SE&I Trade Decisions is listed because inclusion of specific pharmaceutical countermeasures is dependent on the decision process listed above. For all of these nuances the LoE is set to Strong.

Non-Assumed Edge LoE Evaluation

Once the DAG edges that are subject to assignment of LoE score by assumption are removed, there is a set of edges that are non-assumed for LoE scoring. 36 edges within the Renal Stone DAG are within this category. These are considered in this section broken into two categories. The first category includes

those edges that represent causal links in the environmental-physiologic chain that drives renal stone occurrence and determines whether the presence of stones will lead to changes in Mission Level Outcomes. The second category considers the available evidence that specific countermeasures included in the DAG will have the expected effect on risk reduction at their intersection points with the environmental-physiologic chain.

Specific Edge Evidence

When evaluating evidence with regards to causal inference for specific claims shown in the DAG, it is important to keep in mind that the LoE of the arrow drawn between two nodes is not an open-ended question. An open-ended question example for this chain of events would be "What is the strength of evidence that supports the assertion that nephrolithiasis can lead to ureterolithiasis?" The answer to this question is that the evidence is very strong indeed – when considered over the whole of the human population, medical evidence, fundamental physics of fluids and chemistry of precipitation, and the totality of our knowledge regarding this question. This would always result in a LoE of 1 which implies coherence in the totality of our evidence base.

However, asking a question like this tends to lead to unreasonable considerations in the context of mission risk, i.e. every next step in the chain of causation becomes an inevitability. For the purposes of risk management, the question should be re-asked with constraints defined.

What is the strength of evidence that supports the assertion that nephrolithiasis will lead to ureterolithiasis given the following constraints – 1. Typical NASA astronaut population, 2. Standard environmental conditions experienced in spaceflight, and 3. Specified mission duration (in this case up to 3 years for a Mars mission). These constraints correspond to the traditional person, place, and time rubric that is used to describe the necessary conditions for meeting the Specificity requirement for causality (3).

When asked like this, other necessary questions flow naturally:

- How long does it take for a non-stone former to become a stone former?
- What environmental conditions induce this change and how do they map to the expected operational environment?
- How long does it take for an asymptomatic stone that has formed within the calyx of the kidney to move to the ureter?
- What are the chances that any or all of these things will occur within the mission timeframe?

To answer these questions, we must also evaluate our understanding of Mechanism and Reproducibility in the available evidence base.

Our evidence base for the renal stone risk in spaceflight is based largely on proxy outcomes. An example of a proxy outcome is when we rely on urine chemistry changes to act as a surrogate for an outcome we have not been able to measure yet – incidence of renal stone formation in space when compared to incidence of renal stone formation terrestrially. However, using proxy outcomes makes an important assumption. Namely that the mechanisms we understand to be at work in terrestrial environments are functioning in the same way in the spaceflight environment. This may be a good or bad assumption, and the only way to truly tell the difference is to measure actual outcomes in the spaceflight environment, in a Reproducible fashion.

For terrestrial renal stone formation, a multitude of studies have demonstrated that urine chemistry profiles are a reasonable proxy outcome and these are documented in the prior evidence report (17). Whether this is generalizable to the NASA astronaut population in-mission who experience altered gravity and other unique spaceflight environmental conditions is a reasonable question to ask. According to Barratt's textbook, among 357 astronauts, 22 experienced at least one episode of kidney stones with a total of 36 episodes (18). But this must not be mistaken for strong evidence that kidney stones are a higher risk in spaceflight. A deeper look at the studies shows that as of 2007 there had been 14 events in the NASA astronaut population – 7 pre-flight, 7 post-flight, and 0 in-flight (19). At the time of this writing there are no USOS cases of kidney stone in spaceflight. This leads to a lack of coherence in the evidence base – to date there have been no *proven* symptomatic renal stones in spaceflight. There has been one case of suspected symptomatic renal stone in a cosmonaut in flight (17,18,20). There have been no cases of renal stone progression to more concerning diseases such as infection, sepsis or renal failure.

Facing a lack of data in this domain it is appropriate and reasonable to use the terrestrial data that is available along with modeling that has been performed based on the understood mechanisms. In doing so we must clearly state where Mechanism, Reproducibility, and Specificity criteria have and have not been met by the existing evidence. Appropriate scoring of the evidence base that supports claims about mission level outcomes is a key part of communicating the uncertainty that exists currently.

Th next sections are split into two parts for clarity. The first section, "Environmental-Physiologic Chain Evidence," documents evidence supporting the specific DAG hypothesized claims regarding the physiologic processes that are mapped in the DAG.

The second section, "Countermeasures Evidence," documents evidence that supports or refutes the claims that countermeasures will be effective in lowering risk for the scenarios in which they apply (see the ConOps documentation). Where appropriate specific Scenarios from the Concept of Operations Document are referenced for clarity.

For each section, the LoE is considered from the perspective of whether the aggregate evidence base has met any of the specific criteria for causation – Mechanism, Reproducibility, Specificity, and Coherence. The criteria for Temporality and Analogy were applied for inclusion in the DAG itself and form the basis for the minimum LoE of *Weak* (level 4). These are not considered explicitly here.

Note that where two or more edges are listed at the beginning of a paragraph, it means that the LoE for each of them are considered within that following paragraph.

Environmental-Physiologic Chain Evidence

Altered Gravity -> Bone Remodeling

The association of bone remodeling with an altered gravity field has been well documented in the literature and in publicly available NASA evidence books for Bone Fracture and the historical evidence book for Early Osteoporosis. (21,22).

"Atypical bone changes observed with space flight and in healthy, young persons includes

- Increased bone resorption with uncoupled bone formation response (depressed)

- Reductions in bone mineral density targeted to weight-bearing bones
- Accelerated rates of bone loss and delayed recovery in hip trabecular bone
- Reductions in bone mineral density in males, especially at sites rich in trabecular bone
- Increased excretion of calcium with stable or reduced parathyroid hormone"

This process affects multiple Human System Risks and is primarily of interest in the Renal Stone risk because of the causal chain that affects calcium levels within the blood and eventually urine. In the interest of space, readers are referred to the prior evidence books for a complete review of the evidence that supports the causal connection between Altered Gravity and Bone Remodeling. At this point there is coherence among the literature sources that is well documented. LoE is *Strong*.

Nutrients -> Bone Remodeling

The effects of nutrients on bone remodeling are well known generally. The development of Rickett's with the lack of vitamin D has been long documented and understood at a strong level of coherence (23). Th research in spaceflight has also been extensive and is reviewed fully in several other sources and the relationship between bone mineral loss and the elevation of calcium in the urine has also been well documented (21,22,24–28). These are referenced here for completeness, and the LoE score is rated as *Strong*.

Bone Remodeling -> Urine Chemistry

The physiology and regulation of bone remodeling processes are well understood mechanistically and are reviewed in depth elsewhere (21,22). There are multiple studies both terrestrially and in spaceflight that establish the causal link between bone remodeling and changes in urine chemistry. This has been well studied and documented over multiple programs (24,25,29–33). Smith et al. in 2014 reported on a study of 23 astronauts on ISS expeditions 6-14 that documented changes in bone, calcium and vitamin D metabolism, and renal stone risk using markers of urinary chemistry changes as a proxy (26). A subsequent publication of studies on ISS reached 42 astronaut subjects (33 men and 9 women) for missions ranging from 49-215 days in space and found that urinary supersaturation markers were typically increased for both males and females post-flight and that there were not significant differences in response between the sexes (27). Changes in bone remodeling and increases in urinary calcium and calcium oxalate supersaturation have been documented extensively in prior renal stone evidence reports (17) in spaceflight, thus meeting the criteria for specificity to the spaceflight environment The causal mechanism of calcium release from bone is appreciated, and the results have been reproducible. Coherence has been reached for this edge. LoE is *Strong*.

Hostile Closed Environment -> Hydration

Humidity -> Hydration

The link between Hostile Closed Environment and Hydration depends on the atmospheric conditions within the spacecraft. These conditions are set by the vehicle design, in particular the Environmental Control and Life Support Systems (34). These systems determine conditions that may affect renal stone formation including temperature and humidity.

Temperature is not included in the DAG explicitly, but it will be considered here because it is a sub-feature of the Closed Hostile Environment node. Seasonal variation in renal stone occurrence around

the world has been well documented (35–39). In one study, temperature elevations specifically correlated with increased relative risk of renal stones (35). The relative risk was 1.37 in Chicago (95% CI, 1.07 –1.76) and 1.47 in Philadelphia (95% CI, 1.00 – 2.17) at temperatures of 30ºC compared with 10ºC (40).

A retrospective analysis of 182 military personnel in Kuwait and Iraq from March- August 2003 showed a mean time of 93 days to the onset of urinary calculi in previous non-stone formers (39). The average temperatures were 10 degrees Celsius hotter than the average temperatures in the US during this study and the humidity was near zero in the desert environments (39).

A Korean study evaluated the effect of seasonal variation and climate parameters on urinary tract stone events using a the Korean Health Insurance Review and Assessment Service (41). The data showed seasonal trends with a sharp incline in June, a plateau from July to September, and a sharp decline after September. Analysis suggested that ambient temperature ($r = 0.557$, $p < 0.001$) and relative humidity ($r = 0.513$, $p < 0.001$) were significantly associated with symptomatic stone cases. After adjustment for trends and seasonality, ambient temperature was the only climate factor associated with the stone attack cases in ARIMA regression test ($p = 0.04$). Threshold temperature was estimated as 18.4 °C. Risk of urinary stone attack significantly increases 1.71% (1.02-2.41 %, 95% confidence intervals) with a 1 °C increase of ambient temperature above the threshold point (41). A similar study in Taiwan from 1999-2003 found that ambient temperature was the only environmental variable that correlated with stone events (38). These suggest that humidity may play less of a role in stone formation, and by inference in Hydration status, than has previously been surmised.

NASA-STD-3001 levies two technical requirements related to the atmospheric environment: [V2 6012] provides environmental parameters that keeps the internal habitat at safe levels of temperature and humidity for protection of crew health: 18°C -27°C and 25 -75% humidity. [V2 6013] provides environmental parameters that take into consideration crew performance, specifying temperature and humidity limits in which humans can achieve thermal comfort and not have their performance of routine activities affected by thermal stress: 20°C -25°C and 30 -60% humidity (42).

There is little quantified data identified to suggest that humidity plays a significant factor in stone formation. The DAG however shows a more detailed pathway through Hydration -> Urine Concentration -> Urine Chemistry -> Mineralized Renal Material -> Nephrolithiasis. Humidity is known to affect insensible losses of water for humans and because of that it has been speculated that it may play a role in dehydration of astronauts and by proxy increased risk of renal stones. Given the lack of quantitative data available from the literature to support Humidity -> Hydration in the ranges expected by the 3001 standards, the LoE for this is rated *Speculative*.

However, this research suggests that given a temperature based correlation of renal stone events with a gradient starting around 18 degrees C, there is at least *Weak* evidence that temperature should be included in this DAG. It is also found that both temperature and humidity should be displayed as intermediate factors between Hostile Closed Environment and Hydration by the guidelines set forth by the HSRB (16). Therefore Figure 4 shows a recommended update to the Renal Stone DAG for consideration:

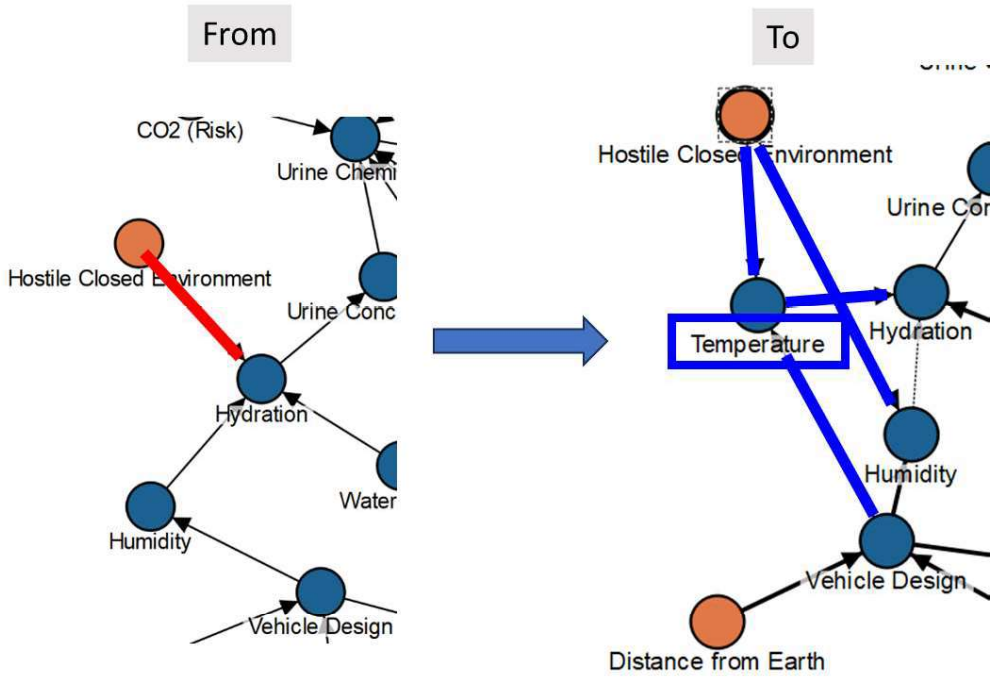

Figure 4: Recommended update to the Renal Stone DAG based on the focused literature review performed here. Red shows edges to be removed. Blue shows edges and nodes to be added.

CO2(Risk) -> Urine Chemistry

The CO2 (Risk) as a whole does not contribute to urinary chemistry (here as a whole means that not all of the nodes within the CO2 risk contribute causally). Specifically, the node for Ambient CO2 Level is considered to have effect on the acid-base balance of the blood and urine. The node within the NASA Standard 3001 Technical brief shows typical spacecraft CO2 partial pressures range from 2.3-5.3 mmHg (43). The outdoor Earth environment is at 0.23 mmHg of CO2. So, the difference is an order of magnitude larger than what we experience outside on Earth. Because bicarbonate exchange in the nephrons of the kidney are responsible for metabolic control of the body's acid-base balance, there has been speculation that elevated CO2 levels may affect renal stone formation by affecting the pH of the urine chemistry. This review was unable to find an evidence-based link between ambient CO2 level and urinary chemistry changes for the levels expected on the ISS. It is possible that future evidence may emerge. At this time the LoE supporting this causal link is *Speculative*.

Hydration -> Urine Concentration

Urine Concentration -> Urine Chemistry

Changes in hydration affect urinary solute concentrations and osmolality thus affecting urine chemistry. This has been demonstrated in spaceflight (25,29,44,45). Compared to specimens collected prior to flight, 24-hour urine specimens collected from Shuttle crewmembers on the day of landing have demonstrated. Increased calcium, decreased citrate, decreased magnesium, decreased pH, decreased volume (17,46). This has been repeated in long duration astronauts as well (47) and is extensively reviewed in other places to the level of mechanistically informing fluids, biochemistry, and probabilistic models for prediction (17,30,48). The LoE score for these connections is rated *Strong*.

Microbiome -> Urine Chemistry

Evidence is available to suggest a role for the gut microbiome in renal stone formation. In particular colonization with Oxalobacter Formigenes has been found to correlate with decreased calcium oxalate stone formation (49–52). The mechanism is suspected to be metabolism of oxalate by this species. Other microbiota likely play a role, both in the gut and in the urinary tract (53,54). This is an emerging area of understanding, and while mechanisms are proposed in the literature, there is much that is unknown in this domain. The evidence that it will meaningfully affect Mission Level Outcomes in the Renal Stone risk is still considered *Speculative*.

Urine Chemistry -> Mineralized Renal Material

Mineralized Renal Material -> Nephrolithiasis

A mechanism for the formation of mineralized renal material (MRM) based on Randall's plaque formation and reaction with calcium oxalate supersaturation has been reasonably well studied in the literature (31,55,56). The LoE for Urine Chemistry -> MRM is scored as *Strong*.

The formation of MRM from Randall's Plaques was first proposed in 1937 (57). Since then it has been demonstrated that these plaques are nidus points for growth of Calcium Oxalate crystallization in the renal papillae (55,58). The growth of MRM and subsequent break from renal surfaces leading to renal stone formation has been well documented elsewhere (17,18,59).

The question of whether this process occurs in the astronaut population is informed by the number of post-flight renal stone events that have been documented (18). The focus on post-flight stones rather than pre-flight stones is because no astronauts with a prior history of nephrolithiasis are admitted to service. The number of post-flight stones that occurred as of 2015 were 32 with only a single event occurring in less than 90 days post-return (18).

The nephrolithiasis mean incidence rate from IMED is 0.00396 events/person-year, SD 0.00046 (60).

Twelve total in-career stone events were documented and 19 post-career events were documented, but timeframe to post-career events is not provided (18). The relevance of post-career events to in-mission renal stone risk is uncertain given that the longest DRM mission duration, that of a Mars mission, is approximately 3 years long. Evidence shows that the development of MRM is occurring and leading to nephrolithiasis in the astronaut population, but it is unclear if it is due solely to exposure to the spaceflight environment or if it is also a function of age and other factors. Because of this the LoE is scored as *Moderate*.

Nephrolithiasis -> Ureterolithiasis

Ureterolithiasis -> Urine Flow

Urine Flow -> Medical Illness

The question of whether Nephrolithiasis is causal for Ureterolithiasis is an open-ended question that does not lead to meaningful discussion of the evidence in the context of HSRB DRMs. Is this likely to occur within the mission timeframe for an asymptomatic stone? At this point we have assumed that all the prior causal factors have occurred, and a renal stone has separated from the wall of the kidney and is now present inside the kidney. These stones are asymptomatic and with a few exceptions (large

staghorn calculi for example) they do not progress to affect urine flow and cause medical illness until a stone enters the ureter. The evidence that this can occur is well documented and understood (61).

The necessary timeframe for formation of new stones from prior non-stone formers is relevant in the context of mission durations of interest to NASA. If MRM and Nephrolithiasis are unlikely to form within the mission timeframe or relevance, then the low likelihood of stone formation would drive down risk. Clinical information on time to stone formation for non-stone formers includes one study by Evans that considered 182 soldiers in the deserts of Iraq and Kuwait from March – August 2003 (high temperatures and low humidity environment). This study found 218 symptomatic stones with a mean time to formation of symptomatic stones of 93 days with a standard deviation of ±42 days (39).

For stones that are located in the kidney but are asymptomatic, there is some evidence in the literature that informs estimates of time to passage or time to symptoms.

Dropkin et al. retrospectively analyzed 110 patients who elected expectant management of 160 stones (62). The stones had an average size of 7.0±4.2 mm and the average follow up time was 41±19 months. Forty-five (28% of total) stones caused symptoms during follow up. 3 stones (3% of asymptomatic subgroup, 2% of total stones) caused painless silent obstruction that required intervention after an average of 37±17 months. Location within the kidney was found to be the only significant predictor of spontaneous passage or symptom development. Upper pole/mid renal stones were more likely than lower pole stones to become symptomatic (40.6% vs 24.3%, $p > 0.047$) and to pass spontaneously (14.5% vs 2.9%, $p > 0.016$) (62).

Much of the literature considers asymptomatic stone growth to be a relevant variable, but for the context of risk in spaceflight the most relevant variable is time to symptoms as an asymptomatic stone does not progress along the causal chain towards affecting Mission Level Outcomes. Selby et al. retrospectively analyzed time to passage for 550 patients found to have asymptomatic stones on CT scan and identified a median time to a stone event (symptomatic passage or development of symptoms) of 4.7 years after the stone was identified (63).

These data contribute to the consideration of whether an asymptomatic stone that does form in spaceflight will progress to symptoms or medical illness in a meaningful timeframe. The evidence that this will happen in the astronaut population, in-mission for the NASA DRMs, in a meaningful timeframe is in question. As no documented stones have occurred in spaceflight, there is no specificity and no reproducibility at a clinical level in spaceflight to date. Additionally, given available evidence on time to symptoms from the literature specificity is further removed for most of the DRMs. The evidence neither supports nor refutes increased likelihood for a Mars mission. From that perspective, for all DRMs the Evidence that nephrolithiasis in-mission is likely to progress to ureterolithiasis is rated as *Weak*.

Stones that leave the kidney and progress to the ureter have a chance of obstructing the ureter. Stones above 5 mm diameter have an increasing likelihood of causing Hydronephrosis. This is a medical condition associated with increased fluid pressure inside the kidney that can, if untreated, lead to infection and possibly renal failure (64).

Given this question it is relevant to ask how long after historical short and long duration spaceflight are renal stones occurring in the astronaut population. The last update at the Human System Risk Board in April 2022 showed 43 stone events total observed in 29 crew members who had flown in space. 26 of

the 43 events occurred more than 1 year after return from space. 7 symptomatic stone events occurred within 1 year of spaceflight, and all of those stones were between 2-4 mm in diameter by CT scan (65).

Additional details from the 2016 HSRB update indicated that at that time 19 of 36 stone events were found post-career in short duration flyers (66). Given potential confounders including age, this evidence suggests that most stones are occurring after long periods post-flight and in short-duration flyers. This challenges our understanding of the mechanisms and timeframes involved in whether the spaceflight environment actually causes an increase in symptomatic stone formation in space missions at a rate that is different than would be expected terrestrially. This data underscores a lack of coherence between the urinary chemistry data interpreted from a terrestrial viewpoint and clinical symptomatic disease in the spaceflight domain. Given the lack of specificity of evidence in spaceflight, these pathways are scored *Weak* in LoE.

Individual Factors -> Nephrolithiasis

Genetic predispositions to renal stone disease are known to occur. For example, primary hyperoxaluria type 1 is a rare genetic form of calcium oxalate kidney stone disease. It is caused by a deficiency in the liver-specific enzyme, alanine:glyoxylate aminotransferase (AGT) (67). Pathogenic variants in the HOGA1 gene are responsible for primary hyperolaxluria type III which is inherited in an autosomal recessive fashion. This is most often expressed in childhood, but presentation can be delayed until adulthood (68). Cysteine stones have a heritable link through mutations in genes SLC3A1 and SLC7A9 (69). Potential genetic factors related to urinary chemistry are also being explored though the evidence is currently weak (70). A review suggests that polymorphisms of 11 genes are associated with increased calcium kidney stones through effects on renal handling of nutrients and water that likely lead to a supersaturation state (71).

It is possible that the astronaut selection process at NASA catches heritable renal stone disease through questions on family history, but at the time of this writing NASA cannot use genetic information to select out astronaut candidates or potential mission candidates who are already in the astronaut pool due to the Genetic Information Non-Discrimination Act (72). They can use that information to inform personalization of countermeasures (72,73). It is clear that a personal history of symptomatic stones can be used for that purpose.

The evidence that this will contribute meaningfully to any of the HSRB Design Reference Missions (DRMs) is at this point *Weak*. Mechanism is understood, but specificity and reproducibility have not been established for relevant spaceflight missions or HSRB DRMs. Further research in this area can help to improve our understanding of the potential genomic impacts for the Renal Stone risk.

Medical Illness

There are a variety of types of medical illnesses that are relevant to the renal stone risk. Figure 5 shows the Narrative risk in panel A. that uses the generic term ‘Medical Illness’ as the node name. Panel B. shows an expansion of the known sub-nodes of specific illnesses and their additional relationships. This is a Detailed DAG that is based on and consistent with the Narrative DAG used for the Renal Stone risk.

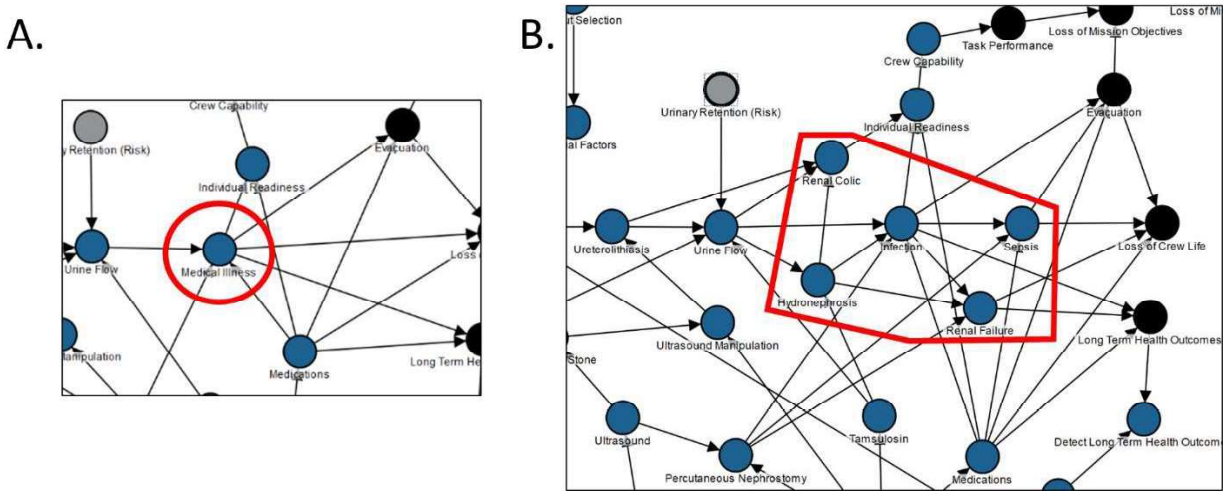

Figure 5: Panel A. shows a subset of the HSRB Narrative DAG focused on the Medical Illness node (red circle). Panel B shows the medical conditions nested within that node (red shape) and their additional relationships. Pane B is an example of a Detailed DAG that is consistent with the Narrative Renal Stone DAG under consideration here.

The relevant medical conditions that are shown in Figure 5 include renal colic, hydronephrosis, infection (includes urinary tract infections such as cystitis and pyelonephritis), renal failure, and sepsis. Because this level of detail is not provided in the Narrative DAG, these are discussed here for completeness and clarity of relationships and better explain the LoE assignments for edges coming out of the 'Medical Illness' node.

Medical Illness -> Individual Readiness

Both ureterolithiasis and hydronephrosis can lead to renal colic which is pain associated with a renal stone (64). This often includes nausea and vomiting as additional symptoms. The duration of symptoms for a stone that will spontaneously pass is generally no longer than 14 days (64). NSAIDs and opioids are a mainstay of treatment for pain and antiemetics respectively. Given the lack of spaceflight data on the effects of nephrolithiasis on Individual Readiness, we rely on terrestrial data used to inform probabilistic models. Table 5 shows the estimates for functional impairment in the IMED database from the Clinical Information Findings Form (CLIFF) for Nephrolithiasis (74).

Table 5: Nephrolithiasis CLIFF shows the summary of Mission End States for ISS treatment scenarios including untreated Best Case and Untreated Works Case scenarios.

The table below summarizes the treated and untreated best and worst case scenarios.

	Clinical Phase I Diagnosis & Initial Treatment[1]		Clinical Phase II On-going Treatment / Convalescence[2]		Clinical Phase III Recovered / Mission End State[3]		
	FI* (%)	Duration (hrs)	FI* (%)	Duration (hrs) (Min - ML - Max)	FI* (%)	EVAC** (%)	LOCL** (%)
ISS-based Treatment (best case scenario %: 36 - 85)	100	0.75	2 - 39	3 - 13.5 - 24	0	0	0
ISS-based Treatment (worst case scenario %: 15 - 64)	100	0.75	21 - 61	72 - 96 - 120	0 - 61	100	0
Untreated Best Case	0	0	21 - 61	3 - 13.5 - 24	0 - 39	100	0
Untreated Worst Case	0	0	43 - 85	72 - 96 - 120	43 - 85	100	0

Functional impairment according to IMED assumptions is expected to be 100% for the first 45 minutes of an event. Then in the worst-case scenario untreated it is expected to be between 43-85% impaired for potentially up to 120 hours (5 days). The evidence that this will result in meaningful impairment of a crewmember at a time that will lead to potential loss of mission outcomes (Consequence Level = 3) depends on where those 5 days fall in relation to critical mission tasks. Assuming that it may last up to 14 days, the likelihood and consequence that reaches 3 for a 1000-day Mars mission should be assessed against the number of mission critical days expected based on mission critical tasking that cannot be taken up by another crew-member if needed. This calculation is beyond the scope of this document. Because this evidence is based on terrestrial data only, it lacks specificity. In this sense the LoE is scored as *Weak*.

Medical Illness -> Evacuation

One Russian cosmonaut is thought to have had a renal stone that passed spontaneously. He was being prepared for evacuation (18,20). One study with the Integrated Medical Model assessed a 923-day mission with 4 crew and found the probability of reaching consideration of evacuation from nephrolithiasis alone to be 1:59 (75). The same study found for a 426 day mission with 4 crew that probability dropped to 1:130 (75). Given the lack of nephrolithiasis in flight and the dependence on incidence modeling using terrestrial numbers for these estimates, the LoE is scored as *Weak*.

Medical Illness -> Loss of Crew Life

Medical Illness -> Long Term Health Outcomes

For a Medical Illness to lead to Loss of Crew Life or Long-Term Health Outcomes, the progression shown in Panel B of Figure 5 to either Renal Failure or Sepsis must occur. This is most likely to happen with an impacted stone and the development of an infection in mission. There has been one notable case of urosepsis in mission during Apollo 13 when Fred Haise wore a condom catheter too long (28). This was not related to renal stones and because he was traveling back to Earth at the time the question of adequate treatment resources was not faced at that time.

The Sepsis CLIFF includes probabilities for mission end states including LOCL (consequence 5) shown in Table 6. Probability of LOCL in the worst case scenario with ISS level treatment is 29-70% and in the

untreated worst case scenario it is 100% (76). Because there have not been any meaningful cases of sepsis or renal failure in mission, the numbers here rely on terrestrial data. Sepsis is treated as a fixed rate event at 0.0024 events / person-year and in IMM is independent of other factors. This is all cause sepsis and there is insufficient information to describe the fraction of that total that would be due to nephrolithiasis alone beyond saying that it would be lower. There is no CLIFF for Renal Failure.

Table 6: Sepsis CLIFF shows the summary of Mission End States for ISS treatment scenarios including untreated Best Case and Untreated Works Case scenarios.

The table below summarizes the treated and untreated best and worst case scenarios.

	Clinical Phase I Diagnosis & Initial Treatment[1]		Clinical Phase II On-going Treatment / Convalescence[2]		Clinical Phase III Recovered / Mission End State[3]		
	FI* (%)	Duration (hrs)	FI* (%)	Duration (hrs) (Min - ML - Max)	FI* (%)	EVAC** (%)	LOCL** (%)
ISS-based Treatment (best case scenario %: 66.4)	100	1	2 - 36	24 - 96 - 168	0	0	0
ISS-based Treatment (worst case scenario %: 33.6)	100	1 - 2	16 - 58	0 - 12 - 24	0 - 58	100	29 - 70
Untreated Best Case	0	0	16 - 58	48 - 60 - 72	16 - 58	100	0 - 100
Untreated Worst Case	0	0	38 - 75	0 - 12 - 24	38 - 75	100	100

The evidence here lacks specificity, reproducibility, and mechanism (the PRA data not dependent on preceding conditions like sepsis). For these reasons the LoE that supports nephrolithiasis leading to LOCL or Long-Term Health Outcomes is considered *Speculative*.

Medical Prevention Capability -> Water Intake

NASA Standard 3001 has current requirements for a minimum amount of hydration that must be provided to astronauts through spacecraft systems (Figure 6). However, it is not always possible to achieve these levels. For renal stone prevention, the requirement for water intake is 2.5 L/day per crewmember.

NASA-STD-3001 Volume 2, Rev C Table 4 – Water Quantities and Temperatures
Technical Requirements in **bold boxes** are the focus of this technical brief

Technical Requirement	Quantity (quantities are mutually independent)	Temperature		
		Hot	Nominal	Cold
Potable Water for Hydration	Minimum 2.5 L (84.5 fl oz) per crewmember per day *(allocation to include 600 mL per meal per crewmember to be available as Hot Water)*	between 68 ºC (155 ºF) and 79 ºC (175 ºF) **	between 18 ºC (64 ºF) and 27 ºC (80.6 ºF)	maximum temperature of 16 ºC (60 ºF)

Figure 6: NASA-STD-3001 V2 Rev C requirement for potable water for hydration (77,78).

Figure 7 shows the average water intake per crewmember in past missions as evidence of what has been achieved through the systems engineering trade space deliberations in the past.

Average Water Intake on Past Spaceflight Programs (range overlaid on graph above)

	Apollo	Skylab	Shuttle	ISS (E1-13)	ISS (E14-25)	ISS (E26-37)
# Astronauts	33*	9	32	19	19	17
Water L/day	~ 1.6 +/- 0.2	~ 2.8 +/- 0.5	~ 2.2 +/- 0.7	~ 2 +/- 0.5	~2.1 +/- 0.4	~ 2.3 +/- 0.6

- Intake includes water directly consumed and water used to rehydrate food
- For Apollo, data was only based on one mission (n of 3); assumed to be average for all missions
- E stands for Expedition, ~6 month missions on International Space Station (ISS)
- Data adapted from Human Adaptation to Spaceflight, The Role of Nutrition, Smith, Scott, M. et al, NP-2014-10-018-JSC

Figure 7: Evidence of average water intake per crewmember on past spaceflight programs (77).

Note that only during Skylab has the required amount of hydration per crewmember per day been achieved on average throughout missions. This evidence suggests that systems engineering trade space decisions do affect the availability of water intake and therefore affect the risk of renal stone formation. This data is specific to the spaceflight environment, the mechanism is well understood, and throughout multiple missions the data has been reproducible. The LoE is coherent and is scored as *Strong*.

Countermeasures Evidence

K+ Citrate -> Urine Chemistry (Scenario #2)

Potassium citrate and its effects on urine chemistry have been extensively evaluated both terrestrially and in spaceflight (18,19,29,79–89). The causal link between changes in urine chemistry and the use of potassium citrate is well understood mechanistically, has been explored in the spaceflight environment, and has had multiple studies confirming the effects of potassium citrate on urinary chemistry. One in-flight study on 30 long duration crew members demonstrated that potassium citrate "decreased urinary calcium excretion and maintained the calcium oxalate supersaturation risk at preflight levels compared to that in controls. Increased urinary pH in the treatment group decreased the risk of uric acid stones." (89)

Critically, terrestrial data also demonstrates that potassium citrate as a treatment does result in decreased renal stone incidence. Figure 8 shows two equivalent DAGs for visual clarity that illustrate the causal pathway to nephrolithiasis.

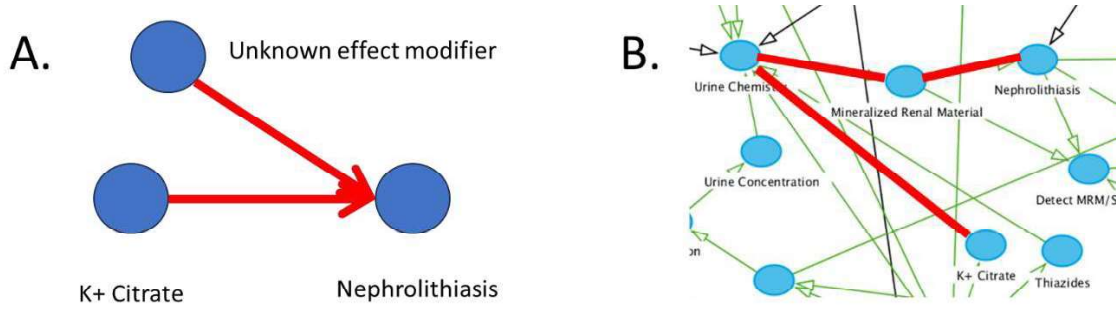

Figure 8: The effect of potassium citrate on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.

There are several terrestrial studies worth discussing that demonstrate the equivalence of these pathways and enable a quantitative estimate of effect size for potassium citrate on nephrolithiasis probability of occurrence.

Pak et al. studied 89 participants and found that with potassium citrate therapy stone passage rate declined from 5.14-7.41 stones/patient year before potassium citrate treatment to 0.66-1.33 stones/patient year during treatment, and 75.0-91.7% of patients were in remission (90). They had a subgroup of 37 patients (Subgroup 2) that were similar to the astronaut population in that they did not have significant co-morbidities to consider. That subgroup demonstrated a decrease from pretreatment 1.17 +- 2.03 stones/year (duration 3 years) to 0.37+-1.53 stones/year (duration 1.8 years) showing remission of 82% and a reduced stone formation rate of 93% (90).

A review of 11 studies by Preminger et al. in 1985 showed new stone formation was virtually eliminated by potassium citrate therapy (a decrease from 0.52 to 0.02 stones per patient per year, a remission rate of 96 per cent, $p > 0.001$) (91). New stone formation continued in 39 per cent of the patients during conservative or placebo trials. In patients participating in conservative or placebo trials new stone formation decreased by only 54 per cent (from 0.54 to 0.25 stones per patient per year). Conservative therapy here is defined as diet modifications and increased water intake without other therapy.

In 1997 Ettinger et al. performed a prospective double blinded study of 64 patients randomized to either placebo or potassium-magnesium-citrate therapy (81). They found that when compared with placebo, the relative risk of treatment failure for potassium-magnesium citrate was 0.16 (95% confidence interval 0.05 to 0.46). Treatment failure here is defined as stone recurrence. Potassium-magnesium citrate had a statistically significant effect (relative risk 0.10,95% confidence interval 0.03 to 0.36) even after adjustment for possible confounders, including age, pretreatment calculous event rate and urinary biochemical abnormalities (81).

Robinson et al. retrospectively evaluated 1480 patients at the Comprehensive Kidney Stone Center between 2000 and 2006(83). 503 met study inclusion criteria based on 24-hour urinary profiles. Mean potassium citrate therapy duration was 41 months (range 6 to 168). They found a significant change in urinary metabolic profiles as soon as 6 months after the onset of therapy including increased urinary pH (5.90 to 6.46, $p < 0.0001$) and increased urinary citrate (470 to 700 mg a day, $p < 0.0001$). The stone formation rate decreased after the initiation of potassium citrate from 1.89 to 0.46 stones per year ($p < 0.0001$) (83).

Importantly, the American Urologic Society guidelines in 2014 suggest that patients with renal stones should be offered potassium citrate as a treatment option and grade their level of evidence as level B (92).

From this available evidence the mechanism of changes in urine chemistry as it relates to renal stone formation is well understood, has been reproduced in multiple studies, and with the Whitson study in spaceflight also has reached specificity for the environment and population. The evidence base for this link reaches the level of coherence and the LoE score is *Strong* that potassium citrate will modify urine chemistry in a favorable profile (proxy outcome) and by clinical demonstration in multiple studies it probably will decrease the likelihood of renal stone occurrence in spaceflight (target outcome).

Thiazides -> Urine Chemistry (Scenario #2)

Thiazide diuretics are a commonly used medication for control of hypertension. The mechanism of action is well understood as they inhibit the Na+/Cl- cotransporter in the renal distal convoluted tubule (DCT) (93,94). Changes in urine chemistry occur with the sodium retention and transport of chloride ions into the urine. The blockage of the Na+/Cl- channel causes an increase in sodium and water retention in the lumen and a decrease in Na in the DCT. At the same time, blockage of the Na+/Cl- channel increases the flow of ions through the Na+/Ca++ channel, resulting in increased calcium reabsorption into the interstitium in exchange for Na return to the DCT (95). This results in decreased urinary calcium and has been the basis for the use of Thiazide diuretics for renal stone treatment (95).

A 2009 Cochrane Review of 5 prospective randomized double blind controlled studies examining the effect of thiazide use on urine chemistries (96). These were in concert with dietary modifications (4 studies) and with a neutral potassium salt (1 study). The conclusions indicated there was a significant decrease in the number of new stone recurrences in those treated with thiazides (RR 1.61, 95% CI 1.33 to 1.96). The stone formation rate also showed a statistically significant decrease in the patients treated with thiazides (MD -0.18, 95% CI -0.30 to -0.06). Thiazides plus potassium salts significantly decreased calciuria and vitamin D levels. There is little doubt that thiazides affect urine chemistry. The question specificity for useful application for risk reduction in spaceflight missions requires more insight into quantitative effects of stone reduction.

Quantitative estimates of the effects of thiazides on stone reduction are available, but there is disagreement among experts in the field of the magnitude of benefit (97). In 1981 Brocks et al. published a randomized double-blinded study of 62 patients that showed no difference in the clinical course of idiopathic renal calcium stone formation between a thiazide group and a placebo group (98). Similarly, Sholtz et al. performed another randomized double blinded study with 51 patients over a year and found the expected calcium decrease without and difference in stone formation or passage between thiazide and placebo groups (99). A later meta-analysis in 1999 found thiazides to be effective in the prevention of recurrent stones (100). A later review by Knoedler and Krambeck identified ten randomized controlled studies assessing thiazide effects on stone prevention (97). These results are shown in Table 7.

Table 7: Randomized, controlled trials for thiazide-type diuretics in stone prevention (97). Copied without permission.

Year	Author	Treatment/dose	Outcome (RR)
1981	Brocks et al.	Bendroflumethiazide 2.5 mg TID	None
1982	Schloz et al.	HCTZ 25 mg BID	None
1984	Laerum et al.	HCTZ 25 mg BID	0.39
1984	Wilson et al.	HCTZ 100 mg QD	0.48
1985	Robertson et al.	Bendroflumethiazide 2.5 mg TID	0.38
1986	Mortenson et al.	Bendroflumethiazide 2.5 mg TID	None
1988	Ettinger et al.	Chlorthalidone	0.23
1992	Ohkawa et al.	Trichlormethiazide 4 mg	0.42
1993	Borghi et al.	Indapamide 2.5 mg daily	0.21
2006	Fernandez-Rodrigue et al.	HCTZ 50 mg QD	0.56

A separate double-blind randomized Norwegian study of 50 recurrent stone formers did find a clinically significant difference between thiazide and placebo groups. The probability of not forming a new stone during the treatment period was 45% for the placebo group and 75% for the thiazide group. The Quality of Evidence (QoE) of this study was unable to be assessed.

A 2022 systemic review by Ferre et al. reviewed 5 prospective randomized, double blinded studies using thiazides in 441 patients from 1987 – 2009 (101). These were different from the studies in Table 7. Four of the studies were done in individuals with pre-existing renal stones and one was in post-menopausal women with osteopenia. This review assigned Quality of Evidence (QoE) scores. The meta-analysis suggested that thiazide diuretics were likely to increase the number of stone-free patients (RR 1.61, 95% CI 1.33-1.96, moderate QoE). Notably, this only produced a slight decrease in stone formation rate (mean difference -0.18, 95% CI -0.30 - -0.06, Low QoE) (101). Importantly, the American Urologic Society guidelines in 2014 suggest that patients with renal stones should be offered thiazides as a treatment option and grade their level of evidence as level B (92).

Figure 9 shows two equivalent DAGs for visual clarity that illustrate the causal pathway to nephrolithiasis.

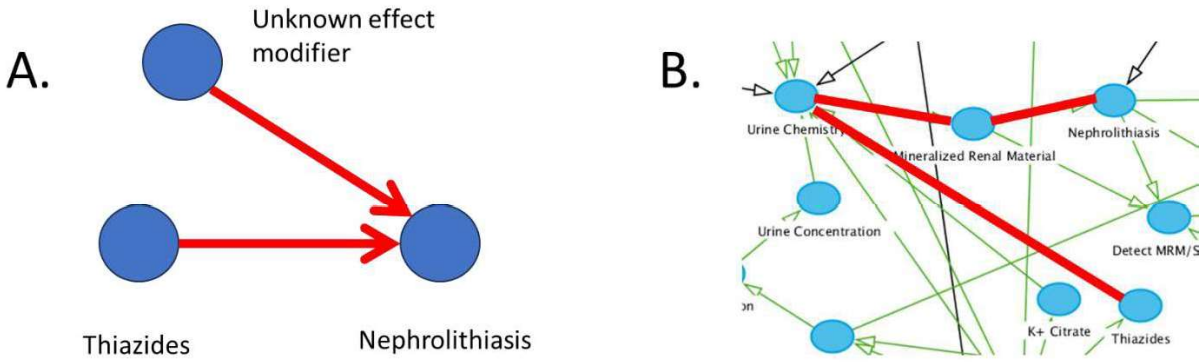

Figure 9: The effect of thiazide diuretics on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.

The studies in Table 7 that showed no effect, taken with the modern review of other similar studies from Ferre et al who graded QoE suggest that there is some lack of coherence in the overall literature on the effectiveness of thiazides for renal stone treatment, and more importantly the generalizability of this information to an astronaut population in the spaceflight environment for the mission durations of interest. There is a notable of data on usage in the spaceflight environment. Publicly available information on the in-flight calculus accessory treatment kit includes many of the other medications considered here, but notably does not include thiazide diuretics (18). In total the evidence for effectiveness of thiazides changing urinary chemistry in a manner that eventually affects nephrolithiasis is considered *Weak*. To achieve a Moderate LoE score some use or research in the spaceflight environment is warranted to achieve specificity.

Bisphosphonates -> Bone Remodeling (Scenario #2)

Resistive Exercise -> Bone Remodeling (Scenario #2)

Bisphosphonates are a well understood class of pharmaceuticals that inhibit osteoclastic resorption of bone that have been used in spaceflight as a countermeasure for bone resorption (21,22,102). In effect they act to keep calcium within the bones, resulting in changes in calcium levels in blood and urine which is why they are of interest in the Renal Stone DAG.

Okada et al. studied the effects of bisphosphonates in bedrest subjects in 2008 but this was primarily looking at bone remodeling effects (103). Okada et al. later studied the effects of alendronate and exercise in spaceflight specifically considering urinary factors on 17 ISS astronauts (104). Originally there were 18 subjects, but one astronaut in the study stopped taking the alendronate because of gastrointestinal (GI) issues. This study found that excretion of oxalate, uric acid, and calcium was higher in the 11 subjects who used the exercise device (ARED) alone compared with those who used ARED plus alendronate and suggested that there appears to be a relationship between urinary bone resorption markers and the excretion of calcium, oxalate, and uric acid (104).

Whether Bisphosphonates are likely to reduce nephrolithiasis because of these changes in the context of spaceflight is a broader question. Figure 10 shows the path tracing (Panel B.) from Bisphosphonates and Resistive Exercise through Urine Chemistry, MRM, to Nephrolithiasis. Panel A shows the simplified equivalent for Bisphosphonates alone with all other effect modifiers shown in a single node.

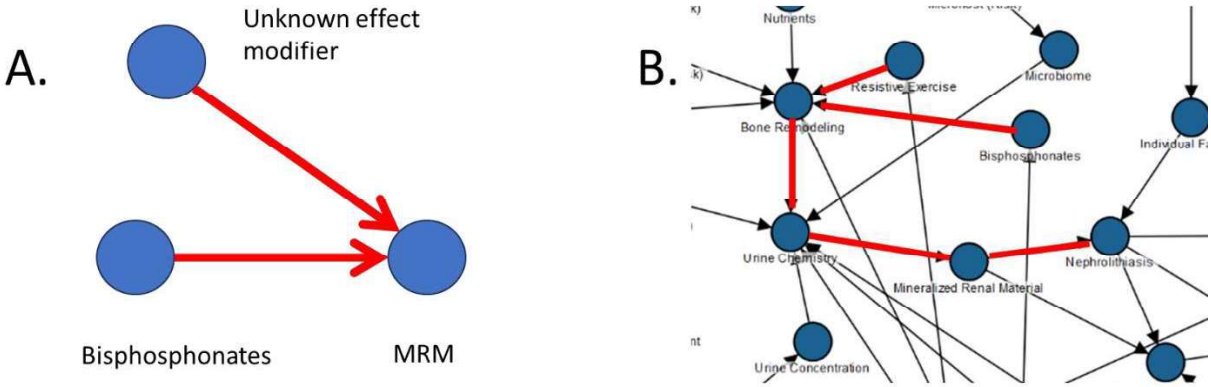

Figure 10: The effect of bisphosphonates and resistive exercise on nephrolithiasis is shown in a simplified DAG (Panel A.) and the equivalent detailed sub-DAG from the official Renal Stone DAG (Panel B.) Unknown Effect Modifier node illustrates all the other effect modifiers that must be considered when evaluating causal inference.

Whether bisphosphonates clinically demonstrate a meaningful reduction in renal stone formation or symptoms is a separate question. In 2020 Kovacevic et al. showed ex vivo that bisphosphonates inhibited calcium salt formation in the urine (105). Prochaska et al. did a cross-sectional analysis of 2294 participants in the Nurses Health Study II and concluded that Among participants with low bone density, bisphosphonate use was associated with lower risk of incident kidney stone but was not independently associated with 24-hour urine calcium excretion. The multivariate adjusted relative risk for no bisphosphonate use was 1.39 (95% confidence interval [95% CI], 1.20 to 1.62) and with bisphosphonate use it was 0.68 (95% CI, 0.48 to 0.98) (106). Another study showed decreases in calciuria and bone markers favorable to renal stone formation using bisphosphonates with and without thiazides (107).

Whether Bisphosphonates will be used in multi-year missions is unclear because of known side-effects. GI symptoms are common with these medications. Osteonecrosis of the jaw (ONJ) is a known side effect that can occur with increasing incidence over longer usage periods (108). Reviewing five available studies, Gupta and Gupta found that the risk ranges from greater than 1% at 12 months to 11% after four years of treatment. Taking zoledronic acid alone increases the risk of osteonecrosis to 21% after the third year. There appears to be a difference between oral and IV dosing (108). A separate estimate suggests that patients taking oral bisphosphonates appear to have between 1:1000 to 1:10000 chance of developing ONJ while those taking IV bisphosphonates may have an incidence as high as 1:10 to 1:100 (109). This is relevant because Zoledronic acid has been suggested as a countermeasure for bone protection. In the context of a 3-year long Mars mission this information may affect the risk-benefit calculation. If they are not included for reasons of unacceptable side effect risk, then no benefit to renal stone risk reduction will be available.

The overall evaluation of the evidence shows some mechanistic understanding, but little reproducibility or specificity to long duration spaceflight. While the connection between Bisphosphonates and Bone Remodeling is well understood terrestrially, from the perspective of risk reduction application in human spaceflight, the evidence is considered *Weak* that it will be used and provide effective renal stone risk reduction.

Tamsulosin -> Urine Flow (Scenario #5, Part 2)

Tamsulosin is a smooth-muscle inhibitor (alpha-blocker) that has been used clinically to improve the passage of renal stones. The mechanism of action is well-understood.

Wang et al. performed a systematic review in 2018 of eight randomized controlled trials totally 1,384 patients (110). The pooled risk of stone passage in the tamsulosin arm was 85% versus 66% in the placebo arm, but substantial heterogeneity existed across trials. After stratifying the studies by stone size, the meta-analysis of the large stone subgroup (5 to 10 mm; N=514) showed a benefit of tamsulosin (risk difference = 22%; 95% confidence interval 12% to 33%; number needed to treat=5). The meta-analysis of the small stone subgroup (<4 to 5 mm; N=533) indicated no benefit (risk difference=–0.3%; 95% confidence interval –4% to 3%). This suggests that for small stones there is likely to be less benefit from Tamsulosin administration.

In 2019 Cui et al. also performed a large meta-analysis that included 56 randomized controlled trials for a total of 9,395 patients (111). Tamsulosin treatment was associated with a higher stone expulsion rate (RR 1.44, 95% CI 1.35-1.55, p <0.01), a shorter stone expulsion time (weighted mean difference -0.73, 95% CI -1.00--0.45, p <0.01), a lower incidence of ureteral colic (weighted mean difference -0.81, 95% CI -1.24--0.39, p <0.01) and fewer incidences of requiring subsequent treatment interventions (RR 0.68, 95% CI 0.50-0.93, p = 0.017). There was not a significant difference between the Tamsulosin group and the control group in the overall incidence of side effects (RR 1.14, 95% CI 0.86-1.51, p = 0.36). They also found a stronger benefit in the stone expulsion rate for tamsulosin among patients with stones greater than 5 mm (RR 1.44, 95% CI 1.22-1.68, p <0.01) and no effect for stones 5 mm or less (RR 1.08, 95% CI 0.99-1.68, p <0.01).

Terrestrial clinical evidence suggests that tamsulosin is beneficial for relieving obstruction by larger stones (>5mm) through helping them pass more quickly. Larger stones are less common than small stones. Tamsulosin is also included in the in-flight calculus accessory treatment kit and is present on the ISS. Evidence on usage in flight was not available but given there are zero reported USOS incidents of renal stone, the use in spaceflight is assumed to be zero here. In this case with the lack of data in the spaceflight environment, the evidence supporting the claim that Tamsulosin will improve medical symptoms and decrease renal stone risk is scored *Weak*.

Medications -> Individual Readiness (Scenarios #2 and #5 Parts 2 and 3)

Medications -> Evacuation (Scenarios #2 and #5 Parts 2 and 3)

Medications -> Loss of Crew Life (Scenarios #2 and #5 Parts 2 and 3)

Medications -> Long Term Health Outcomes (Scenarios #2 and #5 Parts 2 and 3)

The category node ‘Medications’ in this case refers to symptomatic medications for control of pain and nausea, fluid hydration, and in some cases antibiotics and medical expulsive therapies which are the mainstays of initial treatment for symptomatic renal stones (61). These types of medications are listed in the ISS inflight calculus accessory treatment kit and are shown in Table 8 (18).

Table 8: Medications contained in the inflight calculus accessory treatment kit. Modified from Jones et al. (18)

Antiemetic	**Ondansetron IV**
	Ondansetron ODT
	Promethazine IM

	Promethazine PR
Analgesic	Ketorolac IV
	Ketorolac PO
	Morphine IV
Antibiotics	Nitrofurantoin PO
Other	Tamsulosin PO
	Potassium Citrate PO
	Lactated Ringers Solution IV

Another publicly available source of information on the medications on the ISS is from Stingl et al. in 2015 who evaluated the ISS formulary for possible pharmacogenomic issues (112). In addition to the medications from Table 8, Sulfamethoxazole was listed as an antibiotic (likely from sulfamethoxazole-trimethoprim) and ibuprofen and acetaminophen/hydrocodone, and dilaudid were listed as analgesics.

Each of the above medications has flown and been used in space before, so there is strong evidence that they will be available and are at least reasonably effective. There is some question as to whether these medications will remain effective throughout the duration of a Mars mission (113). In the context of total risk reduction for individual readiness, the side effects of all these potential medications must be considered. One study of the exploration medical conditions and the medications used to treat them showed that the top medications with behavioral health and performance impacts are also medications commonly used to treat renal stones including Ibuprofen, hydrocodone and acetaminophen (Vicodin), Trimethoprim and sulfamethoxazole (Bactrim), promethazine, and dilaudid (114). This implies that treatment of an ongoing stone for symptomatic relief only is not likely to return a crew member to full functionality. This was an exploratory study, and the methods are not strong, but it suggests a need for better understanding of the performance impacts in the future. Hence, the evidence that medication treatments will significantly impact Individual Readiness is currently *Weak*.

In the case of the evidence that these medications will significantly alter a decision to evacuate an ill astronaut, the evidence is *Speculative* at best. It is considered that in LEO DRMs, symptomatic treatment is likely to be viewed as a stabilizing measure to prepare for evacuation. In Lunar DRMs, the decision to evacuate may be a decision to remove to a higher level of care (i.e. from the lunar surface back to a Gateway vehicle) may be more pragmatic and enable a wait-and-see time. In Mars, the evacuation option is not available.

For the cases of LOCL and Long-Term Health outcomes, the breakdown of the Medical Illness node into the specific medical conditions as seen in Panel B. of Figure 5 must be considered in detail. Antibiotics and fluids are the only medications that will treat infection and possibly prevent or treat sepsis or renal failure, and these are unlikely to be provided in quantities meaningful for the treatment of sepsis given constraints on mass and volume. However, this level of analysis is beyond the scope of this evidence report as the detailed sub-DAG shown in Figure 5 has not been officially approved by the HSRB. For these cases the LoE is scored as *Speculative*.

Ultrasound -> Detect MRM/Stone (Scenario #3 and #4)

This causal link assumes a specific claim - assuming an Ultrasound is provided, crewmembers can detect MRM or a stone. For DRMs where real-time guidance is an option, evidence must demonstrate that this can be done with real-time guidance. For DRMs where real-time guidance is not an option, evidence must demonstrate that this can be done without real-time guidance and possibly with minimal or Just-in-time (JIT) training.

Ultrasound trained clinical practitioners on-site at Johnson Space Center routinely detect and measure MRM in the astronaut cohort as part of ongoing medical care (115–117). Figure 11 shows data from the Lifetime Surveillance of Astronaut Health (LSAH) illustrating MRM detected in astronauts in pre-flight and annual exams. Size and identification markers for ultrasound include the presence or absence of shadowing and the twinkle/spectral signal (115,118–120).

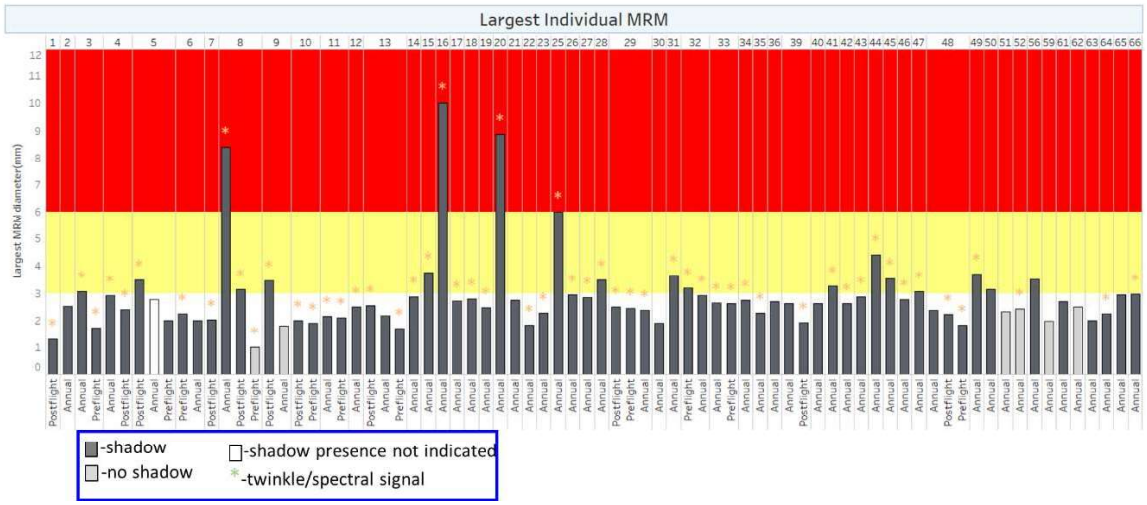

Figure 11: LSAH data on the size, location, and measurements of mineralized renal material in US astronauts (66). Different parameters of ultrasound indicators of MRM presence are shadow and twinkle/spectral signal.

The feasibility of detecting MRM by a well-trained clinician in the terrestrial environment is well demonstrated but does not address the ability of untrained astronauts to capture clinical images that are of high enough quality to be independently analyzed (by ground support or artificial intelligence). No studies were identified that had demonstrated AI utility in diagnosing renal stones from ultrasound images, though there is significant AI work in image diagnosis in other clinical domains (121–123).

There is evidence at the level of animal studies that suggests that the ISS environment may make it more difficult to detect the twinkle/spectral artifact. In one animal study using pigs, the twinkle artifact decreased in visibility as the CO2 atmospheric levels increased to a threshold around 0.8% CO2 which is approximately 5.3 mmHg ppCO2. In this experiment 4 pigs were implanted with stones and imaged. The twinkle artifact faded after 9-25 minutes of exposure to 0.8% CO2 driven by an increase in the carrier gas and returned after the O2 levels were restored (124). ISS has reached this level of CO2 in the past in ambient conditions, but other issues drove re-evaluation of the standards (125). Current NASA-STD-3001 Volume 2 Rev C [V2 6004] limits the average 1-hour CO_2 partial pressure ($ppCO_2$) in the habitable volume to no more than 3 mmHg (43). Given this data comes from animal studies in a different environment,

this particular study sheds light on possible mechanisms, but there has not been reproducibility or specificity observed in humans or the spaceflight environment.

Throughout the life of the International Space Station (ISS) ultrasound has been utilized as a research and medical imaging device (126). Typically, astronauts have been guided from the ground through ultrasound image capture and those images have been analyzed on the ground by experienced clinical personnel. Using this methodology, high quality images of the renal and genitourinary tracts have been successfully captured by astronauts in-mission and demonstrated to be valid in weightlessness (127,128).

For missions that lack a real-time support capability (i.e. Mars missions), the evidence is less clear regarding whether astronauts will be able to perform diagnostic, monitoring, and possibly interventions using ultrasound given the level of training that is required. In 2015 Hurst et al. performed an evaluation of image quality and time to image capture for remote guided and computer guided operators (129). Theis initial data suggests that image quality was acceptable in both modalities. An on-orbit assessment was conducted in April 2020 and June 2022 with Autonomous Medical Officer Support (AMOS) software developed by the Exploration Medical Capabilities Element (ExMC) at NASA. The crewmembers involved did not receive any prior training and had no support. They were able to obtain 25 high-quality images of bladder and kidneys using the software alone (130). However, no mention is made of the capture of images of MRM or of a stone specifically.

The evidence in this case lacks specificity to adequate image capture in the space environment by astronaut personnel, although the initial steps to demonstrating that have been taken. If Ultrasound can be shown as a successful tool in the spaceflight environment to at least detect the presence of stones, then it can be used as a monitoring method and clinical trigger for in-mission preventive interventions to keep the stone from becoming symptomatic. LoE to support this claim is currently scored as *Weak* when considered for the case of autonomous imaging for the Mars DRM.

Detect MRM/Stone -> Ultrasound manipulation (Scenario #3 and #4)

Ultrasound Manipulation -> Ureterolithiasis (Scenario #3 and #4)

Even if they can detect a stone, does the evidence suggest that they can successfully manipulate it to relieve symptoms and decrease medical risk? Hand-held ultrasound technology designed to push or break a renal stone with focused ultrasound beams has been advancing through clinical trials for applications in terrestrial medicine (131). The utility of this technology in a spaceflight mission assumes that a beam focuser for the ultrasound has been provided in the medical treatment capability. As this is a small, low power device that typically fits over the probe of an ultrasound machine, it is reasonable to assume this may be included if evidence of risk reduction can be demonstrated. Applications include repositioning a stone to an area less likely to progress to the ureter (i.e. inferior pole of the kidney (62)), pushing a stone out of the proximal or distal ureter, or possibly breaking a stone into smaller pieces that are able to pass with minimal symptoms (131).

In 2016 Harper et al. attempted to use this technology to reposition stones in the kidney in a first in human trial. They reported successful repositioning of stones in 14 of 15 subjects. “Of the 43 targets, 28 (65%) showed some level of movement while 13 (30%) were displaced > 3 mm to a new location. Discomfort during the procedure was rare, mild, brief, and self-limited. Stones were moved in a controlled direction with over 30 fragments being passed by 4 of 6 subjects who previously had a

lithotripsy procedure. The largest stone moved was 10 mm. One patient experienced pain relief during treatment of a large stone at the UPJ. In 4 subjects a seemingly large stone was determined to be a cluster of small passable stones once moved." (132)

In 2022 Hall et al. performed a prospective unblinded study of 29 subjects who received either ultrasonic propulsion alone (n = 16) or with burst wave lithotripsy bursts (n = 13). They report observable stone motion in 19 (66%). Stone passage occurred in 18 (86%) of the 21 distal ureteral stone cases with at least 2 weeks follow-up in an average of 3.9±4.9 days post-procedure. Fragmentation was observed in 7 of the burst wave lithotripsy cases. Average pain scores (0–10) dropped from 2.1±2.3 to 1.6±2.0 (P= .03). Side effects were minimal including hematuria on initial urination post-procedure and mild pain. In total, 7 subjects had associated discomfort with only 2.2% (18 of 820) propulsion bursts. Figure 12 illustrates the clinical positioning both terrestrially and as-intended for spaceflight for the procedure.

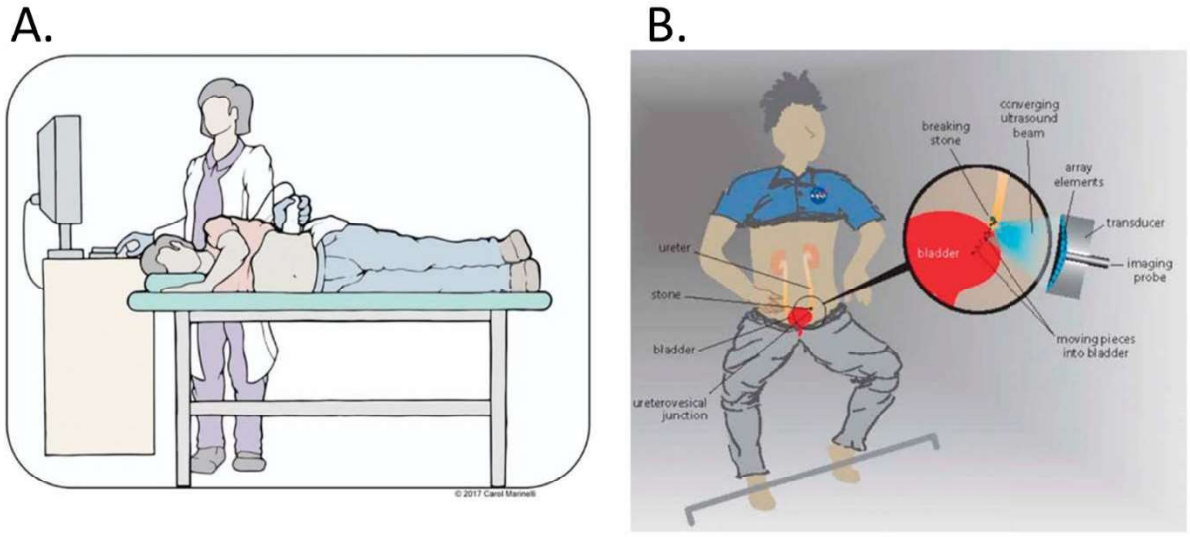

Figure 12: Figure modified from Hall et al.(133) showing clinical positioning and use of ultrasonic stone propulsion and transcutaneous burst wave lithotripsy in A. terrestrial setting and B. spaceflight setting.

Given the recency of this technology, the Technology Readiness Level is 5-6 given the demonstrations discussed here (134). The technology is expected to advance in the future. Mechanism is understood, but reproducibility and specificity are lacking at this time. The LoE that supports the assertion that ultrasonic propulsion will meaningfully reduce renal stone risk is currently *Weak*.

Ultrasound -> Percutaneous Nephrostomy (Scenario #5, Part 3)

Percutaneous Nephrostomy -> Medical Illness (Scenario #5, Part 3)

In keeping with the prior discussion on autonomous ultrasound imaging, the evidence regarding the effectiveness of percutaneous nephrostomy (PCN) for risk reduction when autonomous performance is required is thin. PCN is a medical procedure where a clinician uses imaging guidance to place a catheter through the back into the renal pelvis and allow urine to pass from the body without passage through the ureters or bladder (135,136). This is not required in all cases of renal stones but could be indicated in rare situations where a rental stone becomes stuck and obstructs the passage of urine. Panel B. in Figure 5 shows an expansion of the Medical Illness node out into specific medical conditions that are

associated with renal stones. These include renal colic, hydronephrosis, infection, sepsis and renal failure. In the case of a stone that is unable to pass on its own and becomes lodged in the ureter, hydronephrosis can develop, and the likelihood for infection increases. Given the breadth of MRM sizes shown in Figure 11, it is conceivable that stones in the astronaut corps with sizes > 5 mm can form and possibly obstruct.

Terrestrially these types of stones are treated with a variety of approaches including extracorporeal shock wave lithotripsy, flexible ureteroscopy, and PCN. PCN relieves hydronephrosis and decreases the likelihood of infections and is used to treat patients who are either in or at risk of sepsis with an obstructing stone (18,61,137). The purpose of this intervention is then to reduce the likelihood of progression to sepsis and renal failure, two events that would be exceedingly difficult to treat with the mass, volume, loss of real-time communications, and training restrictions that are a reality of an eventual Mars mission (138). For LEO DRMs, occurrence of the medical conditions that lead to consideration of PCN would likely result in an evacuation for definitive care on Earth. In a Mars mission where evacuation is not feasible, the provision of PCN as a medical capability may be lifesaving.

In 1998 Pearle et al. randomized 42 patients with obstructing calculi and clinical signs of infection including fever and elevated white blood cell count to PCN vs. retrograde ureteral catheterization to assess differences between the techniques (139). For the PCN group, average time to normal temperature was 2.3 days and time to normal white blood count was 2. Those PCN patients stayed an average of 4.5 days.

Placing a PCN is not without risk. Efesoy et al. retrospectively evaluated four hundred and fifteen percutaneous nephrostomy tube placements performed in 354 patients (165 men and 159 women) suffering from obstructive uropathy over a 10-year period in Turkey. They found that overall technical success, major and minor complications rates were 96.1%, 11.1%, and 7.7% for their experienced operators (136). Major complications included 10 cases where the tube needed to be replaced because of blood clots, 7 cases of macroscopic hematuria requiring blood transfusion (a medical capability which is unlikely to be available in a Mars mission(140)), 6 cases that needed tube replacement due to mechanical displacement, 5 cases of urosepsis, 2 cases of retroperitoneal hematoma that required blood transfusion, and 1 case of injury to a neighboring organ or vessels (136). Minor complications included temporary hematuria, fever, colicky pain, vaso-vagal symptoms and urinary extravasation that did not require additional intervention.

Sousa Morais et al. prospectively evaluated PCN (18 patients) against retrograde ureteral stent (RUS) placement (36 patients) and found that PCN was associated with a higher rate of spontaneous stone passage when adjusted for stone size and location and it was better tolerated and associated with fewer urinary symptoms when compared with RUS. Patients in RUS group experienced more urinary symptoms, mostly hematuria (68.7% vs 16.7% in PCN group < .001) and dysuria (78.3% vs 16.7% in PCN group, $p < .001$).

Determining if the evidence supports the use of PCN as a meaningful form of risk reduction in a Mars mission is a challenge. This procedure is under consideration because it requires a small kit and ultrasound, minimizing the mass and volume taken for a low likelihood, high consequence event. In the case that an ultrasound and a PCN kit are provided, the question remains - Can they successfully place a PCN under ultrasound guidance without real-time guidance. Lerner et al. performed initial studies into the differences between experiences operators and naïve operators for percutaneous placement of a

drain by video training and remote guidance (141). The techniques used are like PCN but were performed on phantoms and not on real humans. Of 27 naïve subjects, all were able to complete the simulated procedure with time to completion different between experienced operators (2 mins) and naïve operators (~5.8 mins). This was designed as a proof-of-concept study only.

Moeen et al. performed a review of the literature recently that suggests that achieving competence for safe percutaneous renal access requires approximately 50 cases and pelvicalyceal system dilatation, which can be assessed by ultrasound prior to considering PCN (142). Whether that level of training can be provided to non-astronauts in a meaningful fashion is unclear. PCN is more likely to be a procedure that is restricted to a physician astronaut on a mission and given the low likelihood that an obstructing stone will occur in one of these missions it may not be worth the mass, volume, and training investments for overall risk reduction. Based on the factors discussed, the mechanism by which PCN can be implemented and affect medical illness are understood and supported by the evidence. However, there is no evidence showing specific success with the astronaut population or spaceflight environment and no reproducibility of results in either analog or spaceflight settings for the population in question. The LoE scores for Ultrasound -> PCN and PCN -> Medical Illness meaningfully reducing risk in a Mars mission are *Speculative*.

Water Intake -> Hydration (Scenario #2)

Water Intake -> Urine Flow (Scenario #5, Part 2)

The relationship between water intake, hydration status and renal stone development is well understood mechanistically and matches clinically observed data. Focused literature review showed a significant amount of data that supports the link between Water Intake and Nephrolithiasis directly from clinical studies. Figure 13 shows two equivalent DAGs highlighted by red lines.

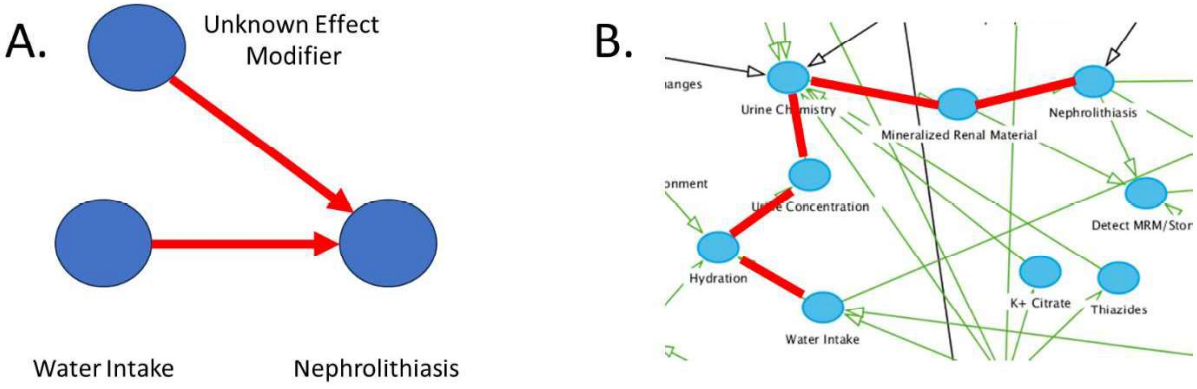

Figure 13: Comparison between DAG visualizations for the Water Intake effect on Nephrolithiasis. The image on the right is from the Renal Stone DAG and shows a higher level of mechanistic detail than the image on the left, but they are functionally the same.

The pathway from Water Intake to Nephrolithiasis is functionally the same between the two images, but the image on the right has additional nodes that show a different level of detail. The advantage of additional detail is that different countermeasures that work at different points along the mechanistic pathway can be differentiated from each other.

Goodenow-Messman et al. produced a computational probabilistic biochemistry of CaOx crystal precipitation, growth, and agglomeration (48). This model was trained on data from 1517 astronauts' 24-hour urine samples. Model development like this demonstrates a strong understanding of *Mechanism* of formation. The model was able to calculate incidence rate ratios for the increase in water intake that would be needed to reduce CaOX IRR to the same level as pre-flight values. Their simulations predict that in-flight fluid intake alone would need to increase from current prescriptions of 2.0–2.5 L/day to ~3.2 L/day to approach the CaOx IRR of the pre-flight population. Bone protective interventions would reduce CaOx risk to pre-flight levels if Ca excretion alone is reduced to <150 mg/day or if current levels are diminished to 190 mg/day in combination with increasing fluid intake to 2.5–2.7 L/day.

In a secondary analysis of 78,293 women from the prospective Women's Health Initiative Observational Study, 1,952 non-stone forming women were found to have kidney stones in follow up. This analysis found that the risk of kidney stone was decreased 13% to 31% ($p = 0.002$) with higher water intake after adjusting for nephrolithiasis risk factors (143).

Xu et al. reviewed 15 relevant studies (10 cohort and 5 case-control studies) in a meta-analysis with 9601 cases and 351,081 total participants. In the dose-response meta-analysis, they found that each 500 mL increase in water intake was associated with a significantly reduced risk of kidney stone formation (relative risk (RR) = 0.93; 95% CI: 0.87, 0.98; $P < 0.01$) (144).

The evidence that Water Intake will be an effective countermeasure for Renal Stone risk management is considered *Strong*.

LoE Scored DAG

From the discussions above, the resulting LoE scores are compiled in Table 9.

Table 9: LoE scores for all other edges.

Starting Node	Ending Node	LoE Score
Altered Gravity	Bone Remodeling	1
Bisphosphonates	Bone Remodeling	3
Bone Remodeling	Urine Chemistry	1
CO2 (Risk)	Urine Chemistry	4
Detect MRM/Stone	Ultrasound Manipulation	3
Hostile Closed Environment	Hydration	2
Humidity	Hydration	4
Hydration	Urine Concentration	2
Individual Factors	Nephrolithiasis	2
K+ Citrate	Urine Chemistry	1
Medical Illness	Individual Readiness	3
Medical Illness	Evacuation	3
Medical Illness	Loss of Crew Life	4
Medical Illness	Long Term Health Outcomes	4
Medical Prevention Capability	Water Intake	1
Medications	Medical Illness	1
Medications	Individual Readiness	3

Medications	Evacuation	4
Medications	Loss of Crew Life	4
Medications	Long Term Health Outcomes	4
Microbiome	Urine Chemistry	4
Mineralized Renal Material	Nephrolithiasis	2
Mineralized Renal Material	Detect MRM/Stone	2
Nephrolithiasis	Detect MRM/Stone	2
Nephrolithiasis	Ureterolithiasis	3
Nutrients	Bone Remodeling	1
Percutaneous Nephrostomy	Medical Illness	4
Resistive Exercise	Bone Remodeling	1
Tamsulosin	Urine Flow	3
Thiazides	Urine Chemistry	3
Ultrasound	Detect MRM/Stone	3
Ultrasound	Percutaneous Nephrostomy	4
Ultrasound Manipulation	Ureterolithiasis	3
Ureterolithiasis	Urine Flow	3
Urine Chemistry	Mineralized Renal Material	1
Urine Concentration	Urine Chemistry	2
Urine Flow	Medical Illness	3
Water Intake	Hydration	1
Water Intake	Urine Flow	2

The results of scoring based on assumptions from Tables 1-4 and the focused literature review in Table 5 are shown in a combined visualization in Figure 14.

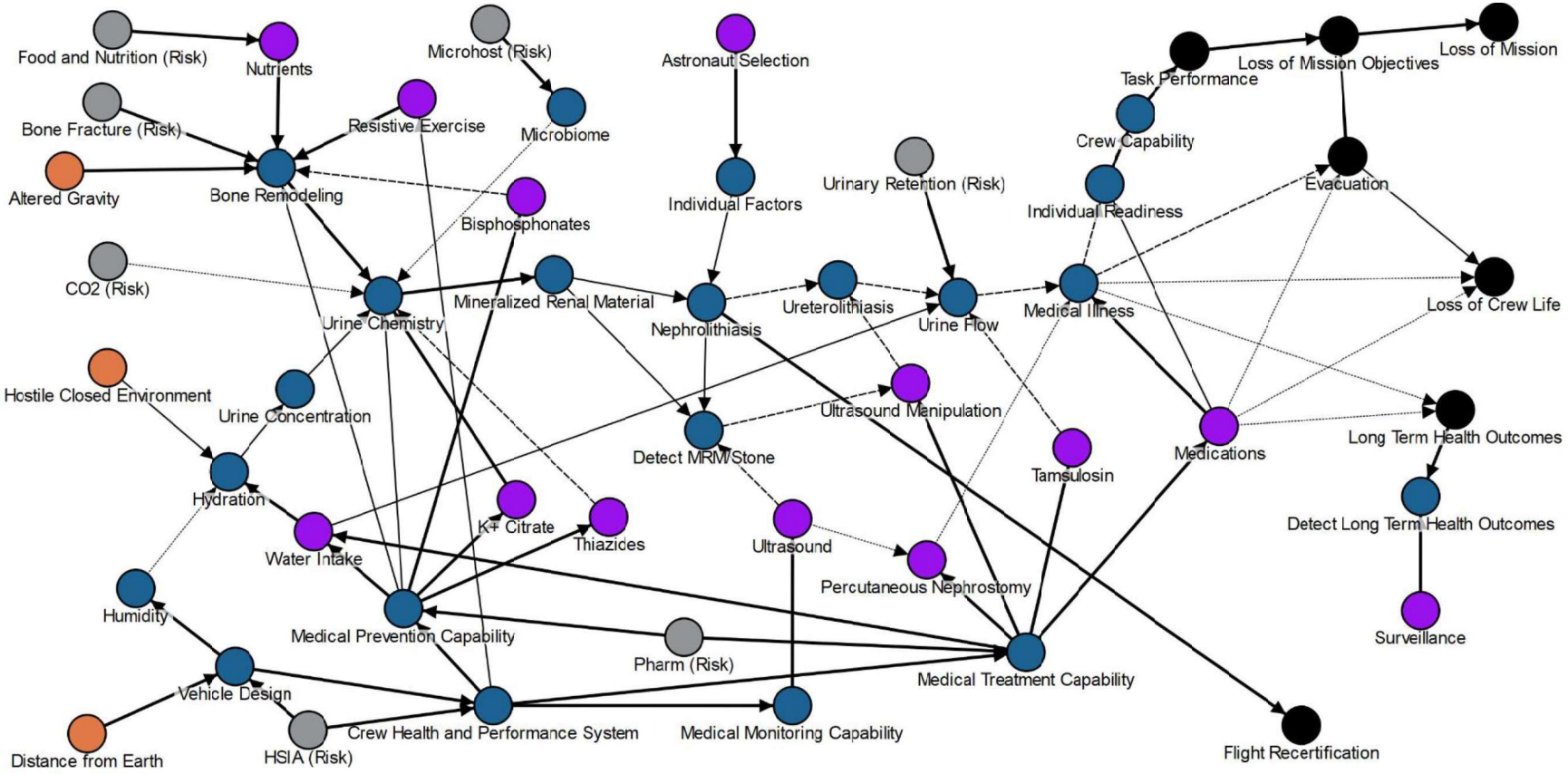

Figure 14: Visualization of the LoE Scoring on the Renal Stone DAG.

Visualizing the edges of a DAG based on LoE scoring is intended to highlight areas where either knowledge or capability gaps exist. The value of this exercise is in communicating to interested stakeholders a visual roll-up of the evidence base and its uncertainty in a single image. It is important to keep in mind that the visualization of LoE is in no way interpretable as strength or magnitude of effect from one node on another.

It is hoped that this approach for evaluating evidence in the context of the DAGs, scoring LoE for edges, and visualizing those scores for the purpose of communicating uncertainty in our understanding of the flow of risk will be used for other risks beyond the Renal Stone Risk.

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APPENDIX B:

Concept of Operations for the Prevention, Diagnosis and Treatment of Renal Stones for Mars Missions

Human Research Program

Verify this is the correct version before use

September 2023
Baseline

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

Human Research Program
Exploration Medical Capability (ExMC)
Renal Stone ConOps

Submitted By:

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Date

Concurrence By:

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Approved By:

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Date

CHANGE HISTORY

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Change/ Revision	Date	Description of Change	Pages Affected
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1 INTRODUCTION

1.1 Purpose

The purpose of this document is to provide a Concept of Operations (ConOps) that encompasses the prevention, mitigation, and management of kidney stones in a Martian mission scenario to assist in updating the information used by the Human Research Program (HRP) and Human System Risk Board (HSRB).The ConOps includes a set of scenarios that incorporate recent terrestrial and space-based medical data regarding kidney stones.

1.2 Scope

This ConOps explores the utilization and integration of medical system functionalities to prevent, monitor, diagnose, and treat renal stones in the context of a Mars mission. The document describes these system functionalities during nominal and off-nominal (emergency) operations in the pre-, in-, and post-flight mission phases.

1.3 Authority

This document was managed by the ExMC Systems Engineering (SE) Team, was reviewed by the Renal Stone Risk Custodian Team (RCT), and was approved by the ExMC Element.

Document Heritage

- 09/12/2023 Renal Stone Risk Custodian and ExMC Leadership Review
- 10/3/2023 MOG presentation
- 10.xx.2023 ExMC Control Board Approval

2 APPLICABLE AND REFERENCE DOCUMENTS

2.1 Applicable Documents

Applicable documents contain provisions or other pertinent requirements directly related to and necessary for the performance of the activities specified by the document. The following documents, of the exact issue and revision shown, form a part of this specification to the extent specified herein.

Document Number	Revision/ Release Date	Document Number
	January 2016	NASA Clinical Practice Guidelines for Prevention of Nephrolithiasis
HEOMD-007	Revision 2, 09/28/2021	HEOMD Strategic Campaign Operations Plan for Exploration
HEOMD-415	Revision 1, 01/24/2022	Reference Surface Activities for Crewed Mars Mission Systems and Utilization
HEO-DM-1002	9/28/2020	Mars Mission Duration Guidance for Human Risk Assessment and Research Planning Purposes
NASA STD 3001 - V1 Rev. B	1/5/2022	NASA Space Flight Human-System Standard, Volume 1: Space Flight Human- System Standard: Crew Health
NASA STD 3001 - V2 Rev C	4/8/2022	NASA Space Flight Human-System Standard, Volume 2: Human Factors, Habitability, and Environmental Health

Document Number	Revision/ Release Date	Document Number
HRP 48021	4/2019	Medical System Concept of Operations for Mars Exploration Mission-11

2.2 Reference Documents

Reference documents contain supplemental information and provide guidance in the application of this concept of operations. These documents may or may not be specifically cited within the text of this document, and a complete list is provided in Appendix B.

2.3 Order of Precedence

All specifications, standards, exhibits, drawings or other documents that are invoked as "applicable" in this specification are incorporated as cited. All documents that are referred to within an applicable document are considered to be for guidance and information only. In the event of a conflict between the text of this specification and an applicable document cited herein, the text of this document takes precedence.

3 MISSION DESCRIPTION AND ASSUMPTIONS

3.1 Mission Description and Assumptions

This section identifies the system stakeholders, the stakeholder needs, system goals, and assumptions used by the team to develop this Renal ConOps.

3.1.1 Renal ConOps Stakeholders

The stakeholders and their association with this ConOps are outlined in the table below.

Table 1 Renal ConOps Stakeholders

Stakeholder	Summary
ExMC	ExMC, under the umbrella of HRP, is tasked with working with the HSRB to update the information regarding the risk of renal stones in spaceflight for a long-duration Mars mission using prevention, diagnostic, monitoring, and treatment strategies.
HSRB	The HSRB is working with ExMC to update the information regarding the risk of renal stones in spaceflight for a long-duration Mars mission.
SD	Responsible for implementing renal stone prevention, diagnostic, monitoring , and treatment strategies for mission success.
HRP	NASA program focusing on research findings to address the effects of the spaceflight environment on the human body, focusing on Mars.
OCHMO/HMTA	Arbiters of risk on behalf of NASA Programs.
Crew Office	Must ultimately accept the risk.
Moon to Mars Program Office	Has oversight over Artemis and Mars missions, so they establish the DRMs.

3.1.2 Stakeholder Need

As exploration missions take astronauts further into deep space, there is a need to develop strategies for the prevention, mitigation, diagnosis and management of kidney stones, which possibly carry an increased risk due to physiological changes in spaceflight, that may arise during missions. This isdetailed further in the Renal Stone Evidence Report (73).

3.1.3 System Goals

System goals identify the end the activity team works toward while specificying the system. They are based on constraints levied on the system by stakeholder needs, mission architecture, and stakeholder expectations. They provide a foundation for system development and influence the choice of metrics used to measure performance of the solution. The specific goals for this ConOps are as follows:

Goal #1: Perform pre-flight renal stone monitoring and prevention
Further implement and develop monitoring and mitigation strategies for renal stone formation in astronauts pre-flight. This would involve pre-flight testing and evaluations, which may involve astronaut screening with respect to kidney stones.

Goal #2: Prevent in-mission renal stone formation
Develop preventative strategies to decrease the likelihood of renal stone formation through, for example, diet, exercise, pharmacological supplementation, and optimal hydration

Goal #3: Diagnose renal stones in-mission
Develop strategies to diagnose renal stone formation during flight

Goal #4: Treat renal stones in-mission
Develop strategies to treat renal stones in-mission, as well as manage long-term health consequences that may arise in-mission due to stone formation.

Goal #5: Provide In-mission Training of renal stone diagnosis and treatment
Develop familiarization and just-in-time training modalities for diagnosing and treating renal stones in-mission.

Goal #6: Monitor and treat renal stones post-flight
Develop strategies and capabilities for monitoring and treating renal stones post-flight.

3.1.4 System Objectives

The overarching objective of this ConOps is to provide guidance for Mars missions in the context of preventing, diagnosing, and treating renal stones in spaceflight. The specific goals related to this objective are outlined in Section 3.1.3.

3.1.5 System Description

The Medical System will interface with other subsystems within the greater Crew Health and Performance (CHP) System as well as subsystems outside the CHP System. These interactions are captured in Figure 1 below, which shows not only the Medical System interfaces but also the subsystems within the Medical System.

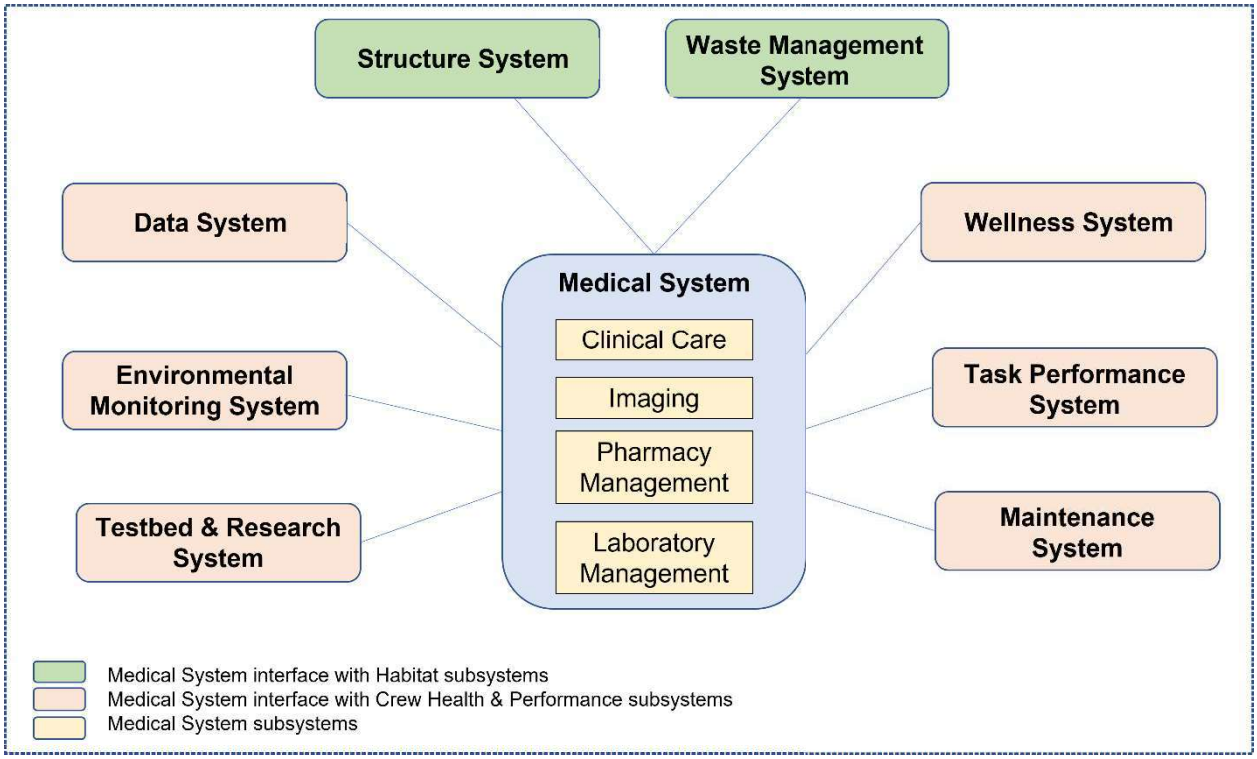
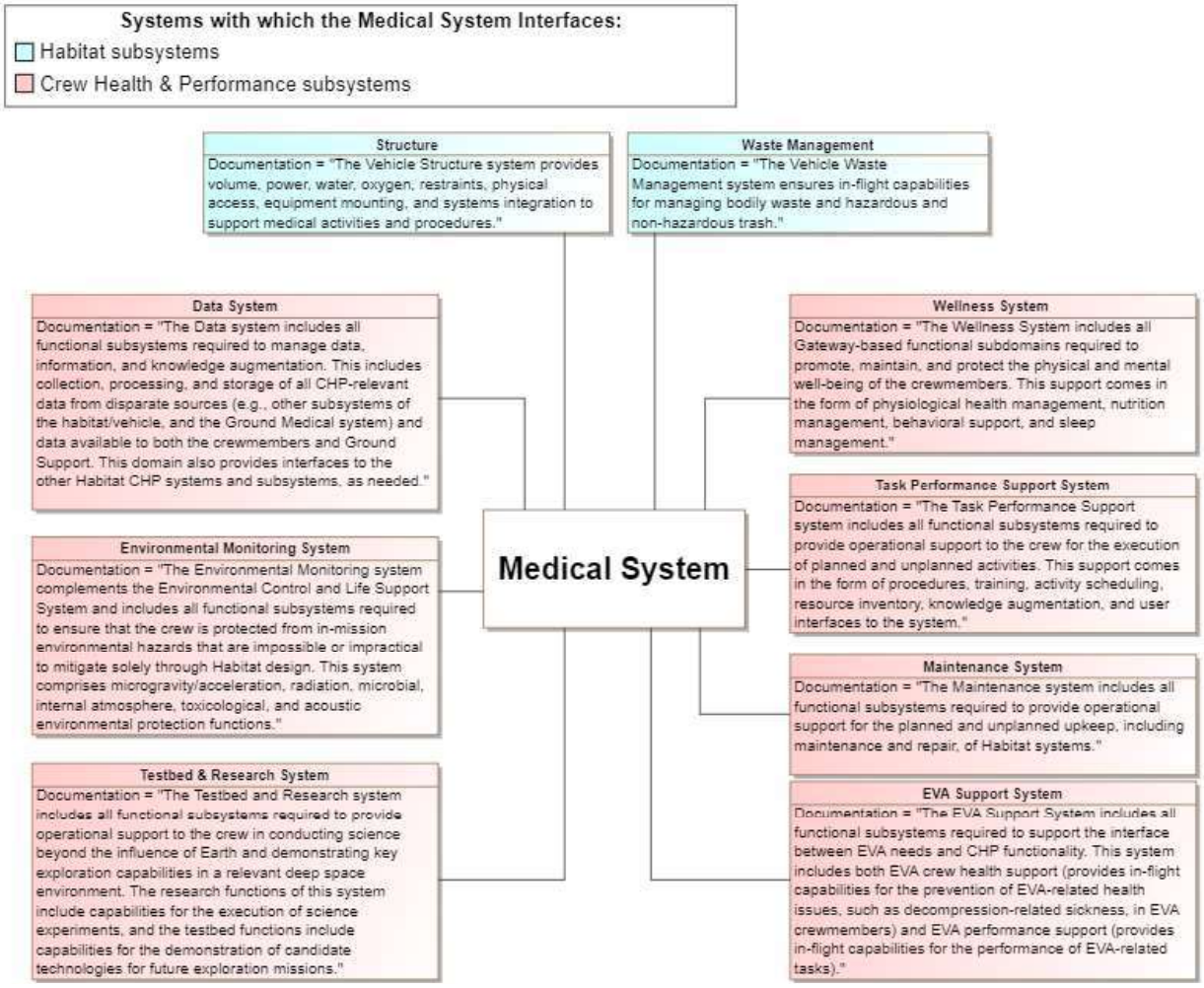


Figure 1 Medical System Context Diagram



The Habitat Medical System, which includes both the Medical System in the deep space transport vehicle and the Medical Systems in the Mars surface habitat and pressurized rover, is responsible for medical care of in-mission crewmembers, including the prevention, diagnosis, treatment, monitoring and long-term management of medical conditions, namely, renal stones for the purposes of this ConOps, for both clinical and well-being aspects of health. This system's resources include crewmembers, hardware, software, skillsets, knowledge, and information required to provide clinical care, imaging, laboratory management, and pharmaceutical management. These subsystems of the Medical System are described in further detail in Table 2.

Table 2 Habitat Medical System Description

Subsystem	Description
Clinical Care	Provides in-mission capabilities for the prevention, diagnosis, treatment, monitoring, and long-term management of medical conditions.
Imaging	Provides in-mission capabilities for diagnostic imaging in support of the provision of clinical care. Includes all hardware, software, and analysis capabilities required for the capturing and processing of diagnostic images.
Laboratory Management	Provides in-mission capabilities for laboratory analysis in support of the provision of clinical care. Includes all hardware, software, and analysis capabilities required for the collection and processing of biological samples.
Pharmacy Management	Provides in-mission capabilities for the administration of pharmaceuticals in support of clinical care. Includes all medications and the mechanisms used to prepare and deliver them and track their use.

3.1.6 Assumptions

The assumptions for the Mars Renal ConOps capture mission and operations characteristics that have not been explicitly defined by stakeholders or driving documentation and are as follows:

1. Risks integrating with the Renal Stone Risk are green for Mars missions (e.g., Nutrition, Pharmacy, Bone).
2. There is no definitive care option once the astronauts leave Earth (i.e., little to no possibility for an abort)
3. Both diagnostic and propulsive ultrasound capabilities are available and CMO is able to detect a renal stone in the ureter. Additionally, propulsive ultrasound is FDA approved by this time and found to be successful in relocating renal stones in ureteropelvic junction or proximal ureter back to kidney in spaceflight
4. Renal stone prevention measures will include pre-flight and in-mission ultrasound screening and the regular use of anti-resorptive medications and potassium citrate. Pharmaceutical stability and pharmacokinetics/pharmacodynamics (PK/PD) considerations are outside the scope of the renal risk. Here, it is assumed that pharmaceutical stability and PK/PD are adequately addressed
5. The available exercise capabilities will be comparable to those available on the ISS.
6. Drinking water will be available for adequate hydration and can be up-titrated to decrease the risk of renal stones (up to 3.5 L/day per crewmember for a high-risk crewmember)
7. Urine dipstick for the detection of urinary calcium oxalate levels will be available as a resource (at a minimum) and will remain stable throughout the duration of the mission.
8. Point of care blood tests are available to evaluate for a complete blood count and basic metabolic panel.
9. Pharmaceuticals for renal stone prevention/treatment will be available and will fit within the mass and volume constraints of the medical system. Pharmaceutical stability and pharmacokinetics/pharmacodynamics (PK/PD) considerations are outside the scope of the renal risk. Here, it is assumed that pharmaceutical stability and PK/PD are adequately addressed
10. The sodium in the diet will be comparable to that in the diets of astronauts on the ISS.
11. Familiarization and just-in-time training capabilities for renal stone detection will be available
12. The crew will include two Crew Medical Officers (CMOs)
13. The CMOs will have had prior, ground-based training on ultrasound use and nephrostomy tube placement.
14. The astronauts have no previous history of significant renal stones and do not have metabolic or anatomic abnormalities related to the renal or urinary systems.

15. Crewmembers will be able to view a database of health records and medical data during the mission. This information can be stored either in a local database in the vehicle and habitat or a shared database with earth. This is important for administering health care when needed in a delayed communications paradigm. Updating crew health data refers to a crewmember sending health records and data to the database manually or via automated means.
16. A four-person crew is assumed, with the option of both females and males that could be of different nationalities.
17. To improve the in-mission scanning capability and accuracy, pre-flight scans of each crewmember will be loaded into the in-mission ultrasound system.

3.2 Mission Phases and Environments

This ConOps focuses primarily on the Mars transit phase of the mission and secondarily on the Martian surface phase. The environmental parameter assumptions are described in Table 2 below, many of which have been pulled from HEOMD-007 and HEOMD-415.

Assumptions	Name	Description
Travel Duration	Travel to the Martian Surface	Mission duration is expected to be 730-1224 days (HEO-DM-1002).
Crew Composition	Number of Crew Members	Four crew members per mission (2 orbital, 2 planetary surface)
	CMOs	Minimum of 2 CMOs during all mission phases
Communications	Nominal Communications	Due to the distance from, Earth-nominal communications will have a ~20-minute one-way delay.
	Off-nominal Communications	Anything above nominal (> 20 minutes) communications.
	Communication Outages	Due to the placement of Earth and Mars, communications may be unavailable or impossible when blocked by solar activity (solar conjunction). Mission objectives and activities must be planned around the position of Mars, Earth, and the sun. The risk of communication loss could be a result of unplanned activity or poor planning if solar conjunction is not considered. This loss of communication could last anywhere from a day to several weeks.
	Bandwidth	There will be a maximum defined bandwidth that will limit communications between the crew and the ground.
Evacuation	Emergency Evacuation	There will be no emergency evacuations.
Medical System Technologies	Autonomy	The Medical System will allow the crew autonomy over their medical care.
	Technological Abilities	Technologies, such as artificial intelligence, could assist in various situations and activities involving the crew. The use of technological assistance could be a lifesaving asset during a mission. The use of AI to create probabilities and models may aid the crew in decision making or consultation.
	Crew Health and Performance Management	Crew health and performance will be maintained throughout all mission phases, including during communication delays to Earth, and in an environment

Assumptions	Name	Description
		that does not allow emergency evacuation or terrestrial medical assistance.
	Modularity	Modular components can be transported to the site of an injured member if necessary.

3.3 Renal Scenarios

These ConOps scenarios present a broad, but not comprehensive, set of activities and functionalities envisioned for a Mars Design Reference Mission (DRM) and guide successful mission design as it relates to the support provided for renal stone prevention, diagnosis, monitoring and treatment. The scenarios are characterized by the timing, location, scheduling and activity systems they describe, as detailed below in Table 3.

Table 3 Scenario attributes

Attribute Category	Attribute	Definition
Activity Timing	Preflight	Occurs prior to launch
	In-missionmission	Occurs between launch and landing on Earth
	Postflight	Occurs after landing
Activity Scheduling	Planned	Expected or required to occur
	Unplanned	Not expected nor required to occur but addressed on an as-needed basis
Activity Systems	Ground	Requires only Ground CHP domains
	Autonomous	Requires only Habitat CHP domains
	Semi-autonomous	Requires Ground CHP and Habitat CHP domains
Activity Location (In-mission Only)	Extravehicular	Occurs external to the vehicle or habitat
	Intravehicular	Occurs internal to the vehicle or habitat

The scenario tree shown in Figure 2 outlines the 6 scenarios according to Table 3.

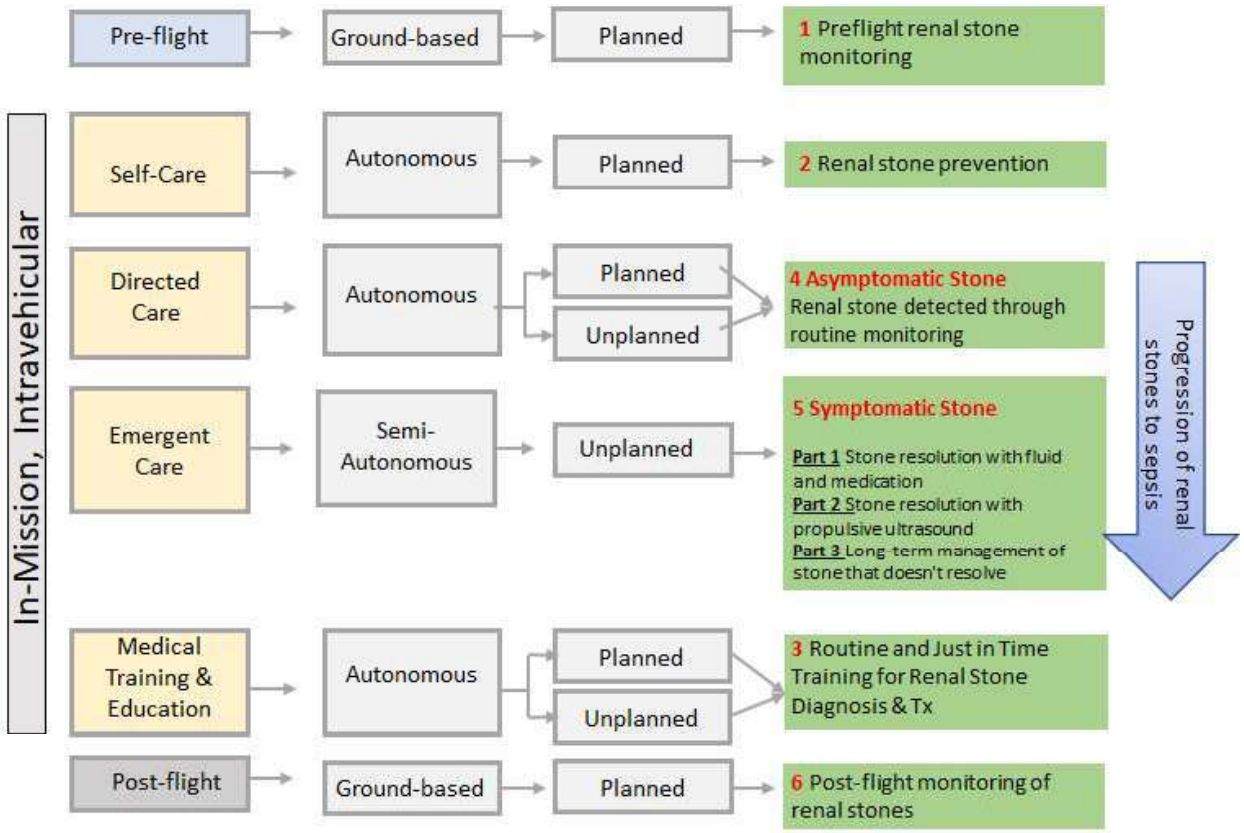


Figure 2 Scenario tree

Figure 3 below displays an outline of the scenarios from the standpoint of the progression of renal stones from a best-case to worst-case scenario.

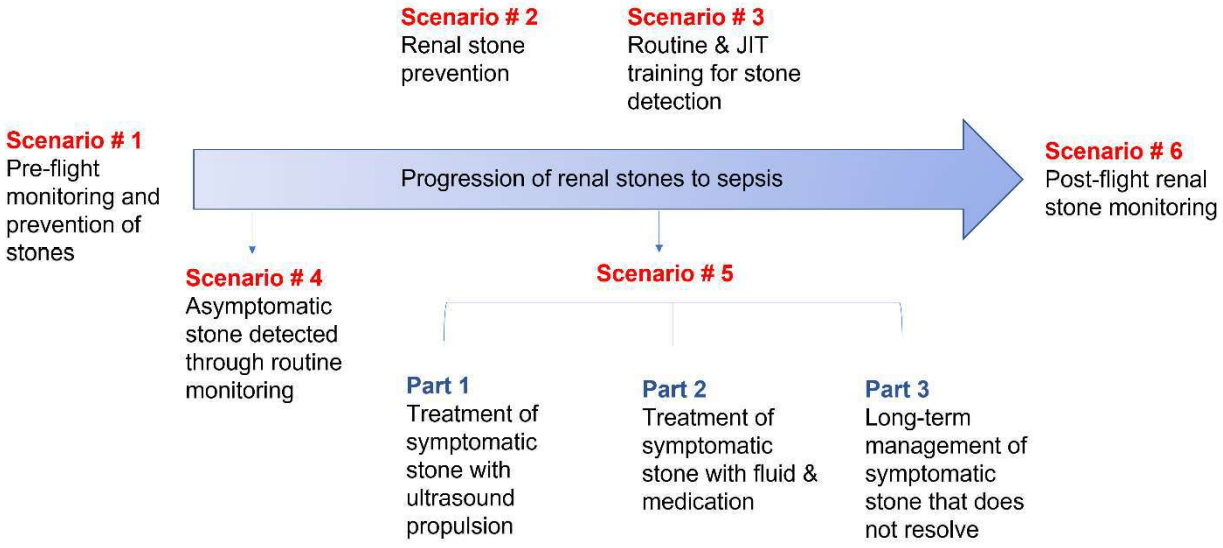


Figure 3 Scenario Tree Outline

3.3.1 Scenario 1: Pre-flight Monitoring and Prevention of Renal Stones

Currently, astronauts receive yearly screening ultrasounds to evaluate for possible mineralized renal material (MRM), and, additionally, receive a screening ultrasound at 6 months before launch. According to the NASA Clinical Practice Guideline for the Monitoring and Management of Renal Stones, history of recurrent stones, multiple stones, a metabolic abnormality, or anatomic abnormality may be cause for restriction of fight duties. In the same way, for astronaut candidate applicants, a history of a renal calculus is disqualifying. In current astronauts, it is disqualifying for flight until resolved.

In this case, the planned crewmembers of a Mars transit flight receive an ultrasound approximately 6 months prior to launch. They have no history of kidney stones, or metabolic/anatomic renal or urologic abnormalities. Urinary oxalate levels have remained in the low-risk status. No significant MRMs/renal stones were seen on the crewmembers' ultrasounds, so they are cleared for flight from a renal and urological perspective.

3.3.2 Scenario 2: Renal Stone Prevention

Two months into the Mars transit phase of the flight, a crewmember is notified by the scheduling system that her daily exercise activity is scheduled to start in 10 minutes. She acknowledges the notification through the scheduling system and then translates to her private crew quarters to prepare for this activity. She dons her exercise clothes, retrieves her headphones and fills a water bag using the potable water dispenser before translating to the exercise system.

The crewmember touches the user interface display to activate the exercise device. The interface displays her personal exercise prescription, which had been loaded into the Medical System pre-flight and has been modified periodically as needed while in transit. The exercise prescription was established for each crewmember to ensure maintenance of aerobic capacity and cardiovascular health, as well as mitigate bone loss, which also aids in the prevention of renal stone formation. She currently exercises 2.5 h/day. As she exercises, she makes sure to drink plenty of water from her drink bag. In addition to exercising to mitigate bone loss, staying adequately hydrated is another important preventative measure for renal stone formation. Her baseline water intake is 2.5-3 L/day.

Upon exercise completion, the crewmember disconnects the loading mechanism for the exercise device and stows the harness. She heads to the hygiene area to get cleaned up and don her other clothes before heading to the kitchen area for dinner with her crewmates. The crew menus are carefully selected preflight (and adjusted as needed inflight) to ensure adequate consumption of foods that meet certain thresholds for important micronutrients. In particular, for renal stone mitigation, levels of potassium, citrate, oxalate and sodium are carefully monitored. The crewmember also follows guidelines for bisphosphonate intake.

In addition to adequate hydration and exercise, as well as carefully monitored nutrient intake, the crewmember also self-administers periodic urinary chemistry tests to identify elevated urinary calcium oxalate levels, which could lead to renal stone formation. Periodic ultrasounds are also performed to assess the presence of asymptomatic stone formation. So far into this flight, the crewmember has had no elevated calcium oxalate levels or indication of stone formation on ultrasound, so no changes are made to her exercise prescription, water and nutrient intake, urine chemistry testing or ultrasound scan frequency. This decision is confirmed by use of the Glenn model, which shows a low risk of renal stone formation for this crewmember based on the required input parameters (e.g., urine chemistry testing, fluid intake).

3.3.3 Scenario 3: Training for Renal Stone Detection

In preparation for their upcoming flight, the crewmembers are scheduled for an ultrasound training session to review the procedures for renal stone detection. During the training session, the crewmembers take turns performing scans on each other, with limited supervision from the support team (e.g., flight surgeons and training managers). They are directed by the training module on how to properly prepare for and perform the scan, as well as how to use the medical system to analyze the scans and make any appropriate diagnoses.

The crew is 3 months into the Mars transit phase of the mission, and the crew medical officers (CMOs) have a scheduled medical familiarization training session to review the procedure for performing routine ultrasound scans to assess renal stone formation. The two CMOs translate to the module of the transit vehicle that houses the medical equipment and locate the ultrasound device and necessary accessories to perform a training scan. They also access the renal stone detection training tutorial in the medical system. They take turns reviewing the training material and performing scans on each other until the training objectives are complete, namely, the achievement of correct visualization of the kidneys and collecting system. They indicate completion of the training in the scheduling system, which sends an update to the Medical System records. The updated training record is downlinked to the Ground Medical System, thereby synchronizing the onboard and ground electronic health records. The CMOs stow the ultrasound equipment and move on to the next scheduled task for that morning.

One month later, a crewmember reports abdominal pain of an intensity and at a location that makes the CMO suspicious of a potential renal stone. A decision is made to perform an ultrasound examination to assess stone formation. Prior to performing the assessment, the CMO decides to perform a just-in-time training session to review the procedural steps performing an ultrasound scan for renal stone detection. He accesses the Medical System from his personal computing device and locates the training material for this procedure. He reviews the material, which includes procedural guidance on where to position the probe, the specific images that need to be captured, and example images of expected anatomy as well as anatomy indicative of renal stone presesnce. After completing the training, the training record is updated in the Medical System. He locates and unstows the ultrasound equipment and asks the symptomatic crewmember to join him in the medical bay to perform the scan. The symptomatic crewmember is placed on an oxygen mask during the scan to aid kidney stone's twinkling effect ultrasound uses to identify kidney stones. The images are interpreted by the CMO with input from onboard AI algorithms (informed by preflight baseline scans), and the images are also sent down to the Ground for secondary review.

3.3.4 Scenario 4: Renal Stone Detection Through Routine Monitoring

A crewmember and a crew medical officer (CMO) are alerted via their personal computing devices that the crewmember has an upcoming scheduled renal ultrasound exam that is periodically performed during the mission as a preventative measure. They translate to the location in the Mars transit habitat where the medical equipment and supplies are stored and retrieve the ultrasound machine and medical computing device to prepare for the exam.

The CMO enters her credentials into the medical computing device and opens the crewmember's record in the medical exam application. As she prepares for the exam, she elects to receive direction from the Medical System regarding imaging device configuration and how to capture the required images. The CMO then begins the exam, and all captured images (from US and CT scans) are automatically stored in and analyzed by the Medical System, which uses his pre-flight baseline images as a reference. The collected data are also scheduled for automated downlink to the Ground Medical System when communication becomes available.

The CMO identifies a small (2 mm) renal stone in the renal collecting system that is also verified by the analysis performed by the Medical System. She asks the crewmember whether he has experienced any renal stone-associated symptoms, which he denies, and also asks him to perform a routine spot urinary calcium check to measure oxolate levels. This test result comes back indicating low risk for stone formation; however, because a stone was found via ultrasound, the CMO places the crewmember on a protocol provided by the Medical System of increased fluid intake closer to 4 L/day, potassium citrate, and more frequent spot urinary calcium checks and ultrasound scans. Additionally, a point of care blood test is performed, looking for elevated white blood cell count, creatinine level, and electrolyte levels to evaluate for the secondary affect of infection and/or acute kidney injury due to kidney stone. These values are within normal limits. The crewmember is also placed on a stricter nutrition protocol to decrease calcium intake, and she was told to eliminate consumption of tea in particular due to elevated oxalate levels. These mitigation measures are initiated in an effort to keep the stone from increasing in size and even possibly to reduce the size.

If a urine spot check came back positive or an ultrasound scan showed the stone to be increasing in size or obstructing, the increased fluid intake and potassium citrate dose would be titrated accordingly. Fortunately, the stone remains stable in size for the remainder of the mission, and the urine chemistry tests always yield negative results.

3.3.5 Scenario 5: Treatment of symptomatic renal stone

PART 1: Tx of stone with ultrasound propulsion

While performing routine scientific experiments during the return to Earth transit phase of a mission, a crewmember experiences right-sided flank pain. She continues her work, attempting to manage the pain by changing position and stretching, but the pain does not subside. The crewmember contacts one of the CMOs and requests an evaluation, and they both translate to the medical bay. The CMO employs the Clinical Decision Support System (CDSS) within the Medical System and collects a history of symptoms, as well as performs a focused physical exam. Based on the input, the CDSS provides a differential diagnosis, with kidney stones presenting as the most likely cause of the crewmember's pain and advises testing urine for signs of infection or kidney stone and ultrasound to look for a kidney stone or evidence of a stone causing urinary obstruction (hydronephrosis). The CMO locates the ultrasound equipment and prepares for the exam, which does reveal a **6-mm** kidney stone in the **proximal ureter**.

The urinalysis exam, which was performed to detect CaOx levels, hematuria or infection, was negative. Additionally, a point of care blood test is performed, looking for elevated white blood cell count, creatinine level, and electrolyte levels to evaluate for the secondary affect of infection and/or acute kidney injury due to kidney stone was performed and within normal limits. The CMO reviews the clinical diagnostic notes and re-engages the CDSS to determine the next treatment step. Because the stone is located in a favorable position (proximal or distal ureter) for ultrasound propulsion to be a treatment option, this is the step recommended by the CDSS. The goal of ultrasound propulsion is to move the stone from its obstructive position and facilitate its passage either into the bladder (in the case of very small stones or debris, potentially in distal ureter near bladder) or back into the kidney in the case of symptomatic proximal ureteral stones.As he prepares to perform this procedure, the CMO recruits the other CMO on board to assist. They are guided in the procedure by the Medical System, which displays the procedural instructions. If the procedure is successful, the stone will be redirected back into the kidney from the ureter, thereby decreasing pain and obstruction. However, after multiple attempts, the CMOs are unable to reposition the stone back into the kidney with the ultrasound.

PART 2: Tx of stone with fluid and medication

The CMO consults the CDSS to determine the next treatment step. Because ultrasound propulsion of the stone failed, the next step is traditional treatment, which consists of administering medication along with increased fluid intake of at least 4 L/day, using IV fluids if oral intake is not tolerated. The crewmember is started on tamsulosin (0.4 mg/day; alpha-blocker) to attempt to hasten the stone passage along with analgesia for pain management and an anti-nausea medication as needed. This treatment plan would be effective until passage of the stone, which would be within about 14 days. The goal would be to manage the crewmember's pain and nausea to a degree such that the crewmember could resume normal duties. However, the crewmember's pain only intensifies over the next 2 weeks to the extent that it is affecting the ability to carry out mission objectives, despite the above pain medications and even introduction of an opioid for symptomatic management.

PART 3: long-term mgmt. of stone that does not resolve

The CMOs both consult the CDSS again. With attempts to manage the pain with medication and facilitate stone passage with tamsulosin and increased fluids having failed, the CDSS suggests repeating the ultrasound to check for stone location and kidney pathology. One of the CMOs sends a message to the Ground to notify flight controllers, including the flight surgeon, of the crewmember's status, including the ongoing pain. He then prepares for the ultrasound exam by locating and unstowing the necessary equipment per the guidance provided by the medical system, as well as preparing the crewmember on the exam table using the attached restraints. As the exam equipment is being prepared, in-situ blood analysis is also performed, including assessments of kidney function, electrolyte levels, and blood cell counts, which indicate signs of infection.

The CMO commences the ultrasound exam using the appropriate probe and captures images that are analyzed by the Medical System software. Based on the analysis results and the CMO's recognition of the dilated renal pelvis and calyx as signatures from the training information, the CMO diagnoses the crewmember with hydronephrosis of the kidney. The CMO also realizes that the stone is no longer visible at the proximal ureter/ureteropelvic junction, where it had first been found about 2 weeks prior. The repeat urinalysis showed increased white blood cells and red blood cells, significant for likely secondary infection. Labs show a mild elevation in WBC count and a slightly

elevated creatinine level, signaling an acute kidney injury. Blood electrolytes are within normal limits. In this situation, there is likely to be an obstructing kidney stone causing hydronephrosis with secondary infection.

Antibiotics are immediately started to address the infection, and the CDSS recommends that a percutaneous nephrostomy (PCN) be performed with ultrasound guidance to insert a tube to drain urine percutaneously to prevent worsening infection/sepsis. One of the CMOs sends a message to the Ground to notify them of the decision to perform this procedure emergently, and both CMOs begin preparing the medical bay for the procedure and locating the necessary supplies.

The crewmember is prepped for the procedure by placing him in the prone position, and 1% lidocaine is administered for anesthesia. Patient given a dose of pain medication prior to procedure. An 18G needle is inserted through a microcatheter into the dilated calyx using ultrasound guidance with a linear probe. The drainage tube is inserted without complications, and pain medication is administered for post-procedure pain relief. To keep the catheter clean, it is flushed 3-4 times a day with 20 mL of saline and drained with intermittent suction. Crewmember did have some task time affected during the period of PCN placement, but he was able to complete most assigned tasks. One month after tube placement, the crewmember performs a routine straining of his urine and finds that he has passed the stone. Upon consult with the CMO, it is determined to leave the tube in place for the remaining 2 weeks of the transit back to Earth to allow for the formation of granulation tissue for at least 6 weeks after placement.

3.3.6 Scenario 6: Post-flight Renal Stone Monitoring

Upon arriving back in Houston after their mission, the crewmembers report to the JSC Flight Medicine Clinic for additional postflight medical data collection and testing. The crewmember in Scenario 3.3.5 with the PCN is followed closely by urology within 2 days of landing for an evaluation and further workup as well as removal of the drainage tube. The clinic staff collect routine post-flight blood and urine samples, and the flight surgeon as well as subject matter experts and specialists, periodically perform additional postflight exams to assess crewmember health and readaptation to Earth's gravity. One of these exams is an ultrasound assessment, performed by urologists, to monitor for possible renal stone formation that developed in-mission.

The flight surgeons assigned to the crewmembers perform these assessments shortly after landing and then periodically thereafter and ensure that the crewmembers are continuing their renal stone prevention measures (including good water intake, adequate exercise, and nutritional supplementation).

APPENDIX A1: ACRONYMS AND ABBREVIATIONS

CTP	Common Technical Process
DRM	Design Reference Mission
CaOx	Calcium oxolate
CDSS	Clinical Decision Support System
CHP	Crew Health and Performance
CMO	Crew Medical Officer
ConOps	Concept of Operation
CT	Computed tomography [scan]
DRM	Design Reference Mission
ExMC	Exploration Medical Capability
FDA	Food and Drug Administration
HEOMD	Human Exploration and Operations Mission Directorate
HMTA	Health and Medical Technical Authority
HRP	Human Research Program
HSRB	Human System Risk Board
ISS	International Space Station
JSC	[Lyndon B.] Johnson Space Center
L	liter
mg	milligram
mm	millimeter
MOG	Medical Operations Group
MRM	Mineralized Renal Material
NASA	National Aeronautics and Space Administration
OCHMO	Office of the Chief Health and Medical Officer
PK/PD	Pharmacokinetics/pharmacodynamics
RCT	Risk Custodian Team
SD	Mail designation for Space Medicine Directorate
SE	Systems Engineering
STD	Standard

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