RESEARCH ARTICLE

Urologic Innovation in the Spaceflight Environment: Challenges, Opportunities, and Future Directions

Authors

Zachary B Kahlenberg, MD[1] : Octav Cristea, MD, FRCSC[2] : Danielle J Carroll, MD, FAWM[3],[4,5] : Emmanuel Urquieta, MD, MS, AFAsMA[6],[7] : Nabil K Bissada, MD[8] : Jeffrey A Jones MD, FACS, FACPM, FAsMA[9]

Affiliations

[1] Baylor College of Medicine – Department of Surgery
[2] Emory University School of Medicine – Department of Surgery
[3] University of California San Diego – Department of Surgery
[4] University of Colorado Boulder – Department of Aerospace Engineering Sciences
[5] Orbital Biodesign, LLC.
[6] Translational Research Institute for Space Health
[7] Baylor College of Medicine – Department of Emergency Medicine / Center for Space Medicine
[8] Baylor College of Medicine – Department of Urology
[9] Baylor College of Medicine – Department of Urology / Center for Space Medicine

Corresponding Author:

Jeffrey A Jones, MD, FACS, FACPM, FAsMA
OCL Deputy Executive for Inpatient Services
Chief of Urology- OCL/MEDVAMC
Professor Baylor College of Medicine
Scott Dept of Urology/Center for Space Medicine
Jamail-Abramson Chair in Urology Research
Captain, US Navy Reserves
Fleet Logistics Support Wing Surgeon
USNR Aerospace Medicine Specialty Leader

Office VA: 713 791-1414 #2-4196
BCM: 713 798-8425
Email: jajones@bcm.edu

ABBREVIATIONS

BWL – Burst Wave Lithotripsy
EVA – Extra-Vehicular Activity
Gy- Gray
ISS – International Space Station
JAXA – Japanese Aerospace Exploration Agency
LEO – Low Earth Orbit
mSv – milliSieverts
NASA – National Aeronautics and Space Administration
NSAID- Non-Steroidal Anti-Inflammatory Drug
ONWM – Off- Nominal Waste Management System
Sv- Sieverts
STS – Space Transportation System
UP – Ultrasonic Propulsion
UWMS – Universal Waste Management System
UCD – Urine Collection Devices
WCS – Waste Collection System

ABSTRACT

The coming decades are poised to usher in an era of commercial spaceflight and extended duration missions beyond low-earth orbit. Urologic challenges and conditions have been central to the history of human spaceflight, and their effective management will continue to play a key role in future endeavors. Voiding equipment, such as the Universal Waste Management System aboard the International Space Station, is emblematic of the significant technical strides that have been made to improve the usability and functionality of non-terrestrial waste elimination and containment devices. Detailed investigations over the past few decades have demonstrated that crew members are at an increased risk of developing nephrolithiasis due, in large part, to the effects of microgravity. Renal calculi and their potentially debilitating effects represent one of the most significant urologic complications that could impact the success of future long duration missions. Other urologic conditions, such as urinary tract infections, urinary retention, and urinary incontinence have been well documented during flight and pose their own challenges. While preventive measures remain central to all mitigation strategies, imaging and treatment modalities such as a S-Mode ultrasound, burst wave lithotripsy, and ultrasonic propulsion are being developed and evaluated as in-flight countermeasures for urologic pathology. Parabolic flights have been conducted to develop and evaluate the feasibility of using surgical and endoscopic techniques to treat urologic conditions in microgravity. Although less often discussed, occupation-related delayed conception and the risk of radiation-induced gamete damage suggests that there may be a need for NASA to adopt a policy for Assisted Reproductive Technology for both male and female astronauts. The last 60 years of human spaceflight have provided a unique opportunity for discovery and medical technology innovation. This paper serves to highlight the advancements that will help pave the way for the next 60 years of human spaceflight.

1. INTRODUCTION

Since the inception of NASA in 1958 and the subsequent establishment of the human spaceflight program, there has been an ongoing need for the development, innovation, and refinement of in-flight medical technology, particularly with regard to urologic concerns. As the broader aeromedical community has learned from past crewed missions, the microgravity environment leads to alterations in the 'normal' voiding physiology experienced on the Earth's surface. In addition to posing a challenge for the elimination and collection of human waste, the changes observed in the physiology of urinary elimination have contributed to the development of a number of urologic health conditions that pose a risk to astronaut health and performance. These conditions will become especially salient as mission duration continues to increase and as mission profiles shift to exploration beyond low-earth orbit (LEO) in the decades to come. In this review, we discuss the most common urologic challenges and conditions affecting spaceflight crews and highlight the variety of management and mitigation strategies that have been proposed and employed, including imaging and diagnostic innovations, as well as surgical treatment modalities. We conclude our review with a discussion of future challenges and opportunities in the field.

2. VOIDING IN MICROGRAVITY AND ASSOCIATED EQUIPMENT

Voiding physiology in microgravity differs in important ways from its terrestrial counterpart. Without gravity, capillary action, aided by negative pressure, becomes the predominant mode by which urine travels ex vivo.[1,2] As such, there was an early need for the development of in-flight waste elimination systems. In the early 1960s, urine collection devices (UCDs) analogous to current condom (aka "Texas") catheters were utilized to collect urine within the pressure suit. However, these UCDs were prone to leakage and unsuitable for female use due to a lack of a watertight interface. UCDs were subsequently replaced with other urine storage devices, such as Disposable Absorption Containment Trunks and Maximal Absorptive Garments (MAGs). Although MAGs (aka "space diapers") were worn in NASA's Launch and Entry and Extravehicular Activity space suits, they were made famous for a "discommoding" reason: this technology reduced the morbidity of many with earthbound incontinence. It was not until the 1980s that onboard Waste Collection Systems (WCS) began to resemble a toilet. The USSR preceded the United States in space toilet design and implementation: the first Soviet orbital toilets were custom-made, such that a number of cosmonauts had their buttocks measured for their personal toilets. In the absence of gravity, airflow is utilized to aid in the collection of waste. These WCSs allow for the collection and separation of both urine and fecal matter without the use of gender-specific interfaces.[3] On the International Space Station (ISS), urine separated from fecal matter can then be recycled and converted into drinking water.[4]

NASA's need for constant innovation and the improvement of existing technology led to the first Space Transportation System (STS) Shuttle Orbiter WCS, followed by the development the Universal Waste Management System (UWMS) for the ISS in 2015 (Figure 1). The development of the UWMS was a partnership between the Advanced Exploration Systems program at NASA headquarters, the Orion Program, the ISS Program, and Collins Aerospace. Initial objectives for the UWMS were for it to be lighter, smaller, more efficient, easily maintainable, and to improve the human interface relative to that of prior space toilets. Weighing in at 115 lbs., the UWMS is 50 lbs. lighter than the Shuttle WCS. In addition to reducing total mass, the UWMS utilizes a smaller footprint of 5 cubic feet relative to the 12 cubic feet of the Shuttle WCS.[5] The use of highly efficient, low friction fans in the dual fan separator component allows the UWMS to achieve power targets of 274 watts for steady-state operation and 380 watts for peak power.[5] Another important aspect of the UWMS was a focus on crew interfaces with the device. Even before the initial start date of the project in 2015, NASA had already conducted extensive crew evaluations on the commode seat and the urine funnel.

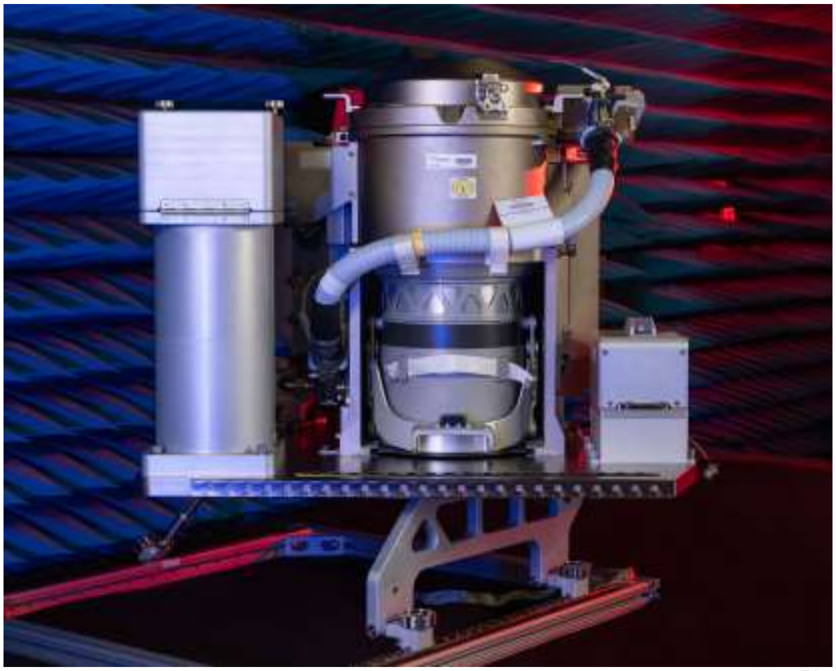

Figure 1 - UWMS with Integration Hardware for use on ISS.[52]

In addition to waste management advancements onboard the spacecraft, NASA's Orion program is aiming to develop a solution for waste storage and containment in the setting of vehicle cabin depressurization scenario for emergent Lunar-Earth return in which astronauts may be forced to remain inside their pressure suit until landing back on Earth. An external device called the Off-Nominal Waste Management System (ONWM) aims to achieve just that. The ONWM was created and is currently being tested to allow for the controlled removal and storage of urine from a pressurized suit in the event of a depressurization scenario for up to four crew members and a maximum of six days. The ONWM utilizes both suit-internal and suit-external hardware to be able to achieve the end result of urine evacuation away from the pressurized suit (Figure 2). The suit-external hardware is comprised of a series of flex hoses and quick disconnects to facilitate the flow of urine from the pressurized space suit to the pressure-less external environment. The pressure differential from the pressurized suit to the depressurized cabin acts as the main driving force for the flow of urine. Finally, a 1 liter bladder tank with a four way valve is utilized as a means to draw urine away from the crewmember while simultaneously serving as a rigid barrier between the pressurized suit and the pressure-less enviornment.[6] The external bladder tank was designed with an internal flexible bladder that serves to divide the tank into two hemispheres thereby separating the pressurized suit from the external vacuum of space. The four way valve controls the flow of urine from the space suit to the lower pressure tank and then from the tank to the zero-pressure environment in the cabin, all without jeopardizing the pressurized environment within the space suit.[6]

Figure 2 - ONWM Functionality Evaluation.[53]

3. URINARY TRACT INFECTIONS AND VOIDING DYSFUNCTION

Urinary tract infections (UTIs) have been observed throughout the history of human spaceflight. Fred Haise, the lunar module pilot of Apollo 13, developed a urinary tract infection during the mission that progressed to pyelonephritis, with lethargy, fevers, and flank pain persisting throughout the duration of the mission. Post-mission urine cultures demonstrated *Pseudomonas aeruginosa* as the causative organism, and he was subsequently treated with a successful course of antibiotics.[7] In 1985, Russian cosmonaut Vladimir Vasyutin underwent a pre-mature de-orbit from the space station Salyut 7 due to a case of prostatitis.[1] Over the years, a number of US_astronauts aboard the Space Shuttle and ISS have been diagnosed with UTIs, all of which have been treated successfully with antibiotics and none of which required early mission_termination.[8] On the Space Shuttle, diagnostic capabilities were limited to urine dipsticks that could be used to confirm the presence of pyuria, urinary nitrites and blood. Diagnostic modalities aboard the ISS are more robust, allowing for basic biochemical analysis of the blood and, with guidance from the ground, the use of ultrasound to image the genitourinary organs to rule out any complicating factors, such as a concomitant renal calculus.[9] Treatment options include oral antibiotics, such as ciprofloxacin, as well as broad spectrum intra-venous antibiotics, such as ceftriaxone, imipenem and amikacin.[8]

A number of cases of urinary retention have been observed during flight, several of which have required in-flight intervention via urinary catheterization. The causes of urinary retention are multifactorial and include dehydration, delayed voiding (due to work schedules or WCS availability), the use of various pharmacologic agents, and underlying predisposing factors, such as benign prostatic hyperplasia.[1–3] Anticholinergic medications (scopolamine and promethazine), which are used to treat space motion sickness, and alpha-adrenergic agonists, which are used to treat nasal congestion and head fullness, can both contribute to the development of urinary retention. Urinary retention can result from or be the cause of a urinary tract infection. Left untreated, acute urinary retention can be incapacitating and lead to a number of sequalae, including acute renal failure. Shuttle medical kits used to manage acute urinary retention were mainly limited to indwelling urethral catheterization. More recently ISS Medical Accessory Kits have also included non-ballooned straight catheters to allow clean intermittent catheterization without the necessity of leaving an indwelling catheter. At least one spaceflight extra-vehicular activity (EVA) included a crewmember utilizing an indwelling urinary catheter during the spacewalk due to pre-EVA urinary retention. In the event that initial urethral catheterization fails, contingency management procedures for urinary retention have been developed and tested in simulated microgravity conditions by using ultrasound guidance and a percutaneously inserted suprapubic catheters.[3] Moving forward, an emphasis on pre-flight screening and risk mitigation are of importance to decrease the incidence of in-flight urinary retention as well as urinary tract infection.

According to data from Space Shuttle missions STS-1 through STS-114 there were a total of 9 cases of in-flight urinary incontinence, all of which occurred in female crew members. The majority of these cases were described as stress urinary incontinence. Of note, many of these reports describe minimal post-void wetness that was noted immediately after a desired void; it is unclear if these cases represent true stress incontinence or if they resulted from the collection of urine in the distal vagina (due to lack of gravitational forces) that was subsequently expelled with increased abdominal pressure. There have been discussions with female crewmembers about applying perineal pressure after completion of voiding, in order to assist in clearing any vaginal backflow of urine when using the various funnel adaptors attached to the reduced pressure hoses of the various on-orbit waste management systems. These crewmembers typically did not experience any urinary leakage in full gravity. It was therefore speculated that the new urinary soiling in microgravity may have been due exclusively to vaginal pooling of urine during micturition. Currently, clothing and other protective measures prevent leaked urine from entering and contaminating the orbiter atmosphere, as well as from damaging electronic hardware which otherwise might have presented a health hazard for the crew and further jeopardized mission outcomes.

4. URINARY CALCULI

Formation of urinary calculi represents one of the most consequential medical conditions that can affect spaceflight crews. Urinary calculi develop when the complex biochemical environment in the urine becomes supersaturated with minerals that can precipitate out of solution to form crystals. A variety of factors can contribute to this state, including decreased urinary volume, increased concentration of stone forming/promoting agents (e.g. calcium, oxalate, sodium, uric acid; [Figure 3]), decreased concentration of substances that inhibit stone formation (e.g. citrate), or anatomic abnormalities that promote urinary stasis.[10] Multiple aspects of the spaceflight environment contribute to the risk of calculus formation, including microgravity, dehydration, and fluid shifts.[11] Of these, the most salient and intractable is microgravity. Bone demineralization in weightlessness is a well-described phenomenon, whereby the absence of gravity-induced loading of the musculoskeletal system leads to bone resorption, calcium loss, and calcinuria-increasing urinary supersaturation .[12–14]

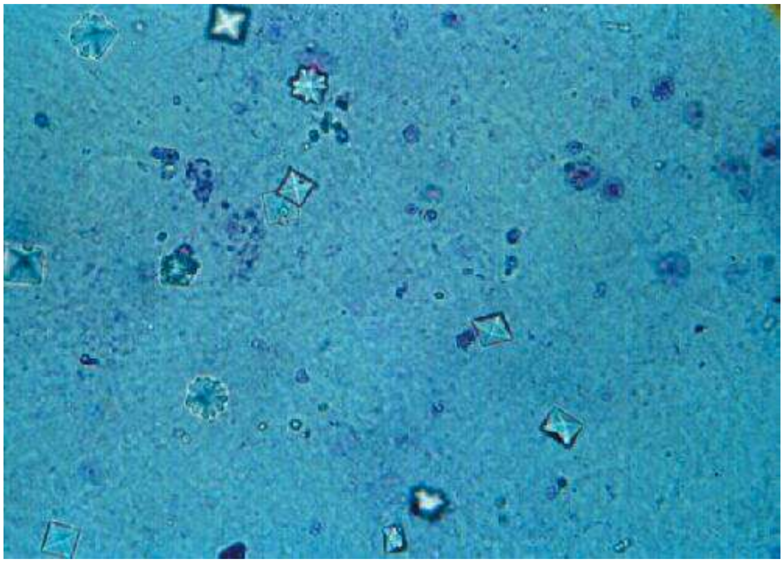

Figure 3 - Calcium oxalate crystals and one uric acid crystal under magnification. These are the most likely minerals to precipitate during microgravity.[54]

Renal calculi may initially be asymptomatic but can present with debilitating symptoms when passed into the renal pelvis or the ureter and cause an obstruction of the affected kidney. This can result in intractable pain, nausea, and vomiting. If combined with a superimposed urinary tract infection, it can lead to urinary sepsis and even death. The occurrence of a symptomatic renal calculus is, therefore, not only of consequence to the health of the affected crewmember, but to the mission integrity as a whole.[15] NASA's probabilistic risk assessment model identifies renal calculi formation as one of the events most likely to cause a medical evacuation from the ISS.[16] In addition, crews participating in long-duration missions beyond LEO in the coming decades may not have medical evacuation as a readily available option. The development of strategies to prevent urinary calculi and to manage them during flight is therefore of paramount importance.

An understanding the fundamental principles underlying stone formation points the way towards potential mitigation strategies. In the general population, up to 10% of adults are afflicted with renal calculi and, among stone formers, over 80% demonstrate at least one abnormal urine biochemical parameter.[17] The rate of stone recurrence is estimated at >50% over the course of a 10 year period[18]; as such, a history of renal stones or the presence of any anatomic abnormality that can increase the risk of stone formation are grounds for rejection during the astronaut selection process[8]. However, despite these measures, a number of astronauts have developed renal calculi. As of 2015, there have been 36 documented renal calculi among 22 members of the US astronaut corps, although to date none have occurred during flight.[8] In 1982, a Russian cosmonaut aboard Salyut 7 experienced what is suspected to have been an episode of renal colic, but the stone passed spontaneously and medical evacuation was avoided.[19] Urinary studies performed on Space Shuttle crews as well as on ISS expedition members have demonstrated a shift in urinary biochemical parameters associated with spaceflight that is conducive to stone formation, including decreased urinary volumes, decreased pH, excess calcium, and decreased citrate levels.[20–22]

Preventive strategies include behavioral, dietary, and pharmacologic measures.[23] Crewmembers are encouraged to maintain adequate hydration status throughout the duration of the mission, and intravenous fluids are available in limited quantities in the event that oral intake cannot be maintained, such as in the setting of severe space motion sickness. The development of increasingly more effective resistive devices, designed to function in microgravity, alongside a rigorous daily exercise regimen, has been successful in improving astronaut bone health and serves to minimize the extent of bone demineralization. A diet that moderates sodium, oxalate, and animal protein intake also serves to promote a urinary environment that is less conducive to stone formation.[23] A number of pharmacologic interventions have also been evaluated during spaceflight. Potassium citrate is frequently used as a preventative measure in recurrent stone formers, functioning by increasing urinary pH and urinary citrate levels. A randomized double-blind placebo-controlled study was conducted on the ISS and space station Mir. This involved 30 long-duration spaceflight crew members who received daily administration of a low-dose (20 mEq) of potassium citrate. Urinary samples collected before, during, and after flight demonstrated decreased urinary calcium levels and increased urinary pH in the treatment group, as compared to controls, indicating that prophylaxis with potassium citrate may decrease the risk of urinary stone formation in spaceflight crews.[24] To date, potassium citrate remains the only pharmacologic countermeasure approved by NASA for in-flight renal stone prevention, and is used in crew members who are felt to be at increased risk for stone formation based on previous history or urinary biochemical parameters.[8] In addition to the above, bisphosphonate therapy during spaceflight has also been evaluated as a measure for mitigating bone loss. Building on earlier research from bed-rest analogues studies,[25] NASA and JAXA researchers collaborated to evaluate the effect of alendronate administration, in combination with resistive exercise training, on bone health and bone resorption indicators among astronauts who spent a mean of 5.5 months on the ISS. The group found that among the 7 astronauts who received alendronate, the expected bone loss was attenuated across all measures, including urinary calcium excretion, which was decreased compared to controls.[26,27]

While prevention remains the central pillar of urinary calculus mitigation strategies, the risk of an in-flight event cannot be completely eliminated. The means for dealing with such an event, should it occur, exist to a limited extent on the ISS, and various interventional strategies continue to be investigated. An in-flight calculus accessory treatment kit available aboard the ISS contains an array of medications that can be used to treat a crew member suffering from an obstructive renal calculus.[8] The kit includes antiemetics, analgesics (including NSAIDs and narcotics), antibiotics, and alpha-blockers, the latter of which have been show to aid in the spontaneous passage of distal ureteric calculi (Figure 4).[28] As previously discussed, intravenous fluids are also available in limited quantity, should they be required to stabilize a dehydrated and unwell crewmember. The goal of all these interventions would be to support the afflicted crew member in the hope that the offending calculus will pass spontaneously.[29]

The feasibility of bypassing the obstructing calculus via placement of a ureteric stent in the microgravity environment has been explored and subsequently demonstrated in a porcine model in parabolic flight.[30,31] However, the feasibility of performing this on human subjects during spaceflight has not been established and the ISS currently does not have the flexible endoscope, dedicated light source or disposable stents required for this procedure; but a multi-purpose flexible endoscope and stent could be easily justified for exploration missions.

Figure 4 - Stability Kit 3 before flight to ISS on STS-121.[55]

5. IMAGING IN SPACE

Imaging technology in the form of ultrasonography is available onboard the ISS, with demonstrated efficacy for obtaining images of the genitourinary system during flight.[9] Newer developments, discussed in greater detail below, seek to blend diagnostic and therapeutic capabilities into a single ultrasound probe to provide a noninvasive method for definitive stone management on upcoming long-duration missions beyond LEO.[32]

Current ground-based technologies for the imaging of kidney stones include plain-film X-rays, Computed Tomography (CT), or ultrasonography. Of these, however, only ultrasonography can be deployed in the spaceflight environment due to mass, power, volume, and cost constraints (Figure 5). Standard B-mode ultrasound has been used on Earth for the detection of kidney stones; despite its enhanced portability and versatility in the spaceflight setting, however, there are limitations in its sensitivity for detecting stones, particularly those that are smaller.[33] To date, NASA has utilized its calculus accessory kit on STS and ISS missions as a means of managing symptomatic nephrolithiasis. As previously described, this accessory kit contains antiemetics (ondansetron, promethazine), analgesics (ketorolac, morphine), antibiotics (nitrofurantoin), among several other pharmacologic agents (tamsulosin, potassium citrate, and lactated Ringer's solution)[34]. While this accessory kit is effective for symptomatic management and treatment of smaller stones that are more likely to pass spontaneously, larger stones may necessitate further treatment to prevent deterioration of the crewmember's condition. To help address the limitations of spaceflight-ready imaging and treatment modalities for kidney stones, researchers at the University of Washington and other academic centers are currently developing technologies such as S-mode ultrasound, burst wave lithotripsy (BWL), and ultrasonic propulsion (UP). [35]

Figure 5 - Inflight utilization of ultrasound imaging. Dr Ashot Sargsyan performs abdominal imaging on NASA/JSC's KC-135, zero-g aircraft.[56]

Traditional B-mode ultrasound, while sufficiently portable to allow for implementation in spaceflight, can be of limited diagnostic utility due to its overall poor sensitivity in stone detection. Unlike S-mode, B-mode ultrasound is mechanically optimized for detection of soft tissue abnormalities, compromising its ability to distinguish firm objects, particularly small renal stones.[33] Conversely, S-mode ultrasound is capable of more reliably detecting subtle changes in high-density structures such as stones, at the exclusion of soft-tissue resolution and contrast capabilities .[36] S-mode ultrasound was developed through the use of a standard flexible Verasonics® ultrasound system and the addition of a custom Density Ray Line Imaging algorithm, overlaid with targeted filtering and smoothing algorithms – a process known as spatial compounding).[35] Although S-mode ultrasound is still undergoing testing, early versions have demonstrated promising results: among renal stones <5mm and 5-10mm in diameter, sensitivity rates of 74% for stone detection and 70% for shadow detection have been observed; 74% of stone measurements and 88% of shadow measurements have fallen within 2mm of CT documented stone dimensions, suggesting good concordance by current terrestrial standards.[37]

While the existing inflight management protocol for nephrolithiasis (pharmacologic intervention alone) may be effective for small stones, planning for upcoming long-duration interplanetary missions mandates the development of a treatment plan for larger stones, for which spontaneous passage is unlikely. The terrestrial standard of care for treatment of large or refractory renal stones includes modalities such as ureteroscopic lithotripsy, percutaneous nephrolithotomy, and shock wave lithotripsy, depending on stone size and location. Due to equipment mass, associated cost with transportation, and level of training required for effective implementation, these options are impractical for spaceflight missions in the immediate future. Burst wave lithotripsy, which employs brief bursts of low-frequency, broadly focused ultrasound, is currently being tested for viability as a noninvasive inflight treatment option for larger kidney stones. Ongoing in vitro studies evaluating BWL-induced fragmentation of artificial stones show promise: following treatment, all resulting stone fragments measured less than 2mm, and 87% were under 1mm in greatest dimension. In vivo studies in pigs have demonstrated the feasibility of real-time imaging feedback during BWL therapy, enabling the operator to monitor for injury while permitting visual confirmation of effective stone fragmentation.[35]

By means of short, focused ultrasonic bursts, UP can be utilized to reposition stones within the collecting system. In an FDA feasibility study of 15 patients in the United States, stones were successfully moved (passed or repositioned to a target location) in 14 of 15 patients; no associated adverse events were reported.[38] While UP alone is not intended to provide definitive management of stones, it may serve as a potent tool to facilitate relief of an acute obstruction, passage of smaller stones, and/or follow-on therapy after BWL stone fragmentation in-flight.

In the near term, until such time as a low-profile, low-mass, flight-ready lithotripsy system is available, management of stone-induced ureteral obstruction must be achieved with temporizing measures, such as placement of ureteral J-J stent to relieve the obstruction. This can be accomplished with a portable ultrasound and flexible cystoscope as was demonstrated in parabolic (0-g simulated) flight on the KC-135 at JSC in 1999.[30] As recently as June 3, 2021, the next generation of low-profile, portable ultrasound equipment – the Butterfly iQ – was launched to the ISS as part of a SpaceX Dragon cargo resupply payload by way of a collaborative partnership with the Translational Research Institute for Space Health.[39] The Butterfly iQ probe plugs directly into a smartphone or tablet, allowing for rapid uploading and transmission of images from the ISS to ground personnel for further analysis and evaluation. While this diagnostic paradigm will need to be adapted to the exploration-class mission setting, the advent of a low-mass, versatile, user-friendly alternative to standard ultrasound equipment provides additional flexibility for scope-based interventions.

6. SURGICAL INTERVENTION IN SPACE

Some urologic issues arising during spaceflight might require interventional treatment. A surgical procedure has never been required or performed on a human in space, however parabolic flights have suggested that surgery would be technically feasible during spaceflight. Parabolic flights can temporarily reproduce microgravity conditions in an aircraft by alternating upward and downward arcs. These flights have been used to model renal stone formation in animals as well as surgical procedures, control of fluids, changes in fine motor control, and restraint of instruments, patient, and physician.[40,41] Additional studies with parabolic flights have been conducted to develop and test the feasibility of using functional endoscopes and ultrasound to pass a ureteral catheter or stent to bypass an obstructive stone (Figure 6).[30] As highlighted above, non-surgical interventions using ultrasound to either fragment or reposition kidney stones represent a newer approach.[42]

Figure 6 – Simulated laparoscopic surgery study on NASA/JSC's KC-135 zero-g aircraft. Pictured are surgeons J Jones, MD and M. Campbell, MD (inverted) during a parabolic flight surgical skills assessment.[57]

Other conditions that might require surgery in space are likely to be rare. However, as we venture beyond LEO – back to the Moon and onward to Mars – additional logistical challenges will arise. For instance, telemedicine and telesurgery will not be feasible during a mission to Mars given long communications delays, expected to be around 20 minutes each way. Other technologies, such as autonomous medical systems, might need to be considered to fill this gap.[43]

7. REPRODUCTIVE CHALLENGES

Although the reproductive consequences of extended spaceflight exploration are currently unknown, variables such as occupation-related delayed conception and radiation-induced gamete damage suggests that there is a need for NASA to adopt a policy for Assisted Reproductive Technology for their astronauts.

The average age for incoming female astronauts is currently 32.8 years, with an average age of 38.3 at the time of the first mission.[44] Many prefer to delay conception until undertaking their first spaceflight, and are therefore nearing or beyond the age of 40 before they desire a pregnancy. The delay in conception for female astronauts is potentially consequential, in that the per-cycle fecundability for natural and assisted cycles begins to considerably decline in females starting at the age of 32. According to information from NASA, the average age for conception in female astronauts after successful spaceflight is 41-42 years.[1] By this age, the probability of genetic defects and miscarriage approaches 40%.

In addition to delayed conception, another issue that poses a potential risk to both male and female astronauts is radiation induced gamete damage. On Earth, the geomagnetosphere provides shielding from the highly ionized heavy particles that characterize the space radiation environment. During spaceflight, however, astronauts are exposed to much higher doses of radiation. Furthermore, this particle radiation has greater potential to induce nuclear damage in the gametes of both sexes.[44,45] Future missions to Mars will subject crewmembers to an annual dose of 425mSv/year or more.[45] In addition to the constant and cumulative exposure to radiation in the form of galactic cosmic rays, crews will also be at risk of sudden intense bursts in the form of solar particle events (SPEs). Doses ranging from 150 mSv to 650mSv to gonadal tissue in men and women respectively are sufficient to induce temporary infertility.[44]

For women, assisted reproductive technology in the form of oocyte and embryo cryopreservation stand to circumvent the issues of radiation-induced gamete damage and age-related issues of conception.[45] For male astronauts, sperm cryopreservation technology is available based on current technology and can be easily implemented. Health records from NASA show that 25% of female astronauts have utilized assisted reproductive technologies, the cost of which was incurred by the individual. Other suggested measures include: barring-younger astronauts from deep-space missions, mandating the use of hydrogen-based materials to shield pelvic organs during spaceflight, and conducting periodic on-board physical exams focused on reproductive health.[45,46]

8. ONGOING DEVELOPMENTS AND FUTURE DIRECTIONS

If the last several years are any indication, the 2020s will continue to be marked by a revolution in space habitat, life support, and propulsion technology which, for the first time in human history, will permit NASA and other space agencies around the globe to undertake long-duration, exploration-class missions beyond the confines of Earth's geomagnetosphere. Not surprisingly, this endeavor is fraught with challenges: NASA has outlined several primary concerns, known as "red risks," which provide the foundation for the evolving landscape of aeromedical capabilities.[47,48] The "five main hazards of spaceflight and the space exposome" include: i) space radiation, ii) isolation and confinement, iii) altered gravity fields, iv) hostile or closed environments, and v) distance from Earth. From a logistical perspective, distance will pose the greatest challenge by far, particularly where in-flight medical diagnostics and therapeutic interventions are concerned.

Artemis missions will remain within close enough contact to terrestrial resources to permit frequent communication,[49] should the need arise. The shift to deep space missions in the coming decades, however, will mandate robust, autonomous medical capabilities that can facilitate interplanetary operations in excess of 30 months' duration.[50] In anticipation of evolving needs, support of technological development should be prioritized to include advancing in-flight therapeutic capabilities for modalities such as BWL and UP, which may to permit definitive treatment of ureterolithiasis and avoid the need for serial application of temporizing measures. Urogynecologic and reproductive considerations, to include fertility preservation and risk mitigation related to birth defects, would likely benefit from updated policies that better reflect our evolving understanding of the effects of spaceflight on these physiologic processes.[45] Advanced reproductive technologies continue to develop in the terrestrial setting at an extraordinary pace, due in large part to increased demand seen among women who have elected to postpone childbearing in pursuit of career opportunities; as these processes evolve, active members of the astronaut corps should have access to burgeoning technologies in support of their own reproductive, gynecologic, and urologic health.[44] Ongoing development of imaging technology, too, should be prioritized – perhaps in the form of a hybrid, low-profile, Butterfly iQ-like device with integrated BWL or UP-based capabilities. A narrow-caliber, multi-purpose endoscope that is capable of cystourethroscopy and retrieval of small stones, as well as a variety of other interventional and surgical applications, would prove tremendously useful in the spaceflight setting. As terrestrial ureteroscopic technology continues to advance, a streamlined mechanism should be developed for adoption and adaptation of these new technologies to the microgravity environment in order to further mitigate procedural risk and promote long-term crew health.[51]

9. CONCLUSIONS

The last 60 years of human spaceflight have provided a unique opportunity for innovation and discovery in medical technology. Our understanding of urologic physiology, pathophysiology, imaging, and therapeutics have advanced, in part, due to the unique constraints and challenges of spaceflight. Our evolving knowledge of nephrolithiasis, reproductive physiology, as well as telemedicine and telesurgery, will provide key resources and capabilities to prepare future astronauts for missions to the Moon, Mars, and deep space. Urologic care necessitates a unique set of clinical, diagnostic, and surgical tools that will continue to advance the space medicine field, while spinning-off new technologies to terrestrial patients.

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REFERENCES

1. Jones JA, Jennings R, Pietryzk R, Ciftcioglu N, Stepaniak P. Genitourinary issues during spaceflight: a review. *Int J Impot Res*. 2005;17 Suppl 1:S64-67. doi:10.1038/sj.ijir.3901431
2. Stepaniak PC, Ramchandani SR, Jones JA. Acute urinary retention among astronauts. *Aviat Space Environ Med*. 2007;78(4 Suppl):A5-8.
3. Maciolek KA, Best SL. How Do Astronauts Urinate? The History of Innovations Enabling Voiding in the Void. *Urology*. 2019;128:8-13. doi:10.1016/j.urology.2018.11.065
4. Volpin F, Badeti U, Wang C, et al. Urine Treatment on the International Space Station: Current Practice and Novel Approaches. *Membranes (Basel)*. 2020;10(11). doi:10.3390/membranes10110327
5. Stapleton TJ, Broyan JL, Baccus S, Conroy W. Development of a Universal Waste Management System. In: *43rd International Conference on Environmental Systems*. American Institute of Aeronautics and Astronautics; 2013. doi:10.2514/6.2013-3400
6. Anderson SA, Kaufman CA, Johnson KM. Urine Removal from Suited Crew in Orion Vehicle Depressurization Scenario. :9.
7. Johnston RS, Dietlein LF, Berry CA, Parker JF, West V. Biomedical Results of Apollo. Published online January 1, 1975. Accessed June 22, 2021. https://ntrs.nasa.gov/citations/19760005580
8. Jones J, Pietrzyk RA, Cristea O, Whitson PA. Chapter 18: Renal and Genitourinary Concerns. In: Barratt MR, Baker E, Pool SL, eds. *Priciples of Clinical Medicine for Spaceflight*. Springer Nature; 2020.
9. Jones JA, Sargsyan AE, Barr YR, et al. Diagnostic ultrasound at MACH 20: retroperitoneal and pelvic imaging in space. *Ultrasound Med Biol*. 2009;35(7):1059-1067. doi:10.1016/j.ultrasmedbio.2009.01.002
10. Khan SR, Pearle MS, Robertson WG, et al. Kidney stones. *Nat Rev Dis Primers*. 2016;2:16008. doi:10.1038/nrdp.2016.8
11. Whitson PA, Pietrzyk RA, Pak CYC, Cintron NM. Alterations in Renal Stone Risk Factors after Space Flight. *The Journal of Urology*. 1993;150(3):803-807. doi:10.1016/S0022-5347(17)35618-5
12. Smith SM, Heer M, Shackelford LC, et al. Bone metabolism and renal stone risk during International Space Station missions. *Bone*. 2015;81:712-720. doi:10.1016/j.bone.2015.10.002
13. Smith SM, McCoy T, Gazda D, Morgan JLL, Heer M, Zwart SR. Space Flight Calcium: Implications for Astronaut Health, Spacecraft Operations, and Earth. *Nutrients*. 2012;4(12):2047-2068. doi:10.3390/nu4122047
14. Smith SM, Zwart SR, Heer M, Hudson EK, Shackelford L, Morgan JL. Men and Women in Space: Bone Loss and Kidney Stone Risk After Long-Duration Spaceflight: BONE LOSS AND KIDNEY STONE RISK IN SPACEFLIGHT. *J Bone Miner Res*. 2014;29(7):1639-1645. doi:10.1002/jbmr.2185
15. Lehnhardt K. HRR - Risk - Risk of Renal Stone Formation. Accessed May 1, 2021. https://humanresearchroadmap.nasa.gov/risks/risk.aspx?i=81
16. Butler D, Kertsman E. Medical Updates to the International Space Station Probabilistic Risk Assessment Model Using the Integrated Medical Model. Presented at the: Presentation to the Multilateral Medical Operations Panel, NASA Johnson Space Center; 2011; Houston Texas.
17. Scales CD, Smith AC, Hanley JM, Saigal CS. Prevalence of Kidney Stones in the United States. *Eur Urol*. 2012;62(1):160-165. doi:10.1016/j.eururo.2012.03.052

18. Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Intern Med*. 1989;111(12):1006-1009. doi:10.7326/0003-4819-111-12-1006
19. 9780929776002: Diary of a Cosmonaut: 211 Days in Space (English and Russian Edition) - AbeBooks - Lebedev, Valentin Vital Evich: 0929776003. Accessed June 22, 2021. https://www.abebooks.com/9780929776002/Diary-Cosmonaut-211-Days-Space-0929776003/plp
20. Whitson PA, Pietrzyk RA, Sams CF. Urine volume and its effects on renal stone risk in astronauts. *Aviat Space Environ Med*. 2001;72(4):368-372.
21. Whitson PA, Pietrzyk RA, Morukov BV, Sams CF. The risk of renal stone formation during and after long duration space flight. *Nephron*. 2001;89(3):264-270. doi:10.1159/000046083
22. Pietrzyk RA, Jones JA, Sams CF, Whitson PA. Renal stone formation among astronauts. *Aviat Space Environ Med*. 2007;78(4 Suppl):A9-13.
23. Kidney Stones: Medical Mangement Guideline - American Urological Association. Accessed June 22, 2021. https://www.auanet.org/guidelines/guidelines/kidney-stones-medical-mangement-guideline
24. Whitson PA, Pietrzyk RA, Jones JA, Nelman-Gonzalez M, Hudson EK, Sams CF. Effect of potassium citrate therapy on the risk of renal stone formation during spaceflight. *J Urol*. 2009;182(5):2490-2496. doi:10.1016/j.juro.2009.07.010
25. Okada A, Ichikawa J, Tozawa K. [Kidney stone formation during space flight and long-term bed rest]. *Clin Calcium*. 2011;21(10):1505-1510. doi:CliCa111015051510
26. Leblanc A, Matsumoto T, Jones J, et al. Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. *Osteoporos Int*. 2013;24(7):2105-2114. doi:10.1007/s00198-012-2243-z
27. Sibonga J, Matsumoto T, Jones J, et al. Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. *Bone*. 2019;128:112037. doi:10.1016/j.bone.2019.07.013
28. Sur RL, Shore N, L'Esperance J, et al. Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. *Eur Urol*. 2015;67(5):959-964. doi:10.1016/j.eururo.2014.10.049
29. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. *AJR Am J Roentgenol*. 2002;178(1):101-103. doi:10.2214/ajr.178.1.1780101
30. Jones JA, Johnston S, Campbell M, Miles B, Billica R. Endoscopic surgery and telemedicine in microgravity: developing contingency procedures for exploratory class spaceflight. *Urology*. 1999;53(5):892-897. doi:10.1016/s0090-4295(99)00024-2
31. Jones JA, Kirkpatrick AW, Hamilton DR, et al. Percutaneous bladder catheterization in microgravity. *Can J Urol*. 2007;14(2):3493-3498.
32. Chen TT, Samson PC, Sorensen MD, Bailey MR. Burst wave lithotripsy and acoustic manipulation of stones. *Current Opinion in Urology*. 2020;30(2):149-156. doi:10.1097/MOU.0000000000000727
33. Ray AA, Ghiculete D, Pace KT, Honey RJD. Limitations to ultrasound in the detection and measurement of urinary tract calculi. *Urology*. 2010;76(2):295-300. doi:10.1016/j.urology.2009.12.015
34. Jones J, Jennings R, Baker E. Renal, Genitourinary, and Gynecological Health Issues. *Biomedical Results of the Space Shuttle Program*. eds Stepaniak P, Risin, D. NASA 17Nov 2013; ISBN-13 978-0615866130

35. Simon JC, Dunmire B, Bailey MR, Sorensen MD. Developing Complete Ultrasonic Management Of Kidney Stones For Spaceflight. *J Space Saf Eng*. 2016;3(2):50-57. doi:10.1016/S2468-8967(16)30018-0

36. Dunmire B, Lee FC, Hsi RS, et al. Tools to Improve the Accuracy of Kidney Stone Sizing with Ultrasound. *J Endourol*. 2015;29(2):147-152. doi:10.1089/end.2014.0332

37. May PC, Haider Y, Dunmire B, et al. Stone-Mode Ultrasound for Determining Renal Stone Size. *J Endourol*. 2016;30(9):958-962. doi:10.1089/end.2016.0341

38. Harper JD, Cunitz BW, Dunmire B, et al. First in Human Clinical Trial of Ultrasonic Propulsion of Kidney Stones. *J Urol*. 2016;195(4 Pt 1):956-964. doi:10.1016/j.juro.2015.10.131

39. The Butterfly iQ Catches a Ride on the SpaceX Dragon to Space. Accessed June 22, 2021. https://ir.butterflynetwork.com/news/news-details/2021/The-Butterfly-iQ-Catches-a-Ride-on-the-SpaceX-Dragon-to-Space/default.aspx

40. Campbell MR, Billica RD, Johnston SL. Surgical bleeding in microgravity. *Surg Gynecol Obstet*. 1993;177(2):121-125.

41. Campbell MR, Dawson DL, Melton S, Hooker D, Cantu H. Surgical instrument restraint in weightlessness. *Aviat Space Environ Med*. 2001;72(10):871-876.

42. Sorensen MD, Bailey MR, Hsi RS, et al. Focused Ultrasonic Propulsion of Kidney Stones: Review and Update of Preclinical Technology. *J Endourol*. 2013;27(10):1183-1186. doi:10.1089/end.2013.0315

43. Hamilton D, Smart K, Melton S, Polk JD, Johnson-Throop K. Autonomous medical care for exploration class space missions. *J Trauma*. 2008;64(4 Suppl):S354-363. doi:10.1097/TA.0b013e31816c005d

44. Ronca AE, Baker ES, Bavendam TG, et al. Effects of Sex and Gender on Adaptations to Space: Reproductive Health. *J Womens Health (Larchmt)*. 2014;23(11):967-974. doi:10.1089/jwh.2014.4915

45. Barbrow ST. Radiation Effects on Astronautic Fertility in Space: Deep Space Policy. 2020;16(1):5.

46. Vuolo M, Baiocco G, Barbieri S, et al. Exploring innovative radiation shielding approaches in space: A material and design study for a wearable radiation protection spacesuit. *Life Sciences in Space Research*. 2017;15. doi:10.1016/j.lssr.2017.08.003

47. Patel ZS, Brunstetter TJ, Tarver WJ, et al. Red risks for a journey to the red planet: The highest priority human health risks for a mission to Mars. *npj Microgravity*. 2020;6(1):1-13. doi:10.1038/s41526-020-00124-6

48. Milstead L. Human Research Program Integrated Research Plan. NASA. Published March 2021. Accessed June 22. https://humanresearchroadmap.nasa.gov/Documents/IRP_Rev-Current.pdf

49. Baird D. Artemis I: Demonstrating the Capabilities of NASA's United Networks. NASA. Published October 5, 2020. Accessed June 22, 2021. http://www.nasa.gov/feature/goddard/2020/artemis-i-demonstrating-the-capabilities-of-nasa-s-united-networks

50. Mars.nasa.gov. Trip to Mars. Accessed June 22, 2021.https://mars.nasa.gov/mars2020/timeline/cruise/

51. Khoder WY, Bader M, Sroka R, Stief C, Waidelich R. Efficacy and safety of Ho:YAG laser lithotripsy for ureteroscopic removal of proximal and distal ureteral calculi. *BMC Urol*. 2014;14:62. doi:10.1186/1471-2490-14-62

52. NASA. *Universal Waste Management System*. https://techport.nasa.gov/view/93128]

53. Anderson S, Kaufman C, Johnson K. *Urine Removal from Suited Crew in Orion Vehicle Depressurization Scenario*. - https://ntrs.nasa.gov/api/citations/20200001583/downloads/20200001583.pdf

54. Nemon J. *Preparing To Stock The Medicine Cabinet for Long-Duration Missions*. - https://www.nasa.gov/mission_pages/station/research/news/Medication_ISS.html

55. Johnson M. *Using Ultrasound to Zap Kidney Stones and Other Health Problems in Space*. https://www.nasa.gov/mission_pages/station/research/news/b4h-3rd/hh-ultrasound-to-zap-kidney-stones

56. Kirkpatrick AW, Jones JA, Sargsyan A, et al. Trauma sonography for use in microgravity. *Aviat Space Environ Med*. 2007;78(4 Suppl):A38-42.

57. A.Rafiq, T. J. Broderick, D. R. Williams, C.R. Doarn, J.A. Jones, R.C. Merrell: Assessment of surgical skills in parabolic gravity. Aviation, Space, Environ Med 76(4) April 2005; p.385-91.