Cases in Space Medicine:

Right Lower Quadrant Abdominal Pain in a Female Crewmember on the International Space Station

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You are a NASA flight surgeon working on console at Mission Control during an International Space Station (ISS) mission. You have completed extensive NASA and military or civilian aerospace medical training to address almost any anticipated medical contingency, and can summon advice from space medicine experts located around the world. Your present duties include providing medical support for two male astronauts and one female cosmonaut who are working on the ISS for a planned 6-month flight. These three highly dedicated and motivated crewmembers underwent very rigorous medical examinations at the time of their selection and annually thereafter to obtain and maintain medical certification for flight. You have also performed annual and pre-flight medical exams, in-flight periodic health status exams, exercise monitoring, private medical conferences, biomedical monitoring during spacewalks, and monitoring of vehicle environmental parameters and daily crew schedules.

One of the crewmembers, a 37-year-old Russian female, designated Flight Engineer 2 (FE2), who has been on orbit for 2 months, has just requested an unscheduled private medical conference (PMC) with you, the flight surgeon, via private space-to-ground voice loop from the ISS. The BME, who is the only person on SURGEON console in MCC, requests that the private medical conference be relayed to your house by phone. It is 3 AM local time when the phone rings and the BME is on the line stating that FE2 has requested an unscheduled PMC. Because the Russian flight surgeon is unavailable at this time, the BME has also arranged for Russian-English translation services to be provided in case there is a communication problem with the native

speaking female Russian Soyuz pilot. The Crew Medical Officer (CMO) on the ISS is conversant in Russian and has received 40 hours of medical training in areas of emergency procedures and general medical procedures. You release the BME from the private communication loop and commence the medical conference with FE2, who expresses serious concerns about her lower right quadrant pain which has progressed from a 2/10 to 8-9/10 in severity over a 5 hour period. During the PMC, FE2 denied ever having extreme pain like this in the past and states that it is completely unbearable and no maneuver, or position improves it.

You have her complete medical record on a notepad computer at your house and quickly review during the conversation that FE2 had a mother who died from colon cancer at the age of 56, a father who has a history of multiple episodes of nephrolithiasis starting at age 45, which were all treated medically, and a brother who has had one episode of diverticulitis. FE2 weight = 75 Kg, height = 172 cm., is premenopasual and married with 2 children (Gravida 2 – Para 2 females ages 9 and 12 both healthy). FE2 has been in perfect health up to this PMC with no outstanding medical issues. FE 2 consumes a daily calcium pill along with a multivitamin as per prescription from the Russian flight surgeon.

FE2 denies experiencing any shortness of breath, palpitations, fatigue, or weakness and symptoms of presyncope. She denies dysuria, urgency, frequency, vomiting, chills shakes, diarrhea, and constipation. She describes her pain as undulating cramps and CVA severe pain and is often associated with nausea. She took aspirin 325mg 10 minutes prior to calling the Flight Surgeon with no noticeable effect on her

pain. The limited upmass from the recent grounding of the Shuttle fleet has caused the crew to conserve water. Upon further questioning, FE2 notes that her busy schedule has prevented her from drinking the minimum of 2 liters of fluids you recommend the crew to consume daily.

Question 1. Based on your limited knowledge at this time, your differential diagnosis should include which of the following potentially life-threatening causes?

A. Aortic dissection
B. Appendicitis
C. Ruptured Ovarian Cyst
D. Diverticulitis
E. Ectopic pregnancy (2 months since launch)
F. Renal Obstruction
G. Acute Cholecystitis
H. Gastritis
I. Small Bowel Obstruction.
J. All of the above

The history of FE2's pain and the HPI causes you to consider many of the above maladies in the differential diagnosis. You realize that several of these can be ruled out with diagnostic imaging. After the PMC you transfer the control of the private voice from the ISS back to the BME and phone the flight director from your car as you drive to MCC.

Question 2. While driving to MCC in your car, you think of additional information that should be obtained from the medical record or directly from the patient. What

characteristics in the family or past medical history raise concern with this case prompting a more detailed history?

A. Family history of kidney stones
B. Diet (Russian's diet is rich in meat, a source of uric acid, NaCl, etc)
C. Preflight Stone Risk Profile
D. Geographic, environmental conditions
E. Family history of cholelithiasis
F. Family history of peptic ulcer
G. A history of any diet supplements of Vitamins
H. Recent or chronic medications
I. All the above

After you arrive at MCC, a video PMC is conducted and during the medical examination of FE2 by the CMO under your guidance, the following information is obtained.[13] You provide guidance on how to listen for bowel sounds and the technique for palpation and percussion of the abdomen, however this proves to be very difficult for a non-physician under microgravity conditions with high ambient noise levels in the ISS (65-70 dBA) with a patient is uncooperative due to extreme discomfort.

On examination it is noticed that the patient is very anxious, diaphoretic, writhing in pain, and speaking in short sentences. She points to her lower abdomen and right costovertebral angle (CVA) as the location of pain. She cannot get comfortable and feels like the pain is "deep inside her". She is tearful and requesting "anything" for pain control.

BP= 150/97 by automated blood pressure cuff
HR = 160 regular
RR = 24

Temp = 98.2
O_2 Saturation via pulse oximetry = 99% on 100% O_2 by non-rebreather mask.
Urine is positive for blood, white cells, positive nitrites by dipstick, specific gravity= 1.030. Urine output is about 100 ml over the last 30 minutes.
CMO reports no bowel sound heard and severe tenderness on right CVA percussion. Patient refuses all other examination maneuvers. Under your real-time guidance, the CMO performs an abdominal exam on FE2. A pelvic exam is differed at this time due to the extreme pain and discomfort FE2 is experiencing and the inexperience of the CMO.

Question 3. Given the previous circumstances surrounding the medical exam, what history and reported physical findings would you trust as accurate?

A. Absent bowel sounds
B. CVA tenderness
C. Rebound tenderness
D. Murphy's sign
E. Severe colicky flank pain
F. "tinkling" bowel sounds
G. Fever
H. Pulsatile midline abdomen
I. Abdominal tenderness
J. Volume Status

Using private communications with the CMO, you advise him that FE2 is experiencing an acute abdominal event and ask him to deploy the Ambulatory Medical Pack (AMP) and wait for medication orders. The AMP contains many oral and IM medications which could potentially be prescribed for FE2.

Question 4: What supportive medical treatment would you offer the FE2 at this time?

A. ASA 325 mg PO
B. Tylenol 325 mg PO
C. Ibuprofen 400 mg PO
D. Naprosyn 250 mg PO
E. Prednisone 10 mg PO
F. IV Ketorolac Tromethamine 30mg IV
G. Phenergan 50 mg IM
H. IV fluid 0.9NS at 500 ml/hr

I. Morphine 0.05 to 0.1 mg/kg IM Q3-6h
J. Meperidine 0.5 to 1.0 mg/kg IM Q3-4h
K. Lorazepam 2 mg PO
L. Foley catheter

Due to the privacy maintained during the PMC, the Flight Director has not been able to hear or see any of the conversation between you and the crew. The Flight Director asks you about this and you advise him that, at the moment a “mission impact” medical condition is being evaluated and an expedited return to Earth may need to be considered. The space shuttle left the ISS 30 days ago after completing a routine resupply mission, with the next shuttle launch to the ISS expected in 2 weeks to install more components of the ISS. The default emergency return vehicle is the Russian Soyuz, which is afforded a nominal landing opportunity in Kazakhstan only every 19 to 21 hours. FE2 is the Soyuz commander with the most experience in navigating the Soyuz during launch, docking, undocking and landing. The flight director informs you that we are only 6 hours away from when the Soyuz would need to undock from ISS to make the next Primary Landing Site (PLS) opportunity in Kazakhstan or Russia otherwise the next PLS opportunity will be in 25 hours from now. You inform the Flight Director that FE2 was given 10 of Morphine IM 30 minutes ago by the CMO and therefore is probably not qualified to activate and fly the Soyuz. The Flight Director spends the next 30 minutes in an emergency conference with the rest of the flight control team at Mission Control and the ISS Commander, and subsequently orders the MCC prepare to abandon the ISS until told to stand down. The flight director informs you that he will need to make a GO/NOGO deorbit decision in 3 hours and to advise the flight control team what resources you need to accomplish this.

After a discussion with the BME, you advise the Flight Director that a more informed decision can be obtained by using the Health Research Facility (HRF) ISS ultrasound unit currently being flown in the laboratory module. One hour later GC reports the HRF ultrasound team is in MCC and that the ultrasound system is ready for use. Using real time guidance from a sonographer on console in MCC, the CMO was able to obtain clinically useful images for evaluation by a radiologist who was also called into MCC. The ultrasound images obtained real-time, rule out any gross vascular, hepatic, gastro-intestinal and ovarian pathology. Of interest was a significant dilation of the right renal calyces and an echogenic mass in the proximal ureter measuring 4 to 5mm. Doppler images of the bladder showed classic left ureteral jets, indicating patency between the bladder and left kidney. Unfortunately no jets were found on the right which is consistent with a right ureteral obstruction. Although the patient is clearly obstructed, you cannot tell whether it is a "complete" obstruction without contrast. The classic sign is a very delayed nephrogram. Seeing a column of urine does not indicate degree of obstruction. Seeing a column of urine does not indicate degree of obstruction. FE2 is not taking fluid because of nausea and is still complaining of severe abdominal and flank pain. There are no other echogenic masses seen in the renal parenchyma or abdomen.

Question 5. Based on the results of the diagnostic imaging what is this patient's prognosis?

A. No Problem – the patient should pass this stone easily without any complications

B. Permanent obstruction requiring emergent lithotripic or surgical intervention is required to save the patients renal function.
C. Acute Tubular Necrosis
D. Acute Renal Failure
E. Could pass the stone with a trial of therapy (IV fluids, paincontrol)
F. Patient is at high risk for pyelonephritis
G. Not enough information at this time

Three hours have passed since your initial discussion with the flight director and he has asked you to speak with him privately regarding the status of FE2. You inform the flight director that you are very confident that FE2 is suffering from an acute right renal obstruction secondary to urolithiasis. You explain that this medical problem may not resolve on orbit, however, treatment has been started. FE2 is not able to perform any mission related duties and will require 24 monitoring and medical support.

Question 6. Based on the results of the diagnostic imaging you instruct the CMO to perform which of the following?

A. Start a Morphine 2-5 mg IV q15min (limited by RR <16 bpm and systolic BP <100 mm Hg) prn for pain relief .
B. Morphine 10 mg. IM q6h PRN
C. IV NS TKVO
D. IV NS 500 ml/hour
E. Augmentin 500 mg X 2 stat then Q8H
F. Ciprofloxacin 500mg PO BID
G. Amikacin/ceftriaxone IV
H. Vitals q1h
I. Vitals q15min
J. Vitals q5min

K. Ketorolac/Tromethamine 30 mg IV initially, followed by 15 mg IV q8h prn
L. Ketorolac/Tromethamine 15 mg IM initially, followed by 15 mg IM q8h prn

You now feel that FE2 has an adequate pain control plan for the next 24 to 28 hours but unfortunately is now not able to "fly" the Soyuz under the influence of these medications. NASA management has called the flight director for an update of the situation because the media is now covering this event on national TV.

Question 7. The Flight Director asks you which of the following options you would medically consider is appropriate over the next 24 hours.

A. Contingency deorbit to Continental United States within 3 hours with 1 minute of 8-10 G_x exposure
B. Nominal Soyuz deorbit to Kazakhstan or Russia in 6 hours with 3 minutes 3.8 G_x exposure.
C. Manage the problem on orbit as contingency deorbiting is dangerous
D. Wait for the Space Shuttle to return in 14 days
E. Miss the next PLS and re-evaluate in 12 hours.
F. No recommendation is possible at this time

You have discussed the results of the ultrasound with the experts in MCC, Medical Operations management and the Russian medical support team in Mission Control Moscow. It is the consensus of these experts that the size of the obstructing kidney stone is small enough to attempt a "trial of therapy" consisting of IV fluids loads and aggressive pain management. Your recommendation to the Flight Director is to stand-down from the plan to deorbit to the next PLS in Kazakhstan, however, a nominal Soyuz deorbit in 25 hours will be needed if FE2's symptoms do not improve. You advise him that we have no means of removing a small stone on orbit and the supply of pain control medications will not last greater than 32 hours. You also suggest that a

contingency deorbit of 8 to 10 G_x exposure with knees above the head for a patient suffering from an acute renal obstruction may become intolerable to the patient. You also remind him that an emergency deorbit to other parts of the world may not be effective since there is no guarantee that the crew will be rescued by globally deployed military resources for as long as 24 hours after landing.

The flight Director is reminded by CAPCOM that the commander (CDR) who is assisting the CMO is also the backup Soyuz pilot and that he will need to be released from patient care to prepare for the possibility of having to fly the Soyuz and prepare the ISS for abandonment since FE2 is incapacitated. The Flight Director orders the MCC to stand-down for a next PLS landing but to prepare for a PLS landing in 25 hours when the opportunity occurs again. CAPCOM instructs the CDR that he is released from medical duties unless a medical emergency is declared. FE2 is stable with pain controlled with Morphine IM and IV fluids.

Approximately 16 hours after the initial medical event you have become concerned about the lack of improvement in FE2 and the deterioration of her vitals signs. The last physical exam conducted by the CMO under your guidance by video conference shows the following.

On examination it is noticed that the patient is anxious, diaphoretic, pale and vomiting. Patient complains of chills and shakes with occasional rigors. Her pain is about 9/10 and it has been 5 hours since her last IM injection of morphine. She states her pain has "moved" to be more into the pelvis and midline but continues to have and right CVA discomfort. She states that this is the worst pain she has ever experienced in her life.

BP= 100/60 by automated blood pressure cuff
HR = 175 regular
RR = 24
Temp = 103.4
Approximately 250 mls of urine output over the last 6 hours
O_2 Saturation via pulse oximetry = 99% on 100% O_2 by non-rebreather mask.
The urine is still positive for blood, white cells, nitrites and ketones by dipstick, Specific gravity = 1.0010

CMO reports no bowel sound heard and severe pain on right CVA percussion. Patient refuses all other examination maneuvers. Urine samples are positive for blood, white cells, nitrates and ketones by dipstick.

Question 8. Based on the physical exam information prescribe the flowing treatment for the non-physician CMO to provide:?

A. Continue IV NS 500 ml/hour
B. Augmentin (500 mg PO X 2 STAT then Q8H)
C. IV Amikacin (7.5 mg per kg Q12H)
D. Ceftriaxone (100 mg/kg/day, up to 2 g/day IV, as a single daily dose)
E. Ciprofloxacin (500 mg PO BID)
F. Phenergan (25 mg IV STAT)
G. Phenergan (25 mg IM STAT)
H. Repeat the ultrasound exam
I. Inform flight director we are definitely going to need to deorbit for next PLS
J. Wave off the current deorbit and reassess for next PLS

You inform the flight director that the medical management team feels that deorbit to next PLS is the only option available now that the patient is showing signs of a complete right urinary obstruction with a likely diagnosis of pyelonephritis with possible urosepsis. You understand that the presence of blood in the urine can cause false positive nitrites to be indicated on a urine dip stick but the clinical presentation is

nonetheless very consistent with infection. You prescribe double gram negative coverage consisting of Amikacin/ceftriaxone IV since urospesis is potentially fatal within hours. The flight director instructs the flight control team to start procedures to deorbit to next PLS and prepare the ISS for abandonment.

Approximately 6 hours prior to the undock and planned abandonment of the ISS(18 hours after the last PLS opportunity), FE2 reports a very sudden decrease in pain and becomes quite sleepy. FE2 is requesting time to sleep and you suspect that she may have passed the stone and the narcotics may now be sedating FE2 in the absence of pain but you are also concerned that she is becoming obtunded secondary to a possible sepsis. A second ultrasound was performed 30 minutes later and showing restoration of flow in the right ureter was confirmed by the large ureteral jets seen on the right side. You ask the CMO to discontinue all narcotic pain medications because they are making FE2 excessively drowsy now that her pain has abated.

You notify the Flight Director that FE2 no longer has an obstruction of her right kidney but there is still a possibility that she still may be suffering from serious urosepsis. You further suggest that a medical GO/NOGO decision for next PLS should be not canceled until you can confirm that FE2's condition has definitely improved.

During the next 4 hours you discontinue pain meds, but maintain IV hydration and NSAIDs and continue to prepare for deorbit. You advise the CMO not to perform any oral reentry fluid-loading countermeasures on FE2. An adequate supply of IV analgesics and anti emetics are placed in the Soyuz for the deorbit to next PLS which will confine the crew of three in a very small capsule for up to 3 hours. You guide the

CMO though another physical exam using the videoconferencing system and the following information is obtained:

On examination it is noticed that the patient is relaxed and in relatively good humor. Patient no longer has any complaints of chills, shakes or nausea. Her pain is about 1/10 and it has been 4 hours since her last IM injection of morphine. She states her pain has all but gone but still has some very mild right CVA discomfort. She is very thirsty.

BP= 120/75 by automated blood pressure cuff
HR = 85 regular
RR = 16 non-labored
Temp = 99.6
Approximately 1950 mls of urine output since her pain decreased.
O_2 Saturation via pulse oximetry = 99% on 100% O_2 by non-rebreather mask.

CMO reports bowel sounds present and minimal pain on right CVA percussion. The urine is still positive for blood, white cells, mild nitrates and ketones by dipstick, Specific gravity = 1.0021.

Question 9. Based on the recent physical exam and diagnostic imaging information you prescribe which of the flowing treatments for FE2?

A. Continue IV NS 500 ml/hour
B. Continue IV Amikacin/ceftriaxone
C. Start Ciprofloxacin 500mg PO BID
D. Vitals q1h
E. Vitals q15min
F. Discontinue Oxygen
G. Continue Ketorolac/Tromethamine 15 mg IM q8h prn
H. Discontinue Ketorolac/Tromethamine
I. Repeat the ultrasound exam
J. Remove Foley catheter but strain urine for stones.
K. Wave off the current deorbit and reassess for next PLS

You inform the flight director that FE2 is improving and her last exam indicated that her infection is resolving due to the resolution of her kidney obstruction. The next PLS deorbit is not indicated at this time, however you advise for the flight control team to consider future next PLS deorbits until the situation is completely resolved. The Flight Director orders that the flight control team stand down from next PLS but be ready to consider the next available deorbit which is 21 hours from now.

FE2 was advised to increase fluid intakes and monitor her urine to keep it clear and very well diluted. She remained on orbit until nominal end of mission and had an uneventful landing at Kazakhstan.

Question 10.) After her mission, you advise FE2 that she?

A. is disqualified from long duration spaceflight
B. is disqualified from short duration spaceflight
C. is potentially waiverable for short duration flight
D. should receive Renal Stone Risk assessment
E. should receive a CT – fine 2mm renal slices
F. should receive a Nephro – tomogram
G. should receive a Spiral CT with pyelogram phase,
H. should receive a Metabolic stone work up
I. no workup necessary since it was spaceflight which caused this

The acute renal obstruction completely resolved and FE2 was returned to all mission duties except EVA because of the risk of dehydration for this activity. FE2 retired from the space agency and is in the process of writing her memoirs about being an ISS crew member. She has not had any repeat episodes of acute renal obstruction to date.

The most sensitive preflight study for determining if stones exist is a non-contrast renal CT. It is sensitive enough to show calculi forming on the papilla which is commonly referred to as “Randall’s plaque”.[35] The use CT is becoming more frequent for ruling out the presence of pathological calcium in soft tissues such as coronary arteries.[8,24,43] Unenhanced helical CT allows rapid and accurate determination of whether a stone is present anywhere in the urinary tract.[1] This screening test requires no contrast medium and takes only 5 to 10 minutes of imaging time, making it cost effective. Future astronaut selection may need to employ this modality to help prevent incidents like this from occurring in space again.

ANSWERS / DISCUSSION

Answer. J - All the above

Question 1. Based on your limited knowledge at this time, your differential diagnosis should include which of the following potentially life-threatening causes?

A. Aortic dissection
B. Appendicitis
C. Ruptured Ovarian Cyst
D. Diverticulitis
E. Ectopic pregnancy (2 months since launch)
F. Renal Obstruction
G. Acute Cholecystitis
H. Gastritis
I. Small Bowel Obstruction.
J. All of the above

All of the conditions posited in the question fit within the differential diagnosis of the presenting symptoms and must be considered. Each is potentially life-threatening and would be a disastrous oversight to miss. Many of the entities in this list are treatable with the proper knowledge and equipment. Aortic dissection is not commonly found in this age group of females and the possibility of an ectopic pregnancy 8 weeks after launch is obviously not a consideration in this scenario. Nonetheless, all of these diagnoses would fit within the differential of a left lower quadrant acute abdomen in a premenopausal female.

Answer I – all the above

Question 2. While driving to MCC in your car, you think of additional information that should be obtained from the medical record or directly from the patient. What characteristics in the family or past medical history raise concern with this case prompting a more detailed history?

A. Family history of kidney stones
B. Diet (Russian's diet is rich in meat, a source of uric acid, NaCl, etc)
C. Preflight Stone Risk Profile
D. Geographic, environmental conditions
E. Family history of cholelithiasis
F. Family history of peptic ulcer
G. A history of any diet supplements of Vitamins
H. Recent or chronic medications
I. All the above

Human exposure to microgravity results in alterations in renal function, fluid redistribution, bone loss, and muscle atrophy, all of which contribute to an altered urinary milieu and the potential for renal stone formation during and immediately after flight. Since the early flights of Gemini it has been known that the unloading of bone in microgravity causes a commensurate hypercalcuria which seems to continue almost indefinitely during short and long duration missions. You recall the fact that renal stones have been found in 12 active US astronauts and many of these happened within 9 to 120 months post flight.[33] The Russians have experienced multiple renal stone events with one actually happening during a mission almost causing an abort due to intractable symptoms. The in-flight episode resolved spontaneously and the mission was completed.

In-flight changes include decreased urine volume and increased urinary secretion of calcium, phosphate, potassium, and sodium. Microgravity possibly alters renal stone protein inhibitor excretion rates increasing the risk of crystallization. Increased

concentration of urinary constituents may be caused by either low urine volume (dehydration, dry climates) or by increased urinary chemical excretion (hypercalcuria, hyperoxaluria, hyperuricosuria, cystinuria). Decreased urine solubility can be induced by an abnormal urine pH (uric acid and phosphate-containing calculi can be precipitated by acidic, and alkaline, urine respectively).

Diet may play a significant role in the pathogenesis of kidney stones. High protein and salt intake increase the risk of calcium stone formation. High purine diets (meat, fish, chicken) lower urinary pH and cause increased excretion of uric acid. Vitamin B6 deficiency leads to increased formation and excretion of oxalate. Dehydration, excessive vitamin C intake, calcium supplementation, and calcium containing antacids may also lead to stone formation.

The reduced gravity environment combined with FE2's poor oral intake of fluids causes you to suspect that she may have has very concentrated urine with possibly high concentrations of calcium which is promotes the growth microlithiasis. Therefore, your presumptive diagnosis is acute renal obstruction secondary to a kidney stone formed while living in the ISS.

A family history of nephrolithiasis may be useful in determining the etiology of this patient's presentation. Selection history and physical examination are quite extensive and most likely any significant family history would have been already know. FE2 was cleared of any evidence of renal tubular acidosis, hyperparathyroidism, chonic urinary tract infections and hypercalcuria at selection. She had a negative Renal Stone Risk workup (ref) which unfortunately does not always identify all individuals who will eventually have idiopathic or stress induced nephrolithiasis.

Question 3. Given the previous circumstances surrounding the medical exam, what history and reported physical findings would you trust as accurate?

A. Absent bowel sounds
B. CVA tenderness
C. Rebound tenderness
D. Murphy's sign
E. Severe colicky flank pain
F. "tinkling" bowel sounds
G. Fever
H. Pulsatile midline abdomen
I. Abdominal tenderness
J. Volume status

Each of the exam findings listed makes sense on Earth however pathophysiology in some organ systems (i.e. change of pain with position) is predictably altered in microgravity. This medical emergency requires care to be provided by the CMO using step-by-step instructions from a capable physician at the Mission Control Center via two-way audio and video. Some of these findings are changed or made useless by the conditions posited in the question. Ambient noise and inadequate CMO training are likely to make abnormal ausculatory bowel sound findings unreliable at best. There also is a normal 1- to 2-liter cephalad fluid shift from the legs (primarily the thighs) that takes place in the first 8 to 24 hours of space flight[28] and remains until landing. This shift in fluid towards the heart is paradoxically accompanied by about a 5- to 7- mmHg decrease in central venous pressure (CVP)[3] with no clinically significant changes in cardiac output. The bedside examination of the jugular venous pressure (JVP) on Earth is a reliable indicator of right atrial pressure and helps determine volume status because the vena cava acts as a venous hydrostatic column

of blood. Jugular venous distension is a normal response to space flight that persists throughout the mission and would not be helpful in determining changes in central volume status.

Urgent urologic consultation is indicated when fever suggests infection or an obstructed kidney or intravenous pyelography shows a nonfunctioning kidney (completely obstructed ureter), a partially obstructed ureter in a patient with only one kidney, or urine extravasation. The following table is useful in helping determine the nature and possible cause of abdominal pain.

Table 1 Typical Presentations of Abdominal Pan

Symptom	Peptic ulcer	Renal colic	Biliary colic	Appendicitis	Gastroenteritis
Colicky pain	No	Yes	Yes	No	Yes
Localized pain	Yes	Yes	Yes	Yes	No
Fever	No	No	No	Yes	Not frequent
Diarrhea	No	No	No	Not frequent	Yes
Abdominal tenderness	Yes	No	Not frequent	Yes	Not frequent

Answer – F,H, I,L

Question 4: What supportive medical treatment would you offer the FE2 at this time?

A. ASA 325 mg PO
B. Tylenol 325 mg PO
C. Ibuprofen 400 mg PO
D. Naprosyn 250 mg PO
E. Prednisone 10 mg PO
F. IV Ketorolac Tromethamine 30mg IV
G. Phenergan 50 mg IM
H. IV fluid 0.9NS at 500 ml/hr
I. Morphine 10 mg Q6H PRN pain
J. Meperidine 0.5 to 1.0 mg/kg IM Q3-4h
K. Lorazepam 2 mg PO
L. Foley Catheter

All the treatments above are used to control inflammation or pain under many medical circumstances. A premenopausal female with acute onset of debilitating abdominal/pelvic pain and tenderness presents a pain management problem given the wide differential diagnosis. ASA is contraindicated in several of the diagnoses being considered and the patient has already taken ASA with little effect. Tylenol alone with probably not be effective with this level of pain but could be considered for adjunctive pain control.

The presumptive diagnosis is renal colic however an acute bowel obstruction may be further exacerbated with opiates. Regardless, the first step in management of acute renal colic is to alleviate the patient's pain with analgesics, such as Morphine. Patients with nausea and vomiting who cannot tolerate oral rehydration and oral analgesics should receive IV fluids and analgesics.

Nonsteroidal anti-inflammatory agents (NSAIDS), such as Ketorolac Tromethamine , may be considered in cases of uncontrolled renal colic. Oral NSAIDS may not be tolerated but decrease pain by reducing GFR and therefore urine output, almost immediately. The use of ASA with NSAIDS in the face of a possible post obstructive nephropathy may increase nephrotoxicty.

FE2 should be encouraged to force fluids (2 to 3 L/day) to dilute urine and encourage passage of the presumed stone. A Foley catheter is clearly indicated in this situation to monitor urine output. Typically urine should be filtered through a strainer, stocking, or filter paper so a passed stone can be retained for evaluation; however this is not easily accomplished in microgravity. It is always important to be alert for infection or obstruction. Infection may occur with fever or white cells in urine, and obstruction may detected using ultrasound. Stones smaller than 5 mm usually pass spontaneously. Those between 5 and 10 mm have a 50% chance of passing spontaneously. Larger stones usually need to be removed surgically. Be aware that other causes of pain (eg, lumbosacral strain, dissection of the aorta, malingering) can masquerade as renal colic.

Meperidine in this setting is not the first drug of choice for pain control due to its propensity to induce nausea and vomiting. Lorazepam would have little effect on the pain and would only be advised if the patient need concurrent anxiolytics.

Answer – C,D,E,F

Question 5. Based on the results of the diagnostic imaging what is this patient's prognosis?

A. No Problem – the patient should pass this stone easily without any complications
B. Permanent obstruction requiring emergent surgical intervention is required to save the patients renal function.
C. Acute Tubular Necrosis
D. Acute Renal Failure
E. Could pass the stone with a trial of therapy (IV fluids, paincontrol)
F. Patient is at high risk for pyelonephritis

The probability that a renal stone will pass spontaneously over a prolonged period of time (usually 3 months or more) depends on the size of the stone. The likelihood of spontaneous passage is about 80% for stones smaller than 4 mm, 59% for stones between 4 and 6 mm, and 21% for stones larger than 6 mm.[38] Stones smaller than 5 mm may be initially managed with fluids and analgesics. Hydronephrosis, which is commonly seen, is not an indication for immediate endoscopic, surgical or lithotripic intervention but should be followed closely. A urinary tract infection concurrent with an obstructed stone requires immediate removal because the risk of urosepsis and irreversible renal injury is exceedingly high. The type of intervention chosen depends upon the size, location, and type of stone as well as the clinical features of the patient (eg, body habitus, infection).

An upper ureteral stone is generally treated using extracorporeal shock wave lithotripsy (ESWL) with a greater than 90% stonefree rate. Stone removal using retrograde ureteroscopy is generally reserved for stones in which ESWL has failed to resolve, for cystine stones, or for distally located stones causing obstruction. Stones located in the midureter are in close proximity to the pelvic bones which can absorb a significant amount of the energy of the ESWL shock wave. Ureteroscopic stone removal is the preferred modality in these locations especially for stones larger than 10 mm or when stents are required to relieve intractable pain or obstruction or to treat infection.[38]

The management of the distal ureteral stone in FE2 is complicated by the environment of the ISS and the available resources. Most certainly a trial of fluids and analgesia is prudent but the limited ability to return to Earth may cause you to be more conservative in your approach. This patient can develop acute renal failure of her right kidney and most certainly acute tubular necrosis. Acute pylonephritis in the setting of obstruction needs to be promptly treated in a hospital setting. This patient has pyuria but no fever or sign of sepsis. Clearly a failure of medical therapy on-orbit would incur a mission cost of several 100 million dollars if FE2 requires urological intervention on Earth.

Answer – B,D,F,I,L

Question 6. Based on the results of the diagnostic imaging you instruct the CMO to perform which of the following?

A. Start a Morphine 2-5 mg IV q15min (limited by RR <16 bpm and systolic BP <100 mm Hg) prn for pain relief .
B. Morphine 10 mg. IM q6h PRN
C. IV NS TKVO
D. IV NS 500 ml/hour
E. Augmentin 500 mg X 2 stat then Q8H
F. Ciprofloxacin 500mg PO BID
G. Amikacin/ceftriaxone IV
H. Vitals q1h
I. Vitals q15min
J. Vitals q5min
K. Ketorolac Tromethamine 30 mg IV initially, followed by 15 mg IV q8h prn
L. Ketorolac/Tromethamine 15 mg IM initially, followed by 15 mg IM q8h prn

Terrestrial diagnosis of nephrolithiasis is usually based upon a intravenous pyelogram, unless the patient is allergic to contrast media or has substantial risk of a contrast-induced renal failure.[41] Renal ultrasound imaging is usually adequate for determining the presence of nephrolithiasis. Ureteral calculi, especially in the distal ureter, and stones smaller than 5 mm are not always observed on ultrasound.

The role of supranormal hydration in the management of renal/ureteral colic is debatable however, hypovolemic patients need adequate restoration of circulating volume to prevent further exacerbation of a supersaturated urine environment. Typical workup of a patient suffering from renal colic includes a urinalysis, CBC, and electrolyte, BUN, creatinine, and serum calcium levels. Unfortunately, most of these

are not available on orbit. Urine cultures should be obtained because urinalysis alone may not be sufficient to exclude a urinary tract infection. Obtaining a urine sample for post mission stone risk profile would be helpful; unfortunately there is no refrigeration capability on the ISS for urine sample storage.[14]

If the patient has vomiting, dehydration, fever, signs of infection, or a complete obstruction, de-orbit for hospitalization in indicated and urgent on-orbit treatment should be initiated.

The cornerstone of management of renal/ureteral colic is analgesia and can be accomplished most effectively with parenteral narcotics or nonsteroidal anti-inflammatory drugs (NSAIDs). Morphine sulfate is the renal colic narcotic analgesic drug of choice for parenteral and intramuscular use however, its use may be require you to address nausea, emesis, and urinary retention.

Ketorolac tromethamine is the only NSAID approved for parenteral use for renal colic in the United States, and it is often effective when used for renal colic with an onset of action being clinically evident within 10 min. Antiemetic agents such as metoclopramide HCl, and prochlorperazine may also be added as needed. It should be understood that promethazine may impair the passage of a stone due to its potential side effect of urinary retention.

A urinary tract infection behind an obstructing stone is an emergency and healthy adults can develop urosepsis and die within 4 hours. Terrestrial medical standards require that stenting or percutaneous drainage be performed immediately. Attempts to remove a stone should not be performed if an infectious process is ongoing. Urosepsis, once started, will not resolve without renal drainage. Since these

procedures aren't available in space, it is probably prudent to start all patients who present with renal colic on oral antibiotics. If tolerated, oral antibiotics in this setting may be appropriate and Ciprofloxacin provides good gram negative coverage. Augmentin has Clavulinate which in the face of renal obstruction may complicate its pharmacodynamics. Intravenous antibiotics are not indicated at this time and the delivery of many intravenous fluids and medications concurrently by a non-physician CMO in microgravity will be difficult.

Although not commonly used for this illness on Earth, prednisone may be added to help reduce ureteral inflammation and calcium channel blockers, such as nifedipine, also relaxes ureteral smooth muscle. Amelioration of both ureteral inflammation and ureteral muscle tone appears to facilitate stone passage. More recently, the use of selective alpha blockers such as Tamsulosin HCL (Flomax®) or Alfuzosin HCL (Uroxatral®) has become standard of care for increasing the passage of stones, however, these drugs are not currently manifested on the ISS.

This patient is stable and IM injections of an NSAID and analgesia are appropriate. Intravenous fluids should be given aggressively. Should FE2 pass the stone a significant post obstructive dieresis may occur with a dramatic increase in urine flow and possible electrolyte loss via the affected kidney.

Answer: E

Question 7. The Flight Director asks you which of the following options you would medically consider is appropriate over the next 24 hours.

A. Contingency deorbit to Continental United States within 3 hours with 1 minute of 8-10 G_x exposure
B. Nominal Soyuz deorbit to Kazakhstan or Russia in 6 hours with 3 minutes 3.8 G_x exposure.
C. Manage the problem on orbit as contingency deorbiting is dangerous
D. Wait for the Space Shuttle to return in 14 days
E. Miss the next PLS and re-evaluate in 12 hours.
F. No recommendation is possible at this time

You recommend against a contingency deorbit to the continental United States due to the risks of this off nominal event to the other crewmembers, as well as the unknown effect of FE2 suffering from renal colic during an exposure to +8 G_x for at least one minute. The renal colic of FE2 is still presently uncontrolled, and she is the only crewmember who is the most qualified to fly the Soyuz. Maintaining adequate pain control of a crew member during a Soyuz reentry would be very challenging to a non-physician CMO, and the very confined space would prevent the CMO from monitoring or managing the patient. Your recommendation to the Flight Director is for a nominal Soyuz deorbit from the ISS to Kazakhstan since a contingency deorbit of 8 to 10 G_x exposure with knees above the head for a patient suffering from renal colic may be extremely uncomfortable. Nominal landings to Earth using the Soyuz are only supported at Kazakhstan because of limitations in its navigational software. It could take more than 24 hours for a US military recovery crew to reach all other contingency

landing sites throughout the world which may not be acceptable for patients suffering from nephrolithiasis and possible gram negative sepsis.

Answer: A,C,F,I,J,K,M

Question 8. Based on the physical exam information prescribe the flowing treatment for the CMO to provide:?

A. Continue IV NS 500 ml/hour
B. Augmentin 500 mg PO X 2 STAT then Q8H
C. IV Amikacin/ceftriaxone
D. Start Ciprofloxacin 500mg PO BID
E. Vitals q1h
F. Vitals q15min
G. Vitals q5min
H. Discontinue Oxygen
I. Continue Ketorolac/Tromethamine 15 mg IM q8h prn
J. Repeat the ultrasound exam
K. Use a strainer to “catch” any stones
L. Wave off the current deorbit and reassess for next PLS
M. Inform flight director we are definitely going to need to deorbit for next PLS

FE2 is most likely suffering urosepsis until proven otherwise and prompt antibiotic treatment in required. Phenergan should be given to help control the nausea and vomiting, however, the Flight Surgeon is aware of the potential for precipitation of Ketorolac Tromethamine and Phenergan in the same IV. FE2 is receiving regular doses of intravenous Ketorolac/Tromethamine and therefore ASA is not indicated. Coadministration with aspirin increases the risk of inducing serious gastrointestinal NSAID-related side effects and probenecid may increase the renal toxicity of NSAIDs

therefore Augmentin should be avoided since the FE2 already took ASA earlier. Ciprofloxacin has been shown to be very effective in treating complicated urinary tract infections and uncomplicated acute pylonephritis.[42] Amikacin/ceftriaxone could be administered if FE2 cannot ingest oral antibiotics, however, managing several IV medications at the same time on the ISS is difficult for the CMO to administer and Flight Surgeon to monitor. Nonetheless ,given the potential for rapid deterioration of FE2's vitals in such a hazardous environment, an immediate dose of IV Amikacin/ceftriaxone is indicated even though Amikacin induced nephrotoxicity and ototoxicity are potential complications .[34]

Answer: A,B,C,D,F,G,K

Question 9. Based on the recent physical exam and diagnostic imaging information you prescribe which of the flowing treatments for FE2?

A. Continue IV NS 500 ml/hour
B. Continue IV Amikacin/ceftriaxone
C. Start Ciprofloxacin 500mg PO BID
D. Vitals q1h
E. Vitals q15min
F. Discontinue Oxygen
G. Continue Ketorolac/Tromethamine 15 mg IM q8h prn
H. Discontinue Ketorolac/Tromethamine
I. Repeat the ultrasound exam
J. Remove Foley catheter but strain urine for stones.
K. Wave off the current deorbit and reassess for next PLS

FE2 should be encouraged to drink fluids PO and IV normal saline should be continued until FE2 can tolerate PO fluids. IV antibiotics are appropriate for at least the next 24 hours given her previously septic presentation. Starting a course of PO Ciprofloxacin now is appropriate since her IV antibiotics may get discontinued later. FE2 is stable and vitals q1h is appropriate. IM NSAIDS will be helpful in controlling the inflammatory response to her obstruction and can be discontinued in 24 hours. A repeat ultrasound exam in 12 to 24 hours is advised to confirm bilateral urethral jets and a resolution of the calyceal dilation. Next PLS should be waived given the improvement in FE2's condition.

Question 10.) After her mission, you advise FE2 that she?

A. is disqualified from long duration spaceflight
B. is disqualified from short duration spaceflight
C. is potentially waiverable for short duration flight
D. should receive Renal Stone Risk assessment
E. should receive a CT – fine renal slices (2mm)
F. should receive a Nephro – tomogram
G. should receive a Spiral CT with pyelogram phase,
H. should receive a Metabolic stone work up
I. no workup necessary since it was spaceflight which caused this

You advise the patient that the minimally invasive modalities for stone removal are generally successful in removing calculi. The usually quoted recurrence rate for urinary calculi on Earth is 50% within 5 years and 70% or higher within 10 years. Metabolic evaluation and treatment are indicated for patients at greater risk for recurrence, including those who present with multiple stones, those who have a history of previous stone formation, and those who present with stones at a younger age, however, this is not the case for FE2. The most important aspect of medical therapy is maintaining an increased fluid intake and high urinary volume. Without an adequate urinary volume, no amount of medical or dietary therapy is likely to be successful in preventing nephrolithiasis. Increasing fluid intake and dietary moderation can cut the stone recurrence rate by 60%. This phenomenon is known as the “stone clinic effect”. FE2 should be counseled to seek immediate medical attention if he or she experiences flank or abdominal pain or notes visible blood in the urine.

Of significance is the fact that spaceflight alone may be the only risk factor responsible for this case of nephrolithiasis. During a long duration mission in space, calcium excretion (both urinary and fecal) is increased when compared to measurements taken before flight, [17] which results resulted in a net loss of calcium from the body causing . This is a great concern for bone loss and also elevated urinary calcium which can increase the risk of forming kidney stones[47]. The Multilateral Space Medicine Board has disqualified FE2 from further ISS missions.

Discussion

Renal and ureteral stones are a common problem and recent studies establish the occurrence of kidney stone disease has increased in many industrialized countries[40]. Patients typically present with the classic symptoms of renal colic and hematuria, however other presentations can be asymptomatic or have atypical symptoms such as vague abdominal pain, acute abdominal pain, nausea, difficulty urinating, penile pain, or even testicular pain. Nephrolithiasis is a relatively common problem and approximately 12 percent of men and 5 percent of women will have at least one symptomatic stone by the age of 70.[16] The National Health and Nutritional Examination Survey reports that the prevalence of nephrolithiasis is increasing in the United States from 3.8 percent in the period 1976 to 1980 to 5.2 percent in the years 1988 to 1994.[40] Of patients with nephrolithiasis, eighty percent form stones which are composed primarily of calcium oxalate or, less often, calcium phosphate.[6,16] The incidence of nephrolithiasis increases with age, and is higher in men , and in Caucasians[39] with Hispanics and Asians being at an intermediate risk. It has been estimated that 7 to 10 of every 1,000 hospital admissions are due to nephrolithiasis.[22] Nephrolithiasis is most likely to occur when one or more factors contribute to supersaturation of the urine, the formation of calcium crystals, and their subsequent aggregation into an overt stone. Urine supersaturation can be increased by dehydration, hyperfiltration (too much calcium delivered), inadequate reabsorption in the tubules or over secretion of oxalate, phosphate, cystine or uric acid. Asymptomatic subjects can excrete tiny crystal nuclei; however, this process is

accelerated in nephrolithiasis prone patients who tend to excrete larger crystal aggregates and are more likely to have calcium oxalate crystals in the urine.[36] Most certainly many of these risk factors can occur in space flight.[11,12,25,31,46-49] A significant factor which contributes to the formation of certain stones is the urine pH. Most subjects excrete acidic urine throughout the day which promotes the precipitation of uric acid and can increase the risk for formation of calcium stones. Conversely, calcium phosphate stones precipitate in relatively alkaline urine, and calcium oxalate stones are not pH-dependent.

It is unclear how crystals which have formed in the renal tubules eventually become a stone, rather than being washed away by the high rate of urine flow. One hypothesis is that crystal aggregates become large enough to anchor at the end of the collecting ducts and then increase in size over time.[2,20,21,44]This renal tubule crystal anchoring is thought to occur at sites of epithelial cell damage by binding to hyaluronan[2,44] which is induced by the crystals themselves[23,26]. Another hypothesis supports the formation of a crystal nidus by nanobacteria, a class of atypical bacteria commonly found in kidney stones which is independent of stone composition[18,19]. In a study by Ciftcioglu et al[5] of 72 consecutive kidney stones, 97 percent tested positive for nanobacteria.

In the absence of gravity, such as space flight, a rapid loss of bone mineral and osteopenia occurs through a mechanism which not completely understood.[27,29,45] The unloading of the skeleton in microgravity may result from increased bone resorption, decreased bone formation, or both, however the analysis of bone from animals during space flight has not yielded consistent results. There have been fewer studies of the effects of weightlessness on human bone metabolism because of the inherent

difficulties in procuring bone biopsies from astronauts while in orbit. Most bone biopsy studies have focused on immobilized patients such as those with spinal cord injury or normal subjects undergoing prolonged bed rest.[32] More recently, the availability of biochemical assays for assessing bone resorption and formation activities has been used in assessing the skeletal response to both simulated weightlessness[10] and long duration space flight.[4,7]

This microgravity induced loss of bone calcium and phosphorus could promote the formation of nephrolithiasis, in part by causing secondary hypercalciuria and hyperphosphaturia.[30,31] Pak et al[31] analyzed 24-h urine samples for stone-forming risk factors in 104 male applicants before the final selection into the astronaut corps. Of interest was abnormal supersaturation of urine with calcium oxalate in 25.0% of applicants, brushite in 36.5%, and monosodium urate in 66.3% of applicants which predisposes them to nephrolithiasis from precipitation of calcium salts. The supersaturated urine was secondary to both "metabolic" and environmental factors. Metabolic factors included hypercalciuria in 11.5%, hyperoxaluria in 2.9%, hyperuricosuria in 18.3% and hypocitraturia in 5.8% of applicant. Environmental factors included low urine volume of less than 2 L.d-1 in 84.6%, high urinary phosphate in 24.4%, and high urinary sodium in 10.6% of applicants. Pak et al[31] found that the majority nephrolithiasis risk factors among astronaut applicants were environmental.

Hwang et al[15] studied the effect of prolonged bedrest of risk factors for nephrolithiasis. The crystallization of calcium salts was examined in eight normal subjects during 5 weeks of bedrest. The mean urinary calcium excretion increased in the first week from

5.68 to approximately 7.50 mmol/day and remained elevated thereafter. Mean urinary phosphorus excretion increased by the second week from 2.70 to approximately 30.6 mmol/day and remained elevated. Urinary sodium, magnesium and uric acid excretion increased slightly and pH, oxalate, and citrate remained relatively unchanged. Nonetheless, urinary saturation of calcium phosphate, calcium oxalate, and monosodium urate increased significantly during bedrest. The inhibitor activity against nucleation of brushite and calcium oxalate was not increased by bedrest, therefore propensity for the crystallization of stone-forming calcium salts is enhanced by bedrest. This suggests that gravitational unloading of the musculo-skeletal system in microgravity may confer increased risk for the formation of calcium-containing renal stones.

Whitson et al examined 24 hr urine samples from 365 astronauts pre and post flight from4 to 17 day Shuttle missions.[49] They found that urinary supersaturation levels of stone forming salts were reduced when urine volumes exceeded 2 liters per day. Of interest is the need for daily exercise countermeasures and the increase risk for calcium oxalate and uric acid stone formation with exercise which is not currently followed with fluid compensation.[37] Another interesting potential risk for stone formation is during 6 to 8 hr Extravehicular Activities (EVA) where dehydration is possible since fluid compensation is usually less than 2 liters.

(add a small blurb about sepsis in space leo versus mars… refer to white paper[9]

Note From the Authors:

This case was presented to acquaint the reader with the tremendous challenges that face the flight surgeon when supporting a space mission. The limited crew training time, medical hardware, and drugs manifested to deal with the previous medical event predicate that aggressive primary and secondary prevention strategies need to be developed to protect a 40-billion-dollar asset like the International Space Station.

Reference List

1. Ahamad NA, Ather MH, Rees J. Unenhanced helical computed tomography in the evaluation of acute flank pain. Int J Urol 2003 Jun;10:287.

2. Asselman M, Verhulst A, De Broe ME, et al. Calcium oxalate crystal adherence to hyaluronan-, osteopontin-, and CD44-expressing injured/regenerating tubular epithelial cells in rat kidneys. J Am Soc Nephrol 2003 Dec;14(12):3155-66.

3. Buckey JC, Gaffney AF, Lane LD, et al. Central Venous Pressure in Space. NEJM 1993;328(25):1853-4.

4. Caillot-Augusseau A, Vico L, Heer M, et al. Space flight is associated with rapid decreases of undercarboxylated osteocalcin and increases of markers of bone resorption without changes in their circadian variation: observations in two cosmonauts. Clin Chem 2000 Aug;46(8 Pt 1):1136-43.

5. Ciftcioglu N, Bjorklund M, Kuorikoski K, et al. Nanobacteria: an infectious cause for kidney stone formation. Kidney Int 1999 Nov;56(5):1893-8.

6. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N Engl J Med 1992 Nov;327(16):1141-52.

7. Collet P, Uebelhart D, Vico L, et al. Effects of 1- and 6-month spaceflight on bone mass and biochemistry in two humans. Bone 1997 Jun;20(6):547-51.

8. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study. Radiology 2005 Aug;236(2):477-84.

9. Feldman CL, MacCallum G, Hartley LH. Comparison of the standard ECG with the EASI cardiogram for ischemia detection during exercise monitoring. Computers in Cardiology. Lund, Sweden. Piscataway, NJ: IEEE Computer Society Press, 343-5.

10. Fukuoka H, Nishimura Y, Haruna M, et al. Effect of bed rest immobilization on metabolic turnover of bone and bone mineral density. J Gravit Physiol 1997 Jan;4(1):S75-81.

11. Gazenko OG, Grigoriev AI, Egorov AD. Physiological Effects of Weightlessness on Humans During Space Flight. Fiziol Cheloveka 1997;23(2):138-46.

12. Grigoriev AI, Egorov AD. Mechanisms of Homeostasis Formation During Prolonged Exposure to Weightlessness . Aviat. Space Environ. Med. 1998;32(6):20-6.

13. Harris BA, Billica RD, Bishop SL, et al. Physical Examination During Space Flight. Mayo Clin. Proc. 1997;72:301-8.

14. Hoyer JR, Pietrzyk RA, Liu H, et al. Effects of Microgravity on Urinary Osteopontin. J Am Soc Nephrol 1999;10:S389 - S393.

15. Hwang TI, Hill K, Schneider V, et al. Effect of prolonged bedrest on the propensity for renal stone formation. J Clin Endocrinol Metab 1988 Jan;66(1):109-12.

16. Johnson CM, Wilson DM, O'Fallon WM, et al. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int 1979 Dec;16(5):624-31.

17. Johnson RS, Dietlein LF. Biomedical Results from SkyLab. NASA Washington D.C. 1977;SP - 377:313-23.

18. Kajander EO, Ciftcioglu N. Nanobacteria: an alternative mechanism for pathogenic intra- and extracellular calcification and stone formation. Proc Natl Acad Sci U S A 1998 Jul;95(14):8274-9.

19. Kajander EO, Ciftcioglu N, Aho K, et al. Characteristics of nanobacteria and their possible role in stone formation. Urol Res 2003 Jun;31(2):47-54.

20. Khan SR, Kok DJ. Modulators of urinary stone formation. Front Biosci 2004 May;9:1450-82.

21. Kok DJ, Khan SR. Calcium oxalate nephrolithiasis, a free or fixed particle disease. Kidney Int 1994 Sep;46(3):847-54.

22. Kreutzer ER, Folkert VW. Etiologic diagnosis of renal calculus disease. Curr Opin Nephrol Hypertens 1993 Nov;2(6):949-55.

23. Kumar V, Yu S, Farell G, et al. Renal epithelial cells constitutively produce a protein that blocks adhesion of crystals to their surface. Am J Physiol Renal Physiol 2004 Sep;287(3):F373-83.

24. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005 Sep;162(5):421-9.

25. Leach CS, Citron NM. Endocrine System and Fluid and Electrolyte Balance. Space Biology and Medicine, Humans in Spaceflight. 1 ed. Vol. 3. 1. Reston VA and Moscow: American Institute of Aeronautics and Astronautics and Nauka Press, 1996:89-104.

26. Lieske JC, Toback FG. Regulation of renal epithelial cell endocytosis of calcium oxalate monohydrate crystals. Am J Physiol 1993 May;264(5 Pt 2):F800-7.

27. Marie PJ, Jones D, Vico L, et al. Osteobiology, strain, and microgravity: part I. Studies at the cellular level. Calcif Tissue Int 2000 Jul;67(1):2-9.

28. Moore PT, Thornton WE. Space Shuttle Inflight and Postflight Fluid Shifts Measured by Leg Volume Changes. Aviat. Space Environ. Med. 1987;58(9, Suppl.):A91-6.

29. Morey ER, Baylink DJ. Inhibition of bone formation during space flight. Science 1978 Sep;201(4361):1138-41.

30. Pak CY. Medical prevention of renal stone disease. Nephron 1999;81 Suppl 1:60-5.

31. Pak CY, Hill K, Cintron NM, et al. Assessing applicants to the NASA flight program for their renal stone-forming potential. Aviat Space Environ Med 1989 Feb;60(2):157-61.

32. Palle S, Vico L, Bourrin S, et al. Bone tissue response to four-month antiorthostatic bedrest: a bone histomorphometric study. Calcif Tissue Int 1992 Sep;51(3):189-94.

33. Pietrzyk RA, Jones JA, Sams CF, et al. Characteristics of Renal Stone Formation Amoung U.S. Astronauts. Unpublished Results 2005.

34. Ramakrishnan K, Scheid DC. Diagnosis and management of acute pyelonephritis in adults. Am Fam Physician 2005 Mar;71(5):933-42.

35. Randall A. The origin and growth of renal calculi. Ann. Surg. 1937;105:1009-27.

36. Robertson WG, Peacock M. Calcium oxalate crystalluria and inhibitors of crystallization in recurrent renal stone-formers. Clin Sci 1972 Oct;43(4):499-506.

37. Sakhaee K, Nigam S, Snell P, et al. Assessment of the pathogenetic role of physical exercise in renal stone formation. J Clin Endocrinol Metab 1987 Nov;65(5):974-9.

38. Singal RK, Denstedt JD. Contemporary management of ureteral stones. Urol Clin North Am 1997 Feb;24(1):59-70.

39. Soucie JM, Thun MJ, Coates RJ, et al. Demographic and geographic variability of kidney stones in the United States. Kidney Int 1994 Sep;46(3):893-9.

40. Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 2003 Jun;63(5):1817-23.

41. Stewart C. Nephrolithiasis. Emerg Med Clin North Am 1988 Aug;6(3):617-30.

42. Talan DA, Klimberg IW, Nicolle LE, et al. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol 2004 Feb;171(2 Pt 1):734-9.

43. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary Calcium Independently Predicts Incident Premature Coronary Heart Disease Over Measured Cardiovascular Risk Factors Mean Three-Year Outcomes in the Prospective Army Coronary Calcium (PACC) Project. J Am Coll Cardiol 2005 Sep;46(5):807-14.

44. Verhulst A, Asselman M, Persy VP, et al. Crystal retention capacity of cells in the human nephron: involvement of CD44 and its ligands hyaluronic acid and osteopontin in the transition of a crystal binding- into a nonadherent epithelium. J Am Soc Nephrol 2003 Jan;14(1):107-15.

45. Vico L, Hinsenkamp M, Jones D, et al. Osteobiology, strain, and microgravity. Part II: studies at the tissue level. Calcif Tissue Int 2001 Jan;68(1):1-10.

46. Whedon GD, Lutwak L, Rambaut P, et al. Effect of weightlessness on mineral metabolism; metabolic studies on Skylab orbital space flights. Calcif Tissue Res 1976 Sep;21 Suppl:423-30.

47. Whitson PA, Pietrzyk RA, Pak CY. Renal stone risk assessment during Space Shuttle flights. J Urol 1997 Dec;158(6):2305-10.

48. Whitson PA, Pietrzyk RA, Pak CY, et al. Alterations in renal stone risk factors after space flight. J Urol 1993 Sep;150(3):803-7.

49. Whitson PA, Pietrzyk RA, Sams CF. Urine Volume and its Effects on Renal Stone Risk in Astronauts. Aviat. Space Environ. Med. 2001;72:368-72.