

Hypothetical Case of Pancreatitis During a Long Duration Lunar Mission

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INTRODUCTION: This peer-reviewed hypothetical case was written to help the readership understand the challenges of dealing with quite common yet very debilitating diseases during space missions. This scenario is based on a real case of an astronaut who had previously flown in space and developed acute pancreatitis after being dehydrated from wilderness survival training. Many astronauts experience life threatening illness and injury before and after flight and, as space missions become longer and more remote, it is only a matter of time before these events occur during a mission. Future exploration space mission planners need to anticipate that these common catastrophic medical events will occur.

CASE REPORT: You are a flight surgeon working on console at Mission Control during a long duration lunar mission. You have completed extensive space, military, and civilian aerospace medical training to address almost any anticipated medical event and can summon advice from medical experts located around the world. One crewmember is a 37-yr-old man who just completed an 8-h moonwalk and now describes a constant 7/10 dull epigastric pain with radiation around the left flank to his back. His pain is getting progressively worse and he is presently sitting with his trunk flexed and knees drawn up in extreme distress. Working with the flight director, you must decide in the next 12 h whether to recommend the multibillion-dollar mission be aborted and have the crew return to Earth immediately to save your patient.

KEYWORDS: space medicine, pancreatitis, space exploration, lunar mission, epidemiology, medical care, critical care, abdominal pain.

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You are a flight surgeon working on console at the Mission Control Center during a lunar exploration mission. You have completed extensive space, military, and civilian aerospace medical training to address almost any anticipated medical event and can summon advice from space medicine experts located around the world. Your present duties include providing medical support for two male and two female astronauts who are working on the lunar surface for a planned 6-mo stay. You also have conducted annual and preflight medical exams, in-flight periodic health status exams, exercise monitoring, private medical conferences, biomedical monitoring during moonwalks, and monitoring of the vehicle's environmental parameters and the crew's daily schedules.

One crewmember is a 37-yr-old man who arrived with his crew on the lunar surface 5 wk ago from Earth via a platform orbiting around the Moon. Today he participated in a physically demanding 8-h moonwalk to repair a failing solar panel array. He has completed six moonwalks since his arrival on the lunar surface, including three in the past week. Following his return to the lunar habitat he underwent a routine private medical conference with you via private space-to-ground video

conference from the lunar base. During the medical conference the patient denied any medical concerns except for dry lips and right forearm and shoulder soreness thought to be secondary to stiffness of the space suit when pressurized. The patient has been self-prescribing ibuprofen 400 mg every 6–8 h over the last week. Following his medical conference, he proceeds to eat a meal consisting of pasta with tomato and meat sauce. The patient has an unremarkable past medical and family history with no abdominal surgeries or procedures.

As you are just about to leave Mission Control 2 h later, the patient requests another unscheduled private video conference. He describes a constant 7/10 dull epigastric pain with radiation

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around the left flank to his back. During the medical conference, the patient denied ever having pain like this in the past and states his pain is getting worse; sitting with his trunk flexed and knees drawn up slightly improves the pain.

Currently, the patient denies a history of chest pain, shortness of breath, cough, constipation, diarrhea, dysphagia, dyspepsia, hematemesis, hematochezia, melena, or reflux. He feels nauseated but has not vomited. He also denies any dysuria, urgency, frequency, chills, shakes, diarrhea, or constipation. He took 500 mg of acetaminophen 20 min before calling you with no noticeable effect on his pain. You recall the lunar crew has been forced to conserve water because the reduced power from the solar panel failures resulted in a reduction of water recycling. The patient informs you that he has been restricting his recommended fluid intake of $2.5 \text{ L} \cdot \text{d}^{-1}$ for all moonwalks to minimize voiding in his space suit.

The lunar crew medical officer is a physician/geologist who participated in a hybrid space medical training program (E/R, aerospace, trauma, surgical, internal medicine, and occupational medicine) for this mission. With guidance from you (4–5 s communication delay), the medical officer examines the patient, who has presumptive abdominal pathology, under one-sixth Earth-gravity ($1/6 \text{ g}$) conditions with high ambient noise levels in the lunar habitat.

Examination

The patient is sitting with his trunk flexed and knees drawn up and appears quite anxious, pale, and diaphoretic. He points to his epigastric area as the location of pain.

- Vitals: Temperature 37.2°C ($\sim 99^{\circ}\text{F}$), pulse is 100 bpm, respiration rate is 18/min, blood pressure is 120/80 mmHg, pulse oximetry is 97%.
- Heart: Regular rate and rhythm, no murmurs, rubs, or gallops noted. Jugular veins are maximally distended to the ears, there is no pedal edema – the patient's legs are very skinny.
- Lungs: Equal breath sounds bilaterally, no adventitious sounds noted, no cyanosis.
- Abdomen: Bowel sounds unknown, epigastric tenderness to light palpation, no percussion tenderness. No Gray Turner's or Cullen's sign. Rebound tenderness not present.
- Neurological: No focal weakness or sensory deficiency, reflexes normal. Cranial nerve exam is grossly normal.

Question 1. Which of the following would you include in your differential diagnosis?

- A. Acute appendicitis.
- B. Small bowel obstruction.
- C. Acute pancreatitis.
- D. Mesenteric thrombosis.
- E. Renal colic.
- F. Aortic aneurysm dissection or rupture.
- G. Esophageal perforation.
- H. Pulmonary embolism.
- I. Pericarditis.
- J. Gastric or duodenal ulceration.

K. Angina/Myocardial infarction.

L. Esophageal spasm.

M. Gastroesophageal reflux disease.

N. Diaphragmatic hernia.

O. Parasitic infection: malaria, amoebiasis, giardiasis, cryptosporidiosis.

P. Bacterial infection: *E. coli*, *C. difficile*, salmonella, shigella; uncommon: *Yersinia*, *Campylobacter*.

Q. Decompression sickness (bends).

Each condition on the differential diagnosis represents a possible cause of severe epigastric pain. Some are potentially life threatening and would be disastrous to misdiagnose. Small bowel obstruction is unlikely in this individual as he provides no history of abdominal surgery requiring a waiver and denies pulsating pain consistent with obstruction. Small bowel surgeries secondary to bowel obstruction have been waived for long-duration space travel in the past.

Acute superior mesenteric artery embolic occlusion is typically associated with unremitting, intense midabdominal pain, nausea, vomiting, and often explosive diarrhea, and physical examination early in its course tends to be unimpressive. This diagnosis is unlikely given that the patient does not have any known vascular risk factors; however, a gas embolic occlusion is theoretically possible given the history of repeated moonwalk space suit decompressions. Decompression sickness can occur anywhere in the body, but is most frequently observed as joint pain in the shoulders, elbows, knees, and ankles and accounts for about 60–70% of all altitude cases.

Enteric infection is unlikely since he consumes the same food as everyone else. Stress-induced erosive gastritis complicated by nonsteroidal anti-inflammatory medications is possible and should be considered. Given the reduced gravity environment, classic findings like Gray Turner's or Cullen's sign may not manifest themselves classically due to the nondependent nature of free-fluid movement in the body.

Due to the privacy maintained during the medical video conference, the Flight Director is unable to hear any of the conversation between you, the medical officer, and the patient. After the conference you advise the Flight Director that a potential mission impact medical condition is being evaluated and an expedited return to Earth may need to be considered. The lunar exploration spacecraft and the lunar habitat have the capabilities to support a medical evacuation back to the lunar orbiting platform and then the Crew Exploration Vehicle to return to Earth. Ventilation, oxygenation, and inotropic support is provided by all vehicles. The Flight Director informs you that we are 12 h away from when they would need to launch from the lunar surface to make the next Earth return opportunity, which would take 4 d. The next window of opportunity to return to Earth from the Moon would be in 5 d. You inform the Flight Director that the patient was given 10 mg of intramuscular morphine 30 min ago by the medical officer and may require further medical and pain management and, therefore, an alternative pilot should start preparing for launch. The Flight Director spends the next 30 min in an emergency conference with

the flight control team and orders the teams to prepare for a complete evacuation of the crew back to Earth. The Flight Director informs you that he will need to make a GO/NOGO evacuation decision in 8 h.

Question 2. Which of the following laboratory investigations would you perform?

- A. Complete blood count (CBC).
- B. Na^+ , Cl^- , HCO_3^- , K^+ , BUN, creatinine, glucose.
- C. Ca^{2+} , Mg^{2+} , HPO_4^{2-} .
- D. EKG.
- E. Liver function.
- F. Liver enzymes.
- G. Lipase.
- H. Blood gases.
- I. Lactate.
- J. Troponin.
- K. D-dimer.

Having the capability to measure various blood parameters is important in helping to prioritize the differential diagnosis. A CBC is useful in identifying overall blood counts and indicators of infection. Hematocrit provides an indication of hydration status. Electrolytes, including Na, K, Cl, and HCO_3^- , are important for monitoring of critical cellular functions. Liver analysis, including alanine transaminase, aspartate transaminase, alkaline phosphatase and total bilirubin, also are useful in helping to rule in or rule out hepatobiliary pathology. Lipase is primarily produced by the pancreas and is an important marker for identifying pancreatitis. Blood gases are helpful in monitoring a patient's acid-base status and are also useful in identifying pulmonary and kidney pathology. The other tests can help rule out other less likely causes of acute abdominal pain. New microarray technology permits the evaluation of any standard lab available in most terrestrial tertiary care centers. All are normal except lipase, which is 1122 (U/L).

Question 3. Elevated lipase raises a concern for which of the following in this scenario?

- A. Acute pancreatitis.
- B. Salivary gland damage.
- C. Autoimmune pancreatitis.
- D. Chronic alcoholism.
- E. Renal colic.
- F. Hepatitis.
- G. Multiple endocrine neoplasia syndrome.

In each of these conditions, the labs ordered are useful in helping prioritize the differential diagnosis. The lipase level is approximately five times the upper limit of normal. Although a limited number of diagnoses can result in a lipase elevation, only pancreatitis is typically associated with a greater than threefold increase over baseline.³⁶ Other causes of elevated lipase include kidney disease, as lipase is excreted by the renal system.

Acute pancreatitis is a disease associated with significant morbidity and mortality and accounts for health care costs of \$2.5 billion and 275,000 admissions in the United States each

year. In severe cases, the mortality rate can be as high as 30%.¹⁸ Indeed, there have been several reports of commercial airline passengers with an acute abdomen secondary to pancreatitis and one individual who required medical evacuation from U.S. Amundsen-Scott South Pole Station in the Antarctic due to gallstone pancreatitis.⁴⁴

Up to 40% of patients with acute pancreatitis are labeled as idiopathic because of an inability to diagnose the corresponding etiology.¹⁸ The idiopathic descriptor is used when there is no apparent history of alcohol abuse or medication use, and when abdominal ultrasound reveals no characteristic abnormality of the gallbladder or biliary tree (i.e., no gallstones or duct dilation). Hypercalcemia and hypertriglyceridemia must also be absent. It is now apparent that a proportion of idiopathic pancreatitis is secondary to Sphincter of Oddi dysfunction,⁹ hereditary pancreatitis, cystic fibrosis, or autoimmune causes; however, the most prominent etiology within the idiopathic group remains a biliary source, in the form of biliary sludge or microlithiasis.²⁸ Originally described by Conrad⁸ in 1979, sludge can account for more than 60% of “idiopathic” cases.²⁸ Biliary sludge is defined as a mixture of particulate matter and bile due to solute precipitation. This mixture migrates caudally from the gallbladder to the common bile duct and eventually forms a mechanical obstruction of the main pancreatic duct drainage, and consequently increases intraductal pressure leading to stasis of acinar secretions, intraductal activation of pancreatic enzymes, and auto-digestion of the pancreas. Typically, this particulate matter is composed of cholesterol monohydrate crystals, calcium bilirubinate granules, other calcium salts, gall-bladder mucus, or small gallstones (< 2 mm) in the gallbladder.⁴⁰ The sensitivity of conventional transabdominal ultrasound for gall-bladder sludge is only ~55% and is even lower for sludge in the common bile duct. Ierardi *et al.*²⁶ studied 50 patients with ‘idiopathic’ pancreatitis observed over an 18-mo period using conventional ultrasonography and secondary harmonic imaging. They found that standard transabdominal ultrasonography had a sensitivity of 77.3%; however, the same procedure using secondary harmonic imaging increased this to 85.4% with a positive predictive value of 100%. Endoscopic ultrasonography has a sensitivity of 96%, with the ability to assess for parenchymal abnormalities as well, but has the disadvantage of being an invasive procedure, and is limited in its availability.¹⁹ Diagnosis and treatment decisions are commonly based on evidence from ultrasound alone.²⁸ Because the presence of biliary sludge increases the probability of recurrent pancreatitis,²⁸ a plan for early therapy and definitive intervention is essential.⁶ In fact, recent recommended practice in cases of minor (i.e., self-limiting with normal calcium, lipids, and IgG4) idiopathic pancreatitis is to perform mandatory laparoscopic cholecystectomy.¹ Despite a negative ultrasound, approximately 44% of these patients will go on to be diagnosed with microlithiasis on pathology, and 75% of these patients treated with cholecystectomy will not have recurrence of pancreatitis.^{1,39}

Several congenital abnormalities of the pancreas have been associated with idiopathic pancreatitis. Of these, pancreas

divisum is the most common anatomic variant of the human pancreas associated with idiopathic pancreatitis, occurring in 5–10% of the Caucasian population.¹² Pancreas divisum is caused by the failure of the dorsal and ventral pancreatic ducts to fuse such that most of the pancreas drains through the minor papilla (via the duct of Santorini). It is thought that this results in a relative stenosis of pancreatic drainage and, therefore, an increased risk of pancreatitis. The incidence of pancreas divisum ranges from 5 to 25% in patients with idiopathic acute pancreatitis.¹⁰ The management of pancreas divisum is controversial, because the precise risk of pancreatitis associated with this common anatomic variant is unclear. Symptomatic patients are treated conservatively initially, followed by either a surgical or endoscopic sphincterotomy/stent/Puestow procedure. Other anatomic anomalies that may increase the risk include duodenal duplication cysts, choledochal cysts, and choledochoceles.

Recently, several gene mutations that confer a significant risk of pancreatitis have been linked with familial pancreatitis.¹⁸ The index of suspicion for hereditary pancreatitis is higher in the setting of recurrent acute idiopathic pancreatitis with no other cause identified, early age of onset, and a positive family history of pancreatitis. Mutations in the cationic trypsinogen gene (PRSS1) result in increased autoactivation of cationic trypsinogen, and are associated with an 80% lifetime chance of acute pancreatitis and 40% lifetime risk of pancreatic cancer.⁴² These mutations are inherited in an autosomal dominant fashion.²⁵ Other mutations of the pancreatic secretory trypsin inhibitor/serine protease inhibitor Kazal Type 1 (PST1/SPINK1) and the cystic fibrosis transmembrane receptor (CFTR) increase the relative risk of pancreatitis 12 to 80 fold (vs. 1000 fold for PRSS1 mutations).⁷ The overall frequency of these alleles in the general population is as yet unknown and genetic testing is currently available for only the three most common PRSS1 mutations. Of note, patients with CFTR mutations have been reported to present initially with acute pancreatitis in the absence of other symptoms and in the presence of a normal sweat test.

The most common etiology of acute pancreatitis in adults are cholelithiasis (gallstones) and ethanol. Other common causes include the following:

- Alcohol
- Biliary tract disease
- Hyperlipidemia
- Hereditary
- Hypercalcemia
- Trauma
 - External
 - Surgical
 - Endoscopic retrograde cholangiopancreatography
- Ischemia
 - Hypoperfusion
 - Atheroembolic
 - Vasculitis
- Pancreatic duct obstruction

- Neoplasms
- Pancreas divisum
- Ampullary and duodenal lesions
- Infections
- Venom
- Drugs
- Idiopathic

While excessive ethanol consumption has been recognized as one of the major risk factors for the development of both acute and chronic pancreatitis, the magnitude of the effects of ethanol consumption remains unclear.¹⁴ Approximately one-third of the cases of acute pancreatitis in the United States have been attributed to ethanol. The chronic consumption of ethanol of 80 g/d over a 6- to 12-yr period has been estimated to increase the relative risk of chronic pancreatitis threefold, with an absolute risk of 2–3% over 20 to 30 yr.^{27,43} In the astronaut population, this degree of alcohol consumption (equivalent to 3 to 5 beers/day) is unlikely to be a major cause of pancreatitis.

Gallstones represent the other major predisposing factor for the development of pancreatitis in adults. In the setting of symptomatic gallstones, an elective laparoscopic cholecystectomy is typically performed due to the risk of recurrent symptoms and the low risk of the procedure itself. In individuals with asymptomatic gallstones, the annual rate of acute events has been previously estimated at 1–4% per year.⁴⁵

In the military aviator population, concerns have been raised about the development of acute complications of asymptomatic gallstones during flight. This led to the historical recommendation in the U.S. Air Force that pilots undergo an elective cholecystectomy for asymptomatic gallstones.³³ However, a subsequent review of this policy estimated the incidence of asymptomatic gallstones in the military aviator population to be 2–3%, with an associated occurrence of 0.1–0.7% of acute events,³³ with the prediction of 0.1 to 0.6 individuals having acute symptoms in flight and that the surgical risk was greater than the risk to flying safety or mission completion. Medical waivers have been allowed for asymptomatic cholelithiasis in U.S. military aviators and NASA astronauts, except selection physical exams. One retrospective review of 79 waivers was performed over a 2-yr period by Farr *et al.*,¹⁷ where 71% were requested for previous cholecystectomy and 29% for cholelithiasis. Aviators with symptomatic cholelithiasis are not eligible to return to flying status until they are asymptomatic postcholecystectomy. Most waivers were granted (83.5%) unless they had other disqualifying conditions and none of the aviators that were granted waivers had them revoked later due to symptomatic cholelithiasis (follow-up from 1 to 9 yr, mean 2.6 yr). Chadha *et al.*⁵ performed abdominal ultrasound imaging as an adjunct to routine physical examination among 2598 (2339 men, 259 women, mean age 20.3 ± 1.8 yr) young adults undergoing initial medical examination for civilian and military aviation duties in India and found cholelithiasis in 9 subjects (0.34%). These candidates with cholelithiasis were declared temporarily unfit pending evaluation to rule out any underlying causes. Other well-known risk factors for pancreatitis are in the list above.

The presumed cause of this patient's epigastric pain is acute pancreatitis. Using the onboard ultrasound under real-time tele-mentored guidance from experts on Earth, the medical officer conducts an abdominal ultrasound exam that includes biliary secondary harmonic imaging.^{24,34} The exam reveals sub-optimal distention of the gallbladder with possible "pseudo-thickening" of the gallbladder wall. No gallstones are present and ducts are not dilated; however, the exam is positive for biliary sludging. Although difficult to visualize, there is some evidence to support enlargement of the pancreatic head. No pancreatic pseudocysts or masses are noted. Renal calculi are not visualized.

Question 4. What would you recommend the medical officer perform?

- A. Recommend for immediate return to Earth.
- B. IV fluid resuscitation.
- C. Prophylactic antibiotic therapy.
- D. Monitor vitals every 30 min.
- E. Monitor urine output.
- F. Monitor oxygenation.
- G. Estimate the 24- and 48-h prognosis based on patient's presentation.

Acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. The overall mortality of acute pancreatitis is approximately 2%, but can approach 30% among patients with persistent failure of an organ system (i.e., lasting more than 48 h).¹⁸ In most cases, however, the disease is self-limited and will usually subside within 3 to 7 d after initiation of treatment. Conservative measures include analgesics for pain and intravenous fluids to maintain intravascular volume. In severe acute pancreatitis, the early phase is often associated with a systemic inflammatory response, causing third-space fluid sequestration and acute lung injury with pulmonary edema.¹⁸ Extra-pancreatic complications of acute pancreatitis include shock, renal insufficiency, respiratory insufficiency, cardiac complications, common bile duct obstruction, gastrointestinal bleeding, stenosis of an adjacent hollow organ (duodenum, colon, ureter, ileus of the small intestine), fat necrosis, and pancreatic encephalopathy.

Infection secondary to pancreatic necrosis is often seen later in the course of the disease. The role of prophylactic antibiotics was historically controversial,² but mounting evidence suggests against the routine use of prophylactic antibiotic in computed-tomography (CT) proven acute necrotizing pancreatitis.³⁵ In fact, even in patients with known infected necrotizing pancreatitis who undergo necrosectomy, antibiotic use has not been shown to definitively alter outcomes relative to noninfected necrotizing pancreatitis patients who also undergo surgery.¹³ The possibility of acquiring a common antibiotic induced *Clostridium difficile* diarrhea in the microgravity environment during the return to Earth is a definite hazard. Infection complicating pancreatic necrosis typically presents 7 to 14 d into the course of the illness. Infected necrosis may also present later in the course and other infections (such as pancreatic abscess or infected pseudocyst) are

seen more than 4 wk after the onset of illness.⁴ Studies have demonstrated a wide variation in bacterial infiltrates and a general shift from enteric organisms, including Gram-negative rods and anaerobic bacteria, to organisms of increasing resistance patterns and gram-positive species.¹³ In severe acute pancreatitis, the prevalence of enteric organisms has been linked to increased intestinal mucosal permeability. Organisms translocate across the colonic mucosa into the portal venous system and seed necrotic pancreatic tissue.¹³ In general, guidelines recommend against the use of antibiotics in acute pancreatitis, regardless of necrotization or degree of severity, unless accompanied by a concurrent extrapancreatic infection, or in some cases of infected necrotizing pancreatitis.^{11,38}

Predicting the outcome of acute pancreatitis is difficult. Several methods have been developed, including Ranson's criteria, Glasgow score, Apache II score, Atlanta classification, bedside index of severity in acute pancreatitis (BISAP), harmless acute pancreatitis score (HAPS), and CT severity index (CTSI). In 1974, Ranson *et al.*³² identified a group of prognostic signs to help identify patients with severe pancreatitis. Of these 11 parameters, 5 are measured at the time of admission, and the remaining 6 are measured within 48 h of admission (**Table I**).

Mortality is directly related to the number of signs present (**Table II**). The acute physiology and chronic health evaluation (APACHE II) score and the Glasgow score are based on modifications of Ranson's original 11 signs, yet both are difficult to implement and have poor sensitivity on initial presentation.³⁰ A contrast-enhanced CT scan provides a valuable estimate of the severity and prognosis in cases of moderate-to-severe acute pancreatitis; however, such devices are unlikely to be available on long duration space missions. It should be noted that the absolute level of serum amylase or lipase does not correlate with severity.⁴¹

In every case of pancreatitis that is not exceptionally mild, the patient should be hospitalized for observation, which reinforces the need to stabilize and transport the patient back to Earth. Furthermore, early therapy incorporating intravenous hydration, hemodynamic monitoring, electrolyte and acid-base correction, analgesia, antiemetics, nutritional assessment, and arguably early PO intake (within 24 h) as tolerated, is crucial for improving prognosis. Most physicians would agree that, in the case of acute pancreatitis, it is prudent to admit the patient overnight to monitor disease severity and progression, with severe cases of acute pancreatitis mandating intensive care unit admission. One key point to remember is prognostic criteria are derived from findings observed in a terrestrial environment.

Without additional laboratory and imaging data it is difficult to diagnose the severity of the pancreatitis. Knowing that the risk of serious acute pancreatitis is approximately 20%, you decide to initiate IV fluid resuscitation and monitor vitals, including pulse oximetry, for the next 4 h. You discuss the plan with the Flight Director and agree to re-evaluate the patient's medical status in 4 h. Meanwhile the Flight Director continues with preparations for an emergency evacuation from the Moon in 8 h.

You re-evaluate the situation 4 h later with the assistance of the lunar medical officer caring for the patient. He complains of

Table I. Ranson's Criteria.

UPON ADMISSION:
1. Age > 55. The incidence of acute pancreatitis increases with age and is greatest over the age of 55.
2. Blood glucose > 200 mg · dl ⁻¹ . Hyperglycemia (blood glucose > 200 mg · dl ⁻¹) is common and is due to multiple factors, including impaired insulin secretion, increased glucagon release, and an increased output of adrenal glucocorticoids and catecholamines.
3. WBC count > 16,000/mm ³ . Leukocytosis (WBC count > 16,000/mm ³) occurs frequently and is a marker of systemic inflammation.
4. Serum LDH > 700 IU%. Lactate dehydrogenase (LDH) is an enzyme that catalyzes the interconversion of lactate and pyruvate in the presence of NAD/NADH. Elevated serum LDH (Serum LDH > 700 IU%) is from tissue necrosis.
5. SGOT > 250 SF units % (56 units/dl). Serum glutamic oxaloacetic transaminase (SGOT), also known as aspartate transaminase (AST), is a liver enzyme released into circulation as a result of hepatocellular injury or death. Elevated serum glutamic oxaloacetic transaminase [SGOT > 250 SF units % (56 units/dl)] typically results from an ischemic liver injury.
AFTER 48 HOURS:
1. HCT decrease > 10%. The release of vasoactive inflammatory mediators from pancreatic tissue causes changes in capillary membrane permeability, leading to extra vascular and peritoneal space fluid loss, causing hypovolemic shock and hypotension. Hematocrit (HCT) provides a measure of hemoconcentration.
2. Serum Ca ²⁺ < 8 mg % (mg · dl ⁻¹). Hypocalcemia [Serum Ca ²⁺ > 8 mg % (mg · dl ⁻¹)] occurs in approximately 25% of patients and its pathogenesis is incompletely understood. It is primarily thought to be caused by saponification of fats in the retroperitoneum due to fatty acid breakdown from pancreatic enzymes; however, hypoalbuminemia is also thought to be a contributing factor.
3. Base deficit > 4 mEq · L ⁻¹ . Base deficit is a measure of circulatory inadequacy and reflects increased anaerobic metabolism associated with tissue hypoperfusion.
4. BUN increase > 5 mg % (mg · dl ⁻¹). Decreased intravascular volume and hypotension will have a direct effect on the glomerular filtration rate (GFR), resulting in an increased BUN. The result is decreased renal perfusion, causing oliguria.
5. Estimated fluid retention > 6L. Fluid retention is secondary to increased vascular permeability caused by vasoactive inflammatory mediators. The volume of fluid administered is determined by arterial blood pressure, central venous pressure, and urine output.
6. Arterial O ₂ tension < 60 mm · dg ⁻¹ . The release of vasoactive inflammatory mediators from pancreatic tissue causes changes in capillary membrane permeability, resulting in pulmonary edema. Approximately 25% of patients have hypoxemia (arterial O ₂ tension < 60 mm · dg ⁻¹), which may cause the onset of ARDS.

8/10 epigastric pain with some relief after the morphine that was administered 4 h ago. Upon examination it is noted that the patient is sitting upright and appears anxious, pale, and diaphoretic. He points to his epigastrium and right upper quadrant as the location of pain and complains of increased shortness of breath.

Table II. Mortality Rates Correlate with the Number of Criteria Present.

NUMBER OF CRITERIA	MORTALITY
0–2	1%
3–4	16%
5–6	40%
7–8	100%

Re-Evaluation

- Vitals: Temperature is 39.3°C (102.7°F), pulse is 120 bpm, respiratory rate is 26, blood pressure is 96/70 mmHg, pulse oximetry is 89%.
- Heart: regular rate and rhythm, no murmurs, rubs, or gallops noted.
- Lungs: Equal breath sounds bilaterally with bilateral global fine crackles.
- Abdomen: No bowel sounds present. Epigastric tenderness to light palpation, no percussion tenderness. No Gray Turner's or Cullen's sign. Rebound tenderness not present.
- Neurological: No focal weakness or sensory deficiency.

The medical officer also reports that the patient has received 4 L of normal saline IV with only 180 cc of urine output over the last 8 h.

Question 5. Which of the following concerns you the most regarding this patient?

- Urine output less than 50 ml · h⁻¹.
- Temperature of 39.7°C (102.7°F).
- Hypovolemia.
- Possible pulmonary edema.
- Third spacing of fluids.
- Retroperitoneal bleed.
- Hypotension.

The management of pancreatitis in microgravity (Space Shuttle, ISS, or the Crew Exploration Vehicle) or partial gravity (Moon 1/6 g, Mars 1/3 g) presents a unique diagnostic and treatment challenge. Diagnosis will most likely be clinically derived, based on history and physical exam performed by the crew medical officer. However, the clinical evaluation of an acutely ill crewmember will be difficult, as traditional methods of assessing volume status, such as the jugular venous pulsation or transabdominal ultrasonography of the inferior vena cava, may no longer be possible or valid. Basic laboratory testing may be available and the use of abdominal ultrasound may have limited utility during an acute episode of pancreatitis (ileus may obstruct a retroperitoneal view.)

Widely used clinical scoring schemes that aim to prognosticate patient outcomes from acute pancreatitis, such as Ranson's criteria, contain a variety of measures that may not be available on space vehicles over the next decade (white blood cell count, LDH, AST, BUN, etc.). Moreover, these scoring systems are validated with populations of often significantly differing demographics and medical histories/comorbidities than those typically selected for spaceflight. In addition, since individuals in low-gravity/microgravity may have low venous reserve because of cardiovascular adaptations, the effects of third spacing due to pancreatitis might magnify the clinical presentation of shock (hypovolemic or septic). Early therapy will likely involve intravenous hydration, hemodynamic monitoring, electrolyte and acid-base correction, analgesia, antiemetics, and nutritional assessment. Definitive therapy typically requires cholecystectomy, preferably laparoscopic.³⁷ Obviously these modalities will

not be available during spaceflight and rapid return to Earth is the only real option.

Edema and orthopnea are findings that change with body orientation relative to the gravitational vector, and it is unlikely that these changes would be profound in the reduced gravity of the Moon. There is also a normal 1- to 2-L cephalad fluid shift from the legs (primarily the thighs) that takes place in the first 8 to 24 h of spaceflight and remains until landing.²² This shift in fluid toward the heart is paradoxically accompanied by about a 5 to 7 mmHg decrease in central venous pressure²² with no clinically significant changes in cardiac output. The bedside examination of the jugular venous pressure on Earth is a reliable indicator of right atrial pressure because the vena cava acts as a venous hydrostatic column of blood. Jugular venous distension is a normal response to spaceflight that persists throughout the mission and would not be helpful in determining changes in right atrial pressure and right ventricular preload.^{22,23}

This case presents a unique medical management dilemma. An astronaut in space is hypovolemic relative to Earth-normal²² and, with the release of vasoactive inflammatory mediators from pancreatic tissue, the capillaries in the peripheral tissue and the lungs become 'leaky'. The cephalad fluid shifts in a reduced gravity environment may divert any administered intravenous fluid to the lungs. Therefore, there is a fine balance between reducing fluid resuscitation and worsening a hypovolemic shock state versus giving too much fluid, thereby exacerbating a possible low-pressure pulmonary edema. This patient most likely has low-pressure pulmonary edema secondary to cytokine-evoked changes in alveolar permeability, affecting capillary Starling fluid forces. This low-pressure pulmonary edema may be further exacerbated by the well-known cephalad fluid shifts secondary to reduced gravity.

The signs and symptoms also point to acute cholangitis as a result of biliary stasis and subsequent infection that needs to be treated aggressively especially when further complicated by pancreatitis. Any patient with suspected cholangitis should be treated with broad-spectrum antibiotics to cover Gram-negative aerobic enteric (*Enterobacter*, *Klebsiella*, *Escherichia coli*), Gram-positive *Enterococcus*, and anaerobic organisms (*Bacteroides fragilis*, *Clostridium perfringens*). Endoscopic decompression of the gallbladder also should be considered. Recent work by the authors has validated the placement of percutaneous drains in the gallbladder in a porcine model with the NASA reduced gravity research aircraft using remote expert guidance.¹⁵ The drains in that study were placed by nonmedical personnel who were remotely guided by surgical experts in real time using ultrasound or microlaparoscopy.

You are concerned that the patient is in the early stages of developing acute respiratory distress syndrome and may have already developed third spacing with a mild fever. You are also concerned that he has a decreased reserve fluid volume due to cephalad fluid shifts in 1/6 gravity, yet his low-pressure pulmonary edema might not tolerate any additional fluids at this point. You realize this situation has the potential to become much worse and decide it is necessary to transfer the patient to a more definitive medical care facility on Earth. After

discussing the patient's case with outside experts, acute cholangitis cannot be ruled out; therefore you direct the medical officer to insert a percutaneous drain into the gallbladder for decompression using the remote ultrasound guidance team in mission control. You also instruct the medical officer to administer broad spectrum intravenous antibiotics.

You advise the Flight Director of your concerns and that the quickest Earth return is strongly recommended because the patient may develop imminent life-threatening symptoms which can only be treated in a terrestrial critical care facility. Fortunately, over the last 4 h, the flight control team has successfully configured the lunar vehicle for the next optimal launch opportunity to rendezvous with the lunar orbiting platform. The Flight Director orders the crew to abandon the lunar base and return to Earth.

Question 6. What do you warn the medical officer about the patient's condition during the return to Earth?

- A. Progressive hypoxia from pulmonary edema.
- B. Infection and possible sepsis.
- C. Acidosis.
- D. Anemia.
- E. Fluid third spacing.
- F. Fluid shift in microgravity.
- G. Kidney failure.
- H. Diarrhea.
- I. Cardiovascular collapse.
- J. Depletion of medical resources.
- K. Agitation and a reduced level of consciousness.
- L. Review plans for palliation and possible death.

The incidence of pulmonary complications secondary to acute pancreatitis varies from 15 to 55%³¹ and ranges in severity, including hypoxia, atelectasis, pleural effusion, and severe acute respiratory distress. The pathogenesis of these complications is not completely understood, but has been attributed to cytokine release resulting in increased lung microvascular permeability.²⁹ Early onset pleural effusion is suggestive of a poor outcome from acute pancreatitis.³ Pleural effusions are visualized in all lung zones in microgravity since there are no dependent fluid shifts with posture as on Earth.²⁴ Ranson's original study reported that 58% of patients with acute pancreatitis were hypoxic within 48 h after admission.³² In more severe cases of acute pancreatitis, patients can develop acute respiratory distress (P_aO_2/F_iO_2 ratio less than 200 mmHg) with mortality rates of 30–40%.²⁰

Lung physiology is sensitive to gravity as it induces large gradients in blood flow, alveolar size, ventilation, and gas exchange. Experiments in weightlessness have demonstrated that topographic differences of lung expansion, ventilation distribution, and pulmonary perfusion are reduced.^{16,21} In this case, transporting the patient from a 1/6 gravity environment to weightlessness would most likely worsen his pulmonary function since all regions of the lung would become equally susceptible to pulmonary edema. In 1 G, when patients have basilar crackles secondary to acute or low- or high-pressure pulmonary edema, the midlung pressure is typically around 20 cm H₂O with the bases closer to 30 cm H₂O.²³ With increased alveolar permeability, a normal midthoracic pulmonary venous pressure

of 20 cm H₂O in microgravity may produce sudden global alveolar flooding. This theoretically implies that in low gravity/microgravity, the auscultation of crackles anywhere in the thorax in the setting of fluid overload and/or increased alveolar permeability may be a harbinger of impending fulminant pulmonary edema. If this fulminant pulmonary edema is secondary to increased alveolar permeability causing acute respiratory distress syndrome, then the patient might benefit from positive airway pressure to offset low left atrial pressure alveolar flooding.

The launch from the lunar surface and rendezvous with the orbiting platform is uneventful and after a successful lunar-Earth trajectory burn, the crew is now 4 d away from re-entry to Earth. The patient starts complaining of increased shortness of breath 6 h after leaving the lunar surface and experiencing microgravity and is observed to be confused. The medical officer now reports that his oxygen saturation is now 85% and dropping. The patient is successfully placed on continuous positive airway pressure with a fractional inspired oxygen of 80% from a cabin atmosphere oxygen concentrator. He remains barely stable during this time with a mild fever, oxygen saturation of 88% on continuous positive airway pressure by mask, and a urine output less than 50 ml · h⁻¹. The crew arrives 2 d later into Earth orbit and the patient has remained hypoxic from respiratory distress. The commander initiates a deorbit burn to re-enter over the Pacific Ocean 25 miles west of Los Angeles. The recovery team transports the patient to a tertiary care facility via air ambulance where he is intubated, placed on inotropic support, antibiotics, and later receives a laparotomy to remove infected necrotic tissue. The etiology of his pancreatitis is eventually declared to be biliary sludging secondary to dehydration. The patient received a prophylactic cholecystectomy and assumed an “inactive” status in the astronaut corps and later retired. You also retire and reflect on how hard this medical event would have been during a Mars mission, which would not have an abort option.

Summary

During a long duration lunar mission, the occurrence of acute pancreatitis in a crewmember would represent substantial challenges in medical management and have a sizeable impact on the mission itself. To prevent or reduce the risk of this possibility, it would be reasonable to screen for risk factors as part of the selection process, as well as assessing and managing risk factors during routine health maintenance visits. The difficulty arises with risk factors that are not well defined, such as common anatomic anomalies like pancreas divisum, or conditions such as microlithiasis for which routine abdominal ultrasound is not sufficiently sensitive. The presence of a rare mutation that places an individual at a markedly increased risk of pancreatitis raises the question of whether this and other medical illnesses should be genetically selected out for long duration missions.

Strategies for the prevention of acute pancreatitis in the astronaut/aviator population would consist of those interventions that seek to prevent the onset of the disease and those that aim to prevent recurrent episodes of acute pancreatitis. The approach for primary prevention includes identifying and managing risk factors for pancreatitis, such as alcohol use and

hypercholesterolemia, which are also important in the long-term health of any individual. In the astronaut population, the treatment of asymptomatic gallstones with a laparoscopic cholecystectomy would be reasonable to consider in the setting of a long duration mission, given the low risk of complications associated with the surgery. The prevention of recurrent episodes of pancreatitis and the potential implications for flight status depend on the underlying etiology of the acute episode. For example, the risk of recurrent acute pancreatitis due to biliary sludge in the case discussed warrants a laparoscopic cholecystectomy for the prevention of further episodes. Evidence does not exist whether this is truly preventive for missions greater than 1 yr.

Afterword

This hypothetical case report is presented in the style of “You are the Flight Surgeon” to help the readership understand the challenges of dealing with medical conditions that might be encountered during spaceflight. This scenario is based on a real case of an astronaut who had previously flown in space and developed acute pancreatitis after being dehydrated from wilderness survival training. Many astronauts experience life threatening illness and injury before and after flight and, as space missions become longer and more remote, it is only a matter of time before these events occur during a mission. This hypothetical lunar mission medical simulation allowed for an extremely unrealistic “return to Earth” scenario, which is not an option for a Mars mission. Future exploration space mission planners need to anticipate that these common catastrophic medical events will occur. We hope this will generate interest and more articles for and about space flight surgeons.

ANSWERS TO QUESTIONS

- 1.) A, C, E, F, G, H, I, J, K, L, M, N.
- 2.) All of them.
- 3.) A.
- 4.) A, B, D, E, F, G.
- 5.) All of them.
- 6.) All of them.

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