Clinical Finding Form (CliFF)

Branch Baseline

ICL26_Cholelithiasis/Biliary Colic, Acute

Acute cholecystitis is acute inflammation of the gallbladder, most commonly associated with obstruction of the cystic duct by gallstones or biliary sludge. Risk factors include female gender, obesity, hormone replacement therapy, severe hypertriglyceridemia, sickle cell disease, obesity surgery, sudden and significant weight loss, and gallbladder carcinoma. Acute cholecystitis may result in complications if not identified and treated promptly. Common disease-related complications can include severe sepsis, gangrenous cholecystitis, and gallbladder perforation with resultant bile peritonitis. Up to 18% of men and 25% of women have gallstones and most are asymptomatic [i.e. free of biliary colic] . A small number with gallstones (about 1.5% per year) will be treated for gallstone-related complications or symptoms. Gallstones may cause severe epigastric or right upper quadrant pain, acute cholecystitis, acute cholangitis, or gallstone pancreatitis. . While gallbladder cancer is rare, gallstones are a risk factor for this malignancy. Acalculous cholecystitis is gallbladder inflammation without stones and is seen primarily in critically ill patients. It requires a high degree of clinical suspicion, is difficult to diagnose, and is associated with a high mortality rate. There have not been any cases of biliary colic or cholecystitis reported in flight. In comparing these closely related conditions, biliary colic and cholecystitis share a spectrum of symptoms and no exact time course or definition exists to separate them, although based off of a systematic review by (Sanders, 2007), biliary colic pain lasts approximately less than 8 hours and acute cholecystitis pain lasts approximately greater than 8 hours. Further, a meta-analysis performed by (Colli, 2012) utilized a 2 hour interval to measure successful medical management of biliary pain with NSAIDs. An article published in UpToDate by (Zakko, 2021) notes that biliary colic pain lasts for at least 30 minutes. Therefore, it was estimated that biliary colic presents in a minimum window of 0.5 hours and a maximum window of 8 hours. Once the signs and symptoms of biliary colic last beyond 8 hours, the crew member is likely experiencing acute cholecystitis. About 10 to 15% of the adult Western population will develop asymptomatic gallstones over the course of their lifetime (Halldestam, 2004; Sanders, 2007; Zakko, 2021). (Zakko, 2021) puts the annual incidence of gallstone diagnosis in America at 1 million persons per year, which we may interpret as roughly equating to an 0.6%, all-inclusive annual risk of Cholecystitis-- likely a gross over-estimate in an astronaut population clinically screened for Cholecystitis and generally absent of risk factors. We estimate the annual 'complication' rate from Cholecystitis, i.e. an RTDC-surrogate of hospitalization, at 1.5% per year (Halldestam, 2004).

INCIDENCE DATA INCLUDED IN THE MODEL

The model imports the following incidence information from the MEDPRAT Evidence Library Database: incidence data category, space adaption status, EVA status, incidence data type, incidence and occurrence distribution data and incidence data characteristics. Data category defines the type of data available for incidence calculations (i.e. raw data vs. adjusted data). Space adaptation identifies medical events that where onset occurs in the first 5-7 days of flight and does not reoccur. EVA-related incidence values identify medical events that occur only during an EVA. Incidence values types vary by data category and define the number of medical events per person-year (rates) or medical events per person at-risk (proportion) for each medical condition. Incidence values can be modified by crew characteristics such as gender sex and certain crew medical history characteristics. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crewmember in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the MEDPRAT Technical Description Document.

INCIDENCE DATA

SPACEFLIGHT LITERATURE

Occurrences of biliary colic in the astronaut population are very low, and, therefore, the Bayesian process, preflight and in-flight astronaut data (obtained from Lifetimes Surveillance of Astronaut Health (LSAH) was utilized as the experimental data for spaceflight incidence in combination with a variety of sources, including the general U.S. population, U.S. Navy submarine data, and the analog astronaut population at the NASA Johnson Space Center (Gilkey, 2012). The probability distribution describing this rate in the general population was determine from a study published in the Canadian Medical Association Journal that used data from the Canadian Institute for Health Information, the Ontario Health Insurance Plan Physicians Claims Database and the Registered Persons Database to determine the annual incidence rates of acute cholecystitis, acute biliary pancreatitis, and acute cholangitis per 100,000 people from 1988 to 2000. Data concerning incidence of severe gallstone disease in the astronaut corps were obtained from the LSAH. There were no occurrences of severe gallstone disease in in-flight astronauts and no occurrences at any stage in female astronauts. The 3 pre-flight occurrences of gallstone disease in men were all 3 to 6 years preflight (Gilkey, 2012). A limitation to this incidence calculation is that an assumption was made that gallstone disease occurs at some characteristic constant rate over the period of interest (Gilkey, 2012).

ANALOG LITERATURE

A review of the Naval Aerospace Medical Institute (NAMI) Biomedical Database waiver requests for gallbladder disease over a 13 year period (April, 1988 to August, 2000) was conducted by (Farr, 2002). The Naval avation personnel were chosen to represent an astronaut analog population. Among the database waiver request review, 79 aviation personnel had submitted waiver requests for gallbladder disease. Of the 79, 56 (70.9%) had a diagnosis of previous cholecystectomy and 23 (29.1%) had a diagnosis of Cholecystitis. Of the 56 with previous cholecystectomy, laparoscopic cholecystectomy was the most common procedure in 36 (64.3%). Waivers were granted to 11 (47.8%) of the aviators with Cholecystitis and 51 (91.1%) with cholecystectomies. Waivers were not recommended in 12 aviators with Cholecystitis due to symptomatic common bile duct stone (1), symptomatic Cholecystitis (5), asymptomatic Cholecystitis (1), and other disqualifying conditions (3). No explanation was evident for 2 aviators. Of the aviators who received waivers for Cholecystitis or cholecystectomy had their waivers revoked later because of symptoamtic Cholecystitis or retained common bile duct stone (Farr, 2002).

TERRESTRIAL LITERATURE

According to an NIH study, hospitalization rates with mention of gallstones increased with age, were similar for blacks and whites and were 58% higher for women than men (Everhart, 2008). Generally, patients with symptomatic gallstones (ie biliary colic) or complications (ie cholecystitis or gallstone pancreatitis) warrant surgical intervention (Bellows, 2005). Biliary colic is alleviated by cholecystectomy in the majority of cases, whereas medical management methods are mostly palliative and are not widely supported (Bellows, 2005). Nearly 1 in 10 asymptomatic gallstones in the general population may be expected to develop symptoms or complications that require treatment within 5 years (Halldestam, 2004). Age may be inversely related to incidence of complications and both biliary colic and cholecystitis may be more common in women. During a prospective cohort study performed by Halldestam (2004), 14 of 123 patients with known gallstones, choelsterolosis or sludge were admitted to the hospital over an 87 month average period and were treated for symptoms or complications related to gallstones, 7 of those indications being biliary pain, 1 with biliary colic and 3 with cholecystitis (Halldestam, 2004). In a similar study by Alli (2017) utilizing the NY State Planning and Research Cooperative System (SPARCS) longitudinal administrative database, approximately 4.88% of patients underwent laparascopic cholecystectomy for biliary colic, 72.81% for calculous cholecystitis, and 8.98% for acalculous cholecystitis over a 19-year period (Alli, 2017). Further, a study by Noel (2016) utilized a nation-wide registry of the total number of cholecystecomies in Sweden between 1998 and 2013 and indications were prospectively collected during years 2006 to 2013 in the National Registry for Gallstone Surgery and ERCP. This study resulted in a mean adjusted annual rate of 85 admissions per 100,000 persons with an indication of biliary colic and 38 admissions per 100,000 persons for cholecystitis.

OVERALL INCIDENCE SUMMARY

INCIDENCE

7.69E-4 and SD 4.65E-6 for males; mean 1.266E-3 and SD 7.683E-6 for females

INCIDENCE SUMMARY

From the GRC Bayesian modeling of astronaut data using terrestrial sources for informing the priors, the posterior distributions for the sex-specific incidence rates are log-normally distributed with mean 7.69E-4 and SD 4.65E-6 for males and mean 1.266E-3 and SD 7.683E-6 for females.

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type
General
Segment
All
Env. Exposure
NA

Sex
Male
Crowns
Any
Contacts
Any

Pregnancy
Any

Incidence Distribution

Occurrence Dist
Poisson
Incidence Dist.
Log-Normal
Mean
0.000769
SD
4.65E-06

Log-Normal
(Mean): 0.000769
(SD): 4.65E-06

Incidence Details

Incidence Type
General
Segment
All
Env. Exposure

NA

Sex
Female
Crowns
Any
Contacts
Any

Pregnancy
Any

Incidence Distribution

Occurrence Dist
Poisson
Incidence Dist.
Log-Normal
Mean
0.001266
SD
7.683E-06

Log-Normal
(Mean): 0.001266
(SD): 7.683E-06

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Gilkey, et.al., 2012	Spaceflight	3
Halldestam, et.al., 2004	Terrestrial	2
Alli, et.al., 2017	Terrestrial	2
Noel, et.al., 2016	Terrestrial	2
Farr, et.al., 2002	Analog	1
Everhart, 2008	Terrestrial	2

A study by (Gilkey, 2012) utilizes data specific to astranauts, in addition to data among a variety of populations that are less representative of astronauts, such as a general population in Ontario, Canada (Urbach, 2005) which are less representative of the astronaut population. (Halldestam, 2004) provides data from a Swedish population without explicitly stating prior health conditions, making it unclear how well the population represents astronauts, and the paper also reports prevalence periods rather than incidence data. (Alli, 2017) determines incidence based on data registry of a general population in New York, which is likely overestimating incidence data for astronauts. A study performed by (Noel, et.al., 2016) utilizes a nation-wide registry for a general Swedish population requiring hospitalization, likely also overestimating incidence for astronauts. (Everhart, 2008) utilizes U.S. national surveys of patients requiring hospitalizations, which also likely overestimates the incidence among astronauts. A review conducted by (Farr, 2002) on Naval Aerospace Medical Institute (NAMI) Biomedical Database waiver requests over a 13 year period for gallbladder disease represents a somewhat reliable analog population.

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTATIVE MEASURES

Pre-flight preventive screening measures found at https://lsda.jsc.nasa.gov/MRID. To evaluate health status pre-, in-, and post-flight, astronauts undergo ultrasounds of abdomen and retroperitoneum; pelvis (female); thyroid, carotid vasculature; deep veins (upper extremity venous: bilateral internal jugular veins, entire subclavian-axillary axis, and lower extremity venous: bilateral deep veins).

BEST CASE SCENARIO DEFINITION

A course of uncomplicated biliary colic which resolves spontaneously or causes minimal disturbance requiring only symptomatic pain management.

WORSE CASE SCENARIO DEFINITION

Acute cholecystitis with likely complications requiring significant pain management, antibiotic administration, and likely definitive surgical management.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

Chlolelithiasis

BEST CASE/WORST CASE PROBABILITY COMMENTS

According to (Bellows, et.al., 2005), surgery for acute cholecystitis was historically discouraged. More than 20% of patients fail to respond to conservative management and experience recurrent cholecysitis during the intervening period. According to a study by (Halldestam, et.al., 2004), 123 individuals were identified with gallstones, choelsterolosis or sludge and were followed over an average 87 month period. Of those 123 patients, 14 were hospitalized and treated for symptoms or complications related to gallstones, 8 of these involving biliary related pain and 3 involving acute cholecystitis. It was determined that a ratio of roughly 25% of patients with biliary colic may develop acute cholecystitis, with 75% presenting only with biliary colic. It is estimated that 1.5% of patients with gallstones develop symptomatic disease each year and an estimated 3.8% to 12% develop acute cholecystitis within 5 to 10 years (Bellows, 2005; Haldestam, 2004).

TABLE 3.BEST/WORST CASE PROBABILITY LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Halldestam, et.al., 2004	Terrestrial	3
Noel, et.al., 2016	Terrestrial	2

The probability of worst case scenario was calculated based on a study by Halldestam (2004) reporting hospitalization rates of patients previously identified to have gallstones over an average of 87 months, in which 14 were hospitalized, 8 with biliary colic or recurrent biliary pain and 3 with acute cholecystitis. The ratio was determined to be 75% best case scenario and 25% worst case scenario. The study's results were determined to be reliable, involved a generally healthy population, and followed patients with the target condition over time for a representative, predictable approach. Noel (2016) utilized mean annual hospitalization rates for the best and worst case scenarios over a 16 year period, with a probability closer to 70% best case and 30% worst case, however the data less reliably represents this probability determination. Lastly, a more dated study cited by Bellows (2005) reported that in a randomized clinical study comparing surgery with observation for patients with symptomatic, noncomplicated gallstone disease, approximately 20% of patients in the observation group had recurrent biliary pain requiring hospital admission. Given that this data was less recent than that of Halldestam (2014), it was decided to utilize the 75/25 probability rather than the prior 80/20 of Bellows (2005).

TABLE 4. CLIFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	Composite Incidence	Condition Probability %	CP1: Diagnosis		CP2: Treatment			CP3: Condition End State				
			TI%	Duration	TI%	Duration		TI%	RTDC		LOCL	
			Preset	Preset	Preset	Min	Max	Preset	Min%	Max%	Min%	Max%
Treated Best Case (TBC)	7.69E-4 and SD 4.65E-6 for males; mean 1.266E-3 and SD 7.683E-6 for females	75 - 75	100	1.456	9.73957	0.5	7.5	5.60723	0	0	0	0
Treated Worst Case (TWC)		25 - 25	100	1.29	50	8	240	0	100	100	0	2.1
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.456	25.7109	1	8	5.60723	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.29	100	8	240	100	100	100	0	20

TABLE 4 KEY

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

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

Clinical Phase General Comments:

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

Clinical Phase 1: Initial Assessment and Diagnosis:

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%. In the untreated case, there is no diagnosis performed, therefore Task Impairment and Duration will always be " not applicable."

Clinical Phase 2: Stabilization, Treatment, and Convalescence:

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

Clinical Phase 3: Condition End State:

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

SCENARIO OVERVIEW COMMENTS

Capabilities exists to treat biliary colic and uncomplicated acute cholecystitis. Diagnosis may be made clinically, and augmented via right upper quadrant ultrasound possibly supported by serologic data. Therapy includes supportive care in the form of PO/IM/IV analgesia; anti-emetics; IV fluids and potentially antibiotics. Definitive surgical management via cholecystectomy is reserved for the most complicated and/or recurrent cases, and will likely not a capability. This was the rationale for the 100% worst case RTDC. Percutaneous drainage for gallbladder infections and infectious complications may be a half-measure capability for future long-duration missions.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Biliary colic and cholecystitis share a spectrum of symptoms and no exact time course or definition exists to separate them, although based off of a systematic review by (Sanders, 2007), biliary colic pain lasts approximately less than 8 hours and acute cholecystitis pain lasts approximately greater than 8 hours. Further, a meta-analysis performed by (Colli, 2012) utilized a 2 hour interval to measure successful medical management of biliary pain with NSAIDs. An article published in UpToDate by (Zakko, 2021) notes that biliary colic pain lasts for at least 30 minutes. Therefore, it was estimated that biliary colic presents in a minimum window of 0.5 hours and a maximum window of 8 hours. Once the signs and symptoms of biliary colic last beyond 8 hours, the crew member is likely experiencing acute cholecystitis. About 10 to 15% of the adult Western population will develop asymptomatic gallstones over the course of their lifetime. (Halldestam, 2004; Sanders, 2007; Zakko, 2021). (Zakko, 2021) puts the annual incidence of gallstone diagnosis in America at 1 million persons per year. We may interpret this risk as roughly equating to an 0.6%, all-comer annual risk of Cholecystitis, which is likely a gross over-estimate in an astronaut population clinically screened for Cholecystitis and generally absent of risk factors. Many papers have cited an annual ‘complication’ rate from Cholecystitis at 1-4%, specifically (Zakko, 2021 [UpToDate], and (Sanders, 2007) a BMJ Clinical Review. The source article for this range was (Halldestam, 2004), but the actual risk of an RTDC-surrogate [i.e. hospitalization] was closer to 1.5% per year. The definition of ‘complication’ includes “recurrent biliary pain, acute biliary colic, acute cholecystitis, bile duct stones with jaundice, gallstone pancreatitis and adenocarcinoma of the gallbladder.’ They summarize their findings that the “cumulative risk of being admitted to hospital and treated for complications or symptoms” was 7.6% (2.8-12.4%) during the first 5 years of follow-up; roughly equating to 1.5% per year assuming a linear curve for cumulative risk. This study was of a Scandinavian population. One limitation is that 18 of the original 123 individuals followed were lost to follow-up (3) or died (15)—with only one mortality linked to GB disease [carcinoma of the gallbladder]. In summary, we therefore may estimate the annual risk of gallbladder stone formation with a ‘hospitalization’-requiring complication at 0.6% * 1.5% = 0.009%. HOWEVER, by definition, this analysis will not impact RTDC, as: BC definition is “A course of uncomplicated biliary colic which resolves spontaneously or causes minimal disturbance requiring only symptomatic pain management.” By definition we assume that this equates to an RTDC of 0% for both treated and untreated. By definition, BC LOCL for this condition is 0%.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

According to a systematic review by (Sanders, 2007), biliary colic symptoms lasting greater than 8 hours are likely representative of the earliest conversion of biliary colic to cholecystitis. A review conducted by (Overby, 2010) recommends that for mild to moderately severe acute cholecysitis, surgery should be performed between 24 and 72 hours from symptom onset for patients who are not critically ill. Therefore, the low end duration for treated acute cholecystitis was determined to be 8 hours and the high end was established at 72 hours. WC definition is “Acute cholecystitis with likely complications requiring significant pain management, antibiotic administration, and likely definitive surgical management,” and by definition, equates to an RTDC of 100%. LOCL for acute cholecystitis can be as low as 0% and as high as 2.1% in patients who undergo standard of care, which consists of both hospitalization and surgical intervention (i.e. cholecystectomy) (Halpin, 2014; Riall, 2010).

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Regarding untreated biliary colic, literature has established a mean shortest duration period of approximately 1 hour (Akriviadis, 1997). It is also known that if biliary colic pain lasts longer than approxiamtely 8 hours, then it has likely converted to acute cholecystitis. Thus, the longester duration period is 8 hours (Sanders, 2007). These duration points are specific to a single episode of biliary colic, not recurrence. It should be noted that a study by (Akriviadis, 1997) reported a mean duration for recurrence of biliary pain to be 7.25 hours if left untreated. Treatment of biliary colic with NSAIDs may reduce the rate of gallstone-related complications, as high as 50% in the short term, however this disease modifying therapy has not been established in general treatment guidelines thus far (Colli, 2012). About 10 to 15% of the adult Western population will develop asymptomatic gallstones over the course of their lifetime. (Halldestam, 2004; Sanders, 2007; Zakko, 2021). (Zakko, 2021) puts the annual incidence of gallstone diagnosis in America at 1 million persons per year. We may interpret this risk as roughly equating to an 0.6%, all-comer annual risk of Cholecystitis, which is likely a gross over-estimate in an astronaut population clinically screened for Cholecystitis and generally absent of risk factors. Many papers have cited an annual ‘complication’ rate from Cholecystitis at 1-4%, specifically (Zakko, 2021 [UpToDate], and (Sanders, 2007) a BMJ Clinical Review. The source article for this range was (Halldestam, 2004), but the actual risk of an RTDC-surrogate [i.e. hospitalization] was closer to 1.5% per year. The definition of ‘complication’ includes “recurrent biliary pain, acute biliary colic, acute cholecystitis, bile duct stones with jaundice, gallstone pancreatitis and adenocarcinoma of the gallbladder.’ They summarize their findings that the “cumulative risk of being admitted to hospital and treated for complications or symptoms” was 7.6% (2.8-12.4%) during the first 5 years of follow-up; roughly equating to 1.5% per year assuming a linear curve for cumulative risk. This study was of a Scandinavian population. One limitation is that 18 of the original 123 individuals followed were lost to follow-up (3) or died (15)—with only one mortality linked to GB disease [carcinoma of the gallbladder]. In summary, we therefore may estimate the annual risk of gallbladder stone formation with a ‘hospitalization’-requiring complication at 0.6% * 1.5% = 0.009%. HOWEVER, by definition, this analysis will not impact RTDC, as: BC definition is “A course of uncomplicated biliary colic which resolves spontaneously or causes minimal disturbance requiring only symptomatic pain management.” By definition we assume that this equates to an RTDC of 0% for both treated and untreated. By definition, BC LOCL for this condition is 0%.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Regarding the duration for untreated acute cholecystitis, the shortest known symptomatic duration of acute cholecystitis is 8 hours (Sanders, et al, 2007). If left untreated, symptoms may abate in approximately 7 to 10 days (Salam, et al, 2021). Therefore, the duration of untreated acute cholecystitis was defined as ranging from 8 to 240 hours. It should be noted that observation alone (vs. surgical intervention) leads to a higher rate of gallstone-related complications and untreated acute cholecystitis frequently leads to complications (Halpin, 2014; Salam, et al, 2021). WC definition is “Acute cholecystitis with likely complications requiring significant pain management, antibiotic administration, and likely definitive surgical management,” and by definition, equates to an RTDC of 100%. According to a systematic review by (Halpin, 2014), the mortality for delayed surgical intervention was as low as 0%. A study by (Riall, et al, 2010) reported an in-hospital mortality rate as high as 2.7% for those who did not undergo cholecystectomy, although these patients did recieve nonsurgical therapy. Another study performed by (Schmidt, et al, 2011) resulted in a 24% mortality rate over a 14-month period for those who did not undergo surgical intervention; however, a systematic review performed by (Halpin, 2014) noted that this study's evidence was low quality. (Halpin, 2014) also reported an overall mortality of 20% from complications related to untreated acute cholecystitis, which are notably frequent (Salam, et al, 2021). Therefore, the low end UTWC LOCL was reported as 0% and a high end UTWC LOCL was approximated at 20%.

TABLE 5. CLINICAL PHASE II DURATION LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Colli, et al, 2012	Terrestrial	3
Bellows, et al, 2005	Terrestrial	
Overby, et al, 2010	Terrestrial	
Akriviadis, et al, 1997	Terrestrial	
Sanders, 2007	Terrestrial	
Riall, et al, 2010	Terrestrial	
Salam, 2021	Terrestrial	

(Colli, 2012) utilized a large sample size among a detailed systematic review of multiple RCTs, but does note a lack of high quality RCTs and presence of consistent heterogeneity among studies that may partially flaw the results. (Bellows, 2005) is an American Family Practice article and, therefore, peer reviewed and pooled from recent data for reliable evidence, however no specific study was cited from the duration data utilized. (Overby, 2010) also consists of a review of evidence for clinical guidelines and similarly did not specifically report a study for the duration data. The study by (Akriviadis, 1997) utilizes a small sample size with limited medical history noted, but does consist of ages similar to those of the target astronaut population, and was therefore deemed overall low quality evidence. A systematic review by (Sanders, 2007) performed a detailed search strategy choosing up to date articles and large populations of ages 19+ and was considered reliable data but may not be entirely representative of the astronaut population. The study by (Riall, 2010) consists of a large population with reliable data; however, the mean age of the population studied is 77 years, which is less representative of the target population and was conducted over a 10-year period, which is less realistic of spaceflight mission timelines. (Salam, 2021) is an article published by UpToDate and was deemed reliable, although no specific studies were cited by the data pooled from the article. Further, all citations inovlve terrestrial data and, therefore, are not simlar to the spaceflight environment.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Halldestam, et al, 2004	Terrestrial	3
Royal College of Surgeons, 2016	Terrestrial	
Friedman, et al, 1993	Terrestrial	
Zakko, 2021	Terrestrial	

An study by (Halldestam, 2004) utilies a large population with ages somewhat consistent with the target astronaut population. Articles utilized by the Royal College of Surgeons (2016), a literature review by (Friedman, 1993), and an article published by (Zakko, 2021) in UpToDate were all deemed reliable evidence, although no specific populations or studies were cited from the data pooled for RTDC. Further, all citations inovlve terrestrial data and, therefore, are not simlar to the spaceflight environment.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Riall, et al, 2010	Terrestrial	2
Halpin, 2014	Terrestrial	
Schmidt, et al, 2011	Terrestrial	

The study by (Riall, 2010) consists of a large population with reliable data; however, the mean age of the population studied is 77 years, which is less representative of the target astronaut population and was conducted over a 10-year period, which is less realistic of spaceflight mission timelines. A systematic review performed by (Halpin, 2014) utilizes a moderate sized population, but was regarded as low quality evidence and the population is only somewhat representative of the target astronaut population. A study by (Schmidt, 2011) consists of a small sample size, an age range somewhat similar to the target astronaut population, and was deemed as low quality evidence by the editor as well as a systematic review by (Halpin, 2014). Further, all citations inovlve terrestrial data and, therefore, are not simlar to the spaceflight environment.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope

Overview

Cholecystitis, or gallstones, are an incredibly common gastrointestinal morbidity affecting up to 6% of men and 9% of women (Everhart 1999). Gallstones may be asymptomatic, lead to intermittent biliary colic (consistent with our best-case definition), or lead to future morbidities such as cholecystitis, choledocholithiasis w/ or w/out cholangitis, and pancreatitis. For asymptomatic patients, Cholecystitis, are detected incidentally on abdominal imaging. Biliary colic is characterized by an intense, dull discomfort in the right upper quadrant/epigastric region that may radiate to the back (right shoulder blade) and is often associated with nausea, vomiting, and diaphoresis. Fatty meals may trigger the pain as it causes the gallbladder to contract. When associated with fever, leukocytosis concern elevates for cholecystitis, cholangitis, or pancreatitis. The presence of jaundice and serum chemistries can also help distinguish between gallstone-related morbidities.

CNES: None

Diagnostic Scope and Resourcing

The medical history should review any personal history of GI complaints, dietary restrictions, and current medications. Workup begins with vital signs, an abdominal exam, and a pelvic exam if the abdominal pain is not localized to the right upper quadrant. Abdominal ultrasound is highly sensitive (76-99%) and specific (99%) (Shea 1994). As with the pelvic exam, pelvic ultrasound should be considered if gynecologic pathology is in the differential diagnosis. Non-contrast CT will not be possible in spaceflight. Reasonable laboratory evaluations to evaluate for Cholecystitis and its sequelae as well as key morbidities in the differential include a complete blood count with differential, basic metabolic panel, liver function panel, lipase, urinalysis, and urine pregnancy. Per the definitions, BC and WC diagnostic work up will be the same.

Clinical Phase 1 Duration and Rationale
This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows:

CP1 BC (Treated or Untreated): 1.456
CP1 WC (Treated or Untreated): 1.29

The CP1 WC duration is longer than the BC duration because the diagnosis is clearer and includes less work-up in the differential diagnosis. The highest scope of practice required for diagnosis includes the interpretation of the ultrasounds which is SOP 5 (attending).

Treatment Scope and Resourcing
Conservative management terrestrially includes pain control with oral modalities. In addition to mild pain medications like NSAIDs and Tylenol, oral narcotics may be needed acutely. Oral hydration and PO antiemetics are also needed in the best-case scenario. Lastly, unique to this condition is that ursodiol dosed a 10mg/kg/day can relieve symptoms in many patients within a few weeks by changing the viscosity of bile as well as assisting with the dissolution of gallstones.

In the worst-case scenario, intravenous narcotics for pain control and IV antiemetics may also be needed. Further, as the WC scenario sees an escalation of Cholecystitis to cholecystitis, conservative treatment will include intravenous antibiotics followed by oral antibiotics. Surgical management with a cholecystectomy will not be possible with current resourcing. However, if antibiotics are not adequately treating the WC scenario, insertion of a percutaneous drain may be possible. The gallbladder is punctured via the Seldinger technique and a pigtail drain is placed within the gallbladder. Cholecystostomy tube placement has proven been shown to be effective in resolving an acute episode in ~30% of cases. If this capability is elected for, it may also require sedation. Percutaneous stone clearance through the tube tract may be beyond the scope of practice in spaceflight. Terrestrially, patients who are good surgical candidates should undergo interval cholecystectomy once inflammation has subsided, and thus this could be considered upon RTDC.

Communications and Support Needs

While a best-case scenario may only require ground communication for confirmation of diagnosis and management, ground support with video or pictures will be necessary for the worst-case scenario to help guide management and guide RTDC decisions as the diagnosis warrants surgical management.

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IMM CLIFF RECONCILATION COMMENTS

(Gilkey, 2012) remains the best for space data incidence, and this was reflected in the historic IMM CliFF. As this data is the prime driver for incidence distributions in the IMM and this current CliFF, there remains little essential difference in risk assessment. (Alli, 2007; Everhart, 2008; Noel, 2016) are new updates to this database. (Farr, 2002) was cited in the IMM CLiFF as analog data.

LIMITATIONS SUMMARY

For biliary colic, the mainstay of treatment is supportive care and therefore the risk assessments across our parameters is likely similar to terrestrial care, given the capabilities. For incidence, this analysis is limited by the fact that it assumes a constant rate of occurrence for gallstone disease without accounting for physiological and environmental risk factors for disease (Gilkey, 2012). For worst case scenarios representing complex pathology, the uncertainties around diagnostic and therapeutic capabilities limit the accuracy of risk assessment. For example, ultrasound diagnostic limitations by the user in assessing anatomic measurements which greatly affect diagnosis and prognosis. Likewise, the ability for ultrasound-guided percutaneous drainage is a likely capability for long duration missions, but this uncertainty is a limitation in formulating precision in risk assessment. Regarding TWC [CP2] duration, there remained limited certainty of capacity for invasive procedures on-board [i.e. percutaneous drainage]. Given that, we assume the maximum duration should be pegged to supportive care measures for a gallbladder 'cool-off', and was set at a maximum 10-day course of antibiotics= 240 hours.

TABLE 8. TASK IMPAIRMENT CALCULATION BASED ON AFFECTED HUMAN SYSTEMS TASK CATEGORIES (HSTC)

Clinical Phase 2: Treatment												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)							145					
Untreated Best Case (UTBC)		664		89			145		13			
Treated Worst Case (TWC)	223	664	113	89	854	44	145	5	13	6		
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	Affected HSTCs (Continued)								TI Calculation			TI Score
	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)	132						34	211	522	3763	0.138719	13.8719
Untreated Best Case (UTBC)	132		414	22			34	211	1724	3763	0.458145	45.8145
Treated Worst Case (TWC)	132	564	414	22	196	34	34	211	3763	3763	1	100
Untreated Worst Case (UTWC)	132	564	414	22	196	34	34	211	3763	3763	1	100

Clinical Phase 3: Condition End State												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)												
Treated Worst Case (TWC)												
Untreated Worst Case (UTWC)	223	664	113	89	854	44	145	5	13	6		
	Affected HSTCs (Continued)								TI Calculation			TI Score

	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)								211	211	3763	0.0560723	5.60723
Untreated Best Case (UTBC)								211	211	3763	0.0560723	5.60723
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)	132	564	414	22	196	34	34	211	3763	3763	1	100

TABLE 8 KEY
Human System Task Category (HSTC) Definitions: Cognitive-Simple: Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems. Cognitive-Complex: Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems. Communication: Tasks requiring primarily communication, via hearing and speaking. Interpersonal Skills: Tasks requiring interpersonal, social interaction between crew including complex technical tasks that require extended crew interaction. Vision: Tasks in which visual information is required. Hearing: Tasks in which primarily auditory information is required, excluding communication, e.g. hearing alarms, medical auscultation, OOHAs. Cardiopulmonary: Tasks requiring greater-than-baseline cardiopulmonary effort, e.g. physically strenuous activities. Dentition: Tasks requiring use of teeth for mastication. GI (Gastrointestinal): Tasks requring use of the alimentary sytem, e.g. solids/liquids consumption and solids excretion. GU (Genitourinary): Tasks requiring use of the male/female genitourinary systems. Hand (Dominant): Tasks performed using primarily the hand, requiring use of the dominant hand (piloting, medical procedures, dental procedures). Hand (Any): Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness. Upper Extremity: Tasks requiring specific use of the upper extremities, excluding hands. Lower Extremity: Tasks requiring specific use of the lower extremities (excluding ambulation and standing in the presence of gravity), e.g. using exercise equipment. Ambulation and Standing (g): Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity. Translation and Stabilization (microgravity): Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity. Don/Doff Equipment: Tasks requiring the donning of personal equipment (including pressure suit, exercise harness, EVA equipment, etc). Pressure Ops: EVA/contingency tasks performed while pressurized in a suit.

Criteria for Assignment of Conditions to HSTCs (any of the following):
1) Is affected crew member physically incapable of performing the human system task category, without impairment, with the condition?
2) Would the treatment (e.g. medications) impair the crewmember's ability to perform the human system task category? (Does not apply to UTx)
3) Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated human system task category
4) Would performing tasks in an associated task category worsen the condition? (If so, it is affected).
5) Does pain associated with the condition impair any further human system categories?

TASK IMPAIRMENT COMMENTS

CP2: No comment. CP3: No comment.

EVIDENCE COLLECTION PROCESS

Mesh terms that most closely resembled the best-case and worst-case scenarios, and associated Conditions Included but Not Explicitly Stated (CNES), were utilized to build incidence, duration, RTDC, and LOCL searches by best- and worst-case.

Incidence:
Databases searched for spaceflight and analog incidence data included: PubMed, Google Scholar, NASA Technical Reports Server (NTRS) public search, Defense Technical Information Center (DTIC), and Barratt MR, Baker E, Pool SL. Principles of Clinical Medicine for Space Flight. New York, NY: Springer; 2019. 2nd Edition. Databases searched for terrestrial incidence included: DynaMed, PubMed, and Google Scholar.

Duration, RTDC, LOCL:
Databases searched for duration, RTDC, and LOCL included: Dynamed, Cochrane, PubMed, and Google Scholar. Note, that if duration, RTDC, or LOCL data was found in a DynaMed search, the other search engines were not included. Relevant articles were selected and reviewed. If applicable, the article was included in the CLiFF.

LEVEL OF CONFIDENCE (LOC) SCORING

Articles obtained to update the evidence behind this CLiFF were scored by ExMC editors, based on their applicability to the Exploration Spaceflight environment using the following grading scale:

4 – Confident
3 – Somewhat confident
2 – Neutral
1 – Somewhat unconfident
0 – Not confident

The following considerations factor into the grading scale above:

• How closely does the paper describe the medical condition as defined by the IMPACT 1.0 Condiltion List (relevance)?
• How closely does the population included resemble the astronaut population?
• Quality of the paper (number of subjects, methods, etc.)
• How much does the editor trust the source of the evidence?
• How closely does the editor think that the data represents the exploration spaceflight environment?
• Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

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ACRONYMS

ACRONYM	PHRASE
AAOMS	American Association of Oral and Maxillofacial Surgeons
AMA	American Medical Association
ARCL	All Remaining Conditions List
ARS	Acute Radiation Sickness
BHP	Behavioral Health and Performance
CAC	Coronary Artery Calcium
CHS	Crew Health and Safety
CL	Condition List
CliFF	Clinical Finding Form
CMO	Crew Medical Officer
COMFORT	Clinical Outcome Metrics for Optimization of Robust Training
CP1	Clinical Phase 1
CP2	Clinical Phase 2
CP3	Clinical Phase 3
CRL	Clinical Resource Level
CRT	Capability Resource Table
CST	Clinical Science Team
DCS	Decompression Syndrome
DRM	Design Reference Mission
ED	Emergency Medicine Doctor
EL	Evidence Library
EMCL	Exploration Medical Condition List
EMT	Emergency Medical Technician
EVA	Extravehicular Activity
EXMC	Exploration Medical Capability
HRP	Human Research Program
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List
ICU	Intensive Care Unit
IMCL	iMED Condition List
iMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT-MD	Impact Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	Intravenous
JSC	Johnson Space Center
LEO	Low-Earth orbit
LEVA	Lunar Extravehicular Activity

LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEVA	Medical Extravehicular Activity
NASA	National Aeronautics and Space Administration
N/A	Not Applicable
NP	Nurse Practitioner
OBGYN	Obstetrics and Gynecology
OR	Occurrence Rate
PA	Physician Assistant
PDQ	Pain Disability Questionnaire
PFCL	Proposed Future Conditions List
PPE	Personal Protective Equipment
PTRS	Project Technical Requirements Specification
PRL	Pharmaceutical Resource Level
QTL	Quality Time Lost
RCL	Removed Conditions List
REP	Rochester Epidemiology Study
RTDC	Removal to Definitive Care
SANS	Spaceflight-Associated Neuro-ocular Syndrome
SAS	Space Adaptation Syndrome
SEVA	Spaceflight Extravehicular Activity
SME	Subject Matter Expert
SoP	Standard Operating Procedure
SPE	Solar Particle Event
TBD	To Be Determined
TI	Task Impairment