Clinical Finding Form (CliFF)

Branch: Baseline

ICL8_Appendicitis

Appendicitis is acute inflammation and subsequent infection of the appendix, a small outpouching of the colon. It is caused by a blockage of the lumen of the appendix which results in increasing pressure, inflammation of surrounding structures, and eventual perforation. The typical presentation is gradual onset of abdominal pain, decreased appetite, and local tenderness in the right lower abdomen. The terrestrial standard of care is surgical removal of the inflamed appendix. Although appendectomy is one of the most common surgeries performed worldwide, the technical challenge of the procedure and anesthesia prohibits non-surgeons from performing it. Medical management with antibiotics and bowel rest has been successful in select cases in remote analog and traditional medical environments. No confirmed cases of appendicitis have been reported in US spaceflight. (Marshburn, 2008) (Campbell, 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

Through 2012, there have been 2 cases of appendicitis in American astronauts on Earth in 1644 person-years recorded. No cases have ever occurred in flight. Bayesian analysis (Gilkey, 2012) from that incidence rate estimated a spaceflight incidence of 9.34 x 10^-4 events/person-year. Note that there have not been any new cases since these numbers were calculated; with 9 more years (2012-2021) of appendicitis-free spaceflight the actual risk may be lower. The Russians have experienced two cases in spaceflight that were clinically suspicious for appendicitis. The first case resolved on its own and was presumed to be ureterolithiasis, whereas the second case required evacuation from the Space Station and was ultimately diagnosed as prostatitis (Campbell, 2004).

ANALOG LITERATURE

(Campbell, 2004) provides the most relevant review of analog populations. Incidence was as high as 43.0 cases / 1 million person-days, on average between 4 and 10 cases / 1 million person-days, with US submariner data having an incidence around 9.8 cases / 1 million person-days and US incidence data as high as 5.6 but declining with age. (Lugg, 1975) had a large data set but the data preceded modern diagnostics, definition, and treatment of appendicitis; as such, they showed an unusually high incidence that is not seen in any other study.

TERRESTRIAL LITERATURE

(Ferris, 2017) is a systematic review of 120 studies that are geographically and chronologically stratified. For Americans and Canadians, the incidence from 1980 to 2014 was between 82-111 cases per 100,000 person-years. This is lower than the European incidence and Australian incidence. Incidence in this systematic review are comparable with other manuscripts that were reviewed.

OVERALL INCIDENCE SUMMARY

INCIDENCE

Mean 9.34E-4 SD 1.03E-4

INCIDENCE SUMMARY

From the GRC Bayesian modeling of astronaut data using terrestrial sources for informing the priors, the posterior distributions for the incidence

rate of appendicitis is log-normally distributed with mean 9.34E-4 and SD 1.03E-4. Evidence: Gilkey 2012 – Bayesian analysis of inflight, preflight, and terrestrial incidence data. Posterior distribution defined as log-normal with the following parameters. Since this condition utilizes the results of a Bayesian analysis, the posterior distribution can be expressed directly through the reported parameters.

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type
General

Segment
All

Env. Exposure
NA

Sex
Any

Crowns
Any

Contacts
Any

Pregnancy
Any

Incidence Distribution

Occurrence Dist
Poisson

Incidence Dist.
Log-Normal

Mean
0.000934

SD
0.000103

Log-Normal
(Mean): 0.000934
(SD): 0.000103

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Ferris, 2017	Terrestrial	3
Gilkey, 2012	Spaceflight	4
Campbell, 2004	Analog	3
Lugg, 1975	Analog	2

(Ferris, 2017) is the best general population incidence paper since it incorporates the most recent data, stratifies it by geographic region, and has a good sample size. (Gilkey, 2012) is the best overall paper to inform incidence as it was specifically designed to obtain spaceflight-relevant data for IMM and incorporated astronaut population data to generate a risk of appendicitis. Since then, no cases of appendicitis have occurred, so the risk may be lower than documented in this paper. Notably, because there has not been a case of appendicitis in space, the study used a Bayesian analysis to calculate the likely risk of it occurring by combining baseline incidence data in analogous populations and the two cases in astronauts that had appendicitis on earth. (Campbell, 2004) is our best review of analog populations, and it builds on the work done by (Lugg, 1975) via a systematic review of incidence data in a variety of populations (military, Antarctic, etc.). (Lugg, 1975) is an analog population, but demonstrated an inexplicably high incidence, and was from a different era of medical diagnostics and treatment.

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

Measures utilized for prevention may potentially include preflight screening and selection, in-flight treatments, and prophylactic appendectomy. Disqualifying conditions: Chronic diseases or disorders of the alimentary tract are possibly disqualifying and will require evaluation. History of intestinal obstruction if due to any chronic or recurrent disease will be similarly evaluated. Surgery to relieve childhood pyloric stenosis, intussusceptions, or volvulus is not disqualifying if there are no sequelae. (NASA, 2007) In-flight treatments: Antibiotic administration may be a treatment or temporizing therapy for mild uncomplicated cases of appendicitis. Antibiotic prophylaxis to prevent appendicitis has not been described. Other: Prophylactic appendectomy has been utilized by some Antarctic programs in an attempt to decrease the risk of developing appendicitis during exploration of remote environments. At this time prophylactic appendectomy for long duration flights is not recommended, but may be considered for exploration class missions. (Campbell, 2004). CT imaging can screen for pre-flight appendicoliths, which put patients at higher risk of developing appendicitis; however, only 40% of patients with acute appendicitis had an appendicolith on their diagnostic CT. (Ranieri, 2021)

BEST CASE SCENARIO DEFINITION

Appendicitis which responds to conservative medical treatment (antibiotics and symptomatic treatment).

WORSE CASE SCENARIO DEFINITION

Appendicitis resulting in a perforation or intra-abdominal infection

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

A Hand-search for non-operative appendicitis systematic reviews found two papers, (Prechal, 2019) and (Podda, 2017). Both found a similar complication rate and need for secondary appendectomy after initial treatment with antibiotics - 37.4% of patients returning in one year in (Prechal, 2019), and 22.5% in (Podda, 2017). Notably no statistically significant differences were found when comparing antibiotics to surgery for overall post-intervention complications in both studies, leading the authors to conclude that antibiotic treatment can be a reasonable alternative in select patients with proven uncomplicated appendicitis, which is a standard that is not applicable to spaceflight with current technology.

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

Citation	Source	LOC Value
Podda, 2017	Terrestrial	2
Prechal, 2019	Terrestrial	2

Both papers are systematic reviews of non-operative treatment of appendicitis compared to appendectomy. Populations are terrestrial inpatients. As the non-operative approach to appendicitis grows in popularity, these data likely underestimate the amount of people that may be treated without surgery. These papers have large population sizes (Podda compares 1743 antibiotic therapy to 1875 surgical, Prechal evaluated a total of 1430) with clearly defined endpoints. It is difficult to extrapolate these data to spaceflight as terrestrial appendicitis patients have an early and clear diagnosis by (typically) CT imaging, which is a lynchpin of the treatment pathway decision.

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)	Mean 9.34E-4 SD 1.03E-4	62.6 - 77.5	100	1.83	21.552	168	240	0	0	29	0	0
Treated Worst Case (TWC)		22.5 - 37.4	100	1.83	50	168	240	0	100	100	0	8.7
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.83	83.4573	168	504	100	5	29	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.83	100	168	504	100	100	100	0	50

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

Terrestrially, someone with suspected appendicitis will be evaluated by physical examination, laboratory tests, and oftentimes a CT of the abdomen and pelvis with IV contrast. In pediatrics, ultrasound can be utilized to (unreliably) detect appendicitis as well but this is not typically performed in adults due to body habitus. If appendicitis is diagnosed, then antibiotics will be started while awaiting surgical removal of the appendix, which typically occurs within 24 hours of diagnosis, if not sooner. In spaceflight, the physical examination and history will be the mainstays of diagnosis, and lab tests (particularly an elevated white blood cell count) can further increase the suspicion for intra-abdominal infection. There is no availability of confirmatory testing, so treatment and RTDC decisions will need to be made based on clinical data and flight surgeon experience/comfort. RTDC in the perforated appendicitis (worst case) is more clear, as the astronaut will have severe tenderness and possibly a fever. The milder cases are more challenging, and it is unclear how long we wait to see if antibiotics will resolve the issue in the austere spaceflight setting.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

In the treated best-case scenario, someone is diagnosed with appendicitis, then treated with IV antibiotics, then transitioned to oral antibiotics when they show clinical improvement (Flum, 2020 and Di Saverio 2020). Treatment duration is 10 days. RTDC chance is dependent on how long the crew will be on-mission; RTDC is somewhere between 3 to 8% at 90 days, and as high as 29% at one year. Zero patients died in the Treated Best Case Scenario since they would be defined as the worse case scenario before death would occur. Also note that conservative is the only treatment method for patients that are unsafe to go to surgery (i.e. poor surgical candidates, perforated appendicitis), which is a factor that will raise the complication rate in these analyses. Some high risk patients with perforated appendicitis are treated with a surgical drain and antibiotics.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The terrestrial standard of care for treatment of appendicitis is surgery. The course of symptom onset to surgery is usually within three days, but can be up to a week. Delay to surgery increases complications, risk of perforation, and mortality (Alore 2018), with the predominant outcome of delay being an increase in intraabdominal infections. By definition, Worst Case treated or untreated appendicitis does not directly cause LOCL, but rather results in a perforation and complicated intraabdominal infection. (Claridge, 2014) has an overall mortality rate of 8.7% for intraabdominal infection in a population treated with antibiotics (40-year old antibiotics) mean age 54 and 50% male. (Berry, 1984) cites a perforation rate of 28%. (Papaziogas, 2009) and (Bickell, 2006) cite a rupture risk of 5-6%. We can use these data to estimate the chance of a case being a Best Case Scenario or Worst Case Scenario.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Appendicitis studies end at 72-hours from symptom onset, as patients with continuing abdominal pain at that point are brought to surgery. Because of this, a hand search was performed for duration of peritonitis symptoms in both SBP and liver abscess as a proxy for duration of nonsurgically-treated appendicitis, as both diseases cause peritonitis that is not treated surgically. Hand searches were performed to determine duration of peritonitis, but this outcome was not tested for in studies. (Li, 2016) states that the longest duration treatment for peritonitis was 21 days, so this represents the only possible upper bound we can set on how long someone would have symptoms of an abdominal infection. The RTDC of the best case is set to 0% by definition. LOCL is 0% by definition.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Appendicitis studies end at 72-hours from symptom onset, as patients with continuing abdominal pain at that point are brought to surgery. Because of this, a hand search was performed for duration of peritonitis symptoms in both SBP and liver abscess as a proxy for duration of nonsurgically-treated appendicitis, as both diseases cause peritonitis that is not treated surgically. Hand searches were performed to determine duration of peritonitis, but this outcome was not tested for in studies. (Li, 2016) states that the longest duration treatment for peritonitis was 21 days, so this represents the only possible upper bound we can set on how long someone would have symptoms of an abdominal infection. No literature was identified that provides information on the minumum length of time an untreated perforated appendicitis would resolve on its own, so the TWC minimum time was utilized. UTWC LOCL estimated from a paper about appendicitis from before the antibiotic era. Unfortunately, it is not a very rigorous paper, and does not cite sources for many statements. RTDC is set to 100%, as perforated appendicitis is a surgical emergency. In the absence of the standard of care terrestrial treatment for perforated appendicitis - surgery - antibiotics, IV fluids, and pain medication can be given; however, this has not been demonstrated to resolve perforated appendicitis.

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

Citation	Source	LOC Value
Di Saverio, 2020	Terrestrial	3
Flum, 2020	Terrestrial	
Li, 2016	Terrestrial	
Papaziogas, 2009	Terrestrial	
Temple, 1995	Terrestrial	

The treated duration has the most certainty, as the length of antibiotic treatment for appendicitis is well documented in large, multi-center studies and published guidelines, for example (DiSaverio, 2020) and (Flum, 2020). The untreated Duration of Clinical Phase 2 is not found in the literature because on Earth, Best Case appendicitis is treated with surgical removal of the appendix before it becomes Worst Case, which is not possible in spaceflight. The duration of peritonitis can be used as a proxy for the duration of untreated appendicitis, and is available in the literature. The duration of antibiotic treatment for symptomatic peritonitis found in (Li, 2016) was 14-21 days, so 21 days was used as the untreated duration. The lower limit of 14 days was used as the UTWC lower limit. Both (Temple, 1995) and (Papaziogas, 2009) find that spontaneous resolution of untreated appendicitis first occurs around 12 hours after symptom onset (UTBC lower limit).

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Di Saverio, 2020	Terrestrial	3
Flum, 2020	Terrestrial	
Bickell, 2006	Terrestrial	
Papaziogas, 2009	Terrestrial	

The RTDC of Worst Case (perforated appendicitis) was set to 100%, as this is a surgical emergency that is disabling and life threatening. The Best Case RTDC is the chance that the patient progresses to the worst case. (DiSaverio, 2020) and (Flum, 2020) both show a one-year complication rate of between 27 and 29% for appendicitis treated with antibiotics. They also give a lower limit for complication of 5-6% at one month after appendicitis onset. The TBC lower limit is 0% because successful eradication of infection in the appendix does not result in increased risk for appendicitis.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Claridge, 2014	Terrestrial	2
Jackson, 1940	Terrestrial	

Death due to appendicitis on Earth occurs from severe intraabdominal infection and complications of surgery. There is no literature on mortality of non-treated appendicitis. We approximated the mortality of TWC by using the mortality rate of abdominal infections of 8.7% found in (Claridge, 2014). The only article found on appendicitis not treated with either surgery or antibiotics is (Jackson, 1940), a low-power study from the pre-antibiotic era, that lists the risk of death from perforated appendicitis as approaching 50%.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope Overview Appendicitis remains one of the most common surgical emergencies and is calculated to occurring in about 6.7-8.6% of humans terrestrially. Specific inciting agents are still unknown, however, dietary fiber intake, environmental pollutants, intestinal dysbiosis, other intestinal infections, immune alterations, or even some aberrant expression of genes like PITX2 have been associated with appendicitis. It is unknown how these associations (alone or in combination) lead to uncomplicated appendicitis versus frank gangrene and appendiceal perforation. While operative management has long been the standard of care, non-operative management is imperative, especially in low-resource settings such as spaceflight. CNES: None Diagnostic Scope and Resourcing Several clinical prediction tools have been described for appendicitis. The Alvarado (MANTRELS) score is the best known, however, a recent metanalysis by Kularatna revealed that the AIR score was the most performant and pragmatic terrestrially (Bessoff 2020). The AIR score, like many other algorithms, requires knowing the % of polymorphonuclear leukocytes (PMNs) which is often included in a CBC with differential. It is currently believed this will be possible to evaluate during spaceflight. Another approach by Tzanakis et al 2005 reveals an algorithm that does not require the differential and evaluates a) Ultrasound positive for appendicitis (6 points), b) RUQ tenderness (4 points), c) rebound tenderness (3 points), and d) WBC >12,000 (2 points) . If 8 points or

greater, >95% sensitive and >97% specific for appendicitis. In the setting of concern for appendicitis in space, ground support communications can assist with choosing one of these diagnostic algorithms best appropriate for the diagnostic capabilities available during the flight. In general, both the best case and the worst-case scenarios will involve diagnostic capabilities inclusive of vital signs, an abdominal physical exam, a CVA tenderness exam, a serum CBC with differential, a basic metabolic panel, liver function panel, lipase, urinalysis, urine pregnancy test, and abdominal/pelvic ultrasound to not only evaluate for appendicitis, but also for cant miss diagnoses in the differential. A serum CRP or abdominal CT scan will likely not be available. Importantly, because of how we have defined best case and worst-case appendicitis, the diagnostic scope and resourcing will be identical. 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): 1.83 hours CP1 WC (Treated or Untreated): 1.83 hours The highest diagnostic scope of practice will include the evaluation and interpretation of appendicitis on ultrasound, which is scoped at level 5, which is the level of an experienced attending physician. Treatment Scope and Resourcing Many cases of appendicitis terrestrially, even in low-resource settings, are still treated with laparoscopic or open appendectomy. However, initiating treatment with antibiotics in order to avoid surgery is now first line. One of the main concerns with this terrestrially is the risk of recurrence, however, our team is more immediately concerned with acute treatment failure or recurrence within a short time period. Reliable data exploring this is incredibly important as our treatment scope will not include appendectomy. A best-case scenario would involve antibiotics and symptom control including pain management (inclusive of narcotics if needed) and nausea management as well as fluid hydration. As the worst-case scenario definition requires surgical management that would not be available in spaceflight, the highest scope would involve these same resources and additional consideration of ultrasound-guided percutaneous drainage of the abscess that has failed antibiotics. A sedation bundle would likely be needed to accomplish this procedure. While there is elevated risk of complications from this procedure and high complexity for a CMO who may have only received just-in-time training, the worst-case definition is considering a patient who has failed antibiotics and thus may die from appendicitis without further intervention. The antibiotic bundle will include antibiotics active against enteric gram-negative aerobic and facultative bacilli, enteric gram-positive streptococci, and obligate anaerobic bacilli. There are a legion of varying antibiotic regimens often ranging from 7-10 days of IV and oral antibiotics (Talan 2019, Solomkim 2010), and we have provided five regimens that utilize ertapenem, piperacillin/tazobactam, levofloxacin, ciprofloxacin, metronidazole, and ceftriaxone. Pain management bundles will include acetaminophen, NSAIDs, oral narcotics, and IV narcotics. Communications and Support Needs Ground support may be required for assistance with interpretation of the diagnostic ultrasound and/or assistance with performance of the ultrasound-guided percutaneous drain placement if needed during the worst-case scenario. REFERENCES Bessoff KE, Forrester DJ. Appendicitis in Low-Resource Settings. Surg Infect. 2020;21(6):523-532. Tzanakis NE, Efstathiou SP, Danulidis K, et al. A new approach to accurate diagnosis of acute appendicitis. World J Surg 2005;29:1151–1157. Solomkin JS et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010; 50(2):133-64. Talan DA et al. Methods of conservative antibiotic treatment of acute uncomplicated appendicitis: a systematic review. J Trauma Acute Care Surg. 2019; 86(4):722-736.

IMM CLIFF RECONCILATION COMMENTS

Attached is the draft CLiFF for ICL 8 – Appendicitis, as well as relevant articles and the IMM CLiFF on the same topic. The IMM CLiFF reported an estimated incidence of appendicitis in spaceflight of 0.000934 events per person-year with a standard deviation of 0.000103, which appears to be wholly based on the incidence determined by the Gilkey 2012 Bayesian analysis of this condition (an incidence of 0.000935 events per person-year, SD 0.000104). Given that the Gilkey study included astronaut data through 2012 and we have had no additional cases in 9 years, the new incidence may be slightly lower than previously estimated. Since the IMM CLiFF, there have been no additional analog nor spaceflight data published. A large terrestrial systematic review of 120 appendicitis incidence studies (Ferris, 2017) found a pooled North American incidence of appendicitis of 0.001 events per person-year. Since these data were from the general population, they will overestimate the risk in astronauts. Additionally, studies of antibiotic only treatment of appendicitis have been published in the interim, and demonstrate the safety of treating proven uncomplicated appendicitis with antibiotics rather than surgery (Prechal, 2019) (Podda, 2017).

LIMITATIONS SUMMARY

The fundamental limitations of this CLiFF center around the terrestrial standard of care dictating diagnosis by CT imaging and treatment with surgery, both of which are unavailable in spaceflight with current technology and training. Although appendicitis can be a clinical diagnosis with a classic presentation and examination, a number of other conditions (renal colic, ascending urinary tract infection, ovarian torsion, mesenteric appendicitis, etc.) can appear identically. Although antibiotic treatment of early uncomplicated appendicitis has been demonstrated to be safe, the terrestrial literature hinges on a clear diagnosis. Durations of antibiotic treated for the best case are well-established; however, no literature addressing an untreated or antibiotic-only treated complicated/perforated perforation exists, so proxies were utilized for duration . The LOCL estimate has significant limitations as well given that there is no literature to inform the untreated situations, which requires us to utilize a rough surrogate. RTDC is similarly problematic. The decision to return an astronaut will be a clinical judgment call given the spectrum with which appendicitis can present clinically and numerous logistical factors.

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)		664					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		414	22			34	211	1622	3763	0.431039	43.1039
Untreated Best Case (UTBC)	132	564	414	22	196	34	34	211	2518	3763	0.669147	66.9147
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)	223	664	113	89	854	44	145	5	13	6		
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)									0	3763	0	0
Untreated Best Case (UTBC)	132	564	414	22	196	34	34	211	3763	3763	1	100
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