Clinical Finding Form (CliFF)

Branch: Baseline

ICL117_Urinary Tract Infection

Urinary tract infections encompass multiple pathologies including an infection of the lower urinary tract (involving the urethra or bladder; urethritis or cystitis) or an ascending infection from the bladder through the ureters to the kidneys leading to pyelonephritis. "Uncomplicated" UTIs are defined as UTIs that occur in non-pregnant hosts with no structural or functional abnormalities, and who have not been instrumented (ex. with a catheter or cystoscope). All other UTIs are considered "complicated". Other risk factors for UTI in men include benign prostatic hypertrophy (BPH) or a stricture causing obstruction, and being uncircumcised. While some forms of prostatitis can be closely related or even considered to be UTIs, prostatitis is covered under a separate condition (ICL #77). The overwhelming majority of infections in females are caused by E. coli (Schaeffer 2007, Foxman, 2010). Other organisms include members of the family Enterobacteriaceae, streptococci and staphylococci species, and yeast. Importantly, the microgravity environment predisposes astronauts to UTIs by promoting the formation of urinary tract calculi and relative dehydration through fluid shifts and decreased oral intake. There are well-documented past cases of UTIs during spaceflight in both men and women as we will cover below

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

IMM LSAH data requests revealed 5 events over 37.31 person-years in males and 7 events over 8.18 person-years in females. IR males: 0.134 (95%CI: 0.0491, 0.297) and IR females: 0.8557 (95%CI: 0.3743, 1.693). The HSRB Urinary Retention Analysis also reported 1 event in males and 8 in females over STS and ISS up to EXP 38. Males experienced one event 31.565 person-years of spaceflight and females experienced one UTI per 7.757 person-years of spaceflight. IR males: 0.03168 (0.001585, 0.1562) and IR females: 0.1289 (95%CI: 0.0065, 0.6358) (Cole, 2016). It is not surprising that the counts from the 2 sources are slightly different. Though the urinary retention data includes some more recent missions, because the LSAH data request was a more expansive search covering more person-time, we decided to utilize this data for our composite incidence decisions below.

ANALOG LITERATURE

Boulware 2003 evaluated the incidence rate of UTIs in hikers revealing an IR: 0.01562 (95%CI: 0.002619, 0.05161), however this low rate is calculated based off only 2 total events. Lyon 2010 evaluated medical reports from 232 wilderness expeditions and revealed 19 urinary tract infections and a IR: 0.1634 (95%CI: 0.1013, 0.2504). The spaceflight data was felt to be more characteristic of spaceflight incidence for this condition and thus this data was not utilized.

TERRESTRIAL LITERATURE

Foxman's 2010 review estimated incidence from the NHANES to be 0.126 in women and 0.03 in men. Suskind 2016, Medina 2019, and Schaeffer 2016 all provide prevalence data and/or incidence data without enough detail to calculate incidence with confidence intervals. The spaceflight data was felt to be more characteristic of spaceflight incidence for this condition thus terrestrial data was not used for composite incidence calculation.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.858 and SD 0.3311

INCIDENCE SUMMARY

As discussed above, the spaceflight data was decided to be used alone in the composite incidence decision. The Bayesian posterior distribution for the male incidence rate given the spaceflight data (5 events over 37.31 person-years) under an uninformative prior is Gamma(shape=4.839, rate=35.981) with mean 0.1345 and SD 0.06114. The Bayesian posterior distribution for the female incidence rate given the spaceflight data (7 events over 8.18 person-years) under an uninformative prior is Gamma(shape=6.715, rate=7.827) with mean 0.858 and SD 0.3311.

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.
Gamma
Mean
0.134488
SD
0.0611371

Gamma
(Shape): 4.839
(Rate): 35.981

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.
Gamma
Mean
0.857928
SD
0.331076

Gamma

(Shape): 6.715
(Rate): 7.827

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Medina, 2019	Terrestrial	2
Foxman, 2010	Terrestrial	3
Katchman, 2005	Terrestrial	2
Suskind, 2016	Terrestrial	2
Butler, 2015	Terrestrial	2
Boulware, 2003	Analog	2
Lyon, 2010	Analog	3
Suchulz, 2014	Analog	2
Cole, 2016	Spaceflight	3

Numerous data is available for analysis in the terrestrial, analog, and spaceflight populations for UTI. Given the low n, it is difficult to combine spaceflight data into a composite incidence with terrestrial data and thus one or the other must be chosen. While it is possible that the spaceflight incidence may be artificially high 2/2 a low n, the 4-6-fold increase in incidence over terrestrial males and females is concerning enough to warrant conservative estimates regarding incidence as there may be factors unique in spaceflight that increase the risk of UTIs occurring. Thus, the spaceflight incidence alone was chosen and separated by sex as the incidence rates are very different in males and females both in space and terrestrially. A high level of confidence is still not chosen given the low n in spaceflight.

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

L-45/30 pre-flight, a urinalysis is collected and evaluated. If findings concerning for a urinary tract infection are noted, this would be sent for culture and treated pre-flight.

BEST CASE SCENARIO DEFINITION

Urinary tract Infection (UTI) responsive to oral antibiotics.

WORSE CASE SCENARIO DEFINITION

UTI or pyelonephritis requiring IV antibiotics.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

Pyelonephritis

BEST CASE/WORST CASE PROBABILITY COMMENTS

There are two ways to evaluate data regarding the worst-case scenario which in this case is the chance of pyelonephritis: a) looking at overall rates of pyelonephritis upon first diagnosis as a percentage of UTIs, or b) by looking at patients undergoing treatment for a UTI who then experience escalation to pyelonephritis. Ikaheimo's prospective study in 1996 revealed that of the 147 UTIs diagnosed, that 138 were cystitis and 5 were pyelonephritis (a proportion of 3.6%) at initial diagnosis prior to treatment. Reviews by Belyayeva, Czaja, and Foxman reveal that pyelonephritis rates are 1-5% of that of UTIs. Lastly, Katchman 2005 performed a meta-analysis revealing that 2 out of 582 cases progressed to pyelonephritis with treatment yielding a WC percentage of 0.34%. Choosing a BC/WC scenario also requires understanding the reality of the scenario. A higher incidence of pyelonephritis in terrestrial populations may be because of delayed diagnosis and difficulty with access to care. It is very unlikely that an astronaut would have an asymptomatic underlying UTI that progresses to pyelonephritis. Thus taking all of this data into account, understanding that there is a high likelihood of astronauts being diagnosed with a UTI and beginning treatment before pyelonephritis would occur, and understanding the increased risk of UTI in spaceflight populations, a WC percentage chance of 1% was felt to be reasonable.

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

Citation	Source	LOC Value
Katchman, 2005	Terrestrial	3
Ikaheimo, 1996	Terrestrial	2
Belyayeva, 2021	Terrestrial	3
Czaja, 2007	Terrestrial	3
Foxman, 2014	Terrestrial	3

While there is overall confidence in this BC/WC decision, however, there is not high confidence given that the majority of data to guide this decision are reported at first diagnosis rather than evaluation of the progression of the illness as would be more applicable to a spaceflight WC scenario.

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)	male mean 0.1345 and SD 0.06114, female mean 0.858 and SD 0.3311	99 - 99	100	0.81	9.11507	72	336	0	0	0	0	0
Treated Worst Case (TWC)		1 - 1	100	1	30.6139	168	336	0	0	8.8	0	8.7
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.81	30.7733	96	1008	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1	39.41	168	1008	39.41	7	40	4.1	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

The standard of care for treatment of lower and upper urinary tract infections includes antibiotics and hydration. Fortunately, most UTIs in spaceflight should be uncomplicated given that terrestrial complicated UTIs often involve anatomical abnormalities of the urinary tract, indwelling catheters/stents, systemic disease, pregnancy, or multi-drug resistant bacteria. A stone could make for a complicated UTI in spaceflight, and as renal stones may be more common in spaceflight, this may increase the risk of a complicated UTI. Nephrolithiasis, in the absence of concomitant infection, is considered a separate condition. While the incidence varies between men and women, the treatment courses also vary for men and women and this is reflected in the table above and explanations below.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Milo's Cochrane Review in 2005 revealed that while UTIs can be cured in as little as 3 days, that treatment for 5-10 days could be considered for treatment of women in whom eradication of bacteriuria is important, and thus a TBC range of 3-10 days was chosen. In Grigoryans 2014 study, the authors discuss that while therapy longer than 7-14 days may not be beneficial in women with acute UTI, that there has not been adequate evidence to suggest treatment for a shorter duration in men, thus this longer duration was chosen for men. The American Urological Association confirms such a range of 7-14 days in men (AUA, 2020). RTDC and LOCL is not expected for treated best case scenarios.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

Some studies endorse treatment durations for complicated UTI's and pyelonephritis as short as 7 days. This duration likely selects for clinical courses that, on average, are less clinically severe. More severe UTI's generally require a minimum of 24-48 hours of IV antibiotics (or until 24 hours fever-free) followed by completion of an oral course of antibiotics for a total of 7-14 days. This range was chosen as the CP2 duration for TWC (Eliakim-Raz 2013, Sandberg 2012, and Talan 2000). The surrogate that was chosen for RTDC is the failure of IV antibiotics to treat the usual UTI pathogens. It is anticipated that broad spectrum IV antibiotics, including vancomycin, meropenem and ertapenem, will be manifested on exploration missions. Since the vast majority of UTI's are caused by gram negative organisms, resistance to carbapenems such as ertapenem is thought to be the most likely cause of treatment failure. Another cause of possible treatment failure is late presentation, but the crew will be closely monitored on board and through telemetry; therefore, this scenario is thought to be an unlikely risk for RTDC. A study by Shields, et al, 2021, described the burden of illness in US hospitals due to carbapenem-resistant (CRE) gram negative urinary tract infections and found that 4.4% involved CRE organisms. Based on this study, a range of 0 (since no cases of treatment failure have been seen on US spaceflights) to 8.8% was assigned, which yields a mean value of 4.4%. A study by Eliakim-Raz, et al (2019) found a 30 day all-cause mortality rate of 8.7% (85/976) from complicated UTI's (including pyelonephritis). This was used as the upper limit for LOCL as the study included older adults who are presumably less healthy than astronauts. The lower limit for LOCL was taken as 0% as no cases of treatment failure have been reported during spaceflight.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

In a study not looking at bacterial clearance but in symptomology, Little 2010 revealed that women in TBC scenarios on average had symptoms for 3.32 days while UTBC duration was 5.38 days. Two other studies (Koradia 2019 and Hoffman 2020) evaluated the natural history of untreated UTI and placebo vs. probiotics for UTI. Together these studies revealed that the earliest resolution of a UTI was 4 days and the latest was 6 weeks. Together these studies revealed that the earliest resolution of a UTI was 4 days and the latest was 6 weeks. Though the duration is longer in comparison to treated best case scenarios, per the definitions of best-case scenario, RTDC or LOCL would not anticipated.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Duration is difficult to assess in UTWC scenarios as pyelonephritis is not a condition which will continue to remain stable without a definitive end state in a patient without treatment. Pyelonephritis will either spontaneously resolve if one is fortunate, or it will progress to sepsis which is beyond the scope of this CLiFF. Because no formal range can be decided upon by the data, the range of UTBC was chosen to also be used for UTWC. With regards to definitive end states, there is also a paucity of data to suggest a range of RTDC (or hospitalizations which is the surrogate for RTDC) in patients without treatment. Thus, the range of hospital admissions in the terrestrial public (even with treatment) was chosen for this population. This would be 7-40% depending upon the study (Medina 2019, Czaja 2007, Hooten 1997). Lastly, as with the TWC scenario choosing a mortality rate is also difficult given the mostly likely reason for mortality in the setting of pyelonephritis is an escalation to sepsis. Buonaiuto 2014 reported that in their study of patients 26% developed severe sepsis and 12.5% developed septic shock. In that study attributable mortality was 4.1%. Other terrestrial articles have provided a range of 10-20% (Foxman 2003, Efsthathiou 2003) for mortality in the setting of pyelonephritis. Given the fact that this is untreated worst case, utilizing these ranges was felt to be reasonable when choosing LOCL from untreated pyelonephritis.

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

Citation	Source	LOC Value
Little, 2010	Terrestrial	3
Grigoryan, 2014	Terrestrial	
Milo, 2005	Terrestrial	
AUA, 2020	Terrestrial	
Koradia, 2019	Terrestrial	
Hoffman, 2020	Terrestrial	
Eliakim-Raz, 203	Terrestrial	
Sandberg, 2012	Terrestrial	
Talan, 2000	Terrestrial	

While the duration may be variable depending upon the type of antibiotic or lack of antibiotic, between the number of studies cited, there is reasonable confidence for the duration of treated scenarios. Duration of untreated situations is always challenging. While there is some evidence for best case scenarios based off placebo-controlled studies, the worst-case scenario is problematic as explained above. Overall, we feel there is some confidence in this duration, and thus a 3 was given.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Medina, 2019	Terrestrial	2
Czaja, 2007	Terrestrial	
Hooten, 1997	Terrestrial	

Hospitalization is not necessarily a perfect surrogate for a rate needing to be chosen for RTDC as many patients may be admitted to the hospital not because they are in urgent need of care, but more for observation while antibiotics are started unless they get sicker. Further, hospital admission rates may be elevated given patients may present late to care terrestrially or patients being older or having medical complications. If an astronaut experiences pyelonephritis and receives prompt diagnosis and antibiotics, the risk of RTDC is likely lower than the conservative estimates provided by hospitalization rate. Thus, neutral confidence level was provided.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Efsthathiou 2003	Terrestrial	3
Ramakrishnan 2005	Terrestrial	
Foxman, 2003	Terrestrial	

Hospitalization is not necessarily a perfect surrogate for a rate needing to be chosen for RTDC as many patients may be admitted to the hospital not because they are in urgent need of care, but more for observation while antibiotics are started unless they get sicker. Further, hospital admission rates may be elevated given patients may present late to care terrestrially or patients being older or having medical complications. If an astronaut experiences pyelonephritis and receives prompt diagnosis and antibiotics, the risk of RTDC is likely lower than the conservative estimates provided by hospitalization rate. Thus, neutral confidence level was provided.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview Urinary Tract Infection – A urinary tract infection is a bacterial infection of the bladder (cystitis) and/or kidneys (pyelonephritis). Best-case scenario involves a Urinary tract Infection (UTI) responsive to oral antibiotics. Worse-case scenario involves a UTI or pyelonephritis requiring IV antibiotics. Sepsis / urosepsis is not discussed here as sepsis is its own condition. CNES: N/A Diagnostic Scope and Resourcing In the best-case scenario, diagnosis is based on history and physical examination of the abdomen and costovertebral angle as well as a urinalysis. In the worst-case scenario, diagnosis is based on history, physical examination - abdomen, costovertebral angle, and digital rectal exam (with suspicion for prostatitis

in male) - urinalysis and lab tests to look for complications or other differential diagnoses. Ultrasound can also be helpful in diagnosis when looking for urinary retention or evidence of a ureteral stone. 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): 0.81 hours CP1 WC (Treated or Untreated: 1.00 hours This CRT includes a scope of practice code of 3 (which correlates to an "Experienced ED/ICU nurse" and was included for physical exam and laboratory interpretation, ultrasound performance, and management decisions. Treatment Scope and Resourcing Terrestrially, uncomplicated urinary tract infections and pyelonephritis can be treated with oral antibiotics after a screening urinalysis. Complicated UTIs, such as those in men, with associated urinary obstruction, sepsis, or resistant bacteria, will require IV antibiotics, laboratory testing, and close monitoring. In space, ureteral stones, functional obstruction, and challenges with sanitation make urinary tract infections more common across both genders, and inherently more complicated. Without the ability to culture bacteria for proof of appropriate antibiotics, empiric antibiotic choices must be made on the best available information and ground based support. Pain is variable depending on the patient but can be treated with NSAIDs, acetaminophen, and Pyridium. In the worst case, the pain of pyelonephritis can be treated with narcotic pain medications. Communications and Support Needs Communication with ground based support through audio or video would contribute to the management decisions, while video assistance may assist with ultrasound interpretation. REFERENCES 1. Kang CI, Kim J, Park DW, et al. Clinical Practice Guidelines for the antibiotic treatment of community-acquired urinary tract infections. Infect Chemother 2018;50(1):67-100. 2. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–e120. 3. Up To Date. Acute complicated urinary tract infection including pyelonephritis in adults. Updated March 19, 2021. Available at https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults?search=pyelonephritis%20treatment&source=search_ result&selectedTitle=1~150&usage_type=default&display_rank=1#H945200358. Accessed on May 22, 2021.

IMM CLIFF RECONCILATION COMMENTS

The previous IMM was reviewed and sources were reviewed and utilized during the creation of this updated CLiFF.

LIMITATIONS SUMMARY

One major limitation of this effort is that our preliminary spaceflight data reveals that UTI may be more common in spaceflight compared to our terrestrial data despite the astronaut population being an overall healthier population. Time will help elucidate whether this increased incidence is valid. Another limitation of the effort is that there are strong epidemiologic and treatment data that differ between men and women and thus this CLiFF could be arguably split into two CLiFFs, however, as a singular condition, a range was chosen to accommodate both men and women. A large limitation is that the surrogate for RTDC of hospitalization may be conservative an inflate estimates of the need for RTDC as discussed above. As with many other conditions, one of the biggest limitations is how to decide on the best numbers in untreated worst-case scenarios. This is not only complicated by a paucity of data attempting to infer results without treatment of pyelonephritis, but difficulty in deciding what numbers to choose for duration, RTDC, and mortality when pyelonephritis is a condition that will either resolve or progress to sepsis which is another condition. Thus, lastly, one of the largest limitations is that there may be overlap between our mortality data and that featured in the sepsis CliFF as theoretically, all of the mortality experiences from pyelonephritis is in the setting of progression to sepsis.

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)												
Untreated Best Case (UTBC)		664					145			6		
Treated Worst Case (TWC)		664					145					
Untreated Worst Case (UTWC)	223	664		89			145		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							211	343	3763	0.0911507	9.11507
Untreated Best Case (UTBC)	132							211	1158	3763	0.307733	30.7733
Treated Worst Case (TWC)	132							211	1152	3763	0.306139	30.6139
Untreated Worst Case (UTWC)	132							211	1483	3763	0.3941	39.41

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		89			145		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)									0	3763	0	0
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)	132							211	1483	3763	0.3941	39.41

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.

REFERENCES

Reference
Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019;11:1756287219832172. Published 2019 May 2. doi:10.1177/1756287219832172
Foxman, B. The epidemiology of urinary tract infection. Nat Rev Urol 7, 653–660 (2010). https://doi.org/10.1038/nrurol.2010.190
Katchman, E. A. et al. Three-day vs longer duration of antibiotic treatment for cystitis in women: systematic review and meta-analysis. Am. J. Med. 118, 1196–1207 (2005).
Suskind, A. M., et al. (2016). "Incidence and Management of Uncomplicated Recurrent Urinary Tract Infections in a National Sample of Women in the United States." Urology 90: 50-55.
Butler, C. C., et al. (2015). "Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey." Br J Gen Pract 65(639): e702-707.
Cole, R. e. a. (2016). "NASA Astronaut Urinary Conditions Associated with Spaceflight."
Boulware DR, Forgey WW, Martin WJ. Medical risks of wilderness hiking. The American Journal of Medicine. 2003;114:288-293.
Lyon RM, Wiggins CM. Expedition Medicine—the Risk of Illness and Injury. Wilderness & Environmental Medicine. 2010;21:318-324.
Schutz S, et. al. Pattern of Passenger Injury and Illness on Expedition Cruise Ships to Antarctica, Journal of Travel Medicine, Volume 21, Issue 4, 1 July 2014, Pages 228–234
Schaeffer, A. J. and L. E. Nicolle (2016). "CLINICAL PRACTICE. Urinary Tract Infections in Older Men." N Engl J Med 374(6): 562-571.
Ikaheimo R, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clin Infect Dis. 1996; 22(1):91-9.
Belyayeva M, Jeong JM. Acute Pyelonephritis. StatPearls Publishing. 2021.
Little, P. et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observation study. BMJ. 2010; 340:b5633.
Grigoryan, L., et al. (2014)." Diagnosis and management of urinary tract infections in the outpatient setting: a review." JAMA 312(16): 1677-1684.
Talan, D. A., et al. (2000). "Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial." JAMA 283(12): 1583-1590.
Sandberg, T., et al. (2012). "Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomized, open-label and double-blind, placebo-controlled, non-inferiority trial." Lancet 380(9840): 484-490.
Eliakim-Raz, N., et al. (2013). "Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-- 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials." J Antimicrob Chemother 68(10): 2183-2191.
Ramakrishnan, K. and D. C. Scheid (2005). "Diagnosis and management of acute pyelonephritis in adults." Am Fam Physician 71(5): 933-942.
Foxman, B., et al. (2003). "Acute pyelonephritis in US hospitals in 1997: hospitalization and in-hospital mortality." Annals of Epidemiology 13(2): 144-150.
Efsthathiou SP et al. Acute pyelonephritis in adults. Prediction of mortality and failure of treatment. Arch Intern Med 2003; 163(10):1206-1212.
Eliakim-Raz, N., et al. (2019). "Risk factors for treatment failure and mortality among hospitalized patients with complicated urinary tract infection: a multicenter retrospective cohort study (RESCUING Study Group)." Clinical Infectious Diseases 68(1): 29-36.
Koradia, P., et al. (2019). "Probiotic and cranberry supplementation for preventing recurrent uncomplicated urinary tract infections in premenopausal women: a controlled pilot study." Expert review of anti-infective therapy 17(9): 733-740.
Hoffmann, T., et al. (2020). "Natural history of uncomplicated urinary tract infection without antibiotics: a systematic review." British Journal of General Practice 70(699): e714-e722.
Buonaiuto, V. A., et al. (2014). "Clinical and epidemiological features and prognosis of complicated pyelonephritis: a prospective observational single hospital-based study." BMC infectious diseases 14(1): 1-8.
American Urological Association University. Adult UTI. Published 5.2012 and amended in 4.2020. https://www.auanet.org/education/auauniversity/for-medical-students/medical-students-curriculum/medical-student-curriculum/adult-uti
Czaja CA, et al. Population-based epidemiologic analysis of acute pyelonephritis. Clin Infect Dis. 2007; 45(3):272-280.
Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am 1997;11:551-81.
Buonaiuto, V. A., et al. (2014). "Clinical and epidemiological features and prognosis of complicated pyelonephritis: a prospective observational single hospital-based study." BMC infectious diseases 14(1): 1-8.
Kang CI, Kim J, Park DW, et al. Clinical Practice Guidelines for the antibiotic treatment of community-acquired urinary tract infections. Infect Chemother 2018;50(1):67-100.

Reference
Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–e120.
Up To Date. Acute complicated urinary tract infection including pyelonephritis in adults. Updated March 19, 2021. Available at https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults?search=pyelonephritis%20treatment&source=search_ result&selectedTitle=1~150&usage_type=default&display_rank=1#H945200358. Accessed on May 22, 2021.
Shields, R.K., Zhou, Y., Kanakamedala, H. et al. Burden of illness in US hospitals due to carbapenem-resistant Gram-negative urinary tract infections in patients with or without bacteraemia. BMC Infect Dis 21, 572 (2021). https://doi.org/10.1186/s12879-021-06229-x
Eliakim-Raz N, Babitch T, Shaw E, Addy I, Wiegand I, Vank C, Torre-Vallejo L, Joan-Miquel V, Steve M, Grier S, Stoddart M, Nienke C, Leo VDH, Vuong C, MacGowan A, Carratalà J, Leibovici L, Pujol M; RESCUING Study Group. Risk Factors for Treatment Failure and Mortality Among Hospitalized Patients With Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group). Clin Infect Dis. 2019 Jan 1;68(1):29-36. doi: 10.1093/cid/ciy418. PMID: 29788118.

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