Clinical Finding Form (CliFF)

Branch: Baseline

ICL68_Herpes Zoster Reactivation (Shingles)

Herpes zoster (HZV) is caused by the varicella virus which can remain latent in the dorsal root ganglia for years and then be reactivated in adults who had a primary infection (chickenpox) in their youth. It can cause a self-limited infection that, while uncomfortable, usually only causes a rash in a single dermatomal distribution. More invasive infections can result in meningoencephalitis, involvement of the auditory and visual systems, and a widely disseminated rash. Facial involvement can result in post-herpetic neuralgia that can last for months or even years. Due to the current average age of current astronauts, the timing of the Varicella vaccine creation (rolled out in the U.S. in 1995), and the extremely high incidence of prior exposure to HZ, most astronauts are at risk for HZ reactivation. While there is laboratory evidence that astronauts may be more at risk due to a compromised immune system, potentially from the stress of spaceflight and the spaceflight environment itself, there have been no reported cases of herpes zoster during spaceflight.

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

A significant amount of work has been performed by Rooney, Mehta, and Crucian et. al. seeking to understand the potential for HZ reactivation in spaceflight as current astronauts were likely to have had Chicken Pox before the advent of the vaccine and are thus at risk for HZ reactivation. Fortunately, while their effort has revealed that ~30-60% of astronauts may show laboratory evidence of reactivation or viral shedding from Herpes viruses in saliva and urinary samples during spaceflight, there have been no reported clinical cases of HZ reactivation. While spaceflight incidence is currently zero, spaceflight studies showing an increase in laboratory HZ reactivation, a possible increase in cold sores (caused by a different Herpes virus; Herpes Simplex Virus), and analog studies (discussed below) raise our level of concern and force a conservative interpretation when creating our best estimates of risk.

ANALOG LITERATURE

We evaluated to analog manuscripts regarding clinical reactivation of HZ in Antartica (Reyes et al 2017) and at elevation (Singh et al 2018) and see that the risk is increased 7-10-fold above the terrestrial incidence values of Americans at sea level. Clinical Herpes Zoster in Antarctica as a Model for Spaceflight revealed 5 cases with an incidence rate of 33.3 per 1000 py. From this information, we can estimate the person-years at 150.1502 (after age and sex-adjustment to the 2010 census). IR: 0.0333 (95%CI: 0.0108, 0.0778). Unfortunately, we cannot obtain a true incidence rate from the Singh publication at present as it reports on percentages of all skin outpatient department cases as opposed to in terms of the underlying at risk population.

TERRESTRIAL LITERATURE

While HZ is seen more often in older populations (>50 y/o), immunocompromised or immunosupressed (i.e. HIV/AIDs, pregnancy, cancer chemotherapy), there is robust terrestrial evidence evaluating HZ reactivation by age and gender in the United States (Johnson et al 2015). In <50 year olds, Johnson provides an annual incidence of 2.4 per 1000 person years. 60% of these cases are in women and 40% in men.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.03331 and SD 0.01501

INCIDENCE SUMMARY

Since there are no reports of HZV reactivation during spaceflight, terrestrial data was used to calculate the composite incidence. A manuscript by Reyes, et al., was chosen to be the source of incidence data since it used a similar population to astronauts in an analog environment. Two papers showed up to a 10 times higher risk for reactivation in analog populations, possibly due to increased stress compared with the general population. The Bayesian posterior distribution from Reyes 2017 given the reference evidence (5 events over 150.15 person-years) under an uninformative prior is Gamma(shape=4.925, rate=147.85) with mean 0.03331 and SD 0.01501.

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.
Gamma

Mean
0.0333108

SD
0.01501

Gamma
(Shape): 4.925
(Rate): 147.85

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Reyes, et al. 2017	Analog	3
Singh, et al. 2018	Analog	2
Mehta, et al. 2007	Spaceflight	3
Johnson, et al. 2015	Terrestrial	1
Drolet, et al. 2010	Terrestrial	1
Rooney, et al. 2019	Spaceflight	3
Leung, et al. 2011	Terrestrial	1
Kawai, et al. 2016	Terrestrial	1

As extensively explained with the other incidence captions, the level of confidence in spaceflight, analog, and terrestrial is complicated. While we have reasonable confidence that Mehta and Rooney are truly showing laboratory evidence of HZ reactivation, these studies cant be used to calculate clinical spaceflight incidence risks and the current clinical reactivation incidence in spaceflight is 0. While the analog populations agree with the spaceflight data that reactivation risk may be elevated, the studies are limited by low numbers and both the population and environment are different from the astronaut population and spaceflight environment. The terrestrial data is much more robust, however, despite the increase in numbers, we also do not have high confidence in these incidence rates would apply well to spaceflight given the spaceflight and analog data that is available.

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

There are no formal pre-flight preventive screening measures noted on MRID.

BEST CASE SCENARIO DEFINITION

An uncomplicated course of herpes zoster over several days which causes minimal disturbance with localized pain and may require treatment with antiviral and/or pain medications.

WORSE CASE SCENARIO DEFINITION

A prolonged course of herpes zoster accompanied by symptoms of either persistent disruptive pain, e.g. post herpetic neuralgia (PHN), or ocular and neurological complications (peripheral motor neuropathy, Ramsay Hunt syndrome, or HZ ophthalmicus).

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

The difficulty in evaluating best/case worst case is the fact that while we can find incidence rates for all of the varying complications from HZ reactivation (post-herpetic neuralgia [~5-30%], peripheral motor neuropathy [~3%], Ramsay Hunt sundrome [very rare], HZ opthalmicus [~10%], etc), there is a paucity of data combined incidence of complicated HZ reactivation. One study in Italy found a combined complications rate of 26% in all age groups (Paparatti et al, 1999). Given that terrestrial stressors (and thus spaceflight stressors) will likely increase the rates of some of these complications, while lower ages (as characteristic of our astronauts) converseley decreases the rate of complications from HZ reactivation, assuming an average worst case of 20% is reasonable. This is further substantiated when looking into the Paparatti data further, the complication rate for those aged 35-44 was 14.9% while 45-54 year olds was 23.9%.

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

Citation	Source	LOC Value
Drolet, et al. 2010	Terrestrial	2
Rowbatham, et al. 1998	Terrestrial	2
Kong, et al. 2020	Terrestrial	2
Kawai, et al. 2014	Terrestrial	2
Paparatti U, et al. 1999	Terrestrial	3

As clinical HZ reactivation has yet to occur in spaceflight, complications stemming from reactivation are even more rare and thus the level of confidence dimishes even further that any terrestrial study could apply to astronauts. A neutral LOC value was chosen because astronauts are simultanously under increased stressors that may theoretrically increase the risk of complications while also being of a demographic (age, health, etc) that would decrease this risk. The Paparatti manuscirpt was given a 3 given these authors were able to evaluate combined complication rate by age group.

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 0.03331 and SD 0.01501	80 - 80	100	0.66	3.25538	168	240	0	0	0	0	0
Treated Worst Case (TWC)		20 - 20	100	1	13.832	240	2160	0	0	0.002	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.66	13.832	168	336	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1	34.7863	240	2160	26.761	0	0.025	0	0

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

Given the variability in duration and severity of HZ reactivation symptomatology, durations, RTDC, and LOCL are largely based around expert opinion and analysis of previous meta-analyses. As with most every condition, the worst case scenario is not presumed to be the absolute worst imaginable case, however the median presentation that meets the WC definition provided.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Data supporting best-case treated scenarios indicate that the condition will generally resolve within 7-10 days with antivirals and symptomatic control with pain medications. There is no concern for RTDC or LOCL in treated best-case scenarios.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The worst-case definition includes a number of distinct complications of HZ reactivation that all have differing timings. While continued neuropathic pain can persist for longer than 3 months, symptoms lasting a maximum of 3 months was felt to be a reasonable consideration for a maximum treated worst-case scenario. Bouhassira et al 2012 found that pain symptoms dropped to 11.6%, 8.5%, 7.4%, and 6.0% at 3, 6, 9, and 12 months, respectively. This was not broken down by age, and thus there is likely <10% chance that symptoms would remain for longer than 3 months in the astronaut population. A large meta-analysis (Kawai et al, 2014) revealed a range of hospitalization rates from 0.2-2.5 per 10,000 person-years and mortality rates of 0.0017-0.0465 per 10,000 person-years. As this meta-analysis also includes all ages, these numbers are likely elevated beyond our expectations in a health astronaut population.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

In early studies of acyclovir vs. placebo, they found that acyclovir shortened the duration of pain symptoms and decreased the risk of HZ complication, hence why it is now the standard of care. Upon evaluating a meta-analysis of these trials (Wood et al, 1996), it is notable that the relief from moderate pain without treatment lasted until 14 days and thus we extend the duration to 336 hours for UTBC. Upon review of the best case scenario definition, we would not expect RTDC or LOCL.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

The worst-case definition includes a number of distinct complications of HZ reactivation that all have differing timings. While we expect <10% of individuals <60 to still have remaining symptoms beyond 3 months with treatment, there is limited data to guide untreated worst case scenario durations. In a young and healthy astronaut population, there is likely <10% chance that symptoms would remain for longer than 3 months. Given that the Wood et al 1996 meta-analysis of early placebo-controlled trials showed that the median time to being pain free was 67 days in the placebo groups, it is likely that as with the treated groups, that untreated WC scenario duration has a low likilihood of extending beyond 90 days (or 2160 hours). Rare cases can extend for many months or years, however, given the astronaut population is young and healthy, this range feels reasonable. Furthermore, based off of Kawai's 2014 meta-analysis of 28 studies evaluation hospitalization and mortality rates, UTWC carries an RTDC risk of 25/100,000 (or 0.025%) and mortality rate of 0.465/100,000 (or 0.000465%).

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

Citation	Source	LOC Value
Schmader, 2018	2	3
Huff, et al. 1988	3	
Schmidt SA, et al. 2016	3	
Wood, et al. 1996	3	
Helgason, et al. 2000	3	

Fortunately, there are a number of studies still available for review that compared acyclovir with placebo for HZ in the 1980s and 1990s. Wood et al, 1996 provided a meta-analysis of these trials, and between this and the other studies, we can be reasonably confident in our duration intervals. The main limitations include: 1. that most studies do not separate outcomes by age and cmplication rate and duration of complications is affected by age, 2. That the duration and diversity of complicated symptoms in the worst case scenario can have very braod ranges and very variable

outcomes, and 3. our main meta-analysis (Wood et al 1996) doesnt robustly evaluate complicated HZ symptpms.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Kawai, et al. 2014	4	3
Schmidt SA, et al. 2016	3	
Helgason, et al. 2000	3	
Schuster, et al. 2016	3	
Drolet, et al. 2010	3	

Though the astronaut population is significantly different from the average HZ reactivation patient, we have reasonable conifdence regarding RTDC rates that are based around the need for hospitalization for symptom management.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Kawai, et al. 2014	4	3
Schmidt SA, et al. 2016	3	
Helgason, et al. 2000	3	
Schuster, et al. 2016	3	

Though the astronaut population is significantly different from the average HZ reactivation patient, we have reasonable conifdence regarding the LOCL data.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview
In addition to the more commonly known shingles, Herpes Zoster can also lead to other complications such as Ramsay Hunt syndrome, post-herpetic neuralgia, peripheral motor neuropathy, and VZV ophthalmicus. Mehta et al have numerous studies over the last two decades raising the concern of reactivation of VZV during or after spaceflight. Ramsay Hunt syndrome (RHS) is manifested by facial palsy, inner ear dysfunction, periauricular pain, and herpetiform vesicles on the pinna. It occurs in 4/100,000 people, and without proper treatment, only 20% will achieve complete recovery. These symptoms are thought to be caused by inflammation, edema, and compression of CN 7. Involvement of other CNs is rare. Postherpetic neuralgia (PHN) is a chronic neuropathic pain syndrome that results from VZV reactivation that persists for 3 months or more after the onset of rash in the same affected dermatome. In most of the cases, pain improve progressively and is categorized in 3 types: 1) constant pain (burning, aching, throbbing), 2) intermittent pain (stabbing, shooting, electric-shock-like pain), or 3) stimulus-evoked pain such as allodynia or hyperalgesia. HZ ophthalmicus represents up to 25% of reactivation zoster cases and presents with periorbital vesicular rash, conjunctivitis, keratitis, uveitis, and ocular cranial-nerve palsies. This may lead to chronic ocular inflammation, loss of vision, and debilitating pain. It should be noted that vaccination in astronauts older than 50 years could be considered as a preventative strategy and possibly in astronauts younger than 50 if the higher risk of reactivation in space outweighs the risk of vaccination.

CNES: None

Diagnostic Scope and Resourcing
The best-case scenario includes an uncomplicated course of shingles, while the worst-case scenario may include the numerous complications above. In the best-case scenario, a history and skin physical exam are all that are required for diagnosis. In the worst case, a focused neurological exam and eye exam may be necessary depending upon the symptomology and location of the reactivation. Tzanck smears, DFA, VZV PCR, or antibody levels will not be available. Furthermore, MRI or lumbar puncture will also not be available.

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): 0.66 hours
CP1 WC (Treated or Untreated): 1.00 hour

While the diagnostic scope of practice for the best case may have been 1, for the worst case, given the complexity of interpretation of the neurologic and eye exam with complicated VZV, the scope of practice is 5 (experienced procedure trained generalist attending).

Treatment Scope and Resourcing
In the best-case scenario, symptom management include valacyclovir, cool compresses/wet dressings, and topical moisturizers/lotions like calamine may be necessary. Tylenol or NSAIDS can be used for pain. In the worst case, oral steroid tapers, neurologic medications such as gabapentin, pregabalin, or topical lidocaine can be used, and an ultrasound-guided stellate ganglion nerve block can be performed for facial pain if the reactivation occurs there. Additionally, oral narcotics can be used for pain if needed in addition to the Tylenol and NSAIDs. However, other anticonvulsants, antidepressants, topical capsaicin, botulinum toxin, intrathecal blocks, electronic neuromodulation (TENS, PNS, SCS), and radiofrequency are unlikely to be possible during spaceflight. Supportive medications beyond valacyclovir for VZV ophthalmicus are covered under ICL 49 – eye irritation.

Communications and Support Needs
While real-time video and audio loop communications are desired for diagnosis and treatment of the worst-case scenario where consultation with ground specialists can be helpful for facilitating treatment and healing was considered necessary given the limited diagnostic and treatment capabilities in-flight.

IMM CLIFF RECONCILATION COMMENTS

The sources within the previous CLiFF were evaluated and often used unless newer or more robust trials were located. Ultimately, we elected to be more conservative with higher duration maximum estimations and actually lower with RTDC and mortality rates upon reviewing the newest data.

LIMITATIONS SUMMARY

Limitations are extensively discussed when applicable throughout the CLiFF above, however, some other limitations not specifically addressed include: • Once an episode occurs, the incidence of further cases will likely increase significantly. This is true because HZV is a highly contagious virus and adequate protective gear may not be available on board. Also, once an individual has a case of reactivation, his/her risk of another case increases. • The use of HZV vaccination for those eligible can decrease the risk of infection and affect the incidence calculation. • The composite incidence would predict a case of HZV reactivation within 33 person-years of spaceflight. There have been no reports of a case in nearly 50 person-years to date. • The worst case includes many of the complications from HZV, but not all of them (e.g., encephalitis). Each of these complications are unique and have different durations. This made defining an “average” worst case problematic.

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										
Treated Worst Case (TWC)		664										
Untreated Worst Case (UTWC)	223	664	113	89			145					
	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)							34	211	245	3763	0.0651076	6.51076
Untreated Best Case (UTBC)	132						34	211	1041	3763	0.276641	27.6641
Treated Worst Case (TWC)	132						34	211	1041	3763	0.276641	27.6641
Untreated Worst Case (UTWC)	132						34	211	1611	3763	0.428116	42.8116

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)		664										
	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	1007	3763	0.267606	26.7606

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