Clinical Finding Form (CliFF)

Branch: Baseline

ICL2_Abnormal Uterine Bleeding

Chronic, nongestational abnormal uterine bleeding (AUB) has been shown to affect 5-25% of reproductive-aged women in the United States and thus represents one of the most common gynecologic complications that may impact female crewmembers during spaceflight. The etiology may be structural (polyps, adenomyosis, leiomyomas, and malignancy/neoplasia) or nonstructural including coagulopathy, ovulatory dysfunction, endometrial disorders, or be iatrogenic. AUB can range from unpredictable intermenstrual spotting to catastrophic hemorrhage depending upon the etiology. While effort is placed to mitigate the risk of AUB via pre-flight assessment and consideration of hormonal contraceptive options, it can still occur with or without the use of exogenous hormones.

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

There is no formal incidence of AUB during spaceflight. Steller et al (2020) cite the incidence of leiomyoma; iron deficiency anemia, ovarian cysts; and [lack of data on] endometriosis. While both Steller 2020 and Jennings 2000 discuss rare occurrences (at least two episodes) of AUB in spaceflight, true incidence values are unknown and likely suffer from underreporting. Even with this limitation, spaceflight AUB incidence is clearly lower than the terrestrial population data of 5-25%. This also may be from hormonal suppression, however, the number of astronauts using cyclical, continuous, or no hormonal contraception is also unknown.

ANALOG LITERATURE

Three analog studies were reviewed. The first followed a group of flight attendants (Lauria 2006) who frequent high altitudes and are more subject to cosmic radiation; though not at the level of low earth orbit or deep space. The two other studies reported incidence for female soldiers deployed in the Iraq war (Thomson 2006, Nielsen 2009). The studies were chosen for the high stress environment and for most soldier's high preference to suppress menstruation during deployment which is most reflective historically of the astronaut population. With that said there are other studies that show that daily compliance with oral contraceptive pills (which was most likely) was also difficult, and thus some rates of AUB may be iatrogenic in nature from imperfect use of the hormonal modalities. Ultimately, these analog studies, whilst informative, were not used in the composite incidence given their low numbers, the factor that they were survey data, and that some information was missing in order to full utilize it in the calculations. Overall, these showed a possible incidence range of about 21-25% in line with terrestrial data.

TERRESTRIAL LITERATURE

An English cross sectional study (Shapley 2004) and a retrospective Dutch study (de Vries 2008) were chosen as terrestrial incidence studies for AUB. These studies showed an incidence range of 5-25%.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.05197 and SD 0.003205

INCIDENCE SUMMARY

The Bayesian posterior distribution for the incidence rate given the terrestrial study (270 cases over 5192.308 person-years) under an uninformative prior is Gamma(shape=262.94, rate=5059.37) with mean 0.05197 and SD 0.003205. This condition is for females only. Composite IR 0.052 (95%CI: 0.046, 0.058). Producing a formal composite incidence for AUB in spaceflight is extremely limited. Not only do spaceflight, analog, and terrestrial data all suffer from reporting bias and not being robustly tracked, but the data is not separated out by whether one is using no hormonal contraception, cyclical hormonal contraception, or continuous hormonal contraception. Further it may depend upon the type of hormones whether progestogens alone or an estrogen and a progestogen in combination. Lastly, rates of AUB may depend upon a patient's history, socioeconomic factors such as access to care, and compliance. The astronaut population has extensive work-up pre-flight to mitigate inflight AUB, traditionally use continuous hormonal contraceptives, and are extremely compliant (Steller 2020). For all of these reasons, even our most conservative estimate may be incorrect. As the de Vries 2008 study is our only non-survey-based level 3 evidence, this incidence was ultimately chosen.

TABLE 1. INCIDENCE MODEL

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
0.0519709

SD
0.00320503

Gamma
(Shape): 262.94
(Rate): 5059.37

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Lauria et al, 2006	Analog	2
Thomson et al, 2006	Analog	2
Nielsen et al, 2009	Analog	2
Shapley et al, 2004	Terrestrial	2
de Vires et al, 2008	Terrestrial	3

As explained in Table 1 caption, available data is largely based off of survey data which leads to level of confidence scores of 2 given the inherent limitations of these studies.

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

It is recommend all astronauts undergo screening for a personal and family history of bruising/bleeding (inclusive of AUB), have a pre-flight transvaginal ultrasound to evaluate for anatomical/structural causes, and undergo testing for anemia or iron-deficiency as these can all be managed pre-flight. Consideration of testing for bleeding disorders can be conducted if indicated by the history.

BEST CASE SCENARIO DEFINITION

Irregular bleeding between menses, menses > 8 days in length, or heavy menses (requiring tampon/pad changes < Q2H, or passing clots larger than the size of a quarter), that resolves spontaneously or with medications.

WORSE CASE SCENARIO DEFINITION

Irregular bleeding between menses, menses > 8 days in length, or heavy menses (requiring tampon/pad changes < Q2H, or passing clots larger than the size of a quarter), that requires mechanical/surgical intervention.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

Irregular menses; Menorrhagia

BEST CASE/WORST CASE PROBABILITY COMMENTS

Calculating a worst-case probability is also complicated by similar limitations as discussed above. Most studies, including Majoribanks et. al.'s Cochrane reviews are evaluating patient satisfaction with control of their AUB after differing medical and surgical management. Dood et al, 2014 discusses a large Canadian study evaluating how many patients required endometrial ablation or hysterectomy in the setting of AUB which was 4%. With that said, as our team was reviewing RTDC surrogates, AUB necessitating hospitalization and evacuation in the military is also a good surrogate for the WC scenario in which AUB fails medical management and requires mechanical/surgical intervention. In the military, hospitalization/evacuation for AUB ranges from 6-15% (Dorsey et al 2013, Stahlman et al 2017), whereas in terrestrial data, the incidence of hospitalization for AUB is 10-fold less (1.3 per 1000; Whiteman et al 2010) and (4.78 per 1000; Louoto et al 1994). Again as the astronaut population and spaceflight environment both differ from terrestrial and analog populations, a conservative maximum worst-case scenario estimate of 5% is reasonable. Given the extensive screening for crewmembers pre-flight and that no worst-case scenario AUB has been seen in spaceflight to date, the minimum worst-case scenario was assigned 0%. Thus, a worst-case scenario range of 0-5% was assigned.

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

Citation	Source	LOC Value
Dood et al, 2014	Terrestrial	2
Majoribanks et al, 2016	Terrestrial	2
Dorsey et al, 2013	Analog	2
Stalhman et al, 2017	Analog	2
Whiteman et al, 2010	Terrestrial	2
Luoto et al, 1994	Terrestrial	2

Given the paucity and lack of understanding of the spaceflight environment on menses and AUB in addition to the various limitations discussed throughout this CLiFF, it is difficult to have a higher level of confidence level than 2 (neutral) as BC/WC probability is being chosen by expert opinion in the setting of this data.

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 0.05197 and SD 0.003205	95 - 100	100	1.33	2.80361	0.33	336	0	0.13	6	0	0
Treated Worst Case (TWC)		0 - 5	100	2.17	50	336	8760	0	50	100	0.001	100
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.33	5.60723	0.33	336	5.60723	6	15	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	2.17	11.7327	672	8760	7.97236	100	100	90	100

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

As discussed below in the individual section and the limitations section, while AUB may be one of the most common reasons that women seek medical care (occurring in 5-25% of all women), it can often be managed terrestrially either pharmacologically or surgically with high success. Though AUB will try to be prevented through optimal pre-flight screening and consideration of hormonal modalities, if AUB occurs during spaceflight, management options will be very limited.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

A best-case shortest duration may brief (0.33 hours) in that intermenstrual spotting is considered in the duration while the best-case longest duration may be up to two weeks with AUB managed by hormonal modalities. There is robust analog data to evaluate RTDC with evacuations from the operational theatre in the military or in using hospitalization as a surrogate for bleeding that is bad enough to warrant consideration of evacuation (Dorsey et al 2013, Stahlman et al, 2017). With that said the hospitalization and evacuation rate in the military for AUB ranges from 6-15% whereas in terrestrial data, the incidence of hospitalization for AUB is ~10-fold less than the incidence of having AUB (0.13%; Whiteman et al 2010; 0.48%; Louoto et al 1994). As diagnostics and management will be limited during spaceflight, adopting both data sets is reasonable for a TBC min and max (0.13-6%), while UTBC may require the most conservative WC range (6-15%). LOCL with treatment in the best case scenario is presumed to be 0%, as by definition, it resolves.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The worst case definition specifically warrants mechanical or surgical intervention for excessive AUB that is refractory to expectant and medical management (best-case definition). Terrestrially, such patients can be managed safely with surgical management and the risk of death from non-obstetrical uterine bleeding is very low (GBD, 2017). In spaceflight, with exception of a few minor procedures such placement of a foley balloon and vaginal packing for uterine tamponade, surgical management is not an option. This holds heavy implications for worst case scenarios meeting our definition in that AUB that requires such intervention nearly obligates RTDC, and without RTDC would lead to eventual LOCL. It is possible that pharmacologic management may temporize AUB to allow for RTDC and it is possible that the AUB can stop spontaneously, however, there is not data that is capable of answering such questions under this definition (i.e. AUB significant enough to warrant surgery that is temporized by pharmacologic management or resolves spontaneously). Thus the range for both RTDC and LOCL chance are based on Global Burden of Disease Study authors for the minimum chance and true worst case scenario for the maximum chance. Further, the duration decisions are also severely limited by definition constraints. AUB significant enough to warrant mechanical/surgical intervention likely is from a pathologic cause that will continue cause AUB until treated. Again if not abiding by a completely rigid interpretation of the definition, it is possible that the AUB could abate after temporary mechanical tamponade and resolve. Thus, a very broad duration range from 14 days to 1 year was chosen. Our authors note that with a completely rigid definition, there would be almost no range of duration, RTDC, and LOCL as these would be 100%.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

A best-case shortest duration may brief (0.33 hours) in that intermenstrual spotting is considered in the duration while the best-case longest duration may be up to two weeks as with TBC. This range has limited accuracy in that while this is an untreated scenario, the best-case definition still is considering the best case that may resolve spontaneously. 14 days is a reasonable choice in that AUB can range from spotting between menses or having menses >8 days for months, to one large bleed one time. There is robust analog data evaluating RTDC with evacuations from the military operational theatre or in using hospitalization as a surrogate for bleeding that is bad enough to warrant consideration of evacuation (Dorsey et al 2013, Stahlman et al, 2017). As we are considering an untreated scenario, utilizing the conservative hospitalization and evacuation rates from the analog studies of 6-15% are reasonable. LOCL without treatment in a best-case scenario is still presumed to be 0%, especially if RTDC is presumed to be occurring, however, would not be for worst case scenarios.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

As explained in the TWC section, AUB severe enough to warrant mechanical/surgical management is very rare and very serious. The complete lack of treatment for bleeding this severe with no pharmacologic or procedural management is catastrophic. There is no data to guide duration, RTDC, or LOCL in this setting. A duration of 1-12 months was chosen given the small chance that it could abate spontaneously. However, RTDC would remain 100%, and LOCL must approach 100%. A range of 90-100% was chosen by expert clinical opinion. While the terrestrial literature supports spontaneous resolution of AUB without treatment that may sound encouraging, this literature is for all patients with AUB, irrespective of severity. This data does NOT review the resolution rates in patients presenting with bleeding at the severity level of this definition and then also receiving no treatment.

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

Citation	Source	LOC Value
Munro, 2006	terrestrial	1
Lethaby, 2019	Terrestrial	
Yousefi, 2020	Terrestrial	
Lukes, 2010	Terrestrial	

Given the nuance associated with the best- and worst-case definitions as well as the paucity of understanding in how spaceflight may affect AUB, there is low confidence in the duration range, RTDC chance, and the LOCL.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Dorsey et al, 2013	Analog	1
Stalhman et al, 2017	Analog	
Whiteman et al, 2010	Terrestrial	
Luoto et al, 1994	Terrestrial	
de Vries, 2008	Terrestrial	
Stang, 2012	Terrestrial	

Given the nuance associated with the best- and worst-case definitions as well as the paucity of understanding in how spaceflight may affect AUB, there is low confidence in the duration range, RTDC chance, and the LOCL.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
GBD, 2017	Terrestrial	1
Wijeratne, 2018	Terrestrial	

Given the nuance associated with the best- and worst-case definitions as well as the paucity of understanding in how spaceflight may affect AUB, there is low confidence in the duration range, RTDC chance, and the LOCL.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview Abnormal uterine bleeding can range from spotting in between menses to catastrophic uterine bleeding leading to significant anemia and its associated complications. While the optimal strategy is to try and decrease the risk of future AUB pre-flight, this common pathology may occur despite pre-flight surveillance and with or without the use of hormonal contraceptives. CNES: none Diagnostic Scope and Resourcing In the best-case scenario, a history and physical exam (inclusive of abdominal exam and pelvic exam), in addition to an ultrasound of the pelvis and a urine pregnancy test would be recommended. In the worst case scenario, given the significant bleeding, vital signs and a CBC would also be necessary. 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): 1.33 hours CP1 WC (Treated or Untreated): 2.17 hours The highest scope of practice that would be necessary is SOP 5 (experienced procedure-trained generalist attending). Treatment Scope and Resourcing Routine management of abnormal uterine bleeding may often depend upon the cause of the AUB, whether anatomical (polyps, adenomyosis, leiomyomas, or malignancy) or non-structural. However, treatment is going to be largely limited to pharmacologic management. This may include a burst taper of norethindrone/ethinyl estradiol or medroxyprogesterone, followed by initiation of a daily oral contraceptive pill to follow the episode. Tylenol may also be used for discomfort, and NSAIDS like ibuprofen can not only be used for mild pain but also should be used every 6 hours throughout menses, if heavy, and can help to decrease the amount of blood flow. In a worst case scenario where AUB is leading to a significant bleed that is not responding to hormonal modalities and may even require mechanical/surgical intervention, many additional treatment options may be implemented. In addition or hormonal options and NSAIDs, adding doxycycline and TXA should be considered. Further, considering uterine tamponade via foley catheter in the uterus and packing. Oral hydration, IV hydration, or even a whole blood transfusion from a crewmate could be considered in the absolute worst case. If transfusion were to be considered, then a bundle of treatment

options for mild blood transfusion reactions should be included. Unfortunately, beyond potentially removing an IUD or subdermal implant that may be contributing to AUB, other procedural options or surgical management are not currently available. Further, other forms of heterologous blood transfusion, cell saver, or more advanced management of TRALI/TACO/AHTR are also not currently possible. Communications and Support Needs Real-time video and audio loop communications may be necessary for the diagnosis and treatment of worst case scenarios where consultation with ground specialists is possible.

IMM CLIFF RECONCILATION COMMENTS

The old IMM CLiFF was reviewed which contained many informative analog and terrestrial studies for review and implementation into the current effort. Unfortunately, because the definitions changed (which made the worst case of AUB for the current CLiFF more severe), it has dramatically changed the duration, RTDC, and LOCL outcomes.

LIMITATIONS SUMMARY

This CLiFF is first limited by no formal tracking of AUB in spaceflight. While there have been a few occurrences of AUB, there are minimal published details surrounding these events and an incidence cannot be calculated. It is possible that there may also be reporting bias and that the spaceflight incidence of AUB may be higher than presumed. Another limitation is that the age, health, and pre-flight screening and mitigation decrease the risks of AUB in comparison to outcomes in the terrestrial literature. A third limitation is the fact that terrestrial literature on AUB does not specifically analyze their outcomes in the setting of no hormonal contraception, cyclical hormonal contraception, continuous hormonal contraception, or even type of contraception (i.e.. progesterone alone vs. combination estrogen and progesterone). Lastly, while the best-case and worst-case definitions are reasonable, especially terrestrially, another limitation of the CLiFF is being able to calculate and understand what the inability to perform surgical management of this condition would have on duration, RTDC, and LOCL in worst case scenarios.

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)												
Treated Worst Case (TWC)	223	664	113	89	854	44	145	5	13	6		
Untreated Worst Case (UTWC)				89			145			6		
	Affected HSTCs (Continued)								TI Calculation			TI Score
	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)								211	211	3763	0.0560723	5.60723
Untreated Best Case (UTBC)								211	211	3763	0.0560723	5.60723
Treated Worst Case (TWC)	132	564	414	22	196	34	34	211	3763	3763	1	100
Untreated Worst Case (UTWC)	132							211	583	3763	0.15493	15.493

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)				89								
	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)								211	211	3763	0.0560723	5.60723
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)								211	300	3763	0.0797236	7.97236

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