Clinical Finding Form (CliFF)

Branch: Baseline

ICL50_Eyelid And Anterior Eye Infection

The eye is comprised of three layers: the exterior fibrous layer (cornea and sclera), the middle vascular layer (choroid, ciliary body, and iris) and the internal layer (retina). The lens partitions the anterior structures (iris, anterior chamber, and cornea) from the posterior structures (vitreous, retina, choroid, and optic nerve). This CLiFF concerns infections related to the eyelids and the anterior structures of the eye. Conditions that this CliFF encompasses include hordeola, infectious conjunctivitis, preseptal cellulitis, infectious uveitis, infectious keratitis. Infection means a disease caused by a pathogen or microorganism. Consequently, non-infectious causes such as autoimmune uveitis, allergic conjunctivitis and ulcerative keratitis (corneal ulcer) are not covered here. Further, herpes zoster opthalmicus is covered in the CLiFF entitled “Herpes Zoster Reactivation.” Infectious conjunctivitis, which is covered in the best-case scenario refers to inflammation resulting from infection of the conjunctiva: the thin, clear membrane that lies against the anterior part of the sclera and inside the eyelids (Azari et al., 2020). Cases of conjunctivitis are characterized by hyperemia, edema, and discharge. The worst-case scenario can refer to a case of preseptal (or periorbital) cellulitis, but markedly not orbital cellulitis. Preseptal and orbital cellulitis are distinct clinical diseases, though have overlapping clinical features and therefore can be difficult to differentiate. Preseptal cellulitis involves infection of the eye lids and surrounding skin not involving the orbit (the structures anterior to the orbital septum). Orbital cellulitis involves the contents of the orbit (fat and ocular muscles) (Baiu et al., 2020). For simplicity, this CLiFF covers only category 1 of the Chandler classification system.

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

Spaceflight literature were derived from two LSAH data gathering events (Walton, 2010; Saile et. al, 2017) and a NASA white paper (Antonsen et al., 2017). Unfortunately, the authors of this CLiFF did not have direct access to the data from those LSAH events. Consequently, information was taken detailing these events from previous IMM CLiFF entitled "Eye Infection.” Of note, this IMM previously covered herpes zoster opthalmicus which is now covered in the worst-case scenario of the CLiFF ‘Herpes Zoster Reactivation’ and was not covered in this condition. From the Walton LSAH pull there were 5 events: “3 styes, 1 blepharitis caused by hair and eyelid pustules.” From the Saile LSAH pull, there were seven more events: three from ISS and four from STS. On ISS, two events involved an extended infection treated with tobramycin/dexamethasone drops and ciprofloxacin. The other case involved keratitis that was treated with ciprofloxacin drops. On STS, two events were styes, one event was a report of "eye goop" and one event was recorded as "eye infection." Treatments for these events on STS are unavailable. The statistician of this CLiFF was also able to contact the authors of Antonsen et al. and verify the data (which was also based on the prior LSAH events). During her analysis it was observed that in the Antonsen et al. paper Table 1 was mislabeled as 'ISS through Exp 40' when it should read ' ISS expeditions 9 and 14 through 40'; this CLIFF corrects for that error. Antonsen et al. was rated less than the LSAH pulls as they categorized events as “eye abnormalit[ies]” as opposed to specific pathologies. At the time of this CLIFF completion, a repeat LSAH data gathering event was not possible and missions past 2017 are not represented.

ANALOG LITERATURE

Although analog studies included larger sample sizes, studies did not accurately reflect condition environments or spaceflight populations. As a result, spaceflight data was rated much higher than analog data in the incidence calculation. In Psolka et al. (2007), a retrospective review was conducted of 107 United States military personnel who were referred to the Walter Reed Army Medical Center ophthalmology service between January 1, 2003 and September 30, 2005 with non-battle pathologies. During this time, there were five cases of infectious keratitis (4.7%), one case of blepharitis (0.9%), one case of viral conjunctivitis (0.9%), four cases of anterior uveitis (3.7%), and one case of toxoplasmosis uveitis (0.9%) found in the 33 months of this study. The total number of cases in this study may underestimate true incidence as patients were initially evaluated by their “primary service” and not every ocular event likely warranted an ophthalmology referral. In a prospective epidemiological study describing the distribution and rates of medical conditions suffered during a physically demanding 25-week Naval Special Warfare Center indoctrination training of male U.S. Navy SEALs, Linenger et al. (1993) reported one “eye infection” event in 482 trainee-months at risk (0.2 per 100 trainee months). Another study (Tansey et al., 1979) analyzed medical reports from 885 Fleet ballistic missile submarine patrols from 1963-1973 and compared them to illness rates found in crewmembers on surface-level vessels. Within this timespan there were nine reported events of “keratoconjunctivitis,” three cases of “iridocyclitis” and one case of “uveitis” out a total of 48 eye medical cases in a total of 7,650,000 man-days. There are no details whether these cases were secondary to infection, trauma, or autoimmune pathologies. The authors did comment that they believed the reporting of medical conditions on submarines was artificially low secondary to the lack of medical personnel and fear of retribution. In

Thomas et al. (2003), a retrospective analysis was conducted of the medical records between January 1, 1997 and September 30, 2000 of 1389 officers and 11,952 enlisted crew members. This accounted for a total of 215,086 and 1,955,521 person-days at sea, respectively. The subjects in this study were a highly screened, healthy population and the study was conducted to develop epidemiological data to determine risk in space medicine. “Disorders of the eye and adnexa” had a reported six officer events for 1.0/100 person-years and 54 enlisted men events for 1.0/100 person-years. Unfortunately, there were no further details regarding the types of pathologies involved. A retrospective analysis (Aslam et al., 2005) of medical records presenting to a British Army Field Hospital during Operation Telic, study period March 27 and May 1 2003, reported that conjunctivitis was the most frequent non-traumatic presentation, 22.22% (10 cases out of 45 eye complaints). Other cases reported include two corneal abscesses, two sties, one iritis, one episcleritis, one dacrocystitis and seven “other.” Unfortunately, despite the relevance of the population of this study, an incidence can not be calculated as there is not enough information provided to calculate person-years. Lastly, a study analyzing medical visit data between 1996-2005 of active-duty personnel via the Defense Medical Surveillance System (Hilber et al., 2010) described “other conjunctivitis” and “punctate keratitis” as two of the top-ten most frequent diagnoses of eye complaints (6.3% and 7.6% of all ocular injuries in 2005). Still, it is not known whether these presentations were secondary to infection versus traumatic injuries.

TERRESTRIAL LITERATURE

Terrestrial literature came from large retrospective studies with data gathered from nationally representative databases. These studies encompassed populations with increased rates of comorbid conditions. There were no metanalysis incidence data available for this condition. McGwin et al. (2005), analyzed the data from the Consumer Product Safety Commission’s National Electronic Injury Surveillance System (NEISS) All Injury Program in the year 2000 and found that the rate of emergency department treated eye injury in the United States was 3.15 per 1000 population (95% confidence interval, 2.66-3.63). “Conjunctivitis” accounted for 9.9% of these presentations. Chana et al. (2016) reviewed data from 2006-2011 in the U.S Nationwide Emergency Department Sample (NEDS) for ocular problems. There were over 11,929,955 ED visits for ophthalmic conditions during this timeframe; of these, 3,343,900 (28.0%) visits were for “conjunctivitis” and 450,831 (3.8%) visits were for “external hordeolum.”

OVERALL INCIDENCE SUMMARY

INCIDENCE

0.2638 person-years; SD: 0.07658 person-years

INCIDENCE SUMMARY

Spaceflight data: • IMM – 12 events (5 in Walton and 7 in Saile) over 45.49 person-years. IR: 0.2638 (95%CI: 0.1429, 0.4485) • Antonsen report – 5 events in Table 2, which matches Walton (as expected). No relevant counts in Table 1. Because the IMM captures more events, those numbers were used in the analysis. Gamma(shape=11.866, rate=44.983) with mean 0.2638 and SD 0.07658 is the Bayesian posterior distribution given the inflight data (12 events over 45.49 person-years) under an uninformative prior.

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
0.263789

SD
0.076578

Gamma
(Shape): 11.866
(Rate): 44.983

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Walton, et al. 2010	Spaceflight	4
Saile et al., 2017	Spaceflight	4
Antonsen et al., 2017	Spaceflight	3
Psolka et al., 2007	Analog	2
Linenger et al., 1993	Analog	2
Tansey et al., 1979	Analog	2
Thomas et al., 2003	Analog	1
Aslam et al., 2005	Analog	0
Hilber et al., 2010	Analog	1
McGwin et. al, 2005	Terrestrial	1
Channa et al., 2016	Terrestrial	1

Spaceflight incidence data was rated the highest as there was an appropriate sample size that occurred in space. Analog and terrestrial studies did not accurately reflect the highly screened crewmembers or the spaceflight environmental conditions. Further, there was concern that analog and terrestrial studies would exert an overwhelming influence on the final incidence distribution given their large number of poorly representative subjects.

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

Crewmembers undergo several preflight ocular examinations. Firstly, at L-21/18 m an MRI (3T or better using specific ocular imaging protocols) is obtained. Then at L-21/18 m and L-9/6 m an eye exam is conducted which is inclusive of the following testing: refraction (manifest and cycloplegic), visual acuity (distance and near), Amsler grid, threshold visual fields, pupil reflexes, contrast sensitivity, biomicroscopy (slit lamp), extraocular muscle balance, tonometry, optical biometry, retinal photography, dilated fundoscopic examination and optical coherence tomography (high resolution) including spontaneous venous pulsations (SVP) videography. Also, at L-9/6 m, 2-D ultrasound imaging and contact lens or spectacle fitting is performed. Lastly, at L-90/30 d the best corrected visual acuity, color vision, refraction (manifest), biomicroscopy (slit lamp), tonometry, fundus exam (undilated) and OCT (if any baseline scans need to be repeated) tests are performed. Of note, crew-members are trained to conduct vision testing, fundoscopy and 2-D ultrasound so that they can conduct in-flight eye examinations. All astronauts must undergo annual medical examination that includes a medical history review and clinical laboratory testing.

BEST CASE SCENARIO DEFINITION

Mild eyelid infection or bacterial/viral conjunctivitis that may require symptomatic treatment.

WORSE CASE SCENARIO DEFINITION

Moderate or severe eye infection which requires antibiotic or antiviral treatment.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None.

BEST CASE/WORST CASE PROBABILITY COMMENTS

In the precursor CLiFF entitled ‘Eye Infection’ the worst-case probability was calculated to be 14.29% (1/7) as “there were 7 events and 1 of them were worst case. Since we now have worst case scenarios, which did not have before, we can use the empirical data so the worst case would be 14.29% (1/7).” The specifics of that worst case are currently unknown as details were not documented in the prior IMM CLiFF. However, the authors of this effort find fault in the prior calculation as it neglected the previous five cases found in the Walton LSAH pull. Adjusting for this, the worst-case scenario happened 8.3% (1/12) of the time. In Chana et al, orbital cellulitis (authors did not separate preseptal cellulitis from the less frequent and more concerning orbital cellulitis) was responsible for 0.9% of all ophthalmic cases presenting to an emergency department based on the Nationwide Emergency Department Sample (NEDS) 2006-2011. Similarly, abscess of the eyelid accounted for 1.0% of these cases. The best-case scenario counterparts, conjunctivitis (conjunctivitis, unspecified and acute conjunctivitis, unspecified) and hordeolum externum, accounted for 25% and 3.8% of cases, respectively. Thus the estimated probability of the worst-case scenario based on data from this study would be 6.2% ((0.9%+1.0%)/(0.9%+1.0%+25%+3.8%)). This is in good agreement with our spaceflight data. Of note, the data in this definition does likely include post-septal/true orbital cellulitis cases which is not covered in the CLiFF condition (anterior eye infections only).

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

Citation	Source	LOC Value
Walton, et al. 2010	Spaceflight	4
Saile et al., 2017	Spaceflight	4
Channa et al., 2016	Terrestrial	2

Both spaceflight and terrestrial data were obtainable to determine the worst-case probability. Ultimately, spaceflight data was rated higher, but the terrestrial data seemed estimate the worst-case relatively well.

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 0.2638 SD 0.07658	92 - 92	100	1.1	0	24	336	0	0	0	0	0
Treated Worst Case (TWC)		8 - 8	100	1.1	15.9049	48	336	0	0	3.6	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	1.1	15.9049	24	336	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.1	49.4552	48	840	49.4552	0	100	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

The best case is an acute bacterial or viral conjunctivitis, hordeolum externum or blepharitis that easily resolves and does not require a prolonged course of antibiotics. In terrestrial conditions, subjects may not even present for medical care and rarely pursue emergency department evaluation. In the worst case, a preseptal cellulitis or an eyelid abscess develops requiring a course of systemic antibiotics. Other conditions associated with the worst case but are even more rare in frequency include infectious iridocyclitis, infectious uveitis, infections keratitis and infectious dacryocystitis. The RTDC surrogate for this CLiFF is hospitalization.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

By definition, the treated best case only requires symptomatic treatment and will resolve on its own without therapeutic intervention. Viral conjunctivitis, the most common overall cause of infectious conjunctivitis, bacterial conjunctivitis or hordeolums/styes are included in the best-case scenario. Most symptoms of viral conjunctivitis last between 3-7 days although infected individuals can transmit the pathogen 14 days from the time of inoculation (Azari et al., 2020). These cases are often treated with artificial tears, antihistamines containing eye-drops, or cold-compresses. Although most cases of acute bacterial conjunctivitis have strong recommendations to be treated with topical antibiotics (Azari et al., 2013), this scenario only allows for symptomatic treatment. In more than 60% of cases, spontaneous cure of bacterial conjunctivitis will happen in 1-2 weeks without any complications (Azari et al., 2020; Schiebel, 2003). Hordeolum or styes can resolve within several days (as little as one) with warm compresses (Carlisle et al., 2015; Lindsley et al., 2017). RTDC or LOCL is not expected for this condition.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

The worst case is a moderate or severe eye infection that requires antibiotic or antiviral treatment. Most treatment regimens for infectious bacterial conjunctivitis can range from 2-10 days (Sheikh et al., 2012; Rose, 2007). There are no controlled trials evaluating the duration of antimicrobial therapy in preseptal cellulitis and duration is usually modified with response to treatment. Most recommendations are for a course of 5-7 days in a combination of nasal decongestants and saline nasal irrigation (Gordan et al., 2020; Howe et al., 2004). However, since the upper-bound of this duration was shorter than the treated best case, duration was increased to be aligned with the other condition. Most infections fulfilling the definition for worst will be preseptal cellulitis. The most common bacterial infections causing preorbital cellulitis are gram positives (staphylococcus aureus, streptococcus pneumoniae, and streptococcus pyogenes). It is planned that vancomycin will be carried onboard exploration missions. Vancomycin will treat each of these bacterial except for vancomycin-resistant strains of staphylococcus aureus (VRSA). A review article (Shariati, et al. 2020) states that 3.6% of staphylococcus aureus isolates were VRSA. This could result in treatment failure and the need for RTDC. Thus, the treated worst case RTDC is 0 to 3.6%. LOCL is not expected for this condition unless it leads to sepsis or orbital cellulitis which are separate conditions.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Since the treatment for the best-case scenario only involved symptomatic treatment and not therapeutic management, the duration and other parameters are not expected to differ.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

We expect the duration for the untreated worst case to be no less than the treated worst case. In a retrospective observational case series design, the medical records of 54 consecutive patients seen over a 6-year period at the Dean McGee Eye Institute (DMEI) with a diagnosis of adenoviral keratoconjunctivitis were reviewed (Butt et al., 2006). The median duration of disease from onset of the conjunctivitis to resolution of symptomatic subepithelial keratitis was 5 weeks (840 hours). These patients were not treated with any antivirals or antibiotics. The untreated worst case can result in vision compromise; we would expect RTDC should this happen. Therefore, the worst-case estimate for RTDC is 0-100%, accounting for uncertainty. LOCL is not expected for ocular conditions.

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

Citation	Source	LOC Value
Azari et al., 2020	Terrestrial	
Azari et al., 2013	Terrestrial	

Citation	Source	LOC Value
Schiebel, 2003	Terrestrial	3
Carlisle et al., 2015	Terrestrial	
Lindsley et al., 2017	Terrestrial	
Sheikh et al., 2012	Terrestrial	
Rose, 2007	Terrestrial	
Gordan et al., 2020	Terrestrial	
Howe et al., 2004	Terrestrial	
Butt et al., 2006	Terrestrial	

Available studies to determine durations for treated cases involved retrospective studies and review papers. There were no available consensus guidelines for this condition. One cochrane review was available regarding antibiotic treatment for bacterial conjunctivitis (Sheikh et al., 2012). Due to the increasingly more rigorous Institutional Review Board guidelines of American institutions, literature for untreated best and worst cases were limited and this information was often extrapolated from single, low-powered studies.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Channa et al., 2016	Terrestrial	1
Shariati et al., 2020	Terrestrial	

RTDC for the treated and untreated best case are expected to be zero given the conditions' definition; as such articles were not reviewed for this condition. The remaining scenarios used a retrospective reviews to determine RTDC. The authors performed a Medline search of all reports of vancomycin-resistant Staphylococcus aureus globally from 1997-2019. However, their results are likely an overestimation of resistant bacteria that would be found in a healthy, non-hospitalized cohort. As such, it was used as an upper bound of the RTDC probability. (Shariati, 2020)

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	3

Based on the definitions, loss of crew life is not expected for any of the scenarios associated with this CLiFF.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope Overview Worst Case Definition: Moderate or severe eye infection which requires antibiotic or antiviral treatment. Best Case Definition: Mild eyelid infection or bacterial/viral conjunctivitis that may require symptomatic treatment. This is an eye infection (such as conjunctivitis). The delineation between best and worst case simply involves antibiotics or not. Note: We are not currently scoping for contact lens associated infections in this condition. Diagnostic Scope and Resourcing In the best-case scenario, diagnosis is based on history and physical examination. In the worst-case scenario, diagnosis is based on history and physical examination. 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): 1.1 hours This is the longest reasonable time to complete this task for an experienced clinician adjusted for being in the spaceflight environment to do the following: 1 - Take a proper history of the patient 2 - Perform a physical on the patient CP1 WC (Treated or Untreated): 1.1 hours This is the longest reasonable time to complete this task for an experienced clinician adjusted for being in the spaceflight environment to do the following: 1 - Take a proper history of the patient 2 - Perform a physical on the patient The highest scope of practice code used in this CRT which includes interpretation of diagnosis, performing diagnostic tests and performing treatment would be a three, nurse level. Treatment Scope and Resourcing In the best-case scenario, treatment is limited to mild pain medications and lubrication. The worst case scenario, treatment will include ophthalmic as well as systemic pain medication, eye lubrication, and ophthalmic antibiotic therapy. Communications and Support Needs In the best-case and worst-case scenario, initial diagnosis and cleaning is uncomplicated and likely within the scope of care of onboard crew members. Later diagnosis of damage will require ground communications.

IMM CLIFF RECONCILATION COMMENTS

This CLiFF is the successor to the previous IMM CLiFFs entitled "Eye Infection." CLiFF condition definitions for the ocular conditions were changed from the previous IMM effort. Previously, the “Eye Infection” CLiFF included herpes zoster opthalmicus; this is now covered in the worst-case scenario of the CLiFF entitled “Herpes Zoster reactivation.” Based on an updated review of the literature, the authors of this CLiFF also significantly changed the expected duration period of the scenarios.

LIMITATIONS SUMMARY

• Literature regarding the untreated worst-case scenario was extremely limited and several parameters are based on subject matter expert opinion. • The worst-case definition was not explicitly defined to one type of pathology, allowing for a wide range of uncertainty. • There is some possible overlap with other ocular CLiFF definitions. • There could be under-reporting of past spaceflight cases as many episodes may have been mild and self-limited. • Viral conjunctivitis can be very contagious, so once any episode occurs, the incidence of further cases will likely increase significantly. • It can be problematic to determine whether the pathologic causes of styes or blepharitis is caused by obstruction, inflammation or true infection.

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)					854							
Treated Worst Case (TWC)					854							
Untreated Worst Case (UTWC)		664			854							
	Affected HSTCs (Continued)								TI Calculation			TI Score
	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)									0	3763	0	0
Untreated Best Case (UTBC)	132							211	1197	3763	0.318097	31.8097
Treated Worst Case (TWC)	132							211	1197	3763	0.318097	31.8097
Untreated Worst Case (UTWC)	132							211	1861	3763	0.494552	49.4552

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			854							
	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	1861	3763	0.494552	49.4552

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