

Clinical Finding Form (ClIFF)

Branch

Baseline

ICL70_Mouth Ulcer

There is an IMM ClIFF for Mouth Ulcer. The incidence data from the IMM LD68 ClIFF is based on spaceflight data (LSAH) and will be used in this ClIFF for incidence. Terrestrial study is used for data for best case/worst case percentages and CP2 durations. RTDC and LOCL is not expected for this condition.

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 data used for incidence. There is an IMM ClIFF for Mouth Ulcer. The incidence data from the IMM LD68 ClIFF is based on spaceflight data and will be used in this ClIFF for incidence.

ANALOG LITERATURE

Analog literature not used.

TERRESTRIAL LITERATURE

Terrestrial study is used for data for best case/worst case percentages and CP2 durations. The Treatment of Chronic and Recurrent Oral Aphthous Ulcers. Altenburg, et al. Dtsch Arztebl Int 2014; 111; 665-73. DOI:10.3238/arztebl.2014.0665. (Altenburg, 2014). LOC = 3 (somewhat confident).

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.1984 and SD 0.06726

INCIDENCE SUMMARY

The posterior distribution for the incidence rate given the spaceflight data (9 events over 45.49 person-years) under an uninformative prior is Gamma(shape=8.701, rate=43.856) with mean 0.1984 and SD 0.06726.

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

0.198399

SD

0.0672598

Gamma

(Shape): 8.701

(Rate): 43.856

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Saile, et al. 2017	Spaceflight	4

Spaceflight data from LSAH.

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 preflight preventive measures.

BEST CASE SCENARIO DEFINITION

A mouth ulcer causing minimal discomfort that may require topical treatment.

WORSE CASE SCENARIO DEFINITION

A mouth ulcer with moderate to severe pain that requires oral pain medication or for the crewmember to be on a soft or liquid diet.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

Best case/worst case percentages based on a terrestrial study. The Treatment of Chronic and Recurrent Oral Aphthous Ulcers. Altenburg, et al. Dtsch Arztebl Int 2014; 111; 665-73. DOI:10.3238/arztebl.2014.0665. (Altenburg, 2014). Small ulcers of the minor-type (Mikulicz) are less than 1 cm in diameter (usually 2–5 mm) and heal spontaneously in 4–14 days. They account for 80–90% of all recurrent oral aphthous ulcers. Therefore best case/worst case percentage = 80-90%/10-20%.

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

Citation	Source	LOC Value
Altenburg, 2014	Terrestrial	3

Best case/worst case percentages are based on a terrestrial study. LOC = 3 (somewhat confident).

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 0.1984 and SD 0.06726	80 - 90	100	0.5	0	96	336	0	0	0	0	0
Treated Worst Case (TWC)		10 - 20	100	0.5	0	240	1008	0	0	0	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.5	0.478342	96	336	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	0.5	26.0962	240	1008	0	0	0	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

There is an IMM Cliff for Mouth Ulcer. The incidence data from the IMM LD68 Cliff is based on spaceflight data and will be used in this Cliff for incidence. Terrestrial studies are used for data for best case/worst case percentages and CP2 durations. RTDC and LOCL is not expected for this condition.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

CP2 durations based on terrestrial study. RTDC and LOCL not expected.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

CP2 durations based on terrestrial study. RTDC and LOCL not expected.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

CP2 durations based on terrestrial study. CP2 durations based on treated best case scenario. RTDC and LOCL not expected.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

CP2 durations based on terrestrial study. CP2 durations based on treated worst case scenario. RTDC and LOCL not expected.

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

Citation	Source	LOC Value
Altenburg, 2014	Terrestrial	3

CP2 durations based on terrestrial study. (Altenburg, 2014)

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	4

RTDC is not expected for this condition.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	4

LOCL is not expected for this condition.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

ICL - 70, Mouth Ulcer

Definitions:

Best Case: Definition: A mouth ulcer causing minimal discomfort that may require topical treatment.

Worst Case: Definition: A mouth ulcer with moderate to severe pain that requires oral pain medication or for the crewmember to be on a soft or liquid diet.

Capabilities and Resourcing Scope

Overview

Ulcerated lesions (or aphthous stomatitis or "canker sores") of the oral cavity can be secondary to several etiologies including trauma, immune dysregulation, medications, infection, or neoplasm (Fitzpatrick et al. 2019; Baccaglini et al. 2011). Acute ulcers are episodes lasting less than 6-weeks while chronic ulcers are those of longer duration (Bruce et al. 2015; Edgar et al. 2017). Chronic ulcerations are usually secondary to systemic inflammatory (i.e. Bechet syndrome, systemic lupus erythematosus, inflammatory bowel disease, etc.) or malignant pathologies that would not be expected in spaceflight populations. Ulcerations are classified as being "minor" if there are less than 1 cm in diameter and "major" if greater than 1 cm in diameter. There are no consensus guidelines available for management of aphthous ulcerations. For patients with minor, isolated episodes (as in the best-case scenario), treatment can typically involve ensuring adequate oral hygiene, pain control with topical therapies and avoidance of exacerbating factors such as further trauma. In the worst-case scenario, a major ulcer can limit calorie intake secondary to oral pain. However, dehydration and hypovolemic shock are not part of this condition and are resourced in a separate CRT.

CNES: None

Diagnostic Scope and Resourcing

In the best case, diagnosis will be made via history and physical exam. Given the benign nature of this condition, ground communications are not resourced for the best case. The worst case is similarly diagnosed in spaceflight. In terrestrial conditions, a biopsy may occur to help with the differential (Bruce et al. 2015); however, this is not possible secondary to the lack of histology and expertise available in spaceflight. Ground communications were not resourced in the worst-case scenario given the low task impairment.

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): 0.50 hours

This is the longest reasonable time to complete the task for an experienced clinician (adjusted for being in the spaceflight environment) 1) to remove a crewmember from duties 2) obtain a history and 3) examine the patient.

CP1 WC (Treated or Untreated): 0.50 hours

This is the longest reasonable time to complete the task for an experienced clinician (adjusted for being in the spaceflight environment) 1) to remove a crewmember from duties 2) obtain a history and 3) examine 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 four: this is at intern/PA/NP level. Although most cases will be at an EMT level, the occasional worst-case may require cautery and knowledge of topical corticosteroids.

Treatment Scope and Resourcing

In the best-case scenario, treatment is limited to topical anesthetics and steroids. In the worst case, resources for cautery, HSV reactivation (which is not herpes zoster, as this is covered in a separate CRT), any mild pain management are resourced. Both scenarios make note that crewmembers should be placed on a bland diet, however in the worst case, a soft diet is instituted as well.

Communications and Support Needs

Diagnosis and course of treatment is uncomplicated for both best- and worst-case scenarios. CRT group consensus was not to resource ground communications for this condition.

REFERENCES

Baccaglini, L., R. V. Lalla, A. J. Bruce, J. C. Sartori-Valinotti, M. C. Latortue, M. Carrozzo, and R. S. Rogers. 3rd. 2011. 'Urban legends: recurrent aphthous stomatitis', Oral Dis, 17: 755-70.
Bruce, A. J., T. S. Dabade, and N. M. Burkemper. 2015. 'Diagnosing oral ulcers', Jaapa, 28: 1-10.
Edgar, N. R., D. Saleh, and R. A. Miller. 2017. 'Recurrent Aphthous Stomatitis: A Review', J Clin Aesthet Dermatol, 10: 26-36.
Fitzpatrick, S. G., D. M. Cohen, and A. N. Clark. 2019. 'Ulcerated Lesions of the Oral Mucosa: Clinical and Histologic Review', Head Neck Pathol, 13: 91-102.

IMM CLIFF RECONCILIATION COMMENTS

There is an IMM Cliff for Mouth Ulcer. The incidence data from the IMM LD68 Cliff is based on spaceflight data (LSAH) and will be used in this Cliff for incidence. Terrestrial study is used for data for best case/worst case percentages and CP2 durations. RTDC and LOCL is not expected for this condition.

LIMITATIONS SUMMARY

There is limited data related to untreated 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)									5	13		
Treated Worst Case (TWC)												
Untreated Worst Case (UTWC)		664		89					5	13		
	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)									18	3763	0.00478342	0.478342
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)								211	982	3763	0.260962	26.0962
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)												
	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	T1 Decimal	T1 %
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)									0	3763	0	0

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 requiring use of the alimentary system, 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 Condition List (relevance)?
- How closely does the population included resemble the astronaut population?
- Quality of the paper (number of subjects, methods, etc.)
- How much does the editor trust the source of the evidence?
- How closely does the editor think that the data represents the exploration spaceflight environment?
- Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

REFERENCES

Reference

Saile L., Boley L., Kerstman E. Integration RWS ISS STS Observed Incidence V2. 2017. (Saile, 2017). The Treatment of Chronic and Recurrent Oral Aphthous Ulcers. Altenburg, et al. Dtsch Arztebl Int 2014; 111; 665-73. DOI:10.3238/arztebl.2014.0665. (Altenburg, 2014).

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