

Mouth Ulcer Cliff

Branch Baseline

Ulceration is a breach in the oral epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness, especially when eating spicy foods or citrus fruits. Erosion is the term used for superficial breaches of the epithelium. Soreness varies enormously in relation to oral ulceration. Some patients with large ulcers complain little; others with minimal ulceration complain bitterly of discomfort. Sometimes there is a psychogenic influence. Recurrent aphthae may have an underlining minor degree of immunological dysregulation. (Scully, 2005)

Aphthae is a term of ancient origin referring to ulceration of any mucosal surface. (Bruce, 2003)

Herpes Simplex Virus 1 (HSV-1) causes infections in up to 15% of the population from reactivations of HSV latent in the trigeminal ganglion. Reactivating factors include fever, sunlight, menstruation, trauma, and immunosuppression. Herpes labialis is often called 'cold' sores due to reactivation caused by upper respiratory tract infection with fever. They are infectious. (Scully, 2005)

Most ulcers of local cause are acute, single, have an obvious etiology, last less than three weeks and heal spontaneously. Most mouth ulcers are inconsequential. (Scully, 2005)

Incidence Data Included in the Model

The model imports the following incidence information from the IMM database: incidence data category, space adaption status, incidence data, 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. fixed data). Space adaptation identifies medical events that onset occurs in the first 5 days of flight and does not reoccur. Incidence values vary by data category and define the number of medical events per person-year or medical events per person-at-risk for each medical condition. Incidence values can be modified by crew characteristics such as gender. 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 crew member 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 IMM Technical Description Document.

Incidence

Data Category:	In-flight
Space Adaptation:	No
Incidence Type:	Rate

Distribution Data

Incidence:	Gamma
Occurrence:	Poisson

Data Characteristics

Events:	9
Person Years:	45.49
Space Flight Incidence Rate (Events / Person Years):	$9 / 45.49 = 0.197845680369312$

Incidence Comments

Mouth ulcers had occurred among US astronauts in flight. Of a total of 9 events, 3 were aphthous ulcers, and 6 cold sores. (Walton, 2010)

Our incidence is higher than in analog populations: Richardson's in the UK Navy (Richardson, 2005), Chaffin's in the US Army (Chaffin, 2001), and Deutsch's (Deutsch, 2008) in the US submarine force.

Integrated real world system incidence data (Saile, 2017)

Updated the Person-Years based on the revised real world system integrated incidence data. The integrated person years changed from 18.17 to 18.13 so the conditions person years changed from 45.53 to 45.49 (Saile L., 2017)

Information Regarding Prevention

Disqualifying conditions include:

Active or history of marked stomatitis, leukoplakia, or severe recurrent ulcerations (e.g. aphthous or herpetic) of the mouth that may interfere with the performance of duties. (International Space Station Program, 2009)

Prevention:

At 6 months before launch crewmembers undergo examination, if treatment is deemed necessary, all such treatment is completed 3 months before launch. All astronauts are expected to maintain optimal physical and oral health and to follow oral hygiene practices (Hodapp, 2008)

Incidence Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
Walton, 2010	1	Incidence
Saile L., 2017	1	Incidence

Alternative Incidence Data

The first detailed study of common oral connective tissue and mucosal lesions in US adults reported that more than 10% of the 23,616 white Americans who participated in a mass screening examination had at least one oral lesion. In 1986 aphthous ulcer prevalence per 1,000 population was 3.1 (3.3 for males and 3.0 for females). Herpes simplex (labialis) prevalence per 1,000 population was 2.5 (2.4 for males and 2.6 for females (Bouquot, 1986).

The Third National Health and Nutrition Examination Survey, or NHANES III, employed a complex, multistage sample of 33,994 civilian, non institutionalized people from 19,528 households using procedures based on the World Health Organization's Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases. Lesion prevalences differed significantly by age, sex, race/ethnicity, denture wearing and tobacco use. When lesion-specific prevalences are cited in the literature, they should be stratified by covariates known to be associated with them. The literature is devoid of credible prevalence data for the adult general population. (Shulman, 2004)

The 17,245 subjects aged 17 years and older who received an oral mucosal examination are projected to represent 182,292,666 people in the U.S. population. After adjusting for the design effect, we can project that 28.24 percent of the U.S. population has at least one clinically recognized lesion. The point prevalence for recurrent aphthous ulcerations was 0.89 percent, standard error 0.104, 95% Confidence Interval (CI) 0.69 to 1.09. Prevalence (adjusted odds ratio) by age cohorts, 30-39, 40-49, and 50-59 was 1.17 (95% CI 0.95-1.46), 1.34 (95% CI 1.06 to 1.70), and 1.40 (95% CI 1.14 to 2.01) respectively. By gender prevalence in males was 1.28 (95% CI 1.16 to 1.40), and 1.0 in females (Shulman, 2004). No CI published.

The point prevalence for herpes labialis was 1.61 percent, standard error 0.145, 95% Confidence Interval (CI) 1.33 to 1.90 (Shulman, 2004).

Analog populations

Richardson (Richardson, 2005) reviewed the dental morbidity experienced by U.K. Armed Forces serving in Iraq from deployment on Operation Telic in January 2003 until the end of phase 1 on May 1, 2003. U.K. Armed Forces dental teams treated 1800 emergency patients, including 135 prisoners of war. A total of 1523 of these were regular troops and 101 were reservists or Royal Fleet Auxiliary troops. This gave morbidity rates of 148 cases per 1,000 personnel per year for the Royal Navy/Royal Marines and 160 cases per 1,000 per year for the Army. Lost restorations and fractured teeth were by far the most common problems experienced, followed by pericoronitis, pulpitis, and periapical pathological conditions. Both the rates of morbidity and the types of problems experienced were very similar to those reported by other nations in previous conflicts.

Ulcerations accounted for 1.2% (n 17) of total dental emergencies. Richardson estimated morbidity rate 148 cases per 1000 person-years Royal Navy and Marines (0.148 per person-years); and 160 cases per 1000 person-year in the Army, which is 0.148 and 0.16 per person-years respectively. We estimated the ulceration rates (1.2% of 0.148) at 0.001776 per person-year and (1.2% of 0.16) 0.00192. Of a total of 426 conditions causing moderate or serious operational impact, six (1.4%) were ulceration. We estimated the proportion rate to be 35% (6/17).

Chaffin (Chaffin, 2001) studied retrospectively dental emergencies experienced by 2449 US soldiers in Bosnia, in 2000, deployed 201.95 days. The overall emergency rate was 156 per 1000 soldier-year, 0.156. ICD-9 codes were not included; an emergency is any condition that prompts a soldier to leave their duty station. The true emergencies like extreme pain due to infection, irreversible pulpitis or trauma represented 25% of patients seen. These conditions would have required evacuation without on site dental care. Based on the 9% other dental emergencies (n=19), we estimated an incidence of 0.01404. We may be overestimating because there is no information on which conditions are included under "other". Of all dental emergencies 18.5 % required palliative care. There is no information on the type of emergencies requiring pain medication. We cannot infer from the types of treatment rendered, e.g. no treatment indicated, or other treatment, which ones if any were used to treat oral aphthae or cold sores.

Deutsch (Deutsch, 2008) determined that of 5187 total medical consultation in the US submarine Force 3% were due to dental reasons. Incidence density rates were determined using the number of initial visits as the numerator, and the total number of person-days underway was the denominator. When excluding revisits 109, 3% of 3562, initial visits were for dental conditions. Visits for "Other" include cyst, aphthae, and baby tooth, tooth pain from sinus, lip infection or tongue. They accounted for 27 initial visits; or 1.2 per 100,000 person days at sea (Table III); or 0.00438 person-years.

In ICD-9 code 528 is for oral soft tissues disease. Code 528.2 Oral aphthae includes aphthous stomatitis, canker sore, periadenitis mucosa necrotica recurrens, recurrent aphthous ulcer, and stomatitis herpetiformis. It excludes: herpetic stomatitis (054.2). (Centers for Disease Control and Prevention (CDC), 2008)

Dental studies do not consider aphthae to be a dental emergency. Code 528.2 was separated out from all 528 codes. Rate by ICD-9 code 528.2, *Aphthae*, was 0.3 per 100,000 person days at sea (n 6), (Table VII) (Deutsch, 2008); or 0.001095 person-years.

The remainder of code 528 had an initial visit rate of 0.1 per 100,000 person days at sea (n 3), (Table VII); or 0.000365 person-years.

Evacuations (EVACs) were reported at 7-9%. The nature of dental EVACs was not reported. Not all evacuations are due to emergencies. (Deutsch, 2008)

Tansey did an analysis of 10 years of data collected on Polaris submarines, 1963-1973. (Tansey, 1979) There were 2 incidents of stomatitis from a total of 50 dental events reported, or 4%. These incidents caused 14 sick days.

Thomas reported on the health events occurring among highly screened, healthy US submariners. ICD9-codes 520-528 had a total rate of 0.8 for officers and 1.5 for enlisted men per 100 person-years, 0.008 and 0.015 per person-year respectively. Code for aphthous ulcer falls under this category but data were not broken down by type of condition. The majority of the medical events reported among officers and enlisted men could be considered minor and non-life threatening, with little or no impact on unit mission. (Thomas, 2003)

Treatment and Outcomes

Based on the best evidence available best and worst case percentage ranges are assigned. The medical condition is divided into three clinical phases in all three clinical phases a functional impairment is assigned. The clinical phase I and II's functional impairments remain for the duration for that respective clinical phase. The function impairment in clinical phase III represents final impairment for this medical condition and remains for the rest of the mission. Other mission end states include evacuation and loss of crew life.

The IMM checks medical resource availability once the number of medical events and scenarios has been established. If there is not sufficient essential resources called out in the ClIFF, then the medical condition will go down an untreated best or worst case scenario pathway.

The table below summarizes the treated and untreated best and worst case scenarios.

	Clinical Phase I Diagnosis & Initial Treatment ¹		Clinical Phase II On-going Treatment / Convalescence ²		Clinical Phase III Recovered / Mission End State ³		
	FI* (%)	Duration (hrs)	FI* (%)	Duration (hrs) (Min - ML - Max)	FI* (%)	EVAC** (%)	LOCL** (%)
ISS-based Treatment (best case scenario %: 90 - 100)	100	0.25	0 - 15	24 - 48 - 72	0	0	0
ISS-based Treatment (worst case scenario %: 0 - 10)	100	0.25	5 - 30	72 - 156 - 240	0 - 15	0	0
Untreated Best Case	0	0	5 - 30	24 - 48 - 72	0 - 15	0	0
Untreated Worst Case	0	0	20 - 50	72 - 156 - 240	0 - 20	0	0

¹Clinical Phase I: Clinical phase I covers only the initial assessment of the affected crew member to define his or her medical condition, and completion of appropriate initial treatment to stabilize the crew member. While the affected crew member is being assessed, he or she is not able to perform any assigned tasks, thus Functional Impairment during this phase is considered 100%. In the untreated case, there is no diagnosis performed or treatment given, therefore Functional Impairment and Duration will always be "not applicable".

²Clinical Phase II: On-going Treatment and Convalescence- During clinical phase II, the affected crew member is receiving any appropriate follow-on treatment for his or her medical condition to allow the crew member to recover as much as he or she is able to recover in the ISS environment. Clinical phase II also encompasses relapses or reoccurrences of the same original medical condition in clinical phase I necessitating additional treatment or recovery time due to unsuccessful primary treatment response. The duration in Clinical Phase II is expressed in minimum, most likely (ML) and maximum hours. This was updated for future capabilities in IMM but is currently not being used by the model.

³Clinical Phase III: Recovered/Mission End State- Clinical phase III is reached once the affected crew member has recovered from the medical condition as much as he or she is able to recover in the ISS environment. This may or may not be recovery from the given medical condition to the full extent possible. If this "recovered" state results in an evacuation or loss of the crew member, this will be noted in the mission end state results.

*Functional Impairment (FI) is a measure of the affected crew member's health and performance ability.

**Two mission end state results are addressed in the ClIFF: 1) Evacuation (EVAC) - crew and patient are evacuated from the spacecraft due to the medical condition, and 2) Loss of crew (LOCL) - death of affected crew member due to medical condition. EVAC is considered as an end state result if any of the following criteria are met: 1) potential LOCL, 2) potential significant permanent impairment, or 3) potential intractable pain. Probability distributions are assigned for each range of values within the Table of Treatments and Outcomes.

Refer to the Integrated Medical Model Technical Document for more information on how risk is reported by the IMM, Crew Health Index (CHI) and Quality Adjusted Mission Time calculations.

Definition and Probability of Best and Worst Case Scenario: (includes definitions of best and worst case scenarios and identifies the probability of those scenarios.)

Scenario Comments

Best case scenario describes a crewmember with a mouth ulcer and minimal discomfort that may require topical treatment.

Worst case scenario is a mouth ulcer with moderate to severe pain. Discomfort may require topical treatment, oral pain medication or for the crewmember to be on a soft or liquid diet.

Percentages of how often best versus worst case scenarios occur

Based on in-flight data (Walton, 2010), we assume 9 cases were best cases. If the next case is a worst case, 10% (1/10) would have been worst case. If the next case is a best case, we would have 0% of worst cases. To allow for uncertainty, we are estimating 0 to 10% for our worst case scenario. Thus the best case percentage is 90 to 100%.

Richardson's study (Richardson, 2005) estimated types of morbidity causing moderate or serious operational impact among regular troops. 35% (6/17) of aphthous ulceration are included in this category, which is higher than our estimate of worst case.

Best Case Comments

Mouth ulcer is a temporary condition and it is not listed in the AMA Guides for Permanent Impairment. Our functional impairments calculation follows the IMM mild non-space adaptation template and Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region (American Association of Oral and Maxillofacial Surgeons, 2008). We are deviating from the template in Clinical Phase III for all scenarios, except in the best case. Ulcers are expected to resolve with topical treatment (treated worst case scenario); they may resolve spontaneously over a certain period of time (untreated best case scenario), and are assigning impairment class 0 to 2 to allow for soft or liquid diet (untreated worst case scenario). Mastication disorders ratings are based on Table 11-7, p.269 (American Medical Association, 2008). For further description of gradings refer to the ClIFF Appendix.

By definition, functional impairment (FI) is 100% during **Clinical Phase I**. Duration is estimated to be 15 minutes, to follow the procedure indicated in the ISS Medical checklist, i.e. oral exam and topical medication. **Clinical Phase II**, FI is estimated in 5 to 30%. Duration is estimated in 24 to 72 hours, 1 to 3 days. Terrestrial clinical guidelines (Scully, 2003 3557 /id {Scully, 2005}) refer to a few days; we arbitrarily assigned 24 to 72 hours. During **Clinical Phase III**, total recovery is expected; by definition FI is 0%. By definition, EVAC and LOCL are not expected in the best case scenario (In-flight Compilation Lockdown revised, 2010).

Worst Case Comments

Mouth ulcer is a temporary condition and it is not listed in the AMA Guides for Permanent Impairment. Our functional impairments calculation follows the IMM mild non-space adaptation template and Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region (American Association of Oral and Maxillofacial Surgeons, 2008). We are deviating from the template in Clinical Phase III for all scenarios, except in the best case. Ulcers are expected to resolve with topical treatment (treated worst case scenario); they may resolve spontaneously over a certain period of time (untreated best case scenario), and are assigning impairment class 0 to 2 to allow for soft or liquid diet (untreated worst case scenario). Mastication disorders ratings are based on Table 11-7, p.269 (American Medical Association, 2008). For further description of gradings refer to the ClIFF Appendix.

By definition, functional impairment (FI) is 100% during **Clinical Phase I**. Duration of treatment is 10 minutes based on the procedures indicated in the ISS Medical checklist, similar to the best case scenario. During **Clinical Phase II** FI is estimated at 5 to 30%. Terrestrial guidelines (Scully, 2003 3557 /id {Scully, 2005}) refer to a longer duration than for the minor ulcers; we arbitrarily assigned 72 to 240 hours, 3 to 10 days. (Scully, 2005) During **Clinical Phase III**, the pain may not resolve completely thus FI is 0-15%. By definition, EVAC and LOCL are not expected (In-flight Compilation Lockdown revised, 2010).

Untreated Best Case Comments

Mouth ulcer is a temporary condition and it is not listed in the AMA Guides for Permanent Impairment. Our functional impairments calculation follows the IMM mild non-space adaptation template and Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region (American Association of Oral and Maxillofacial Surgeons, 2008). We are deviating from the template in Clinical Phase III for all scenarios, except in the best case. Ulcers are expected to resolve with topical treatment (treated worst case scenario); they may resolve spontaneously over a certain period of time (untreated best case scenario), and are assigning impairment class 0 to 2 to allow for soft or liquid diet (untreated worst case scenario). Mastication disorders ratings are based on Table 11-7, p.269 (American Medical Association, 2008). For further description of gradings refer to the ClIFF Appendix.

During **Clinical Phase II**, FI is estimated at 5 to 30%. Duration is estimated at 24 to 72 hours, one to 3 days, similar to the treated best case. During **Clinical Phase III**, the pain may not resolve completely and FI is estimated at 0 to 15%. By definition, EVAC and LOCL are not expected for this scenario (In-flight Compilation Lockdown revised, 2010).

Untreated Worst Case Comments

Mouth ulcer is a temporary condition and it is not listed in the AMA Guides for Permanent Impairment. Our functional impairments calculation follows the IMM mild non-space adaptation template and Guidelines to the Evaluation of Impairment of the Oral and Maxillofacial Region (American Association of Oral and Maxillofacial Surgeons, 2008). We are deviating from the template in Clinical Phase III for all scenarios, except in the best case. Ulcers are expected to resolve with topical treatment (treated worst case scenario); they may resolve spontaneously over a certain period of time (untreated best case scenario), and are assigning impairment class 0 to 2 to allow for soft or liquid diet (untreated worst case scenario). Mastication disorders ratings are based on Table 11-7, p.269 (American Medical Association, 2008). For further description of gradings refer to the ClIFF Appendix.

During **Clinical Phase II**, FI is estimated at 20 to 50%. Duration is estimated from 72 to 240 hours, 3 to 10 days, similar to the treated worst scenario. During **Clinical Phase III**, the pain may improve or may not completely resolve. FI is estimated at 0 to 20%. The majority of the medical events reported among officers and enlisted men could be considered minor and non-life threatening, with little or no impact on unit mission. (Thomas, 2003). EVAC and LOCL are not expected for this scenario (In-flight Compilation Lockdown revised, 2010).

Treatment and Options Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
Lopez, 2010	1	EVAC
American Association of Oral and Maxillofacial Surgeons, 2008	3	FI
American Medical Association, 2008	3	FI
Walton, 2010	1	BCWC

Additional Comments

We searched PubMed using the terms aphthous or stomatitis, AND incidence OR prevalence, AND clinical guidelines, AND astronauts, AND microgravity.

A second search was conducted using the terms oral herpes simplex OR herpes labialis, AND incidence OR prevalence, AND clinical guidelines, AND astronauts, AND microgravity.

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Benzocaine Swab Stick Oral 20%, 0.15 mL swab	5	10	24	Yes	No	Topical anesthetic
Silver nitrate stick 75%/25%	0	1	10	Yes	Yes	To chemically cauterize ulcer
Tylenol (Acetaminophen) 325 mg	0	8	250	Yes	Yes	Oral pain medication

Resource Comments

ISS medical checklist includes Mouth Ulcers - Stomatitis as a medical condition. All resources included are addressed in the ISS medical checklist (MOD, 2011).

Our search for clinical guidelines yielded results for recurrent aphthous stomatitis (RAS). Mouth ulcers are a minor condition and very common. Treatment is symptomatic.

Comparison of the Med Checklist and current treatment process.

Terrestrial guidelines for aphthous ulcers (Scully, 2003) recommend identifying etiology and avoiding it, mouthwash, topical steroids and anesthetics. Treatment in ISS is similar, except for the mouthwash which is not available.

Terrestrial standards of care for cold sores report that spontaneous healing occurs in 10 to 14 days (Scully, 2005); treatment is indicated to reduce fever and control pain

Required Resources Level of Evidence (LOE)

The IMM level of evidence appropriate assessment of the quality of the IMM input data. Since IMM incorporates input data from a wide variety of sources including astronaut population, terrestrial or analog populations, and external models, an innovative approach to assess the quality of input data was required. Information obtained from the astronaut population and/or space flight is the more relevant so it is assigned the highest level of evidence and less relevant data sources are assigned a lower level of evidence.

Citation	LOE Value	LOE Category
NASA Mission Operations Directorate (MOD), 2011	2	Resources
Scully, 2005	3	Resources

Level Of Evidence

Input Data	LOE Average	Description	Range
Incidence	1	Excellent	1-2
Functional Impairment	3	Good	2.1-3
Best Case / Worst Case	1	Fair	3.1-4
EVAC / LOCL	1	Poor	4.1-5
Resources	2.5		
QUALITY OF EVIDENCE	1.7		

Reference List

Reference

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