Clinical Finding Form (CliFF)

Branch	Baseline

ICL74_Otitis Media

Otitis Media (OM) is inflammation or infection of the middle ear. Acute otitis media (AOM) is usually a result of dense bacterial colonization at the nasopharynx and eustachian tube dysfunction that occurs during a viral upper respiratory tract infection (Schilder, 2016). In more than 50% of cases, bacteria such as Streptococcus pneumoniae, nontypeable Haemophilus influenzae can be isolated from the middle ear fluid (Jacobs, 1998). Presentations of AOM typically include recent onset ear pain and muffled or decreased hearing. An episode of upper respiratory tract infection or exacerbation of seasonal allergic rhinitis often proceeds these symptoms. Diagnosis is often made with otoscopic exams in suspected individuals. Management of AOM in adults usually involves analgesics for pain and oral antibiotics (Pichichero, 2003). The global average AOM incidence rate is estimated at 10.8 episodes/100 person-year, with more than 50% of cases occurring in children under 5 years of age (Monasta, 2012). Despite the high incidence, most cases of AOM are uncomplicated and self-resolving (Rosenfeld, 2003). Although rare, complications of AOM include extracranial infections (e.g. mastoiditis, mastoid abscess, fistulas) and intracranial infections (e.g. meningitis, brain abscess) (Dongol, 2020).

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

The space literature for this assessment includes three articles detailing incidence of OM in space crew populations. Although each study provides data that may be applicable to the astronaut population, extrapolating results to long duration missions may be difficult due to limited information in this domain. The Antonsen, 2017 study examined astronauts during inflight missions inclusive of the: Space Shuttle Program, Mir, and ISS (through Expedition 13 in 2006) reported 3 events . NASA case files by Berry, 1975, on the other hand, reported 1 inflight event during the Apollo mission. Crucian, 2016 examined astronauts participating in the ISS Program through Expedition 37/38, reported 6 events of “ear-related” conditions which includes OE and OM among 46 US astronauts on board the International Space Center. With a total of 20.57 flight years, incidence was 0.3 events/flight year. This data is limited due to the lack of data on OM alone.

ANALOG LITERATURE

Thomas, 2003 examined an isolated military population on a submarine, population used as an analog for crew members on long-term space missions from a space shuttle with minimal accessibility to terrestrial care. A total event number of 120 "disorder of ear and mastoids" were reported for 2,170,607 person-days at sea. Pinto, 2019 provides incidence data on OM with effusion among a population of aircrew members who are repetitively exposed to varying pressures and altitudes. An incidence of 9.65% was reported.

TERRESTRIAL LITERATURE

Systematic review by Monasta in 2012 reported AOM incidence rate of 5.26% in North America. Tong, 2018 offers an overview of OM cases in insured and Medicare patients by examining ED and primary care visits for OM in the general public. They reported an overall incidence of 60.5/1000 person-year. Among the 18-49 age group, incidence was 33.1/ 1000 person-year.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.11 and SD 0.04954

INCIDENCE SUMMARY

The Bayesian posterior distribution for the incidence rate given the spaceflight data (5 events over 45.49 person-years) under an uninformative prior is Gamma(shape=4.93, rate=44.821) with mean 0.11 and SD 0.04954. (95%CI: 0.4027E-1, 2.436E-1) •Spaceflight – Antonsen report and LSAH data requests. The Antonsen report corresponds directly to the 2 LSAH data requests. Table 2 represents IMM categorizations of symptoms in the earlier request and matches exactly to Walton. Table 1 represents a different interpretation of the same data as the second data request. Specifically, the same set of reports that were passed to the IMM Team and used to inform Saile, were passed to another group for creation of Table 1. These two sets could therefor have slightly different numbers from differing interpretations. Since Saile has more specific counts relating to Otitis Media, I used that rather than Table 1. Antonsen Table 2 (and Walton) – 3 cases of Otitis Media. Saile – 1 additional case. Total events 4 over 45.49 person-years (all flights up through ISS Expedition 40). IR: 8.793E-2 (95%CI: 2.794E-2, 21.21E-2) •Spaceflight – Crucian. ISS expeditions up to 37/38Since this paper doesn't specify Otitis Media but rather ear related pain, congestion, or itchiness, and overlaps in time with the LSAH requests, I am dropping this reference to not double count. •Spaceflight – Berry. Apollo era 1 report of otitis media over Apollo missions. This case was not included in the LSAH requests or Antonsen report. Will include this additional case within the final spaceflight numbers. 1 event over 0.856 person-years. IR: 1.168 (95%CI: 0.05845, 5.762)

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
0.109993

SD
0.0495384

Gamma
(Shape): 4.93
(Rate): 44.821

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Antonsen, 2017	spaceflight	4
Berry, 1975	spaceflight	4
Crucian, 2016	spaceflight	4
Lewis, 2013	spaceflight sim Extravehicular Activity	3
Hoiberg, 1986	analog	1
Thomas, 2003	analog	3
Pinto, 2019	analog	3
Monasta, 2012	terrestrial	2
Tong, 2018	terrestrial	2

The study by Antonsen, 2017 receives a level 4 rating value because the study population is astronauts during inflight missions inclusive of: the Space Shuttle Program, Mir, and ISS (through Expedition 13 in 2006), representing a wide range of dates and missions. The study did not categorize or give incidence data on WC vs BC, however. Likewise, the analysis by Berry, 1975 (aka Johnston 1975) receives a 4 because the population examined was astronauts during inflight missions taking place during the Apollo era. Although this is a good representation of spaceflight incidence, the missions were shorter in duration and there was no WC vs BC data. Crucian, 2016 receives a level 4 value because it is also a population of astronauts with incidence inflight and spans missions from ISS Program through Expedition 37/38. However, this study combines OE and OM for incidence and does not include WC vs BC data. Lewis, 2013 was given a 3 because it is simulated data of space crews on lunar or NEA missions. The data is from a model run to estimate WC scenarios. Hoiberg, 1986 receives a level 1 rating because it is a military diving population, which is analogous to a space crew as the population is working in isolated environments. However, the difference of water exposure in navy divers may account for incidence of OM. This paper has WC data in the form of whether patients needed hospitalization or discharge from duties, but is not useful for incidence calculation. Thomas, 2003, receives a 3 rating because the population closely resembles space crews as isolated and removed from extensive medical care with a high risk/cost of evacuation. Pinto, 2019 receives a 3 because the population is aircrew members who are often exposed to rapid changes in elevation and pressure--with readily available access to medical care. Monasta, 2012 is a systematic review of global incidence of OE. It provides valuable terrestrial data of OM incidence and WC data, therefore receiving a 2 rating. Tong, 2018 is a retrospective study looking at incidence of OM and was given a 2 as the study examined incidence of OM in the general population in a large-scale retrospective chart review.

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

Hearing assessment test and physical exams of the ear are performed as part of preflight medical requirements.

BEST CASE SCENARIO DEFINITION

Acute otitis media that resolves with a single course of antibiotics and responds to non-opioid analgesics.

WORSE CASE SCENARIO DEFINITION

Severe acute otitis media that is accompanied by pain that cannot be controlled with non-opioid analgesics, causes hearing loss, or requires more than one course of antibiotics.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None

BEST CASE/WORST CASE PROBABILITY COMMENTS

The majority of AOM, even without treatment, are self-limiting and uncomplicated. Complications of OM including extracranial and intracranial infection are rare, with incidence reported between 0.032% to 0.78% (Leskinen, 2005; Dongol, 2020). Generally, complication rates in adult are believed to be less than 0.5% (Hafidh, 2006). With the use of proper antibiotics and analgesics, complication rates, mortality, and disease duration are significantly decreased (Monasta, 2012). Retrospective cohort study by Park et al. found prevalence of sensorineural hearing loss associated with AOM to be 9.6%. However, 87.5% of these cases significantly improved after initial treatment, with a mean recovery duration of 18.6 days (Park, 2014), leaving only around 1.2% with longer-term clinically significant hearing impairment. With these terrestrial data, it can be estimated that with treatment, WC probability will be rounded up to about 2% if not less.

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

Citation	Source	LOC Value
Lewis, 2013	spaceflight sim EVA	3
Hoiberg, 1986	terrestrial	2
Andersen, 2009	terrestrial	2
Mostafa, 2009	terrestrial	3
Leskinen, 2005	terrestrial	2
Dongol, 2020	terrestrial	3
Park, 2014	terrestrial	2

Lewis, 2013 does not represent an actual space mission, but rather simulated data for WC scenarios which is helpful for considering the incidence of WC vs BC. The model was designed to estimate necessity to evacuate and LOCL so this WC data is directly applicable, though it was all simulated. Hoiberg, 1986 receives a level 2 rating for this component of the CLiFF, as this paper had WC data in the form of whether patients needed hospitalization or discharge from duties. The report details how often an enlisted diver was able to return to duty after treatment, if they required hospitalization or if they required time off from duty. Though this population does not exactly represent space crews, it is reasonable to consider the WC outcomes will be similar in any population. Andersen, 2009 receives a 2, the paper has incidence for OM in adult populations and includes chronic OM. Mostafa, 2009 receives a 3 because it is a 10 year study with a large number of patients who presented with OM. WC data is given in rate of complications, the mortality and significant morbidity incidence is most relevant for WC data. Dongol, 2020 is a retrospective chart review study looking at complications associated with acute and chronic OM. It provides relevant data for WC probability in the terrestrial population. Park, 2014 receives a 2 because it is a retrospective chart review study of sensorineural hearing loss incidence among adults with acute OM, providing relevant WC data.

TABLE 4. CLIFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

			CP1: Diagnosis		CP2: Treatment			CP3: Condition End State				
			TI%	Duration	TI%	Duration		TI%	RTDC		LOCL	
Case Scenario	Composite Incidence	Condition Probability %	Preset	Preset	Preset	Min	Max	Preset	Min%	Max%	Min%	Max%
Treated Best Case (TBC)	mean 0.11 and SD 0.04954	98 - 98	100	0.62	6.77651	24	312	0	0	0	0	0
Treated Worst Case (TWC)		2 - 2	100	1.62	30.295	24	1008	0	0	2	0	0.01
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.62	27.9298	24	504	0	0	0.2	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	1.62	48.4188	24	1008	9.77943	0	50	0	1

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 scenario involves OM that is uncomplicated and can either resolve spontaneously or cause minimal disturbance and is treated with one course of antibiotics and does not require opioids for pain management. This is true for the vast majority of OM cases terrestrially. The cornerstones of treatment will likely include symptomatic management of pain. Given a paucity of data regarding spaceflight or analog OM leading to a return to definitive care, OM that was severe enough that it might warrant hospital admission due to CNS infection/risk of bilateral hearing loss was chosen as the surrogate for RTDC. CNS infection is the most critical complication of OM and was therefore a surrogate and provided data for LOCL.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

In summary, with appropriate treatment, patients with OM should expect to have significant symptomatic relief within 24 hours (Szmuilowicz, 2019), most cases resolve within 72 hours but some may require treatment for up to 2 weeks (Burrows, 2013). OM has low morbidity and in a treated best case scenario, by definition, RTDC would not be expected, nor would mortality. For both BC RTDC and LOCL, the low and high end are 0%. RTDC and mortality for BC OM is not expected so the data for RTDC and LOCL are demonstrated in the WC scenario. The populations of the included studies did not all approximate the populations of space crews, but a concerted effort was made to include those with age groups more similar to space crews.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

For WC data, the duration, RTDC and LOCL reported were more representative of the higher end of the spectrum of rates. Required duration of antibiotic therapy for intracranial infection secondary to OM is up to 6 weeks (Arlotti, 2010). Minimum duration was based on the assumption that antibiotics would be effective but that opioid analgesics were necessary for pain control. WC treated OM RTDC minimum is 0% because this group is receiving treatment and even though they may require opioids for pain control and multiple rounds of antibiotics, RTDC is very unlikely. The populations of the included studies did not all approximate the populations of space crews, but a concerted effort was made to include those with age groups more similar to space crews. Dongol, 2020 reported an overall OM complication incidence of 0.78%. Even though the likelihood of an intracranial infection is very low, when it does occur, 100% of patients are hospitalized (Leskinen, 2005). A 2% mortality associated with intratemporal and intracranial complications was reported by Leskinen and colleagues. Study by Monasta et al. reported a 1.6/10 million OM complication mortality in North America (Monasta, 2012). These terrestrial data cannot adequately represent those of space crew members. However, they are valuable as it is apparent that complications from OM can be significantly reduced with proper treatment. LOCL from OM will have a minimum of 0%. Although unlikely, conservatively calculated maximum will be approximately 0.01% (2%x0.78%). RTDC will have a maximum of 2% (2% x100%).

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

Several of the articles were found through hand-searching when they came up during other search parameters. Several of the studies involved pediatric populations so they are not analogous to the space crew populations. Although the incidence of OM in children is significantly higher than in adults, the duration of symptoms, rates of clearance vs complications or recurrence have not been compared and it is reasonable to consider these parameters may be more similar in adults and children. For that reason and because the majority of studies are in children, studies with pediatric populations were included. For duration of UTBC symptoms; many clear symptoms of acute OM within 24 hours and by 336 hours, the majority have clinically recovered (Rosenfeld, 2003). Rosenfeld, 2003 was in a pediatric population but the meta-analysis reviewed many papers and provides reliable data. Gower, 1983 found mortality data of untreated OM cases specifically related to CNS infections. Of all the hospital admissions, 0.2% were for CNS infections (Gower, 1983). By definition for BC the minimum RTDC is 0%, though RTDC increases with CNS infections, which are also very rare. Hence, the RTDC minimum is 0% and the maximum 0.2%. Although, best case denotes treatment, it is our assumption that a base case scenario would have no mortality and all mortality will be reflected in WC. For that reason, LOCL is 0%.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

Several of the articles for estimating the untreated worst case scenario were encountered during novel PubMed searches, not through the original search strategy. Although the incidence of OM in children is significantly higher than in adults, the duration of symptoms, rates of clearance vs complications or recurrence have not been compared and it is reasonable to consider these parameters may be more similar in adults and children. For that reason and because the majority of studies are in children, some studies or large review articles with pediatric populations were included. For duration of UTWC symptoms; many patients clear symptoms of AOM within 24 hours though Fradis, 1997 found that 58.5% of patients still had clinical signs and symptoms of OM after three weeks. Gower, 1983, found mortality data of untreated OM cases specifically related to CNS infections. Since mortality from OM is directly related to the type of CNS infection, the overall mortality of OM due to CNS infections was chosen. The type of infection with the highest mortality, sigmoid sinus thrombosis, has a mortality of 50%, however, the incidence of sigmoid sinus thrombosis is <<1% (Devasagayam, 2016). According to simulation by Lewis, 2015, untreated OM has a 50% probability of evacuation and 1% of LOCL.

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

Citation	Source	LOC Value
Szmuilowicz, 2019	terrestrial	3
Burrows, 2013	terrestrial	
Rosenfeld, 2003	terrestrial	
Fradis, 1997	terrestrial	

The overall grade for duration level of evidence is a 3 because several of the papers, Szmuilowicz, 2019 and Burrows, 2013, have study populations experiencing AOM in adults. These papers were well representative of the treated data for duration because the sample size for incidence was high. Additionally, the condition, OM was well represented in all of the studies for duration. The papers detailed how the diagnosis of OM was established and left little doubt it was a different condition. Rosenfeld, 2003, is a meta-analysis of OM and although the population is pediatric, it is an analysis with large sample sizes and patient presentations that well represent OM. This data is a good representation for what duration of OM will be in space flight. The populations of the studies were not space crews, but most of the studies were in adults.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Ren, 2018	terrestrial	2
Leskinen, 2005	terrestrial	
Lin, 2009	terrestrial	
Karaman, 2012	terrestrial	
Gower, 1983	terrestrial	
Ren, 2018	terrestrial	
Oliveira Penido, 2015	terrestrial	

The RTDC level of evidence receives an overall confidence rating of 2, neutral. Several of the studies have populations that do not closely represent the space crew populations. Ren, 2018 includes children, Lin, 2009 and Karaman, 2012, include older adults (up to 94 years old). Although the extremes of age are included in several of the paper, the wide span of ages captures the average ages of space crew members. Leskinen, 2005 has a small sample size (n=50). The cases do well-represent OM and the possible complications. There were also several studies with data regarding OM and CNS infection in the pre-antibiotic era (Ren, 2018 and Gower, 1983). This data was helpful in determining untreated RTDC. Because of some of the papers having a wide range of ages or smaller sample sizes, the overall confidence rating is somewhat confident.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Leskinen, 2005	terrestrial	3
Seven, 2005	terrestrial	
Kanganarak, 1995	terrestrial	
Gower, 1983	terrestrial	
Rudin, 1987	terrestrial	
Oliveira Penido, 2015	terrestrial	
Devasagayam, 2016	terrestrial	

The LOCL level of evidence receives an overall confidence rating of 3, somewhat confident. Leskinen, 2005 has a small sample size (n=50). Several of the other studies included populations that are not analogous to a space crew population. Seven, 2005 and Kangsanarak, 1995 both include children in their studies. Gower, 1983 and Rudin, 1987 are older studies and the population may not well-represent the current general population, but these studies provided valuable data regarding untreated cases. The cases do well-represent OM and the possible complications that cause mortality (CNS infections).

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Capabilities and Resourcing Scope Overview: Otitis Media is an infection of the middle ear. Terrestrially this is most often viral but may occasionally involve a bacterial infection. In space materials will need to account for the possibility of bacterial infection to enable effective treatments. CNES: NONE Diagnostic Scope and Resourcing: Diagnosis relies on history and physical exam with particular attention paid to the ear nose and throat. In flight audiometry may also be useful in diagnosing otitis media this is true for both best and worst cases. 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): 0.62 hours for set up history, physical exam including an otic and pharyngeal exam CP1 WC (Treated or Untreated): 1.62 for a set up history, physical exam including an otic and pharyngeal exam This condition requires a Scope of Practice 4 to manage and rule out other similar presenting conditions, assess treatment response, and assess fitness for duty. Treatment Scope and Resourcing: The best case requires antibiotics in case of a bacterial infection as well as symptomatic treatment with pain medications and anti-fever medications. The worst case adds a second line antibiotic and is presumed to occur after failure to treat with the initial best case antibiotic. Ceftriaxone and Levofloxacin are included for this. Communications and Support Needs: Communications are not expected to be necessary beyond the routine medical ground communications for the best case. However, in the worst case consultation with a ground expert will be helpful in determining the need for additional antibiotics. References: Centers for Disease Control and Prevention. Antibiotic prescribing and use in doctor's offices. https://www.cdc.gov/antibiotic-use/community/for-hcp/outpatient-hcp/pediatric-treatment-rec.html (Accessed on July 10, 2021) Lin K, Moonis G, Lustig LR. Mastoiditis. In: Infections of the Ears, Nose, Throat, and Sinuses, Durand ML, Deschler DG (Eds), Springer International Publishing AG, Cham, Switzerland 201

IMM CLIFF RECONCILATION COMMENTS

The best-case scenario definition has changed from rapidly improved uncomplicated AOM treated by antibiotics with pain controlled by Ibuprofen to AOM that resolves with a single course of antibiotics and responds to non-opioid analgesics. This broadens the scope of best-case scenarios, as some cases of AOM require a longer duration of treatment while remaining manageable with one course of antibiotics and without opioid use. Therefore, while IMM assigned up to 20% probability of WC scenarios, with a proper treatment course, most of these cases will recover without complications and lingering symptoms. For this reason, WC probability for this CLiFF was assigned after evaluating existing data regarding complications and prolonged hearing impairment incidence rate from treated AOM. 2% probability was assigned, a number much lower than 20%.

LIMITATIONS SUMMARY

Most available studies examining OM reflect terrestrial and pediatric populations, which are not generalizable to the spaceflight population. Also, there was no available data regarding number of cases that were uncontrolled with non-opioid analgesics. This is a subjective point of quantification, and likely the necessity of opioid analgesia for OM would be provider and patient dependent if any studies did exist. Therefore it was difficult to discern the likelihood of the BC and WC in spaceflight. Similarly, given that a course of antibiotic therapy for OM may vary in duration, the definition of requiring a second course of antibiotics could be better defined (i.e. if only 3 days is given at first, and then a further 3 days prescribed - would this still qualify as a second course and that patient would meet definition for worst case while another patient prescribed 14 days initially would not?). We may consider re-wording the definition of worst case scenario to state "remains symptomatic after more than 14 days of antibiotic treatment."

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)						44						
Untreated Best Case (UTBC)		664				44						
Treated Worst Case (TWC)		664		89		44						
Untreated Worst Case (UTWC)	223	664	113	89		44	145	5				
	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	255	3763	0.0677651	6.77651
Untreated Best Case (UTBC)	132							211	1051	3763	0.279298	27.9298
Treated Worst Case (TWC)	132							211	1140	3763	0.30295	30.295
Untreated Worst Case (UTWC)	132				196			211	1822	3763	0.484188	48.4188

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)			113			44						
	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)								211	368	3763	0.0977943	9.77943

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.

REFERENCES

Reference
American Medical Association. Ear, Nose, Throat, and Related Structures. Guides to the Evaluation of Permanent Impairment. 6th ed. Chicago: American Medical Association Press; 2008. p. 247-79.
Agrawal S, Husein M, MacRae D. Complications of otitis media: an evolving state. J Otolaryngol 2005 Jun;34 Suppl 1:S33-S39.
Antonsen, Erik, et al. Risk of Adverse Health Outcomes and Decrements in Performance due to In-Flight Medical Conditions - Human Research Program Exploration Medical Capabilities Element - 2017
Arlotti M, Grossi P, Pea F, et al. Consensus document on controversial issues for the treatment of infections of the central nervous system: bacterial brain abscesses. Int J Infect Dis 2010; 14 (S4):S79–S92.
Berry, Charles A. Biomedical Results of Apollo - Richard S. Johnston, Lawrence F . Dietlein, M.D., and M.D. - 1975
Bluestone CD, Rosenfeld RM, Bluestone CD. Evidence-Based Otitis Media. BC Decker Inc; 2003. p. 121
Crucian B, Babiak-Vazquez A, Johnston S, Pierson DL, Ott CM, Sams C. Incidence of clinical symptoms during long-duration orbital spaceflight. Int J Gen Med. 2016;9:383-391. Published 2016 Nov 3. doi:10.2147/IJGM.S114188
de Zinis LOR, Gamba P, Balzanelli C. Acute Otitis Media and Facial Nerve Paralysis in Adults. Otology & Neurotology 2003;24:113-7.
Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke. 2016 Sep;47(9):2180-2. doi: 10.1161/STROKEAHA.116.013617. Epub 2016 Jul 19. PMID: 27435401.
Dongol K, Rayamajhi P, Gurung U. Complications of Acute and Chronic Otitis Media in a Tertiary Referral Center in Nepal. Turk Arch Otorhinolaryngol. 2020;58(4):234-240. doi:10.5152/tao.2020.5761
Gower D, McGuirt WF. Intracranial complications of acute and chronic infectious ear disease: a problem still with us. Laryngoscope. 1983 Aug;93(8):1028-33. doi: 10.1288/00005537-198308000-00010. PMID: 6877010.
Hafidh MA, Keogh I, Walsh RM, Walsh M, Rawluk D. Otogenic intracranial complications. a 7-year retrospective review. Am J Otolaryngol. 2006 Nov-Dec;27(6):390-5. doi: 10.1016/j.amjoto.2006.03.004. PMID: 17084222.
Hoiberg A. Consequences of U.S. Navy diving mishaps: decompression sickness. Undersea Biomed Res. 1986 Sep;13(3):383-94. PMID: 3775971.
Inglesby DC, Antonucci MU, Spampinato MV, et al. Spaceflight-Associated Changes in the Opacification of the Paranasal Sinuses and Mastoid Air Cells in Astronauts. JAMA Otolaryngol Head Neck Surg.2020;146(6):571–577. doi:10.1001/jamaoto.2020.0228
International Space Station Integrated Medical Group. Medical Checklist ISS- All Expeditions. Houston: National Aeronautics and Space Administration; 2008.
International Space Station Program. Medical Standards and Certification Procedures For Space Flight Participants. NASA; 2002.
Jacobs MR, Dagan R, Appelbaum PC, Burch DJ. Prevalence of antimicrobial-resistant pathogens in middle ear fluid. Antimicrob Agents Chemother. 1998;42(3):589–595.
Kangsanarak J, Navacharoen N, Fooanant S, Ruckphaopunt K. Intracranial complications of suppurative otitis media: 13 years' experience. Am J Otol. 1995 Jan;16(1):104-9. PMID: 8579165.
Leskinen K, Jero J. Acute complications of otitis media in adults. Clin Otolaryngol. 2005 Dec;30(6):511-6. doi: 10.1111/j.1749-4486.2005.01085.x. PMID: 16402975.
Lin YS, Lin LC, Lee FP, Lee KJ. The prevalence of chronic otitis media and its complication rates in teenagers and adult patients. Otolaryngol Head Neck Surg. 2009 Feb;140(2):165-70. doi: 10.1016/j.otohns.2008.10.020. PMID: 19201282.
Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, Grasso D, Barbiero C, Tamburlini G. Burden of disease caused by otitis media: systematic review and global estimates. PLoS One. 2012;7(4):e36226. doi: 10.1371/journal.pone.0036226. Epub 2012 Apr 30. PMID: 22558393; PMCID: PMC3340347.
Park, J.H., Park, S.J., Kim, Y.H. et al. Sensorineural hearing loss: a complication of acute otitis media in adults. Eur Arch Otorhinolaryngol 271, 1879–1884 (2014). https://doi.org/10.1007/s00405-013-2675-x
Penido Nde O, Chandrasekhar SS, Borin A, Maranhão AS, Gurgel Testa JR. Complications of otitis media - a potentially lethal problem still present. Braz J Otorhinolaryngol. 2016 May-Jun;82(3):253-62. doi: 10.1016/j.bjorl.2015.04.007. Epub 2015 Sep 9. PMID: 26420564.
Pichichero ME, Casey JR. Acute otitis media disease management. Minerva Pediatr. 2003 Oct;55(5):415-38. PMID: 14608265.
Pinto JA, Nunes HDSS, Soeli Dos Santos R, Cavallini A, Freitas G, Knoll D, Duarte C. Otitis Media with Effusion in Aircrew Members. Aerosp Med Hum Perform. 2019 May 1;90(5):462-465. doi: 10.3357/AMHP.5266.2019. PMID: 31023406.
Ren Y, Sethi RKV, Stankovic KM. Acute Otitis Media and Associated Complications in United States Emergency Departments. Otol Neurotol. 2018 Sep;39(8):1005-1011. doi: 10.1097/MAO.0000000000001929. PMID: 30113560; PMCID: PMC6097248.
Rosenfeld RM, Kay D. Natural history of untreated otitis media. Laryngoscope. 2003;113:1645–1657. doi: 10.1097/00005537-200310000-00004

Reference

Rudin R, Svärdsudd K, Tibblin G, Hallén O. Middle ear disease in samples from the general population. Prevalence and incidence of otitis media and its sequelae. The study of men born in 1913-23. Acta Otolaryngol. 1983 Sep-Oct;96(3-4):237-46. doi: 10.3109/00016488309132896. PMID: 6605651.

Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. Nat Rev Dis Primers. 2016;2(1):16063. Published 2016 Sep 8. doi:10.1038/nrdp.2016.63

Szmuilowicz J, Young R. Infections of the Ear. Emerg Med Clin North Am. 2019 Feb;37(1):1-9. doi: 10.1016/j.emc.2018.09.001. PMID: 30454772.

Thomas TL, Garland FC, Molé D, Cohen BA, Gudewicz TM, Spiro RT, Zahm SH. Health of U.S. Navy submarine crew during periods of isolation. Aviat Space Environ Med. 2003 Mar;74(3):260-5. PMID: 12650274.

Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with acute otitis media in the United States during 2008-2014. BMC Health Serv Res. 2018 May 2;18(1):318. doi: 10.1186/s12913-018-3139-1. PMID: 29720156; PMCID: PMC5932897.

Vikram BK, Khaja N, Udayashankar SG, Venkatesha BK, Manjunath D. Clinico-epidemiological study of complicated and uncomplicated chronic suppurative otitis media. J Laryngol Otol 2008 May;122(5):442-6.

Williamson I, Benge S, Mullee M, Little P. Consultations for middle ear disease, antibiotic prescribing and risk factors for reattendance: a case-linked cohort study. Br J Gen Pract 2006 Mar;56(524):170-5.

Zernotti ME, Casarotto C, Tosello ML, Zernotti M. [Incidence of complications of otitis media]. Acta Otorrinolaringol Esp 2005 Feb;56(2):59-62.

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