Anaphylaxis Cliff

Branch Baseline

Anaphylaxis is an acute, life-threatening, IgE-mediated allergic reaction that occurs in previously sensitized people when they are re-exposed to the sensitizing antigen. Symptoms include stridor, dyspnea, wheezing, and hypotension. The diagnosis is clinical. Bronchospasm and upper airway edema are treated with inhaled or injected β-agonists and sometimes endotracheal intubation. Hypotension requires IV fluids and vasopressors. History of atopy does not increase risk of anaphylaxis but increases risk of death when anaphylaxis occurs.

Anaphylactoid reactions: These reactions are clinically indistinguishable from anaphylaxis but do not involve IgE and do not require prior sensitization. They occur via direct stimulation of mast cells or via immune complexes that activate complement. The most common triggers are iodinated radiographic radiopaque dye, aspirin, other NSAIDs, opioids, blood transfusions, Ig, and exercise. (Merck Manual, 2009)

An anaphylactic reaction in space would be a significant medical emergency. The most likely sensitizing antigen for a crewmember would be on board medication. Other potential antigens are tracers and markers used in life sciences experiments. Crewmembers are tested for these common allergens before flight, but that does not fully obviate the risk of an anaphylactic reaction, particularly with repeated exposures. Another risk factor is that immune dysregulation occurs in space flight. The clinical manifestations of a vasodilation-induced hypotension in microgravity are not known, but presumably would present differently than in a 1g environment. (Marshburn, 2008) ISS Medical Kits contain the needed equipment and medication required to treat an anaphylactic reaction in space. (International Space Station Integrated Medical Group, 2008)

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:	Fixed
Space Adaptation:	No
Incidence Type:	Rate

Distribution Data	
Incidence:	Fixed
Occurrence:	Poisson

Data Characteristics	
Fixed Rate:	0.000491

Incidence Comments

Decker studied anaphylaxis episodes and categorized the subjects based on age and then gender. The main reference currently used by the IMM model is a 2008 study by Decker **(Decker, 2008)** who conducted a population-based incidence study in Rochester, Minnesota, from 1990 through 2000. Anaphylaxis episodes were identified on the basis of symptoms and signs of mast cell and basophil mediator release plus mucocutaneous, gastrointestinal tract, respiratory tract, or cardiovascular system involvement.

Two hundred eleven cases of anaphylaxis were identified (55.9% in female subjects). The mean age was 29.3 years (SD, 18.2 years; range, 0.8–78.2 years). The overall age-and sex-adjusted incidence rate was 49.8 (95% CI, 45.0–54.5) per 100,000 person-years. Age-specific rates were highest for ages 0 to 19 years (70 per 100,000 person-years).

For age 30 to 39, total incidence was 53.3 (66.1 female, 40.3 male). For age 40 to 49, total incidence was 49.1 (53.3 female, 44.7 male). For age 50 to 59, total incidence was 40.4 (54.9 female, 24.6 male). All incidence values are per 100,000 person years. The overall age range for 40 to 49 was used in the model as it is most representative of our astronaut population age range.

Ingested foods accounted for 33.2% (70 cases), insect stings accounted for 18.5% (39 cases), medication accounted for 13.7% (29 cases), radiologic contrast agent accounted for 0.5% (1 case), “other” causes accounted for 9% (19 cases), and “unknown” causes accounted for 25.1% (53 cases). The “other” group included cats, latex, cleaning agents, environmental allergens, and exercise. There was an increase in the annual incidence rate during the study period from 46.9 per 100,000 persons in 1990 to 58.9 per 100,000 persons in 2000 ($P = .03$).

Information Regarding Prevention

Disqualifying conditions include: In general, any medical condition that, in the judgment of the Aerospace Medical Board (AMB), may compromise mission operations or crew safety, or require urgent medical treatment while resident on the ISS; history of sensitivity or demonstrated allergy of sufficient severity which could interfere with performance of duties. In skin, any skin disorder, acute or chronic, that is severe enough to cause interference with duties or wearing of flight equipment. In lungs and chest: active asthma. Any history of asthma requires pulmonary evaluation. (NASA, 2007)

Other: All crew members are tested before flight for their responses to common medications in the space shuttle and ISS medical kit to determine any unexpected allergic reactions. Other antigens that could initiate an anaphylactic response are tracers and markers used in life sciences experiments.

Terrestrially, anaphylaxis causes shock through vasodilation, which increases the capacity of the veins and capillaries, greatly reduces venous return to the heart, and leaves the vena cava empty. Pumphrey et al observed that some deaths occurred in anaphylaxis cases after an upright posture was assumed; he hypothesized that when venous return is so severely compromised epinephrine cannot circulate and is thus ineffective (Pumphrey, 2003). Clinical manifestations of vasodilation induced hypotension in microgravity are unknown, but presumably the presentation would be different without a gravity gradient to exacerbate orthostatic hypotension (Marshburn, 2008)

Providing medical care in emergency situations in microgravity is challenging given the longer time to retrieve needed medical supplies. The medical kits contain epinephrine 1:1000 and diphenhydramine, steroids and beta agonists aerosols packaged together in an easily accessible location and restrained on nomex fabric pallets (Marshburn, 2008).

The best strategy to control hypersensitivity reactions is prevention. While these steps can minimize the likelihood of an allergic reaction they cannot eliminate the possibility of an in-flight event. Potential consequences of a hypersensitivity reaction during flight can be quite serious (Sams, 2008). A severe allergic reaction could be disastrous during a space missions (Marshburn, 2008).

We have anecdotal reports of anaphylactic events among astronauts on the ground. One occurred in 1996 during preflight testing with radiotracers; causes might have been insulin or indocyanine green and was successfully treated with epinephrine. A similar milder reaction occurred in 1993, by another crew member’s voluntary report. It is unknown if epinephrine was used in the 1993 case (Burrough, 1998).

During the Apollo era seven cases of urticaria occurred (Johnston, 1975). We have not been able to determine the urticaria definition used for these cases nor have additional information about treatment.

A committee of anaphylaxis experts assembled by the World Allergy Organization has examined the evidence from the medical literature concerning the appropriate use of epinephrine for anaphylaxis. The Committee strongly believes that epinephrine is currently underutilized and often dosed sub-optimally to treat anaphylaxis, is under-prescribed for potential future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that the therapeutic benefits of epinephrine exceed the risk when given in appropriate intra-muscular doses (Kemp, 2008).

Medications included in the ISS Medical Kit which could potentially cause an allergic reaction are: silvadene, tobradex ophthalmic, penicillin, Tarivid (Ofloxacin), amoxicillin, bactrim, aspirin, ibuprofen (motrin), diclofenac sodium, or misoprostol (contraindicated if allergic to aspirin), Polytrim ophthalmic, and erythromycin (International Space Station Integrated Medical Group, 2008).

Immune dysregulation occurs in space flight. Numerous cellular and other changes lead to impaired cell-mediated immunity. Hypersensitivities, autoimmunity, and allergies are potential adverse clinical events that may be related to prolonged dysregulation of the immune system (Williams, 2009).

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
Decker, 2008	4	Incidence

Alternative Incidence Data

Note: A Bayesian Analysis for Anaphylaxis has been requested and results are pending. It will replace Decker's data when available.

Since anaphylaxis is not a reportable event, incidence and prevalence are unknown. Those with mild reactions do not seek medical treatment (Neugut, 2001). A review of the literature found that the occurrence of anaphylaxis in the US is not as rare as is generally believed. On the basis of their figures, the problem of anaphylaxis may, in fact, affect 1.21% to 15.04% of the US population.

The objective of a study by Mulla and Simon (Mulla, 2007) was to determine the annual hospital discharge rate and risk factors for anaphylaxis outcomes throughout Florida. Annual hospital discharge rate for anaphylaxis was 2.8/100,000 population. Hospital mortality rate was 0.86%. Median length of stay (LOS) was 1 day. 464 patients who were hospitalized in Florida for anaphylaxis and discharged in 2001 were identified using a statewide database and ICD-9-CM (International Classification of Diseases, 9th revision, Clinical Modification) codes. Linear regression was used to determine the predictors of length of stay (LOS). Relative risks (RR) for ventilator-assisted respiration and anaphylaxis due to food were calculated using binomial regression.

Asthmatics had increased risk of receiving ventilator-assisted respiration (adjusted RR = 2.72, p = 0.04). Likelihood of hospitalization for anaphylaxis increased with age for both sexes (p < 0.0001). Patients who were <18 years old were three times as likely to be hospitalized for food anaphylaxis (versus other causes) compared to patients who were 71+ years old (adjusted RR = 3.25, p = 0.004). The likelihood of hospitalization increased with age.

Burrough reported 1 terrestrial incident among US astronaut crew/27.36 person-years = 0.0365497076023392 (Burrough, 1998)

The clinical epidemiology of acute allergic reactions in the emergency department (ED) is uncertain. The National Hospital Ambulatory Medical Care Survey (Gaeta, 2007) was used to identify a nationally representative sample of ED visits between 1993 and 2004 with the objective to characterize ED visits for acute allergic reactions and to evaluate national trends in ED management. Cases with a diagnosis of acute allergic reaction were identified by International Classification of Diseases, Ninth Revision (ICD-9) codes (9950[vl1] , 9951, 9952, 9953, 9956[vl2]). A total of 12.4 million allergy-related ED visits occurred from 1993 to 2004, representing 1.0% (95% confidence interval, 0.93%-1.10%) of all ED visits or 1.03 million ED visits per year. The number of allergy-related ED visits remained relatively stable, averaging 3.8 per 1,000 US population per year (95% confidence interval, 3.4-4.1; P for trend = .39). Although 63% of all visits were coded as urgent, only 4% required hospitalization. Anaphylaxis coding was rare (1%) and small sample size precluded any detailed analysis. The 52 actual cases represented approximately 12,000 visits per year. Or approximately 143000 anaphylaxis cases per 12.4 million total allergy cases during more than 12 years. 50% of anaphylaxis cases received epinephrine and 13% received a beta-agonist. Only 33% of patients who sought care in the ED and were coded as having anaphylaxis (995.0 or 995.6) were admitted overnight to the hospital. ED staff prescribed medications in 87% of visits, especially histamine, blockers (62%; P for trend = .29). Increases were noted from 1993 to 2004 for corticosteroids (22% to 50%; P < .001), histamine2 blockers (7% to 18%; P < .001), and inhaled beta-agonists (2% to 6%; P = .008). Epinephrine use was infrequent and declining (19% to 7%; P = .04). Confidence intervals or age ranges for anaphylaxis are not published in the study.

Between 1993 and 2004, significant variability has occurred in ED management of acute allergic reactions. Results are thought to significantly underestimate the true burden of anaphylaxis. ED physicians use the diagnoses of allergic reaction or acute allergic reaction with multiple system organ that should instead be diagnosed as having anaphylaxis. Epinephrine is underused for severe acute allergic reactions in the ED. Results are confined to ED visits and not to all cases of acute allergic reactions in the general population.

An observational follow-up study encompassing approximately 8 million person-years based on the UK General Practice Research Database (Peng, 2004) for the period January 1, 1994, to December 31, 1999, quantified the frequency, type, and severity of a clinical diagnosis of anaphylaxis. Based on 675 cases of anaphylaxis, we estimate the incidence to be 8.4 per 100 000 person-years. Approximately 10% of cases had hypotension and shock that required urgent treatment providing an incidence of approximately 1 per 1 million person-years. Age ranges are not published. Some common symptoms include weakness, dizziness, flushing, angioedema, urticaria, nasal congestion, and sneezing. Severe symptoms include upper respiratory tract obstruction, hypotension, vascular collapse associated with angioedema and urticaria, gastrointestinal distress, cardiovascular arrhythmias, and/or arrest. Peng concluded that anaphylaxis is an uncommon illness that has multiple causes and can be life-threatening.

Peng estimated based on the random sample of 120 case histories reviewed, that 675 had an acute episode of anaphylaxis. From these findings, we calculated a crude estimate of the incidence of anaphylaxis to be 675 per 8 million person-years at risk (8.4 per 100 000 person-years).

Most common cause of anaphylaxis was insect sting or bite, which accounted for 32% of cases. All but 2 cases occurred in June through September. The second most common cause was medicines (30%). Penicillin (n = 5) and nonsteroidal anti-inflammatory drugs (n = 4) were the most frequent causes. Allergy to food was estimated to represent 22% of cases. More than half of these were due to nuts, primarily peanuts. Shellfish and dairy products accounted for most of the remaining cases. Other causes were present in the remaining 16% of cases.

Based on the computer-recorded information and the records received, Peng estimated that 65% to 70% of patients were either hospitalized or seen in the emergency department. More than half were treated with epinephrine and prescribed adrenaline 0.15-mg self-injection device to be available for immediate use when necessary. The possibility that some cases of anaphylaxis may not have been recorded in the GP computer record, particularly those that occurred in hospital cannot be ruled out.

Our previous incidence data (Johnson, 2004) were based on a study by Yocum (Yocum, 1999). The purpose of his study was to describe the epidemiology of anaphylaxis in Olmsted County residents from 1983 through 1987. This was a retrospective population-based cohort study. The medical records of 1255 Olmsted County residents identified by computer-linked, medical diagnostic indices (the Rochester Epidemiology Study) were reviewed retrospectively to identify residents whose clinical episodes met the criteria for anaphylaxis. He determined the incidence and rate of occurrence of anaphylaxis, rate of recurrence, prevalence of atopy, cause of anaphylaxis, frequency of referral to an allergy specialist, hospital admission rate, and case-fatality rate. There were 133 residents who experienced 154 anaphylactic episodes during the 5-year period: 116 residents had 1 episode of anaphylaxis, 13 residents had 2 episodes, and 4 residents had 3 episodes. The anaphylaxis occurrence rate was 30 per 100,000 person-years (95% confidence interval, 25-35). There were 110 residents who had a first lifetime episode of anaphylaxis (that was medically evaluated) during the years 1983 to 1987. The average annual incidence rate of anaphylaxis was 21 per 100,000 person-years (95% confidence interval, 17-25). Atopy was present in 53% of the cohort, and allergy consultation was obtained in 52%. A suspect allergen was identified in 68% of the cohort, most frequently a food, medication, or insect sting. The hospitalization rate was 7%, and 1 patient died. Conclusion: The incidence of anaphylaxis is less than 1%, and death rarely occurs. People with atopy experience anaphylaxis more frequently than people without atopy. Anaphylaxis frequently is not recognized by patients and physicians.

The American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group (Lieberman, 2006) performed a qualitative review by hand of the major epidemiology studies of anaphylaxis to improve understanding of the epidemiology of anaphylaxis. This review was restricted to articles in the English language, selected by the committee and dated back to 1968. There was no specific criterion used for selection except the determination of the members of the committee. Data on anaphylaxis incidence and prevalence are sparse and often imprecise. Findings are based on diverse study designs and are not entirely comparable. These factors have contributed to widely varying estimates of the frequency of this important condition. The roundtable discussion led to an improved estimation of the frequency of anaphylaxis: approximately 50 to 2,000 episodes per 100,000 persons or a lifetime prevalence of 0.05% to 2.0%. The largest number of incident cases is among children and adolescents. In addition to under-diagnosis, they noted under-treatment, especially for those at highest risk (i.e., those without immediate access to treatment with epinephrine). Anaphylaxis is a relatively common problem, affecting up to 2% of the population. Further data on epinephrine dispensing could improve current estimates. Another way to improve current understanding would be through better population-based study designs in different geographic regions. A recurring theme was the importance of broader access to self-injectable epinephrine for high-risk populations. A new epidemiological approach to estimate anaphylaxis incidence by epinephrine prescriptions to patients outside the hospital in Canada during a 5 year period, resulted in 0.95% of this defined general population had injectable epinephrine dispensed for out-of-hospital treatment. Epinephrine dispensing rates across were higher: 1.44%, for individuals younger than 17 years of age, 0.9% for individuals 17 to 64 years of age (inclusive), and 0.32% for those age 65 years or older (Simons, 2002).

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 %: 99 - 100)	100	0.25 - 0.5	3 - 46	0.75 - 0.875 - 1	0	0	0
ISS-based Treatment (worst case scenario %: 0 - 1)	100	0.5 - 1	48 - 100	1 - 36.5 - 72	0 - 70	100	0 - 100
Untreated Best Case	0	0	21 - 70	0.75 - 0.875 - 1	0 - 46	50 - 100	10 - 100
Untreated Worst Case	0	0	48 - 100	1 - 36.5 - 72	48 - 100	100	100

[1]Clinical 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".

[2]Clinical 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.

[3]Clinical 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

The **best case scenario is defined** as an anaphylactic event involving a reaction of the respiratory or cardiovascular systems that responds to initial treatment with epinephrine.

The **worst case scenario is defined** as an anaphylactic event involving a reaction of the respiratory or cardiovascular systems that does not respond to initial treatment with epinephrine..

Anaphylaxis has varied clinical presentations but respiratory and cardiovascular collapse cause the most concern because they are the most frequent cause of fatalities. Urticaria and angioedema are the most common manifestations but may be delayed or absent in rapidly progressive anaphylaxis. Anaphylaxis often produces signs and symptoms within minutes to exposure to an offending stimulus but some reactions may develop >30 minutes after exposure. Late phase, or biphasic reaction, occurs 8 to 12 hours after the initial attack. Protracted and severe anaphylaxis might last up to 32 hours despite aggressive treatment. Increased intravascular permeability allows transfer of as much as 50% of the intravascular fluid into the extravacular space within 10 minutes. Hemodynamic collapse may occur rapidly with little or no cutaneous or respiratory manifestations. Symptoms not immediately life threatening may progress rapidly. Anaphylactic reactions to food almost always occur immediately. Symptoms might then subside only to recur several hours later. (Lieberman, 2005)

16 to 35% of individuals who inject epinephrine require a second dose (Kounis cited in Simons).

There appears to be a correlation between time of onset after exposure and severity of reaction. In 75% of cases the principal causes of death are asphyxia from upper airway edema and hypoxia from severe bronchospasm. In 25% of deaths there is circulatory failure with hypotension (Netzel, 1986).

Pumphrey et al noted that in cases of fatal anaphylaxtic shock, the time from anaphylaxis onset to cardiac arrest was between 4 and 80 minutes (10 to 20 minutes in the majority of cases). Asphyxial deaths took from 10 to 360 minutes (with a median of 35 minutes) from time of anaphylaxis onset to the first manifestations of repiratory arrest (Pumphrey, 2003).

Allergic angina and allergic myocardial infarction are referred to as Kounis Syndrome. The true frequency has not been determined and reporting to a national registry is not required. A literature search showed 150 reported cases (Kounis, 2006). Kounis Syndrome is not included in this CliFF.

Percentages of how often best versus worst case scenarios occur is estimated as 0 to 1% based on terrestrial data (Mulla, 2007); (Gaeta, 2007).

Best Case Comments

Anaphylaxis is a multi-system medical condition and it is not included as a condition in the American Medical Association guides to the Evaluation of Medical Impairment. The calculation of functional impairments (FI) follows the IMM standard template for severe conditions, except in the case of treated worst case scenario; it requires combining two tables. Pulmonary Dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008) and Consciousness and Awareness ratings are based on Table 13-4, p. 327 (American Medical Association, 2008). Combined FI ratings are calculated using the Combined Values Chart as indicated in Appendix A, pp 604-606 (American Medical Association, 2008). For detailed information on calculation and description of grading refer to the CliFF Appendix.

In **Clinical Phase I**: By definition functional impairment (FI) is 100% based on time required for initial evaluation and treatment using the ISS Medical Checklist procedures. Duration is estimated between 15 to 30 minutes for initial evaluation and initial treatment (Injecting epinephrine). **Clinical Phase** II: 45 minutes to 1 hour is the estimated duration for continued treatment and follow up clinical evaluation. FI is estimated as 3 to 46 %. **Clinical Phase III**: 0% functional impairment based on complete resolution of anaphylaxis with treatment available on ISS. By definition EVAC and LOCL are not expected in this scenario.

Worst Case Comments

Anaphylaxis is a multi-system medical condition and it is not included as a condition in the American Medical Association guides to the Evaluation of Medical Impairment. The calculation of functional impairments (FI) follows the IMM standard template for severe conditions, except in the case of treated worst case scenario; it requires combining two tables. Pulmonary Dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008) and Consciousness and Awareness ratings are based on Table 13-4, p. 327 (American Medical Association, 2008). Combined FI ratings are calculated using the Combined Values Chart as indicated in Appendix A, pp 604-606 (American Medical Association, 2008). For detailed information on calculation and description of grading refer to the CliFF Appendix.

In **Clinical Phase I**: By definition functional impairment (FI) is 100% based on time required for initial evaluation and treatment using the ISS Medical Checklist procedures. Duration is estimated between half to one hour for initial evaluation and stabilizing treatment. **Clinical Phase II:** duration is estimated as1 to 72 hours of functional impairment based on the treatment of moderate to severe shock following the ISS procedures and the maximum time indicated for ACLS on board. FI combined values are 48-100% based on the fact that this scenario involves airway compromise and may require intubation **Clinical Phase III**: 0 to 70% functional impairment. EVAC is estimated in 100%. Anaphylaxis is a Class III event requiring evacuation if occurring on orbit (Johnston, 2008). LOCL is estimated in 0 to 100% of cases considering the unpredictability of response for an anaphylactic event.

Untreated Best Case Comments

Anaphylaxis is a multi-system medical condition and it is not included as a condition in the American Medical Association guides to the Evaluation of Medical Impairment. The calculation of functional impairments (FI) follows the IMM standard template for severe conditions, except in the case of treated worst case scenario; it requires combining two tables. Pulmonary Dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008) and Consciousness and Awareness ratings are based on Table 13-4, p. 327 (American Medical Association, 2008). Combined FI ratings are calculated using the Combined Values Chart as indicated in Appendix A, pp 604-606 (American Medical Association, 2008). For detailed information on calculation and description of grading refer to the CliFF Appendix.

In **Clinical Phase** II: 45 minutes to 1 hours is the estimated similar to best case treated scenario. FI is estimated in 2 to 46 %, however, there is no treatment available. **Clinical Phase III**: FI combined values is 0 to 46%. Anaphylaxis is unlikely to resolve without treatment. EVAC is estimated in 50 to 100%, based on terrestrial data of 50% of patients seen in the ED required treatment with Epinephrine (Gaeta, 2007)and 65 to 70% hospitalization (Peng, 2004). LOCL is estimated in 10 to 100% based on terrestrial data indicating that 10% of events go into hypovolemic shock (Peng, 2004).

Untreated Worst Case Comments

Anaphylaxis is a multi-system medical condition and it is not included as a condition in the American Medical Association guides to the Evaluation of Medical Impairment. The calculation of functional impairments (FI) follows the IMM standard template for severe conditions, except in the case of treated worst case scenario; it requires combining two tables. Pulmonary Dysfunction ratings are based on Table 5-4, p.88 (American Medical Association, 2008) and Consciousness and Awareness ratings are based on Table 13-4, p. 327 (American Medical Association, 2008). Combined FI ratings are calculated using the Combined Values Chart as indicated in Appendix A, pp 604-606 (American Medical Association, 2008). For detailed information on calculation and description of grading refer to the CliFF Appendix.

In **Clinical Phase** II: 1 to 72 hours is the estimated duration similar to the worst case treated scenario. FI is estimated in 48 to 100 % and there is no treatment available. **Clinical Phase III**: FI combined values remains 48 to 100%. Anaphylaxis is unlikely to resolve without treatment. EVAC is estimated in 100%, based on Anaphylaxis being a Class III medical event (Johnston, 2008). LOCL is estimated in 10 to 100% based on terrestrial data indicating that 10% of events go into hypovolemic shock (Peng, 2004).

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
American Medical Association, 2008	3	FI
American Medical Association, 2008	3	FI
American Medical Association, 2008	3	FI
Johnston, 2008	4	EVAC
Gaeta, 2007	4	BCWC
Peng, 2004	4	EVAC
Mulla, 2007	4	BCWC

Additional Comments

We searched PubMed using the keywords anaphylaxis or anaphylactic shock and incidence, and anaphylactic shock or anaphylaxis and epidemiology. We refined the search by relevance and date. A PubMed search using the keywords anaphylaxis or anaphylactic shock and space medicine yielded no results.

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Albuterol inhaler (Proventil) 90 mcg, 6.7 gm	1	1	3	Yes	Yes	bronchodilator, to relieve wheezing
Ambu bag and mask	0	1	1	No	Yes	hand-held device used to provide positive pressure ventilation to a patient who is not breathing or is breathing inadequately
Benadryl 50 mg/mL, 1mL injectable	1	2	6	Yes	Yes	to stop severe allergic reaction, intramuscular
Blood Oximeter	1	1	1	No	Yes	monitors the oxygen saturation of a patient's blood
Blood Pressure Cuff (regular, large)	1	1	2	No	Yes	Measure blood pressure
Blood Pressure Monitor	1	1	1	No	Yes	Measure blood pressure
BZK wipes	4	10	60	Yes	No	Cleanse skin.
Dexamethasone (Decadron) 10mg injectable	1	6	20	Yes	Yes	steroid anti-inflammatory, to inject intravenously or intramuscularly
ECG Monitor (Device, USB Charge Cable, Lead Set Cable, Cue Card)	1	1	1	No	Yes	Measure and monitor ECG
Endotracheal Stylet	0	1	1	No	Yes	Means to maintain open airway and provide ventilation
Endotracheal Tube 7.0/8.0	0	1	4	Yes	Yes	Establish and maintain patent airway and ventilation
EpiPen 1:1000	1	3	3	Yes	Yes	to stop severe allergic reaction, subcutaneous
EtCO2 Monitor with EMMA adapter	0	1	1	No	Yes	Monitor end tidal CO2
Gauze pads (4x4)	0	6	50	Yes	No	to absorb blood or fluids from skin
IV administration set	0	1	3	Yes	Yes	To administer IV fluids and emergency medications.
IV Cap	0	1	5	Yes	No	To attach IV fluids to Y-type catheter
IV Catheter (18G, 20G, or 22G)	0	1	14	Yes	Yes	IV fluid administration
IV Fluid 1L (1000mL)	0	5	5	Yes	Yes	For IV hydration and for administering emergency medications into bloodstream.
IV Fluid Air Filter	0	1	3	Yes	No	To filter air from IV set
IV pressure infuser	0	1	1	No	No	IV Fluids infusion
Ketamine 50 mg/mL, 10 mL multi dose vial	0	0.3	6	Yes	Yes	For sedation in case of intubation/ventilation.

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
King Supraglottic Airway (SGA) Tube (size 3/size 4)	0	1	2	Yes	Yes	Establish and maintain patent airway and ventilation
Laryngoscope (blade)	0	1	1	No	Yes	Used injunction with a handle to help visualize the vocal cords during insertion of ET tube.
Laryngoscope handle	0	1	1	No	Yes	Used injunction with a handle to help visualize the vocal cords during insertion of ET tube.
Medical tape	0	1	5	Yes	No	Used to anchor IV catheter and administration set to patient.
Nasal Airway (6mm, 7mm)	0	1	2	No	Yes	Airway management
Needle (23G)	0	3	20	Yes	Yes	For medication administration.
Nitrile gloves (large, medium, and small) (pair)	1	2	30	Yes	No	Personal Protective equipment for CMO
Oral Airway	0	1	2	No	Yes	Airway management
Pack of 12 ECG electrodes	1	1	5	Yes	Yes	Measure and monitor ECG
PEEP Valve	0	1	1	No	Yes	Provide positive pressure during ventilation
SGA Cue Card	0	1	1	No	Yes	Guidance for use of supraglottic airway
Sharps container	1	1	40	No	No	To dispose of medical waste such as used medical needles, scalpels, IV catheters, razors, vials
Stethoscope	1	1	2	No	Yes	Audible evaluation of lungs
Suction Cartridge	0	1	1	No	Yes	Provide medical suction
Suction device	0	1	1	No	Yes	Help remove mucous from airway.
Suction device collection bag	0	1	2	Yes	No	Help remove mucous from airway.
Suction device syringe	0	1	1	No	Yes	Help remove mucous from airway.
Suction tip - mouth (curette)	0	1	1	No	Yes	Provide oral suction
Suction Tubing - Endotracheal Tube	0	1	1	Yes	Yes	Provide airway suction
Surgical Lubricant	0	1	6	Yes	No	Lubricates the bottom of ILMA mask, roof of the mouth, and ET tube.
Syringe (35cc)	0	1	1	Yes	Yes	Inflation of SGA tube
Syringe (3cc)	0	6	20	Yes	Yes	IV flush and medication administration
T-adapter	0	1	1	No	Yes	Connection for ventilation tubing
Thermometer	1	1	1	No	No	Measures body temperature.
Tongue depressor	0	1	20	Yes	No	Assists inthe examination of airway.

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Tourniquet	0	1	1	No	No	To stop blood flow and engorge vein, this facilitates IV insertion
Valium (Diazepam) 5 mg/mL, 2 mL syringe	0	1	2	Yes	Yes	For sedation with intubation
Variable Oxygen System	0	1	1	No	Yes	Anicillary supplies for the oxygen administration
VOS Intubated Patient Hardware (Ventilator/Respirator)	0	1	1	No	Yes	Mechanical Ventilation
Zantac (Ranitidine) 150 mg	4	0	60	Yes	Yes	To cover H2-receptor blockade

Resource Comments

The sources of the resource table data was derived from the ISS Medical Checklist (Mission Operations Directorate (MOD), 2011).

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

Level Of Evidence

Input Data	LOE Average
Incidence	4
Functional Impairment	3
Best Case / Worst Case	4
EVAC / LOCL	4
Resources	2
QUALITY OF EVIDENCE	**3.4**

Description	Range
Excellent	1-2
Good	2.1-3
Fair	3.1-4
Poor	4.1-5

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