Seizures Cliff

Branch Baseline

A seizure is an episode of neurologic dysfunction caused by abnormal neuronal activity that results in a sudden change in behavior, sensory perception, or motor activity. The clinical spectrum of seizures includes simple and complex focal or partial seizures and generalized seizures. (Pillow, 2011) There have not been any reported cases of seizures occuring in the US space program.

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:	Model
Space Adaptation:	No
Incidence Type:	Rate

Distribution Data	
Incidence:	Lognormal
Occurrence:	Poisson

Data Characteristics	
Mean:	0.00027
Standard Deviation:	2.88E-05

Incidence Comments

Evaluating the probability that an astronaut may experience a seizure during an exploration mission is necessary because this condition may greatly affect crewmember performance, health, and morale. An estimate of the probability of an astronaut experiencing a seizure was evaluated using data from the general population (Hauser, 1993), as well as astronaut data from the Lifetime Surveillance of Astronaut Health (LSAH) (Mason, 2011). The incidence rates of seizure from these sources were combined using a Bayesian update approach, numerical Bayesian update code WinBUGS, to estimate the appropriate representation for the rate of seizure for the time. By making the constant rate assumption, a Poisson probability distribution could be assumed to govern the probability of seizure (Gilkey, 2012).

The incidence of first unprovoked seizures among individuals 40-54 years of age was slightly higher in males (29) than females (25); however, for the purpose of this estimate the incidence rate of seizures among males and females was averaged (2.7× x 10e-4 events per person-year). Because there is not a significant variation in the incidence of seizure between males and females, the average incidence rate was considered appropriate. The incidence of seizure is related to age— incidence rates were high among infants younger than 1 year and highest among persons older than 75 years of age. Confidence interval information was not available for first unprovoked seizures, therefore the error factor was estimated from 95% confidence interval constructed from total population data for epilepsy. A person experiencing a single unprovoked seizure was not diagnosed with epilepsy and thus was not included in the confidence interval data. The incidence rate of a first unprovoked seizure was 33% higher than the incidence rate of epilepsy, which is primarily due to the addition of those individuals who experienced only one unprovoked seizure. Data for this estimate was averaged from three age ranges: 40-44, 45-49, and 50-54 yielding and average age of 47 years. The error factor was estimated to be 1.19 from a 95% confidence interval constructed from male and female data from population age 40-54 years (Gilkey, 2012).

The mean incidence rate of seizure among astronauts was **0.00027** events per person-year. Standard deviation is **0.0000288**. 95% Confidence Interval is 2.25 x 10e-4 – 3.19 x 10e-4 (Gilkey, 2012).

Limitations include assuming an average incidence rate of seizure irrespective of environmental conditions and the cause of seizure, and the calculation of the error factor was determined using epilepsy data, not unprovoked seizure data, as the paper did not have confidence interval information on first unprovoked seizure data. Additionally, data regarding repeated occurrences of seizures could influence the predicted rate of incidence since it is known that the occurrence of a single seizure greatly increases the likelihood of subsequent seizures. Use should be treated with understanding of these limitations; however, it is likely a reasonable representation of the rate of seizure incidence given the occurrence data available and given the assumptions made during construction of the estimate (Gilkey, 2012)

Information Regarding Prevention

Selection criteria

Disqualifying conditions in the neurologic disorders area include: any neurologic disorder that may interfere with the performance of duties; tumors of the nervous system; vascular disorders of the nervous system (e.g. arteriovenous malformation, intracranial aneurysms, familial cavernous angioma, and temporal arteritis). Sporadic cavernous angiomas require neurologic evaluation. History of cerebrovascular accident (stroke, TIA, or subarachnoid hemorrhage). Asymptomatic disease of the carotid or vertebral arteries requires neurologic evaluation. Seizure disorders or history of seizure disorders, including absence seizures**.** History of traumatic brain injury with associated intracerebral hemorrhage with persistent neurologic deficits; or intracranial hemorrhage requiring surgery or with persistent neurologic deficits (e.g. subdural or epidural hematoma). (International Space Station Program, 2009); (NASA, 2007) (International Space Station Program, 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
Gilkey, 2012	2	Incidence

Alternative Incidence Data

Analog Populations

In the US Air Force no flying personnel with the diagnosis of epilepsy have received waivers to date. In aviators with provoked seizures and a history of childhood seizures, consideration for a waiver to return to flying duties is entertained. In the US Air Force database, a total of 65 cases were noted that carried a diagnosis of seizure disorder of some sort requesting a flying waiver. Of that total, 25 were granted a waiver for an approval rate of 38.5%. Ten waiver applicants were for initial pilot training, six were for a trained pilot or navigator and the remaining nine were for non-pilot aircrew. In each of the 25 cases, the history was for childhood febrile or infantile seizures or for provoked seizures. There were no listed approved waivers for the diagnosis of epilepsy. (American Society of Aerospace Medicine Specialists, 2008)

An analysis of 10 years of data collected on US Navy Polaris submarine patrols over the ten year period 1963-1973 reported a total of 1685 medical events treated. Illness rates are indicated as new/cases/1000 man-days. There were a total of 53 neurological events during the 1963-73 period. There were three seizure events; one of unknown etiology caused one sick day, one grand mal epilepsy, caused 2 sick days, and one post traumatic epilepsy caused 7 sick days. Illness rate and rate of days lost were significantly higher than those observed in the surface population ($P < 0.05$) (Tansey, 1979). Our estimate rate per person year is 0.0000007 (3 seizures/4,410,000 person-days). Four EVACs occurred but there is no information by condition.

A study was conducted to examine the risk of undergoing an epileptic seizure as a function of differing levels of occupational stress (physical and mental) in new military recruits with no previous history of epilepsy or with epilepsy in remission for over 2 years. The medical records of over 300,000 18-year-old men recruited to the Israeli Army between mid-eighties and mid-nineties were used to assemble a cohort, which was followed for a period of 30 months. The severity of epilepsy at recruitment was determined according to four categories, 0 (no history of seizures) and 1-3 (history of seizures with different relapse-free periods, with or without treatment). The soldiers were subdivided according to their occupational categories into: combat units (CU), maintenance units (MU), and administrative units (AU). The annual incidence rates per 100,000 in category 0 were 317, 298, and 401 in AU, MU, and CU, respectively. The incidence of seizures in category 0 was higher (relative risk [RR] = 1.29, CI = 1.03-1.62) in CU compared to AU and MU. No differences were found for seizure recurrence among various occupational groups. The increased risk of seizures in CU compared to AU and MU may indicate contribution of service conditions in CU, like physical and mental stress. The equivalent rates of seizure relapse, regardless of the type of occupation, suggest the need for minimal occupational restrictions for epilepsy patients who have been free of seizures for long periods (Moshe, 2008). Rates per person-year are 0.00317, 0.00298, and 0.00401 respectively.

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 %: 82 - 90)	100	0.33 - 0.5	1 - 20	0.33 - 24.165 - 48	0	100	0
ISS-based Treatment (worst case scenario %: 10 - 18)	100	0.5 - 0.75	11 - 50	0.5 - 24.25 - 48	0 - 50	100	1 - 4
Untreated Best Case	0	0	11 - 35	0.33 - 24.165 - 48	0 - 20	100	0
Untreated Worst Case	0	0	31 - 100	0.5 - 24.25 - 48	31 - 100	100	0 - 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

Best case is defined as a seizure that responds to drug therapy and does not recur.

Worst case is defined as a seizure that does not respond to initial drug therapy and/or recurs.

Of note, all seizures occurring within 24 hours are considered a single seizure. (Adams, 2007)

Best case/worst case percentages

The percentages of worst versus best case were determined using the rate of recurrence established in the in the United Kingdom at 10-18%. (Bonnett, 2010)

Best Case Comments

The functional impairments (FI) calculation for Seizures follows the IMM severe non-space adaptation template. Seizures affect consciousness, which is the basis for our FI calculations. Consciousness and awareness ratings are based on Table 13-4, p. 327.

Episodic Loss of Consciousness or awareness ratings are based on Table 13-5, p. 328. (American Medical Association, 2008)

By definition during **Clinical Phase I**, FI is 100% and duration is estimated to be 20-30 minutes for diagnosis evaluation for neurological impairment and initial treatment. During **Clinical Phase II**, Functional Impairment is estimated in 1-20%. Duration s estimated at 20 minutes to 24 hours. By definition, during **Clinical Phase III** complete recovery and 0% functional impairment is expected. By definition, EVAC is a consideration based on health concerns and the potential to compromise flight safety. It is estimated at 100%. LOCL is not expected for this scenario.

Worst Case Comments

The functional impairments (FI) calculation for Seizures follows the IMM severe non-space adaptation template. Seizures affect consciousness, which is the basis for our FI calculations. Consciousness and awareness ratings are based on Table 13-4, p. 327; Episodic Loss of Consciousness or awareness ratings are based on Table 13-5, p. 328. (American Medical Association, 2008)

By definition during **Clinical Phase I**, FI is 100% and duration is estimated to be 30 to 45 minutes for diagnosis evaluation for neurological impairment and initial treatment following the ISS Medical Checklist procedures and clinical experience. During **Clinical Phase II**, FI is estimated at 11 to 50%. Duration is estimated at 0.5-48 hours, based in the time estimated to arrange for evacuation. During **Clinical Phase III**, some or incomplete recovery is expected, with functional impairment estimated at 0-50%. EVAC is expected for 100% of worst case scenario. Sudden epilepsy deaths have been estimated at less than 1% (Jehi, 2010) and in newly diagnosed epilepsy the standardized mortality ratio (SMR) is 2.6; 95% Confidence interval1.8-3.5. (Rakitin, 2011)To allow for uncertainty LOCL is estimated at 1 to 4%.

Untreated Best Case Comments

The functional impairments (FI) calculation for Seizures follows the IMM severe non-space adaptation template. Seizures affect consciousness, which is the basis for our FI calculations. Consciousness and awareness ratings are based on Table 13-4, p. 327; Episodic Loss of Consciousness or awareness ratings are based on Table 13-5, p. 328 (American Medical Association, 2008).

During **Clinical Phase II**, Functional Impairment is estimated at 11-36%. Duration is 20 minutes to 48 hours similar to the treated best case scenario. During **Clinical Phase III** functional impairment is estimated at 0 to 20%. EVAC of a crew member with seizures is estimated at 100% for in-hospital evaluation, similar to the treated best case scenario. LOCL is not expected and it is estimated at 0%.

Untreated Worst Case Comments

The functional impairments (FI) calculation for Seizures follows the IMM severe non-space adaptation template. Seizures affect consciousness, which is the basis for our FI calculations. Consciousness and awareness ratings are based on Table 13-4, p. 327; Episodic Loss of Consciousness or awareness ratings are based on Table 13-5, p. 328 (American Medical Association, 2008). During **Clinical Phase II**, FI is estimated at 31 to 100%. Duration is estimated at 0.5-48 hours, similar to the treated worst case scenario. During **Clinical Phase III**, no recovery is expected, with functional impairment remaining at 31-100%. EVAC is expected for 100% of worst case scenario. LOCL is estimated at 0-100% without treatment available.

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
Jehi, 2010	4	EVAC
Rakitin, 2011	4	EVAC
Bonnett, 2010	4	BCWC

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Blood Oximeter	1	1	1	No	Yes	To measure blood oxygen levels.
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	5	10	60	Yes	No	Cleanse skin.
CMRS	0	1	1	No	No	Restrain crew member to ensure safety
ECG Monitor (Device, USB Charge Cable, Lead Set Cable, Cue Card)	0	1	1	No	Yes	Measure and monitor ECG
Gauze pads (4x4)	1	7	50	Yes	No	To absorb blood or fluids from skin
Levetiracetram (Keppra) 500mg	30	30	30	Yes	Yes	Seizure control and prevention
Medical tape	0.1	3	5	Yes	No	Single-coated adhesive tape to secure IV
Nitrile gloves (large, medium, and small) (pair)	1	1	30	Yes	No	Personal Protective equipment for CMO
Pack of 12 ECG electrodes	0	1	5	Yes	Yes	Measure and monitor ECG
Sharps container	1	1	40	No	No	To dispose of medical waste such as used medical needles, scalpels, IV catheters, razors, vials
Syringe (3cc)	0	1	20	Yes	Yes	To flush IV catheter as needed
Valium (Diazepam) 5 mg/mL, 2 mL syringe	1	2	2	Yes	Yes	To treat seizures
Variable Oxygen System	0	1	1	No	Yes	Administration of oxygen

Resource Comments

The table was revised on 9/21/2011 to include IV tubing, and adding rationales.

Seizures is included as a medical condition in the ISS Medical Checklist. All resources included in the table are included in ISS Medical checklist (International Space Station Integrated Medical Group, 2008)and/or ISS Checs Catalog. (Mission Operations Directorate (MOD), 2011).

Comparison of terrestrial guidelines versus ISS treatment

Electroencephalography is recommended for patients presenting with a first seizure, and neuroimaging is recommended for adults before starting antiepileptic medications. These tests are not available on board. Patients with a normal neurologic examination, normal test results, and no structural brain disease do not require hospitalization or antiepileptic medications. (Adams, 2007) (American Society of Aerospace Medicine Specialists, 2008) The treatment recommended in the ISS medical checklist is similar to terrestrial guidelines except that lacking tests and imaging, medications are started immediately.

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	2
Functional Impairment	3
Best Case / Worst Case	4
EVAC / LOCL	4
Resources	2
QUALITY OF EVIDENCE	**3**

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

Reference List

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