Visual Impairment and/or Increased Intracranial Pressure (VIIP)(space adaptation) Cliff

Branch Baseline

During the last 4 years, pre-flight and post-flight retinal exams have been conducted in NASA astronauts. Disc edema, globe flattening, choroidal folds, cotton wool spots, nerve fiber layer thickening, and hyperopic shift have all been observed in astronauts on long-duration missions during in-flight and/or post-flight exams. Although the etiology is unclear, multiple mechanisms have been proposed (Mader, 2011).

The first explanation for the fundoscopic changes is that the findings are a result of elevated intracranial pressure (ICP) due to microgravity exposure (Mader, 2011). Terrestrially, idiopathic intracranial hypertension (IIH) is a well-defined syndrome characterized by signs and symptoms of intracranial hypertension (headache, papilledema) and elevated ICP (pressure 25 cm), and lack of neurologic findings or neuroimaging abnormalities (Friedman, 2002). The ophthalmic findings in astronauts are consistent with findings in IIH, and four astronauts demonstrated ICP >20 cm post-flight (Mader, 2011).

Despite the similarities, many differences exist between the astronaut population and terrestrial patients with IIH, and other etiologies should be considered. An alternative explanation is that localized events at the level of the intraorbital optic nerve cause optic nerve head edema without elevated ICP. Under microgravity conditions, cerebrospinal fluid (CSF) may enter intraorbital portion of the subarachnoid space, but outflow may be impeded causing an optic nerve compartment syndrome with resultant disc edema and globe flattening (Mader, 2011).

A third etiology for ophthalmic findings in long duration space flight is ocular hypotony, or intraocular pressure (IOP) <6.5 mmHg (Mader, 2011). Low IOP has been seen in astronauts post-flight (Nicogossian, 1993)Fundoscopic changes, including papilledema, vascular tortuosity, and choroidal folds, have been observed with ocular hypotony (Costa, 2007).

Hyperopic changes are also documented in 11% of short-duration and 34% of long-duration missions. Multiple theories exist as to the cause such as posterior globe flattening, axial shortening with normal aging, changes in corneal refractive power with atmospheric changes, lenticular changes due to fluid shifts, or choroidal expansion (Mader, 2011).

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:	Raw Data
Space Adaptation:	Yes
Incidence Type:	Proportion

Distribution Data	
Incidence:	Beta
Occurrence:	Bernoulli

Data Characteristics	
Occurrence Hour Range:	288 to 1464
Peak Occurrence Hours:	900
Events:	40
Persons At Risk:	188
Space Flight Incidence Rate (Events / Persons at Risk):	40 / 188 = 0.212765957446809

Incidence Comments

Fifteen events occurred in 44 crewmembers at risk. The numerator is the number of long duration crewmembers with mild, moderate or severe post flight refraction changes and the denominator is the number of astronauts on long duration flights reporting subjective visual changes between 1989 and 2009 (Table 2) (Mader, 2011)

The above incidence data was updated on 4/5/2017 with the integration of additional VIIP events (additional 19 ISS and 6 STS events) and crew at risk (additional 144 persons at risk) from the updated observed RWS data set.(Saile, 2017)

The SA Occurrence range min changed from 504 to 288. This change was based on the includsion RWS STS mission data. The shortest mission STS mission that was included in the data pull was STS 132 which was 12 days. This SA Occurrence range change made a change in the SA Peak Occurrence from 1008 to 900. The peak occurrence was calculation was (min+max/2)+24.

Seven cases of eye changes were described in detail after long duration space flight (identified as longer than 30 days). The following describes the pertinent findings in those seven cases. After 6 months aboard ISS, 7 astronauts complained of visual changes which included: 5 with disc edema, 5 with choroidal folds, 3 with cotton wool spots, 6 with nerve fiber layer thickening, and 6 with decreased near vision. Out of 5 astronauts with disc edema, 2 demonstrated bilateral grade 1 disc edema, 3 were unilateral grade 1, and one was unilateral grade 3. Disc edema was graded based on the modified Frisen scale (Mader, 2011)

Modified Frisen Scale is included in the CliFF Appendix

Information Regarding Prevention

Selection criteria

Disqualifying conditions in the eye category include: disease of either eye or supporting structure that may interfere with the performance of duties; any condition of the eyelids that impairs normal eyelid function; chronic blepharitis or blepharospasm; dacrocystitis; herpetic ulcer or history of herpetic ulcer; and inflammation of the uveal tract (iris, ciliary body, choroid), acute, chronic or recurrent with the exception of uncomplicated post-traumatic iritis. Conjunctivitis, chronic or recurrent, and chronic or recurrent keratitis require special consideration by the MSMB (International Space Station Program, 2011)

Disqualifying conditions in the neurologic disorders area include: any neurologic disorders 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. 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, 2011)

Vehicle requirements

Currently no in-flight treatment has been used for in-flight papilledema but “space anticipation glasses” are currently being used for decreased visual acuity. Based on multiple crew members with elevated intracranial pressure post-flight, it has been hypothesized that space flight induced intracranial hypertension may have contributed to papilledema (Mader, 2011)

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
Mader, 2011	1	Incidence
Saile, 2017	1	Incidence

Alternative Incidence Data

Studies of an American-based terrestrial population indicate that the incidence of idiopathic intracranial hypertension (IIH) is 0.9 cases per 100,000 person-years. In females aged 15 to 44, the incidence is 3.3 to 3.5 cases per 100,000 person-years. For males aged 15 to 44, the incidence is 0.3 cases per 100,000 person-years (Durcan, 1988); (Radhakrishnan, 1993).

The incidence of IIH is greater in obese individuals. For obese females aged 15 to 44, the incidence is reported as 7.9 cases per 100,000 person-years. For obese females aged 20 to 44, the incidence is 14.9 to 19.3 cases per 100,000 person-years. For obese males aged 20 to 44, the incidence is 1.5 cases per 100,000 person-years. Of the patients in the studies, 67% to 70% were obese (Durcan, 1988); (Radhakrishnan, 1993).

A recent study of 2 groups of atypical patients with IIH: those with a normal body mass index (BMI) and those at least 50 years of age included 407 consecutive adult patients. 18 IIH patients had normal BMI and 19 (5%) were 50 years or older. No patient with IIH with a normal BMI had severe visual loss in either eye. Older patients were less likely to receive any treatment and they were more likely to have persistent disc edema at last follow-up (median Frisén grade: 1 vs. 0, $p = 0.002$), but had similar, if not better, visual outcomes compared with younger patients. The authors concluded that patients with normal body mass index and those 50 years or older make up a small proportion of patients with idiopathic intracranial hypertension (IIH), but appear to have better visual outcomes than more typical patients with IIH. 17% of subjects (n 3) with BMI less than 25 received CSF shunting, and 11% (n 2) optic nerve sheath fenestration (Bruce, 2010).

A multicenter study to compare the characteristics of idiopathic intracranial hypertension (IIH) in men versus women included 721 consecutive patients, including 66 men (9%) and 655 women (91%). Visual acuity and visual fields at presentation and last follow-up were significantly worse among men. The relative risk of severe visual loss for men compared with women was 2.1 (95% CI 1.4–3.3, $p = 0.002$) for at least one eye and 2.1 (95% CI 1.1–3.7, $p = 0.03$) for both eyes. Logistic regression supported sex as an independent risk factor for severe visual loss. The authors concluded that men with idiopathic intracranial hypertension (IIH) are twice as likely as women to develop severe visual loss. Men and women have different symptom profiles, which could represent differences in symptom expression or symptom thresholds between the sexes. 15% of men (n 10) received CSF shunting, and 21% (n 14) optic nerve sheath fenestration vs. 16% and 15% respectively among women. (Bruce, 2009)

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 %: 85.37 - 87.81)	100	2 - 3	0 - 7	72 - 372 - 672	0 - 7	0	0
ISS-based Treatment (worst case scenario %: 12.19 - 14.63)	100	2 - 3	28 - 85	72 - 372 - 672	28 - 85	0 - 1	0
Untreated Best Case	N/A	N/A	0 - 27	72 - 372 - 672	0 - 27	0	0
Untreated Worst Case	N/A	N/A	28 - 85	72 - 372 - 672	28 - 85	0 - 1	0

[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 visual acuity changes and/or papilledema grades 0-2.

The worst case scenario is visual acuity changes and papilledema grades 3 or above.

The **percentages of how often best versus worst case scenario occur** based on Real World System data set, there were 25 events and 5 of them were worst case. Since we now have worst case scenarios, which did not have before, we can use the empirical data so the worst case scenario would be 20% (5/25). Thus the best case scenarios would be 80% (20/25) (Saile L., 2017).

Best Case Comments

The functional impairments calculation for Visual Impairment and/or Increased Intracranial Pressure (VIIIP) combines both the IMM mild and severe non-space adaptation templates and deviates from the standard template. Best case and untreated best case scenarios are mild; while worst case and untreated worst case are severe. Impairments of the Visual System and of the Whole Person are based on Table 12-10, p.307. On Clinical Phase (CP) II best case is assigned class 0; worst case classes 2-4; untreated best case classes 0-1; untreated worst case classes 2-4. No changes are expected during CP III; thus impairments are the same as in CP II for all scenarios. (American Medical Association, 2008)

By definition, in Clinical Phase I, FI is 100%. Duration to follow procedures specified in ISS checklist, i.e. dilated Panoptic video fundoscopy, visual acuity, eye ultrasound, is estimated in 2-3 hours (Ebert, 2012). During Clinical Phase II, FI is estimated at 0 to 7%. Based on currently available space flight data, this impairment is expected to persist for the duration of the mission (Mader, 2011). Duration is estimated at 72-672 hours, 3 to 28 days. In Clinical Phase III, FI remains 0 to 7%. EVAC and LOCL are not expected for the best case scenario.

Worst Case Comments

The functional impairments calculation for Visual Impairment and/or Increased Intracranial Pressure (VIIIP) combines both the IMM mild non-space adaptation and severe templates and deviates from the standard template. Best case and untreated best case scenarios are mild; while worst case and untreated worst case are severe. Impairments of the Visual System and of the Whole Person are based on Table 12-10, p.307. On Clinical Phase (CP) II best case is assigned class 0; worst case classes 2-4; untreated best case classes 0-1; untreated worst case classes 2-4. No changes are expected during CP III; thus impairments are the same as in CP II for all scenarios. (American Medical Association, 2008)

By definition, in Clinical Phase I, FI is 100%. Duration to follow procedures specified in ISS checklist, i.e. dilated Panoptic video fundoscopy, visual acuity, eye ultrasound, is estimated in 2-3 hours (Ebert, 2012). During Clinical Phase II, FI is estimated at 28 to 85%. This event will be classified as Class IIb or IIc; indicating that it may require the astronaut to return at next available opportunity or may necessitate emergent evacuation if it does not improve or worsens (Johnston, 2008). Based on currently available in-flight data, this visual impairment is expected to persist for the duration of the mission (Mader, 2011). Our estimated duration is 72 to 672 hours, 3 days to 4 weeks to cover both Class IIb and Class IIc probabilities. In Clinical Phase III, FI is remains 28-85%. Hospitalization has occurred among the astronaut corps for transient exercise induced visual loss (Johnston, 2008); no relationship to idiopathic intracranial hypertension (IIH) is made, but it serves as reference because the event was vision loss. No EVAC has occurred to date for VIIP cases. However, EVAC would be considered for progressive worst case scenarios of VIIP. Terrestrially, CSF shunting was performed in 15% to 17% of IIH cases, and optic nerve eye sheath fenestration was performed in 11% to 21% of IIH cases. (Bruce, 2010); (Bruce, 2009). Therfore, EVAC is estimated as 0 to 21% to account for uncertainty. Loss of crew life is not expected for this medical condition.

Untreated Best Case Comments

The functional impairments calculation for Visual Impairment and/or Increased Intracranial Pressure (VIIIP) combines both the IMM mild non-space adaptation and severe templates and deviates from the standard template. Best case and untreated best case scenarios are mild; while worst case and untreated worst case are severe. Impairments of the Visual System and of the Whole Person are based on Table 12-10, p.307. On Clinical Phase (CP) II best case is assigned class 0; worst case classes 2-4; untreated best case classes 0-1; untreated worst case classes 2-4. No changes are expected during CP III; thus impairments are the same as in CP II for all scenarios. (American Medical Association, 2008)

Duration, EVAC and LOCL are similar to the treated best case scenario. During Clinical Phase II and III, without treatment on board (space anticipation glasses), FI is estimated at 0 to 27%. EVAC and LOCL are not expected.

Untreated Worst Case Comments

The functional impairments calculation for Visual Impairment and/or Increased Intracranial Pressure (VIIIP) combines both the IMM mild non-space adaptation and severe templates and deviates from the standard template. Best case and untreated best case scenarios are mild; while worst case and untreated worst case are severe. Impairments of the Visual System and of the Whole Person are based on Table 12-10, p.307. On Clinical Phase (CP) II best case is assigned class 0; worst case classes 2-4; untreated best case classes 0-1; untreated worst case classes 2-4. No changes are expected during CP III; thus impairments are the same as in CP II for all scenarios. (American Medical Association, 2008)

Because there is no current treatment on board, FI, duration, EVAC and LOCL are similar to the treated worst case scenario. During Clinical Phase II, FI is estimated at 28-85%. Duration is 72-672 hours. In Clinical Phase III, FI remains 28-85%. EVAC 0-21% and LOCL 0%.

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
Johnston, 2008	2	EVAC
Bruce, 2010	4	EVAC
Bruce, 2009	4	EVAC
Saile L., 2017	1	BCWC

Additional Comments

Diagnosis of elevated intracranial pressure in-flight remains a current challenge. Additional research involving imaging and idiopathic intracranial hypertension (IIH), revealed a strong specificity of posterior globe flattening and diagnosis of IIH. In a terrestrial study presence of posterior globe flattening on contrast-enhanced magnetic resonance venography (MRV) increased the odds of having IIH by 50-fold. Specificity of posterior globe flattening on MRV and diagnosis of IIH was 100% and sensitivity was recorded at 43.5% (Agid, 2006).

Although MRI technology on ISS is currently not available and invasive testing such as lumbar punctures is still too risky in-flight, research into use of ultrasonography is currently ongoing. Review of recent literature into the subject has provided positive results into the accuracy of ultrasonography and diagnosis of raised intracranial pressures. A recent NASA study has confirmed that in a porcine model sonography is a feasible noninvasive method for evaluating acute changes in intracranial pressure (Hamilton, 2011). A meta-analysis published in 2011 (Dubourg, 2011) reviewed 6 studies and 231 patients to evaluate the efficacy of ultrasonography of optic nerve sheath diameter (ONSD) and diagnosis of intracranial hypertension. This study determined a mean sensitivity of 90% and specificity of 85% for intracranial hypertension. It also showed that the technique is reproducible and had a median intra-observer reliability of 0.2 mm and inter-observer reliability of 0.2 to 0.3 mm. Another study (Bauerle, 2011) showed a similar sensitivity of 90% and specificity of 84% for detecting idiopathic intracranial hypertension in patients with a greater than 5.8 mm ONSD. This study also showed the potential usefulness of ultrasonography in monitoring treatment of elevated intracranial pressure.

Research is continuing to discover new ways to assess papilledema. Current practice assesses the degree of papilledema by the Frisén scale and fundoscopic examination. A 2011 study showed that ultrasonography had a high degree of sensitivity to differentiate papilledema from other causes of swollen discs (Neudorfer, 2011). It has also been shown that optical coherence tomography (OCT) may allow for more accurate staging of early lower grade abnormalities (Scott, 2010). Although OCT is currently unavailable on ISS, it has been suggested by the Visual Impairment Pressure Summit and is under assessment by the space medicine hardware team (Fogarty, 2011)

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
BZK wipes	1	1	60	Yes	No	to wipe contact end of Scanhead
Cyclopentolate 1% 15mL bottle	0.039	0.08	1	Yes	Yes	Pupil dilation for exam
Eye Chart	1	1	1	No	Yes	evaluate vision
Otoscope (Head, Handle, and USB cable)	1	1	1	No	Yes	Light source for eye exam
Penlight	1	1	2	No	Yes	eye exam
Penlight Blue Filter	1	1	2	No	Yes	eye exam
Proparacaine eye drops 0.5%, 15mL bottle	0.013	0.013	1	No	No	eye anesthetic
Refresh artificial tears (Carboxymethylcellulose) 0.5%, 0.4mL bottle	1	1	40	Yes	Yes	to rinse eye
Space anticipation glasses	1	1	6	No	Yes	to compensate for visual changes (hyperopic shift)
Tonometer	1	1	1	No	Yes	to measure the pressure inside the eye, which is called intraocular pressure (IOP)
Tonometer tip cover	1	1	150	Yes	Yes	to protect the eye while using the tonometer
Tropicamide 1%	1	1	2	Yes	Yes	to dilate pupil prior to eye exam
Ultrasound machine	1	1	1	No	Yes	To evaluate posterior globe flattening and optic nerve sheath diameter

Resource Comments

Based on multiple crew members with elevated intracranial pressure post-flight, it has been hypothesized that space flight induced intracranial hypertension may contributed to papilledema (Mader, 2011). Therefore acetazolamide has been deemed a possible treatment. Further studies are needed to consider the risks of using acetazolamide in-flight. Elevations in creatinine have been observed in astronauts post-flight (Gans, 2011). It has been theorized that due to an already elevated calcium load on astronauts' kidneys, acetazolamide may increase the risk for kidney stones/kidney damage in-flight (Clark, 2008)

ISS Medical checklist procedures include the use of tonometer, visual acuity and visual fields testing charts, ultrasound and Panoptic Ophtalmoscope to perform the eye exam (Mission Operations Directorate (MOD), 2011).

All resources are available on board; although some are part of the personal IMAK kits.

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	1
Functional Impairment	3
Best Case / Worst Case	1
EVAC / LOCL	3.33333333333333
Resources	2
QUALITY OF EVIDENCE	**2.06666666666667**

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

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