Herpes Zoster Reactivation (shingles) Cliff

Branch Baseline

Herpes zoster is infection that results when varicella-zoster virus reactivates from its latent state in a posterior dorsal root ganglion. The first infection of the varicella-zoster virus results in chicken pox. Reactivation of this virus in the cranial nerve or dorsal root ganglia results in a painful rash known as herpes zoster (HZ) (Insinga, 2005).

To date there have not been any confirmed cases of herpes zoster reported in the US space program (Powers, 2010). Systemic and topical antiviral agents, and analgesics are available on ISS (International Space Station Integrated Medical Group, 2006).

Incidence Data Included in the Model

The model imports the following incidence information from the IMM database: incidence data category, space adaption status, incidence data, incidence and occurrence distribution data and incidence data characteristics. Data category defines the type of data available for incidence calculations (i.e. raw data vs. fixed data). Space adaptation identifies medical events that onset occurs in the first 5 days of flight and does not reoccur. Incidence values vary by data category and define the number of medical events per person-year or medical events per person-at-risk for each medical condition. Incidence values can be modified by crew characteristics such as gender. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crew member in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the IMM Technical Description Document.

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

Distribution Data	
Incidence:	Gamma
Occurrence:	Poisson

Data Characteristics	
Events:	3
Person Years:	45.49
Space Flight Incidence Rate (Events / Person Years):	3 / 45.49 = 0.065948560123104

Incidence Comments

The source fo othe incidence data is a compliation of available in flight medical events (Walton, 2010).

Integrated real world system incidence data (Saile, 2017).

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

Information Regarding Prevention

Disqualifying conditions include: Any acute or chronic infections or any communicable disease until healed and not associated with functional deficit or communicable state; recurrent corneal ulcers including herpetic ulcers; infections of the skin, systemic or superficial, if communicable, extensive, or not amenable to treatment (International Space Station Program, 2009).

Contingency measure(s): The Health Stabilization Program (implemented for Apollo 14) requires partial isolation of the crew in the weeks prior to launch. The crew is limited to interact with selected and screened primary contacts. This program is effective for reducing the number of acute infections. However, latent viruses are already integrated into the host cells prior to selection. One case of herpes zoster rash was identified during the pre-flight isolation period (Hawkins, 1975)(Mehta, 2004).

Zostavax, a new vaccine for the prevention of HZ and post herpetic neuralgia (PHN), was approved by the FDA in May 2006. The vaccine contains live attenuated Oka/Merck varicella zoster virus (VZV) virus. Each individual receives a 0.65 mL SC injection containing 19 400 PFU. Vaccination is recommended for persons reporting a previous episode of zoster (Harpaz, 2008).

The Shingles Prevention Study was a randomized, double blind, placebo controlled Phase 3 study. There were a total of 38 546 patients aged 60 years or older who were randomized to receive the vaccine. The mean follow up time was 3.1 years. The primary outcomes were prevention of HZ / PHN and burden of disease (Harpaz, 2008) (Oxman, 2005).

Another proposed countermeasure is the use of active hexose correlated compound; a nutritional supplement extracted from Basidiomycetes mushrooms. There is limited clinical evidence that it could serve as a functional biological response modifier. Specifically, it has been shown to increase the total number of dendritic cells and enhance the activity of natural killer cells (Terakawa, 2008). Although the exact mechanism is not understood it may induce a Th1 differentiation of the immune system. This could help offset the proposed effects of space flight in the immune system. One study demonstrated that hind limb-unloaded mice showed enhanced resistance to Klebsiella (K) pneumoniae (Aviles, 2003). Further confirmation is required in longer, randomized, placebo controlled trials.

Other: Several studies have demonstrated subclinical reactivation of VZV in astronauts. In addition, multiple complications of herpes zoster have potential for significant mission impact.

Latent virus infections were first mentioned by Ginsberg in 1971 (Ginsberg, 1971). In fact, an episode of thoracic herpes zoster occurred 2 days prior to space flight in a healthy 47 year old astronaut among 81 astronauts. More specifically, subclinical reactivation of VZV has been identified. Saliva samples were examined for VZV DNA in 8 astronauts (7 men and 1 woman) before, during, and after 3 STS missions. During and after space flight 61 of 200 (30%) of saliva samples were positive for VZV DNA in all 8 astronauts (Mehta, 2004).

Asymptomatic VZV shedding has also been identified. In another study, saliva samples were examined for VZV DNA and infectious VZV in 3 astronauts before, during, and after a 13 day STS mission. During and after space flight VZV DNA was detected in 2 of the 3 astronauts. Infectious VZV was also cultured from one of the post flight samples. Interestingly, the third astronaut had previously developed HZ prior to the flight (Cohrs, 2008).

A further study demonstrated the reactivation of VZV without an increase in VZV antibodies. Saliva samples were examined for VZV DNA before, during, and after a 14 day Soyuz taxi mission. There was a significant increase in VZV DNA during and after space flight without a significant increase in VZV antibodies (Mehta, 2007).

Incidence Level of Evidence (LOE)

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

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

Alternative Incidence Data

One Herpes Zoster prodromal phase, was anecdotally reported in ISS, the rash phase occurred post flight but it is unconfirmed (Powers, 2010).

A bayesian analysis was done in 2010 at Glenn Research Center. HZ is a skin disease more commonly known as shingles. While the cause for reactivation is unknown, higher incidence rates are found among the elderly and reactivation is generally associated with a weakened immune system. Due to the virus living in the nerve, HZ is extremely painful. To ensure enough medications are supplied for any and all shingles outbreaks during a space mission, the probability of HZ incidences must be calculated.

To improve the estimate of the rate of occurrence in the astronaut corps and provide an approximation suitable for use in the GRC-IMM modeling effort, the following approach was taken with the aid of the numerical Bayesian update code WinBUGS. The first step was to perform a Bayesian update on the pre-flight astronaut data for HZ incidence with the general population data from Insinga et al (Insinga, 2005)An update was performed for the male, the female, and the total data. The posteriors from this step described the incidence rate of HZ among the astronaut corps during pre-flight. The means, 5^{th} percentiles, and 95^{th} percentiles from this first step then served as the priors for the second step and were used to perform a Bayesian update on the in-flight astronaut data. This update was performed once for each gender category, and yielded the incidence rates of HZ among the astronauts while in-flight. . The mean rate for HZ per person-year for males, females, and both are 0.0025, 0.0032, and 0.0029, respectively (Gilkey, 2010).

This model should be considered rather limited because it assumes an average rate of HZ. The understanding of this limitation of this model is necessary for any use of this model. In spite of the limitations, this model is likely a reasonable approximation of HZ incidence. This model could also be used as a baseline for any future studies relating to HZ (Gilkey, 2010).

Perez-Farinos et al. - In the period from 1997 to 2004, a total of 9856 cases of varicella and 1798 cases of herpes zoster (HZ) were reported to the Madrid Region SGPN. The standardized annual herpes zoster incidence rates ranged from 249.9 (95% CI: 217.9 – 282.0) to 359.4 (95% CI: 322.3 – 396.6) cases per 100000 person-years (Figure 1 in Perez-Farinos). In all, 59.2% of cases occurred among females, and 40.8% among males. We included the 2004 rate of 359.4 per 100,000 in 2004 (Fig 1). Peak incidence is 75-84 followed by 65-74 age cohort (Fig 5 in Perez-Farinos') (Perez-Farinos, 2007).

Yawn - Retrospective study with a total of 1669 adult residents with a confirmed diagnosis of HZ were identified between January 1, 1996, and December 31, 2001, in Olmstead County. Most (92%) of these patients were immuno-competent and 60% were women. When adjusted to the 2005 US adult population, the incidence of HZ was 3.6 per 1000 person-years (95% confidence interval, 3.4-3.7), with a temporal increase from 3.2 to 4.1 per 1000 person-years from 1996 to 2001. Incidence rate by age cohort is 2.3/1000 for the 40-49, 4.7 for the 50-59, and 7.1 for the 60-69 age cohorts respectively. Table 4; the incidence of HZ and the rate of HZ-associated complications increased with age, with 68% of cases occurring in those aged 50 years and older. Post herpetic neuralgia occurred in 18% of adult patients with HZ and in 33% of those aged 79 years and older. Overall, 10% of all patients with HZ experienced 1 or more non pain complications (Yawn, 2007).

Insinga identified 9,152 incident cases of HZ (3.2 per 1,000 person-years) (95% confidence interval [CI], 3.1 to 3.2 per 1,000). Annual HZ rates per 1,000 person-years were higher among females (3.8) than males (2.6) (P<.0001). HZ rates rose sharply with age, and were highest among individuals over age 80 (10.9 per 1,000 person-years) (95% CI, 10.2 to 11.6). The incidence of HZ per 1,000 person-years among patients with evidence of recent care for transplantation, HIV infection, or cancer (10.3) was greater than for individuals without recent care for these conditions (3.0) (P<.0001).

Insinga presented rate per 1000 person-years adjusted for 2000 US population (95% CI) by age: 40.49 2.9 (2.7, 3.0), 50-59 4.6 (4.4, 4.8), 60-69 6.9 (6.6, 7.2) (Table 3 in Insinga) (Insinga, 2005).

Mullooly estimated age-specific herpes zoster (HZ) incidence rates in the Kaiser Permanente Northwest Health Plan (KPNW) during 1997–2002 and tested for secular trends and differences between residents of two states with different varicella vaccine coverage rates. Herpes zoster incidence rates per 100,000 person-years by age and sex, 1997–2002, KPNW were age 40-49, male 296.6, female 326.1; age 50-59, male 474.8, female 602.8 , with 95% confidence interval. (Fig 1 in Mullooly's) Washington residents by age group 40–49 348.3 SE 44.5; 50-59 595.9 SE 59.5 (Mullooly, 2005).

The gender specific incidence rate was consistently higher for female, around 60% versus 40% male. Incidence increases with age, but rates are not consistent across studies.

While these general population figures are a decent guideline, it is important to recognize that astronauts are in excellent health, so their incidence rate may not be the same. Many cases of zoster occur in the 60+ years population, which is not typical of the astronaut pool.

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 %: 50 - 75)	100	1	0 - 16	168 - 204 - 240	0	0	0
ISS-based Treatment (worst case scenario %: 25 - 50)	100	1 - 2	2 - 38	240 - 480 - 720	0 - 16	1 - 3	0
Untreated Best Case	0	0	2 - 38	168 - 204 - 240	0 - 16	0	0
Untreated Worst Case	0	0	18 - 59	240 - 480 - 720	18 - 59	100	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 defined as having an uncomplicated course of herpes zoster which resolves spontaneously over the course of several days and causes minimal disturbance with localized pain.

The **worst case scenario** is defined as a prolonged course of herpes zoster accompanied by symptoms of either persistent disruptive pain, e.g. post herpetic neuralgia (PHN), or ocular and neurological complications (peripheral motor neuropathy, Ramsay Hunt syndrome, or HZ ophthalmicus).

Most common complications are ocular and neurological as well as skin super-infections (Weinberg, 2007). There is no agreement in the incidence of complications. PHN increases with age, 6.5% for the general population and 11.7% for the 55-74 age cohorts. Up to 18% of adults have PHN with duration of 30-90 days and 10% of non-pain complications (Yawn, 2007). 3% of patients with HZ are hospitalized (Harpaz, 2008) (Yawn, 2007). Eye involvement reports also varied: 10-25% Yawn (Yawn, 2007); 10-20% (Liesegang, 2008); and 5-10% (Insinga, 2005).

The **best and worst case scenario percentages are** based on Real World System data set, there were 2 events and 1 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 50% (1/2). Thus the best case scenarios would be 50% (1/2) (Saile L., 2017).

Because Herpes Zoster causes severe pain the functional impairments (FI) calculation deviates from the IMM standard template. Skin disorders ratings are based on Table 8-2 p.166 (American Medical Association, 2008). Complex Regional Pain Syndrome (UEI) is based on Table 15-26, p.454, Table 15-24 and Table 15-25 in p 453. UEI was selected because majority of Herpes Zoster cases affect the trunk. The CRPS (UEI) ratings are then converted to percentage of Whole Person Impairment (WPI), which are based on Table 15-1, p 385 (American Medical Association, 2008). Combined FI ratings are calculated combining the Skin and Whole Body Impairment using the Combined Values Chart as indicated in Appendix A, pp 604-606. (American Medical Association, 2008)

Best Case Comments

In Clinical Phase I, a 100% functional impairment is recognized until the crewmember receives a diagnosis and appropriate treatment. Since HZ is a clinical diagnosis, an accurate diagnosis requires a medical history and a physical examination. During a space flight mission a PMC would be arranged allowing the flight surgeon to obtain a description of symptoms and a visual (through video) of the vesicular rash. The differential diagnosis would be broader if the characteristic vesicular rash was not present. Duration of approximately 1 hour encompasses the time it takes to diagnose and stabilize the affected crewmember using ISS checklist protocols, (International Space Station Integrated Medical Group, 2006). In Clinical phase II, FI is estimated in 0 to 16%, based in Skin impairments grading combined with Complex Pain Regional (CPRS-UE) pain as described. Class 0, 0%, Skin disorder signs have been present in the past but are currently present <1% of the time, no medication is necessary, no interference with activities of daily living. Class 1, 1 to 9%, signs and symptoms are present 1 to 30% of the time; may intermittently require treatment with topical medications; when signs and symptoms are present there is minimal interference with ADLs. Pain grading ranges from none to mild. Duration values are approximately 7-10 days (Dworkin, 2007) (Yawn, 2007). This is reasonable for a crew member with a limited clinical course with complete resolution and no expectations of an additional episode. For Clinical Phase III, full recovery is reached at this point in the disease, the FI for best case scenario is estimated to be 0% (American Medical Association, 2008). By definition, mission end state resulting in crewmember evacuation (EVAC), and/or loss of crew (LOC) is considered to be 0%.

Worst Case Comments

In Clinical Phase I, a 100% functional impairment is assigned similar to best case scenario. Duration of approximately 1 to 2 hours encompasses the time it takes to diagnose and stabilize the affected crewmember using ISS checklist protocols, (International Space Station Integrated Medical Group, 2006).

In Clinical phase II, FI is estimated in 2 to 38%, based in Skin impairments grading combined with Complex Pain Regional (CPRS-UE) pain as described. Class 1, 1 to 9%, signs and symptoms are present 1 to 30% of the time; may intermittently require treatment with topical medications; when signs and symptoms are present there is minimal interference with ADLs. Class 2, 11 to 27%, signs and symptoms are present > 30 to 60% of the time; often require treatment with topical or systemic medications; when signs and symptoms are present there is mild interference with some ADLs. Pain is graded from mild to moderate. Duration is estimated in 10-30 days (Dworkin, 2007) (Harpaz, 2008).

For Clinical Phase III, full recovery may not be reached, the FI for worst case scenario is estimated to be 0 to 16% based in Skin grading and mild pain (American Medical Association, 2008). Class 0, 0% Skin disorder signs have been present in the past but are currently present <1% of the time, no medication is necessary, no interference with activities of daily living. Class 1, 1 to 9%, signs and symptoms are present 1 to 30% of the time; may intermittently require treatment with topical medications; when signs and symptoms are present there is minimal interference with ADLs.

Mission end-state resulting in crewmember evacuation (EVAC) is estimated in 1-3%, considering the rate of hospitalization for herpes zoster in terrestrial population. In the studies revised, age ranges were not similar preventing to calculate an average hospitalization rate except for the high limit of the range. Our rate was obtained from studies in Spain,3.4% for age 30-49 and 2.3% for age 50--59 (Gil, 2009), Italy 1.31% for 0-49 cohort, 3.83% for the 50-54 cohort, and 5.28 for the a55-59 cohort, overall 1.3% of total cases among immune competent patients in the age range 0-85+ (Gialloreti, 2010), in the United Kingdom the hospitalization rate for the 45-64 age cohort is 2.4, and in Canada 2.8% (Brisson, 2001). Loss of crew (LOC) is considered to be 0%.

Untreated Best Case Comments

In Clinical phase II, FI is estimated in 2 to 38%, based in Skin impairments grading combined with Complex Pain Regional (CPRS-UE) pain as described. Class 1, 1 to 9%, signs and symptoms are present 1 to 30% of the time; when signs and symptoms are present there is minimal interference with ADLs. Class 2, 11 to 27%, signs and symptoms are present > 30 to 60% of the time; when signs and symptoms are present there is mild interference with some ADLs. Pain is graded from mild to moderate. Treatment is not available in this scenario. Duration is estimated in 7-10 days (Dworkin, 2007) (Harpaz, 2008). For Clinical Phase III, full recovery may not be reached, the FI for worst case scenario is estimated to be 0 to 16% based in Skin grading and mild pain (American Medical Association, 2008). Class 0, 0% Skin disorder signs have been present in the past but are currently present <1% of the time, no medication is necessary, no interference with activities of daily living. Class 1, 1 to 9%, signs and symptoms are present 1 to 30% of the time; when signs and symptoms are present there is minimal interference with ADLs. Mission end state resulting in crewmember evacuation (EVAC) and Loss of crew life (LOCL) is considered to be 0%.

Untreated Worst Case Comments

In **Clinical phase II, FI** is estimated in 18 to 59%, based in Skin impairments grading combined with Complex Pain Regional (CPRS-UE) pain as described. Class 2, 11 to 27%, signs and symptoms are present > 30 to 60% of the time; when signs and symptoms are present there is mild interference with some ADLs. Class 3, 30-42%, signs and symptoms are present > 60 to 90% of the time; when signs and symptoms are present there is moderate interference with some ADLs. Pain is graded as moderate to severe. This scenario requires treatment which is not available. Duration is estimated in 10-30 days (Dworkin, 2007) (Harpaz, 2008).

In **Clinical Phase III**, FI is same as in clinical phase II, 18 to 59%. EVAC is estimated to be 100% considering the need to treat the crew member and possible complications. LOCL is estimated in 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
Harpaz, 2008	4	BCWC
Gil, 2009	4	EVAC
Gialloreti, 2010	4	EVAC
Brisson, 2001	4	EVAC
Saile L., 2017	1	BCWC

Additional Comments

We searched PubMed using the keywords herpes zoster and incidence, herpes zoster and epidemiology, and herpes zoster and space medicine. We then refined by relevance and date. Individual searches were conducted for primary sources from several articles.

The Resource Table (RT)

Resource	Units Required Best Case	Units Required Worst Case	Units Available At Start Of Mission	Consumable	Essential	Rationale
Camera	1	1	1	No	No	To document rash, or wound
ECG Monitor (Device, USB Charge Cable, Lead Set Cable, Cue Card)	1	0	1	No	Yes	Measure and monitor ECG
Effexor XR (Venlafaxine XR) 75 mg capsules	0	60	60	Yes	Yes	Pain relief, post herpetic neuralgia,
Pack of 12 ECG electrodes	1	0	5	Yes	Yes	Measure and monitor ECG
Tylenol (Acetaminophen) 325 mg	28	0	150	Yes	Yes	Pain relief
Valacyclovir 1 gm tablet	21	21	60	Yes	Yes	Antiviral.
Vicodin HP (Hydrocodone/ Acetaminophen HP) 10 mg/660 mg	0	30	30	Yes	Yes	Pain relief

Resource Comments

Herpes Zoster treatment is not listed as a specific procedure in the ISS checklist but the resources were derived the content list in the med kit. Zovirax and Valtrex are included in the Contents List (Mission Operations Directorate (MOD), 2011). Of note, use of Zovirax ointment is not recommended in terrestrial clinical guidelines (Dworkin, 2007).

The ranges for quantity of analgesic medications were determined using a standard daily dose for 7-10 days and considering the resources available in the ISS medical resources and variability in severity of complications.

The pharmaceutical treatment of HZ incorporates antiviral and analgesic medication as required. Any confirmed case of HZ should initially be treated with antiviral medication within the first 48-72 hours (Dworkin, 2007). VZV antiviral medications are nucleoside analogues that are phosphorylated by viral thymidine kinases terminating viral DNA replication. The goal of therapy is to promote rapid healing of lesions, decrease severity of pain associated with acute neuritis and reduce the risk of developing PHN. Acyclovir is the prototypical antiviral medication but has poor bioavailability. Valacylovir, a pro-drug of acyclovir, has increased oral bioavailability and is the current standard of care for HZ. Dosing of Valacyclovir is 1000 mg PO 3 times a day (TID) for 7 days (Dworkin, 2007). At present, there is only one course of antiviral therapy available in the ISS medical supplies.

In the best case scenario a combination of Valacyclovir, acetaminophen, and ibuprofen would likely be adequate treatment for sustained analgesia. In comparison, a severe case of HZ or any of the worst case scenario complications would require additional analgesic medications. Although many of these medications are suitable for adequate analgesia they are disqualifying for performance of mission critical assigned tasks. This would effectively decrease the crewmember's FI for the duration of treatment in addition to any FI caused by the medical condition.

The pharmacotherapy for PHN has been reviewed in several systematic reviews (He, 2008) (Hempenstall, 2005) (Saarto, 2007). The current best evidence for analgesic efficacy is tricyclic antidepressants, opioids, Gabapentin, Pregabalin, and Tramadol. Besides opioids, none of these medications are available on the ISS. However, corticosteroids and other antidepressants are included in the ISS medical resources. But, in a Cochrane review of corticosteroids for preventing PHN, there was no significant difference between the corticosteroid and control groups for the presence of PHN after 6 months (RR 1.27, 95% CI 0.20 to 7.97). (He, 2008)Venlafaxine (Effexor), a SNRI antidepressant, would be a suitable alternative to standard of care tryciclics. A Cochrane review of antidepressants for neuropathic pain included 3 studies with pain relief measurements of Venlafaxine. The effectiveness showed a significant effect for Venlafaxine compared to placebo, RR 2.2 (95%CI 1.5 to 3.1) for neuropathic pain –not specific PHN related pain. (Saarto, 2007)The doses of Venlafaxine used were 75 mg, 150 mg and 225 mg.

Evidence based practice articles have included anti-epileptics (Dilantin) for treatment of post-herpetic neuralgia (Dworkin, 2007) (Harpaz, 2008) (Pavan-Langston, 2008) (Schmader, 2008) (Stankus, 2000); however they are not included in clinical guidelines (Dworkin, 2007).

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
Dworkin, 2007	3	Resources

Level Of Evidence

Input Data	LOE Average
Incidence	1
Functional Impairment	3
Best Case / Worst Case	2.5
EVAC / LOCL	4
Resources	2.5
QUALITY OF EVIDENCE	**2.6**

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

Reference List

Reference
American Medical Association. Guides to the Evaluation of Permanent Impairment. 6th ed. Chicago: American Medical Association Press; 2008.
American Medical Association. Skin. In: Rondinelli R, editor. Guides to the Evaluation of Permanent Impairment. 6th ed. Chicago: American Medical Association Press; 2008. p. 159-82.
American Medical Association. Upper Extremities. In: Rondinelli R, editor. Guides to the Evaluation of Permanent Impairment. 6th ed. Chicago: American Medical Association Press; 2008. p. 383-492.
Aviles H, Belay T, Fountain K, Vance M, Sun B, Sonnenfeld G. Active hexose correlated compound enhances resistance to Klebsiella pneumoniae infection in mice in the hindlimb-unloading model of spaceflight conditions. J Appl Physiol 2003 Aug;95(2):491-6.
Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 2001 Oct;127(2):305-14.
Cohrs RJ, Mehta SK, Schmid DS, Gilden DH, Pierson DL. Asymptomatic reactivation and shed of infectious varicella zoster virus in astronauts. J Med Virol 2008 Jun;80(6):1116-22.
Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007 Jan 1;44 Suppl 1:S1-26.
Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007 Dec 5;132(3):237-51.
Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis 2010;10:230.
Gil A, Gil R, Alvaro A, San MM, Gonzalez A. Burden of herpes zoster requiring hospitalization in Spain during a seven-year period (1998-2004). BMC Infect Dis 2009;9:55.
Gilkey KM, McRae MP, Griffin EA, Kalluri AS, Myers JG. Bayesian Analysis For Risk Assessment of Selected Medical Events in Support of the Integrated Medical Model Effort. Technical Paper. Cleveland, OH: National Aeronautics and Space Administration, Glenn Research Center; 2012. Report No.: NASA/TP-2012-217120.
Ginsberg HS. Immune states in long-term space flights. Life Sci Space Res 1971;9:1-9.
Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). 2008 Jun 6. Report No.: 57.
Hawkins WR, Zieglschmid JF. Clinical Aspects of Crew Health. In: Johnston RS, Dietlein LF, Berry CA, editors. Biomedical Results of Apollo. NASA SP-368 ed. Washington D.C.: NASA; 1975. p. 46-84.
He L, Zhang D, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2008;(1):CD005582.
Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2005 Jul;2(7):e164.
Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med 2005 Aug;20(8):748-53.
International Space Station Integrated Medical Group. Medical Checklist ISS- All Expeditions. Houston: National Aeronautics and Space Administration; 2008.
International Space Station Program. Medical Standards for ISS Crewmembers - MED Vol A. 3.2 ed. NASA; 2011.
Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. Ophthalmology 2008 Feb;115(2 Suppl):S3-12.
Mehta SK, Cohrs RJ, Forghani B, Zerbe G, Gilden DH, Pierson DL. Stress-induced subclinical reactivation of varicella zoster virus in astronauts. J Med Virol 2004 Jan;72(1):174-9.
Mehta SK, Pierson DL. Reactivation of Latent Herpes Viruses in Cosmonauts During a Soyuz Taxi Mission. MICROGRAVITY SCIENCE AND TECHNOLOGY 2007 May 6;XIX(5/6):215-8.
Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997-2002. Epidemiol Infect 2005 Apr;133(2):245-53.

Reference

NASA Mission Operations Directorate (MOD). International Space Station Integrated Medical Group Medical Checklist. Mission Operations Directorate (MOD), Systems Operations Data File (SODF) . 6-24-2011. Houston, TX, National Aeronautics and Space Administration (NASA).

Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005 Jun 2;352(22):2271-84.

Pavan-Langston D. Herpes zoster antivirals and pain management. Ophthalmology 2008 Feb;115(2 Suppl):S13-S20.

Perez-Farinos N, Ordobas M, Garcia-Fernandez C, Garcia-Comas L, Canellas S, Rodero I, et al. Varicella and herpes zoster in Madrid, based on the Sentinel General Practitioner Network: 1997-2004. BMC Infect Dis 2007;7:59.

Powers E. Zoster Case Notes. Watkins S, editor. 2010. 10-7-2010.

Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev 2007;(4):CD005454.

Saile L., Boley L, Kerstman E. Integration RWS ISS STS Observed Incidence V2. 2017.

Saile L., Boley L, Arellano J, Kerstman E. iMED Best and Worst Case Percentage Update. 2017.

Saile L, Boley L, Kerstman E. Integration RWS ISS STS Observed Incidence. 2017.

Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. J Pain 2008 Jan;9(1 Suppl 1):S3-S9.

Stankus SJ, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. Am Fam Physician 2000 Apr 15;61(8):2437-8.

Terakawa N, Matsui Y, Satoi S, Yanagimoto H, Takahashi K, Yamamoto T, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. Nutr Cancer 2008;60(5):643-51.

Walton M, Kerstman E, IMM. In-flight Compilation v20100414_Incidence_calculation. 2010.

Weinberg JM. Herpes zoster: epidemiology, natural history, and common complications. J Am Acad Dermatol 2007 Dec;57(6 Suppl):S130-S135.

Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 2007 Nov;82(11):1341-9.