Clinical Herpes Zoster in Antarctica as a Model for Spaceflight

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INTRODUCTION: Antarctica is a useful analog for spaceflight, as both environments are remote, isolated, and with limited resources. While previous studies have demonstrated increased asymptomatic viral shedding in both the Antarctic and spaceflight environments, clinical manifestations of reactivated viral disease have been less frequently identified. We sought to identify the incidence of clinical herpes zoster from viral reactivation in the Antarctic winter-over population.

METHODS: Medical records from the 2014 winter season were reviewed for the incidence of zoster in U.S. Antarctic personnel and then compared to the age-matched U.S. population.

RESULTS: Five cases of clinical herpes zoster occurred in the Antarctic Station population of 204 persons, for an incidence of 33.3 per 1000 person-years vs. 3.2 per 1000 person-years in the general population. Four cases were in persons under age 40, yielding an incidence of 106.7 per 1000 person-years in persons ages 30–39 compared to an incidence of 2.0 per 1000 person-years in the same U.S. age group.

DISCUSSION: Immune suppression due to the stressful Antarctic environment may have contributed to the increased incidence of herpes zoster in U.S. Antarctic personnel during the winter of 2014. Working and living in isolated, confined, and extreme environments can cause immune suppression, reactivating latent viruses and increasing viral shedding and symptomatic disease. Such changes have been observed in other austere environments, including spaceflight, suggesting that clinical manifestations of viral reactivation may be seen in future spaceflight.

KEYWORDS: viral reactivation, herpes zoster, isolation, confinement, extremes, spaceflight.

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Antarctica is a useful spaceflight analog. Personnel stationed in Antarctica are exposed to significant environmental stressors, isolation, and limited resources, similar to conditions found in spaceflight. Multiple previous studies have demonstrated that personnel working in isolated regions, including both Antarctica and space, can have dysregulation of stress hormones, cytokines, and other inflammatory markers that can lead to reactivation of latent viruses.[7,8,12]

For example, Shearer et al.[12] examined the balance between serum anti-inflammatory and inflammatory cytokines in 21 persons stationed at Australia's Casey Station in Antarctica during the Antarctic winter and found that the inflammatory response observed was likely suboptimal and insufficient to provide antiviral protection. This study suggested that these changes may have been associated with stress related to the winter isolation.[12] Similarly, Mehta et al.[8] demonstrated increased Epstein-Barr virus (EBV) shedding in the saliva of 16 subjects wintering at 2 Australian Antarctic stations.

There have also been several studies examining viral reactivation in Space Shuttle astronauts and, more recently, in astronauts flying long duration missions aboard the International Space Station (ISS). Examples of immunologic changes observed during spaceflight include altered plasma cytokines[3,7] and altered neutrophil and monocyte function.[6] Mehta et al.[7] demonstrated statistically significant elevation in measured

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plasma cytokines over baseline levels in astronauts on short-duration (9–14 d) flights.

In more recent work, Crucian et al.[3] examined the levels of various plasma cytokines and other immune markers in 28 astronauts during 6-mo missions aboard the ISS and concluded that there is a clear pattern of immune changes with spaceflight, though the exact mechanism of immune dysregulation is unclear. These immunologic changes may be associated with increased shedding of varicella zoster virus (VZV)[2] and EBV[11] during the stress of spaceflight.

In other work, an in vitro spaceflight model environment demonstrated that radiation and microgravity may also play a role in initiating viral reactivation.[1] The decreased immune function of crewmembers, combined with DNA damage from radiation and viral reactivation, may create a combination of factors that could increase the risk for reactivation of latent viruses.

While increased viral shedding is of scientific interest in these environments, there is concern that viral reactivation may lead to clinically significant manifestations in a setting where medical resources are limited. One virus that may reactivate with significant clinical impact is VZV. Most individuals are exposed to VZV during their early childhood, either through vaccination or clinically as chicken pox. After primary infection or vaccination, VZV becomes latent in the cranial nerves, dorsal roots, and autonomic ganglia.

The period of latency and subsequent reactivation of VZV varies from individual to individual, dependent upon viral load, time since initial exposure, re-exposure to VZV shed from the community, and advancing age.[4,5,9] VZV-specific immunity decreases with advancing age, immunosuppression, or stress. When immune function is sufficiently suppressed, VZV can reactivate at any ganglion in the neuraxis and erupt along the associated dermatome as the characteristic painful, vesicular rash of herpes zoster (HZ).[9]

The incidence of HZ between men and women has been varyingly reported in the literature as the same, and also as higher in women.[5] However, in the work by Insigna et al.,[5] the 30- to 39-yr-old age group has essentially the same incidence between men and women. In this work, the majority of cases occur in this age range.

HZ can present in a myriad of ways, making diagnosis and treatment in remote locations all the more difficult. Delayed treatment in healthy individuals is rarely fatal, but HZ can become painful to the point of incapacitation. Remote locations such as Antarctic stations and spaceflight missions have reduced capacity for diagnosis and treatment of disease because they lack the advanced diagnostic and treatment capabilities found in most Western medical facilities. Further, personnel may delay reporting of early manifestations of disease due to the increased work responsibilities and minimal staffing during winter in Antarctica or during spaceflight. These factors can lead to delayed diagnosis and intervention, and a subsequent increased risk for functional impairment and extended illness.

This paper will discuss the clinical manifestations of VZV reactivation leading to an increased incidence of clinical HZ seen in U.S. Antarctic personnel, likely related to stress-associated mechanisms. The clinical epidemiological data presented here demonstrates the problem of viral reactivation in isolated populations living in extreme environments, and further demonstrates a clinical issue associated with high viral load in remote, stressful environments that may also be seen in spaceflight.

METHODS

Data for this report were obtained from review of the patient register and medical records of individuals wintering over at U.S. Antarctic Program stations (McMurdo, Palmer, and South Pole) during the winter season from March to October 2014. Collected data include age, sex, and details of symptomatic HZ presentation. Population data were provided by the National Science Foundation's U.S. Antarctic Program. This work was classified as exempt research by the Office of Research Subject Protections Institutional Review Board at the University of Texas Medical Branch in Galveston, TX (UTMB IRB #14-0537).

Given the similar isolated, high-workload, and extreme winter conditions at each location, station populations were analyzed in aggregate. HZ incidence rates were calculated by dividing the number of diagnosed HZ cases by the number of person-years spent at U.S. Antarctic Program stations during the 2014 winter. Rates were then sex and age-adjusted to the 2010 U.S. population.[13] Regression analyses using a Poisson distribution were used to calculate 95% confidence intervals (CI) and to compare incidence of HZ among Antarctic personnel with the general U.S. population. All statistical analyses were performed using STATA version 12.0 (College Station, TX).

RESULTS

During the 2014 winter season, 204 personnel were stationed at U.S. Antarctic Program stations. The mean age of all personnel was 40 yr (range 20–70), and 75% ($N = 154$) were men. **Table I** shows the incidence of HZ overall and by age, and **Fig. 1** compares HZ incidence among the Antarctic personnel vs. the general U.S. population. There were five total cases of HZ in 2014, translating to a significantly higher ($P < 0.0001$) overall incidence rate of 33.3 cases per 1000 person-years (95% CI 10.8–77.8) compared to the general U.S. population rate of 3.2 per 1000 person-years (95% CI: 3.1–3.2[5]).

Four of the cases occurred in personnel ages 30–39 yr. The incidence rate in this age cohort was 106.7 cases per 1000 person-years (95% CI 29.1–237.4), which was significantly higher ($P < 0.0001$) than similar ages of individuals in the U.S. population, where the incidence rate was 2.0 cases per 1000 person-years (95% CI: 1.8–2.2[5]). The remaining case occurred in an individual in the 60–70 yr age range and translated to an incidence of 77.3 cases per 1000 person-years (95% CI 2.0–430.4)

Table I. Incidence of Herpes Zoster in U.S. Antarctic Personnel, Winter 2014.

AGE (yr)	NUMBER OF PERSONNEL	PERSON-YEARS	NUMBER HZ CASES (%)	RATE PER 1000 PERSON-YEARS* (95% CI)
20–29	46	28.1	0 (0.0)	-
30–39	61	36.7	4 (6.6)	106.7 (29.1 - 237.4)
40–49	49	29.7	0 (0.0)	-
50–59	37	21.9	0 (0.0)	-
60–69	11	6.7	1 (9.1)	77.3 (2.0 - 430.4)
Overall**	204	123.1	5 (2.5)	33.3 (10.8 - 77.8)

Overall and age-specific zoster cases in Antarctic personnel during the winter-over of 2014.
* Age-specific rates for all personnel are sex-adjusted to the 2010 U.S. Census.
** Overall rate is age- and sex-adjusted to the 2010 U.S. Census.

in that age group, which has an overlapping confidence interval for similar ages of persons in the general U.S. population, where the rate is 6.9 cases per 1000 person-years (95% CI 6.6–7.2[5]).

DISCUSSION

The incidence of HZ in winter-over personnel at U.S. Antarctic Program stations was 10 times the incidence in the general U.S. population, and the difference in the 30- to 39-yr-old age group was much greater still. This age group typically has a robust immune response that suppresses the VZ virus—until exposed to stressors. Winter-over is generally accepted as the most stressful period of residence in Antarctica[10] and was likely a major contributor. The single case of HZ in a person in the 60 to 69-yr-old age group, while possibly triggered by stress, was not unexpected, as this age group more readily manifests HZ due to decreasing immune response with age. These relationships are shown in the conceptual model of **Fig. 2** and suggest that viral reactivation under stress may be a common occurrence, even in younger and immunocompetent persons.

Previous studies in the Antarctic have evaluated the increased incidence of immune alterations and asymptomatic viral shedding in immunocompetent adults in Antarctica.[8,12] This study demonstrates symptomatic, clinical reactivation of VZV in an environment where only asymptomatic shedding has previously been published. This is particularly interesting given that Antarctic expeditioners undergo rigorous medical screening prior to deployment and are thus considered a generally healthy population. The U.S. population ranges from 63–100% seropositive for VZV, depending on the reporting method used.[4] The prevalence of latent VZV in U.S. Antarctic Program personnel is unknown; however, it likely mirrors the general U.S. population from which they are selected.

Due to the isolated environment and limited diagnostic and treatment capabilities, many persons in the Antarctic winter-over population may be at increased risk for a complicated or longer clinical course of reactivated HZ. Further, those personnel who are VZV seronegative prior to deployment are also at greater risk for a primary episode of VZV due to their own reduced immune function and potential novel virus exposure secondary to an increase in viral shedding from other station personnel.

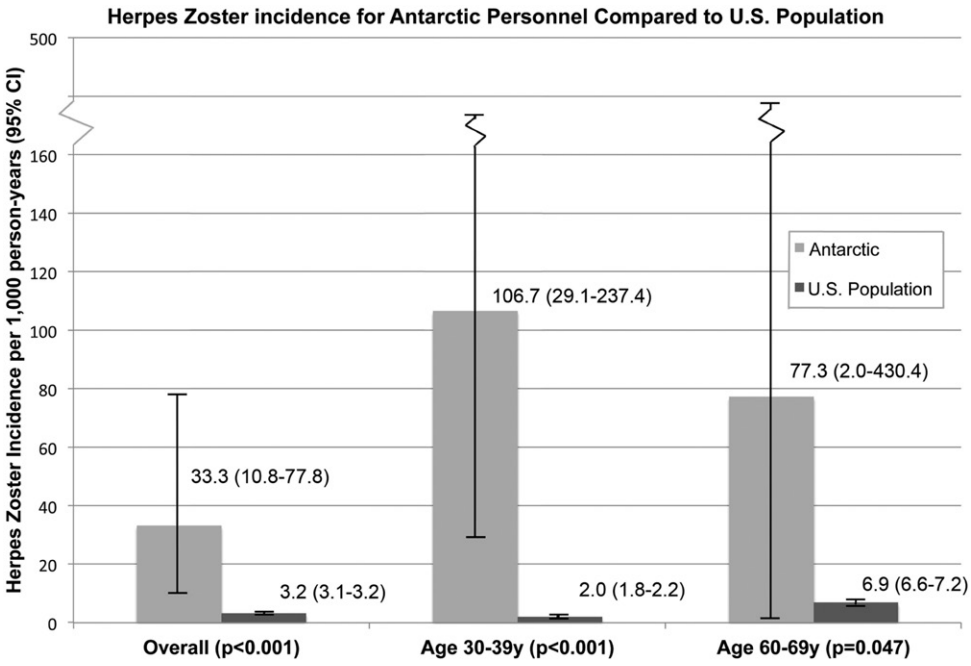

Fig. 1. Herpes zoster incidence for Antarctic personnel compared to U.S. population. Error bars represent the 95% confidence intervals.

The conceptual model of viral reactivation under stressful conditions shown in Fig. 2 was adapted from Gilden et al.[4] and Insinga et al.[5] Stress for deployed personnel in Antarctica is similar to other persons deployed to extreme environments. Stressors include isolation from their usual social context, confinement to the remote location, and exposure to an extreme physical environment; in combination, these stressors are referred to as I-C-E: Isolation–Confinement–Extremes.[10] The effects of stress on the body include the release of stress hormones (such as glucocorticoids, adrenaline, prolactin, and growth hormone), changes in the expression of cytokines, reduction of

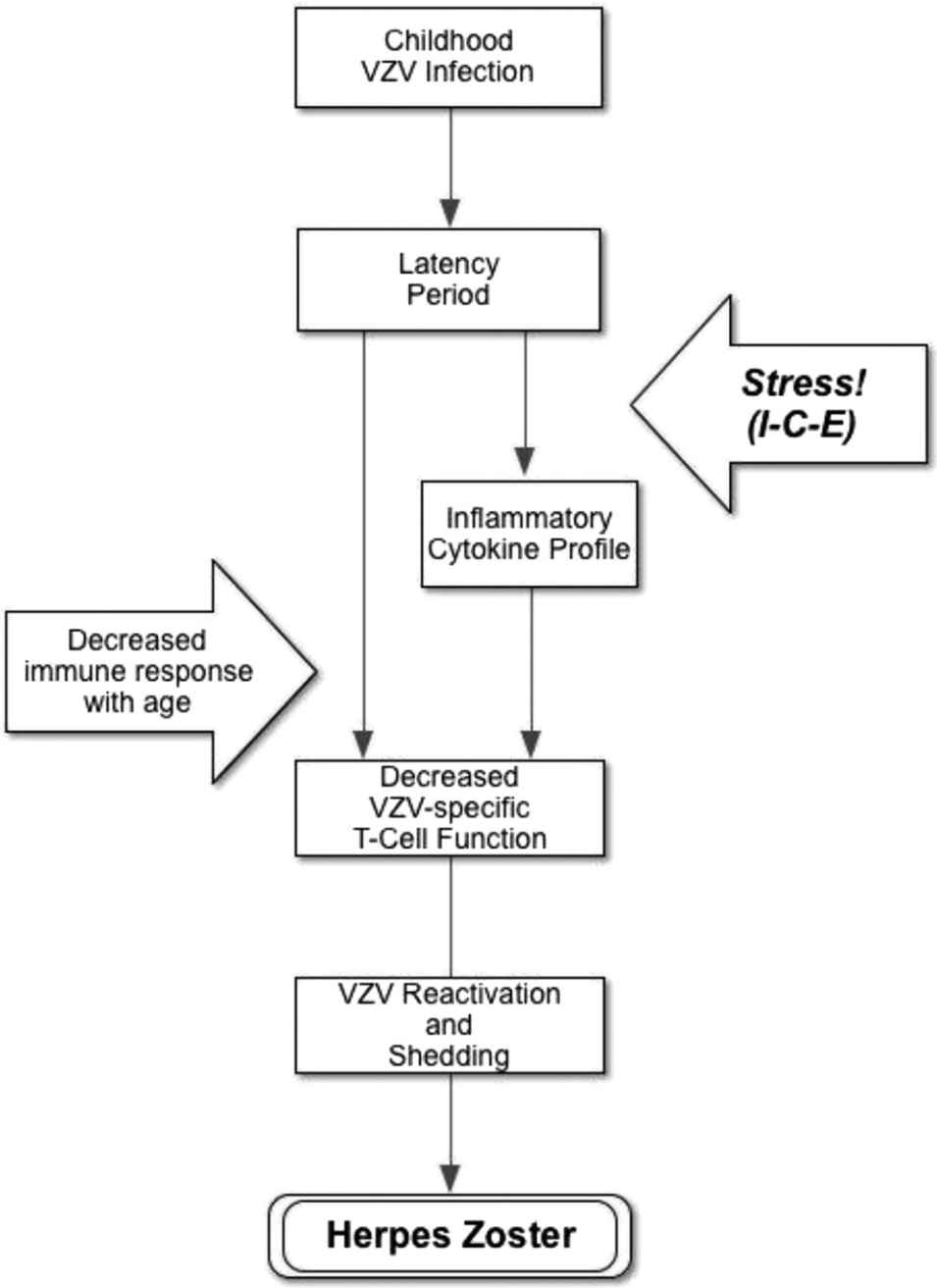

Fig. 2. Stress reactivation of herpes zoster. A conceptual model of viral reactivation under conditions of I-C-E, adapted from previous work by Gilden et al. and Insinga et al.[4,5] I-C-E, Isolation–Confinement–Extremes. VZV, Varicella zoster virus.

NK cell activity, reduced lymphocyte and antibody production, and reactivation of latent viruses.[9,14]

VZV-specific T-lymphocytes are important for maintaining suppression of VZV in ganglia;[4,9] thus, immunocompromised hosts are at greater risk for clinical manifestations of HZ. T-lymphocyte mediated immunity declines with age, which is why VZV reactivation is more common in the elderly. This may be related to immunosenescence or reduced numbers of circulating T-lymphocytes; however, is not necessarily related to decreased levels of VZV IgG antibodies.[4]

T-lymphocyte mediated immunity may also be suppressed under stressful conditions[14] such as conditions experienced by Antarctic personnel. As previous evidence has shown similar immune responses during spaceflight, this suggests that astronauts may also be at risk for clinical manifestations of reactivated viruses like VZV. Given that the spaceflight environment has even more limited medical resources than the Antarctic, this raises significant concerns regarding stocks of appropriate pharmaceuticals, the increased potential for a virus-naïve individual to experience the primary manifestations of viral illnesses, and the potential for significant mission impact with clinical manifestations of HZ or similar viral illnesses.

There are important limitations to the data presented here. A total of only 5 cases of HZ were observed in an Antarctic population of 204 persons. While this is a statistically significant increase in incidence compared to the general population, further analysis of subpopulation cohorts, including sex, job function, or similar, is severely restricted by small sample size. In addition, we do not know the age of initial exposure to VZV and whether the individuals in either the Antarctic or U.S. population data were vaccinated or infected through clinical disease, and therefore cannot comment on whether these factors played a role in reactivation incidence. Studies with more robust population data and larger sample sizes could better define such relationships. Finally, with previous work demonstrating comparable conditions and medical events between the Antarctic and spaceflight environments, we have presented a discussion regarding potential implications for spaceflight; however, it is unknown whether similar rates of clinical manifestations of disease will occur in the space environment.

While data are limited and further study is indicated, the results presented here suggest that viral reactivation with clinical manifestation is possible in both remote terrestrial environments and in spaceflight. The elevated incidence of clinical HZ

in winter-over personnel at U.S. Antarctic stations may be related to the stress inherent in I-C-E environments, which can result in the activation of the neurohumoral stress axis, down regulation of T-cell mediated immunity, and reactivation of latent viruses.

The ability to treat the clinical manifestations of viral reactivation in an austere setting is crucial, and antiviral medications and other pharmaceutical interventions that are currently an important part of the U.S. Antarctic medical capability should also be available during long-duration spaceflight. Further, due to the potential for increased morbidity from HZ in these isolated environments, prophylactic vaccination against HZ for personnel operating under conditions of I-C-E may be helpful. While spaceflight-specific data would be ideal, Antarctica may be the best place on Earth to perform these investigations on a larger and more cost-effective scale.

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