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Research paper

Pre-travel counseling for immunocompromised travelers: A 12-year single-center retrospective review☆

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KEYWORDS
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Abstract *Background:* Immunocompromised travelers (ICTs) are medically complex and challenging for travel medicine providers. Our study hypothesizes that ICTs have high-risk travel itineraries and do not have adequate immunity against vaccine-preventable infections.
Methods: This retrospective review of 321 ICTs from 2004 to 2015 included patients with solid organ transplant (SOT, n = 134), connective tissue disease (CTD, n = 121), inflammatory bowel disease (IBD, n = 46), and human immunodeficiency virus (HIV, n = 20). Variables included immunosuppressive medications, hepatitis A and B vaccination and serology, gamma-globulin use, and antimalarial and antidiarrheal prophylaxis. Chi-square analysis was used for categorical variables and Kruskal–Wallis for continuous variables.
Results: Malaria-endemic regions accounted for 38.9% (125/321) of travel destinations. High-risk activities were planned by 37.4% (120/321) of travelers. A significant proportion of HIV patients [70.0% (14/20)] visited friends and relatives, whereas other ICTs traveled for tourism. Hepatitis A and B vaccination rates were 77.3% (248/321) and 72.3% (232/321). Post-vaccination hepatitis A and B serologic testing were completed by 66.1% (41/62) and 61.1% (11/18) of travelers, respectively.
Conclusion: ICTs demonstrate differences in travel patterns and risk. Serologic testing was uncommon, and vaccination rates were low. Providers should screen ICTs early for upcoming travel plans and advise vaccine completion prior to departure.

Abbreviations: ICT, immunocompromised traveler.

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Highlights

- Immunocompromised patients have high-risk travel patterns.
- There were low rates of hepatitis A and B vaccination and serologic testing.
- Healthcare providers should screen immunocompromised patients early for upcoming travel plans.

Introduction

In 2015, there were 1.2 billion international arrivals [1], and of those, 60 million were undertaken by American citizens [2]. There has also been an increase in the number of immunocompromised individuals, such as recipients of solid organ or stem cell transplants [2]. In a 2008 study, 27% of solid-organ transplant (SOT) recipients reported international travel [3]. Although travel-related infections can occur in a quarter of international travelers [4], as few as 8% seek pre-travel consultation [5]. Compared to immunocompetent hosts, immunocompromised travelers (ICTs) are at an even higher risk of travel-related or opportunistic infections; therefore, pre-travel consultation for this population is especially important. However, according to a 2015 Australian survey of 254 ICTs, only 68.6% sought pre-travel consultation [6]. Pre-travel healthcare for ICTs presents various challenges, such as contraindications to live vaccines; inadequate serologic response to inactivated vaccines; and drug interactions among immunosuppressive, antimalarial, and antidiarrheal medications [6—8]. However, pre-travel consultation is strongly indicated, as this may help ICT avoid acquiring serious infections abroad [9].

Our single-center study aims to assess pre-travel healthcare among ICTs at the Mayo Travel and Tropical Medicine Clinic (TTMC). A prior study was performed on 49 ICTs seen at the Mayo TTMC between 4/1/1999 and 12/1/2003. This study found an overall low rate (45.0%) of completion of hepatitis B vaccination among SOT recipients [10]. The current study builds upon the results of this prior study. Our hypothesis was that ICTs have high-risk travel itineraries and do not have adequate immunity against vaccine-preventable infections.

Methods

Study design, setting, and participants

This single-center retrospective study included adults over 18 years of age who received pre-travel counseling at the Mayo TTMC between 1/1/2004 and 12/31/2015. All travelers who were immunocompromised were identified through the Advanced Cohort Explorer (ACE), which is an institutional search engine for medical records. Immunocompromising conditions included solid organ transplant (SOT), inflammatory bowel disease (IBD), connective tissue disease (CTD), and human immunodeficiency virus (HIV). The following were excluded due to low sample size (less than 5 cases): patients on chemotherapy for malignancies and travelers who had recently undergone stem cell and bone marrow transplants. The study was approved by the Mayo Clinic Institutional Review Board. Informed consent was waived given the minimal risk to subjects in this retrospective chart review.

Data collection

Demographic information included age, gender, and ethnicity. Primary measures included type of immunosuppression; number of immunosuppressive medications; travel details including duration, destination, and malaria endemicity; pre-travel recommendations including vaccinations, serologic test results, gamma-globulin use, provision of malaria and travelers' diarrhea prophylaxis, and advised trip cancellations. Immunosuppressive medications included cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, steroids, methotrexate, and tumor necrosis factor-alpha (TNF-α) inhibitors. We documented patients' purpose for travel such as tourism, visiting friends and family (VFR), missionary work or business. High-risk travel was defined as any activity that may increase the risk of blood or body fluid exposures, food/waterborne illness, tuberculosis, zoonotic diseases, or bodily injuries. Examples include traveling to a rural or remote area without ready access to healthcare, camping or hiking in a densely wooded or rural area, or swimming or wading in fresh water. Based on risk assessment, the travel medicine provider would, in some instances, recommend canceling the trip altogether, which was recorded as an advised trip cancellation.

Data analysis

Descriptive statistics were used to define the primary measures for each cohort. Primary measures were compared among the different groups of ICTs using Kruskal—Wallis for continuous variables and chi-square testing for categorical variables. Multivariate analysis was performed to adjust for baseline demographic differences among ICT subgroups. JMP® 10.0.0 was used for statistical analysis.

Results

Sample description

There were four groups of ICTs studied. First, there were 134 SOT recipients. Transplanted single organs included kidney (n = 65), liver (n = 34), heart (n = 21), lung (n = 6), and pancreas (n = 1). The remaining 7 patients had multiple organs transplanted. Median time between

transplantation and travel was 2.9 years (interquartile range, IQR, 25%–75% = 1.1–8.3 years).

The second group included 121 CTD patients. Examples of connective tissue diseases included rheumatoid arthritis (n = 37), polymyalgia rheumatica (n = 18), systemic lupus erythematosus (n = 14), psoriatic arthritis (n = 5), granulomatosis with polyangiitis (n = 5), and Sjogren's disease (n = 3). A significant number of CTD patients (n = 35) had an unclassifiable disease.

The third group included 46 IBD patients, which included both ulcerative colitis and Crohn's disease. This sample size was relatively small, and as the overlap between these two diseases may be somewhat difficult to discern clinically, the IBD group was not further subdivided into Crohn's disease versus ulcerative colitis.

The fourth and smallest subgroup included the HIV patients (n = 20). This small group had well-controlled HIV, with a median CD4 count of 495 cells/μL (IQR 25%–75% = 284–641 cells/μL). The median viral load was less than 20 copies/mL (IQR 25%–75% = undetectable –95 copies/mL).

There were significant baseline differences among the four groups of ICTs (Table 1). First, there were more patients with SOT (n = 134) and CTD (n = 121) compared to those with IBD (n = 46) and HIV (n = 20). Overall, sample sizes were small. Patients with IBD were significantly younger (median age 35 years) compared to solid organ transplant recipients (median 55.5 years, p = 0.0006) and connective tissue disease patients (median 55.0 years, p < 0.0001). There were also significant differences in gender among the four groups: compared to the SOT group, the CTD and IBD groups had a lower proportion of males. Lastly, though determination of statistical significance was limited by a small sample size (n = 20), the HIV group had less Caucasians (25.0%, 5/20) compared to the SOT group (79.9%, 107/134).

Table 1 Baseline characteristics of all immunocompromised travelers (n = 321).

Characteristic	All groups (n = 321)	Solid organ transplant (n = 134)	Connective tissue disease (n = 121)	Inflammatory bowel disease (n = 46)	HIV[a] (n = 20)	p value
Age, years (median, Q1–Q3[b])	53.0 (40.0–63.0)	55.5 (45.0–63.0)	55.0 (40.5–68.5)	35.5 (28.5–57.5)	49.0 (42.3–57.0)	0.0001[c]
Gender	49.8% male	64.9% male	29.8% male	47.8% male	75.0% male	0.0001
Proportions	(160/321)	(87/134)	(36/121)	(22/46)	(15/20)	
Odds ratios (OR, 95% CI)[d]		Reference	0.23 (0.13–0.38)	0.50 (0.25–0.98)	1.62 (0.59–5.23)	
% Caucasian						
Proportions	79.4% (255/321)	79.9% (107/134)	83.5% (101/121)	91.3% (42/46)	25.0% (5/20)	0.0001
Odds ratios (OR,95% CI)		Reference	1.27 (0.67–2.41)	2.65 (0.87–8.03)	0.08 (0.03–0.25)	

[a] HIV = human immunodeficiency virus.
[b] Q1–Q3 = interquartile range (25%–75%).
[c] A nonparametric comparison for all pairs using the Dunn method revealed that it was the group of inflammatory bowel disease patients who had a significantly different age compared to solid organ transplant recipients (p = 0.0006) and connective tissue disease patients (p < 0.0001).
[d] OR = odds ratio. 95% CI = 95% confidence interval.

Hepatitis A

Forty-eight percent (154/321) of ICTs had a prior history of vaccination or immunity to hepatitis A. Of the 167 ICTs with no prior documentation of hepatitis A immunity, 95.2% (159/167) were advised vaccination based on a travel itinerary with significant hepatitis A exposure risk. Of these 159, 94 (59.1%) patients completed the vaccine series during the study period, and 47 received one of the two vaccine doses. There were only 4.8% (8/167) of travelers who were not advised hepatitis A vaccination, as they traveled to an economically developed nation with adequate community sanitation and, therefore, a low risk of hepatitis A acquisition. Healthcare providers consulted the Centers for Disease Control and Prevention (CDC) and Shoreland Travax® traveler reports to determine if hepatitis A vaccination was recommended for a certain destination. There were no significant differences in vaccine series completion rates among groups. Prior to travel to an area endemic for hepatitis A, 295/313 (94.2%) received at least one or two doses of the hepatitis A vaccine or had prior immunity. During the study period, 248/321 (77.3%) of all ICTs completed the hepatitis A vaccination series or had prior documentation of immunity or disease.

Hepatitis A serology was recommended for 65.9% (62/94) of ICTs who completed vaccination series. Of these 62 ICTs, the majority included SOT (45.2%, 28/62) and CTD (40.3%, 25/62) patients. Of the 62 ICTs for whom serologic testing was recommended, only 41 (66.1%) completed the test. The rate of serologic immunity against hepatitis A was 50.0% after two doses of vaccine.

Gamma-globulin was discussed and recommended to 18.9% (30/159) of ICTs with no prior hepatitis A immunity and imminent travel. Of the 30 ICTs who were advised gamma-globulin administration, 60% were SOT recipients (18/30) followed by CTD (30.0%, 9/30) and IBD (10.0%, 3/30) patients. In the end, only 14 ICTs actually received gamma-globulin. The remaining 16 ICTs did not follow up to complete the gamma-globulin administration.

Hepatitis B

Overall, 72.3% (232/321) of ICTs completed the hepatitis B virus (HBV) vaccination series or had prior documentation of immunity or disease before travel (Table 2). There was a significant difference ($p = 0.0025$) in rates of vaccine completion among those with SOT (81.3%, 109/134), CTD (65.3%, 79/121), and IBD (58.7%, 27/46). In univariate analysis, SOT recipients had higher odds of having completed the hepatitis B series prior to travel, compared to the CTD and IBD groups (Table 2). In a multivariate model including age, gender, race, and type of immunosuppression, SOT recipients had a higher odds [OR 3.94 (95% CI 1.78, 8.85), $p = 0.0007$] of completing the hepatitis B vaccination series, compared to IBD patients. SOT recipients also had a higher odds [OR 2.12 (95% CI 1.14, 4.02), $p = 0.0177$] of completing the hepatitis B vaccination series, compared to CTD patients.

A significant number [62.9% (202/321)] of ICTs had evidence of prior HBV immunity through vaccination or prior positive serologic testing. Of the 119 ICTs with no prior immunity, 49.6% (59/119) were advised to undergo vaccination due to a travel itinerary with potential risk for acquiring HBV. The remaining 50.4% (60/119) were not advised hepatitis B vaccination due to a lower-risk itinerary. Of the 59 ICTs who were advised vaccination, 49.2% (29/59) completed the 3 doses of vaccine.

Of the 18 ICTs who were advised to undergo serologic testing, the majority were SOT recipients (61.1%, 11/18), followed by CTD patients (22.2%, 4/18). Eleven of eighteen ICTs completed the recommended serologic testing. Though limited by a very small sample size, evidence of serologic immunity against hepatitis B after three doses of vaccine was low (12.5%, 1/8). Seroconversion rates in immunocompetent patients after hepatitis B vaccination range between 85% and 90% [11]. However, seroconversion rates are lower with increased age (>60 years), male gender, overweight (body mass index over 25 kg/m^2), tobacco use, and chronic medical conditions. Seroconversion rates in adults over the age of 60 years may vary between 30% and 80% [12].

Other pre-travel vaccines

Based on prior vaccination records, serologic testing, or birth before 1957, 86.6% (278/321) of ICTs had prior immunity to measles, mumps, and rubella (MMR) (Table 2).

Table 2 The study focused on the following vaccine-preventable infections: hepatitis A, hepatitis B, measles, mumps, rubella, varicella-zoster, and yellow fever. Pertinent information for each infection is summarized below for unique travelers (n = 321), not for number of travel episodes (453).

	All groups (n = 321)	Solid organ transplant (n = 134)	Connective tissue disease (n = 121)	Inflammatory bowel disease (n = 46)	HIV[a] (n = 20)	P value
Completion of hepatitis A series prior to travel	77.3% (248/321)	74.6% (100/134)	77.7% (94/121)	76.1% (46/121)	95% (19/20)	0.2447
Completion of hepatitis B series prior to travel	72.3% (232/321)	81.3% (109/134)	65.3% (79/121)	58.7% (27/46)	85% (17/20)	0.0025
OR (95% CI)[d]		Reference	0.43 (0.24–0.77)	0.33 (0.16–0.68)	1.30 (0.35–4.78)	
History of immunity to MMR[b]	86.6% (278/321)	85.8% (115/134)	91.7% (111/121)	78.3% (36/46)	80.0% (16/20)	0.0966
History of immunity to VZV[c]	73.8% (237/321)	86.6% (116/134)	61.2% (74/121)	69.6% (32/46)	75.0% (15/20)	<0.0001
OR (95% CI)		Reference	0.24 (0.13–0.45)	0.35 (0.16–0.80)	0.47 (0.16–1.57)	
Medical exemption noted for yellow fever	19.6% (63/321)	16.4% (22/134)	22.3% (27/121)	21.7% (10/46)	20% (4/20)	0.6684

[a] HIV = human immunodeficiency virus.
[b] MMR = measles, mumps, rubella.
[c] VZV = varicella-zoster virus.
[d] OR = odds ratio. 95% CI = 95% confidence interval. These values were calculated only if the p-value for whole-group comparisons was significant (<0.05).

Based on prior vaccination records or serologic testing, immunity to primary varicella caused by varicella-zoster virus (VZV) was 73.8% (237/321) among all ICTs. There were significant differences ($p < 0.0001$) in rates of VZV immunity among those with SOT (86.6%, 116/134), CTD (61.2%, 74/121), and IBD (69.6%, 32/46) The SOT group had higher odds of having history of immunity to VZV compared to the CTD and IBD groups (Table 2). In a multivariate model including age, gender, race, and type of immunosuppression, SOT recipients had a higher odds [OR 3.96 (95% CI 2.09, 7.76), $p < 0.0001$] of having VZV immunity, compared to CTD patients. SOT recipients also had a higher odds [OR 3.40 (95% CI 1.45, 7.92), $p = 0.0049$] of having VZV immunity, compared to IBD patients.

Among all ICTs, medical exemption for yellow fever vaccination was documented for 19.6% (63/321). There were no significant differences among groups. Out of these 63 ICTs for whom yellow fever vaccination was contraindicated, 15.9% (10/63) were advised to cancel their itinerary.

Immunosuppressive medications

SOT recipients were on the highest number (median 3) of immunosuppressive medications at the time of travel compared to those with CTD (median 1), IBD (median 1), and HIV (median 0, $p < 0.0001$). Commonly prescribed immunosuppressive medications for SOT recipients included calcineurin inhibitors (88.8%, 119/134), mycophenolate mofetil (64.2%, 86/134), and low-dose steroids (61.2%, 82/134, prednisone < 20 mg/day). Commonly prescribed immunosuppressive medications for CTD patients included low-dose steroids (62.0%, 75/121, prednisone < 20 mg/day), methotrexate (23.1%, 28/121), and high-dose steroids (12.4%, 15/121, prednisone > 20 mg/day). Commonly prescribed immunosuppressive medications for IBD patients included azathioprine (54.4%, 25/46) and TNF-α inhibitors (50%, 23/46) (Table 3).

Antimalarial and antidiarrheal medications

Rates of antimalarial (38.9%, 125/321) and antidiarrheal (93.1%, 299/321) prescriptions were similar among all groups, and discussion of potential drug interactions with immunosuppressive medications was documented in 5.3% (17/321) of visits (Table 4). The most common antimalarial prescribed was atovaquone-proguanil (63.2%, 79/125). The most common antidiarrheal antibiotics were quinolones (54.8%, 164/299).

Travel itineraries

Three hundred twenty-one ICTs traveled abroad 453 times and visited 561 locations. International regions were classified based on the GeoSentinel Surveillance System [13]. The most popular region of travel was Sub-Saharan Africa (15.3%, 86/561 visits). Travel itineraries varied among the four groups of ICTs. Only 20.0% (4/20) of HIV patients traveled for the purpose of tourism, whereas 69.4% (93/134) of SOT recipients, 57.9% (70/121) of CTD patients, and 67.4% (31/46) of IBD patients traveled for tourism ($p = 0.0002$).

Seventy five percent (15/20) of HIV patients were non-Caucasian, and most (70.0%, 14/20) traveled abroad to visit friends and relatives (VFR). A majority of HIV patients (40.0%, 8/20) stayed in a private home while traveling, compared to 17.9% (24/134) of SOT recipients, 15.7% (19/121) of CTD patients, and 8.7% (4/46) of IBD patients ($p = 0.0194$).

HIV patients departed shortly after their pre-travel visit (median 20.5 days), whereas other ICTs had more time between pre-travel visit and departure (e.g. 41.5 days for SOT recipients) ($p = 0.0055$). In addition, HIV patients traveled for longer durations (median 29.5 days) compared to SOT recipients (12.0 days), CTD patients (14.0 days), and IBD patients (9.5 days) ($p = 0.0001$). There were no significant differences in high-risk travel activities, malaria

Table 3 Comparison of immunosuppressive medication use: There were 453 unique travel episodes among 321 travelers. Although medications varied for individual patients with different episodes of travel, comparisons were based on numbers of unique travelers (n = 321), and duplicate travel episodes (453) were removed.

	All groups (n = 321)	Solid organ transplant (n = 134)	Connective tissue disease (n = 121)	Inflammatory bowel disease (n = 46)	HIV[a] (n = 20)
Number of immunosuppressive medications at time of travel (median,[b]Q1-Q3)	1 (1—2)	3 (2—3)	1 (1—2)	1 (1—2)	0 (0—0)
Calcineurin inhibitor	38.3% (123/321)	88.8% (119/134)	3.3% (4/121)	0	0
Mycophenolate mofetil	30.2% (97/321)	64.2% (86/134)	9.1% (11/121)	0	0
Azathioprine	15.3% (49/321)	9.0% (12/134)	9.9% (12/121)	54.4% (25/46)	0
Low-dose steroids (<20 mg/day)	49.8% (160/321)	61.2% (82/134)	62.0% (75/121)	6.5% (3/46)	0
High-dose steroids (>20 mg/day)	4.9% (16/321)	0.8% (1/134)	12.4% (15/121)	0	0
Methotrexate	10.3% (33/321)	0	23.1% (28/121)	10.9% (5/46)	0
TNF-α[c] inhibitor	10.6% (34/321)	0	9.1% (11/121)	50% (23/46)	0

[a] HIV = human immunodeficiency virus.
[b] IQR = interquartile range, 25%—75%.
[c] TNF-α inhibitor = tumor necrosis factor-alpha inhibitor, including infliximab, etanercept, adalimumab, etc.

Table 4 Comparisons of antimalarial and antidiarrheal medications prescribed. 125 of 321 ICTs traveled to malaria-endemic regions, and all 125 were prescribed an antimalarial medication.

	All groups (n = 321)	Solid organ transplant (n = 134)	Connective tissue disease (n = 121)	Inflammatory bowel disease (n = 46)	HIV[a] (n = 20)
Antimalarial prescribed	38.9% (125/321)	33.6% (45/134)	46.3% (56/121)	32.6% (15/46)	45.0% (9/20)
Atovaquone-proguanil	63.2% (79/125)	66.7% (30/45)	60.7% (34/56)	80.0% (12/15)	33.3% (3/9)
Doxycycline	15.2% (19/125)	11.1% (5/45)	16.1% (9/56)	0% (0/15)	55.6% (5/9)
Chloroquine	16.0% (20/125)	15.6% (7/45)	17.9% (10/56)	20.0% (3/15)	0% (0/9)
Mefloquine	5.6% (7/125)	6.7% (3/45)	5.4% (3/56)	0% (0/15)	11.1% (1/9)
Antidiarrheal prescribed	93.1% (299/321)	91.0% (122/134)	95.9% (116/121)	91.3% (42/46)	95.0% (19/20)
Quinolone	54.8% (164/299)	51.6% (63/122)	58.6% (68/116)	59.5% (25/42)	42.1% (8/19)
Azithromycin	42.8% (128/299)	42.6% (52/122)	41.4% (48/116)	40.5% (17/42)	57.9% (11/19)
Rifaximin	1.7% (5/299)	4.1% (5/122)	0% (0/116)	0% (0/42)	0% (0/19)
Cefixime	0.7% (2/299)	1.6% (2/122)[b]	0% (0/116)	0% (0/42)	0% (0/19)
Discussed potential drug interactions or side effect profile	5.3% (17/321)	9.0% (12/134)	2.5% (3/121)	2.2% (1/46)	5.0% (1/20)
Significant interaction emphasized	52.9% (9/17)[c]	66.7% (8/12)[d]	0% (0/3)	0% (0/1)	100.0% (1/1)[e]

[a] HIV = human immunodeficiency virus.
[b] Cefixime was prescribed for two patients due to concern for QTc prolongation.
[c] Despite discussion of a potentially significant drug interaction, none of these patients reported any travel-associated illness or adverse drug event.
[d] All eight drug interactions involved antidiarrheal medications (quinolone or azithromycin) interacting with calcineurin inhibitors to cause QTc prolongation.
[e] The noted interaction involved atazanavir reducing atovaquone levels.

risk, or advised trip cancellations. None of the 15 travelers, who were advised to cancel their trips, continued to go to high-risk destinations against medical advice.

Discussion

Sample description

Pre-travel healthcare for ICTs presents various challenges. The ICT population is very diverse in terms of age, ethnic groups, travel itineraries, travel purpose, and immunocompromising medical conditions (e.g. SOT, CTD, IBD, and HIV), which require individualized recommendations for overseas travel. Even within the individual subgroups, there were additional nuances that may affect clinical care. For example, the SOT group contained a variety of transplanted organs, including heart, liver, kidney, and lung. The CTD group was composed of a range of rheumatologic conditions such as rheumatoid arthritis and polymyalgia rheumatica, which are managed differently. It is important to keep these differences in mind while we standardize and individualize pre-travel recommendations.

Hepatitis A and B vaccines and serologic responses

Ideally, ICTs should be administered the complete hepatitis A vaccine series, confirmed to have serologic positivity four weeks prior to travel, or administered gammaglobulin if seronegative [14]. Intramuscular gammaglobulin provides short-term (85—90%) protection against hepatitis A and may be considered for ICTs with inadequate time before departure to high-risk areas or ICTs who are unlikely to respond to vaccination due to severe immunosuppression [15].

Among ICTs, hepatitis B surface antibodies (HBsAb $>$ 10 mIU/mL) should be confirmed after completing HBV vaccination series [14]. Although this threshold level of HBsAb has been protective in clinical trials, other mechanisms such as cellular immunity may also contribute. Levels of HBsAb may wane over time, but the patient may still remain protected [16]. For patients with a negative HBsAb after the primary vaccination series, management options include rechecking HBsAb levels after a "booster" HBV vaccine dose. If this repeated HBsAb level remains negative, patients can reinitiate either the standard 3-dose series or a new vaccination series consisting of higher doses (40 mcg) in a four-dose (0, 1, 2, and 12 months) series. In immunocompromised hosts, the latter is the most commonly advised strategy [17]. The ICT should receive detailed counseling on how to avoid blood and body fluid exposure [18].

The SOT subgroup was prescribed the most immunosuppressive medications, which tended to be calcineurin inhibitors, mycophenolate mofetil, and low-dose steroids. This higher degree of immunosuppression may explain the low seropositivity rates of hepatitis A and B, although the sample size is small. Given the low rates of serologic testing, many ICTs miss the opportunity to confirm immunity to vaccine-preventable infections.

There is overall low adherence to recommendations for serologic screening of ICTs. In a 2015 Australian survey of 254 ICTs, 96.7% were not tested for measles, 92.1% were not tested for varicella, and 40.7% were not tested for hepatitis B virus serology [6]. Consistent with other studies, our study also revealed a low rate of hepatitis A and hepatitis B serologic testing in the patients who did not already have prior evidence of immunity. When serologic screening is performed, the results may be suboptimal. Of the 8 ICTs with negative hepatitis A antibody testing after 2 doses of vaccine, 87.5% (7/8) were SOT recipients. Of the 7 ICTs with negative hepatitis B surface antibody testing after 3 doses of vaccine, 57.1% (4/7) were SOT recipients. As stated previously, SOT recipients were on the highest number of immunosuppressive medications, which typically consisted of mycophenolate mofetil, tacrolimus, and prednisone. This severe immunosuppression may explain the lack of seroconversion for hepatitis A and B, though the sample size is very small. Knowledge of the typical immunosuppressive regimens for different ICT subgroups may facilitate risk stratification and individualized pre-travel counseling.

In a 2015 study of 85 Dutch ICTs, the overall serologic response rate to hepatitis A vaccination was 76.5%, which was moderate. Serologic response rates may be higher when all doses are completed and when the interval between vaccination and antibody measurement is longer (3—6 months), as ICTs may need more time to mount a protective immune response. Therefore, ICTs may benefit from pre-travel vaccination several months earlier than immunocompetent travelers [19]. A suggested approach to hepatitis A and B vaccination is depicted in Fig. 1.

Issues with live vaccines

Another challenge is that live vaccines are contraindicated, and inactivated vaccines may not produce an adequate immune response [6]. In a 2015 American study of 486 ICTs, pre-travel healthcare providers considered yellow fever and measles/mumps/rubella (MMR) to be contraindicated in 42% and 10% of ICTs, respectively. Out of 149 ICTs traveling to countries endemic for yellow fever, 34% received the yellow fever vaccine. No SOT recipients received the yellow fever vaccine [2]. In comparison, in our study, contraindications to yellow fever were documented in 19.6% (63/321) ICTs. Of these 63 ICTs for whom yellow fever vaccination was contraindicated, 15.9% (10/63) were advised to cancel their itinerary. For those ICTs who were considered at relatively low risk for yellow fever exposure, a written waiver was provided in the World Health Organization International Certificate of Vaccination or Prophylaxis. None of our ICTs were advised or received MMR or VZV vaccination, but the majority of them had already had a history of immunity.

Novel immunomodulatory medications are being developed and may change the issues we face in terms of vaccine efficacy, drug interactions, and adverse effects. For example, although calcineurin inhibitors have been the mainstay of immunosuppression for solid organ transplant recipients for many years, their multiple toxicities, such as nephrotoxicity and hypertension, have encouraged the transplant community to search for alternative immunosuppression regimens. One example is belatacept, which is the daughter protein of abatacept and binds CD86 and CD80. Belatacept has been studied in kidney and liver

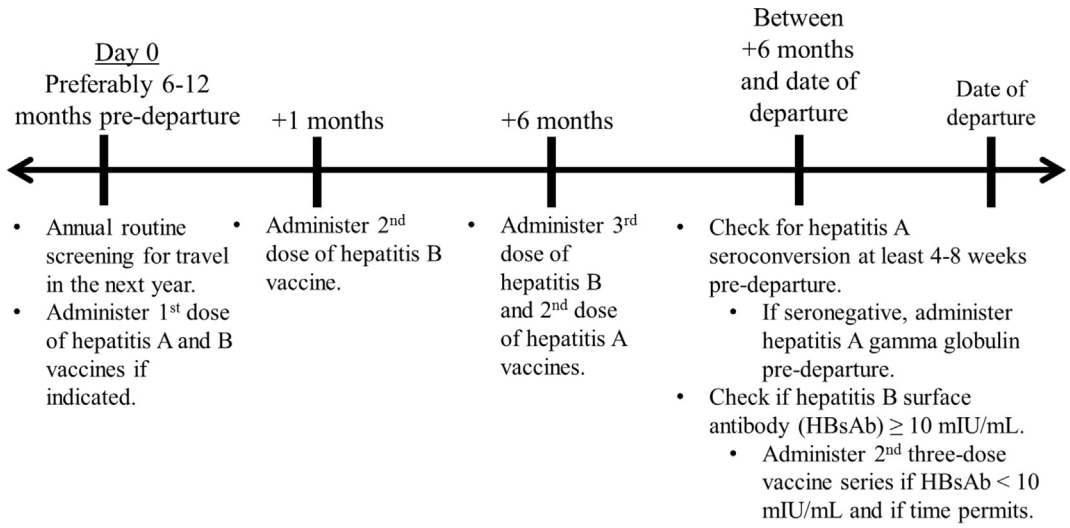

Figure 1 Suggested approach to hepatitis A and B vaccination and serologic testing for immunocompromised travelers [14].

transplant recipients and is a promising alternative immunosuppressive agent that preserves renal function. However, its use may be associated with higher rates of cytomegalovirus infection and post-transplant lymphoproliferative disease, associated with Epstein—Barr virus [20]. Given the relative novelty of such agents, we must wait to see how these novel agents will be tolerated in a population of immunocompromised travelers and whether they will affect immunity in response to vaccinations.

Medication interactions with malaria chemoprophylaxis

Another challenge for ICTs would involve drug interactions. Travel-related medications, such as antimalarial and antidiarrheal prophylaxis, may interact with immunosuppressive regimens [6]. In our study, potential interactions were documented as discussed in only 5.3% (17/321) of ICT visits. Given the low rate of documentation, it is difficult to determine whether our travel medicine providers considered drug interactions when prescribing antimalarial and antidiarrheal medications. For example, atovaquone-proguanil was the most commonly prescribed antimalarial for all ICTs (Table 4), which may be due to its high tolerability, efficacy, and lack of significant drug interactions with common immunosuppressive medications such as calcineurin inhibitors. On the other hand, mefloquine was least commonly prescribed, which may be due to its lower tolerability, efficacy, or significant drug interactions, particularly its ability to increase levels of calcineurin inhibitors [21]. However, it is difficult to conclude the exact reasons for certain prescribing patterns, and the choice of antimalarial medications is also largely dictated by rates of chloroquine resistance in certain regions of the world.

Medication interactions with antidiarrheal antibiotics

In terms of antidiarrheal medications, both commonly prescribed medications (quinolones and azithromycin) have interactions with calcineurin inhibitors [21]. As noted in Table 4, the majority of significant drug interactions involved fluoroquinolones or azithromycin interacting with calcineurin inhibitors to cause QTc prolongation. The benefits of antidiarrheal medications may have been perceived to be greater than the risk of travelers' diarrhea and were, thus, prescribed. Given the relatively short duration of treatment for traveler's diarrhea, these interactions may not be clinically significant. For two patients, cefixime was prescribed due to the concern for drug interactions and to avoid QTc prolongation with azithromycin or quinolones. Fortunately, none of these patients with potential drug interactions experienced any illness related to travel or medication use. All 125 ICTs who traveled to malaria-endemic regions were prescribed antimalarial prophylaxis, and 93.1% (299/321) were prescribed antidiarrheal medications.

Reducing risk of other travel-related infections

Lastly, ICTs travel to similar high-risk areas compared to immunocompetent travelers. In the 2015 study of 486 ICTs and 30,702 immunocompetent travelers, leisure travel to regions of low socioeconomic development was common in both groups. However, SOT recipients were less likely to travel to destinations with low U.N. human development indices and were more likely to travel on cruise ships, which may suggest a more cautious approach [2]. Our results revealed a significant percent of ICTs traveling to malaria-endemic regions (38.9%, 125/321) and reporting high-risk outdoor activities (37.4%, 120/321).

To complicate matters further, there are many disease- and location-specific risk factors for which patients may need counseling. For example, living in a stilt house with plants or muddy floors may predispose a patient to *Leishmania* infection, and patients should be advised to avoid this form of accommodation during pre-travel counseling [22]. If a VFR traveler is returning home to stay with family in a tuberculosis-endemic region, he or she should be counseled on the risk of acquiring tuberculosis, the need to

stay in well-ventilated areas, and post-travel testing for tuberculosis exposure [23].

Limitations

Our study was limited by its retrospective, single-center design, and some missing data. Many patients did not have complete details regarding their vaccination history as they may have been completed outside of our institution. Our study also missed the significant proportion of travelers who likely never seek pre-travel consultation prior to departure. In addition, small sample size was a problem, as there was a relatively low number of HIV patients (n = 20) compared to other groups. ICTs with HIV appeared to form a unique subgroup of non-Caucasian VFRs who traveled to their countries of origin for longer durations. However, definitive conclusions could not be drawn due to the small sample size. Also, the fact that this was a single-center study makes it difficult to generalize findings to a wider population.

Potential interventions

A larger, prospective, possibly multi-center study would be needed to discern unique characteristics of ICT subgroups. Since many patients do not complete their vaccination series or serologic testing prior to travel, a proactive process for reminders may need to be developed for high-risk patients traveling to high-risk areas. Such detailed follow-up would enable travel medicine providers to help decrease post-travel illnesses in these patients. Awareness among primary care providers may also help improve pre-travel care for high-risk patients.

Conclusions

Many ICTs within our population continue to travel to high-risk and malaria-endemic regions, although travel patterns vary within ICT groups. Rates of vaccination series completion could be improved, and serologic testing for hepatitis A and B were low. Though our study was done on small sample sizes at a single center, this study provides a basis for increased awareness for ICT pre-travel counseling and future recommendations by thoroughly describing the ICT population's demographics, travel itineraries, and medication use. Based on this single-center study, our recommendation is that healthcare providers for immunocompromised patients should screen for any anticipated international travel within the upcoming one year. ICTs, especially SOT recipients, should be seen at a travel medicine clinic at least six months before their scheduled departure date so that they can complete any needed hepatitis A or B vaccination series and/or serologic tests. For ICTs who have negative HBsAb serology after initial hepatitis B vaccination, reinitiating the series would be indicated if there is sufficient time before departure. The role of gamma-globulin in ICTs is limited and should be further clarified.

Ethics

The study was approved by the Mayo Clinic Institutional Review Board. Informed consent was waived given the minimal risk to subjects in this retrospective chart review.

Authorship statement

EMT participated in study design, data collection, data analysis, and manuscript preparation. JRM participated in data analysis and manuscript revision. AV participated in study design, data analysis, and manuscript revision.

Conflicts of interest

AV is an inventor for Travel Health and Wellness, LLC.

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