

# The Immune Suppressed Traveller

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# Declaration of Conflict

- I do not accept gifts, meals etc., from industry
- Any honoraria, regardless of source, are treated identically, they go into a fund to support the U of A link with Makerere University in Uganda
- I am involved in pharmaceutical research studies in HIV

# Why This Topic?

- A growing number of patients with previous cancer therapy, on corticosteroids or other immune suppressive drugs, transplant recipients and HIV-infected individuals, are travelling more adventurously.
- The information available on which to base the advice you give them, is very limited.

# Have Transplant, Will Travel (Toronto) travel outside US, Canada

J Travel Med 2004;11:37-43

- 36% had recently travelled outside US/Canada
- Only 66% of transplant recipients sought pre-travel advice; (80% of those who didn't were going to the tropics)
  - 78% who got advice, got it from transplant team
- 18% took along presumptive Rx for diarrhoea
- 3% took antimalarials
- 4% got Hep A vaccine, 5% live vaccines
- 5% ran out of immune suppressive medication

# HIV-infected Travellers (TO) outside US, Canada

CMAJ 2005;172:884-8.

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- 44% sought health advice; only 13% from a travel clinic
- 6% ran out of medications
- Only 21/56 who should have taken malaria prophylaxis received it

# Objectives

- To define what we mean by immune suppressed
- To identify some of the issues specific to certain conditions (e.g. HIV, transplant)
- To touch on the impact of immune suppression on specific travel-related diseases and travel health interventions
- To introduce you to the new CATMAT guidelines

# Warning!

- Some of this is dense and boring and supported by limited evidence (not me, the subject matter!).

# KJ, 52 y.o. Indian born Canadian

- Renal transplant 2003
  - Transplant functioning well on cyclosporine, low dose prednisone
- Plans 6/52 visit to her home area in rural Punjab



# FP, 59 y.o. semi-retired businessman

- HIV-infected
  - On antiretroviral therapy
  - Stable CD4 >400, undetectable viral load
- Plans E. African safari with his partner

# HV, 72 y.o. Red Deer woman

- On prednisone 40 mg. daily for vasculitis
- Plans a 2 week Amazon cruise

# Definition of “Immune Suppressed” for This Discussion

## Immune Suppressed

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- HIV infection (depends on CD4 count)
- Transplantation (depends on organ, timing)
- Corticosteroid therapy
- Cytotoxic therapy (methotrexate etc.)
- TNF  $\alpha$  inhibitors (Remicaid etc.)
- Splenectomy

## Not

- Age, diabetes, cirrhosis or most previously treated cancers

# Main interactions between immune suppression & travel health advice

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- Potential for increased susceptibility to infections & measures to mitigate these risks
- Vaccine concerns
  - safety of live vaccines
  - possible decreased vaccine efficacy
- Other potential problems include access to specialised drugs and the potential for complex drug interactions

# The Immune Suppressing Diseases



# Cancer

- People shouldn't (and usually won't) travel during acute chemo- or radiotherapy course
- Most cancers, cured or in remission, are associated with minimal immune suppression
- Hormonal therapies (breast, prostate cancer) not immune suppressive
- \*Hodgkins disease, some lymphomas, have sequelae of cell mediated immune deficiency even after cure (ask the oncologist)
- Some treatments may be immune suppressive (corticosteroids etc; see below)

# HIV specific issues

- Discrimination, immigration requirements
  - [http://travel.state.gov/travel/tips/brochures/brochures\\_1230.html](http://travel.state.gov/travel/tips/brochures/brochures_1230.html)
- Susceptibility to infection correlates with CD4 cell count:
  - > 500 ~ normal, 200-500 = mild-mod, <200 = substantial, <50 = severe
- Antiretroviral drugs
  - Assured supply
  - Drug interactions (clinical significance not clear)
    - Ritonavir ↓ atovaquone levels; Atovaquone ↑ zidovudine levels (a colleague is working on HIV/malaria interactions)
- Risk of conditions with ↑ risk in HIV infected
  - TB, endemic fungi;
  - & pneumococcal disease, non-typhoidal Salmonella

# Transplant Patient

- Depends on transplanted organ; time post-transplant
- Degree of immune suppression:
  - Successful stem cell (bone marrow) > 2 years < renal < heart or liver < lung or small intestine < recent stem cell
- May have compromised renal (or liver) function
- Drug interactions with immune suppressives are common
  - Chloroquine ↑ cyclosporine levels → ? Pre-travel blood levels
  - So do azithromycin & cipro, but short courses probably not a problem
- Vaccine stuff
  - Timing—routine vaccines coordinated with Tx program
  - Live vaccines a concern
  - Monitoring seroconversion, double dosing (hep B),



# Splenectomy

- Main risk is pneumococcal sepsis
- ↑ risk of malaria of little practical importance because risk is high for any non-immune

# Other Immunosuppressive Agents

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- Methotrexate
- Azathiaprine (Imuran)
- Cyclophosphamide (Cytosan)
  - Difficult to estimate or quantitate degree of immune suppression, but can be severe
- Note: patients on high dose hydroxychloroquine (Plaquenil) for rheumatic disease do not need chloroquine and should probably not take mefloquine

# TNF $\alpha$ Inhibitors (Remicaid etc.)

- Increased risk of TB activation and endemic fungal infections

## Corticosteroids (many indications)

- Consensus re significant immune suppression:
  - Dose  $\geq$  20 mg./day prednisone or equivalent
  - Duration  $\geq$  2 weeks
  - Advice analogous to HIV with CD4  $<200$
  - Probable increased risk of TB
  - Risk of *Strongyloides* hyperinfection

# The Travel-Related Diseases

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# Travellers' Diarrhoea

- Patients with renal dysfunction e.g. transplant patients on cyclosporine, at increased risk of renal failure from dehydration
- HIV and other immunosuppressed hosts at ↑ risk of invasive, bacteremic non-typhoidal *Salmonella*, less commonly, *Campylobacter*
- Profound immunosuppression turns *Cryptosporidia* (and *Microsporidia*) from an acute, self-limited disease to a chronic one
- No clear association with other “routine” organisms such as toxinigenic *E. coli*, *Giardia* & *Entameba*
- Diarrhoea treatments probably OK for almost all immunosuppressed patients (? Bismuth)

# TD: advice

- Reinforce usual advice, especially re: hydration
- You could make a case for Dukoral™ here, at least for prosperous travellers.

# Malaria

- Splenectomy associated with ↓ clearance of malaria parasites
- HIV associated with increased risk & density of parasitemia (malaria also associated with ↑ HIV replication)
- But it doesn't really impact travel advice since falciparum malaria is a life threatening illness even in the immune competent

# TB

- Risk of TB **exposure**
  - approximates local transmission risk, e.g. 3%/year in some low income country settings
  - Some activities, e.g. health care in high prevalence countries, **very high** risk, possible risk of MDR (or XDR) TB exposure
- Risk of TB activation/reactivation
  - HIV most potent factor known for the reactivation of latent tuberculosis infection; ~ 50% risk depending on HIV therapy
  - HIV also associated with increased risk of progressive 1<sup>e</sup> disease, & re-infection post Rx
  - Other immune suppressive conditions, e.g. transplant, Remicaid, also ↑ risk of TB activation
- Tuberculin skin test less sensitive in the immune suppressed
  - (sensitivity of Quantiferon™ not yet clear in this setting)



# TB—Advice

- Inform travellers, especially the profoundly immune suppressed re: risk
- Avoid health care and other high risk settings
- Do before-and-after skin tests
- High index of suspicion for TB if unexplained illness develops

# Strongyloides

- The only helminth (worm) that can cause opportunistic infection
- Latent infection can persist for decades, usually in immigrants from tropical LIC's
- Life threatening “hyperinfection” can then occur with immunosuppression
- Immunosuppressed travellers should probably be warned particularly against walking barefoot

# Travel-Related Diseases without Significant Interaction

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- Dengue
- Worms other than *Strongyloides*

# STI's

- Some, especially syphilis, can behave more aggressively in the immune suppressed

# Exotic diseases

- Brucellosis, scrub typhus, leptospirosis—no recognized association
- Chagas' disease (*T. cruzi*) can cause brain abscesses in AIDS and transplant patients; infection almost never seen in travellers
- African trypanosomiasis (sleeping sickness), very rare in travellers, may have poorer treatment response in the presence of HIV
- Leishmaniasis clearly associated with HIV, may be transmitted by needle sharing, different species, more resistant to treatment, in presence of HIV
- Endemic fungi: *Histoplasma*, *Penicillium* ↑ risk of disease

# Vaccines

- Don't work as well in the immune suppressed
  - In HIV, Hep A & B vaccine response correlates with CD4 count
  - Transplant patients: timing is critical
  - Hence occasional consideration of use of immune globulin (Hep A, measles)
- Killed vaccines are safe (if sometimes less effective than in normal hosts)
  - Theoretical concerns about enhancing HIV replication or transplant rejection appear not clinically validated

# Specific Vaccines in the Immune Suppressed

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- DPT--update
- Dukoral—consider for the wealthy & risk intolerant immune suppressed traveller
- Hep A—of course.
  - Marked fall-off in response with immune suppression
  - Consider ISG if very immune suppressed
- Hep B: double dose for the immune suppressed
- Rabies: check serologic response
- Typhoid & polio: injectables

# Live Vaccines

- Live vaccines should be given to immune suppressed travellers only after an individualized assessment of **exposure risk and degree of immunosuppression**



# Vaccines, cont'd

- BCG—never
- Measles
  - Disease common in many low income countries
  - Disease very severe in immune suppressed
  - **One** case report of vaccine-related disease in HIV
  - So, in immunosuppressed travellers:
    - Assess immunity (history, serology if unclear)
    - Consider vaccine in HIV patients with CD4 > 200 or equivalent
    - Possible role for ISG

# Live Vaccines

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- Yellow Fever
  - Inform immunosuppressed travellers of risk
  - Mosquito avoidance (mostly daytime)
  - Give a waiver certificate if exposure risk very low or negligible (east Africa safari areas)
  - Give the vaccine to high risk travellers with  $CD4 > 200$  or equivalent

# KJ, 52 y.o. Indian born Canadian

- Renal transplant 2003
  - Transplant functioning well
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# KJ

- Assume or confirm Hep A immunity
- Mefloquine or Atovaquone/Proguanil probably OK; consider early initiation or loading & measurement of levels
- Safety of bismuth unclear if creatinine clearance reduced.
- Vaccines: typhoid (injectable), JEV if indicated, polio, consider meningococcal—
- Maybe this is a Dukoral candidate, if prosperous and risk-averse!
- She should have been TST tested pre-transplant—do post travel TST

# FP, 59 y.o. semi-retired businessman

- HIV-infected
  - On antiretroviral therapy: tenofovir, lamivudine, ritonavir & atazanavir
  - Stable CD4 >400, undetectable viral load
- Plans E. African (Tanzania) safari with his partner

# FP, the plan

Near normal host; main concerns would be immigration issues, assured medication supply, drug interactions

- Usual diarrhoea advice & preparations
- Mefloquine probably first choice for prophylaxis (theoretical drug interaction concerns with atovaquone/proguanil)
- Usual vaccines (he would be expected to respond) except I would be inclined to give yellow fever a miss since his exposure risk is near zero.)
- TB a concern if he has close contact with locals in crowded settings
- Reinforce safe sex

# HV, 55 y.o. Red Deer woman

- On high dose steroids
- Plans a 2 week Amazon cruise

# H.V.

- Inform re: risk including yellow fever
- Encourage itinerary that minimizes jungle exposure
- Emphasize mosquito protection
- I think I would give her a YF vaccine waiver
- Consider ISG (hep A)
- Other interventions as per routine



# Conclusions

- You are likely to see increasing #'s of immune suppressed travellers
- They can be pretty complicated
- Their physicians may not be up to speed on travel related issues, but should provide information re: degree of immune suppression
- Resources
  - CATMAT guidelines
  - A drug interaction program
  - Canadian immunization guidelines
  - The physician or program re: degree of immune suppression