Pre-Transplant Donor and Recipient Evaluation

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Objectives

- To understand **common** contemporary scenarios in donor derived infections that may affect screening decisions
- To know how the recent **CDC/PHS guidelines** may impact safety of organ donation
- To elaborate what perioperative transplant professionals can do to **mitigate the risk** of disease transmission

Disclosures

None

Infection in Transplantation

- 25% of cadaver kidneys have bacterial contamination at time of transplant
- Occurs in 70% of patients in the first year
- Remains a leading cause of death
- Risks
  - Epidemiologic exposure and history
  - Net state of immunosuppression
  - Time after transplant
  - Efficacy of prophylaxis

ID COP Guidelines. Am J Transplant. 2013

Case 1

- Transplant recipient identified with post-transplant HCV and HIV infection with no obvious risk factors. Negative pre- transplant testing
- Reported to OPO, UNOS, and CDC
- Donor – Look-back Assessment
  - Negative serology for HIV & HCV
  - Appropriately labeled as “high risk” by PHS Guidelines
  - Subsequent testing of post-transfusion serum was + for HIV and HCV by PCR
- All other recipients tested + for HIV & HCV

Ison et al. Am J Transplant. 2011; 11: 1218–1225

Case 1: Something to fear?

The ugly

- Transplant recipient identified with post-transplant HCV and HIV infection with no obvious risk factors. Negative pre- transplant testing
- Reported to OPO, UNOS, and CDC
- Donor – Look-back Assessment
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  - Appropriately labeled as “high risk” by PHS Guidelines
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4 cases of HIV transmitted since HIV antibody testing

- All occurred when testing consisted of HIV Ab NOT molecular (NAT) testing

- Factors that may lead to HIV transmission
  - Hemodilution
  - Living donor tested, then converts after testing and before donation
  - HIV Ab test negative (window period) before seroconversion

Limitations of organ donor screening

- Restricted timeline
- Different screening paradigms
- Donor history
- Incomplete data collection
- Serology-based screening
- Variable NAT capacity and practice
- No expectation for “Zero Risk”

Ison et al. Am J Transplant. 2009; 9: 1929-1935.
Ison & Nalesnik. Am J Transplant. 2011; 11

Definition

CDC high risk

- **1994:** CDC published guidelines for preventing HIV transmission through Organ Transplant
- 'Further recommendations should be made to reduce the already LOW RISK of HIV transmission by transplantation'
- **2013:** Revised guidelines

Seem et al, Public Health Reports. 2013; 128

Definition

CDC high risk (revised 2013)

- **Men who have sex with men** (MSM) – men who have had sex with another man in the preceding ~~5 years~~ 12 months
- **Hemophiliac** – persons with hemophilia who have received human derived clotting factor concentrates
- **Injection drug use** – nonmedical IV/IM/SC injection of drugs in the preceding ~~5 years~~ 12 months
- **Commercial sex worker** – persons having sex in exchange for money or drugs in preceding ~~5 years~~ 12 months
- **High risk sex** – exposed in preceding 12 months to known/suspected HIV infected blood or persons in above four categories
- **New STD** – syphilis, gonorrhea, chlamydia, genital ulcers in preceding 12 months
- **Incarcerated** – Inmate of correctional system for at least 72 hours and in the past year
- **Hemodialysis** last 12 months (for HCV)

Seem et al, Public Health Reports. 2013; 128

Window period

- Between acquisition of infection, and serologic detectability:
  - HIV: 22 days
  - HCV: 66 days

- With NAT (molecular) testing:
  - HIV: 9 days (8-10)
  - HCV: 7 days

Window period

HIV risk

- HIV ELISA: 0.09 – 12.1 per 10,000

- HIV NAT (molecular): 0.04 – 4.9 per 10,000
  - Injection drug users: 4.9
  - Men who have sex with men: 4.2
  - Commercial sex workers: 2.7
  - Incarcerated: 0.9
  - Blood exposure: 0.6
  - High risk sex: 0.3
  - Hemophiliacs: 0.035

Window period

HCV risk

- HCV ELISA: 0.26 – 300.6 per 10,000

- HCV NAT (molecular): 0.027 – 32.4 per 10,000
  - Injection drug users: 32.4
  - Men who have sex with men: 3.5
  - Commercial sex workers: 12.3
  - Incarcerated: 0.8
  - Blood exposure: 0.4
  - Hemophiliacs: 0.027

Patient attitudes

Turn down high risk donors

- In focus groups, patients felt unprepared to receive organ offers, especially from high risk donors (HRD)
- They want information about HRD behaviors, kidney quality and probability of undetected infection
- Patients weighed opinion of their nephrologist most heavily when deciding about organ offers
- Conclusion: Lack of preparedness contributes to patient apprehension toward HRD organs
- Need for ongoing education
  - Patients
  - REFERRING NEPHROLOGISTS – the most trusted source of information

Clin Transplant 2012 Ros et al (Johns Hopkins)

What is high risk?

Odds of…

	Per 10,000
Being struck by lightening in your lifetime (80 years)	1
Dying in a plane crash in your lifetime	2
Dying in a car accident	125
Dying crossing the street	16
Missing HIV with a NAT test	0.04 – 5
Missing HCV with a NAT test	0.03 – 32
Dying if no liver transplant and MELD 20-29 in next 3 months	2,000
Dying if on waitlist and no kidney transplant in 1 year	900

Most recent case of HIV transmission was in a living donor

- Living donor had history of syphilis, and history of sex with male partners
- Initial evaluation and serologic tests were negative 10 weeks before donation
- Donation and transplant occurred, febrile illness in recipient, HIV positive test in recipient and donor – genetically identical strains
- After transmission documented, living donor reported unprotected sex with one man during year before donation (including interval between testing and donation) with unknown HIV status

Case 2

- Patient is a 46 year-old Chinese male
- Underwent cadaveric renal transplant
- CMV D+/R–
- Prophylaxis: Valganciclovir
- 9 days post-transplant
- Donor has + blood cultures drawn the day prior to donation
- Positive for Pseudomonas aeruginosa

Case 2

The good

- Patient is a 46 year-old Chinese male
- Underwent cadaveric renal transplant
- CMV D+/R–
- Prophylaxis: Valganciclovir
- 9 days post-transplant
- Donor has + blood cultures drawn the day prior to donation
- Positive for Pseudomonas aeruginosa

- Positive result on cultures
- Day of transplant
- Took several days to convey results to recipient centers
- Patient was receiving ciprofloxacin for a probable UTI, which covered the bacteria with no serious sequelae

Case 3

- Patient is a 56 year-old Chinese female with cirrhosis from chronic hepatitis B
- On liver transplant waiting list
- PPD 10mm
- Had BCG as a child
- AST 50, ALT 200, Tbili 2.0, MELD 30
- What do you do?

Case 3

The good

- Patient is a 56 year-old Chinese female with cirrhosis from chronic hepatitis B
- On liver transplant waiting list
- PPD 10mm
- Had BCG as a child
- AST 50, ALT 200, Tbili 2.0, MELD 30
- What do you do?

Recipient Evaluation / Diagnosis

- 2-step TST (≥5mm is positive) or IGRA; likely disregard prior BCG status
- CXR
- Careful history: risk factors, travel / residence to endemic countries, contact to active TB case, past prior rx/dx
- Symptom review
- If evidence for “old” granulomatous disease, e.g. apical thickening/scarring/nodularity:
  - Obtain sputa for AFB
  - If sputa neg / CXR stable, then expedite treatment
  - Even if TST / IGRA neg, would consider LTBI treatment, esp if TB risk factors present

- Yehia BR, Blumberg EA. Mycobacterium tuberculosis infection in liver transplantation. Liver Transpl. 2010 Oct;16(10):1129-35.
- Subramanian AK, Morris MI; AST Infectious Diseases Community of Practice. Mycobacterium tuberculosis infections in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:68-76.

Donor Evaluation / Diagnosis

- Living
  - Careful history: risk factors, travel / residence to endemic countries, contact to active TB case, past prior rx/dx
  - Symptom review
  - TST or IGRA
- Deceased
  - Careful history from family if possible, as above
  - IGRA
  - CXR
  - Cultures (if above abnl)

- Yehia BR, Blumberg EA. Mycobacterium tuberculosis infection in liver transplantation. Liver Transpl. 2010 Oct;16(10):1129-35.
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LTBI treatment options

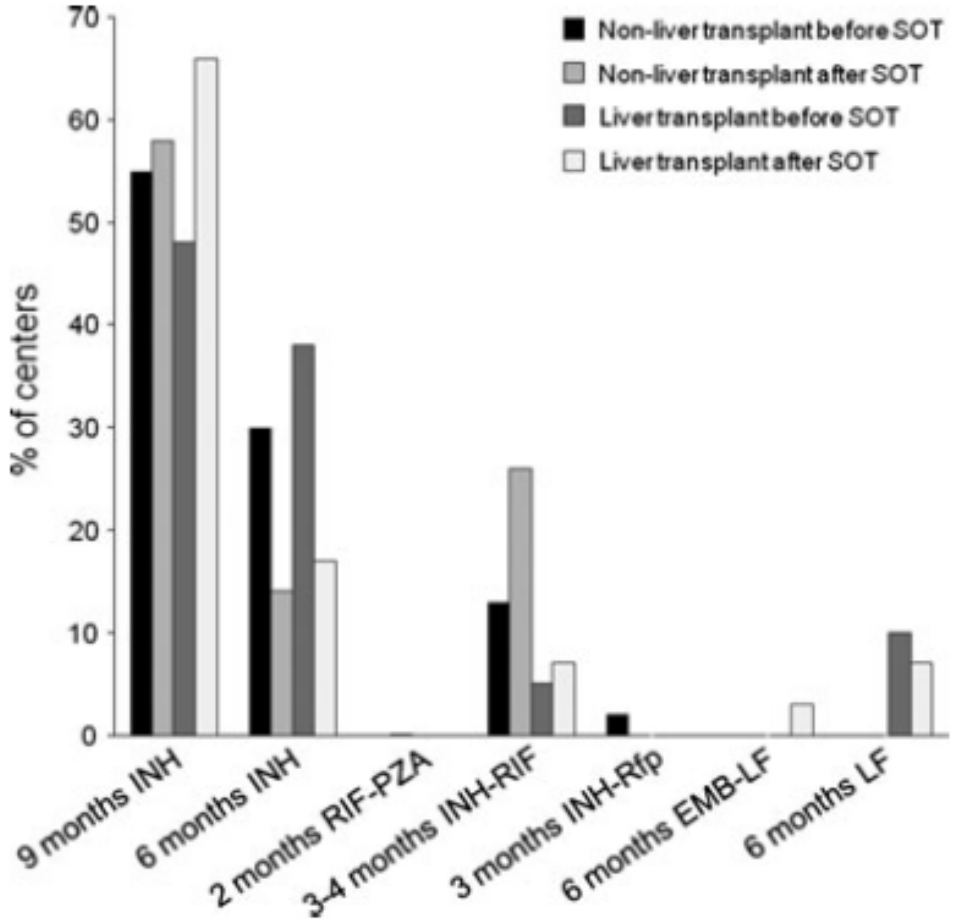
- Isoniazid (INH)

Alternatives (with less data):

- Rifampin (RIF)
- Isoniazid-Rifapentine (3HP)
- Fluoroquinolone +/- ethambutol (MDR)

* Centers for Disease Control and Prevention (CDC). Targeted Tuberculin Testing and Treatment of Latent TB Infection.
* Centers for Disease Control and Prevention (CDC). Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2011 Dec 9;60(48):1650-3.
* Yehia BR, Blumberg EA. Mycobacterium tuberculosis infection in liver transplantation. Liver Transpl. 2010 Oct;16(10):1129-35.

LTBI treatment is varied



Boillat-Blanco N, Aguado JM, Aubert JD, Sester M, Grossi P, Kamar N, Pascual M, Manuel O; ESCMID Study Group of Infection in Compromised Hosts. European survey on the management of tuberculosis in solid-organ transplant recipients and candidates. Transpl Int. 2013 Aug;26(8):e69-70.

INH

- Preferred treatment for LTBI→ 9 months
- Concern for risk of hepatotoxicity, however, studies suggest low risk in compensated cirrhosis.

- Stucchi RS, Boin IF, Angerami RN, Zanaga L, Ataide EC, Udo EY. Is isoniazidcsafe for liver transplant candidates with latent tuberculosis? Transplant Proc.c2012 Oct;44(8):2406-10.
- Jahng AW, Tran T, Bui L, Joyner JL. Safety of treatment of latent tuberculosis infection in compensated cirrhotic patients during transplant candidacy period. Transplantation. 2007 Jun 27;83(12):1557-62.
- Singh N, Wagener MM, Gayowski T. Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis. Transplantation. 2002 Sep 27;74(6):892-5.

INH safety / efficacy

- Meta-analysis: 7 studies (2 prospective, 5 retro)
- 224 patients with positive pre-transplant TST
  - ≥6 mo INH: 61 (no development of active TB)
  - <6 mo INH: 16
  - RIF: 5
  - No rx: 143 (5.1% developed active MTB)
- INH ≥6 mo associated with decreased risk of active TB (8.2% absolute RR, p=0.02)
- 6% pts d/c'd INH due to hepatotoxicity; 1 pt with drug-induced liver failure

Holty JE, Gould MK, Meinke L, Keeffe EB, Ruoss SJ. Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. Liver Transpl. 2009 Aug;15(8):894-906.

INH + Rifapentine (3HP)

- Recommended as an equal alternative to INH x 9 mo in healthy patients ≥12 yo and HIV-infected patients not on ART.
- Not recommended in the following:
  - Children <2yo
  - HIV-infected patients on any ART
  - Pregnant or planning to become pregnant
  - Contact to INH/RIF resistant cases
  - No / limited data on transplant / immunocompromised

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

	INH-RPT	INH
No. of patients	3,986	3,745
Administration	Directly-observed therapy	Self-administered therapy
Frequency	Weekly	Daily
Duration	12 weeks	9 months

Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66. Slide courtesy, Dr. Neha Shah

Pre-transplant evaluation

- HIV
- HBV: HBsAg, HBSAb, HBcAb
- HCV
- Herpesvirus: HSV, VZV, CMV, EBV
- Syphilis
- Toxoplasma gondii (heart)

- Urinalysis
- Urine culture
- TST or IGRA
- CXR
- Sputum or BAL (lung)

- Blood cultures (depends)
- Others (next talk)

HIV positive recipient evaluation

Eligibility criteria for HIV-infected transplant candidates

Meet center-specific criteria for specific organ transplant

HIV-related criteria

- Kidney: CD4+ T-cell count greater than 200 cells/μL
- Liver: CD4+ T-cell count greater than 100 cells/μL (CD4+ T-cell count >200 cells/μL if history of opportunistic infection or malignancy)
- HIV RNA suppressed for kidney transplant recipients
- HIV RNA suppressed for liver transplant recipients, or expected to be suppressed if unable to tolerate cART
- Stable antiretroviral regimen
- No active opportunistic infection or neoplasm
- No history of chronic cryptosporidiosis, primary central nervous system lymphoma or progressive multifocal leukoencephalopathy

Other

- Liver (HCV): BMI greater than 21 kg/m^2, no need for combined kidney transplant, no HCV+ donor

Chin-Hong PV et al, Infect Dis Clinics NA, 2013

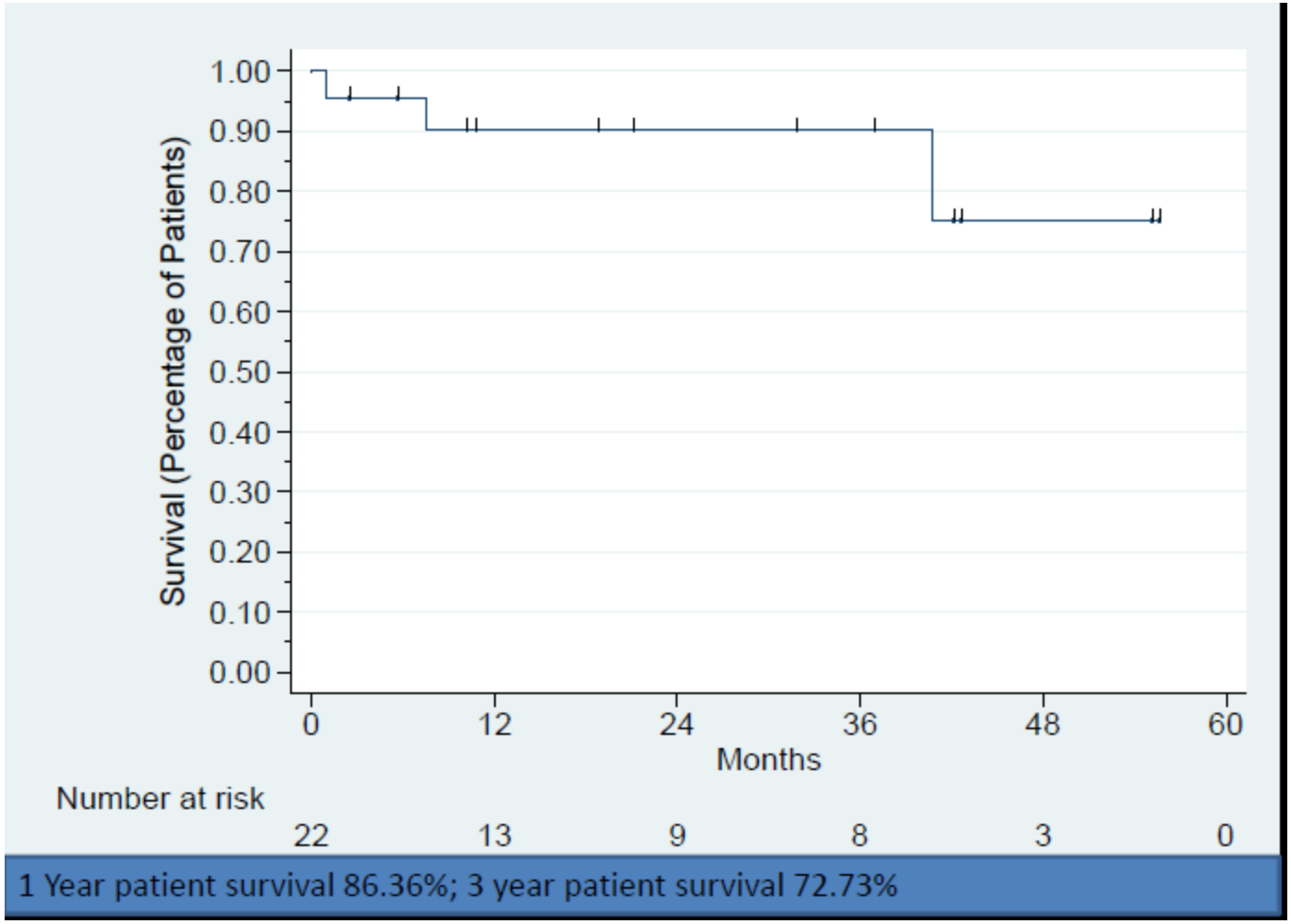
HIV to HIV transplant in South Africa

	Patient 1	Patient 2	Patient 3	Patient 4
Age	47	56	37	29
Sex	male	male	male	female
CD4 count (baseline)	288	258	132	147
CD4 count (12 mo)	253	119	112	220
HIV viral load (12 mo)	<50	<50	<50	<50
Immunosuppression	tacrolimus	tacrolimus	tacrolimus	tacrolimus
Clinical status	alive with functioning graft	alive with functioning graft	alive with functioning graft	alive with functioning graft

Muller E et al, NEJM; 2010; 362

HIV to HIV transplant in South Africa

Patient survival



courtesy E Muller

Obama lifts ban on HIV organ transplants

SF Gate

November 21, 2013

HIV-positive organ donation: HOPE Act signed into law

Slate

November 22, 2013

What happened

- 1988: Amendment to the National Organ Transplant Act of 1984 banned the transplant of any organ from a person with HIV
- February 14, 2013: Bipartisan Hope Act introduced in both houses of Congress
- Drafted by Rep. Lois Capps (D-CA) [RN], Senators Barbara Boxer (D-CA) and Tom Coburn (R-OK) [MD]
- Potential for almost **500** people on the donor list to receive organs from HIV-infected donors every year
- November 21, 2013: President Obama signs S.330: the HIV Organ Policy Equity Act

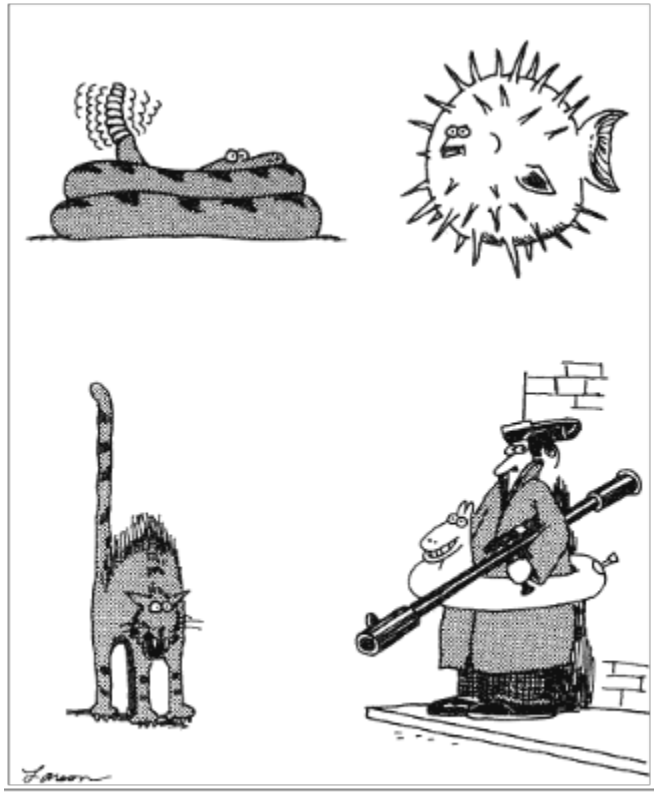
What transplant professionals can do peri-operatively

- Ensure **donor screening** performed
  - Review medical & social history
  - Physical examination
  - Screening of blood samples of donor and recipient
  - Serology
  - Nucleic Acid Testing (NAT)
  - LTBI assessment
- Define the **increased risk** donor
  - OPTN-defined increased risk donor
  - New definitions
  - Increased risk of transmission of other infections may affect peri-transplant antimicrobials
- Screen high-risk recipients **post-transplant**

Screening 123

1. The "**Big 3**": HIV, Hep B, Hep C
2. The **givens**: CMV, EBV, HSV, VZV, toxoplasma, syphilis, bacteria

To be continued...



How nature says, "Do not touch."

Hocevar S et al, Ann Intern Med; 2014; 160(4)
Kotton C, Ann Intern Med; 2014; 160(4)

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