Emerging Infections in Transplantation

Michael Wong, MD

Emerging Infections

- Human infections that are emerging in immunocompromised patient populations:
  - MTB
  - CDAD
  - KPC
- Enzootic and Endemic conditions
  - LCMV
  - T cruzi
  - Strongyloides

Case 1
- 56 yr old, HCV with ESLD, s/p RFA for HCC, history of reactive PPD 30 yrs ago, and completed only 2 weeks of INH therapy for LTBI. MELD with points is 32.
- Sent to me for “ID clearance” for TXP.
  - “I didn’t believe the doctor”
- Foreign born, left country of origin at age 22, family history positive for grandfather with active MTB when he was a child; told no problem since he received the BCG vaccine
- On CXR, he has a clear Gohn complex.

What do you do?

MTB following SOT

- Increasing migration patterns of populations with globalization from areas of high-endemicity (e.g., Haiti, South Africa, Eastern Europe) to the US
- Routine screening in primary health care settings lax including in immigrant populations
- Significant confusion and lack of understanding regarding the BCG, PPD and even the concept of LTBI exists among healthcare providers
Singh and Paterson, Clin Infect Dis 1998
- Large lit review, 511 cases of MTB following SOT with primary source being recipient reactivation of disease
- Exception, Lung and heart/lung where donor was source (9%)
- Risk factors were ALG therapy and non-US borne recipients
- Outcomes poor if disease presented as dissemination

Torres-Ciseneros et al. Clin Infect Dis 2009
- REISTRARE Experience-4388 SOT
- 21 active MTB infections post SOT
- Incidence 251-2000/100,000 with highest rate in lung txp recipients
- MV analysis revealed age of recipient and Lung TXP to be most consistent risk factors

Lopez de Castilla et al, Transpl Infect Dis 2009
- NYC/Columbia Med Ctr experience-4925 SOT from 1988-2005
- 13 cases of MTB disease with case rate 264/100,000
- Majority were reactivation in kidney recipients (largely non-US borne recipients)

NYC Experience
Lopez de Castilla et al, Transpl Infect Dis 2009
Median time to MTB disease post transplantation was 12 months

Singh and Paterson experience
Median time to disease post transplantation was 11.5 months

Back to our case

The recipient had no findings suggestive of active MTB disease on evaluation and sputa smears. He went forward with transplantation that was unremarkable, and was started on INH LTBI therapy rather than RIF at the end of Month +1 when his steroids were discontinued

Chosen to minimize the drug-drug interactions of RIF and his IS, with the understanding he was at higher risk for LFT issues with INH.

He completed 9 months of INH therapy and had no untoward complications while on therapy
Case 2

- 55 yr old Cuban born gentleman, presents with fevers to 103, 35# weight loss, and mental status changes and CHF
- Initial labs demonstrate WBC 110,000, 90% blasts; BMBx consistent with AML
- Exposure history: low risk employment (IT support), lives with family who are well, no MTB exposures, has pet parrot of 25 yrs at home. Had not travelled or returned to Cuba
- Let Cuba in the massive boat exodus in the 1980s. The immigrants were all co-housed in Florida based detention and corrections centers.

Numerous studies obtained large effusion that was more evident on CT was sampled. MTB PCR was positive from the effusion, probe positive from sputum and AFB blood cultures all positive on the same day (hosp day 8). Had prolonged course of antiMTB therapy, complicated by sterile abscesses that developed after his induction chemotherapy and counts returned (? IRIS equivalent).

NB: This was a treatment nightmare; while he was receiving induction and consolidation chemotherapy (IDA: ARA then HIDAC), his antiTB regimen as outlined to Amoxicillin monotherapy (ETB and PZA were continued during induction chemos). Ultimately went on to have a successful sibling matched allogeneic HSCT, and doing well now 4 years from HSCT.
Case 3

- 55 yr old s/p OLT for complications associated with Laennec’s cirrhosis, complicated by failure to thrive only. Developed diarrhea on day +35 at rehab facility which was attributed to MMF.
- Neither he nor records acknowledged significant diarrhea though in retrospect he was having up to 10 watery bowel movements daily.
- Admitted to our hospital with acute abdomen and fevers to 103.
- CT demonstrated toxic megacolon and stool markedly C diff tox + by EIA.

- He was also GN septic, and went on to have a total colectomy with diverting ileostomy; at surgery, pseudomembranes were seen into the distal ileum.
- Course further complicated with non-albicans candida sepsis, but after combined tigecycline/micafungin/CDAD therapy, he survived and is doing well now 14 months post OLT.

CDAD following OLT

- 32 pts developed CDAD (5-1999 days post OLT).
- 30/32 (93.8%) developed CDAD within first year post OLT.
- Risk factors:
  - Early (< day 28):
    - major intraabdominal bleed (P<0.001),
    - biliary complication (P=0.034),
    - bile leak (P=0.026),
    - Concurrent systemic infection (P<0.001),
    - OLT redo (P=0.031).
  - Intermediate onset cases (days 29-365) were more likely to have similar risk factors that were clearly ongoing and more chronic technical issues.
  - Late onset cases (>365 days): only 3 cases; severe disease, multiple post transplant complications (drug-related ITP, recurrent biliary stricture with stenting and prolonged systemic antimicrobial exposure).

12 studies from 1994-2006
- 1963 patients with CDAD, no denominator data provided
  - Mix of allogeneic and autologous HSCT recipients
  - CDAD confirmed in 141 (7.18%)
  - 13 died from CDAD complications
    - Gorschluter et al, 2001
    - Median time to onset was between 4 to 45 days
    - Arango, 2006; Yuen, 1998
    - Other major cause of diarrhea was GVHD (45%)
Clostridium difficile-associated disease in allogeneic hematopoietic stem-cell transplant recipients: risk associations, protective associations, and outcomes

Erik R. Dubberke, Kimberlay A. Reske, Anand Srivastava, Justin Sathu, Robert Gatti, Rebecca M. Young, Lauren C. Rakes, Britan Dieckgraefe, John DiPersio and Victoria J. Fraser

Department of Medicine, Washington University School of Medicine, St Louis, MO, USA

Table 1. Predictor variables associated with CDAD on univariate analysis (p < 0.10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n = 97)</th>
<th>Cases (n = 27)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>10 (10%)</td>
<td>13 (38%)</td>
<td>3.1 (1.24-6.6)</td>
</tr>
<tr>
<td>Long duration of hospitalization</td>
<td>1 (1%)</td>
<td>4 (11%)</td>
<td>0.00 (0.3-74.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>46 (47%)</td>
<td>16 (25%)</td>
<td>0.03 (0.1-1.3)</td>
</tr>
<tr>
<td>Receipt of a growth factor during admission</td>
<td>41 (42%)</td>
<td>9 (25%)</td>
<td>0.65 (0.1-2.0)</td>
</tr>
<tr>
<td>Receipt of third-generation methotrexate during admission</td>
<td>35 (36%)</td>
<td>10 (29%)</td>
<td>1.2 (0.5-3.1)</td>
</tr>
<tr>
<td>VTE</td>
<td>4 (4%)</td>
<td>12 (32%)</td>
<td>0.32 (0.1-0.4)</td>
</tr>
<tr>
<td>Receipt of corticosteroids during admission</td>
<td>22 (23%)</td>
<td>4 (11%)</td>
<td>0.46 (0.1-1.3)</td>
</tr>
</tbody>
</table>

Table 2. Multivariable analysis of variables associated with CDAD on logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factor</td>
<td>0.1 (0.00-1.1)</td>
</tr>
<tr>
<td>Death with diagnosis methotrexate</td>
<td>4.0 (1.1-14.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.01 (0.1-163)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.2 (1.2-12.7)</td>
</tr>
</tbody>
</table>

CDAD: Clostridium difficile-associated disease

Figure 1. Kaplan-Meier analysis of survival after C. difficile associated diarrhea (CDAD). Survival beyond CDAD. Median survival from CDAD onset.

Table 3. Associated with death (n = 100)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (continuous)</td>
<td>0.0 (0.1-1.0)</td>
</tr>
<tr>
<td>Death (CDAD)</td>
<td>3.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Death with diagnosis methotrexate</td>
<td>24.8 (3.0-2.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.01 (0.1-163)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.2 (1.2-12.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24.5 (3.0-1.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24.8 (3.0-2.6)</td>
</tr>
</tbody>
</table>
CDAD

- Increasing frequency in both solid and liquid organ transplant recipients
- Infections associated with poorer outcomes including higher rates of graft loss, and death
- Risk factors appear to be diverse and variable

Case report

Fatal cross infection by carbapenem-resistant
Klebsiella in two liver transplant recipients

A.A. Matthews, M.G. Coon, J. Brinton, M. Kline, D. Wray

Background
- Klebsiella spp. are often associated with bloodstream infections and healthcare-associated infections in immunocompromised patients.
- Carbapenem-resistant Klebsiella species have emerged as a significant threat in recent years.

Case report
- Two liver transplant recipients developed carbapenem-resistant Klebsiella infections.
- Both patients were treated with appropriate antimicrobial therapy.
- Despite treatment, one patient succumbed to multi-organ failure.
- The other patient recovered with prolonged hospitalization.

Conclusion
- Carbapenem-resistant Klebsiella infections are a serious concern in transplant recipients.
- Effective prevention and treatment strategies are essential to improve outcomes.

References
- Additional studies on the epidemiology and management of carbapenem-resistant Klebsiella infections in transplant recipients are recommended.

Authors' correspondence
- A.A. Matthews, Department of Medicine, University of California, San Francisco, CA 94143, USA. Email: amatthews@ucsf.edu
MMWR
July 25, 2008 / 57(29);799-801

- A 45-year-old Dominican Republic-born recipient, HIV, HBV, and HCV negative, ESRD presumed from HTN received one of a pair of kidneys in mid-February 2008.
- Course uncomplicated; in follow-up at 1 month, complained of some fevers, fatigue, and nausea.
- Admission labs at end of March demonstrated leukopenia, profound transaminitis, and some blood and protein in his urine.

- Extensive initial work-up was unrevealing; liver and kidney biopsies were unremarkable except for inflammatory changes in the liver.
- At the same time, report from NEOB that the paired recipient was in the ICU at another local hospital.
Donor Review

- Donor packet revealed the donor was living in a local shelter, and was found down outside the shelter.
- In ED, he was febrile to 102 and had a witnessed seizure;
  - BAC was elevated and assumed to be the cause of the seizure;
  - CXR demonstrated infiltrate and assumed aspiration PNA cause of the fever.
- In ICU, he remained unresponsive. Head imaging was unremarkable except for some atrophy.
  - L.P. demonstrated protein >100, glucose 30, and CSF pleocytosis at 150, mononuclear cell predominance.
  - Routine cultures and studies negative.
  - Assumed by local ID and Neurologist to be consistent with seizure.

- In ED, he was febrile to 102 and had a witnessed seizure;
  - BAC was elevated and assumed to be the cause of the seizure;
  - CXR demonstrated infiltrate and assumed aspiration PNA cause of the fever.

Serologies of the paired recipient returned LCMV positive, prompting the notification to us, MDPH and CDC.

- CDC proved the Donor had acute LCMV and transmission was to both recipients with positive evolving serologies and plasma PCR detection in prior stored and serial specimens.

- Both recipients died from complications of LCMV.
  - Our recipient rapidly developed acute renal failure not related to IS modification or AR;
    - in spite of this, we treated with IV RBV per emergent IND.
    - Minimal hemolysis was experienced.
    - At post, his liver was necrosing; his kidney was completely necrotic.
    - In surveillance, LCM viremia cleared.

Liver Biopsy IHC (4/18/08): LCMV Positive
Arenaviruses

- Generally associated with rodent-transmitted disease
- First arenavirus to be isolated was LCMV in 1933
- LCMV 110-130 nm

Vero E6 tissue culture cell infected with an arenavirus. Image shows extracellular virus particles budding from the cell surface.

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Transmission of Lymphocytic Choriomeningitis Virus by Organ Transplantation

- Australia
- 3 organ recipients died
- A new arenavirus was detected - Unbiased High-Throughput Sequencing
- Donor with no symptoms, no virus detected, IgM+ and IgG+

Subsequent sequence analysis at CDC revealed this to be LCMV. Personal communications, P Rollin
**T. cruzi (Chaga’s disease)**

- Endemic in Latin America
- Transmitted by the Triatome or “kissing” bug which defecates the eggs as it feeds; we scratch the eggs into the wound
- Causes smooth muscle paralysis (megacolon, myocarditis, heart blocks, distal esophagitis)
- Transmission reported in SOT and HSCT by donors and blood transfusions

**WHO estimates**
- 16-18 million persons infected with *T. cruzi*
- Incidence of 300,000 persons/year
- Mortality ~50,000 per year
- Distribution is in South and Central America, but seropositivity through blood bank screening ranges from 1.7% in Sao Paolo Brazil, to 53% in Santa Cruz, Bolivia
- The risk to the recipient population is dependent upon the geographic location of the center, and the donor history.

- 404 deceased donors in So Cal
- 25% donors are Hispanic
- 6 (1.5%) were EIA+ for *T. cruzi*
- 1 had active disease

Nowicki et al. Transplantation 2006;81:477-8

**Chaga’s Disease**

- **Acute phase:**
  - incubation period of 7 to 10 days.
  - Local skin swelling: chagomas.
  - Romana’s sign: unilateral periorbital edema and swelling of the eyelid if conjunctival inoculation
  - Other symptoms include: fever, myalgias, sweating, hepatosplenomegaly.
  - Cardiac involvement is present in over 90 percent of those in whom the diagnosis is made.
  - Variable signs of cardiac failure secondary to myocarditis
  - Frequency and severity of myocarditis are inversely proportional to age
  - Very rarely, can present as meningencephalitis.
  - Recovery is spontaneous in over 95% of those acutely infected with normalization of ECGs.
Indeterminant form:
- Persons who are asymptomatic but are seropositive for the disease
- 2% per year will have slowly developing evidence of end organ involvement (GI, cardiac)
- In one report, 38.3% of persons who were seropositive but asymptomatic at time of diagnosis developed signs and symptoms of cardiac involvement within 10 years.

Chronic disease (cardiac)
- Biventricular failure
- High rate of sustained and nonsustained dysrythmias with sudden death reported in up to 55% of persons with cardiac disease
- Ventricular aneurysms may be found
- Mural thromboembolism reported in 44% of autopsy pts with embolic CVA complications reported in up to 56% of pts with chronic cardiac disease

Diagnostics
- FOCUS IFA: highly reliable with results >1:256 with sensitivity >93% at this level
- CDC IFA and EIA: essentially confirmatory with sensitivities and specificities >95%
- PCR appears to be the new gold standard in endemic regions.
  - 194 patients at high risk for chronic Chagas' disease
  - Serology negative in 80 pts (41%)
  - 12 of the 80 (15%) were positive by PCR.
  - 3 of the 12 (25%) had clinical signs and symptoms that suggested Chagas' heart disease.
- It is available through the CDC.

As pertains to Transplantation

- Reactivation reported in:
  - 9-16% of KI
  - 50-100% hearts
  - 17% autologous HSCT
  - 40% allogeneic HSCT
  - Surveillance recommended to include at minimum the direct Strout test (assessment for parasitemia)
  - PCR is being suggested as a suitable surveillance tool
  - Suggestion in endemic areas to preemptively treat with a positive result


In spite of potential transmission through HSCT or with SOT, or reactivation occurring post-transplant, outcomes can be reasonably good with recognition pre-transplantation, good surveillance (PCR vs smear for parasitemia), and treatment


- Reactivation or disease mitigation with use of azoles (fluconazole, voriconazole) as these are structural similar to benznidazole.
As pertains to Renal transplantation

Renal Transplant experience, Argentina

- 23 seropositive recipients
  - 5 reactivated between day 35 to month 29
  - Reactivation defined by parasitemia (3), cutaneous disease (2)
  - All treated with benznidazole for 21-30 days and repeated with parasitemia recurrence
  - 10 became seronegative over time
- 16 seronegative recipients received organs from seropositive donors
  - Transmission occurred in 3 pts (18.75%)
  - All had parasitemia

Strongyloides

*Strongyloides stercoralis*—very small threadlike roundworm that is found throughout the tropic and subtropical regions of the world. Typical infestation is from very few parasites.

Females tend to burrow into the small bowel or colon wall and either encyst or every couple of weeks release an egg that may or may not hatch in the gut. Transmission is rarely through the fecal-oral route, but more often by the adolescent worm burrowing through the skin.

In most cases, SHS is from recipient specific hyperparasitism following exposure to immunosuppressive or cytoreductive therapies.

- Donor associated infections include:
  - Recipient SHS following intestinal transplant
    - Recipient survived the infection
  - Recipient SHS following heart transplantation
    - Recipient died from the infection

While transmission through SOT is rare, if the recipient is infected, exposure to steroids and IS can result in hyperparasitism which is life-threatening.

- Some suggestion that there may be a steroid dependent promotor region that is upregulated on the female nematode.

- Gravid females become highly active, migrating through tissue planes
- Can present with GN sepsis, ‘sterile’ sepsis, and cyclic hypereosinophilia (improved with steroids; exacerbated with steroid withdrawal)

- Other agents also implicated including ALG, biologics including rituximab, and cytoreductive chemotherapy


Conclusions

Syndromic Approaches to donor/recipient evals

- CNS disease-
  - Arboviruses, rabies, LCMV, leptospirosis, NIPAH virus, toxoplasma

- Sepsis Syndromes
  - Acute hepatitis E, brucella, coxiella, leptospirosis, tularemia, Chaga’s disease, strongyloidiasis, toxoplasma

- Unexplained hepatitis
  - Hepatitis C, leptospirosis, Bartonella, Brucella, Coxiella, LCMV, Nipah, leishmaniasis, Babesia, anaplasma

- Eosinophilia
  - Strongyloidiasis, acute viral infections, endemic mycoses.
In all cases, need:

1) GOOD social history for both donor and recipient.
   - A good history should be done by the Donor site as part of the organ procurement process
     - Rabies case in 2004,
     - The New England LCMV case in 2006
     - Our LCMV in 2008

2) careful review of the labs and radiographic studies; while not specific, there may be enough circumstantial information to clear or not clear a potential donor
   - GESITRA, European ID Society recommendations now to forego any lung harvest if granuloma present.

Rarely associated with SOT, but in 2004, 4 recipients became infected when the organs of donor were transplanted into them.

The donor presented 4 days prior to harvesting to the local ED where he complained of headache and difficulty swallowing; no exposure history was provided at that time.

Toxicology screen revealed cocaine. He decompensated rapidly, developing seizures and requiring intubation. Head CT demonstrated intracranial hemorrhage.

3 organ recipients and 1 iliac artery recipient died from rabies

Prior reports include infection from corneal transplantation.

Rabid bat rate in NE
   - In 2006, 4% (34/756) of the bats submitted to the Rabies Laboratory at the State Laboratory Institute (SLI) were positive.
   - This past summer, we saw a patient from Quincy who caught a bat in her home that was rabid.