What’s hot in adult infectious diseases?

Ted Steiner, M.D.
Associate Professor, Associate Head
UBC Infectious Diseases
May 5, 2012
Disclosures

- Honoraria from Amgen, Wyeth
- Consultant for Optimer, Iroko
- Research support from Merck
Topics--What’s new in:

- *Staph aureus*
- *C. difficile*
- Viral infections
- Transplant ID
- Antibiotic-resistant GNRs
- Vaccines
- Emerging infections
- Odds & Ends
What’s new in *Staph aureus*?

- Which patients with *S. aureus* bacteremias need a TEE?
- What to do about vancomycin MIC creep in MRSA?
- What to do about recurrent *S. aureus* skin infections?
Predictors for IE in nosocomial SAB

- Problem: how to predict which patients with hospital-acquired SAB are likely to have IE and require a TEE
- Patients analyzed from two large prospective cohorts (INSTINCT and SABG)
- Simplified criteria for IE:
  - Prolonged bacteremia (>4 days to neg blood cx)
  - Permanent intracardiac device
  - Hemodialysis
  - Spinal infection or osteomyelitis

Results of study

- 798 patients analyzed
- 546/798 met one or more criteria
  - 53 with echo-confirmed IE
  - 14 of these were due to IV catheters
- 212 were negative for all criteria
  - Only 1 with confirmed IE
- Negative predictive value of 0 criteria: 99.2%
- Conclusion: TEE may be dispensable in low-risk patients

What to do about MRSA with moderate vancomycin MICs?

- IDSA Guidelines for MRSA published in Jan, 2011
  - Vancomycin for infections with MIC ≤ 2
  - Combination with rifampin or gentamicin not recommended
  - Alternative to vancomycin (e.g. daptomycin for bacteremia, linezolid or clindamycin for pneumonia) in cases of clinical failure or MIC > 2
  - Evidence for alternatives in cases of clinical failure or reduced vanco/dapto susceptibility is all grade B/C

- Emerging data on alternatives sorely needed!
Problem: what about vancomycin MIC of 1.5-2.0?

- These isolates are “susceptible” but outcomes may not be as good

  - 22 studies included in analysis
  - MIC associated with mortality (only when excluding MSSA) when comparing ≥1.5 to <1.5
  - Mortality difference driven by BSI and MICs ≥2
Is there a benefit of daptomycin over vancomycin?

- **Case-control study** (Moore et al, Clin Infect Dis 2012;54(1):51-8)
  - MRSA BSIs with vancomycin MIC ≥ 1.5
  - Cases: received daptomycin (*usually switched from vanco*)
  - Controls: treated with vancomycin
- Daptomycin group: lower 60-day mortality (P = 0.022)
- Problems: reasons for switch from vancomycin to daptomycin; effect of early deaths; dapto group more likely to get ID consultation?
  - Also, low number of cases with MIC 2—underpowered in this subgroup
MRSA: conclusions

- Still insufficient evidence demonstrating superiority of alternatives to vancomycin in all cases of MIC 1.5
- Alternatives may be better when MIC=2
  - But is it too late by the time the E-test is done?
- Switching from vanco to dapto in cases of clinical failure justified; evidence for initial therapy lacking
- Still insufficient evidence regarding other alternative drugs for MRSA bacteremias
  - Clinical successes are common
What to do about daptomycin failure?

- **Dhand et al** *(Clin Infect Dis 2011; 53(2):158-163)*
  - Used combination daptomycin plus anti-staph β-lactam in 7 patients with breakthrough bacteremia on daptomycin
  - Demonstrated increased daptomycin binding and activity with combination

- RCT of vanco vs dapto underway
What do we do about recurrent *Staph aureus* SSTIs?

**Household Versus Individual Approaches to Eradication of Community-Associated *Staphylococcus aureus* in Children: A Randomized Trial**

*Clinical Infectious Diseases* 2012;54(6):743–51

Stephanie A. Fritz,¹ Patrick G. Hogan,² Genevieve Hayek,¹ Kimberly A. Eisenstein,¹ Marcela Rodriguez,¹ Emma K. Epplin,¹ Jane Garbutt,¹,² and Victoria J. Fraser²

Departments of ¹Pediatrics and ²Medicine, Washington University School of Medicine, St Louis, Missouri

(See the Editorial Commentary by Miller, on pages 752–4.)

---

**Prospective Investigation of Nasal Mupirocin, Hexachlorophene Body Wash, and Systemic Antibiotics for Prevention of Recurrent Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections**

Loren G. Miller,⁶ Jennifer Tan,⁶ Samantha J. Eells,⁶ Esther Benitez,⁶ and Allen B. Radner⁶

Harbor-UCLA Medical Center, Torrance, California, USA⁶; Los Angeles Biomedical Research Institute, Torrance, California, USA⁶; and Natividad Medical Center, Salinas, California, USA⁶.
Whom to decolonize?

- Fritz et al: Children with recurrent MSSA OR MRSA SSTIs randomized to solo or family decolonization
  - 5d regimen of mupirocin and chlorhexidine plus hygiene education
  - Decolonization in 50% of each group but household group had fewer recurrences (52% vs 72% at 1 yr)
  - Many patients with SSTIs had no detectable colonization
Does eradication work?

- Miller et al—nonrandomized, prospective trial of 31 patients with ≥2 recurrent MRSA SSTIs
- Given 10d intranasal mupirocin, 3% chlorhexidine, plus doxy, TMP-SMX, or minocycline
- Recurrences in 5 patients: 0.03 infections/month vs. 0.84 before therapy
- Limitations: no control group; no cultures done; different regimens
- Promise: supports our clinical experience.
What’s new in *C. difficile*?

- Fidaxomicin approved in US
  - Likely soon in Canada
- New guidelines for stool transplantation
- New information on course of the NAP1/BI/027 epidemic
Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poinier, Michael S Samara, Karl Weiss, Pamela Sears, Sherwood Garbach, for the OPT-80-004 Clinical Study Group
More good news about fidaxomicin

- Concomitant antibiotics delay response to vanc/fidax and increase risk of relapses
- Fidax superior to vanc in clinical cure (95% vs 79%) in presence of concomitant antibiotics
- Lower relapse rate with fidax (17% vs 29%)
The not-so-good news

- More recent paper (Petrelli et al, CID, April 2012)
- Analysis of all subjects combined from the Phase III Fidaxomicin vs. Vancomycin trials
- Benefit of fidaxomicin highest in non-NAP1/BI cases (16.6% vs 27.4%; p = .007)
- Recurrence rate not significantly different in NAP1/BI cases (23% vs 31%; p=0.2)
- Studies not powered to answer this question
Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection in 26 Patients

Methodology and Results

---

Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for Recurrent *Clostridium difficile* Infection

Lawrence J. Brandt, MD, MACG1, Olga C. Aroniadis, MD1, Mark Mellow, MD, FACP2, Amy Kanatzar, BA2, Colleen Kelly, MD3, Tina Park, MD3, Neil Stollman, MD, FACP45, Faith Rohlke, BA6 and Christina Surawicz, MD, MACG7

CONCLUSIONS: **FMT is a rational, durable, safe, and acceptable treatment option for patients with recurrent CDI.**

*Am J Gastroenterol* advance online publication, 27 March 2012; doi:10.1038/ajg.2012.60

---

Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD1, Alexa R. Weingarden1, Michael J. Sadowsky, PhD1,2 and Alexander Khoruts, MD2,3

*Am J Gastroenterol* advance online publication, 31 January 2012; doi:10.1038/ajg.2011.482
Has the epidemic finally peaked?

Figure 1. Trends in hospital stays associated with Clostridium difficile infection (CDI), 1993–2009

What’s new in viral infections?

- HIV
  - Comparison of TB prophylaxis regimens
  - Timing of ARVs during TB treatment
  - Effect of early treatment on transmission (it works!)

- Hepatitis C
  - New guidelines based on newer drugs
What’s new in hepatitis C?

● New drugs!
● Better drugs!

AASLD Practice Guideline

An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases

Marc G. Ghany, David R. Nelson, Doris B. Strader, David L. Thomas, and Leonard B. Seeff
HIV and TB studies

- **Martinson et al** *(NEJM 2011:365(1);11-20)*
  - Compared 4 prophylaxis regimens in HIV+/PPD+ patients
  - Low rate of active TB disease in all 4 groups
  - Continuous INH protective in the long term; shorter courses had higher adherence

- **When to start ARVs in TB** *(NEJM 2011; 365:1471-1481)*
  - CD4<200 randomized to 2 wks vs 8 wks
  - Improved survival in 2 wks group, but more IRIS
  - Differed from earlier studies only showing a benefit with CD4<50
  - Consensus: start early when very immune suppressed, but with caution
What’s new in transplant ID?

- Still no definitive answers on:
  - Best regimens for prophylaxis for fungal infections in HSCT/leukemias
  - Best approach to CMV in SOT
  - Optimal diagnosis of invasive fungal infection
  - Empiric antifungal therapy vs. pre-emptive therapy
  - Optimal treatment for invasive fungal infection (Which drugs? Alone or in combination?)
Is combination therapy for IA superior?

- Multicentre trial results just presented at ECCMID (poster)—K. Marr et al (MSG)
- RCT compared Voriconazole + anidulafungin to Vori + placebo in proven or probable IA
  - MITT: diagnosis confirmed as proven or probable by day 7
  - Subgroups: diagnosed by tissue, culture, or GM only
- Primary endpoint: 6 week mortality in MITT
Results of trial

- Primary endpoint (6 wk mortality): combo therapy 19.3% vs monotherapy 27.5% (P = 0.0868)
- Subgroup with probable IA diagnosis based on GM alone (majority of subjects): combo therapy significantly better (15.7% vs 27.3%; P = .037)
- Global response composite marker (clinical and radiographic improvement): monotherapy better (43% vs 33%; P = 0.078)
  - Unequal censoring of cases likely contributed
- No significant toxicity differences between arms
Combo therapy: conclusion

- By strict statistical criteria: no demonstrated survival benefit of combo Rx vs voriconazole monotherapy
  - However, a strong trend!
- In subgroup based on GM alone, there was a statistically significant survival benefit
  - Were the patients with positive culture or histopath too advanced already? 28%/33% mortality in single/combo arms
- Practice patterns already changing in some institutions—but publication still pending
- What about other combinations?
What’s new in resistant GNRs?

Carbapenem-resistant Gram-negative bacilli in Canada 2009–10: results from the Canadian Nosocomial Infection Surveillance Program (CNISP)

L. F. Mataseje¹, E. Bryce², D. Roscoe³, D. A. Boyd⁴, J. Embree⁵, D. Gravel⁶, K. Katz⁷, P. Kibsey⁶, M. Kuhn⁷, A. Mouchill⁸, A. Simor⁹, G. Taylor⁹, E. Thomas¹⁰, N. Turgeon¹¹ and M. R. Mulvey¹¹ on behalf of the members of the Canadian Nosocomial Infection Surveillance Program†

¹Public Health Agency of Canada, Winnipeg, MB, Canada; ²Vancouver General Hospital, Vancouver, BC, Canada; ³University of Manitoba, Winnipeg, MB, Canada; ⁴Public Health Agency of Canada, Ottawa, ON, Canada; ⁵North York General Hospital, Toronto, ON, Canada; ⁶Victoria General Hospital, Victoria, BC, Canada; ⁷Moncton Hospital, Moncton, NB, Canada; ⁸Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ⁹University of Alberta Hospital, Edmonton, AB, Canada; ¹⁰Children’s and Women’s Health Center, Vancouver, BC, Canada; ¹¹Hotel-Dieu de Quebec du CHUQ, QC, Canada
20 hospital sites across Canada submitted all suspected carbapenem-resistant *Pseudomonas*, *Acinetobacter*, and Enterobacteriaceae.

- Vitek often overestimated MIC versus broth dilution or E-test.
- Majority of *Pseudomonas* resistance was not due to transmissible carbapenemases.
- Majority of *Acinetobacter* resistance was due to ESBLs.
- A few clustered outbreaks identified.

Conclusion: we have been fairly lucky—so far . . .
• 15-50% of *Klebsiella pneumoniae* isolates from BSI are carbapenem resistant in EU
• Increasing incidence of NDM-1 isolates
Some good news . . .

What Is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

- Systematic review of studies of colistin for VAP
- No significant difference between colistin and comparator antibiotics in mortality, microbiologic success, or nephrotoxicity
- Still no good RCT data
What’s new in vaccines?
Vaccines: the good news


- Successful trial of meningococcal group A conjugate vaccine (N Engl J Med 2011; 364:2293-2304)


Vaccines: the bad news

- Failure of HSV2 vaccine
- Vaccine-associated Polio (12 years later)
- Ongoing public outcry over vaccines
- Ongoing outbreaks of vaccine-preventable diseases
HSV vaccine trial

- HSV2 glycoprotein (gD-2) vaccine
- Two prior studies on serodiscordant couples: significant reduction in HSV2 disease in HSV1/2 seroneg. Women
- Current trial: HSV1/2 seronegative women randomized to gD-2 or hep A vaccine

NEJM 2012, 366(1):34-43
Results

- Vaccine protective against HSV-1 genital disease (58% efficacy CI 12-80) but not HSV-2 disease
- Risk factors for acquisition of HSV-1: >5 lifetime sexual partners, age 18-22; NOT geography, ethnicity, history of partner with HSV, oral sex, etc.
- Risk factors for HSV-2: >5 partners in past year, history of STI, nonwhite race, and living in U.S.

NEJM 2012, 366(1):34-43
Vaccine-associated Polio

- 44 yo woman with CVID on maintenance IVIg developed progressive weakness over several days
- EMG suggested anterior horn-cell disease
- Multi-organ failure, eventual withdrawal of ventilatory support
- Stool sample on day 74 identified vaccine-associated poliovirus type 2 with reversion at two sites to wild-type—estimated infection 12 years prior
- Patient’s child had received OPV 12 years prior

Emerging infections

- *E. coli* O104:H4 and HUS
- Schmallenberg virus
- New Ehrlichia strain
- And one “un-emerging” infection
E. coli O104:H4 and HUS

- An enteroaggregative strain that acquired the Stx2 phage
- High rate of HUS (22%), predominantly in adult women
- Acquired from sprouts
- Reasons for high HUS incidence still unknown
- Expresses an ESBL and R to TMP/SMX but S to FQ
  - We still don’t know whether or not to treat these!
Schmallenberg virus

- Novel orthobunyavirus causing outbreak of livestock disease in northern Europe
- Causes fever, diarrhea, congenital malformations
- No evidence of spread to humans
- Related virus unable to infect humans
Identified via PCR surveillance of suspected cases—found atypical sequences and created specific ELISA

4 patients developed clinical illness c/w Ehrlichiosis
  - Fever, headache, lymphopenia, thrombocytopenia
  - Two were SOT recipients

All 4 survived—improved on Doxycycline

Strain related to *E. muris*
And the unemerging infection . . .

- XMRV and Chronic fatigue
  - Since the initial report in 2009, several laboratories were unable to reproduce the results
  - Follow-up publications identified XMRV sequences as a contaminant of common lab reagents and demonstrated how false results were obtained
  - Two authors of original study asked to retract
  - *Science* finally retracted article in Dec. 2011
Odds & Ends

- Another rabies survivor
- Are antibiotics as good as appendectomy for acute appendicitis?
- Can “big brother” make you wash your hands?
- New IDSA guidelines for rhinosinusitis
- And: the most important papers NOT to get published
Another rabies survivor!

11 yo girl with swallowing difficulty—progressed to ascending flaccid paralysis
Rabies diagnosed based on + IgG and IgM (serum/CSF)
Recovered after ketamine-induced coma—remained unvaccinated
Can Abx cure appendicitis?

- Noninferiority RCT of Amox/Clav vs surgery
- Primary endpoint: peritonitis within 30d: abx not non-inferior (8% vs 2%, CI 0.3-12.1)
- 32% of patients in Abx group required surgery within 1 year
- No differences in disability, hospital stay, pain
- Video cameras placed outside every room of MICU
- Each room entry noted by electronic sensor, and automatically scored as pass/fail/not assessable
- Feedback provided real time via LED boards, and multiple daily emails to supervisors
Conclusion: it works!
But: did it have any impact on nosocomial infections?
What about patient and HCW privacy concerns?
IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

- More stringent definition of when to treat
- Change in recommended Abx
  - Amox/Clav or Doxycycline
- Change in duration for adults (5-7d)
- Antihistamines/decongestants not recommended
And what hasn’t been published:
Can H5N1 spread between humans?

- **Fouchier group (Rotterdam)**
  - Identified cluster of mutations in H5 that allowed spread between ferrets
  - Initial report: fatal high level transmission
  - Later: softened

- **Kawaoka group (Wisconsin)**
  - Identified random mutations in H5 that allowed adherence to human tracheal cells
  - Then made chimeric virus with H1N1 pandemic strain and demonstrated spread between ferrets (but slow and nonlethal)
Debate on H5N1

- Reported mortality of H5N1 around 59%
- If mutant virus carried even 10% that level, this would still be devastating
- Concerns about accidental or intentional release and potential for pandemic spread
- Outcome: papers to be published,
  - “horse already out of the barn”
- Virus made CL4 in Canada—rest of the world?
Let’s hear it for evidence-based medicine