What's hot in adult infectious diseases?

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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

Clin Infect Dis 2011;53(1):1–9

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

Clin Infect Dis 2011;53(1):1–9

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 bactermia, 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
- Meta-analysis by van Hal, Lodise, and Paterson (Clin Infect Dis. 2012;54(6)755-71)
  - 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 ß-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,[1] Genevieve Hayek,[1] Kimberly A. Eisenstein,[1] Marcela Rodriguez,[1] Emma K. Epplin,[1] Jane Garbutt,[1,2] and Victoria J. Fraser[2]

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

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

AAC

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,[a,b] Jennifer Tan,[b] Samantha J. Eells,[b] Esther Benitez,[c] and Allen B. Radner[c]

Harbor-UCLA Medical Center, Torrance, California, USA[a]; Los Angeles Biomedical Research Institute, Torrance, California, USA[b]; and Natividad Medical Center, Salinas, California, USA[c]

Whom to decolonize?

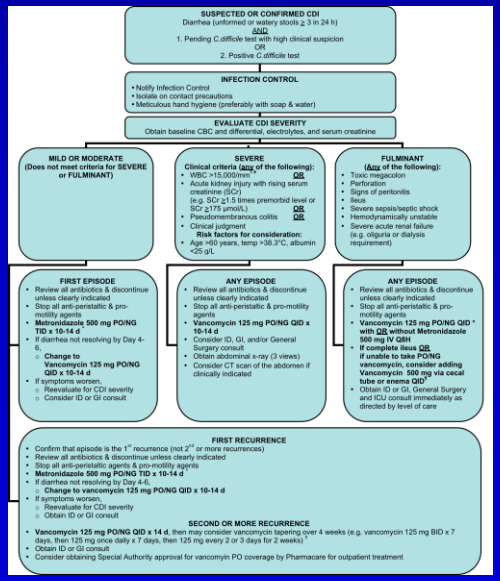
- Fritz et al: Children with recurrent MSSA OR MRSA SSTIs randomized to solo or family decolonization
- 5d regimen of mupirocin and chlorhexidine plus hygeine education
- Decolonization in 50% of each group but household group had fewer recurrences (52% vs 72% at 1 yr)
- Many patients with SSTIs had 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



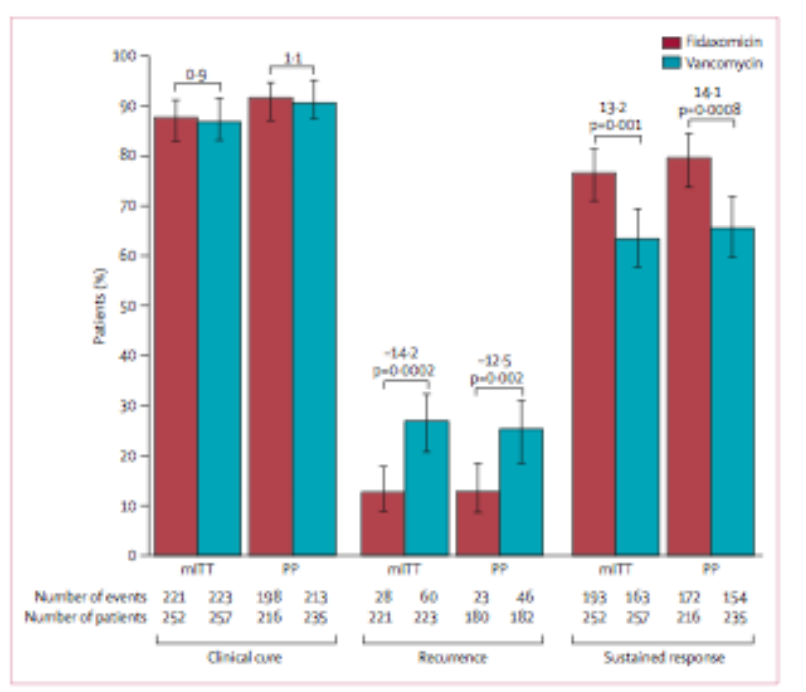
Fidaxomicin

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 Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group

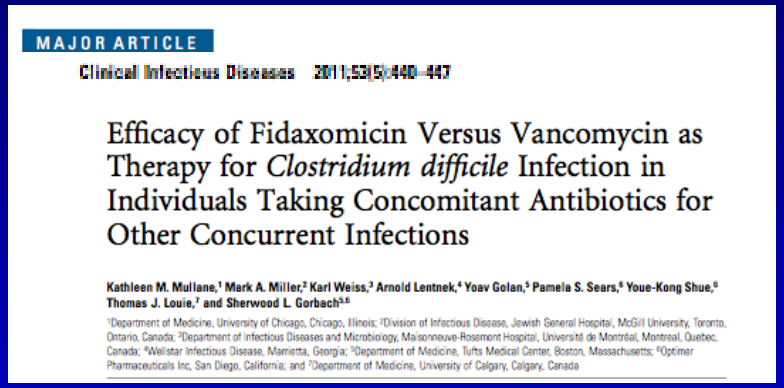
Lancet Infect Dis 2012; 12: 281–89

Published Online February 8, 2012 DOI:10.1016/S1473-3099(11)70374-7



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% v 79%) in presence of concomitant antibiotics
- Lower relapse rate with fidax (17% vs 29%)



MAJOR ARTICLE

Clinical Infectious Diseases 2011;53(5):440–447

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Kathleen M. Mullane,[1] Mark A. Miller,[2] Karl Weiss,[3] Arnold Lentnek,[4] Yoav Golan,[5] Pamela S. Sears,[6] Youe-Kong Shue,[6] Thomas J. Louie,[7] and Sherwood L. Gorbach[5,6]

[1]Department of Medicine, University of Chicago, Chicago, Illinois; [2]Division of Infectious Disease, Jewish General Hospital, McGill University, Toronto, Ontario, Canada; [3]Department of Infectious Diseases and Microbiology, Maisonneuve-Rosemont Hospital, Université de Montréal, Montreal, Quebec, Canada; [4]Wellstar Infectious Disease, Marietta, Georgia; [5]Department of Medicine, Tufts Medical Center, Boston, Massachusetts; [6]Optimer Pharmaceuticals Inc, San Diego, California; and [7]Department of Medicine, University of Calgary, Calgary, Canada

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

(*J Clin Gastroenterol* 2012;46:145–149)

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

Lawrence J. Brandt, MD, MACG[1], Olga C. Aroniadis, MD[1], Mark Mellow, MD, FACG[2], Amy Kanatzar, BA[2], Colleen Kelly, MD[3], Tina Park, MD[3], Neil Stollman, MD, FACG[4,5], Faith Rohlke, BA[6] and Christina Surawicz, MD, MACG[7]

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

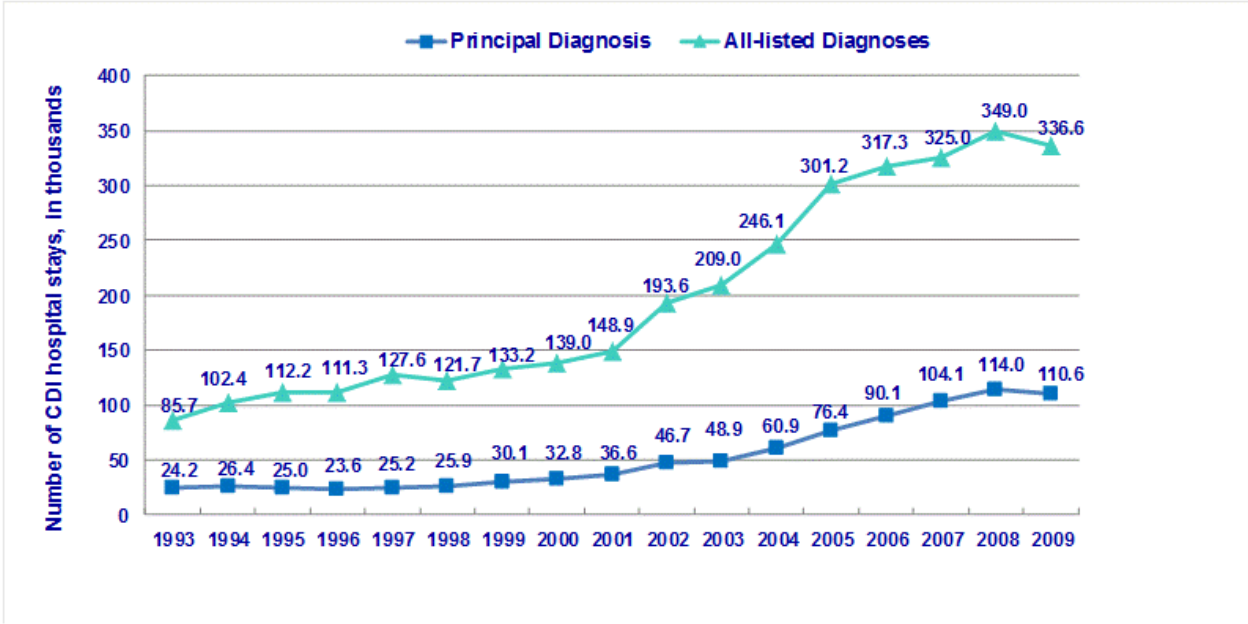
Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD[1], Alexa R. Weingarden[1], Michael J. Sadowsky, PhD[1,3] and Alexander Khoruts, MD[2,3]

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



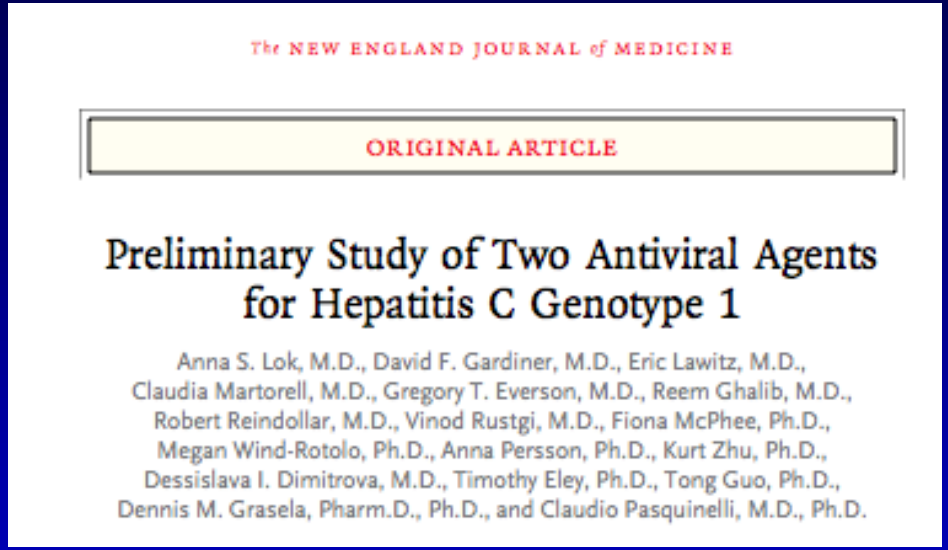
Source: AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 1993–2009

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!

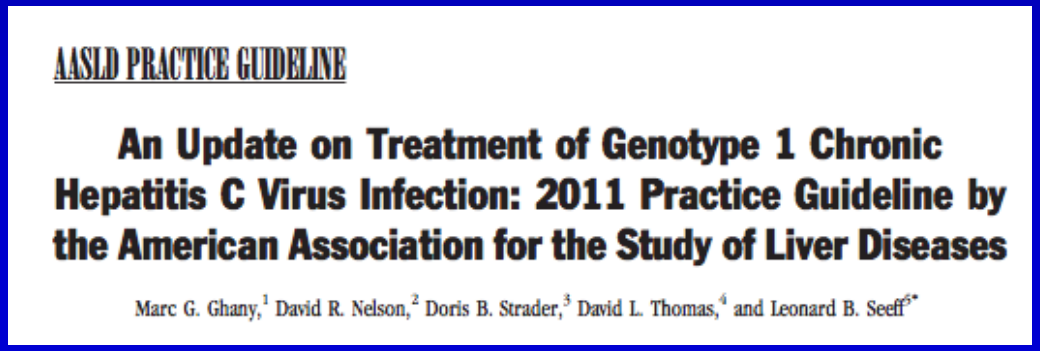


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1

Anna S. Lok, M.D., David F. Gardiner, M.D., Eric Lawitz, M.D., Claudia Martorell, M.D., Gregory T. Everson, M.D., Reem Ghalib, M.D., Robert Reindollar, M.D., Vinod Rustgi, M.D., Fiona McPhee, Ph.D., Megan Wind-Rotolo, Ph.D., Anna Persson, Ph.D., Kurt Zhu, Ph.D., Dessislava I. Dimitrova, M.D., Timothy Eley, Ph.D., Tong Guo, Ph.D., Dennis M. Grasela, Pharm.D., Ph.D., and Claudio Pasquinelli, M.D., Ph.D.



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,[1] David R. Nelson,[2] Doris B. Strader,[3] David L. Thomas,[4] and Leonard B. Seeff[5]*

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?

J Antimicrob Chemother
doi:10.1093/jac/dks046

Journal of Antimicrobial Chemotherapy

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

L. F. Mataseje[1], E. Bryce[2], D. Roscoe[2], D. A. Boyd[1], J. Embree[3], D. Gravel[4], K. Katz[5], P. Kibsey[6], M. Kuhn[7], A. Mounchili[4], A. Simor[8], G. Taylor[9], E. Thomas[10], N. Turgeon[11] and M. R. Mulvey[1]* on behalf of the members of the Canadian Nosocomial Infection Surveillance Program†

[1]*Public Health Agency of Canada, Winnipeg, MB, Canada;* [2]*Vancouver General Hospital, Vancouver, BC, Canada;* [3]*University of Manitoba, Winnipeg, MB, Canada;* [4]*Public Health Agency of Canada, Ottawa, ON, Canada;* [5]*North York General Hospital, Toronto, ON, Canada;* [6]*Victoria General Hospital, Victoria, BC, Canada;* [7]*Moncton Hospital, Moncton, NB, Canada;* [8]*Sunnybrook Health Sciences Centre, Toronto, ON, Canada;* [9]*University of Alberta Hospital, Edmonton, AB, Canada;* [10]*Children's and Women's Health Center, Vancouver, BC, Canada;* [11]*Hotel-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 . . .

Not so in Europe . . .

•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

Diana F. Florescu,[1] Fang Qiu,[2] Megan A. McCartan,[3] Cezarina Mindru,[1] Paul D. Fey,[4] and A. C. Kalil[1]

[1]Infectious Diseases Division, [2]Biostatistics Department, [3]Department of Pharmaceutical and Nutrition Care, and [4]Pathology Microbiology Department, Nebraska Medical Center, Omaha

Clinical Infectious Diseases 2012;54(5):670–80

- 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

- Rotavirus vaccine: quantification of intussusception risk (N Engl J Med 2011; 364:2283-2292)
- Successful trial of meningococcal group A conjugate vaccine (N Engl J Med 2011; 364:2293-2304)
- Successful trial of group B meningococcal vaccine Lancet. 2012 Feb 18;379(9816):617-24.
- Promising new Norovirus vaccine N Engl J Med 2011; 365:2178-2187
- Efficacy of HPV in preventing anal intraepithelial neoplasia N Engl J Med. 2011;365(17):1576-85.

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

N Engl J Med 2011; 364:2316-2323

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, congential malformations
- No evidence of spread to humans
- Related virus unable to infect humans

N Engl J Med 2011;365:422-9.

- 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*

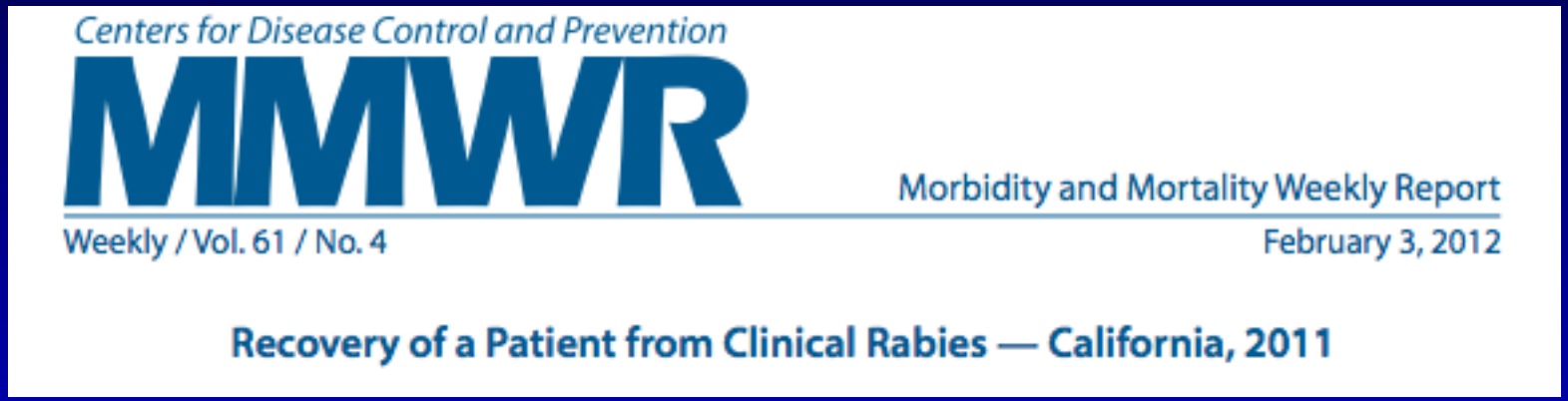
And the unemerging infection . . .

- 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

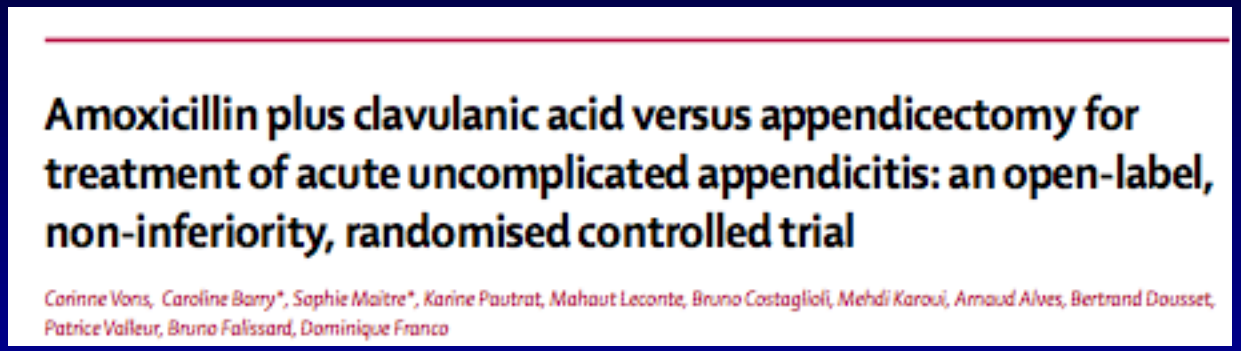
- Another rabies survivor
- Are antibiotics as good as appendectomy for acute appendicitis?
- Can “big brother” make you wash your hands?
- New IDSA guidelines for rhinosinusitis
- And: the most important papers NOT to get published

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?



Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial

Corinne Vons, Caroline Barry, Sophie Maitre*, Karine Pautrat, Mahaut Leconte, Bruno Costaglioli, Mehdi Karoui, Arnaud Alves, Bertrand Dousset, Patrice Valleur, Bruno Falissard, Dominique Franco*

Lancet 2011; 377: 1573–79

- 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

Using High-Technology to Enforce Low-Technology Safety Measures: The Use of Third-party Remote Video Auditing and Real-time Feedback in Healthcare

Donna Armellino,[1] Erfan Hussain,[2] Mary Ellen Schilling,[1] William Senicola,[3] Ann Eichorn,[5] Yosef Dlugacz,[5] and Bruce F. Farber[4]

Clinical Infectious Diseases 2012;54(1):1–7

- 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

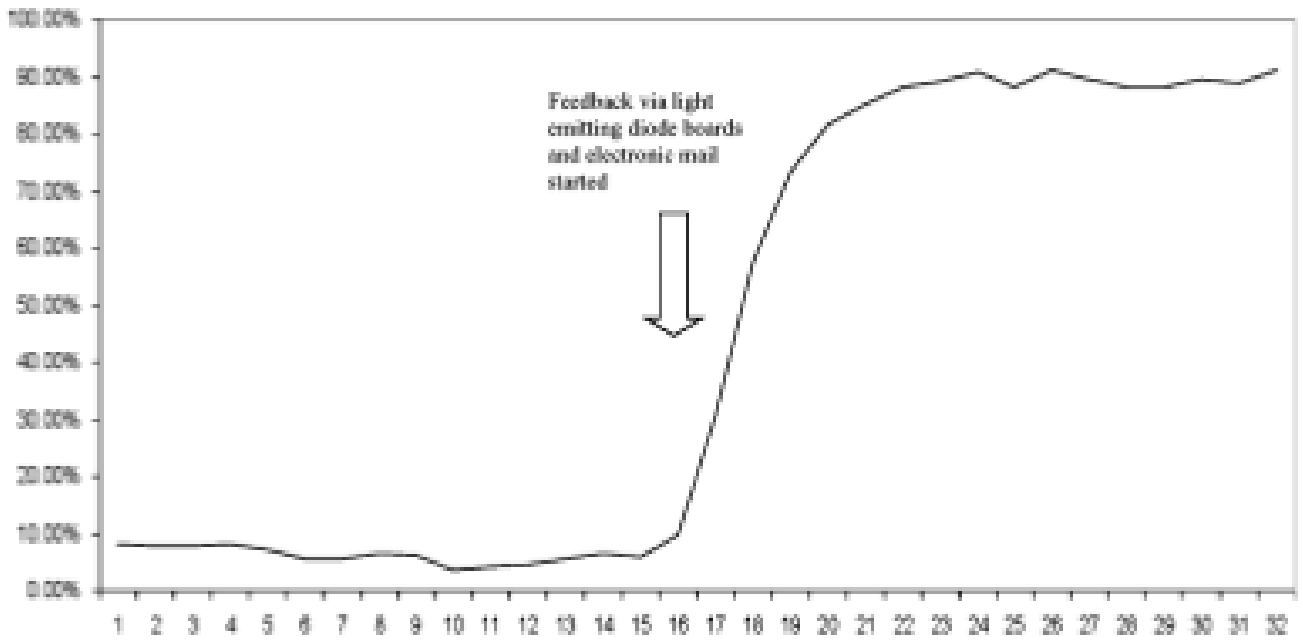
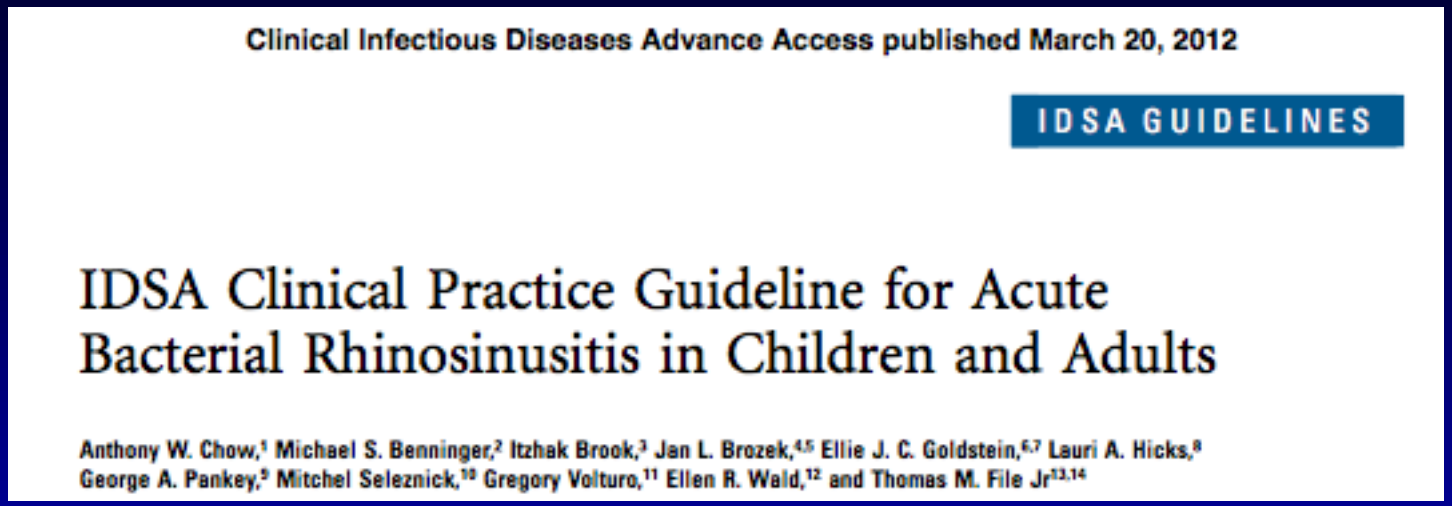


Figure 3. Hand hygiene compliance by week during impact period following feedback.

Conclusion: it works!
But: did it have any impact on nosocomial infections?
What about patient and HCW privacy concerns?



Clinical Infectious Diseases Advance Access published March 20, 2012

IDSA GUIDELINES

IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

Anthony W. Chow,[1] Michael S. Benninger,[2] Itzhak Brook,[3] Jan L. Brozek,[4,5] Ellie J. C. Goldstein,[6,7] Lauri A. Hicks,[8] George A. Pankey,[9] Mitchel Seleznick,[10] Gregory Volturo,[11] Ellen R. Wald,[12] and Thomas M. File Jr[13,14]

- 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