Infectious Disease Update – 2010

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Outline of Talk

• HPV Vaccination: Herd Immunity and Genital Warts
• N95 versus Surgical Masks for Prevention of Influenza
• Macrolides versus Other Atypical Coverage in Combination Rx for Severe Community Acquired PNA
• New *Clostridium difficile* Treatment Guidelines
• Melanoma and Photosensitivity from Voriconazole
• Preventing Surgical Site Infections in *Staphylococcus aureus* Nasal Carriers
• The next bad bug: *Klebsiella pneumoniae* carbapenemase-producing bacteria

“Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human HPV vaccine national program for young women”

Fairley CK, Hocking JS, Gurrin LC et al.
HPV Vaccine - Background

- HPV vaccine trials: show high level efficacy, high level efficacy in prevention of precancerous cervical lesions and early (in situ) cervical cancer (serotypes 16 and 18, 70% invasive cervical CA)
- Two vaccines available (Gardasil®, quadrivalent HPV4)(HPV 6, 11, 16, 18); (Cervarix®, bivalent HPV 2) (HPV 16, 18)
- Either HPV2 or HPV4 is recommended by ACIP is recommended for routine vaccination of pre-adolescent girls (age 9 -12) and “catch-up” vaccination for girls and women age 13 – 26

HPV Vaccine- Background

- Policy decisions regarding which vaccine to use should be based upon population based efficacy studies
- Population-based studies have not previously been preformed to demonstrate effects on prevalence of genital warts in an at risk population to help determine cost effectiveness of HPV4

Study Methods

- Retrospective analysis Melbourne STD treatment center, 1/04 – 12/08; 36,055 visits for STDs
- Australia rolled out no-cost HPV4 vaccine to 12-18 y.o. females in school based programs starting 7/07
- HPV vaccine was also available for boys aged 9 – 15 by end of 2007 at cost of approximately $300
- By end of 2007, approximately 70% of at risk girls/women between age 12 and 17 were vaccinated
- Primary analysis: change in quarterly prevalence of genital warts before and after 12/07 in four groups (women < 28, > 28, MSM, MSW)
Conclusions

- Significant reduction in genital warts prevalence in girls/women aged 9 – 26 in pre/post vaccine period
- Similar (but lesser) reduction in risk in heterosexual partners of these women suggest herd immunity
- Reduction in genital warts reduce clinic visits, morbidity related to treatment, possible reduction in transmission of other STDs
- No reduction in prevalence in MSM or women > age 28 suggest direct vaccine effect on prevalence in vaccinated population
- No reduction in genital HSV in women > age 28 or in their heterosexual partners suggests no change in acquisition risk for HPV infection
- Further studies should focus on effect of adolescent male population in development of herd immunity

“Surgical Mask vs N95 Respirator for Preventing Influenza among Health Care Workers”

Loeb M, Dafoe N, Mahony J et al.
Background: surgical mask versus N95 respirators for preventing infection in HCWs:

**Droplet Isolation (Surgical Mask for HCW):**
- Aerosol (particle size > 10 µm; droplet nuclei)
- Large particles/droplets generated by coughing, sneezing, suctioning
- Mask/protective eyewear/private room
- Usually recommended IC precaution for:
  - Respiratory viruses (flu, RSV, paraflu)
  - Respiratory bacteria (meningococcus, pertussis)

**Respiratory Isolation: (N95 Respirators for HCW):**
- Particle size < 10 µm; aerosol
- Larger distance particle spread; deposits into alveoli versus upper airways
- Usually in conjunction with negative pressure rooms
- Usually recommended precaution for:
  - TB
  - Varicella, measles
  - SARS, Avian Flu (H5N1)

Background: surgical mask versus N95 respirators for preventing influenza A H1N1 2009:
- Extremely controversial—many opinions and no data
- WHO and SHEA recommend surgical mask
- CDC, IOM, and VA recommend N95 respirators
- N95 respirators require fit testing for each model used
- National shortage of 3M respirators has huge cost implications

Study Design
- Study subjects: full-time RNs in EDs, med and peds units, 8 tertiary care Ontario Hospitals; open-label RCT
- 446 nurses randomized to N95 vs surgical mask for all patient care, flu 1/12/09 – 4/23/09
- Primary endpoint: laboratory confirmed influenza (nasal PCR and serology)
- Study stopped because of emerging concerns over flu A H1N1 2009
- 30% of nurses recently vaccinated for seasonal influenza at study entry
- Trained auditor to monitor use of assigned strategy in study participants
### Results

<table>
<thead>
<tr>
<th></th>
<th>Surgical Masks (n= 212)</th>
<th>N95 Respirator (n = 210)</th>
<th>Absolute Risk Difference % (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory-confirmed influenza</td>
<td>50 (23.6)</td>
<td>48 (22.9)</td>
<td>-0.73 (-8.8 – 7.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>RT PCR Influenza A</td>
<td>5 (2.4)</td>
<td>1 (0.5)</td>
<td>-1.88 (-4.13 – 0.36)</td>
<td>0.22</td>
</tr>
<tr>
<td>RT PCR Influenza B</td>
<td>1 (0.5)</td>
<td>3 (1.4)</td>
<td>0.06 (-0.89 – 2.81)</td>
<td>0.37</td>
</tr>
<tr>
<td>Influenza-like illness*</td>
<td>9 (4.2)</td>
<td>2 (1.0)</td>
<td>-3.29 (-6.31 – 0.28)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* Influenza-like illness: presence of both cough and temperature 38º or greater

Loeb M et al, JAMA 2009; 302:1865-1871

### Caveats/conclusions

- Other potential confounders not measured:
  - hand hygiene
  - gown, glove, and eye shield use
- Not generalizable to invasive procedures (bronchoscopy, intubation, suctioning) involving airway
- Majority of circulating strains during study period not A 2009 H1N1
- May have impact on policy decisions for next flu season
- Higher incidence ILI in surgical mask arm remains unexplained

### "Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia"

Martin-Loaches I, Lisboa T, Rodriguez A et al.
Background

- Macrolides (azithromycin) have been associated with mortality benefits in studies of patients with severe CAP
- Addition of a macrolide to a beta-lactam has previously been shown to improve outcomes in bacteremia pneumococcal pneumonia in 2 prospective and 3 retrospective cohort studies
- IDSA/ATS guidelines recommend beta lactam (ceftriaxone, ampicillin/sulbactam, or cefotaxime) therapy plus either respiratory quinolone or macrolide in patients with severe CAP (Clin Infect Dis 2007; 44:S27-72)
- There are no prior studies comparing azithromycin with respiratory quinolones with background beta-lactam therapy in ICU patients with CAP

Study design

- Multicenter, prospective observational cohort in 27 ICUs in 9 European countries of patients requiring MV for severe CAP
- Immunocompromised patients, patients with viral PNA or TB were excluded
- 218 subjects requiring MV; of these 165 (75%) had severe sepsis
- 43 subjects received monotherapy; 175 subjects received combination therapy
- Positive blood cultures in 9.2%; microbiologic diagnosis in 45%:
  - Streptococcus pneumoniae (32.4%)
  - Staphylococcus aureus (22.5%)
  - Hemophilus influenzae (10.8%)

Potential mechanisms

- Antiinflammatory effects of macrolides
- Coverage for atypical pathogens probably not responsible (respiratory quinolones also cover these pathogens)
- ? Reduced pneumococcal toxin production by macrolide (doxy or respiratory quinolones do not reduce α-pneumolysin in vitro; J Antimicrob Chemoth 60:1155-1158)
Other findings

- Mortality in ICU was 26.1% in macrolide group compared with 46.3% in quinolone group (p <0.05)
- Cox regression analysis (adjusted by etiology and severity) found macrolide use associated with lower ICU mortality (HR 0.48, 95% CI 0.23-0.97, P=0.04)
- Macrolides also associated with decreased ICU mortality in patients with severe sepsis
- Has led to revision of SFVAMC ICU empiric CAP guidelines

"Clinical Practice Guidelines for Clostridium difficile Infectious in Adults: 2010 Update by SHEA and IDSA"

Elements of new guidelines

- Changing epidemiology of C. difficile disease since 2005
- Review of new testing methodologies
- Identification of patients with severe uncomplicated disease for whom PO vancomycin should be used instead of metronidazole:
  - WBC > 15K, Cr > 1.5 x premorbid level
- Revised treatment guidelines for patients with severe complicated disease
- Limit use of metronidazole for treatment of only 2 relapses

Recommendations for the treatment of Clostridium difficile infection

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supporting clinical data</th>
<th>Recommended rx</th>
<th>Strength of recommendation</th>
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<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>WBC &lt; 15K and Cr &lt; 1.5 x baseline</td>
<td>PO metronidazole 500 mg PO TID x 10-14 d</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC &gt; 15 K or Cr &gt; 1.5 x baseline</td>
<td>PO vancomycin 125 mg PO TID x 10 – 14 d</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, fever, ileus, megacolon</td>
<td>PO vanco 500 mg PO or via NGT qid PLUS IV metronidazole 500 mg IV q8h, consider rectal vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>First recurrence</td>
<td>Same as for initial episode</td>
<td>Same as for initial episode</td>
<td>A-II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Vancomycin in a tapered and or pulsed regimen</td>
<td>Vancomycin in a tapered and or pulsed regimen</td>
<td>E-III</td>
</tr>
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“Melanoma associated with long-term voriconazole therapy”

Miller DD, Cowen EW, Nguyen JC et al.
Arch Dermatol 2010; 146:300-4.
Voriconazole: background

- FDA approved 2002; drug of choice for invasive aspergillosis
- Also used to treat invasive fungal infections (candidemia, esophageal candidiasis, crypto, endemic mycoses, other molds)
- Major "holes" are Zygomyces (agents of mucormycosis) and some Candida sp. (C. glabrata and C. krusei)
- Toxicities include visual disturbances, nausea, vomiting, transaminitis; multiple drug interactions
- Photosensitivity reactions in 6% (associated with long term administration)
- Other cutaneous toxicities: cheilitis, xerosis, pseudoporphyria, squamous cell carcinoma

Case reports: melanoma associated with voriconazole use

Case 1
- 39 yo woman presented with severe photosensitivity and lentigenes
- Previously worked as CHP Officer
- Developed cocci meningitis in August, 1992 initially treated with fluconazole; relapse in 2004 treated with voriconazole
- Developed severe erythema in sunexposed areas
- After 35 months of therapy developed melanoma on R helix
- Solar lentigos, melanocytic nevi, also found
- Second and third melanomas subsequently diagnosed
- After 2nd melanoma, voriconazole changed to posaconazole

Case 1

Case 1

Case 1
Case reports: melanoma associated with voriconazole use

Case 2
- 21 year old with CGD started on vori for pulmonary aspergillosis 3/02
- Developed lentigines on sun exposed areas, intermittent blistering of lips
- After 55 months of vori treatment, at age 20, patient developed L forearm melanoma in situ
- Extensive brown lentigines in sun exposed areas
- Subsequently vori changed to posaconazole

Other observations/conclusions
- Erythema and blistering lentigines characteristic of voriconazole toxicity
- Lesions similar to patients with xeroderma pigmentosum
- Similar to photosensitivity, erythema, xerosis, cheilitis in solid organ transplantation
- Similar to reactions of PUVA and psoralen in treatment of psoriasis
- Probably warrants switch to alternative agent (usually fluconazole or posaconazole) in patients who develop photosensitivity reactions to voriconazole
“Preventing surgical site infections in nasal carriers of *Staphylococcus aureus*”

Bode LGM, Kluytmans J, Wertheim H et al.  

**Background: Staphylococcal decolonization prior to surgery**

- Nasal carriers of *Staphylococcus aureus* associated with relative risk of 7.1 for developing skin and soft tissue infections
- 20 – 30% of general population are nasal carriers, and 60% of people are intermittent carriers
- Prior studies of mupirocin in orthopedic and cardiac surgery patients have demonstrated reduction in postoperative SSIs by 45% (Van Rijen M et al, Cochrane Review, 2009)
- Nasal screening may not identify all carriers in recent CA-MRSA era
  - many patients with active CA-MRSA infections are not nasally colonized prior to developing infection
  - nasal screening may not be practical prior to surgery if results cannot be available immediately
Who and how to decolonize?

- Other indications for decolonization might include:
  - recurrent SSTI with CA-MRSA despite optimized wound care and hygiene measures;
  - ongoing transmission among household members or other close contacts despite wound care and hygiene measures
- Decolonization strategies might include nasal decolonization (mupirocin), body decontamination (chlorhexidine or dilute bleach) or both
- Oral antibiotics are generally not recommended for decolonization (concerns about toxicities and resistance) and have not been well studied
- Decolonization studies with topical therapies are urgently needed in various settings

Study Design

- RCT, double blind, nasal mupirocin BID plus chlorhexidine soap QD x 5 days, versus placebo; rx every 3 weeks while hospitalized
- 5 hospitals in the Netherlands, 10/05 – 6/07
- Inclusion criteria:
  - positive nasal swab for S. aureus by real time PCR on admission or up to 7 days prior to admission AND
  - ability to start intervention within 24 hours AND
  - expected hospitalization > 4 days
- 87% of subjects were admitted to surgical services; 917 subjects randomized
- Exclusion: < age 18, pregnancy, breastfeeding, chlorhexidine allergy, nasal foreign body, prior mupirocin < 4 weeks
- Primary endpoint: hospital acquired S. aureus infections

Results: relative risk of hospital acquired Staphylococcal infection and localization (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Mupirocin-Chlorhexidine (n=504), n (%)</th>
<th>Placebo (n=413), n (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-acquired S. aureus infection</td>
<td>17 (3.4)</td>
<td>32 (7.7)</td>
<td>0.42 (0.23 – 0.75)</td>
</tr>
<tr>
<td>Deep Surgical Site Infection</td>
<td>4 (0.9)</td>
<td>16 (4.4)</td>
<td>0.21 (0.07 – 0.62)</td>
</tr>
<tr>
<td>Superficial Surgical Site Infection</td>
<td>7 (1.6)</td>
<td>13 (3.5)</td>
<td>0.45 (0.18 – 1.11)</td>
</tr>
</tbody>
</table>
Other findings/conclusions:

- Overall 60% reduction in risk of hospital-acquired *S. aureus* infections
- All-case mortality not different in 2 groups
- Other endpoints:
  - Time to infection shorter in placebo group (p=0.005)
  - Mean duration of hospitalization shorter in treatment arm (12.2 vs. 14 days, p = .04)
- Limitation: no MRSA in Netherlands; real-time PCR not available in most hospitals; independent effects of mupirocin and chlorhexidine cannot be measured
- Risk/benefit ratio probably favors this intervention in high risk patients (open heart surgery, orthopedic/neurosurgical procedures with implants)

“Guidance for Control of Infections with Carbapenem-Resistant or Carbapenemase-Producing *Enterobacteriaceae* in Acute Care Facilities”

Wledo W, Hernandez M, Lopez E et al. 
MMWR 2009; 58:256-60.

A short history of recent bad bugs:

- MRSA, VISA, VRSA
- Penicillin and cephalosporin resistant *S. pneumoniae*
- VRE
- MDR *Pseudomonas aeruginosa* and *Acinetobacter baumanii*
- ESBL producing *E. coli* and *Klebsiella* species

AND NOW:

- *Klebsiella pneumoniae* carbapenemase-producing bacteria (KPCPB)
KPCPB facts

- First described in North Carolina in 1996, rapid worldwide dissemination
- Transposon mediated gene (bla<sub>kpc</sub>) codes for carbapenemase
- Most commonly detected in Klebsiella sp.
- 8% all Klebsiella isolates were CRKP in 2007 vs. < 1% in 2000

KPCPB facts

- Has led to nosocomial outbreaks in Israel, Greece, NYC hospitals (approximately 30% of K. pneumoniae isolates in NYC hospitals are carbapenemase-producing) with high morbidity/mortality
- Requires specialized testing for diagnosis/difficult to detect
- Spread of carbapenemases to other GNRs has been documented (Enterobacter sp., E. coli, Citrobacter sp., Serratia sp., Pseudomonas sp.)
- Most isolates are multidrug resistant (colistin and tigecycline may still be active)
- Sporadic cases in California have been described
**Modified Hodge Test**

1. Prepare a 1:10 dilution of McF 0.5 suspension of E. coli ATCC 25922.
2. Swab onto MHA plate to create lawn as for disk diffusion test. Place ertapenem or meropenem (best) disk on lawn.
3. Streak test culture (1-2 mm) from edge of disk outward (use 1 mcl loop).
4. Incubate overnight.
5. Look for growth of E. coli around ertapenem streak - indicates carbapenem-hydrolyzing enzyme.