Disclosure

- No actual or potential conflict of interest in relation to this program/presentation
- I will be discussing off-label uses and/or investigational use of the following medications in my presentation:
  - Rifaximin
  - Cholestyramine
  - Colestipol
  - Tigecycline
  - IVIG
  - CDAL/ID81
  - Actoxumab
  - Beduximab
  - LFF571
  - CB183,315

Objectives

- At the completion of this program, the participant will be able to:
  - Select appropriate antibiotic therapy for hospital-acquired pneumonia based on the updated IDSA guidelines
  - Explain how procalcitonin can be used to de-escalate and limit duration of antibiotic therapy for select disease states
  - Describe treatment principles for *Clostridium difficile* based on patient characteristics
Topic #1: Updated IDSA Hospital-Acquired Pneumonia (HAP) and Ventilator-Acquired Pneumonia (VAP) Guidelines

2005 vs 2016 HAP/VAP Guidelines

- Main differences
  - GRADE methodology
  - Removal of healthcare-associated pneumonia (HCAP)
  - Local antibiograms
  - Shorter courses of therapy
- Other differences
  - Procalcitonin
  - Double-coverage for Pseudomonas Aeruginosa
- Not intended for immunosuppressed patients

Why do we care?

- HAP/VAP among most common hospital-acquired infections (22%)
- 10% of ventilated patients diagnosed with VAP
  - Negative patient outcomes: mortality
    - All-cause mortality associated with VAP: 20-50%
    - Meta-analysis: attributable mortality 13%
  - Negative patient outcomes: length of stay
    - Prolongs mechanical ventilation by 7.6-11.5 days
    - Prolongs hospitalization by 11.5-13.1 days
- Cost
  - ~$40,000 per patient
- 50% of HAP patients develop serious complications
- HAP in ICU patients: mortality rate approaches that of VAP
GRADE Methodology

**Table 1: Interpretation of Strong and Weak (Conditional) Recommendations**

|**Patients** |
|---|---|
| Test-negative patients and no clinical evidence of infection | Strong Recommendation |
| Test-negative patients and clinical evidence of infection | Weak Recommendation |
| Test-positive patients and no clinical evidence of infection | Strong Recommendation |
| Test-positive patients and clinical evidence of infection | Weak Recommendation |

**GRADE Methodology/Level of Evidence**

- For the purposes of this presentation:
  - Strong Recommendation (SR)
  - Weak Recommendation (WR)
  - High-quality evidence (H)
  - Moderate-quality (M)
  - Low-quality evidence (L)
  - Very low-quality evidence (V)

**Removal of Healthcare-Associated Pneumonia (HCAP)**

- Contact with healthcare system ≠ MDRO
- Neither sensitive nor specific to identify at-risk patients
- Outcomes likely due to age/comorbidities
- Validated risk factors
- Underlying patient characteristics
- Likely will be included in updated CAP guidelines
- Spring 2018
HCAP

- First defined in 2005 IDSA/ATS guidelines
  - Consensus-derived criteria
  - Low quality of evidence
  - Not prospectively validated

- Co-chair of guideline committee publicly disavowed HCAP entity shortly after publication in 2005

2005 HCAP Strategy

- Original definition
  - Hospitalized for ≥ 2 days in past 90 days
  - Resident of SNF or LTCF
  - Home infusion therapy
  - Wound care in past 30 days
  - HD in past 30 days
  - Family member with MDRO

- Recommended treatment
  - Dual anti-pseudomonal coverage PLUS MRSA coverage

2005 HCAP Strategy

- Cumulative antibiotic use associated with development of C. difficile infection
  - HR 2.5 [95% CI 1.6-4.0] for patients on 2 antibiotics
  - HR 3.3 [95% CI 2.2-5.2] for patients on 3-4 antibiotics

- Multicenter observational study demonstrated increased rate of overall 28 day mortality in patients with HCAP receiving triple antibiotic therapy as recommended by IDSA/ATS guidelines
Pathogens in HCAP

- 2014 meta analysis and systematic review (24 studies; n = 22,456 patients)
  - Assessed frequency of MDRO in HCAP vs CAP groups
    - MRSA, Enterobacteriacae, Pseudomonias
    - Mortality and ICU admissions

Pathogens in HCAP

- No organisms met specified threshold for correlation (AUC 0.75)
- HCAP definition not sufficiently sensitive or specific to identify risk of MDRO
- Adjusted analysis found no difference in MDR rate
  - Studies with high prevalence in HCAP also had high prevalence in CAP

Mortality in HCAP

- HCAP associated with increased mortality overall
  - Less so when adjusted for higher mean age and # co-morbidities common in HCAP patients
  - No mortality differences when excluding studies that mandated culture positive infection
HCAP Summary

- HCAP definition poor at determining who might have these pathogens
- Overtreat areas of low MDR prevalence
- Undertreat areas of high MDR prevalence
- Need to look at other risk factors
- Excess mortality of HCAP primarily attributable to age and comorbidities

HAP: Initial Treatment
Coverage: Staphylococcus Aureus (MRSA, MSSA)

MRSA
- MRSA risk, prior IV abx >20% MRSA, high risk for mortality (SR, VL)
- Vancomycin, Linezolid (SR, VL)

MSSA
- Empiric (SR, VL)
- Piperacillin/tazobactam
- Ceftepime
- Levofloxacin
- Imipenem
- Meropenem

HAP: Initial Treatment
Coverage: Pseudomonas aeruginosa/other gram negative bacilli (SR, VL)

Double Coverage
- IV abx ≤ 90 days
- High risk mortality (SR, VL)
- Structural lung disease

Antibiotic Selection
- Beta-lactams/Cephalosporins
- Piperacillin/tazobactam
- Ceftepime
- Ceftriaxone
- Carbapenems, Fluoroquinolones
- Aminoglycosides
- Aztreonam
HAP: Length of Therapy

- 7 day course (SR, VL)
- Clinical criteria + procalcitonin vs clinical criteria alone (WR, L)
  - Control group in studies had abx durations of 9-15 days
  - Unclear if procalcitonin useful for stopping antibiotics prior to 7 days
- Procalcitonin not recommended for use in determining when to initiate antibiotics

Initial Treatment: VAP
Coverage: Staphylococcus Aureus (SR, L)

**MRSA**
- Prior IV abx
- Septic shock
- 5+ days hospitalization
- MRSA (if)
- High risk for mortality (W, VL)
- Vancomycin
- Linezolid

**MSSA**
- Empiric (W, VL)
  - Pipericillin/tazobactam
  - Cefepime
  - Levofloxacin
  - Imipenem
  - Meropenem

Coverage: MSSA

Initial Treatment: VAP
Coverage: Pseudomonas aeruginosa/other gram negative bacilli (SR, L)

Double Coverage
- Prior IV abx
- Septic shock
- ARDS
- 5+ days hospitalization
- Unlikely to 20% GN resistance
- High risk for mortality (W, VL)
- Structural lung disease

Antibiotic Selection
- Beta-lactams/Cephalosporins
  - Pipericillin/tazobactam
  - Cefepime
  - Cefazolin

Carbapenems/Fluoroquinolones
- Imipenem
- Meropenem
- Aztreonam
VAP: Length of Therapy

- 7 day course (SR, M)
  - Clinical status
  - Radiographic findings
  - Laboratory findings
- Clinical criteria + procalcitonin vs clinical criteria alone (WR, L)
  - Control group in studies had abx durations of 9-15 days
  - Unclear if procalcitonin useful for stopping abx prior to 7 days
- Procalcitonin not recommended for determining when to initiate antibiotics

VAP: Risk Factors NOT Associated with MDRO

- Re-intubation
- Immunosuppression
- Chronic respiratory failure
- Tracheostomy
- Diabetes Mellitus
- Recent corticosteroids
- Addressed in several studies

Inhaled Antibiotic Therapy

- Use:
  - VAP
    - GNB ONLY susceptible to aminoglycosides/polymyxins (WR, VL)
    - Use systemic + inhaled
  - Adjunctive
    - Not responding to systemic abx alone
Conclusion

“It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgement with respect to particular patients or special clinical situations.”

Topic #2: Procalcitonin

What is it?

- Precursor to calcitonin
  - Rapidly produced/released in response to endotoxic/pro-inflammatory cytokines
    - Detectable within 2-4 hours
    - Peaks within 6-24 hours
    - Inhibited by interferon-gamma
- FDA approval
  - Lower respiratory tract infections
  - Sepsis
Current Thresholds

<table>
<thead>
<tr>
<th>Sepsis/Septic Shock</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.05</td>
<td>Normal reference value</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>Local bacterial infection possible; low risk</td>
</tr>
<tr>
<td>0.5 and &lt; 2</td>
<td>System infection possible; moderate risk</td>
</tr>
<tr>
<td>2 and &lt; 10</td>
<td>Systemic infection likely; high risk</td>
</tr>
<tr>
<td>≥ 10</td>
<td>Severe bacterial sepsis or septic shock</td>
</tr>
</tbody>
</table>

Example Algorithm

Current Thresholds-Lower Respiratory Tract Infection

<table>
<thead>
<tr>
<th>Lower Respiratory Tract Infections</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td>Absence of infection</td>
</tr>
<tr>
<td>&gt; 0.1 and &lt; 0.25</td>
<td>Bacterial infection unlikely</td>
</tr>
<tr>
<td>&gt; 0.25 and &lt; 0.5</td>
<td>Bacterial infection possible</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>Presence of bacterial infection</td>
</tr>
</tbody>
</table>
Example Algorithm

Limitations

- False elevations
  - Newborns (>72 hours)
  - Trauma, surgery, cardiac shock, burns
  - Treatment with agents that stimulate cytokines
  - Malaria/fungal infections
  - Acute graft vs host disease
  - Medullary thyroid tumors
  - Small cell lung cancer
  - Renal insufficiency (AKI, CKD, ESRD)

- Missed infections
  - Organisms that lack a cell wall
    - Mycoplasma
    - Chlamyphila

Procalcitonin in Renal Insufficiency

- Acute Kidney Injury (AKI)
- Chronic Kidney Disease (CKD)
- End Stage Renal Disease (ESRD)
Acute Kidney Injury (AKI)

  - Single center retrospective study
  - 393 patients
  - Diagnostic accuracy of procalcitonin significantly lower in AKI than in non-AKI

- Heredia-Rodriguez, et al.
  - Case-control study (cardiac surgery patients)
  - 440 patients (SIRS, severe sepsis, septic shock)
  - SCr > 2, median procalcitonin levels similar between infected/non-infected patients

Chronic Kidney Disease

- Serum procalcitonin levels are significantly higher in CKD patients without a history of dialysis or infection compared with healthy individuals
  - On average:
    - 36% CKD without infection have procalcitonin ≥ 0.5
    - 36-100% CKD with infection have procalcitonin ≥0.5
- Contou D, et al.
  - Observational, prospective single center study
  - 135 CKD patients
  - Procalcitonin ≥ 0.85 strong independent predictor of infection

End Stage Renal Disease

- Adult patients on chronic HD without infection have average procalcitonin baselines ranging from 0.26 to 1.0 ng/ml prior to starting the dialysis session
  - Higher in infected ESRD vs non-infected ESRD
  - Level did not correlate with severity of infection
- Levels drop significantly after renal replacement therapy (RRT)
  - High-permeability of procalcitonin through dialysis filter
  - Magnitude of drop in levels depends on method of RRT
    - Most significant for patients on HD
  - Measure levels before dialysis; may be falsely low for up to 48 hours
- Optimal threshold
  - Lee et al: 0.75 ng/ml (sensitivity 76.2%, specificity 80%)
General Principles

- Any threshold increase will increase sensitivity but decrease specificity
- Unnecessary antibiotics
- Use other test results, clinical signs and symptoms, and sound judgment

Topic #3: Clostridium Difficile
Refresher: Guidelines (ACG vs IDSA/SHEA)

Mild/moderate
- ACG: metronidazole PO x 10 days
- IDSA/SHEA: metronidazole PO x 10-14 days

Severe
- ACG: vanco or fidaxomicin x 10 days
- IDSA/SHEA: vanco x 10-14 days

Severe, complicated
- ACG: vanco + metronidazole IV + vanco PR + vanco intra-colon
- IDSA/SHEA: vanco + metronidazole IV

Recurrences

First recurrence (ACG/IDSA/SHEA)
- Same agent
- Stratified by disease severity

Second recurrence (or more) (ACG/IDSA/SHEA)
- Vancomycin (pulse/taper)
- No metronidazole
- Fecal transplant (ACG only)

Hines VA Score

- Prospective observation by Fujitani et al.
- Strongest correlation between Hines VA Index and prediction of severe CDI
- Severe CDI: score of ≥ 3

<table>
<thead>
<tr>
<th>Hines VA Index</th>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38°C)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Resis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Leukocytes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC &lt; 15,000/mm³</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>WBC ≥ 15,000/mm³ but &lt; 30,000/mm³</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>WBC ≥ 30,000/mm³</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CT scan findings (thickened colonic wall, colonic dilation, ascites)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Two or more</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
**Metronidazole**

- **Dose:** 500 mg PO/IV TID
  - PO for mild/moderate
  - IV for severe/severe complicated
  - Higher levels in unformed stool
  - Cumulative neurotoxicity
  - May have less impact on microbiome/colonization resistance
  - Resistance reported in some strains

---

**Vancomycin**

- **Dose:** 125 mg PO QID or 500 mg PO QID
  - High concentration in stool
  - Recurrence rates of ~20%
  - "Pulse and taper"

---

**New/Adjunctive/Alternative Agents**

- Fidaxomicin
- Rifaximin
- Nitazoxanide
- Cholestyramine/Colestipol
- Tigecycline
- IVIG
- Fecal Microbiota Transplant
- Monoclonal Antibodies
- New Drug Developments
- Protective Agents
Fidaxomicin

- FDA approval
  - Two large, double-blind, randomized, non-inferiority trials
    - Possible reduction of recurrences
      - Post-hoc exploratory ITT time-to-event meta-analysis of combined data
  - Dose: 200 mg BID
    - “Chaser”: 200 mg BID x 10 days AFTER vancomycin
  - Not absorbed
  - More effective in patients on concomitant antibiotics?
    - Two phase III trials
      - Cure rate: 90% fidaxomicin vs 79.4% for vanco
      - Relapse rate: 16.9% for fidaxomicin vs 29.2% for vanco
  - Cost

Rifaximin

- Dose: 400mg TID
  - Alternative for metronidazole-unresponsive
    - Prospective pilot trials
    - “Chaser”:
      - 400mg BID x 14 days
  - Patients with multiple recurrences/previous treatment strategies failed
  - Not absorbed
  - Somewhat flora sparing
  - Resistance issues

Nitazoxanide

- Dose: 500mg PO BID or 250mg PO QID
  - Similar response rates to metronidazole/vancomycin
    - Small studies
  - Efficacy in patients who failed treatment with metronidazole
Cholestyramine/Colestipol

- Adjunctive treatment only
- Toxin binding
  - Also binds vancomycin

Tigecycline

- Dose
  - 50mg IV Q12H
  - 100mg IV LD then 500mg IV Q12H
- Broad-spectrum
- Patients w/ severe, intractable CDI for whom previous standard treatment failed
  - Limited case reports
- Adjunct to standard treatment
- Limitations/drawbacks:
  - Resistance
  - Cost
  - Increased mortality w/ use (recent FDA warning)

IVIG

- MOA: binding/neutralization of toxin by IgG anti-toxin A antibodies
- Dose: 300-500mg/kg x 1-6 days
- Recurrent/refractory primarily
  - More effective: colon-restricted, low APACHE 2 score

<table>
<thead>
<tr>
<th>1st Criteria (IVIG for 1-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
</tr>
<tr>
<td>Albumin &lt; 2.5</td>
</tr>
<tr>
<td>WBC &gt; 15</td>
</tr>
<tr>
<td>Temp &gt; 38.3</td>
</tr>
<tr>
<td>Pseudomembranous colitis on colonoscopy</td>
</tr>
<tr>
<td>ICU patient</td>
</tr>
</tbody>
</table>
Fecal Microbiota Transplant

- 2013 ACG guidelines: 3+ recurrences
- 90-93% cure rates reported

Monoclonal Antibodies

- Targeted against toxins A and B
- Reduced relapse rates
  - Treated w/ mAbs + metronidazole/vanco
  - CDA1 and CDB1: 7% relapse vs 25%
    - Randomized, double-blind, placebo-controlled
- Actoxumab + Bezlotoxumab
  - Phase III clinical trials
  - Efficacy in preventing recurrent disease

New Drug Developments

- LFF571
  - Semisynthetic thioppeptide
  - Narrow-spectrum (flora sparing)
  - High fecal concentrations
  - Phase II trials (current)
    - Efficacy/safety in patients w/ moderate CDI
- CB-183 315
  - Cyclic lipopeptide
  - Great in-vitro activity against c.diff than vancomycin or metronidazole
  - Limited activity against intestinal flora
  - Phase II trials
    - Lower relapse rates compared to vancomycin
    - Phase III trials (current)
      - Efficacy compared to vancomycin
Protective Agents

- Doxycycline
  - Cohort study: ceftriaxone vs ceftriaxone/doxycycline
    - 27% reduced risk
- Metronidazole
- Linezolid
  - Retrospective study: major heart surgery patients
  - Treated w/ linezolid = less development of CDI

Appendix

Probiotics

References