Game Changing Publications of 2014 – 2015

Infectious Diseases

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Disclosures

• Nicholas Torney has no potential or actual conflicts of interest to disclosure in relation to this presentation.

Objective

• Describe how the current infectious disease literature can be applied to your practice.
Article Inclusion Strategy

Themes in 2014-2015

• Gram negative resistance
• HIV
• HCV DAAs
• Rapid molecular diagnostic tests
• Vaccines
• New antimicrobial agents
• Antimicrobial stewardship

Society of Infectious Diseases Pharmacists

Significant publications on infectious diseases pharmacotherapy in 2014

Khai Phu, Richard McCabe, David E. Gordon, Phyllis E. Guinan, Ashley M. Lockwood, Katherine K. Perez, Nancy Y. Vong, and Samuel L. Aronson, on behalf of the Houston Infectious Diseases Network

Each year, a substantial number of infectious diseases pharmacotherapy research is published in peer-reviewed journals encompassing a range of topics in infectious disease (ID). A PubMed search conducted in January 2015 using the keywords “infectious disease” and “HIV” identified 5,824 and 3,695 articles published in 2014 and 2013, respectively. The aim of this paper is to provide an overview of the most significant publications in the field of infectious diseases pharmacotherapy in 2014. The list of the most significant publications is based on a combination of peer review scores, impact factors, and clinical relevance. This year, 28 publications were identified as significant. These publications will be discussed in detail, with a focus on their impact and relevance to the field of infectious diseases pharmacotherapy.
Included Articles

• Has the paper already impacted practice?

• Does it have the potential to impact practice?

START Trial
Strategic Timing of Antiretroviral Treatment Trial

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group

Patient Groups

HIV-Positive ART-Naïve patients with CD4+ count >500 cells/mm³

Immediate ART Group (n=2326)
ART initiated immediately after randomization

Deferred ART Group (n=2359)
ART deferred until CD4+ count declines to <350 cells/mm³ or AIDS develops

Results

<table>
<thead>
<tr>
<th>Primary Events (%)</th>
<th>Early Treatment</th>
<th>Delayed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0%</td>
<td>n=96</td>
<td>n=42</td>
</tr>
<tr>
<td>1.0%</td>
<td>1.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>2.0%</td>
<td>57% Reduction</td>
<td></td>
</tr>
</tbody>
</table>

Hazard of Developing AIDS, Serious Non-AIDS Events, or Death

ART Use and HIV RNA Level

CD4+ Count

Conclusion

“Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count.”


CAP-START

The New England Journal of Medicine

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults


Background

- CAP diagnosis admit to a non-ICU bed
- Cluster-randomized, crossover trial
- Performed in 7 hospitals in the Netherlands from Feb 2011 – Aug 2013

β-lactam

- Amoxicillin
- Amoxicillin/clavulanate
- 3rd generation cephalosporins

β-lactam–macrolide

- Azithromycin
- Erythromycin
- Clarithromycin

Respiratory Fluoroquinolone

- Levofloxacin
- Moxifloxacin

Results

- **Primary Outcome – 90 Day mortality**
  - \( \beta\)-lactam
  - \( \beta\)-lactam–macrolide
  - Fluoroquinolone

  - No difference in length of stay between groups

- **Atypical pathogens** isolated in 2.1% of patients

- Empirical atypical coverage reduced by \(~70\%\) during \( \beta\)-lactam strategy periods

Discussion / Conclusion

- **Limitations**
  - Low isolation of atypical pathogens
  - Lower rates of resistance in the Netherlands

- **Potential Impact**
  - Reduce ubiquitous use of azithromycin for CAP
  - New IDSA CAP guidelines – projected Fall 2016
Daptomycin and IBW Dosing

Daptomycin Dosing Based on Ideal Body Weight versus Actual Body Weight: Comparison of Clinical Outcomes

Jennifer J. Ng, Lucas J. Schulte, Marcus I. Haas, Barry C. Jr, David R. Amato, Kevin A. Block, Jeffrey Y. Fujii

University of Wisconsin Hospital and Clinics, Madison, Wisconsin; UW-Madison, Madison, Wisconsin; Wisconsin, USA; Statistical Data Analysis Center, University of Wisconsin-Madison, Madison, Wisconsin, USA


Background and Design

• University of Wisconsin changed to IBW dosing in July 2010
• Retrospective cohort analyzing clinical outcomes with ABW dosing vs. IBW dosing


Group Comparison

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ABW (n=63)</th>
<th>IBW (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% clinical success</td>
<td>88.9</td>
<td>89.1</td>
<td>0.97</td>
</tr>
<tr>
<td>% clinical cure</td>
<td>57.1</td>
<td>69.6</td>
<td>0.19</td>
</tr>
<tr>
<td>% microbiological success</td>
<td>90.8</td>
<td>91.5</td>
<td>0.48</td>
</tr>
</tbody>
</table>

• Mean length of stay = no difference

Study Limitations

- Single Center
- Insufficient power to detect significant differences in clinical outcomes or adverse events
- Heterogeneity in causative pathogen and infection source.
- Deep-seated infections excluded (endocarditis and prosthetic-device infections)
- Low number of *S. aureus* infections


Dapto and IBW Dosing

- Potential Advantages
  - Reduced toxicity in obese patients
  - Reduced Cost $$
- IBW dosing shows promise…but,
  - Prospective, randomized study needed?


Clinical Microbiology
Rapid Pathogen Identification From Positive Blood Cultures

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing


Background / Study Design

- Prospective RCT – Mayo Clinic
- **3 groups**
  1. Control
  2. Rapid Multiplex PCR
  3. Rapid Multiplex PCR + Real-Time Stewardship

- Baseline Interventions (all groups)
  - MALDI-TOF pathogen identification
  - M-F antimicrobial stewardship interventions
    - Prospective audit and feedback
    - Restricted antimicrobial authorization

What's Detected?

FilmArray® Blood Culture Identification Panel (BioFire Diagnostics)

FilmArray (BioFire) Verigene Nanosphere

<table>
<thead>
<tr>
<th>Gram Stain prior to processing</th>
<th>Unnecessary</th>
<th>Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hands on time</td>
<td>2 minutes</td>
<td>&lt; 5 minutes</td>
</tr>
<tr>
<td>Run time</td>
<td>1 hour</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>Technology</td>
<td>rmPCR</td>
<td>Gold Nanoparticle</td>
</tr>
<tr>
<td>Pathogens detected</td>
<td>8 Gram (+)</td>
<td>11 Gram (+)</td>
</tr>
<tr>
<td></td>
<td>1 Gram (-)</td>
<td>5 Gram (-)</td>
</tr>
<tr>
<td></td>
<td>5 candida spp.</td>
<td>4 Gram (-)</td>
</tr>
<tr>
<td>Resistance mechanisms detected</td>
<td>mecA</td>
<td>KPC</td>
</tr>
<tr>
<td></td>
<td>vanA, vanB</td>
<td>CTX-M</td>
</tr>
<tr>
<td></td>
<td>mecA</td>
<td>KPC</td>
</tr>
<tr>
<td></td>
<td>vanA, vanB</td>
<td>NMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OXA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIM</td>
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BioFire vs. Verigene

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Standard Blood Culture Bottle processing</td>
</tr>
</tbody>
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Impact

• Most bang for your buck:
  – Rapid molecular diagnostics coupled with real-time stewardship intervention
• Most interventions were made during the day… may not need 24/7 coverage.

T2 Magnetic Resonance

T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Blood to Bug Detection

Rapid Identification of *Candida* spp.

- **T2Candida**
  - Detects 5 *candida* spp. from **whole blood** in 3-5 hrs
  - *Albicans*
  - *Glabrata*
  - *Krusei*
  - *Parapsilosis*
  - *Tropicalis*

Study Design

- Blood cultures gathered from 1801 hospitalized patients

- **250 manually spiked** with <1 – 100 CFUs/mL of 5 different *candida* spp.
Results

- Sensitivity 91.1%
- Specificity 99.4%
- Limit of Detection
  - Ranged from 1-3 CFUs/mL depending on species
- T2MR not shown to be altered by antifungal agents

Potential Impact

- Questions that need answering:
  - What is T2MR’s place in therapy?
  - What patients do you test?
  - Cost/benefit

- Stewardship Impact

- On the horizon
  - T2 Bacteria?

Clinical Micro Pipeline

- Whole Genome Sequencing (WGS)

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