Epidemiologically Important Gram-negative Bacteria

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The war against infectious diseases has been won!

William H. Stewart
Surgeon General, 1967
The introduction of antibacterial drug therapy in the 1940s led to a dramatic reduction in illness. The emergence of drug-resistant bacteria is reversing the trend.

The current antibiotic crisis differs from those in the past because several different organisms are involved and because there are no immediate solutions on the horizon.
The prevalence of antimicrobial-resistant human pathogens is rapidly increasing, but the discovery and development of new antimicrobial drugs have slowed dramatically.

“Despite many accomplishments…It is now clearer than ever that the human species is in the midst of a war with the microbial world—a resilient foe that will never be completely defeated.”

Anthony Fauci, NIH
### Table 5. Distribution of Rank Order of Selected Pathogens Associated National Healthcare Safety Network, by Type of HAI, 2009–2010

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall No. (%) of pathogens</th>
<th>Overall Rank</th>
<th>CLABSI No. (%) of pathogens</th>
<th>CLABSI Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>12,635 (15.6)</td>
<td>1</td>
<td>3,735 (12.3)</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>9,351 (11.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>9,261 (11.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella (pneumoniae/oxytoca)</td>
<td>6,470 (8.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>6,111 (7.5)</td>
<td></td>
<td>1,365 (4.5)</td>
<td>8</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>5,484 (6.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>4,275 (5.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>3,821 (4.7)</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Candida spp. or NOS</td>
<td>3,408 (4.2)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>3,314 (4.1)</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>2,409 (3.0)</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>2,051 (2.5)</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>1,737 (2.1)</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>1,490 (1.8)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>9,304 (11.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>81,139 (100)</td>
<td></td>
<td>30,454 (100)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** CAUTI, catheter-associated urinary tract infection; CLABSI, central line–associated blood stream infection.

* A rank is not given if pathogen is not in the top 14 reported for the specific HAI type listed (https://nhsn.data/stat.html).

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**NHSN 2009/2010: Antibiotic-resistance**

Percent Organisms, *Imipenem-resistant*

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CLABSI</th>
<th>VAP</th>
<th>CAUTI</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td>26.1</td>
<td>30.2</td>
<td>21.3</td>
<td></td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>62.6</td>
<td>61.2</td>
<td>74.2</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>12.8</td>
<td>11.2</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

Sievert D et al. ICHE, 2013; 34:1

**Percent Organisms, Fluroquinolone-resistant**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CLABSI</th>
<th>VAP</th>
<th>CAUTI</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td>30.5</td>
<td>32.7</td>
<td>33.5</td>
<td>30.7</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>41.8</td>
<td>35.2</td>
<td>31.2</td>
<td></td>
</tr>
</tbody>
</table>

Sievert D et al. ICHE, 2013; 34:1

NHSN 2009/10: Antibiotic-resistance

**Percent Organisms, Cefepime/ceftazidime**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>CLABSI</th>
<th>VAP</th>
<th>CAUTI</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella</td>
<td>28.8</td>
<td>23.8</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>19.0</td>
<td>16.3</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

Sievert D et al. ICHE, 2013; 34:1
Outline of talk

• Mechanisms of resistance
• E. coli
  – ESBL
• Klebsiella
  – KPC/CRE
• Pseudomonas
• Acinetobacter
• Reasons for spread of resistance
• Methods to reduce resistance
Mechanisms of Resistance

• Decreased permeability of the outer membrane
  – important for *Pseudomonas aeruginosa*

• Alteration of the target site
  – Important for penicillin-resistant *Streptococcus pneumoniae*

• Efflux

• Production of a bacterial enzyme
B-lactamase Production

- Encoded within a chromosome
  - inducible
  - important for *Citrobacter*, *Enterobacter*, *Serratia*, *Pseudomonas*, *Acinetobacter*
- Acquired on a plasmid or transposon
  - usually produced all the time (non-inducible)
  - potentially transferable to other bacteria

Plasmid-mediated B lactamases

- First described: TEM-1, TEM-2, and SHV-1
  - resistance to penicillins
  - 1st generation cephalosporins
  - 2nd generation cephalosporins
  - *easily inhibited by clavulinic acid, sulbactam or tazobactam*
- Now, more than 200 B lactamases have been documented (http://www.lahey.org/Studies/)
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E. coli

- 2nd most common pathogen of nosocomial infections
- Sites of nosocomial infection
  - surgical site infections
  - blood stream infections
  - urinary tract infections
- Common pathogen in ICU’s
Klebsiella

• Common isolate
• Sites of nosocomial infection
  – surgical site infections
  – pneumonia
  – UTI

KPC: Epidemiology

• First reports in 2004 in New York
• In 2007 CDC data, 8% of all *Klebsiella* isolates were reported to be carbapenem resistant, compared to just under 1% in 2000.
KPC Epidemiology

% Klebsiella with Carbapenem Resistance

- 2001: < 1%
- 2007: 8%

Srinivasan et al. ICHE, 2009; 29:1099

2010 Location of Carbapenem-Resistant Enterobacteriaceae (CRE) caused by KPC enzyme; CRE caused by other enzymes noted
KPC: Resistance

• Most commonly seen in *Klebsiella pneumoniae*
• KPC confers resistance to penicillins, cephalosporins and carbapenems
• Present on a plasmid

KPC: Microbiological detection

• Difficult to identify for laboratories which has important clinical implications
  – Ertapenem better method than imipenem or other carbapenems
• New MIC breakpoints
KPC: Infection control

• Difficult to determine if infection control measures should be the same for KPC as for ESBL-producing *Klebsiella*

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Pseudomonas

• Common isolate
  – 9% of nosocomial infection site isolates
  – most common cause of nosocomial gram-negative pneumonia
• Sites of nosocomial infection
  – bacteremia
  – surgical site infections
  – pneumonia

Monotherapy
Combination Therapy

Antibiotic Options for Pseudomonas

- Due to mechanism of resistance, resistance can evolve
  - Hence, repeat cultures
- Role of double antibiotic coverage
  - Practiced by many but documentation of effectiveness poor
Antibiotic Options for Pseudomonas

- At University of Maryland:
  - 90% susceptible to cefepime
  - 75% susceptible to ciprofloxacin
  - 79% susceptible to imipenem
  - 78% susceptible to piperacillin/tazobactam

Pseudomonas bacteremia

Combination Therapy: Fact or Fiction
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Combination beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilf et al</td>
<td>1982-1986</td>
<td>Y</td>
</tr>
<tr>
<td>Bodey et al</td>
<td>1972-1981</td>
<td>N</td>
</tr>
<tr>
<td>Chatzinikolaou et al</td>
<td>1991-1995</td>
<td>N</td>
</tr>
<tr>
<td>Vidal et al</td>
<td>1991-1994</td>
<td>N</td>
</tr>
<tr>
<td>Kuikka et al</td>
<td>1992-1996</td>
<td>N</td>
</tr>
</tbody>
</table>

**Conclusions of Bacteremia Data:**

- Minimal to no effect of combination therapy on cure of infection or mortality
- Instituting effective treatment up-front is what is important
- Patients with pseudomonas pneumonia as primary source have poorer outcome
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Acinetobacter

- Gram-negative coccobacillus
- Was often viewed as a colonizer
- HAS ARRIVED as a nosocomial pathogen
- *Acinetobacter baumannii* is the most common
- Present in returning troops from the Middle East
Maryland, 2010

358 MV-patients
40 Healthcare Facilities

Thom, KA et al. *ICHE*. 2012; 33:883

Maryland, 2010

34% (121/358) of patients with *A. baumannii*

Thom, KA et al. *ICHE*. 2012; 33:883
Increasing Incidence in US

- CDC National Nosocomial Infections Surveillance report the following increases in *Acinetobacter*
  - Proportion of *Acinetobacter* ICU pneumonia increased from 4% in 1986 to 7% in 2003
  - Proportion of *Acinetobacter* UTIs and SSIs also increased
  - Increase noted at multiple US hospitals and not confined to 1 geographic region
- Over 30% of Maryland vented patients colonized with *Acinetobacter*

Gaynes R, Clinical Infectious Diseases 2005;41:848.
Thom K, ICHE 2012;33:883

Increasing Incidence Worldwide

- SENTRY antimicrobial surveillance program involves 5 geographic regions
- 11% of *Acinetobacter* were carbapenem resistant in 2001
- Imipenem-resistant Acinetobacter spp. rates increased from 6.4%, 12.6%, and 0.0% in the 1997-1999 period to 84.9%, 71.4%, and 50.0% in 2008-2010 in Argentina, Brazil, and Chile, respectively.

Gales AC Clinical Infectious Diseases 2001;32(S2):104.
Diagn Microbiol Infect Dis. 2012
Increasing Incidence Worldwide

- Middle East
- Australia
- South Africa

Attributable Mortality

<table>
<thead>
<tr>
<th>Reference</th>
<th>Clinical Setting</th>
<th>Cases</th>
<th>Controls</th>
<th>Attributable Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grupper et al. 2007</td>
<td>Nosocomial BSI ICU, med-surg wards</td>
<td>52 cases of AB-BSI</td>
<td>52 Matched Controls w/o AB</td>
<td>36.5%</td>
</tr>
<tr>
<td>Playford et al. 2007</td>
<td>Infection/Colonization General ICU</td>
<td>66 cases of Infection or Colonization</td>
<td>131 Matched controls w/o AB</td>
<td>20%</td>
</tr>
<tr>
<td>Sunenshine et al. 2007</td>
<td>MDR-AB infections 3* Care Hospitals Baltimore, MD</td>
<td>96 cases of MDR-AB Infections</td>
<td>91 Susceptible-AB</td>
<td>8.4%</td>
</tr>
<tr>
<td>Kwon et al. 2007</td>
<td>CR-AB BSI 3* Care Hospitals Korea</td>
<td>40 cases of CR-AB Infection</td>
<td>40 Imipenem-susceptible</td>
<td>25-30%</td>
</tr>
<tr>
<td>Robenshtok et al. 2006</td>
<td>Nosocomial BSI Israel</td>
<td>112 cases of AB-BSI</td>
<td>90 controls w/ Klebsiella BSI</td>
<td>22.7%</td>
</tr>
<tr>
<td>Blot et al. 2001</td>
<td>Nosocomial BSI ICU Belgium</td>
<td>45 cases of BSI</td>
<td>90 Matched Controls w/ AB</td>
<td>7.8%</td>
</tr>
</tbody>
</table>
Transmissibility compared to other organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>HCW Room Entries</th>
<th>Hand + Before (%)</th>
<th>Gown and/or Glove + After (%)</th>
<th>Hands + After Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. baumannii</td>
<td>199</td>
<td>1.7%</td>
<td>38.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>133</td>
<td>0%</td>
<td>8.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>VRE#</td>
<td>94</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>MRSA#</td>
<td>81</td>
<td>2%</td>
<td>19%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>


After Contact with Patients Infected/Colonized with …

... MDR Acinetobacter baumannii
40% of Gloves/Gowns were Contaminated
4% of Hands were Contaminated after removal of gloves

... MRSA
18.5% of Gloves/Gowns
1% of Hands Contaminated

... VRE
8.5% of Gloves/Gowns
No Hands Contaminated
Acinetobacter

- carbapenems are/were the antibiotic of choice
  - Many are now resistant
- Ampicillin-sulbactam susceptibility should be looked at
- Tigecycline data is not encouraging

Outline of talk

- Mechanisms of resistance
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Spread of Resistance

• Reasons for spread of resistant bacteria
  – excessive antibiotic use
  - poor hygiene and failure of infection control practices

Hand-disinfection is the single most important means of preventing the spread of infection

CDC
Do Certain Antibiotics Lead to Emergence of Resistance?

- Answer is likely yes but as to specific ones it is uncertain due to poor study design
  - variable and incorrect control group selection
  - lack of statistical control for confounding and collinearity of antibiotics
  - lack of adjustment for time at risk
  - lack of adjustment for severity of illness
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• As much as possible and consistent with first-rate medical care, we must starve these bacteria of the lifeblood that promotes their persistence— the unrelenting selective pressure exerted by overuse of antibiotics

Lou Rice, CID 2000;31:762.
12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults

1. Vaccinate
2. Get the catheters out
3. Target the pathogen
4. Practice antimicrobial control
5. Use local data
6. Access the experts
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say "no" to vanco
10. Stop treatment when cured
11. Isolate the pathogen
12. Contain your contagion

Then What Antibiotic Recommendations Should I Be Making?

- Limit duration of antibiotics
- Limit unnecessary use of broad-spectrum agents
- Controversial issues:
  - Two agents versus one
  - Empiric antibiotic choice/Inadequate therapy
  - Importance of dosing frequency of antibiotics and their effect on resistance

Prevent Transmission
Use Antimicrobials Wisely
Diagnose & Treat Effectively
Prevent Infections

Campaign to Prevent Antimicrobial Resistance in Healthcare Settings
How To Prevent Resistance

• Improve handwashing compliance
• Find novel ways to decrease patient-to-patient transmission
• Limit duration of antibiotics

How To Prevent Resistance

• Limit unnecessary use of broad-spectrum agents
• IN GENERAL, LIMIT THE USE OF ANTIBIOTICS BOTH IN THE HOSPITAL AND OUTSIDE THE HOSPITAL
Infection control questions about untreated Gram-negative bacteria

• Should I be placing these patients on contact isolation precautions?
• Should I be performing active surveillance culturing?
• Should I be focusing my efforts on antimicrobial stewardship or infection control?
• Should we be cohorting these patients?
• Should I be culturing hospital personnel?

Infection control policies at University of Maryland

• CHG bathing all units
• Universal glove and gown in MICU
• Acinetobacter, CRE screening in the MICU, SICU and trauma units
• Isolate Gram-negative patients susceptible to two or fewer of zosyn, cefepime, imipenem
• GO TO THE INTRANET OR SPEAK TO US ABOUT THESE POLICIES
“Your infection may be antibiotic-resistant, but let’s see how it responds to intensive litigation.”
References:

• “A good general review of resistance” Chen LF. Pathogens resistant to antimicrobial agents. Epidemiology, molecular mechanisms, and clinical management. Infect Dis Clin North Am. 2011, Pages 647–676

• SHEA compendium on guidelines for preventing healthcare-associated infections http://www.shea-online.org/PriorityTopics/CompendiumofStrategiesetoPreventHAIs.aspx

References

References


References

• “Interesting article on the benefits of short term therapy (8 days) for ventilator-associated pneumonia” JAMA. 2003;290:2588
• Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. Am J Respir Crit Care Med 2000;162:505-11. Article that shows that patients with low-likelihood of ventilator-associated pneumonia did as well or better with 3 day course of antibiotics versus a longer course.
References


References

References
