C. difficile and CRE infection: Tackling the Superbugs

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Update on progress of city-wide stewardship projects

• Focus on a better understanding of antimicrobial resistance in the Houston area

• We received a huge boost this past year from CDC-sponsored grants to the Texas Dept of State Health Services and the City of Houston Health Department

• CRE:
  • characterize resistance mechanisms of CRE from at least 10 hospitals in the Houston area
  • This is just getting started, will briefly go through methodology
  • If anyone wants to participate (aka, send samples), let me know!

• C difficile infection (CDI):
  • Active, state-wide surveillance system to detect emerging epidemics of CDI
  • Houston-wide outbreak investigations of CDI
  • Lots of data to present!
  • Still looking for more sites, let me know!
Carbapenem-resistant *Enterobacteriacea*

- Carbapenemases belong to 3 classes of beta-lactamases
  - Class A – serine active site
    - KPC
  - Class B – “metallo-beta-lactamases”
    - IMP
    - VIM
    - NDM
  - Class D – serine active site
    - OXA-48

- KPC
  - USA
- IMP
  - Europe, Latin America
- VIM
  - Greece, Italy, Turkey, Spain
- NDM
  - India – emerging globally
- OXA-48
  - Europe, Latin America
CREs are in Houston

- Emergence of KPC-producing Klebsiella pneumoniae in Texas
  - Hirsch et al. DMID 2011
- .... and identification of New Delhi Metallo-B-lactamase production in Enterobacteriaceae at a major cancer center
  - Aitken et al. CID 2016
- “Six isolates with the blaKPC-2 gene were identified from 84 blood stream Klebsiella pneumoniae isolates”
  - Henrietta Abodakpi and Vincent Tam. Carmig meeting 2017
- However, no active surveillance system exists to characterize CREs in Houston.
CRE and Houston: 2017 goals

• To develop a network of hospitals submitting carbapenem-resistant Gram-negative isolates for characterization of CRE-resistant genes

• UH COP will coordinate with health-systems to collect Klebsiella and Escherichia isolates with phenotypic resistance to carbapenems

• Isolates will be further tested using the molecular PCR diagnostic, Cepheid Expert Carba-R:
  • Detects: KPC, NDM, VIM, IMP-1, OXA-48

• Goal is to collect >300 isolates per year as part of ongoing surveillance

• Interested in participating: kgarey@uh.edu
C diff Goals for 2017

• Develop a state-wide surveillance network for emerging epidemic strains (TX Dept of State Health Services)

• Develop an outbreak reporting network for *C. difficile* strains from Houston hospitals (Houston Department of Health)
Before we get started, a few words on C. diff strain typing

• **Ribotyping**
  • Strains produce band patterns based on the size variation of the 16S-23S rDNA intergenic spacer region
  • Example: ribotype 027
  • Moderate level of discrimination

• **Multilocus variable number tandem repeat analysis (MLVA)**
  • Utilizes naturally occurring variation in the number of tandem repeated DNA sequences found in many different loci in the genome. Different lengths of variable number of tandem repeats (VNTR) regions determines strain differences
  • Highly discriminatory, no temporal analysis possible

• **Whole genome sequencing (WGS)**
  • DNA sequence of conserved areas of genome
  • Highly discriminatory, temporal analysis possible with reference strains.

Rodriguez et al. Microbial Patho 2016;97:59-78
How to use these tools: did one patient give the other C diff?

Scenario 1: Ribotype: ribotype 027
Answer: No. Stop

Scenario 2: Ribotype: 027
MLVA different 027
Answer: Maybe
Answer: No. Stop

Scenario 3: Ribotype: 027
MLVA same 027
WGS (vs. historic control) 20 BP difference 30 BP difference
Answer: Maybe
Answer: Yes. Who gave it to who
Answer: Pt 1 gave it to patient 2!
Now, let’s start using some of these tools

• Nursing home outbreak
• Houston surveillance
• Environmental surveillance
Nursing home outbreak

• In 2016, we were consulted on an increased number of CDI cases at a nursing home (n=4). One patient was originally symptomatic with three subsequent cases developing over the next month. This was the first case of CDI occurring at this nursing home ever!

• Is an outbreak occurring?

• Sample sent to UH
  • Six stool samples
  • 50 environmental samples

RESULTS: ALL STOOL SAMPLES WERE POSITIVE FOR RIBOTYPE 027!
MLVA confirmed outbreak in patient and environmental samples

<table>
<thead>
<tr>
<th>Center</th>
<th>StrainID</th>
<th>Ribotype</th>
<th>A6&lt;sub&gt;cd&lt;/sub&gt;</th>
<th>B7&lt;sub&gt;cd&lt;/sub&gt;</th>
<th>G8&lt;sub&gt;cd&lt;/sub&gt;</th>
<th>C6&lt;sub&gt;cd&lt;/sub&gt;</th>
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<td>17</td>
<td>16</td>
<td>15</td>
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</tbody>
</table>

Patient sample
We were able to provide some conclusive proof that the environmental was contaminated

<table>
<thead>
<tr>
<th>Environmental source</th>
<th>Positive C. difficile growth</th>
<th>Ribotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rm 616 Handrails on bed</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm616 Bendside table surface- fixed table beside the bed</td>
<td>No</td>
<td>XXXX</td>
</tr>
<tr>
<td>Rm616 Remote control on recliner chair</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 616 Doorway outside floor</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 616 Shower seat surface</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 616 Doorway inside floor</td>
<td>No</td>
<td>XXXX</td>
</tr>
<tr>
<td>Rm 616 wheelchair arms</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 616 light switches</td>
<td>No</td>
<td>XXXX</td>
</tr>
<tr>
<td>Rm 616 bedside table surface - mobile used for meals</td>
<td>No</td>
<td>XXXX</td>
</tr>
<tr>
<td>Rm 616 Toilet hand rails</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 616 Tube syringe</td>
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<td>XXXX</td>
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<tr>
<td>Rm 502 Doorway- outside floor</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 502 Doorway- inside floor</td>
<td>Yes</td>
<td>F027</td>
</tr>
<tr>
<td>Rm 502 Bedside table surface-mobile used for meals</td>
<td>Yes</td>
<td>F027</td>
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<td>Rm 502 bed hand rails</td>
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<td>Rm 502 sink surface area</td>
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<td>Rm 502 inside door knob</td>
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<td>Rm 502 toilet hand rails</td>
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<td>Rm 502 bathroom floor</td>
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</tr>
<tr>
<td>Admin. Office copier surface</td>
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<td>XXXX</td>
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</table>
Follow-up

• Based on these results, the nursing home is currently going through an institution-wide terminal clean
  • Will repeat the environmental sampling protocol when terminal clean is done to confirm eradication of ribotype 027 from the environment

• Interesting hypothesis:
  • In this case, the patient likely spread ribotype 027 to the environment (and not the other way around)
  • We should be able to confirm this with WGS
Health system *C. diff* surveillance

- Approximately 40 hospitals submitting leftover stool from *C. diff* positive patients on a monthly basis
- Samples are cultured for *C diff*, confirmed toxigenic by PCR, and ribotyped
- Clinical meta-data: Age, gender, collection date, admission date, hospital variables (location, testing method, etc)
- Approximately 1,200 samples submitted in 2016
Texas 2016

*C. diff* ribotype distribution

- Houston-Galveston (n=501)
- Dallas Fort-Worth (n=209)
- San Antonio (n=72)
This global surveillance system can also be used to assess hospital-level outbreaks

Reports sent quarterly to participating hospitals

<table>
<thead>
<tr>
<th>Month-yr</th>
<th>F001</th>
<th>F002</th>
<th>F005</th>
<th>F010</th>
<th>F012</th>
<th>F014-020</th>
<th>F015</th>
<th>F017</th>
<th>F019</th>
<th>F027</th>
<th>F053-163</th>
<th>F054</th>
<th>F056</th>
<th>F078-126</th>
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<td>0</td>
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<tr>
<td>09-2016</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
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<td>7</td>
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<td>11-2016</td>
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<td>3</td>
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<td>29</td>
<td>3</td>
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</table>

Interpretation: This hospital saw an increase in ribotype 027 in Sept-Nov. Was this an outbreak?

**Answer:** No!
This surveillance system will also allow us to answer some amazing research questions.

The 027 epidemic was caused by the emergence of two separate ribotype 027 lineages (FQR1 and FQR2).

How did C diff ribotype 027 arrive in Houston?

Endres et al. Carmig 2017
Did you ever notice how much time and effort we spend cleaning patient rooms? (Probably not enough but we do try our best)

If we use appropriate germicidal solutions, we do the bacteria come back so fast?
*C. difficile* is becoming more common in the community setting

- CDC: 10 US states identified 984 patients with community-acquired CDI (No previous antibiotics: 36%; No outpatient healthcare exposure: 18%).

How do patients get infected in the first place? Where are C diff strains coming from?

- Leeds, England: Whole genome sequencing of 1223 cases of CDI. This allows for a highly discriminatory way to see where C diff strains are coming from.

New thoughts on CDI transmission

Symptomatic Patient with CDI → Patient → Asymptomatic Patient with CDI

Healthcare workers → Patient

Hospital environment

Slide courtesy of Eric Kao
Prevalence of *C. difficile* (CD) from various environmental samples. Samples collected from 30 households throughout Houston, TX

Alam, Anu, and Garey. *Anaerobe* 2014
Is C. diff ubiquitous in our environment?

• We hypothesized the community environment may contain a large burden of *C. difficile* contamination.

• The objectives of the study was to assess community environmental contamination of toxigenic *Clostridium difficile*
  
  • Sub-aims
    • compare strain relatedness to clinical strains (ribotype)
    • assess virulence in a mouse model.
Methods

• Environmental contamination
  • Assessed C. difficile prevalence in
    • Public areas (public parks)
    • Chain stores, fast-food restaurants
    • Homes (3-5 samples)
      • Kitchen and bathroom
      • Cleaning supplies
      • Shoe soles
      • Door steps
• Clinical isolates
  • Diarrheal stool from hospitalized patients with positive *C. difficile* toxin test obtained from two healthcare systems in Houston (7 hospitals)

• Microbiology
  • Stool and environmental isolates incubated anaerobically for *C. difficile* (confirmed with PCR)
  • *C. difficile* isolates characterized by fluorescent PCR-ribotyping
Results, number of samples

<table>
<thead>
<tr>
<th>Isolate source</th>
<th>Number</th>
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<tbody>
<tr>
<td>Environmental</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>1173</td>
</tr>
<tr>
<td>Chain stores</td>
<td>230</td>
</tr>
<tr>
<td>Fast-food restaurants</td>
<td>125</td>
</tr>
<tr>
<td>Parks</td>
<td>540</td>
</tr>
<tr>
<td>Clinical isolates</td>
<td>613</td>
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</table>
Community environmental contamination of toxigenic *C. difficile*

**p<0.001** compared to either chain stores, fast-food restaurants, or other commercial stores

Alam et al. OFID 2017, In press
Home environmental contamination of toxigenic *C. difficile*

**p<0.001** comparing shoe soles and doorsteps to cleaning supplies, kitchen and restroom samples
Ribotype distribution of clinical vs. environmental *C. difficile* isolates

- Community environmental (n=344)
- Hospital environmental (n=74)
- Clinical isolates (n=615)

![Bar chart showing ribotype distribution](chart.png)
Cytotoxicity of environmental vs. clinical isolates by ribotype

Environmental Isolates

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>Isolate</th>
<th>Isolate with toxin A&amp;B neutralizing antibody</th>
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<td>027</td>
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Clinical Isolates

<table>
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Most of the other environmental samples have been conducted in Europe.

How do our results compare to Europe?

Paris, France
Berlin, Germany
Houston, TX
Lucky for me, I had a student do an internship in Paris and Berlin last Summer!
# Houston vs. Europe

**C. difficile environmental prevalence**

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<tr>
<th>Environment</th>
<th>Houston</th>
<th>Europe</th>
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<tbody>
<tr>
<td>Overall*</td>
<td>21%</td>
<td>219/1040 (21%)</td>
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<tr>
<td>Parks</td>
<td>32%</td>
<td>97/235 (41%)</td>
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<tr>
<td>Houses</td>
<td>n/a</td>
<td>61/175 (35%)</td>
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<tr>
<td>General Public</td>
<td>16%</td>
<td>27/200 (14%)</td>
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<tr>
<td>Fast Food</td>
<td>n/a</td>
<td>10/125 (8%)</td>
</tr>
<tr>
<td>Chain Stores</td>
<td>n/a</td>
<td>21/250 (8%)¹</td>
</tr>
</tbody>
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An Epidemiological Survey of Environmental *Clostridium difficile* in Berlin and Paris

Community environmental studies on potentially pathogenic *Clostridium difficile*
Conclusions

• Houston has taken the lead for active surveillance of threat level urgent pathogens.
  • Partnership with City and State Health departments has been invaluable
  • This HASS meeting and our group collective has been an amazing strength for our ability to garner this support

• These surveillance systems will improve patients care and add to science

• Each of these surveillance efforts has room to grow
  • Want to participate: email me!
  • kgarey@uh.edu
Acknowledgements