Outbreak Case Study

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**Ralstonia Outbreak Investigation Background**

- CDC notified of 5 cases of recovery of Ralstonia spp. From respiratory cultures obtained from patients at one pediatric hospital.
- No previous cases in 5 years.
Question 1

• Is this an outbreak?

Epidemic Curve of *Ralstonia* Cases–
Question 2

- What can an epidemic curve tell you?
- Sometimes, quite a lot

Common Source Outbreak
Person-to-Person Transmission

Mixed Common Source and Person-to-Person Transmission of the Same Disease
Intermittent Exposure to Common Source

Epidemic Curves in Healthcare Outbreaks

- Caveat emptor- epi curves can be tricky in healthcare outbreaks.
- Usually, the number of cases is very small and the reaction is quick, so there’s not much help in the epi curve.
Top 3 reasons to do an Epidemic Curve in a Healthcare Outbreak

- They are easy to do and might help point you in a direction.
- You will get instant epi bonus points.
- Trish is going to ask for it.

Question 3

- What the heck is *Ralstonia*?
**Ralstonia spp. Background**

- Gram-negative bacillus
- Water environment
- Prior healthcare-associated outbreaks
- Low virulence
- Increasing cause of serious illness

Image from DHQP courtesy of Janice Carr

**Ralstonia spp. Microbiology**

- *Ralstonia* genus proposed in 1995 (formerly *Pseudomonas* and *Burkholderia*)

- R. insidiosa
- R. pickittii
- R. eutropha
- R. paucula
- R. campinensis
- R. basilensis
- R. mannitolilytica
- R. metallidurans
- R. oxalatica
- R. gilardii
- R. tainwanensis
- R. solanacearum

- Can be difficult to identify using standard biochemical techniques
- Tendency to form biofilms in plastic piping*
- Can pass thru 0.45 and 0.2 micron filters

*Anderson, et al 1990
**Ralstonia spp. Outbreaks**

- Previous outbreaks in hospital due primarily to contaminated solutions
- *R. pickettii*  
  - 55 outbreaks  
  - 366 patients  
  - 4 deaths  
  - Bacteremia, endocarditis, meningitis, pneumonia, osteomyelitis, septic arthritis
- *R. mannitolilytica**  
  - Respiratory infections in Cystic fibrosis patients  
  - Meningitis, hemoperitoneum


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**Remember Papers Are Your Friend**

- Always remember that just about anything you will have to investigate has been investigated before.
- If you’ve seen one healthcare outbreak, you’ve seen one healthcare outbreak.
- BUT, the lessons learned and methods used can be very helpful.
What’s Your Case Definition?

Case Definition

• Any patient admitted to the hospital with a culture that grew Ralstonia spp. from any site in the previous 6 months.
Why?

- Ralstonia is pretty rare so there is little downside to including all cases in your definition.

How Will You Find Cases?
Case Finding

• Is easy in this case-
• Microbiologically driven case definition means you can use lab records for case finding.

Now What?

• Line list.
• What do you want to know initially and why?
## Line List

<table>
<thead>
<tr>
<th>Item</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Respiratory Diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>NICU</td>
<td>2</td>
</tr>
<tr>
<td>CICU</td>
<td>3</td>
</tr>
<tr>
<td>Ventilator exposure within 30 days</td>
<td>4</td>
</tr>
<tr>
<td>Vapotherm device exposure in 30 days</td>
<td>4</td>
</tr>
<tr>
<td>Nasogastric feeds</td>
<td>3</td>
</tr>
<tr>
<td>Inhaled medications</td>
<td>3</td>
</tr>
</tbody>
</table>
What do you need to learn more about now?

**Vapotherm 2000i Background**

- Delivers humidified oxygen via nasal cannula
- Widely used by pediatric and neonatal clinicians
  - 13 countries
  - 5,000 units in 900 hospitals in United States
- Portable, multi-use device

Diagram from Vapotherm, Inc
Vapotherm 2000i Background

Water flow from Water Reservoir to Water Pump, then to Heater. Air flow from Oxygen Supply through Cartridge with 0.01 micron filter. Water flow from Heater to Cartridge, then humidified oxygen to patient.

Vapotherm Filter-Cartridge

- Vapor transfer humidification of oxygen
- “Air and water are separated by a biological barrier . . . essentially no risk of bacterial contamination . . .”
- Tap water used in device circuit
Vapotherm Reprocessing

- Entire device (including cartridge) reusable
- Reprocess between patient use
- Quaternary ammonium with 10 minute dwell time

Is It Time to Notify Others?

- Do you have enough information at this point to alert any external partners about what’s going on?
- What are the potential benefits?
- What are the potential down sides?
Is It Time to Notify Others?

- Yes.
- Always helpful to alert your state and/or local health department when you suspect an outbreak.
- That’s exactly what this facility did.
- State health department called CDC.
- CDC put out calls for other potential cases - other pediatric facilities responded.
- FDA also notified.

Do You Need an Analytic Study?
Do You Need an Analytic Study?

- This outbreak has factors that make an analytic study helpful:
- No clear common factor
- Potential association with a medical device.

What Type of Study?
What Type of Study?

- Case control study makes the most sense given small number of cases.

Who Are Controls?

- What factors need to be controlled for (e.g. what might you want to match for)?
- Length of hospital stay?
- Underlying health status?
- Birth weight/ gestational age?
- Facility location?
Colonization Status and Control Selection

- All of the case patients were felt to be colonized and not infected.
- What if there was widespread colonization in the facility at the time the cases were diagnosed?
- How would that impact your study?
- What could you do about it?

Our Controls

- Matched on length of hospital stay
  - Because cases had relatively long lengths of stay before infection, we thought it was important to select controls that also had long lengths of stay and hence, we hoped, similar exposure risks.
- Control had to have at least one respiratory culture that did not grow Ralstonia.
  - Based on discussions with the facility staff, we were worried about included potentially recognized cases as controls.
## Case Control Study- Univariate Demographics

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=5)</th>
<th>Controls (n=20)</th>
<th>Cochran-MH p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex*</td>
<td>3 (60%)</td>
<td>11 (58%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean age (days)</td>
<td>594</td>
<td>804</td>
<td>0.81**</td>
</tr>
<tr>
<td>Respiratory chief complaint</td>
<td>3 (60%)</td>
<td>9 (45%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>2 (40%)</td>
<td>10 (50%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Cardiac ICU</td>
<td>3 (60%)</td>
<td>3 (15%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pediatric ICU</td>
<td>0</td>
<td>6 (30%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Ward unit</td>
<td>0</td>
<td>1 (5%)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*Sex not recorded for one control  
**Independent sample t-test

## Case Control Study- Univariate Exposures

<table>
<thead>
<tr>
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<th>Cases (n=5)</th>
<th>Controls (n=20)</th>
<th>Odds Ratio* (95% CI)</th>
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<tbody>
<tr>
<td>Vapotherm use within 30 days</td>
<td>4 (80%)</td>
<td>1 (5%)</td>
<td>17.8 (2.2, 141.8)</td>
</tr>
<tr>
<td>Ventilator use within 7 days</td>
<td>4 (80%)</td>
<td>18 (90%)</td>
<td>0.3 (.01, 8.2)</td>
</tr>
<tr>
<td>Oral feeding</td>
<td>0</td>
<td>2 (10%)</td>
<td>0.8 (.06, 10.9)</td>
</tr>
<tr>
<td>Naso-gastric feeding</td>
<td>3 (60%)</td>
<td>10 (50%)</td>
<td>2.0 (0.1, 30.6)</td>
</tr>
<tr>
<td>Inhaled Medication</td>
<td>3 (60%)</td>
<td>13 (65%)</td>
<td>0.8 (0.1, 3.9)</td>
</tr>
</tbody>
</table>

*Logit estimate for Cochran-Mantel-Haenszel statistic
## Case Control Study- Multivariate

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases (n=5)</th>
<th>Controls (n=20)</th>
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<td>0.8 (0.1, 3.9)</td>
</tr>
<tr>
<td>Cardiac ICU</td>
<td>3 (60%)</td>
<td>3 (15%)</td>
<td>5.1 (0.71, 37.5)</td>
</tr>
</tbody>
</table>

*Logit estimate for Cochran-Mantel-Haenszel test statistic

### What Might Help Close the Case Now?
What Might Help Close the Case Now?

- Environmental samples.
- What would you culture?

Field Investigation
Environmental Samples

<table>
<thead>
<tr>
<th>Source</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapotherm devices (n=4)</td>
<td><em>Ralstonia mannitolilytica</em></td>
</tr>
<tr>
<td><em>(Cleaned and Patient ready)</em></td>
<td></td>
</tr>
<tr>
<td>Sink water</td>
<td>GNR (oxidase +, not <em>Ralstonia</em>), Diptheroid, <em>P. aeruginosa</em></td>
</tr>
<tr>
<td>Ice machine</td>
<td>GNR (oxidase +, not <em>Ralstonia</em>)</td>
</tr>
<tr>
<td>Mechanical ventilators</td>
<td>No growth</td>
</tr>
<tr>
<td>Respiratory solutions</td>
<td>No growth</td>
</tr>
<tr>
<td>New Vapotherm cartridges</td>
<td>No growth</td>
</tr>
<tr>
<td>Vapotherm disinfectant</td>
<td>No growth</td>
</tr>
</tbody>
</table>
Outbreak Related
• 18 of 22 (82%) hospitals
• 31 of 38 (82%) cases
• 12 states

National Investigation Methods

• *Ralstonia search*
  - Epi-X dispatch
  - Data collection forms distributed electronically
  - Clinical cases or contaminated machines
  - Isolates requested for identification

• National case definition
  - Culture-confirmed *Ralstonia*
  - Colonization or infection in patient
National Investigation
Clinical Cases

Possible Sources of Intrinsic Contamination

Filter Cartridge
Manufactured in Minneapolis, MN
Water involved in assembly
High temperature manufacture
Drying with HEPA-filtered air
CDC unable to culture organisms from unopened cartridges

Vapotherm Device
Assembled in Galway, Ireland
Water involved in calibration
Now uses filtered water
Tap water used previously

Sphingomonas spp. from water sample
B. cepacia recovered from tap swab
What Happened?

- Once Ralstonia was introduced, the reprocessing protocol recommended by the company was not sufficient to remove it.
- Ralstonia spp. can be somewhat resistant to disinfectants and have a propensity to form biofilms.

What Happened?

- The company issued a national recall for the devices.
- Manufacturing protocols were changed to prevent introduction of organisms.
- In-use reprocessing protocols were changed to more stringent methods.