Microbial Genetic Data and Infection Prevention
What are the applications?

Outline
1. Whole Genome Sequencing technology
2. Infection Prevention and Control applications
3. Microbiology testing for antimicrobial genes
4. Metagenomic analysis

Current journal articles - AJIC

The new frontier of diagnostics: Molecular assays and their role in infection prevention and control
S Das, DR Shibib, MO Vernon
AJIC, Feb 01, 2017 pp. 158-169

Infection Control in the new age of genomic epidemiology
P Tang, M Croxen, M Hasan, W Hsiao, L Hoang
AJIC Feb 01, 2017 pp. 170-179
What?

“Molecular Epidemiology”

* Use of molecular methods coupled with conventional epidemiologic tools to identify potentially linked cases and aid in the investigation of outbreaks – or possible horizontal transmission events

Outbreaks using new molecular methods

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole Genome Sequencing

MRSA Transmission on a Neonatal Intensive Care Unit: Epidemiological and Genome-based Phylogenetic Analyses
U Nubei et al. *PLOS ONE* Jan 2013, Vol 8, Issue 1
How do we most effectively assess whether and how an organism is being transmitted?

1. Epidemiologic investigation
   • delineate human contacts
   • search for environmental exposures
   • Patient location

2. Strain relatedness

Strain-relatedness in Infectious Diseases Epidemiology

- organisms generally accumulate progressive genetic change over time
- can infer timing, and therefore direction of transmission
- genetic differences can be detected phenotypically or by a number of DNA-analysis based techniques:
  • phenotypically (antibiotic resistance)
  • restriction endonuclease digestion (PFGE)
  • multi-locus sequencing
  • whole genome sequencing

David Haslam, MD

Pulse field gel electrophoresis (PFGE)

DiversiLab Typing (repPCR-based)

Courtesy of Joel Mortensen, PhD
Whole genome sequencing of bacterial isolates to assess transmission, antibiotic resistance, virulence.

WGS allows reconstruction of transmission path.
CCHMC Examples

• CICU possible horizontal transmission event
• Cystic Fibrosis MRSA
• NICU *Staphylococcus aureus* transmission

CICU possible horizontal transmission event
August 2016

• 2 CICU patients isolated *Enterobacter spp.* with a very similar antibiotic susceptibility pattern
• Microbiology lab alerted Infection Preventionist

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<th>Patient 1</th>
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| • Admitted 6/21/16  
  • Dx: Hypoplastic left heart syndrome  
  • 200/300 pod  
  • 8/8/16 blood and ETI  
  • 8/11/16 wound  
  • Mediastinitis w/secondary BSI  
  • Enterobacter aerogenes  
  • Enterobacter aerogenes  
  • Enterobacter aerogenes  
  • Enterobacter aerogenes  
  • Enterobacter aerogenes  
  | • Admitted 8/2/16  
  • Dx: AV valve defect  
  • 100 pod  
  • 8/12/16 blood and ETI  
  • 8/13/16 wound  
  • Mediastinitis w/secondary BSI  
  • Enterobacter aerogenes  
  • Enterobacter aerogenes  
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  • Enterobacter aerogenes  |
Investigation

- Reviewed patient locations
  - Pods
  - ORs
  - Cardiac cath lab
- Met with CICU leadership
  - Shared staff between patients
- Met with Cardiac Fellows
- Observations
  - Portable ultrasounds
  - Portable sonograms
  - Hand hygiene
  - PPE compliance
- Tracked TEE probes
- Sent clinical isolates for WGS

Investigation conclusions

- *Enterobacter* isolates were not related
- Epidemiology did not show a clear link between patients
- Infection Control investigations revealed some lax practices
  - Hand hygiene
  - PPE
  - Equipment cleaning
Cystic Fibrosis MRSA relatedness

- 2014 new CF guidelines released – changes implemented
- April 2014 – Feb 2016
  - MRSA isolate from respiratory culture on all CF patients
  - Serial isolates – every 3 months
- 212 isolates from 70 unique patients – 13 pairs of siblings
- 24 isolates were first-time acquisitions, rest were colonized
- Whole Genome Sequencing

Objective: Examine relatedness of MRSA isolates to determine possible horizontal transmission events

Population dynamics of Staphylococcus aureus in Cystic Fibrosis patients to determine transmission events utilizing whole genome sequencing
A. Ankrum and B. Hall

Results and Conclusions

- Define “same strain” in the context of our patient population
  - Not an outbreak scenario
  - Long-term colonization mixed with new acquisition
  - No established cut-off values
- Determine if any patients had the “same” strain
  - ≤ 70 SNPs = “same” strain
  - Only siblings had the “same” strain
- Longitudinal isolates revealed strain retention during the study period
- Conclusion: during the study period, there was NO transmission of MRSA between CF patients except between siblings
Antibiotic resistance and virulence gene content of Staphylococcus aureus isolated from Cystic Fibrosis patients

• WGS allows detailed investigation of genes present in infecting and colonization strains from patients with different outcomes

Bacterial WGS allows rapid profiling of antibiotic resistance potential

• Correspondence between genotype and phenotype very high

Prediction of Staphylococcus aureus Antimicrobial Resistance by Whole-Genome Sequencing

• Prediction of antibiotic susceptibility by WGS was as accurate as in vitro testing


Prediction of antibiotic susceptibility by WGS was as accurate as in vitro testing.
**Staphylococcus aureus transmission in the NICU**

**Epidemiology**

- **Virulence Factors**
  - Adhesive Pili
  - Beta-Lactamase
  - Penicillin-binding Proteins
  - Virulence Factors

- **Resistance**
  - Antibiotic

- **Pod Construction**
  - Fomites
  - Families
  - Other Visitors
  - Healthcare Workers

**NICU and Staph aureus**

- 59 beds, 8 pods, 20 private rooms
- 95% full 95% of the time
- MRSA/MSSA screening
  - On admission
  - Weekly
- Screening stops if MRSA positive
- Culture on screening media switched to molecular in October 2016 (higher sensitivity)
- Staph aureus is the #1 cause of HAIs
- Relative risk analysis: 50x greater risk of infection if colonized
- In 2016 there were 58 healthcare-acquired bacterial infections in the NICU
  - 24% were attributed to S. aureus

Orlando, FL
S. aureus burden in our NICU

- February 2017 (point prevalence)
- 94 patients
  - 22 MRSA (23%)
    - 21 healthcare acquired (since admission)
    - 1 (present on admission)
  - 22 MSSA (23%)
    - 15 healthcare acquired (since admission)
    - 7 (present on admission)
  - 50 neither (54%)

S. aureus NICU study

- 2014 - present
- Saved all S. aureus isolates
  - Screening isolates
  - Clinical isolates (blood, wound, ETT)
  - Whole Genome Sequencing
- >800 isolates
- Objective: determine transmission events and study the epidemiology of acquisition

Preliminary Results

- 1751 admissions during the study period
  - 67 (3.8%) cases of acquired MRSA
  - 179 (10.2%) cases of acquired MSSA
- Strains available for sequencing
  - MRSA isolates – 68 patients
    - 34 acquired
    - 34 positive admission screens
  - MSSA isolates – 143 patients
    - 90 acquired
    - 53 positive admission screens

Matt Washam MD, MPH
Infection Prevention Forum 3/23/2017

Matt Washam MD, MPH

• MRSA from 68 patients
  • 57 with one isolate
  • 11 with multiple isolates

• Transmission events:
  • 9 identified (2-3 patients)
  • 39 (58%) infants with unique MRSA isolates
  • 29 (42%) with evidence of infant-to-infant transmission

Visualization of ‘identical’ isolates by force network graph

Preliminary Conclusions

• Line insertion / maintenance bundles and ventilator care are working
• Colonizing strains match infecting strains
• Contact precautions do not seem to affect direct infant-to-infant transmission
• Increasing terminal bed space cleaning frequency may drive lower acquisition rates
• Preventions focusing on eliminating influx of Staph into the NICU are key
  • 100% hand hygiene compliance
  • Routine HCW and parent decolonization?

Matt Washam MD, MPH
Clinical testing for detection of antibiotic resistance genes
Identification of ESBL, AmpC, and Carbapenemase enzymes in Gram-Negative Bacilli

Joel Mortensen, PhD.

Check-Points System

• Multiplex PCR followed by microarray detection
• Identifies extended spectrum beta-lactamases (ESBLs), AmpCs, and carbapenemases
• Input: Extracted DNA from isolated Gram-negative bacilli

Joel Mortensen, PhD.

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Next Steps

- Research applications
  - Long term antimicrobial use
  - Patients with Central Venous Catheters
  - Patients with long term urinary catheters

- Orderable laboratory test
  - Enterobacteriaceae isolates from blood with phenotypic resistance to 3rd/4th/5th generation cephalosporins
  - May expand to urine culture isolates

Joel Mortensen, PhD.

Patient	Name:	_______________________	 	 	 DOB:	__________________ _________
MRN:	______________________________	 	 	 Accession	Number:	_______ ________
Site:	_______________________________	 	 	 Collection	Date:	______ ____________
Organism	Identification:	______________________________________________
Genes	Detected:	 	 	 	 	 Susceptibilities:	 ⃝	Vitek2						⃝	E‐test

Notification:	__________________________________________________________________________
Comment:
- For questions regarding antimicrobial selection, please contact the Antimicrobial Stewardship program or the Infectious Disease service.
- For questions regarding this test, please contact the laboratory at (513) 636‐7658.

This test was performed using the Check‐points Check‐MDR CT103XL Test.
This multiplex PCR assay of the CT103XL was validated for use by the Cincinnati Children's Hospital Medical Center Diagnostic Disease Testing Laboratory.

Signature of Reviewer:	___________________________________
Joel E. Mortensen, Ph.D.
Director, Diagnostic Infectious Diseases Testing Laboratory

Checkpoints Check MDR CT103XL detects the following:

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Joel Mortensen, PhD.
What does this mean for Infection Prevention?

- Currently we isolate patients with Enterobacteriaceae resistant to 3rd/4th generation Cephalosporins
- Checkpoints system only run on isolates with this profile
- Potential exists for identification of Carbapenem-resistance genes that were not phenotypically expressed
- Patient isolation upgraded to “strict contact”

Metagenomics

Application of a suite of genomic technologies and bioinformatics tools to directly access the genetic content of entire communities of organisms (Microbiome)


Precision Metagenomics
High-risk inpatient samples have markedly increased prevalence of pathogenic organisms

Average distribution of organism abundance, by patient group

Species Composition in Healthy Children compared to High Risk GI Diseases

Heidi Andersen, MD
Patient examples with ‘normal’ microbial community

Patient examples with pathogen domination

Heidi Andersen, MD

IF: JM had Hirschprung disease with intestinal failure (subsequent intestinal transplant) who had numerous SSI due to E coli, Candida, Pseudomonas, and VRE. Many line changes. Ultimately dealt with persistent Pseudomonas, VRE and Candida bloodstream infections.

What if we knew his intestine was loaded with the organisms causing his recurrent (and ultimately fatal) infections?

Enterococcus faecium
Pseudomonas aeruginosa
Candida albicans

What if we knew his intestine was loaded with the organisms causing his recurrent (and ultimately fatal) infections?

Enterobacter, Candida, and Pseudomonas prompting gut decontamination while waiting for a liver transplant

Enterobacter cloacae
Enterococcus faecalis
Pseudomonas aeruginosa

Heidi Andersen, MD
Very few antibiotic-resistance genes detected in patients with a healthy microbiome, but patients with pathogen dominance generally have very high ARG counts.

High burden of ARG in patients with pathogen-dominated microbiota.

Metagenomics in Children with High-Risk Gastrointestinal Diseases:

1. Children with high-risk gastrointestinal diseases have marked reduction in species diversity and anaerobe abundance compared to healthy children.
2. Reduced anaerobe abundance is associated with an increased risk of bloodstream infection. Increased pathogen abundance is associated with an increased risk of subsequent bloodstream infection (Hazard analysis).
3. Antibiotic exposure is associated with a significant reduction in anaerobe abundance within the gut microbiome.

Metagenomic surveillance of high-risk patients reveals:

1. Colonization and subsequent dominance with pathogenic bacteria is common.
2. High-level abundance of antimicrobial resistance genes is common in colonized patients.
3. Intestinal domination by an MDR pathogen almost always occurs before the patient becomes ill.
4. Presumed patient-to-patient transmission within the hospital appears to be much more common than expected (E. coli, E. faecium, E. faecalis, Pseudomonas aeruginosa, Klebsiella pneumoniae).
Metagenomic surveillance has the capacity to prevent MDR infection and improve outcomes by:

1. Isolating colonized patients to prevent transmission
2. Identify impending dominance of MDR pathogen and prevent inappropriate antimicrobial exposure
3. Displace pathogenic organism by targeted probiotics or fecal transplantation

Heidi Andersen, MD

Moving forward, metagenomic surveillance has the capacity to improve outcomes in children with high-risk of invasive infection

1. Identify patients at risk of invasive infection (HAI prevention?)
2. Preserve and/or replenish anaerobe abundance by antimicrobial stewardship, targeted probiotics, or next generation fecal transplantation

Heidi Andersen, MD

Conclusion

1. Whole Genome Sequencing will become more mainstream in the near future
   - Outbreak investigations
   - Transmission events
2. Detection of antimicrobial resistance genes may facilitate quicker isolation practices
3. Metagenomics will drive understanding of microbiomes and disease
   - May help initiate practices to prevent HAIs
4. Clinical microbiology will move towards whole genome sequencing for organism identification and antibiotic resistance
   - Faster
   - Predictive
   - Strain relatedness
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