New Antimicrobials and Rapid Diagnostics: Implications for Antibiotic Stewardship

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Disclosures

- While product trade names are used in this lecture, I have received no compensation from these agencies and my presentation in no way should represent the direct marketing of any of these products.
Objectives

• To review the utility of rapid respiratory viral panels and compare them to standard viral swab tests
• To discuss rapid meningoencephalitis panels and their utility in rapid antimicrobial de-escalation and patient discharge
• To discuss the utility of stool panel PCR tests
• To discuss the potential stewardship impact of rapid blood culture tests and procalcitonin use as well as new antimicrobials for drug resistant pathogens
• Take home points
Background

- FDA first approved multiplex PCR panels for respiratory pathogens in 2008
- In the last 10 years we now have panels for meningoencephalitis, GI pathogens, and blood cultures which are becoming mainstream
Its Flu Season 2018...

• A 42yo woman presents to the ED with a c/o 48 hours of cough, headache, fever to 103F
  • Did not receive seasonal influenza vaccine
  • Works as an elementary school teacher
  • Went to a “minute clinic” and flu swab was negative
  • What next?
Rapid Flu Swab Testing

• The CDC estimates the sensitivity of rapid influenza testing to be ~50-70%
Rapid Diagnostics

- BioFire® FilmArray Respiratory Viral Panel
  - PCR based test, results in 45min
  - 97.1% sensitivity, 99.3% specificity
  - Reduction in mean ICU days per ICU visit from 9.2 to 6.2 days after panels introduced
  - Decrease in duration of empiric antibiotic use from 3.2 days to 2.7 days after initiation of testing
- Negative tests save ~$8,104/patient
- Positive tests save ~$9,109/patient

THE BIOFIRE RESPIRATORY PANEL MENU

Overall 97.1% Sensitivity and 99.3% Specificity
Sample Type: Nasopharyngeal swab in transport media

VIRUSES:
- Adenovirus
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus 229E
- Coronavirus OC43
- Human Metapneumovirus
- Human Rhinovirus/Enterovirus
- Influenza A
- Influenza A/H1
- Influenza A/H3
- Influenza A/H1-2009
- Influenza B
- Parainfluenza Virus 1
- Parainfluenza Virus 2
- Parainfluenza Virus 3
- Parainfluenza Virus 4
- Respiratory Syncytial Virus

BACTERIA:
- *Bordetella parapertussis*
- *Bordetella pertussis*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

* Available only on the BioFire Respiratory Panel 2
Opportunities

• Potential rapid de-escalation of empiric antimicrobials if a viral source can be confirmed

• Prior to PCR tests, judicious empiric use of oseltamivir based on symptoms alone
  • Push towards rapid treatment regardless of flu swabs, especially in “bad” flu seasons

• Some evidence of emerging oseltamivir resistance in 2015-2016 H1N1 cases

• Oseltamivir cost - $157.65 for a 5 day course
56yo man presents to the ED with a c/o 2 days of debilitating headache, fevers to 102F, neck pain, and now his spouse reports he has had some confusion and disorientation.

LP done in the ED demonstrates 336 WBCs, 92% lymphocytes, protein 65, glucose 55.

Patient is started on IV ceftriaxone, vancomycin, ampicillin, and acyclovir.

And now the wait begins...
Scenario Cont’d.

• Gram stain can be performed quickly but CSF cultures will take up to 72 hours
  • Most likely a viral etiology – but all droplet/contact isolation remains in place
• HSV PCR is sent to an outside lab in Utah
• Lab has already called and said they don’t have enough CSF to run the Lyme test you added on
• Infection control is calling asking about prophylaxis for 17 hospital employees
• Patient is feeling much better on day 2 and is asking about discharge
  • He has a trip planned with his entire family in 4 days and wants to know the plan
Rapid Diagnostics

- **BioFire® FilmArray Meningitis/Encephalitis Panel**
  - 1 test, 14 bacterial/viral/fungal targets
  - Results in ~1-3 hours
    - Traditional testing around 13 hours, however most sent out of state so turnaround is often 3-5 business days pending receipt of specimen and if batch has been run for the day
  - 2 min of hands-on time in the lab
FilmArray® Meningitis/Encephalitis Panel

1 Test. 14 Targets. All in about an hour.

Bacteria
- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Viruses
- Cytomegalovirus (CMV)
- Enterovirus
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus
- Varicella zoster virus (VZV)

Fungi
- *Cryptococcus neoformans/gattii*
How Does This Work?

• PCR based testing, reagents stored “freeze dried” in the machine
  • Buffer solution and CSF inserted into the machine
  • Machine extracts and purifies all nucleic acids and two separate PCR tests are performed against standard reagents

• Overall 94.2% Sensitivity and 99.8% Specificity
  • Sample size? Only 0.2mL
Implications/Stewardship

• Within 3 hours we will know with reasonable certainty that patient is negative for the most common bacterial culprits
  • Reassurance to infection control and staff
  • Broad spectrum IV antibiotics can be streamlined or discontinued
• The often 3-5 day wait for outside labs to return HSV PCR and VZV PCR studies is now reduced to almost immediate results
  • Empiric antivirals can be discontinued where appropriate
• PICC lines, when needed, can be placed 2-3 days sooner and discharge plans can be expedited
Another Clinical Scenario

• A 64yo man presents to the ED with a c/o watery diarrhea with cramping for the past 2 days
• Up to 10 watery stools per day, foul smell, no blood
• Granddaughter with diarrhea last week
• Recent travel to Puerto Rico 2 weeks prior, no illnesses while abroad
• Recent dental procedure for which he took 1gm of amoxicillin last week as he has a prosthetic mitral valve
Stool Testing

• Differential in this patient could include foodborne illness, viral gastroenteritis, traveler’s diarrhea, and c.diff

• Empiric therapies could include antimicrobials for infectious processes as well as empiric c.diff treatment
  • Possibly holding off on either/or empiric therapy given the possibility of exacerbating the underlying culprit

• Traditional stool studies/cultures could take 1-3 days to result and lack sensitivity
The Biofire GI Panel Menu

Overall 98.5% Sensitivity and 99.2% Specificity

Sample Type: Stool or Cary Blair

Bacteria:
- Campylobacter (jejuni, coli, and upsaliensis)
- Clostridium difficile (toxin A/B)
- Plesiomonas shigelloides
- Salmonella
- Yersinia enterocolitica
- Vibrio (parahaemolyticus, vulnificus, and cholerae)
  - Vibrio cholerae

Viruses:
- Adenovirus F40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)

Diarrheagenic E. coli/Shigella:
- Enteraggregative E. coli (EAEC)
- Enteropathogenic E. coli (EPEC)
- Enterotoxigenic E. coli (ETEC) Iht/st
- Shiga-like toxin-producing E. coli (STEC) stx1/stx2
  - E. coli O157
- Shigella/Enteroinvasive E. coli (EIEC)

Parasites:
- Cryptosporidium
- Cyclospora cayetanensis
- Entamoeba histolytica
- Giardia lamblia
Opportunities

• Potential for de-escalation of empiric therapies or initiation of targeted therapies sooner
• Reduction of testing such as CTs, further diagnostics if a probable cause is found
• Reduction in length of stay if symptomatically improving
• Shorter time in isolation for “ruled out” patients
  • Less waste, less expenditure of nursing time with isolation requirements
Onto Sepsis...

• Recommendations of Surviving Sepsis Campaign:
  • “We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.”
    • Appropriate cultures (including 2 sets of blood cultures) should be obtained prior to first dose if no substantial delay in therapy
  • “We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.”
  • “We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours.”
    • Avoid starch containing solutions
Traditional Management

- Empiric, broad spectrum and potentially toxic antibiotics
  - Usually started in the ED, often within 1 hour of patient arrival
- Up to 48-72 hours for identification and susceptibility testing
- Increased incidence of resistance, c.diff, acute nephrotoxicity and other antibiotic-associated adverse reactions
Lactic Acid, Procalcitonin

- When sepsis is suspected, lactic acid/serum lactate levels and procalcitonin levels can be drawn
  - Initial lactic acid levels should be trended until resuscitation has normalized lactate in patients with elevated levels as a marker of tissue hypoperfusion
- Procalcitonin is a peptide precursor of calcitonin and is usually below the level of detection in healthy persons
  - Procalcitonin rises in response to an inflammatory stimulus, especially of bacterial origin
  - 85% sensitive and 91% specific for differentiating patients between SIRS and sepsis
  - Low levels can be used to support de-escalation or shortening antibiotic duration in patients without obvious bacterial source of sepsis
Procalcitonin Algorithm

BioFire® FirmArray Blood Culture ID Test

- Rapid testing for 24 common gram positive, gram negative, and fungal pathogens
- Includes testing for 3 resistance markers
  - mecA (methicillin resistance)
  - VanA/B (vancomycin resistance)
  - KPC (carbapenem resistance)
- 98% sensitive, 99.9% specific
- Does not immediately test full sensitivity

Aggregated Prospective Performance from the FilmArray® Blood Culture Identification Panel Clinical Trial. Data on File, BioFire Diagnostics.
FilmArray Blood Culture Identification Panel

1 Test. 27 Targets. All in about an hour.

- Gram-Positive Bacteria
  - Enterococcus
  - Listeria monocytogenes
  - Staphylococcus
    - Staphylococcus aureus
    - Streptococcus
      - Streptococcus agalactiae
      - Streptococcus pyogenes
      - Streptococcus pneumoniae

- Gram-Negative Bacteria
  - Acinetobacter baumannii
  - Haemophilus influenzae
  - Neisseria meningitidis
  - Pseudomonas aeruginosa

- Yeast
  - Candida albicans
  - Candida glabrata
  - Candida krusei
  - Candida parapsilosis
  - Candida tropicalis

- Antibiotic Resistance Genes
  - mecA - methicillin resistant
  - vanA/B - vancomycin resistant
  - KPC - carbapenem resistant

Identify Pathogens from Positive Blood Cultures in About 1 Hour

The FilmArray Blood Culture Identification Panel (BCID) tests for a comprehensive list of 24 pathogens and 3 antibiotic resistance genes associated with bloodstream infections. With just one test you can identify pathogens in 9 out of 10 positive blood cultures in about an hour with only 2 minutes of hands-on time.

- Simple: 2 minutes of hands-on time
- Easy: No precise measuring or pipetting required
- Fast: Turnaround time of about 1 hour
- Comprehensive: 27 target BCID panel

For In-vitro Diagnostic Use
FDA Cleared | CE IVD Marked

If you are interested in a free, no obligation demonstration of the FilmArray in your laboratory visit www.biofiredx.com or call 1-800-736-6544. FREE Demo!
Proven Effect of Antimicrobial Stewardship and the BioFire BCID Panel

Antimicrobial stewardship programs (ASP) optimize antimicrobial use to achieve the best clinical outcomes. The BioFire BCID Panel rapid pathogen identification, in combination with locally-derived treatment guidelines set by an ASP, can result in appropriate antimicrobial interventions. At Mayo Clinic, BioFire BCID Panel results reported with templated comments improved antimicrobial escalation, reduced treatment of contaminants, and decreased the use of broad-spectrum antimicrobials; addition of antimicrobial stewardship enhanced antimicrobial de-escalation.

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<tr>
<th>Prospective Randomized Study Arms</th>
<th>Timeline in Hours Post Gram Stain Result</th>
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<tr>
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<tr>
<td>Traditional Methods</td>
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<td>BCID</td>
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<td>BCID+Stewardship</td>
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- Organism Identification
- Antimicrobial Escalation
- Antimicrobial De-Escalation
- Antimicrobial Susceptibility Report

Adapted from Banerjee R, et al. Clinical Infectious Diseases 2015;61(7):1
Opportunities

• In one study, median time to the reduction/de-escalation of antibiotics onto optimal therapy was reduced by 33.5 hours

• Empiric selection can be narrowed very quickly if no resistance markers identified

• If KPC identified – rapid acquisition of necessary salvage therapies if not on formulary

• Savings of up to $3,000 per patient when possible CoNS contaminants are present

Newer Antimicrobials for Resistant Pathogens

• Ceftazidime/avibactam (Avycaz)
  • Salvage therapy for CRE organisms
  • $855/day

• Meropenem/vaborbactam (Vabomere)
  • Salvage therapy for CRE organisms
  • $930/day

• Ceftolozane/tazobactam
  • MDR pseudomonas infections
  • $378/day
Take Home Points

• There are now rapid diagnostic testing products on the market for the expedited identification of respiratory, meningeal, diarrheal, and blood culture pathogens

• Improvement in patient outcomes with proper targeted therapies and durations

• Use of rapid diagnostics can dramatically decrease cost to institutions with de-escalation of therapies and expedited discharge plans of care
Questions?