Syndromic Testing: The Key to the Right Diagnosis
the Most Appropriate Therapy
the Best Patient Care

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VP, Global Microbiology, bioMerieux
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Disclosure

- Employee of bioMerieux/BioFire
- Stock in Luminex
Objectives:

- Explain the concept of a syndrome and why syndromic testing is a powerful tool for the diagnosis of infectious diseases
- Classify when syndromic testing is indicated
- Outline how syndromic testing provides better patient care and saves healthcare costs
What is a Syndrome?

A *syndrome* is a set of *symptoms* and *signs* that are correlated with each other and, often, with a specific disease.

### Symptoms
- Headache
- Shaking chills
- Feverish
- Runny nose
- Cough
- Tired
- Muscles aches

### Signs
- Temperature 103.5
- Tachycardia
- Pulse ox 92%
- Wheezing, rales
- High WBC count
- Chest x-ray
- Elevated ESR
Syndrome: Symptoms and Signs

*Symptoms* and *signs* are often nonspecific; but often, combinations of them are at least suggestive of certain diagnoses, helping to narrow down what may be wrong or being specific even to the point of being pathognomonic.
Symptoms and signs are often nonspecific, and even combinations of them are at least suggestive of certain diagnoses (e.g. pneumonia, sepsis), but not specific enough to determine exact cause to appropriately guide medical interventions, including therapy.
Diagnosis: Signs and Symptoms, Demographics and History

- Age
- Sex
- Past medical history
- Comorbidities
- Immune status
- Risk of exposure
- Animal (pet) exposure
- Behavioral risk factors
- Patient location
- Season
- Travel history
- Vaccination history
# Meningitis/Encephalitis: Targeted List of Suspected Pathogens

<table>
<thead>
<tr>
<th>Traveler</th>
<th>Foreign born</th>
</tr>
</thead>
<tbody>
<tr>
<td>All above +&lt;br&gt; L. monocytogenes&lt;br&gt; CMV, EBV&lt;br&gt; HIV&lt;br&gt; HHV-6&lt;br&gt; Polyomaviruses (BK)&lt;br&gt; Aspergillosis&lt;br&gt; Nocardiosis&lt;br&gt; Cryptococcosis&lt;br&gt; Toxoplasmosis&lt;br&gt; Neurosyphilis&lt;br&gt; Gram negatives&lt;br&gt; Gram positives&lt;br&gt; ++++++++</td>
<td>S. pneumoniae&lt;br&gt; N. meningitidis&lt;br&gt; H. influenzae (NT)&lt;br&gt; EV, PeV&lt;br&gt; HSV-1, 2&lt;br&gt; EBV, CMV&lt;br&gt; Arboviruses</td>
</tr>
</tbody>
</table>
Key Syndromes

- Respiratory infections
- Gastrointestinal infections
- Meningitis/encephalitis
- Sepsis
- HAP/VAEs (VAP)
- Febrile infant
- Bone and joint infections
- Sexually transmitted infections
- Undifferentiated fevers

............................................
Key Syndromes

- Respiratory infections
- Gastrointestinal infections
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- Sepsis
- HAP/VAP
- Febrile infant
- Bone and joint infections
- Sexually transmitted infections
- Undifferentiated fevers
Undifferentiated Patient in ED

Age 69: history of mild COPD, one hospitalization in last year for pneumonia
Cough, shortness of breath, fever, chest pain, elevated WBC, elevated lactate

- Infectious
  - Bacterial
  - Viral
- Respiratory w/wo sepsis
- Non-infectious
  - PE
- Other
  - Acute asthma/bronchitis
  - Acute exacerbation of COPD
- Cardiac
  - CHF
  - ACS

SOB: shortness of breath
CHF: congestive heart failure
ACS: acute coronary syndromes
PE: pulmonary embolism
COPD: chronic obstructive pulmonary disease
Age 69: history of mild COPD, 1 hospitalization in last year for pneumonia
Cough, shortness of breath, fever, chest pain, elevated WBC, elevated lactate

SOB: shortness of breath
CHF: congestive heart failure
ACS: acute coronary syndromes
PE: pulmonary embolism
COPD: chronic obstructive pulmonary disease
Respiratory Tract Infections

<table>
<thead>
<tr>
<th>Site</th>
<th>Infectious Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharynx</td>
<td>rhino, corona, entero, RSV, parainfl, influ A, B</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>GAS, C. diptheriae, C. pneumoniae, M. pneumoniae, EBV, adeno, rhino, corona, entero, RSV, parainfl, influ A, B, entero, hMPV, HSV, CMV</td>
</tr>
<tr>
<td>Middle ear and paranasal sinususes</td>
<td>S. pneumoniae, H. influenzae, S. aureus, M. catarrhalis, GAS, rhino, corona, entero</td>
</tr>
<tr>
<td>Eye</td>
<td>H. influenzae, S. pneumoniae, S. aureus, Moraxella sp., adeno</td>
</tr>
<tr>
<td>Epiglottis</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>Larynx-trachea</td>
<td>S. aureus, adeno, rhino, corona, entero, RSV, parainfl, influ A, B, hMPV</td>
</tr>
<tr>
<td>Bronchi</td>
<td>S. pneumoniae, H. influenzae, M. pneumoniae, C. pneumoniae, adeno, rhino, corona, entero, RSV, parainfl, influ A, B, hMPV, measles</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>adeno, rhino, corona, entero, RSV, parainfl, influ A, B, hMPV, measles</td>
</tr>
<tr>
<td>Lung (alveoli)</td>
<td>Bacterial, viral, mycobacterial, fungal, parasitic</td>
</tr>
</tbody>
</table>
### Virus Differentiation by Clinical Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rhinovirus (n=580)</th>
<th>Respiratory syncytial virus (n=1655)</th>
<th>Adenovirus (n=902)</th>
<th>Parainfluenza virus 1 (n=94)</th>
<th>Parainfluenza virus 2 (n=49)</th>
<th>Parainfluenza virus 3 (n=315)</th>
<th>Influenza A virus (n=544)</th>
<th>Influenza B virus (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>18%</td>
<td>16%</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
<td>14%</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Wheezy bronchitis</td>
<td>22%</td>
<td>12%</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Otitis media</td>
<td>23%</td>
<td>59%</td>
<td>24%</td>
<td>27%</td>
<td>20%</td>
<td>30%</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Non-specified acute respiratory infection</td>
<td>14%</td>
<td>32%</td>
<td>37%</td>
<td>27%</td>
<td>22%</td>
<td>50%</td>
<td>44%</td>
<td>53%</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>3%</td>
<td>34%</td>
<td>1%</td>
<td>2%</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>37%</td>
<td>53%</td>
<td>10%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>2%</td>
<td>0%</td>
<td>30%</td>
<td>1%</td>
<td>0</td>
<td>2%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Fever without a focus</td>
<td>2%</td>
<td>1%</td>
<td>5%</td>
<td>10%</td>
<td>0</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Febrile convulsion</td>
<td>1%</td>
<td>2%</td>
<td>7%</td>
<td>4%</td>
<td>0</td>
<td>5%</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Fever ≥38°C</td>
<td>44%</td>
<td>63%</td>
<td>81%</td>
<td>77%</td>
<td>76%</td>
<td>63%</td>
<td>94%</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Rhinovirus infections are from 1987 to 2006; other respiratory virus infections are from 1980 to 1999. Modified from reference 51, with permission of John Wiley and Sons.*

**Table 2:** Occurrence of pneumonia and other findings in 4277 children with laboratory-confirmed viral respiratory infection at Turku University Hospital, Finland

Differentiation by Radiography

4 y/o: alveolar infiltrates
human rhinovirus

6 y/o: alveolar infiltrates
EV-D68

7 y/o: alveolar infiltrates
human metapneumovirus

9 y/o: alveolar and interstitial infiltrates
adenovirus
Differentiation by Radiography

62 yr old
Pericardial effusion
hMPV

57 yr old
Left pleural effusion
hMPV

52 yr old
Interstitial infiltrates
hMPV

62 yr old
bilateral lower lobe opacities
hMPV
Co-circulation of Respiratory Viruses

- RSV
- EV/RV
- AdV
- FluA-09
- FluA-H3
- FluA-NT
- FluB
- HMPV
- Para-1
- Para-2
- Para-3
- Para-4
- Corona
“Few influenza infections were recognized clinically: only 28% of inpatient children with laboratory-confirmed influenza and 17% of outpatient children had been given a diagnosis of influenza by the treating physician.”

Traditional Viral Diagnostics

**Rapid Antigen**
- influenza A, B, RSV
  - Sensitivity: 15%-80%

**DFA**
- influenza A, B, RSV, AdV, hMPV, PIV-1, 2, 3
  - Sensitivity: 35%-85%

**Culture**
- influenza A, B, RSV, AdV, hMPV, PIV-1, 2, 3, CMV, HSV, EV/R
  - Sensitivity: 50%-85%
Improves Diagnostic Yield

**Multiplex MDX**

- influenza A, B
- RSV, adeno, hMPV
- para 1, 2, 3, 4
- CMV, HSV, EV/R
- coronaviruses: OC43, 229E, NL63
- HKU-1, SARS, MERS
- Bocavirus, ???
- influ subtyping
- H1, H3, 2009H1

**Sensitivity** 80-99%

No viruses detected:
- Rap Ag: 3
- IF: 8
- Culture: 7
- RP: 17

Respiratory Virus Detection in Immunocompromised Patients with Respiratory Panel Compared to Conventional Methods

Sarah P. Hammond, a,b,c Lisa S. Gagne, a Shannon R. Stock, b Francisco M. Marty, a,b,c Rebecca S. Gelman, b,c Wayne A. Marasco, b,c Mark A. Portitz, d and Lindsey R. Baden a,b,c

All samples

NPA

Standard          FA RP
## Improves Diagnostic Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flu A</td>
<td>H1N1</td>
<td>Flu A</td>
<td>H1N1</td>
</tr>
<tr>
<td>Rapid Ag</td>
<td>20.7%</td>
<td>17.8%</td>
<td>93.6%</td>
<td>93.6%</td>
</tr>
<tr>
<td>DFA</td>
<td>48.6%</td>
<td>46.7%</td>
<td>94.5%</td>
<td>94.5%</td>
</tr>
<tr>
<td>R-Mix</td>
<td>82.7%</td>
<td>88.9%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>RVP</td>
<td>97.8%</td>
<td>97.8%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

62 y/o previously healthy woman (elementary school teacher) with one-day history of progressively worsening anterior chest pain – sharp, constant, worsens with deep breaths

Temp 40.1, tachycardic at 108, sat 88%

Chest X-ray: small, bilateral, pleural effusions associated with a large pericardial effusion

CT: diffuse bilateral ground glass opacities and pleural effusions

Echo revealed pericardial thickening
Table 3

Rates per 10 000 of ED visits and hospitalizations in patients aged 18–49 years, 50–64 years, and 65+ years.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>RSV Infection</th>
<th>HMPV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient* N = 24</td>
<td></td>
</tr>
<tr>
<td>18–49</td>
<td>13.18 (6.7, 25.3)</td>
<td>2.11 (1, 4.2)</td>
</tr>
<tr>
<td>50–64</td>
<td>12.76 (4.4, 35.4)</td>
<td>6.71 (3.3, 13.4)</td>
</tr>
<tr>
<td>65+</td>
<td>33.96 (11.7, 90.8)</td>
<td>18.96 (10.4, 34)</td>
</tr>
<tr>
<td>Total 50+</td>
<td>19.48 (9.9, 40.8)</td>
<td>11.24 (7.1, 17.7)</td>
</tr>
<tr>
<td>Total 18+</td>
<td>15.44 (9.3, 25.4)</td>
<td>5.5 (3.7, 8.1)</td>
</tr>
</tbody>
</table>

*Patients originally evaluated in the ED and then admitted were counted in both the ED and hospital because they used resources in both healthcare settings.
Addresses the “Fear Factor”

Majority of testing was for out patients: sick and worried well
October 2013:
- 53 year-old woman is seen in ED complaining of difficulty breathing, flu-like symptoms
- Admitted due to hypoxia and history of COPD and DM
- Husband was seen in ED for similar symptoms three days earlier
- Niece admitted to hospital in Texas with acute respiratory distress
- Other family members similar symptoms after a family trip to Saudi Arabia

August 2007: 2 Influenza as Isolated
- Patient back from three-week visit to mainland China
- Patient back from two-week visit to rural Afghanistan
January 2013

- Three-month-old female, history of prematurity
- Fever, cough, runny nose of two days’ duration
- Sneezing, fever, wheezing, irritable
- Seen in ED and diagnosed with acute bronchiolitis
- Cohorted in PICU
- Improves over next three days
- Develops severe respiratory distress, intubated
- Five other improving babies in PICU worsen
More than 20% of infants with bronchiolitis are infected with two or more respiratory pathogens. Of these, more than 10% have been described to be co-infected with hMPV.
## Detect Mixed Infections

<table>
<thead>
<tr>
<th>Virus</th>
<th>Number (%)</th>
<th>Mixed Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu A (H1N1-pdm09)</td>
<td>1937 (35.9%)</td>
<td>Adeno(3), E/R(98), 229E(3), HKU-1(5), hMPV(2), P1(4), P3(6), P4(5), RSV(1)</td>
</tr>
<tr>
<td>Flu A H1N1</td>
<td>6 (0.1%)</td>
<td>Adeno(1), E/R(1)</td>
</tr>
<tr>
<td>Flu A H3N2</td>
<td>153 (2.8%)</td>
<td>E/R(6), hMPV(1)</td>
</tr>
<tr>
<td>Flu B</td>
<td>6 (0.1%)</td>
<td>P3(2)</td>
</tr>
<tr>
<td>Entero/Rhino (E/V)</td>
<td>829 (15.4%)</td>
<td>Flu A(57), H1N1(6), H3N2(6), P1(5), P2(1) P3(12), P4(5), hMPV(6), Adeno(4)</td>
</tr>
<tr>
<td>hMPV</td>
<td>89 (1.7%)</td>
<td>E/R(7), RSV(1), H3N2(1), A (UST)(2)</td>
</tr>
<tr>
<td>Parainfluenza 3</td>
<td>149 (2.8%)</td>
<td>E/R(17), Flu B(2), RSV(2), A (UST)(3)</td>
</tr>
<tr>
<td>Parainfluenza 1</td>
<td>67 (1.2%)</td>
<td>E/R(8), A (UST)(4)</td>
</tr>
<tr>
<td>Parainfluenza 4</td>
<td>40 (0.7%)</td>
<td>E/R(8), A (UST)(5)</td>
</tr>
<tr>
<td>Parainfluenza 2</td>
<td>7 (0.1%)</td>
<td>E/R(1)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>58 (1.1%)</td>
<td>E/R(7), H1N1(1), A (UST)(3)</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>33 (0.6%)</td>
<td>Types: NL63(2), 229E(14), HKU-1(15)</td>
</tr>
<tr>
<td>RSV</td>
<td>18 (0.6%)</td>
<td>P3(2), hMPV(1), A (UST)(1)</td>
</tr>
<tr>
<td>Negative</td>
<td>2179 (40.4%)</td>
<td></td>
</tr>
</tbody>
</table>
Defines Supportive Care

<table>
<thead>
<tr>
<th></th>
<th>OP</th>
<th>EDD</th>
<th>PU</th>
<th>PICU</th>
<th>Hosp</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV+</td>
<td>41.7%</td>
<td>33.8%</td>
<td>13.0%</td>
<td>11.5%</td>
<td>24.5%</td>
</tr>
<tr>
<td>hMPV+</td>
<td>3.0%</td>
<td>38.2%</td>
<td>38.8%</td>
<td>20.0%</td>
<td>58.8%*</td>
</tr>
</tbody>
</table>

(*P=<0.01)

OP: Out patient
EDD: Emergency department discharge
PU: Pediatric unit
PICU: Pediatric intensive care unit
Hosp: Hospitalized

Monitor viral infections over time
Establish seasonal patterns
Establish baseline prevalence
Establish thresholds for above normal incidence levels
Monitor numbers of test requests
Use this data in combination with syndromic surveillance to identify natural or biothreat events
Trigger response to EMS, system leadership, infectious disease, laboratory, public health agencies
What is a Syndrome?

Why is Syndromic Testing so Powerful?

How do we use Syndromic Testing to Provide Better Patient Care and Save Healthcare Costs?
Age 69: history of mild COPD, one hospitalization in last year for pneumonia
Cough, shortness of breath, fever, chest pain, elevated WBC, elevated lactate

SOB: shortness of breath
CHF: congestive heart failure
ACS: acute coronary syndromes
PE: pulmonary embolism
COPD: chronic obstructive pulmonary disease
Mortality Risk with Inappropriate Therapy

Empiric Antimicrobial Therapy

- Initiate **broad spectrum antibiotic** therapy ASAP
- Antimicrobial stewardship to ensure appropriate targeted antimicrobial usage once pathogen identified

- Improve Outcome
- Avoid Antibiotic Resistance
- Avoid Antibiotic Associated Complications
Mortality Risk with Inappropriate Therapy

K. Pneumoniae (KPC)
- Amikacin: R
- Ampicillin: R
- Cefazolin: R
- Cefoxitin: R
- Ceftazidime: R
- Ceftriaxone: R
- Cefepime: R
- Colistin: S
- Doripenem: R
- Ertapenem: R
- Gentamicin: R
- Imipenim: R
- Levofloxacin: R
- Meropenem: R
- Piperacillin/tazobactam: R
- Tobramycin: R

Mortality Risk with Inappropriate Therapy

K. Pneumoniae (KPC)
- Amikacin: R
- Ampicillin: R
- Cefazolin: R
- Cefoxitin: R
- Ceftazidime: R
- Ceftriaxone: R
- Cefepime: R
- Colistin: S
- Doripenem: R
- Ertapenem: R
- Gentamicin: R
- Imipenem: R
- Levofloxacin: R
- Meropenem: R
- Piperacillin/tazobactam: R
- Tobramycin: R

Developed recommendations for empiric therapy for bloodstream infections based on:

- Local antibiogram
- Multiplex molecular assay to detect Gram positive, Gram negative and Candida spp. from positive bottle culture bottles

“Combining rapid pathogen ID with locally derived treatment guidelines, an application of these guidelines would have resulted in appropriate antimicrobial intervention for 99.2% of blood cultures growing organisms detected by the blood culture panel.”

Southern RS et al. Diagn Microbiol Infect Dis (2014), http://dx.doi.org/10.1016/j.diagmicrobio.2014.11.004
Unanticipated Multiplex PCR Identification of Polymicrobial Blood Culture Resulting in Earlier Isolation, Susceptibilities and Optimization of Clinical Care

1° Gram Stain
- Gram+ cocci

Rapid Blood ID System
- MRSA
- VRE
- *P. aeruginosa*
- *Streptococcus sp.*
- *Candida tropicalis*
- *Candida glabrata*

2° Gram Stain
- Gram+ cocci clusters
- 1 Budding Yeast

Subculture
- MRSA
- VRE
- *P. aeruginosa*
- *Streptococcus sp.*
- *Candida tropicalis*
- *Candida glabrata*

Critical Diagnosis: Meningitis/Encephalitis

The causative agents of meningitis or encephalitis should be rapidly identified to guide appropriate patient management but are many times impossible to identify based on clinical indications alone due to overlapping symptoms\(^1,2\)

Delays in appropriate therapy can be associated with adverse outcomes\(^1\)

- **Bacterial\(^2\)**
  - Permanent brain and nerve damage
  - Behavioral changes
  - Cognitive disabilities
  - Lack of muscle control
  - Seizures

- **Viral\(^2,3\)**
  - Brain damage, including behavioral and personality changes and memory and speech problems
  - Focal neurological signs
  - Seizures

- **Fungal\(^4\)**
  - Increased intracranial pressure
  - Hydrocephalus
  - IRIS
  - Blindness, sometimes with optic atrophy

Early diagnosis facilitates timely and appropriate therapeutic interventions and can minimize the risks of adverse outcomes and mortality\(^2\)

---

IRIS=immune reconstitution inflammatory syndrome.

Twenty-three-day-old male presents to ED
Parents note: fever, fussy, failure to nurse, diaper rash
Possible seizure, lethargic
Non-responsiveness
Very ill looking, Temp 40.1 °C
CSF: WBC 243 cu/mm, glucose 85 mg/mL, protein 112 mg/dL
Gram stain: numerous WBCs, 85% lymphocytes, 15% PMNLs

T1WMR: Extensive hemorrhagic infarction of WM and cortex

Day 3

CSF Positive for: HSV-1
Three-year-old female, presented in August to the ED with fever, vomiting, rash and irritability

Parents say symptoms developed rapidly and have persisted for two days

Not very ill looking

Temp 38.1 °C

Slight nuncal rigidity, light rash

CBC: normal

CSF: WBC 15 cu/mm, glucose 85 mg/mL, protein 85 mg/dL

CSF: Gram stain: Few WBCs, 90% lymphocytes, 10% PMNLs; no bacteria seen

PCR Positive
Held in 18-24 hr short stay room
Abx D/C
Discharged
### Impact of a Diagnostic Cerebrospinal Fluid Enterovirus Polymerase Chain Reaction Test on Patient Management

**Table 3.** Subset Analysis of Patients With a Discharge Diagnosis of Viral Meningitis and With Enterovirus (EV) Polymerase Chain Reaction (PCR) Test Results Available Before Discharge

<table>
<thead>
<tr>
<th></th>
<th>EV-Negative</th>
<th>EV-Positive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Median, h</td>
<td>67</td>
<td>42</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time from PCR test to discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>90</td>
<td>.002</td>
</tr>
<tr>
<td>Median, h</td>
<td>59.73</td>
<td>11.38</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients who received computed tomographic scan or magnetic resonance imaging</td>
<td>16 (84.2)</td>
<td>9 (10.0)</td>
<td>.001</td>
</tr>
<tr>
<td>No. (%) of patients who received a chest or abdominal x-ray film</td>
<td>9 (47.4)</td>
<td>19 (21.1)</td>
<td>.02</td>
</tr>
<tr>
<td>No. (%) of patients who received an electroencephalogram</td>
<td>7 (36.8)</td>
<td>0 (0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median, d/patient</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>


Pediatric patients
Diagnosing Meningitis and Encephalitis: Diagnostics

- CSF analysis is a fundamental method in diagnosing meningitis or encephalitis, but only small volumes are obtained by lumbar puncture\(^1\)–\(^3\)
- CSF samples are considered high-priority and are processed immediately\(^4\)

**CSF Examination**\(^5\)
- Cell count
- Protein
- Glucose

**CSF Culture**\(^5,\)\(^6\)
- Pathogen-specific media
  - Bacterial culture
  - Viral culture
  - Fungal culture

**Gram Stain**\(^7\)
- Crystal violet
- Iodine
- Alcohol
- Safranin

**India Ink Stain**\(^5\)

**Rapid Latex Agglutination Test**\(^8\)
- Positive
- Negative

**Traditional PCR**\(^5\)

---

CSF=cerebrospinal fluid; PCR=polymerase chain reaction.

Challenges in Diagnosing Meningitis and Encephalitis Infections

- Meningitis and encephalitis often present with similar symptoms, sometimes as flu-like symptoms\(^1\)
- The causative agents underlying the disease may not be distinguishable based on clinical symptoms alone\(^2\)
- Challenges associated with currently available testing methods\(^1,3\):
  - Time-consuming
  - Technically complex/requires specific expertise
  - Lack sensitivity and specificity
  - Accuracy may be affected by antibiotic administration
  - Small volume of CSF obtained
  - Physician must choose which tests to select based on symptoms and available CSF volume
  - Need to order multiple tests specific for suspected organisms

CSF=cerebrospinal fluid.

Impact on Patient Care Costs: Respiratory Testing

- **Cost reduction:**
  - Hendrickson, K. J.: Up to 50% reduction in hospital days, 30% reduction in antibiotic use and 20% reduction in unnecessary diagnostic tests and procedures

- **Impact on appropriate therapy:**
  - Gonzales, R et al.: Out of 41 million antibiotic prescriptions, 22.6 million (55%) were estimated to have been prescribed for infections unlikely to have a bacterial etiology
## Antimicrobial Stewardship: Reduction in Use

<table>
<thead>
<tr>
<th></th>
<th>Hospitalization Days</th>
<th>Antibiotic Use</th>
<th>Antibiotic Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>RSV+</strong></td>
<td>5.3</td>
<td>2</td>
<td>54%</td>
</tr>
<tr>
<td><strong>RSV -</strong></td>
<td>24.4</td>
<td>3</td>
<td>69%</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.035</td>
<td></td>
<td>0.021</td>
</tr>
</tbody>
</table>

Antibiotics used less, less overall duration and were discontinued one day earlier in patients once diagnosed as RSV+.

Antimicrobial Stewardship

Comparison of Turnaround Time (TAT) and Time to Oseltamivir Discontinuation between Two Respiratory Viral Panel (RVP) Testing Methodologies

Testing schedule
- RVP A: 2-3x/week
- FVP B: 24/7

TAT
- RVP A: 46.4 hr
- RVP B: 3.1 hr \( (p < 0.001) \)

Time to oseltamivir DC
- RVP A: 4 days
- RVP B: 2 days \( (p < 0.001) \)

Cost savings
- RVP B: $34.16/patient
### Implementation of RVP in a Core Laboratory Improves Testing Turnaround Time and Patient Care

#### RP compared to limited batch PCR testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Samples Viral Negative</th>
<th>Samples Viral Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-RP</td>
<td>Post-RP</td>
</tr>
<tr>
<td>TAT</td>
<td>1129 mn</td>
<td>377 mn</td>
</tr>
<tr>
<td>Result in ED</td>
<td>17.9%</td>
<td>52.7%</td>
</tr>
<tr>
<td>ED LOS</td>
<td>248 mn</td>
<td>277 mn</td>
</tr>
<tr>
<td>Abx Pres</td>
<td>75.2%</td>
<td>80.5%</td>
</tr>
<tr>
<td>Abx Use</td>
<td>3.1 d</td>
<td>3.1 d</td>
</tr>
<tr>
<td>Inpatient LOS</td>
<td>3.2 d</td>
<td>3.2 d</td>
</tr>
<tr>
<td>Time in Iso</td>
<td>60 h</td>
<td>43 h</td>
</tr>
</tbody>
</table>

Comprehensive, faster diagnosis, impact on patient treatment, LOS and infection control

Antimicrobial Stewardship: Treat or Not

- Five-year-old male with severe abdominal pain and vomiting
- Diarrhea for three days’ duration, no visible blood
- Parents noted fever over two days
- Irritable, won't eat or drink
- Temperature 39.8 °C
- Abdomen distended
- Severe rt quadrant tenderness
- Elevated hematocrit, WBC 18,000
- Electrolyte imbalance: dehydrated
- Slightly hypertensive
- Stool occult blood weakly positive

DIFFERENTIAL DIAGNOSIS

BACTERIAL INFECTION: TREAT OR NOT TREAT (STEC VS SHIGELLA)
NON-INFECTIONOUS CAUSE: ENDOSCOPY/SURGERY
APPENDICITIS: SURGERY
22/571 case-patients (4%)

Median age with appendectomy was higher (11.5 years, IQR 9–18 years) than median age of patients without appendectomy (8 yrs, IQR 2–17 yr)

Appendectomy was strongly and significantly associated with lower right pain

Yersiniosis patients were >70 times more likely to report an appendectomy than the reference group not exposed to yersiniosis (RR 73.5; \( P<0.001 \)).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Hospitalization</th>
<th>Appendectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio(^a) (95% CI(^b))</td>
<td>( P ) value(^c)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.5 (0.4 -0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.9 (0.6 -1.2)</td>
<td>0.406</td>
</tr>
<tr>
<td>Pain in lower right abdomen</td>
<td>2.7 (1.9-3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tenesma</td>
<td>0.9 (0.6-1.2)</td>
<td>0.428</td>
</tr>
<tr>
<td>Fever</td>
<td>2.0 (1.5-2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.7 (1.3 -2.1 )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visible blood in stool</td>
<td>0.9 (0.5 -1.9)</td>
<td>0.871</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>1.2 (0.9-1.7)</td>
<td>0.154</td>
</tr>
</tbody>
</table>

\(^a\) Odds ratios estimated using multivariable logistic regression

\(^b\) Exponentiated estimate

\(^c\) \( P \) value estimated using multivariable logistic regression
35-year-old male with no significant past medical history

Complained of acute onset of severe watery diarrhea, vomiting, muscle cramps

No visible blood in stool, no fever

Slightly tachycardic, hypertensive

Dehydrated

Stool occult blood weakly positive

Physician’s assistant

Returned from two-week humanitarian mission in Haiti three days previous to onset of symptoms

Another colleague was now complaining of similar symptoms
Clinical Course

- ED: IV fluids, oral rehydration
- After 24-hour severe symptoms continued, patient admitted, treated with doxycycline
- Day 2: stools are bloody, fever, cramps and abdominal pain
- Not responding to therapy: switched to azithromycin
- Slowly responds and discharged day 6
- Day 21: returns to the ED with progressive, symmetric ascending paralysis

- 40-70% of all Guillain Barré syndrome cases are preceded by an acute infectious illness
  - 22-53% are upper respiratory infections
  - 6-26% are gastrointestinal infections, one of the most common being enteritis due to *Campylobacter* spp.
  - Culture: *V. cholerae*, PCR positive for *V. cholerae* and *C. jejuni*
Diagnostic Challenges: Gastrointestinal Infections

- Limited clinical guidelines for the diagnosis and treatment of patients with suspected infectious diarrhea\(^1\)

- Challenges associated with currently available testing methods\(^1-4\)

  - Time-consuming
  - Labor-intensive
  - Technically complex/requires specific expertise
  - Low yield
  - Lack sensitivity and specificity
  - Limited coverage
  - Confounded by:
    - Overlapping symptomology
    - Need to order multiple tests specific for suspected organisms
    - Unavailability of tests for many organisms

---

Current GI Diagnostic Methods
Complicated and Incomplete

Lack Comprehensive Coverage

<table>
<thead>
<tr>
<th>Organism</th>
<th>Stool Culture</th>
<th>O&amp;P</th>
<th>EIA</th>
<th>DFA</th>
<th>Traditional PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrheagenic E. coli</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Vibrio</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersinia entercolitica</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norovirus GI/GII</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus F 40/41</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus A</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrovirus</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Sapovirus</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Approximately 70% of E. coli STEC O157 only: .
DFA=direct fluorescent antibody; EIA=enzyme immunoassay; O&P=ova and parasite; PCR=polymerase chain reaction.
## Cost of GI Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Reagent Costs</th>
<th>Media Prep Stains</th>
<th>TAT</th>
<th>Tech Time Costs</th>
<th>Number Samples Tested</th>
<th>Cost (low to high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>$12 $15 $10</td>
<td>Media Ag ID</td>
<td>3-5 d</td>
<td>$50 $10 $5</td>
<td>1</td>
<td>$62 $25 $15</td>
</tr>
<tr>
<td>O&amp;P</td>
<td>$15 $15</td>
<td>Smear Ag</td>
<td>1 d</td>
<td>$50 $5</td>
<td>3</td>
<td>$195 $60</td>
</tr>
<tr>
<td>Virus</td>
<td>$35 $15</td>
<td>Culture</td>
<td>14 d</td>
<td>$15</td>
<td>1</td>
<td>$50</td>
</tr>
<tr>
<td></td>
<td>$15 $15</td>
<td>Ag</td>
<td>1 d</td>
<td>$5</td>
<td>1</td>
<td>$20</td>
</tr>
<tr>
<td></td>
<td>$150</td>
<td>PCR</td>
<td>5 d</td>
<td>$5</td>
<td>1-5</td>
<td>$155 to $775</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>5 to 14 d</td>
<td></td>
<td></td>
<td>$582 to $1202</td>
</tr>
</tbody>
</table>

Replacement not an “add on” test
How well does physician selection of microbiologic tests identify *Clostridium difficile* and other pathogens in paediatric diarrhoea? Insights using multiplex PCR-based detection
How well does physician selection of microbiologic tests identify *Clostridium difficile* and other pathogens in paediatric diarrhoea? Insights using multiplex PCR-based detection
# Benefits of Rapid Comprehensive Syndromic Testing

**LABORATORY**
- Comprehensive
- Fast
- Easy
- Reduces labor
- Better sensitivity
- Better specificity
- Expands testing capabilities
- Provides better services
- Increases income

**ADMINISTRATORS**
- Cost saving
- Improves services
- Pleases “customers”
- Decreases ancillary testing
- Better test utilization
- Promotes antimicrobial stewardship
- Improves P4P outcome
- Infection control
- Surveillance and preparedness

**PHYSICIAN/PATIENT**
- Comprehensive
- Fast/accurate
- Affects patient management
- Improved outcomes
- Rule in or rule out
- Unexpected diagnosis
- Decreases “fear factor”
- Improves therapy selection
- Decrease unnecessary Abx
Laboratory Testing Networks

- Community Hospital
- Community Hospital
- Community Hospital
- Community Hospital
- Community Hospital

- Tertiary Care
- Core Lab
- Tertiary Care

- Physicians’ Offices
- Nursing Homes
- Clinics
- Emergency Centers
- Reference Testing

Outreach
Hospital Lab
RRL
“Point of Impact” Testing
Laboratory Testing Networks

Tertiary Care

Core Lab

Tertiary Care

Community Hospital

Community Hospital

Community Hospital

Community Hospital

Community Hospital

Physician’s Offices

Nursing Homes

Clinics

Emergency Centers

Reference Testing

Outreach

Hospital Lab

RRL
QUESTIONS