Sorting Signal from Noise

Laboratory Interpretation from an Infectious Disease Perspective

Ryan Gentry, MSN, RN, CPNP
Objectives

• Discuss the diagnostic approach for:
  – Infectious mononucleosis
  – Tick-borne diseases
  – *Streptococcal* pharyngitis
  – Influenza
Clinical Pearls

• Diagnostic approach:
  – Are the symptoms/illness caused by a microbe
  – If so, what is the most likely microbe
  – How can I optimize/target therapy

• Obtaining specimens:
  – Appropriate transport media and volume
  – Before antibiotics whenever possible
  – Appropriate test
Laboratory Diagnosis of Infections

Pathogenic organism

DNA

RNA

Detection of antibodies (e.g., ELISA)

Oligonucleotide probe

Target nucleic acid

Detection of nucleic acids (e.g., DNA hybridization)

in vitro nucleic acid amplification (e.g., PCR, NASBA)

DNA sequencing

Microscopy

Culture

Biochemical characteristics

U. Raischl '65
Susceptibility Data Interpretation

Minimum Inhibitory Concentration (MIC)

What is the MIC?

MIC definition: Lowest concentration of agent to inhibit growth

http://astro.temple.edu/~jasanog/ID/MIC%20broth%20dilution.png
# Susceptibility Data Interpretation

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Interp</th>
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<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
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# Susceptibility Data Interpretation

<table>
<thead>
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D Test
D Test
Case 1 - Interpret This Test

• A 17 year old boy has sore throat and fever to 40°C
• A rapid streptococcal antigen test (RST) is positive and his pediatrician gives him amoxicillin
• 2 days later, he remains febrile, vomiting w/ a morbilliform rash
• In your office, he appears ill with exudative pharyngitis and cervical adenopathy
• His conjunctivae are icteric, and liver edge is palpable
What is causing his symptoms?

A. Group A *Streptococcus* (GAS)
B. Parvovirus
C. Cytomegalovirus (CMV)
D. Epstein-Barr virus (EBV)
E. Coxsackievirus A16
Epstein-Barr Virus Infection

• Gammaherpesvirus
• Most common cause of infectious mononucleosis
• Humans: only reservoir
• 90% of adults are infected, usually early in life
EBV Clinical Manifestations

• Infectious mononucleosis
  – Fever, pharyngitis with petechiae, exudative pharyngitis, lymphadenopathy, and hepatosplenomegaly (most commonly in teens)

• Infants and young children often present with mild to severe viral respiratory symptoms
EBV Laboratory Values

- Leukocytosis
- Predominance of lymphocytes
  - Increased percentage of atypical lymphocytes
EBV Testing

- Serologic: VCA IgG and IgM*, EA*, EBNA
- Limited sensitivity of the Monospot test in first 2 weeks of symptoms
  - Positive for up to 18 months
  - Younger children may not produce heterophile Ab
- Reserve PCR for immunocompromised host

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<th>Test</th>
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<th>Negative</th>
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<td>18-21.9</td>
<td>&lt;18</td>
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<tr>
<td>EBV VCA IgM</td>
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<td>36-43.9</td>
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<td>EBV Nuclear Antigen IgG (EBNA)</td>
<td>&gt;21.9</td>
<td>18-21.9</td>
<td>&lt;18</td>
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</table>
# EBV Testing

Serum Epstein-Barr Virus (EBV) Antibodies in EBV Infection

<table>
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<tr>
<th>Infection</th>
<th>VCA IgG</th>
<th>VCA IgM</th>
<th>EA (D)</th>
<th>EBNA</th>
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<td>No previous infection</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Acute infection</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Recent infection</td>
<td>+</td>
<td>+/-</td>
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</tr>
<tr>
<td>Past infection</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
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</table>
Treatment EBV Mononucleosis

- Supportive
- Avoid contact sports
  - Splenic rupture
  - 3-4 weeks - individualize
- **Dexamethasone** only for airway obstruction
- Antivirals have no clinical impact in immunocompetent patients
Case 2- Fever and Rash

• A 10 year-old from Kansas City, MO (no travel) had a tick bite last week and now has fever, rash, headache, and hyponatremia. Which of the following is most likely:
  A. Rocky Mountain Spotted Fever (RMSF)
  B. Babesiosis
  C. Tularemia
  D. Lyme
Questing
Tick-Borne Illnesses

- RMSF
- Ehrlichiosis
- Tularemia
- Lyme disease

Image obtained from: Red Book® 2015, online
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RMSF and Ehrlichia

- Rocky Mountain Spotted Fever
  - *Rickettsia rickettsii*
    - Gram negative coccobacillus
    - Invades the endothelial cells that line the blood vessels
- Ehrlichiosis
  - *Ehrlichia chaffeensis*
    - Gram negative cocci
    - Invades WBC in order to replicate
RMSF and Ehrlichia

- **Clinical Manifestations**
  - Fever, rash, headache, myalgia, and respiratory symptoms
  - Systemic capillary and small vessel endothelial damage (ie, vasculitis) with increased microvascular permeability is the primary pathologic feature of severe infection
  - Encephalitis
- Can become life threatening rapidly
- Risk factors for severe disease include late diagnosis, glucose-6-phosphate dehydrogenase deficiency, male gender, and treatment with sulfonamides
**RMSF**

- The characteristic RMSF rash
  - May start as blanching macules
  - Usually petechial and spreads from distal extremities to trunk
- 3-18% of patients present with fever, rash, and history of tick bite
Laboratory Findings Associated with RMSF and Ehrlichiosis

- Thrombocytopenia
- Mildly elevated hepatic transaminase levels
- Hyponatremia
- Anemia (may occur late in illness)
- Leukopenia (absolute)
Diagnosis

• Diagnosis is made by history and clinical symptoms

• Confirmation of diagnosis is made by acute and convalescent serology
  – Antibodies (serology) are detectable in serum 7 to 14 days after onset of illness
  – Serology should be obtained again in 2-3 weeks
  – An increase in antibody titer is positive
RMSF and Ehrlichia Treatment

- Treatment should be initiated *immediately* whenever RMSF or ehrlichiosis is suspected and is continued for 7-10 days
  - Doxycycline is the drug of choice for any age
    - 2.2 mg/kg/dose every 12 hours (max 100mg per dose)
  - A clinical response is usually seen in 24-72 hours; for patients who fail to respond, consider an alternate diagnosis
Tularemia

• Clinical manifestations:
  – Abrupt onset of fever, chills, myalgia, and headache.

• Common forms of tularemia infection:
  – Ulceroglandular syndrome
  – Glandular syndrome
Tularemia - Recognition
Tularemia Treatment

• Gentamicin is the drug of choice
  – Only available in IV formulation

• Oral ciprofloxacin
  – Uncomplicated ulceroglandular tularemia

• Relapses of tularemia can occur after therapy with any antibiotic, so close follow-up is recommended
Lyme

- *Borrelia burgdorferi*
Lyme

• Disease forms
  – Early localized: erythema migrans (EM) - distinguish from tick reaction which is itchy, small and does not expand in size
  – Early disseminated: multiple EM, Bell’s palsy, heart block, meningitis
  – Late: arthritis (pauciarticular, large joints-joint effusions are smaller than with septic joints and fewer WBC in synovial fluid)
Clinical Manifestations

“Classic” erythema migrans rash  Facial palsy  Swollen knee
Lyme: Diagnosis and Treatment

• Should you test everyone with nonspecific signs and symptoms?

• Serologic testing not necessary if patient has EM and resides in or traveled to Lyme endemic area- just treat

• Test those if residence or travel to Lyme endemic area AND tick exposure AND symptoms consistent with early disseminated disease or late Lyme disease
Two-Tiered Testing for Lyme Disease

First Test

- Enzyme Immunoassay (EIA)
- Immunofluorescence Assay (IFA)

OR

Positive or Equivocal Result

Negative Result

Consider alternative diagnosis OR
If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum

Second Test

- Signs or symptoms ≤ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms > 30 days
  - IgG Western Blot ONLY

National Center for Emerging and Zoonotic Infectious Diseases
Division of Vector Borne Diseases | Bacterial Diseases Branch
## Perils of Tick Panels

### Tick-Borne Ab Panel, S

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Value</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrlichia Chaffeensis (HME) Ab, IgG</td>
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</tr>
<tr>
<td>Anaplasma phagocytophilum Ab, IgG,S</td>
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</tr>
<tr>
<td>Babesia microti IgG Ab, S</td>
<td>&lt;1:64</td>
<td></td>
</tr>
</tbody>
</table>

### Lyme Disease Serology, S

- **Negative**
  - Serologic response to B. burgdorferi infection is not detected, but cannot rule out early infection during which low or undetectable antibody levels to B. burgdorferi may be present. If clinically indicated, a new serum specimen should be submitted in 7–14 days.

- **Received:** 21 Aug 2014 14:09
- **Reported:** 21 Aug 2014 14:12
Case 3- Pharyngitis

• 3 year-old female presents to your office with sore throat, cough, congestion, fever, + daycare exposure, and an older brother (age 5) with similar symptoms. Which of the following is most likely:
  A. Viral pathogen
  B. Bacterial pathogen
Pharyngitis

• Viral pathogens
  – 80% of cases (children and adults)
  – Examples: enteroviruses, adenovirus, herpes

• Bacterial pathogens
  – GAS most common bacterial cause of pharyngitis
    – Age 5-11 years
    – Gonococcus (teens)
Features of GAS Pharyngitis

- Pharyngeal erythema
- Exudate
- Tender cervical LAD
- Strawberry tongue
- Palatal petechiae
GAS Diagnosis

• Rapid antigen detection test (rapid strep)
• Bacterial culture
• Antistreptolysin O (ASO)
  – do not use to diagnose
Pharyngitis: GAS

• Chronic pharyngeal carriers have GAS present in the pharynx but have no evidence of infection
• Up to 1/4 of school-aged children can be chronic pharyngeal carriers of GAS
• Carriers are not considered infectious and typically do not respond to therapy
Pop Quiz!

• What is the percentage of GAS resistance to PCN?
  A. 0%
  B. 25%
  C. 50%
  D. 75%
  E. Approaching 100%
GAS Treatment

• No documented resistance of GAS to penicillin
  – Amoxicillin or PCN drug of choice
  – Once daily amoxicillin preferred

• Response to antimicrobial therapy for GAS pharyngitis is expected within 24 hours
  – Return to school (the next day after starting Abx)

• PCN allergy
Would you Perform a Rapid Strep?

A. An 18 month-old with croupy cough and sore throat who attends daycare where 3 toddlers were diagnosed with GAS pharyngitis

B. A 9 year old with fever to 103°F, severe sore throat and rhinorrhea

C. A 5 year old with headache and abdominal pain similar to that experienced last month when he had strep throat

D. A 10 year old with fever to 101°F, sore throat, pharyngeal erythema
Case 4: A Coughing Child

• A 6 year-old child presents to your office in January with sudden onset of high fever accompanied by rigors, headache, malaise, diffuse myalgia, and nonproductive cough. Which of the following is most likely:

A. Respiratory syncytial virus (RSV)
B. Rhinovirus
C. Herpes virus (HSV)
D. Influenza
Eww

What can I do?
Influenza

- Infects 5-20% of the US population annually
- Influenza types
  - Type A
    - Subtype H and N
  - Type B
- Antigenic drift
  - Minor genetic variation
- Antigenic shift
  - Major genetic change
Clinical Manifestations

• Influenza
  – Sudden onset of fever, chills, headache, myalgias, cough, sore throat, and congestion
  – Incubation period 1-4 days
  – Viral shedding
    • 24 hours prior to symptoms, peak within 72 hours
Diagnostic Tests

• Rapid Antigen Testing:
  – Typically available in provider offices and ED/UCCs
  – Vary in terms of sensitivity and specificity when compared with viral culture or PCR
  • Sensitivities are approximately 50-70%
Diagnostic Tests

- The sensitivity and specificity vary with rapid tests depending upon the prevalence
  - False-positive test results
    - When prevalence is low
  - False-negative test results
    - When disease prevalence is high
- PCR is most sensitive and specific (expensive)
Treatment - Oseltamivir

- **RECOMMEND** treatment ASAP to children:
  - Hospitalized (any duration)
  - High risk groups (any severity)

- **CONSIDER** treatment for clinical influenza:
  - Any healthy child with presumed influenza
  - Siblings at home:
    - < 6 months old
    - High risk
Influenza Vaccine

• An ounce of prevention!

• Seasonal vaccine recommendations:
  – All persons ≥ 6 months of age
    • Cocooning
  – High risk groups
    • Age, chronic illness, immunosuppression, pregnant women

• Efficacy: 50-65%
Closing Remarks

When in doubt, just ask!
Acknowledgements

Wife and children for coping with me during preparation of this presentation

Dr. Mary Anne Jackson
Gina Weddle, DNP, APRN
Dr. Angela Myers
Dr. Jennifer Schuster
References

Red Book (2015)


Infectious Diseases Society of America (IDSA)

American Academy of Pediatrics (AAP)

Centers for Disease Control and Prevention (CDC)
Questions?

So when they told me to bring an ID I totally misunderstood