Hot Topics in Infectious Diseases

Ryan Dare, MD
Assistant Professor, UAMS
No conflicts of interest
Outline

• *C diff* treatment guideline update

• Hepatitis A outbreak in Arkansas

• Antibiotic Stewardship: Clinical Pearls
Outline

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• Hepatitis A outbreak in Arkansas

• Antibiotic Stewardship: Clinical Pearls
• 26yo M with history of recurrent sinus infections presents the Emergency Department with 5 day history of diarrhea. He complains of profuse watery, non-bloody bowel movements ~8x per day. No recent sick contacts or travel. He works at Park Plaza mall in security.

• On presentation, Temp 100.2F BP 115/82 HR 87 RR 17. On exam, he is well appearing, normal HEENT exam, RRR, no murmurs, lungs are clear bilaterally, abdomen is soft and non-distended though slightly tender on palpation diffusely, hyperactive bowel sounds are present, no HSM, no rashes, no lower extremity edema.

• Initial labs revealed a WBC of 10,500 cells/mL and serum creatinine of 1.1 mg/dL. Stool culture was negative for salmonella, shigella, and campylobacter. C diff A/B toxin and C diff antigen were both present. He has never had C diff before.

How would you initially treat this patient?

A. Metronidazole 500mg IV q8h x10d
B. Vancomycin 125mg PO q6h x10d
C. Metronidazole 500mg PO q8h x10d
D. Vancomycin 500mg PO q6h x10d
E. Fidaxomicin 200mg q6h x10d
*Clostridium difficile* Infection (CDI) in USA

- Most common hospital acquired infection
- $4.8$ Billion in excess cost for hospitals each year
- 453,000 infections annually
- 20% of patients reside in nursing homes
- 20% of patients have recurrence
- 30 day mortality rate is 6%
  - 9.1% if ≥ 65yo
  - 80% of *C diff* related deaths are in patients ≥ 65yo

Lessa et al. NEJM 2015; 372: 825-34
https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html
Figure 1. Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure.\(^\text{11}\) CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.
Clostridium difficile colonization

- 3% of adults in general population
- 10% of adults residing in hospitals or LTCFs
- Acts as reservoir for environmental contamination
- Colonized patients at time of admission are less likely to develop CDI during admission compared to newly colonized patients that were not colonized at time of admission.
**Clostridium difficile** Infection (CDI) Risk Factors

- Antibiotics increase risk 7-10x
  - Clindamycin (OR 16-20)
  - Fluoroquinolones (OR 5-6)
  - Cephalosporins (OR 4-6)
- Age ≥ 65 (RR 8.65)
- Renal Impairment (SCR > 1.2)
- PPI or H2 Blocker (RR 2.75)
- Female (RR 1.26)
- Caucasian (RR 1.72)
- Lack of *C diff* antibody
- Recent GI surgery or manipulation
- Healthcare exposure
- Immunosuppressed
- Comorbidities (IBD....)
- Obesity
- Enteral feeding

Brown et al, AAC 2013
Deshpande et al, JAC 2013
Lessa et al. NEJM 2015; 372: 825-34
NAP 1 strain (NAP1/BI/027)

- CDI more virulent starting 2003
- Increased toxin production
- CDI Incidence doubled
- CDI recurrence increased
- Mortality increased 4x
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,1 Dale N. Gerdin,2 Stuart Johnson,2,3 Johan S. Bakken,4 Karen C. Carroll,5 Susan E. Coffin,6 Erik R. Dubberke,7 Kevin W. Garey,8 Carolyn V. Gould,1 Ciaran Kelly,9 Vivian Loo,10 Julia Shaklee Sammons,6 Thomas J. Sandora,11 and Mark H. Wilcox12

1Centers for Disease Control and Prevention, Atlanta, Georgia; 2Edward Hines Jr Veterans Administration Hospital, Hines, and 3Loyola University Medical Center, Maywood, Illinois; 4St Luke's Hospital, Duluth, Minnesota; 5Johns Hopkins University School of Medicine, Baltimore, Maryland; 6Children's Hospital of Philadelphia, Pennsylvania; 7Washington University School of Medicine, St Louis, Missouri; 8University of Houston College of Pharmacy, Texas; 9Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; 10McGill University Health Centre, McGill University, Montréal, Québec, Canada; 11Boston Children's Hospital, Massachusetts; and 12Leeds Teaching Hospitals NHS Trust, United Kingdom
Preferred Diagnostic Testing

Target Population:
• Unexplained diarrhea
• New onset
• ≥ 3 unformed stools in 24hr period

Detection Method:
• Multi-step algorithm
  – GDH plus Toxin (reflex NAAT if discordant)
  – NAAT plus Toxin
  – NAAT alone is not recommended*

Repeat Testing:
• No repeat testing within 7d of prior test
Infection Prevention and Control

- CDI patients require private rooms with dedicated toilet
- If cohorting is required, consider other organisms (MRSA, VRE, ESBL...) as well
- Contact isolation (gowns and gloves) on room entry
- Continue isolation for at least 48 hours after diarrhea has resolved
- During endemic setting: Soap and water or alcohol-based product
- During CDI outbreak: Soap and water
- Use disposable equipment. Sporicidal disinfectant for non-disposable equipment
- Terminal room cleaning (sporicidal) during epidemics
- Measure cleaning effectiveness to ensure quality of environmental cleaning
- Antimicrobial stewardship program must be in place
NO Recommendation for:

- Screening asymptomatic patients for carriage
- Discontinuation of PPIs if needed
- Providing probiotics for primary prevention
CDI Treatment

• **Initial CDI:**
  – Vancomycin 125mg PO q6h x10d
  – Fidaxomicin 200mg PO q12h x10d

• **Fulminant CDI:**
  – Vancomycin 500mg PO q6h
  – Vancomycin 500mg/100ml NS PR q6h (If ileus is present)
  – Metronidazole 500mg IV q8h (not oral)

• **Recurrent CDI:**
  – Vancomycin 125mg PO q6h x10d (if metronidazole used for primary infection)
  – Vancomycin as a tapered and pulsed regimen (if vanc used for primary infection)
  – Fidaxomicin 200mg PO q12h x10d (if vanc used for primary infection)

• **Multiple recurrences of CDI:**
  – Vancomycin as a tapered and pulsed regimen
  – Fidaxomicin 200mg PO q12h x10d
  – Fecal Microbiota transplantation

• **Metronidazole is no longer first line:**
  – Strong Recommendation
  – Meta-analysis of 2 RCTs including 843 patients
  – Clinical Cure inferior with metronidazole (78%) vs vanc (87%) (p=0.002)
  – Metronidazole for non-severe CDI only if vanc or fidaxomicin NOT available

• **Discontinue inciting antibiotic agent ASAP**
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Outline

• *C diff* treatment guideline update

• **Hepatitis A outbreak in Arkansas**

• Antibiotic Stewardship: Clinical Pearls
Clinical Hepatitis A described as a unique presentation compared to Hepatitis B

Hepatitis A Virus (HAV) identified, Picornaviridae

HAV Vaccine Approved Europe

HAV Vaccine Approved USA

Hepatitis A

• Human reservoir

• Transmission is fecal-oral
  – Person-Person
  – Contaminated Food/Water

• Transmission Risk:
  – IVDU
  – MSM
  – Raw or undercooked shellfish, vegies, foods
  – Close quarters (Military, Dorms, SNFs)
  – Daycare
Hepatitis A Presentation

Signs and Symptoms
- Nausea/Vomiting/Diarrhea
- Fever
- Malaise/Anorexia
- Abdominal Pain
- Dark urine (bilirubinuria)
- Pale Stools
- Pruritus

Physical Exam
- Jaundice
- Hepatomegaly (80%)
- Arthralgia (rare)
- Rash (rare)

Labs
- AST and **ALT >1000 IU/dL**
- Total Bilirubin elevation
- Alk Phos ~400 U/L
- ESR and CRP elevation
- Elevated acute phase reactants

Tong et al, JID 1995; 171: S1-15
Hepatitis A Clinical Illness

![Graph showing the stages of hepatitis A clinical illness with timelines for IgM anti-HAV, IgG anti-HAV, and ALT levels, as well as periods of viremia and viral shedding in stool.](image-url)
Hepatitis A Case Definition

Acute illness:

1. Presentation consistent with viral hepatitis:
   - Fever, HA, malaise, anorexia, N/V/D, abdominal pain.
   - Jaundice +/- elevated ALT or AST

2. Positive IgM  OR  Link to lab-confirmed patient

Hepatitis A Vaccine

• High risk individuals
  – Travelers
  – MSM
  – Drug users
  – Occupation (lab)
  – Liver Disease
  – Clotting factor disorder

• Children (1 yo)
  – 1996: Areas with consistently high transmission rates
  – 1999: Areas with transmission rates > national avg
  – 2006: Entire country

MMWR 1996/45(RR15)
MMWR 1999/48(RR12)
MMWR 2006/55(RR07)
Hepatitis A vaccine

• **Single Antigen:**
  – 2 Doses for adults (>18yo) at 0 and 6m

• **Combo Hep A/Hep B:**
  – 3 Doses for adults (>18yo) at 0, 1, and 6m
Post Exposure Prophylaxis

Within 2 weeks of exposure:

- Vaccinate (Single antigen-1 dose)
  - all individuals >12 months old

- Immunoglobulin (0.1ml/kg)
  - Infants <12 months
  - Pregnant
  - Immunocompromised or chronic liver disease
Hepatitis A Incidence USA

FIGURE 1. Incidence* of reported acute hepatitis A cases — National Notifiable Diseases Surveillance System, United States, 1966–2013

* Rate per 100,000 population. Rate (number of cases) in 1971 (peak), 1996 (first Advisory Committee on Immunization Practices [ACIP] recommendation for hepatitis A vaccination) and 2011 (low) were 28.9 (59,606 cases), 11.7 (31,032 cases), and 0.4 (1,398 cases), respectively.

Murphey et al, MMWR 2016/65(1): 29-41
Impact of Vaccination Campaign

FIGURE 3. Incidence* of reported acute hepatitis A cases, by county — National Notifiable Diseases Surveillance System, United States, 1987–1997† (pre-vaccine) and 2007

* Rate per 100,000 population.
† Annual average incidence.

Murphhey et al, MMWR 2016/65(1): 29-41
Outbreak of Hepatitis A Virus (HAV) Infections among Persons Who Use Drugs and Persons Experiencing Homelessness

Distributed via the CDC Health Alert Network

June 11, 2018, 0800 ET (8:00 AM ET)

CDCHAN-00412

Summary

The Centers for Disease Control and Prevention (CDC) and state health departments are investigating hepatitis A outbreaks in multiple states among persons reporting drug use and/or homelessness and their contacts. This Health Alert Network (HAN) Advisory alerts public health departments, healthcare facilities, and programs providing services to affected populations about these outbreaks of hepatitis A infections and provides guidance to assist in identifying and preventing new infections.
States with Active Hepatitis A Outbreaks

https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm. As of 09/03/2018
Arkansas Active Hepatitis A Outbreak

https://www.healthy.arkansas.gov/programs-services/topics/hepatitis-a. As of 09/03/2018
Arkansas Hepatitis A Cases by Week February-September 2018

[Bar chart showing the number of hepatitis A cases per week from February to September 2018.]
## Arkansas Hepatitis A Outbreak

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Men</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>Women</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Pregnant Women</td>
<td>&lt; 5</td>
<td>N/A</td>
</tr>
<tr>
<td>Black or African American</td>
<td>&lt; 5</td>
<td>N/A</td>
</tr>
<tr>
<td>White</td>
<td>106</td>
<td>91</td>
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<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Number Who Use Drugs</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Number who Inject Drugs</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>Number who Shared Injection Equipment</td>
<td>&lt; 5</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of Food Handlers</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Number Co-infected With Hepatitis C</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Number Co-infected With Hepatitis B</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Number Hospitalized</td>
<td>62</td>
<td>53</td>
</tr>
<tr>
<td>Number of Men Who Have Sex With Men</td>
<td>&lt; 5</td>
<td>N/A</td>
</tr>
<tr>
<td>Number Jailed Past 2 Months</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Number of Homeless Individuals</td>
<td>&lt; 5</td>
<td>N/A</td>
</tr>
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### Median, Min, Max

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.8</td>
<td>14.9</td>
<td>71.3</td>
</tr>
</tbody>
</table>
Arkansas Hepatitis A Outbreak

- First Case February, 2018
- Northeast Arkansas: Clay->Greene->Craighead
- Associated with recreational drug use
  - IV Drug Users, Construction workers
  - 70% meth and Marijuana
  - 28% co-infected with HCV
- 8 Food Workers (8 Restaurants)
  - All with recreational drug use
  - No food-borne transmission documented
- Clinically more severe than prior Hep A outbreaks
  - 117 Cases (all Genotype 1B)
  - >50% Hospitalized
  - 5 Co-acquired infections (2 HBV, 2 HCV, 1 HIV)
  - 1 Death
ADH Response

• ADH Recommendations for post exposure prophylaxis:
  – 1x dose of Hepatitis A Vaccine within 2 weeks of exposure
  – Immunoglobulin within 2 weeks of exposure
    • <1yo, pregnant, immunocompromised, liver disease

• Vaccination campaign
  – Free vaccines provided by ADH
  – >30 vaccine clinics in affected areas thus far
  – High priority: Food workers, illicit drug use, homeless, incarceration, + Contact
  – Targeting all Greene Co. individuals (19-60yo)
  – Targeting all high risk individuals in Clay and Craighead Co.

• Vaccination Response:
  – Clay Co: 100% food handlers vaccinated
  – Greene Co: >13K vaccinated (population ~25K)
  – Craighead Co: >8K Food-Workers

• Hand-hygiene: Critical!!!
  – Soap and water recommended (hand gel not effective)
Outline

- *C diff* treatment guideline update
- Hepatitis A outbreak in Arkansas
- **Antibiotic Stewardship: Clinical Pearls**
Oral Outpatient Antibiotic Prescriptions Dispensed in U.S. Community Pharmacies Per 1000 Population: All Antibiotic Classes, 2014

Arkansas ranks 46th in number of antibiotic RXs dispensed

1,155 RX per 1,000 pop

269.4 million Abx RXs:
838 per 1000 persons

Increase in Antibiotic Resistance

MRSA = methicillin-resistant Staphylococcus aureus; VRE = Vancomycin-resistant enterococci
FQRP = Fluoroquinolone-resistant Pseudomonas aeruginosa

Centers for Disease Control and Prevention
Number of Antibacterial NDAs* Approved

*NDAs = new drug applications

Adapted from: CL Ventola. P&T 2015; 40(4):277-83
Antimicrobial Stewardship

• Coordinated interventions to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.
Symptom-Free Pee
LET IT BE
#SymptomFreeLetItBe
If any of these are met, Treatment Duration......

5-7d (adults)
IV->PO Antimicrobials

- Azithromycin
- Bactrim (tmp/smx)
- Clindamycin
- Doxycycline
- Fluconazole
- Levofloxacin/Ciprofloxacin
- Linezolid
- Metronidazole
2016 HAP/VAP Guidelines

Treatment Duration....

7d

- Strong Recommendation
- Meta-analysis of 6 RCTs including 1088 patients
  - Short (7-8d) course compared to long (10-15d) course
  - Similar 28d mortality, PNA recurrence, tx failure, LOS
  - Longer courses had increased risk of recurrent PNA due to MDROs

Kalil et al. CID 2016
FLUOROQUINOLONE ANTIBIOTICS
Use of MRSA Nares in patients with suspected pneumonia

• MRSA colonization predicts future clinical infection

• MRSA nares PCR became available ~2009

• Sensitivity ~90%\textsuperscript{1-5}

• Negative Predictive Value >95%\textsuperscript{1-5}

• Data from mixed clinical settings:
  – Med/Surg, Stepdown, and ICU
  – CAP, HCAP, HAP, and VAP
  – Proven and suspected pneumonia

1. Dangerfield et al. AAC 2014
3. Tilahun et al. AJCC. 2015
5. Smith et al. JCC. 2017
Which of these is considered a contaminant in blood culture???

- *Staph aureus*
- *Candida*

*Staph aureus* and Candida are never considered blood culture contaminants and should be treated aggressively.
Procalcitonin

• FDA approved for:
  – Acute respiratory infection – at antibiotic initiation, and for follow up
  – Severe sepsis/Septic shock – at antibiotic initiation, and for follow up

• Use outside of these indications has little interpretable value

Schuetz et al. BMC Medicine 2011 9:107
Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia

- Sensitivity: 67%
- Specificity: 67%
- PPV: 53%
- NPV: 78%

<table>
<thead>
<tr>
<th>Group</th>
<th>n patients</th>
<th>PCT median (ng/ml)</th>
<th>PCT IQR (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>409</td>
<td>0.09</td>
<td>&lt;0.05, 0.54</td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>67</td>
<td>0.20</td>
<td>&lt;0.05, 0.87</td>
</tr>
<tr>
<td>Typical bacteria</td>
<td>169</td>
<td>2.5</td>
<td>0.29, 12.2</td>
</tr>
<tr>
<td>Mycobacterial/fungal</td>
<td>15</td>
<td>0.19</td>
<td>&lt;0.05, 0.68</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,075</td>
<td>0.14</td>
<td>&lt;0.05, 0.61</td>
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</table>
Approximately 10% of all U.S. patients report having an allergic reaction to a penicillin class antibiotic in their past.

However, many patients who report penicillin allergies do not have true IgE-mediated reactions. When evaluated, fewer than 1% of the population are truly allergic to penicillins.

Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.

Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of broad-spectrum antibiotics in patients labeled “penicillin-allergic” is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.

Correctly identifying those who are not truly penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics.
Vanc + Pip/Tazo Nephrotoxicity

Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-Tazobactam or Cefepime

Diane M. Gomes,1 Carmen Smotherman,2 Amy Birch,1,3 Lori Dupree,1,3 Bethany J. Della Vecchia,1,3 Dale F. Kraemer,2,4 and Christopher A. Jankowski1,3,*

1UF Health Jacksonville, Jacksonville, Florida; 2Center for Health Equity and Quality Research, Jacksonville, Florida; 3University of Florida College of Pharmacy, Jacksonville, Florida; 4Department of Neurology, University of Florida, Jacksonville, Florida

- 224 patients
  - Vanc + Zosyn: 39 of 112 (34.8%)
  - Vanc + Cefepime 14 of 112 (12.5%)
  - P value 0.003
Pharmacist Driven Vancomycin Dosing Protocol

<table>
<thead>
<tr>
<th></th>
<th>Before Protocol, % (n=177)</th>
<th>After Protocol, % (n=25)</th>
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<tbody>
<tr>
<td><strong>1st Vanc trough 07/2016</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-therapeutic</td>
<td>17.5</td>
<td>16</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>40.5</td>
<td>60</td>
</tr>
<tr>
<td>Supra-therapeutic</td>
<td>42</td>
<td>24</td>
</tr>
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Before Vanc Protocol

- Subtherapeutic: 17.5%
- Therapeutic: 40.5%
- Supratherapeutic: 42%

After Vanc Protocol

- Subtherapeutic: 16%
- Therapeutic: 60%
- Supratherapeutic: 24%
Pseudomonas coverage is not needed on all patients
The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.
Hot Topics in Infectious Diseases

• New *C. diff* guidelines recommend oral vancomycin as initial therapy rather than metronidazole

• Growing Hep A outbreak in NE Arkansas linked to recreational drug use. Vaccination campaign underway.

• Be mindful of unnecessary antibiotic exposure as antibiotics are a limited resource. The more that antibiotics are used today, the less likely they will still be effective in the future.
Return of Antimicrobial Activity

EFFECT OF ZOSYN USAGE ON PSEUDOMONAS SUSCEPTIBILITY

% OF PSEUDOMONAS ISOLATES SUSCEPTIBLE TO ZOSYN

ZOSYN USAGE (DEFINED DAILY DOSE)

Susceptibility

DDD of Zosyn