Clostridium difficile and Influenza

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May 14-15, 2018
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Clostridium difficile
What is *C. difficile*?

- Anaerobic spore-forming bacillus
- Some strains can produce toxins
  - Toxin A - enterotoxin
  - Toxin B – cytotoxin
- Toxin B
  - 10x more potent than toxin A
  - Strains without toxin A as virulent as those with both toxins
- ~10-30% of *C. difficile* strains do not produce any toxins
  - Not pathogenic
- Most common bacterial infectious diarrhea in nosocomial settings
Risk Factors

- Antimicrobial exposure
- Acquisition of *C. difficile*
- Advanced age
- Severe illness
- Immunosuppression
- Tube feeds
- Gastric acid suppression
What diseases result from *C. difficile*?

• Asymptomatic carriage
  – Colonization with non-toxin producing *C. difficile*
  – Up to 20% of hospitalized adults
  – Up to 50% of long-term care facility residents

• *C. difficile* infection (CDI) – symptomatic illness

• *C. difficile*-associated disease (CDAD) – spectrum of illnesses
  – pseudomembranous colitis (PMC)
  – toxic megacolon
  – perforations of the colon
  – sepsis
  – death (rarely)
What are the main clinical symptoms of CDI?

• Watery diarrhea (3 loose stools in 24 hours)

• Other manifestations
  – lower abdominal pain and cramping
  – low-grade fever
  – Nausea
  – anorexia
How does *C. difficile* spread and cause disease?

Susceptible host (>1 risk factors)

- Loss of normal protective flora
  (Antibiotic use or decreased stomach acidity)

- Exposure to *C. difficile* spores
  (Bedside items, caregivers’ hands)

- Ingestion of spores
  (Transmission via fecal-oral route)

- Proliferation of *C. difficile* bacteria
  (Secretion of toxins A and B)

- Profound colonic inflammatory response
  (Diarrhea results)
C. difficile Infection Incidence Among Hospitalized Patients by Age Group (Age <18, 18-64, >65 years) --- United States, 2001-2010
Deaths Caused by C. difficile Infections --- United States, 1999-2010

*Age-adjusted Rate of *C. difficile* as the Primary (Underlying) Cause of Death.

Source: CDC National Center for Health Statistics, 2012
Why the increase in *C. difficile* incidence and mortality?

- Increasing use of antibiotics
  - Across all age groups
- Aging population in all medical care settings
  - SNF, acute inpatient care and outpatient
- Introduction of a new hypervirulent *C. difficile* strain BI/NAP1/027
  - First detected in Pittsburgh (2000)
  - Spread widely leading to large outbreaks in 2000s
  - Produces more toxin (23x more toxin B)
  - Produces another toxin (binary toxin)
Diagnosis of CDI

• Suspect CDI in patients with
  – Acute diarrhea
  – CDI risk factors
  – No alternative explanation (e.g., laxatives)

• Send liquid unformed stool for testing

• Do not test asymptomatic patients with formed stool
  – Asymptomatic carriage is common and does not warrant treatment

• Stool assays may remain positive after clinical recovery
  – Testing for cure or repeated testing during same episode is not warranted
Common *C. difficile* diagnostic tests

- EIA for *C. difficile* toxins A and B (2 hours)
  - 79-80% sensitive
  - 99% specific
- Nucleic acid amplification test such as PCR (1 hour)
  - Detects toxin genes; does not test for active toxin production
  - Cannot distinguish toxin producing from non-producing strains
  - Can result in overdiagnosis of CDI
- Other tests: EIA for *C. difficile* GDH antigen, toxigenic culture, and endoscopy
Treatment of CDI

• Stop inciting drugs (20-25% respond)
• Preferred antibiotics
  – Vancomycin
  – Fidaxomicin
  – If above unavailable – metronidazole
• Fecal microbiota transplantation
  – Preferred for recurrent CDI despite appropriate antibiotic therapy
• Surgery for complications
Infection Control and Prevention:
Core Prevention Strategies

Guidelines for prevention and control of *C. difficile* and multi-drug resistant organisms available on LA County DPH website: http://publichealth.lacounty.gov/acd/docs/LAC%20Guidelines_AcuteCare206-2-09rev.pdf

- Antimicrobial stewardship program (~50% antibiotic use unnecessary)
- Hand hygiene **with soap and water** (not sanitizer)
- Contact precautions for duration of diarrhea
- Disinfection equipment/environment
- Laboratory-based alert system for immediate notification of positive test results
- Education about CDI: HCP, housekeeping, administration, patients, families
Supplemental Prevention Strategies

- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)
- Presumptive isolation for symptomatic patients
- Evaluate and optimize testing for CDI
- Implement universal glove use on units with high CDI rates
- Use sodium hypochlorite (bleach 1:10) – containing agents for environmental cleaning
Common Challenge: Patient Placement

• Long-term care placement should not be refused based on *C. difficile* status; instead:
  – Place resident in private room
  – If private room unavailable
    • Cohort with other CDI-positive patients
    • Provide a dedicated bedside commode
Influenza
The Influenza Virus

• Genome ~13,000 base pairs
• Viral replication highly error prone (~1/10,000 bp)
• Advantages
  – Increased adaptability to selection pressures (e.g. antivirals)
  – Evade host immunity
• Influenza survives as a population of viruses, not a single virus
  – Requires continuous viral surveillance
  – Necessitates frequent updates to the vaccine
Antigenic “Drift” and “Shift”

Drift

• Point mutations (1/10,000 bp)
• Minor changes, within subtypes
• Occurs in A and B subtypes
• May cause epidemics

⇒ Occurs frequently

Shift

• Major change, new subtypes
• Exchange of gene segments
• Occurs in A subtypes only
• May cause pandemics

⇒ Occurs infrequently
Influenza A Virus Divided into Subtypes

• Based on surface glycoproteins
  – Hemagglutinin (H) – vaccines induce antibodies to block this protein
  – Neuraminidases (N) – Antiviral drugs inhibit this protein

• Current human subtypes:
  – A(H1N1)pdm09
  – A(H3N2)
Classifying Influenza B Viruses

• Not divided into subtypes
• Characterized by lineage (geographic origin) and strain
• Currently circulating influenza B viruses belong to two lineages
  – B/Victoria
  – B/Yamagata
WHO Nomenclature for Naming Influenza Viruses

A/Beijing/32/92 (H3N2)

- Antigen type
- Year of isolation
- Geographic origin
- Strain number
- Virus subtype (for A viruses)
  - Hemagglutinin subtype
  - Neuraminidase subtype
Pandemic Influenza

• Emergence and spread of “novel” influenza A virus
  – Results from antigenic shift
  – Sustained and efficient human-human transmission
• Potential for global spread within months
• Potential to kill millions - All age groups
• Two modern pandemics
  – “Spanish” pandemic – H1N1 in 1918
  – “Hong Kong” pandemic – H3N2 in 1958
Challenges with Counting Influenza Cases, Hospitalizations, and Deaths

• Many flu hospitalizations/deaths occur 1-2 weeks after illness
  – Secondary bacterial infection
  – Exacerbation of underlying chronic illness

• Most people with flu-related complications are not tested for flu

• Commonly used flu tests not highly sensitive – result in false negative results

• No requirement to report individual cases or deaths
Impact of Influenza in the U.S.
• Best obtained by modelling

- Deaths: 12,000 – 56,000
- Hospitalizations: 140,000 – 710,000
- Cases: 9,200,000 – 35,600,000

(CDC estimates for 2010–2016)
Overview of Influenza Surveillance in LA County

- Begins in October and ends mid-May
- Surveillance concentrated during this period
  - Year round surveillance activities
- Data collected and analyzed weekly
  - Published weekly or bi-weekly during flu season through *Influenza Watch*
Influenza Surveillance Data Sources

• Sentinel surveillance
  – Laboratory-based reporting – 9 participating laboratories
  – Influenza-associated fatalities – reportable since 2010
  – Outbreak surveillance

• Syndromic surveillance
  – ED visits for influenza-like illness (ILI) symptoms

• P&I Deaths – death certificate data

• Other – Kaiser Permanente, Biofire
LA County Laboratory-Based Sentinel Surveillance, 2012-13 to 2017-18

- Used to define the beginning and end of flu season
  - % positive >5% or <5%

Respiratory Specimen Surveillance 2012-2018
Influenza Positive Tests from Sentinel Laboratories
Los Angeles County, 2017-18 Season
Proportion of ILI Emergency Department visits by week, LAC, 2013 to 2018

Number per 1,000 ED patients

MMWR week

2017-18
2016-17
2015-16
2014-15
2013-14

Acute Communicable Disease Control Program

4/5/2018
Influenza-Associated Deaths in LA County, 2012-13 to 2016-17

- 239 influenza-associated deaths in 2017-18 season
  - 193 (81%) aged 65+ years
Influenza Vaccination Recommendations for 2017-18 Season

• All persons aged >6 months without contraindications should be vaccinated annually

• Timing of vaccination: Ideally before onset of influenza activity

• Vaccine formulation
  – Live attenuated vaccine not recommended
  – Higher dose formulation for elderly and immunocompromised
  – CDC does not state preference between trivalent or quadrivalent vaccine (theoretical benefit to quadrivalent)
Seasonal Influenza Vaccine Effectiveness (VE) for 13 Seasons, 2004-05 to 2016-17

*Interim 2016-2017 VE Estimates (4/20/2016-4/9/2017) were presented to ACIP in June 2017

**Interim early estimates may differ from final end-of-season estimates
2017-18 Interim Seasonal Influenza VE

Vaccine effectiveness

Overall 36%
A(H3N2) 25%
A(H1N1) 67%
B 42%
A vaccine *not* given is 100% *not* effective
What is Considered a Flu Outbreak in a SNF?

- >1 case of laboratory confirmed flu in the setting of a cluster (≥2 cases) of ILI in a 72 hour period

- LAC Department of Public Health responded to
  - 30 flu outbreaks at SNFs during the 2016-17 flu season
  - 73 flu outbreaks at SNFs from Nov 2017 to Mar 2018
Laboratory Confirmation of Influenza

- Recommended tests (in order of preference):
  - rRT-PCR – most sensitive and accurate test
  - Immunofluorescence
  - Rapid antigen tests
    - Low sensitivity (62%)
    - High specificity (98%)
Antiviral Chemoprophylaxis During Outbreaks

• To all non-ill residents regardless of vaccination status
• Minimum 2 weeks and continued for 7-10 days after last known case identified
• Consider for all staff regardless of vaccination status if outbreak caused by a strain that is not well matched by the vaccine
Other Outbreak Control Measures

- Droplet precautions for ill residents
- Place ill residents in a private room or cohort with other ill residents
- Dedicate separate staff to ill and non-ill residents
- Limit group activities and serve meals in room
- Avoid new admissions to facility or unit with ill residents (7 days after symptom onset of last ill resident)
Influenza Outbreak Prevention

- *Vaccinate* all residents and staff
- *Surveillance* of all residents, staff, and visitors for ILI during flu season (Oct-May)
- *Test* for flu anytime resident develops ILI
- *Exclude* ill staff and visitors from facility
Questions?