Clostridium Difficile Primer: Disease, Risk, & Mitigation

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Special Thanks: Drs. Parodi, Dryjanski, Rieg
Objectives

1. Understand the pathophysiology of C. difficile infections
2. Describe risk factors for C. diff
3. Describe strategies to mitigate C. diff
4. Understand the epidemiology of C. diff and antibiotic overuse
Microbiology & Pathophysiology

- Spore-forming anaerobe
- Ingestion of spores $\rightarrow$ toxins A and B $\rightarrow$ disease
- Epidemiology:
  - colon colonization 3% in healthy adults
  - 20-40% for hospitalized patients
Clinical Syndromes

- Mild to severe diarrhea
- Life threatening colitis
- Toxic megacolon/ intestinal perforation

- Clues to severe disease:
  - Ileus
  - WBC >20,000
  - Sepsis
  - Renal failure
  - Pseudomembranes by endoscopy/biopsy
Available Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Detection</th>
<th>Time required</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxin</td>
<td>Toxin B</td>
<td>24–48 h</td>
<td>Relatively sensitive and specific, but delayed results and technically complex</td>
</tr>
<tr>
<td>Toxin-culture</td>
<td>Toxigenic <em>C. difficile</em></td>
<td>3–5 days</td>
<td>Sensitive, but delayed results and technically complex</td>
</tr>
<tr>
<td>EIA-toxin A or A/B</td>
<td>Toxin A or A/B</td>
<td>Hours</td>
<td>Rapid, inexpensive, specific but relatively insensitive</td>
</tr>
<tr>
<td>EIA-GDH</td>
<td><em>C. difficile</em></td>
<td>Hours</td>
<td>Rapid, inexpensive, relatively sensitive, but not specific, especially in nosocomial cases</td>
</tr>
<tr>
<td>EIA-GDH + EIA toxin A/B</td>
<td><em>C. difficile</em> &amp; toxins</td>
<td>Hours</td>
<td>Rapid, inexpensive, need alternative toxin test for pos/neg result</td>
</tr>
<tr>
<td>RT-PCR toxin B gene</td>
<td>Toxigenic <em>C. difficile</em></td>
<td>Hours</td>
<td>Rapid, very sensitive, need clinical correlations for positive tests</td>
</tr>
</tbody>
</table>

**Endoscopy:** Sensitivity 50%, Specificity approaches 100%
Yearly *Clostridium difficile*-related Mortality by Listing on Death Certificates, United States, 1999–2004

CDI Costs to Healthcare

- US annual hospital healthcare cost estimated at $1.1-3.4 billion
- Median increase LOS 10-12 days
  - If surgery needed increase LOS 20.9 days
- Increase ICU LOS regardless of surgery
- Excess drug costs
- Median excess cost for each hospitalization: $27,120
  - $3,797-7,197 inpatient costs/180 days follow up

Kyne et al Clin Infect Dis 2002;34:346
Dubberke et al Infect Control Hosp Epidemiol 2009;30:57
Dubberke et al Clin Infect Dis 2008;46:497
Pakyz MD Consult 2009
Patients risk factors to acquire C. difficile Infection (CDI)

“old information”
- Aged > 65 years
- “Multiple Comorbidities”
- “Antibiotic classes”
- PPI?

New*
- Aged > 68 years
- LOS >24 days
- White (non-Hispanic); female
- Asians (lowest risk, but high mortality)
- Higher in: dementia, PVD, SNF, exposure to multiple abx classes
- “HO- C. diff” misses many “HA” C. diff (i.e. post discharge C. diff is an issue)

1. Tartof, Rieg, Yu, et al., A Comprehensive Assessment Across the Healthcare Continuum: Risk of Hospital-Associated Clostridium difficile Infection Due to Outpatient and Inpatient Antibiotic Exposure”, Infection Control & Hospital Epidemiology, October 2015, pp 1 – 8
Risk of *C. difficile* Diarrhea According to Antibiotic Class

- **Odds Ratio**
  - Cephalosporins: 3.8
  - Fluoroquinolones: 3.9
  - Clindamycin: 1.6
  - Macrolides: 1.3

Outpatient and Inpatient Abx: Risk

### Outpatient Medications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Days of Use</th>
<th>Relative Risk</th>
<th>P value</th>
<th>Adjusted Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEPHALOSPORINS</td>
<td>1-10</td>
<td>1.0 (0.9-1.2)</td>
<td>0.25564</td>
<td>1</td>
</tr>
<tr>
<td>CEPHALOSPORINS</td>
<td>11+</td>
<td>1.3 (1.0-1.6)</td>
<td>0.25564</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient Fluoroquinolones</td>
<td>1-10</td>
<td>1.3 (1.2-1.4)</td>
<td>0.08002</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient Fluoroquinolones</td>
<td>11+</td>
<td>0.9 (0.7-1.2)</td>
<td>0.08002</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient Lincosamides</td>
<td>1-10</td>
<td>1.6 (1.3-2.1)</td>
<td>0.08044</td>
<td>1</td>
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<tr>
<td>Outpatient Lincosamides</td>
<td>11+</td>
<td>1.3 (0.9-2.0)</td>
<td>0.08044</td>
<td>1</td>
</tr>
<tr>
<td>PENCILLINS</td>
<td>1-10</td>
<td>0.9 (0.6-1.5)</td>
<td>0.7396</td>
<td>0</td>
</tr>
<tr>
<td>PENCILLINS</td>
<td>11+</td>
<td>1.4 (0.6-3.3)</td>
<td>0.7396</td>
<td>0</td>
</tr>
<tr>
<td>PENCILLINS, Broad Spectrum</td>
<td>1-10</td>
<td>1.1 (0.9-1.3)</td>
<td>0.11769</td>
<td>0</td>
</tr>
<tr>
<td>PENCILLINS, Broad Spectrum</td>
<td>11+</td>
<td>1.4 (0.9-1.9)</td>
<td>0.11769</td>
<td>0</td>
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<tr>
<td>Outpatient Tetracyclines</td>
<td>1-10</td>
<td>1.0 (0.8-1.2)</td>
<td>0.97081</td>
<td>0</td>
</tr>
<tr>
<td>Outpatient Tetracyclines</td>
<td>11+</td>
<td>1.0 (0.8-1.4)</td>
<td>0.97081</td>
<td>0</td>
</tr>
<tr>
<td>Absorbable Sulfonamides</td>
<td>11+</td>
<td>1.0 (0.7-1.4)</td>
<td>0.29587</td>
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<tr>
<td>Absorbable Sulfonamides</td>
<td>11+</td>
<td>1.0 (0.7-1.3)</td>
<td>0.29587</td>
<td>1</td>
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<tr>
<td>Outpatient Amoxicillin &amp; Pot</td>
<td>1-10</td>
<td>1.3 (1.0-1.6)</td>
<td>0.1136</td>
<td>0</td>
</tr>
<tr>
<td>Outpatient Amoxicillin &amp; Pot</td>
<td>11+</td>
<td>0.6 (0.4-0.9)</td>
<td>0.1136</td>
<td>0</td>
</tr>
<tr>
<td>Cephalosporins, 1st Generation</td>
<td>1-10</td>
<td>1.0 (0.8-1.2)</td>
<td>0.89247</td>
<td>1</td>
</tr>
<tr>
<td>Cephalosporins, 1st Generation</td>
<td>11+</td>
<td>1.0 (0.8-1.5)</td>
<td>0.89247</td>
<td>1</td>
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<tr>
<td>Lincosamides</td>
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<td>1.1 (0.8-1.9)</td>
<td>0.76694</td>
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<tr>
<td>Lincosamides</td>
<td>11+</td>
<td>0.2 (0.7-2.3)</td>
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<tr>
<td>Outpatient Macrolides</td>
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<td>0.5 (0.5-0.8)</td>
<td>0.00621</td>
<td>1</td>
</tr>
<tr>
<td>Outpatient Macrolides</td>
<td>11+</td>
<td>0.2 (0.2-1.3)</td>
<td>0.00621</td>
<td>1</td>
</tr>
<tr>
<td>Nitrofurans Derivatives</td>
<td>1-10</td>
<td>0.7 (0.7-1.6)</td>
<td>0.02942</td>
<td>0</td>
</tr>
<tr>
<td>Nitrofurans Derivatives</td>
<td>11+</td>
<td>1.0 (0.4-2.2)</td>
<td>0.02942</td>
<td>0</td>
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<tr>
<td>Absorbable Sulfonamides</td>
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<td>1.0 (0.7-1.2)</td>
<td>0.72546</td>
<td>0</td>
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<tr>
<td>3rd Generation Cephalosporins</td>
<td>1</td>
<td>1.7 (1.4-1.7)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cephalosporins, 4th Generation</td>
<td>1</td>
<td>1.0 (0.8-1.2)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chemotherapeutics, Antibacterial, Misc</td>
<td>1</td>
<td>0.5 (0.1-3.9)</td>
<td>0.50332</td>
<td>0</td>
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<tr>
<td>Cyclic Lipopeptides</td>
<td>1</td>
<td>2.1 (0.7-6.6)</td>
<td>0.24903</td>
<td>0</td>
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<tr>
<td>Glycyclolides</td>
<td>1</td>
<td>0.0 (0.0-1)</td>
<td>0.45177</td>
<td>0</td>
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<tr>
<td>Lincosamides</td>
<td>11+</td>
<td>1.3 (1.1-1.5)</td>
<td>0.00646</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values in bold type are statistically significant.

**Medications with a "1" value in the 'Adjustment indicator' column have been adjusted for: sex, age, race, Charlson Comorbidity Score, skilled nursing facility transfer, statin, history of hospitalization. Medications with a "0" value indicates that the estimate is a crude estimate.*

Tartof, Rieg, Yu, et al., A Comprehensive Assessment Across the Healthcare Continuum: Risk of Hospital-Associated *Clostridium difficile* Infection Due to Outpatient and Inpatient Antibiotic Exposure, Infection Control & Hospital Epidemiology, October 2015, pp 1 – 8
Do not underestimate: Cumulative Antibiotic Exposures Over Time and multiple classes

- Overall reduction of total dose as well as number and days of antibiotic exposure and the substitution of high-risk antibiotic classes for lower-risk alternatives may reduce the incidence of hospital-acquired CDI.

  CID 2011:53 (1 July) d Stevens et al

- Expounded upon with more granular antibiotics risk and number of classes exposed as increase risk in 2015

- Antimicrobial Stewardship Teams can help pick the most appropriate abx in the fastest amount of time to help avoid both extended LOS and multiple abx exposure
AND speaking of costs and waste

- 50% of all antimicrobial use is inappropriate
- 30-50% of hospitalized pts receive antibiotics
- Antibiotics account for ~30% of hospital pharmacy costs
- USA one of world’s top spenders on antibiotics
What antibiotics do

- Alter gut flora in quantity, composition, diversity and ability to resist colonization with C. diff
- 100 trillion bacteria colonize gut essential for immune cell development and function
- Complex ecosystem in symbiosis with host is altered with antibiotics
CALIF LAW: ASP requirements
per CDPH ASP subcommittee, Sacramento

“Ideal” Quality Metrics: CDC, SHEA, ?CMS

- Usage patterns of **broad-spectrum** antibiotics
- Usage measured by either Defined Daily Dosing (DDD) or Days of Therapy (DOT) is collected for antibiotics; results are examined for appropriate use. The institution **monitors antibiotics** determined to be of importance to the resistance ecology of that facility
- Multi-Drug **Resistant Organisms** (MDRO) rates and trends
- SCIP measures (performance)
- Medical Use Evaluations (MUEs) for total and **class-specific antibiotics** used
- A **risk assessment** for each facility is performed and includes the above parameters as well as a definition of the scope of practice of a facility
- An antibiogram is developed consistent with guidelines issued by the Clinical and Laboratory Standards Institute; there is documentation to indicate that it is distributed to the Medical Staff and is being used for **education**

CA SB 1311: 1 MD, 1 pharmD, ASP education, working committee by 2016
Basic ASP Workflow

ID Pharmacist

- Daily Surveillance of all pts on antibiotics
- Identifies “Opportunity” Cases

ID Physician

- Confirms Need for Intervention
- Consult/Education Attending MD; Report to PharmD

Attending MD

- Changes or Amends Order

Monitor case through stay

Document Intervention

Review Chart
### Decrease Use/Cost for Targeted Drugs and Class*

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Difference</th>
<th>Difference for Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonal</td>
<td>Zosyn</td>
<td>-14,598</td>
<td>-32.1%</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>-1,429</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
<td>-4,904</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>-299</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>434</td>
<td></td>
</tr>
<tr>
<td>Anti-MRSA</td>
<td>Vancomycin</td>
<td>-2,032</td>
<td>-11.7%</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>-1,698</td>
<td></td>
</tr>
<tr>
<td>Antifungal</td>
<td>Caspofungin</td>
<td>1174</td>
<td>-2.1%</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>-1,189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>-297</td>
<td></td>
</tr>
<tr>
<td>Quinolone</td>
<td>Moxifloxacin</td>
<td>-808</td>
<td>-20.2%</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>-299</td>
<td></td>
</tr>
</tbody>
</table>

*Required by State Law and TJC

Source: Southern California Pharmacy Analytics and Program Office DCSO
Cost Differences between Pilots and “controls”

<table>
<thead>
<tr>
<th></th>
<th>Prior Yr</th>
<th>Non ASP1 ICU ID MD</th>
<th>ASP lost PharmD</th>
<th>NonASP2</th>
<th>WLA</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per cent Change</td>
<td></td>
<td>2.3%</td>
<td>8.5%</td>
<td>1.9%</td>
<td>-23.9%</td>
<td>-20.5%</td>
</tr>
</tbody>
</table>
How Important is ASP/IDpharmacist?

Overall Abx use (cost/1000 pt days)

- Never had ASP
- ASP, 7/2010
- lost IDpharmD
- ASP with IDpharmD
Ranking By Consumption: Pros & Cons
SCAL KP abx use compared to USA

Drug Utilization: Quinolones

Drug Utilization: Piperacillin/Tazobactam
SCAL KP vs USA, part 2

Drug Utilization: Carbapenems

Drug Utilization: Vanco (systemic)
ASP = Patient Safety
(Not Just about “taking away Antibiotics”)
ASP: NOT Just a COST THING:
pre ASP (2010) vs post ASP

Hospital Standardized Mortality Ratio* and % mortality:

- ICD9 principal diagnosis for Infections
  - 38 Strep septicemia
  - 38.1 Staph septicemia, unspecific
  - 38.11 Staph aureus septicemia
  - 38.4 Septicemia gram-neg unspecified NOS
  - 38.42 Septicemia E. coli
  - 38.49 Septicemia other gram-neg org
  - 38.8 Other spec septicemia
  - 38.9 Septicemia uns
  - 38.19 Other staph septicemia
  - 38.2 Pneumococcal septicemia
  - 38.43 Septicemia pseudomonas
  - 42 HIV & specific infection
  - 8.45 Clostridium difficile intestine infection
- ICD9 principal diagnosis for Respiratory disease
  - 481 Pneumococcal pneumonia
  - 482 Pneumonia due to klebsiella
  - 482.1 Pneumonia due to pseudomomas
  - 486 Pneumonia organism NOS
  - 518.5 Pulm insuf follow trauma/surg
  - 518.81 Respiratory failure
  - 482.41 Other bacterial pneumonia
  - 482.83 Pneumonia due to gm-neg bacteria
  - 485 Bronchopneumonia organism uns
  - 491.21 Chronic bronchitis with Acute exacr
  - 496 Chronic airway obstruction NE
  - 507 Pneumonitis due to inhalation of food/vomit
  - 511.9 Unspecified pleurisy pleural effusion
  - 515 Postinflammatory pulm florosi
  - 518.82 Other pulmonary insufficiency NOS
  - 518.84 Other diseases of lung

- Sepsis/bacteremia/CDI:
  HSMR 74 → 70.24

- Resp Infections:
  HSMR 65.38 → 49.64

- **Overall Sepsis Mortality:**
  Pre-ASP 2010: 14.6%
  postASP: 13.4% (2011)
  **10.6% (2012)**

*Medicare WLA medicare inpatient data, highest at risk demographic

Yu, et al., Am J Health Syst Pharm June 15, 201471:1019-1028
C. diff Treatment

- **Mild Disease**
  - Metronidazole 500mg po q8 10-14d

- **Severe Disease**
  - WBC >15,000
  - Cr >1.5x baseline
  - Vanco liquid solution 125 mg po qQID 10-14d

- **S/S ileus or toxic megacolon**
  - Vanco liquid pngt 125-500mg q6 PLUS
  - Flagyl 500mg iv Q8
  - Surgery consult

- **Xfactors:**
  - IVIG/Vanco enemas
  - Rifaximin ‘chaser’ w/Vanco
  - Fidaxomicin
    - Non-inferior to Vanco
    - Decrease reoccurrence?

- **Bacteriotherapy?**
  - Recalcitrant cases
  - Supported by med lit (Am J Gastro, June 2012)

Environmental Prevention

- Hospital infection control:
  - Single room with bathroom
  - Barrier precautions
  - Terminal room clean w/ 1:10 bleach
  - AND soap and water for hand hygiene
Cdff decrease: 'Combination Therapy'

NHSN Defined Hospital Onset C. difficile
Jan 2012 - Jun 2013

ASP 2011

ASP/pharmD PPI reduction
ASP/PCT
EVS Bleach validation

Rate Hospital Onset C. diff./10,000 Patient Days

Jan-12 | Feb-12 | Mar-12 | Apr-12 | May-12 | Jun-12 | Jul-12 | Aug-12 | Sep-12 | Oct-12 | Nov-12 | Dec-12 | Jan-13 | Feb-13 | Mar-13 | Apr-13 | May-13 | Jun-13
---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
16.5 | 21.1 | 11.1 | 10.6 | 17.5 | 8.2 | 11.0 | 11.5 | 13.9 | 13.9 | 5.1 | 7.2 | 2.7 | 4.9 | 8.5 | 3.3 | 5.6

ASAP Regional Rate 2012
How Important is BLEACH…?

Bleach cleaning stopped

Environmental Contamination

- Room contamination
  - 49% rate if sx CDI v. 29% rate asx colonization
  - Placement in a room w/ a prior CDI occupant RR 2.35

- More recent studies: Contamination rates vary between 2.5%-75%
  - Rooms occupied by noninfected/colonized patients may be contaminated

- Environmental survival of spores: up to 5 months

Shaughnessy ICHE 2011;32:201
Prolonged Isolation?

- Continued shedding 1-4 weeks after completion of treatment
- Amount of shedding probably matters
  - Asx carriers shed less--isolation not routinely recommended
- Previously sx pt who remains hospitalized--unresolved

Sethi ICHE 2010;31:21-7
Summary: C. difficile 3X Plan

- **Decrease in C. difficile/HAI rates**
- **Decrease Morbidity and Mortality**
- **Increased Patient Safety**

**Hand Hygiene:**
Hospital Admin support and enforcement
HAI bundles

**Contact Plus Isolation and EVS Cleaning**

**Antimicrobial Stewardship Program**

- **Decrease in C. difficile/HAI rates**
- **Decrease Morbidity and Mortality**
- **Increased Patient Safety**
Which of the following may help prevent spread of C. diff?
(A) Wash hands with alcohol
(B) Bleach rooms after
(C) Wash hands with soap and water
(D) No need to use gloves when entering the room
(E) B and C
Which of these antibiotics is considered high risk for C. diff?

(A) Cipro
(B) Clindamycin
(C) Ceftriaxone
(D) Doxycycline
(E) A, B, C > D
Which of the following are potential reasons why *C. diff* remains an issue in many acute care hospitals?

(A) Antibiotic overuse
(B) Uneven room cleaning ("terminal room bleach cleaning")
(C) *C. diff* spore shedding even after the diarrhea stops
(D) All of the above
Antibiotic Stewardship is required by CA state law SB 1311. What can small hospitals do to prevent C. *diff*?

(A) Reinforce hand hygiene  
(B) Focus on ONE broad spectrum antibiotic for overuse  
(C) Ensure EVS is cleaning C. *diff* patient rooms  
(D) Contact isolation precautions for C. *diff* suspect  
(E) All of the above
Figure 1. Model antimicrobial prescribing practice pathway in acute hospitals. Note: The above figure outlines a proposed pathway to monitor and influence antimicrobial prescribing within a hospital or healthcare organization’s clinical governance structure. In particular, the multidisciplinary AMT should be a subgroup of and report to the DTC. There should also be a clear path of communication with the Infection Control Committee where there may be overlapping interests or expertise. An Antimicrobial Pharmacist® should take the lead in coordinating the implementation and audit of antimicrobial practice, and as such the use of existing pharmacy structures is essential to support this activity; the antimicrobial pharmacist should also report to the Chief Pharmacist. Local investment is likely to be required to support the establishment of lead antimicrobial pharmacists. In some hospitals there may be specialty-based lead pharmacists who could link with ward-based pharmacists.
The Big Picture: What IS Affordable Healthcare?

- Why do we need ASP?
  - MDROs
  - C. Diff
  - Preserve anti-infectives
  - Cost effective/mortality
- How should we look at ASP?
  - Self-assessment (vs. "rank")
  - Quality enhancement
  - Future subspecialty
  - Regulation ?= job security
  - Sepsis campaign Equalizer

We can Do BETTER:
- Invest In The Future
  - Decreased NIMs/ HAIs
  - Improved patient safety/care
  - Waste : less