Outcomes in Community-acquired *Clostridium difficile* Infection

Darrell S. Pardi, MD, MS
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic Rochester
Disclosures

• Research support
  • ViroPharma, Merck, Salix

• Honoraria
  • Salix, Optimer

• Rochester Epidemiology Project
  • National Institute of Aging R01 AG034676

• Acknowledgement: Sahil Khanna
Outline

• CA-CDI Epidemiology
• Current definition of CA-CDI
• Modes of Transmission in the Community
• Outcomes in CA-CDI
Epidemiology of Community-Acquired CDI
Background: Epidemiology of CA-CDI

- Increasing incidence of hospital-acquired CDI
- Increasing reports on community-acquired CDI
- Few well-done population based studies assessing epidemiology of community-acquired CDI
  - Variable definitions, data sources
- Fewer studies comparing HA- to CA-CDI or reporting on outcomes in CA-CDI
Epidemiology of CA-CDI – Prior Studies

• Incidence estimates range from 7-46/100,000 in studies from UK, Canada, US
  • No difference in urban vs. semi-rural incidence\(^1\)
  • Higher in females\(^2-4\)

• CA-CDI represents 11-30% of CDI

• 24-48% had no documented antibiotic exposure

---

1) Wilson J Antimciob Chemo 2008  
2) Kutty Emerg Inf Dis 2010  
3) MMWR 2005  
4) MMWR 2008 (Conn)
Epidemiology of CA-CDI – Prior Studies

• CA-CDI younger\textsuperscript{1,2}, less recurrence (12% vs 22\%)\textsuperscript{2}

• Incidence higher in spring-summer than fall-winter\textsuperscript{3}

• C. difficile second only to Giardia as identified cause of diarrhea in a community\textsuperscript{4}

• According to GPRD, incidence increased from <1/100,000 in 1994 to 22/100,000 in 2004\textsuperscript{5}

\textsuperscript{1} Naggie Infection 2010 \hspace{1cm} \textsuperscript{2} Dumyati Emerg Inf Dis 2012
\textsuperscript{3} MMWR 2008 (Conn) \hspace{1cm} \textsuperscript{4} Riley J Hyg 1986
\textsuperscript{5} Dial JAMA 2005
Epidemiology of CA-CDI – Prior Studies

• Antimicrobials, malignancy, exposure to high-risk persons, and remote health care exposure were independently associated with CA-CDI

• PPI use was a/w CA-CDI incidence in one study (OR 3.5) not in three others

1) Naggie Infection 2010  
2) Dial CMAJ 2006 (UK)  
3) Wilcox J Antimicrob Chemo 2008  
4) Kutty Emerg Infect Dis 2010  
The Epidemiology of Community-acquired C. difficile infection: A population-based Study


Am J Gastroenterol 2012;107:89-95
Specific Aims

• Estimate the incidence of CDI in a population-based cohort
  • Overall
  • Community-acquired
  • Hospital-acquired

• Assess associations of demographics, risk factors and outcomes with mode of acquisition
Methods

• All cases of CDI in Olmsted County residents from 1991-2005 identified
• Retrospective chart review
• Definite CDI diagnoses
  • Positive *C. difficile* stool assay (EIA)
  • Diarrhea (≥ 3 loose stools in 24 hours)
• Nursing home residents excluded
• Community acquired: symptom onset in community (> 4 wk after discharge) or <48 hours of hospitalization
Surveillance definitions

Symptom onset: CA-CDI

Admission

Discharge

48 h

4 wks

12 wks

HA-CDI

Indeterminate

CA-CDI

McDonald et al, Infect Control Hosp Epidemiol 2007
Rochester Epidemiology Project

- Mayo Clinic and Olmsted Medical Group provide all medical care to Olmsted County residents
- Access to records of all providers and all patients
- Computer linkage of all inpatient, outpatient, ER encounters for all patients and all providers
- Includes lab results, diagnoses, procedures, prescriptions
Results

• Patient characteristics
  • 385 definite CDI cases
  • Median age: 50 yrs (range 1 – 102)
    • 31.2% were > 65 years
  • 76% female
Overall CDI Incidence Increased with Age and Time

\[ p < 0.001 \]
Community-acquired CDI in Olmsted County

- 41% of cases were community-acquired
- ~ 5% indeterminate (4-12 wks post D/C)
  - Higher than prior reports
  - Younger (50 vs. 72 years)
  - More female (76% vs. 60%)
  - Less comorbidity (3.3 vs. 1.3)
  - Less antibiotic exposure (78% vs. 94%)
CA-CDI Incidence Increased with Age and Time

CA-CDI incidence in keeping with prior studies (7-46/100,000)
Age-Specific Incidence Rates over Time

Crude Incidence Rates (per 100,000 person-years)
CA-CDI: Less Acid Suppression and Antibiotic Exposure

![Bar chart showing comparison between Hospital-acquired and Community-acquired CA-CDI with respect to Acid Suppression and Prior Antibiotic use. The chart indicates a significant difference (*) with p<0.001.]
The Epidemiology of *Clostridium difficile* infection in Children: A Population-based study

Methods

• Retrospective chart review of all cases of CDI in Olmsted County children from 1991-2009

• Definite CDI diagnosis
  • Positive *C. difficile* stool assay
  • Diarrhea (≥ 3 loose stools / 24 hours)
Results

- 92 cases, 75% (n=69) were community-acquired
  - Median age 1.9 yrs (vs 4.2, p = 0.05)
  - 51% were female (vs 30%, p=0.08)
  - 25% had no abx exposure (vs 13%, p=0.22)
  - 15% on acid suppression (vs 35%, p=0.04)

- Caveat: Pediatric carriage
Risk factors – Pediatric CDI

- Antibiotic exposure: 76%
- Gastric acid suppression: 20%
- Hospitalization: 25%
Pediatric CA-CDI Incidence (age & sex adjusted)

Per 100,000 person-years

Annual Incidence
Modes of Transmission in Community-Acquired CDI
Modes of Transmission in CA-CDI

• Consumption
• Person-to-person
• Animal-to-person
• Environment-to-person

Otten Epidemiol Infec 2010
Modes of Transmission in CA-CDI

• Consumption
  • 5.5% water, 2.3% raw vegetables in South Wales¹
  • 20% of ground meat samples in Ontario and Quebec stores²
  • 6.1% beef, veal samples from Canadian stores³
  • 42% meat samples from Arizona⁴

3) Rodriguez-Palacios Emerg Inf Dis 2009   4) Songer Emerg Inf Dis 2009
Modes of Transmission in CA-CDI

- Person-to-person
  - Important in hospitals, difficult to distinguish from environmental spread
  - Exposure to colonized or infected persons in the community
    - Health care workers¹
    - Patients: spouse and children attack rate 5-6/1000 (RR 7.6 and 90.6) for 3 mo after dx²
    - Exposure to high-risk persons a/w CA-CDI³

Modes of Transmission in CA-CDI

• Person-to-person
  • Infants and children
    • 48% kids in Japanese day-care centers colonized\(^1\)
    • 13% of newborns carried toxigenic strains\(^2\)
    • 19% of pediatric oncology pts colonized\(^3\)
    • Exposure to colonized infant risk factor for recurrent CDI in mother\(^4,5\)

Modes of Transmission in CA-CDI

• Animal-to-person
  • 19% dogs colonized with toxigenic C. difficile\(^1\)
  • CDI reported in 0-40% of dogs, 2-38% of cats\(^1\)
  • Also reported in horses, cows, other species
  • Low rates (0-1.7%) in cattle, sheep, pigs, poultry, horses in South Wales\(^2\)
  • One case of transmission from human to dog\(^3\)

Modes of Transmission in CA-CDI

• Environment-to-person
  
  • Environmental contamination found in day care centers\(^1\) and Vet hospitals \(^2\)
  
  • 31-34% of households have \(\geq 1\) sample + \(^3\)
  
  • 27-88% of water, 21% of soil, and 50% of swimming pools samples + in South Wales\(^4\)
  
  • House and yard samples of ill child + \(^5\)

Ingestion of toxigenic *C. difficile* spores or vegetative cells

- Consumption
  - Food
  - Water
- Environment-to-person
  - In the home
  - External to home
- Animal-to-person
- Person-to-person

Susceptible → Gl exposure → Colonized → Cleared

Colonized → Diseased → Deceased

Clinically resolved Colonized

Relapse

Non-human reservoirs

Human reservoirs

Otten Epidemiol Infec 2010
Outcomes in Community-Acquired CDI
CA-CDI Outcomes – Prior Studies

• Connecticut\textsuperscript{1}:
  • 46\% hospitalized, 12\% ICU
  • 2\% colectomy, 2\% mortality
  • Age >65, fever, hospitalization in prior year (>3-12 months) a/w need for hospitalization

• Monroe County, NY\textsuperscript{2}:
  • 19\% required hospitalization
  • no deaths or complications

1) MMWR 2008  2) Dumyati  Emerg Infect Dis 2012
CA-CDI Outcomes – Prior Studies

• North Carolina:
  • 38% required hospitalization\(^3\)

• Durham VAMC:
  • Lower 60-day all-cause mortality than HCFA
  • (3 vs. 17%; \(p = 0.06\))\(^4\)

CA-CDI Outcomes – Prior Studies

Summary

- 19-46% required hospitalization
  - Elderly, fever predictive
- Colectomy 0-2%
- Mortality 0-3%

Outcomes in Community acquired
Clostridium difficile infection

Khanna S, Pardi DS, Aronson S, Kammer P, Baddour L
Aliment Pharmacol Ther 2012;35:613-8
Specific Aims

• Compare outcomes in CA-CDI to HA-CDI
  • Need for hospitalization
  • Risk of severe, severe complicated CDI
  • Treatment failure
  • Recurrence
• Assess predictors of these outcomes
Outcomes definitions

• Severe CDI
  • Peripheral WBC ≥ 15,000 / mm³
  • Creatinine rise ≥ 50% from baseline

• Severe-complicated CDI
  • Hypotension, ileus, toxic megacolon, perforation, need for ICU admission, surgery or death

Outcomes definitions

• Treatment failure
  • Change in treatment within 14 days
    • Non-response
    • Intolerable drug side effects

• Recurrent CDI
  • Diagnostic criteria met within 8 weeks of initial diagnosis after symptom resolution

Outcomes in CA-CDI

- Hospitalization: 40%
- Severe CDI: 20%
- Severe Complicated: 4%
- Treatment failure: 20%
- Recurrence: 28%

*Metro 22% vs vancomycin 7%
CA-CDI: Less Severe than HA-CDI

* p<0.001
Elderly with CA-CDI have worse Outcomes

* p<0.001

- Severe
- Hospitalized for CA-CDI

Green bars: Age < 65
Blue bars: Age > 65

©2010 MFMER | slide 43
### Predictors of Hospitalization (Univariate)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hospitalized (n=63)</th>
<th>Not hospitalized (n=94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>64</td>
<td>44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>79%</td>
<td>73%</td>
<td>0.45</td>
</tr>
<tr>
<td>Charlson Comorbidity index</td>
<td>2.06</td>
<td>0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Antibiotic exposure</td>
<td>68%</td>
<td>85%</td>
<td>0.01</td>
</tr>
<tr>
<td>Severe CDI (%)</td>
<td>33%</td>
<td>12%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

No differences in initial treatment, treatment failure or recurrence
Predictors of Hospitalization (Multivariate)

* Unit odds ratio for every 10-year increase in age
** Unit odds ratio for every one-unit increase in Charlson Comorbidity index
Predictors of Hospitalization - Summary

• Older patients, more comorbidities, elevated WBC or creatinine more likely to require hospitalization

• Prior antibiotic exposure less in those who required hospitalization
  • ?novel risk factor(s)
Age Predicts Severe CA-CDI

Severe CDI

- Occurred in 20% of CA-CDI
- Older (median 69.5 vs 50 yrs, p=0.001)
- No differences in
  - Gender
  - Prior antibiotic exposure
  - Charlson Comorbidity index
Age and Comorbidities Predict Severe-Complicated CA-CDI

Severe-complicated CDI

- Occurred in 7 (4%) of all CA-CDI (4 deaths)
- Older (80 vs 49 yrs, p=0.006)
- Higher Comorbidity Index (5.8 vs 1.1, p<0.0001)
- No differences
  - Gender
  - Prior antibiotic exposure
CA-CDI Outcomes in children

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CA-CDI</th>
<th>HA-CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3%</td>
<td>26%</td>
</tr>
<tr>
<td>Complicated</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>17%</td>
<td>26%</td>
</tr>
</tbody>
</table>

24% | 3% vs 26% | 4.3% | 17% vs 26%
Summary

• 10-40% of CDI is CA

• Compared to HA-CDI, CA-CDI were
  • Younger, more often female
  • Less likely to have severe infection
  • No differences in response or recurrence rates
  • Less likely to have antibiotic (PPI) exposure
    • Suggests other undefined risk factors
  • Food, water, soil, animals?
Summary

• 20-45% of CA-CDI requires hospitalization

• Hospitalized CA-CDI
  • Older, more comorbidities, higher likelihood of severe CDI

• Severe CDI uncommon in young CA-CDI, more common in elderly CA-CDI
Conclusions

• Incidence of CA-CDI is increasing
• Many without antibiotic exposure
• Clinicians must broaden mindset on CDI risk factors
• CA-CDI can be associated with complications and poor outcomes
• Age, comorbidities, fever, elevated WBC, rising creatinine predict poor outcomes
• Patients with these risk factors should be managed aggressively and monitored closely