“Clostridium difficile: what are the best preventive and therapeutic options”

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19th INFECTION AND SEPSIS SYMPOSIUM, Porto 26/28 Fevereiro 2014
“Clostridium difficile: - what are the best preventive and therapeutic options”

DISCLOSURES:

Travel Grants and Speaker Honoraria: Alere, Abbvie, BMS, Gilead, Janssen-Cilag, MSD

Advisory Boards: BMS, Gilead, Janssen-Cilag
“Clostridium difficile: - what are the best preventive and therapeutic options”

OVERVIEW

1. *Clostridium difficile* Associated Diarrhea (CDAD): - HOW AND WHY DOES IT OCCUR?

2. PREVENTIVE OPTIONS:
   - focus on the PATIENT
   - focus on the ENVIRONMENT

3. THERAPEUTIC OPTIONS

4. TAKE HOME MESSAGES
CDAD - HOW AND WHY DOES IT OCCUR?

- Hospitalized patient
- Exposure to *Clostridium difficile*
  - Contaminated HCW hands
  - Contaminated environment
- ABs (+ PPIs)
- Alteration of gut flora (antibiotics)
- > 65 years
- Comorbidities
  - Severe underlying disease
  - Immunosuppression
- Acquisition of *Clostridium difficile*
- Clinical risk factors
  - Insufficient immune response
- CDAD
- Asymptomatic colonization

*Clostridium difficile*: pathophysiology and natural history - T.G. Frazier, J.F. Swiencicki

[www.clevelandclinicmeded.com](http://www.clevelandclinicmeded.com)
Diverse Sources of C. difficile Infection Identified on Whole-Genome Sequencing
Eyre DW, Cule ML, Wilson DJ, et al

Use of Multilocus Variable Number of Tandem Repeats Analysis Genotyping to Determine the Role of Asymptomatic Carriers in Clostridium difficile Transmission
Curry SR, Muto CA, Schlackman JL, et al
Clin Infect Dis. 2013;57:1094-1102


"...45% OF C. DIFFICILE CASES WERE GENETICALLY DISTINCT FROM ALL PREVIOUS CASES...
...asymptomatic carriers appear to have played an important role in transmission...”

“Standard teaching is that Clostridium difficile infection ...reflects a failure of infection control, but IT MAY BE MORE CLOSELY RELATED TO ANTIBIOTIC CONTROL. ...”

CDAD - HOW AND WHY DOES IT OCCUR?
RESERVOIRS: PATIENTS and CONTAMINATED ENVIRONMENT

LOW SUSPICION
LOW SENSITIVITY TESTS

LATE DIAGNOSIS

MULTIPLE ANTIBIOTICS
Continuous PPIs

PATIENT

Overcrowded wards, insufficient staff and equipments

Non compliance with good practice procedures

Spores persistence/difficult irradication

INADEQUATE ISOLATION (local, duration)

High risk patients, readmissions, recurrent CDAD

ENVIRONMENT

INSTITUTIONAL COOPERATION

Hand Hygiene

Isolation/Contact Precautions

Cleaning and Desinfection

EDUCATE

MOTIVATE

STAFF

EARLY DIAGNOSIS

Adequate use of ABs and PPIs

GLOVES, PROTECTIVE CLOTHING, INDIVIDUAL ROOM OR COHORT

SODIUM HYPOCHLORITE

HYDROGEN PEROXIDE AFTER DISCHARGE?

WATER AND SOAP

SURVEILLANCE

ENVIRONMENT

PATIENT

ANTIMICROBIAL STEWARDSHIP

OPTIMIZE DIAGNOSIS

PROTOCOL APPROACH FOR PATIENT WITH DIARRHEA

Guide to preventing clostridium difficile infections, APIC 2013 www.apic.org
Outbreak of *Clostridium difficile* PCR ribotype 027 - the recent experience of a regional hospital

Mónica Oleastro¹, Marta Coelho², Marília Gião², Salomé Coutinho², Sandra Mota³, Andrea Santos¹, João Rodrigues¹, Domitília Faria²

*(Waiting acceptance to be published)*

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Figure 5 – Evolution of the consumption of ceftriaxone and levofloxacin in the hospital from the third trimester of 2011 to the first semester of 2013.
“...The risk of acquiring *Clostridium difficile*, methicillin resistant *Staphylococcus aureus*, and multidrug-resistant gram-negative rods individually was reduced, but not significantly.”

**COMMENTS:**

- **BACTERIAL RECONTAMINATION - EARLY AND INEVITABLE**...
- **HIGH ANTIBIOTIC PRESSURE?**
- **COMPLIANCE WITH OTHER INFECTION CONTROL MEASURES?**
THERAPEUTIC OPTIONS

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Christina M. Surawicz, MD¹, Lawrence J. Brandt, MD², David G. Binion, MD³, Ashwin N. Ananthakrishnan, MD, MPH⁴, Scott R. Curry, MD⁵, Peter H. Gilligan, PhD⁶, Lynne V. McFarland, PhD⁷, Mark Mellow, MD⁸ and Brian S. Zuckerbraun, MD¹⁰

*Am J Gastroenterol* 2013;108: 478-498

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast¹, M. P. Bauer², E. J. Kuijper³, on behalf of the Committee⁴

*Clin Microbiol Infect* 2014;20(Suppl.2):I-6

[www.escmid.org](http://www.escmid.org)
THERAPEUTIC OPTIONS

• Treatment strategies depend on the severity of the disease

• Identify early clinical markers of severity

Derivation and validation of a simple clinical bedside score (ATLAS) for Clostridium difficile infection which predicts response to therapy

“... These variables include: age, treatment with systemic antibiotics, leucocyte count, albumin and temperature (ATLAS).” (score 0 to 10)

Miller MA, Louie T, Mullane K et al BMC Infect Dis 2013;13:148  
www.biomedcentral.com
THERAPEUTIC OPTIONS

“... the continuation of non C. difficile antibiotics and use of PPIs in patients diagnosed with CDAD are associated with unfavorable clinical outcomes...”


“...26% of patients received only unnecessary antimicrobials, and 45% of total non-CDI antimicrobial days included unnecessary antimicrobials.”

THERAPEUTIC OPTIONS

GENERAL MEASURES:

• 1st STOP UNNECESSARY ANTIBIOTICS AND PPIs

• Avoid anti-motility drugs

• Oral or enteric feeding should be continued (if no ileus or significant abdominal distension)

• Fluid resuscitation, electrolyte replacement
## THERAPEUTIC OPTIONS

### ASSESS SEVERITY AND TREAT ACCORDINGLY

<table>
<thead>
<tr>
<th>MILD</th>
<th>MODERATE/SEVERE</th>
<th>COMPLICATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years, No severe comorbidities</td>
<td>&gt;65 years, fever &gt; 38.5°, hypotension</td>
<td>Leuc &gt; 35000 or &lt; 2000 uL</td>
</tr>
<tr>
<td>Leucocytes &lt; 15000 uL</td>
<td>Pain/abdominal distension</td>
<td>Lactates &gt; 5</td>
</tr>
<tr>
<td>Creatinine &lt; 1.5 mg/dl or &lt; 1.5x baseline</td>
<td>Albumin &lt; 3 mg/dL and at least 1 of following:</td>
<td>Shock</td>
</tr>
<tr>
<td></td>
<td>Leucocytes &gt; 15000 uL</td>
<td>Ileus</td>
</tr>
<tr>
<td></td>
<td>Creat &gt; 1.5 mg ou &gt; 1.5 x baseline</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td></td>
<td>Abdominal plain xR – distension</td>
<td>Perforation</td>
</tr>
<tr>
<td></td>
<td>Fibrosigmoidoscopy or CT scan:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous colitis</td>
<td></td>
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<tr>
<td></td>
<td>/colonic distension</td>
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</table>

- **METRONIDAZOL**
- **VANCOMYCIN** + **SURGERY**

- If need to continue other AB prefer vancomycin or fidaxomicin
- Metronidazol and fidaxomicin may be less effective with 027 ribotype - of importance in outbreaks
ASSESS TREATMENT RESPONSE – stool frequency / stool consistency, parameters of disease severity/no new signs of severe disease

IT MAY TAKE WEEKS FOR STOOL CONSISTENCY AND FREQUENCY TO BECOME ENTIRELY NORMAL, TESTING SHOULD NOT BE DONE TO ASSESS TREATMENT RESPONSE

Failure to respond to metronidazol in 5-7 days change to vancomycin

RATE OF 1st RECURRENCE 10-20%; after 1st recurrence 45-50%

Mortality and recurrences related to continuous use of ABs, PPIs, old age, comorbidities, severe underlying disease, ribotype??
SEVERE DISEASE ORAL ADMINISTRATION NOT POSSIBLE

1st relapse the same as 1st episode, assess severity!

2nd and recurrent relapses – taper or pulse vancomycin, consider fidaxomicin, FECAL TRANSPLANTATION recommended after 3rd relapse

Surgery – total colectomy vs laparoscopic ileal diversion with colonic lavage

Vancomycin oral tube 500mg qid or enema + metronidazol iv

COMPLICATED DISEASE
FECAL MICROBIOTA TRANSPLANTATION

The first documented case of confirmed RCDI treated with FMT was reported in 1983.

"LONG-TERM FOLLOW-UP OF COLONOSCOPIC FECAL MICROBIOTA TRANSPLANT FOR RECURRENT CLOSTRIDIUM DIFFICILE INFECTION"
Brandt LJ, Aroniadis OC, Mellow M et al.
Am J Gastroenterol 2012; 107: 1079 - 87

"...By 2011, approximately 325 cases of FMT had been reported worldwide, including approximately 75% by colonoscopy or retention enema, and 25% by nasogastric or nasoduodenal tube, or by esophagogastroduodenoscopy. Overall, mean cure rates to date are approximately 91% ..."
PROBLEMS WITH AVAILABLE THERAPY:

EFFICACY?...

METRONIDAZOL AND VANCOMYCIN - high rates of relapse/refractory disease
FIDAXOMICIN - no data to support use in severe disease

COST?...

“IS FIDAXOMICIN WORTH THE COST? AN ECONOMIC ANALYSIS”
Sarah Bartsch, Craig A. Umscheid, Neil Fishman. Bruce Y.Lee
Clin Infect Dis, 2013 May 23

PRACTICALITY?...

“FECAL MICROBIOTA TRANSPLANTATION: A PRACTICAL UPDATE FOR THE INFECTIOUS DISEASE SPECIALIST”
T.Moore, A.Rodriguez, J.Bakken
CID (2014)58(4):541-545
THERAPEUTIC OPTIONS

ALTERNATIVE THERAPIES:

TEICOPLANIN - rate of response similar to vancomycin, small series, licensed indication for CDAD since 2013

TIGECYCLINE IV - severe, refractory disease, limited case reports

IMMUNOGLOBULINS IV - reported to be successful in small series, could help if hypogammaglobulinemia present

PROBIOTICS (saccharomyces boulardii, lactobacillus) - insufficient evidence, contra-indicated in immunodepressed and CVC

Toxin binding resins - colestipol
Polymers - tolevamer
Fusidic acid
Nitazoxanide
Rifaximin
THERAPEUTIC OPTIONS

SUMMARY:

Vancomycin = fidaxomicin B-II

Vancomycin A-I

THERAPEUTIC OPTIONS

FUTURE OPTIONS:

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: ‘RePOOPulating’ the gut

Petrof E.O. et al. Microbiome 2013;1:3
www.microbiomejournal.com

Fecal transplant pills effective for *C difficile*


“In vitro activity of CADAZOLID against clinically relevant *Clostridium difficile* isolates and in an in vitro gut model of *C. difficile* infection”

“Clostridium difficile: what are the best preventive and therapeutic options”

**TAKE HOME MESSAGES:**

- Prevent is better than treat!
- Practice good antimicrobial stewardship
- Optimize clinical and diagnostic tools
- Infection control bundles and treatment protocols
- Continuous education and motivation of HCWs
- Close communication with primary care and other healthcare facilities, report cases, use same bundles/protocols
- Keep on surveillance – N cases/10 000 patient days (ESCMID)
AKNOWLEDGEMENTS

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THANK YOU!

And don´t forget FANTAS!

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