Double trouble:

C. difficile in IBD

Shomron Ben-Horin MD
IBD Service, Gastroenterology Department
Sheba Medical Center, Tel-Aviv University, Israel
Introduction

IBD denotes chronic immune-driven inflammatory diseases of the digestive tract:

- Crohn’s Disease
- Ulcerative Colitis
- Indeterminate colitis
IBD manifestations

Crohn’s disease:
(Inflammation anywhere in GI tract, penetrates through intestinal wall)

- Inflammatory
- Penetrating (abscess, fistula)
- Stricturing (intestinal obstruction)

Ulcerative colitis:
(Inflammation restricted to the colon and only of mucosa !)

- Inflammatory
Normal Colon
Crohn’s colitis
Capsule endoscopy

Ulcer on capsule

Ulcer on colonoscopy
Infections and IBD flares

Many enteric pathogens can precipitate and/or simulate an IBD flare

Screening flaring patients for infectious agents has been advocated

Mylonaki M, Eur J Gastroenterol Hepatol 2004
Epidemiology of C. difficile in IBD

Widely varying incidence in IBD patients:

- Hospitalized IBD patients .......... 1 to 5.7% \(^{(1-5)}\)
- Relapsing outpatients .............. 5.5 to 60% \(^{(6-8)}\)
- Newly diagnosed pediatric IBD ..... 47% \(^{(9)}\)

References:

[1] – Ott C, Digestion 2011

Epidemiology of C. difficile in IBD

Nguyen GC, Am J Gastroenterol 2008
Rodemann JF, Clin Gastroenterol Hepatol 2007
Ananthakrishnan AN, Gut 2008
Bossuyt P, J Crohn Colitis, 2009
Repeated tests for CDAD

Because of rather low sensitivity of EIA, some ID and GI specialists advocate repeat testing of negative cases.

Mylonakis E, Arch Intern med 2001
Binion D, Best Pract Gastroenterol 2011
Manabe YC, Ann Intern Med 1995
Repeated tests for negative results lead to reduced PPV (because positives are taken out)

1\textsuperscript{st} test.......PPV = 75%
2\textsuperscript{nd} test......PPV = 45%
3\textsuperscript{rd} test.......PPV = 25%
4\textsuperscript{th} test........PPV = 5%

Litvin M, Infect Control Hosp Epidemiol 2009
Peterson L, Ann Intern Med 2009
Predominantly in colonic IBD (UC, Crohn’s colitis)
Immuno-suppressants – inconclusive predisposition
Only 30-60% with prior antibiotic exposure

Pascarella F, J Pediatr 2009
Issa M, Clin Gastroenterol Hepatol 2007
Nguyen GC, Am J Gastroenterol 2008
Kelsen JR, Inflamm Bowel Dis 2011
Impact of C. difficile on IBD: In-hospital mortality
Impact of C. difficile on IBD: In-hospital mortality

In two more studies: Odds ratio of 3.9 to 6.3 for dying in hospital

Ananthakrishnan AN, Gut 2008
Jen MH, APT 2011
Nguyen GC, Am J Gastroenterol 2008
Impact of C. difficile on IBD: Bowel surgery

In two more studies: Odds ratio 1.8 for surgery in one, but no increased colectomy in another

Ananthakrishnan AN, Gut 2008
Ott C, Digestion 2011
Kariv R, J Crohn Colitis, 2011
Manifestations of C. difficile in IBD

Indistinguishable from “regular” IBD flare:
   Bloody diarrhea common
   Pseudomembranes in less than 15% of IBD-CDAD

Issa M, Clin Gastroenterol Hepatol 2007
Ben-Horin S, J Crohn Colitis 2010
European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

ECCO Statement 01 70
Screening for C. difficile is recommended at every flare in patients with colonic disease [EL3, RGD].
What is the cause of symptoms in IBD-CDAD?
What is the cause of symptoms in IBD-CDAD?

Is it C. difficile infection in quiescent IBD?
What is the cause of symptoms in IBD-CDAD?

Is it *C. difficile* infection in quiescent IBD?

Is it *C. difficile* infection also triggering IBD flare? (2 simultaneous processes)
What is the cause of symptoms in IBD-CDAD?

Is it *C.* difficile infection in quiescent IBD?

Is it *C.* difficile infection also triggering IBD flare? (2 simultaneous processes)

Is it IBD flare with *C.* difficile bystander colonization?
What is the cause of symptoms in IBD-CDAD?

Survey of 169 North American Gastroenterologists:

- Isolated IBD flare: 65
- Isolated infection: 9
- Simultaneous C. difficile & IBD flare: 18
- Other explanations: 8

Yanai H & Ben-Horin S, Inflamm Bowel Dis 2011
Is it *C. difficile* colonization or infection?

In 4143 prospectively tested (non-IBD) hospitalized patients:
- 3% had asymptomatic *C. difficile* colonization
- 2.8% had *C. difficile* infection

Loo VG, N Engl J Med 2011
Is it *C. difficile* colonization or infection?

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- 3% had asymptomatic *C. difficile* colonization
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Presence of *C. difficile* with diarrhea = Infection
Presence of *C. difficile* without diarrhea = Colonization

Loo VG, N Engl J Med 2011
Is it *C. difficile* colonization or infection?

Presence of *C. difficile* **with** diarrhea = Infection
Presence of *C. difficile* **without** diarrhea = Colonization

But flaring IBD patients all have diarrhea when tested – so perhaps they have *C. difficile* colonization (not infection)??
Is it C. difficile colonization or infection?

Presence of C. difficile with diarrhea = Infection
Presence of C. difficile without diarrhea = Colonization

But flaring IBD patients all have diarrhea when tested – so perhaps they have C. difficile colonization (not infection)??

And if so, does C. difficile colonization only marks a worse IBD??
C. difficile in IBD: pathogen or By-stander?

High rate of Toxicogenic C. diff cultured in asymptomatic IBD out-patients (8.2% Vs. 1% in healthy controls, p=0.02)

None developed CDAD after 6 months follow-up

Clayton EM, Am J Gastroenterol 2009
Is C. diff a marker of severe IBD or a trigger of it?

More IBD-CDAD patients require therapy escalation within 6-12 months after hospitalization compared to those with IBD alone (OR 2.3-4.2, P<0.001)

Risk of C. difficile infection increases in severe IBD

Banaszkiewicz A, Inflamm Bowel Dis 2011
Risk of C. difficile infection increases in severe IBD

Banaszkiewicz A, Inflamm Bowel Dis 2011
Risk of C. difficile infection increases in severe IBD

Banaszkiewicz A, Inflamm Bowel Dis 2011
So … does CDAD make IBD worse or worse IBD have more C. difficile?

The hen and egg dilemma! – Who came first?
We still have to find the chicken that started it all.....
Treatment of CDAD
Treatment of CDAD

Discontinuation of offending antibiotics

C. difficile-antibiotics:
- Metronidazole
- Vancomycin
- Fidaxomycin

- Nitazoxanide
- Bacitracin
- Teicoplanin
- Fusidic acid
- Rifaximin

Similar efficacy to Vanco in small scale studies – Non-inferiority not proven
Treatment of severe CDAD

Vanco is superior to Metro in severe disease

Zar F, Clin Infect Dis 2007
A flaring hospitalized IBD patient with C. difficile…

Should we be giving only antibiotics or antibiotics+steroids?

(Is it only CDAD or is it CDAD triggering IBD?)
Therapeutic choices – Survey of 169 American Gastroenterologists

Antibiotics alone: 61%
Corticosteroids + antibiotics: 39%

Yanai H, Inflamm Bowel dis 2011
European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

ECCO Statement OL76
In CDAD it remains to be established whether concomitant therapy with immunomodulators should be withheld [EL5, RG D]
Outcome of combination AB+IM vs. AB alone

Multi-center retrospective European study of 155 hospitalized IBD-CDAD patients treated by AB or AB+IM

12/155 met composite adverse outcome (colectomy/Death)

Ben-Horin S, Clin Gastroenterol Hepatol 2009
Results – Primary outcome

Ben-Horin S, Clin Gastroenterol Hepatol 2009
61 YO Crohn’s colitis patient
A flare not-responsive to oral prednisone
C. Difficile + in stool. On sigmoidoscopy:
Food for thought….

61 YO Crohn’s colitis patient
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Prednisone stopped. Metro initiated. 5 days improvement
Then… fever again, increased bowel movements
Re-endoscoped:

Berdichevski T & Ben-Horin S, Endoscopy 2010
Food for thought….

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Then… fever again, increased bowel movements
Re-endoscoped:

C. Difficile negative. >> response to IV hydrocortisone (+Metro)

Berdichevski T & Ben-Horin S, Endoscopy 2010
Take home messages

C. difficile is (probably) more common in colonic IBD than general hospitalized population

C. difficile causes / marks a more severe IBD outcome and increased mortality

Optimal therapy for CDAD-IBD remains to be determined (Antibiotics+corticosteroids or antibiotics alone)
Thank you for your attention