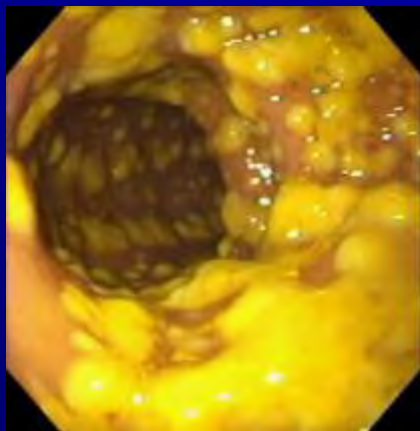


Double trouble:

C.difficile in IBD



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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)

Strictureing (intestinal obstruction)

## Ulcerative colitis:

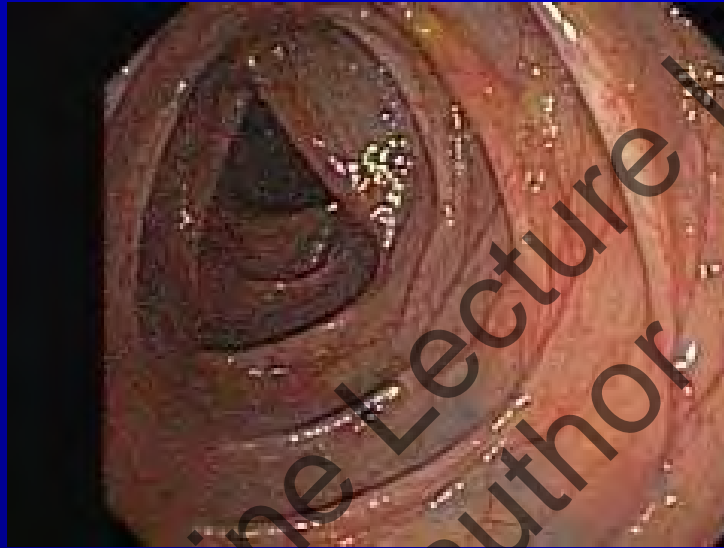
(Inflammation restricted to the colon and only of mucosa !)

Inflammatory

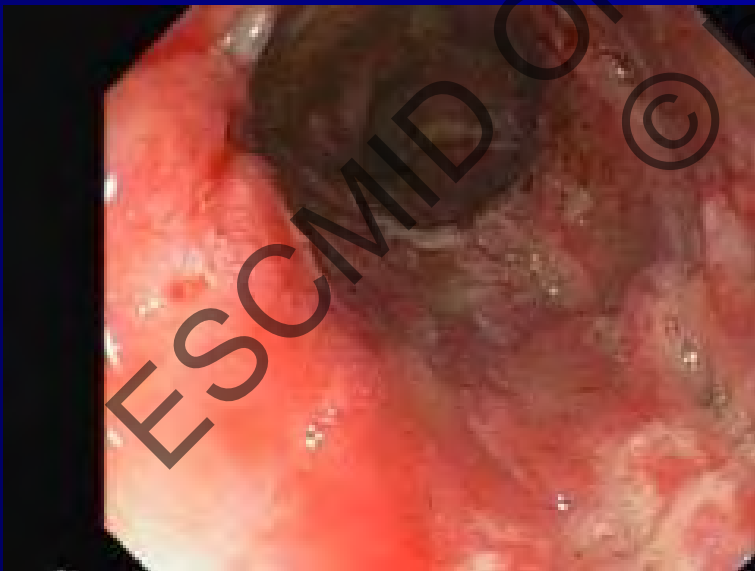
## Normal Colon



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Crohn's colitis

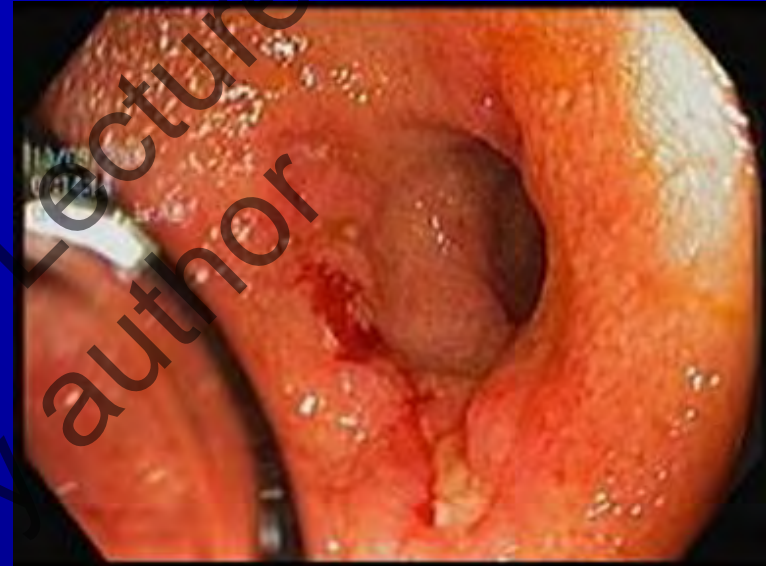


# Capsule endoscopy

Ulcer on capsule



Ulcer on colonoscopy



07 Jul 08



PillCam® COLON

# Infections and IBD flares

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

Screening flaring patients for infectious agents has been advocated



# Epidemiology of C.difficile in IBD

Widely varying incidence in IBD patients:

Hospitalized IBD patients ..... 1 to 5.7%<sup>(1-5)</sup>

Relapsing outpatients..... 5.5 to 60%<sup>(6-8)</sup>

Newly diagnosed pediatric IBD.....47%<sup>(9)</sup>

[1] – Ott C, Digestion 2011

[2] - Nguyen GC, Am J Gastroenterol 2008

[3] – Navarro-Llavat M, digestion 2009

[4] - Ananthakrishnan AN, Gut 2008

[5] – Rodemann JF, CGH 2007

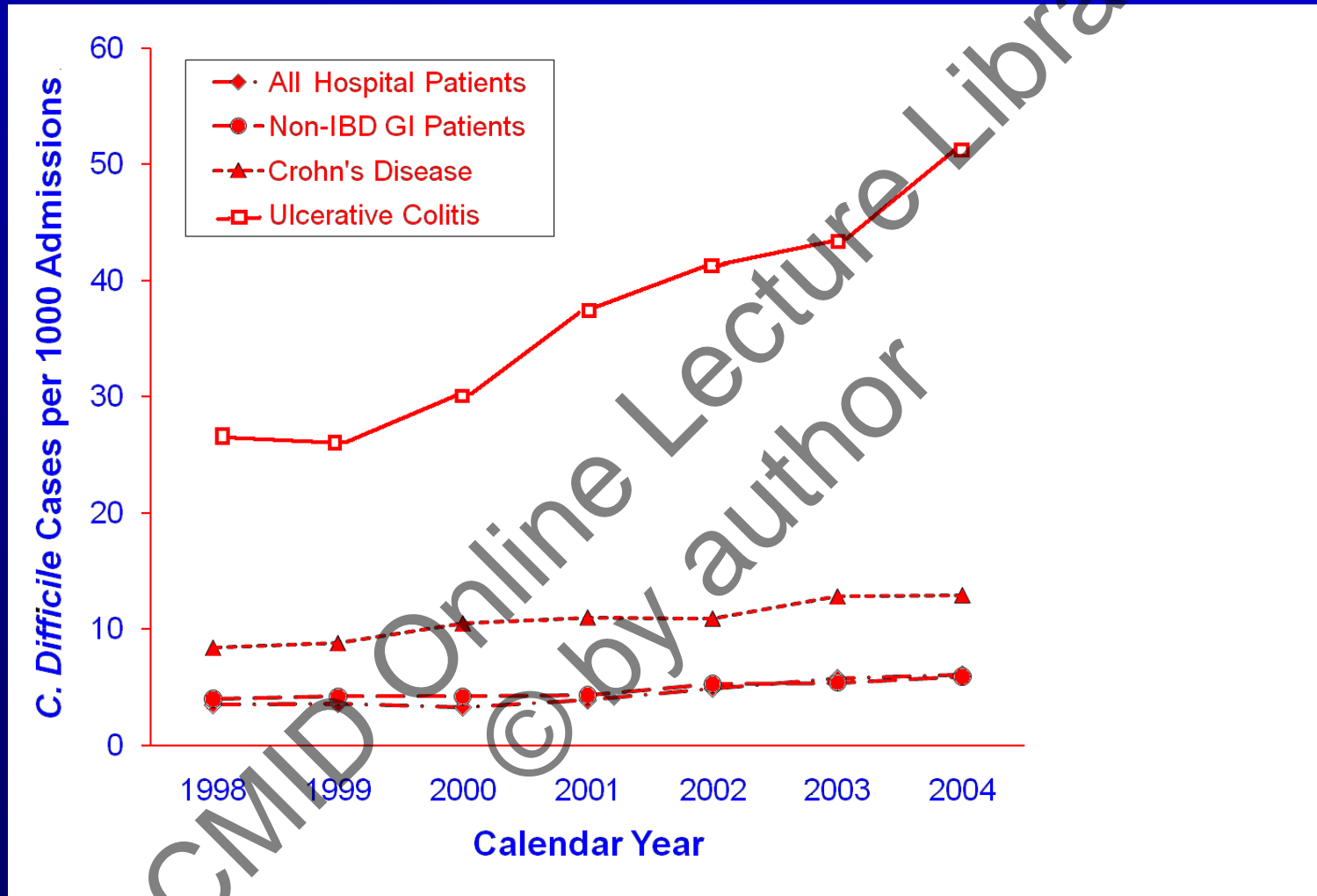
[6] – Wultanska D, Eur J Clin Microbiol Infect Dis 2010

[7] – Meyer AM, J Clin Gastro 2004

[8] – Mylonaki M, Eur J Gastroenterol Hepatol 2004

[9] – Banaszkiwicz A, Inflamm Bowel Dis 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 CDAD

Repeated tests for negative results lead to reduced PPV  
(because positives are taken out)

1<sup>st</sup> test.....PPV = 75%

2<sup>nd</sup> test.....PPV = 45%

3<sup>rd</sup> test.....PPV = 25%

4<sup>th</sup> test.....PPV = 5%

# Epidemiologic peculiarities of C.difficile in IBD

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

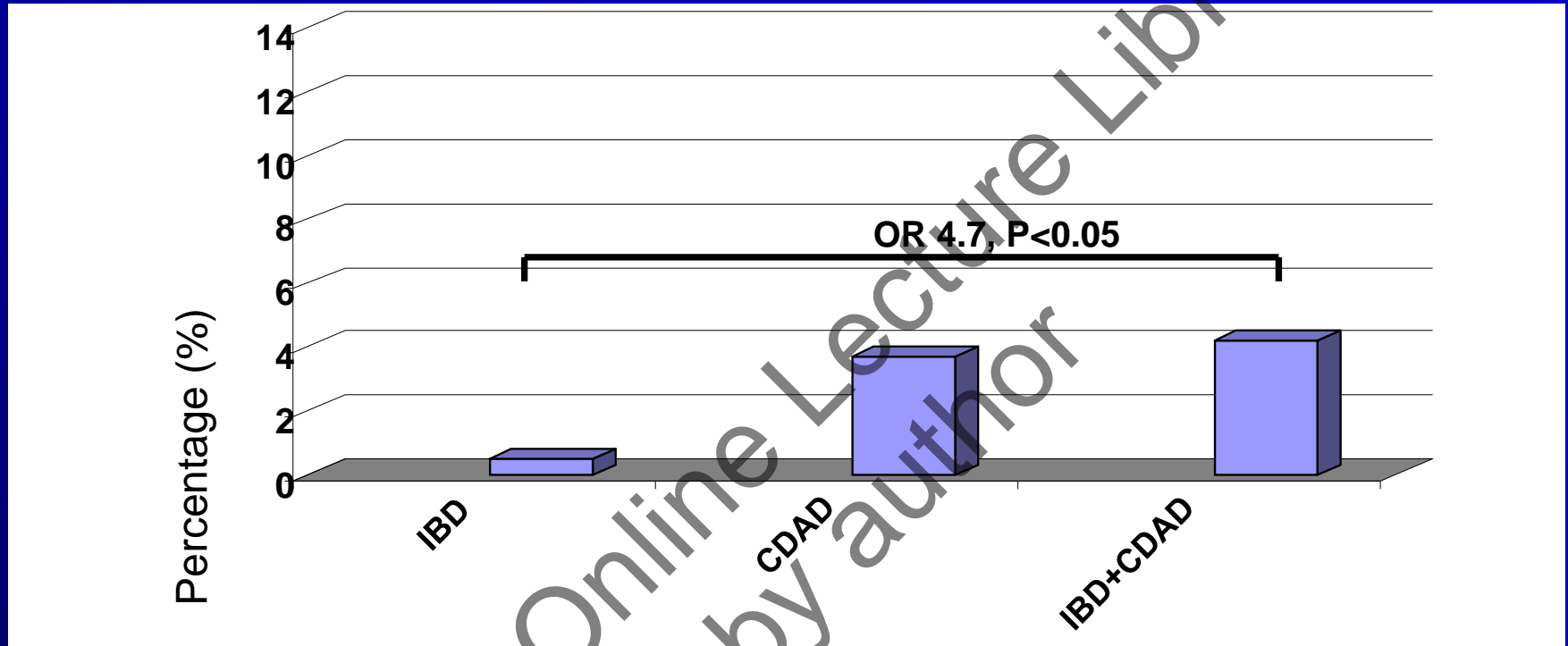
Nguyen GC, Am J Gastroenterol 2008

Kelsen JR, Inflamm Bowel Dis 2011

# Impact of C.difficile on IBD: In-hospital mortality

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# Impact of C.difficile on IBD: In-hospital mortality



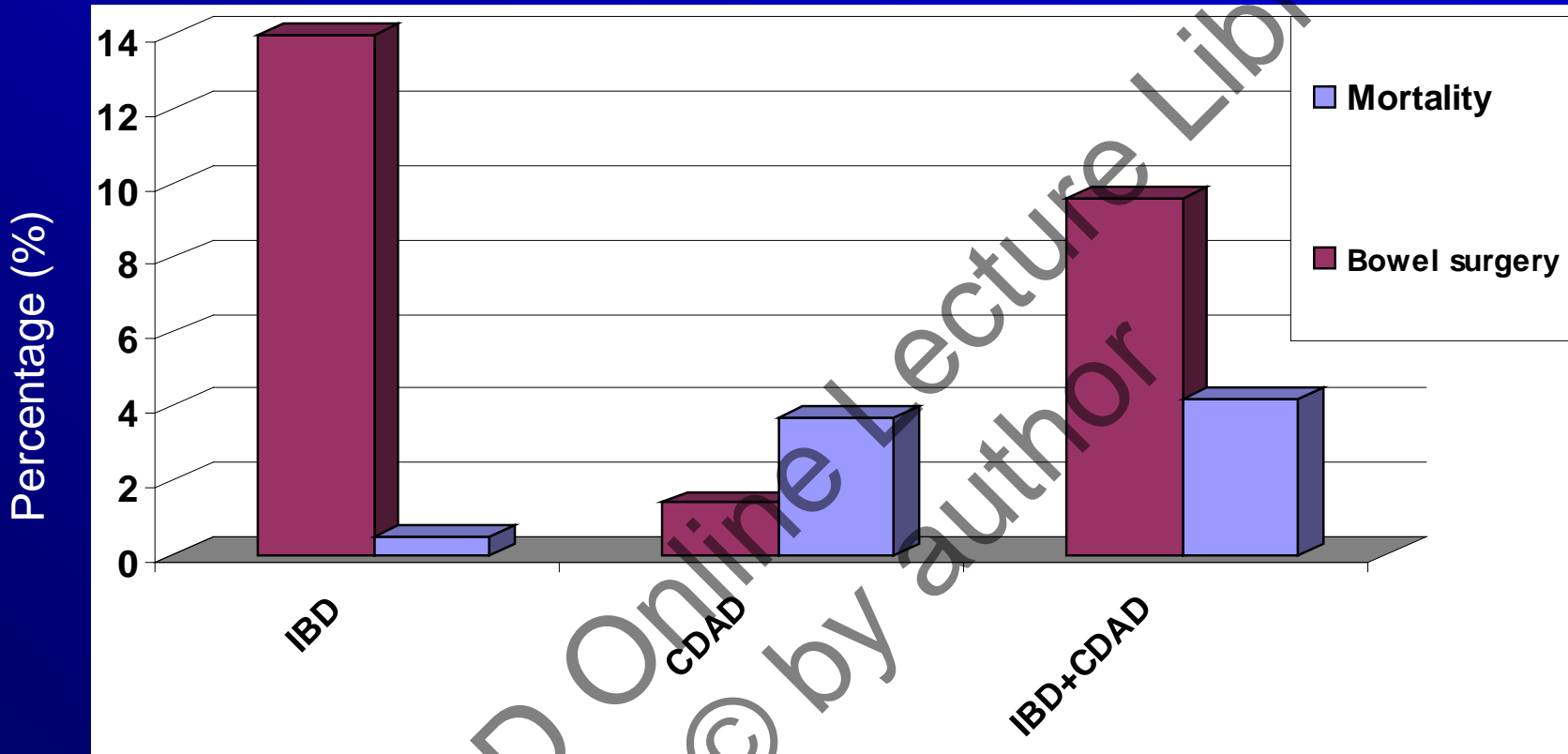
In two more studies: Odds ratio of 3.9 to 6.3 for dying in hospital

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



# Manifestations of C.difficile in IBD

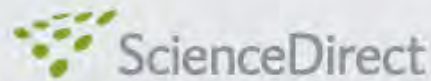
Indistinguishable from “regular” IBD flare:

Bloody diarrhea common

Pseudomembranes in less than 15% of IBD-CDAD



available at [www.sciencedirect.com](http://www.sciencedirect.com)



SPECIAL ARTICLE

## 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 ?

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What is the cause of symptoms in IBD-CDAD ?

Is it C.difficile infection in quiescent IBD ?

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# 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 ?

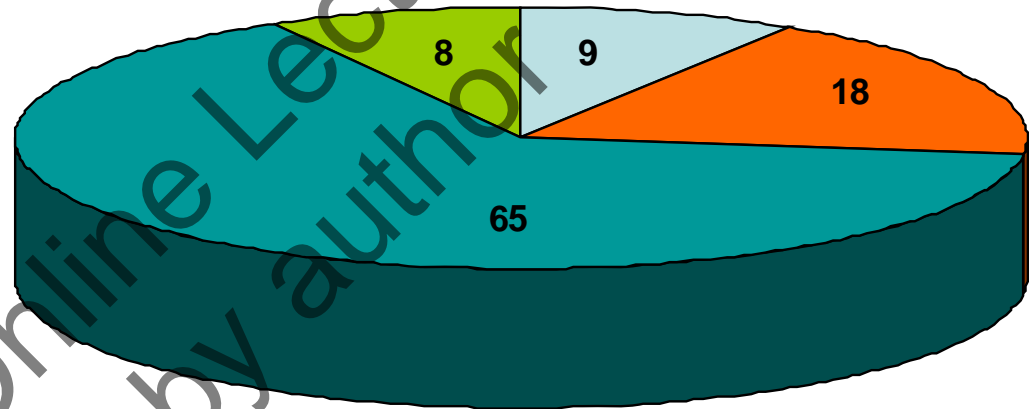
Is it C.difficile infection also triggering IBD flare ?  
(2 simultaneous processes )

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
- Isolated infection
- Simultaneous C.difficile & IBD flare
- Other explanations



# 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



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Presence of *C.difficile* with diarrhea = Infection

Presence of *C.difficile* without diarrhea = Colonization

# 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

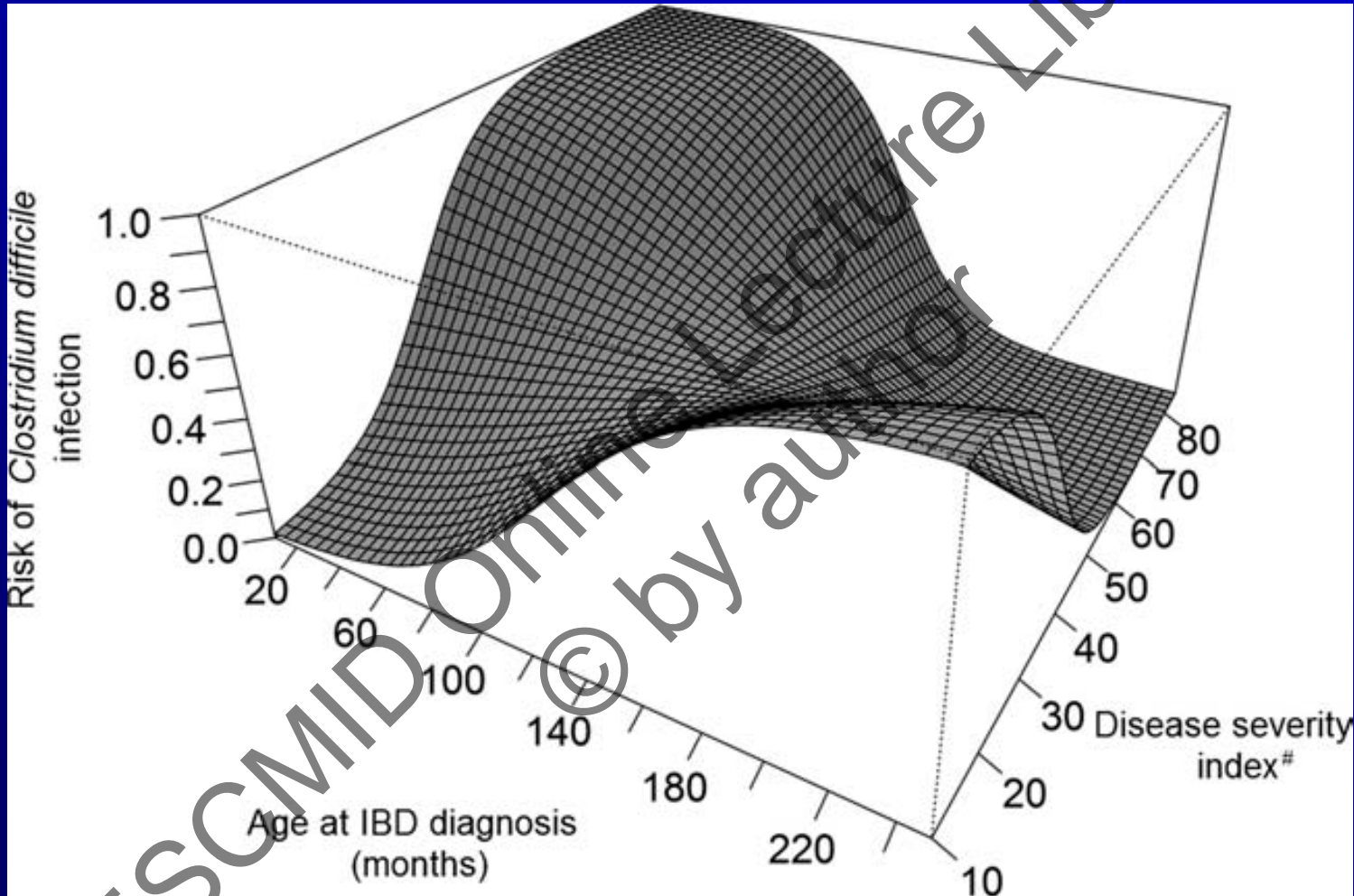
# Is C.diff a marker of severe IBD or a trigger of it ?

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

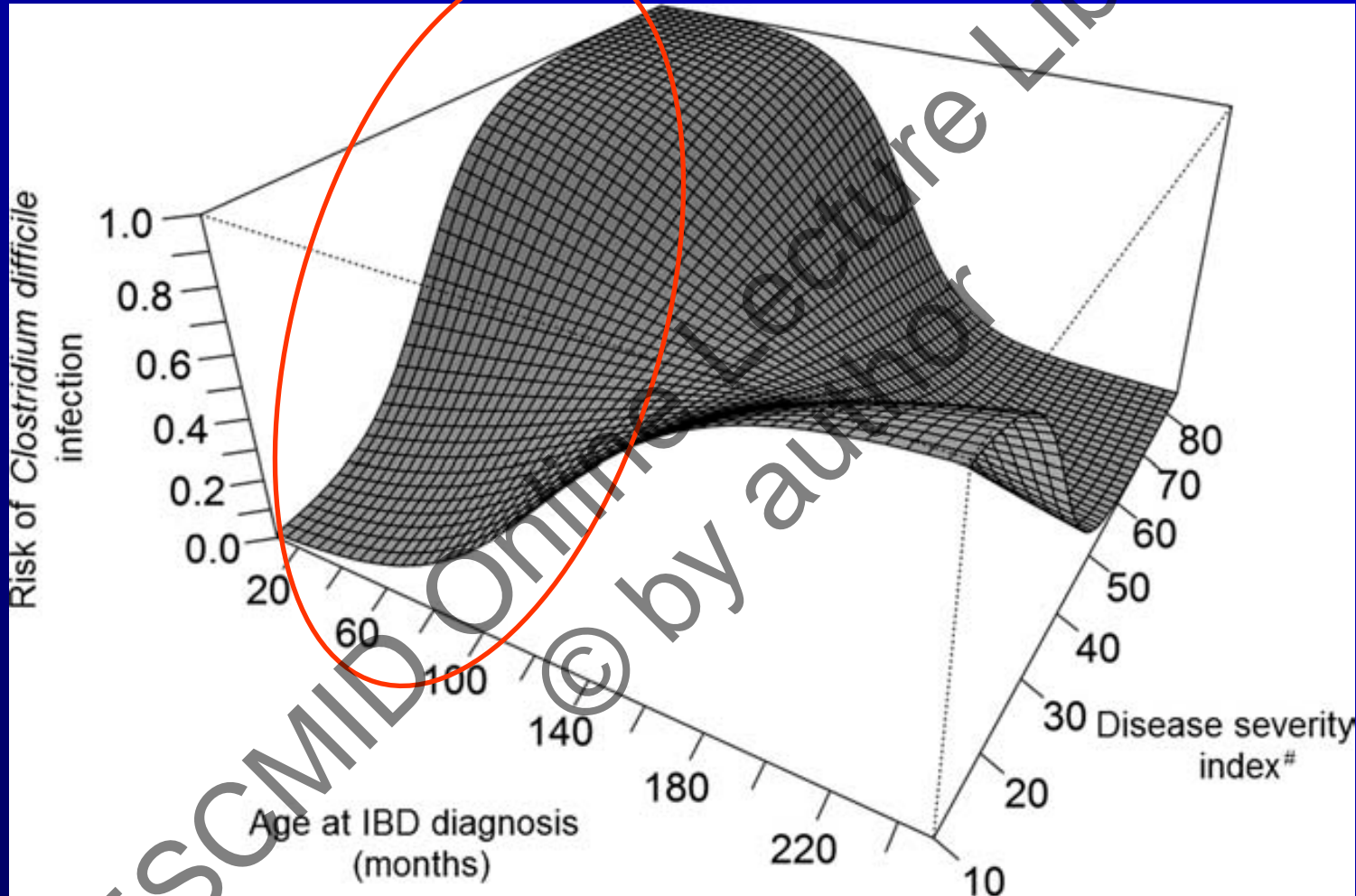
[1] – Kelsen JR Inflamm Bowel Dis 2010

[2] – Navaneethan U, J Crohn Colitis 2012

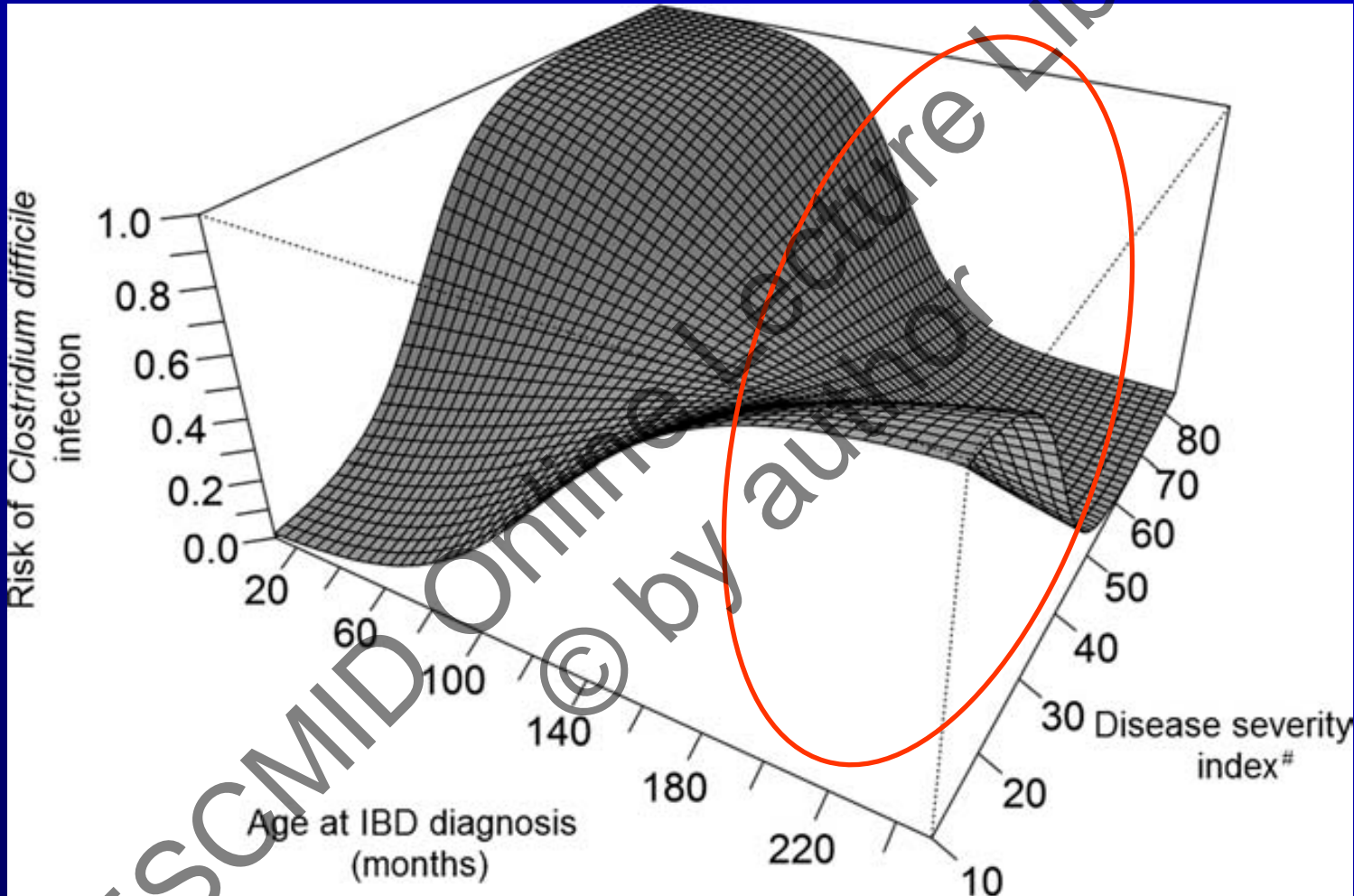
# Risk of C.difficile infection increases in severe IBD



# Risk of C.difficile infection increases in severe IBD



# Risk of C.difficile infection increases in severe IBD





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.....



By: Kyle Bean

# Treatment of CDAD

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# Treatment of CDAD

Discontinuation of offending antibiotics

C.difficile-antibiotics:

Metronidazole

Vancomycin

Fidaxomicin

Nitazoxanide

Bacitracin

Teicoplanin

Fusidic acid

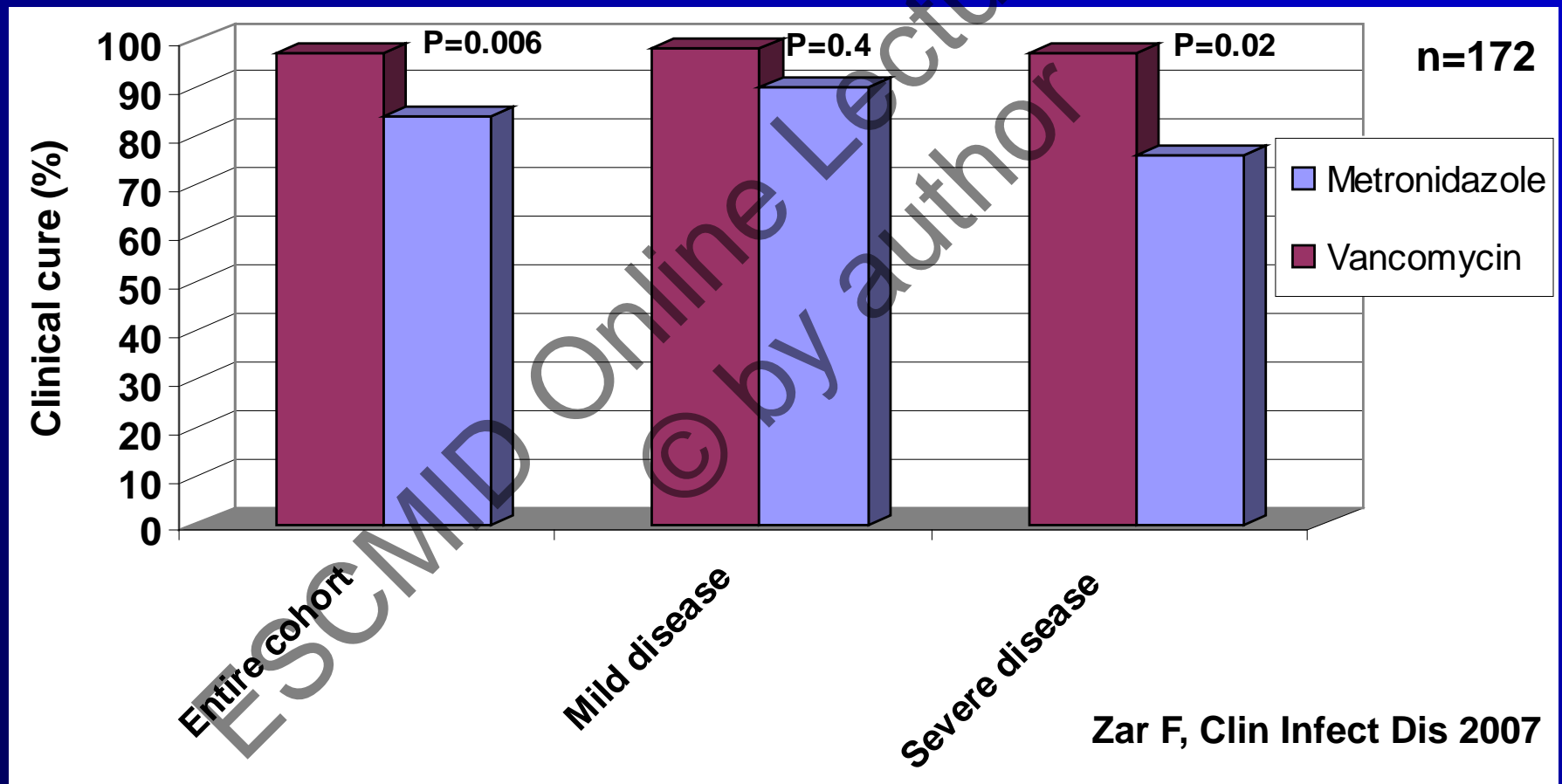
Rifaximin



Similar efficacy to Vanco in small scale studies – Non-inferiority not proven

# Treatment of severe CDAD

Vanco is superior to Metro in severe disease



# Treatment of CDAD in IBD

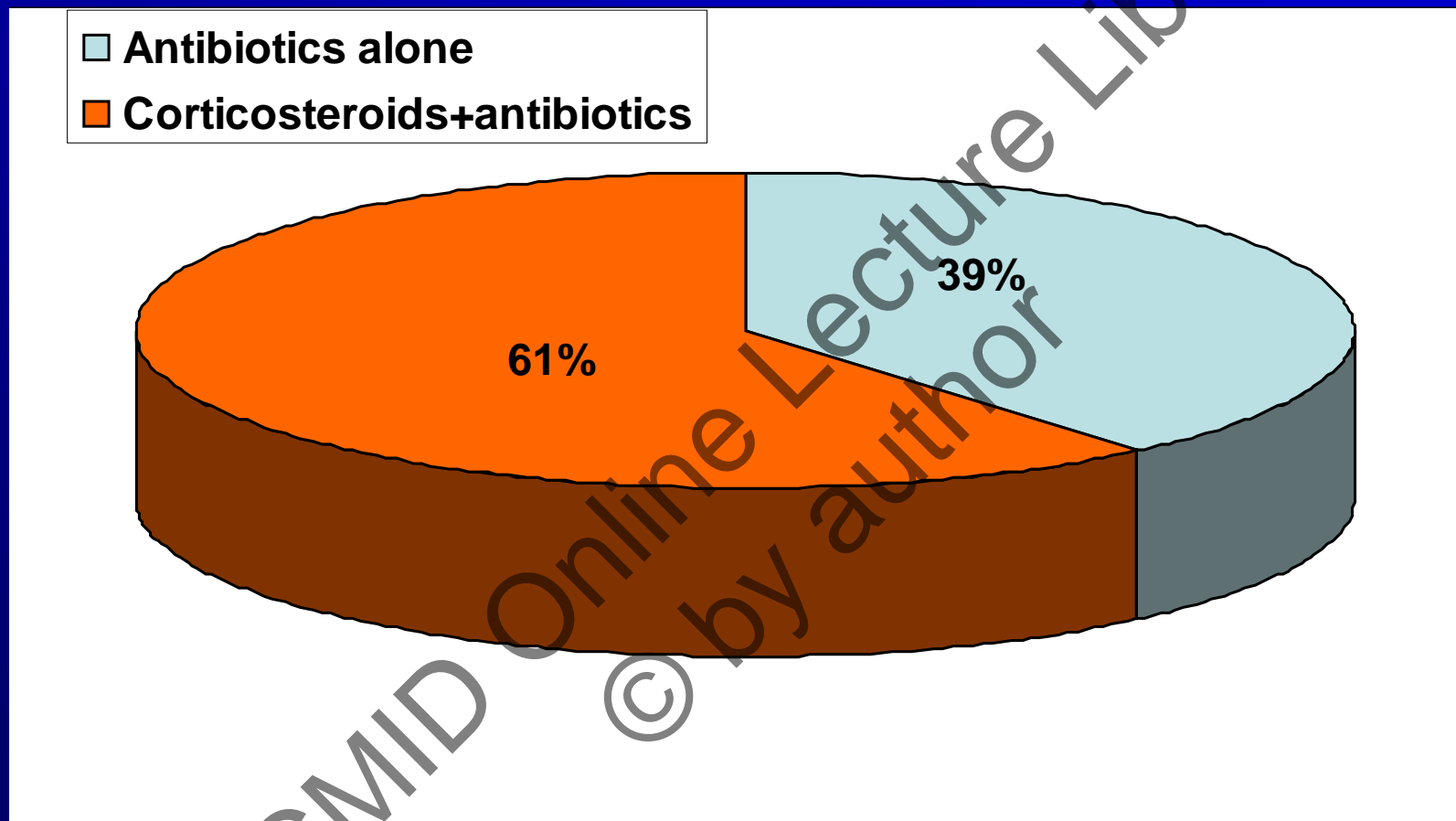
A flaring hospitalized IBD patient with C.difficile...

Should we be giving only antibiotics or antibiotics+steroids ?

(Is it only CDAD or is it CDAD triggering IBD?)

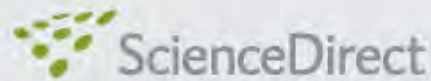
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# Therapeutic choices – Survey of 169 American Gastroenterologists





available at [www.sciencedirect.com](http://www.sciencedirect.com)



SPECIAL ARTICLE

## European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease

ECCO Statement OI 75

In CDAD it remains to be established whether concomitant therapy with immunomodulators should be withheld [EL5, RG D]



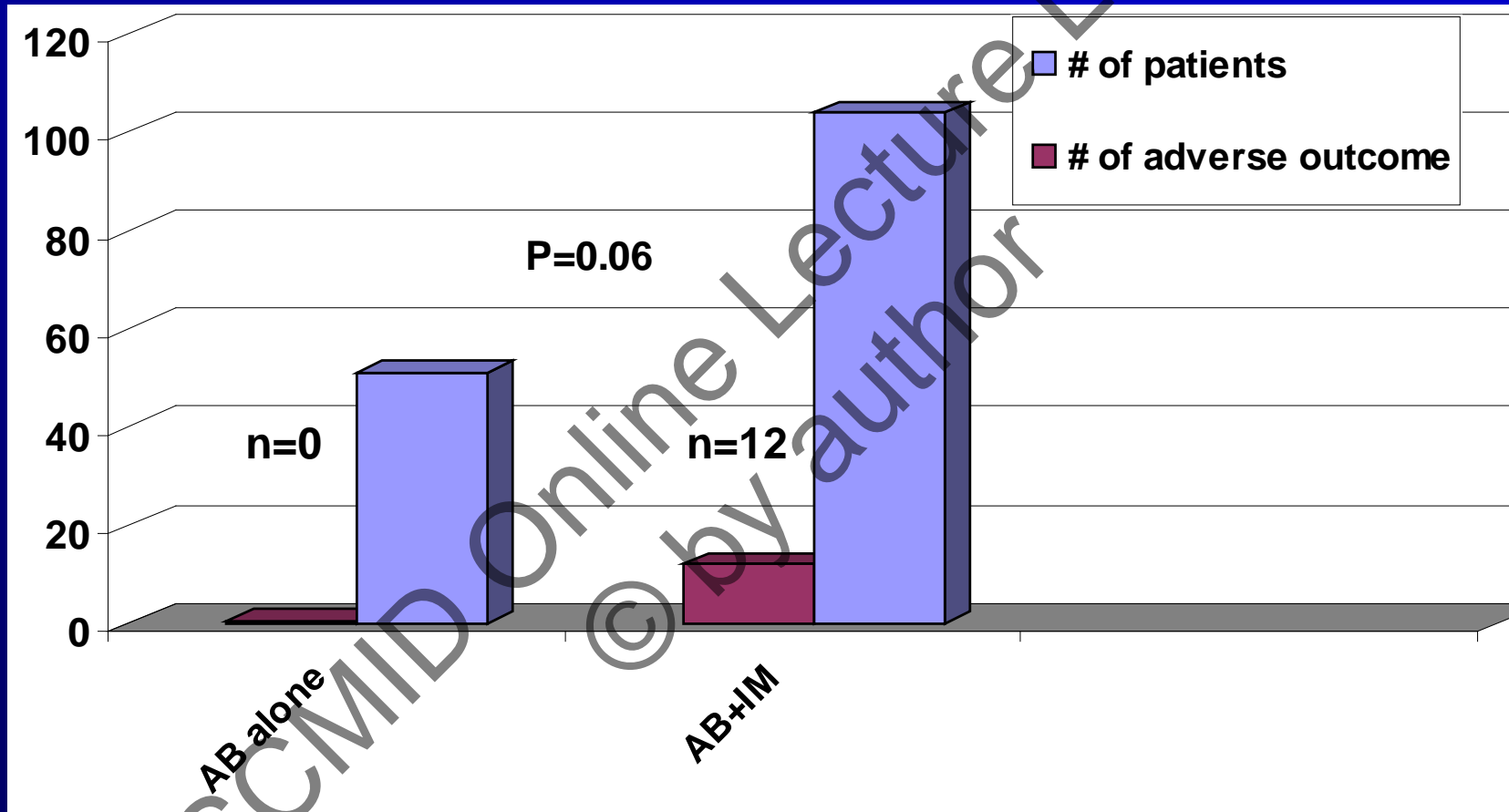


## Outcome of combination AB+IM vs. AB alone

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)

# Results – Primary outcome



# Food for thought....

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

A flare not-responsive to oral prednisone

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Prednisone stopped. Metro initiated. 5 days improvement

Then... fever again, increased bowel movements

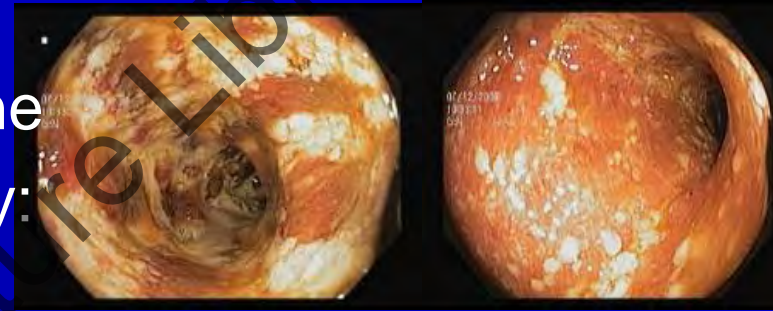
Re-endoscoped:

# Food for thought....

61 YO Crohn's colitis patient

A flare not-responsive to oral prednisone

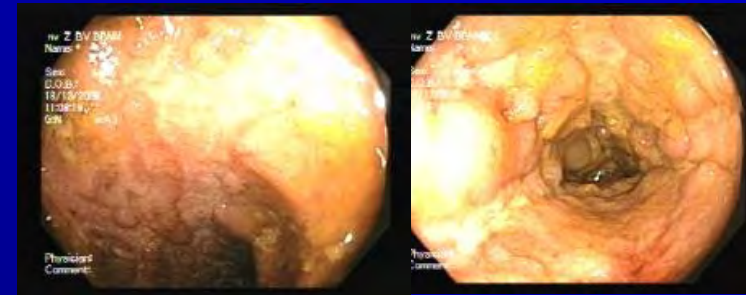
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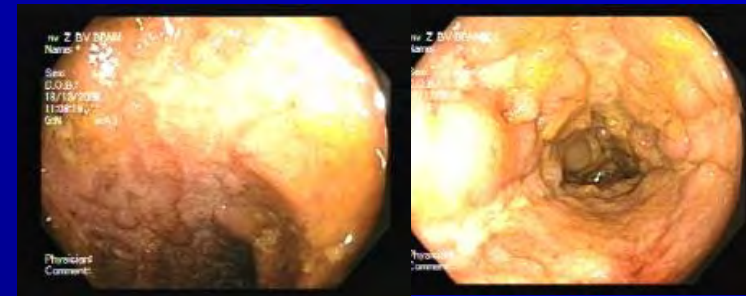
C. Difficile + in stool. On sigmoidoscopy:



Prednisone stopped. Metro initiated. 5 days improvement

Then... fever again, increased bowel movements

Re-endoscoped:



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

# 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

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