Update on Diverticular Disease: New Concepts New Science New Guidelines

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New Guidelines

Gastroenterology 2015;149:1944–1949

AGA SECTION

American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis

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Stuff we thought we knew…..

“Diverticulosis is caused by low dietary fiber intake”

The “Fiber Deficiency Hypothesis”

- Evidence **for**:
  - Worldwide striking geographic correlation with low dietary fiber intake
  - Developed in the west after the introduction of grain milling
  - Humans & animals on low-fiber diets: only species to get diverticula
  - Lower rates diverticular disease in vegetarians
- Burkitt and Painter: stool weights & transit times in Brits (low fiber diet) vs rural Ugandans (high fiber diet)

	Transit time	Stool Weight	Risk diverticulitis
UK patients	80 hours	110 gm/d	increased
Ugandans	34 hours	450 gm/d	decreased

- Also supported by rodent data (lifelong low vs high fiber diet)
  - Low-fiber diet: 45% developed diverticula
  - High-fiber diet: 9% developed diverticula
- Popular and logical thesis, but evidence supporting is actually poor

Painter NS, Burkitt DP. Br Med J 1971;2:450–54

Peery: cross-sectional colonoscopy: dietary risks for diverticulosis

- 2100 colonoscopies 1998-2010, telephone dietary hx post exam
- Dose dependent **increase** in tics with **increased** fiber
  - APR: 1.30 (1.13-1.50) for highest vs lowest fiber quartile
  - Also, increased BMs associated with increased tics
  - No association with fat, red meat or physical activity
- *Problems*: diet assessed decades after development of tics, and patients aware of dx, and might have learned (or been told) that fiber helps symptoms.
- Post-facto association does not prove causality.
- And even if high-fiber doesn't prevent diverticulosis, may still be effective in TREATMENT of patients with diverticulosis, and have other health benefits as well

Peery AF et al. Gastroenterology 2012;142:266-272

Can dietary fiber prevent *complications*?

- 2 large prospective cohort studies showing inverse relationship b/w fiber intake and diverticular ***complications***
- **HPFU**, >43K men, US, 1988-1992, no prior colonic dz
  - RR for symptomatic disease in highest vs lowest fiber quintiles = 0.63 (.44-.91) (insoluble fiber, esp cellulose)
- **EPIC-Oxford Study**, 47K M & F, UK, 12 year follow up
  - 812 cases (806 hospitalizations, 6 deaths)

	Adjusted Relative Risk
– Highest vs lowest fiber intake:	0.59 (.46-.78)
– Vegetarians vs meat eaters:	0.69 (.55-.86)

Aldoori WH et al. J Nutr 1998;128:714-19
Crowe FL et al. BMJ 2011;343:

The Guidelines Weigh in:

Question 4. Should a High-Fiber Diet, Rather Than a Regular Diet, Be Advised in Patients With a History of Acute Diverticulitis?

The AGA suggests a fiber-rich diet or fiber supplementation in patients with a history of acute diverticulitis. (*Conditional recommendation, very low quality of evidence*).

Are there other important risk factors for Acute Diverticulitis besides fiber?

- ? NSAIDs, opioids, and steroids
- ? Genetic risk
- ? Obesity
- ? Physical inactivity
- ? Geography/Season (? low vit D levels)
- ? Toilet position

NSAIDs as risk factor

- Many prior studies and meta-analyses consistently show NSAID use as significant risk factor for diverticular **bleeding**.
- Recent meta-analysis (23 studies):
  - Increased risk bleeding with NSAIDs (OR 2.69), and ASA (OR 3.24)
  - But **also** increased risk of *perforation* or *abscess* with NSAIDs (OR 2.49), steroids (OR 9.08) and opioids (OR 2.52)

Kvasnovsky CL, Papagrigoriadis S, Bjarnason I et al. Colorectal Dis 2014;16:189-96.

AGA Guidelines Say:

Question 6. Should Aspirin Be Avoided in Patients With a History of Acute Diverticulitis?

The AGA suggests against routinely advising patients with a history of acute diverticulitis to avoid the use of aspirin. (*Conditional recommendation, very-low quality of evidence*).

Question 7. Should Nonaspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Be Avoided in Patients With a History of Acute Diverticulitis?

The AGA suggests advising patients with a history of diverticulitis to avoid the use of nonaspirin NSAIDs if possible. (*Conditional recommendation, very-low quality of evidence*).

Genetic risk factors?

- Swedish Twin Registry linked to Inpatient Registry[1]
  - >100K twins; 2300 had dx of diverticular disease
  - OR for developing DD if monozygotic twin affected = 7.15 (4.8-10.6) (3.2 for same gender dizygotic twins)
  - Estimate hereditability at 40%
- Danish Registry[2], >10K siblings, 900+ twins
  - RR for developing DD if monozygotic twin affected = 14.5 (8.9-23) (5.5 for dizygotic twins)
  - Estimated hereditability at 53%

1. Granlund J et al. Aliment Pharmacol Ther 2012; 35:1103-07
2. Strate LL et al. Gastronenterology 2013;144:736-742.

Physical Activity and DD

- 47K US males (HPFU) 40–75 years, free of diverticular disease at entry, followed 18 years
- RR in highest quintile of **total** activity 0.75 (0.58–0.95) for diverticulitis, and 0.54 (0.38–0.77) for bleeding when compared to the lowest quintile
- **Vigorous** activity inversely related to AD (RR=0.66, 0.51–0.86), and bleeding (RR=0.61)
- *Conclusion*: physical activity lowers the risk of diverticulitis and diverticular bleeding. Vigorous activity appears to account for this association.

Strate LL et al. Am J Gastroenterol. 2009 May ; 104(5): 1221–1230

Question 11. Should Vigorous Physical Activity Rather Than Regular Activity Be Encouraged in Patients With a History of Acute Diverticulitis?

The AGA suggests advising patients with diverticular disease to consider vigorous physical activity. (*Conditional recommendation, very low quality of evidence*).

DDW 2016: Obesity ↑risk c/w low fiber diet

- 451 pts, 1st time screening colon at UNC, no prior diverticulitis
- 43% had diverticulosis (older, male more likely)
- There was no association between dietary fiber intake and diverticulosis (OR=1.1; 95% CI 0.6-1.8) when comparing the highest quartile of intake with the lowest.
- Obese BMI (≥30) increased risk of diverticulosis (OR=3.1; 95% CI 1.7-5.8) compared to those with a normal BMI.
- Highest quartile of waist circumference, c/w those in the lowest, also had increased risk (OR=1.9; 95% CI, 1.1-3.2).
- *Conclusions*: “Obesity, particularly abdominal obesity, significantly increased the risk of diverticulosis.”

DDW 2016 Abstract #28 Peery AF et al. Obesity Is a Risk Factor for Colonic Diverticulosis. Gastroenterology 150(4), S10

Higher Serum Vitamin D Levels Are Associated With a Reduced Risk of Diverticulitis

- Multicenter study (1993-2012), 9116 patients with uncomplicated diverticulosis and 922 patients who developed diverticulitis requiring hospitalization.
  - Multivariate logistic regression comparing serum 25(OH)D levels
- Patients with uncomplicated diverticulosis had significantly higher mean pre-diagnostic serum levels of 25(OH)D (29.1 ng/mL) than patients with diverticulitis who required hospitalization (25.3 ng/mL; $P < .0001$)
- RR for diverticulitis: 0.49 (95% CI 0.38-0.62; p< .0001)

Maguire LH, Strate L et al. Clin Gastroenterol Hepatol 2013;11:1631-5

SSAT 2016: Posture during defecation

- 757 patients undergoing colonoscopy (Turkey)
- Diverticulosis (D) in 12.5%, majority sigmoid.
- Frequency of sitting during defecation (Western type toilet) was higher in D group (72.2% vs 53.5%; p=0.007).
- “Use-time” of Western-type toilet was longer in the D-group compared to the non-D group (p=0.04).
- *Conclusion*: “Sitting during defecation (Western type toilet) seems to increase the risk of DD. To optimize the anorectal angle, placing a footstool during defecation may have a protective role against diverticula formation”.

SSAT 2016 Mo1759 Ozturk O et al. Posture During Defecation is a Risk Factor for Colonic Diverticular Disease. Gastroenterology 150(4), S1242

Squatty-Potty

$15M in sales (2015)

Now also in inflatable for travel, and “tao bamboo”

What we thought we knew…..

“10-25% of patients with diverticulosis will develop diverticulitis”

Risk of Acute Diverticulitis

- Estimates based on older data, true denominator unknown
- Retrospective review LA-VAMC 1996-2011
- 2222 pts with baseline diverticulosis (97%M)
- Diverticulitis during 11 year follow up:
  - Liberal criteria: 4.3%
  - Strict criteria: 1.0% (CT or surgery confirmed)
- Median time to event (AD): 7.1 years
- Risk highest in younger patients

Shahedi K, Fuller G, Bolus R et al. Clin Gastroenterol Hepatol 2013;11:1609-13.

What we thought we knew…..

“Patients with diverticular disease should avoid seeds and nuts”

Risk of seeds / nuts

- ACG Practice Guidelines 1999[1]
  - "Controlled studies that support this belief are lacking….no role for 'elimination' diet"
- Strate et al 2008[2] [USHP F/U Study]
  - 47,000 men free of DD on entry, followed 18yrs
  - 801 incident cases of diverticulitis
  - Hazard ratio for highest vs lowest consumption
    - Nuts: 0.80 (0.63 – 1.01), p=0.04
    - Popcorn: 0.72 (0.56 – 0.92), p=0.007
- Not only 'no association' but may actually protect

1. Stollman NH, Raskin JB. *Am J Gastroenterol*. 1999;94(11):3110.
2. Strate LL et al. *JAMA*. 2008;300(8):907.

Question 5. Should Consumption of Nuts and Popcorn Be Avoided in Patients With a History of Acute Diverticulitis?

The AGA suggests against routinely advising patients with a history of acute diverticulitis to avoid consumption of nuts and popcorn. (*Conditional recommendation, very-low quality of evidence*).

What we thought we knew…..

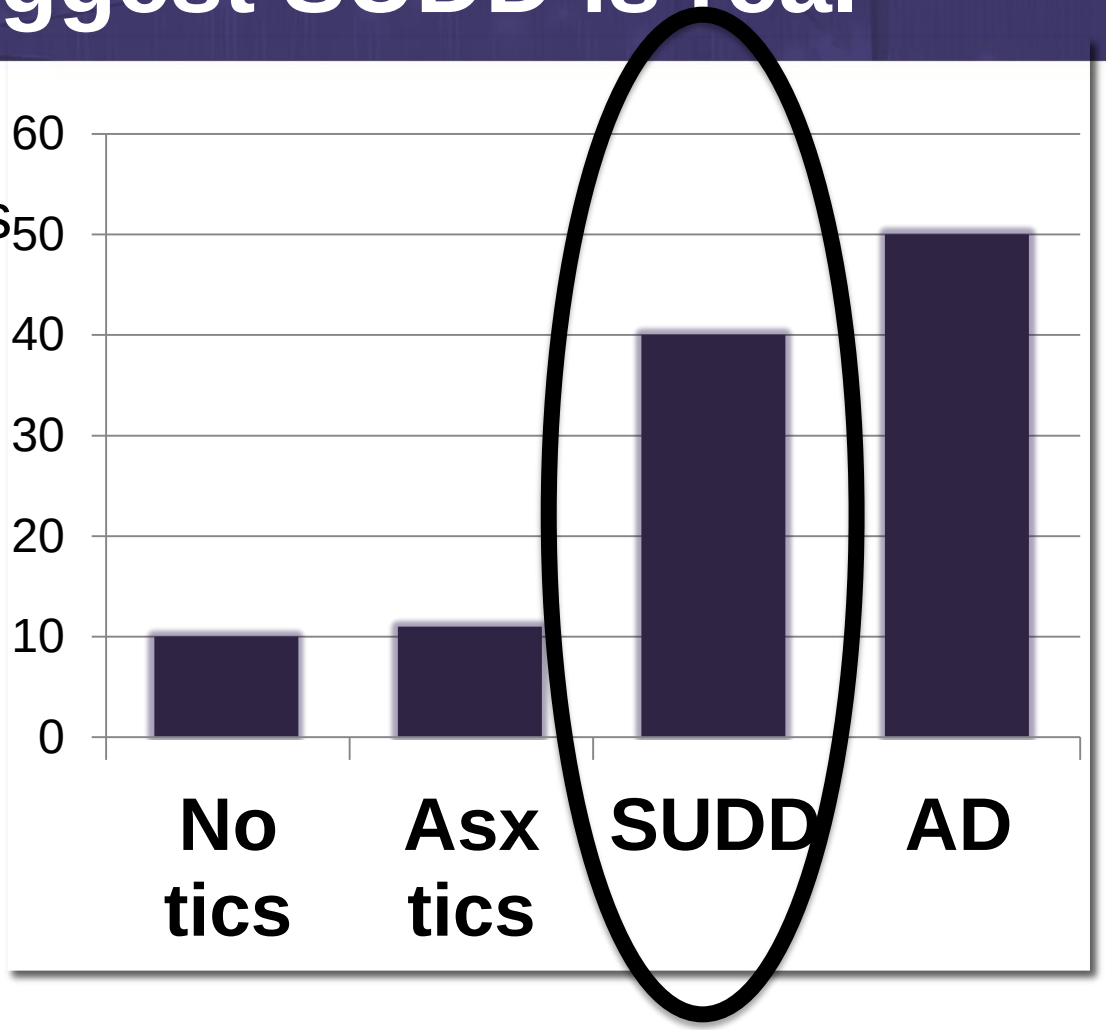
"Diverticulosis is binary (all or none), either incidental asymptomatic finding….or causes acute diverticulitis"

Symptomatic Uncomplicated Diverticular Disease (SUDD)

- SUDD: lower abdominal symptoms in absence of overt inflammation (by vital signs, labs, CT)
- Now recognizing a continuum of inflammation, with evidence for subclinical inflammation in SUDD patients
- Possible mechanisms:
  - Inflammatory damage to enteric nerves (and aberrant re-innervation leading to visceral hypersensitivity)
  - Altered neuropeptides
  - Muscle hypertrophy with increased intraluminal pressure
  - Microbiota alterations

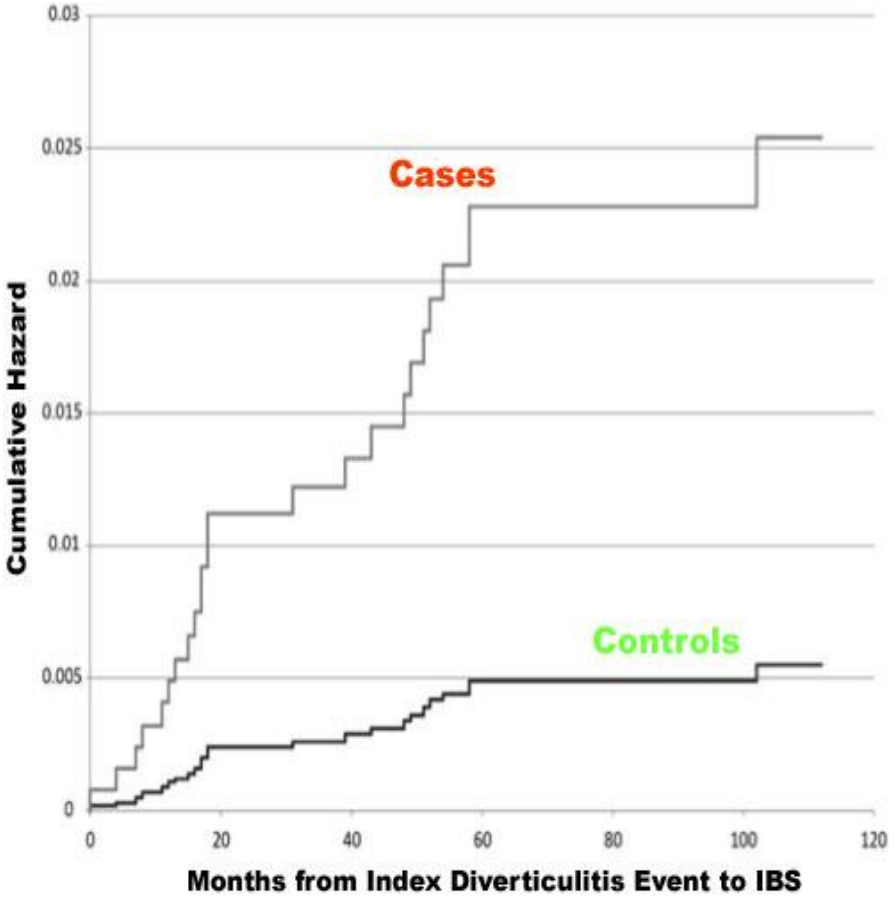
Consistent results of abnormal markers suggest SUDD is real

- Fecal calprotectin
- Mucosal lymphocytes
- Galanin
- Substance P
- Neuropeptide K
- TNF-α
- VIP
- PACAP
- Neurokinin 1
- Barostat pain threshold
- Post-cibal motility



Is SUDD a "post–diverticulitis IBS"?

- Retrospective review 1100 pts with AD LAVAMC (1996-2011), no prior Dx of IBS (96% men, mean 64 yrs)
- 1100 controls, f/u 6 years
- Hazard Ratio for subsequent:
  - IBS = 4.7 (CI 1.6-14.0, P=0.006)
  - Mood disorder = 2.2 (1.4-3.5, P<.001)
- Supports hypothesis that AD might trigger long-term IBS and/or functional GI Sxs



Cohen E, Fuller G, Bolus R et al. Clin Gastroenterol Hepatol 2013;11:1614-9.

DDW 2016: Tics and IBD/SUDD

- 451 pts, 1st time screening colon at UNC
- No prior diverticulitis
- 5% met Rome III for IBS
- Pts with diverticulosis had an increased risk of IBS (OR 2.1; 95% CI 0.9- 5.0) compared to patients without diverticulosis.
- *Conclusions*: “colonic diverticula were associated with an increased risk of irritable bowel syndrome…these results suggest that diverticula may be associated with GI symptoms”.

DDW 2016 1135 Peery AF et al. Colonic Diverticula Are Associated with Irritable Bowel Syndrome. Gastroenterology 150(4), S230 - S231

Emerging Treatments for SUDD

- If there is indeed a symptomatic state of DD marked by low-grade inflammation, and/or visceral hypersensitivity and/or abnormal motor function, can we intervene in such patients?
- Historically, we've prescribed fiber or anti-spasmodics, although data in support is weak
- ? Antibiotics, ? Probiotics ? Anti-inflammatories

Treatment with mesalamine

- Many studies, mainly European, have evaluated 5-ASA either after acute diverticulitis or in SUDD patients
- Generally favorable results, but
  - Data very heterogeneous
  - Most not double blinded or placebo controlled
  - Subjective endpoints (SUDD, certainly)
  - Dose / regimen unclear

High(er) quality European data emerging…

- RDBPCT 96 pts 1st episode AUD
- 5-ASA 800mg BID 10d/month vs PBO x 24 months
- Diverticulitis 24 months:
  - 5ASA: 13%
  - PBO: 28% (NS)
- Statistically sig decrease in:
  - Symptoms at 24 months (p=0.02)
  - Additional GI drug use (p<0.03)

- RDBPCT 210 patients w/ SUDD
- 5-ASA 1.6gm/day vs PBO with or without Lactobacillus casei (LC), 10d/month x 12 months
- Recurrence of SUDD at 12 months:
  - 5ASA + LC: 0%
  - 5ASA + PBO: 14%
  - PBO + LC: 15%
  - PBO + PBO: 46%

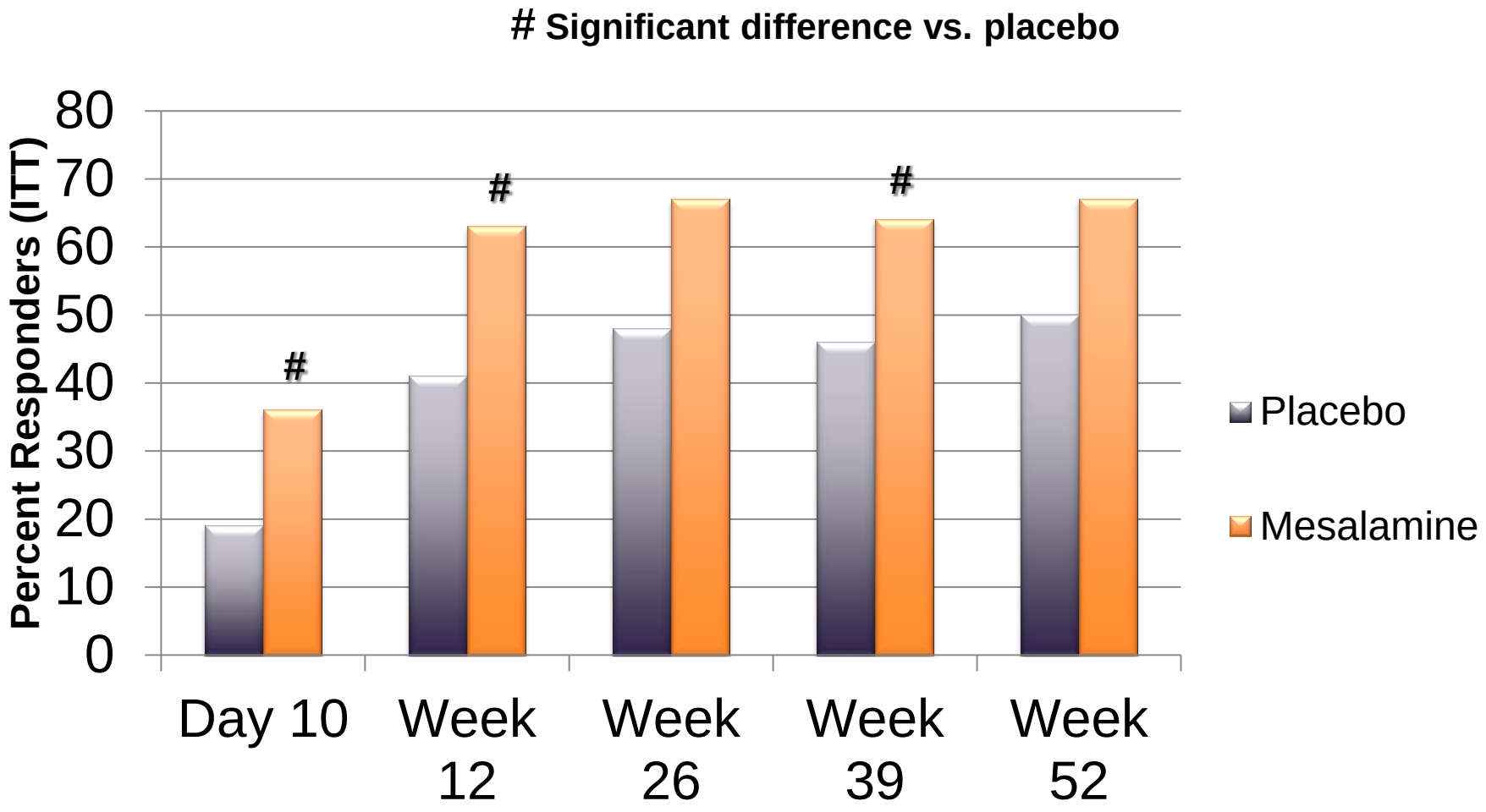
Parente F et al. Int J Colorectal Dis 2013;28:1423-31
Tursi A et al. Aliment Pharacol Ther 2013;38:741-51

DIVA Trial

- 52 week, randomized, multi-center, double-blind, placebo-controlled, proof-of-concept study (first in US)
- Required CT scan confirmed AD, excluded IBS Dx
- Patients randomized to:
  - Standard care (abx, dietary advice as per local MD)
  - Standard care, plus mesalamine 2.4gm QD
  - Standard care, plus mesalamine 2.4gm QD plus *B. infantis* QD
- 12 week Rx with 40 week additional f/u
  - Lower GSS at all time points with 5ASA but NS (no effect probiotics)
  - Significant increase in **symptom responders** (GSS=0 or 1) at some (but not all) time points
  - No effect on **acute diverticulitis** recurrence rates or surrogate markers

Stollman N et al. J Clin Gastroenterol 2013; 47;621-9.

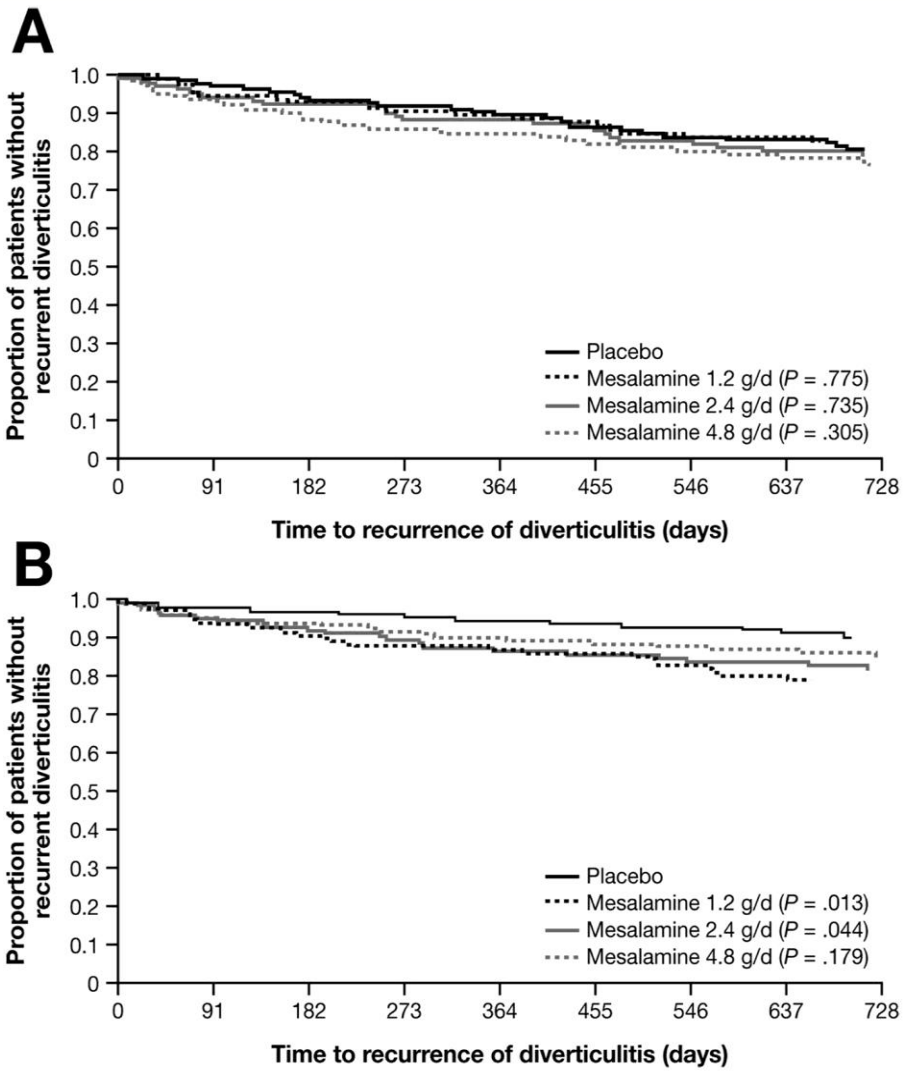
Global Symptom Score Responders



Responder = score of 0 or 1 for all symptoms

5-ASA for AD: The ‘final answer’?

- Phase III RDBPC studies (PREVENT 1 and 2)
- >1000 patients with ≥1 episode of acute uncomplicated diverticulitis
- Randomized to receive mesalamine (1.2, 2.4, or 4.8 g/d) or placebo
- Primary endpoint: proportion of patients free of recurrent diverticulitis, defined as surgical intervention or positive CT scan
- No dose of 5ASA superior to PBO for reducing AD at 104 weeks
- No decrease in symptoms or time to recurrence (although not primary endpoint)



Raskin JB, Kamm MA, Jamal MM et al. Gastroenterology 2014;147:793-802

DDW 2016: 5-ASA for AD

- Systematic review of five RCTs of 5-ASA to prevent recurrent AD (not SUDD)
- Pooled OR was 0.95 (95% CI 0.60 to 1.49)
- Quality of evidence by GRADE approach was "moderate".
- Conclusion: “We have found no evidence to support a role for mesalamine in the prevention of recurrent diverticulitis”.

DDW 2016 Tu1074 Khan MA et al. No Role of Mesalamine in Prevention of Recurrent Diverticulitis: Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. Gastroenterology 150(4), S834

Question 8. Should Mesalamine Rather Than Placebo Be Used in Patients With a History of Acute Uncomplicated Diverticulitis?

The AGA recommends against the use of mesalamine after acute uncomplicated diverticulitis. (*Strong recommendation, moderate quality of evidence*).

Rifaximin in SUDD (400mg BID, 7 d/month)

Meta-analysis: 4 PRCTs, 1660 pts

Difference in:	Pooled Rate
Sx relief (1 year) p<0.0001 NNT=3	29% (CI 24 - 34%)
All Complications p=0.03 NNT=59	2% (CI -3.2 - -0.1%)
Diverticulitis p=0.0057 NNT=50	2% (CI -3.4 - -0.6%)

- Systematic Review 31 studies (6 PC)
- Significant improvement in Sxs and greater prevalence of Sx-free patients at 1 year with fiber plus rifaximin in comparison with fiber alone.
- Cumulative data from 11 RCTs: significant benefit of rifaximin and fiber for 1-year rate of AD:
  - 11/970 (1.1%) vs 20/690 (2.9%); P = .012)
  - NNT of 57

Bianchi M et al. Aliment Pharmacol Ther 2011;33:902-10
Maconi G. Dis Colon Rectum 2011;54:1326-38.

Question 9. Should Rifaximin Rather Than Placebo Be Used in Patients With a History of Acute Uncomplicated Diverticulitis?

The AGA suggests against the use of rifaximin after acute uncomplicated diverticulitis. (*Conditional recommendation, very-low quality of evidence*).

Probiotics for SUDD and diverticulitis

Protocol	DD Stage	Follow up (N)	Outcome
Lactobacillus paracasei F19 with fiber	SUDD	6 mos (50)	Improved symptoms
L. casei, 5-ASA, or both[2]	SUDD	12 mos (210)	Increased remission rate SUDD
L. casei plus 5-ASA[3]	SUDD	24 mos (75)	Increased remission rate
VSL#3 plus balsalazide[4]	SUDD	2 mos (30)	Improved symptoms
L. Acidophilus plus *L. helviticus* plus *Bifidobacterium*[5]	SUDD	6 mos (45)	Prevented recurrence, improved symptoms
B. infantis[6]	AD	12 mos (40)	No effect + 5-ASA

1. Annibale B et al. Minerva Gastroenterol Dietol 2011 Mar;57:13-22. 2. Tursi A et al.Aliment Pharmacol Ther 2013;380:741-51. 3. Tursi A et al. Hepatogastroenterology. 2008;55:916-920. 4. Tursi A et al. Int J Colorectal Dis. 2007;22:1103-1108. 5. Lamiki P et al. J Gastrointestin Liver Dis. 2010;19:31-36. 6. Stollman N et al. J Clin Gastroenterol 2013; 47;621-9.

Question 10. Should Probiotics Rather Than Placebo Be Used in Patients With a History of Acute Uncomplicated Diverticulitis?

The AGA suggests against the use of probiotics after acute uncomplicated diverticulitis. (*Conditional recommendation, very low quality of evidence*).

What we thought we knew…..

"Antibiotics (with activity against anareobes and GNR) are ***required*** in acute diverticulitis"

Retrospective, case-controlled study

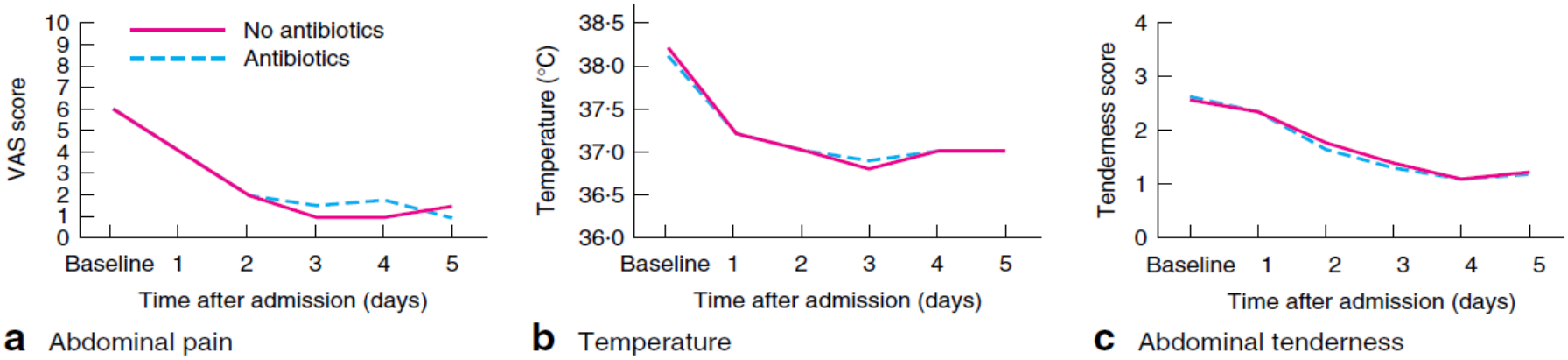
- 272 patients with “mild AD, CT confirmed” admitted to two different Dutch Hospitals ‘with different treatment regimens re Abx’
- 191 patients: (-) Abx
- 81 patients: (+) Abx
- Treatment failure: 4% vs 6% (NS)
- NSAIDs: OR 7.25 (CI 1.22-46.9, P=0.037) for recurrence
- “Abx can be omitted in selected patients with mild colonic diverticulitis…”

De Korte N et al. Colorectal Dis 2012;14:325-30.

Are Antibiotics Obligate?

- First PRCT: 623 Swedish patients (but unblinded)
- CT-confirmed acute diverticulitis without complications
- **No** antibiotics vs antibiotics at MD's discretion for ≥7 days

	Abscess, perforation (*P* = 0.3)	Recurrent diverticulitis (*P* = 0.88)
No antibiotics	6 (1.9%)	47 (16.2%)
Antibiotics	3 (1.0%)	46 (15.8%)



Chabok A et al. British Journal of Surgery 2012;99:532.

Question 1. Should Antibiotics Be Routinely Used in Patients With Acute Uncomplicated Diverticulitis?

The AGA suggests that antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis. (*Conditional recommendation, low quality of evidence*).

What we thought we knew…..

“Elective prophylactic / curative surgery should be considered after a second attack of confirmed diverticulitis”

When to consider surgery?

- Prior guidelines, including ASCRS and ACG recommended 'considering' prophylactic surgical resection after 2nd attack'
- Most recent ASCRS recommendations[1]
  - "The decision to recommend elective sigmoid colectomy after recovery from uncomplicated acute diverticulitis should be individualized."
  - "Routine elective resection based on young age (<50 years) is no longer recommended."
- Markov Model (WA State database)[2]
  - Colectomy after **fourth** (rather than 2nd) episode → 0.5% fewer deaths and saved $1,035/patient.

1. Feingold D et al. Dis Colon Rectum 2014;57:284-294. 2. Salem L et al. J Am Coll Surg 2004;199:904-12

DDW 2016: Risk of elective surgery?

- Has been poorly characterized
- NISQIP database 2011-2013
  - 15K elective cases, no bleeding or infection
  - 24% < 50 years old
  - 76% overweight or obese
  - 68% laparoscopic
  - Colostomy in 8% (higher in open cases)
  - Mortality 0.3%

SSAT 2016 Mo1764 Peery AF et al. Short Term Complications After Elective Surgery for Acute Diverticulitis; Gastroenterology 150(4), S1243 - S1244

Question 3. Should Elective Colonic Resection Be Performed After an Initial Episode of Acute Uncomplicated Diverticulitis?

The AGA suggests against elective colonic resection in patients with an initial episode of acute uncomplicated diverticulitis. The decision to perform elective prophylactic colonic resection in this setting should be individualized. (*Conditional recommendation, very-low quality of evidence*).

MEN'S JOURNAL ENTERTAINMENT 06/08/2016

How Brock Lesnar Beat Diverticulitis And Rebooted his UFC Career

By **Taylor Kubota**

"Lesnar has had a long, traumatic journey with diverticulitis. It has hindered his physical abilities for years and he had major surgery to address it. Many athletes would not come back from a medical issue this severe. Lesnar? Well, he's scheduled to participate in WWE SummerSlam in August."

"In my mind and in my heart, I never lost to a foe. I never lost to an opponent. I lost to diverticulitis. That was my opponent that beat me," he told ESPN.

Summary / Take home points

- Fiber deficiency may not be as important a CAUSE of diverticulosis as previously thought.
- Adequate fiber intake likely IS effective at decreasing ***complications*** of diverticulosis
- NSAIDS significant risk factor for diverticular bleeding AND diverticulitis/abscess
- Genetics may play a significant role in susceptibility, as may obesity, Vit D, toilet type
- Acute Diverticulitis is probably not as common as we thought
- Nuts and seeds: no need to avoid

Summary / Take home points

- SUDD: a possible subclinical inflammatory state
- PDV-IBS may be a form of PI-IBS
- Mesalamine doesn’t prevent recurrent diverticulitis, but may improve symptoms
- Rifaximin and probiotics: role TBD, may also improve Sxs, likely doesn’t reduce recurrence
- Antibiotics: not **obligate** in mild diverticulitis
- Surgery: recommended later, case-by-case basis