Antibiotics should be used for acute uncomplicated diverticulitis

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What is acute diverticulitis?

Diverticulitis is a microperforation of a diverticulum!

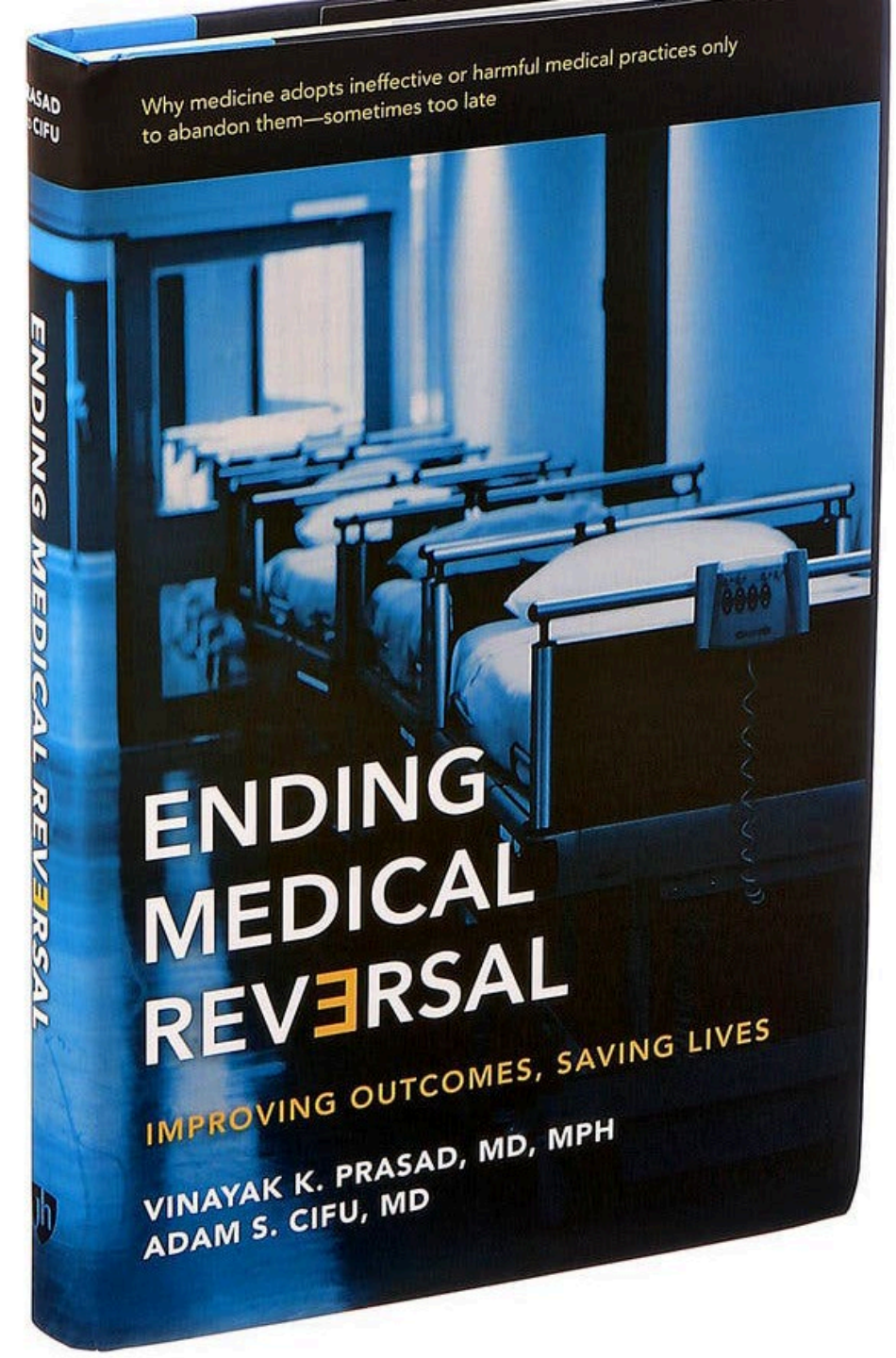
Abdominal perforations should be treated with antibiotics.

Some argue that acute diverticulitis may have inflammatory etiology.

- Metronidazole reduces post op recurrence in Crohn's disease
- Ciprofloxacin and metronidazole are routinely used to treat pouchitis
- Even if the inciting event is inflammatory, this leads to infectious complications

What are our goals in treating patients with acute diverticulitis?

- Symptom resolution
- Reduce need and duration of hospitalization
- **Reduce the risk of progression to complicated disease**
- **Reduce the risk of recurrence**
- **Reduce the risk of long term complications (stricture, fistula, need for surgery, post-diverticulitis functional bowel disease)**



Are we ready for medical reversal?

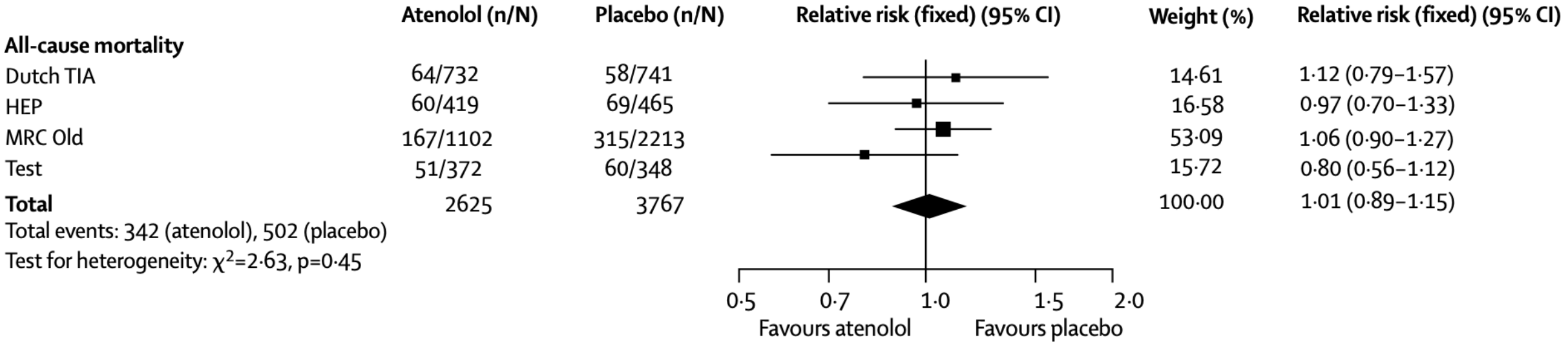
Medical reversal: when an accepted therapy is overturned

- Overturned therapy is typically based on weak data to start that is accepted before being rigorously evaluated
  - Surrogate endpoints
  - Poorly designed studies
  - Single center trials
  - Observational studies

Do we have data to support medical reversal for the treatment of diverticulitis?

Let's first look at other examples of medical reversal: atenolol for hypertension

- Historically, atenolol lowered blood pressure and was the trial standard
- LIFE trial: losartan vs. atenolol for 4 years in patients with HTN and LVH determined by ECG
  - Similar BP reductions: 30.2/16.6 mm Hg (losartan) and 29.1/16.8 mm Hg (atenolol)
  - But, lower rates of death, MI, and stroke in those treated with losartan



Bo Carlberg, et al. Lancet. 2004.

Bjorn Dahlof, et al. Lancet. 2002.

Medical reversal: estrogen replacement therapy for post-menopausal women

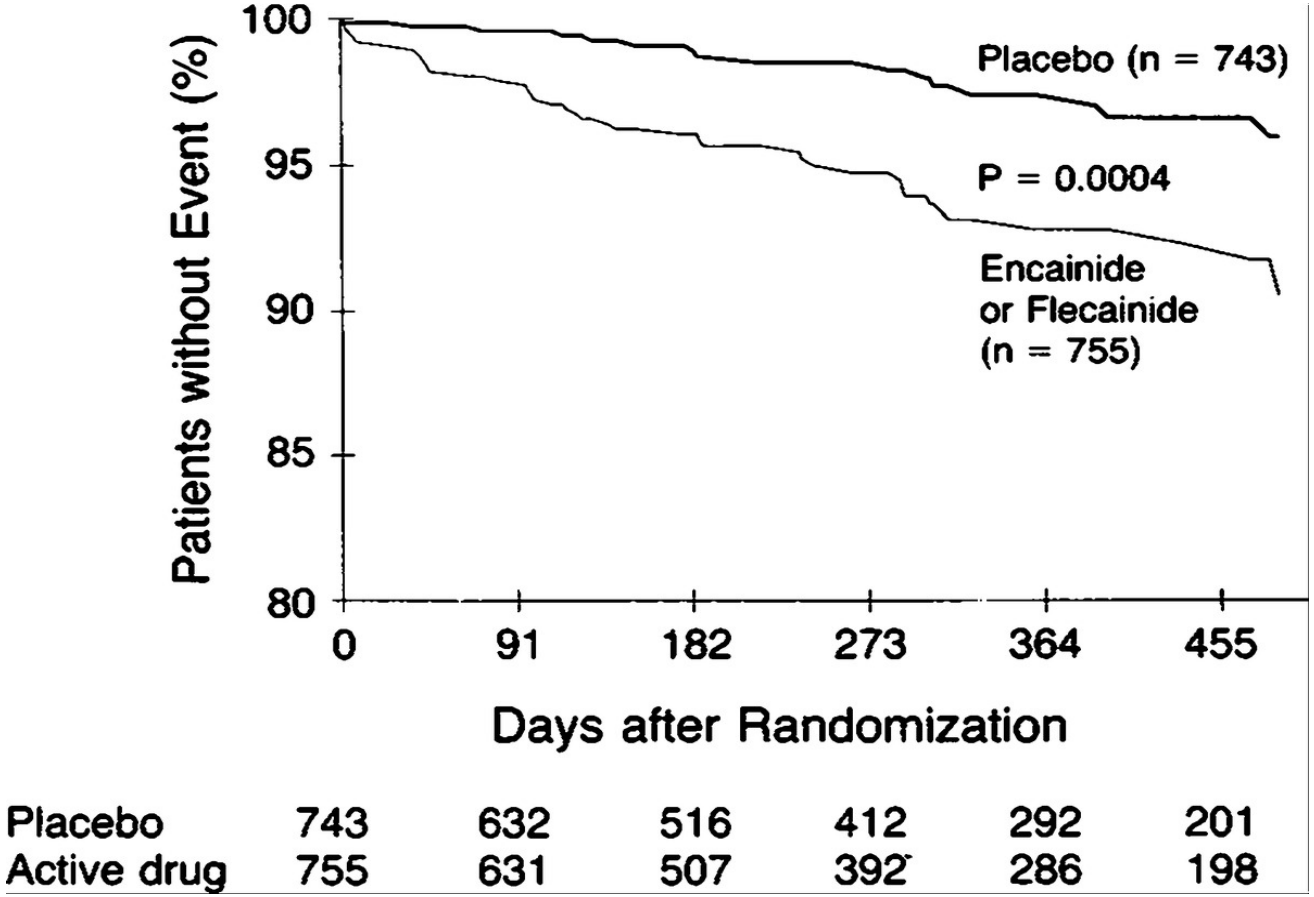
- Nurses' Health Study: estrogen users had 40% fewer heart attacks (observational data)
- But, the Women's Health Initiative tested this in a randomized controlled – estrogen + progesterone vs. placebo
  - Trial ended early: estrogen/progesterone arm had higher rates of stroke, breast cancer, cardiac events, and PE

F Grodstein, et al. Ann Int Med. 2000.

JoAnne Manson et al. JAMA. 2013.

Medical reversal: flecainide after MI

- PVCs are associated with higher risk of death after MI
- Flecainide and encainide were used to suppress PVCs
- CAST trial: encainide and flecainide decreased PVCs but increased risk of death



Debra Echt et al. NEJM. 1991.

Are we ready to abandon antibiotics in acute uncomplicated diverticulitis?

AGA and ACP guidelines *suggest* no antibiotics for acute uncomplicated left sided diverticulitis

Conditional recommendation, low quality of evidence

Unblinded studies

Sequence of randomization not appropriately concealed

Small number of events

Let's analyze the three randomized, controlled trials that have looked at this!

1 Antibiotics vs. no antibiotics: AVOD study group

Study Design:

- Open label, multicenter RCT in Sweden and Iceland
- 620 patients with diverticulitis:
  - 38 C or higher
  - Admitted to the hospital
  - High WBC and CRP
  - CT demonstrating diverticulitis
  - Excluded: high fever, affected general condition, sepsis, pregnancy, immunosuppressive therapy
- Interventions:
  - No antibiotic arm: IV fluids
  - Antibiotic arm: IV antibiotics during admission then oral antibiotics on discharge for 7 days total

A Chabok et al. British Journal of Surgery. 2012.

1 Antibiotics vs. no antibiotics: RCT in Sweden and Iceland

Results:

	No antibiotics ($n = 309$)	Antibiotics ($n = 314$)	P†
Complications	6 (1·9)	3 (1·0)	0·302
Sigmoid perforation	3 (1·0)	3 (1·0)	0·985
Abscess	3 (1·0)	0 (0)	0·080
Sigmoid resections	7 (2·3)	5 (1·6)	0·541
During hospital stay	1 (0·3)	3 (1·0)	0·324
During follow-up	6 (1·9)	2 (0·6)	0·148
Hospital stay (days)*	2·9(1·6)	2·9(1·9)	0·717‡
Recurrent diverticulitis	47 of 290 (16·2)	46 of 292 (15·8)	0·881

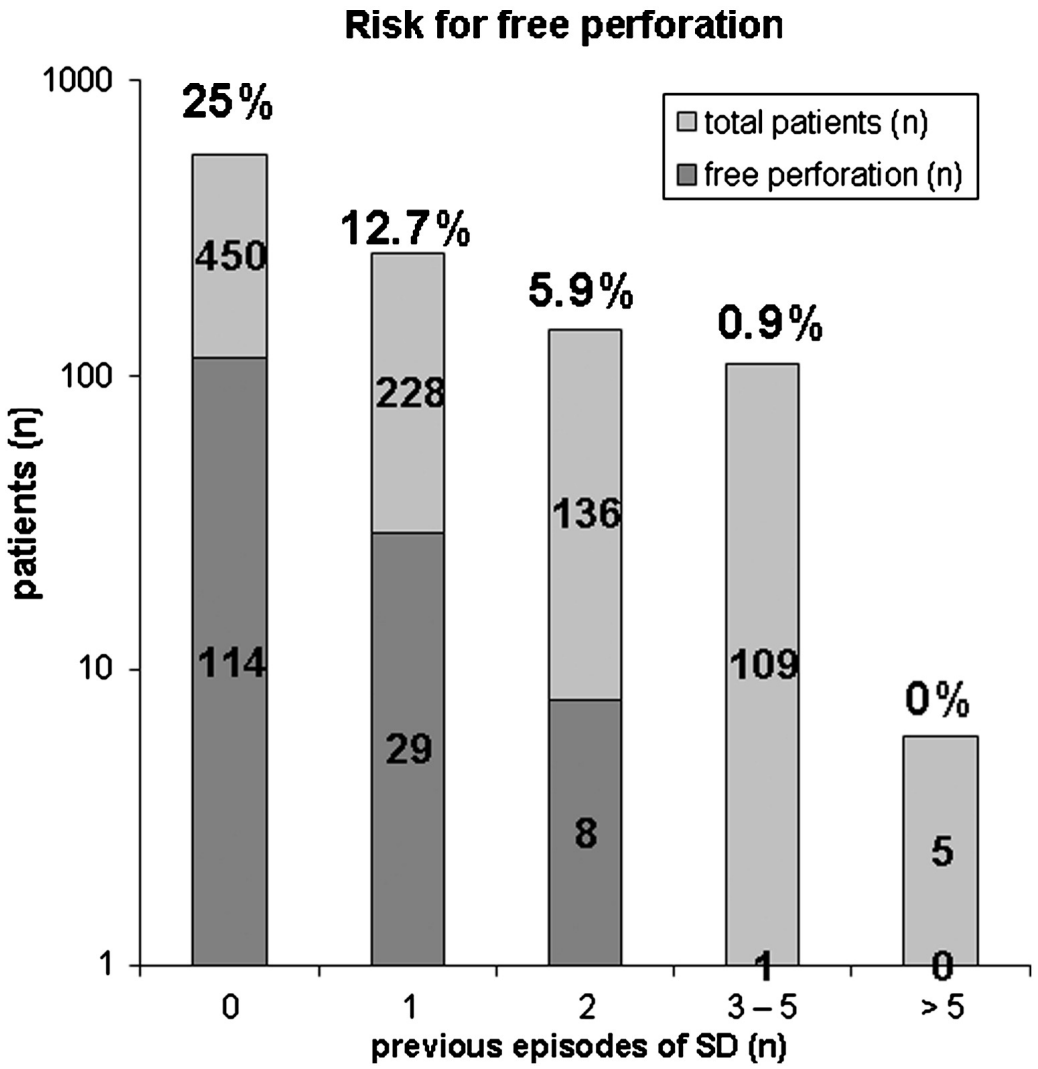
10 patients in the no-antibiotic arm were given antibiotics for rising CRP, pain, or fever

1 Antibiotics vs. no antibiotics: RCT in Sweden and Iceland

	No antibiotics ($n = 309$)	Antibiotics ($n = 314$)	P¶
Age (years)	57·1(13·2)	57·4(12·8)	0·853
Sex ratio (M : F)	110 : 199	110 : 204	0·882#
Co-morbidity*‡	91 (29·4)	92 of 312 (29·5)	0·992#
Previous diverticulitis*	137 of 306 (44·8)	110 of 309 (35·6)	0·020#
Body mass index (kg/m^2)	28·2(4·4)	27·9(4·4)	0·437
WBC ($\times$ 10^9 cells/l)	12·3(3·3)	12·6(3·1)	0·276
CRP (mg/l)	91(61)	100(62)	0·070
Body temperature (°C)	38·1(0·6)	38·1(0·6)	0·350
Abdominal pain†	6 (4–8)	6 (5–8)	0·503**
Tenderness score§	3 (2–3)	3 (2–3)	0·950**

More patients in the no-antibiotic arm had prior episodes of diverticulitis

Complications are more likely to occur with the first episode of diverticulitis



Jorg-Peter Ritz, et al. Surgery. 2011.

2 Antibiotics vs. no antibiotics: DIABOLO RCT in the Netherlands

- 528 patients with first episode of diverticulitis
- Both treating provider and patient were unblinded
- Randomized to no antibiotics vs IV antibiotics for 38 hours then p.o. amoxicillin-clavulanic acid
- Results:
  - No difference in time to recovery (median 12 days with antibiotics, 14 days without)
  - No difference in emergency surgery (3 patients with antibiotics, 2 patients without, p=0.55)

L Daniels et al. Br J of Surgery. 2017.

2 Antibiotics vs. no antibiotics: DIABOLO RCT in the Netherlands

But, in long-term follow up there was a trend towards higher rates of elective surgery if antibiotic were withheld!

- Colonic obstruction
- Ongoing diverticulitis
- Recurrent diverticulitis

	No antibiotics	Antibiotics	P-value
Elective surgery	7.7%	4.2%	0.09

Six patients in no-antibiotic arm were excluded from this analysis, 4 of whom underwent sigmoid resection!

Rate of major adverse event after elective sigmoid resection for diverticulitis: 17%

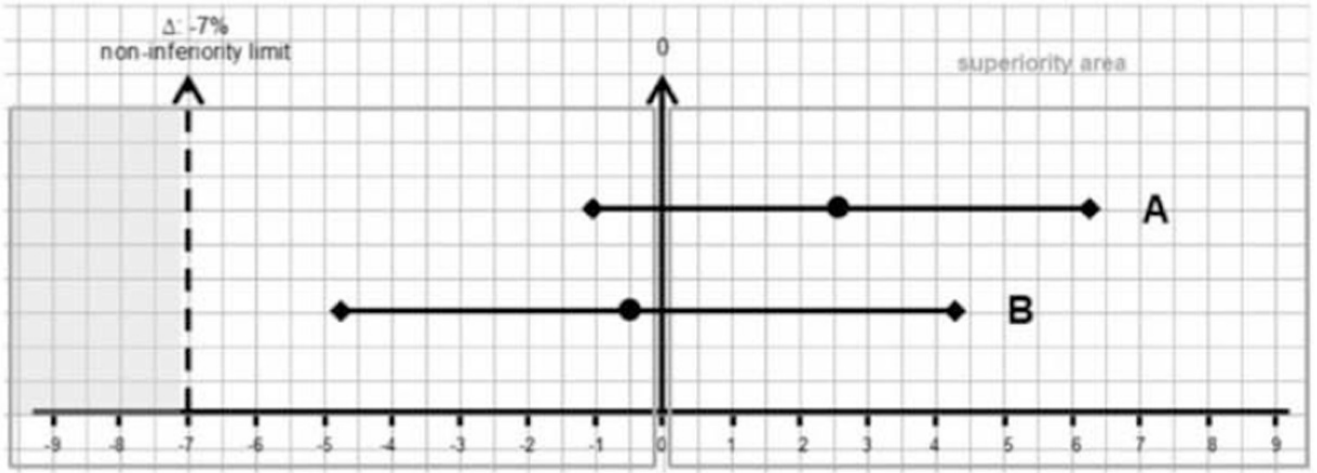
- Post op abscess: 4%
- Anastomotic leak: 3%
- Ostomy: 7%

L Daniels et al. Br J of Surgery. 2017.

Anne Peery. Am J of Gastroenterology. 2018.

3 Antibiotics vs. no antibiotics: DINAMO study

- Open-label, non-inferiority RCT
  - Pre-specified non-inferiority margin 7%
  - Primary endpoint: admission to hospital
- Randomized in ED after CT confirmed diverticulitis and adequate symptom control
  - Ibuprofen (600 mg q8h) + acetaminophen (1 g q8h) vs. ibuprofen/acetaminophen + amox/clav for 7 days



90-days FU	ATB-Group (%)	Non-ATB-Group (%)	p	CI 95% (ATB-Group (%) – Non-ATB-Group (%))
(A) Admission	14/238 (5·8%)	8/242 (3·3%)	0·19	2·58 (6·32 to -1·17)
(B) ED revisit	16/238 (6·7%)	17/242 (7%)	1	-0·3 (4·22 to -4·83)

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Laure Mora-Lopez. Ann Surg. 2021.

3 Antibiotics vs. no antibiotics: DINAMO study

- Non-inferiority design can be exploited: in an analysis of 182 non-inferiority trials, only 2% of novel or experimental interventions were inferior!
- Hospitalizations as an endpoint is important but can itself be a surrogate endpoint
  - Need to be cautious when extrapolating the benefit of reduced hospital admissions to better outcomes
  - In an analysis of 55 trials reporting both hospitalization and mortality in response to an intervention:
    - Concordance in 60% (both hospitalization and mortality increase or decrease together)
    - Discordance in 40%
      - Lower mortality but more hospitalization: 13%
      - Higher mortality but fewer hospitalization: 26%

Lars Hemkens et al. CMAJ. 2013.

Scott Aberegg et al. J Gen Int Medicine. 2018.

To Summarize:

1. AVOD trial:
    a. Open label
    b. Small number of events
    c. High rate of prior diverticulitis in the no-antibiotic arm
        a. Complications are more likely to occur in the first episode, driving down the number of events in the no-antibiotic group
2. DIABOLO trial:
    a. Unblinded
    b. Trend toward higher rates of elective surgery in long-term follow up which indicates ongoing symptoms or complications and carries substantial risks
3. DINAMO trial:
    a. Open label
    b. Non-inferiority
    c. Hospitalization was the primary endpoint

We are not yet ready for medical reversal for uncomplicated diverticulitis

The available data is just not strong enough for us to abandon antibiotics.

Withholding antibiotics carries substantial risk for the patient, not just in the short term but long term as well.