Spectrum of Diverticular Disease

ACG Postgraduate Course
January 24, 2015

Lisa Strate, MD, MPH
Associate Professor of Medicine
University of Washington, Seattle, WA

Outline

• Traditional theories and updated perspectives
• Diverticulitis
• Recurrent diverticulitis
• Post-diverticulitis irritable bowel syndrome
• Symptomatic uncomplicated diverticular disease (SUDD)
Traditional View: Limited Acute Attacks

**Diverticulosis**
30-50% of Americans > 60 yrs

- **Uncomplicated**
  - Asymptomatic 75%

- **Complicated**
  - Diverticulitis 25%
  - Bleeding 5%
  - Diverticular Colitis <1%

Traditional View: Pathophysiology

- **Diverticulosis** → Obstruction / Trauma → Bacterial stasis → Microperforation → Inflammation
Updated View: A Disease Spectrum

**Diverticulosis**

- **Asymptomatic**
  - Symptomatic (SUDD)
  - Diverticular Bleeding
  - Diverticular Colitis

- **Diverticulitis**
  - Recurrent Diverticulitis
  - Functional Bowel Disorders
  - Mood Disorders

Evolving Pathophysiologic Mechanisms

**Diverticular Disease**

- Altered Microbiota
- Low-grade inflammation
- Diverticular Disease
- Altered motility
- Visceral hypersensitivity

*Strate et al Am J Gastroenterol 2012*
Updated View: A Disease Spectrum

**Diverticulosis**

- Asymptomatic
- Diverticular Bleeding
- Diverticular Colitis

**Diverticulitis**

- Symptomatic (SUDD)
- Recurrent Diverticulitis
- Irritable Bowel Syndrome
- Mood Disorders

Progression to Diverticulitis is Uncommon

- 2222 Prevalent Diverticulosis on colonoscopy
- Median time to event: 7 years
- 95 (4%) Diverticulitis 6/1000 patient years
- 23 (1%) CT-confirmed Diverticulitis 1.5/1000 patient years

Are Antibiotics Necessary for Acute Uncomplicated Diverticulitis?

Multicenter randomized trial in Sweden
623 patients with CT proven uncomplicated L-sided diverticulitis

<table>
<thead>
<tr>
<th></th>
<th>Antibiotics N=314</th>
<th>No Antibiotics n=309</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication (abscess, perforation)</td>
<td>3 (1.0%)</td>
<td>6 (1.9%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Length of stay</td>
<td>3 days</td>
<td>3 days</td>
<td>0.72</td>
</tr>
<tr>
<td>Recurrence in 1 year</td>
<td>46 (16%)</td>
<td>47 (16%)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Updated View: A Disease Spectrum

- **Diverticulosis**
  - Asymptomatic
  - Symptomatic (SUDD)
    - Diverticular Bleeding
    - Diverticular Colitis
  - Diverticulitis
    - Recurrent Diverticulitis
    - Irritable Bowel Syndrome
    - Mood Disorders
Recurrence is Not More Serious Than Incident Disease

### Outcomes of Patients with Incident Hospitalization for Diverticulitis

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (n=20,135)</th>
<th>&lt; 40 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent admission</td>
<td>19%</td>
<td>27%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>More than 1 recurrence</td>
<td>3.8%</td>
<td>6.0%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrence with emergency colectomy</td>
<td>4.4%</td>
<td>6.7%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abscess</td>
<td>7.4%</td>
<td>11.2%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>2.7%</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

A population-based administrative cohort (CHARS) in the state of Washington

Anaya, Flum Arch Surg 2005

---

Timing of Elective Colectomy

Decision analysis based on data from the population-based CHARS study

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Age, y</th>
<th>Cost per patient ($)</th>
<th>QALYs per patient</th>
<th>Cost/QALY ($)</th>
<th>Colectomies (%)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective colectomy after first episode</td>
<td>50</td>
<td>10,829</td>
<td>18.3</td>
<td>591.9</td>
<td>5.7</td>
<td>2.93</td>
</tr>
<tr>
<td>Elective colectomy after second episode</td>
<td>50</td>
<td>5,230</td>
<td>18.7</td>
<td>279.6</td>
<td>3.1</td>
<td>2.00</td>
</tr>
<tr>
<td>Elective colectomy after third episode</td>
<td>50</td>
<td>4,272</td>
<td>18.8</td>
<td>227.4</td>
<td>2.4</td>
<td>1.65</td>
</tr>
<tr>
<td>Elective colectomy after fourth episode</td>
<td>50</td>
<td>4,199</td>
<td>18.8</td>
<td>223.3</td>
<td>2.4</td>
<td>1.57</td>
</tr>
<tr>
<td>Elective colectomy after first episode</td>
<td>35</td>
<td>10,124</td>
<td>22.1</td>
<td>427.8</td>
<td>5.9</td>
<td>0.71</td>
</tr>
<tr>
<td>Elective colectomy after second episode</td>
<td>35</td>
<td>6,113</td>
<td>23.4</td>
<td>200.7</td>
<td>4.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Elective colectomy after third episode</td>
<td>35</td>
<td>4,866</td>
<td>23.5</td>
<td>207.0</td>
<td>4.0</td>
<td>0.74</td>
</tr>
<tr>
<td>Elective colectomy after fourth episode</td>
<td>35</td>
<td>4,695</td>
<td>23.5</td>
<td>199.6</td>
<td>3.9</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Note: QALY, quality-adjusted life-years.

Wait until at least 4 episodes

Salem, Flum J Am Coll Surg 2004S
Diminished Role of Surgery in Recurrent Diverticulitis

- 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.

*Practice guideline Amer. Society of Colon & Rectum Surgeons: Feingold, et al. Dis Colon Rectum 57(3); 2014: 284*

Evolving Pathophysiologic Mechanisms Diverticular Disease

- Altered Microbiota
- Low-grade inflammation
- Diverticular Disease
- Altered motility
- Visceral hypersensitivity
- S-ASA
- Probiotics
- Non-absorbable antibiotics

*Strate et al Am J Gastroenterol 2012*
Summary: Prevention of Recurrent Diverticulitis

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Fiber</th>
<th>5-ASA</th>
<th>Rifaximin</th>
<th>Probiotics</th>
</tr>
</thead>
</table>

Type of evidence: Indirect evidence from patients without previous diverticulitis
Small Randomized Trials Meta-analyses
Small trials rifaximin + fiber in patients with SUDD
Small randomized trial

Quality of evidence: Low
Moderate
Low
Low


Mesalamine Does NOT Prevent Recurrent Diverticulitis: PREVENT1 and PREVENT2

- 590/592 pts with ≥ 1 episode of diverticulitis in prior 2 yrs
- Mesalamine 1.2g, 2.4g or 4.8g
- 104 weeks (2 years)
- Diverticulitis diagnosed by CT

Raskin JB. Gastroenterology 2014;147:793
Updated View: A Disease Spectrum

**Diverticulosis**

- Asymptomatic
- Symptomatic (SUDD)
- Diverticular Bleeding
- Diverticulitis
- Recurrent Diverticulitis
- Irritable Bowel Syndrome
- Mood Disorders
- Diverticular Colitis

IBS and Diverticular Disease

- Motor abnormality
  - Irritable bowel syndrome → Diverticulosis
- Altered colon structure/pressures
  - Diverticulosis → Irritable bowel syndrome
- Post-inflammatory/visceral hypersensitivity
  - Diverticulitis → Irritable bowel syndrome

Simpson et al Br J Surg 2003;90:899
**Post-Diverticulitis Irritable Bowel Syndrome**

Retrospective study of 1100 cases of diverticulitis and 1100 controls without a prior diagnosis of functional bowel disease followed for average of 6 years

**IBS:**
Adjusted HR 4.7 (95% CI, 1.6-14)

**Functional GI Diagnosis:**
Adjusted HR 2.4 (95% CI, 1.6-3.6)

---

**Post-Diverticulitis & Mood Disorders**

Retrospective study of 1100 cases of diverticulitis and 1100 controls without a prior diagnosis of functional bowel disease followed for average of 6 years

**Depression/Mood Disorder:**
Adjusted HR 2.2 (95% CI, 1.4-3.6)
Post-Diverticulitis Quality of Life

Updated View: A Disease Spectrum

Diverticulosis

- Asymptomatic
- Symptomatic (SUDD)

Diverticulitis

- Recurrent Diverticulitis
- Irritable Bowel Syndrome
- Mood Disorders

Diverticular Bleeding

Diverticular Colitis

Symptomatic Uncomplicated Diverticular Disease (SUDD)

- Subtype of diverticular disease with persistent abdominal symptoms attributed to diverticula in the absence of macroscopic colitis or diverticulitis
- Greater interest in Europe (UK and Italy) than US
- Variably applies to those with and without prior diverticulitis

*Spiller RC Dig Dis. 2012;30:64*

IBS vs SUDD

<table>
<thead>
<tr>
<th></th>
<th>IBS</th>
<th>SUDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Young</td>
<td>Older</td>
</tr>
<tr>
<td></td>
<td>Female &gt;&gt; Male</td>
<td>Female = Male</td>
</tr>
<tr>
<td>Colon structural changes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevalence of symptoms</td>
<td>100%</td>
<td>15% of diverticulosis pts</td>
</tr>
<tr>
<td>Rome criteria</td>
<td>100%</td>
<td>15%</td>
</tr>
<tr>
<td>Pain pattern</td>
<td>Frequent recurrences, short-lived</td>
<td>Long remissions, prolonged (&gt;24hrs)</td>
</tr>
<tr>
<td>Pain location</td>
<td>Diffuse</td>
<td>Left lower quadrant</td>
</tr>
<tr>
<td>Bowel alteration</td>
<td>Diarrhea &amp; constipation</td>
<td>Diarrhea &gt; constipation</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*Spiller RDig Dis 2012:30:64-69*  
*Tursi A J Clin Gastroenterol 2014*
### Summary: Treatment of SUDD

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Fiber</th>
<th>5-ASA</th>
<th>Rifaximin</th>
<th>Probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>?Prevent</td>
<td></td>
<td>Prevent</td>
<td>Prevent</td>
<td>Prevent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of evidence</th>
<th>Fiber</th>
<th>5-ASA</th>
<th>Rifaximin</th>
<th>Probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small studies; often combined with other therapy</td>
<td></td>
<td></td>
<td>One small randomized Trials</td>
<td>Few small randomized trial</td>
</tr>
<tr>
<td>One small randomized Trials</td>
<td></td>
<td></td>
<td>One trial rifaximin + fiber; One RCT</td>
<td></td>
</tr>
<tr>
<td>Few small randomized trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Fiber</th>
<th>5-ASA</th>
<th>Rifaximin</th>
<th>Probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Mesalamine & Lactobacillus casei Maintain Remission in SUDD

- 210 Italian patients with SUDD and no prior diverticulitis
- Treated 10 days/month x 12 months

**Graph:**

- Mesalamine+Lactobacillus (n=54)
- Lactobacillus (n=55)
- Mesalamine (n=51)
- Placebo (n=50)

Tursi A. Aliment Pharmacol Ther 2013;38:741
The Spectrum of Diverticular Disease

- Diverticulosis
- Diverticulitis
- Altered Microbiota
- Altered Motility
- Hypersensitivity
- Inflammation
- Recurrent Diverticulitis
- Segmental Colitis

Summary

- Diverticular disease represents a spectrum of disorders with chronic manifestations
- Manifestations range from “functional” to frankly inflammatory
- Altered microbiota, chronic inflammation, visceral hypersensitivity and altered motility may play a role
- New treatment paradigms exist but few proven effective therapies
Updated View: A Disease Spectrum

Diverticulosis

Asymptomatic Diverticulitis

Symptomatic (SUDD) Recurrent Diverticulitis

Diverticular Bleeding Diverticular Colitis

Irritable Bowel Syndrome Mood Disorders

Diverticular Bleeding Associated with Cardiovascular Risk Factors

- Pathophysiology involves vascular injury and not mucosal inflammation
- Vessel histology consistent with arteriosclerosis
- Risk factors include:
  - Obesity
  - Physical inactivity
  - Hypertension
  - Hyperlipidemia
  - Diabetes

Strate et al. Gastroenterol 2008; 136:115
Strate et al. Am J Gastroenterol 2009; 104:1221
Yamada et al Dis Colon Rectum 2007; 51:116
Updated View: A Disease Spectrum

Diverticulosis

Asymptomatic

Symptomatic (SUDD)

Diverticular Bleeding

Diverticulitis

Recurrent Diverticulitis

Mood Disorders

Irritable Bowel Syndrome

Diverticular Colitis

Diverticular Colitis or Segmental Colitis Associated with Diverticular Disease

- Chronic mucosal inflammation similar to IBD confined to a segment of (left) colon with diverticulosis with sparing of the rectum and proximal colon
- Diverticula are not inflamed (no diverticulitis)
- Relationship with IBD is unclear
  - IBD with coincidental diverticulosis
  - Segmental colitis is a form of IBD (10% develop IBD)
  - Segmental colitis is a form of diverticulitis

Peppercorn et al. AJG 1992
### IBD vs. Segmental Colitis

#### Similarities
- Endoscopic findings
- Histology findings
- Treatment
  - 5-ASA
  - Antibiotics
  - Anti-TNF

#### Differences
- Older age in SCAD
- SCAD spares rectum
- Lower relapse rate
- SCAD usually
  - No fever
  - No ↑ ESR, CRP

*Tursi, et al. Dig Dis Scie 2011*