Medical and Endoscopic Management of Upper GI Bleeding

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ACG Annual Meeting 2013
Upper GI Bleeding: Pre-endoscopic Medical Therapy

- Proton pump inhibitors
- Erythromycin
- Antibiotics
- Octreotide
ACG Practice Guideline

Management of Patients With Ulcer Bleeding

Loren Laine, MD, and Dennis M. Jensen, MD

This guideline presents recommendations for the step-wise management of patients with overt upper gastrointestinal bleeding. Hemodynamic status is first assessed, and resuscitation initiated as needed. Patients are risk-stratified based on features such as hemodynamic status, comorbidities, age, and laboratory tests. Pre-endoscopic proton pump inhibitor (PPI) may be considered to decrease the need for endoscopic therapy but does not improve clinical outcomes. Upper endoscopy is generally performed within 24 h. The endoscopic features of ulcers direct further management. Patients with active bleeding or non-bleeding visible vessels receive endoscopic therapy (e.g., bipolar electrocoagulation, heater probe, sclerosant, clips) and those with an adherent clot may receive endoscopic therapy; these patients then receive intravenous PPI with a bolus followed by continuous infusion. Patients with flat spots or clean-based ulcers do not require endoscopic therapy or intensive PPI therapy. Recurrent bleeding after endoscopic therapy is treated with a second endoscopic treatment; if bleeding persists or recurs, treatment with surgery or interventional radiology is undertaken. Prevention of recurrent bleeding is based on the etiology of the bleeding ulcer. *H. pylori* is eradicated.

ASGE Guidelines

The role of endoscopy in the management of acute non-variceal upper GI bleeding

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When few or no data exist from well-designed prospective trials, emphasis is given to results from large series and meta-analysis, or to expert opinion for outcomes patients with non-variceal UGIB has been demonstrated to improve patient outcomes. This updated ASGE guideline focuses on the role of GI endoscopy in patients with acute non-variceal UGIB. This guideline will not address obscure GI bleeding or the role of endoscopy in the management of variceal bleeding, both of which are discussed in existing ASGE practice guidelines. UGIB refers to GI blood loss having an origin proximal to the ligament of Treitz. Acute UGIB can manifest as hematemesis, “coffee ground” emesis, the return of red blood via a nasogastric tube, or stool with or without hematochezia.
**Medical Therapy:**

**PPIs**

“Pre-endoscopic intravenous proton pump inhibitor (e.g., 80 mg bolus/ 8mg/hr infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012

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**PPIs and Upper GI Bleeding**

- 240 patients with peptic ulcer disease
  - Active bleeding or visible vessel at EGD
- Injection plus thermal therapy
  - Successful hemostasis
- Randomized to
  - Omeprazole 8mg/hour IV
  - Placebo

PPIs and Upper GI Bleeding

- Cohort of patients with upper GI bleeding
- Randomized to
  - Omeprazole 80 mg bolus followed by 8 mg/hr infusion vs placebo
  - Used both high dose bolus and infusion protocol
- Endoscopy

Lau JY, Leung WK, Wu JCY, NEJM, 2007
PPIs and Upper GI Bleeding

<table>
<thead>
<tr>
<th></th>
<th>PPIs</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic therapy overall</td>
<td>19.1%</td>
<td>28.4%</td>
<td>0.007</td>
</tr>
<tr>
<td>In those with ulcers:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active bleeding</td>
<td>6.4%</td>
<td>14.7%</td>
<td>0.01</td>
</tr>
<tr>
<td>Clean Based ulcers</td>
<td>64.2%</td>
<td>47.4%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Use of PPIs before endoscopy... bolus followed by IV infusion decreases the need for endoscopic therapy and decreases the proportion of patients with higher risk stigmata

Lau JY, Leung WK, Wu JCY, NEJM, 2007

PPIs and Upper GI Bleeding

Numbers of Ulcers Found during the First Endoscopic Examination

PPIs and UGI Bleeding: Outcomes Without Endoscopy Therapy

- Meta-analysis of randomized trials of patients with UGIB who did not receive endoscopic hemostatic therapy
- PPI therapy associated with
  - Reduced rebleeding (Odds ratio 0.38, NNT=10)
  - Reduced need for surgery (Odds ratio 0.62, NNT=17)
- PPI therapy had no effect on mortality
- PPIs may improve outcomes when endoscopy not done


PPIs and Upper GI Bleeding

- Cochrane meta-analysis
- 6 randomized controlled trials (N=2223)
- Compared pre-endoscopic PPI and control in patients with suspected UGI bleeding

Steedharan A, Martin J, Leontiadis, Cochrane Database Syst Rev 2010
PPIs and Upper GI Bleeding

Pre-procedure PPI
- Reduced rate of high risk stigmata identified at endoscopy (active bleeding, non-bleeding visible vessel, adherent clot)
  - PPI: 37%
  - Control: 47%
  - OR 0.67
- Reduced need for endoscopic therapy
  - PPI: 8.6%
  - Control: 11.7%
  - OR 0.68

Steedhan A, Martin J, Leontiadis, Cochrane Database Syst Rev 2010

No significant effect on mortality, rebleeding or need for surgery

<table>
<thead>
<tr>
<th></th>
<th>PPI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>6.1%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>13.9%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Surgery</td>
<td>9.9%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Steedhan A, Martin J, Leontiadis, Cochrane Database Syst Rev 2010

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Medical Therapy:
PPIs

“PPIs do not improve clinical outcomes such as further bleeding, surgery or death”

PPIs should not replace the need for adequate resuscitation and early endoscopy

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Barkun AN, GIE, 2008

Medical Therapy:
PPIs

“If endoscopy will be delayed or cannot be performed, IV PPI is recommended to reduce further bleeding”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Erythromycin Prior to Endoscopy in UGI bleeding

- Prokinetics may improve visualization at endoscopy
- IV erythromycin
  - Motilin-like activity
  - Systematic review of 3 studies
  - Dosing: 3mg/kg (or 250 mg IV) over 5 or 30 minutes, 20-60 minutes prior to EGD

Results:
- Quality of visualization of mucosa significantly better
- Meta-analysis showed modest but significant benefit in diagnosis at the first endoscopy (RR = 1.13, NNT=9)
- Decreased need for repeat upper endoscopy
- No difference in:
  - Blood transfusion requirements
  - Length of hospital stay
  - Need for surgery
  - Adverse events
Medical Therapy: Erythromycin

“Intravenous infusion of erythromycin (250 mg approx. 30 minutes before endoscopy) should be considered to improve diagnostic yield and decrease the need for repeat endoscopy. However, erythromycin has not consistently been shown to improve clinical outcomes”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012

Antibiotics and Variceal Bleeding

• Antibiotics indicated prophylactically before endoscopy
  – Reduces:
    • Infections (45% vs 14%)
    • Rebleeding (78% vs 33% at 7 days)
    • Mortality (24% vs 15%)
• Typical choice is a quinolone

Garcia-Tsao, ACG Guidelines, AJG, 2007
Octreotide in Non-variceal Upper GI Bleeding

- Meta-analysis, 14 trials, 1829 patients
- Overall relative risk of further bleeding
  - Favors octreotide
  - OR 0.53 (0.43-0.63)
- Other investigator blinded trials (seven)
  - Favor octreotide
  - OR 0.73 (0.67-0.81)

Octreotide may diminish the risk of bleeding in non variceal upper GI bleeding

Imperiale T, Ann Int Med, 1997

Medical Therapy for UGI Bleeding: Summary

- PPIs (80 mg IV bolus followed by an 8 mg/hour IV infusion for 72 hours) are effective in patients with high risk stigmata to decrease bleeding
- PPIs should be used in combination with endoscopic therapy for optimal outcomes
- Therapy with erythromycin may result in a higher diagnostic yield when there is a high probability of fresh blood or a clot in the stomach
- Antibiotic prophylaxis before therapy for variceal bleeding is indicated
Endoscopy in the Management of Upper GI Bleeding

- **Highly effective**
  - Reduces blood transfusion requirements
  - Reduces length of ICU stays
  - Reduces the length of hospital stay
- **Diagnosis**
  - Identifies bleeding source frequently
- **Prognosis**
  - Allows prediction of risk of recurrent bleeding
- **Therapy**
  - Injection, thermal, mechanical

Endoscopic Stigmata of Bleeding Peptic Ulcer

**Endoscopic Findings Predict Rebleeding**

<table>
<thead>
<tr>
<th>Stigmata (Identified at endoscopy)</th>
<th>Risk of rebleeding if untreated</th>
<th>Surgery</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial spurting bleeding</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial oozing bleeding</td>
<td>55% (17-100%)</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Non-bleeding visible vessel (NBVV)</td>
<td>43% (8-81%)</td>
<td>34%</td>
<td>11%</td>
</tr>
<tr>
<td>Sentinel clot</td>
<td>22% (14-36%)</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Flat pigmented spot</td>
<td>10% (0-13%)</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Clean based ulcer</td>
<td>5% (0-10%)</td>
<td>0.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Laine L, Peterson WL, NEJM, 1994

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**Indications for Endoscopic Therapy**

<table>
<thead>
<tr>
<th>Stigmata</th>
<th>Endoscopic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>Yes</td>
</tr>
<tr>
<td>Non bleeding visible vessel</td>
<td>Yes</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>Consider</td>
</tr>
<tr>
<td>Flat spot</td>
<td>No</td>
</tr>
<tr>
<td>Clean base</td>
<td>No</td>
</tr>
</tbody>
</table>

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
**Indications for Endoscopic Therapy**

- **Actively bleeding ulcer**
  - Meta-analysis of endoscopic therapy vs no endoscopic therapy
    - Endoscopic therapy favored
    - Significant decrease in further bleeding (RR 0.29, NNT=2)
    - Decreased need for surgery
- **Non-bleeding visible vessel**
  - Endoscopic therapy leads to significant decrease in further bleeding (RR 0.49, NNT = 5)


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**Indications for Endoscopic Therapy**

**Adherent clot**
- Meta-analysis of endoscopic therapy shows no significant benefit
- Heterogeneity in studies
  - Two US studies
    - Significant benefit from endoscopic hemostasis
    - 3% rebleeding vs 35% with medical therapy
  - European and Asian studies
    - No benefit from endoscopic hemostasis
- One study using vigorous irrigation and bolus plus IV infusion PPI following endoscopy vs placebo
  - No rebleeding in the control arm (patient treated medically)

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012

Which Endoscopic Therapy to Choose

• Injection
• Thermal (contact)
  – Heater Probe
  – Bipolar probe
  – Monopolar probe
• Thermal (non-contact)
  – Argon plasma coagulator
• Mechanical
  – Clips
  – Banding
• Combination

Epinephrine Injection

“Epinephrine therapy should not be used alone. If used, it should be combined with a second modality.”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Epinephrine Injection: Technique

- 1:10000 or 1:20000 concentration
- 0.5-2.0 cc aliquots
- Injected in and around the stigmata of recent hemorrhage in ulcer base
- Large volume therapy (30-45 cc) has been reported to be more effective
  - Increased risk

Epinephrine Injection

Epinephrine monotherapy
- Effective at achieving initial hemostasis
- Not more effective than other mono-therapies in initial hemostasis
- Less effective than other monotherapies in preventing further bleeding (RR 1.72)
- Epinephrine in combination with a second modality more effective than epinephrine alone in reducing further bleeding (RR 0.34, NNT=5)

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Epinephrine Injection

• Epinephrine injection prior to thermal/mechanical therapy
  – May slow or stop bleeding allowing improved visualization
  – In adherent clots, pre-injection of epinephrine may reduce the rate of severe bleeding induced by clot removal

• Combination therapy with injection and a second modality may be beneficial even if lesion not bleeding
  – Fluid cushion may reduce the risk of perforation with subsequent cautery
  – Combination probe available

Thermal Therapy

“Thermal therapy with bipolar electrocoagulation or heater probe .... are recommended because they decrease further bleeding, need for surgery and mortality.”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Thermal Therapy

- Bipolar electrocoagulation or heater probe
  - May be called multipolar electrocoagulation (MPEC)
- Meta-analysis of 15 randomized trials
- Significantly more effective than no endoscopic therapy for
  - Initial hemostasis
  - Reducing further bleeding
  - Surgery
  - Mortality
- Bipolar electrocoagulation and heater probe equally effective


Thermal Therapy: Technique

- Endoscope tip as close as possible to bleeding ulcer
- May be applied en face (perpendicular) or tangentially
- Coaptive coagulation
  - Compress vessel and then coagulate
- Probe size
  - 10 French more effective than 7 French
- Most probes allow both thermal therapy and irrigation
Thermal Therapy: 
Technique

- **Power**
  - Bipolar probe: ~ 15 watts for 8-10 second applications
  - Heater probe: 30 joules for 8-10 second applications

- **Multiple applications to ulcer base and around stigmata of recent hemorrhage until**
  - Bleeding stops
  - Vessel flattened
  - Base whitened

Hemostatic Clips

“Clips are recommended because they appear to decrease further bleeding and need for surgery.”

“However, comparisons of clips vs. other therapies yield variable results and currently used clips have not been well studied”

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Hemostatic Clips

- Clips more effective than injection mono-therapy in reducing further bleeding and need for surgery
- Clips
  - May be less effective than thermal therapy at initial hemostasis
  - No different in other outcomes like further bleeding
  - Heterogeneity in studies
  - Newer clips require new studies
- Clips may be preferred over thermal therapy in patients receiving anti-thrombotic therapy

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012

Preferred Modality (Thermal vs Clips)?

<table>
<thead>
<tr>
<th>Modality</th>
<th>Rebleeding odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal plus epi vs epi alone</td>
<td>0.27</td>
</tr>
<tr>
<td>Clips plus epi vs epi alone</td>
<td>0.38</td>
</tr>
<tr>
<td>Thermal plus epi vs thermal alone</td>
<td>0.70 (crosses 1)</td>
</tr>
<tr>
<td>Clips plus epi vs clips alone</td>
<td>1.30 (crosses 1)</td>
</tr>
</tbody>
</table>

- Injection alone not favored
- Thermal or clips alone may be as good as combination
- Equivocal data for adherent clots
Hemostatic Powders

Barkun AN, GIE 2013

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Medical Therapy after Endoscopy

- Following successful endoscopic hemostasis
  - IV PPI therapy (80 mg bolus followed by 8 mg/h continuous infusion) for those with
    - Ulcer with active bleeding
    - Non-bleeding visible vessel
    - Adherent clot
  - IV PPI therapy for 72 hours significantly reduces further bleeding in those groups
  - Oral PPI therapy may be as good as IV PPI therapy in these groups, but needs more study
- Patients with flat spots or clean based ulcers should receive standard PPI therapy

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012
Repeat Endoscopy

• Routine second look endoscopy not recommended
• Repeat endoscopy indicated when clinical evidence of recurrent bleeding
  – Hemostatic therapy should be applied in those with high risk stigmata
• Further bleeding after second endoscopic therapeutic session typically will prompt surgery or interventional radiologic procedure

Laine L, Jensen DM, ACG Guidelines, Management of patients with ulcer bleeding, AJG, 2012

Endoscopic Therapy: Summary

• Endoscopic therapy for bleeding from peptic ulcers with high risk stigmata is effective
• Endoscopic therapy for adherent clots is controversial
• Injection, thermal and mechanical therapies all may play a role
• Epinephrine injection alone is not recommended, but is effective when used in combination with other modalities
• Routine second look endoscopy is not recommended