**Approach to Upper GI Bleeding**

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Co-Medical Director of Endoscopy
University of Virginia
Division of Gastroenterology and Hepatology

**Natural History**

- In 1970, during the BC (before cimetidine) era, 79% of bleeding stopped without intervention

- Our job as gastroenterologists:
  - Stop any remaining bleeding
  - Reduce risk of rebleeding

Schiller et al. BMJ 1970
Background

- GI bleeding is a significant medical problem
  - 300,000 hospitalizations annually
  - Incidence increases with age
  - Rebleeding rates range from 7-16% despite endoscopic treatment
    - Variceal rebleeding (25-29%)
    - PUD rebleeding (20-22%)
  - Mortality: 10-14%


Sources of UGIB

- Non-variceal UGIB
  - Ulcer (33-56%)
  - Erosions (19%)
  - Mallory-Weiss tear (4%)
  - Vascular lesions (3%)
  - Tumor (1%)

- Portal-hypertension
  - Gastric or duodenal varices
  - Gastric antral vascular ectasia (GAVE)

Enestvedt et al. Nonvariceal upper-GI hemorrhage, GIE 2008 (CORI), Barkun A et al. RUGBE, Am J Gastro 2004
Scoring Systems for Risk Assessment

- Blatchford, Rockall
- In general, high risk includes
  - Age >65
  - Shock
  - Poor overall health status, comorbidities
  - Low hemoglobin
  - Fresh blood, elevated urea

Transfusion in UGIB

RCT 921 patients
Restrictive (Hgb <7g/dl) vs Liberal (Hgb <9g/dl)

Restrictive Group:
- improved survival
- lower rebleeding rate (10% v 16%)
- fewer adverse events
- shorter hospital stay

Villanueva C et al, NEJM 2013
### Before Endoscopy

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>IV PPI</th>
<th>Prokinetics</th>
<th>Gastric lavage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Cochrane Review</td>
<td>Meta-analysis</td>
<td>RCT</td>
</tr>
<tr>
<td>Rebleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of high risk stigmata</td>
<td>XX</td>
<td></td>
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</tr>
<tr>
<td>Repeat EGD/Visualization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay/charges</td>
<td></td>
<td></td>
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<tr>
<td>Transfusion requirements</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*S 40 Fr tube with up to 15L of lavage  ** for high risk patients, <24 hours

Before Endoscopy

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<thead>
<tr>
<th>OUTCOMES</th>
<th>IV PPI</th>
<th>Prokinetics</th>
<th>Gastric lavage*</th>
<th>Early endoscopy**</th>
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<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td>RCT</td>
<td>RCT, retrospective</td>
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<tr>
<td>Rebleeding</td>
<td></td>
<td></td>
<td></td>
<td>X (retrospective)</td>
</tr>
<tr>
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* 40 Fr tube with up to 15L of lavage  ** for high risk patients, <24 hours


Timing of Endoscopy

ACG Practice Guidelines

“Patients with UGIB should generally undergo endoscopy within 24 hours of admission, following resuscitative efforts to optimize hemodynamic parameters and other medical problems”

“In patients with higher risk clinical features (e.g., tachycardia, hypotension, bloody emesis or NG aspirate) endoscopy within 12h may be considered to potentially improve clinical outcomes”

International Consensus Recommendations

“In patients receiving anticoagulants, correction of coagulopathy is recommended but should not delay endoscopy”

2012 ACG Practice Guidelines; Barkun AN et al. Ann Intern Med 2010
**Endoscopic Stigmata of Ulcers & Rebleed Risk**

<table>
<thead>
<tr>
<th>Stigmata</th>
<th>Forrest</th>
<th>Prevalence (%)</th>
<th>Rebleed (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleed</td>
<td>1a, 1b</td>
<td>10-20</td>
<td>90</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>2a</td>
<td>15-25</td>
<td>50</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>2b</td>
<td>10-20</td>
<td>25</td>
</tr>
<tr>
<td>Flat spot</td>
<td>2c</td>
<td>10-20</td>
<td>10</td>
</tr>
<tr>
<td>Clean base</td>
<td>3</td>
<td>35</td>
<td>5</td>
</tr>
</tbody>
</table>

* Without treatment


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**Results of Endoscopic Therapy**

Where it all began…

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=23)</th>
<th>MPEC (n=21)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis (%)</td>
<td>3 (13)</td>
<td>19 (90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood Transfusions</td>
<td>5.4 ± 0.9</td>
<td>2.4 ± 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Emergency Intervention (%)</td>
<td>13 (57)</td>
<td>3 (14)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hospital Stay (days)</td>
<td>7.2 ± 1.1</td>
<td>4.4 ± 0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital Cost ($)</td>
<td>7,550 ± 1,480</td>
<td>3,420 ± 750</td>
<td>0.001</td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>3(13)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

For actively bleeding lesions. * MPEC=multipolar electrocoagulation

**Endoscopic Therapy**

- Endoscopic therapy reduces
  - Bleeding (active or recurrent)
  - Need for surgery
  - Mortality
- Results driven by high risk stigmata:
  - Active bleeding (NNT 2)*
  - Visible vessels (NNT 5)*
  - Adherent clot & flat spot—not reduced*


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**Endoscopic Stigmata of Bleeding**

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<td>5</td>
</tr>
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</table>

After clot removal

59% would benefit from therapy

Adherent clot studies

- Four RCTs published 2002-2003:
  - Endo Rx Better = 2 (Jensen (n=32), Bleu (n=56))
  - No difference = 2 (Sung (n=39), Jung (n=19))

<table>
<thead>
<tr>
<th></th>
<th>Retrospective Study 2003</th>
<th>Meta-analysis 2005</th>
<th>Meta-analysis 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>244</td>
<td>240, 6 studies</td>
<td>189, 5 studies</td>
</tr>
<tr>
<td>Location</td>
<td>NYC</td>
<td>US, Spain, Asia</td>
<td>US, UK, Asia</td>
</tr>
<tr>
<td>Endo vs. Medical Rx</td>
<td>138 versus 106</td>
<td>112 versus 128</td>
<td>71 versus 118</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>0.07 (0.02-0.22)</td>
<td>0.39 (0.22-0.69)</td>
<td>0.31 (0.06-1.77)</td>
</tr>
<tr>
<td>FAVORS</td>
<td>Endo Rx</td>
<td>Endo Rx</td>
<td>No Difference</td>
</tr>
</tbody>
</table>

Adherent Clot Summary

- Controversy exists
- Only one study used continuous infusion PPI as control
  - Showed no difference in rebleeding rate
- Current Guidelines: endoscopic therapy may be considered, although intensive PPI therapy alone may be sufficient


Endoscopic therapeutic choices

- Injection
  - Epinephrine (1:10,000) or saline
  - Sclerosant
  - Thrombin/Fibrin Glue
- Thermal
  - Bipolar electrocoagulation (heat + pressure)
  - Heater probe (heat + pressure)
  - APC (heat only)
- Mechanical
  - Clip (theoretical advantage of no tissue injury)
**Injection therapy**

- Epinephrine: 1:10,000 – 1:100,000
- Less effective than:
  - Other monotherapies (NNT 9)
  - When combined with 2nd therapy (NNT 5)
- **TWO IS BETTER THAN ONE**
  - Two modalities—epi + thermal/mechanical
  - Two procedures—2nd look endoscopy if used as monotherapy


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**Thermal Therapy**

- Bipolar electrocoagulation
  - Coaptive coagulation: compress vessel (pressure), then coagulate (heat) to seal
  - Low wattage (15-20W) for 5-10 seconds
- Heater Probe
- Argon Plasma Coagulation
  - Less well-studied
  - No difference in RCT for high risk stigmata when compared to epi + heater probe

Chau C et al. GIE 2003
Thermal Therapy

- When compared to no therapy, reduced:
  - Bleeding (NNT 4)
  - Surgery (NNT 8)
  - Mortality (NNT 33)
- Can be used as monotherapy

Laine L, McQuaid KR. CGH 2009, Chau CH et al. GIE 2003

Endoscopic Hemoclips

- Initial hemostasis lower than other endoscopic treatments:
  - RR 0.78 (0.64 – 0.95)
- When clips do not work well
  - Challenging locations
    - Lesser curvature/posterior wall of stomach
    - Posterior duodenum
    - Retroflexed view
  - Fibrotic lesions

Endoscopic Hemoclips

- No difference in outcomes compared to standard endoscopic therapies (thermal):
  - Rebleeding, surgery, mortality
  - Better than epinephrine monotherapy
- SUMMARY: When able to be placed, clips appear as successful as thermal therapy

Daram SR et al. Surg Endosc 2013

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Endoscopic Hemoclips

<table>
<thead>
<tr>
<th></th>
<th>QuickClip2 (Olympus)</th>
<th>Resolution (BSCI)</th>
<th>Instinct (Cook)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaw span</td>
<td>11 mm</td>
<td>11 mm</td>
<td>16 mm</td>
</tr>
<tr>
<td>Rotation</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Re-opening ability</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MRI conditional</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Ulcer with active oozing
Ulcer with visible vessel
Large ulcer with visible vessel

Mallory Weiss Tear
Mallory Weiss Tear

Vascular Ectasia
Vascular Ectasia

Portal Hypertensive Bleeding

- Esophageal varices
- Gastric varices
- Duodenal varices
- Gastric Antral Vascular Ectasia (GAVE)
High Risk Esophageal Varices

Esophageal Varices with Band Ligation
Gastric Antral Vascular Ectasia

- Conventional approach (sclerosis, banding)
- TIPS (Transjugular Intrahepatic Portosystemic Shunt)
- Endoscopic glue injection: Cyanoacrylate
- BRTO (angiographic retrograde occlusion)
- Surgical shunt: rarely

Gastric Varices
BRTO (Balloon-Occluded Retrograde Transvenous Obliteration)
Complications of therapy

- Endoscopic therapy (8 of 1044, 0.8%) versus no endoscopy (1 of 931, 0.1%): RR 2.12 (0.79-5.70)

<table>
<thead>
<tr>
<th>Modality</th>
<th>n</th>
<th>Induced Bleeding</th>
<th>Perforations</th>
<th>Rate of Cpx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>958</td>
<td>2</td>
<td>0</td>
<td>0.2%</td>
</tr>
<tr>
<td>Sclerosant ± epi</td>
<td>1339</td>
<td>1</td>
<td>6</td>
<td>0.5%</td>
</tr>
<tr>
<td>HP ± epi</td>
<td>1070</td>
<td>2</td>
<td>9</td>
<td>1.0%</td>
</tr>
<tr>
<td>BPEC ± epi</td>
<td>580</td>
<td>1</td>
<td>2</td>
<td>0.5%</td>
</tr>
<tr>
<td>Clips ± epi</td>
<td>373</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Cpx = complications, epi = epinephrine, HP = heater probe, BPEC = bipolar electrocoagulation

New Endoscopic Therapies (aka non-standard therapies)

- Hemospray/EndoClot
  - Disclaimer: Not FDA approved in the United States

- Over-the-Scope closure devices
Hemospray

- Mechanical tamponade effect
- Absorbs water
- Activates clotting cascade

Gastrointestinal Endoscopy 2013 77, 692-700

Hemospray

Sung JJ et al. Endoscopy 2011

ACG Regional Postgraduate Course - Williamsburg, VA
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ACG Regional Postgraduate Course - Williamsburg, VA
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Hemospray

Case series of 16 patients

Sulz MC et al. Endoscopy 2014

Reports using Hemospray/Endoclot

- Peptic ulcer bleeding, primary tx
  - 20 adults, 95% hemostasis, 2 rebleed
- Malignant bleeding
  - 5 patients, 100% hemostasis, one rebleed
- Variceal bleeding
  - 9 patients, 100% hemostasis, zero rebleed
- Post EMR
  - 20 lesions, 90% hemostasis, 3 rebleed

SEAL Survey

- 10 pilot sites across Europe in 2011
- 63 patients with UGIB
  - 30 ulcers, 33 “other” pathology
- 55 (87%) treated as monotherapy
- Primary hemostasis: 85% (47/55)
- Rebleeding rate at 7d: 15%
- Second-line therapy in 8 patients, all with hemostasis


Over the Scope Clip

- Retrospective study, 30 patients
- Conventional Rx failures
- Hemostasis—97%
  - Rebleed—6%
- Reports include use in ulcers, MW tear, dieulafoy, GIST, anastomosis, EMR/ESD, diverticular, post polypectomy

Post-endoscopic Therapy

PPI after endoscopic therapy


- 30-day rebleed rate
  - 6.7% for IV omeprazole
  - 26.5% for placebo
What Dose of PPI?

- RCT 201 patients after endoscopic Rx with epi + thermocoagulation (Forrest 1a/1b/IIa)
- Compared continuous infusion versus bolus

<table>
<thead>
<tr>
<th></th>
<th>High-dose</th>
<th>Stnd-dose</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Recurrent bleed (72h)</td>
<td>5</td>
<td>6</td>
<td>0.77</td>
</tr>
<tr>
<td>Recurrent bleed (30d)</td>
<td>7</td>
<td>7</td>
<td>0.98</td>
</tr>
<tr>
<td>Surgery</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death (bleeding-related)</td>
<td>1</td>
<td>1</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Chen C et al. Alim Pharm & Ther, 2012

High dose versus non-high dose

- Meta-analysis of 1157 patients in 7 studies
- High dose = continuous infusion
- NO difference:
  - Rates of rebleeding (OR 1.30, CI 0.88-1.91)
  - Surgery (OR 1.49, CI 0.66-3.37)
  - Mortality (OR 0.89, CI 0.37-2.13)

Wang, C et al. Arch Int Med 2010
We found that the best dose and route of administration of PPIs cannot yet be determined.

Our results show that, with regards to deaths, rebleeding episodes, emergency surgeries and need for repeat endoscopic treatments, it is not certain if high intravenous dose of PPIs are more, less or equally effective compared to lower (oral or intravenous) dose of PPIs.

Neumann I et al. Cochrane Review 2013

PPI after UGIB Treatment

- PPI decrease rebleed rates
- Current recommendation is for IV PPI bolus (80mg) followed by continuous infusion 8mg/hr for 72 hours
- Further evidence may support non-continuous infusions

When to restart aspirin?

ACG Practice Guideline:
“Early resumption of antiplatelet therapy within 1-3 days after hemostasis, and certainly within 7 days, will be appropriate in most patients with established CV disease”

What about the “highest” risk ulcer bleed?

- RCT (n=105) comparing transcatheter arterial embolization AFTER endoscopic hemostasis in high risk ulcers (Forrest Ia-IIb)

<table>
<thead>
<tr>
<th></th>
<th>STAE</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean transfusion</td>
<td>4.3 units</td>
<td>4.9 units</td>
<td>NS</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>4%</td>
<td>14%</td>
<td>0.10</td>
</tr>
<tr>
<td>Surgery</td>
<td>2%</td>
<td>0%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (30-d)</td>
<td>4%</td>
<td>14%</td>
<td>0.10</td>
</tr>
</tbody>
</table>

How to Prevent Recurrent Ulcer Bleeding?

- **H. pylori**
  - H. pylori therapy
  - Document cure; stop PPI/H2RA

- **NSAID**
  - Stop NSAID; if NSAID required, use coxib/PPI

- **Low-dose aspirin**
  - Primary CV prevention
  - Do not resume aspirin in most patients

- **Idiopathic**
  - Secondary CV prevention
  - Resume aspirin soon after hemostasis (e.g., 1–7 days) in most patients and start PPI

- **Maintenance PPI**

Summary: Approach to Upper GI Bleeding

- PPI therapy should be initiated upon presentation for upper GI bleeding
- Early endoscopy (<24 hours) should be performed in most patients
- Endoscopic therapy should be performed for actively bleeding lesions/visible vessels and considered in adherent clots
New therapies include hemospray and over-the-scope clip
PPI after endoscopy improves outcomes