An Evidence-based approach to Upper GI Bleeding

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Upper GI Bleeding
Consensus Recommendations on UGIB in Ann Intern Med
2003;139:843-857

Incidence

- Decreasing incidence over the past 10 years
  - 77/100,000 in 1993
  - 53/100,000 in 2003
- 250,000 hospitalizations per year in USA
Epidemiology

- Disease of the elderly
  - 20-30 fold increase from 3rd to 9th decade
  - median age ≥ 70 years
- Men more common than women
- Additional major comorbidity in 50%
- NSAID use in > 50%

Outcomes

- Mortality = 3.5%
  - 15,000-30,000 deaths per year in USA
  - No change in rates over past decade
- Recurrent bleeding in 10-20%
- Length of stay = 4-5 days
- Need for surgical intervention as decreased
  - 7% to 4% from 1993 to 2003

Outcomes: Population-based study in Canada

- 1869 patients, 18 centers
- EGD within 24 hours in 76%
- Rebleeding in 14%, surgery in 7%, death in 5%
- High risk PUD: reduced mortality with
  - PPI (OR, 0.18), EGD Rx (OR, 0.31)
Outcomes: importance of comorbidities

• After control of active PUD bleed with EGD Rx and PPI
• 7 day rebleed rate driven by other medical conditions
  – 2.5% in healthy patients
  – 25% with one major comorbidity
  – > 50% with ≥ 2

Gastroesophageal Varices

• 50% of cirrhotics
  – < 40% Childs A; > 80% Childs C
• Incidence of new varices: 5% / year
• Incidence of bleeding: 10–20% / year
  – 1/3 of deaths from cirrhosis
  – Risk related to: Variceal size, “Red color signs”, Childs class, Active ETOH

Variceal Bleeding

Outcomes

• Acute Bleeding Episodes: < 48 hours
  – 50% stop spontaneously
  – Least likely to stop: large varices, Childs C
  – Mortality: 10%
  – Death: aspiration, sepsis, coma, renal failure >> bleeding
• High Risk Period: < 6 weeks
  – Rebleeding: 40 – 50%
  – Increased risk: large varices, age > 60, renal failure, severe or active bleeding on presentation
• > 6 Weeks to 1 year
  – 70% rebleeding
  – Survival similar to cirrhotics who have never bled
Initial Resuscitation

- Intravascular volume replacement
- Airway management
- Blood products

Volume Replacement

- Isotonic crystalloid solutions
- Packed cells to keep Hct 25-30%
  - anticipate nadir
- FFP for PT $\geq 1.5 \times$ control, platelets for count $< 50,000$

Airway Management

- Pulmonary complications a major source of morbidity and mortality
  - $> \text{new CXR infiltrates in } \sim 15\%$
  - Significant cardiopulm complications in 5%
- Endotracheal intubation for altered mental status or massive bleed
- Impact on outcome uncertain
**Initial Risk Assessment**

- **Important Factors**
  - Vital signs
  - Manifestation of bleed
  - Comorbid medical conditions
  - Age
  - Hematocrit
  - Coagulopathy

- **Not important:** ASA/NSAID, anticoagulant, steroid use, stable medical conditions

**Nasogastric Lavage**

- Important for diagnosis and risk assessment if location and severity of bleed is not clear
- False negatives in 10-15% of upper bleeds
- Does not induce bleed, even when varices present
- Large volume lavage in ED not useful, can be dangerous

**Value of NGA Related to Pre-test Probability of High-risk Lesion**

<table>
<thead>
<tr>
<th>Hemodynamic instability</th>
<th>Stable VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGA</td>
<td>HRL LRL</td>
</tr>
<tr>
<td>Clear or bilious</td>
<td>21% 79%</td>
</tr>
<tr>
<td>Coffee grounds</td>
<td>23% 77%</td>
</tr>
<tr>
<td>Bloody</td>
<td>47% 53%</td>
</tr>
</tbody>
</table>

Bloody NG aspirate: sensitivity 48%, specificity 75%, PPV 45% for high-risk lesions.
Clear NG aspirate: PPV 85% and specificity 94% for low-risk lesions
**Triage from Emergency Department**

- Home
- Endo Unit
- Floor
- ICU

**Definition of Low Risk:**
- < 5% Rebleeding, < 1% Mortality

<table>
<thead>
<tr>
<th>Blatchford</th>
<th>Clinical Rockall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP ≥ 110</td>
<td>Systolic BP ≥ 100</td>
</tr>
<tr>
<td>Pulse &lt; 100</td>
<td>Pulse &lt; 100</td>
</tr>
<tr>
<td>Hgb ≥ 12 (women), 13 (men)</td>
<td>Age &lt; 60 years</td>
</tr>
<tr>
<td>BUN &lt; 6.5 mmol/L</td>
<td>Comorbidities: none</td>
</tr>
<tr>
<td>Comorbidities: none</td>
<td>Comorbidities: none</td>
</tr>
</tbody>
</table>

- Retrospective cohort (n = 175) hospitalized with acute NVUGIB
- Scoring of 0: 0% rebleeding

**Discharge w/o Endoscopy?**

**Limitations:**
1. Identify only 8-12% of patients with NVUGIB as “low-risk”
2. ER physicians reluctant to accept risk
3. Concerns: generalizability and validation
Who Requires ICU Admission

- Institution specific
- In general:
  - Ongoing hemodynamic instability despite IV fluids
  - Evidence of active bleeding: hematemesis, Ig volume bloody lavage, hematochezia
  - Significant comorbidities: ischemia, liver, CA
  - Advanced elderly

Early Endoscopy

- Diagnosis
- Risk assessment
- Therapy

Endoscopic Diagnoses at UCSF

7% 6% 5% 12%
10% 11%
19% 30%

DU  pGU  pVarices  pEsophagitis/ulcer  MVT  pGastritis/duodenitis  pMass  pOther

Other: Dieulafoy, vascular ectasia, AE fistula, diverticula, unknown
Ulcer with clean base

Ulcer with red/black spot

Ulcer with adherent clot
Ulcer with visible vessel

Ulcers with active bleeding
Endoscopic Stigmata of Bleeding Ulcers & Rebleed Risk

<table>
<thead>
<tr>
<th>Stigmata</th>
<th>Prevalence (%)</th>
<th>Rebleed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial bleed</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Clean ulcer base</td>
<td>35</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

Rebleeding Rates in RCT’s of Treatment of Adherent Clots

- Mayo Clinic Multicenter Trial N = 56
  - Medical Therapy: 4.8%, Endotherapy: 0.0%, P < 0.05
- UCLA CURE Multicenter Trial N = 32
  - Medical Therapy: 34.3%, Endotherapy: 35.0%
Risk of Rebleed

- Clean base, RR = 1%
- Spot, RR = 3%
- Clot, RR = 15%, < 3% at 72 hrs
- VV + Rx, RR = 15%, < 3% at 72-96 hrs
- BVV + Rx, RR = 20%, < 3% at 72-96 hrs

Endoscopic Therapy

- Monotherapies are ~ equivalent
- Combination therapy may be best for active bleed
- Reduction in rebleeding and mortality of at least 50%
- Routine 2nd look EGD not needed

Endoclips

- Applied directly or tangentially to vessel
- Minimum of 2 applied (usual 2-4)
- Limitations:
  - fibrotic base; posterior bulb or proximal stomach
  - misfires common

From Raju, GIE 2004; 59: 267.
Endoclips

Cipoletta et al. Gastrointest Endosc 2001;53:147-51
* p < 0.05

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Heater Probe</th>
<th>Endoclip</th>
</tr>
</thead>
<tbody>
<tr>
<td>recurrent bleeding</td>
<td>21%</td>
<td>2%*</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Units of blood</td>
<td>4</td>
<td>3*</td>
</tr>
<tr>
<td>Hospital days</td>
<td>7</td>
<td>6*</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Varices

Variceal Bleeding
Sclerotherapy
**Variceal Bleeding**

### EVL vs Sclerotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>EVL / SCL</th>
<th>% Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steigmann</td>
<td>14 / 13</td>
<td>14 / 23</td>
</tr>
<tr>
<td>Laine</td>
<td>9 / 9</td>
<td>11 / 11</td>
</tr>
<tr>
<td>Gimson</td>
<td>21 / 23</td>
<td>10 / 9</td>
</tr>
<tr>
<td>Jensen</td>
<td>14 / 11</td>
<td>20 / 0</td>
</tr>
<tr>
<td>Lo</td>
<td>18 / 15</td>
<td>6 / 20</td>
</tr>
<tr>
<td>Hou</td>
<td>20 / 16</td>
<td>0 / 12</td>
</tr>
<tr>
<td>Fakhry</td>
<td>10 / 12</td>
<td>10 / 8</td>
</tr>
<tr>
<td>Lo</td>
<td>37 / 34</td>
<td>3 / 24</td>
</tr>
<tr>
<td>Pooled</td>
<td>140 / 148</td>
<td>OR 0.56    (0.27-1.14)</td>
</tr>
</tbody>
</table>

*Franschis R, Seminars Liver Disease 1999*

### Prophylactic Antibiotics

- **Increased risk of infections:** sepsis, aspiration pneumonia, SBP, UTIs
- **Meta-analysis:** 5 controlled trials:

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis</th>
<th>Control</th>
<th>Benefit</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total infections</td>
<td>14 %</td>
<td>45 %</td>
<td>31 %</td>
<td>(23-42)</td>
</tr>
<tr>
<td>SBP/bacteremia</td>
<td>8 %</td>
<td>27 %</td>
<td>19 %</td>
<td>(11-26)</td>
</tr>
<tr>
<td>Mortality</td>
<td>15 %</td>
<td>24 %</td>
<td>9 %</td>
<td>(3-15)</td>
</tr>
</tbody>
</table>

- **Optimal Regimen Unknown**
  - Oral / NG quinolone X 5 days
  - IV abx if oral tx not feasible
## Scoring Systems

- Baylor bleeding score 1993
- Cedars-Sinai medical center predictive index 1996
- Rockall score 1996
- Blatchford score 2000

### Rockall

A. Age (0-2)
B. Shock (0-2)
C. Comorbidity (0-3)
D. Diagnosis at EGD (0-2)
E. Stigmata of recent hemorrhage (0-2)

Minimum score: 0  Maximum score: 11  
Risk category: high (≥5), intermediate (3-4), low (0-2)


### Endoscopic Risk Assessment

Rockall et al. Gut 1996;38:316

- Index prospectively derived and validated on > 5,000 patients in United Kingdom in 1994

<table>
<thead>
<tr>
<th>Score</th>
<th>Rebleeding</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>score ≤ 1</td>
<td>3.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>score ≥ 2</td>
<td>4.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>score 3-5</td>
<td>14.7%</td>
<td>6.3%</td>
</tr>
<tr>
<td>score ≥ 6</td>
<td>41.1%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>
Triage after EGD

- Immediate discharge in selected patients

- Optimal length of stay in patients who require admission

Kaiser guidelines for selecting outpatient care

- Endoscopic
  - no high risk EGD features: varices, portal HTN gastropathy, arterial bleeding, visible vessel, adherent clot

- Clinical
  - no debilitation
  - no orthostasis
  - no severe liver disease
  - no serious comorbidity
  - no coagulopathy or anticoag Rx
  - no fresh, voluminous hematemesis or mult melena
  - no Hgb < 8
  - adequate home care

Kaiser Results

- 176 patients treated as outpatients (~25% of all UGIB patients)
- recurrent bleeding in 1 (1%)
- hospitalization in 2 (1%)
- mortality in 0 (0%)

Longstreth GI Endosc
1998;47:219
Early Endoscopy-based Triage: Three RCT’s

• Lee J, GIE 1999
  – N = 110: ER EGD vs routine admission
  – ER EGD: 46% immediate discharge; no rebleeds
  – LOS 1 vs 2 days; costs reduced 40%
• Cipolletta L, GIE 2002
  – N=464 pts underwent EGD w/in 12 hrs: 95 (20%) low risk.
    Randomized to early discharge vs hospital care
  – Recurrent bleeding: 2 % both groups
  – Costs: 90% reduction
• Bjorkman D, GIE 2004
  – N=93: ER EGD vs routine admission
  – ER EGD: 40 % recommended for discharge; ER only discharged 10%

Optimal Length of Stay

• Cedars-Sinai Guideline (Hay et al. JAMA 1997;278:2151)
• Clinical and EGD risk assessment
• Daily reassessment
• Reduction in LOS: 4.6 ± 3.5 days to 2.9 ± 1.3 days
• No adverse events

Does Early EGD (< 24 hours) Improve Outcomes in the Community?
Early EGD Improves Outcomes in High-Risk Patients

- Therapeutic endoscopy
  - Decreased risk of recurrent bleeding or surgery
    - OR = 0.21 (0.10-0.47)
    - OR = 0.37 (0.13-1.06)
  - Reduced ICU length of stay
    - -18% (0-32%)
  - Trend towards decreased mortality

Cooper GS et al. Gastroinest Endos 1999;49:145
Cooper Medical Care 1998;4:462

Early EGD Reduces LOS

Cooper GS et al. Medical Care 1998;4:462
Cooper GS et al. Gastroinest Endos 1999;49:145

Outcomes in California Medicare Patients

- Early EGD versus Late EGD
  - 946 patients
  - 83% underwent EGD and 58% underwent early EGD
  - Adjusted OR for mortality (early versus late)
    - 1.1 (.28, 5.5)
  - Adjusted % change in LOS (early versus late)
    - -26% (-33%, -19%)
PPIs

- > 20 randomized controlled trials
- Considerable heterogeneity with respect to intervention and outcomes measured
- Benefit in most all studies
  - rebleeding, transfusion need
  - surgery
  - death

Meta-Analysis: RCTs of PPI vs Placebo After Endoscopic Therapy of Ulcers with High-risk Stigmata

<table>
<thead>
<tr>
<th>Endoscopic Therapy Followed by High-dose IV PPI</th>
<th>PPI</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>5.2%*</td>
<td>12.8%</td>
<td>0.39 (0.18-0.85)</td>
</tr>
<tr>
<td>Surgery</td>
<td>5.2%*</td>
<td>9.4%</td>
<td>0.53 (0.31-0.90)</td>
</tr>
<tr>
<td>Mortality</td>
<td>5.7%</td>
<td>5.6%</td>
<td>0.98 (0.25-3.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoscopic Therapy Followed By Oral or Low-dose IV PPI vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

Leontiadis G, BMJ 2005
• 21 RCTs: 2915 pts

PPI only versus EGD Rx + PPI

<table>
<thead>
<tr>
<th></th>
<th>PPI</th>
<th>EGD + PPI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleed</td>
<td>9%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PRBCs</td>
<td>2.5</td>
<td>2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LOS</td>
<td>5.0</td>
<td>5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>5.1%</td>
<td>2.6%</td>
<td>NS</td>
</tr>
</tbody>
</table>

• Ann Int Med 2003;139:237-43
RCT: IV PPI Infusion vs Placebo Before EGD

- Endoscopic Tx:
  - Peptic Ulcers: 22.5% (PPI) vs 36.8% (placebo) (p< 0.05)
  - Other bleeding sources: no difference
- Hospitalized < 3 d
  - 61% PPI vs 49% placebo (P< 0.05)
- No effect of PPI on:
  - Urgent endoscopy
  - Transfusions
  - Rebleeding
  - Death


- N = 638 UGIB: 377 PUD (60%)
- Omeprazole 80 mg bolus, 8 mg/hr X 72 hr

Variceal Bleeding

- Octreotide
  - Synthetic SS analogue: 2 hr half-life
  - Bolus 50-100 ug; 50 ug/hr
  - $75/day
  - S75/day
  - Most studies: no reduction in portal pressure or variceal pressure

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Treatment</th>
<th># Pts</th>
<th>% Failure</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beson, NEJM</td>
<td>1995</td>
<td>Scl + Oct vs Scl alone</td>
<td>98/101</td>
<td>13/29*</td>
<td>7/10</td>
</tr>
<tr>
<td>Villanueva, Hepatology</td>
<td>1999</td>
<td>Scl + SS vs SS alone</td>
<td>50/50</td>
<td>7/21*</td>
<td></td>
</tr>
</tbody>
</table>

* = p < 0.05
Conclusions

- IV PPI (continuous infusion) until EGD and then after in those with active bleed, VV, clot for 3 days
- IV octreotide in those with suspected portal HTN, continue for 3 days in confirmed variceal bleed
- EGD within 12-24 hours in all
- Early discharge in those with low risk, observation for 72-96 hours in those with high risk
- Repeat EGD for rebleed