An Evidence-based approach to Upper GI Bleeding

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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%

Causes

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>35%</td>
<td>21%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>21%</td>
<td>43%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>MW Tear</td>
<td>5%</td>
<td>4%</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Varices</td>
<td>4%</td>
<td>11%</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4%</td>
<td>1%</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>AVM</td>
<td></td>
<td>5%</td>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
<td>15%</td>
<td>17%</td>
<td>(w/erosive)</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>No Dx Made</td>
<td>25%</td>
<td>4%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>
Outcomes in Canada
Am J Gastroenterol, 2004

- 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
Outcomes in Italy
Marmo, Am J Gastro, 2008

- 1020 patients from 23 centers
- Rebleeding = 3.2%
- Mortality = 4.5%
  - Rebleeding in only 11% of those that died
  - Age, severe comorbidity predict death
  - Acute PPI use, OR for death = 0.23 (95% CI, 0.09-0.73)

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 ≥ 1.5 x control, platelets for count < 50,000

Airway Management

• Pulmonary complications a major source of morbidity and mortality
  – > new CXR infiltrates in ~ 15%
  – Significant cardiopulm complications in 5%
• Endotracheal intubation for altered mental status or massive bleed
Aggressive Resuscitation

• Small RCT of standard care versus intensive resuscitation
  – No change in timing of EGD
  – Baradarian, Am J Gastro, 2004
• Reduced rate of MI
• Reduced mortality 3% versus 11%, p < 0.05
• No change in LOS

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

**Blatchford**
- Systolic BP ≥ 110
- Pulse < 100
- Hgb ≥ 12 (women), 13 (men)
- BUN < 6.5 mmol/L
- Comorbidities: none

**Clinical Rockall**
- Systolic BP ≥ 100
- Pulse < 100
- Age < 60 years
- Comorbidities: none
Outpatient Management of NVUGIB?

Limitations:
1. Only 8-12% of patients with NVUGIB as “low-risk” by criteria
2. ER physicians reluctant to accept risk
3. Concerns: generalizability and validation
4. Recent Medicare audit (Cooper GS. Gastro, 2009) with OP in ~40% with early EGD in 40%, but 30 day mortality = 6%!!!

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, cancer
  - Advanced elderly
Early Endoscopy

- Therapy
- Accurate risk assessment after specific diagnosis

Who really needs urgent EGD?
Adamopoulos, Eur J Gastro Hepatol, 2003

- Active bleeding at EGD
  - Fresh blood with NG = 6 points
  - Hemodynamic instability = 4 points
  - HgB < 8 g/dl = 4 points
  - WBC > 12K = 3 points
  - < 7 points no bleed and >/= 11 points indicates active bleed with sensitivity of 96%, spec of 98%, PPV of 96%, NPV of 98%
How urgent is urgent?
Targownik, Can J Gastro, 2007

• 169 patients with upper GI bleed and sys BP < 100 mmHg and HR > 100 bpm
• Endo within 6 hours versus 6-24
  – Not an RCT….  
  – No difference in outcomes with respect to:
    • LOS
    • Transfusion
    • Surgery
    • Mortality

Ulcer with clean base
Ulcer with red/black spot

Ulcer with adherent clot
Ulcer with visible vessel

Non-Bleeding Visible Vessel

Vessel
Pseudoaneurysm
Clot
### 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>
Endoscopic Treatments for PUD with High-risk Stigmata (active bleeding / visible vessels)

Injection:
• Epinephrine (1:10000)

Thermal:
• Contact thermocoagulation: MPEC, heater probes

Mechanical:
• Endoclips: loops, bands

Combination:
• Epi injection + thermal or mechanical

Outcomes: Reduction in rebleed, LOS, Tx, Surgery, Mortality by >= 50%

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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.

Monotherapies

Sung, Gut, 2007

- Thermal coag or endoclip is better than injection alone
  - RR of bleed ~1.2-1.5 with inj only
- Thermal coag and endoclip are equivalent
  - Hemostasis in ~80%
  - No difference in rebleed, LOS, surgery, mortality
Combination Therapy vs Monotherapy: Is It Better?

<table>
<thead>
<tr>
<th>Combination</th>
<th>Monotherapy</th>
<th># Trials / N</th>
<th>OR Rebleeding (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi + Thermal</td>
<td>Epi alone</td>
<td>3 / 376</td>
<td>0.363 (0.177-0.727)</td>
</tr>
<tr>
<td>Epi + Clips</td>
<td>Epi alone</td>
<td>4 / 362</td>
<td>0.334 (0.177-0.629)</td>
</tr>
<tr>
<td>Epi + Thermal</td>
<td>Thermal alone</td>
<td>3 / 425</td>
<td>0.699 (0.405-1.206)</td>
</tr>
<tr>
<td>Epi + Clips</td>
<td>Clips alone</td>
<td>3 / 234</td>
<td>1.045 (0.447-2.449)</td>
</tr>
</tbody>
</table>

Pooled Rebleeding 0.597 (0.444-0.802)


Rebleeding Rates in RCT’s of Treatment of Adherent Clots

- Medical Therapy: Mayo Clinic Multicenter Trial N = 56, 34.3% with P < 0.05 vs Endotheraphy 4.8%
- Endotheraphy: UCLA CURE Multicenter Trial N = 32, 35.0% vs 0.0%

P < 0.05
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
IV Erythromycin: 3 RCT’s

*It’s Worth a Try*

- **Coffin B, Gastrointest Endosc 2002**
  - EES 3 mg/kg over 30 min vs control
  - N= 41; 16-20 Fr NG lavage performed
  - EGD Quality Score (0-3): EES 2.5 (0.8) vs control 1.5 (1.3) (p<0.05); decreased 2nd look

- **Frossard JL, Gastroenterology 2002**
  - EES 250 mg over 5 min vs placebo
  - N = 105; no NG lavage
  - “Clear” stomach: 82% vs 33% (p<0.001); decreased 2nd look

- **Carbonell N, Am J Gastroenterol 2006**
  - EES 250 mg over 30 min vs placebo
  - N = 100; 16-20 Fr NG lavage performed
  - Complete clot clearance: 70% vs 48% (p<0.05)
  - No difference in 2nd look

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

Variceal Bleeding
Risk Stratification 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>

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
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
**PPIs**

- > 25 randomized controlled trials
- Considerable heterogeneity with respect to intervention and outcomes measured
- Study outcomes: PPI > placebo, EGD > PPI, PPI + EGD > PPI, EGD + PPI > EGD + placebo
  - rebleeding, transfusion need
  - surgery

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*Kaplan-Meier estimate of the cumulative percentage of patients with recurrent bleeding within 30 days*

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 (0.18-0.87)</td>
</tr>
<tr>
<td>Surgery</td>
<td>5.2%*</td>
<td>9.4%</td>
<td>0.53 (0.31-0.89)</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

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

PPI prior to EGD
Cochrane Syst Rev. 2006

• 5 RCTs, 1512 subjects
• Reduction in EGD stigmata
  – 37.2% vs 46.5%
• No reduction in:
  – Mortality – 6.1% vs 5.5%
  – Rebleed – 13.9% vs 16.6%
  – Surgery – 9.9% vs 10.2%
  – No pooled data on LOS or Tx

Variceal Bleeding

• Octreotide
  – Synthetic SS analogue: 2 hr half-life
  – Bolus 50-100 ug; 50 ug/hr
  – $75/day
  – Most studies: no reduction in portal pressure or variceal pressure
    • Yet it seems to help??
**Variceal Bleeding**

**EGD plus Oct or SS – Better than EGD or SS alone?**

<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>Besson, 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

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**Flowchart:**

1. **Endoscopic Therapy** → **Initial Control** → 80-90%
2. **Rebleeding** → **Endoscopic Therapy** → 75%
3. **Permanent Control** → 25%
4. **Rebleeding** → **Angiography**
Treatment Algorithm

Conclusions

- Aggressive resuscitation if needed and risk assess
- Rarely send home without EGD first
- Early EGD (within 24 hours) in endo unit or ICU depending on risk assessment
- Combination endoscopic therapy as needed
- Early discharge in those with low risk stigmata
- Observation for 72-96 hours in those with high risk
- PPI (IV) 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
- Repeat EGD for rebleed