New Approaches in the Management of Non-Variceal Upper Gastrointestinal Bleeding

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Background

- In 1970, during the BC (before cimetidine) era, 79% of bleeding stopped without intervention
- Our job as medical professionals:
  - Stop any remaining bleeding
  - Reduce risk of rebleeding
- GI bleeding is a significant medical problem
  - 78 cases/100,000 persons (2009)
  - Mortality: 2.1% (2009) for non-variceal UGIB
  - Economic burden: $7.3 billion (2009)
- Rebleeding rates range from 7-16% *despite* endo tx
  - Variceal rebleeding (25-29%); PUD rebleeding (20-22%)

Endoscopic Stigmata and 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


Established Endoscopic Techniques

- Injection (epinephrine)
  - Not to be used as monotherapy
- Coagulation (monopolar, bipolar)
  - Coaptive coagulation
  - APC
- Mechanical (through the scope clips)
  - Can be difficult to place in certain lesions
    - Position: posterior wall stomach/bulb
    - Certain lesions: fibrotic lesions
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

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
New Approaches to UGIB

- Over-the-scope clips
- Ablation
  - radiofrequency ablation
  - cryotherapy
- Stent Placement
- Hemostatic sprays
- Endoscopic suturing
- EUS-guided injection/coil

Over-the-Scope Clip (OTSC)

- First approved in the United States in 2011*
- Various diameters and teeth types
- Requires removal of endoscope and attachment of clip/cap (deployed similar to band ligation devices)
- Porcine model RCT demonstrated efficacy in bleeding compared to standard clips (less time, fewer clips, effective pressure of closure)
- Case series
- No prospective comparison trials

* Approved for closure of GI defects

Kato M et al. GIE 2012; 75: 3-10.
OTSC

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


Radiofrequency Ablation

- Clinical application: GAVE and radiation proctitis
- GAVE
  - Four case series (n=60), mostly after failed APC
  - Successful (no longer transfusion dependent) in 65-86%
  - Requires up to 6 sessions, average 2-3
- Radiation Proctitis
  - Five case series, total of 66 patients (only 10 had failed prior therapy)
  - Average RFA sessions approximately 1.5 (range 1-4)
  - Clinical success (decrease in symptoms) = 64/66 (97%), discontinuation of transfusions 92% (36/39)

Cryotherapy

- Several studies in GAVE and radiation proctitis
- Reasonable rates of success
  - GAVE 50-71%
  - Radiation proctitis 86-100%
- Lack of controlled comparative data


Cryotherapy for Radiation Proctitis

- 71 year old man with history of prostate cancer status post radiation. Reports daily blood in stool.
Wrap-up on Ablation

- Use: GAVE and radiation proctitis
- Ablative techniques include cryotherapy (freezing) and radiofrequency ablation (burning)
- Mostly case reports with no controlled comparative data
- Reasonable success rates to consider after failed treatments (including APC)
- Significantly more costly and less widespread availability compared to APC

Stent Placement

- Feasible in the esophagus due to tubular nature
- Numerous case reports for esophageal varices
- Recent systemic review
  - 12 studies, n=155
  - Hemostasis success within 24h: 96%
  - Technical success for SEMS deployment: 97%
  - Adverse events: 36%
    - Most commonly stent migration (rates 20-80%)
- Survival
  - 30d—68%, 60d—64%

McCarty TR, Njei B. Digestive Endoscopy, 2016
15 Sengstaken-Blakemore tube, 13 SX-ELLA Danis stent

Success (survival at day 15 with control of bleeding)
- Stent (66%) vs. balloon tamponade (20%), p=0.025
- Control of bleeding, transfusional requirements, and adverse events, use of TIPS favored stent group

No difference in 6-week survival (54% vs. 40%, p=0.46)

Hemostatic Spray

- Mechanical tamponade effect
- Absorbs water
- Activates clotting cascade

NOTE: Hemospray is not FDA approved in the United States, Gastrointestinal Endoscopy 2013 77, 692-700
Initial Studies using Hemostatic Spray

- 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


Largest Study using Hemostatic Spray

- 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

Systematic Review of Hemostatic Spray

- Immediate hemostasis 92.3% (180/195)
- Rebleed rate at 7d: 20.6%
- High risk lesions (Forrest 1a, 1b)
  - Immediate hemostasis 95% (53/56)
  - Rebleed rate at 7d: 25% (13/53)
- Safety: based on 243 total cases in GI
  - 5 reported complications:
    - Pain (? Under-reported), biliary obstruction (after use in post-sphincterotomy bleed), perforation, hemoperitoneum, splenic emboli (on day 29)

Chen Y & Barkun AN. Gastrointest Endoscopy Clin N Am 2015: 535-552

Hemostatic Spray

Case series of 16 patients

Sulz MC et al. Endoscopy 2014
Hemostatic Spray take-home points

- Not FDA-approved in the US
- Few complications reported but risks of local injury/vascular injury and embolization
- Advantages: non-contact, can cover area quickly, simple to use (no precise target, does not require en face positioning)
- Disadvantages: high pressure CO2, loss of view after application, only lasts ~24 hours (possible delayed bleeding)
- Biggest disadvantage: NOT readily available

Endoscopic Suturing

- Not widely available
- Technically complex with learning curve
- Even more difficult with compromised visualization in actively bleeding lesions
- Published uses
  - Porcine model: bleeding controlled 17/25 (68%)\(^1\)
    - Failures: penetrated vessel wall (too shallow), loose knot, incorrect position, stomach-wall edema
  - Anastomotic ulcerations with recurrent bleeding (n=2)\(^2\)
  - Post ESD\(^3\)

EUS-guided therapy

- Case reports typically by experts at tertiary care centers
  - Mayo: 17 cases between 2003-2014
  - Remaining case reports: 13 cases
- Ulcers, Dieulafoy lesions, masses/polyps, vascular malformations, malignancy, pseudoaneurysm
- Therapy (Mayo experience):
  - cyanoacrylate (n=5)
  - coil embolization (n=4)
  - hyaluronate (n=3)
  - ethanol (n=3)
  - band ligation (n=2)
  - combination (n=2)

Tissue Glue

- Cyanoacrylate glue
  - Mixed with ethiodized oil (Lipiodol) to slow rate of solidification
  - Used primarily in gastric varices
  - Case series for peptic ulcers:
    - Topical spray therapy (Shida T, Endoscopy 2009)
- Fibrin sealant
  - Contains 2 components (fibrinogen/thrombin)
  - Double-lumen catheter
  - Mostly older trials, none compare to current standard multimodality treatment
  - Use in EUS-guided approaches for pseudoaneurysms
EUS-guided Therapy Results

- Blood flow on Doppler:
  - Complete cessation—12/19 (63%)
  - Decreased flow—7/19 (37%)
- No further bleeding in 15/17 (88%) (f/u 12 mos)

![Figure 1](image1.png)

**Combination Therapy: Endo + IR**

<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>

Laursen SB et al. Scand J Gastroenterol 2014
Use of Doppler

- Prospective Cohort Study, 163 patients (severe PUB)
- + Doppler: high risk – 87.4%, low risk – 42.3%

**TABLE 3: Comparison of Doppler probe results before and after endoscopic hemostasis for different stigmata**

<table>
<thead>
<tr>
<th>Stigma</th>
<th>DEP before hemostasis</th>
<th>DEP after hemostasis</th>
<th>% + after hemostasis</th>
<th>% + before hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active arterial bleed</td>
<td>14</td>
<td>5</td>
<td>35.7</td>
<td>27.4%</td>
</tr>
<tr>
<td>NBV</td>
<td>46</td>
<td>13</td>
<td>27.4%</td>
<td></td>
</tr>
<tr>
<td>Adherent clot</td>
<td>11</td>
<td>2</td>
<td>18.8%</td>
<td></td>
</tr>
<tr>
<td>Flat spot</td>
<td>13</td>
<td>3</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Oozing bleeding</td>
<td>7</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>23</td>
<td>24.2%</td>
<td></td>
</tr>
</tbody>
</table>

DEP: Doppler endoscopic probe
+ = Positive DEP for arterial bleed

*Note that not all patients from Table 1 with positive DEP at baseline were included in Table 2 results because not all had DEP repeated after the endoscopic treatment.

- Can we use Doppler to improve risk stratification and guide endoscopic treatment?

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”

**Rebleeding**

- Log-rank test (P = 0.15)
- Hazard ratio: 1.9 (95% CI: 0.6-6.4)


**Mortality**

- Log-rank test (P = 0.005)
- Hazard ratio: 0.2 (95% CI: 0.04-0.42)
Summary

- Standard endoscopic therapy (injection, coagulation, clips) remain the mainstay of therapy
- Restrictive transfusion improved survival
- New approaches include:
  - OTSC (over the scope clip): ulcers
  - Ablation (cryotherapy, RFA): GAVE, radiation proctitis
  - Stents: esophageal varices
  - Hemostatic Sprays: awaiting approval for use in the US
  - EUS-guided therapy: expert centers
  - Combination therapy: standard endo tx + IR
- Early resumption of aspirin for patients with CV disease