ARTICLE 1
Anticoagulants/Antithrombotics


Introduction
• 7-10x increased risk of intracranial hemorrhage (ICH) if anticoagulated with warfarin
• 60% mortality with intracranial hemorrhage
• Rapid reversal → slow hematoma expansion
• Warfarin inhibits synthesis of Vitamin K dependent coagulation factors
  • Factors II, VII, IX, X

Options for Reversal
• Vitamin K
• Fresh Frozen Plasma (FFP)
• Recombinant Factor VIIa (rFVIIa)
• Prothrombin Complex Concentrate (PCC)

Vitamin K
• Required for any sustained reversal of warfarin related hemorrhage
• Up to 4 hours for desired effects
• Cheap → $15-20 for 10 mg
• IM/SC → No
• ORAL → effective
• IV → faster
  • 5-10 mg if life threatening hemorrhage
  • Administer slowly

Fresh Frozen Plasma (FFP)
• Requires ABO compatibility testing and 30-60 min to thaw
• Poor evidence of effectiveness in ICH
• Slow → 13 – 48 hours for desired effect
• Price → approx. $60
• Minimum dose → 4 Units (15 cc/kg) for 70 kg person
Recombinant Factor VIIa

- Off label use for non-hemophiliac hemorrhage
- Fast → < 1 hour for INR reversal
- Risk of thrombosis → 10 – 20% (high)
- Dose → 90 ug/kg for ICH (maybe less)
- INR not accurate to follow after rFVIIa
- Remain consideration for those pts with religious restrictions
- Approximately $1700 for 1 mg of NovoSeven

Prothrombin Complex Concentrate (PCC)

- Derived from pooled human plasma
- 3 Factor-PCC → contains Factor II, IX, X, Protein C and S, + heparin
- 4 Factor-PCC (Kcentra) → contains Factor II, VII, IX, X, Protein C and S, + heparin
- Approved for use in US → 2013

Prothrombin Complex Concentrate (PCC)

- Rapid reversal of INR
  - Within 10 – 30 minutes
  - Can last up to 6 hours
- Risk of thrombotic adverse events → 1.5% (0.9 – 3.8%)
- Potential for transmission of infectious disease
- Contraindications → DIC, decompensated liver disease, ongoing warfarin tx, HIT
- Expensive → $2000-2500 for 2000 units

Prothrombin Complex Concentrate (PCC)

- Dosing → 25-50 IU/kg
  - Small volume (usually less than 100 mL)
- No need for ABO-compatibility testing
- Repeat INR 15 minutes post-administration of PCC to guide further therapy
- PCC better than FFP and rFVIIa for warfarin reversal for brain hemorrhage
  - Improved neurologic outcomes
  - Reduced hematoma growth

KEY POINTS

- For reversal of life-threatening bleeding related to warfarin to all patients
  - Vitamin K should be administered early via IV route
- FFP should be given when other agents are unavailable
- PCC (preferably 4-factor) is a great option for warfarin reversal, especially in brain hemorrhage
  - Low Volume
  - Faster INR reversal
  - Increasing evidence of superiority to other modalities
- When using 3-factor PCC, consider adding FFP or rFVIIa (lack of factor VII)
  - If used alone, check the INR 15 minutes after administration
ARTICLE 9

Liver


Objective

• Review article
• Define Acute Liver Failure
• Review Evidence, Guidelines, and Specific Recommendations
• Conflicts → lead author on board (2) and speaker (2) different medical/pharmaceutical companies

General Information

• Rare
• 1 in 100,000 (developed world)
• Most common in previously healthy adults in their 30s
• Multiorgan failure and death occurring in up to 50% of cases
• Very limited evidenced-based data to guide management due to rarity
• Survival improved with aggressive critical care and transplant

Definitions

• Fulminant Hepatic Failure → severe liver injury (potentially reversible) with onset of hepatic encephalopathy within 8 weeks of first symptoms, in absence of pre-existing liver disease.
• Hyperacute Liver Failure → usually one week or less; usually caused by acetaminophen toxicity or viral infection.
• Subacute Liver Failure → usually weeks to months; often resulting from idiosyncratic drug reactions or idiopathic causes
  • Consistently worse outcomes, despite coagulopathy/encephalopathy
  • May be confused with chronic liver disease

Causes of Acute Liver Failure

• Viral Infections – Hepatitis A, B, E
  • Predominant cause in developing countries
  • 50% mortality
• Drug-Induced → accounts for 50% of cases in the USA
  • Acetaminophen-Induced → most common, dose dependent (predictable)
  • Idiosyncratic → can be independent of dose (unpredictable)
  • Age, Coagulopathy, Elevated LFTs are risk factors for increased mortality
• Other Causes
  • Acute ischemic hepatocellular injury, hypoxic hepatitis, neoplastic infiltration, acute Budd-Chiari syndrome, heat stroke, mushroom ingestion, Wilson's Disease

Initial Treatment of Acute Liver Failure

• Aggressive supportive/critical care
  • Improve systemic perfusion
    • Fluids, pressor support
  • Airway protection
    • Consider intubation for airway protection in severe encephalopathy
  • Infection control
    • Functionally immunosuppressed
    • Infection will exacerbate encephalopathy
  • Overt bleeding uncommon despite coagulopathy
  • Early consideration to transplant/liver center
Acetylcysteine

- Early treatment improves outcomes in acetaminophen-induced toxicity
- Beneficial to patients with other causes of Acute Liver Failure
  - Complex antioxidant and immunologic effects
  - Improved survival rates among patients with low-grade encephalopathy in randomized controlled trials

Cardio-respiratory Dysfunction

- Low circulatory volumes
  - IVF, pressor support as needed (norepinephrine)
- Echo
- Adrenal insufficiency (possible)
  - Stress dose steroids
- Respiratory Support
  - Early intubation

Neurologic Complications/Encephalopathy

- Acute Liver Failure with high grade encephalopathy
  - Poor Prognosis
- Subacute Liver failure even low grade encephalopathy
  - Poor Prognosis
- Intracranial HTN from Cerebral Edema → Leading Cause of Death
  - Poorly understood; systemic/local toxins, including ammonia
  - May be precipitated or worsened by infection/hypotension
  - Treatment with antibiotics or lactulose may be harmful in ALF (not chronic)
  - Prevent IC-HTN with sedation, 3% NaCl. Consider hypothermia

Renal Dysfunction

- May occur in >50% of patients with Acute Liver Failure
- More common in elderly and those with acetaminophen-induced ALF
- Renal dysfunction often resolves with resolution of liver failure
- If renal replacement therapy required:
  - CRRT (continuous) > intermittent

Treatment

- Aggressive Supportive Care
  - Large volume infusion should be avoided
  - Can lead to hypervolemia and cerebral edema
  - Increased risk of hypoglycemia due to poor glycogen stores
  - May require glucose infusion
  - Balance protein supplementation, while monitoring ammonia levels
- Identify Transplant Candidates before Multiorgan Failure
  - Multiple criteria (King's College, Clichy, Japanese Criteria)
    - Indicators → Encephalopathy, Age, and Severity (coagulopathy/jaundice)
- Liver Transplantation
  - Less than 10% for patients with Acute Liver Failure
  - Survival rates lower than elective liver transplantation

Liver Transplantation

- Articles
General Information/Objectives

- Systematic review and meta-analysis
- Identify evidence based aspects of History, Physical Exam, imaging in diagnosis of SBO
- Determine prevalence of SBO in prospective based ED studies
- Test-treatment threshold to determine when to begin treatment vs further diagnostics to confirm SBO

General Information

- 300,000 admissions in US annually
- 70% admitted through the ED (>200,000/year)
- 2% of all abdominal pain complaints
- 15% of patients admitted to surgical unit from ED have SBO

Causes of SBO
- Adhesions from previous surgery (75% of all cases)
- Neoplasms, hernias, crohn’s disease

High complication rate
- Strangulation → 30%; Bowel Necrosis → 15%

Methods

- Searched articles from 1946-2011 (MEDLINE and EMBASE)
- > 7700 articles → Applied exclusion criteria to screen articles
  - Exclusion Criteria: case studies with insufficient data to develop 2 x 2 table, pediatric population studies, tests not readily available to EP, those focused on single radiographic sign, those focused on treatment, and studies that were not primary research
- 22 FINAL articles (12 prospective, 10 retrospective)
  - QUADAS-2 (quality assessment)
  - Data analyzed/pooled to calculate sensitivity/specificity/likelihood ratios
  - Separate info gathered on prevalence and management of SBO
    - Test/treatment thresholds

Results – History

- No components of history that could reliably/accurately predict SBO
- History of previous abdominal surgery had best combination
  - + LR = 3.86 and − LR = 0.19
- History of constipation
  - + LR = 8.8 and − LR = 0.59
- Very few components of physical exam could be reliably used for diagnosis of SBO
    - Abdominal Distention on physical exam was best sign
      - + LR = 16.8 and − LR = 0.34

Results – Physical

- Very few components of physical exam could be reliably used for diagnosis of SBO
- Abnormal Bowel Sounds
  - + LR = 6.33 and − LR = 0.27
- Abdominal Distention on physical exam was best sign
  - + LR = 16.8 and − LR = 0.34
Results - Imaging

<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>+ Likelihood Ratio</th>
<th>- Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>1.55</td>
<td>0.43</td>
</tr>
<tr>
<td>CT Scan</td>
<td>3.62</td>
<td>0.18</td>
</tr>
<tr>
<td>MRI</td>
<td>6.77</td>
<td>0.12</td>
</tr>
<tr>
<td>Bedside Ultrasound</td>
<td>0.55</td>
<td>0.13</td>
</tr>
<tr>
<td>Formal Ultrasound</td>
<td>14.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

• CT is most sensitive and specific for SBO:
  • Continuous loops of bowel ≥ 2.5 cm present proximal to collapsed loops of bowel (transition point)

Test-Treat Threshold

• Pretest probability for further testing: > 1.5%
• Probability for initiating treatment: > 20.7%

Conclusions

• Causes of SBO: adhesions (most common), neoplasm, hernia, crohn’s
• Abdominal pain + constipation, or Abdominal pain + prior hx of SBO increases chance of SBO
• Physical exam findings of abdominal distention and abnormal bowel sounds increases chance of SBO
• CT is most sensitive and specific for making the diagnosis with finding of transition point.
• US can show SBO with highest likelihood ratio, but will not show transition point

ARTICLE 12

Pericarditis


General Information

• Colchicine historically has been used for treatment of chronic pericarditis
• Prospective trial to look at use of colchicine for acute pericarditis
  • Multi-center, Double blinded, Randomized Control Trial

Methods

• 240 Patients → 120 received colchicine 0.5 mg bid (> 70 kg) (**No loading dose**) vs. placebo + usual therapy (NSAIDS, aspirin, steroids)
  • Follow up at 1 week, 3, 6, 12 months, and then every 6 months
• Primary Outcome → Incessant (persistent) or Recurrent Pericarditis
• Secondary outcomes → symptoms at 72 h, remission within 1 week, # of recurrences, tamponade, etc.
• Inclusion: ≥18 yo + acute first episode
  • First Episode → 2 of the following: typical CP, friction rub, EKG findings, new pericardial effusion
• Exclusion: cancer, severe liver disease, elevated Cv, pregnant, TB, blood dyscrasia, IBD
Definitions

- Recurrent Pericarditis
  - Documented first attack of acute pericarditis
  - Symptom free interval of 6 weeks or longer
  - Evidence of recurrent pericarditis
    - Recurrent Pain + 1 or more of the following:
      - Pericardial Friction Rub, ECG changes, Echo findings of effusion, Elevation in WBC, ESR, or CRP
  - Incessant (persistent) Pericarditis
    - Symptom free interval of less than 6 weeks
    - Evidence of recurrent pericarditis (as above)

Results — Trial Outcomes

- **Primary Outcome** → Recurrent Pericarditis
  - Less frequent in colchicine group (16.7% v 37.5%, p < .001)
  - Relative Risk Reduction in colchicine subset of 0.56 (95% CI)

- **Secondary Outcomes**
  - Statistically significant decrease in symptoms at 72 hours with colchicine
  - Decreased number of recurrences per patient with colchicine
  - Decreased hospitalization with colchicine
  - Colchicine improved rate of remission within 1 week of treatment

- **Results — Trial Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=100)</th>
<th>Colchicine (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pericarditis — n (%)</td>
<td>45 (45.5)</td>
<td>20 (20.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptom free interval of 6 weeks — n (%)</td>
<td>70 (70.0)</td>
<td>70 (70.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Evidence of recurrent pericarditis — n (%)</td>
<td>26 (26.0)</td>
<td>37 (37.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Recurrent pain — n (%)</td>
<td>25 (25.0)</td>
<td>31 (31.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>No. of recurrences per patient</td>
<td>8.8 (4.2)</td>
<td>6.8 (3.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Time from first recurrence — wk</td>
<td>17.4 (10.3)</td>
<td>24.4 (16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Colchicine 0.95 mg — n (%)</td>
<td>17 (17.0)</td>
<td>8 (8.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Echocardiographic pericardium-related</td>
<td>25 (25.0)</td>
<td>18 (18.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hospitalization — n (%)</td>
<td>12 (12.0)</td>
<td>18 (18.0)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

- **Results — Adverse Events**

  - Adverse Events were similar in the two study groups
  - Diarrhea was the most common side effect
    - Occurred in less than 10% of the patients.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=100)</th>
<th>Colchicine (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>52 (52.0)</td>
<td>52 (52.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>19 (19.0)</td>
<td>17 (17.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>19 (19.0)</td>
<td>19 (19.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Physician decision</td>
<td>9 (9.0)</td>
<td>12 (12.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Patient decision</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Conclusions

- Colchicine was shown to reduce the rates of both recurrent and incessant (persistent) pericarditis compared to placebo.
- Colchicine also was shown to reduce length of symptoms, number of recurrences, and hospitalizations.
- Results seen without loading dose (0.5 mg BID), reducing adverse side effects.
Conclusions (cont.)

• Relative Risk Reduction (RRR) – Colchicine Group: 0.56

• Number Needed to Treat (NNT) – 4

• Colchicine (0.5 mg BID x 3 months) + usual treatment for acute pericarditis, significantly reduced rate of persistent and recurrent symptoms