2016 LLSA Review

Articles 1, 9, 11, 12

Brian Felice, MD
Beaumont Health System – Royal Oak
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ARTICLE 1

Anticoagulants/Antithrombotics

- Frumkin K. Rapid reversal of warfarin-associated hemorrhage in the emergency department by prothrombin complex concentrates.*Ann Emerg Med.* 2013;62(6):616-26.

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)

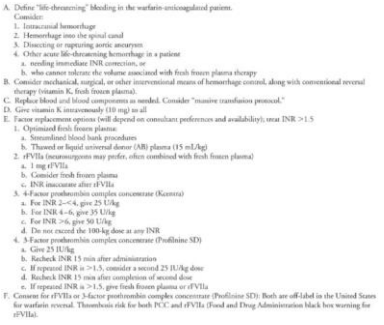
- Derived from pooled human plasma
- 3 Factor-PCC → contains Factor II, IX, X, Protein C and S , + heparin
- 4 Factor-PCC (Kcentra) → contains Factor II, VII, IX, X, Protein C and S, + heparin
- Approved for use in US → 2013

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



A. Define "life-threatening" bleeding in the warfarin-anticoagulated patient.
Consider:
1. Intracranial hemorrhage
2. Hemorrhage into the spinal canal
3. Dissecting or rupturing aortic aneurysm
4. Other acute life-threatening hemorrhage in a patient
   a. needing immediate INR correction, or
   b. who cannot tolerate the volume associated with fresh frozen plasma therapy
B. Consider mechanical, surgical, or other interventional means of hemorrhage control, along with conventional reversal therapy (vitamin K, fresh frozen plasma).
C. Replace blood and blood components as needed. Consider "massive transfusion protocol."
D. Give vitamin K intravenously (10 mg) to all
E. Factor replacement options (will depend on consultant preferences and availability); treat INR >1.5
1. Optimized fresh frozen plasma
   a. Streamlined blood bank procedures
   b. Thawed or liquid universal donor (AB) plasma (15 mL/kg)
2. rFVIIa (neurosurgeons may prefer, often combined with fresh frozen plasma)
   a. 1 mg rFVIIa
   b. Consider fresh frozen plasma
   c. INR inaccurate after rFVIIa
3. 4-Factor prothrombin complex concentrate (Kcentra)
   a. For INR 2–<4, give 25 U/kg
   b. For INR 4–6, give 35 U/kg
   c. For INR >6, give 50 U/kg
   d. Do not exceed the 100-kg dose at any INR
4. 3-Factor prothrombin complex concentrate (Profilnine SD)
   a. Give 25 IU/kg
   b. Recheck INR 15 min after administration
   c. If repeated INR is >1.5, consider a second 25 IU/kg dose
   d. Recheck INR 15 min after completion of second dose
   e. If repeated INR is >1.5, give fresh frozen plasma or rFVIIa
F. Consent for rFVIIa or 3-factor prothrombin complex concentrate (Profilnine SD): Both are off-label in the United States for warfarin reversal. Thrombosis risk for both PCC and rFVIIa (Food and Drug Administration black box warning for rFVIIa).

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

- Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525-34.

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 insuffiency (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 hyponatremia 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

ARTICLE 11

Small Bowel Obstruction

- Taylor MR, Lalani N. Adult small bowel obstruction. *Acad Emerg Med*. 2013;20(6):528-44.

General Information/Objectives

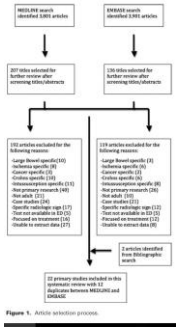
- Systematic review and meta-analysis
- Identify evidence based aspects of History, Physical Exam, imaging in diagnosis of SBO
- Determine prevalence of SBO in prospective based ED studies
- Test-treatment threshold to determine when to begin treatment vs further diagnostics to confirm SBO

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 insuff. 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 SBOs
    - Test/treatment thresholds



Results – History

- No components of history that could reliable/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

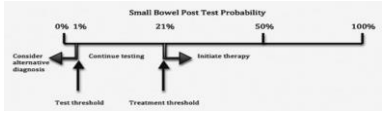
- Very few components of physical exam could be reliably used for diagnosis of SBO
  - Abnormal Bowel Sounds
    - + 6.33 and – LR = 0.27
  - **Abdominal Distention on physical exam was best sign**
    - **+ LR = 16.8 and – LR = 0.34**

Results - Imaging

Imaging Study	+ Likelihood Ratio	- Likelihood Ratio
X-Ray	1.55	0.43
CT Scan	3.62	0.18
MRI	6.77	0.12
Bedside Ultrasound	9.55	0.13
Formal Ultrasound	**14.1**	**0.04**

- **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

- Imazio M, Brucato A, Cemin R, et al; ICAP Investigators. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369(16):1522-8.

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, 1, 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 Cr, 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 in 1 week of treatment

Results – Trial Outcomes

Table 2. Trial Outcomes.*

Outcome	Placebo (N=120)	Colchicine (N=120)	P Value
Incessant or recurrent pericarditis: primary end point — no. (%)‡	45 (37.5)	20 (16.7)	<0.001†
Symptom persistence at 72 hr — no. (%)	48 (40.0)	23 (19.2)	0.001
Remission at 1 wk — no. (%)	70 (58.3)	102 (85.0)	<0.001
Incessant course — no. (%)	20 (16.7)	9 (7.5)	0.046
Recurrent course — no. (%)	25 (20.8)	11 (9.2)	0.02
No. of recurrences per patient	0.52±0.81	0.21±0.52	0.001
Time to first recurrence — wk	17.7±9.0	24.7±11.0	<0.001
Cardiac tamponade — no. (%)	3 (2.5)	0	0.25
Constrictive pericarditis — no. (%)	1 (0.8)	0	1.00
Pericarditis-related hospitalization — no. (%)	17 (14.2)	6 (5.0)	0.02
Mean follow-up — mo	22.3±8.7	22.9±8.7	0.61

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.

Results – Adverse Events

Table 3. Adverse Events.

Adverse Event	Placebo (N=120)	Colchicine (N=120)	P Value
	no. (%)		
Overall	12 (10.0)	14 (11.7)	0.84
Gastrointestinal disorder*	10 (8.3)	11 (9.2)	0.67
Hepatotoxicity†	1 (0.8)	2 (1.7)	
Myotoxicity	0	0	
Alopecia	1 (0.8)	1 (0.8)	
Other	0	0	
Serious adverse event‡	0	0	
Drug discontinuation	10 (8.3)	14 (11.7)	0.52
Physician decision	9 (7.5)	12 (10.0)	
Patient decision	1 (0.8)	2 (1.7)	

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**