Blood, Guts, & Brains:
keeping them straight in the ICU

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What are we talking about?

- Blood
  - DVT Prophylaxis
- Guts
  - Stress Ulcer Prophylaxis
- Brains
  - Critical Care Delirium

DVT Prophylaxis

What is a DVT?

- It is the formation of a blood clot within deep veins, those in the lower limbs, resulting in partial or complete blockage of blood flow in the vein.
- The condition can be resolved if it is recognized and treated properly. However, it can be fatal if the clot breaks off, travels to the lungs, and causes a pulmonary embolism.

http://www.tc.gc.ca/eng/civilaviation/standards/commerce-cabinsafety-dvt-1086.htm Accessed July 8th, 2011.

Approximate Risks of DVT in Hospitalized Patients

Patient Group	DVT Prevalence (%)
Medical patients	10-20
General surgery	15-40
Stroke	20-50
Major trauma	40-80
SCI	60-80
Critical care patients	10-80

Chest 2008.

Risk Factors for VTE

- Surgery
- Acute medical illness
- Trauma
- Immobility
- Cancer
- Venous compression
- Previous VTE
- Increasing age
- Pregnancy
- Estrogen therapy
- SERMs
- ESAs
- IBD
- Nephrotic syndrome
- Obesity
- CVCs

Chest 2008.

Risk Factors for Bleeding

- Active bleeding
- Bleeding disorders
  - e.g. acute liver failure
- Anticoagulation
  - ↑ INR or aPTT
- LP/epidural/spinal
  - Previous 4 hours or next 12 hours
- Acute stroke
- Thrombocytopenia
  - Plt < 75 x 10^9 /L
- Uncontrolled HTN
  - ≥ 230/120 mmHg
- Untreated inherited bleeding disorder
  - e.g. hemophilia

Venous thromboembolism - reducing the risk. 2010 NICE guidelines.

Risk Stratification

Level of risk	DVT risk w/o prophylaxis	Options
Low (mobile patients)	< 10	Early aggressive ambulation
Medium (most surgery and sick patients)	10 – 40	LMWH, LDUH, fondaparinux (mechanical)
High (ortho surgery, major trauma, SCI)	40 – 80	LMWH, warfarin, fondaparinux (mechanical)

Chest 2008.

Factors to consider when choosing an agent

- Risk of bleeding (mechanical DVT prophylaxis?)
- Fondaparinux <u>not</u> recommended in CC
- Hx of HIT
- Renal function
- Heparin bid or tid?
- LMWH dosing based on DVT risk

J Pharm Pract. 2011;24:78-88.

PROTECT

- Double-blinded, placebo-controlled, multi-vcenter RCT
- 3764 ICU patients
- UFH 5000 u bid vs. Dalteparin 5000 u daily
- High-risk groups excluded
  - Major trauma, ortho surgery, SCI

N Engl J Med 2011;364:1305-14..

PROTECT – Results

- Primary:
  - Dalteparin was <u>not</u> superior to heparin in decreasing proximal DVT (5.1 vs. 5.8 % p=0.57)
- Secondary:
  - Fewer PEs with Dalteparin (1.2 vs. 2.3 % p=0.01)
  - No difference in:
    - Major bleeding
    - Death in ICU or hospital

N Engl J Med 2011;364:1305-14..

Bottom Line – DVT Prophylaxis

Stress Ulcer Prophylaxis

What is a Stress Ulcer?

- Gastrointestinal mucosal injury related to critical illness.
- There is a relationship between GI bleeding and severity of disease.
- Likewise there is a strong relationship between bleeding and mortality

www.ccmtutorials.com Pat Neligan, University of Pennsylvania, 2006.

What is the risk of ulceration?

- Clinically significant bleeding in up to 15% of ICU patients with<u>out</u> stress-ulcer prophylaxis
- 1.5 – 8 % with stress-ulcer prophylaxis
- Perforation in < 1 % of surgical ICU patients

J Pharm Pract. 2011;24:78-88.

Who is prophylaxis indicated for?

<u>Definitely:</u>

- Coagulopathy
  - Plt < 50,000 / mm^3
  - INR > 1.5
  - PTT > 2 x normal
- Mechanical ventilation > 48 hrs

<u>Maybe:</u>

- Hypotension
- Sepsis
- Hepatic and /or renal failure
- Head injury w/ GCS < 10
- Thermal injury > 35% of BSA
- Multiple trauma
- Spinal cord injury
- Organ transplant
- ≥ 250 mg hydrocortisone equivilent per day

UW Medical Center Drug Therapy Topics. March 2008.

What are the available options?

- Sucralfate
- H_2 Receptor Antagonists
  - Ranitidine (Zantac)
- Proton Pump Inhibitors
  - Lansoprazole (Prevacid)
  - Pantoprazole (Pantoloc)
- Enteral Feeding ???

Sucralfate

- MOA: forms a protective coating over the gastric mucosa
- Efficacy in SUP:
  - Similar to H_2RAs
  - Better than antacids
- Dose: 1 g ng/og qid
- For the most part, no longer used.

Stress ulcer prophylaxis in the intensive care unit. UpToDate.com, Accessed May 25th, 2011.

H_2 Receptor Antagonists

- MOA: block H_2 receptors on the parietal cell to decrease gastric acid secretion
- Efficacy in SUP:
  - Equivalent to Sucralfate & PPIs
  - Superior Antacids
- Adjust dose for renal function
- Drug of choice for SUP

Stress ulcer prophylaxis in the intensive care unit. UpToDate.com, Accessed May 25th, 2011.

Proton Pump Inhibitors

- MOA: irreversibly bind to and inhibit the H^+-K^+ pump on the parietal cell membrane
- Efficacy in SUP:
  - Equivalent to H_2RAs
- Dosed once daily for SUP
- Drug of choice if bleeding occurs

Stress ulcer prophylaxis in the intensive care unit. UpToDate.com, Accessed May 25th, 2011.

What are the risks of SUP?

- Hospital-acquired pneumonia
- *C. difficile* infection
- Inappropriate long-term Tx:
  - Osteoporosis
  - Drug interactions?
  - Unnecessary cost

When do you stop?

- When no longer indicated !!!
  - e.g. extubation
- Do not order on transfer or discharge unless the patient:
  - had a GI bleed during ICU/hospital stay
  - was taking at home for another indication

Enteral Feeding as SUP?

- Current guidelines based on older data
  - ICU patients kept nil-per-os longer
  - Early feed initiation was uncommon
- MOA: buffer acid, induce natural cytoprotection, improve mucosal blood flow, direct source of mucosal energy
- No prospective clinical trials have evaluated enteral feeding as SUP

Crit Care Med 2010; 38:2222-2228.

2010 Review & Meta-analysis

- 17 studies (1836 patients)
  - H_2RA vs. placebo
  - Adequate TEN given in 3 studies
- Less clinically significant bleeding in H_2RA group vs. placebo
  - Benefit only seen in subgroup not receiving TEN
  - SUP + TEN may increase risk of pneumonia and death
- Caution! Meta-analysis have limitations.

Crit Care Med 2010; 38:2222-2228.

Bottom Line – SUP

- Start when indicated
- Discontinue when the indicating condition is removed

Critical Care Delirium

What is Delirium?

DSM-IV

"a disturbance of consciousness and cognition that develops over a short period of time (hours to day) and fluctuates over time"

Classification of Delirium

- Hyperactive:
  - agitated, restless, emotionally labile
  - pure hyperactive is rare (1.6%)
- Hypoactive:
  - ↓ responsiveness, withdrawal, apathy
  - 43.5%
- Mixed
  - 54.1%

J Am Geriatr Soc 2006, 54:479-484.

Prevalence & Significance

- Reported range of 20-80% depending on severity of illness and diagnostic method used.
- Complications
- Increased mortality

Critical Care 2008, 12(Suppl 3):S3.

Pathophysiologic Theories

- Neurotransmitter imbalance
  - Dopamine vs. Acetylcholine
- Inflammation
  - Inflammatory mediators
- Impaired oxidative metabolism
  - Reduced brain metabolism
- Availability of large neutral amino acids
  - Precursors to neurotransmitters

Critical Care 2008, 12(Suppl 3):S3.

Risk Factors

- HTN
- EtOH abuse
- Severity of illness
- Smoking Hx
- ↑ bilirubin
- Acidosis
- Infection
- Metabolic disturbance
- **Sleep deprivation**
- Anemia
- Hypotension
- Respiratory disease
- Medications:
  - **Sedatives**
  - **Analgesics**
  - Steroids
  - Anticholinergics
  - Metoclopramide
  - H_2RAs

Critical Care 2008, 12(Suppl 3):S3.

Diagnosis

- SCCM recommends that all ICU patients are regularly assessed for delirium.
- Intensive Care Delirium Screening Checklist (ICDSC)
- Confusion Assessment Method for the ICU (CAM-ICU)

Prevention of Delirium (1)

- 852 hospitalized older adults
- Nonpharmacologic strategy
  - Reorientation to time, place, and situation
  - Sleep promotion
  - Remove catheters and restraints
  - Communication aids
  - Early dehydration correction
- 6.1% reduction in delirium vs. usual care
- OR = 0.60 (CI 0.39-0.92)

N Engl J Med 1999, 340:669-676.

Prevention of Delirium (2)

- Use sedation protocols:
  - must incorporate a validated sedation scale
  - use intermittent as opposed to continuous sedation whenever possible
  - promote daily drug holidays
- Avoid benzodiazepine overuse!
- Provide adequate analgesia

Critical Care 2008, 12(Suppl 3):S3.

Prevention of Delirium (3)

- Haloperidol for prevention?
- RCT of 430 elderly hip surgery patients
  - Non-ICU
- No effect on incidence
- Reduced severity and duration of delirium
  - DRS-R-98 score 4 points less ($p<0.001$)
  - delirium duration 6.4 days less ($p<0.001$)

J Am Geriatr Soc 2005 Oct;53(10):1658-66.

Treatment with Haloperidol

- Recommended 1st line by SCCM and APA
- Dosing:
  - 2 mg iv
  - Repeat with double the previous dose every 15-20 minutes while agitation persists
  - Once controlled, switch to q4-6h and taper to d/c over a few days

Critical Care 2008, 12(Suppl 3):S3.

Treatment with Olanzapine

- Non-randomized ICU study
  - Haloperidol vs. olanzapine
    - Both groups received Haldol prn
  - 73 patients
  - given via enteral route
- Resolution of delirium similar
- No adverse effects with olanzapine
  - 6 haloperidol patients had mild EPS symptoms

Intensive Care Med 2004 Mar;30(3):444-9. Epub 2003 Dec 19.

Treatment with Quetiapine

- Prospective, multicenter, randomized, double-blind, placebo controlled study
  - Quetiapine vs. placebo
    - Both groups received Haldol prn
  - 36 patients
- With Quetiapine:
  - Faster delirium resolution (1 vs. 4.5 days $p=0.001$)
  - ↓ Duration of delirium (36 vs. 120 hours $p=0.006$)

Crit Care Med 2010, 38:419-427.

Bottom Line – Delirium

- Prevent
  - minimize risk factors
  - conservative use of benzodiazepines
  - provide adequate analgesia
- Identify
  - regular screening
- Treatment
  - haloperidol
  - olanzapine
  - quetiapine
  - discontinue prior to ICU discharge in most cases

Questions?