MSHP Annual Meeting 2016

Year in Review: Critical Care

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Disclosures

The presenters have no disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Fluid Resuscitation in the Intensive Care Unit (ICU)

Discuss new evidence regarding the use of different fluid resuscitation strategies in critically ill patients

Patient Case

AW is a 42 y/o M admitted to the medical ICU with severe acute pancreatitis. AW receives 5 L of IV NaCl 0.9% and is started on a maintenance infusion at 275 mL/hr. AW's ABG and laboratory values upon arrival to the ICU are as follows:

141	118	30	145	Albumin	2.8 g/dL
4.1	19	1.5		Lactate	2.2 mmol/L

pH 7.32 | PCO_2 32 mm Hg | PO_2 68 mm Hg | HCO_3 18 mmol/L

Which of the following is the best treatment strategy to better manage AW's IV fluid therapy?

A. Switch IV fluid to NaCl 0.9% with 20 mEq/L of KCl at 275 mL/hr
B. Add 1.5 g/kg bolus of Albumin 25%
C. Switch IV fluid to dextrose 5% with NaCl 0.9% at 275 mL/hr
D. Switch IV fluid to lactate ringers at 275 mL/hr

Fluids – General Principles

- Indications and endpoints for fluid resuscitation in the critically ill
  - Intravascular and extravascular resuscitation
  - Maintenance hydration
  - Electrolyte replacement and redistribution
  - Toxins & antidotal therapy
- Indications and endpoints of resuscitation vary amongst ICU subpopulations
- Targeted or guided approach to fluid resuscitation has been shown to improve outcomes compared to the first year medical/surgical/anesthesia intern approach

Types of Fluid

- Crystalloid solutions: Solutions in water of small inorganic ions and small organic molecules
- Colloid solutions: Fluids that contain large molecules which are meant to keep the infusate in the intravascular space for a longer time by exerting an oncotic pressure
  - Human albumin solution and semisynthetics (gelatins, dextrans and hydroxyethyl starch [HES])
- Balanced solutions: Solutions with different electrolyte compositions close to plasma composition
- Buffered solutions: Solutions modified with bicarbonate or bicarbonate precursor buffers, such as maleate, gluconate, lactate or acetate

Guidet B et al. *Crit Care*. 2010;14:325.
Severs D et al. *Nephrol Dial Transplant*. 2015;30:178-87.

Ideal IV Fluid…Does not Exist

- Produces a predictable and sustained increase in intravascular volume
- Chemical composition as close as possible to that of extracellular fluid
- Metabolized and completely excreted without accumulation in tissues
- Does not produce adverse metabolic or systemic effects
- Cost-effective in terms of improving patient outcomes

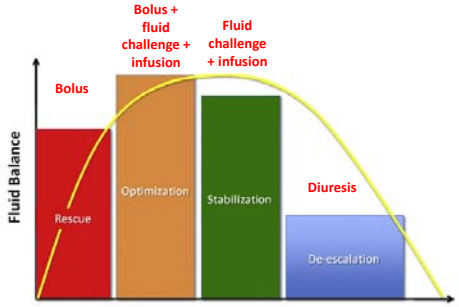
Myburgh JA et al. *N Engl J Med*. 2013;369:1243-51.

Fluid Administration Techniques in the Critically Ill are NOT SO ROUTINE …

- Fluid bolus: a rapid infusion to correct intravascular volume status and shock
  - Typically at least 500 ml over a maximum of 15 min
- Fluid challenge: rapid infusion to correct hemodynamic instability
  - 100–200 ml over 5–10 min with reassessment to optimize tissue perfusion
- Fluid infusion: continuous delivery of IV fluids to maintain homeostasis, replace losses, or prevent organ injury
- Maintenance: fluid administration for the provision of fluids for patients who cannot meet their needs by oral route

Hoste EA et al. *Br J Anaesth*. 2014;113:740-7.

Four Phases of Fluid Therapy: You are always moving on fluids



Hoste EA et al. *Br J Anaesth*. 2014;113:740-7.
Rewa O et al. *Crit Care Clin*. 2015;31:785-801.

Physiological Badness in the Critically ill

- Hyperchloremia is associated with "badness" in critically ill patients
  - Shaw AD et al. *Intensive Care Med*. 2014; 40:1897-1905.
- Non-gap metabolic acidosis is associated with worsened mortality
  - Gunnerson KJ et al. *Crit Care*. 2006;10:R22.
- Normal saline causes a dilutional hyperchloremic metabolic acidosis….
  - Awad S et al. *Clin Nutr.* 2008;27:179-88.

Brill SA et al. *Shock*. 2002 Jun;17(6):459-62.
Hatherill M et al. *Arch Dis Child*. 2005 Dec;90(12):1288-92.

Composition of Crystalloids

	Human plasma	0.9% NaCl	Ringer's Lactate	PlasmaLyte A	PlasmaLyte 148
Osmolarity (mOsm/L)	275-295	308	273	295	294
pH	7.35-7.45	4.5-7.0	6.0-7.5	7.4	4.0-6.5
Na (mmol/L)	135-145	154	130	140	140
Cl (mmol/L)	94-111	154	109	98	98
K (mmol/L)	3.5-5.3	0	4	5	5
Ca (mmol/L)	2.2-2.6	0	1.4	0	0
Mg (mmol/L)	0.8-1.0	0	0	1.5	1.5
HCO_3 (mmol/L)	24-32	0	0	0	0
Acetate (mmol/L)	1	0	0	27	27
Lactate (mmol/L)	1-2	0	28	0	0
Gluconate (mmol/L)	0	0	0	23	23
Na:Cl ratio	1.21:1 to 1.54:1	1:1	1.19:1	1.43:1	1.43:1
Strong ion difference	40 ± 2	0	28	50	50

Myburgh JA et al. *N Engl J Med*. 2013;369:1243-51.
Plasmalyte 148 [package insert]. Baxter Healthcare. 2013.

Chloride-liberal vs. Chloride-restrictive IV Fluid Therapy in the ICU

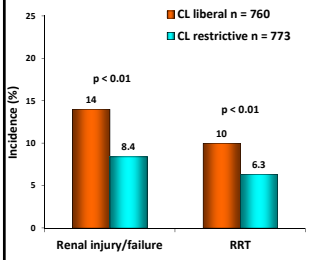
Variable	Cl liberal (n = 760)	Cl Restrictive (n = 773)	P value
Acute kidney injury or failure; no (%)*	105 (14)	65 (8.4)	<0.01
RRT use; no (%)	78 (10)	49 (6.3)	<0.01
ICU LOS hrs; median	42.9	42.8	0.52
ICU mortality; no (%)	65 (9)	59 (8)	0.42
Hospital mortality; no (%)	112 (15)	102 (13)	0.44

* Primary Endpoint: Injury or greater according to RIFLE criteria
LOS = length of stay; RRT = renal replacement therapy

Prospective, open-label, single-centered, before-after study of a chloride liberal (0.9% saline, 4% succinylated gelatin solution, 4% albumin), and chloride restrictive (Hartmann's, Plasma-Lyte 148, 20% albumin) ICU fluid protocol in 1533 patients.

Yunos NM et al. JAMA. 2012;308:1566-1572.

Chloride-liberal vs. Chloride-restrictive IV Fluid Therapy in the ICU



Significant patient characteristics/metrics/outcomes

Variable	Cl liberal	Cl restrictive	P value
ICU LOS*	42.9	42.8	0.52
ICU mortality†	65 (9)	59 (8)	0.42
Hospital mortality†	112 (15)	102 (13)	0.44
NS; L/pt	3.2	0.06	<0.01
Hartmann's; L/pt	0.6	4.6	<0.01
4% albumin; L/pt	0.35	0.1	<0.01
*Data presented in median hrs; †Data presented as n (%)			

Prospective, open-label, single-centered, before-after study of a chloride liberal (0.9% saline, 4% succinylated gelatin solution, 4% albumin), and chloride restrictive (Hartmann's, Plasma-Lyte 148, 20% albumin) ICU fluid protocol in 1533 patients.

Yunos NM et al. JAMA. 2012;308:1566-1572.

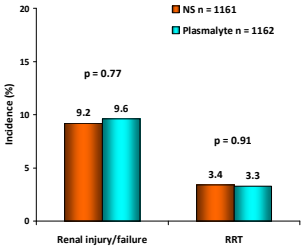
Balanced Solutions do not Cause Hyperchloremia… ***Wrong***

- Mechanisms of hyperchloremic Non Gap Metabolic Acidosis
  - Renal losses: Renal tubular acidosis
  - Gastrointestinal losses
- Yunos et al. Cl liberal vs restrictive before-after analysis

Original analysis	Cl liberal (n = 760)	Cl restrictive (n = 773)	P value
Severe hyperchloraemia (Cl > 114 mmol/l); no (%)	79 (10)	64 (8)	NR
Extended analysis	**Cl liberal (n = 760)**	**Cl restrictive (n = 773)**	**P value**
Severe hyperchloraemia (Cl > 114 mmol/l); no (%)	86 (12)	64 (8)	NR

Yunos NM et al. JAMA. 2012;308:1566-72.
Yunos NM et al. Intensive Care Med. 2015;41:257-64.

NS vs. Plasmalyte 148 in Mixed Medical-Surgical ICU: SPLIT Trial



Significant patient characteristics/metrics/outcomes

Variable	NS	Plasmalyte	P value
ICU LOS*	1.47	1.5	0.58
ICU mortality†	80 (7.2)	76 (6.6)	0.62
Hospital mortality†	112 (15)	102 (13)	0.44
Acidemia (pH < 7.2)†	9 (0.8)	13 (1.1)	0.52
Study fluid; L/pt	2.5	2.6	NS
*Data presented in median hrs; †Data presented as n (%)			

Investigator initiated, multicenter, blinded, cluster-randomized, double crossover study conducted in 4 tertiary ICUs in New Zealand. Patients received blinded NS vs Plasmalyte 148 for routine fluid needs.

Young P et al. *JAMA*. 2015;314:1701-10.

How Much NS is too Much?

- O'Dell and colleagues looked at chloride load and development of hyperchloremeic non gap metabolic acidosis in pediatric meningococcal sepsis
- Established that there is an inverse linear relationship between chloride load and base excess
  - 20 mEq/kg chloride load is needed to decrease base excess by 10 mEql/L = **9 liters of isotonic saline/24hrs**
- Alternatives: 50ml/kg bolus over 1 hour
- Its about dose and speed of chloride load: You have to give the kidneys time to clear chloride, with the barriers of kidney injury and RTA's and GI losses

O'Dell E et al. Crit Care Med. 2007;35:2390-4.
Guidet B et al. Crit Care. 2010;14:325.
Lobo DN et al. Kidney Int. 2014;86:1096-1105.

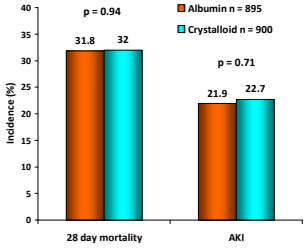
ADDING Balance to NS in Septic Shock

Variable	Saline alone (N = 44,347)	Sal + Bal (N = 3,651)	P value
Two or more vasopressors by day 2; %	32.59	39.09	NR
Mechanical ventilation by day 2; %	40.41	48.32	NR
Total crystalloid by day 2; median (IQR)	5,000 (3,500–8,000)	7,500 (5,000–10,500)	NR
Unadjusted Mortality; %	20.25	17.64	NR
IPW adjusted mortality; % (95 % CI)	20.19 (19.49–20.89)	17.69 (16.40–18.88)	< 0.001
IPM: Inverse probability weighting			

Retrospective analysis of database from the Premier healthcare alliance of adult medical patients with diagnosis of septic shock between January 2006 and December 2010.

Raghunathan K et al. *Anesthesiology*. 2015;123:1385-93.

Albumin Supplementation in Sepsis: ALBIOS Trial



Significant patient characteristics/metrics/outcomes

Variable	Albumin	Crystalloid	P value
Shock†	565 (62.6)	570 (62.8)	NS
ICU LOS; days*	9	9	0.42
90-day mortality†	365 (41.1)	389 (43.6)	0.29
SOFA score*	6	5.62	0.23
Time to pressor cessation; days*	3	4	0.007
Total fluids/ at day 7; mL*	3738	3825	0.1
*Data presented in median; †Data presented as n (%)			

Investigator initiated, multicenter, open label trial conducted in over 100 ICUs in Italy. Patients received albumin 20% supplementation (300 mL) on top of crystalloids vs crystalloid therapy alone with volume resuscitation according to EGDT protocol.

Caironi P et al. N Engl J Med. 2014;370:1412-21.

Patient Case

AW is a 42 y/o M admitted to the medical ICU with severe acute pancreatitis. AW receives 5 L of IV NaCl 0.9% and is started on a maintenance infusion at 275 mL/hr. AW's ABG and laboratory values upon arrival to the ICU are as follows:

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B. Add 1.5 g/kg bolus of Albumin 25%
C. Switch IV fluid to dextrose 5% with NaCl 0.9% at 275 mL/hr
D. Switch IV fluid to lactate ringers at 275 mL/hr

IV Fluids Take Home Points

- Not all crystalloids are created the same
- When you need rapid intravascular volume, NS is the crystalloid of choice
  - Initial fluid resuscitation
  - Fluid challenges depending upon outcomes assessing
- Incorporating balanced solutions may be beneficial in "high" volume resuscitation cases in the optimization and stabilization phases of fluid resuscitation
  - Development or baseline presence of dilutional non gap metabolic acidosis should be a trigger to reduce Cl load and incorporate balanced solutions
- Albumin may have a role in select disease states

Sepsis and Early Goal-Directed Therapy (EGDT)

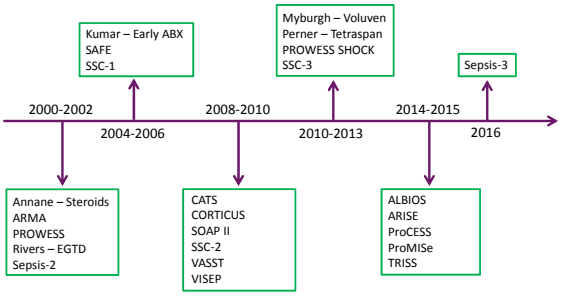
Evaluate new evidence regarding the early management of sepsis and its impact on best practices

Sepsis

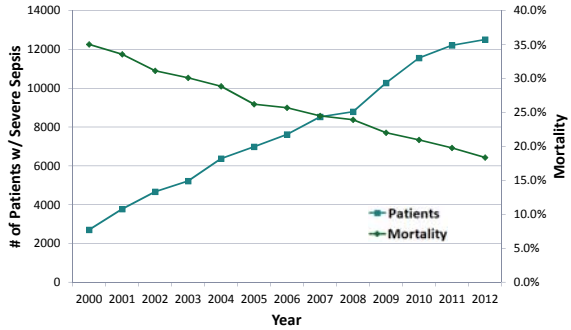
- Was defined as systemic response to infection in presence of two or more of the following (Systemic Inflammatory Response Syndrome [SIRS]):
  - Temperature >38°C or <36°C
  - Heart rate >90 beats per minute
  - Respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg
  - WBC >12 or <4, or >10% bands
- Now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection"

Levy MM et al. Intensive Care Med. 2003;29;530-8.
Singer M et al. JAMA. 2016;315:801-10.

Progress in the Past 1.5 Decades



(Severe) Sepsis Over Time



Kaukonen KM et al. JAMA. 2014;311:1308-16.

Updates in Sepsis: Sepsis-3

- Sepsis-3
  - SIRS criteria problematic
    - Cohort in Australia/New Zealand = 1 in 8 missed
- Removal of severe sepsis
- Septic shock
  - Vasopressors for mean arterial pressure ≥ 65 mm Hg + lactate > 2 mmol/L, in absence of hypovolemia
- Sequential (Sepsis-related) Organ Failure Assessment (SOFA) and quick SOFA (qSOFA)
  - qSOFA for rapid identification

Kaukonen K et al. N Engl J Med. 2015;372:1629-38.
Seymour CW et al. JAMA. 2016;315:762-74.
Singer M et al. JAMA. 2016;315:801-10.

SOFA and qSOFA

SOFA score

	Score
Bilirubin	0-4
Cardiovascular	0-4
GCS	0-4
PaO_2/FiO_2	0-4
Platelets	0-4
SCr	0-4
Urine output	3, 4

FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; PaO_2= partial pressure oxygen; SCr = serum creatinine

- Change in baseline SOFA ≥2

qSOFA score

	Score
Altered mentation	0, 1
RR ≥ 22/min	0, 1
SBP ≤ 100 mm Hg	0, 1

RR = respiratory rate; SBP = systolic blood pressure

- Screening tool to predict patients likely to have poor outcome

Singer M et al. JAMA. 2016;315:801-10.

Surviving Sepsis Campaign – 2016

- Sepsis still identified via organ dysfunction criteria (e.g. lactate > 2 mmol/L)
- qSOFA ≠ definition of sepsis, only identifies patients at risk for ↑ mortality or length of stay
- Preparation for hospitals and fiscal considerations, CMS
- Management stays the same, based on recent guidelines

Dellinger RP et al. Crit Care Med. 2013;41:580-637.
Surviving Sepsis Campaign. March 1, 2016.

Patient Case

MP is a 60 y/o F presenting to the emergency department with signs of sepsis. Based on the Surviving Sepsis Campaign guidelines, which of the following is the most appropriate initial recommendation for management?

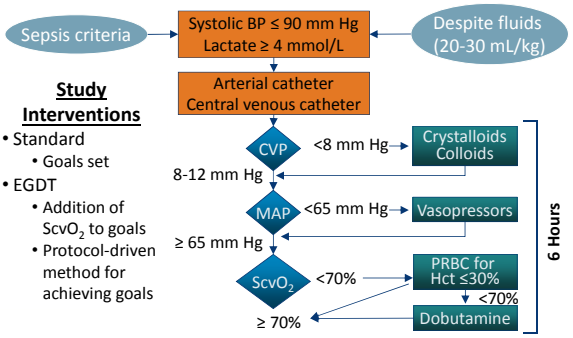
A. Administration of vasopressors, titrated to values obtained from an inserted central venous catheter
B. Administration of antibiotics, tailored to common community-acquired organisms at your institution
C. Administration of albumin, as an initial method of fluid resuscitation
D. Administration of fluids, focused on crystalloid therapy for initial management

Elements of Care for Sepsis

- Resuscitation
  - Early goal-directed therapy (EGDT)
  - Vasopressin
- Infection control
  - Infusion of β-lactams
- Respiratory support
- Central nervous system support
- General supportive care

Angus DC et al. N Engl J Med. 2013;369:840-51.

EGDT: Rivers



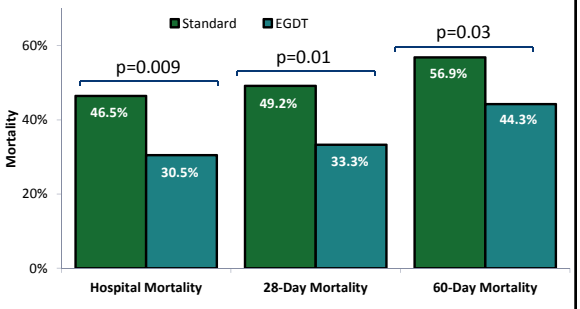
Study Interventions

- Standard
  - Goals set
- EGDT
  - Addition of $ScvO_2$ to goals
  - Protocol-driven method for achieving goals

BP = blood pressure; CVP = central venous pressure; MAP = mean arterial pressure; PRBC = packed red blood cell; $ScvO_2$ = central venous oxygen saturation

Rivers E et al. N Engl J Med. 2001;345:1368-77.

EGDT Outcomes (n = 263)



Rivers E et al. N Engl J Med. 2001;345:1368-77.

Controversies with EGDT

- Unclear intervention leading to study's positive findings
  - Use of a goal-directed protocol
  - Addition of $ScvO_2$ monitoring
    - Lactate clearance non-inferior to $ScvO_2$ as a goal
  - Both?
- High control arm mortality
- Use of CVP as a resuscitation goal
  - Fluid responsiveness better predicted by dynamic markers
- Need for additional research

Durairaj L et al. Chest. 2008;133:252-63.
Huang DT et al. Intensive Care Med. 2013;39:1760-75.
Jones AE et al. JAMA. 2010;303;739-46.

Bigger … but Better?

- ProCESS
  - Emergency departments in US (n = 31)
  - Protocol-based EGDT vs. protocol-based standard therapy vs. usual care
- ARISE
  - Emergency departments (mainly Australia and New Zealand) (n = 51)
  - EGDT vs. usual care
- ProMISe
  - Hospitals in England (n = 56)
  - EGDT vs. usual care
  - Cost-effectiveness analysis

Mouncey PR et al. N Engl J Med. 2015;372:1301-11.
Peake SL et al. N Engl J Med. 2014;371:1496-1506.
Yealy DM et al. N Engl J Med. 2014;370:1683-93.

EGDT Trials

	Rivers	ProCESS	ARISE	ProMISe
Design	SC	MC	MC	MC
# of patients	263	1341	1600	1260
Year	1997-2000	2008-2013	2008-2014	2011-2014
APACHE II	21.4	20.8	15.4	18.7
$ScvO_2$, %	48.6	71	72.7	70
Lactate, mmol/L	7.7	4.8	6.7	7.0
Mortality, %	30.5 vs. 46.5 (Hospital)	21.0 vs. 18.2 vs. 18.9 (60 days)	18.6 vs. 18.8 (90 days)	29.5 vs. 29.2 (90 days)

APACHE = Acute Physiology and Chronic Health Evaluation; $ScvO_2$ = central venous oxygen saturation

Mouncey PR et al. N Engl J Med. 2015;372:1301-11.
Peake SL et al. N Engl J Med. 2014;371:1496-1506.
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Yealy DM et al. N Engl J Med. 2014;370:1683-93.

Surviving Sepsis Campaign 2015

- "Required monitoring…via CVC…does not confer survival benefit in all patients who have received timely antibiotics and fluid resuscitation"
- "Results of ProCESS and ARISE trials have not demonstrated any adverse outcomes…Therefore, no harm exists in keeping current SSC guidelines intact…"

Surviving Sepsis Campaign. May 19, 2015.

Administration of β-lactams

What does your institution do?

A Continuous infusion
B Extended-infusion
C Standard administration

Infusion of β-lactams

- Maximization of PK and PD
  - Continuous vs. prolonged infusion
  - Problems associated with type of infusion
- BLING II (n = 432) and BLISS (n = 140)
  - Prospective, multicenter RCTs
  - Contrasting results
    - BLING II: no difference in mortality (90 days), clinical cure, organ-failure free days, duration of bacteremia
    - BLISS (no RRT): no difference in mortality (14 or 30 days); ↑ clinical cure, ventilator-free days, PK/PD target attainment
- BWH policy

Abdul-Aziz MH et al. Intensive Care Med. 2016.
Dulhunty JM et al. Am J Respir Crit Care Med. 2015;192:1298-1305.
Hohlfelder B et al. Am J Ther. 2016.

Vasopressin

- Significant increases in cost and change in stability/storage
- Vasopressin in sepsis
  - Relative vasopressin deficiency in septic shock
  - VASST
    - Benefit in less severe patients on mortality
  - SSC Guidelines
    - Addition to norepinephrine @ 0.03 units/min

Dellinger RP et al. Crit Care Med. 2013;41:580-637.
Russell JA et al. N Engl J Med. 2008;358:877-87.

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Sepsis Take Home Points

- In the setting of early recognition and early fluids and antimicrobial administration, clinician-driven resuscitation goals most likely sufficient
  - EGDT → usual care
- New changes to definition of sepsis and implications
  - Clinical research
  - Published data

Alcohol Withdrawal Syndrome (AWS) in the ICU

Discuss workhorse and adjunctive pharmacotherapy for the management of alcohol withdrawal in critically ill patients

Patient Case

BH is a 30 y/o M presenting to the emergency department with alcohol withdrawal. His current Clinical Institute Withdrawal Assessment score is 18 and he is still exhibiting signs of diaphoresis and tremulousness, despite receiving a total of 200 mg of intravenous diazepam over the past 3 hours. Which of the following is the best recommendation to prevent progression of this patient's alcohol withdrawal?

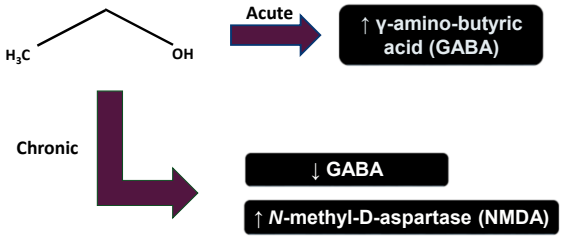
A. Initiate intravenous dexmedetomidine
B. Continue uptitration of IV diazepam
C. Initiate intravenous ethanol 5%
D. Initiate intravenous phenobarbital

Epidemiology

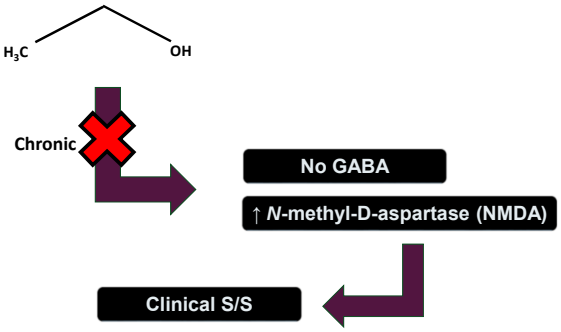
- Alcohol withdrawal syndrome (AWS)
  - Alcohol most frequently abused drug in world
  - Approximately 10% of hospital admissions develop AWS
    - AWS occurs in up to 30% of patients
- Associated with
  - Increased risk of mechanical ventilation
  - Increased infection risk

de Wit M et al. Chest. 2010;138:994-1003.
Foy A et al. QJM. 1997;90:253-61.
Spies CD et al. Anesth Analg. 1999;88:946-54.

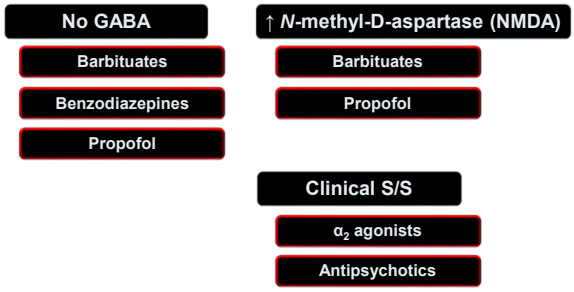
Pathophysiology



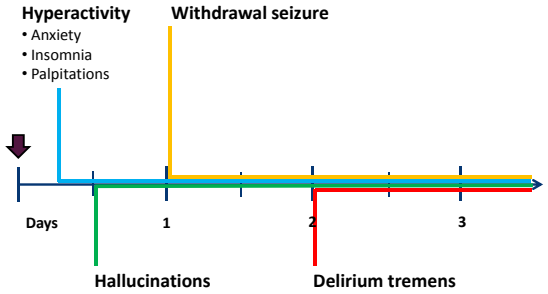
Pathophysiology



Pathophysiology



AWS Symptoms



Severe Alcohol Withdrawal

- "Kindling" effect
- Potential definitions
  - Admission to the ICU for AWS
  - Score on AWS scale
  - Resistant alcohol withdrawal (RAW)
    - >40 mg diazepam within 1 hour for management of AWS
    - Majority require ICU admission (54.9%)

de Wit M et al. Chest. 2010;138:994-1003.
Foy A et al. QJM. 1997;90:253-61.
Wong A et al. J Crit Care. 2015;30:405-9.

Key Aspects for AWS in the ICU

1. Screening for patients at risk of withdrawal
2. Risk assessment/stratification
3. Symptom-triggered & multimodal pharmacotherapy
   - Alcohol withdrawal symptoms
   - Alcohol withdrawal related seizure
   - Alcohol withdrawal related delirium
4. Prevention of Wernicke's encephalopathy/Korsakoff psychosis

Barriers to Management in the ICU

- Screening in the hospitalized setting
- Severity assessment and goal-directed therapy
  - Assessment tools
  - Optimal pharmacological agent and administration technique
- No national standard to guide alcohol withdrawal/delirium in hospitalized patients
  - Local guidelines are needed
- Fear of seizures, delirium tremens, and respiratory depression → under/overdosing
- Resource limitations

Symptom-triggered AWS Tools

- Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)
  - Most widely cited but promising results
  - Not validated in all patients
    - ICU patients
    - Non-communicative patients (for any number of reasons)
- AWS Type Indicator
  - Not as widely cited but promising results
  - Assessment tool triggers multimodal pharmacotherapy depending on AWS type
- Modified Minnesota Detoxification Scale (MINDS)
  - Limited published data but promising results
  - ICU patients

DeCarolis DD et al. Pharmacotherapy. 2007;27:510-8.
Jaeger TM et al. Mayo Clin Proc. 2001;76:695-701.
Stanley K et al. Pharmacotherapy. 2003;23:843-54.
Sullivan JT et al. J Clin Psychopharmacol. 1991;11:291-5.

Risk Factors for Severe AWS

- Previous AWS
- Previous AWS seizure
- History of DT
- History of alcohol rehab treatment
- Previous blackouts
- Concomitant CNS depressant agents
- Concomitant illicit substances
- Recent alcohol intoxication
- (+) blood alcohol level at presentation
- Evidence of ↑ autonomic activity

Maldonado JR et al. Alcohol. 2014;48:375-90.

Goals of Pharmacotherapy

Paradoxical effect: drunkenness and secondary delirium →

Reduce symptoms and potentially reduce risk of delirium tremens →

Prevent seizure →

Supportive management →

Stehman CR et al. Am J Emerg Med. 2013;31:734-42.
commons.wikimedia.org

Potential Considerations

1. Initial underdosing → delirium tremens
   - Initial overdosing → respiratory depression
2. Failure to identify failure of initial agent
   - Use of different medications with different mechanisms
   - Multimodal approach
3. Ethanol for management of symptoms
   - Titration, dosage
   - Intravenous formulation no longer available

Stehman CR et al. Am J Emerg Med. 2013;31:734-42.

General Principles

- Allergies/sensitivities
- Drug interactions
- Drug toxicities
- Individual withdrawal symptomatology
- Kinetics/dynamics
- Medication access availability (IV, IM,PO)
- Patient location (inpatient, inpatient detox, outpatient)
- Severity of illness/comorbidities/organ function
- Severity of withdrawal (mild → DT)

Mayo-Smith MF et al. Arch Intern Med. 2004;164:1405-12.

BZDs and Barbiturates

- Mechanism
  - BZD – frequency of channel opening
  - Barbituates – duration of channel opening
- Short vs. long acting agent
- Route
- Dosing/titration
  - Individualized vs. goal-directed
- Taper for patients with severe or protracted withdrawal
- BZD delirium vs. ICU delirium
  - Use of flumazenil for diagnosis: 72.9% (n = 85)

Mayo-Smith MF et al. Arch Intern Med. 2004;164:1405-12.
Moore PW et al. J Med Toxicol. 2014;10:126-32.
Stehman CR et al. Am J Emerg Med. 2013;31:734-42.

Dexmedetomidine for AWS

Parameter	Notes
Mechanism of action	• α_2 agonist • Data supporting use of clonidine in mild AWS • Improvement of AWS in murine models
Dosing	• Loading dose? • 0.2 – 1.5 mcg/kg/hr continuous infusion • Duration similar to use for ICU sedation
Potential benefit	• Cooperative sedation • Lacks respiratory depression • Different mechanism than BZDs • Polysubstance withdrawal
Potential risks	• Clearance affected by hepatic dysfunction • Effect on hemodynamics (e.g. asystole, bradycardia, hypotension) • Lacks GABA activity (e.g. seizures)
Data	• Limited (primarily retrospective data, small sample sizes) • RCTs (n = 2) indicate ↓ need for BZDs short-term (24 hrs), no difference in length of stay • Not recommended as first-line therapy

Bielka K et al. Ann Intensive Care. 2015;5:33. Wong A et al. Am J Drug Alcohol Abuse. 2015;41:382-91.
Mueller SW et al. Crit Care Med. 2014;42:1131-9.

Phenobarbital for AWS

Parameter	Notes
Mechanism of action	• $GABA_A$ agonist (different site than BZDs) → affects duration of channel opening • NMDA antagonist
Dosing	• Bolus dosing: 10 mg/kg ideal body weight • Dose-escalation: 65 → 130 → 260 mg • Bolus + stable dosing: 260 mg, 130 mg
Potential benefit	• Different mechanism than BZDs • Long t½ allows for self-taper • Targets multiple mechanisms of underlying pathophysiology
Potential risks	• Clearance affected by hepatic dysfunction • Effect on hemodynamics (e.g. bradycardia, hypotension) • Propylene glycol • Respiratory depression (when combined with other agents)
Data	• Use in ED: ↓ need for ICU admission; equivalent outcomes to lorazepam

Hendey GW et al. Am J Emerg Med. 2011;29:382-5. Rosenson J et al. J Emerg Med. 2013;44:592-98.e2.
Gold JA et al. Crit Care Med. 2007;35:724-30..

Propofol for AWS

Parameter	Notes
Mechanism of action	• $GABA_A$ agonist (different site than BZDs) → affects duration of channel opening • NMDA antagonist
Dosing	• Continuous infusion at typical sedation doses
Potential benefit	• Different mechanism than BZDs • Clearance not affected by end-organ dysfunction • Targets multiple mechanisms of underlying pathophysiology
Potential risks	• Effect on hemodynamics (e.g. bradycardia, hypotension) • Lipid formulation: infusion syndrome, triglycerides • Respiratory depression
Data	• Dexmedetomidine vs. propofol: both ↓ in BZD and haloperidol requirements; ↑ hypotension with propofol, ↑ hypotension with dexmedetomidine • BZD vs. BZD + propofol: ↑ ventilation, hospital/ICU length of stay with propofol

Lizotte RJ et al. Clin Pharmacol. 2014;6:171-7.
Wong A et al. Drug Alcohol Depend. 2015;154:296-9.

Select Antipsychotics for AWS

Medication	Route	Typical Dose (Frequency)	Onset (min)	Elimination T1/2 (hrs)	Common Adverse Effects
Haloperidol	IV, IM, PO	0.5 – 80mg/day (q2-q24)	Oral: 1 – 4 hours IV: 20 – 40 mins	21 hrs	Anticholinergic side effects Excessive sedation Extrapyramidal side effects QTc prolongation
Olanzapine	PO, IM	2.5 – 20 mg/day (qday to BID)	Oral: 1 – 4 hours IM: 15 – 45 mins	21 – 54 hrs	Excessive sedation Hyperglycemia QTc prolongation Olanzapine IM: excessive sedation or cardiovascular effects with BZDs
Quetiapine	PO	25 – 750mg/day (q6-q24)	Oral: 1 – 4 hours	4 – 6 hrs	
Risperidone†	PO	2 – 10mg/day (qD-BID)	Oral: 1 – 4 hours	20 – 30 hrs	
Ziprasidone	PO, IM	40 – 160mg/day (qD-BID)	Oral: 1 – 4 hours IM: 15 – 45 mins	2 – 7 hrs	

† IM longer acting agent administered every month
†† Injectable formulations available for intrathecal use

Addolorato G et al. Am J Med. 2006;119:276.e13-8.
Micromedex Healthcare Series.

"Just give them booze. They are going to just leave and go back to the bar. Pharmacy, why can't you supply some vodka for this patient?"

- Anonymous ICU practitioner

www.dominickevans.com, December 2013.

Why not Just Booze?

Parameter	Notes
Mechanism of action	• Likely exact replacement for patient
Dosing	• ? • Not commercially available in intravenous form
Potential benefit	• Works if given enough (prophylaxis and active AWS)
Potential risks	• High degree of patient variability • Impact on thiamine repletion • Increased risk of bleeding in populations; immunosuppressive at high doses • Logistics • No data supporting superiority; not recommended by guidelines • Volume

DiPaula B et al. J Subst Abuse Treat. 1998;15:437-42.
Dissanaike S et al. J Am Coll Surg. 2006;203:186-91.
Hodges B et al. Pharmacotherapy. 2004;24:1578-85.
Mayo-Smith MF et al. Arch Intern Med. 2004;164:1405-12.
Weinberg JA et al. J Trauma. 2008;64:99-104.

Step Up, Multimodal Approach

Adjunctive agents for refractory cases
- Dexmedetomidine
- Propofol (with basal intermediate or long acting benzo or barb)

Adjunctive agents for delirium and noradrenergic symptoms
- Antipsychotics
- Clonidine

GABA agonist backbone (prevention of seizure and treatment of withdrawal symptoms)
- Benzodiazepines or Barbiturates
  - Symptom triggered vs. scheduled dosing
- Propofol (if intubated for medical reason)

AWS Take Home Points

- AWS pharmacotherapy is part of a local guideline
- Multimodal approach targeting individual symptomatology in mild to severe cases
  - Failure of agents
- Symptom management
  - Fluids
  - Nutrition (e.g. thiamine)

Patient Case

BH is a 30 y/o M presenting to the emergency department with alcohol withdrawal. His current Clinical Institute Withdrawal Assessment score is 18 and he is still exhibiting signs of diaphoresis and tremulousness, despite receiving a total of 200 mg of intravenous diazepam over the past 3 hours. Which of the following is the best recommendation to prevent progression of this patient's alcohol withdrawal?

A. Initiate intravenous dexmedetomidine
B. Continue uptitration of IV diazepam
C. Initiate intravenous ethanol 5%
D. Initiate intravenous phenobarbital

References

Fluids

- Awad S. Allison SP, Lobo DN. The history of 0.9% saline. Clin Nutr. 2008;27:179-88.
- Baxter Healtcare. Plasmalyte 148 package insert. Old Toongabbie, New South Wales, Australia; 2013.
- Brill SA, Stewart TR, Brundage SI, Schreiber MA. Base deficit does not predict mortality when secondary to hyperchloremic acidosis. Shock. 2002;17:459-62.
- Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412-21.
- Guidet B, Soni N, Della Rocca G, et al. A balanced view of balanced solutions. Crit Care. 2010;14:325.
- Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10:R22.
- Hatherill M, Salie S, Waggie Z, et al. Hyperchloraemic metabolic acidosis following open cardiac surgery. Arch Dis Child. 2005;90:1288-92.
- Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth. 2014;740-7.
- Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: con. Kidney Int. 2014;86:1096-1105.
- Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369:1243-51.
- O'Dell E, Tibby SM, Durward A, Murdoch IA. Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis. Crit Care Med. 2007;35:2390-4.
- Raghunathan K, Bonavia A, Nathanson BH, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. Anesthesiology. 2015;123:1385-93.
- Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med. 2014;42:1585-91.
- Rewa O, Bagshaw SM. Principles of fluid management. Crit Care Clin. 2015;31:785-801.
- Severs D, Hoorn EJ, Rookmaaker MB. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. Nephrol Dial Transplant. 2015;30:178-87.
- Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med. 2014;40:1897-1905.
- Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701-10.
- Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. Intensive Care Med. 2015;41:257-64.
- Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566-72.

References

Sepsis

- Abdul-Aziz MH, Sulaiman H, Mat-Nor M, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labeled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis [published online ahead of print January 11, 2016]. Intensive Care Med. 2016. doi: 10.1007/s00134-015-4188-0.
- Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840-51.
- Dulhunty JM, Roberts JA, Davis JS, et al. A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis. Am J Respir Crit Care Med. 2015;192:1298-1305.
- Hohlfelder B, Kubiak DW, Degrado JR, Reardon DP, Szumita PM. Implementation of a prolonger infusion guideline for time-dependent antimicrobial agents at a tertiary academic medical center. [published online ahead of print January 16, 2016]. Am J Ther. 2016. doi: 10.1097/MJT.0000000000000377.
- Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29:530-8.
- Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877-87.
- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;23:801-10.

References

EGDT

- Angus DC, Barnato AE, Bell D, et al. A systematic review and metaanalysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med. 2015;41:1549- 60.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
- Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. Chest. 2008;133:252-63.
- Huang DT, Angus DC, Bamato A, et al. Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe. Intensive Care Med. 2013;39:1760-75.
- Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303;739-46.
- Kaukonen K, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and spetic shock among critically ill patients in Australia and New Zealand. JAMA. 2014;311:1308-16.
- Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301-11.
- Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496-1506.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.
- Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;762-74.
- Surviving Sepsis Campaign. Surviving Sepsis Campaign responds to ProCESS trial. http://www.survivingsepsis.org/SiteCollectionDocuments/SSC-Responds-Process-Trial.pdf. May 19, 2015. Accessed March 21, 2016.
- Surviving Sepsis Campaign Executive Committee. Surviving Sepsis Campaign responds to Sepsis-3. http://www.survivingsepsis.org/SiteCollectionDocuments/SSC-Statements-Sepsis-Definitions-3-2016.pdf. March 1, 2016. Accessed March 21, 2016.
- Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol based care for early septic shock. N Engl J Med. 2014;370:1683-93.

References

AWS

- Addolorato G, Leggio, L, Abenavoli L, et al. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med. 2006;119:276.e13-8.
- Bielka K, Kuchyn, Glumcher F. Addition of dexmedetomidine to benzodiazepines for patients with alcohol withdrawal syndrome in the intensive care unit: a randomized controlled study. Ann Intensive Care. 2015;5:33.
- DeCarolis DD, Rice KL, Ho L, Willenbring ML, Cassaro S. Symptom-driven lorazepam protocol for treatment of severe alcohol withdrawal delirium in the intensive care unit. Pharmacotherapy. 2007;27:510-8.
- de Wit M, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. Alcohol-use disorders in the critically ill patient. Chest. 2010;138:994-1003.
- DiPaula B, Tommasello A, Solounias B, McDuff D. An evaluation of intravenous ethanol in hospitalized patients. J Subst Abuse Treat. 1998;15:437-42.
- Dissanaike S, Halldorsson A, Frezza EE, Griswold J. An ethanol protocol to prevent alcohol withdrawal syndrome. J Am Coll Surg. 2006;203:186-91.
- Foy A, Kay J, Taylor A. The course of alcohol withdrawal in a general hospital. QJM. 1997;90:253-61.
- Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med. 2007;35:724-30.
- Handey GW. Dery RA, Barnes RL, Snowden B, Mentler P. A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal. Am J Emerg Med. 2011;29:382-5.
- Hodges B, Mazur JE. Intravenous ethanol for the treatment of alcohol withdrawal syndrome in critically ill patients. Pharmacotherapy. 2004;24:1578-85.
- Hosking J, Ameratunga S, Bullen C, Civil I, Ng A, Rodgers A. Screening and intervention for alcohol problems among patients admitted following unintentional injury: a missed opportunity? N Z Med J. 2007;120:22-30.
- Jaeger TM, Lohr RH, Pankratz VS. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. Mayo Clin Proc. 2001;76:695-701.
- Lizotte RJ, Kappes JA, Bartel BJ, Hayes KM, Lesselyoung VL. Evaluating the effects of dexmedetomidine compared to propofol as adjunctive therapy in patients with alcohol withdrawal. Clin Pharmacol. 2014;6:171-7.

References

AWS (cont.)

- Maldonado JR, Sher Y, Ashouri JF, et al. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol. 2014;48:375-90.
- Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med. 2004;164:1405-12.
- Moore PW, Donovan JW, Burkhart KK, et al. Safety and efficacy of flumazenil for reversal of iatrogenic benzodiazepine-associated delirium toxicity during treatment of alcohol withdrawal, a retrospective review at one center. J Med Toxicol. 2014;10:126-32.
- Mueller SW, Preslaski CR, Kiser TH, et al. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med. 2014;42:1131-9.
- Rosenson J, Clements C, Simon B, et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med. 2013;44:592-98.e2.
- Spies CD, Rommerlspacher H. Alcohol withdrawal in the surgical patient: prevention and treatment. Anesth Analg. 1999;88:946-54.
- Stanley KM, Amabile CM, Simpson KN, et al. Impact of an alcohol withdrawal syndrome practice guideline on surgical patient outcomes. Pharmacotherapy. 2003;23:843-54.
- Stehman CR, Mycyk MB. A rational approach to the treatment of alcohol withdrawal in the ED. Am J Emerg Med. 2013;31:734-42.
- Sullivan JT, Swift RM, Lewis DC. Benzodiazepine requirements during alcohol withdrawal syndrome: clinical implications of using a standardized withdrawal scale. J Clin Psychopharmacol. 1991;11:291-5.
- Weinberg JA, Magnotti LJ , Fischer PE, et al. Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. J Trauma. 2008;64:99-104.
- Wong A, Benedict NJ, Kane-Gill SL. Multicenter evaluation of pharmacologic management and outcomes associated with severe resistant alcohol withdrawal. J Crit Care. 2015;30:405-9.
- Wong A, Benedict NJ, Lohr BR, Pizon AF, Kane-Gill SL. Management of benzodiazepine-resistant alcohol withdrawal across a healthcare system: benzodiazepine dose-escalation with or without propofol. Drug Alcohol Depend. 2015;154:266-9.
- Wong A, Smithburger PL, Kane-Gill SL. Review of adjunctive dexmedetomidine in the management of severe acute alcohol withdrawal syndrome. Am J Drug Alcohol Abuse. 2015;41:382-91.

References of Interest

Cardiology

- Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S465-82.
- Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S444-64. 42 8.
- Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guidelines for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published online ahead of print September 24, 2015]. J Am Coll Cardiol. doi:10.1016/j.jacc.2015.08.856.

Hematology

- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315-52.

Neurology

- Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care. 2016. 24;6-46.
- Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-60.

Nutrition

- Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med. 2016;44:390- 438.

Pain

- Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131-57.