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Clinical Conundrums in Critical Care: Best Practices Not Addressed in Guidelines

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

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Less is More: Low-Dose Thrombolytics in Pulmonary Embolism

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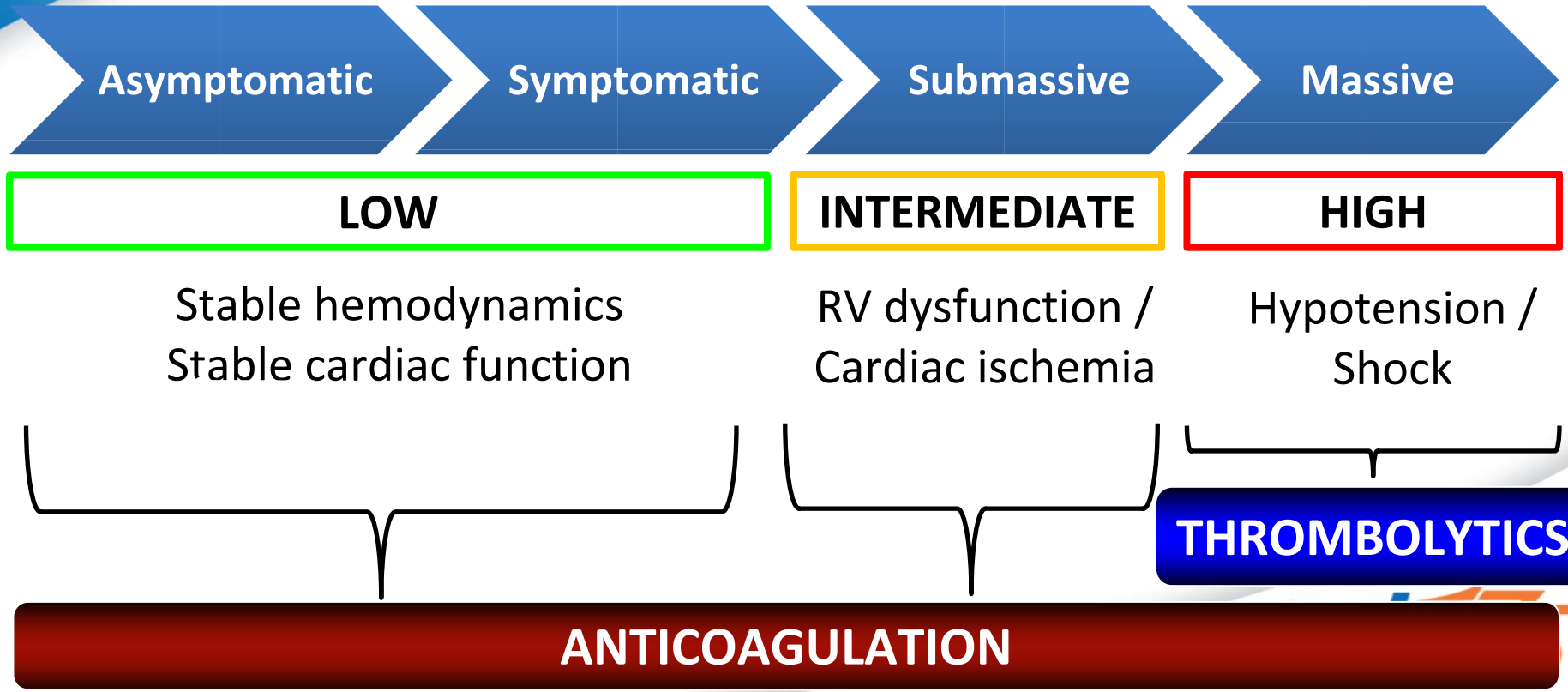
Objectives

- Review the role of thrombolytics in pulmonary embolism (PE)
- Evaluate the safety and efficacy of low-dose vs. standard-dose thrombolytics
- Recommend an evidence-based strategy and role in therapy for low-dose thrombolytics in PE patients

Clinical Spectrum of PE



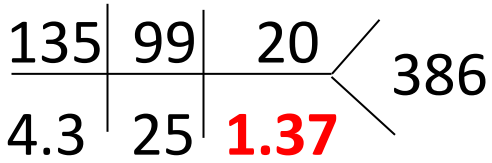
Patient Case

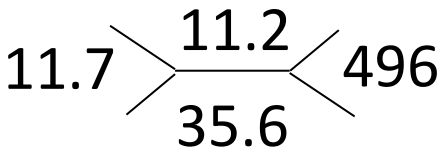
- J.J. is a 76-year old woman who presented from a rehabilitation facility with shortness of breath
- Past medical history
  - Tibia / fibia fracture s/p ORIF (2 weeks ago)
  - DM
  - CML
  - Seizures
  - Diastolic heart failure

Patient Case

- HR=54 RR=25 BP = 124/102 Temp=38.0 SpO2=99% (8 L/min O_2)
- pH = 7.37 pCO2 = 38 pO2 = 66
- CV = Regular rate and rhythm, no murmur
- Respirations = non-labored, ↓ breath sounds R base
- CXR = possible infiltrate R middle lobe

Patient Case





AST = 18

ALT = 16

INR = 1.0

Alk Phos = 104

NT-proBNP = 2599

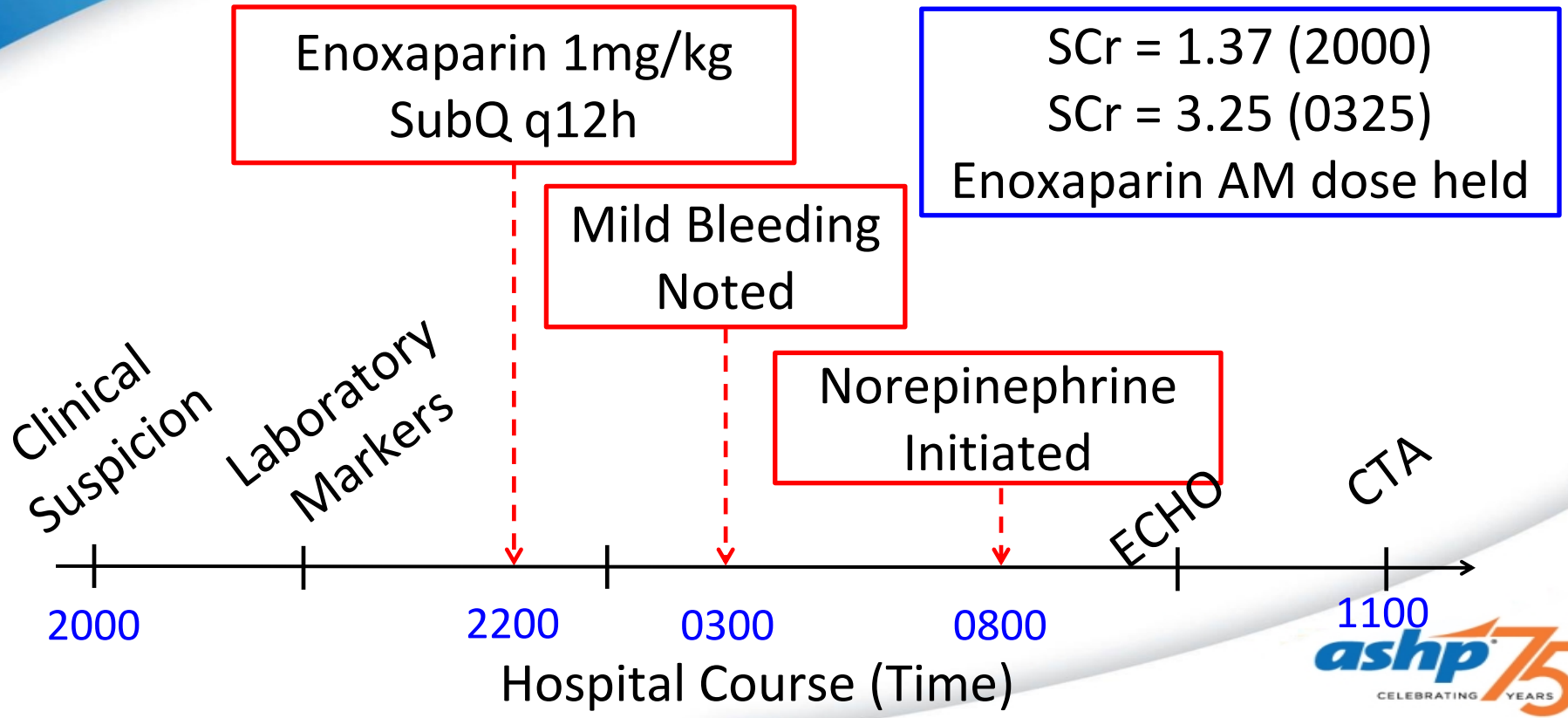
Trop-I = 0.68

Lactate = 6.6

Patient Case

- EKG = NSR, no ectopy, no PR/QRS interval abnormalities, no ischemia
- Sepsis vs. PE -> empiric abx and enoxaparin 1mg/kg SubQ q12h
- Bedside echo
  - Estimated EF >70%
  - Hyperdynamic left ventricle with right ventricle strain
- CXR
  - Possible infiltrate right middle lobe

Course of Events



Contraindications

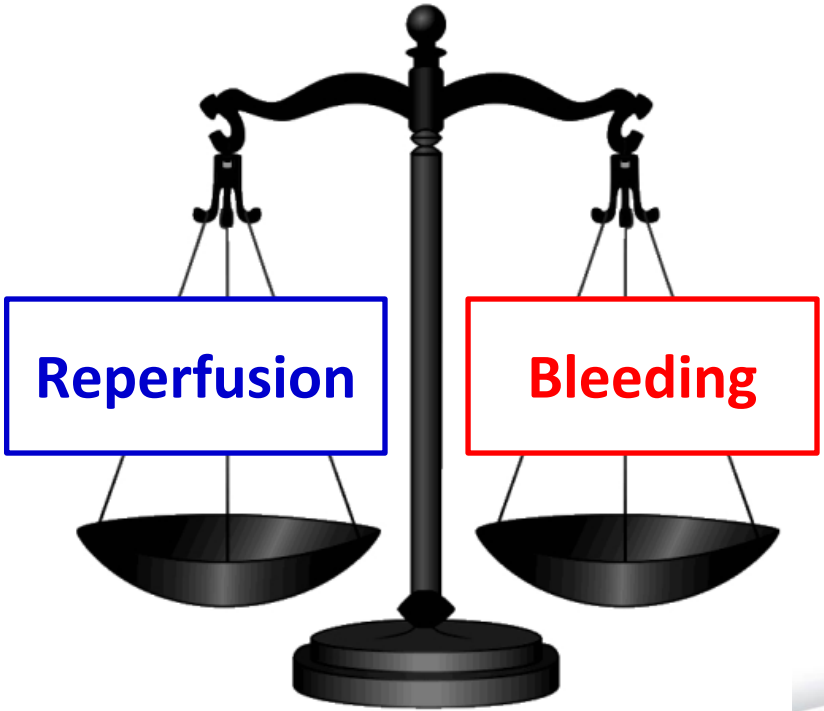
ABSOLUTE

- Internal bleeding
- Recent CVA ≤3 months
- Recent intracranial / intraspinal surgery/trauma
- Uncontrolled HTN
- Intracranial neoplasm
- AV malformation / aneurysm
- Bleeding diathesis

RELATIVE

- Age >75yr
- Current A/C use
- Traumatic/prolonged CPR (<10min)
- Recent internal bleeding (2-4 wk)
- Dementia
- Ischemic stroke (>3mo)
- Major surgery < 3wks

To Lyse or Not To Lyse?



Would you recommend systemic thrombolytic therapy in this patient?

A. Yes (benefit > risk)

B. No (risk > benefit)

C. Not sure / other option

Clinical Practice Guidelines

Clinical Practice Guidelines

- American College of Chest Physicians (2016)
  NO RECOMMENDATION
- European Society of Cardiology (2014)
  NO RECOMMENDATION
- Spanish Society of Pneumology and Thoracic Surgery (2013)
  NO RECOMMENDATION
- UK National Institute for Health and Clinical Excellence (2012)
  NO RECOMMENDATION
- American Heart Association (2011)
  NO RECOMMENDATION

AHA Scientific Statement. Circulation 2011;123:1788-1830
ACCP Guidelines. Chest 2016;149:315-352
ESC Guidelines. European Heart Journal 2014;35:3033-80
NICE Guidelines. National Clinical Guideline Centre (UK). June 2012
SEPAR Guidelines. Arch Bronoconeumol 2013;49:534-47

Low vs. Standard Dose Thrombolysis in Pulmonary Embolism: Clinical Trials

Hemodynamic Effects of Bolus vs 2-hR Infusion of Alteplase in Acute Massive Pulmonary Embolism: A Randomized Controlled Multicenter Trial

Sors H, Pacouret G, Azarian R, et al. Chest 1994;106:712-17

Bolus vs. 2-hr Alteplase Infusion

- Study design
  - Multicenter, randomized, double-blind, double-dummy
- Study population
  - n=53
  - Acute massive PE (≤5 days onset)
  - MPAP ≥20 mmHg

Sors H. Chest 1994;106:712-17

Bleeding Definitions

Major Bleeding

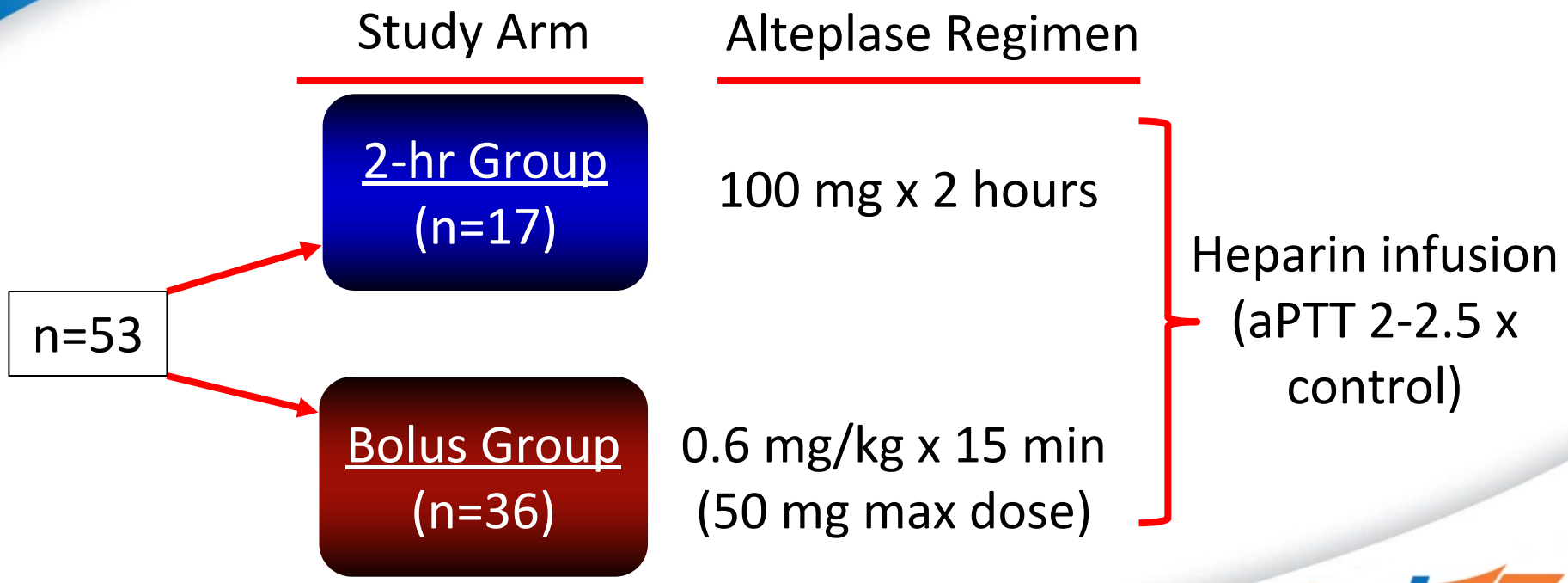
- Intracranial hemorrhage
- ↓HCT x ≥15%
- Any death-related bleeding

Important Bleeding

- Gross hematuria
- Hematemesis
- Retroperitoneal
- ↓HCT x 10-14%

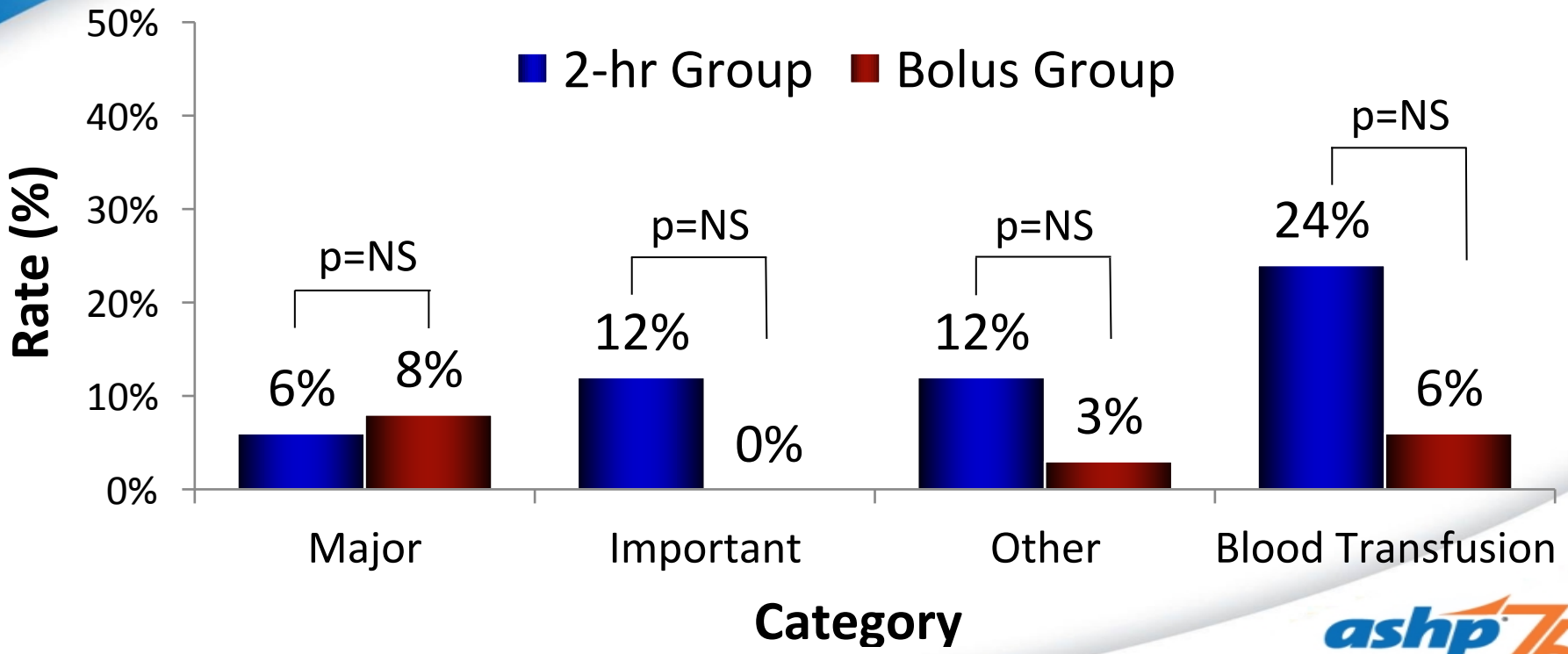
Sors H. Chest 1994;106:712-17

Intervention Groups



Sors H. Chest 1994;106:712-17

Bleeding Events



Sors H. Chest 1994;106:712-17

Reduced Dose Bolus Alteplase vs. Conventional Alteplase Infusion for Pulmonary Embolism Thrombolysis:

An International Multicenter Randomized Trial

Goldhaber SZ, Agnelli, G, Levine MN. Chest 1994;106:718-24. Bolus Alteplase Pulmonary Embolism Group

Bolus Alteplase PE Study Group

- Study design
  - Multicenter, randomized, double-blind, double-dummy
- Study population
  - n=87
  - PE (≤14 days onset)

Goldhaber SZ. Chest 1994;106:718-24

Bleeding Definitions

Major Bleeding

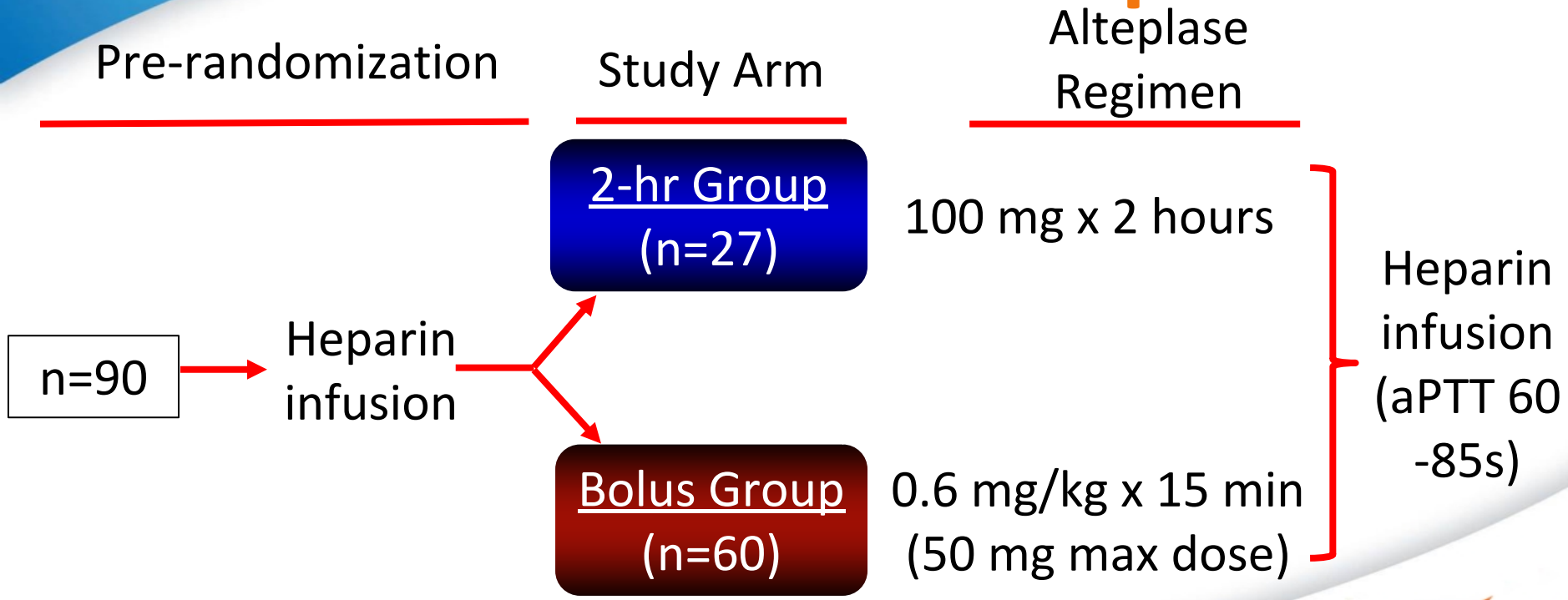
- Intracranial hemorrhage
- ↓HCT x ≥15%
- Any death-related bleeding

Important Bleeding

- Gross hematuria
- Hematemesis
- Retroperitoneal
- ↓HCT x 10-14%

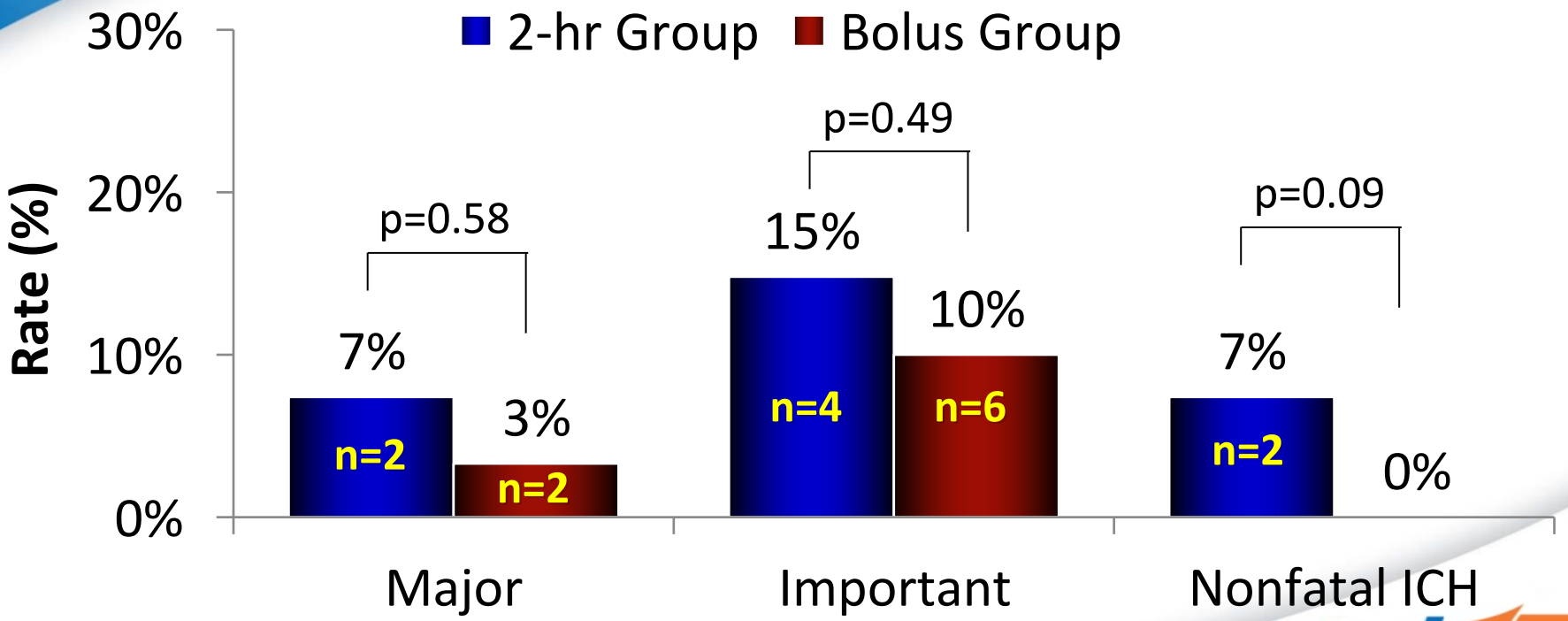
Goldhaber SZ. Chest 1994;106:718-24

Intervention Groups



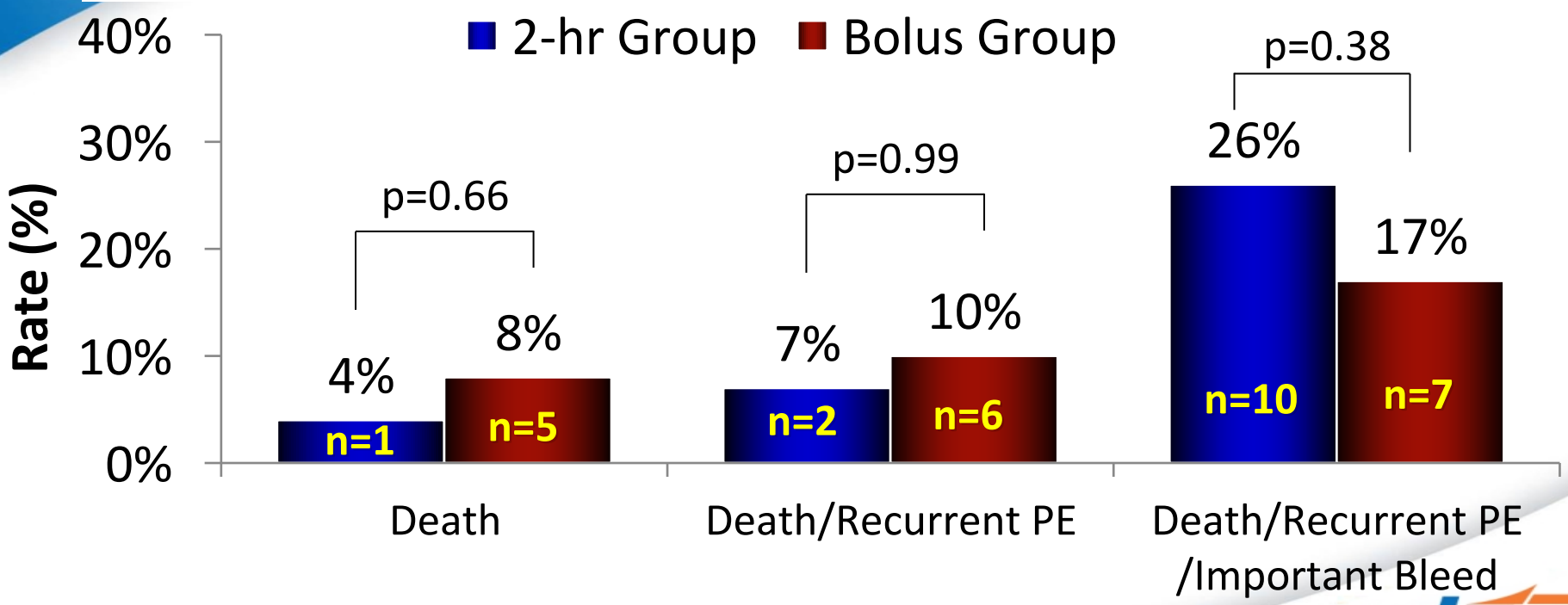
Goldhaber SZ. Chest 1994;106:718-24

Bleeding Events



Goldhaber SZ. Chest 1994;106:718-24

Mortality & Combined Outcomes



Goldhaber SZ. Chest 1994;106:718-24

Study Summary

- No significant differences in imaging studies between groups
  - Perfusion lung scan
  - Angiography
  - Echocardiography
- No significant differences in bleeding rates
- High mortality rate (8%) in bolus group vs. historical data (~2%) resulted in early study termination

Goldhaber SZ. Chest 1994;106:718-24

Mortality Risk Hypothesis

1) Clinically “sicker” bolus group patients at baseline in current study vs. previously published reports
2) 45-min delay in heparinization following bolus t-PA vs. 2-hr group
3) Wide variability and possible inexperience with t-PA among 28 study sites may have contributed to increases adverse events

Goldhaber SZ. Chest 1994;106:718-24

Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism: A Randomized, Multicenter, Controlled Trial

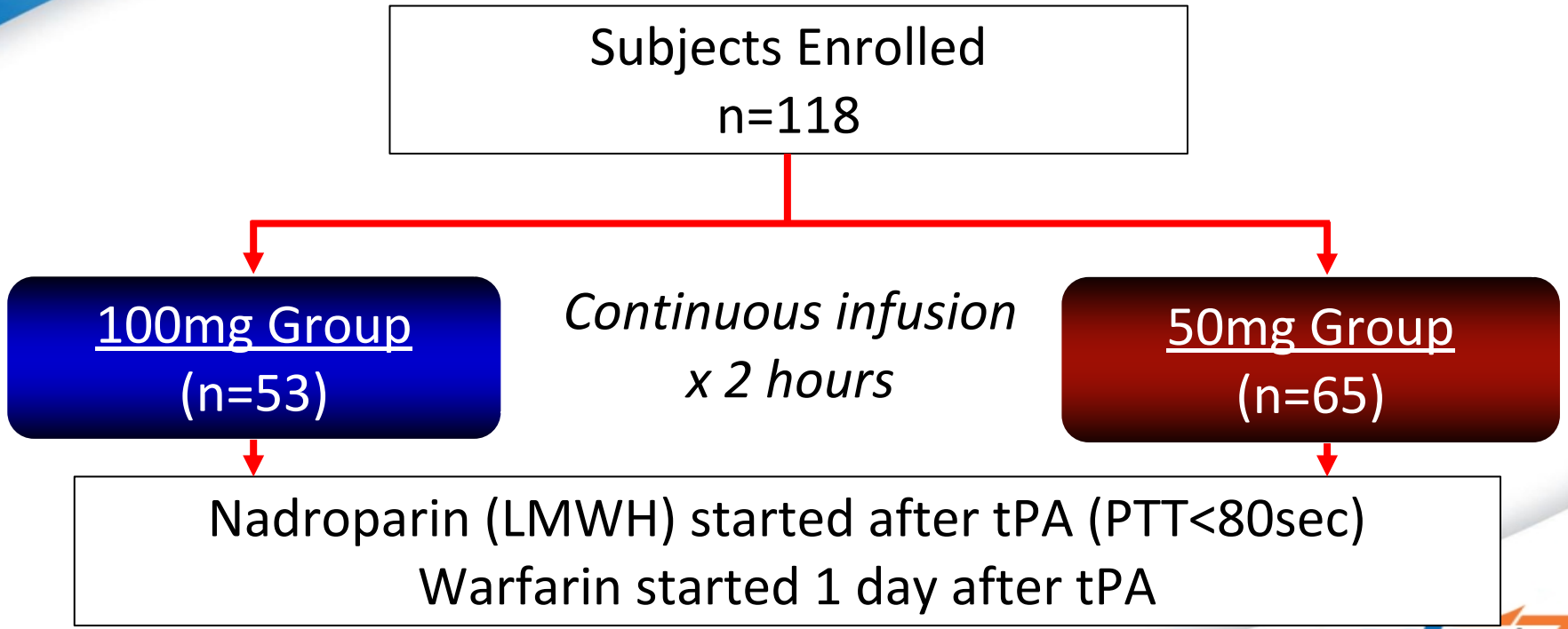
WANG C, ZHAI Z, YANG Y, ET AL. CHEST 2010;137:254-62
CHINA VTE STUDY GROUP

China VTE Study Group

- Study design
  - Multicenter, randomized, open-label
- Study population
  - n=118
  - Acute massive PE (≤15 days onset)
    - Hemodynamic instability
    - Cardiogenic shock
    - Hemodynamic stability with right ventricular dysfunction + PAH
- Primary objective
  - Compare safety & efficacy of low-dose vs. standard alteplase

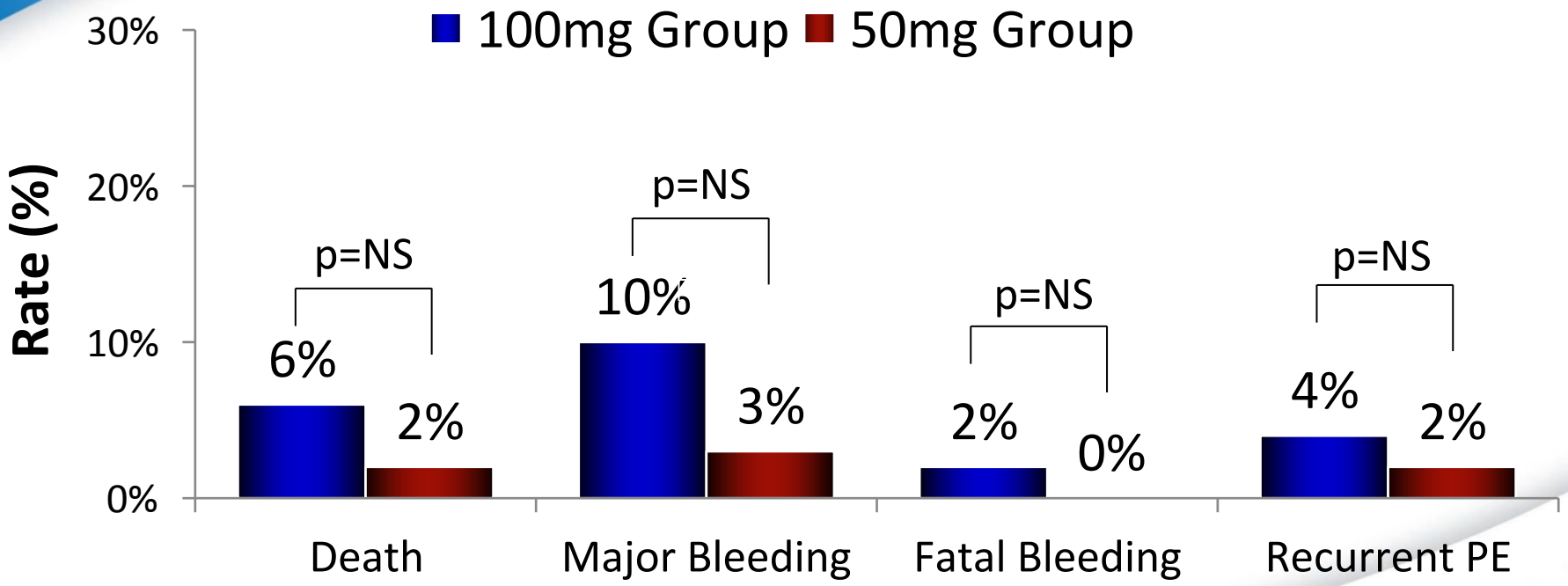
Wang C. Chest 2010;137:254-262

Intervention Groups



Wang C. Chest 2010;137:254-262

Clinical Outcomes



Wang C. Chest 2010;137:254-262

Study Summaries

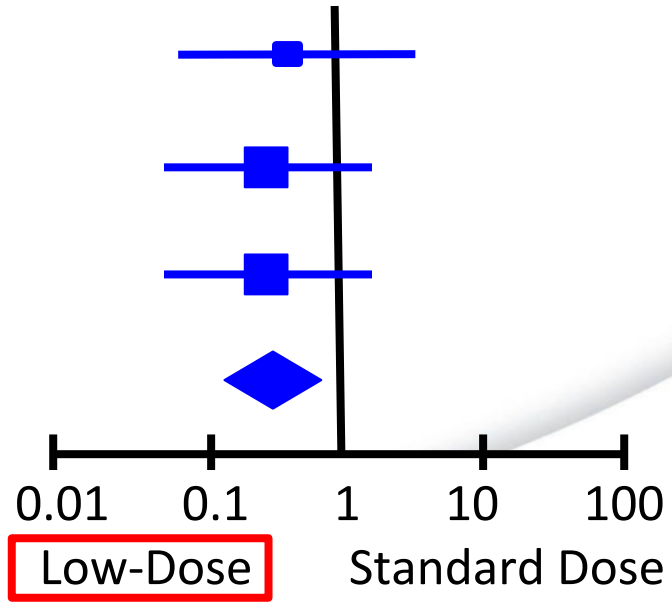
Author (Year)	Low-Dose Group Regimen	PE Severity	Results
Goldhaber (1994)	0.6 mg/kg x 15 min (50 mg max dose)	Hemodynamically Stable	• Equal safety & efficacy • Non-significant ↑ mortality rate
Sors (1994)	0.6 mg/kg x 15 min (50 mg max dose)	Massive*	• Equal safety & efficacy
Wang (2010)	50mg x 2 hrs	Massive ± Submassive	• Equal safety & efficacy

*Severity system graded by angiographic findings inconsistent with present definitions (Miller et al. BMJ 1971;2:681-684)

Meta-Analysis:
Low vs. Standard Dose tPA

Major Bleeding Rates

Study (Year)	Odds Ratio (95% CI)
Goldhaber 1994	0.46 (0.06-3.42)
Sors 1994	0.30 (0.06-1.51)
Wang 2010	0.30 (0.06-1.64)
Subtotal	**0.33 (0.12-0.91)**



Zhang Z. Thrombosis Research 2014;133:357-363

Patient Case

- ICU team decided to administer tPA 50mg over 30 minutes
- Rationale
  - Several relative contraindications with minor bleeding
  - Option to administer additional 50mg over subsequent 30 minutes to equal 100mg tPA standard dose
- Patient responded
  - Hemodynamically stable
  - No further or increased bleeding noted

Key Takeaways

- Key Takeaway #1
  - Low-dose tPA may improve safety without loss of efficacy
- Key Takeaway #2
  - Limited data with low level of evidence should caution use
- Key Takeaway #3
  - Low-dose tPA may be an option in patients with higher bleeding risks

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Dexmedetomidine for Patients Failing Extubation

Gilles L. Fraser, Pharm.D., MCCM
Professor of Medicine, Tufts University
Critical Care Pharmacist
Maine Medical Center
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Bipolar Patient Admitted for Septic Shock

- Hospital course complicated by agitation, followed by oversedation and new onset hallucinations leading to inability to wean from mechanical ventilation which led to the development of pneumonia, tracheobronchomalacia, and ARDS
- Home medications restarted without benefit
- Psychiatry consulted; goal = behavior control without interference with respiratory function
- Tried valproate, but ammonia =160 within 3 days
- Sequentially tried olanzapine, quetiapine, phenobarbital---all failed
- Low dose clonazepam begun with modest benefit during weaning trials

What Other Options Are Available to Facilitate Behavioral Control and Extubation?

A. Propofol
B. Ketamine
C. Dexmedetomidine
D. Haloperidol

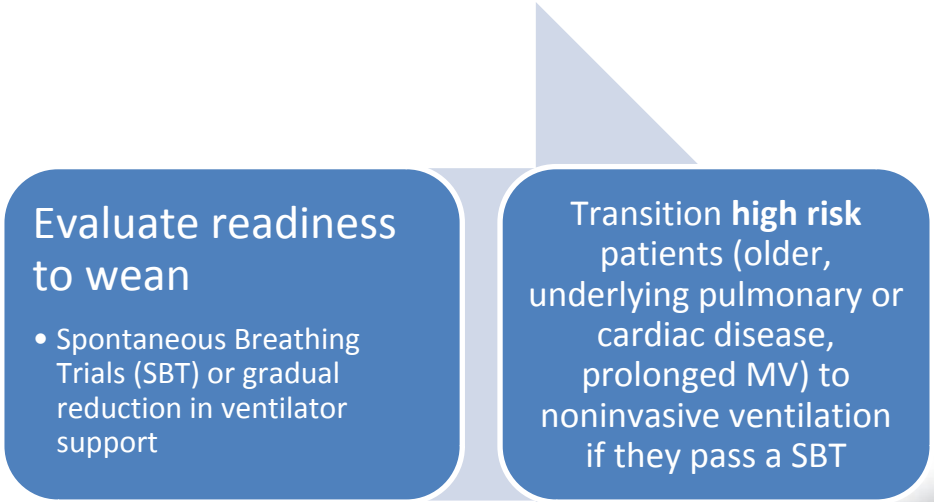
Avoid Mechanical Ventilation (MV) = Avoid Complications

- Ventilator-associated events (VAE)
  - Pneumonia
  - Acute respiratory distress syndrome (ARDS)
  - Fluid overload
  - Atelectasis
- Sleep disorders
- Prolonged time in the ICU
- Patient discomfort

Klompas . Am J Resp Crit Care Med 2015; 192:1420

Facilitating Extubation

- Protocolization saves one day on the ventilator and in the ICU
- Weaning criteria include
  - Improvement in reason for respiratory failure
  - Adequate oxygenation, pH > 7.25, hemodynamic stability without myocardial ischemia
  - Ability to protect airway and spontaneously breathe



Thille. Crit Care 2016; 20:48; Ouellette. CHEST 2017; 151;166

Interesting Facts About MV Weaning

There is a tendency to underestimate readiness to wean

- 50% of patients who self-extubate do not require re-intubation

Other the other hand

- Unexpected extubation may be life threatening for certain ventilator dependent patients

Extubation Failures in the ICU

357 patients with > 24 hours MV	
Overall risk of re-intubation = 17%	• 80% within 48 hours
28% high risk patients were re-intubated	• UNLESS they received non-invasive ventilation (15%)
High risk patients	• Greater than 65 years, underlying cardiac and/or pulmonary disease

Thille. Crit Care 2016; 20:48

Who Fails MV Weaning and Why

- Respiratory muscle fatigue
- Inadequate respiratory drive
- Inability to maintain adequate oxygenation
- Inability to protect airway
- Hemodynamic instability with the potential for ischemia
- Psychological distress including delirium

Sedation May Affect Ability to Wean

- Analgesic needs have been addressed
- All therapeutic options are adequate, but patient response can vary
- Discriminating features = side effects; pharmacokinetics/dynamics
  - Onset/offset
  - Respiratory depression
  - Depth of sedation
  - Hemodynamic instability
  - Allow patient participation
  - Econotoxicity ($$)

Why do patients fail ventilator weaning?

- Inadequate respiratory drive
- Inability to maintain adequate oxygenation
- Inability to protect airway
- Hemodynamic instability with the potential for ischemia
- Psychological distress including delirium

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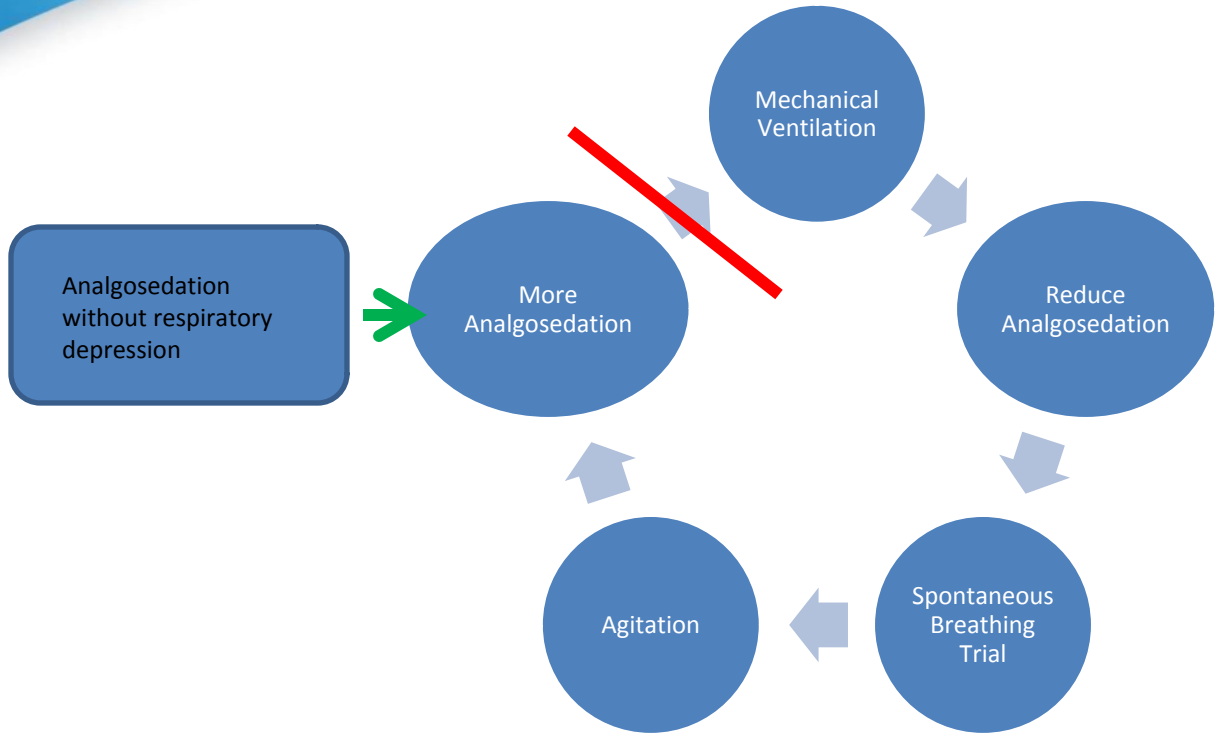
Overview of Therapeutic Choices

Longrois. Multidisciplinary Resp Med 2014; 9:56

	Hemodynamic stability	Analgesia	Preservation of respiratory drive	Promotion of sleep	Delirium avoidance
Propofol	No	No	No	No	Perhaps
Benzodiazepine	Yes	No	No	No	No
Opioids	Yes	Yes	No	No	No
Dexmedetomidine	No	Yes	Yes	Yes	Yes
Ketamine	Yes	Yes	Yes	No	Perhaps

Common Things Go Wrong During a Weaning Trial



Sedative Choice Matters

- 7 year study of 9600 episodes of MV >2 days
  - Sedative agents: benzodiazepines, propofol and dexmedetomidine
- Compared VAE, hospital discharge, death (after risk factor correction)
- Major findings: benzodiazepine use increased MV duration; propofol higher risk for infections
- NO differences in duration of hospitalization nor mortality
- Only 12% of patients received dex; majority = cardiac surgery

Klompas CHEST 2016; 149:1373

Benzodiazepines ≠ Ventilated Patients

- Klompas: higher VAE risk, longer vent time (Chest 2016: 149; 1373)
- Fraser: increased time on the ventilator and in the ICU (CCM 2013:41;S30
- Carson: increased time on the ventilator (CCM 2006:34: 1326)
- Riker: longer time on the ventilator and increased delirium (JAMA 2009:301; 1985)
- Jakob: longer time on the ventilator (JAMA 2012:307; 1151)

Benzos Are NOT Always the Devil's Handiwork

Context is everything. Benzos are GOOD for….

For patients with anxiety related to ventilator weaning

- Prn midazolam
- Low dose clonazepam
  - DO NOT blunt respiratory drive or induce coma

For patients recovering from hemodynamic instability

For patients at risk for gaba agonist withdrawal

No data suggest any negative effect on survival

Propofol

Though this was not considered in the context of liberation from MV

- Easily titratable with predictable offset
- Hemodynamic instability
- Respiratory depression (requires MV for use?)
- 2018 PAD-IS guidelines MAY suggest that there is no significant difference in outcomes between propofol and dexmedetomidine

Dexmedetomidine

Advantages

- Minimal effect on respiratory drive
- Ability to provide “cooperative” sedation
- Opioid sparing
- Sympatholysis

Disadvantages

- Hemodynamic derangement
- Econotoxicity

World's Literature Using Dexmedetomidine for Patients Failing Liberation from Mechanical Ventilatory Support!!

Arpino. J Clin Pharm Therapeutics 2008; 33:25

- **20** agitated patients who failed **MV** weaning
  - 14 (65%) were successfully weaned and extubated with dex
    - 13 within 24 hours of dex initiation
- 4 patients required hemodynamic support
  - 3 were on vasopressors PRIOR to dex initiation

Siobal. Resp Care 2006; 51:492

- **5** agitated patients who failed **MV** weaning
  - All were extubated an average of 2 hour after dex initiation
    - 1 required reintubation for upper airway obstruction
    - 3 required interventions: fentanyl, supplemental oxygen, lower dex dose

Huang. Intern Med 2012; 51:2299

- **62** patients who refused to continue **NIV** due to discomfort
  - Randomized to midazolam vs dex
  - 20 (32%) failed to continue NIV; more often with midazolam p = 0.02
  - Dex induced bradycardia did not require intervention

Yapici. Heart Surgery Forum 2011

- **72** elective cardiac surgery patients failing **MV** weaning (associated with ag
  - Randomized to midazolam vs dex
  - 26% vs 6% (midazolam vs dex) patients failed extubation; no statistics off

Summary
Low Quality Data

- 3 trials; 97 intubated patients—only one was comparative (midazolam)
  - Consistent signal for benefit with dex
- 1 comparative trial; 62 patients who could not tolerate NIV. Dex offered benefit over midazolam

Is Dexmedetomidine Helpful For Agitated Delirious Patients Who Are Ready to Wean?

RCT comparing dex vs placebo for agitated delirium requiring mechanical ventilation	• Two days of dex or placebo, then open label dex • Primary outcome = ventilator-free days
Trial terminated early due to lack of resources	• >21K patients screened and 74 were randomized • 17 hours more vent free days with dex

Reade. JAMA 2016; 315:1460

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What is the Best Choice to Facilitate Behavioral Control and Extubation in Our Bipolar Patient?

(recall that she failed atypical antipsychotics, valproate, and phenobarbital and the only reason for failing to wean is agitation)

A. Propofol
B. Ketamine
C. Dexmedetomidine
D. Haloperidol

What We Did

Dexmedetomidine started with marginal improvement

- Transitioned to clonidine 0.4mg q 6 h
- Behavior controlled, oxygenation improved
- Extubated

Lessons learned

- Limited options dictate an iterative approach
- Maintain medications that seem to offer benefit; abandon those that don’t
- Dex is titratable and if effective supports transition to clonidine

Key Takeaways

- Key Takeaway #1
  - Mechanical ventilation (MV) is uncomfortable and associated with important complications that are largely related to duration/exposure
- Key Takeaway #2
  - Sedation properties/choices may affect the ability to wean from MV
- Key Takeaway #3
  - Dexmedetomidine offers analgosedation without affecting respiratory drive and is easily transitioned to clonidine if necessary

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The Facts and Fallacies of Albumin and Diuresis

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Question

Question

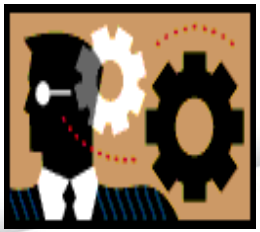
During what decade was albumin first fractionated from human blood?

A. 1890’s

B. 1940’s

C. 1960’s

D. 1980’s



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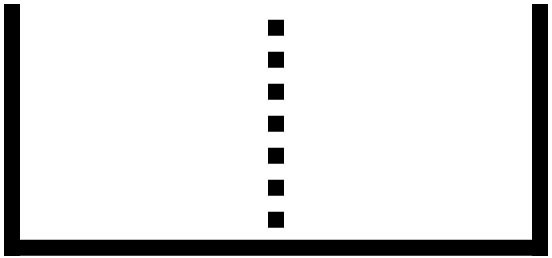
Albumin- 1890's

- Starling built osmometer to measure oncotic pressure of proteins in serum
- Concluded that serum proteins have oncotic pressure of 30-40 mm Hg

"…whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption."



Starling EH. On the absorption of fluids from the connective tissue spaces. J Physiol 1896;19:312-26.

Albumin- 1940’s

CHEMICAL, CLINICAL, AND IMMUNOLOGICAL STUDIES ON THE PRODUCTS OF HUMAN PLASMA FRACTIONATION.

I. THE CHARACTERIZATION OF THE PROTEIN FRACTIONS OF HUMAN PLASMA [1,2]

By EDWIN J. COHN, JOHN L. ONCLEY, LAURENCE E. STRONG, WALTER L. HUGHES, JR., AND S. HOWARD ARMSTRONG, JR.[3]

(Received for publication February 17, 1944)

(*From the Department of Physical Chemistry, Harvard Medical School, Boston*)

The object of the series of investigations herewith reported has been to determine how blood plasma, fractionated into its component parts, may be used with the maximum effect in the treatment of clinical conditions. Extensive experience has demonstrated that plasma is of unquestioned value in the treatment of shock, burns, and diseases in which there has been depletion of one or another of the components of plasma. Moreover, either pooled or convalescent plasma has been injected in man because of either proven or implied effectiveness in the prophylaxis or treatment of certain infectious diseases.

The constituents of plasma are not all equally effective in the treatment of diverse conditions, however. Therefore, the utilization of the whole plasma in therapy may often prove both less effective and less economical than the use of parts thereof. In the treatment of infectious disease, for example, such antibodies as may be present in blood constitute only a small fraction of the plasma globulins. The rest of the plasma has little proven value in the prevention or modification of contagious diseases. In the control of a measles epidemic, injection of the albumin of the plasma, or of the fibrinogen or prothrombin, would appear to serve little purpose.

Conversely, in shock, injection of the human antibodies, though they exert some colloid osmotic pressure, would be far less effective and economical than the injection of an equal amount of albumin. Twice the amount of the immune serum globulins—present in but small amount—would be necessary to produce the same colloid osmotic pressure as the albumin. Albumin is responsible for nearly 80 per cent of the colloid osmotic pressure of the plasma and blood and is thus responsible to a far greater extent than other constituents of the plasma for the maintenance of blood volume.

The significant functions of the blood are by no means all performed by the plasma. The respiratory function of the blood is carried out by the hemoglobin, the carbonic anhydrase, and other proteins within the red cells; and the hematopoietic function of certain of these pro-

Albumin- 1950's to 1970's

A variety of investigations of endogenous/exogenous albumin

- Structure
- Synthesis/processing/secretion
- Distribution
- Catabolism/elimination
- Function

Question

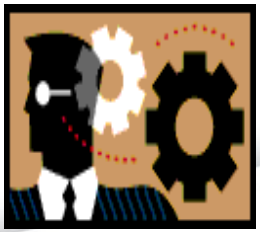
Which of the following properties of albumin is most likely to determine the duration of its intravascular expansion in critically ill patients?

A. Distribution half-life

B. Elimination half-life

C. Antioxidant action

D. Binding actions



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Properties of Albumin

- Synthesized by hepatocytes and controlled by oncotic pressure (blood and beneath glycocalyx)
- Initial distribution half-life in healthy subjects ≈ 5 (3-8) hours, but decreases dramatically (e.g., 300%) in disease states like septic shock
  - Transcapillary escape rate 5%/hour healthy subjects vs. 11%/hour in critically ill patients
- Elimination half-life ≈ 15 (12-18) days in healthy subjects; 9 (5 to 11) in critically ill patients
- Accounts for 50-75% of total protein in plasma and 70% of plasma oncotic pressure

Properties of Albumin

- *The Good, the Bad, and the Ugly*
  - Suppresses effects of cytokines (TNF neutrophil burst)
  - Anticoagulant actions possibly caused by nitric oxide inactivation
  - No neutrophil activation and decreased neutrophil sequestration in lung
  - Transport/binding to endogenous substances (bilirubin, steroids, fatty acids, nitric oxide) and drugs
  - Scavenger for reactive oxygen species
  - Source of amino acids

Erstad BL. Fluid Therapy in the Critically Ill Patient. Erstad BL (ed). Critical Care Pharmacotherapy. American College of Clinical Pharmacy

Properties of Albumin

- Posttranslational modification of albumin products occurs *in vitro* as well as *in vivo*
- One study found 23% oxidized Cys 34 in albumin from healthy volunteers vs. 57% from commercial products
- So, cysteinylation and nitrosylation of commercial products may augment oxidative stress
- Also, concern for loss of N-terminus that yields free radical scavenge
- Denaturation of products another concern (*in vivo* increased pre-denaturation temp decreases overall net negative charge, which decreases cation binding, which decreases oncotic pressure)

Bar-Or et al. Crit Care Med 2005;33:1638

Rezaei-Tavirani et al. J Biochem Mol Biol 2006;39:530

Properties of Albumin

In vivo plasma expansion with albumin products in patients is much different than what is predicted based on fluid distribution by body compartments

- Eg. 50 g of 5% (1000 mL), 20% (250 mL), or 25% (200 mL) albumin infused over 90 minutes in patients immediately after elective surgery
- 5% (1000 mL) given to 10 healthy subjects as control
- Plasma volume before and after albumin administration estimated with ^{131}I-labelled albumin
- Plasma expansion results: 5% = 490 mL; 20% = 470 mL; 25% = 440 mL; 5% control = 500 mL

Lamke & Liljedahl. Resuscitation 1976;5:85

Properties of Albumin

Something to ponder…

Analbuminemia

- Cases of inherited defect
- Many cases not discovered until > 50 years of age
- Common presenting signs/symptoms include osteoporosis, lipodystrophy, fatigue, low BP
- Increased globulins of all types
- Total protein only slightly low
- Colloid oncotic pressure 1/3 of normal
- Rapid disappearance of exogenous albumin

Kallee. J Lab Clin Med 1996;27:470

Question

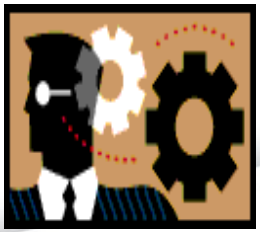
Which of the following “subjects” is most likely to have an improved diuretic response from an albumin/furosemide combination versus furosemide alone?

A. Patient with sepsis-related ARDS

B. Patient undergoing hemodialysis

C. Patient with cirrhosis and ascites

D. An analbuminemic mutant rat



ashp 75 CELEBRATING YEARS

Question

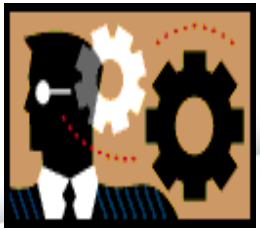
Which of the following conclusions related to albumin use in the clinical setting is most evidenced-based?

A. Decreased mortality vs. furosemide

B. Decreased length of ICU stay vs. furosemide

C. Increased urine output vs. furosemide

D. Transient changes in P/F ratio vs. furosemide



Something Else to Ponder…

Albumin 1980's

- Single dose study in analbuminemic mutant rats and 20 (?) patients with hypoalbuminemia with diuretic "resistance" (not defined)
- Diuresis with furosemide (30 mg), albumin (6 g), and furosemide/albumin combination (equimolar amounts) - improved diuresis with combination

Inoue et al. Kidney Int 1987;32:198

Albumin: Diuretic Resistance

- Patients with cirrhosis and ascites
  - Albumin concentrations ranged from 2.1 to 4.3 g/dl.
  - All patients on sodium restriction and spironolactone
- Randomized crossover design (n=13); furosemide (40 mg), albumin (25 g), combination mixed, or combination infused simultaneously
- No benefit to combination therapy
- No increase in furosemide transport to kidneys as indicated by furosemide excretion rate

Chalasani et al. J Am Soc Nephrol 2001;12:1010

Critically Ill Patients with AKI

- Measured creatinine clearance only reliable predictor of urinary output after furosemide administration
  - Reduction in urinary furosemide with AKI ($p<0.01$)
  - Diuretic response unlikely if CrCl < 20 mL/min

Silbert et al. CCM 2016. DOI 10.1097/CCM.0000000000001823

Furosemide ± Albumin for Acute Lung Injury (ALI)

- RCT with 40 mechanically ventilated ICU patients
- 65% in MICU (sepsis was common cause of ALI as defined by $PaO_2/FiO_2 \leq 300$ mm Hg)
- Treated: 25 g of 25% albumin given over 30 min every 8 hours and 20 mg bolus of furosemide with continuous infusion of 4 mg/hour for 3 days
- Control: NS plus furosemide as above
- Primary endpoint: change in oxygenation (PaO_2/FiO_2)

"The results of this trial are limited primarily by the number of enrolled patients, making conclusions about clinical outcomes unfeasible"

Martin et al. Crit Care Med 2005;33:1681

Furosemide ± Albumin for (ALI)

Martin et al. Crit Care Med 2005;33:1681

Furosemide ± Albumin for ALI

- MICU patients without AKI/CKD (mean P/F=174)
- Fluid intake only variable sig. related to urine output

Furosemide ± Albumin for Sepsis-Induced ARDS

- Two prospective, nonrandomized case series of 28 patients with severe sepsis and ARDS
- Albumin (20%, 200 mL) alone or with furosemide (30 mg) produced "transient improvement in oxygenation and hemodynamics"
- Greatest PaO_2 increase was 13.2 kPa at 5 minutes versus 11.9 kPa at baseline for albumin + furosemide
- Albumin concentrations remained elevated (e.g. 72% of initial concentration at 4 hours), but no sustained improvement in oxygenation (oxygenation had declined to baseline by 4 hours)

Kuper et al. Anaesthesia 2007;62:259

Diuretics ± Albumin for Cirrhosis/Ascites

- Inpatient nonresponders to sodium restriction, bed rest, and potassium canrenoate (aldosterone antagonist similar to spironolactone)
  - Randomized to stepped up dosing of furosemide/canrenoate ± 50 mL 25% albumin daily
- As outpatients, regimens continued for **3 years**!
  - Albumin 25 g/weekly x 1 year then biweekly x 2 years
- Response: disappearance or recurrence of ascites
  - Inpatient: ↑ rate of disappearance with albumin ($p<0.05$)
  - Outpatient: ↓ rate of recurrence ($p<0.05$), ↓readmissions ($p<0.03$), and ↓ LOS ($p<0.001$) with albumin

Gentilini et al. J Hepatol 1999;30:639

Diuretics ± Albumin for Cirrhosis/Ascites

"*However, use of albumin in protocol 2 was very expensive*"

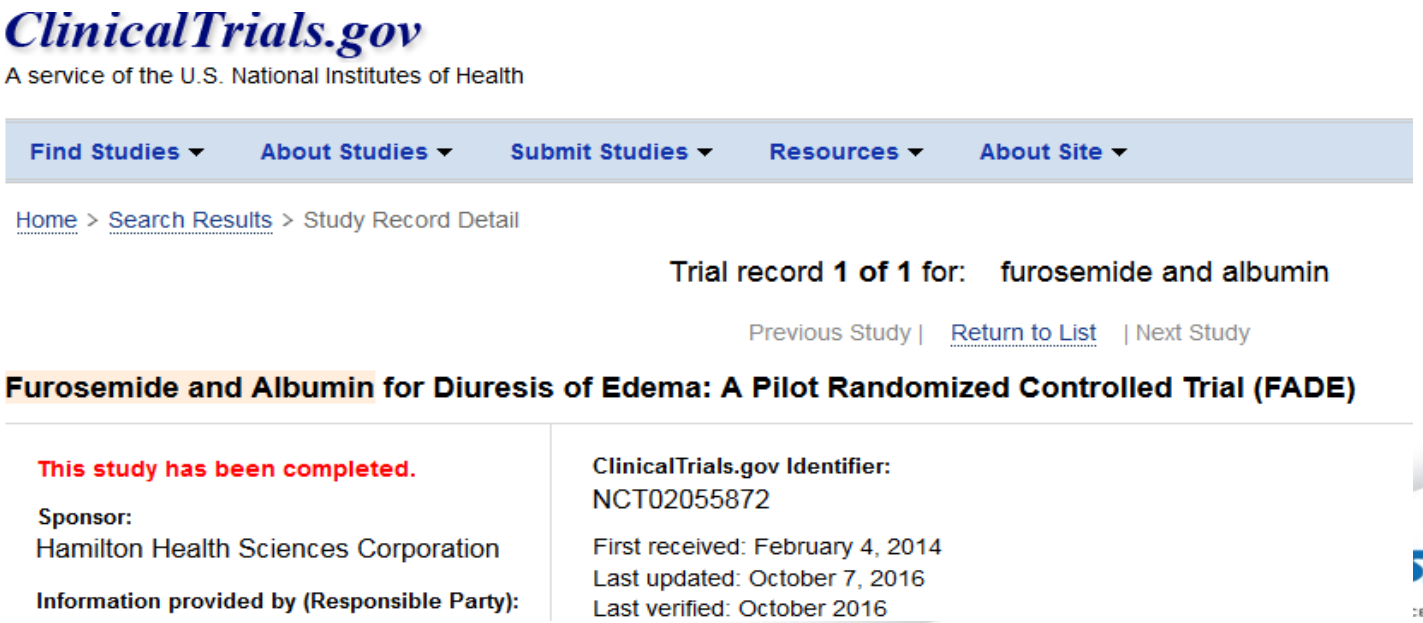
Albumin/Furosemide Metaanalysis

- Limited to crossover trials (24 patients in largest trial)
- Majority of patients had nephrosis or cirrhosis
- Increased urinary volume only < 8 hours

Kitsios et al. J Crit Care 2014;29:253

FADE: Pilot Study to Assess Feasibility

- Furosemide vs. furosemide/albumin (100 mL 25%) for "deresuscitation" of critically ill + hypoalbuminemia



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Trial record **1 of 1** for: furosemide and albumin

Previous Study | Return to List | Next Study

Furosemide and Albumin for Diuresis of Edema: A Pilot Randomized Controlled Trial (FADE)

This study has been completed.

Sponsor:
Hamilton Health Sciences Corporation

Information provided by (Responsible Party):

ClinicalTrials.gov Identifier:
NCT02055872

First received: February 4, 2014
Last updated: October 7, 2016
Last verified: October 2016

Adverse Effects of Albumin

- Hypersensitivity reactions
- Volume overload
- Edema
- Reduction in GFR (with 25% albumin)
- Aluminum toxicity (renal failure)
- Hypocalcemia
- No known transmission of HBV, HCV, or HIV

How to Save Money

Use of this “evidence” to end debate at your institution

Key Takeaways

- Key Takeaway #1
  - Albumin kinetics in patients usually much different than predicted based on theoretical data or normal subjects
- Key Takeaway #2
  - Furosemide kinetics in patients usually much than predicted based on data from rats or normal subjects
- Key Takeaway #3
  - The best evidence for the benefit of an albumin/diuretic combination over diuretic alone is in analbuminemic rats