SCCM Texas Chapter 9TH Annual Symposium Presentations

Closing the Knowledge Gap
Friday & Saturday
September 25th and 26th, 2020
Virtual Symposium via Zoom Webinar

Table of Contents

Consequences of Accidental Leadership

LEWIS J KAPLAN, MD, FACS, FCCP, FCCM
Professor of Surgery
Perelman School of Medicine
University of Pennsylvania
Division of Trauma, Surgical Critical Care and Emergency Surgery

Society of Critical Care Medicine
The Intensive Care Professionals

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Disclosures

- Society of Critical Care Medicine
  - President 2020-2021
- Editorial Board Membership
  - *Critical Care Medicine*
  - *Journal of Trauma and Acute Care Surgery*
  - *Surgical Infections*
- VHA employee
  - Independent views and opinions

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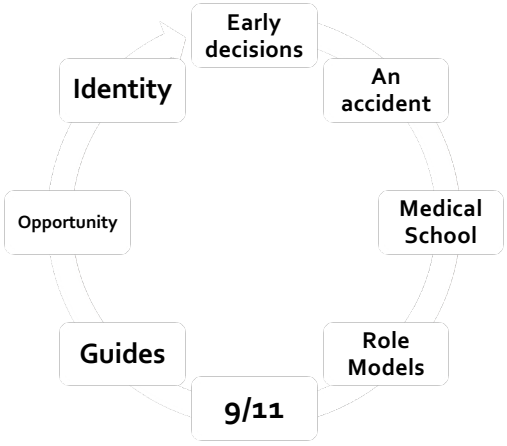
Objectives



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4

Humble Beginnings

1960
Corner soda shop

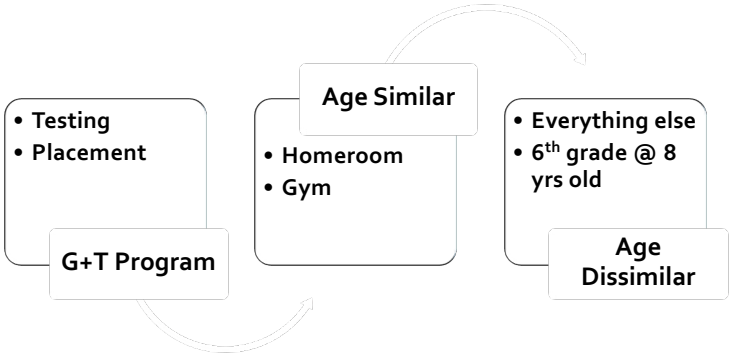
5

On The Pathway …

1965
3 years old

6

Lost In The System

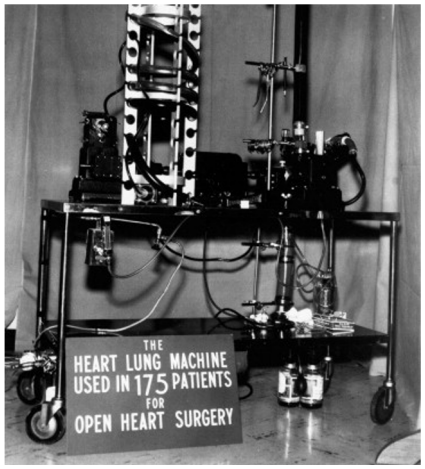


7

The Final Leap …

8

Gibbon
Vertical
Screen
Pump
Oxygenator



DeWall RA. *JTCVS* 2011; 142(2):267-269

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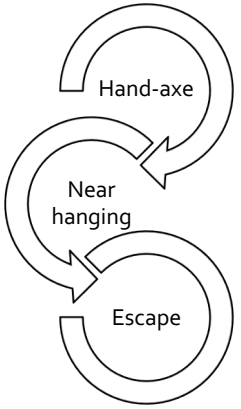
Accidental Displacement



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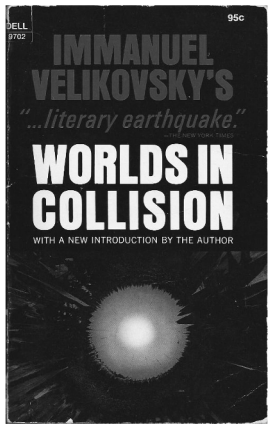
Welcome To 3rd Grade!



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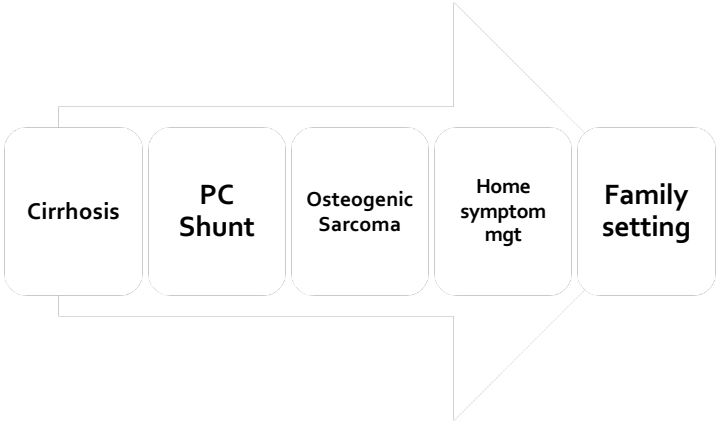
Early PCM Exposure



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Freshman-Sophomore Summer

JHU Gifted and Talented Summer Program

Ted Koppel's son

Early media training

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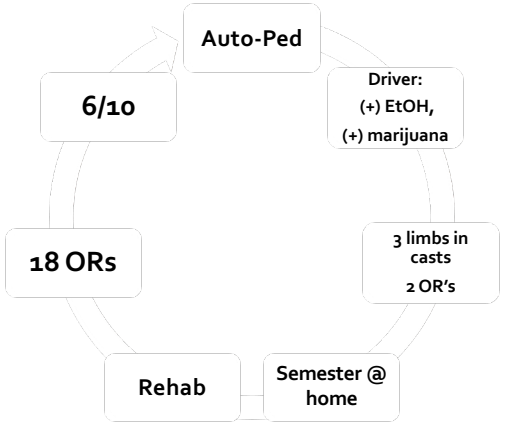
Sophomore Speed Bump



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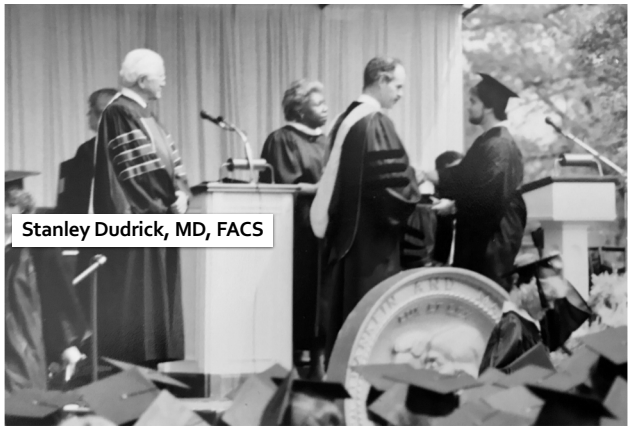
1984: Clueless Graduation



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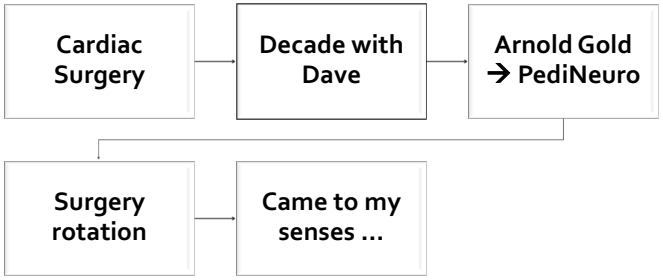
Medical School Path



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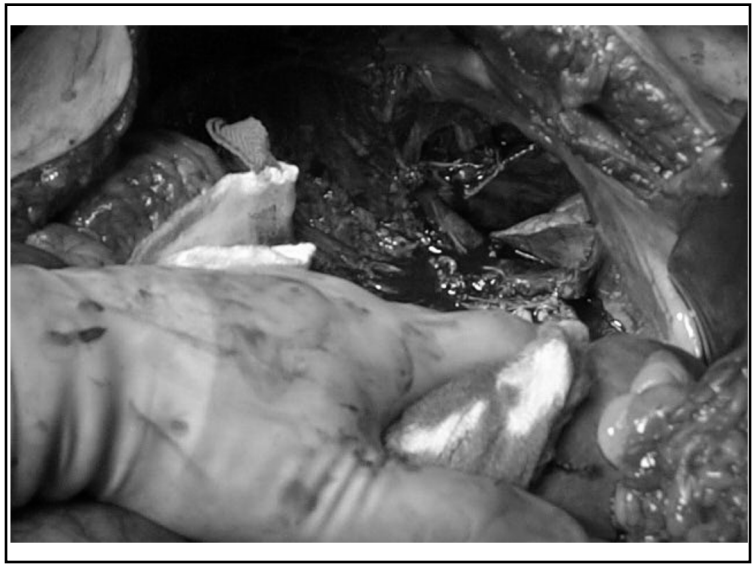

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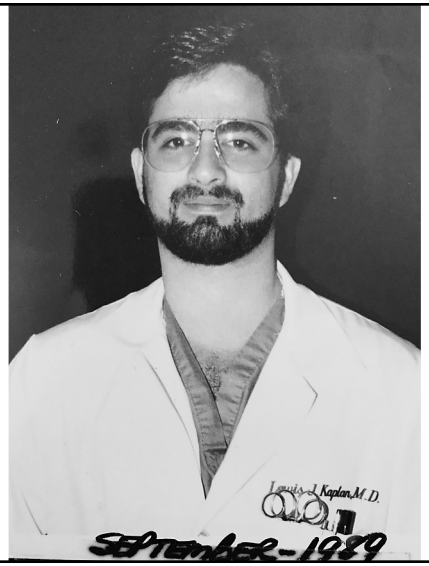

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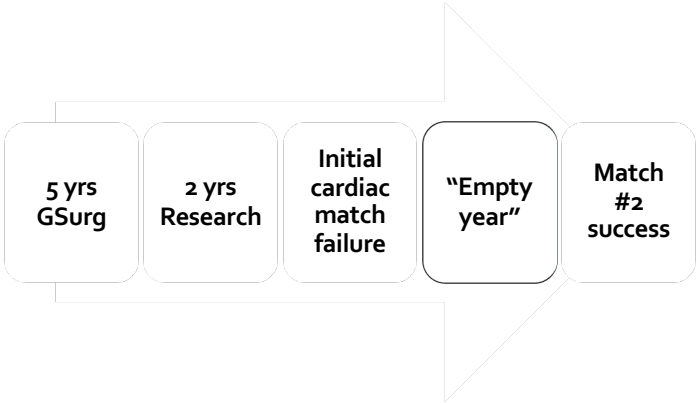
The Road to Injury



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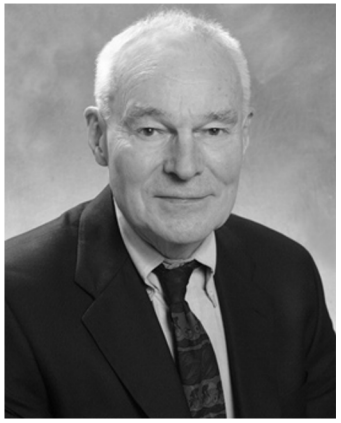
Envision A Different Future



David K Wagner, MD

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It Happened On A Friday

EGS	Trauma	ICU
Rectal injury Dead bowel	GSW chest x 2 SW chest x 1	Sternotomy
Incarcerated hernia + SBO	SW Fem A/V GSW Abd x 2	14 admits

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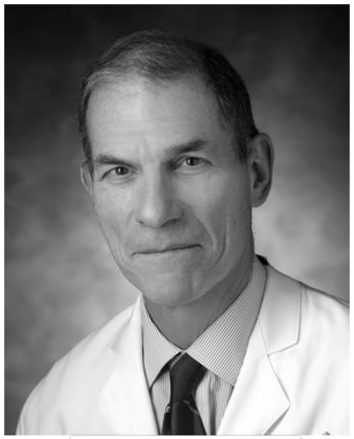
Saturday 1:30PM



Glenn J R Whitman, MD

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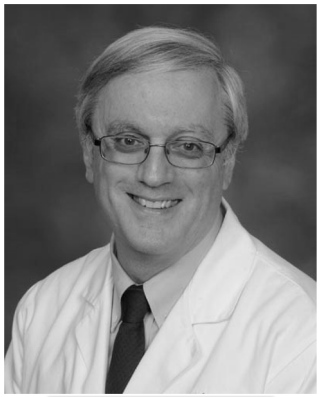
Tuesday



Samuel Tisherman, MD

Ake Grenvik, MD

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UPMC

John A Kellum, MD

Derek Angus, MD

25

Medical College of PA

(and a bunch of other names)

Heatherlee Bailey, MD

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911

27

720th Special Tactics Group

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STORMACT

AIR FORCE SPECIAL OPERATIONS COMMAND

720th SPECIAL TACTICS GROUP

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Tactical Combat Casualty Care

TACTICAL COMBAT CASUALTY CARE

PREHOSPITAL TRAUMA LIFE SUPPORT

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An Untried Course …

- **MCP-HU collapse**
- **Untenable practice**
- **CME deficit**
- **ACS Fall meeting**
  - **U/S**

Heidilee Frankel, MD

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Ivy League Practice

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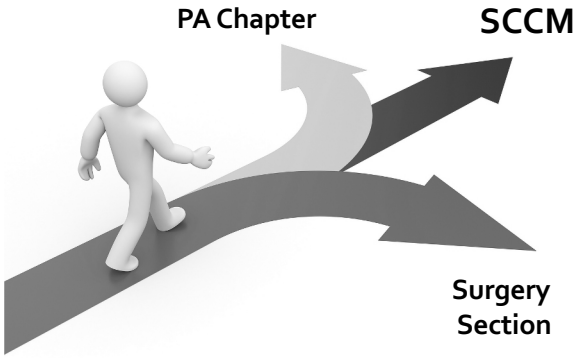
SCCM Meanderings



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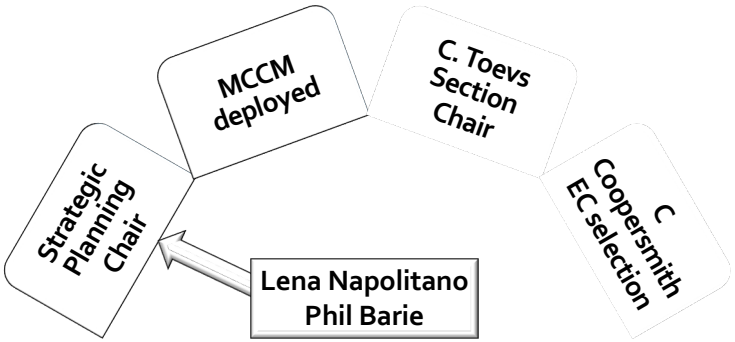
Quadruple Grouping



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Election Mishap

Christine Toevs, MD

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By The Window …

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Immediate Surgical Capability
(172 + 45 + 12 = 229)

Ballistic Helmet

Body Armor
Level III

Not pictured:
Comms
Gloves
Goggles
PRN Tools

Gas Mask

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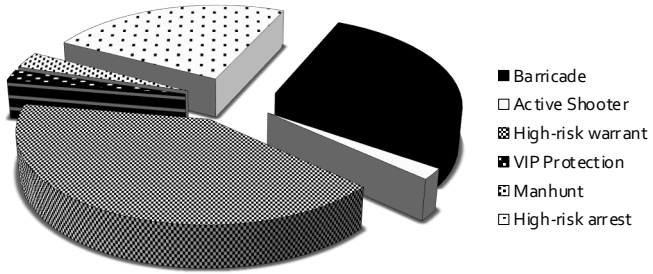
SWAT Activations



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Rotating Role Training

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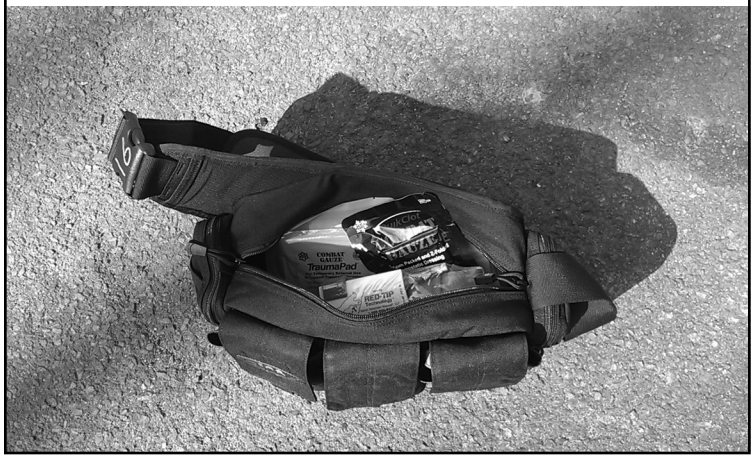
The Go-Bag: Self and Other Care



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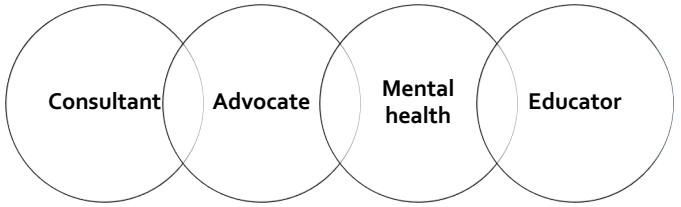
Public Health and Safety



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Pre-Positioned Supplies

45

Back To 1984

S Dudrick	Me
FandM	FandM
EPIC	EPIC
Yale	Yale
PENN	PENN
Distinguished Alumni Award	Distinguished Alumni Award
Wrote my nomination	

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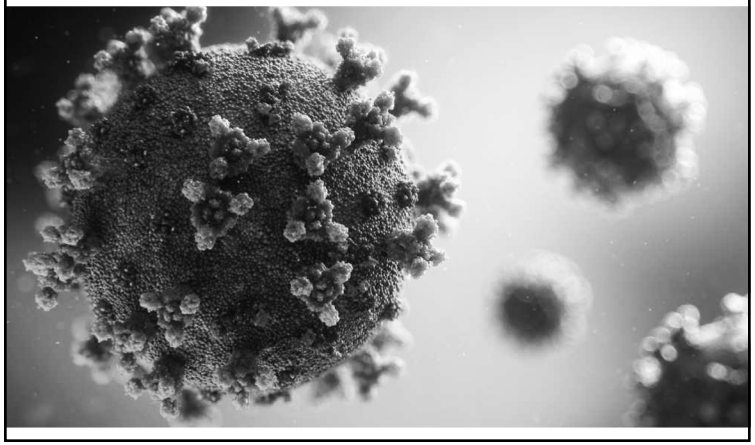
Just One Thing …



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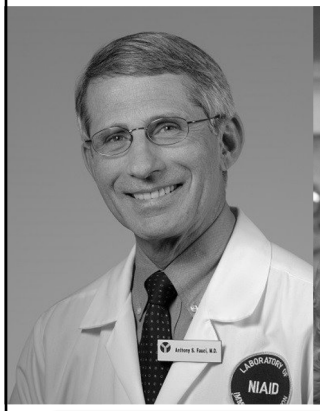
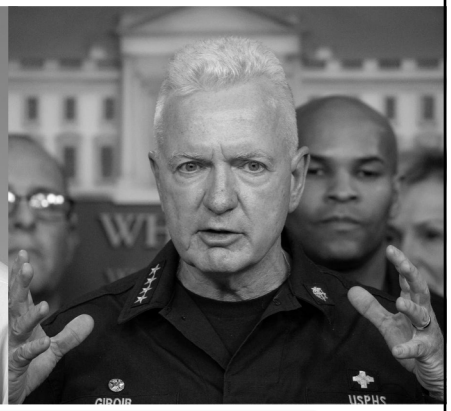
Two Key Leaders





Public Health Management ⟺ Supply and Testing

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Do You Need Some Help?

Neil Halpern, MD

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Novel ICU Spaces

Licensed ICU Beds		
Acute floor	PACU OR	Other spaces

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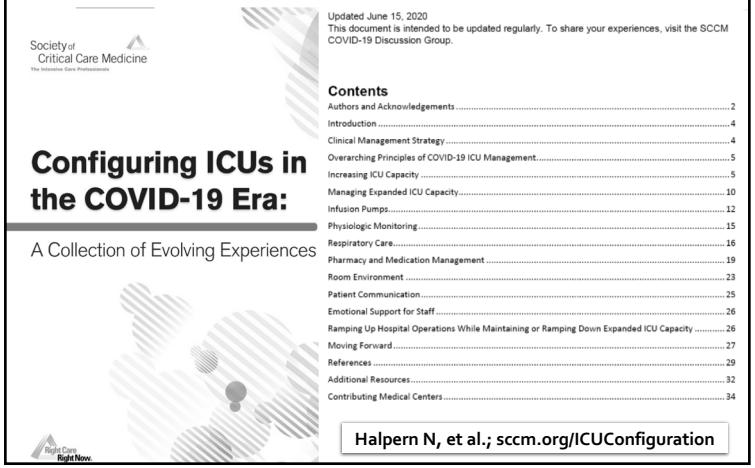
ICU (Re)Configuration



Society of Critical Care Medicine

Configuring ICUs in the COVID-19 Era:

A Collection of Evolving Experiences

Updated June 15, 2020
This document is intended to be updated regularly. To share your experiences, visit the SCCM COVID-19 Discussion Group.

Contents

Halpern N, et al.; sccm.org/ICUConfiguration

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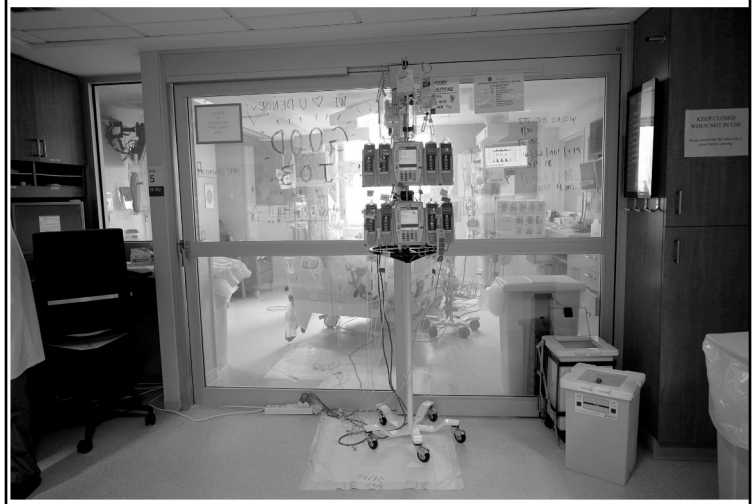

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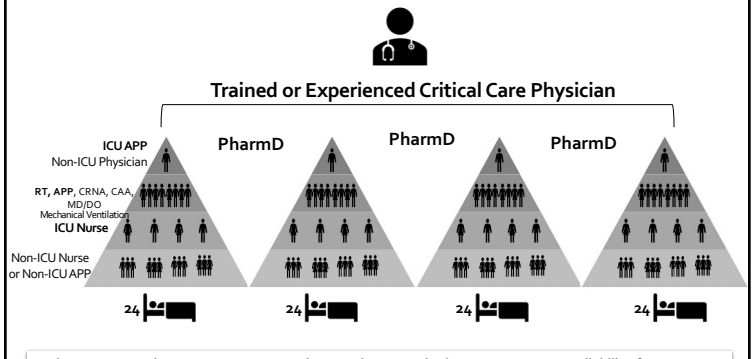
Tiered Staffing Strategy for Pandemic

Caring For The Critically Ill of Injured



Halpern N, Tan K. https://www.sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19

Society of Critical Care Medicine
The Intensive Care Professionals

Modified from the Ontario Health Plan for an Influenza Pandemic Workgroup.
Critical Care During a Pandemic.

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Medical Society Roles

Disaster/Pandemic Adaptations

Webpage redesign Content curation Content generation	Educational product sharing Webinar/On-line education Official organ focused content	SoMe international linkage Expert/leader exportation Process adaptation using virtual platform

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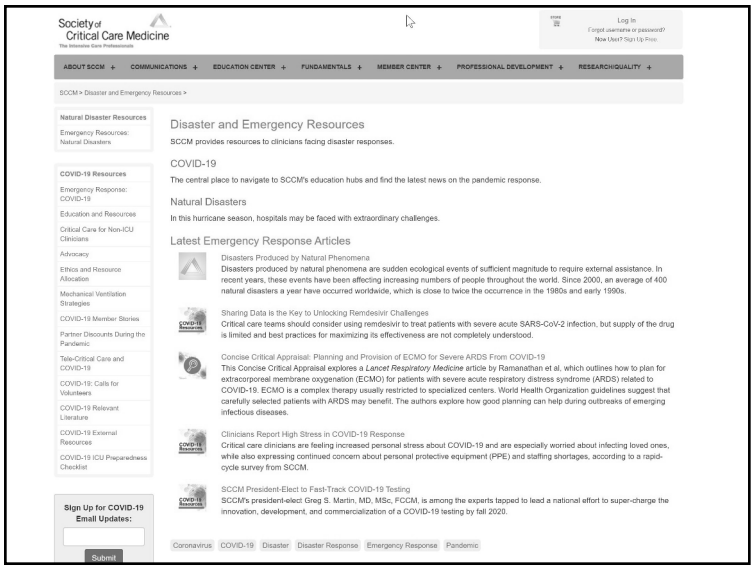

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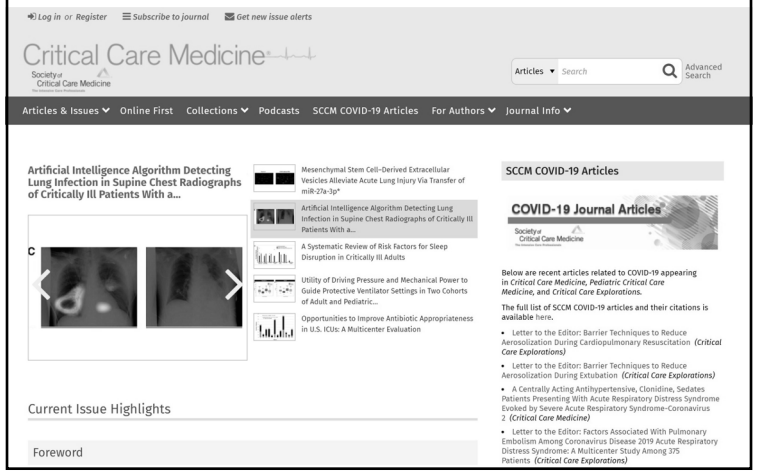
Critical Care Medicine



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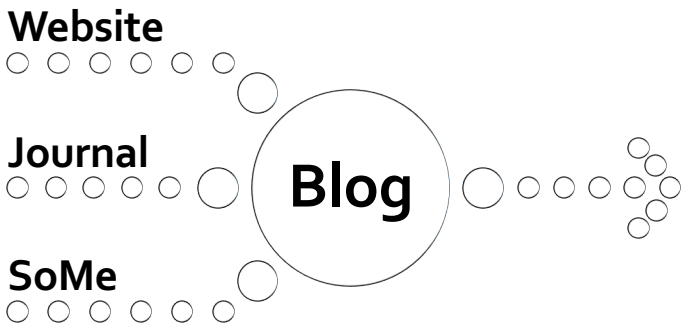
New Approach



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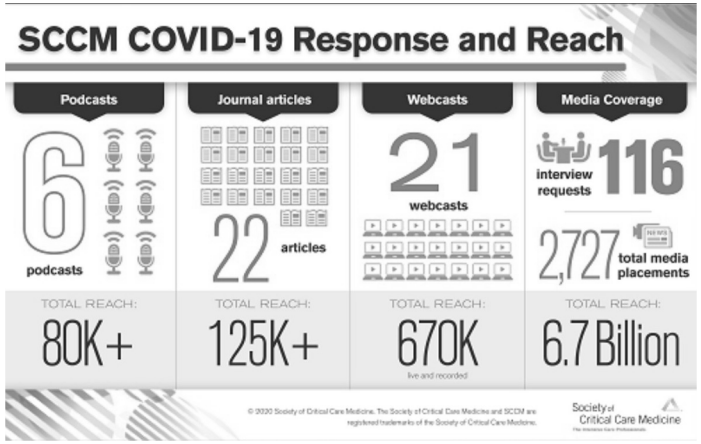
Reach: March-April



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Op-ED

NEWSWEEK MAGAZINE

As the Pandemic Compels Us to Ration Care, Transparency Is Vital to Retain Public Trust | Opinion

BY **LEWIS J. KAPLAN** ON 04/03/20 AT 3:02 PM EDT

Sections

The Washington Post
Democracy Dies in Darkness

PostEverything • Perspective

We need a national dashboard of digital coronavirus data

How can the White House try to manage the pandemic while it's flying blind?

By **Mitchell J. Blutt** and **Lewis J. Kaplan**

April 20, 2020 at 6:00 a.m. EDT

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Society Investigations

OBSERVATIONAL STUDY

Critical Care Clinician Reports on Coronavirus Disease 2019: Results From a National Survey of 4,875 ICU Providers

Kaplan, Lewis J. MD, FACS, FCCP FCCM[1,2]; Kleinpell, Ruth PhD, RN, FCCM[3]; Maves, Ryan C. MD, FCCM, FCCP, FIDSA[4]; Doersam, Jennifer K. MS[3]; Raman, Rameela PhD[5]; Ferraro, David M. MD, FCCP, FCCM[6]

Author Information

Critical Care Explorations: May 2020 - Volume 2 - Issue 5 - p e0125
doi: 10.1097/CCE.0000000000000125

OPEN COVID-19 INFOGRAPHIC Metrics

ONLINE CLINICAL INVESTIGATIONS

Coronavirus Disease 2019 Pandemic Measures: Reports From a National Survey of 9,120 ICU Clinicians

Kleinpell, Ruth PhD, RN, FCCM[1]; Ferraro, David M. MD, FCCP, FCCM[2]; Maves, Ryan C. MD, FCCM, FCCP, FIDSA[3]; Kane Gill, Sandra L. PharmD, MS, FCCM, FCCP[4]; Branson, Richard MSc, RRT, FAARC, FCCM[5]; Greenberg, Steven MD, FCCP, FCCM[6]; Doersam, Jennifer K. MS[1]; Raman, Rameela PhD[7]; Kaplan, Lewis J. MD, FACS, FCCP, FCCM[8] Author Information

Critical Care Medicine: October 2020 - Volume 48 - Issue 10 - p e846-e855
doi: 10.1097/CCM.0000000000004521

COVID-19 Metrics

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Leadership

Guidelines	Webinars	Federal
SSC	SCCM	White House
NIH	ESICM	FEMA
SIS	ACEP	HHS
CHEST	ASHP	CDC
	SIS	

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Uncommon Linkages

Global Sepsis Alliance

World Health Organization

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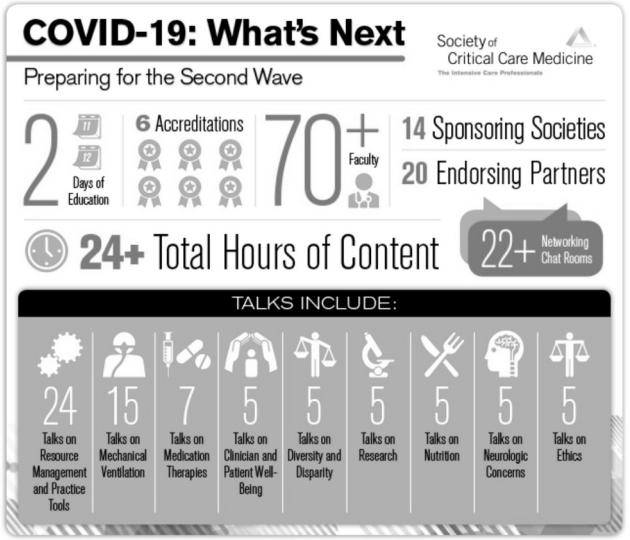

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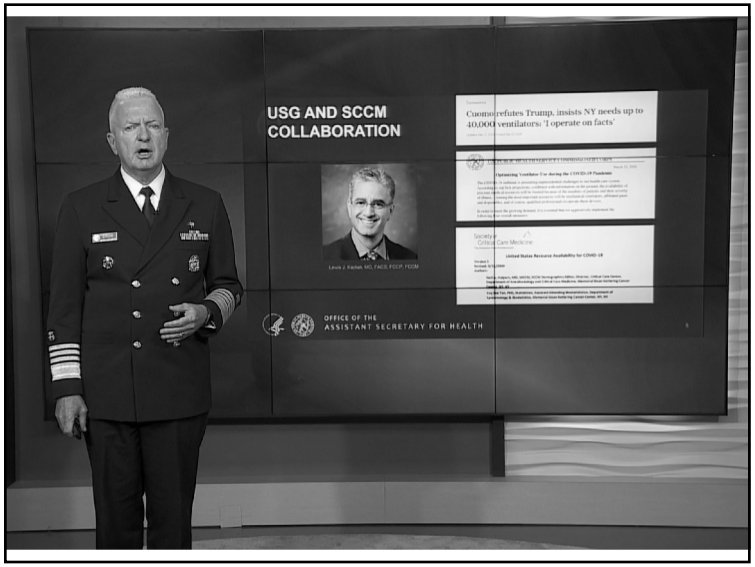

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ADM Brett P Giroir, MD

BE IN "THE ROOM WHERE IT HAPPENS"

- Engagement through professional societies; or coalitions of professional societies, patient advocates, and other stakeholders
- Personal engagement of leadership in specific agencies
  - TV appearances ≠ engagement
  - Journal articles ≠ engagement
- Build long term relationships
  - Federal advisory committees or other special governmental employees (SGEs)
  - Technical assessment panels
- Consider government service
  - Fellowships (ORISE, White House Fellows)
  - The Intergovernmental Personnel Act Mobility Program
  - Full time government appointment (political, career, term appointments)

OFFICE OF THE
ASSISTANT SECRETARY FOR HEALTH

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Maintaining Humanity *and Humility*

PUBLIC HEALTH SERVICE: COVID-19 SUPPORT MISSIONS

First Deployments:

- CDC Quarantine Stations – January 24
- March Air Reserve Base / Travis Air Force Base – January 27

- 8,731 Deployments / 4,136 Officers Deployed as of August 31

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Conclusions

Accidents are opportunities

Coaches, guides and mentors are everywhere

Get to be in the room

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na som tänan väga shukran awiliudo izwis çox sag olun akpé
waad mahadsantahay mahalo 감사합니다 marahaba dhanyavadalu
Благодарам mulţumesc ευχαριστώ kop khun hvala singuila
mèsi הדות danke хвала tack grazie nandri arigatô
salamat po takk thank you Дякую
choukrane
d'akujem gracias merci obrigado gràcies
faleminderit köszönöm teşekkür ederim спасибо dziękuję terima kasih giitu
tapadh leibh dhanyavād Շնորհակալություն motashakkeram
tangio tumas dank u wel kiitos go raibh maith agaibh enachè nuwe
ngiyabonga kakhulu matôndo nirringrazzjak faafetai lava tak

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COVID-19 CRITICAL CARE

APPLYING STANDARDS OF CARE

James H. Henderson II, MD

1

INTRODUCTION

- Unique Scenario
  - Discussing Care Standards in a Non-Standard Scenario
    - Novel Infectious Disease
      - Viral – No Known treatment Options – Similar, but Different
      - Rapid Contagion – High Infectivity
      - World-wide prevalence – Age of Transportation
    - Little Prior Experience – Influenza 1918 - 1922

2

LEARNING OBJECTIVES

1. Discuss why the use of guidelines and standard care for critically ill patients should be applied to patients with COVID-19
2. Discuss why practitioners should have the right to try interventions outside of guidelines in the care of patients with COVID-19
3. Summarize the clinical controversies related to the use of established guidelines versus the right to try other interventions

3

LEARNING OBJECTIVES

Pre-evaluation Questions

1) Which of these therapies are recommended in the current NIH Guidelines for mild to moderate COVID 19 pneumonia patients requiring supplemental oxygen?
   A. Lopinavir/ritonavir
   B. Hydroxychloriquine
   C. Remdesivir
   D. Tocilizumab

1) Dexamethasone 6 mg twice daily for up to 10 days is recommended for the treatment of COVID-19 in patients who are mechanically ventilated?
   A. True
   B. False

4

CONCEPTS

- **Standard of Care**
  - Diagnostic and/or Therapeutic processes that should be followed in the care of patients with particular disorders or in certain clinical circumstances; preferably modified for patient specifics
  - Treatment that is accepted by medical experts as a proper treatment for a specific disease entity and widely accepted by healthcare professionals
- **Clinical Guideline**:
  - IOM: Statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options
  - AHRQ: Systematically developed statements (under the auspices of a recognized appropriate organization) including recommendations intended to optimize patient care and assist physicians and/or other healthcare practitioners assist practitioner and patients to make decisions about appropriate health care for *specific clinical circumstances*

5

CONCEPTS

- Guideline Care
  - Benefits of "Good Guidelines" – Goal: IMPROVE PATIENT CARE AND OUTCOMES (minimize bad outcomes)
    - Systematic Review of Evidence – Evidence Based
    - Systematic Through Expert Review of Validated Literature – balanced evaluations
    - Clear Diagnostic / Therapeutic Recommendations with graded validation
    - Periodic Updates/Review
    - Incorporation of personalized/individualized interpretation
  - Detriments
    - Divergent recommendations – National vs Organization
    - Timeliness of Revision – "Cutting Edge"
    - Limitation of Care and Therapy

6

OBJECTIVE - PERSPECTIVE

- Should we adhere to "Standards of Care" or "Clinical Guidelines" in this Pandemic?
  - General Care
  - Specific Care
- Should individual practitioners have "the right to try"
  - Knowns
  - Unknowns
- What are the Clinical Controversies?
  - Individual
  - Population

7

PERSPECTIVE

- COVID – 19
  - Multiple Broad Treatment Guidelines
    - International: WHO
    - National: NIH, CDC, European
    - Organizational: SCCM, DOD, IDSA
    - Academic: MGH, BWH, UCSF, JHM, UW, Emory
    - Population Specific: AAP, ACOG, ACC,
  - Rapid Expansion of Scientific Literature – WHO lists over 70K publications
    - Over 500 on Respiratory failure / ARDS
    - 366 on Practice Guidelines

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PERSPECTIVE

- COVID – 19
  - Therapies Recommended
    - Remdesivir for patients on low flow oxygen (Strong)
    - Dexamethasone for patients on high flow oxygen (Moderate) or mechanically ventilated (Strong)
    - Convalescent Plasma for patients on oxygen (Weak or uncertain)
  - Adjuncts
    - Antithrombotics: VTE prophylaxis for hospitalized patients; anticoagulation in patients with VTE
    - Prone positioning

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ISSUES

- Should we adhere to "Standards of Care" or "Clinical Guidelines" in this Pandemic?
  - General Care – YES
    - ICU Bundles
    - Mechanical Ventilation
      - ARDS Net – Lung Protective Strategies
      - Prone positioning – pulmonary vasodilators - ECMO
    - Sedation/Paralysis
  - COVID – 19 recommendations
    - Which guideline or recommendation do you follow?

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ISSUES

- Should individual practitioners have "the right to try"
  - Knowns: We always have – that is the Standard of Care
    - FDA approved medications – off label use
    - Novel procedural approaches
    - Does Not invalidate Clinical Guidelines – all are "recommendations"
    - But … what about - missing opportunities, quantifying adverse effects, NNT
  - Unknowns
    - What evidence is available – COVID-19 rapid moves from bench to bedside with multiple therapeutic options
    - Multiple small observational studies early in 2020
    - Now – more multicenter robust prospective blinded trials

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ISSUES

- What are the Clinical Controversies?
  - Individual vs Population
    - Deliver the best "perceived" therapy for the patient
    - Active patient treatment based on limited experimental evidence or pathophysiologic mechanisms
    - Clinical treatments based on witnessed clinical complications
    - Many agents reviewed by small studies
  - Population vs Individual
    - Guideline care based on results of larger or multicenter prospective study
    - Therapies documented to work for overall population
    - Fewer agents reviewed/proven in large studies

12

ISSUES

- Varied Considerations
  - What didn't work – HCQ, Azithromycin, Lopinavir-ritonavir; (+/- tocilizumab)
  - So: what works? We still aren't sure ....
    - Vitamin C, or D
    - Zinc
    - Interferon alfa or beta
    - Anti-IL-6 mAB
    - Anti-IL6 receptors mAB
    - Bruton's Tyrosine Kinase Inhibitors
    - Janus Kinase Inhibitors
    - Ivermectin, Famotidine, Aviptadil, and others

13

LEARNING OBJECTIVES

1) Which of these therapies are recommended in the current NIH Guidelines for mild to moderate COVID 19 pneumonia patients requiring supplemental oxygen?
   A. Lopinavir/ritonavir
   B. Hydroxychloriquine
   C. **Remdesivir**
   D. Tocilizumab
   - Answer C is the correct answer because it is indicated for patients with progression to significant oxygen requirements; but not for mild disease, nor for patients requiring HFNC or Ventilation

1) Dexamethasone 6 mg twice daily for up to 10 days is recommended for the treatment of COVID-19 in patients who are mechanically ventilated?
   A. True
   B. **False**
   - Answer B is the correct answer because daily dosing of dexamethasone is recommended.

14

CONCLUSION

- Primum non nocere
- WE NEED TO KNOW
  - "Insufficient Data"
  - Unique Scenario
    - Registries
    - Clinical trials
- What If?

15

REFERENCES

- NCI Dictionary of Terms
- IOM (Institute of Medicine). 2011. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press.
- Potential benefits, limitations, and harms of clinical guidelines. BMJ 1999;318:527-30
- www.covid19treatmentguidelines.nih.gov
- Drug Treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020; 370:m2980
- Research in the Context of a Pandemic. NEJM DOI:10.1056/NEJMe2024638

16

Treating Critically Ill Patients with COVID-19: The Right to Try

SCCM Texas Chapter Annual Symposium

Michael Sirimaturos, PharmD, BCNSP, BCCCP, FCCM

September 25, 2020

HOUSTON Methodist LEADING MEDICINE

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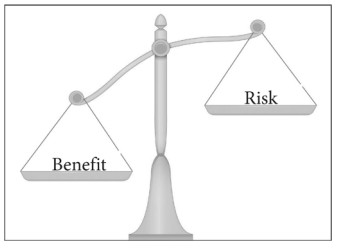
Disclosures

HOUSTON Methodist LEADING MEDICINE

- I have nothing to disclose related to this topic
- I am not an expert on this topic, but appreciate the delicate balance between evidence based medicine and the right to try



https://www.scielo.br/img/revistas/dpjo/v19n5//2176-9451-dpjo-19-05-00136-gf01.jpg

1

1

Learning Objectives

HOUSTON Methodist LEADING MEDICINE

- Discuss why practitioners should have the right to try interventions outside of guidelines in the care of patients with coronavirus disease - 19 (COVID-19)
- Summarize the clinical controversies related to the use of established guidelines versus the right to try other interventions

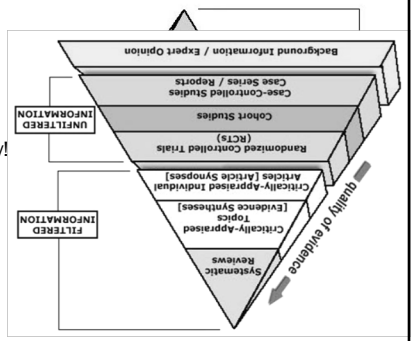
2

2

Standard of Care

HOUSTON Methodist LEADING MEDICINE

- What is the standard in COVID-19?
  - Guidelines?
    - Non existent or limited
  - RCTs, pragmatic trials?
    - Few, take time
  - Observational studies?
    - Not enough or too many!
  - Institutional quality projects/case reports?
  - Prescriber choice?
  - Expert opinion
    - "Doctor knows best?"



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The Right to Try/ Experimental Therapies

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Right to Try

- Ability to try old/new/unproven therapies
- Essential principles
  - Scientific validity
    - Basic science
    - Theoretical efficacy
    - Published literature
    - Application from similar published studies
  - Known risks vs. potential benefit
  - Internal outcomes review
  - Publish results – positive **and** negative

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Right to Try

- Flaws
  - Non-inferiority – Never know if drug actually works
  - Inferiority – Drug is actually harmful/worse than standard of care (SoC)
  - Ethical principles
    - Respect for persons – How informed can the patient be?
      - Fear driven decisions
      - What is actually known about the therapy?
    - Beneficence - Harm may outweigh risks
    - Justice – equitable selection
      - Limited availability at community hospitals
      - Minorities underrepresented

6

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Right to Try

- Benefits
  - Concomitant therapy does not exclude standards of care
  - "Leading medicine" vs. following medicine
  - Identify new treatment options
  - Explore benefits of the unknown
  - Physiology & pathophysiology based therapy
  - Identify appropriate subgroups for benefit
  - Ethical principles
    - Respect for persons – autonomy, informed
    - Beneficence – maximize benefits, minimize risks
    - Justice – equitable selection – may not qualify for other therapy

7

7

Experimental Therapies

8

The Proof is in the Pudding

9

9

Disclosures

- Difficult to be an "expert" on anything COVID
  - Data rapidly changing
  - Clinician + researcher + problem solver + teacher
- Difficult to easily determine effective therapy
  - Heterogeneity of studies
  - Majority of published literature = very small sample size
  - Pre-print > published
    - Peer review lacking
    - Abundance of sub-optimally designed studies
    - Rush to publish early > waiting to meet Power (i.e. no difference)

10

10

Corticosteroids

11

Corticosteroids

- Initial recommendations for steroids = do not use

Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome

Yaseen M Arabi [1,2], Yasser Mandourah [3], Fahad Al-Hameed [4], Anees A Sindi [5], Ghaleb A

Conclusions: Corticosteroid therapy in patients with MERS was not associated with a difference in mortality after adjustment for time-varying confounders but was associated with delayed MERS coronavirus RNA clearance. These findings highlight the challenges and importance of adjusting for

Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients

Nelson Lee [1], K C Allen Chan, David S Hui, Enders K O Ng, Alan Wu, Rossa W K Chiu, Vincent W S

Conclusion: Our findings suggested "early" corticosteroid treatment was associated with a higher subsequent plasma viral load.

doi:10.1164/rccm.201706-1172OC
doi: 10.1016/j.jcv.2004.07.006

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Corticosteroids

- WHO REACT Working Group Meta-Analysis
  - *JAMA*; September 2, 2020
  - 7 Randomized Controlled Trials (RCT)
    - 5 continents; n = 1,703
    - Median age = 60 years (IQR 52-68)
    - Men = 71%
    - SARS-CoV-2 PCR confirmed: 93%
    - Invasive mechanical ventilation (IMV) @ randomization: 91.7%
    - Vasopressors: 47% (RECOVERY – did not record)
    - Antiviral medications: few
    - Risk of bias: low (6/7)

doi:10.1001/jama.2020.17023

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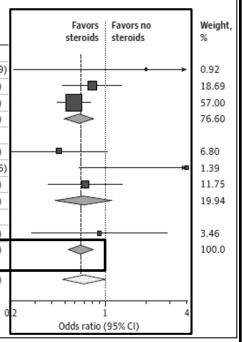
Corticosteroids

- WHO REACT Working Group Meta-Analysis

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



doi:10.1001/jama.2020.17023

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Corticosteroids

- WHO REACT Working Group Meta-Analysis
  - Primary outcome: all-cause mortality at 28 days
    - Steroids vs. placebo: 32.7% vs. 41.5%; OR 0.66; CI 0.53-0.82
      - Low dose steroids: fixed-effect OR 0.61; CI 0.48-0.78
        - » Dexamethasone < 15 mg/d
        - » Hydrocortisone < 400 mg/d
        - » Methylprednisolone < 1 mg/kg/d
      - High dose steroids: fixed-effect OR 0.83; CI 0.53-1.29
  - Secondary outcome: serious adverse events
    - Steroids vs. placebo: 18% vs. 23.4% (6 trials)

doi:10.1001/jama.2020.17023

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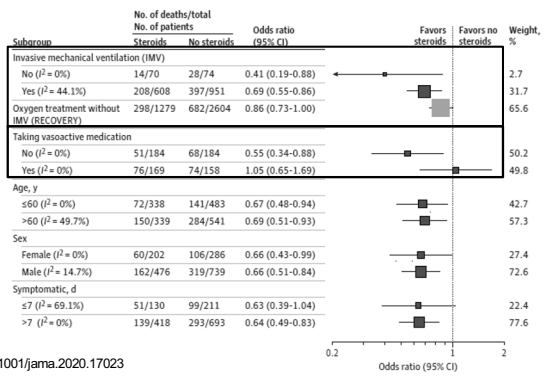
Corticosteroids

- WHO REACT Working Group Meta-Analysis

Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization



doi:10.1001/jama.2020.17023

Corticosteroids

- Takeaways
  - Evidence outside of COVID (i.e. ARDS, adrenal insufficiency)
  - Studies in COVID-19 indicate use is warranted
  - NIH guidelines
    - Recommends: Dexamethasone 6 mg/day x 10 days in vent patients (AI) and if supplemental oxygen (BI)
    - Do not recommend: steroids if not on supplemental oxygen (AI)
  - Do not use → Right to Try → Standard of Care

doi: 10.1056/NEJMoa2021436
National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated Aug 27, 2020). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Sep 21

Remdesivir

Remdesivir (RDV)

- Rationale
  - Broad spectrum antiviral nucleotide analog; activity against coronaviruses
  - Preliminary evidence in SARS & MERS
    - Sheahan 2020 – activity against virus
  - Tested for use in Ebola virus prior to COVID-19

doi: 10.1038/s41467-019-13940-6

Remdesivir (RDV)

- COVID-19
  - SIMPLE-Severe
    - 200 mg x 1, then 100 mg daily for total **5 vs. 10 days**
    - 5 days (n=200) vs. 10 days (n=197)
      - Severe = SpO_2 < 94% or **on supplemental O_2**, but **not on IMV**
      - 10 day group were sicker, higher O_2 needs, & more men
      - Clinical improvement @ day 14 (65% vs. 54%); not significant
      - Post-hoc analysis (vent or ECMO): death 40% vs. 17% (5 vs. 10 days)
    - Takeaways
      - Not placebo controlled; open-label; may improve without therapy
      - Not very "severe" at baseline (no IMV); generalizable to all ICU?
      - 5 days vs. 10 days = equivalent outcomes; 5 days sufficient?

doi: 10.1056/NEJMoa2015301

Remdesivir (RDV)

- COVID-19
  - SIMPLE-Moderate
    - 200 mg x 1, then 100 mg daily for total 5 vs. 10 days
    - 5 days (n=191) vs. 10 days (n=193) vs. **SoC (n=200)**
      - Moderate = SpO_2 > 94% **on room air**
      - Clinical improvement @ day 11 (70% vs. 65% vs. 61%)
        - » 5 day > SoC; OR 1.65, p = 0.026
        - » 5 day = 10 day > SoC @ day 14
      - Low mortality overall (1%)
    - Takeaways
      - Not placebo controlled; open-label
      - Does not translate to ICU; may affect ICU if limited drug supply
      - Clinical improvement @ days 11-14

doi:10.1001/jama.2020.16349

Remdesivir (RDV)

- COVID-19
  - ACTT-1 trial
    - RCT, double-blind, placebo controlled
    - 200 mg x 1, then 100 mg daily for total 10 days
    - RDV (n=538) vs. placebo (n=521)
      - 88.7% had severe disease
      - Median time to recovery: 11 days vs. 15 days; p < 0.001
      - Mortality by day 14: 7.1% vs. 11.9%; not statistically significant
      - Subgroup analysis
        - » Most benefit if on supplemental O_2, but not on IMV/ECMO @ baseline; recovery rate ratio 1.47

doi: 10.1056/NEJMoa2007764

Remdesivir (RDV)

- Takeaways
  - Not FDA approved; currently allowed under Emergency Use Authorization (EUA)
    - 8/28/20 - Expanded to all severity of hospitalized adult & pediatric patients with suspected or confirmed COVID-19
  - Shortens time to clinical recovery; no mortality benefit
    - Potential benefit in opening up hospital beds during pandemic
  - NIH Guidelines
    - Recommend: 5 day course if on supplemental O_2 (AI)
    - Recommend: Prioritize therapy to supplemental O_2 patients over non-invasive O_2 /IMV/ECMO when supplies are limited (BI)
  - Right to Try → Standard of Care

https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklury-remdesivir-include-all-hospitalized
National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated Aug 27, 2020). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Sep 21

Lopinavir-Ritonavir

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Lopinavir-Ritonavir

- Rationale
  - Antiviral; inhibits protease activity of coronavirus
  - Primarily used in HIV
  - Preliminary evidence in SARS and MERS
    - Reduced mortality in conjunction with ribavirin (Chan 2003)
    - Decreased ARDS/death with ribavirin (Chu 2004)
    - Studies were small (n = 41-75), retrospective, and open-label

Chan KS, Lai ST, Chu CM, et al. Hong Kong Med J 2003;9:399-406
doi: 10.1136/thorax.2003.012658
doi: 10.1056/NEJMoa2001282

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Lopinavir-Ritonavir

- COVID-19
  - Cao 2020; RCT
    - n = 100; Lopinavir-Ritonavir x 14d vs. SoC
    - No difference in clinical improvement, viral shedding
    - 13.8% stopped due to adverse effects (i.e. GI intolerance)
    - Underpowered to find difference; stopped early due to RDV
- Takeaways
  - No superiority RCT data in COVID-19
  - Known side effects and drug-drug interactions
  - NIH guidelines
    - Do not recommend: use only in clinical trial (AI)
  - Right to Try → Do not use

doi: 10.1056/NDJMoa2001282
National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated Aug 27, 2020). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Sep 21

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Ascorbic Acid (Vitamin C)

27

Vitamin C

- Rationale
  - Antioxidant; may support host defenses against infection and oxidative stress
  - Infections may decrease Vitamin C concentrations
  - Selective interest recently for repurposing Vitamin C
    - Common cold
    - ARDS
    - Sepsis/septic shock
    - COVID-19

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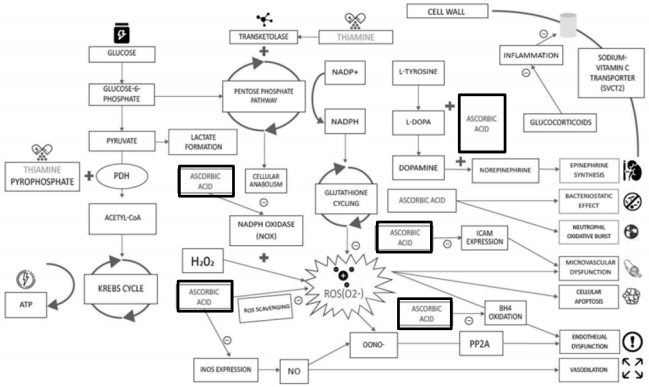
Vitamin C

- Rationale



doi:10.3390/nu12092550

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Vitamin C

- Vitamin C in sepsis

June 2017 Volume 151, Issue 6, Pages 1229–1238

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

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Vitamin C

- Vitamin C in sepsis

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Vitamin C

- Vitamin C in sepsis
  - Marik et al.
  - High dose IV Vitamin C (6 g/day), hydrocortisone, and thiamine vs. standard of care
  - Results: High dose vitamin C cocktail = significant decrease in mortality (40.4% vs. 8.5%)
  - Impact: to be seen
  - Controversy
    - Mega dosage strategy (Vit C 6 g/day) (beneficence?)
    - Too simple? Too good to be true?
    - Single center, non-randomized, retrospective
    - Reproducibility (high rate of mortality at baseline)
    - Generalizability

doi: 10.1016/j.chest.2016.11.036

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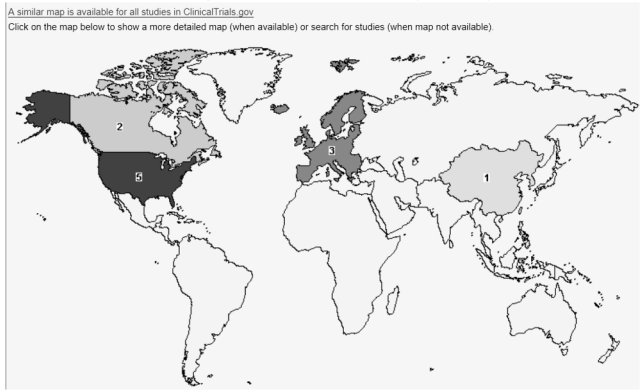
Vitamin C

- Vitamin C in sepsis – Nov 2017 (n=11)



https://clinicaltrials.gov/ct2/results/map?term=ascorbic+acid&cond=Sepsis&map=

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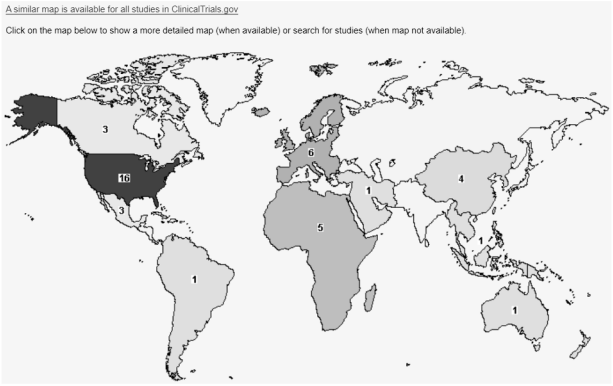
Vitamin C

- Vitamin C in sepsis – Sept 2020 (n=40)



https://clinicaltrials.gov/ct2/results/map?term=ascorbic+acid&cond=Sepsis&map=

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Vitamin C

- Non-COVID-19
  - Common cold
    - Cochrane Systematic Review (Hemila 2013)
      - 29 trials; 11,306 participants; Decreased duration of symptoms
    - Meta-Analysis (Hindawi 2018)
      - 9 trials; Decreased symptom duration only with regular supplementation
  - Sepsis/septic shock
    - Marik, et al., CITRIS-ALI, VITAMINS, ORANGES, HYVCTTSSS

	Marik et al.	CITRIS-ALI	VITAMINS	ORANGES	HYVCTTSSS
Mortality	(+) [1]	(+) [2]	(-) [2]	(-) [2]	(-) [1]
Vasopressor duration	(+) [2]	N/A	(-) [1]	(+) [1]	(-) [2]
SOFA score	(+) [2]	(-) [1]	(-) [2]	(-) [1]	(-) [2]

1 = Primary endpoint; 2 = Secondary endpoint; (+) = in favor of vitamin C; (-) = not in favor of vitamin C

doi: 10.1002/14651858.CD000980.pub4
doi: 10.1001/jama.2019.11825
doi: 10.1016/j.chest.2016.11.036
doi: 10.1001/jama.2019.22176
doi: 10.1016/j.chest.2020.02.049
doi: 10.1016/j.chest.2020.02.065
doi: 10.1155/2018/1837634

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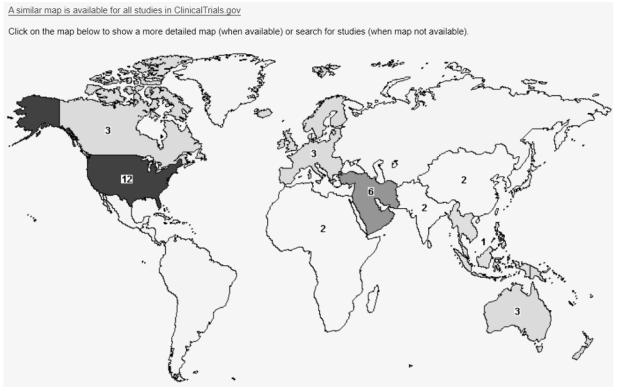
Vitamin C

- Vitamin C in COVID-19 – Sept 2020 (n=33)



https://clinicaltrials.gov/ct2/results/map?term=ascorbic+acid&cond=Covid19&map=

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Vitamin C

- COVID-19
  - No completed RCTs; 33 COVID-19 trials pending

Name	Blinded	Placebo	RCT	Location	Vit C Dose	Primary Outcomes
NCT04357782 (AVoCaDO)	N	N	N	USA	50 mg IV q 6h x 4d	Incidence of adverse events
NCT04323514	N	N	N	Italy	10 g IV x 1	Hospital mortality @ 3d
NCT04342728 (COVIDAtoZ)	N	N	Y	USA	8 g/d divided +/- zinc	Time to 50% reduction in symptoms
NCT04363216	N	N	Y	USA	0.3 g/kg IV x 1, 0.6 g/kg x 1, 0.9 g/kg x 4d	Clinical improvement @ 3d
NCT04395768	N	N	Y	Australia	50 mg/kg IV q 6h x 1d, 100 mg/kg IV q 6h x7d	Death @ 15d & 45d
NCT04264533	Y	Y	Y	China	12 g IV q 12h x 7d	Vent free days @ 28d
NCT03680274 (LOVIT)	Y	Y	Y	Canada	50 mg/kg IV q 6h x 4d	Death & organ dysfunction in septic or COVID-19 @ 28d
NCT04401150 (LOVIT-COVID)	Y	Y	Y	Canada	50 mg/kg IV q 6h x 4d	Death & organ dysfunction @ 28d
NCT04344184 (EVICT-CORONA-ALI)	Y	Y	Y	USA	100 mg/kg IV q 8h x 3d	Vent free days @ 28d

70 kg
63 g/d

28 g/d

Clinicaltrials.gov

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Vitamin C

- Takeaways
  - Increasing number of studies with high dose Vitamin C will add to safety data (or lack thereof)
    - Calcium oxalate (kidney stones)
    - Hypernatremia (sodium ascorbate ~6,800 mg – 15,700 mg Na)
    - "Hyperglycemia" or masked hypoglycemia (interference with oxidative-reduction reaction-based tests)
  - However, "limited major safety issues" + lack of sufficient efficacy data = caution in use
  - NIH guidelines
    - Do not recommend: insufficient data for/against (critically ill) no completed controlled studies
  - Right to Try → ??? (currently IV unavailable)

National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines (updated Jul 17, 2020). From NIH website (https://www.covid19treatmentguidelines.nih.gov/). Accessed 2020 Sep 21

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Back to the Debate

Standard of Care vs. Right to Try

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Standard of Care

- Start of the pandemic
  - No evidence based medicine (EBM) guidelines for COVID-19 available
- Middle of the pandemic
  - Few guidelines
    - Mostly default to preceding standards of care (SoC)
      - Usually appropriate for most conditions/situations
      - Useful in COVID-19?
- End of the pandemic
  - Lots of guidelines!!!
    - Should we wait?

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Standard of Care

- Flaws in limiting to only the standard of care
  - New disease; no or limited known treatments
  - Significant delays in creating standards of care
  - Standard of care limits therapy to the "known"
  - Care is constantly changing during the pandemic
    - Then is it really a standard?
  - Changes made to the SoC are generally based on data from right to try studies
    - Examples
      - Corticosteroids
      - Remdesivir

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Controversies in Guidelines

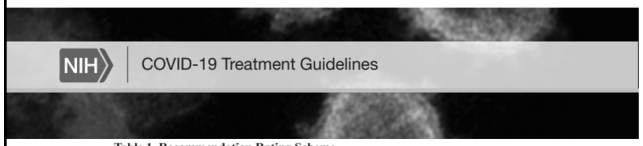

Table 1. Recommendation Rating Scheme

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	III: Expert opinion

Strength of Recommendation	Strong (A)	Moderate (B)	Optional (C)	Quality of Evidence	RCT (I)	Non-RCT (II)	Expert Opinion (III)
(n = 90)							

Should we be limited to guidance of "Strong Opinions" based on no quality of evidence?

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https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed Sept 22, 2020.

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Right to Try

- Failures
  - Right to try therapies that didn't work
    - Non-superiority does not necessarily = harmful
    - Information gained = helpful
      - Institutions stop using unproven/unsafe therapies
      - Move onto other potential beneficial therapies
- Successes
  - Right to try therapies that work
    - Decrease mortality
    - Decrease morbidity
      - Ventilator days = more ventilators for others
      - ICU/Hospital Length of Stay (LOS) = more beds for incoming patients
      - Overall healthcare costs?

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The Real Question

- If you were infected with COVID-19, would you have wanted the right to try…
  - Remdesivir?
  - Corticosteroids?
  - Convalescent plasma?
  - Intermediate dosed DVT prophylaxis?
  - Etc…

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Helpful COVID-19 Resources

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Helpful Resources

- National Institutes of Health (NIH) COVID-19 Treatment Guidelines
  - https://www.covid19treatmentguidelines.nih.gov/
- Centers for Disease Control and Prevention (CDC)
  - https://www.cdc.gov/coronavirus/2019-ncov/index.html
- British Columbia Ministry of Health
  - http://www.bccdc.ca/Health-Professionals-Site/Documents/Guidelines_Unproven_Therapies_COVID-19.pdf

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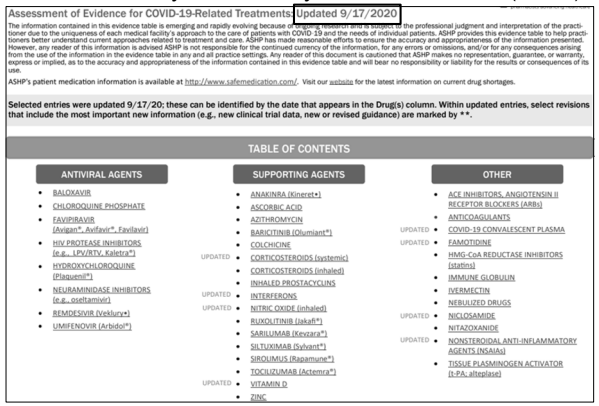
Helpful Resources

- American Society of Health-System Pharmacists (ASHP)



Assessment of Evidence for COVID-19-Related Treatments Updated 9/17/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is designed to support the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

ASHP's patient medication information is available at http://www.safemedication.com/. Visit our website for the latest information on current drug shortages.

Selected entries were updated 9/17/20; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by **.

TABLE OF CONTENTS

ANTIVIRAL AGENTS

- BALOXAVIR
- CHLOROQUINE PHOSPHATE
- FAVIPIRAVIR (Avigan®, Avifavir®, Favilavir)
- HIV PROTEASE INHIBITORS (e.g., LPV/RTV, Kaletra®)
- HYDROXYCHLOROQUINE (Plaquenil®)
- NEURAMINIDASE INHIBITORS (e.g., oseltamivir)
- REMDESIVIR (Veklury•)
- UMIFENOVIR (Arbidol®)

SUPPORTING AGENTS

- ANAKINRA (Kineret•)
- ASCORBIC ACID
- AZITHROMYCIN
- BARICITINIB (Olumiant®)
- COLCHICINE
- UPDATED CORTICOSTEROIDS (systemic)
- CORTICOSTEROIDS (inhaled)
- INHALED PROSTACYCLINS
- UPDATED INTERFERONS
- UPDATED NITRIC OXIDE (inhaled)
- RUXOLITINIB (Jakafi®)
- SARILUMAB (Kevzara®)
- SILTUXIMAB (Sylvant®)
- SIROLIMUS (Rapamune®)
- TOCILIZUMAB (Actemra®)
- UPDATED VITAMIN D
- ZINC

OTHER

- ACE INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)
- ANTICOAGULANTS
- UPDATED COVID-19 CONVALESCENT PLASMA
- UPDATED FAMOTIDINE
- HMG-CoA REDUCTASE INHIBITORS (statins)
- IMMUNE GLOBULIN
- IVERMECTIN
- NEBULIZED DRUGS
- UPDATED NICLOSAMIDE
- NITAZOXANIDE
- UPDATED NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIAs)
- TISSUE PLASMINOGEN ACTIVATOR (t-PA; alteplase)

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table

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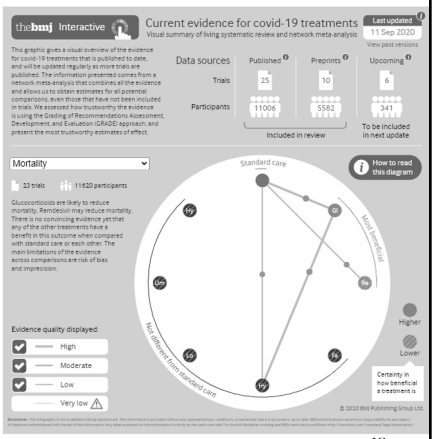
Helpful Resources

- British Medical Journal (BMJ)
  - Living systematic review and network meta-analysis
    - Mortality
    - Mechanical ventilation
    - Adverse events
    - Viral clearance at 7 days
    - Duration of ventilator
    - Length of hospital stay
    - Time to resolution of symptoms
    - Time to viral clearance
    - Length of intensive care stay
    - Admission to hospital



https://www.bmj.com/content/370/bmj.m2980

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Learning Assessment Questions

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Learning Assessment Questions

- Flaws in limiting COVID-19 treatment to standard of care include:
  - A. Delays in trying potentially helpful treatment
  - B. Limits providing therapy to what is already known
  - C. Standards of care during a pandemic are constantly changing
  - D. All of the above

50

50

Learning Assessment Questions

- Flaws in limiting COVID-19 treatment to standard of care include:
  - A. Delays in trying potentially helpful treatment
  - B. Limits providing therapy to what is already known
  - C. Standards of care during a pandemic are constantly changing
  - **D. All of the above**

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51

Learning Assessment Questions

- Thanks to the right to try, corticosteroids like dexamethasone have been determine to be potentially harmful during early phases of COVID-19 (i.e. not on supplemental O_2), but may be beneficial in later stages of disease or in patients with worsening severity of illness (i.e. requiring oxygen support, ARDS, etc.)
  - A. True
  - B. False

52

52

Learning Assessment Questions

- Thanks to the right to try, corticosteroids like dexamethasone have been determine to be potentially harmful during early phases of COVID-19 (i.e. not on supplemental O_2), but may be beneficial in later stages of disease or in patients with worsening severity of illness (i.e. requiring oxygen support, ARDS, etc.)
  - **A. True**
  - B. False

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53

Treating Critically Ill Patients with COVID-19: The Right to Try

Michael Sirimaturos, PharmD, BCNSP, BCCCP, FCCM
September 25, 2020

54

Preparing for Covid-19 Pandemic
A Houston Experience

Steven H. Hsu, M.D.
Assistant Professor of Clinical Medicine
Houston Methodist Hospital
Weill Cornell Medical College

HOUSTON Methodist LEADING MEDICINE

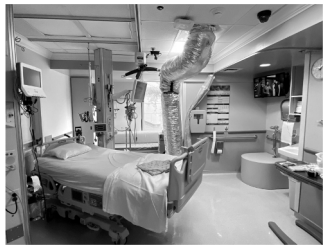
1

Objectives

- Discuss how our hospital system prepared for the pandemic
- Collaboration with other hospital systems
- Future Effort

2

Preparation of the ICU

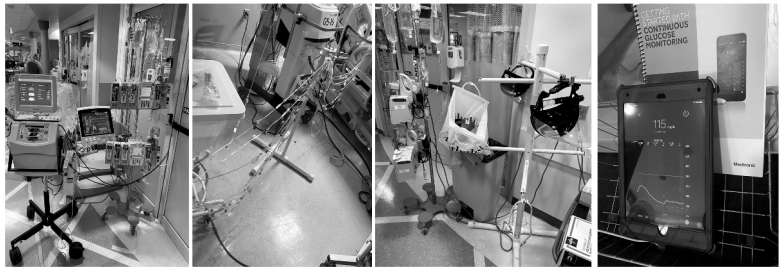


3

PPE Centralization

4

PPE Conservation



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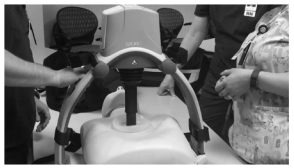
Changes to the ICU



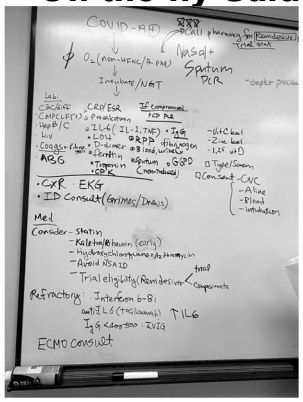
6

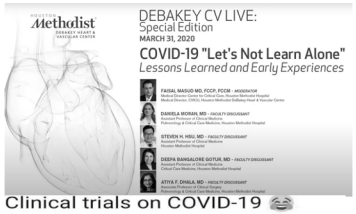
Innovation

Innovative ideas

7

On-the-fly Guideline





8

ECMO in non-ECMO Units

9

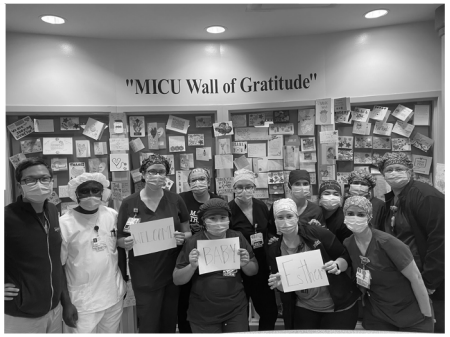
Obstetrics in Covid-19 ICU

Open Forum Infectious Diseases

BRIEF REPORT

Remdesivir Treatment for Severe COVID-19 in Third-Trimester Pregnancy: Case Report and Management Discussion

Grace A. Maldarelli,[1,2] Megan Savage,[2] Shawn Mazur,[2] Corrina Oxford-Horrey,[2,4] Mirella Salvatore,[1,3] and Kristen M. Marks[1,3]



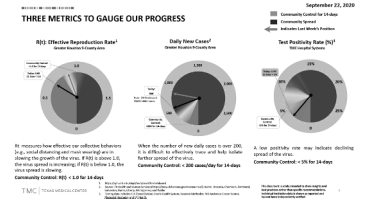
10

Innovation

Telemedicine in ICU

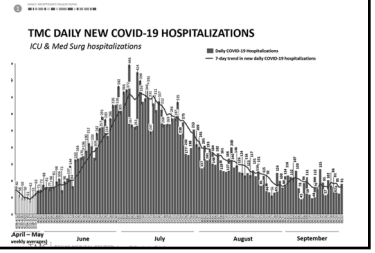
11

TMC Collaboration



TMC EXPECTED PPE NEEDS

	Average daily burn rate[1]	Estimated days available	Status
N95 respirator masks	7,572	274	
Surgical face masks	133,336	144	
Eye protection	4,259	634	
Gowns	55,792	121	
Gloves	1,037,641	45	



12

Community Awareness

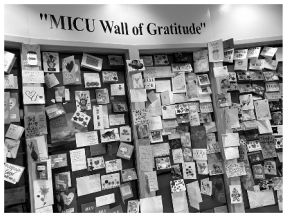
The New York Times

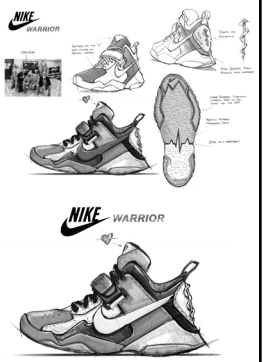
'Feeling Like Death': Inside a Houston Hospital Bracing for a Virus Peak

As young patients fill new virus wards, Houston Methodist is calling nurses to work extra shifts and ramping up its testing efforts.

13

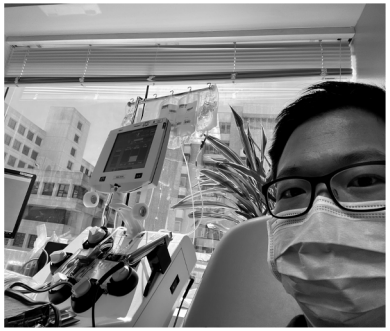
Staff Support





14

Thank you!



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Preparing for the Pandemic: The Texas Experience

1

Critical Care Nursing Preparation During a Pandemic

Susan Smith, DNP, APRN, ACNS-BC
Adult Clinical Nurse Specialist
National Institutes of Health
Clinical Center Intensive Care Unit

2

Learning Objectives

1. ASSESSING RESOURCES
2. MOBILIZING RESOURCES

3

Learning Assessment Question #1

- What percentage of patient care time is provided by nurses?
  - A. 30 percent
  - B. 45 percent
  - C. 60 percent
  - D. 86 percent

4

Learning Assessment Question #1

- What percentage of patient care time is provided by nurses?
  - A. 30 percent
  - B. 45 percent
  - C. 60 percent
  - D. 86 percent
- Answer D is the correct answer. Physicians provide 13%. Critical support staff such as respiratory therapists and pharmacists provide the remainder.

5

Team-based Nursing Care

- Clearly explain the "why" behind moving to team-based care
- Team-based roles must be consistent with scope of practice, both licensed and ancillary
- Assess and support RN learning needs
  - Consider years of experience and home unit
  - Review delegation, communication and team-based behaviors

6

Team-based Nursing Care

- Provide upfront opportunities for redeployed RNs to become part of their new unit's culture.
  - Limit floating
  - Detailed orientation
  - Pilot model
  - Provide a mentor or preceptor

7

ICU Care Team – ICU RN and Non-ICU RN Task List

Goal is to coordinate care and limit time & staff in the patient room

Patient Care Task*	Team Leader (TL) - ICU RN	Non-ICU RN
Team Member Name		
Monitoring	☐ Vital Signs q 4 hr: recording, analyzing for treatment plan ☐ Arterial line: assessing, recording, analyzing ☐ Sedline q 4 hr (if paralyzed) ☐ TOF q 8 hr (if paralyzed) ☐ Collaborating with physician for needs	
Fluids. I&O	☐ CRRT ☐ Analyzing I&O ☐ Flexi-Seal Fecal Management system: insertion, maintenance	☐ Foley insertion ☐ I&O q 4 hr ☐ Assess PIV q 4 hr, & central line/midline daily ☐ Recording liquid stools (Flexi-Seal) ☐ Stool incontinence, skin barrier
Oxygenation/ Ventilation	☐ Chest tubes – analysis ☐ FiO_2 changes, suctioning – collaborating with RT	☐ Supplemental O_2 thru facemask or nasal cannula ☐ Chest tube drainage
Nutrition	☐ Maintain feeding tube and tube feedings for intubated patients (bridle tube) ☐ Collaborate with Dietitian	☐ Feeding tube placement check ☐ Check tube feeding/pump q 12hrs ☐ Feeding non-intubated patients
Medication Administration *(Team Leader reviews)*	Drips that are titrated: ☐ Sedation, Pain management, Paralytics, Vasoactive drips	☐ IV fluids, IV antibiotics, IV steroids ☐ Pain & fever management (non-drip) ☐ Investigational medications ☐ Routine meds
Testing	☐ Labs *(consolidate/ coordinate)*	☐ DFS
ADLs	☐ Positioning / turning / mobility / proning assist ☐ Oral care (intubated pt) ☐ Suctioning	☐ Hygiene, skin protection, incontinence ☐ Positioning/ turning/ mobility / proning assist ☐ Dressings
Transfers	*Department to department, or department to procedure/testing area & back* ☐ Calls report	☐ Transfers patient ☐ If patient maintains ICU status, RT accompanies non-ICU RN
Documentation	☐ Shift assessment - ICU-specifics ☐ What you do – your care ☐ Significant events ☐ Provider communication ☐ Reviewing documentation by team members	☐ Admission & Shift assessment (ICU RN will document ICU-specifics) ☐ What you do – your care
Communication *Concerns/Escalations*	☐ TL escalates to provider and documents ☐ Coordinate family contact with provider	☐ Provider communication, escalated to TL

* *Team huddles at start, midway through, and end of shift. Team leader assigns tasks commensurate with team experience and licensure. Team members inform team leader if unable to perform assigned task in a timely manner*

05/27/2020, 1230 hr at BLANC CMER

8

Date	Room #	Baylor Scott & White Health ICU Care Team: Shift Assignments by Team Role		Patient Name / Label
Patient Care Task*	**Team Leader (TL) - ICU RN**	**Non-ICU RN**	**PCT/Unlicensed**	**RT**
Team Member Name				
Monitoring	☐ Vital Signs q 4 hr; recording, analyzing for treatment plan ☐ Arterial line: assessing, recording, analyzing ☐ Sedline q 4 hr (if paralyzed) ☐ TOF q 8 hr (if paralyzed) ☐ Collaborating with physician for needs			
Fluids, I&O	☐ CRRT ☐ Analyzing I&O ☐ Flexi-Seal Fecal Management system: insertion, maintenance	☐ Foley insertion ☐ I&O q 4 hr ☐ Assess PIV q 4 hr, & central line/midline daily ☐ Recording liquid stools (Flexi-Seal) ☐ Stool incontinence, skin barrier	☐ PO intake & voided output ☐ Stool incontinence, skin barrier	
Oxygenation/ Ventilation	☐ Chest tubes – analysis ☐ FiO_2 changes, suctioning – collaborating with RT	☐ Supplemental O_2 thru facemask or nasal cannula ☐ Chest tube drainage		☐ Vent setting q 4 hr ☐ Hi-flo O_2 checks q 6 hr ☐ Suctioning ☐ Proning Lead - coordinate w/provider & care team
Nutrition	☐ Maintain feeding tube and tube feedings for intubated patients (bridle tube) ☐ Collaborate with Dietitian	☐ Feeding tube placement check ☐ Check tube feeding/pump q 12hrs ☐ Feeding non-intubated patients	☐ Feeding non-intubated patients (only without high O_2 levels)	
Medication Administration *(Team Leader reviews)*	Drips that are titrated: ☐ Sedation, Pain management, Paralytics, Vasoactive drips	☐ IV fluids, IV antibiotics, IV steroids ☐ Pain & fever management (non-drip) ☐ Investigational medications ☐ Routine meds		
Testing	☐ Labs *(consolidate/ coordinate)*	☐ DFS	☐ DFS	☐ ABGs – drawing, analysis, reporting
ADLs	☐ Positioning / turning / mobility / proning assist ☐ Oral care (intubated pt) ☐ Suctioning	☐ Hygiene, skin protection, incontinence ☐ Positioning/ turning/ mobility / proning assist ☐ Dressings	☐ Hygiene, skin protection, incontinence ☐ Positioning/ turning/ mobility / Proning assist	☐ Oral care (intubated patient) ☐ Suctioning ☐ Anchorfast changes
Transfers	*Department to department, or department to procedure/testing area & back* ☐ Calls report	☐ Transfers patient ☐ If patient maintains ICU status, RT accompanies non-ICU RN		☐ Transfers ICU patient with non-ICU RN
Documentation	☐ Shift assessment - ICU-specifics ☐ What you do – your care ☐ Significant events ☐ Provider communication ☐ Reviewing documentation by team members	☐ Admission & Shift assessment (ICU RN will document ICU-specifics) ☐ What you do – your care		
Communication *Concerns/Escalations*	☐ TL escalates to provider and documents ☐ Coordinate family contact with provider	☐ Provider communication, escalated to TL	☐ Escalate to TL	☐ Escalate to TL

* *Team huddles at start, midway through, and end of shift. Team leader assigns tasks commensurate with team experience and licensure. Team members inform team leader if unable to perform assigned task in a timely manner*

03/27/2020, 1230 kz ss BUMC CNER

9

Learning Assessment Question #2

- What is the main activity nurses spend their time on when caring for patients?
  - A. Medication administration
  - B. Care coordination
  - C. Documentation
  - D. Direct patient care

10

Learning Assessment Question #2

- What is the main activity nurses spend their time on when caring for patients?
  - A. Medication administration
  - B. Care coordination
  - C. Documentation
  - D. Direct patient care
- Answer C is the correct answer. At least 23% or more of a nurse's time is spent documenting in the EHR

11

The Advisory Board Group

- *The Nursing Executive Center wishes to thank the following BSWH leaders for their willingness to share this outstanding work with colleagues across the country during this unprecedented time:*
  - *Remy Tolentino, MSN, RN, NEA-BC, Vice President, Nursing Workforce & Leadership Development, Baylor Scott & White Health*
  - *Karen Zwerneman, MSN, RN, NEA-BC, Director, Nursing Leadership Development, Baylor Scott & White Health*
  - *Susan Smith, DNP, APRN, ACNS-BC, Adult Health Clinical Nurse Specialist in the Critical Care Department, Baylor University Medical Center, Dallas*
  - *Scott Williams, MSN, RN, NE-BC, Director of Nursing, Baylor Scott & White Medical Center at Irving*
  - *Leslie Gembol, DNP, RN, NEA-BC, Chief Nursing Office, Temple Region*
  - *Kate Williams, DNP, RN, NPD-BC, Director Center of Nursing Education Innovation & Practice, Temple Region*
  - *Kris Powell, MSN, RN, CEN, NEA-BC, FAEN, Director of Emergency Services, Baylor Scott & White Health - North Texas Division*

12

Life on the COVID unit

By: Brooke Spacek, BSN, RN

1

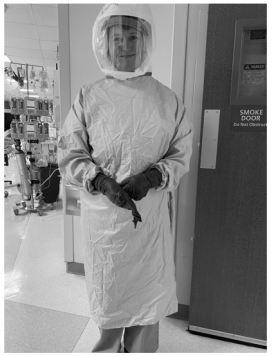
Learning Objectives

- - Summarize a day when caring for a critically ill patient with COVID-19-
- - Describe the psychosocial impact on health care workers as a result of the pandemic
- - List strategies to improve the care of patients and safety of health care workers during the pandemic

2

What do we wear?

- PAPR/N95
- Faceshield if applicable
- Two sets of gloves
- Surgical non-permeable gown
- Booties



3

Protection Plan

- Plenty of PPE (even in the shortage)
- Clustering care
  - Initially limiting contact for self-care patients to as much as every 4 hours
  - For total care patients - every 2 hours
  - Given a lot of grace with moving medications around to fit into clustered care time windows

4

How do we take care of ICU status patients?

- IV poles mostly outside of the room
- Ventilator monitors outside of the room
- Daily Facetime visits for families

5

Daily Norms

- Video monitors inside every room
  - Nurses could use to watch confused patients
  - Healthcare team members could use to talk to patients about their health plan
- Patients provided with Ipads
  - Patients able to use them to communicate with healthcare staff and family members
  - Very useful during comfort care
- GIM physician saw patients in person daily
- Other healthcare team members visited virtually or over the phone
  - Problems with this: more coordination on the nurses' part; nurses had to set up videos properly or show team members how to use equipment; nurses also had to wake patients up frequently so they would answer the phone to talk to team members
- Staff learned how to write backwards when asking for supplies inside the room

6

Easter on the COVID Unit

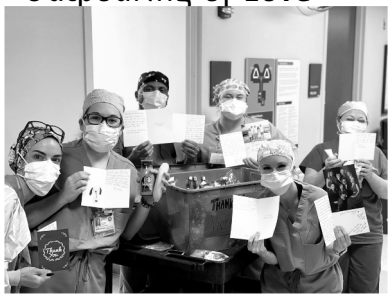
7

Blessing of the Hands

- Came to the unit every day one week to pray over the staff and bless their hands
- Came several times throughout the week for several weeks to check in on how the staff were and to pray over the unit

8

Outpouring of Love



9

End-of-Life Care

- COVID has isolated our patients from their families even during end-of-life
- We now offer the opportunity for 1 family member to visit for up to 4 hours during comfort care

10

Final Thoughts

- COVID has brought this institution together in more ways than one
  - Teamwork; Flexibility; Creativity; Adaptability
- The COVID team is made up of the most caring, selfless people I have ever met (AKA lifelong friends)
- Future Planning
  - We must learn from the mistakes we have made
  - Nurses are on the frontlines- listen to our suggestions
  - Be flexible with your frontline staff members- while many healthcare team members get to work from home or virtually, we HAVE to be there (i.e. have grace with us)
  - Stay mentally healthy- find something that brings you joy and allows you to mentally turn off from work

11

Question 1

Which of the following are potential safety hazards to COVID patient care

- A. Staff inability to quickly enter a room
- B. Staff members do not monitor the monitors
- C. Frequent floating of inexperienced COVID nurses
- D. All of the above

12

Answer

Answer D is the correct answer because all of the above are safety concerns on many COVID floors.

13

Question 2

COVID-19 has not had any significant psychological impact on hospital staff

- A. True
- B. False

14

Answer

Answer B is the correct answer because studies have shown that COVID-19 has in fact increased the emotional and mental stress on medical staff.

15

Questions?

16

Contact Information

Brooke Spacek, BSN, RN

blnell@mdanderson.org

17

Renal dysfunction in Cirrhosis in the ICU setting

Pavan Devulapally MD
Nephrology
San Antonio

1

Learning Objectives

- Describe various presentations of and risk factors for renal injury in the setting of cirrhosis and liver failure
- Discuss treatment strategies for concurrent renal and liver dysfunction

2

What is Cirrhosis

- Advanced state of liver dysfunction due to fibrosis
- Major causes in adults Alcohol and Hepatitis C
- Cause of around 50 k to 70 K deaths every year

3

When to suspect cirrhosis

- History -
- confusion/altered mentation
- Skin and urine color changes
- Abdo distension and Edema
- Physical Exam -
- Juandice ,
- clubbing , HPOA
- spider naevi, caput medusa
- Ascites , edema
- spleenomegaly, hepatomegaly
- dupuytrens
- dark urine
- asterixis

4

Contd … suspicion for cirrhosis

- Labs- bonacini discriminant score with Ascites and spider neavi
- Lower the platelets – higher suspicion with high score
- High INR – higher the score
- ALT to AST ratio - lower the ratio higher the score
- Child pugh score /MELD score

- Imaging
- US seems to be easiest and well tolerated – smallish liver with nodularity
- CT/MR – not very reliable for the diagnosis for cirrhosis

5

Complications usually seen in ICU setting relevant to renal in relation to cirrhosis

- Renal impairment – Hepato renal syndrome type 1 and 2
- Hyponatremia
- Volume overload
- Hypotension
- Variceal hemorrhage
- Spontaneous bacterial Peritonitis
- Hepatic encephalopathy

6

- Definition – HRS 1 and 2
- Pathophysiology and Pathogenesis
- Diagnosis
- Prevention
- Treatment
  1. Albumin
  2. Vasopressors
  3. TIPS (Transjugular Intrahepatic Shunt)
  4. Renal Replacement Therapy
  5. Extracorporeal Liver Support Therapy
  6. Transplantation

7

Hepatorenal syndrome

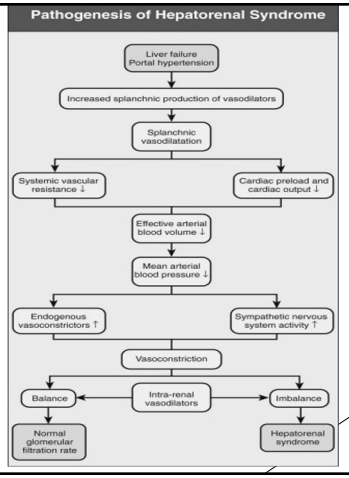
- Renal dysfunction in the absence of histologically obvious renal disease in patients with advanced liver disease.
- Hallmark:May occur in acute liver failure or acute severe alcoholic hepatitis, but usually observed in patients with advanced cirrhosis
- **Renal vasoconstriction-**--lowered renal perfusion/GFR---renal dysfunction
- **Splanchnic arteriolar vasodilation-**decreased systemic resistance and hypotension
- 50% of cirrhosis patients, harbinger of death

8

Hepato renal syndrome
Definition

- Potentially reversible functional renal failure that occurs in patients with acute or chronic liver disease, advanced hepatic failure, and portal hypertension

9



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Definition of Hepatorenal Syndrome Type 1 and Type 2
Type 1 Hepatorenal Syndrome
Doubling of serum creatinine >2.5 mg/dl (220 µmol/l) or a 50% reduction in 24-hr creatinine clearance to <20 ml/min <2 weeks
Frequently follows a precipitating event (e.g. infection)
Median survival without treatment: 2 weeks
Type 2 Hepatorenal Syndrome
Less rapid renal functional deterioration than type 1
Mainly presents with refractory ascites
Median survival without treatment: 4–6 months

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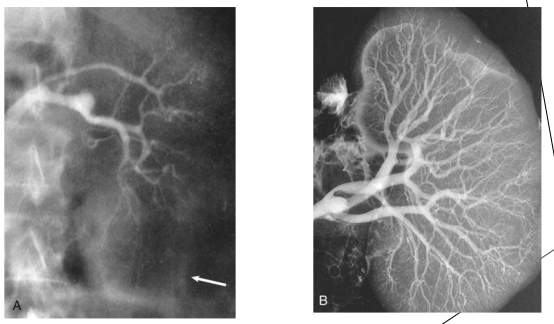
Renal angiogram



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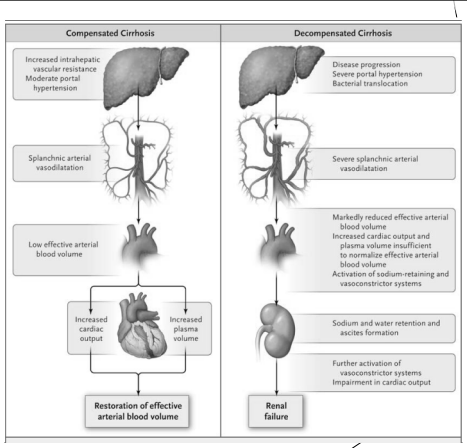

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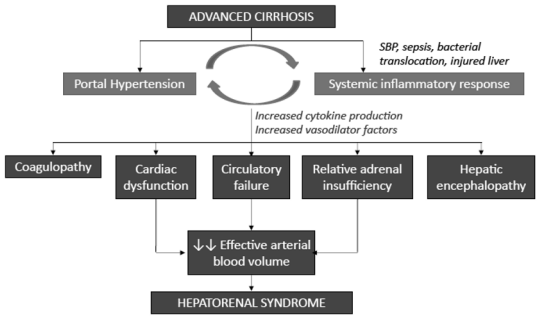

Durnad Et Al Am J Kidney Dis. 2016;67(2):318-328

14

Clinical features

- HRS 1:
- Progressive rise in creatinine
- Normal urine sediment
- No or minimal proteinuria(<500/d)
- Una<10
- Oliguria
- Clinical scenario:
- *Rapid decline of renal function, severe hepatic failure, relative adrenal insufficiency, hyponatremia, borderline to low BP*

15

Precipitating Factors:

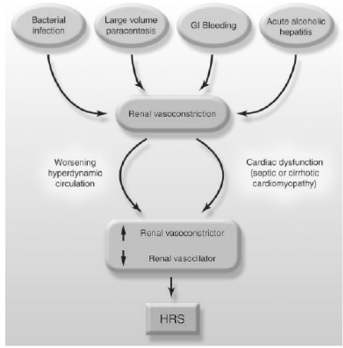

Figure 2. Role of a precipitating factor in HRS.

Clin J Am Soc Nephrol 1: 1066–1079, 2006

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Revised Diagnostic Criteria for Hepatorenal Syndrome

Cirrhosis with ascites
Serum creatinine > 1.5 mg/dl (133 μmol/l)
No improvement in serum creatinine (decrease to a level of 1.5 mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 gm/kg of body weight per day up to a maximum of 100 gm/day.
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasound

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AKI in setting of cirrhosis

- Abrupt rise in creatinine of atleast 0.3mg/dl or 1.5 fold increase from baseline associated with oliguria
- Prerenal:68%
- volume responsive:66%(Infection/Hypovolemia/vasodilators)
- Non volume responsive:34%:HRS I:25% HRS2:9%
- Intrarenal:32%
- Obstructive:<1%
- ***Garcia-Tsao G etal, Hepatology 2008:48***

18

Differential diagnosis

- Diagnosis of exclusion
- Glomerulonephritis
- Vasculitis
- Diabetic nephropathy
- Prerenal
- ATN:contrast/nsaid/aminoglycoside/hypotension/sepsis
- -rapid rise Cr
- -HRS itself can result ATN→low FeNa
- -Sediment:misleading
- Granular/Epithelial cell casts may be seen with raised Bilrubin→Bile Cast nephropathy
- ***Van SlamBock CM etal***
- ***Chicago, KI 2013 March 13***

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Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg bodyweight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc)
- No macroscopic signs of structural kidney injury*, defined as:
  - absence of proteinuria (>500 mg/day)
  - absence of microhaematuria (>50 RBCs per high power field)
  - normal findings on renal ultrasonography

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.
ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.

Angeli P, et al. Gut April 2015 Vol 64 No 4

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Prevention

- Salerno F, Navickis RJ etal
- Clin Gastroenterol Hepatol. 2013;11(2):123.
- In a meta-analysis of 4 RCTs (288 patients), ***albumin infusion prevented renal impairment and reduced mortality among patients with SBP.***
- Fernández J, Navasa M etal
- Gastroenterology. 2007;133(3):818.
- Norfloxacin @ 400mg/d to COL with ascitic fluid protein <1.5g/dl and CTP.9, Bil>3,Creat>1.2, BUN >20,Na<130
- Reduced the 1-year probability of developing SBP (7%vs 61%, P<.001) and HRS(28% vs 41%, P = .02), and improved the 3-month (94% vs 62%, P = .003) and the 1-year (60% vs 48%, P = .05) probability of survival compared with placebo.

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Pentoxifylline (PTX) on short term survival and progression to HRS in severe acute alcoholic hepatitis

Table 3. Mortality and Morbidity in the 2 Treatment Groups

	PTX-treated (n = 49)	Controls (n = 52)	*P*	RR (95% CI)
Mortality				
Hospital deaths [n (%)]	12 (24.5)	24 (46.1)	0.037	0.59 (0.35–0.97)
Deaths with HRS[a] [n (%)]	6 (50)	22 (91.7)	0.009	0.29 (0.13–0.65)
Days to death after randomization (mean ± SD)	29 ± 15.7	33.1 ± 27.3	0.63	
Morbidity				
Diarrhea [n (%)]	4 (8.2)	2 (3.8)	0.31	
Epigastric pain/vomiting [n (%)]	13 (26.5)	5 (9.6)	0.037	1.67 (1.14–2.43)
GI bleeding [n (%)]	6 (12.2)	8 (15.4)	0.43	
Skin rash [n (%)]	1 (2)	0 (0)	0.49	
Headache [n (%)]	4 (8.2)	2 (3.8)	0.31	
Dyspepsia [n (%)]	4 (8.2)	0 (0)	0.052	
Dizziness [n (%)]	4 (8.2)	1 (1.9)	0.16	
HRS after randomization	4 (8.2)	18 (34.6)	0.0015	0.32 (0.13–0.79)
HE after randomization [n (%)]	9 (18.4)	13 (25.0)	0.48	
Days to HE (mean ± SD)	12.8 (6.8)	12.5 (6.0)	0.91	
Withdrawals due to adverse effects [n (%)]	7 (14)	1 (2)	0.028	1.94 (1.37–2.73)

RR, relative risk; HRS, hepatorenal syndrome; GI, gastrointestinal; HE, hepatic encephalopathy.
[a]Includes both patients who were enrolled with and those who subsequently developed irreversible renal impairment.

AKRIVIADIS ET AL. GASTROENTEROLOGY Vol. 119, No. 6

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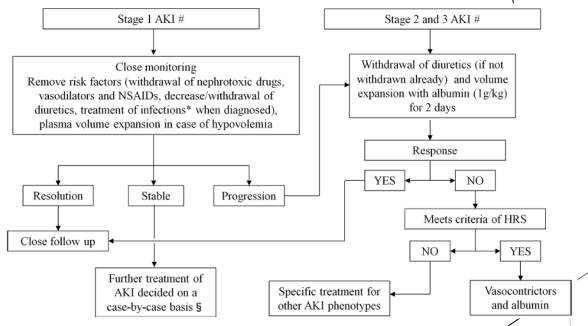

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*Terlipressin, IV 0.5-1 mg q4–6 h to start, doubling every 2 days up to a maximum of 12 mg/day if serum creatinine decreases < 25% after 2 days. Maximum duration of treatment 14 days

Vasopressin, 0.01 U/min to start and titrating the dose upwards to a maximum of 0.8 U/min to achieve an increase of MAP of at least 10 mmHg. Maximum duration of treatment 11 days

Norepinephrine, IV 0.5 mg/h to start, increasing dose by 0.25 to 0.5 mg/h every 4 hours up to maximum of 3 mg/h to achieve an increase of MAP of at least 10 mmHg. Maximum duration of treatment 15 days

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Randomized Studies of Terlipression or Norepinephrine in Patients with HRS

Investigators	Treatment	No. of patients*	Dose of treatment	Duration of treatment (days)	Reversal of HRS† complete/partial	Patients surviving 1/3/6 months	Patients surviving with OLT at 1/3/6 months
Solanki et al., 2003[19]	T	12 (0)	1mg/12 hr	<15	5‡	NA	NA
	P	12 (0)	-	<15	0	0	0
Sanyal et al, 2008[20]	T	56 (0)	1-2 mg/6 hr	6.3	19/NA‡	NA/NA/24	NA/NA/17
	P	56 (0)	-	5.8	7/NA	NA/NA/21	NA/NA/16
Neri et al., 2008[21]	T	26 (0)	1-0.5 mg/8 hr	<19	21/4‡	19/14/11‡	NA
	C	26 (0)	-	<19	5/11	11/5/4	NA
Martin-Llahl et al., 2008[22]	T	23 (6)	1-2 mg/4 hr	7 ± 5	9/1‡	NA/6/NA	NA
	C	23 (5)	-	8 ± 5	1/1	NA/4/NA	NA
Alessandria et al., 2007[26]	T	12 (7)	1-2 mg/4 hr	6 (2-11)	10/0	11/8/8	3/7/8
	N	10 (6)	0.1-0.7 µg/kg/min	5 (2-10)	7/0	8/7/7	7/7/7
Sharma et al., 2008[27]	T	20 (0)	0.5-2 mg/6 hr	7 (4-15)	10/4	11/NA/NA	NA
	N	20 (0)	0.5-3 mg/hr	6.5 (4-15)	10/3	11/NA/NA	NA

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Approach to treatment

- Ideally improvement of liver function
- After diagnosis, pts should be assessed for OLT
- HRS1 pts placed on urgent Tx list
- Bridge to OLT:pharmacotherapy, mechanical shunt,Extracorporeal liver therpay and renal replacement therapy
- Can prolong life for months in non OLT candidates

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Goals of therapy:

- Reversal of renal failure
- Increase MAP by 10-15.Direct correlation noted between rise of MAP and serum creatinine.
- **Velez etal, AJKD 2011 Dec-suggest goal directed therapy**
- Duration:2wks, extended if responsive
- Stop if not responding after 2 wks
- In responders:continue Midodrine indefinitely, shown to improve ascites

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TIPSS

- Parenchymal tract between branches of portal and hepatic vein
- Mortality rate 1-2%, morbidity rate 10%
- Complications: abd bleed, arrhythmia, shunt migration, thrombosis, hemolytic anemia, fever, infection, contrast reaction and nephrotoxicity
- Deterioration of liver function, encephalopathy

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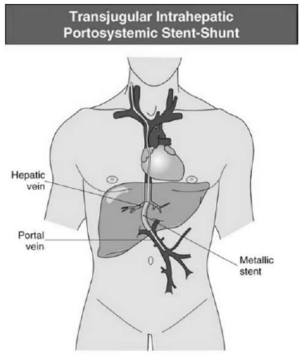
TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)



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Renal replacement therapy - Dialysis

- Remains controversial
- Should be used as a bridge to OLT
- Either int HD or CRRT have similar results

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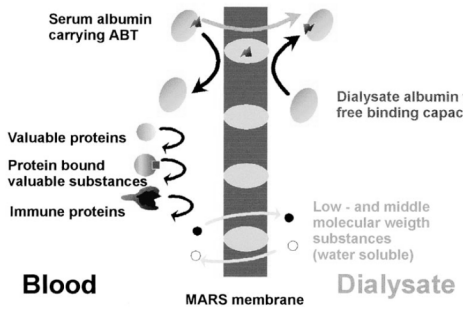

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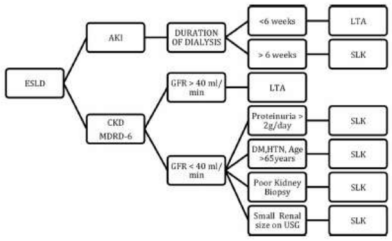
CONTROVERSY OF SLK VERSUS LIVER TRANSPLANTATION ALONE (LTA)



Vichin Puri and James Eason. *Curr Transpl Rep*. 2015.

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Hyponatremia correction

- Hyponatremia is water issue and not a salt issue
- Urine Osm is a useful tool – should be done serially
- As a general rule any osmolality of 300 indicated high ADH state
- Give a 1-2 litres of NS and recheck Urine Osm
- Cirrhosis is a high ADH state and has effective decreased intravascular volume
- Causing ramping of ADH
- Free water/fluid restriction
- Salt tablets
- 3% saline and Tolvaptan
- Use of conivaptan – is controversial but being used at MSTH

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Goal of Correction

No role of trying to correct to serum sodium of 120 currently	Increase should be slow 4-6 units over 24 hrs especially is chronic hyponatremia during acute situation with seizures / neuro issues	3% saline bolus is preferred compared to infusions	If there is a quick correction – try to keep to the goal of 16 mmol in 48 hrs
5% Dextrose and DDAVP are useful tools	Especially with correction in less than 110	Usually 120 and above correction can aggressive	Doesn't seem to carry much of risk of ODS

ODS seems to be an issue between serum sodium between 100 - 110 mmol/l

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“ Thank you for your time and patience – Appreciate the opportunity to present my thoughts - ? Questions ? ”

Thank you Dr Utpal Bhalala and SCCM San Antonio team for the opportunity, help and support with the presentation

Acknowledgements :

- Uptodate, feehaly and johnson textbook of clinical nephrology
- Dr Sudhir Thaduri – transplant Nephrology at university of Alabama
- Dr Chandan Takkar – Professor Nephrology UT – San Antonio

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Learning Assessment Questions

- Common Pathology finding on a renal biopsy of a patient with suspected HRS
  - A. Normal histological pattern
  - B. Presence of electron dense deposits along the glomerular basement membrane

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Learning Assessment Questions

- In patients with cirrhosis and severe symptomatic hyponatremia (serum Na <120), the treatment goal for correction to avoid osmotic demyelinating syndrome (ODS) is recommended to be
  - A. 4 to 6 mmol rise over 24 hours
  - B. 10 to 12 mmol rise over 24 hours

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The Liver and Acute Critical Illness

Brandi McCall, MSN, APRN, AGACNP-BC

1

Objectives

1. Describe sepsis-associated liver dysfunction (SALD)
2. Discuss strategies to mitigate SALD

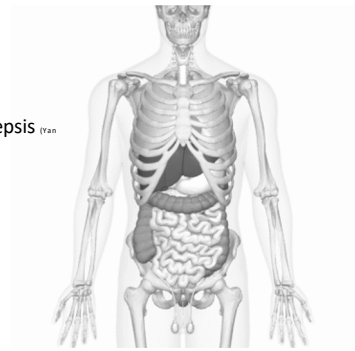
2

Incidence

- SALD: 39.9%
- Liver failure occurs in 8.5% of patients with sepsis (Yan et al., 2014)

Prognosis

- Mortality rates among patients with SALD or hepatic failure range from 54% to 68%
- Mortality rates of patients with cirrhosis and septic shock can be as high as 70% (Yan et al., 2014)



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The Liver as a Guardian

- 2nd line of defense in eliminating invading bacteria and toxins from the body (bacterial translocation)
- Kupffer cells, liver sinusoidal endothelial cells (LSECs), and stellate cells secrete:
  - Cytokines
  - Reactive oxygen species (ROS)
  - Nitric oxide

} **Hepatocyte Injury**

Bacteria enters bloodstream via failed GI barrier → Endothelial, Kupffer, hepatic stellate cells sound the alarm → Additional cells recruited to liver to protect from invading microorganisms → Inflammatory response → Eliminate antigens in bloodstream from gut lumen and liver → Bacterial clearance

4

Liver-Mediated Immunosuppression

Lipopolysaccharide (LPS) and TNF α

LPS is key inducer of inflammation in bacterial infection

Cytokines

- IL-6*
- IL-1β
- IL-12
- IL-18
- Reactive oxygen species
- Nitric oxide
- IFN-γ
- Endothelin-1

Acute Phase Proteins

- CRP
- A1A
- Fibrinogen
- Prothrombin
- Haptoglobin
- Hepcidin
- Ferritin

Ex. CRP flags bacteria for removal and mediates phagocytosis, but also induces ROS and cytokine release from macrophages

Hepatocyte and Endothelial Cell Damage

- Hepatocyte apoptosis (IFN-γ)
- Inhibition of protein C pathway
- ↑ coagulation factor activity
- Suppressed $CD4^+$ and $CD8^+$ T-cell responses

5

The Liver as a Target

- Liver injury occurs secondary to inflammation and hypoperfusion
- Pathology findings
  - Portal inflammation
  - Centrilobular necrosis
  - Lobular inflammation
  - Hepatocellular apoptosis
  - Cholangitis/cholangiolitis
  - Steatosis (Yan 2014)
- Neutrophils are recruited to the liver where they induce the secretion of more cytokines and chemokines, however this can ultimately injure hepatocytes and endothelial cells

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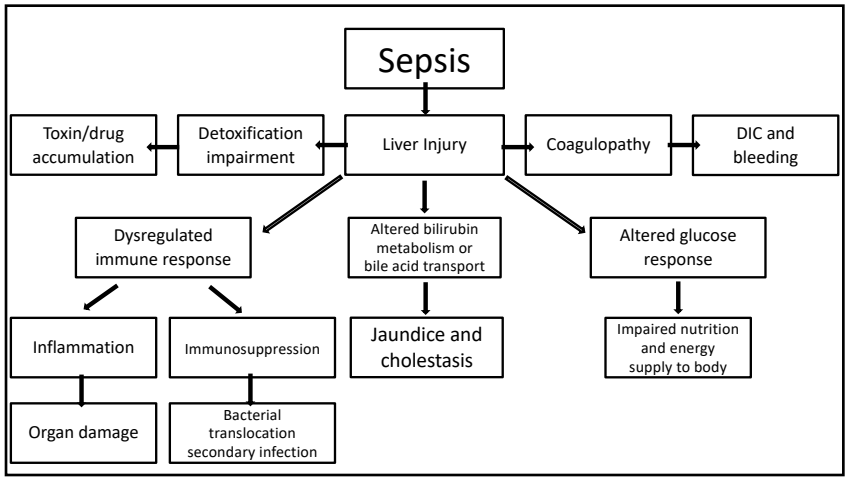

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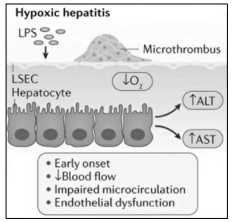
Hypoxic Hepatitis

- "Shock liver", "ischemic hepatitis", or "hypoxic liver injury"
- Liver has ↑ oxygen demand in sepsis
- Demand-delivery mismatch due to
  - ↓ oxygen concentration in blood
  - ↓ hepatic blood flow
  - ↓ oxygen carriers (anemic hypoxia)

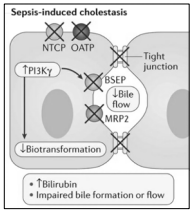


Clinical Criteria for Diagnosis
Underlying cardiac, respiratory, or circulatory failure
Acute elevation ALT/AST > 20x ULN
Exclusion of other causes

8

Sepsis-Induced Cholestasis

- LPS and proinflammatory cytokines impair bile formation and transport
- Proinflammatory cytokines/mediators downregulate hepatocellular transport systems → inflammation linked to hepatocellular cholestasis
- Bilirubin >20 mg/dL indicates cholestatic liver dysfunction
- ↑ ALT, AST, ALP
- Ultrasound, CT, MRI (MRCP) can exclude other causes



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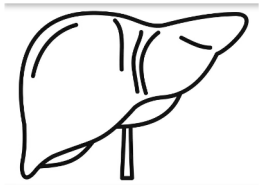
Sequalae of Cholestasis



- Increased serum bile acid concentrations
- Impaired glucose and lipid metabolism
- Suppression of immune response
- Vasodilation
- Impaired renal function
- Increased oxidative stress
- Increased cell membrane permeability

10

Coagulopathy

- Primary cause of coagulopathy in sepsis is microvascular injury secondary to an imbalance of fibrinolysis and coagulation (Woznica et al., 2018)
- Endothelial injury occurs and is characterized by:
  - Loss of vascular tone
  - Capillary obstruction by platelet or fibrin clots
  - Degradation of heparan sulfate leading to a pro-coagulant state
- Increase in APPs leads to inhibition of the protein C pathway
  - Increase of coagulation factor activity (Woznica et al., 2018)

Clinical Findings
Prolonged PT/aPTT
↑ INR > 1.5
↓ Fibrinogen

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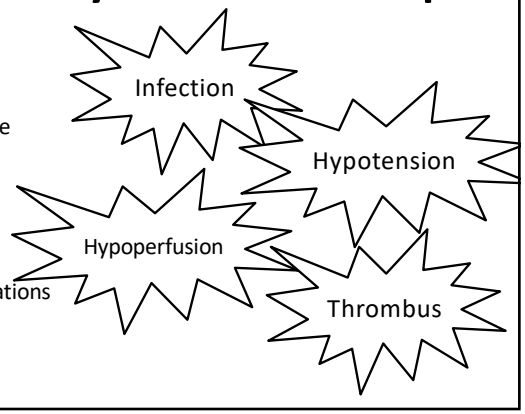
Preventing Liver Dysfunction in Sepsis

- Treat the underlying cause
- Early antibiotic therapy
- Source control
- Avoid hepatotoxic medications



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Fluid Resuscitation

- Balanced crystalloids or saline (Rhodes et al., 2016)
- No strong evidence to support albumin as 1st choice (Simonetto et al., 2019)
- May use albumin if patient requires large amount of crystalloid replacement
- SAFE study – albumin is safe and equally effective (SAFE Study Investigators, 2006)
- ALBIOS trial – albumin + crystalloids did not improve survival (Caironi et al., 2014)
- Albumin is beneficial in patient with cirrhosis and SBP (Simonetto et al., 2019)

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Vasopressors

- Norepinephrine 1st line
  - ↑ venous return
  - ↑ cardiac preload
- Vasopressin
  - Use in conjunction with norepinephrine
  - Mobilization of splanchnic blood pool
- Epinephrine
  - Use with caution in patients with cirrhosis
- Dobutamine
  - Cirrhotics typically have high CO, little benefit from dobutamine
- Angiotensin II
  - ↑↑ vasopressor requirement and ↓ albumin are (-) predictors of response (Khanna et al., 2017)

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Supporting the Patient with Liver Injury

- Early enteral nutrition for hemodynamically stable patients
  - ↓ r/o cholestatic liver dysfunction, jaundice, and formation of sludge in gallbladder
- Glucose concentration monitoring and adequate glucose supply
  - Utilize dextrose infusion as needed
- Correct coagulopathy if bleeding or prior to invasive procedure
  - Vitamin K administration, FFP, cryoprecipitate
- Corticosteroids
  - May result in faster shock resolution and lower vasopressor requirements
  - In patients with liver disease, associated with increase in shock recurrence and GI bleeding (Arabi et al., 2010)

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Special Considerations

- High volume plasma exchange
  - Removal of inflammatory cytokines, bacterial toxins
  - Not enough evidence (Rimmer et al., 2014)
- Prophylactic simvastatin
  - May prevent endotoxemia-induced liver injury, reduce liver inflammation, and prevent microvascular dysfunction
  - Not enough RCT; most studies done in mice (Eladwy et al., 2020) (Bosch et al., 2020) (Nezic et al., 2019)
- Ursodeoxycholic acid
  - Not enough evidence (Nesseler et al., 2012)

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Conclusion

- Liver functions to clear bacteria during sepsis, however the same cells that clear bacteria can result in liver injury
- Manifestations of liver injury: hypoxic hepatitis, sepsis-induced cholestasis, and coagulopathy
- Focus on liver injury prevention by avoiding hepatotoxic medications, optimizing liver perfusion, and treating the underlying infection

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Question 1

Which of the following may indicate sepsis-associated liver dysfunction?

A. Hyperbilirubinemia with cholestasis
B. Serum aminotransferase levels >20 ULN
C. Impaired glucose and lipid metabolism
D. All of the above

Correct Answer: D
Rationale: These are all signs that can develop in response to impaired hepatic synthetic function in the setting of sepsis.

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Question 2

2. Strategies to prevent sepsis-associated liver dysfunction include fluid resuscitation and vasopressor use.

A. True
B. False

Correct Answer: A
Rationale: There is no specific liver-targeted therapy for hypoxic hepatitis and thus prevention and treatment are primarily supportive. To prevent hypoxic hepatitis, maintaining hepatic perfusion is key, and this can be achieved by the use of fluid resuscitation and vasopressors.

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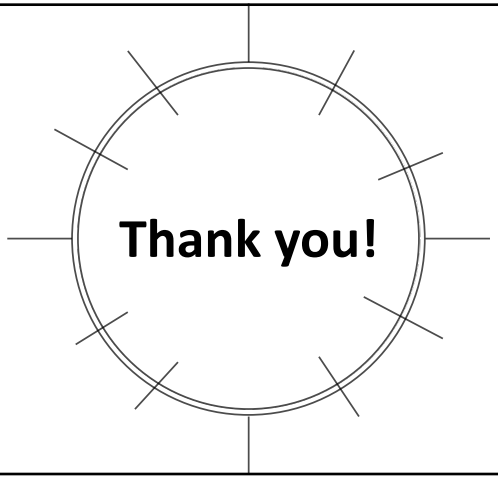

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21

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Yan, J., Li, S., & Li, S. (2014). The role of the liver in sepsis. International reviews of immunology, 33(6), 498-510.

22

Up in Smoke: Managing E-Cigarette or Vaping Associated Lung Injury (EVALI) in the ICU

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1

Objectives

1. Explain the pathophysiology of EVALI
2. Describe the diagnosis of EVALI
3. Discuss treatment strategies of EVALI

2

Case Presentation

April, 2020

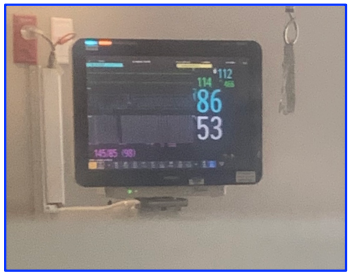
- 30 year old with no previous history complains of 6 days of:

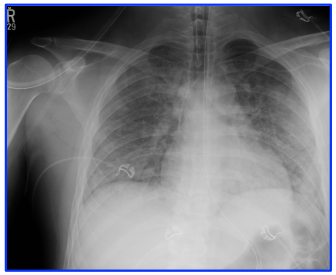
  headache congestion cough dyspnea abdominal pain body aches chills fevers

- No sick contacts. Recently did some shopping at HEB.
- Went to a community hospital and transferred to the ICU at University Hospital for higher level of care due high O2 requirements.

3

Arrival to the ICU





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Labs

- WBC: 19.79 k/dl
- Lymphs: 0.32 (0.9-3.6)
- Lactic acid 1.3
- ALT 100, AST 67, Alk Phos 159

5

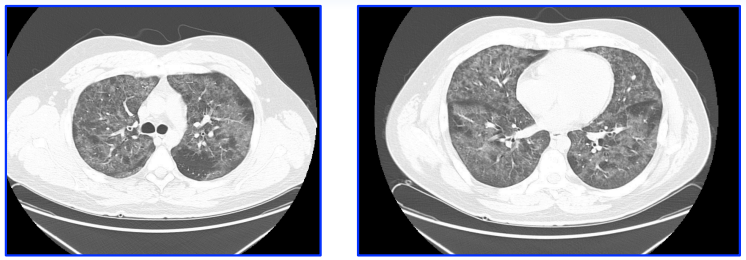
Labs

- Ferritin 499
- LDH: 583
- CRP: 242
- D dimer: 961
- BNP: 29
- Troponin: neg

DOPPLER: Positive
Occlusive thrombosis
of the left brachial vein

COVID 19 pending

6



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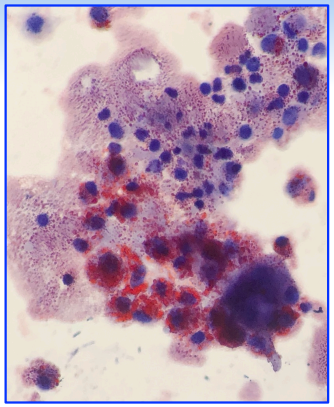
BAL:

Lipid laden

macrophages

(Oil-Red-O stain)



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What therapy to initiate?

a) Azithromycin + ceftriaxone
b) Corticosteroids IV
c) Azithromycin + ceftriaxone + IV corticosteroids
d) None of the above

9

COVID19 test: **negative** THC: **positive**

Next steps?

a) Repeat nasal PCR COVID19 test
b) Repeat nasal PCR COVID19 test + IV steroids
c) Bronch + BAL for Lipid laden macrophages and resend COVID19 test using BAL + IV steroids
d) Treat with IV steroids and DC isolation precautions
e) None of the above

10

Epidemiology

- In 2018, 8.1 million US adults were current e-cigarette users
- First case of EVALI was reported in August 2019
- 2807 hospitalizations in the US as of February 2020
- 68 deaths in the US February 2020

Villarroel M, et al. NCHS Data Brief. 2020 Apr;(365):1-8

11

Pathophysiology

- Incompletely understood
- Caused possibly by nicotine products, tetrahydrocannabinol (THC), cannabidiol (CBD) and vitamin E, propylene glycol, other additives
- E-cigarette have been linked with to:

interstitial lung disease **lipoid pneumonia**
eosinophilic pneumonia **pneumothorax**
diffuse alveolar hemorrhage **asthma exacerbations**
organizing pneumonia **hypersensitivity pneumonitis**

Fryman et al. Chest. 2020 Mar;157(3):e63-e68.

12

Clinical presentation

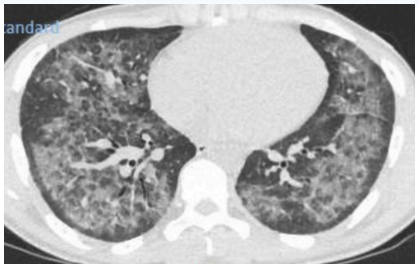
- Variable
- Minimal respiratory symptoms → ARDS
- Days to months after exposure
- May coincide with a change in the device or substance used

Werner AK, et al. N Engl J Med. 2020 Apr 23;382(17):1589-1598.

13

Imaging

CT chest bilateral ground-glass opacities (GGO), with sparing of the lung periphery, and centrilobular ground-glass nodules

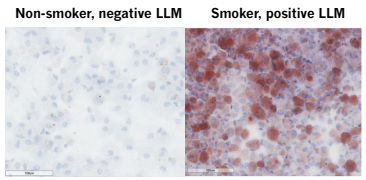


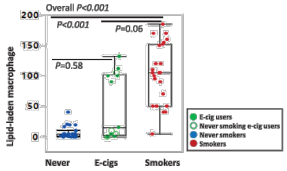
Fryman et al. Chest. 2020 Mar;157(3):e63-e68.

14

Diagnosis (in COVID19 times)

- EVALI remains a diagnosis of exclusion and thorough **history taking** is extremely important. symptoms and clinical manifestations overlap with infectious respiratory diseases, including COVID-19.
- Lipid laden macrophages (oil-red-O stain) are **not exclusive** of EVALI.





Shields P, et al. EBioMedicine. 2020 Sep 9;60:102982.

15

Treatment

- Limited data on treatment
- The majority of patients (particularly in severe disease) received corticosteroids (varying doses).
  - Response is ~ 50 - 80%.
  - May be warranted in severely ill patients when considered safe and feasible, after ruling out life-threatening infections
  - Dosing: methylprednisolone 0.5 to 1 mg/kg per day and tapering over 5 to 10 days, shorter courses are favored

Layden J, et al. N Engl J Med. 2020 Mar 5;382(10):903-916.
Seigel DA et al. MMWR Morb Mortal Wklz Rep. 2019;68(919):2.

16

Conclusions

1. The diagnosis of EVALI relies on an adequate history, clinical awareness and a systematic evaluation of other potential causes.
2. The pathophysiology of EVALI is incompletely understood, but key components of the e-cigarettes have been linked to this disease.
3. Corticosteroids appear to be beneficial in EVALI and should be considered in patients with severe disease

17

ECPR

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1

No Disclosures to Report

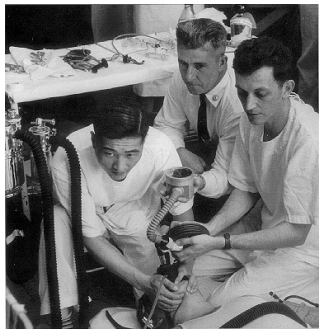
2

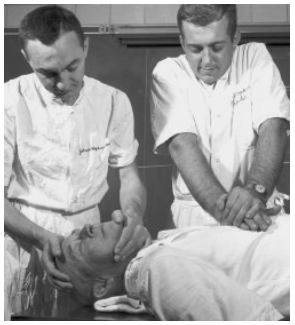
Learning Objectives

- Discuss cardiac arrest and cardiopulmonary resuscitation in children
- Review current evidence for the use of extracorporeal life support during cardiopulmonary resuscitation (ECPR)
- Discuss the concept of high-quality ECPR
- Describe the process of developing an institutional program for high-quality ECPR
- Discuss the future directions of ECPR

3

1950s





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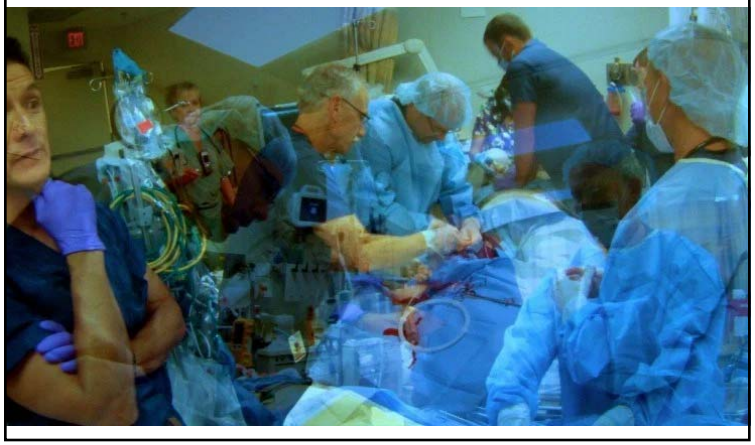

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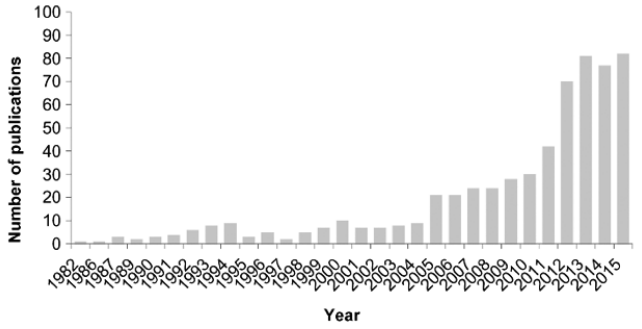

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Why ECPR?

- Failed conventional ACLS
  - CCPR ~25% normal CO
- Pre-morbid status good
- Reversible cause
  - A bridge to definitive treatment

7

ECLS

- *Extracorporeal life support* (ECLS) is an umbrella term for extracorporeal modalities that maintain function of an organ or organ system.
- ECLS is most commonly used as prolonged extracorporeal cardiopulmonary support in patients with cardiac or respiratory failure.

8

ECMO

- *Extracorporeal membrane oxygenation* (ECMO) is a modified form of cardiopulmonary bypass that can be used to deliver oxygen to tissues, eliminate carbon dioxide, and support cardiopulmonary function.

9

CPR

- *Cardiopulmonary resuscitation* (CPR) is a series of lifesaving actions that improve the chance of survival following cardiac arrest.
- The American Heart Association (AHA) 2015 guidelines place emphasis on high-quality chest compressions over artificial ventilation, using the universal sequence C-A-B (compressions, airway, breathing)

10

ECPR

- *Extracorporeal cardiopulmonary resuscitation* (ECPR) is defined as initiation of extracorporeal support during conventional CPR or when repetitive arrest events occur without ROSC for more than 20 minutes

11

The evidence

12

Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis

- Chen et al. 2008
- Taipei
- N= 172
- Prospective observational study
  - Conventional CPR vs ECPR
- ECPR team on call
- Propensity-matching

13

Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis

- Included
  - Cardiac origin (adjudicated)
  - Age 18-75
  - CPR >10minutes
- Excluded
  - Past brain damage
  - Terminal malignancy
  - DNR

14

Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis

- Decision to implement ECPR at discretion of attending MD

15

Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis

- Results
  - ECPR group highly selected
    - Younger
    - More men
    - Less renal disease
    - Less cancer
    - More pressors pre arrest
    - More daytime arrests

16

Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis

- Results
  - ECPR group had more
    - ROSC 93% vs 55%
    - Interventions 61% vs 12%
    - Survival with good neurological function

	Extracorporeal CPR group	Conventional CPR group
N	59	113
CPC status at discharge		
1 or 2*, n (%)	14 (23·7)	12 (10·6)
Odds ratio (95% CI, p value)	2·6 (95% CI 1·1–6·7, p=0·02*)	2·6 (95% CI 1·1–6·7, p=0·02*)
CPC status at 1 year		
1 or 2, n (%)	9 (15·3)	10 (8·9)
Odds ratio (95% CI, p value)	1·9 (95% CI 0·6–5·4, p=0·20)	1·9 (95% CI 0·6–5·4, p=0·20)

www.thelancet.com Vol 372 August 16, 2008

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Propensity-matched

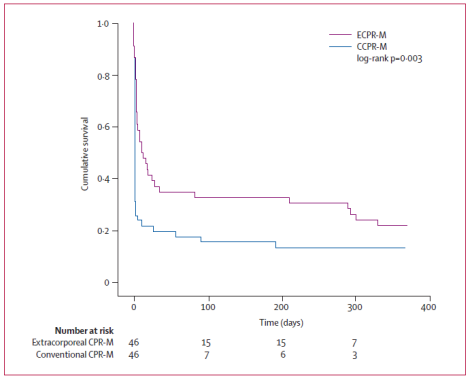

Figure 3: Kaplan-Meier plot of the survival curves in the extracorporeal CPR-M and conventional CPR-M groups for 1 year

- Improved survival out to one year
- No difference in survival with good neurological function

www.thelancet.com Vol 372 August 16, 2008

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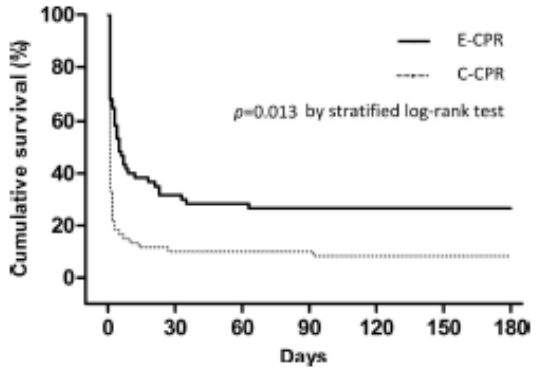
Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation*

- Shin et al. 2011
- Seoul, Korea
- N= 406 (85 ECPR, 321 CCPR)
- Witnessed in-hospital cardiac arrest with CPR >10 minutes
- Included some non-cardiac causes
- Aged 18-80
- No previous neuro injury, malignancy
- No TTM, no CPR quality measured
- Propensity-matched

Crit Care Med 2011 Vol. 39, No. 1

19

Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation*



Crit Care Med 2011 Vol. 39, No. 1

20

Evidence in children

- To date, the pediatric ECPR literature is heavily influenced by selection bias of ECPR candidates.
- Children who receive ECPR for cardiac arrest have survival to hospital discharge rates ranging from 33% to 42% in general ICU patients and from 23% to 55% in cardiac ICU patients.

21

Evidence in children

- Overall, children with cardiac diagnosis have better ECPR outcomes as compared to those with non-cardiac diagnosis

22

Evidence in children

- A study utilizing the get with the guideline - resuscitation (GWTG-R) registry showed improved survival to hospital discharge with the use of ECPR in patients with surgical cardiac diagnoses

23

Evidence in children

- In a study of GWTG-R IHCA database, among the children who were treated with at least 10 minutes of in-hospital CPR, those who received ECPR had greater odds of survival to discharge and favorable neurological outcome than those who received conventional CPR

24

Evidence in children

- AHA 2015 guidelines on CPR recommend "ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment"

25

Evidence in children

- The current guidelines do not support use of ECPR for OHCA in children.

26

Factors determining ECPR Outcomes

- Factors determining ECPR outcomes overlap significantly with those related to outcomes following conventional CPR.
- Additional ECMO related factors such as ICH play a significant role in determining outcomes.

27

Factors determining ECPR Outcomes

- Factors determining ECPR outcomes are
- Pre-arrest factors
- Intra-arrest factors
- Post-arrest factors

28

Factors determining ECPR Outcomes

- Preexisting cardiac disease
- Pre-ECMO arterial blood pH higher than 6.8
- Children with cardiac disease who receive ECPR
  - managed in an intensive care setting after cardiac surgery by a team which is well-trained and experienced in resuscitation and surgical support for cannulation.
- In the ICU, patient deterioration is likely detected quickly and CPR and ECMO can be deployed promptly.
- Monitored environments versus less-monitored environments.
- Respiratory etiology of cardiac arrest with pre-existing hypoxemia.

29

Factors determining ECPR Outcomes

- Important intra-arrest factors -
  - Quality of CPR before and during ECMO cannulation
  - Adequacy of perfusion and the flow of the ECMO circuit.
  - Duration of CPR prior to going on ECMO
- Data are conflicting regarding the impact of CPR duration prior to ECMO cannulation and outcomes following ECPR. As long as the quality of CPR is maintained at high standards, a successful outcome could be expected even after a long duration of CPR prior to ECMO cannulation.

30

Factors determining ECPR Outcomes

- Post-arrest factors include -
  - ECMO complications such as
    - Renal failure that requires renal replacement therapy
    - Need for CPR while on ECMO support
    - Pulmonary hemorrhage
  - Other post-arrest factors that determine outcomes after ECPR are similar to the factors that determine outcomes after conventional CPR
    - Temperature
    - Blood pressure
    - Blood glucose.
- The advantage of ECMO support in patients with cardiac arrest is the ease of tightly regulating post-arrest parameters such as blood pressure and temperature.

31

QCPR

- Quality of care provided during resuscitation frequently does not meet quality of care standards, despite evidence-based CPR guidelines, extensive provider training, and provider credentialing in CPR.

Sutton RM et al, Emerg Med Clin N Am 2012

10/11/20 32

32

QCPR deficiencies

- During adult OHCA CPR, 33% of CC too shallow and delivered only 48% of the time during the arrest
- Similar deficiencies during adult in-hospital arrest care (23% of CC with incorrect rates; 36% of CC too shallow).

33

QCPR Deficiencies

- Ventilation rate exceeds AHA guideline

  Aufderheide TP et al, Crit Care Med 2004
- Laboratory and clinical data suggest that over-ventilation is common and associated with poor cardiac output

  Aufderheide TP et al, Circ 2004
-

34

Successful CPR

- The foundation for successful CPR –
  - **High-quality CPR**
  - Attempted **defibrillation within minutes** of collapse for VF/pulseless VT
  - **Early initiation of CPR**

35

AHA Mantra

- During CPR –
  - Push **Hard** (>5cm)
  - Push **Fast** (at least 100/min)
  - **Minimize interruptions**
  - Allow full chest **recoil**

36

Who should be offered ECPR?

37

ECPR candidate

- In all honesty any critically ill patient who is a potential ECMO candidate could be an ECPR candidate
  - Patients with
    - potentially reversible cardiopulmonary disease
    - preferably with single organ dysfunction and preserved neurologic function
    - no risk of bleeding
- The major difference between ECMO candidacy versus ECPR candidacy are cardiac arrest and CPR-specific factors such as,
  - Witnessed versus Un-witnessed arrest
  - Known versus unknown downtime
  - Quality of CPR
  - Duration of CPR
- The cases which should not be offered ECPR
  - OHCA
  - Significant co-morbidities
  - Trauma, Post-surgical arrest
  - Prolonged CPR before decision to ECPR
  - Futility

38

Who should perform ECPR?

39

How to establish an ECPR program?

- Review factors such as cost-effectiveness and in-house availability of ECMO perfusion and surgical teams, especially at night and on weekends.
- Establish a multi-disciplinary ECPR committee consisting of intensivists, surgeons, perfusionists, nurses and CPR committee members.
- develop multi-disciplinary consultation service

40

How to run a smooth ECPR?

41

How to prepare/train the team on high-quality ECPR?

42

An Extracorporeal Membrane Oxygenation Cannulation Curriculum Featuring a Novel Integrated Skills Trainer Leads to Improved Performance Among Pediatric Cardiac Surgery Trainees

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Sitaram Emani, MD;
Francis Fynn-Thompson, MD;
Ravi R. Thiagarajan, MBBS, MPH;
Annette Imprescia, RN;
Gavin Hayes, BS;
Peter Weinstock, MD, PhD

Introduction: American Heart Association guidelines recommend timely extracorporeal membrane oxygenation (ECMO) cannulation during cardiopulmonary resuscitation for pediatric cardiac arrest refractory to conventional resuscitation. Traditional cannulation training relies on the apprenticeship model. We hypothesized that a simulation-based ECMO cannulation curriculum featuring a novel integrated skills trainer would improve ECMO cannulation during cardiopulmonary resuscitation performance by cardiothoracic surgery trainees.

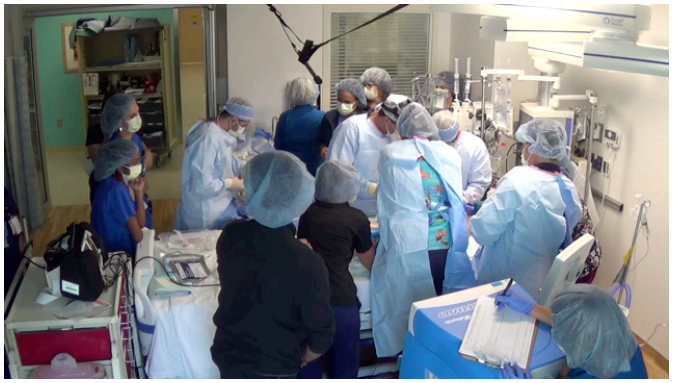
Methods: An embedded surgical neck cannulation trainer, designed in collaboration with expert surgeons, formed the focus for a simulation-based cannulation curriculum. The course included a didactic presentation and 2 neck cannulations during cardiopulmonary resuscitation with video-assisted expert feedback with a further cannulation at 3 months. Primary outcome was time to cannulation on the trainer. Secondary outcomes were performance on a validated Global Rating Scale (GRS) of surgical technique and a novel Composite ECMO Cannulation Score (CECS).

Results: Ten cardiothoracic surgery trainees participated. The trainer was rated as authentic, and sessions was rated as highly useful. Median time to cannulation decreased between cannulation 1 and 2 (15 minutes 24 seconds vs. 12 minutes 15 seconds, P = 0.002). Improvement was sustained at 3 months (13 minutes 36 seconds, P = 0.157 vs. attempt 2). Likewise, GRS increased significantly at attempt 2 versus 1 (77% vs. 62%, P = 0.003) as did CECS (88% vs. 52%, P = 0.002). No deterioration in GRS or CECS was measured at 3 months.

Conclusions: Cardiothoracic surgery trainees found a contextualized ECMO cannulation during cardiopulmonary resuscitation cannulation curriculum to be highly useful and demonstrated sustained improvement in time to cannulation, CECS, and GRS. Further work will focus on determining the clinical impact of this training and defining the optimal interval and number of training sessions.

(*Sim Healthcare* 8:221–228, 2013)

43



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Summary

- ECPR is feasible for patients with refractory cardiac arrest
  - …but it's not easy
- Best available data suggests a possible benefit over conventional CPR
  - …in a highly select population with many potential uncontrolled confounders
- Data from ongoing RCTs will hopefully clarify the true effect

45

Thank You!

46

PREGNANT IN THE ICU: PEARLS FOR THE INTENSIVIST

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MATERNAL FETAL MEDICINE SPECIALIST
ASSOCIATE PROFESSOR BAYLOR COLLEGE OF MEDICINE

1

DISCLOSURES

- ABOG Examiner for Specialty Exam
- Editorial Board Member for *Obstetrics & Gynecology*
- Varda5, LLC, healthcare innovation and education
- Body Wisdom S.A., LLC, health and wellness

2

3

LEARNING OBJECTIVES

- 1. Understand the most common reasons why pregnant women are admitted to the ICU.
- 2. Learn pearls for managing the top critical care issues in pregnancy.

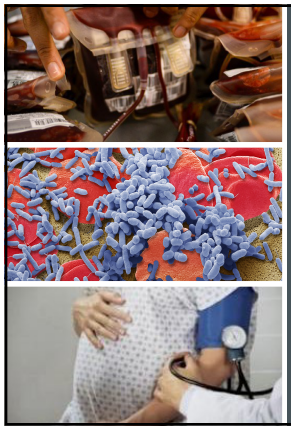
4

PREGNANCY PHYSIOLOGY TO REMEMBER

- Expansion in blood volume
- An increase in minute ventilation
- An increased risk of thrombosis
- Expanding uterus
- Second patient

"Optimizing health of mother will optimize health of fetus."

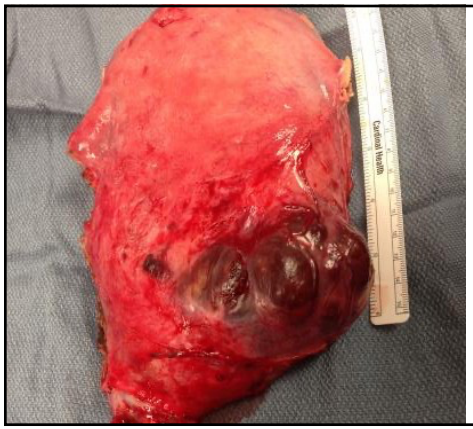
5



TOP REASONS FOR ADMISSION TO ICU

- Obstetric hemorrhage
- Preeclampsia
- Sepsis

6



OBSTETRIC HEMORRHAGE

- #1 leading cause of death from pregnancy world-wide
- Postpartum hemorrhage is the most common cause
  - 4-6% of all pregnancies
  - Uterine atony
  - > 50% of maternal deaths – first 24 hours of delivery
- Morbidly adherent placenta
- Most common reason for admission to ICU

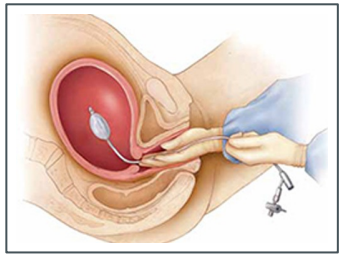
7

PEARLS - BLEEDING, DIC AND OBSTETRICS

- Massive transfusion protocol
- Limit crystalloids
- Permissive hypotension (in non-pregnant)
- Administer FFP early and balanced ratio of blood products
- Goal-directed correction of coagulopathy remains investigational

8

PEARLS - BLEEDING, DIC AND OBSTETRICS



- Hemostatic agents (e.g. TXA, rFVIIa)
- Intrauterine balloon
- Laparotomy with uterine compression sutures and hysterectomy
- Selective arterial embolization

9

PEARLS - BLEEDING, DIC AND OBSTETRICS

- All units should have identification of high risk for hemorrhage on admission
- Recommend all ICU/L&D staff participate in PPH simulation
- Hemorrhage carts, MTP should be available in ICU

10

11

PREECLAMPSIA/ECLAMPSIA AND ICU

- New onset BP elevations in pregnancy: ≥ 140/90 four hours apart with end organ dysfunction
- Severe disease: sustained BP ≥ 160/110, CNS symptoms, liver or renal dysfunction, thrombocytopenia, oliguria
- Chronic hypertension with superimposed preeclampsia
- Eclampsia: New onset seizures in setting of gestational hypertension/preeclampsia

ACOG PB 767 2019

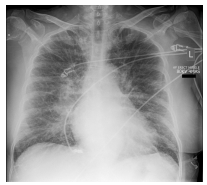
12

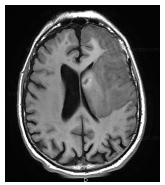
PREECLAMPSIA/ECLAMPSIA AND ICU

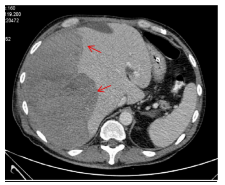
- Hypertensive emergency protocol: Nifedipine, labetalol, hydralazine
  - Must be initiated within 30 minutes of recognition of elevated BPs
  - Oral nifedipine 20 mg q 15 min reduces BP more rapidly than IV labetalol[1]
- Second-line agents: Nicardipine or esmolol by infusion pump[2,3]
- Caution: Nitroprusside[4]

[1]Zuleen. Eur J Obstet Gynecol 2019
[2]Vadhera. Am J Perinatology 2009
[3]Nij Bijvank SW. Obstet Gyn Surv 2010
[4]NIH Publication No. 04-5230 2004

13





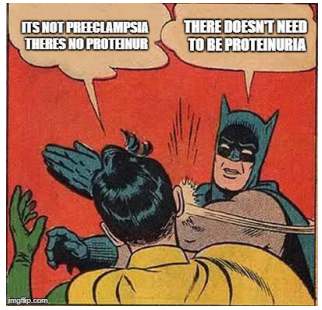


PREECLAMPSIA/ECLAMPSIA AND ICU

- Severe features generally indication for delivery, but must stabilize mother first
- Caution: Pulmonary edema, stroke, liver capsule rupture

https://www.sciencesource.com/archive/Hemorrhagic-Stroke--MRI-SS2870547.html
https://radiopaedia.org/cases/acute-pulmonary-oedema-57?lang=us
https://www.researchgate.net/figure/Abdominal-CT-scan-reveals-hepatic-subcapsular-hematoma-with-dimensions-of-19-178-69_fig2_276458257

14



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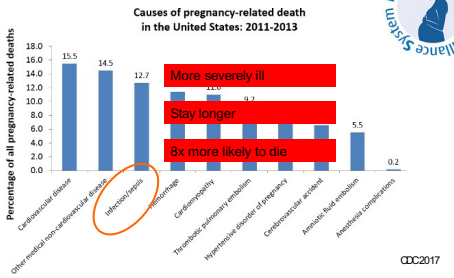
PREGNANCY ASSOCIATED SEPSIS



16

PREGNANCY ASSOCIATED SEPSIS

- Responsible for 75,000 maternal deaths/year (globally)[1]
- Rare event: 0.3-0.6% of sepsis population[2]
  - 1/1,000 births à half progressing to severe sepsis, and 3-4% with septic shock (U.S.)

[1]WHO 2014
[2]Barton JR Obstet Gynecol 2012

17

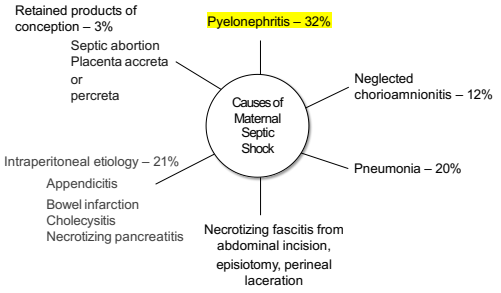
PREGNANCY ASSOCIATED SEPSIS

- For every maternal sepsis death, there is approximately 50 women who have life-threatening morbidity from sepsis (US)[1]
- Both pregnancy-associated severe sepsis and sepsis-related maternal mortality appears to be increasing[2,3]

[1]Barton JR Obstet Gynecol 2012
[2]WHO 2014
[3]Oud L J Clin Med Res 2015

18

Sepsis/Septic Shock in Pregnancy



Barton JR Obstet Gynecol 2012
Synder CC J Mat Fet Neonat Med 2013

19

ORGANISMS ISOLATED FROM EACH STAGE OF PREGNANCY

Table 1. Organisms isolated at each stage of pregnancy

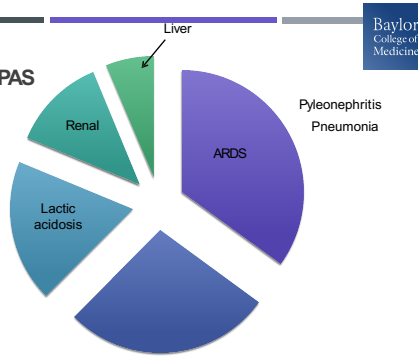
Organism	Antenatal	Intrapartum	Postnatal	All isolates
Escherichia coli	26	22	55	103
Group B *Streptococcus*	2	43	12	57
Anaerobes	4	8	11	23
Staphylococcus aureus	4	5	12	21
Enterococcus faecalis	2	5	6	13
Group A *Streptococcus*	0	2	10	12
Streptococcus milleri	1	4	4	9
Klebsiella pneumonia	1	2	2	5
Proteus mirabilis	0	3	2	5
Haemophilus influenzae	3	1	0	4
Streptococcus pneumoniae	1	0	3	4
Morganella morganii	0	0	3	3
Group C *Streptococcus*	0	1	2	3
Enterobacter species	1	0	2	3
Group G *Streptococcus*	0	0	2	2
Listeria monocytogenes	1	1	0	2
Moraxella species	0	0	2	2
Staphylococcus saprophyticus	0	1	1	2
Acinetobacter baumffi	1	0	1	2
Streptococcus gallolyticus	0	1	0	1
Total	47	99	130	276

- Antenatal
  - *E. coli*
- Intrapartum
  - *E. Coli*
  - *Group B streptococcus*
- Postpartum
  - *E. coli*
  - *Group B streptococcus*
  - *Staph aureus*
  - *Anaerobes*
  - *Group A streptococcus*

Knowles SJ. BJOG 2014

20

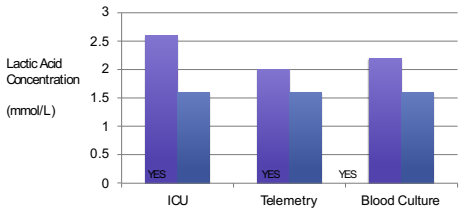
ORGAN INJURY IN PAS



Synder CCJMat Fet Neonat Med 2013

21

- N=850 pregnant or postpartum women
  - 159 had lactic acid measurements
  - Lactic acid positively associated with ICU or telemetry unit admission, aOR per 1 mmol/L increase in lactic acid 2.34 (95% CI 1.33-4.12)



Albright CMAm J Perinat 2014

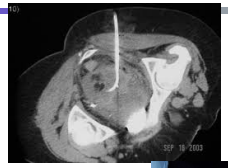
22

SEPSIS AND PREGNANCY – SEPSIS BUNDLE

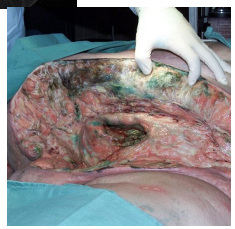
- Appropriate antibiotic therapy
- IVFs: crystalloids; no good evidence on how much
  - 20cc/kg bolus due to risk for pulmonary edema
- Vasopressors: norepinephrine, epinephrine

23

SOURCE CONTROL



- rapid diagnosis of the specific site of infection
- identification of a focus of infection amenable to source control measures
- Minimal target 6-12 hours after diagnosis



24

COVID-19 AND PREGNANCY

- Less likely to manifest fever and myalgia.
- Older age, obesity, chronic hypertension, and pregestational diabetes associated with severe COVID-19 in pregnancy.
- Risk of preterm birth 6% (c/w pregnant without COVID, OR 3.01, 95%CI 1.16-7.85).
- Compared with non-pregnant, pregnant women 60% more likely to require admission to ICU and have nearly double the risk of invasive ventilation.

Allotey, et al BMJ 2020

25

26

OTHER COMMON ICU COMPLICATIONS IN PREGNANCY

- Respiratory failure
- Renal failure
- Maternal cardiac arrest

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RESPIRATORY FAILURE

- Causes
  - Infections
  - Pneumonia
  - Preeclampsia
  - Asthma exacerbation
- Physiologic considerations
  - Decreased FRC
  - Increase minute ventilation

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INDICATIONS FOR INTUBATION

- No specific ABG value
  - Normal pCO_2 values 28-32 mmHg due to mild respiratory alkalosis
  - Normal HCO_3 22 mmol/L
- Elevate head of bed (recruit airways) and give supplemental oxygen

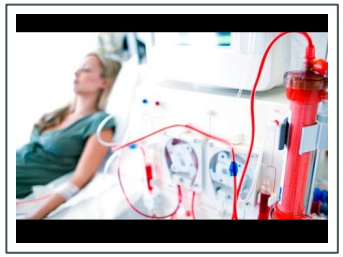
29

INDICATIONS FOR INTUBATION

- Unable to oxygenate patient
- Unable to ventilate
- Unable to maintain work of breathing
- Unable to maintain airway

30

RENAL FAILURE



- Causes of renal failure
  - Sepsis
  - Preeclampsia
  - Hemorrhage
- Indications for renal dialysis
  - Same as nonpregnant patient
  - Generally started earlier, when GFR < 20 ml/min/m^2

31

OBLS
Obstetric
Life Support

MATERNAL CARDIAC ARREST

- Common causes: "BAACC TOLIFE"
- Special procedures "ALIVE AT FIVE"

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BAACC

Bleeding
Anesthesia
AFE
Cardiovascular/cardiomyopathy
Clot/cerebrovascular

TO

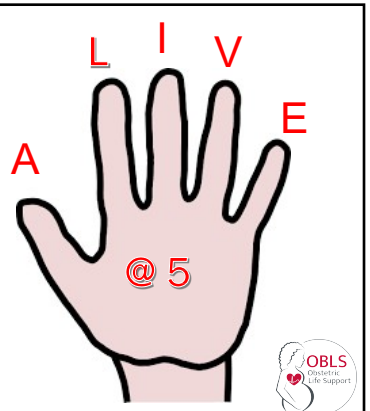
Trauma
Overdose (magnesium sulfate/opioids/other)

LIFE

Lung injury/ARDS
Ions (glucose/K+)
Fever (sepsis)
Emergency hypertension/eclampsia

33

Activate OBLS
Left uterine displacement
IV placement above diaphragm/**I**ntubate early
Verify gestational age and equipment
Extract fetus and placenta at 4 minutes



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POSTPARTUM ICU ADMISSION

- Lactation
- Mother/infant bonding
- Hemorrhage risk
- Care of wounds
- PTSD, anxiety

35

LEARNING ASSESSMENT QUESTION

- Which of the following is the MOST likely etiology for ICU admission?

A. Hemorrhage

B. Sepsis

C. Cardiovascular diseases

C. Hypertension

- Answer A- maternal hemorrhage is the number one cause of maternal morbidity and mortality worldwide, including the United States. Postpartum hemorrhage is the most common cause occurring in 4-6% of all pregnancies, with greater than 50% of maternal deaths from this cause occurring within the first 24 hours of delivery. Postpartum hemorrhage is caused by uterine atony in approximately 70-80% of cases.

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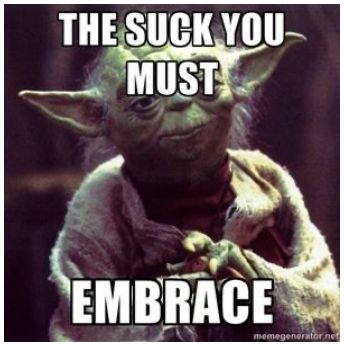

- Thank you!

37

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- Zulfeen Momina, Tatapudi Radha, Sowjanya Ravella. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2019-05-01, Volume 236, Pages 46-52.
- Vadhera RB, Pacheco LD, Hankins GD. Acute antihypertensive therapy in pregnancy-induced hypertension: is nicardipine the answer? Am J Perinatol 2009;26:495–9.
- Nij Bijvank SW, Duvekot JJ. Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature. Obstet Gynecol Surv 2010;65:341–7.
- National Heart, Lung, and Blood Institute. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230 . Bethesda (MD): NHLBI; 2004. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/jnc7full.pdf. Retrieved December 5, 2016.

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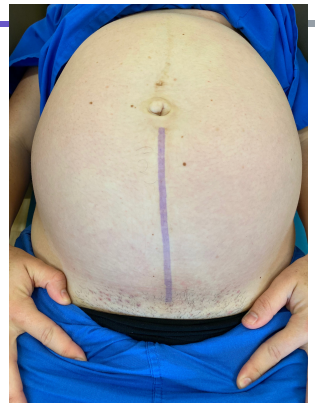
ut

Midline vertical incision



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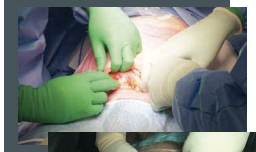
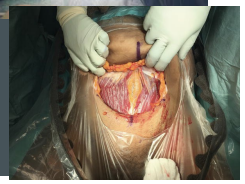
DISSECT





PIERCE

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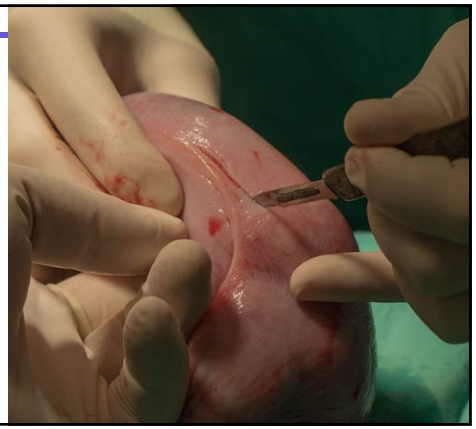
HYSTEROTOMY

Low vertical, or classical uterine incision



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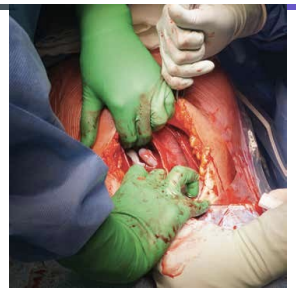
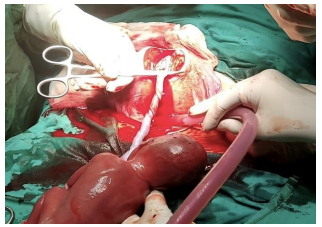


Deliver fetus and placenta



Extend hysterotomy and pierce amniotic sac

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Baylor College of Medicine

MOEWS IN SEPSIS

- 6 published early warning systems specifically designed for use in maternity care
  - Markedly different physiological thresholds, clinical triggers and ability to predict severe worsening of OB sepsis
- Tendency to over detect severe sepsis
  - low PPV– highest 15%

Edwards SEAJOG 2015

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SEPSIS IN OBSTETRIC SCORE (S.O.S)

- modified validated scoring systems based on recognized physiologic changes of pregnancy
- validated pregnancy-specific score to identify risk of ICU admission for sepsis
- score of less than 6 rules out the need for ICU admission

Albright AJOG 2014
Albright AJOG 2017

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www.perinatology.com (calculators)

Variable	High abnormal range				Normal	Low abnormal range			
Score	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	>40.9	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<30
Systolic Blood Pressure (mmHg)					>90		70-90		<70
Heart Rate (beats per minute)	>179	150-179	130-149	120-129	≤119				
Respiratory Rate (breaths per minute)	>49	35-49		25-34	12-24	10-11	6-9		≤5
SpO_2 (%)					≥92%	90-91%		85-89%	<85%
White Blood Cell Count (/µL)	>39.9		25-39.9	17-24.9	5.7-16.9	3-5.6	1-2.9		<1
% Immature Neutrophils			≥10%		<10%				
Lactic Acid (mmol/L)			≥4		<4				

Scoring template for S.O.S., a sepsis scoring system designed specifically for obstetric patients.

Albright AJOG 2014

45

Baylor College of Medicine

ANTIMICROBIAL THERAPY

- Failure to initiate appropriate therapy correlates with increased morbidity and mortality in patients with severe sepsis or septic shock
  - v Consider antimicrobial exposures in last 3 months!
  - v avoid antibiotics used in surgical prophylaxis
  - v cephalosporins will not provide adequate coverage for *Enterococcus* or *Listeria* infections

Dellinger RP. Surviving Sepsis Campaign. CCM Journal 2013

46

OBSTETRIC HEMORRHAGE EMERGENCY MANAGEMENT PLAN

- Stage 0 – all laboring patients
- Stage 1 – EBL/QBL > 500 ml SVD or > 1000 ml C/S or VS changes (by >15%
- Stage 2 – Total blood loss > 1000 ml, or ongoing bleeding with total blood loss
- Stage 3 – Total blood loss > 1500 ml, or > 2 units pRBCs given or VS unstable or suspicion of DIC

CMQCC Obstetric Hemorrhage Emergency Management Plan: Table Chart Format

	Assessments	Meds/Procedures	Blood Bank
Stage 0	Every woman in labor/giving birth		
Stage 1	Blood loss: > 500ml vaginal or >1000 ml Cesarean, or VS changes (by >15% or HR ≥110, BP ≤85/45, O2 sat <95%)		
Stage 2	Continued bleeding with total blood loss under 1500ml		
Stage 3	Total blood loss over 1500ml, or >2 units PRBCs given or VS unstable or suspicion of DIC		

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RENAL PHYSIOLOGIC ADAPTATIONS

Parameter	Pregnancy
Kidney Size	↑ 1-1.5 cm,[24] 30% ↑ volume
Ureteral Dilation	Resembles hydronephrosis[23]
Bladder/Ureter	↑vesicoureteral reflux ↑frequency, nocturia, urgency, dysuria, incontinence
Glomerular filtration rate/ Renal plasma flow	↑ 50%[22] ↓creatinine to ≤0.8 mg/dL ↑excretion of glucose, protein, and amino acids.[22,24,25]
Acid Base Balance	↑bicarbonate excretion[22]
Osmolality	↓threshold for thirst/vasopressin release ↑vasopressin metabolism Hyponatremia

48

- In pregnancy, the most common offending sites
  - Genital 40%
  - Urinary 33%
  - Respiratory 25%

Most common admitting diagnosis to ICU: urosepsis

- The most common offending organisms are:
  - Gram Negatives 52% (E. coli)
  - Gram positives (groups A, B, Gstreptococci; Strep oralis; Staph aureus)
  - Anaerobes (Mycoplasma hominis, Ureaplasma spp., chlamydia spp)
- Most infections tend to be polymicrobial, with most organisms a part of the normal vaginal flora

Oud L. JClin Med Res 2015

49

HEMATOLOGIC CONSIDERATIONS

- Elevated WBC is normal in laboring women (up to 29K, but average around 15K)
- Dilutional anemia
- Platelet count is generally normal, but gestational thrombocytopenia present in 7-12%
- Fibrinogen, clotting factors, d-dimer normally increased
- aPTT shortened, but no changes in PT

Williams Obstetrics, 25e
ACOGPB#207, 2019
Abbassi-Ghanavati M 2009

50

2019 Acute Ischemic Stroke Guideline Update

James C. Grotta, MD

Sept 25, 2020

1

Disclosures

- Mobile Stroke Unit-based acute stroke evaluation & treatment
  - PI for BEST-MSU trial--PCORI
  - Consultant for Frazer Ltd

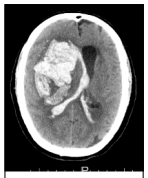
2

Objectives

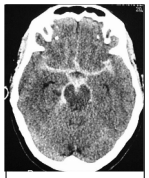
- Explain new recommendations for alteplase administration in "wake-up" stroke patients based on advanced neuroimaging techniques
- Evaluate new recommendations for intravenous tenecteplase in patients eligible for mechanical thrombectomy
- Describe new recommendations for mechanical thrombectomy in patients 6-24 hours post-symptom onset

3

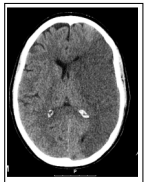
Types of Stroke



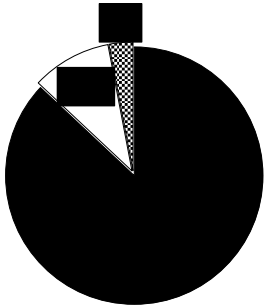
Intracerebral Hemorrhage



Subarachnoid Hemorrhage



Ischemic



AHA Disease Statistics
Circulation 2012;125 (e2-e220)

4

2019 Updated AHA/ASA Guidelines

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair; Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA; Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA; Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA; Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA; Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA; Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA; Andrew M. Southerland, MD, MSc, FAHA; Deborah V. Summers, MSN, RN, FAHA; David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

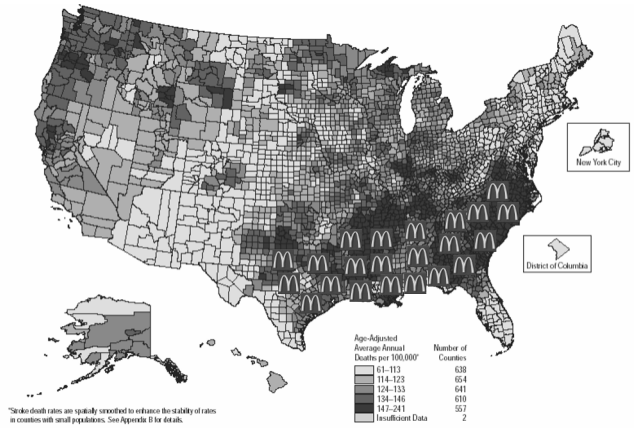
Stroke. 2019; DOI: 10.1161/STR.0000000000000211

5

10 steps for treating acute ischemic stroke

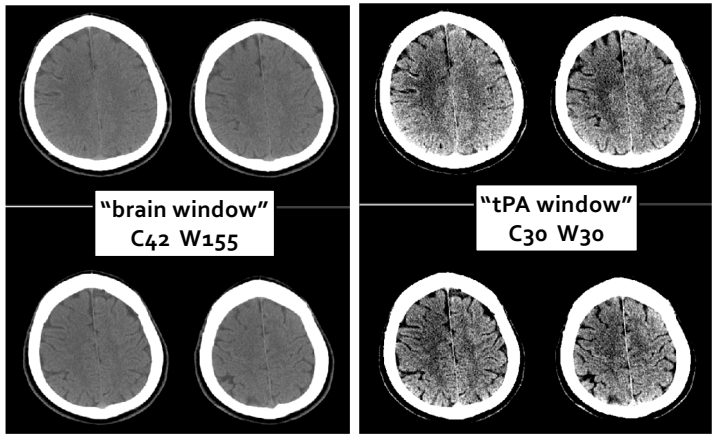
1. Examine the patient and get a history
2. Get a CT scan
3. Give tPA asap, controlling BP < 180/110
4. Get a CTA
5. ET if LVO present
6. Control BP, lipids; DVTp; swallowing
7. Dual antiplatelets X 21 days and then monotherapy
8. Monitor for afib and if present start DOAC
9. Address diet and lifestyle
10. Rehab if possible

6



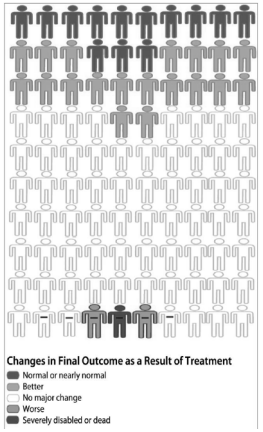
SHINE: -Insulin sliding scale to 130-179 mg/dl is fine;
-Insulin drip to achieve glu 80-130 mg/dl is no better and may produce hypoglycemia

7



8

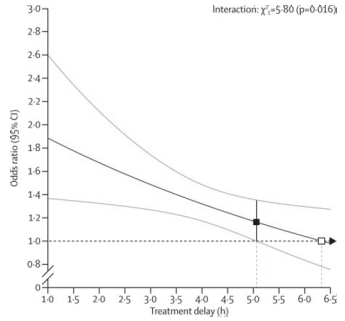
Changes in final outcome as a result of tPA treatment within 3 hours of stroke onset



9

Thousands of patients from clinical trials

Pooled data from 6756 patients in 9 randomized trials of tPA



Emberson et al, Lancet 2014
Lees et al, Stroke 2016

10

tPA vs TNK

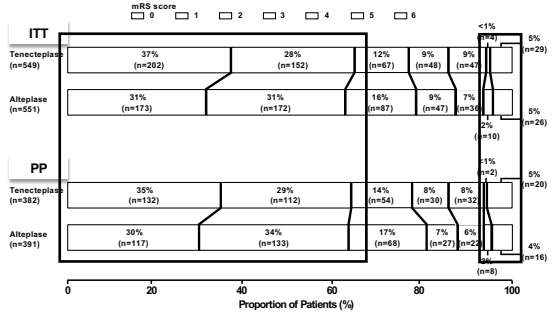
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	IIb	B-R	New recommendation.

Newer/faster is not always better.....

11

TNK

NOR-TEST: Distribution of mRS Scores at 3 Months



ITT=intention-to-treat; mRS=modified Rankin Scale; PP=per-protocol.
Logallo N et al. *Lancet Neurol.* 2017;16:781-788.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*

1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	IIb	B-R	New recommendation.

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Table 1. **Characteristics of the 202 Patients at Baseline.***

Characteristic	Tenecteplase Group (N=101)	Alteplase Group (N=101)
Age — yr	70.4±15.1	71.9±13.7
Male sex — no. (%)	58 (57)	52 (51)
Median NIHSS score (IQR)†	17 (12–22)	17 (12–22)
Cause of stroke — no. (%)		
Cardioembolic occlusion	46 (46)	54 (53)
Large-artery occlusion	21 (21)	18 (18)
Undetermined or other	34 (34)	29 (29)
Median time from stroke onset to hospital arrival (IQR) — min	60 (44–89)	72 (53–104)
Median time from stroke onset to initiation of intravenous thrombolysis (IQR) — min	125 (102–156)	134 (104–176)
Median time from initiation of intravenous thrombolysis to arterial puncture (IQR) — min	43 (25–57)	42 (30–63)
Median time from initiation of intravenous thrombolysis to initial angiographic assessment (IQR) — min	54 (34–67)	56 (40–77)
Interhospital transfer for thrombectomy — no. (%)	27 (27)	23 (23)
Site of vessel occlusion — no. (%)		
Internal carotid artery	24 (24)	24 (24)
Basilar artery	3 (3)	3 (3)
Middle cerebral artery		
First segment	59 (58)	60 (59)
Second segment	15 (15)	14 (14)
Median volume at initial imaging (IQR) — ml‡		
Ischemic core	14 (0–33)	11 (0–24)
Perfusion lesion	145 (105–175)	134 (103–170)

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Results

Table 2. **Outcomes.**

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02

P = 0.002 for noninferiority
P = 0.03 for superiority

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Tenecteplase provides superior recanalization than tPA when given prior to thrombectomy.

- A. True
- B. False

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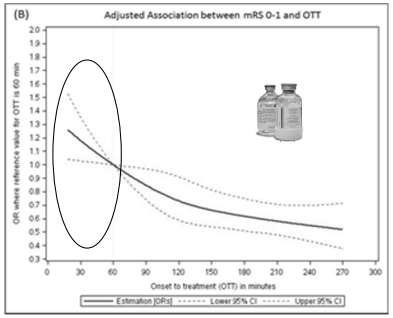
The most potent way to improve tPA outcomes is to give it faster-
Ultra-early treatment in first "golden hour" should be our goal

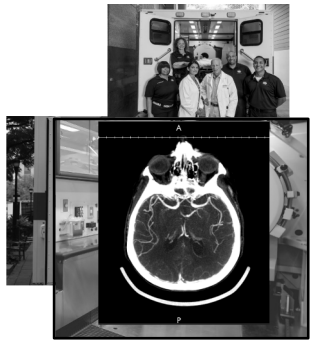


The only way to accomplish this….
Is to bring the treatment to the patient

17

Mobile Stroke Units Don't Need to be Fancy

- ✓ Standard 12 foot ambulance
- ✓ Portable CT scanner
- ✓ Point-of-care laboratory
- ✓ Tele-radiology & neurology
- ✓ VN, RN, CT tech, Medic



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Multifaceted MSU Dispatch Process

911 call → EMS ambulance immediately dispatched per routine → MSU team dispatched to site → MSU team meets EMS ambulance at emergency site

We monitor EMS radio and add ourselves on—rendezvous en route to ED

On-scene FR identifies possible stroke—rendezvous en route to ED

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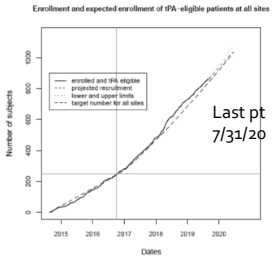
BEST-MSU Study

If I have a stroke and call 911, am I better off if treated in a MSU vs EMS?"

SPECIFIC AIMS

1. How much less disability at 3 months?
2. Health Utilities/Cost-Effectiveness
   - pts followed up to 1 year

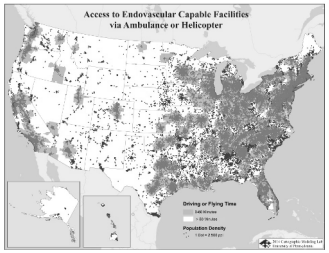


Last pt 7/31/20

20

Telemedicine - Telestroke

- Low tPA treatment rates (6-11%), but up to 29% could be treated
- Only 56% of the US population has access to endovascular hospitals within 1-hour
- Telemedicine acute ischemic stroke evaluation is effective and telestroke-guided tPA administration is beneficial



Kleindorfer Stroke 2004
de los Rios la Rosa Stroke 2012
Adeoye Stroke 2014

4. Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making.	IIa	B-R
5. Administration of IV alteplase guided by telestroke consultation for patients with AIS can be beneficial.	IIa	B-NR

New recommendation.

21

Endovascular Therapy for AIS

Also known as…

Intra-arterial therapy (IAT)

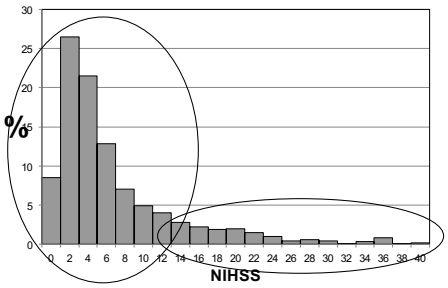
[Mechanical] Embolectomy

[Mechanical] Thrombectomy

22

tPA will remain the most frequent treatment c/w thrombectomy

NIHSS scores in overall population who are candidates for tPA and for ET



Reeves M, Kleindorfer D et al, abstract ISC 2012

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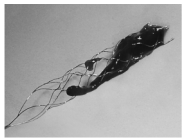
The Landscape of Acute Ischemic Stroke Has Changed!

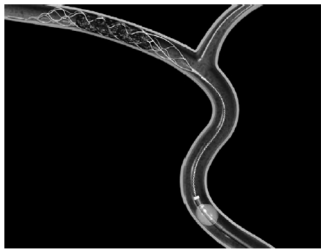
24

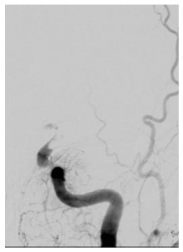
Endovascular Devices – *Stentrievers*

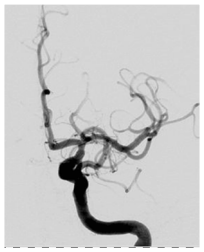
- Very effective for recanalization compared previous devices
  - Large Vessel Occlusions (LVO)
    - Terminal ICA & M1 MCA only

NNT= 2!







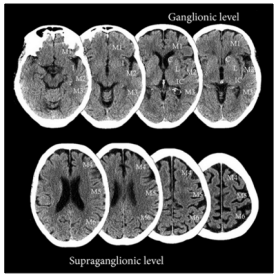


25

0-6 hours from last seen normal/stroke onset and LVO (tICA or M1 MCA) - **RULE OF 6**

1) NIHSS ≥6
2) Near normal non-contrast CT scan (ASPECTS ≥6)
3) Groin Puncture <6 hours from LSN/onset

ASPECTS score



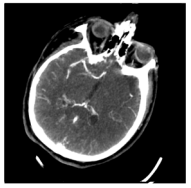
2. When evaluating patients with AIS within 6 hours of last known normal with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6, selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies.	I	B-NR	New recommendation.

26

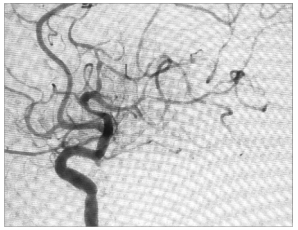
Direct MSU to ET optimizes the acute stroke treatment pathway

65 yo M
Onset 10:35 pm
Rendezvous 11:12 (37 min)
NIHSS 24

tPA (MSU) 11:22 (**47 min from onset**)
CTA (MSU) 11:27
Call to ET team



ED door 11:46
GP 11:56 (**DTGP 10 min**)
Recan 12:26 (111 min)

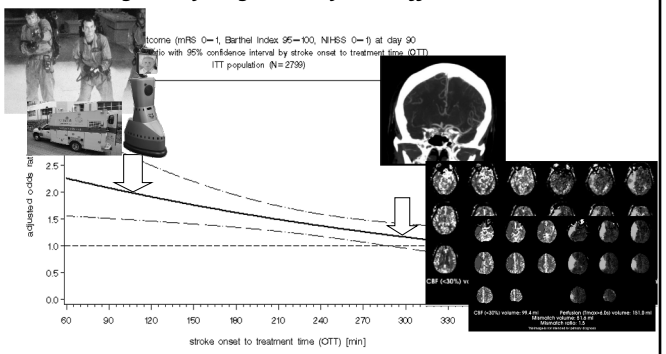


24 hr NIHSS 3

27

Time vs Tissue

"Timing is everything" or "Everyone is different"

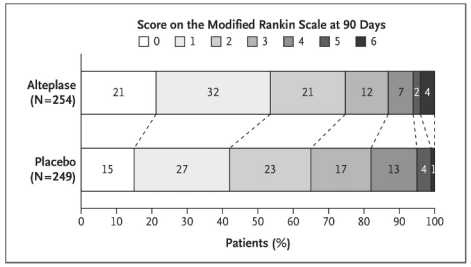


3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.	IIa	B-R	New recommendation.

28

Now 3 trials **with tPA** showing benefit in image-guided selection of patients with wake-up or up to 9 hours from onset

Thomalla et al NEJM 2018, Amiri et al Int J Stroke 2016, Ma et al Int J Stroke 2012



TIMELESS trial of TNK before delayed EVT----
Just starting

29

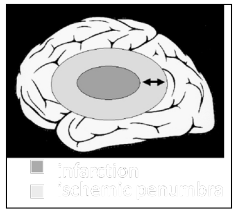
Clinical trials have shown that tPA can be given safely in "wake-up" patients by using any of the following criteria except:

- A. Non-contrast CT
- B. MRI
- C. Clinical exam
- D. CT perfusion

30

6-24 hours LVO – fewer patients with salvageable brain tissue

- Mismatch between infarcted vs. ischemic tissue



- Two RCTs randomized EVT vs. medical management in patients with mismatch
  - DAWN
  - DEFUSE-3

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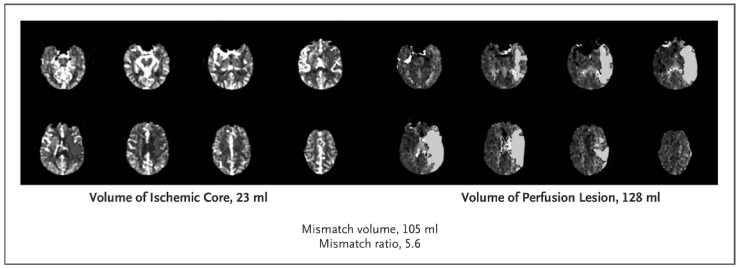
DAWN and DEFUSE-3

- Severe strokes
- Automated software (RAPID – *Ischemia view*) calculated core infarction compared to penumbra



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DAWN Mismatch Definition

1) Age ≥ 80 y; NIHSS ≥ 10; Ischemic core <21 mL

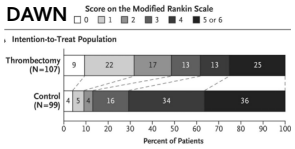
2) Age < 80 y, NIHSS ≥ 10; Ischemic core <31 mL

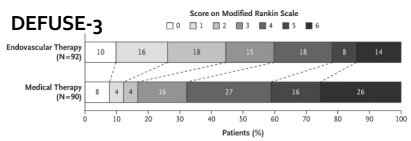
3) Age <80 y, NIHSS ≥ 20; 31≤ Ischemic core<51 mL

- **More aggressive in younger patients**

33

	DAWN 6-24 hours
NIHSS median	17
Functional Independence	49% EVT vs. 13% control
24-hr Recanalization	77% EVT vs. 39% control
Safety – symptomatic ICH	6% vs. 3% (NS)
Mortality	19% EVT vs. 18% control





34

6-24 hours patients

5. CTA with CTP or MR angiography (MRA) with diffusion-weighted magnetic resonance imaging (DW-MRI) with or without MR perfusion is recommended for certain patients.	I	A	New recommendation.

2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging	COR	LOE	New, Revised, or Unchanged
1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	I	A	New recommendation.

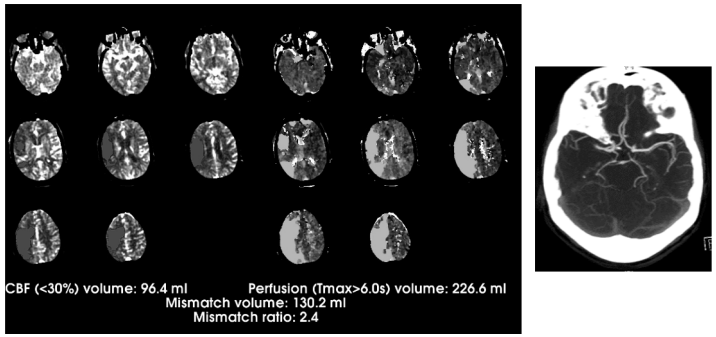
35

Questions after DAWN & DEFUSE-3

1. Treatment time window is extended. How do we change EMS routing patterns? All strokes within 24hrs to a CSC?
2. In the ED, stroke activations for all strokes within 24 hours?
3. What/where is the best imaging for acute stroke?
   - Tertiary hospital/CSC versus community hospital/PSC
4. Other populations not addressed
   - Lower NIHSS scores (ENDO LOW trial)
   - Distal MCA clots (M2, etc)
   - Posterior circulation
   - Large core

36

Anything to save?



Do Large Core strokes benefit from EVT? Unknown.

- **SELECT-2 RCT**
- **TESLA RCT**

37

10 steps for treating acute ischemic stroke

1. Examine the patient and get a history
2. Get a CT scan
3. Give tPA asap, controlling BP < 180/110
4. Get a CTA
5. ET if LVO present
6. Control BP, lipids; DVTp; swallowing
7. Dual antiplatelets X 21 days and then monotherapy
8. Monitor for afib and if present start DOAC
9. Address diet and lifestyle
10. Rehab if possible

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Thank you - Questions?

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(PEDIATRIC) STATUS EPILEPTICUS (in/for the PICU)

Yu-Tze Ng, MBBS
FRACP, FAAN, FAAP, FAES

Professor of Pediatrics
Division of Neurology

1

Outline

- **Definition status epilepticus**
  - **Single prolonged seizure**
    - **Treat with benzodiazepines**
    - **Then treat with first line antiepileptic drugs**
  - **Refractory status epilepticus**
    - **Multiple drug therapies**
    - **Suppressive medication treatments**
- **Auto-immune/inflammatory status epilepticus**
  - **Anti-inflammatory therapies, including steroids and intravenous immunoglobulin**
  - **Novel neurosurgical treatment**

2

Status Epilepticus - Definition

- A seizure that "persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur". - ILAE 1981
- >20-30 minutes
- Operational definition – "Either continuous seizures lasting >5' or ≥2 discrete seizures b/w which there is incomplete recovery of consciousness"

Lowenstein and Alldredge, *NEJM* 1998

3

Refractory Status Epilepticus

- "Seizures persist despite appropriate Rx"
- Does not respond to a BZD/PHT/PB
- >60' duration

Lowenstein and Alldredge, *NEJM* 1998
Sahin et al, *Neurology* 2003
Riviello and Holmes, *Semin Ped Neurol* 2004

4

Pathophysiology

- "Failure of mechanisms that normally abort an isolated seizure"
- Due to excessive glutamate activity and/or excessive GABA antagonists
- Best e.g. ingestion of exogenous toxin of mussels contaminated with domoic acid → patients with RSE – Canada, late 1987

Lowenstein and Alldredge, *NEJM* 1998
Perl et al, *NEJM* 1990

5

Rx: Chaos theory

6

Mortality

- ~20% in adults (22-38% elderly)
- In children ~3-11%
- BUT in RSE, mortality rate ~16-43.5%

Riviello et al, *Semin Ped Neurol* 2004
Chin et al, *Eur J Neurol,* 2004
Maegaki et al, *Neuropediatrics,* 2005
Kang et al, *Yonsei Med J,* 2005
Akbar Asadi-Pooya et al, *Epi and Behav,* 2005
Lowenstein et al, *NEJM,* 1998

7

Rx

- ABCs
- First-line AEDs
- Rx of RSE
- Neurosurgical Rx

8

Positioning

- **Lateral decubitus may be wrong**

- **Adult patients (South Florida)**
- **2 of 733 had aspiration pneumonia**
- **5 of 806 had posterior shoulder dislocation**

- **Conclusion – Implement lateral decubitus position only after seizure cessation**

DeToledo and Lowe, *Neurology* 2001

9

Role of EEG in SE

- STAT EEG only for any unexplained deterioration/alteration of consciousness

- Long-term monitoring as per PICU

10

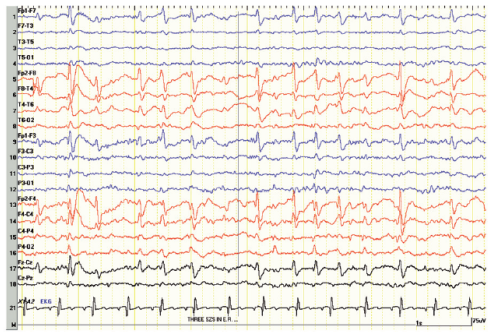


Fig. 1 EEG in a 7-year-old patient with known epilepsy, who had convulsive status epilepticus followed by obtundation and EEG showing generalised (right greater than left) periodic epileptiform discharges suggestive of non-convulsive status epilepticus.

11

Rx - V.A. Study

- 518 patients (384 overt, 134 subtle)
  5-year, randomized, double-blind multicenter trial
- Four groups: IV LZP (64.9%)
  IV PB (58.2%)
  IV DZP & PHT (55.8%)
  IV PHT (43.6%)
- LZP > PHT (P=0.001)
  A comparison of four treatments for generalized convulsive status epilepticus

D. Treiman et al, *NEJM* 1998;339:792-798

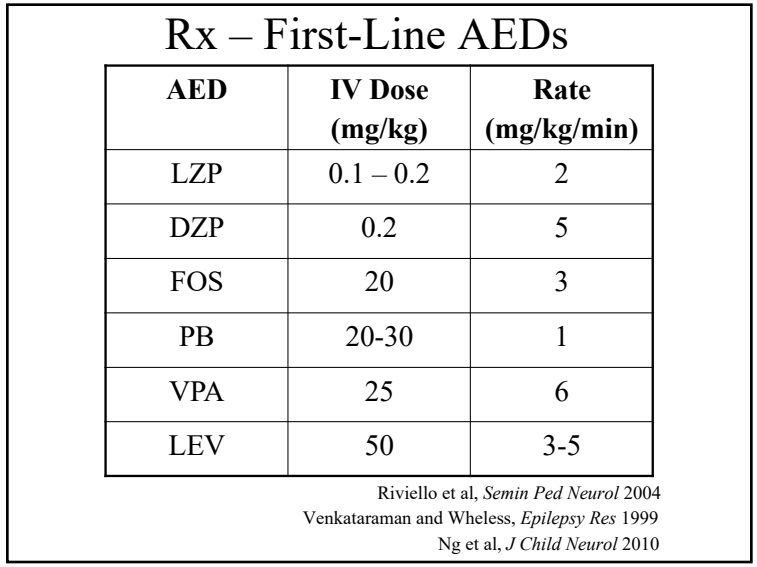
12

Rx – First-Line AEDs

AED	IV Dose (mg/kg)	Rate (mg/kg/min)
LZP	0.1 – 0.2	2
DZP	0.2	5
FOS	20	3
PB	20-30	1
VPA	25	6
LEV	50	3-5

Riviello et al, *Semin Ped Neurol* 2004
Venkataraman and Wheless, *Epilepsy Res* 1999
Ng et al, *J Child Neurol* 2010

13



Original Article

Intravenous Levetiracetam In Children With Seizures: A Prospective Safety Study

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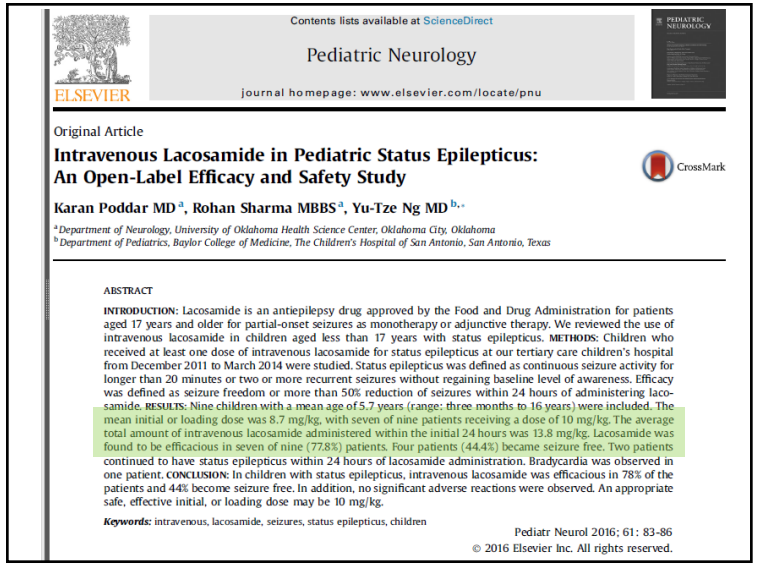
DOI: 10.1177/0883073809348795
http://jcn.sagepub.com
SAGE

Yu-tze Ng, MD, FRACP,[1] Eric V. Hastriter, MD,[1] Javier F. Cardenas, MD,[1] Emily M. Khoury, RN, MN,[1] and Kevin E. Chapman, MD[1]

Abstract

In 2006, intravenous levetiracetam received US Food and Drug Administration (FDA) approval for adjunctive treatment of partial onset seizures in adults with epilepsy, 16 years or older. We have established the safety, tolerability, and dosage of intravenous levetiracetam in children. This prospective study included 30 children (6 months to <15 years of age). Patients were administered a single dose of intravenous levetiracetam (50 mg/kg, maximal dose 2500 mg) over 15 minutes. A blood level of levetiracetam was performed 10 minutes after the infusion. The treated children's average age was 6.3 years (range 0.5-14.8 years). The mean levetiracetam level was 83.3 µg/mL (range 47-128 µg/mL). There were no serious adverse reactions. Minor reactions included sleepiness, fatigue, and restlessness. An apparent decrease in seizure frequency across all seizure types was noted. The dose of 50 mg/kg was well tolerated by the patients and is a safe, appropriate loading dose.

14



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Original Article

Intravenous Lacosamide in Pediatric Status Epilepticus: An Open-Label Efficacy and Safety Study

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ABSTRACT

INTRODUCTION: Lacosamide is an antiepilepsy drug approved by the Food and Drug Administration for patients aged 17 years and older for partial-onset seizures as monotherapy or adjunctive therapy. We reviewed the use of intravenous lacosamide in children aged less than 17 years with status epilepticus. **METHODS:** Children who received at least one dose of intravenous lacosamide for status epilepticus at our tertiary care children's hospital from December 2011 to March 2014 were studied. Status epilepticus was defined as continuous seizure activity for longer than 20 minutes or two or more recurrent seizures without regaining baseline level of awareness. Efficacy was defined as seizure freedom or more than 50% reduction of seizures within 24 hours of administering lacosamide. **RESULTS:** Nine children with a mean age of 5.7 years (range: three months to 16 years) were included. The mean initial or loading dose was 8.7 mg/kg, with seven of nine patients receiving a dose of 10 mg/kg. The average total amount of intravenous lacosamide administered within the initial 24 hours was 13.8 mg/kg. Lacosamide was found to be efficacious in seven of nine (77.8%) patients. Four patients (44.4%) became seizure free. Two patients continued to have status epilepticus within 24 hours of lacosamide administration. Bradycardia was observed in one patient. **CONCLUSION:** In children with status epilepticus, intravenous lacosamide was efficacious in 78% of the patients and 44% become seizure free. In addition, no significant adverse reactions were observed. An appropriate safe, effective initial, or loading dose may be 10 mg/kg.

Keywords: intravenous, lacosamide, seizures, status epilepticus, children

Pediatr Neurol 2016; 61: 83-86
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Rx - RSE

Agent	Loading dose IV (mg/kg)	Maintenance (mg/kg/hr)
Pentobarbital	2-10	0.5-1
MDZ	0.2	0.02-0.4
Thiopental	5	5
Propofol	1-2	2-3 (50 µg/kg/min)

Riviello et al, *Semin Ped Neurol* 2004
van Gestel et al, *Neurology* 2005

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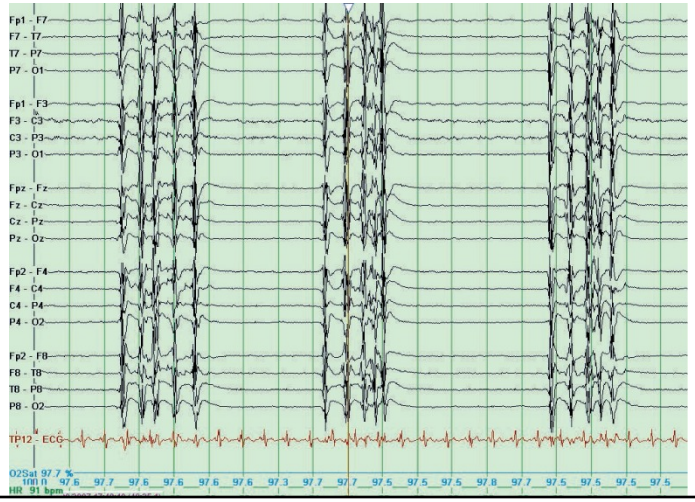
Titrate Burst:Suppression to ?



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Journal of Paediatrics and Child Health

doi:10.1111/j.1440-1754.2012.02559.x

REVIEW ARTICLE

Status epilepticus in childhood

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Abstract: Status epilepticus (SE) remains a life-threatening condition that afflicts both adults and children, and may occur at onset of epilepsy, especially in children. Febrile SE is the most common cause in children, while other symptomatic causes are less frequent compared to adults. The aetiological workup that must be undertaken in all cases includes neuroimaging and electroencephalography. The various electroencephalographic patterns seen in patients with SE along with the out-of-hospital treatment for SE in children and treatment strategies in cases that are refractory to first-line medical treatments are discussed. Medically induced coma may be necessary in refractory cases, although the optimal agents to use and degree of electroencephalographic suppression in children remain unclear. Neurosurgery is not a well-known treatment option that could be considered for refractory cases. Although the prognosis has probably improved over the years, it remains a potential life-threatening emergency.

Key words: children; epilepsy surgery; paediatric; refractory; status epilepticus.

study involving 30 children between the ages of 6 months and 14 years.[9] IV levetiracetam may be a good early or even first choice in children who are actively having seizures or with SE particularly if the exact seizure type is unknown because of its broad spectrum of efficacy. In addition, most neurologists would probably rather continue the patient on levetiracetam upon discharge from hospital as compared to phenobarbitone or phenytoin

Refractory SE

Typically, after two or three high (or at least adequate) doses of IV agents have been used within a few hours, anaesthetic agents are the next line of treatment, if necessary. These involve heavy sedation and medically induced coma requiring intubation, mechanical ventilation and, at times, inotropic support in the intensive care. At this stage of treatment, continuous EEG monitoring is usually necessary. Traditionally, a burst-suppression pattern is targeted with an unknown ratio of burst to suppression. A SE expert advocates for a complete suppression pattern or electrocerebral silence, that is 'flatline' throughout (David Treiman, M.D., pers. comm.); however, patients in complete EEG suppression can have resultant fatal (cardiovascular) complications. We now aim for a suppression-burst pattern perhaps in a ratio of 9:1 that is predominant suppression pattern. IV midazolam may be used to induce coma and a meta-analysis of

used with caution particularly if children are treated for more an 48 h or at a dose of >5 mg/kg/h. Daily testing of muscle izymes and triglycerides should be performed in this setting. The more recently recognised entities associated with SE that e generally refractory to treatment include those associated ith autoimmune encephalopathies. These encephalitides clude those associated with VGKC antibodies, NMDA receptor antibodies, thyroid or paraneoplastic antibodies. While they are extremely rare, they are worth mentioning since these entities require immunomodulatory therapy with either steroids (hence, these conditions are also known as 'steroid responsive encephalopathies') or IV immunoglobulins in addition to standard first- or second-line agents.[8,10]

We have published several clinical studies on the role of neurosurgery in SE.[11,12] We believe that this is an underutilised often unconsidered therapeutic option for the treatment of SE particularly in refractory cases. Although lesional cases are clearly relatively more straightforward to treat by neurosurgical focal resection, cases without an apparent lesion on brain MRI scan (i.e. 'non-lesional' cases) may also undergo successful resection, typically with the help of invasive grids and/or depth wires. Although at times such operations can be life-saving, earlier identification of refractory, epilepsy surgical cases may decrease the need for such heroic measures. Nevertheless, surgical options other than resection, for example multiple subpial transections for eloquent cortex, should be considered and not necessarily only as a last resort. Delaying surgery may be an option for patients whose SE is controlled with medication. However, we believe that surgical intervention should be considered earlier in the course of refractory SE.

Prognosis

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Autoimmune Encephalitis

- Anti-NMDA receptor encephalitis
- Non-Anti-NMDA receptor encephalitis (VGKC, LGI1, CASPR2, $GABA_B$ rec & AMPA rec)
- Rx:

- IV Steroids, IVIg, Plasmapheresis
- Rituximab
- ??? YOYO

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Case 1

- 4 m.o. term baby girl
- P/C:
- Szs since 10 days of life
- 1) Partial - R face and arm jerking, 10-15s
- 2) Tonic-clonic - Stiffens, jerks, fisting, 10-15s
- Each ~5-6/day
- Rx: Failed CBZ, PB
  VPA, ZNS, OXC
- O/E: Hypotonia, head lag
  Wt: 6.5 kg; FOC 41.5 (~50%)

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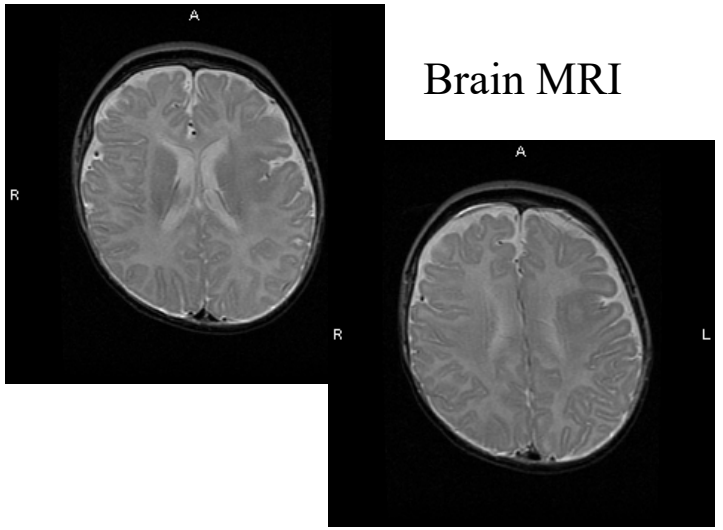
Brain MRI



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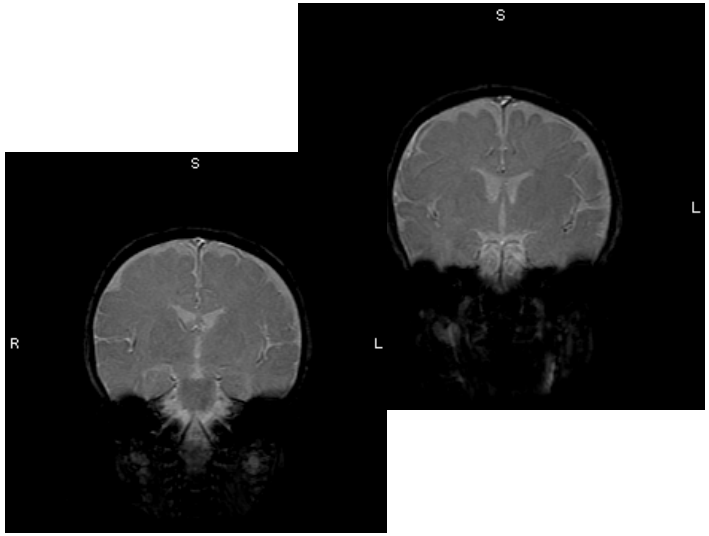

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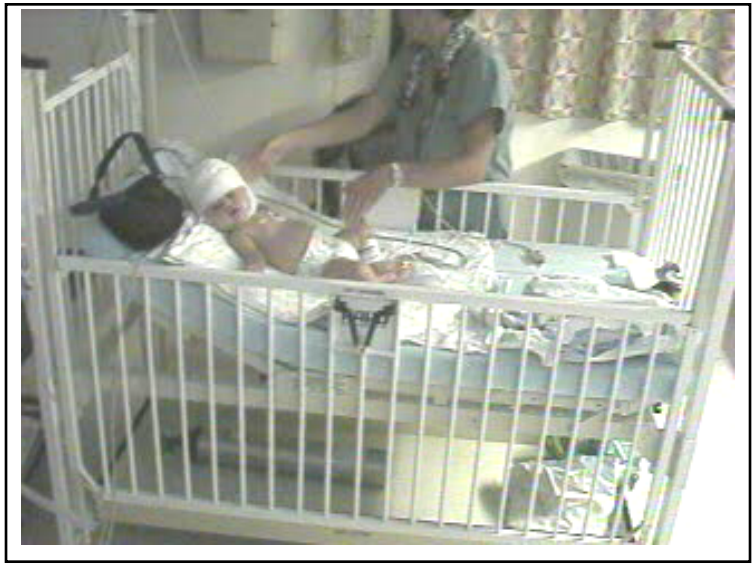

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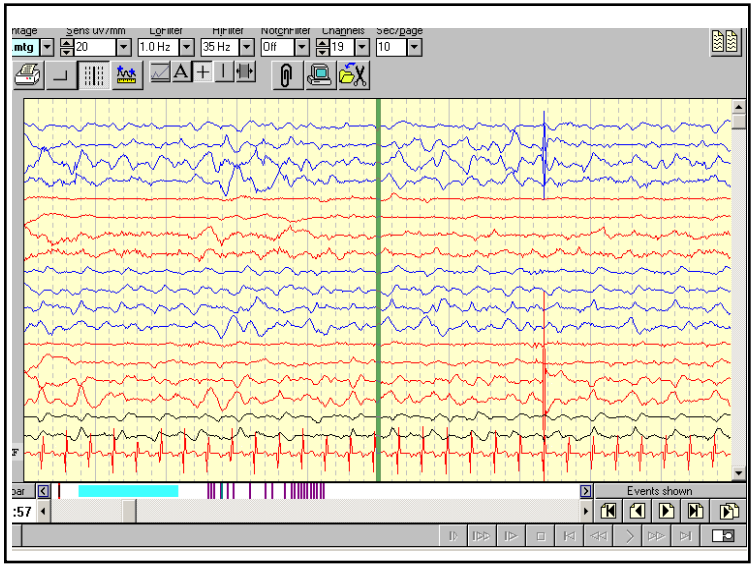
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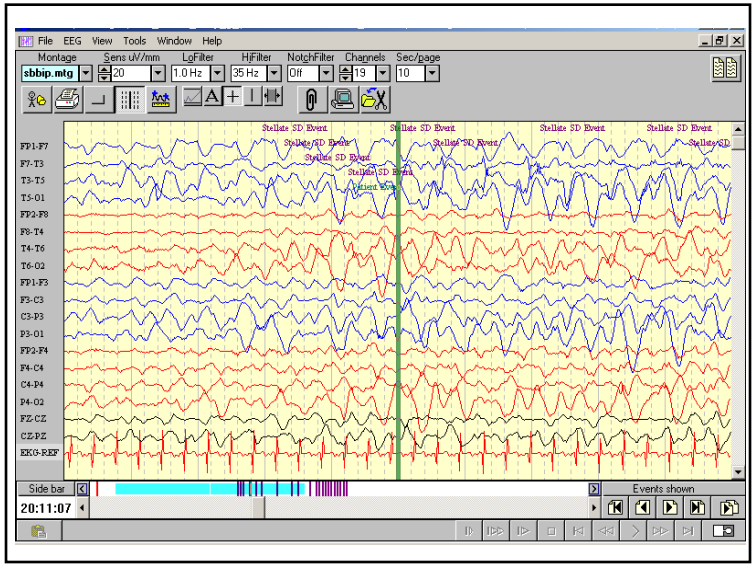
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FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F3
F3-C3
C3-P3
P3-O1
FP2-F4
F4-C4
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P4-O2
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CZ-PZ
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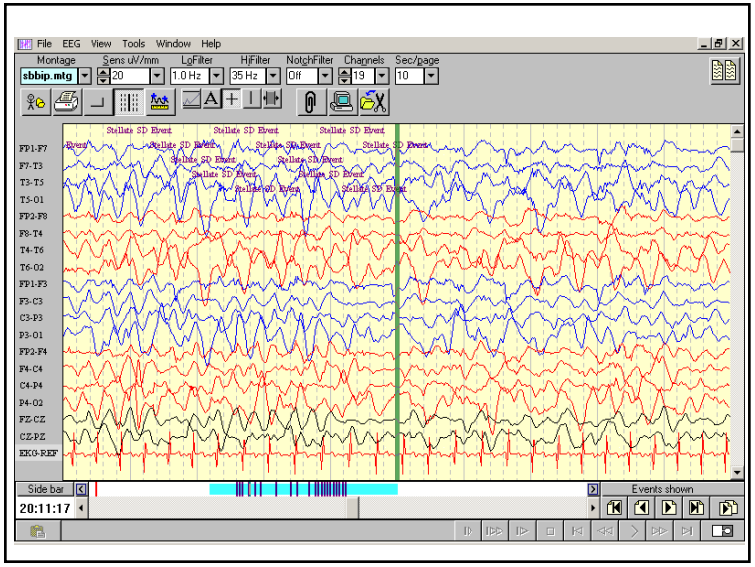
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T6-O2
FP1-F3
F3-C3
C3-P3
P3-O1
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P4-O2
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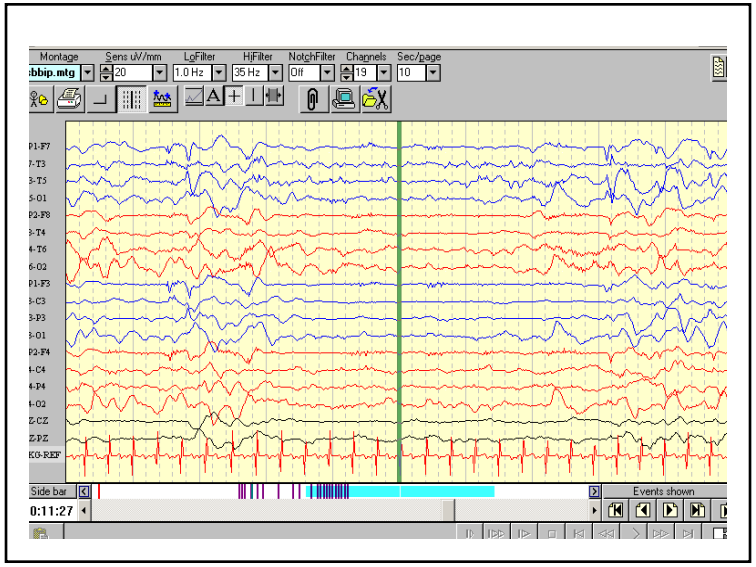
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Management

- High-resolution MRI
- ?Ictal SPECT scan

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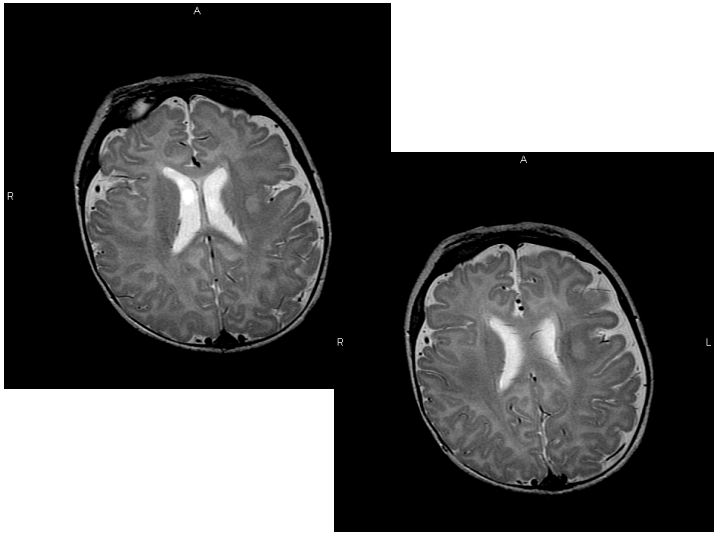

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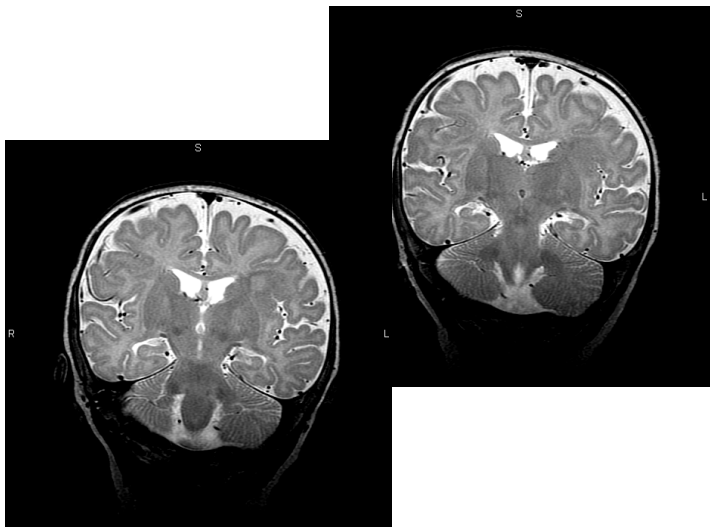

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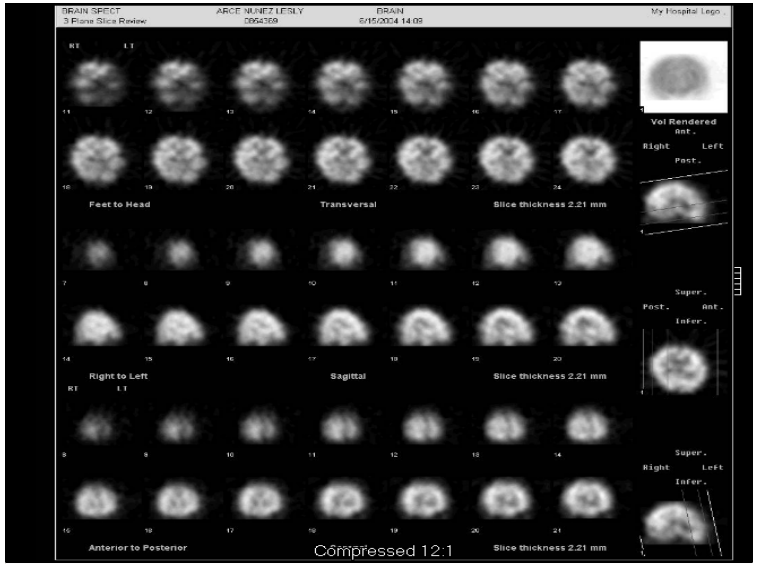

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Rx

- Focal cortical resection performed

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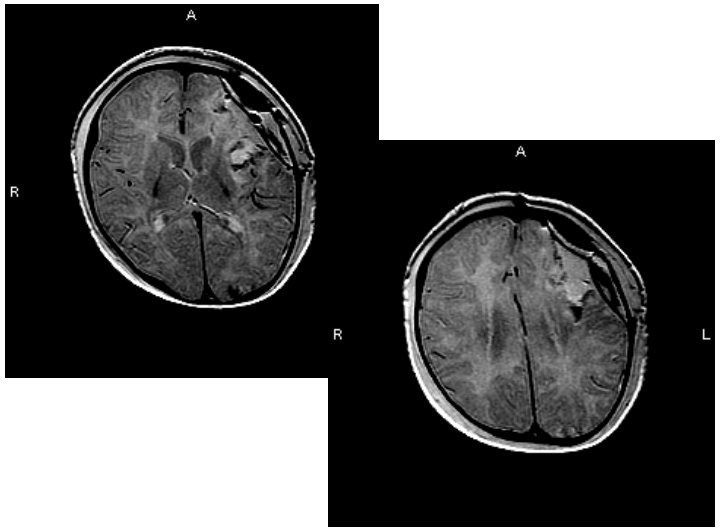

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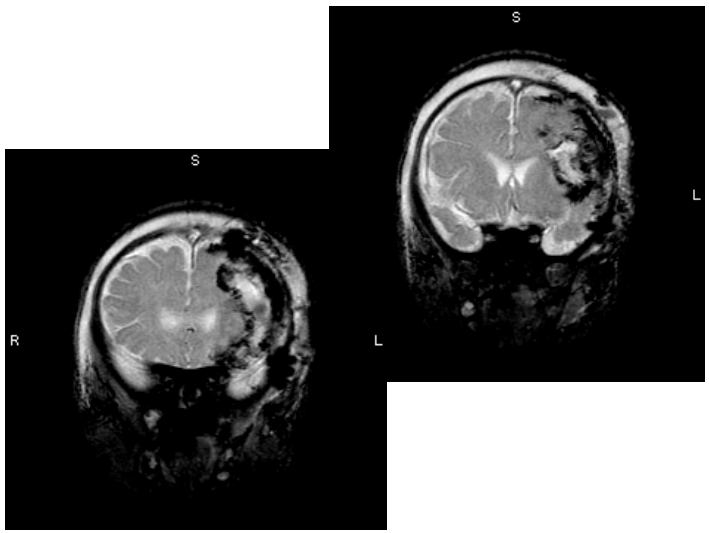

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Outcome

- Transient R hemiparesis
- Patient much more alert, active
- Breakthrough sz (cluster, mouth twitching) with ↓ VPA level
- Discharged home 2 weeks post-op

- Neuropath: Unremarkable gray and white matter

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Middle-term Outcome

- Developmentally delayed, alert
- Mild R hemiparesis
- Failed ketogenic diet
- 50-90% ↓ Sz activity (till >12 mo ago)

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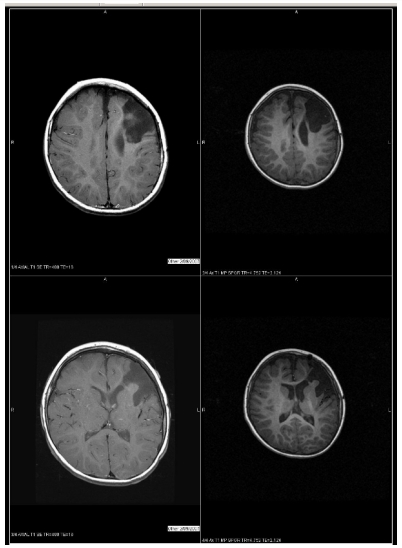

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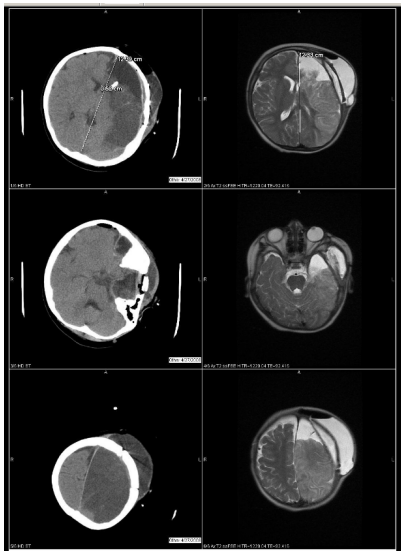

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Longer-term outcome

- Seizure free 15 months
- Now off all AEDs
- L hemiparesis but walking
- Talking more

40

J Neurosurg (5 Suppl Pediatrics) 105:378–381, 2006

Neurosurgical treatment of status epilepticus

YU-TZE NG, M.D., F.R.A.C.P., JOHN F. KERRIGAN, M.D., AND HAROLD L. REKATE, M.D.

Departments of Pediatric Neurology and Pediatric Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona

Five patients (3 published previously)

*Clinical characteristics, surgical procedure, and outcome in five cases of status epilepticus**

Case No.	Age, Sex	Clinical Finding	Diagnosis	Op	Outcome: Seizure Freedom (duration)	Outcome: Neurological/ Neuropsychological
1	4 yrs, F	CPSE	nonlesional FCD (lt parietal)	focal cortical resection	SF (5 yrs)	min lt dorsiflexion weakness, straight-A student
2	7 yrs, M	CPSE	rt hemicortical dysplasia	hemispherectomy	SF (3 yrs)	baseline lt hemiparesis, 2–3 yrs behind academically, in special education
3	30 mos, M	status gelasticus	hypothalamic hamartoma	transcallosal resection, endoscopic resection in 2nd op 19 mos later	SF (9 mos after 2nd op)	normal development, behavioral problems
4	4 mos, F	CPSE	FCD (lt insular)	focal cortical resection	>90% seizure reduction	min rt hemiparesis, developmental delay
5	24 mos, F	EPC	CCM	focal cortical resection	SF (16 mos)	normal

* CPSE = complex partial status epilepticus; EPC = epilepsia partialis continua; FCD = focal cortical dysplasia; SF = seizure free.

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Repeat Neurosurgery for SE

Patient	Age	Sex	Clinical	Diagnosis	Surgery	Outcome
1	4 yr	F	EPC	Non-lesional FCD (L parietal)	Focal cortical resection	SF (4 years)
2	7 yr	M	CPSE	Hemicortical dysplasia	Hemispherectomy	SF (2 years)
3	30 mo	M	Status Gelasticus	Hypothalamic hamartoma	Transcallosal resection **Endoscopic resection**	>90% reduction **Seizure-free**
4	24 mo	F	CPSE	FCD (L insular)	Focal cortical resection	>50% reduction **2nd Sx → Seizure-free**
5	4 mo	F	EPC	Cavernous malformation	Focal cortical resection	SF **9** months)

EPC = Epilepsia partialis continua; FCD = Focal cortical dysplasia; SF = Seizure-free; CPSE = Complex partial status epilepticus

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Conclusions

- Neurosurgical treatment not first line Rx
- Could be (3rd?) 4th, 5th line, rather than "last-resort"
- Can be life-saving
- Focal cortical dysplasias and/or non-lesional cases does not have to mean poorer outcome
- More elective epilepsy surgery may decrease need for "heroic" surgical cases
- 10 Patients with RSE and focal epileptogenesis – 70% SF - Alexopoulos et al, *Neurology* 2005

43

neurocritical care society Neurocrit Care (2007) 7:86–91
DOI 10.1007/s12028-007-0038-4

PRACTICAL PEARL

The role of neurosurgery in status epilepticus

Yu-tze Ng · Ruth E. Bristol · Dewi V. Schrader · Kris A. Smith

Table 1 Summary of previously published neurosurgery performed for different forms and etiologies of status epilepticus

Number of cases	Age(s)	Diagnosis	Seizure type	Surgical procedure	Author
7	5 mo-6.5 yrs	Hemimegencephaly Encephalomalacia, RE, HD	FMSE CPSE IS	Hemi-spherectomy	Alexopoulos et al. [22] Duane et al. [10]
8	2 mo–31 yrs	FCD (lesional on MRI), Tuberous sclerosis - Multiple tubers	CPSE FMSE Tonic	Focal (cortical) resection	Alexopoulos et al. [22] Ng et al. [9] Ng et al. [11] Xa et al. [20] Gorman et al. [27] Krsek et al. [28]
8	3 mo–36 yrs	Non-lesional MRI scan ± FCD (pathology)	FMSE EPC CPSE	Focal (cortical) resection MSTs	Desbiens et al. [25] Ng et al. [10] Costello et al. [26] D'Giano et al. [14] Xa et al. [23]
2	19 yrs, 29 yrs	FCD Non-lesional	EPC NCSE	Isolated MSTs	Molyneux et al. [13] Bristol et al. [15]
1	30 mo	Hypothalamic hamartoma	Status gelasticus	Transcallosal, endoscopic resection	Ng et al. [9, 12]
1	25 yrs	Non-lesional	GCSE	Corpus callosotomy	Xa et al. [23]
1	2 yrs	Cavernous malformation	EPC	Lesionectomy	Ng et al. [9]
2	13 yrs, 30 yrs	Non-lesional	CPSE GCSE	VNS	Winston et al. [29] Patwardhan et al. [30]

FMSE, focal motor status epilepticus; CPSE, complex partial status epilepticus; RE, Rasmussen encephalitis; HD, hemicortical dysplasia; IS, infantile spasms, FCD, focal cortical dysplasia; EPC, epilepsia partialis continua; MSTs, multiple subpial transections; NCSE, non-convulsive status epilepticus; GCSE, generalized convulsive status epilepticus; VNS, vagus nerve stimulation

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Learning Assessment Question 1:

A 5-year-old boy is brought into the ER, with continuous generalized tonic-clonic activity, i.e. convulsive status epilepticus. The first drug that should be administered is:

A.Fosphenytoin
B.Pyridoxine
C.Lorazepam
D.Phenobarbital

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Learning Assessment Question 1:

A 5-year-old boy is brought into the ER, with continuous generalized tonic-clonic activity, i.e. convulsive status epilepticus. The first drug that should be administered is:

A.Fosphenytoin
B.Pyridoxine
C.Lorazepam
D.Phenobarbital

- **Answer C is the correct answer because benzodiazepines are the first drugs that should be used to stop convulsive seizure activity.**

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Learning Assessment Question 2:

- **A 7-year-old girl with a history of absence epilepsy presents in non-convulsive status epilepticus (confirmed on EEG). Which of the following intravenous drugs should be used?**
  - **A. Fosphenytoin**
  - **B. Valproic acid**
  - **C. Phenobarbital**
  - **D. Lacosamide**

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Learning Assessment Question 2:

- **A 7-year-old girl with a history of absence epilepsy presents in non-convulsive status epilepticus (confirmed on EEG). Which of the following intravenous drugs should be used?**
  - **A. Fosphenytoin**
  - **B. Valproic acid**
  - **C. Phenobarbital**
  - **D. Lacosamide**
- **Answer B is the correct answer as the only (from the choices) broad spectrum drug to treat absence seizures and generalized spike-wave activity.**

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Pharmacologic Management of Coagulopathies

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Emergency Medicine Clinical Specialist
Dept. Pharmacotherapy and Pharmacy Services
University Health System

1

1

Disclosure

- I have no conflict of interest relative to the content of this presentation

2

2

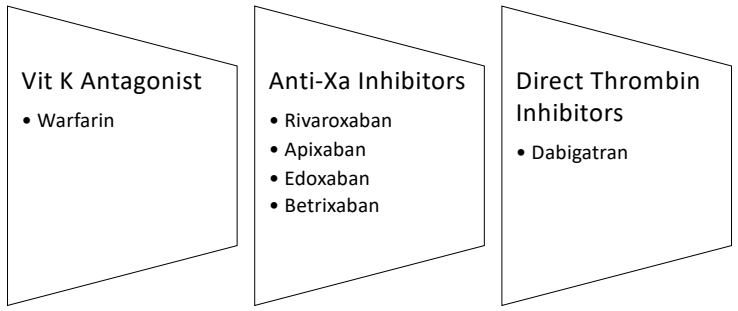
Objectives

- Describe strategies for managing patients **on oral anticoagulants** presenting with hemorrhage
- Detail mechanisms for reversing the effects of vitamin K antagonists and direct oral anticoagulants

3

3

Anticoagulants



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Am J Med. 2015 Dec; 128(12):1300-1305

4

Vitamin K Antagonist (VKA) Reversal

- Four factor prothrombin complex concentrate (4PCC)
  - Standard of care
  - Faster INR normalization and ↓ all cause mortality vs. FFP
- Vitamin K 10 mg IVPB
- 4PCC & IV Vit K work in tandem

	4PCC	IV Vit K
Onset of INR normalization	< 30 min	12 – 14 hrs
Duration	6 – 8 hrs	>48 hrs

Prothrombin complex concentrate. Lexicomp. 2019.
Phytonadione. Lexicomp. 2019
Thromb Haemost. 2016;116(5):879-90.
Circulation. 2013;128(11):1234-43.

5

5

4PCC in the Trauma Bay

- Choose your patients wisely
  - Contraindications
  - PCC can induce DIC absent anticoagulation
- Dosing (max dosing weight 100 kg)

INR 1.4 - <4	INR 4 - 6	INR > 6
25 units/kg	35 units/kg	50 units/kg

Prothrombin complex concentrate. Lexicomp. 2019.
Anesthesiology. 2019; 131(3):543-554
Neurocrit Care. 2016;24(1):6-46

6

6

Assessment Questions

- RL is a 65 kg, 79 yo man with a traumatic subdural hemorrhage s/p fall from 10 ft ladder. RL is on warfarin for atrial fibrillation with an INR of 3. Your hospital uses INR/weight-based dosing (not flat dosing). What is the correct 4-factor PCC dose for RL?
  A. 65 kg x 100 units/kg = 6,500 units
  B. 65 kg x 3 (INR) x 25 units/kg = 4,875 units
  C. 65 kg x 3 (INR) x 35 units/kg = 6,825 units
  D. 65 kg x 25 units/kg = 1,625 units
- Answer D is the correct answer because the 4-factor PCC weight-based dose used for INR 1.4 to <4 is 25 units/kg. 25 units/kg x 65 kg = 1,625 units 4-factor PCC

7

7

Anti-Xa Direct Oral Anticoagulants (DOAC) Reversal

- 4PCC or andexanet alfa?
- 4PCC floods system with inactive clotting factors
  - Is it enough to achieve hemostasis?
- Andexanet alfa is a Factor Xa decoy protein
  - Catalytically inactive
  - High binding affinity for Factor Xa inhibitors

Neurocrit Care. 2016;24(1):6-46
N Engl J Med. 2015;373(25):2413
Ann Pharmacother. 2019;53(9):940-946

8

8

Andexanet Alfa

- FDA approved in May 2018
- Reduces anticoagulant activity
  - Measured by anti-factor Xa activity and thrombin generation
- Onset: ≤ 5 min
- Duration: infusion duration dependent*

N Engl J Med. 2015;373(25):2413
Ann Pharmacother. 2019;53(9):940-946
N Engl J Med. 2019; 380:1326-1335

Andexanet Alfa Dosing

- Two dosing strategies

Dose	Bolus	Infusion
Low Dose	400 mg: 30 mg/min once	480 mg: 4 mg/min x 120 min
High Dose	800 mg: 30 mg/min once	960 mg: 8 mg/min x 120 min

- Dose choice depends on the DOAC and last dose timing

FXa Inhibitor	FXa Inhibitor Dose	Last Dose < 8 hrs ago or unknown	Last Dose ≥ 8 hrs ago
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
Rivaroxaban	> 10 mg/Unknown	High Dose	Low Dose
Apixaban	≤ 5 mg	Low Dose	Low Dose
Apixaban	> 5 mg/Unknown	High Dose	Low Dose

N Engl J Med. 2019; 380:1326-1335

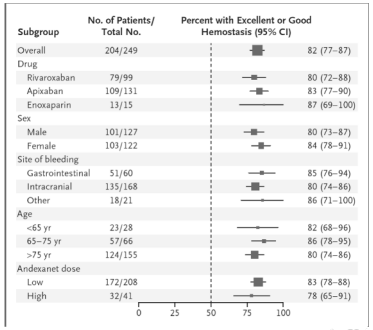
Andexanet Alfa

- Monitoring
- Cost (AWP)
  - Low dose: $29,700
  - High dose: $59,400

N Engl J Med. 2015;373(25):2413
Ann Pharmacother. 2019;53(9):940-946
N Engl J Med. 2019; 380:1326-1335

Andexanet Alfa Efficacy: ANNEXA-4

- Duration
  - Anti-Factor Xa activity
    - 2 hrs after infusion
    - Did not predict efficacy
- Hemostatic outcomes
  - At 12 hours
- Overall mortality: 14%
- No comparator



N Engl J Med. 2019; 380:1326-1335

Anti-Xa Reversal

- Consider DOAC half-life
  - No reversal indicated if last dose > 3 – 5 half lives
    - Caveat: renal disfunction
- Our current practice is 4PCC 50 units/kg
  - Recent internal DUE:
    - 24 hour survival: 92%
    - Survival to hospital discharge: 81%
      - Subgroup of ICH (n=10): 86% survival to hospital discharge

13

Neurocrit Care. 2016;24(1):6-46
Jaeger et al. UHS. 2018. [Unpublished]

13

Andexanet Alfa or 4PCC?

- Limitations in the data for each
- Conflicting society recommendations
- Do not fear "off-label medication use"
- Financial impact should not be ignored

4PCC
(for today)

14

14

Dabigatran Reversal

- Idarucizumab 5g IV
  - Monoclonal antibody binds dabigatran and its metabolites
  - Standard of care
  - Onset: minutes
  - Duration: ≥ 24 hrs

15

N Engl J Med. 2015;373:511
Neurocrit Care. 2016;24(1):6-46
J Am Coll Cardiol. 2017;70(24):3042
Idarucizumab. Lexicomp. 2019.

15

Idarucizumab

- No specific contraindications
- Consider dabigatran half life (12 – 17 hrs)

Last dose taken < 24 hrs ago	• Give idarucizumab 5 g
Last dose taken 24 – 48 hrs ago	• Check a thrombin time (TT) • If TT elevated, give idarucizumab 5 g

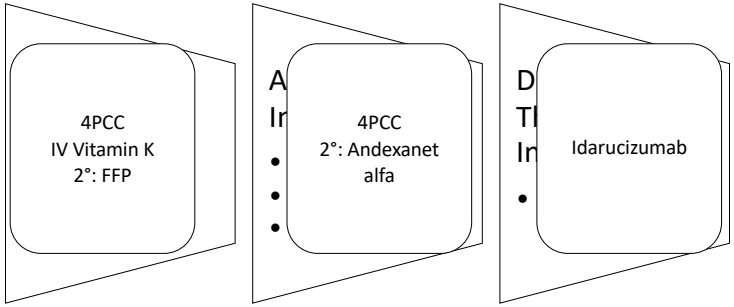
- Consider a second 5 g if bleeding is not controlled & TT ↑↑

16

Neurocrit Care. 2016;24(1):6-46
Idarucizumab. Lexicomp. 2019.
www.entwellbeing.com.au

16

Review



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17

Assessment Questions

- HG is a 43 yo man presents to your trauma bay after an MVC. He requires 4 units of whole blood and is promptly diagnosed grade 3 liver laceration, a grade 2 kidney laceration and significant retroperitoneal bleeding. The property technician finds the patient's medication bottles, one of which is for apixaban 5 mg PO BID for atrial fibrillation. What options do you have to reverse this patient's direct oral anti-Xa inhibitor?
  - A. Nothing but a scalpel
  - B. 4 Factor PCC at 50 units/kg IV
  - C. Andexanet alfa at low dose regimen (400 mg bolus at 30 mg/min followed by 480 mg infusion at 4 mg/min)
  - D. Hemodialysis
  - E. Answer B or C
- Answer E (B or C) is the correct answer because apixaban may be reversed with either 4 factor PCC 50 units/kg or andexanet alfa.

18

18

Innovations in Blood Product Management

September 2020
Donald Jenkins MD FACS
Professor of Surgery
Uniformed Services University
UT Health San Antonio

SCCM Texas

UT Health San Antonio

1

Learning Objectives

- Understand the role of the FDA and the American Association of Blood Banks approval for use of cold stored whole blood and the regulatory compliance associated with this process
- Describe the function of platelets in cold stored whole blood compared to platelet function in apheresis room temperature stored platelets

2

Learning Objectives

- List at least two transfusion triggers for administration of prehospital cold stored whole blood
- Explain the genetic differences leading to Rhesus factor in the human population and the role it plays, especially in the use of Rh+ products in women of child bearing age

3

Acknowledgements

- STRAC (Epley, Schaefer and team) including all EMS, HEMS and trauma centers of South Texas
- COL John Holcomb
- Jim Stubbs, MD, Lisa Button Cathy Berns APRN, CNS, MS and Scott Zietlow MD, Mayo Clinic, Rochester
- Phil Spinella, Mark Yazer and Geir Strandenes, THOR
- COL Andre Cap USAISR
- Elizabeth Waltman and South Texas Blood and Tissue Center
- Dani Cobb, Rachelle Jonas, Caroline Zhu, Doug Pokorny, Susannah Nicholson, Max Braverman and Mark DeRosa UT Health San Antonio
- Bothers in Arms donors

4

Alarhayem AQ et al. 2016

Contents lists available at ScienceDirect

The American Journal of Surgery 2016

journal homepage: www.ajconline.org

Southwestern Surgical Congress

Time is the enemy: Mortality in trauma patients with hemorrhage from torso injury occurs long before the "golden hour"

A.Q. Alarhayem [a], J.G. Myers [a], D. Dent [a], L. Liao [a], M. Muir [a], D. Mueller [a], S. Nicholson [a], R. Cestero [a], M.C. Johnson [a], R. Stewart [a], Grant O'Keefe [b], B.J. Eastridge [a, *]

[a] The University of Texas Health Science Center at San Antonio, Department of Surgery, Division of Trauma, Critical Care, and Acute Care Surgery, United States
[b] University of Washington, Department of Surgery, Division of Trauma and Acute Care Surgery, United States

- NTDB data
- 2.5 million patients retrospective study (2012-14)
- AIS 4 chest and abd, significant TBI excluded
- Prehospital time and mortality

5

5

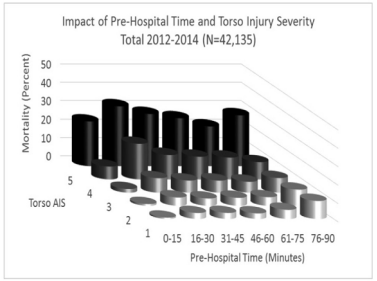


Fig. 1. Mortality Impact of prehospital time and torso injury severity for composite population 2012–2014 (N = 42,135).

Median Prehospital Time = 37 minutes

"We noted a precipitous incremental rise in patient mortality in patients with high-grade injuries at prehospital times 0-15 and 16-30 min, **irrespective of mechanism**."

6

6

Experience and Extrapolation

- 1 January 2015 to 31 August 2017 (32 months) UHS evaluated 16,947 trauma patients.
- 715 of these patients (4.2%) received 1244 units of emergency release blood products (this is before whole blood was available)
- Red cells = 584
- Plasma = 364
- Platelets = 257
- Other = 39

7

Experience and Extrapolation

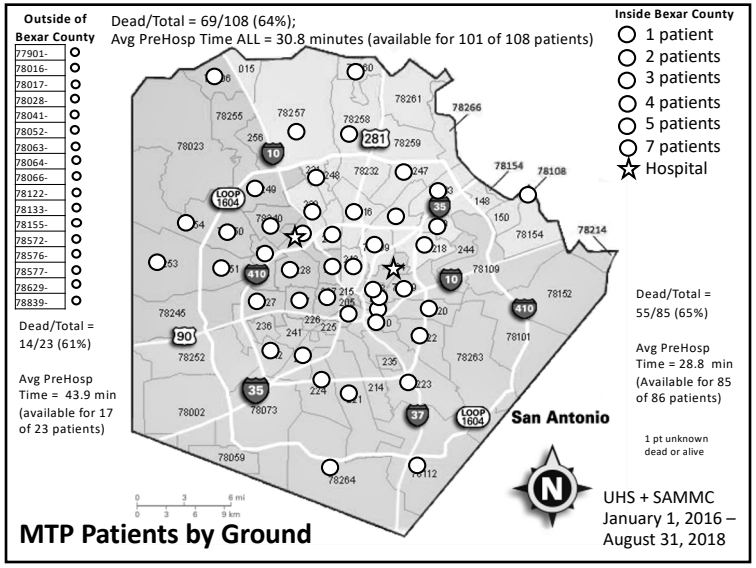
- 289 of those patients died (40%) with an average Injury Severity Score (ISS which has a range of 0-75) of 22
- 124 (17% of emergency release blood product patients and 0.2% of the total) adults required a massive transfusion
  - The mortality in this group was 76%
  - DOA's were excluded (no Lazarus effect)

8

Summary Pediatric Massive Transfusion

- Of 70 pediatric trauma patients:
  - 18 received massive transfusion, defined as 10u of blood products in 24h
    - 7 died (39%)
  - 35 received massive transfusion, defined as 40mL/kg blood products in 24h
    - 14 died (40%)

9



10

Rationale:

Coagulopathy & the "Golden Hour"

- Trauma Induced Coagulopathy (TIC) predicts mortality
- Plasma and RBC resuscitation should occur early in the hemorrhagic / coagulopathic pt
- Catchment area / Rural location provides geographic obstacles

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Hypothesis

- Lack of adequate blood resuscitation in remote regions of STRAC
- Very high mortality in current MTP environment
- No agreed upon transfusion triggers
- No standard hemostatic resuscitation
- No early hemostatic resuscitation

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Answers

- Cold stored whole blood
- Prehospital transfusion protocols need to be written and implemented

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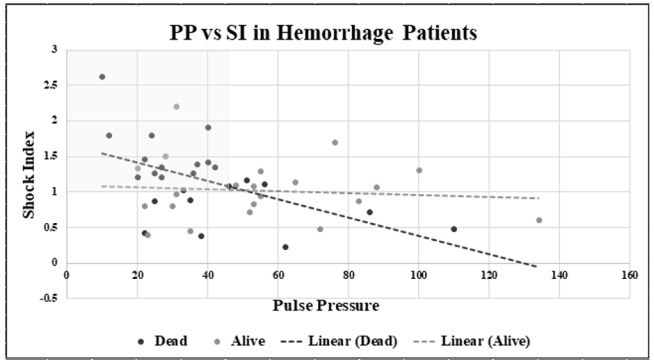
Plot of Pulse Pressure vs Shock Index



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Whole Blood Transfusion Criteria

Transfusion Criteria	
Penetrating Trauma (requires 1 physiologic parameter)	Blunt Trauma (requires 2 physiologic parameter)
Physiologic Parameters	
Patient age ≥ 5	
Single reading of systolic blood pressure (SBP) < 90 mm Hg	
Single reading of heart rate (HR) > 120	
Shock index > 1	
Pulse Pressure < 45	
Positive focused assessment with sonography in trauma (FAST)	
Point of care lactate greater than 5.0 mg/dl	
Known or presumed anticoagulant use; or dual anti-platelet therapy	
Signs of hemorrhage: (high index of suspicion of active internal bleeding or visual evidence of external bleeding)	

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REVIEW ARTICLE

Whole blood for hemostatic resuscitation of major bleeding

Philip C. Spinella,[1,2] Heather F. Pidcoke,[2] Geir Strandenes,[3,4] Tor Hervig,[4] Andrew Fisher,[5] Donald Jenkins,[6] Mark Yazer,[7] James Stubbs,[8] Alan Murdock,[9] Anne Sailliol,[10] Paul M. Ness,[11] and Andrew P. Cap[2]

Trans 2016

- Logistical, economic and clinical benefits of cold stored low titer type O whole blood
- Cold stored for up to 21 days
  - Platelets OK
- Improved function compared to 1:1:1

16

16

Multi-disciplinary and Multi-National Review

SHOCK, Vol. 41, Supplement 1, pp. 70–75, 2014

LOW TITER GROUP O WHOLE BLOOD IN EMERGENCY SITUATIONS

Geir Strandenes,[*†] Olle Berséus,[‡] Andrew P. Cap,[§] Tor Hervig,[*‖] Michael Reade,[¶] Nicolas Prat,[§] Anne Sailliol,[††] Richard Gonzales,[‡‡] Clayton D. Simon,[§§] Paul Ness,[‖‖] Heidi A. Doughty,[¶¶] Philip C. Spinella,[§***] and Einar K. Kristoffersen[*‖]**

[*]Department of Immunology and Transfusion Medicine, Haukeland University Hospital; and [†]Norwegian Naval Special Operation Commando, Bergen, Norway; [‡]Department of Transfusion Medicine, Örebro University Hospital, Örebro, Sweden; [§]US Army Institute of Surgical Research, FT Sam Houston, Texas; [‖]Institute of Clinical Science, The University of Bergen, Norway; [¶]Australian Defense Force Joint Health Command, Canberra, Australian Capital Territory; [**]French Military Medical Service, Clamart, France; [††]Commander French Military Blood Transfusion Center, Clamart, France; [‡‡]Director, US Army Blood Program and [§§]US Army Transfusion Medicine Consultant to the Surgeon General San Antonio Military Medical Center, JBSA–Fort Sam Houston, Texas; [‖‖]Transfusion Medicine Division, Johns Hopkins Medical Institutions, Baltimore, Maryland; [¶¶]NHS Blood and Transplant, Birmingham, England, United Kingdom; and [***]Division of Pediatric Critical Care, Department of Pediatrics, Washington University in St Louis, St Louis, Missouri

Conclusion: Low titer Group O is preferred alternative for emergency transfusions where safe ABO identical transfusions cannot be ensured

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Lactate Clearance

- **Time to clearance clinically and statistically significantly shorter with LTO+WB than with component therapy**
  - **8 vs 13 hours**

Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation
Scheult , Anto, Alarcon, Sperry, Triulzi, and Yazer TRANSFUSION 2018;9999;1–8
doi:10.1111/trf.14779

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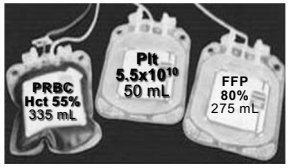
Component Therapy vs. Whole Blood



Component Therapy Gives You
1U PRBC + 1U PLT + 1U FFP + 10 pk Cryo =
- 660 mL
- Hct 29%
- Coag activity 65%
- 750 mg fibrinogen

•Armand & Hess, Transfusion Med. Rev., 2003

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ISBT Science Series
An affiliated publication to Vox Sanguinis
ISBT Science Series (2019) **14**, 308–314

INVITED REVIEW

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DOI: 10.1111/voxs.12501

Platelet functionality in cold-stored whole blood

Einar K. Kristoffersen[1,2] & Torunn Oveland Apelseth[1]
[1]*Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway*
[2]*Department of Clinical Sciences, University of Bergen, Bergen, Norway*

Whole blood is currently being reintroduced as a blood product to be used in massive bleeding situations because it affords plasma, red cells and platelets in a balanced ratio and in a logistical advantageous way. Questions concerning the haemostatic potential of the platelets have arisen, especially in cold-stored whole blood, as this is the major whole blood product in use. When reviewing current knowledge on this, there is an abundance of publications demonstrating that *in vitro*, platelets in cold-stored whole blood have a haemostatic capacity up to 14 days, and even after 21 and 35 days of storage depending on type of additive solution. There is a paucity of data on clinical trials of cold-stored platelets, whereas there is an abundance of previous clinical experience with whole blood, both cold-stored and fresh, as an efficacious and safe product for use in pre- and in-hospital patients with life-threatening bleeding.

Received: 23 April 2019, revised 12 June 2019, accepted 21 June 2019, published online 23 July 2019

Key words: cold storage, massive transfusion, platelet function, platelets, transfusion strategy, whole blood

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- 1:256 titer
- O+
- Male donors
- Cold stored x 35 days
- Waste < 1%

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RBC's vs Whole Blood

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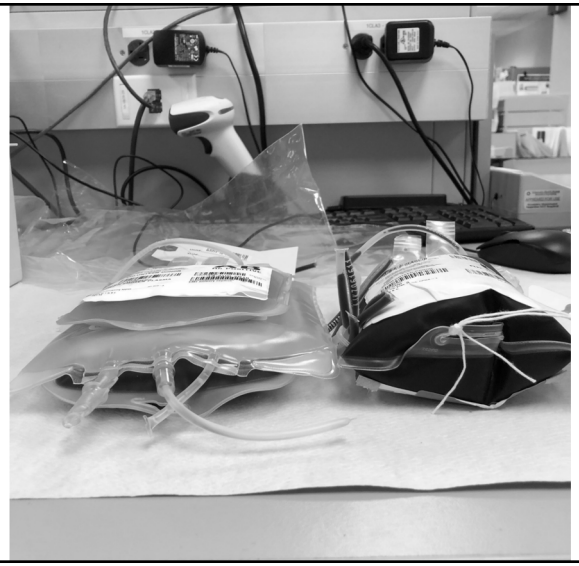

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Advantages of Whole Blood

- Natural
- Organic
- Non-GMO
- Free range
- Gluten Free
- High in protein
- Low in carbs

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Rh Isoimmunization

- Of the 124 patients receiving MTP
  - 26 were women (21%)
  - 18 were age 18-50 (14%)
  - 10 of those 18 died (55%)
  - 16 of the 18 had a type and screen/cross (89%)
  - 1 was Rh negative (6.3%) (she lived)
- Published rate of isoimmunization in Rh- woman 3-6%

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Rh- Data

- Risk of isoimmunization of 0.012 and 0.12 patients/year
- Would take 3000 months (250 years) to have 100 Rh- women of childbearing age receive LTO+WB, and somewhere between 3 and 30 of them would develop isoimmunization without the administration of RhIg
- Without transfusion of LTO+WB in the pre-hospital setting over this time period, nearly 500 women of childbearing age would die of hemorrhage

26

From Yazer at Pittsburgh

0.5% or 3 % risk compared to what?

- San Antonio, Texas
- 250 years to transfuse 100 D- WCP with D+ RBC
- 0.5% fetal risk means 1 fetus dies for every 200 D- WCP transfused with D+ RBCs
- **Would take 500 years for 1 fetus to die!**
- Early intervention with D+ LTOWB would save 1000 women over 500 years!

McGinity AC et al. *J Trauma* 2018: 84:115-119

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Prehospital Cold Stored O+ Whole Blood in San Antonio

- Kicked off January 29 2018
- 18 helicopters
- 2 units each
- Mayo criteria for transfusion
- Women of child bearing potential not excluded—Rh isoimmunization risk versus bleeding to death
- Children 5 years and older

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Whole Blood Workgroup Regional Update

Organization	Type	Status
Acadian Ambulance Service	EMS	Carries LTOWB
Air Evac Lifeteam	Air Medical	Carries LTOWB
Air Methods	Air Medical	Carries LTOWB
Allegiance EMS	EMS	Carries LTOWB
Bandera County EMS	EMS	Carries LTOWB
Bexar County ESD 2	EMS	Carries LTOWB
Bexar County ESD 7	EMS	Carries LTOWB
Bulverde Spring Branch EMS	EMS	Carries LTOWB
Canyon Lake EMS	EMS	Carries LTOWB
Christus Santa Rosa - New Braunfels	Lvl IV Trauma Ctr	Carries LTOWB
Frio Regional Hospital, Pearsall TX	Lvl IV Trauma Ctr	Carries LTOWB
Gonzales County ESD 1 EMS	EMS	Carries LTOWB
Karnes County EMS, Kennedy, TX	EMS	Carries LTOWB
La Salle County EMS	EMS	Carries LTOWB
Methodist Air Care	Air Medicalr	Carries LTOWB
New Braunfels EMS	EMS	Carries LTOWB
San Antonio Fire Department EMS	EMS	Carries LTOWB
San Antonio Military Medical Center	Lvl I Trauma Ctr	Carries LTOWB
Schertz EMS	EMS	Carries LTOWB
Seguin EMS	EMS	Carries LTOWB
University Hospital	Lvl I Trauma Ctr	Carries LTOWB
Wilson County ESD 2	EMS	Carries LTOWB
Wilson County ESD 3	EMS	Carries LTOWB

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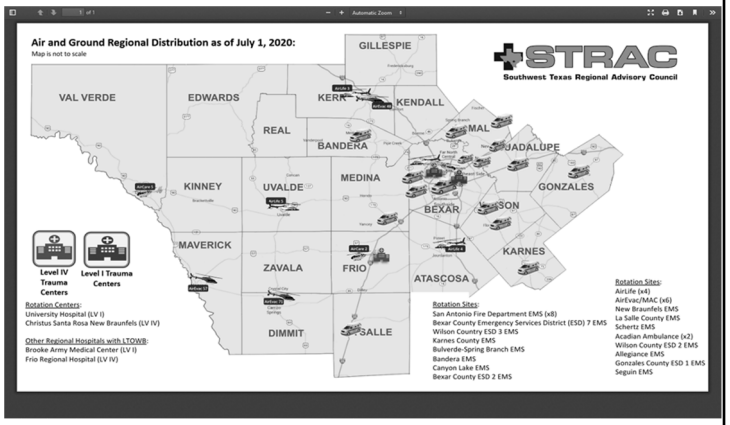

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Contemporary work by Pokorny First Year in Whole Blood Era

- Component therapy emergency transfusion
  - Death rate in trauma room = 24%
  - Time to death = 1 ½ hours
  - Overall mortality 34%
- Whole blood as emergency transfusion
  - Death rate in trauma room = 11%
  - Time to death = 5 ½ hours
  - Overall mortality 27%

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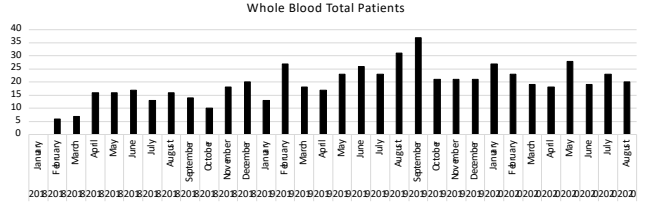
Whole Blood Workgroup

Registry Update (Total Population)

Arrival Year	Arrival Month	Whole Blood	MTP	Emergency Release
2020	August	20	1	23
Total Patients (February 2018 – Present)		**608**	**147**	**779**



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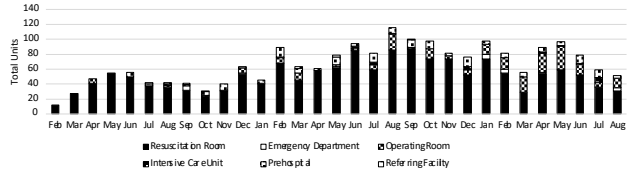
Whole Blood Workgroup

Registry Update (Total Population)

Arrival Year	Arrival Month	TRU	OR	ICU	EC	Prehospital	Referring Facility	Total
2020	August	31	13	0	4	3	0	**51**
Total Units (February 2018 – Present)		1578	236	26	26	174	9	**2049**

Whole Blood Total Units Transfused



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ARMY MEDICINE
Serving To Heal...Honored To Serve

Cold-Stored Platelets for Treatment of Hemorrhage

Better, Safer, Cheaper, Available Now

US Army Institute of Surgical Research

LTC Andrew P. Cap, MD, PhD, FACP
Dr. Heather F. Pidcoke, MD, PhD
Dr. Philip C. Spinella, MD, FCCM

Coagulation and Blood Research Program

October 23, 2013

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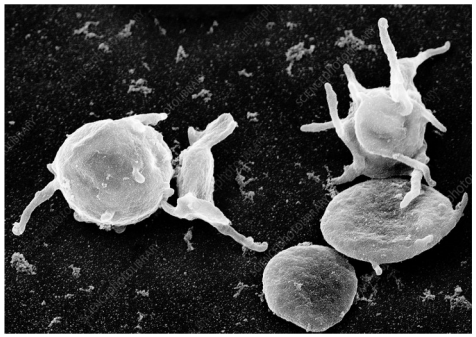

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COLD PLATELETS ARE:

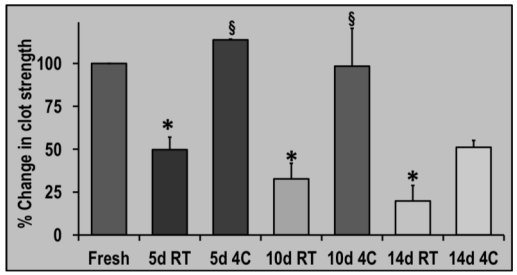
BETTER

- Better hemostatic function:
  - *in vitro* and clinical data demonstrate better:
    - Clot strength
    - TEG
    - Aggregation
    - Metabolics

36

Cold platelets form stronger clots compared to **room temperature (RT)**

∗Compared to Fresh
§Compared to RT



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Becker Study 1973

TABLE 1. *Response of Bleeding Time of Thrombocytopenic Patients to Transfusion of Platelet Preparations*

Platelet Preparations	Number of Patients	Number Improved	Number Not Improved
Fresh	8	6	2
24 hr 22 C	11	7	4
24 hr 4 C	9	6	3
48 hr 22 C	14	4	10
48 hr 4 C	7	4	3
72 hr 22 C	7	1	6
72 hr 4 C	12	8	4
	68	36	32

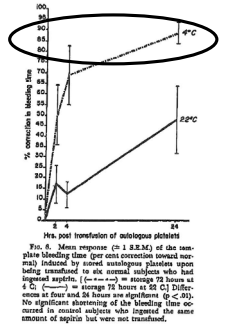

FIG. 6. Mean response (± 1 S.E.M.) of the template bleeding time (per cent correction toward normal) induced by stored autologous platelets upon being transfused to six normal subjects who had ingested aspirin. (– – – –) = storage 72 hours at 4 C; (——) = storage 72 hours at 22 C.] Differences at four and 24 hours are significant. ($p < .01$). No significant shortening of the bleeding time occurred in control subjects who ingested the same amount of aspirin but were not transfused.

89 thrombocytopenic patients
Reduction in clinical bleeding?

84% response rate for 4C-stored vs. 39% for 22C-stored

Becker et al. Transfusion. 1973.

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COLD PLATELETS ARE:

SAFER

- Reduced bacterial growth
  - Less inflammatory material released
- Longer shelf life:
  - could potentially use in critical access hospitals
  - Less waste

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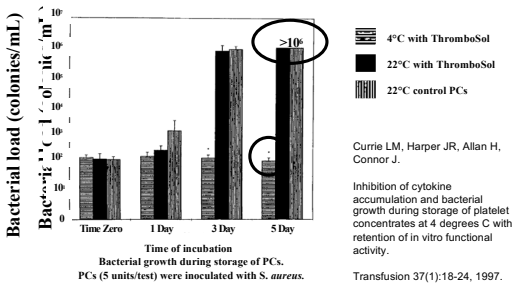
Less bacteria with refrigeration!



Bacterial growth during storage of PCs.
PCs (5 units/test) were inoculated with S. *aureus*.

Currie LM, Harper JR, Allan H, Connor J.

Inhibition of cytokine accumulation and bacterial growth during storage of platelet concentrates at 4 degrees C with retention of in vitro functional activity.

Transfusion 37(1):18-24, 1997.

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Cold Stored Platelets

- At Mayo Clinic since 2015
  - In hospital first
  - Helicopter EMS 2016
- At US Army Institute of Surgical Research
  - 2 week shelf life variance granted by FDA October 2019
- South Texas Blood and Tissue
  - 2 week shelf life license issued by FDA Spring 2020
- At Mayo Clinic
  - 2 week variance approved 2020

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- Cold stored whole blood platelets
  - A. Do not work
  - B. Increase risk of infection
  - C. Are not approved by the FDA
  - D. Are a novel alternative to traditional platelets
- Whole blood
  - A. Is not FDA approved
  - B. Is dangerous
  - C. Has long safety track record
  - D. Has non-functional platelets

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Thank You!

Questions?

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Contact

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The Lethal Diamond: Hypocalcemia and the Lethal Triad

1

Learning objectives:

1. **List physiologic problems in the lethal diamond.**
2. **Discuss the role of calcium in coagulopathy.**
3. **List one reason for adding hypocalcemia to the lethal triad creating the lethal diamond.**

2

Lethal Triad: What is it?

- Lethal triad consists of hypothermia, coagulopathy, and metabolic acidosis
- If this occurs in a trauma patient, increased mortality

3

First, a Case

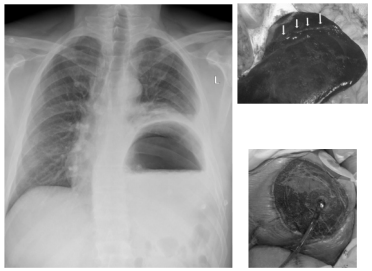
- 16 year old male, s/p MVC, car rolled onto him, late 2018
- On arrival in trauma bay: VS: P150, BP: undetectable Resp: bag-valve mask
- Patient pale appearing, delayed or absent capillary refill
- CPR started
- Massive transfusion started

4

Case

- Patient had large bore IV's placed and massive transfusion protocol (MTP) started
- MTP has 1st box with 4 units PRBC, 2 units FFP and platelets on outside
- OR for bleeding:

Injuries: ruptured diaphragm, ruptured spleen, large segment small intestine devascularized, bleeding mesentery, 2 liters blood



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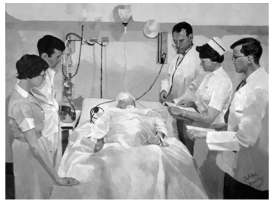
Postop hypothermia, coagulopathy, acidosis

- ABG postop in ICU
- Body Temp: 35.8
- Lactate 7.8, acidosis
- So patient had lethal triad,
- Plus Calcium: 0.69 mmol/L @ 0130
- Patient was noted to get calcium chloride with each PRBC transfusion by 0300



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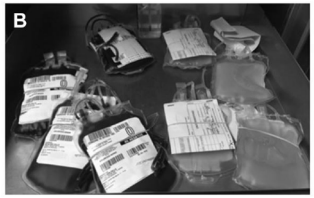
Improving outcomes

- It has been shown to improve outcomes, therapy aimed at the triad improves outcomes
- Coagulopathy: 1:1:1 or WB resuscitation
- Giving PCC or rfVIIa (older)
- Hypothermia: active internal warming, other adjuncts
- Acidosis: bicarbonate, correct with vent



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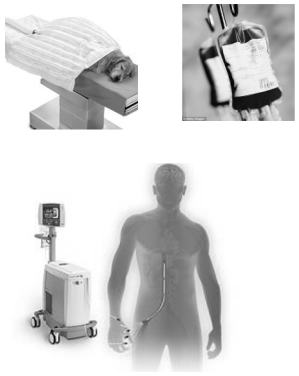
Back to case

- In this case, patient had internal catheter inserted into femoral vein to rewarm. Also active external rewarming with BAIR hugger
- Acidosis treated with Bicarbonate
- Coagulopathy treated with continuing 1:1:1 resuscitation
- Eventually, gave cryoprecipitate with Factor VIIa for a boost. This helped
- Had 4 Code Blue/CPR events
- Repeat surgery early am, to look for any bleeders.
- Total transfusion: over 100 units



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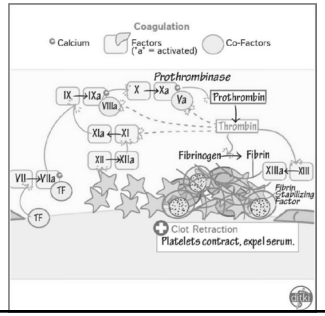
Damage Control resuscitation

- Concept of damage control is to resuscitation to correct coagulopathy
- Just as in damage control surgery, correct the problem
- Frequent ROTEM checks

9

Hypocalcemia

- Hypocalcemia can occur with rapid transfusion of banked blood
- Reason is that citrate is used as anticoagulant in whole blood and PRBC—3g/unit PRBC and 1.66 g/WB.
- Citrate chelates calcium
- Calcium is released by plts in normal clotting, acts as binder to phospholipids and serves as binder to other coagulation factors.



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Bradford Hill Principles for causal relationship

- 1. strength of association
- 2. Consistency- (reproducibility)
- 3. Specificity- Is agent specifically associated with effect
- 4. Temporality—effect occurs after cause
- 5. Biological gradient (dose-response)_Does more or less of agent produce effect in graded response
- 6. Plausibility—Is there a mechanism for effect?
- 7. Coherence—Does laboratory findings correlate with epidemiological findings
- 8. Experiment—Has an experiment been done
- 9. Analogy—Is there a similar finding with similar agents
- 10 Reversibility—If agent or condition is removed is effect removed?

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Hypocalcemia

- Dose response curve of hypocalcemia to number of PRBC transfused. (Kyle et al., 2017)
- Hypocalcemia associated with increased mortality in critically ill and specifically trauma patients (Li, et al, 2015; Lier et al. 2008)
- Hypocalcemia may be present on admission and is associated with increased mortality

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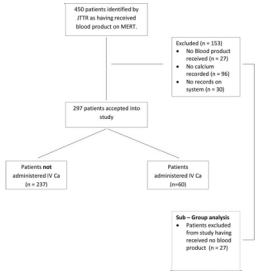
Kyle, 2017



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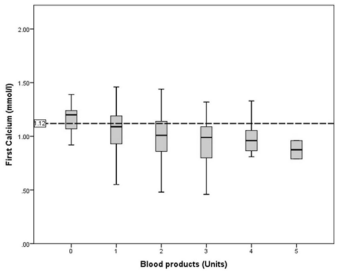
Blood product administration (in units) in the non-treatment group in relation to first recorded serum calcium measurement.



Tony Kyle et al. Emerg Med J 2018;35:176-179

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Studies about hypocalcemia and Trauma mortality

Study	Year	Findings	Bradford Hill
Magnotti Trauma related hypocalcemia	2011	56% of trauma patients on admit had hypocalcemia(CA< 1.0 mmol/L) Lo-Cal group associated with higher mortality (15.5% v 8.7%, p, =.036)	Strength, Temporality
Giancarelli Transfusion related hypocalcemia	2016	97% of MTP patients had hypocalcemia, 71% severe (Ca< .90 mmol/L) Severe hypocalcemic patients had significantly lower plts, pH, higher mortality	Strength, Temporality
Kyle Transfusion induced hypocalcemia	2017	Hypocalcemia in group who did not receive calcium along with blood products transfused en route to facility was70%	Strength, Temporality, Reversibility (Patients who received calcium had less incidence of low calcium)

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Studies about transfusion and calcium

Study	Year	Findings	Bradford Hill
Webster Transfusion related hypocalcemia	2016	Once patient with hypocalcemia got blood products, hypocalcemia significantly increased. Pretransfusion Ica 1.11, after transfusion, 0.98. (p, < .001) 88% hypocalcemia with transfusion.	Strength of association, Specificity, Temporality, Biological gradient
McKay Transfusion related hypocalcemia	2017	85% of trauma patients who received MTP had some hypocalcemia (iCa < 0.86) The extreme hypocalcemic group (iCa< .86) had higher mortality (60% v 4%, p< .01) and more transfusion requirement (14 v 5 units) compared to those with higher ionized calcium	Dose-response or biological gradient, temporal association

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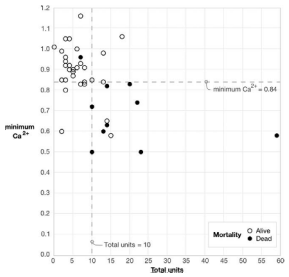
McKay Study



Graph shows higher blood product use with lower ionized calcium, most of mortality with $CA^{2+} < .84$

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Conclusions Hypocalcemia and Trauma

- The recent retrospective studies on trauma patients receiving massive transfusion as well as trauma patients on arrival show a strong association between hypocalcemia and increased mortality and need for further transfusion
- Strength of Association
- Dose Response or Biological Gradient
- Reversibility
- Consistency
- Specificity
- Plausibility--Mechanism

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Experiment

- A double-blind randomized controlled trial has not been done
- Likely difficulty, as giving calcium with transfusions is done frequently
- The interaction with acidosis and coagulopathy is interesting

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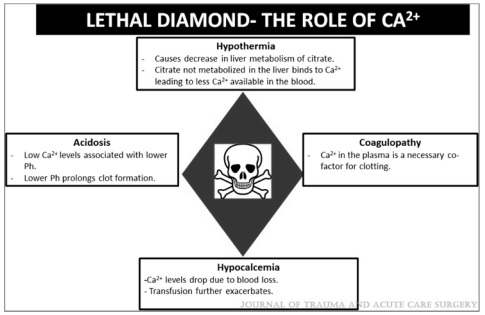
Lethal Diamond



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Our Case

- The patient eventually was able to have closed abdomen.
- Left hospital after two months
- Returned for several more surgeries had postop bleeds
- Diagnosed Factor VII deficiency!
- Went back to high school
- Became bronze medal winner in State Wrestling Championships 2020.
- He signed a wrestling scholarship with Air Force Academy, where he is entering as a freshman.

21

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Learning assessment questions

- 1. Which one is not a component of the lethal triad?
  - A. Metabolic acidosis
  - B. Hypothermia
  - C. Coagulopathy
  - D. Hypokalemia

2. Calcium interacts with factor VIIa of the clotting cascade.
  - A. True
  - B. False

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Use of Vasoactive Therapies: Beyond the Guidelines

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1

Disclosures

No conflicts of interest to disclose

2

Objectives

- Explore the role of new and novel vasopressors, including angiotensin II, compared to traditional vasopressors
- Apply recent evidence on vasopressors to patient scenarios to optimize efficacy and safety
- Review current evidence surrounding vasopressor discontinuation strategies

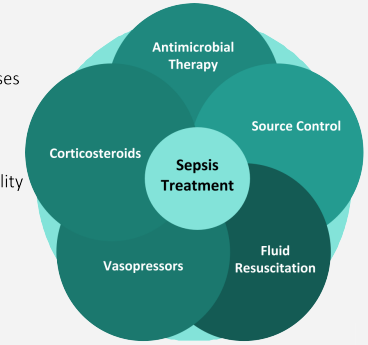
3

Introduction

4

Vasodilatory Shock

- Responsible for ~66% of all shock cases
- Septic shock
  - Majority of vasodilatory shock cases (94%)
  - Significant morbidity and mortality
    - Organ dysfunction
    - Mortality (40-60%)
  - Treatment



Rhodes et al. Crit Care Med 2017;45:486-552.
Rodriguez et al. J Intensive Care Med 2020;35:327-37.

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Vasopressors

- Catecholamines
  - Cornerstone of vasoactive therapy
  - Surviving Sepsis Campaign (SSC) Guidelines
    - First-line: norepinephrine (NE)
  - Risks of catecholamine therapy
    - Tachyarrhythmias
    - Splanchnic hypoperfusion
    - Tissue necrosis

Rhodes et al. Crit Care Med 2017;45:486-552.
Rodriguez et al. J Intensive Care Med 2020;35:327-37.

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Decatecholaminization

- Reducing the use of catecholamines for shock management
  - SSC Guidelines
    - Vasopressin (AVP) recommended second line
      - ↑ mean arterial pressure (MAP)
      - ↓ catecholamine requirement
- Treatment options for patients with catecholamine-resistant vasodilatory shock are limited
  - AVP
  - Corticosteroids
  - Novel vasopressors?

Rodriguez et al. J Intensive Care Med 2020;35:327-37.
Sacha et al. Pharmacotherapy 2020;39:369-81.

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Decatecholaminization with Novel Vasopressors

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Novel Vasopressors

	Mechanism of Action	Half-life (min)	Metabolism	ADRs
Angiotensin II (AT_2)	AT1 receptor agonist	< 1	Aminopeptidase A, angiotensin converting enzyme 2	Thrombosis, HTN, delirium
Selepressin	Selective V1a agonist	90-150	?	Peripheral ischemia, cyanosis, MI
Terlipressin	V1a, V1b, V2 agonist	40	Peptidases	↓ CO, ↑ PVR, ischemic events

ADR: adverse drug reaction; AT1: angiotensin-1; CO: cardiac output; HTN: hypertension; MI: myocardial infarction; PVR: peripheral vascular resistance; V1: vasopressin 1; V2: vasopressin 2

Rodriguez et al. J Intensive Care Med 2020;35:327-37.
Sacha et al. Pharmacotherapy 2020;39:369-81.

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Angiotensin II

- Endogenous renin-angiotensin-aldosterone system hormone
- Binds angiotensin-1 receptor on vascular smooth muscle
  - Potent vasoconstriction
  - ↑ aldosterone, adrenocorticotropic hormone, NE, and AVP release
- Approved in the U.S. for the treatment of severe hypotension

Sacha et al. Pharmacotherapy 2019;39:369-81.
Bauer et al. Pharmacotherapy 2018;38:851-61.

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Angiotensin II for Vasodilatory Shock

- ATHOS-3 Trial
  - International, randomized, double-blind, placebo-controlled trial
  - To determine if angiotensin II (AT_2) improves blood pressure in patients with catecholamine-resistant vasodilatory shock
- Intervention: AT_2 or placebo to increase MAP ≥ 75 mm Hg
  - AT_2 dosing range
    - 0-3 hrs: 20-200 ng/kg/min
    - 3-48 hrs: 1.25-40 ng/kg/min
- Primary endpoint: achievement of MAP goal of ≥ 75 mm Hg or increase MAP of 10 mm Hg from baseline without increase in background vasopressors

Khanna et al. N Eng J Med 2017;377:419-30.

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ATHOS-3 Population

Inclusion Criteria

- ≥ 18 years old
- High-output vasodilatory shock
  - MAP 55 - 70 mm Hg AND
  - Cardiac index ≥ 2.3 L/min/m^2
  - Or, ScvO2 > 70% and CVP > 8 mm Hg
- At least 25 cc/kg volume resuscitation in 24 hr
- Receiving high-dose vasopressors
  - Norepinephrine-equivalent dose (NED) ≥ 0.2 mcg/mg/min for 6 - 48 hr
- Indwelling foley and arterial line

Exclusion Criteria

- Burn > 20 % TBSA
- Acute coronary syndrome
- Bronchospasm
- Liver failure
- Mesenteric ischemia
- Active bleeding
- Abdominal aortic aneurysm
- ANC < 1000 mm^3
- Venoarterial ECMO
- High-dose glucocorticoids

ANC: absolute neutrophil count; CVP: central venous pressure; ECMO: extracorporeal membrane oxygenation; MAP: mean arterial pressure; ScvO2: central venous oxygen saturation; TBSA: total body surface area

Khanna et al. N Eng J Med 2017;377:419-30.

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ATHOS-3 Baseline Characteristics

	AT_2 (N=163)	Placebo (N=158)
Age (years), median (IQR)	63 (52-75)	65 (53-75)
APACHE II score, median (IQR)	27 (22-33)	29 (22-34)
MAP < 65 mm Hg, no. (%)	52 (31.9)	50 (31.6)
Cardiac index (L/min/m^2), median (IQR)	3 (2.6-3.8)	3.2 (2.7-3.9)
Cause of shock - Sepsis, no. (%)	127 (77.9)	132 (83.5)
Exposure to ACE inhibitors/ARBs, no. (%)	26 (15.9)	26 (16.5)

ACE: angiotensin-converting enzyme; APACHE II: Acute Physiology and Chronic Health Evaluation II; ARB: angiotensin-receptor blocker; MAP: mean arterial pressure; NED: norepinephrine-equivalent dose

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Vasopressor Use at Baseline

	AT_2 (N=163)	Placebo (N=158)
NED (mcg/kg/min), median (IQR)	0.33 (0.23-0.56)	0.34 (0.23-0.56)
Distribution, no. (%)		
< 0.35	83 (50.9)	83 (52.5)
≥ 0.35 to < 0.5	34 (20.9)	27 (17.1)
≥ 0.5	46 (28.2)	48 (30.4)
AVP use 6 hr prior to randomization, no. (%)	113 (69.3)	111 (70.3)
Receiving ≥ 2 pressors, no. (%)	114 (69.9)	115 (72.7)
Receiving ≥ 3 pressors, no. (%)	33 (20.2)	32 (20.2)

AVP: vasopressin; NED: norepinephrine-equivalent dose

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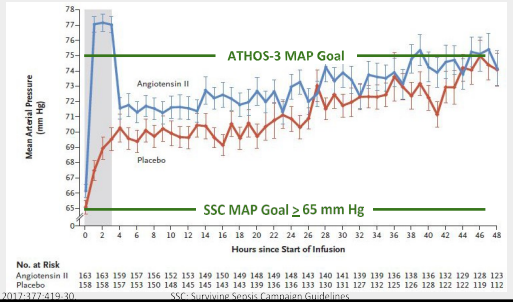
ATHOS-3 Primary Outcome

- MAP response at 3 h: 69.9% AT_2 vs 23.4% placebo (OR 7.95 (4.76-13.3); p<0.01)



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ATHOS-3 Secondary Endpoints

Secondary Endpoints	AT_2 N=163	Placebo N=158	P Value
Change in CV SOFA score at 48 hr	-1.75 ± 1.77	-1.28 ± 1.65	**0.01**
Change in total SOFA score at 48 hr	1.05 ± 5.5	1.04 ± 5.34	0.49
Change in NED at 3 hr	-0.03 ± 0.1	0.03 ± 0.23	**<0.01**
All-cause mortality at day 7, no. (%)	47 (29)	55 (35)	0.22
All-cause mortality at day 28, no. (%)	75 (46)	85 (54)	0.12
Adverse events, no. (%)	142 (87.1)	145 (91.8)	--

Values reported at mean ± standard deviation unless otherwise noted
AT_2: angiotensin II; CV: cardiovascular; NED: norepinephrine-equivalent dose in mcg/kg/min; SOFA: Sequential Organ Failure Assessment

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ATHOS-3 Conclusions

- Patients who received AT_2
  - ↑ MAP response at 3 hours
  - ↓ cardiovascular SOFA score at 48 hrs
  - ↓ catecholamine requirements
- No difference in adverse effects

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ATHOS-3 Critiques and Unanswered Questions

- Small sample size
- Concerns for potential unblinding
- Appropriate antibiotic therapy not reported
- MAP goal > 75 mm Hg
- Lacking improvement in patient-centered outcomes
- Currently only studied as add-on therapy
- Cost
- Safety concerns
  - Not powered to detect differences in mortality or adverse effects

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AT_2 Safety Concerns

Incidence of AT_2 Adverse Reactions Listed in U.S. Package Insert

	AT_2 (N=163)	Placebo (N=158)	Risk Difference %, (95% CI)	P value
Thrombotic events	21 (12.9)	8 (5.1)	**7.8 (1.6 to 14)**	**0.02**
Deep vein thrombosis	7 (4.3)	0 (0)	**4.3 (1.2 to 7.4)**	**0.01**
Thrombocytopenia	16 (9.8)	**11 (7)**	2.9 (-3.2 to 8.9)	0.42
Tachycardia	14 (8.6)	9 (5.7)	2.9 (-2.7 to 8.5)	0.39
Fungal infection	10 (6.1)	2 (1.3)	4.9 (0.8 to 8.9)	0.04
Delirium	9 (5.5)	1 (0.06)	**4.9 (1.2 to 8.6)**	**0.02**
Acidosis	9 (5.5)	1 (0.06)	**4.9 (1.2 to 8.6)**	**0.02**
Hyperglycemia	7 (4.3)	4 (2.5)	1.8 (-2.2 to 5.7)	0.54
Peripheral ischemia	7 (4.3)	4 (2.5)	1.8 (-2.2 to 5.7)	0.54

Data presented as no. (%)

La Jolla Pharmaceutical Company. Giapreza (angiotensin II) [package insert]. SanDiego, CA:2017; Bauer et al. Pharmacotherapy 2018;38:851-61.

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AT_2 Improved Mortality in RRT

- Acute kidney injury (AKI) commonly complicates the course of vasodilatory shock
- AT_2 preferentially vasoconstricts efferent renal arterioles
  - ↑ renal perfusion pressure and filtration
- Post-hoc analysis of ATHOS-3 to asses AT_2 effect on survival and renal recovery
  - Included patients with AKI treated with renal replacement therapy (RRT) at baseline
    - AT_2 = 45 patients, Placebo = 60 patients
  - AT_2 improved survival at 28 days (53% vs 30%; HR 0.52 (0.3-0.87), p=0.01)
  - AT_2 ↑ RRT liberation at day 7 (38% vs 15%; HR 2.9 (1.29-6.52), p=0.01)
- Hypothesis generating for future randomized controlled trials

Tumlin et al. Crit Care Med 2018;46:949-57.
Bauer et al. Pharmacotherapy 2018;38:851-61.

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Serum Renin Levels to Predict AT_2 Response

- Reduced ACE and AT_2 levels have been associated with negative outcomes in sepsis
- Post-hoc analysis of ATHOS-3 (n=255)
  - To determine if ACE insufficiency as identified by serum renin concentration ([SrRenin]) would predict worse outcomes
- Baseline [SrRenin] did not change MAP response at 3 hr
- Patients with [SrRenin] above median study population
  - Independent ↑ risk of mortality (HR 2.15; 95% CI 1.35-3.42)
    - Exogenous AT_2 ↓ mortality risk (51% vs 70%; p=0.01)
  - AT_2 ↑ RRT liberation at day 7 (43% vs 12%; p=0.01)
  - AT_2 ↑ ICU discharge at day 28 (44% vs 22%; p=0.02)
- Hypothesis generating
  - Potential for [SrRenin] to identify patients most likely to benefit from exogenous AT_2

Bellomo et al. Am J Respir Crit Care Med 2020;https://doi: 10.1164/rccm.201911-2172OC [Epub ahead of print]

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AT_2 Conclusions

- Pending SSC Guideline recommendations
- Current place in therapy unknown
  - Increases MAP in catecholamine-resistant vasodilatory shock
  - No improvement in clinically meaningful efficacy data
  - ATHOS-3 underpowered to assess adverse event profile
- Targeted populations requiring further investigation
  - Acute RRT
  - ACE or AT_2 insufficiency
  - Patients on prior ACE-I/ARB therapy

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AT_2 Current Place in Clinical Practice

In which septic shock patient <u>not</u> meeting their MAP goal would it be most appropriate to consider AT_2?

A. Patient in transplant ICU on NE and AVP with CI 1.7 and an elevated renin concentration
B. Patient on NE, AVP, and epinephrine with recent pulmonary embolism diagnosis due to PMH of hypercoagulable state
C. Patient on NE, AVP, and phenylephrine with CI 3.5 and initiated on RRT during ICU admission for AKI
D. Patient with burn wound infection after 30% TBSA burns with CI 3 on NE and AVP

AKI: acute kidney injury; AVP: vasopressin; CI: cardiac index in L/min/m^2; ICU: intensive care unit; NE: norepinephrine; PMH: past medical history; RRT: renal replacement therapy; TBSA: total body surface area

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Novel Vasopressors

	Mechanism of Action	Half-life (min)	Metabolism	ADRs
Angiotensin II (AT_2)	AT1 receptor agonist	<1	Aminopeptidase A, angiotensin converting enzyme 2	Thrombosis, HTN, metabolic alkalosis, delirium
Selepressin	<u>Selective</u> V1a agonist	90-150	?	Peripheral ischemia, cyanosis, MI
Terlipressin	V1a, V1b, V2 agonist	40	Peptidases	↓ CO, ↑ PVR, ischemic events

ADR: adverse drug reaction; AT1: angiotensin-1; CO: cardiac output; HTN: hypertension; MI: myocardial infarction; PVR: peripheral vascular resistance; V1: vasopressin 1; V2: vasopressin 2

Rodriguez et al. J Intensive Care Med 2020;35:327-37.
Sacha et al. Pharmacotherapy 2020;39:369-81

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Selepressin Does Not Improve Outcomes in Septic Shock

	Russell et al. 2017 N=52	SEPSIS-ACT 2019 N = 828
Trial Design	Phase IIa, DB, PC, RCT	Phase IIb/III, blinded, PC, RCT
Inclusion	-Adult septic shock patients -Requiring NE ≥0.1 mcg/kg/min for ≥ 2 hr	-Adult septic shock patients -Requiring NE > 5 mcg/min for > 1 hr despite 1 L fluid resuscitation
Intervention	Patients randomized to one of three fixed-doses of selepressin vs placebo	Selepressin vs placebo w/in 12 h shock onset
Outcomes	-No difference in MAP stabilization, shock resolution time, LOS, mortality -↓ vasopressor requirements -↑ time alive and free of MV at 7 days*	-No difference in ventilator-, vasopressor-, or RRT-free days, LOS, or mortality **Trial terminated early for futility**
ADRs	No difference	No difference

*: with selepressin 2.5 ng/kg/min dose only; ADR: adverse drug reaction; DB: double blind; LOS: length of stay; MAP: mean arterial pressure; MV: mechanical ventilation; NE: norepinephrine; PC: placebo-controlled; RCT: randomized controlled trial; RRT: renal-replacement therapy

Rodriguez et al. J Intensive Care Med 2020;35:327-37. Laterre et al. JAMA 2019;322:1476-85. Russell et al. CriticalCare 2017;21:213-22.

25

25

Terlipressin

- Long-acting vasopressin analog
- Approved in European for treatment of hepatorenal syndrome
- Trials have investigated terlipressin as monotherapy and in combination with other pressors in septic shock (+/- cirrhosis)
  - Heterogeneity in patient populations, dosing and comparator arms
- Effective as mono or combination therapy in ↑ MAP and ↓ vasopressor doses
- Adverse effects
  - ↑ ischemic events
  - ↑ incidence when added to NE
- Further studies warranted in septic shock

Rodriguez et al. J Intensive Care Med 2020;35:327-37.

26

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Recovery Phase of Sepsis:

Vasopressor discontinuation strategies

27

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Recovery Phase of Sepsis

- Weaning and discontinuation of vasopressors
  - Lack of guidance provided by the SSC Guidelines
  - Optimal approach to vasopressor weaning unknown
- Relative AVP deficiency in septic shock
  - Endogenous AVP concentrations
    - Elevated early
    - Decrease to normal ranges within 24-48 h
  - Duration of deficiency unknown
  - May provide rationale to discontinue AVP last or continue beyond shock reversal

Russell et al. N Eng J Med 2008;358:877-87.
Russell et al. Critical Care 2011;15:226-45.

28

28

Summary of Recent Single-Center Trials

Study	Design	Inclusion	Primary Outcome	HypoTN ↑ with AVP DC First?	Change in LOS/Mortality
Hammond et al. 2017 (n=154)	Retrospective cohort	NE + AVP for septic shock	HypoTN • MAP < 60 requiring intervention	Yes (68% vs 11%; p<0.01	No
Bissell et al. 2017 (n=61)	Retrospective cohort	NE + AVP for sepsis or septic shock	HypoTN w/in 24 h • MAP < 60 x 2, addition or increase of vasopressor, fluid bolus	Yes (74% vs 17%; p<0.01)	No
Sacha et al. 2018 (n=585)	Retrospective cohort	NE + AVP for septic shock	HypoTN w/in 24 h • MAP < 60 requiring intervention	No (Yes in MVA)	No
Musallam et al. 2018 (n=80)	Retrospective cohort	NE + AVP for septic shock	HypoTN w/in 24 h • MAP ≤ 65 requiring intervention	Yes (29% vs 62%; p<0.01)	↑ ICU LOS if NE DC first
Jeon et al. 2018 (n=78)	Prospective, DB, RCT	NE + AVP for septic shock	HypoTN at 1 hr • MAP < 65 despite fluids	No (68% vs 23%; p<0.01)	↓

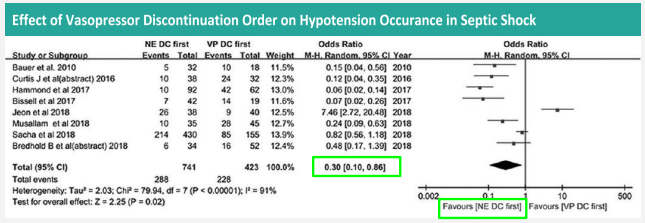
AVP: vasopressin; DB: double-blind; DC: discontinued; HypoTN: hypotension; ICU: intensive care unit; LOS: length of stay; MAP: mean arterial pressure in mm Hg; MVA: multivariate analysis; NE: norepinephrine; RCT: randomized controlled trial

Hammond et al. J Intensive Care Med 2017:https://doi: 10.1177/0885066617714209 [Epub ahead of print]. Bissell et al. J Intensive Care Med 2017:https://doi: 10.1177/0885066617716396 [Epub ahead of print]. Sacha et al. Pharmacotherapy 2018;38:319-26. Musallam et al. Ann Pharmacother 2018;52:233-9. Jeon et al. Critical Care 2018;22:131-42.

29

Meta-Analysis 2020

- Included 1 prospective RCT, 5 retrospective cohorts, 2 retrospective abstracts
- Primary outcome:



- Secondary outcomes: no difference in LOS or mortality

Wu et al. Shock 2020;53:50-7.

30

Recovery Phase of Septic Shock - AVP the MVP?

- Incidence and duration of sepsis-induced AVP deficiency unknown
  - May be favorable to wean AVP last
- Available clinical trials suggest that weaning AVP last:
  - May ↓ recurrence of hypotension
  - No effect on LOS or mortality
- Multicenter, prospective, protocolized RCTs warranted
- Cost-effectiveness of discontinuing AVP last should be considered

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Conclusion

- Dechatecholiminization using novel vasopressors
  - AT_2 only novel vasopressor approved in U.S.
    - ↑ MAP
    - Unknown impact on patient-centered outcomes
    - Optimum patient population for use unknown
    - Further investigation of adverse effects warranted
- Discontinuation of vasopressors in recovery phase of shock
  - Relative AVP deficiency in septic shock
  - Limited evidence investigating optimal weaning strategy
  - Discontinuing AVP last may ↓ incidence of hypotension with no impact on clinical outcomes

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Learning Assessment Questions

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Learning Assessment Question #1

Which of the following is incorrect regarding angiotensin II (AT_2)?

A. AT_2 is an endogenous hormone in the renin-angiotensin-aldosterone system
B. AT_2 administration results in vasoconstriction via the angiotensin-1 receptor and increased release of aldosterone, norepinephrine, and vasopressin
C. AT_2 use is associated with improved mortality in vasodilatory shock
D. AT_2 may not be appropriate for patients with reduced cardiac output

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Learning Assessment Question #2

In adult patients recovering from septic shock receiving vasopressin and norepinephrine, the incidence of hypotension may be decreased if vasopressin is discontinued last

A. True
B. False

35

35

Thank you!

Emily Hodge
emily.hodge@ascension.org

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What's the correct MAP goal in septic shock?

Ashish K.Khanna MD.,FCCP.,FCCM
Associate Professor & Section Head for Research
Department of Anesthesiology, Section on Critical Care Medicine

Wake Forest School of Medicine

1

Disclosures

- Edwards Lifesciences
- Medtronic
- Philips North America
- Zoll Medical
- NIH/NCATS KL2 Wake Forest CTSI

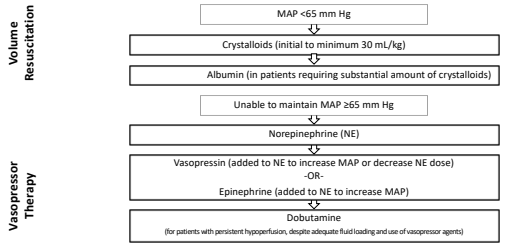
2

Learning Objectives

- Define and describe effects of different degrees of hypotension in critically ill patients
- Explore literature assessing alternate mean arterial pressure goals
- Determine patient populations which may benefit from alternate mean arterial pressure goals

3

Guidelines for Management of Hypotension in Sepsis and Septic Shock →MAP 65mmHg



Rhodes A, et al. Intensive Care Medicine 2017

4

Burden of hypotension in the ICU

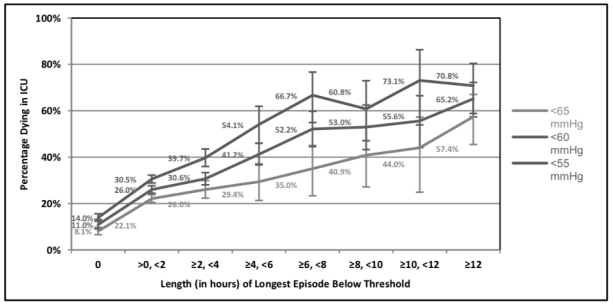
	Length (in hours) of Longest Episode Below Threshold							
	0	>0, <2	≥2, <4	≥4, <6	≥6, <8	≥8, <10	≥10, <12	≥
MAP <65 mmHg								
N	357	1799	1529	776	431	235	159	4
Age (mean)	59.6	65.1	67.1	67.6	68.1	69.5	68.1	6
Severe Sepsis or Septic Shock (%)	55.7	66.6	73.0	71.9	75.9	77.4	81.8	85.4
MAP (mean) at admission	82.4	78.7	74.9	74.4	72.8	68.8	69.2	67.7
MAP <60 mmHg								
N	904	2724	1192	417	161	100	72	155
Age (mean)	61.2	66.5	68.0	69.9	68.4	69.8	69.5	67.9
Severe sepsis or septic shock (%)	58.4	71.0	74.9	79.4	84.5	74.0	79.2	85.2
MAP (mean) at admission	81.0	76.7	72.8	71.5	70.6	64.9	66.4	65.6
MAP <55 mmHg								
N	1799	2917	650	148	69	51	26	65
Age (mean)	63.0	67.4	70.4	69.5	66.6	68.4	67.2	67.6
Severe sepsis or septic shock (%)	62.9	73.9	77.7	79.1	84.1	80.4	76.9	89.2
MAP (mean) at admission	79.4	74.8	71.2	70.1	65.3	62.6	63.0	66.8

62%<65mmHg
37%<60mmHg
18%<55mmHg

Khanna AK, et al. SOCCA 2018 (MIMIC-III Data)

5

Burden of hypotension in the ICU



Khanna AK, et al. SOCCA 2018 (MIMIC-III Data)

6

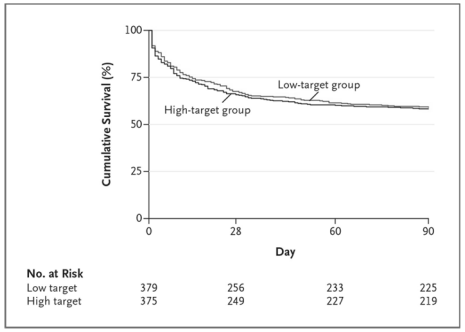
What is an appropriate MAP in the ICU?

Reference	Study design	Number of patients	Targeted MAP, mm Hg	Primary outcomes	Severity score	28-day mortality, %
LeDoux *et al.* [18] (2000)	Prospective cohort	10	65, 75, 85	Regional circulation and oxygen metabolism	APACHE II: 29	70
Bourgoin *et al.* [19] (2005)	Randomized clinical trial	28	65, 85	Regional circulation and oxygen metabolism	APACHE II: 27	NA
Deruddre *et al.* [20] (2007)	Prospective cohort	11	65, 75, 85	Renal perfusion	SAPS II: 57	NA
Jhanji *et al.* [21] (2009)	Prospective cohort	16	60, 70, 80, 90	Microcirculation	APACHE II: 23	62.5
Thooft *et al.* [22] (2011)	Prospective cohort	13	65, 75, 85, 65	Microcirculation	APACHE II: 23	17
Dubin *et al.* [23] (2009)	Prospective cohort	20	65, 75, 85	Microcirculation	APACHE II: 24	50
Asfar *et al.* [24] (2014)	Randomized clinical trial	776	65, 85	28-day mortality	SAPS II: 57	35

APACHE II, Acute Physiology and Chronic Health Evaluation II; MAP, mean arterial pressure; NA, not available; SAPS II, Simplified Acute Physiology Score II.

7

High versus low blood pressure targets



776 septic shock patients

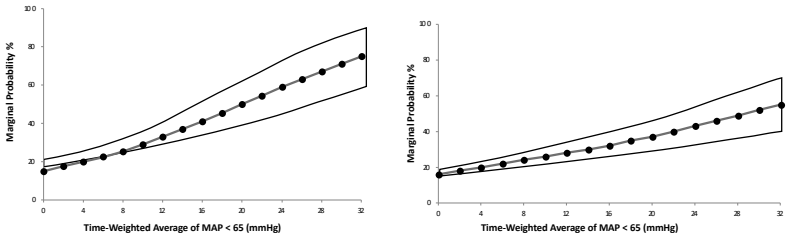
Mean arterial pressure target 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group)

Asfar P, et al. NEJM 2014

8

What is the true threshold of hypotension in the ICU?

Maheshwari K, Khanna AK, Sessler DI et al. Intensive Care Med 2018



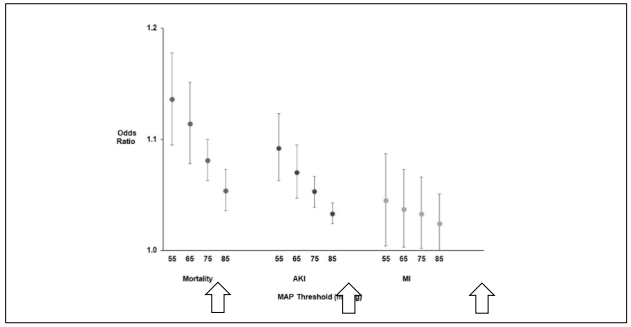
Predicted Marginal Probability of Mortality **Predicted Marginal Probability of AKI**

For Every One Unit Increase in TWA-MAP < 65 mmHg, the Odds of In-hospital Mortality Increased 11.4% (95% CI 7.8%, 15.1%, *p* < 0.001); the Odds of AKI Increased 7.0% (4.7, 9.5%, *p* < 0.001)

9

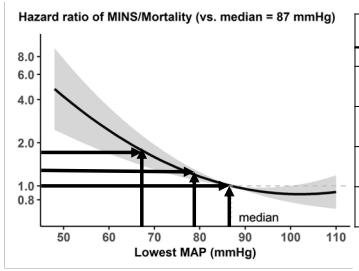
What is the true threshold of hypotension in the ICU?

Maheshwari K, Khanna AK, Sessler DI et al. Intensive Care Med 2018



10

What is the true threshold of hypotension in the postoperative ICU?



	Incidence	Hazard Ratio (95% CI) *		p-value
		Comparing to Median (87 mmHg)		
MINS/mortality	98 (3.5%)	5th percentile (67mmHg)	1.67 (1.26, 2.22)	<0.001*
		25th percentile (78 mmHg)	1.23 (1.12, 1.35)	0.001*
		75th percentile (98 mmHg)	0.88 (0.79, 0.99)	0.095
		95th percentile (109 mmHg)	0.88 (0.64, 1.23)	0.463

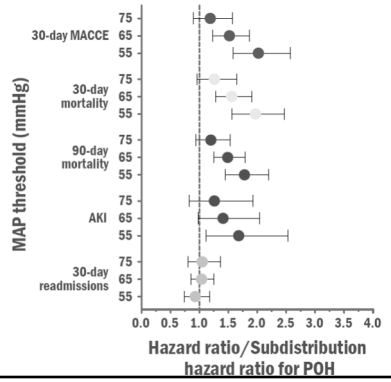
Hypotension associated postoperative outcomes were dependent on intraoperative hypotension

Khanna AK, et al. CCM 2019

11

Hypotension in the postoperative ICU

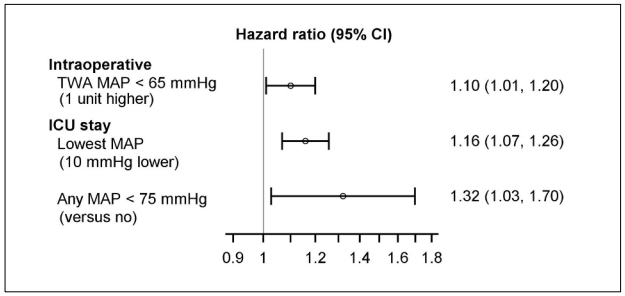
without intraoperative hypotension



Khanna AK., et al (SCCM 2020)

12

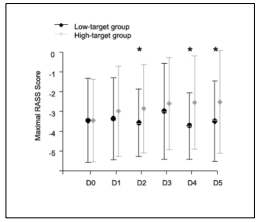
Hypotension in the ICU – Delirium thresholds

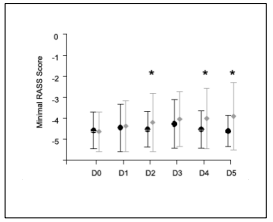


Maheshwari K, Khanna AK, Sessler DI et al.
Anesthesia & Analgesia, 2019

13

Septic shock + sedation does hypotension change arousal outcomes?





532 patients with similar total cumulative sedation in the ICU
RASS difference ? Clinically significant

Jouan Y, Asfar P et al., (SEPSISPAM)
Ann. of Intensive Care 2019

14

Specific situations – Cirrhosis

- Cirrhotic patient – vasodilated, high output, but low MAP
- Thresholds 75-55mmhg (5mm intervals)
- Time - weighted-average MAP: for 1 mm Hg decrease in mean arterial pressure below thresholds
- Adjusted association: significant at all thresholds
- Odds for ICU mortality : 14%, 18%, 26%, 41%, and 74%
- Cumulative time below MAP, for each one hour < MAP thresholds
- Adjusted association significant at : MAP < 65mm Hg and < 60 mm Hg
- Odds for ICU mortality : 10% and 12%
- **Is 65mmHg the sweet spot?**

Patidar K et al., CCM 2020

15

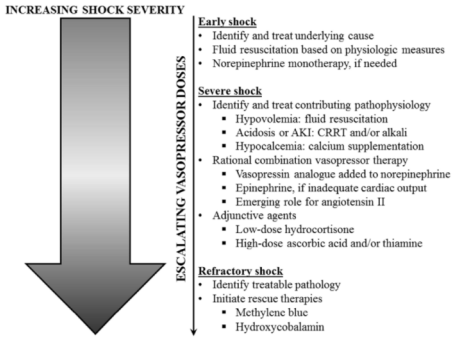
Specific situations – Relative hypotension & kidney injury

- Prospective observational cohort (n=302), >4hrs on vasopressors
- Time-weighted-average mean perfusion pressure (MPP)-deficit (% difference pre-illness basal-MPP and achieved-MPP) during vasopressor- support
- **Pre-illness basal-MPP for the cohort : 45 mmHg - 105 mmHg**
- Every % increase in time-weighted-average MPP-deficit, multivariable-adjusted odds of new significant AKI and MAKE increased by 5.6% (95% confidence interval: 2.2- 9.1; *P*=0.001) and 5.9% (2.2-9.8; *P*=0.002) respectively

Panwar K et al., AJRCCM 2020

16

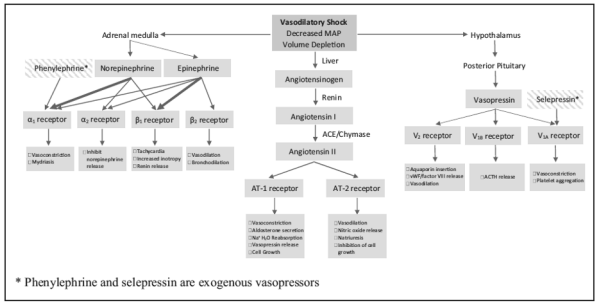
How should I best defend a MAP in the ICU?



Jentzer JC, Khanna AK, et al. Chest 2018

17

A synergistic model Mechanism of actim



Wakefield B, Sacha G, Khanna AK , Current Opinion in Critical Care 2018

18

Intubation in Septic Shock & subsequent Hypotension

	Model 1			Model 2	
Predictor	Coefficient	OR		Coefficient	OR
Intercept	-1.988			-1.733	
APACHE II score, per 1 point increase	0.014	1.01			
Cirrhosis	-0.138	0.87			
Age, per year increase	0.013	1.01		0.012	1.01
Intubation indication = cardiac arrest	1.114	3.04		1.001	2.72
Diuretics in prior 24 hours	0.343	1.41		0.290	1.34
Catecholamine 60 minutes prior to intubation	0.956	2.60		0.917	2.50
Systolic blood pressure					
≥130 mmHg	**0.000**	**1.00**		**0.000**	**1.00**
per mmHg below 130	**0.016**	**1.02**		**0.015**	**1.02**
Etomidate used during intubation	-0.146	0.86		-0.085	0.92

Smischney N, Khanna AK, SCCM Discovery HEMAIR investigators et al. PLOS ONE 2020

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Intubation in Septic Shock & subsequent Hypotension

	Model 3			Model 4	
Predictor	Coefficient	OR		Coefficient	OR
Intercept	-1.961			-1.74	
APACHE II score, per 1 point increase	0.014	1.01			
Cirrhosis	-0.262	0.77			
Age, per year increase	0.012	1.01		0.012	1.01
Intubation indication = shock	0.669	1.95		0.639	1.89
Intubation indication = cardiac arrest	1.000	2.72		0.917	2.50
Diuretics in prior 24 hours	0.379	1.46		0.338	1.40
Pre-intubation hypovolemic shock[c]	0.100	1.11		0.029	1.03
Catecholamine 60 minutes prior to intubation	0.768	2.16		0.740	2.10
Mean arterial blood pressure					
≥95 mmHg	**0.000**	**1.00**		**0.000**	**1.00**
per mmHg below 95	**0.017**	**1.02**		**0.016**	**1.02**
Etomidate used during intubation	-0.237	0.79		-0.174	0.84

Smischney N, Khanna AK, SCCM Discovery HEMAIR investigators et al. PLOS ONE 2020

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Less is more!

Intensive Care Med (2019) 45:1810–1812
https://doi.org/10.1007/s00134-019-05770-3

LESS IS MORE IN INTENSIVE CARE

Less is more: catecholamine-sparing strategies in septic shock

Balasubramanian Venkatesh[1,2,3,4,5*], Ashish K. Khanna[6] and Jeremy Cohen[1,3,5,7]

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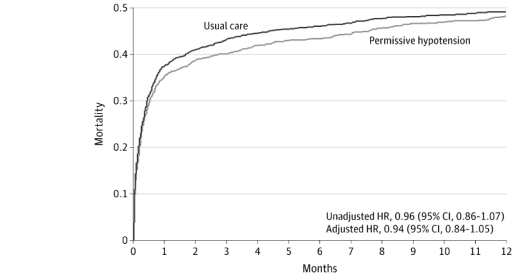
Less exposure to vasopressors may be better?



No. at risk

Permissive hypotension	1283	794	743	721	699	667	631	596	545	509	480	442	409
Usual care	1300	772	727	697	677	642	604	569	525	489	459	435	395

Lamontagne, F et al. JAMA 2020

22

Critical pressures in the ICU → >MAP 65mmHg or greater or ?

Intensive Care Med
https://doi.org/10.1007/s00134-018-5292-8

EDITORIAL

MAP of 65: target of the past?

Pierre Asfar[1*], Peter Radermacher[2] and Marlies Ostermann[3]

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23

Critical pressures in the ICU → >MAP 65mmHg or greater or ?

Khanna *Ann. Intensive Care (2018) 8:116*
https://doi.org/10.1186/s13613-018-0463-x

Annals of Intensive Care

Defending a mean arterial pressure in the intensive care unit: Are we there yet?

Ashish K. Khanna*

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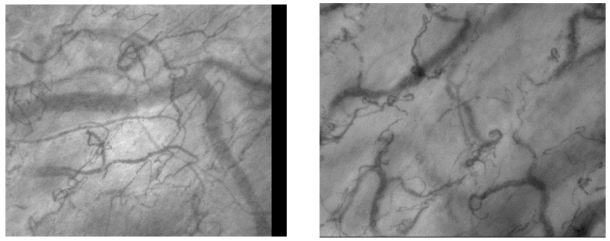
Never forget perfusion!



Healthy **Sepsis-late**

25

The blood pressure story in septic shock

- Surviving sepsis guidelines - MAP of at least 65mmhg
- RCT data no difference in outcomes
- Recent large datasets : association of increasing kidney & myocardial injury/mortality and delirium with mean pressures 85-55mmHg
- Consider relative hypotension and specific organ system injury (cirrhosis)
- Management practices demand a combination of fluids and vasopressors and adjunctive therapy in synergism
- Tissue perfusion may be as important as mean arterial pressure

26

They were simply not names on a list.
They were <u>Us.</u>

200,000 people, 900 healthcare workers…and many more


The New York Times

U.S. DEATHS NEAR 100,000, AN INCALCULABLE LOSS

27

Stay Safe….

10/11/20 28

28

What's the correct MAP goal in septic shock?

Ashish K.Khanna MD.,FCCP.,FCCM
Associate Professor & Section Head for Research
Department of Anesthesiology, Section on Critical Care Medicine

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29

Fluid Resuscitation and De-Resuscitation Strategies

Kevin Proud MD, FCCP
Associate Professor
UT Health San Antonio
South Texas Veterans Health Care System

1

Learning Objectives

- Evaluate recommended fluid resuscitation goals in critically ill patients
- Examine the role of fluid stewardship in critically ill patients
- Assess outcomes of de-resuscitation in critically ill patients
- Examine the role of hemodynamic monitoring tools in starting, monitoring, and ending de-resuscitation as part of fluid stewardship in the ICU

2

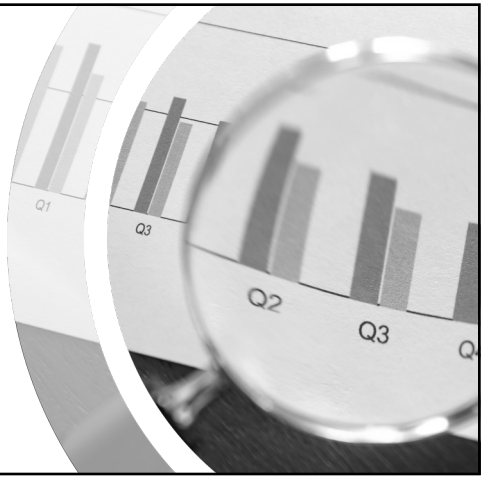
- Question 1
- Which of the following is considered a dynamic end point in fluid resuscitation?
  - Central venous pressure
  - Lactic acid level
  - Pulse pressure variation
  - Heart rate

Question 2

- Using CVP is a well validated why to determine if a patient needs more fluid
  - True
  - False

3

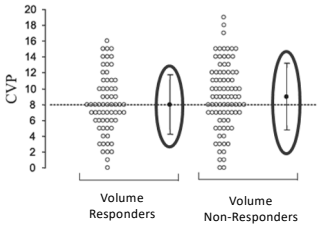
Evaluation of Current Guidelines



4

Fluid Resuscitation Guidelines

- Large change from 2012 to 2016
  - Driven by numerous studies showing CVP is a poor indicator of volume status and fluid responsiveness
- 3 large randomized controlled trials
  - No benefit of EGDT compared to non-CVP based resuscitation (ProCESS, ProMISe, ARISE)



N Engl J Med. 2014:370: 1683-93

N Engl J Med. 2014;371: 1496-1506

N Engl J Med. 2015;372: 1301-1311

Crit Care Med 2007; 35:64-68

5

Surviving Sepsis Campaign

Goals within the first 6hrs

a) Central Venous Pressure 8-12mm Hg
b) Mean arterial pressure > 65 mm Hg
c) Urine output 0.5mL/kg/hr
d) Central/mixed venous oxygen saturation ≥70%/ ≥65%

ProCESS
ProMISe
ARISE

- **Initial Resuscitation with 30ml /kg within the first 3 hours**
- **Subsequent fluids be guided by frequent reassessment of hemodynamic status**
- **Suggest using dynamic variables over static variables**
- **Recommend staring a MAP >65 in patients requiring pressors**
- **Suggest guiding resuscitation to normalize lactate**

Crit Care Med 2013; 41 (2) 580-634

6

Table 1. Fluid Quantities at Different Time Frames in Early Goal-Directed Therapy Sepsis Studies

		0–6 hrs,[a] ml/kg	7–72 hrs, ml/kg	Total cumulative quantity, ml
Rivers[2]	Standard of care	43.8	132.5	13,358 (167.0 ml/kg)
	EGDT	62.2	107.8	13,443 (168.0 ml/kg)
The ProCESS Study Investigators[30]	Standard of care	56.5	54.4	8716 (110.9 ml/kg)
	EGDT	65.6	55.7	9507 (118.8 ml/kg)
ARISE Study Investigators[28]	Standard of care	53.4	48.8	7485 (102.2 ml/kg)
	EGDT	55.7	48.7	7670 (104.4 ml/kg)
ProMISe Study Investigators[29]	Standard of care	52.3	52.7	7809 (97.6 ml/kg)
	EGDT	48.8	54.6	7836 (98.0 ml/kg)

EGDT = early goal-directed therapy.
[a]Includes pre-randomization fluids.

Table 1 Bundle elements with strength of recommendations and under-pinning quality of evidence

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Pharmacotherapy. 2020;40(3):256-269

Intensive Care Med (2018) 44:925–928

7

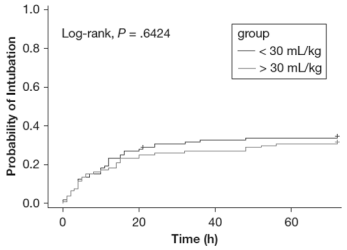
Evaluation of Current Resuscitation Guidelines

- Removal of CVP at target goal
  - Well supported by 3 large RCTs
- Initial resuscitation with 30 ml/kg
  - Largely based on expert opinion
  - Based off pre-randomization amounts in PROMISE/PROCESS/ARISE
  - Lacks clarity on ideal body weigh vs actual bodyweight
  - Felt to represent standard of care, but currently lacks RCT data
- Raises the question for potential harm?

8

Initial Fluid Resuscitation in "At Risk" Groups

- 30 ml/kg does not appear to increase intubation risk in EF <40%, ERSD & cirrhosis
- Septic patients with pre-existing left ventricular dysfunction
  - No difference in fluids given
  - No difference in intubation or mortality

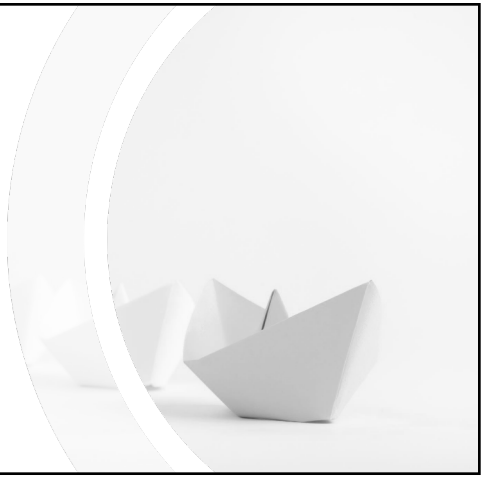


Chest 2020; 157(2):286-292
Critical Care 2014, 18:R79

9

The Role of Fluid Stewardship

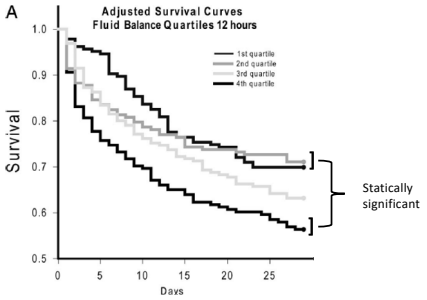
Is there potential harm with over- resuscitation?



10

Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

- **Retrospectively reviewed septic patients requiring vasopressors**
- **Evaluated association of net fluid balance and CVP with mortality**
  - **Fluid balance assessed by quartile**
  - **Corrected for APACHE II score**
- **Overall survivors had less positive fluid balance than non-survivors**
- **At 12hr less positive fluid balance was associated with lower mortality except in patients with CVP <8**
- **Saw optimal survival with positive fluid balance of 3L at 12 hours**



Crit Care Med 2011; 39:259-265

11

Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

Table 4. 12-hr fluid balance: Survivors vs. nonsurvivors within CVP groups

	Net Fluid Balance		
CVP Group	Survivors	Nonsurvivors	*p*
All Patients	3444 (1861–5984) mL	4429 (2537–6560) mL	<.001
CVP <8 mm Hg	3015 (1296–4987) mL	2281 (802–5711) mL	NS
CVP 8–12 mm Hg	2727 (1227–5491) mL	3112 (1559–4809) mL	NS
CVP >12 mm Hg	3975 (2387–6614) mL	5237 (3140–7773) mL	<.001

- Higher CVP (12hr) was associated with higher mortality
- More positive fluid balance and higher CVP (12 hr) was associated with higher mortality…except if CVP <8

Crit Care Med 2011; 39:259-265

12

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

- Randomized control trial
  - Volume expansion with 20-40ml/kg saline vs albumin vs no fluids
  - 3.3% absolute increase in mortality (fluids vs no fluids)
  - 1.45 relative risk of death with volume expansion
  - No difference in mortality at 1 hour
  - 57% positive for malaria

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

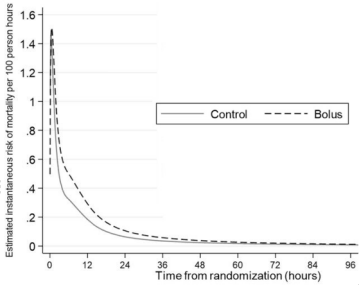
End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value
		no. (%)			
48 Hours					
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)		
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)		
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)		
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)		
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.46 (0.85–2.53)	0.17
4 Weeks					
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.39 (1.11–1.74)	0.004

N Engl J Med. 2011;365(14):1350-1353

13

Mortality risk over time after early fluid resuscitation in African Children

- No difference in peak or early mortality
- Increased mortality 1.6 to 101 hours post-randomization
- The risk of mortality failed to improve as rapidly in the bolus group
- Role for de-resuscitation??



Crit Care. 2019;23(1):377

14

Assess outcomes of de-resuscitation in critically ill patients

15

De-resuscitation Strategies

- Passive
  - Limiting intake
    - More precise (hemodynamic guided resuscitation)
    - Less initial resuscitation
    - Limiting medications and maintenance fluids
- Active
  - Diuresis
  - Fluid removal by renal replacement therapy

16

Fluids and Catheters Treatment Trial (FACTT)

- Then randomized ARDS patients to liberal vs conservative fluid strategy
  - Algorithm based approach to fluid management
- Difference in 7-day cumulative fluid balance
  - Liberal fluid strategy: +7L
  - Conservative strategy: -136cc
- Conservative therapy group got more lasix and had more electrolyte abnormalities

N Engl J Med 2006;354:2564-75

17

FACTT Results

Table 3. Main Outcome Variables.*

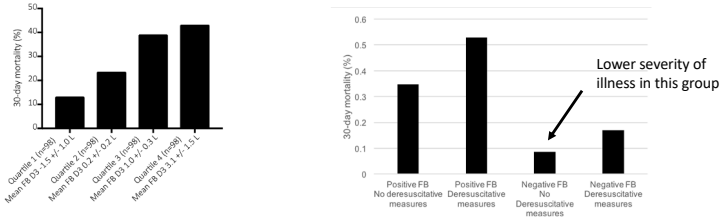
Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
Renal failure	5.5±0.1	5.6±0.1	0.45
Dialysis to day 60			
Patients (%)	10	14	0.06

- No difference in mortality
- No difference in renal failure
- Increase in ventilator free days

N Engl J Med 2006;354:2564-75

18

Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness*



- Fluid balance at day 3 was independent predictor or morality
- Improved outcome regardless if negative fluid balance spontaneous or due to deresuscitation (diuresis or RRT)
- 36% of fluid balance was due to medications, 25% due to fluid boluses (resuscitation)

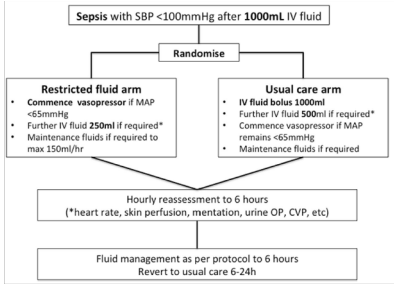
Crit Care Med 2018; 46:1600–1607

19

Restrictive Fluids in Resuscitation (Refresh)

Pilot study: restrictive resuscitation to usual care

- 30% reduction in fluid administration
  - 30ml/kg vs 43 ml/kg (6hr)
  - 40ml/kg vs 61ml/kg (24hr)
- Earlier administration of vasopressor
  - 34 minutes vs 51 minutes (p = 0.001)
- Trend toward less time on pressors
  - 21 hr vs 33hrs (p= 0.13)
- No apparent difference in mortality, RRT, or dose of vasopressors

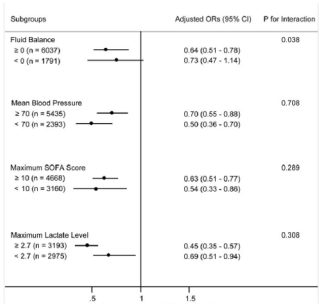


Intensive Care Med (2018) 44:2070–2078

20

Early Diuretic Use and Mortality In Critical Ill Patients With Vasopressor Support: A Propensity Score-Matching Analysis

- Reviewed patients requiring vasopressors within 48hrs of ICU admission
- Looked for association between early diuretic use and mortality
  (Multivariable regression and propensity matching)
- Found that early (loop) diuretic use in patient with a positive fluid balance
  - Early = within 48hrs of admission to ICU
- Benefit not present when negative fluid balance already present
- Authors advised caution in the setting of severe AKI



Critical Care (2019) 23:9

21

Restricted Fluids Following Initial Resuscitation

- Multicenter RCT
  - Septic shock with ongoing vasopressor use after 30ml/kg
  - Restrictive group:
    - Boluses of 250-500ml Fluids only given if
      - MAP < 50 on vasopressors
      - Lactic acid > 4
      - Mottling beyond knee (score >2)
      - Oliguria in the first 2 hours after randomization
  - Mean difference in resuscitation fluids in the first 5 hours after randomization
    - -1.2L compared to the usual care group (primary endpoint)
  - No difference in mortality (exploratory endpoint)
  - Less AKI (exploratory endpoint)

Intensive Care Med (2016) 42:1695–1705

22

Examine the role of hemodynamic monitoring tools in starting, monitoring, and ending de-resuscitation as part of fluid stewardship in the ICU

Warning: Limited data!!!

23

Natriuretic Peptide–driven Fluid Management during Ventilator Weaning

A Randomized Controlled Trial

Patients on mechanical ventilation randomized to daily BNP guided diuresis vs usual care

- If BNP > 200 pg/ml, restricted fluids to <500ml, Lasix titrated to urine output
- Mean of -2.1L fluid balance compared to control group during weaning
- Decreased time to successful extubation (42hrs vs 58hr),
- Increased ventilator free days (57.9 vs 54.9)
- No difference in mortality or need for dialysis/ ARF (creatinine >1.7mg/dL)

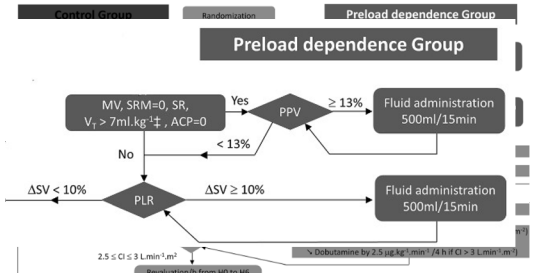
Am J Respir Crit Care Med. 2012;186(12):1256-1263

24

Using Preload Dependence To Titrate Volume Expansion

- Septic Patients randomized:
  - EDGT vs Pre-load assessment based
  - Preload assessment:(pulse pressure variation or passive leg raise)
- Preload dependent resuscitation resulted in
  - Less mean daily fluids: 917cc vs 383cc
  - Less blood transfusion
- Note:
  - 559 admitted only 61 randomized

High exclusion rate!!



SRM = spontaneous respiratory movements
ACP = acute cor pulmonale
SR= sinus rhythm
SV=stroke volume determined with PICCO pus device

Critical Care (2015) 19:5

25

Pre-Load Dependence-Based Resuscitation: Outcomes

	Control (n = 30)	Preload dependence (n = 30)	P
Time to shock resolution (days)	2.0 [1.2-3.1]	2.3 [1.4-5.6]	0.29
Ventilator-free days at day 28	8 [0-21]	14 [0-24]	0.35
Number of days with lactates above upper normal laboratory limit	1 [1-4]	2 [1-4]	0.14
Number of days with pulmonary edema (that is ELWI >10 mL.kg^{-1} PBW)	4 [1-5]	4 [1-6]	0.94
Number of days with organ system failure (that is SOFA ≥6)	4 [3-5]	4 [2-8]	0.61
ICU length of stay (days)	10 [7-20]	14 [6-28]	0.55
In survivors	14 [9-28]	22 [6-28]	0.89
In non-survivors	8 [5-11]	5 [3-17]	0.85
Mortality at day 28	14 (47%)	7 (23%)	0.10

- No difference in time to shock resolution
- Non-significant trend in improved mortality and increased ventilator free days

Critical Care (2015) 19:5

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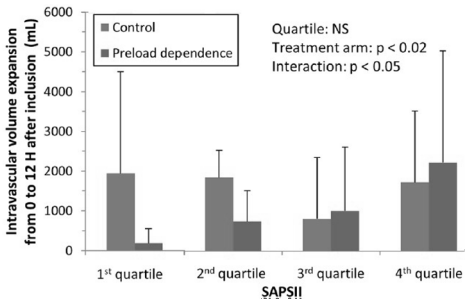
Differences in Initial Resuscitation by Severity



- Sicker patients get more fluids only when pre-load guided

Critical Care (2015) 19:5

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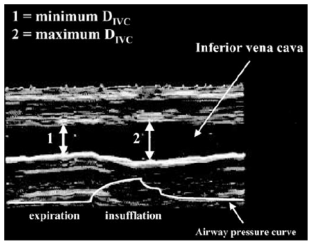
Ultrasound to Predict Fluid Responsiveness



- Data is inconsistent(Heterogeneous)
  - May be useful in ventilated patients
- Most usual in the extremes
  - >42% collapsible
  - > 2.1cm with no collapsibility
  - Large range of indeterminate findings
- Often more useful qualitatively

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Summary

- The optimal amount and timing of fluid resuscitation remains unknown
  - Other endpoints have numerous limitations or lack strong data
- 30 ml/kg for initial resuscitation
  - lacks randomized controlled data in adults
  - Is less than fluids given in large RCT
  - Does not appear result in increased intubation
- There may be benefit early deresuscitation (fluid removal),
  - Strongest data between 48hrs and 72hrs

29

Learning Assessment

Question 1

Which of the following is considered a dynamic end point in fluid resuscitation?

- **Central venous pressure**
- **Lactic acid level**
- **Pulse pressure variation**
- **Heart rate**

Question 2

Using CVP is a well validated why to determine if a patient needs more fluid

- **True**
- **False**

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Questions?

Thank you!

31

Pro/Con Debate: PADIS Guidelines– Do We Always Use Narcotics?

Matthew A. Wanat, PharmD, BCPS, BCCCP, FCCM
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Program Director, Fellowship in Academic Pharmacy
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UNIVERSITY of HOUSTON
COLLEGE OF PHARMACY

1

Learning Objectives

1. Describe the indications for opioids in the critically ill patient
2. Summarize the benefits and limitations of liberalizing opioid use in the critically ill patient

I do not have any conflicts of interest related to this presentation

2

Outline

- Overview of pain
  - Risk factors
  - Assessment of pain
- PADIS guideline recommendations
  - 2013 vs. 2018 guideline comparison
- Using opioids for ICU analgesia
  - Benefits of opioid therapy, monitoring of therapy
  - Limitations of drugs used for multi-modal management

3

Pain in Critically-ill Patients

- Pain in the ICU is complex, based on many individual factors
- Pain experienced throughout continuum of ICU care
  - Disease state related pain
  - Pain at rest
  - Mechanical ventilation
  - Procedural/surgical pain
- Pain affects a patients clinical condition; improved pain control has shown improved patient outcomes
- Frequent assessment of pain needed to optimize care

Devlin JW, et al. *Crit Care Med*. 2018;46(9).
Skrobik Y, et al. *Anesth Analg*. 2010;111.
Delgado SA. *Am J Nursing*. 2020;120(5).

4

Pain Risk Factors

- Age (younger)
- Psychological (anxiety, fear, depression, trauma)
- Comorbidities
- History of surgery
- Delay in time from pain to analgesic therapy
- "Painful procedures"
  - Chest tubes, arterial lines, wound drain removal, turning/repositioning, suctioning
- Opioid use prior to procedure/ICU care

Desbiens NA, et al. *Crit Care Med*. 1996;24.
Puntillo KA, et al. *Am J Respir Crit Care Med*. 2014;189(1).
Devlin JW, et al. *Crit Care Med*. 2018;46(9).

5

Pain Risk Factors

Variable	Increased Pain - Odds Ratio (95% CI)
Age (per decade)	0.85 (0.80-0.91)
Dependencies in activities for daily living (for each additional)	1.09 (1.05-1.13)
Comorbidities (for each additional)	1.06 (1.00-1.11)
Medical Group	
Cardiology	1.00
Surgery	1.72 (1.38-2.13)
Oncology	1.16 (0.90-1.51)
Pulmonary	1.20 (0.98-1.46)
Other medicine	1.24 (1.04-1.49)
Pre-existing Quality of Life	
Excellent	1.00
Very Good	1.15 (0.81-1.63)
Good	1.18 (0.86-1.62)
Fair	1.32 (0.97-1.79)
Poor	1.49 (1.07-2.07
Depression and anxiety (measured with non-linear scales) statistically significant for increased pain.	

Desbiens NA, et al. *Crit Care Med*. 1996;24.

6

Assessment of Pain

- Self-reported pain is gold standard in patients able to communicate
- Behavioral Pain Scale (BPS) and Critical Care Pain Observational Tool (CPOT) should be used in patients not able to report pain
  - Validated across wide range of ICU patients
  - Utilize physical (facial, muscles, movement) surrogates for pain, compliance with ventilator
- Vital signs can be used to trigger pain assessment, but not used as pain assessment
- Reasonable to involve family in assessment of a patient's pain

Puntillo KA, et al. *Crit Care* Med. 2012;40(10).
Barr J, et al. *Crit Care Med*. 2013;41.
Gelinas C, et al. *Seminar Respir Crit Care Med*. 2013;34.
Devlin JW, et al. *Crit Care Med*. 2018;46(9).

7

2013 Pain, Agitation, Delirium Guidelines

- Recommend preemptive analgesia, including procedural, be used (1C,2C)
- Recommend that IV opioids be considered as first line drugs of choice to treat non-neuropathic pain (1C)
- Suggest that non-opioid analgesics be considered to decrease opioids used and side effects (2C)
- Recommend that gabapentin or carbamazepine, in addition to opioids, be used for neuropathic pain (1A)

Barr J, et al. *Crit Care* Med. 2013;41.

8

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16];

- Update from 2013 SCCM guidelines on pain, agitation and delirium
- New sections on immobility and sleep
- 37 total new recommendations
  - 16 recommendations related to pain management
    - Assessment, risk factors, non-opioid adjuvant therapy, procedural pain, non-pharmacologic interventions

Devlin JW, et al. *Crit Care Med.* 2018;46(9).

9

PADIS Guidelines - Adjuvant Pharmacotherapy Recommendations

Recommendation	Level of Recommendation	Quality of Evidence
Suggest using acetaminophen (IV or PO) as an adjunct to an opioid to decrease pain intensity and opioid consumption	**Conditional**	**Very Low**
Suggest using low dose ketamine (1-2 mcg/kg/min) as an adjunct to an opioid for pain management in postsurgical patients	**Conditional**	**Very Low**
Suggest using a neuropathic pain medication with opioids for neuropathic pain	Strong	Moderate
Suggest using neuropathic pain medication with opioids after cardiovascular surgery	**Conditional**	**Low**
Suggest NOT routinely using IV lidocaine as an adjunct to opioids	**Conditional**	**Low**
Suggest NOT routinely using cox-1 selective NSAIDs as an adjunct to opioids	**Conditional**	**Very Low**

Devlin JW, et al. *Crit Care Med.* 2018;46(9).

10

Debate Question

PADIS Guidelines– Can We Safely Liberalize Narcotics?

11

Arguments for Liberalizing Opioids

1. Experience with opioid use; ideal properties

2. Ability to monitor/manage acute side effects

3. Risk of long term dependence from ICU use?

4. Protocolized, team based strategies to optimize pain control

5. Lack of good data with multi-modal therapy options

12

Liberalizing Opioids – Effective Medications for ICU Pain

- Years of experience using opioids as first line analgesics for ICU pain ("mainstay of treatment")
  - Potent, quick acting
  - Available in several dosage forms (IV), equally effective
  - Relatively safe in renal or hepatic dysfunction
- Contain mild sedative and anxiolytic properties, help with anxiety and sedation (analgosedation)
  - Attenuate adverse physiologic responses to pain

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Liberalizing Opioids – Managing Adverse Effects

- Common opioid side effects can be managed
  - Nausea/vomiting
  - Constipation
  - Respiratory depression
  - Pruritus
- Can cause CNS effects, delirium, dependence, ileus, immune effects
- Adjunct pain medications have adverse effects too!

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Liberalizing Opioids – Long Term Dependence?

- Incidence of chronic pain after ICU admission ranges from 30-70%

Chronic Opioid Use After ICU Admission			
Study	Design	Number of Patients	Results
Yaffe PB, et al. 2017	Retrospective cohort	2595 ICU patients (48% surgical, 38% medical) from 2005-2008	Discharge: Intermittent use - 8.6%, Chronic use – 3.6% At 48 months: Intermittent use – 2.6%, Chronic use – 1.8%
Wang HT, et al. 2018	Registry analysis	19,584 patients over age 65, who were chronic opioid users admitted to ICU from 2002-2015	63% of patients filled prescription for opioid at day 180 post discharge; overall lower dose of MME filled
Bonnesen K, et al. 2020	Registry analysis	29,815 patients who underwent cardiac surgery in Denmark from 2003-2016	5.7% of patients with new chronic opioid use at 12 months
Adil MQ, et al. 2020	Retrospective cohort	118 opioid naïve veterans in Houston ICU in 2018	7.6% receiving prescription for opioid at 12 months

Stamenkovic DM, et al. *Front Pharmacol*. 2019;10(23).
Adil MQ, et al. *Fed Pract*. 2020;37(4).
Wang HT, et al. *Crit Care Med*. 2018;46(12).
Yaffe PB, et al. *J Intensive Care Med*. 2017;32(7).
Bonnesen K, et al. *Acta Anaesthesiol Scand*. 2020 Aug 19.

15

Liberalizing Opioids – Use of Protocols

- "We suggest use of an assessment-driven, protocol-based, stepwise approach for pain/sedation"
  - Frequent assessment of pain/sedation
  - Targeted pharmacotherapy choices
    - Analgo-sedation, ICU specific, adjustment of therapy
  - Continuous quality improvement of protocol
- 6 randomized trials
  - Reduced pain intensity (VAS) by 0.35 cm
  - Reduced time on ventilator by 1.25 days
  - Reduced ICU lenth of stay by 2.25 days

Rozendaal FW, et al. *Intensive Care Med* 2009;35(2).
Strom T, et al. *Lancet*. 2010;375(9713).
Egerod I, et al. *Crit Care Med*. 2010;14.
Brook AD, et al. *Crit Care Med*. 2009;27(12)
Skrobik Y, et al. *Anesth Analg*. 2010;111(2).
Diby M, et al. *J Crit Care*. 2008;23(3).

16

17

Arguments Against Multi-Modal Pain Management

- Lack of strong clinical data
  - Low number of studies, patients
  - High risk of bias, difficult to make conclusions
  - Poor "standard of care" used in studies
- Minimal benefit, if any, seen with many therapies
  - Pain scores, opioid consumption, quality of life
- Therapies not without adverse effects
  - Need close monitoring

18

Medication	Number/Type of Studies	Number Receiving Intervention	Key Outcomes	Risk of Bias
Acetaminophen	2 single center trials; 1 double-blinded, 1 un-blinded	**76** (56, 20)	VAS score at 24 hours post-op, median 0.46 lower Mean BPS scores, median 1.98 lower Rescue morphine, OR 0.51, 0.2-1.34 Opioid consumption, med 4.54 MME lower	Serious to very serious
Ketamine	1 single center trial; double-blinded	**41**	VAS score at rest (48 hours), Median 3mm lower Morphine consumption (48 hours), Mean 22 mg less Side effects, no difference	Serious
Neuropathic pain agents	4 single center trials; double-blinded	**91** 49 pregabalin, 30 gabapentin, 12 carbamazepine	NRS Score day 4, median 3.44 cm lower Opioid consumption first 24 hours, median 13.54 MME lower ICU LOS, no difference	Serious
NSAIDs	2 single center trials; double-blinded	**104** 28 diclofenac, 49 ketoprofen, 27 indomethacin	VAS score at 24 hours post-op, median 0.35 lower (-0.91 to 0.21) Opioid consumption at X hours, median 1.6 MME lower	Serious

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Take Home Points

- Lack of data with multi-modal therapies
  - May be effective, need more data
- Multi-modal therapies are not without side effects
- Protocolized treatment of pain and sedation has been shown to be effective in improving outcomes

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Knowledge Assessment Question #1

Which of the following scenarios would be appropriate to use opioids for ICU related pain?

A. Procedural pain management
B. Pain occurring during rest in the ICU
C. Post-surgical pain
D. All of the above

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Knowledge Assessment Question #1

Which of the following scenarios would be appropriate to use opioids for ICU related pain?

A. Procedural pain management
B. Pain occurring during rest in the ICU
C. Post-surgical pain
D. All of the above

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Knowledge Assessment Question #2

Which of the following is true regarding multi-modal pain management?

A. Gabapentin can be used in place of opioids for patients with neuropathic pain.
B. Cox-2 specific NSAIDs have been shown to reduce opioid use and ICU length of stay
C. Ketamine, when added to opioids, has been shown to decrease side effects, pain scores, and time on mechanical ventilation
D. Adjunct lidocaine has not shown a decrease in time on mechanical ventilation or ICU length of stay when added to opioids

23

Knowledge Assessment Question #2

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Pro/Con Debate: PADIS Guidelines – Do We Always Use Narcotics?

Matthew A. Wanat, PharmD, BCPS, BCCCP, FCCM
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Program Director, Fellowship in Academic Pharmacy
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UNIVERSITY of HOUSTON
COLLEGE OF PHARMACY

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TEAMWORK AND TRIAGE DURING CRISIS

SCCM Texas Chapter 9th Annual Symposium: Closing the Knowledge Gap

Anne Rain T. Brown, PharmD, BCCCP, FCCM
Immediate Past-President SCCM Texas Chapter

1

Objectives

- Examine crisis standards of care when faced with difficult triage decisions
- Discuss the role of virtual care in times of crisis
- Outline factors and myths that can undermine teamwork
- List 3 strategies to achieve teamwork during crisis

2

In the current climate, every decision seems to come with a cost
"In a low-resource setting, on all levels of care there's always more demand than supply. One has to choose."

CRISIS STANDARDS OF CARE

COPING WITH CHANGE

CRITICAL CARE TEAMWORK

3

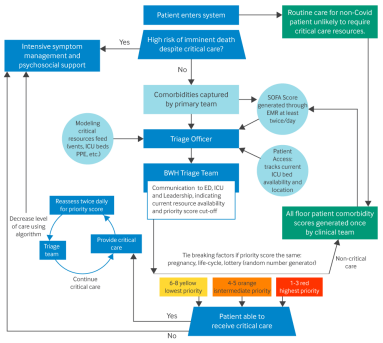
Crisis Standards of Care (CSC)

- A CSC declaration is a recognition that resources are limited and that normal **standards of care** are not possible under the circumstances
- Developed in response to events that can have extended impact which potentially overwhelms the health care system
- 5 key elements of CSC Protocols:
  1. Ethical considerations
  2. Community and provider engagement, education and communication
  3. Legal authority and environment
  4. Indicators and triggers
  5. Clinical process and operations

Milliken A, et al. NEJM Catal Innov in Care Deliv. 2020;10

4

Schematic for Crisis Standards of Care Protocol

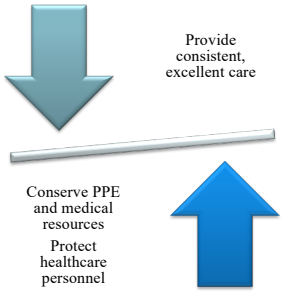


Milliken A, et al. NEJM Catal Innov in Care Deliv. 2020;10

5

Deviation from Standard of Care

- Catastrophic disasters impact all our healthcare systems and daily routines
- COVID-19 presents challenge of providing high-touch care while demanding physical distancing and conserving protective equipment



6

How do deviations from standards affect the clinician at the bedside?

7

Virtual Care in Times of Crisis

- Healthcare workers provide the backbone of a healthy, functioning medical system
- Virtual care may be necessary to address:
  - Lack of access to care during extraordinary circumstances
  - Prevent contagion
  - Minimize exposed providers
- Barriers to virtual care:
  - Lack of complex technology integration
  - Lack of reimbursement for virtual services
  - Discomfort with technology
  - Depersonalization
  - Required interventions

Schwamm LH, et al. The Lancet Digital health. 2020; 2(6):e282-e85

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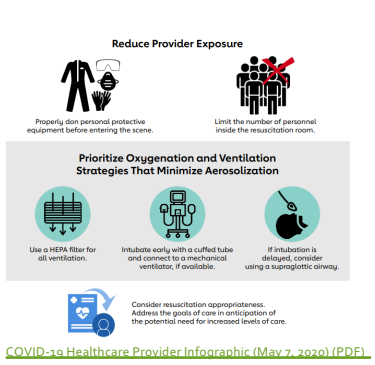
Multidisciplinary Team E-Rounding

https://www.youtube.com/watch?v=1hRsBVgPZZo

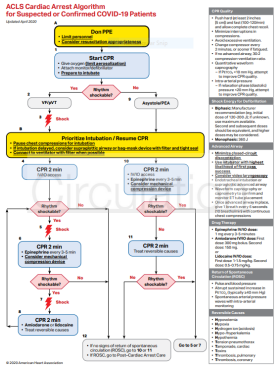
Arora VM, et al. J. Hosp. Med 2020;5;290-291

9

AHA Guidance for COVID-19 Resuscitation



COVID-19 Healthcare Provider Infographic (May 7, 2020) (PDF)



10

Factors and Myths Undermining Teamwork

- Lack of training in group dynamics
- Role and leadership ambiguity or stress
- Lack of interprofessional understanding
- Autonomy struggles
- Fears and Anxiety
- Team too large or too small

Larken GL. AMA J. Ethics 2010;12(6):495-501

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High-Performing Teams

- High-Performing Teams do 4 Things Consistently:
  1. Trust and empower
  2. Share common goals
  3. Make decisions in service of the common good
  4. Foster a sense of belonging

Mitchell, P. et al. 2012. Core principles & values of effective team-based health care. Discussion Paper, Institute of Medicine, Washington, DC. www.iom.edu/tbc.

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Stressors Posed to Healthcare Teams

Individual	• Concern about own health or families • Feelings of being overworked, fatigued, or burnt out
Team	• Lack of team member expertise • Team members that must assume new roles may increase mistakes that both team members and patients experience
Organization	• Insufficient resources, such as PPE, ventilators • Financial repercussions related to loss of revenue from elective procedures and outpatient visits
Work-life	• Concerns about family and friends • Financial concerns due to unemployment or furlough of family members • Social isolation

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7 Teamwork Tips During a Pandemic

- Celebrate all successes-big and small
- Make sure team members understand their roles and priorities
- Don't overlook anyone, including team members who work behind the scenes
- Encourage mutual team monitoring and support
- Foster psychological safety
- Help team members identify and address concerns within their own lives
- Consciously boost team resiliency

Tannenbaum SI, et al. BMJ Qual Saf 2020;0:1–5.

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Coping with Transition and Change

- Acknowledge the change
- Accept your emotions
- Be flexible
- Recognize your strengths
- Manage your stress
- Get help

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Crisis Catalyzing New Innovations

- If there is a silver lining to be found in the COVID-19 crisis, it is that necessity has catalyzed promising new care innovations

FCC ADOPTS $200 MILLION COVID-19 TELEHEALTH PROGRAM

New Program Will Provide Immediate Support to Health Care Providers and Patients Across the Country; Separate Connected Care Pilot Program Will Study Long-Term Role of Telehealth

WASHINGTON, April 2, 2020—This week, the Federal Communications Commission voted to adopt a $200 million telehealth program to support healthcare providers responding to the ongoing coronavirus pandemic. Congress appropriated the funds as part of the CARES Act. Through the COVID-19 Telehealth Program, the FCC will help healthcare providers purchase telecommunications, broadband connectivity, and devices necessary for providing telehealth services. Funding applications from healthcare providers will be processed on a rolling basis.

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Summary

- Crisis standards of care provide framework for making difficult triage decisions in times of crisis and resource shortages
- Strategic foresight and planning are needed to sustain deviations from care
- Incorporation of virtual care will extend into future care throughout healthsystems
- Healthcare clinicians must care for themselves so that they can care for others

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QUESTIONS?

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Question #1

All the following are true regarding crisis standards of care except:

a) Implemented during catastrophic disasters

b) Normal standards of care are not possible

c) Focus of care shifts to meet the needs of individual patients

d) Recognition that resources are limited

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Question #2

High performing teams must:

a) Make decisions that are best for the individual

b) Share common goals

c) Break down team members before they can be built up

d) None of the above

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Stewardship During Pandemics

- Rationing performed by a triage officer or triage committee consisting of 3 steps:
  - Application of exclusion criteria (i.e. irreversible shock)
  - Assessment of mortality risk using SOFA score to determine priority
  - Repeat assessment over time

Truog RD, et al. NEJM. 2020; 382(21):1973-75.

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