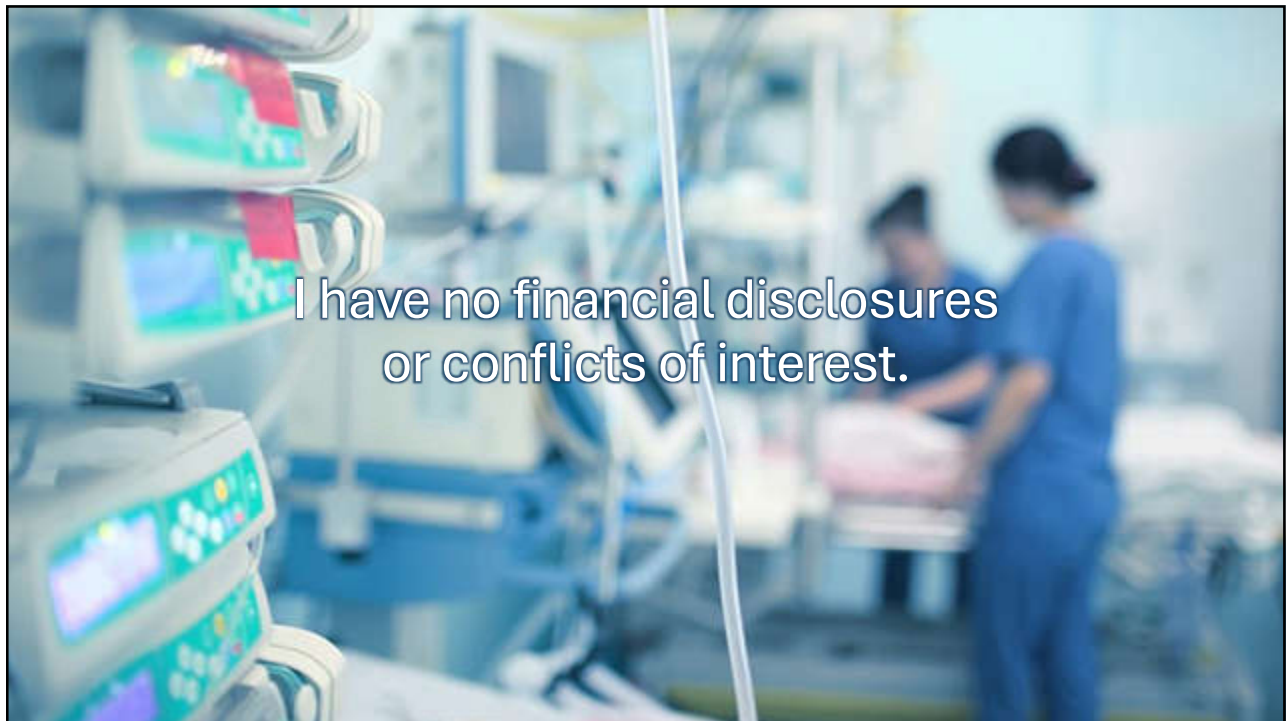




Current Controversies in the Resuscitation of Septic Shock

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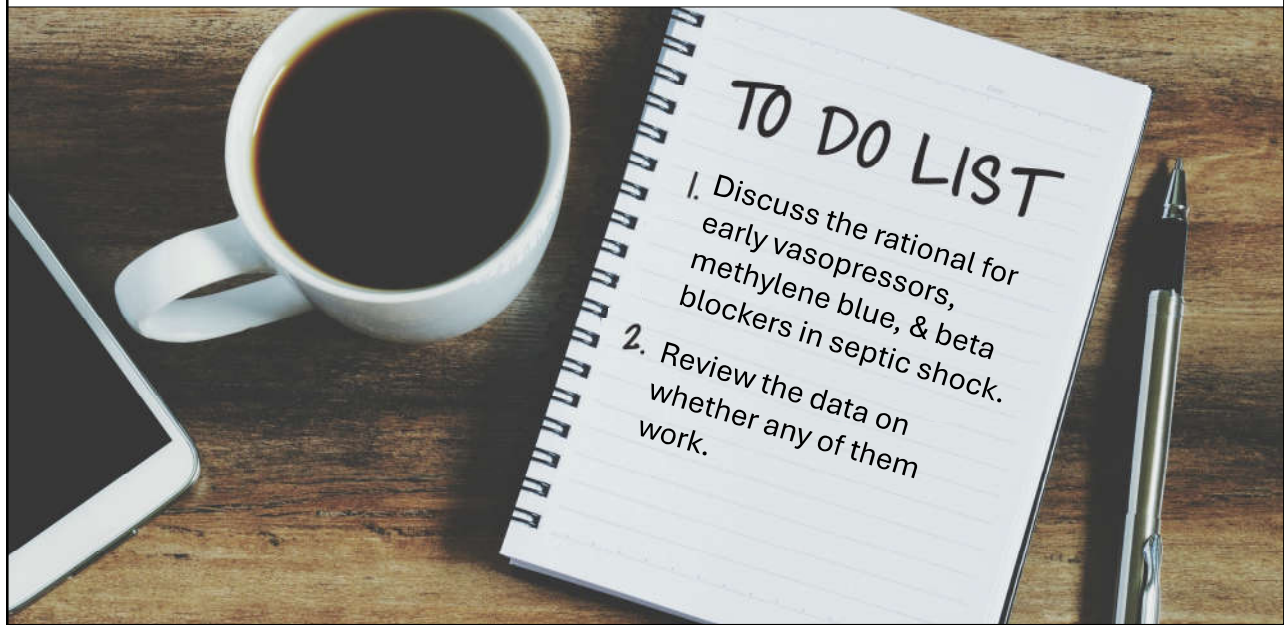
1



I have no financial disclosures
or conflicts of interest.

2

Objectives



3

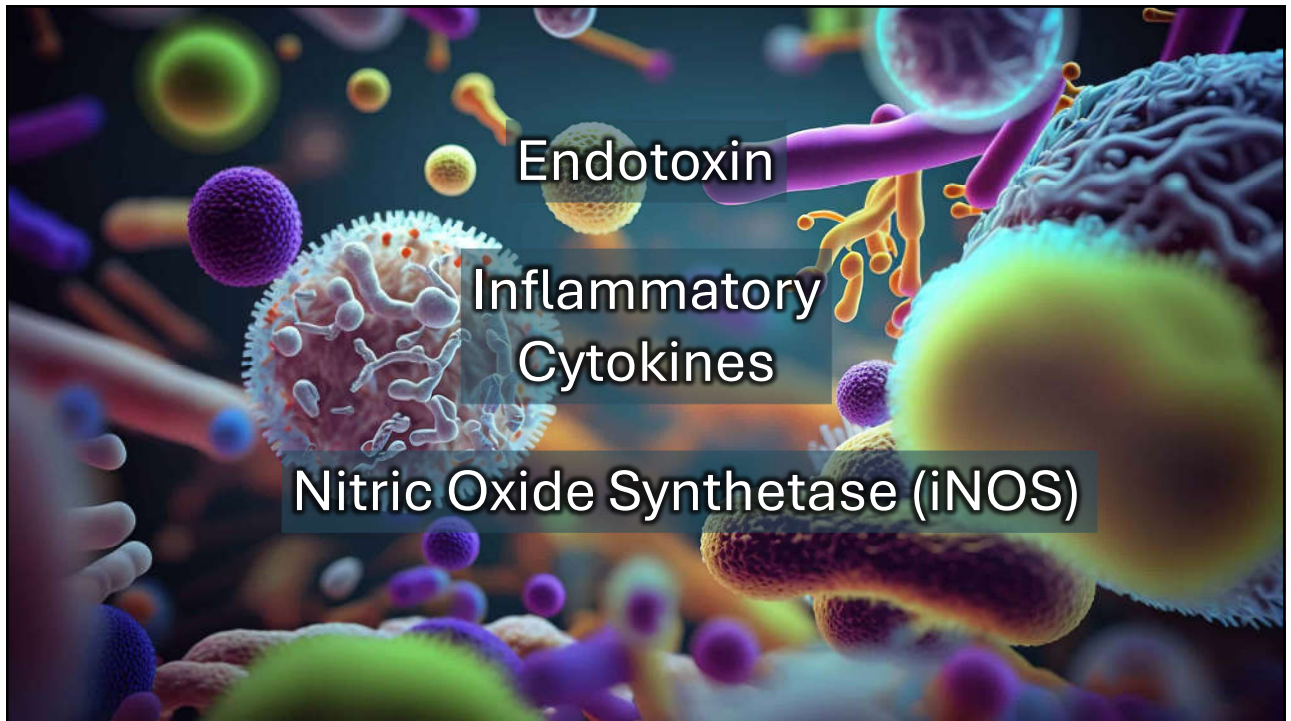


Early Vasopressors

4



5

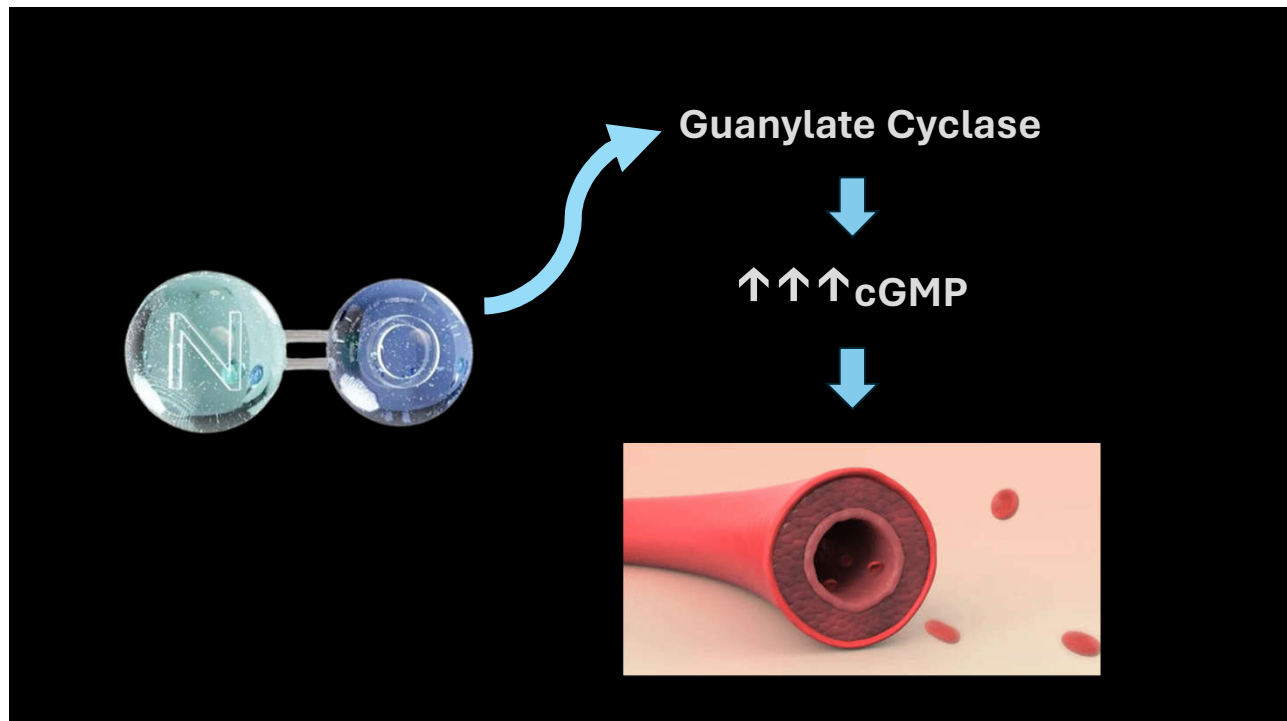


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Nitric Oxide



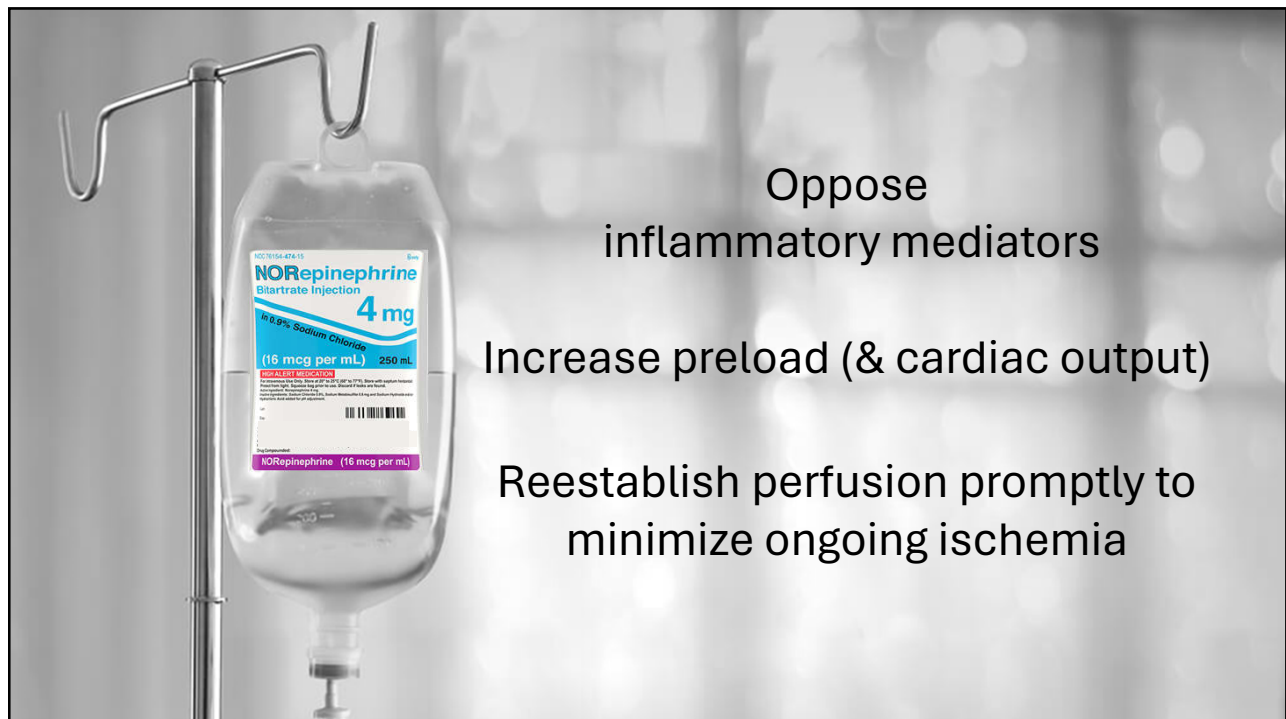
7




8



9



10




Earlier shock control

Decreased IVF / fluid balance

Decreased mortality

Bai et al, Crit Care 2014
Elbouhy et al, Arch Med Res 2019
Ospina-Tascón et al, Crit Care 2020
Permpikul et al, Am J Respir Crit Care Med 2019
Li et al, Crit Care 2020

11



No major adverse events

Peripheral infusion safe

Bai et al, Crit Care 2014
Elbouhy et al, Arch Med Res 2019
Ospina-Tascón et al, Crit Care 2020
Permpikul et al, Am J Respir Crit Care Med 2019
Li et al, Crit Care 2020
Shapiro et al, NEJM 2023

12



Early Vasopressors 

13



Methylene Blue

14



Poisonous Poppers

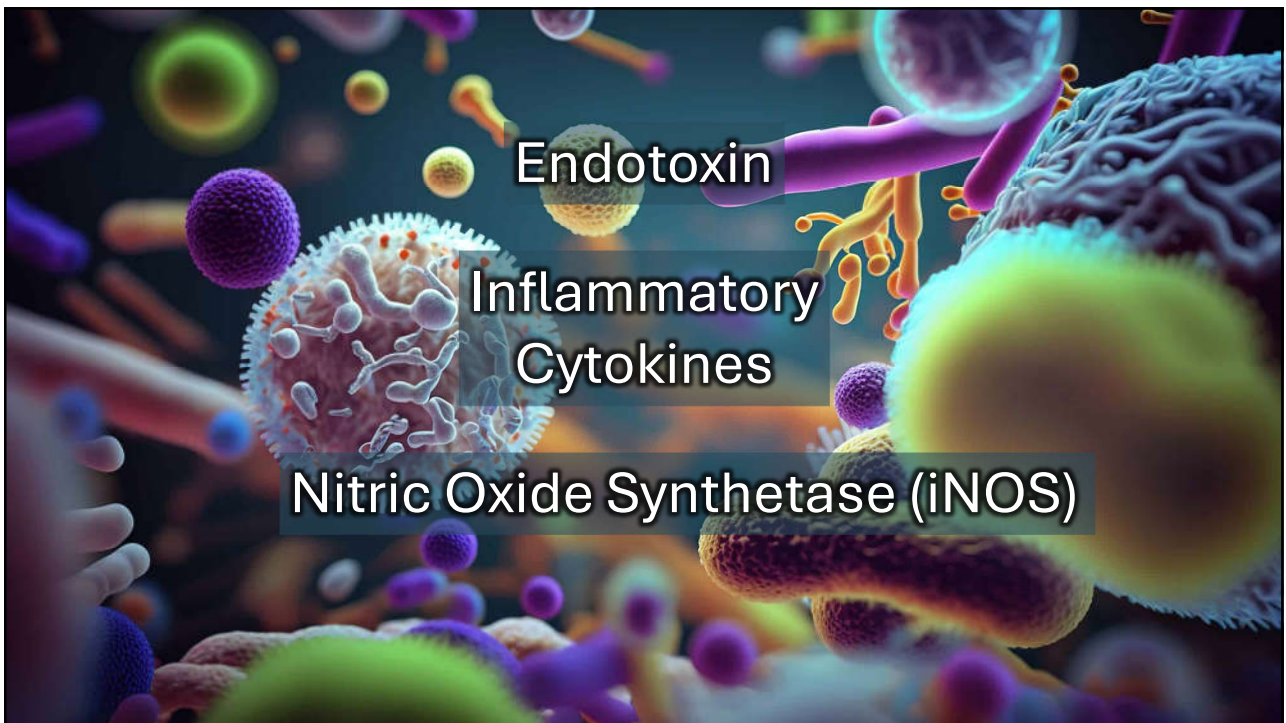
15



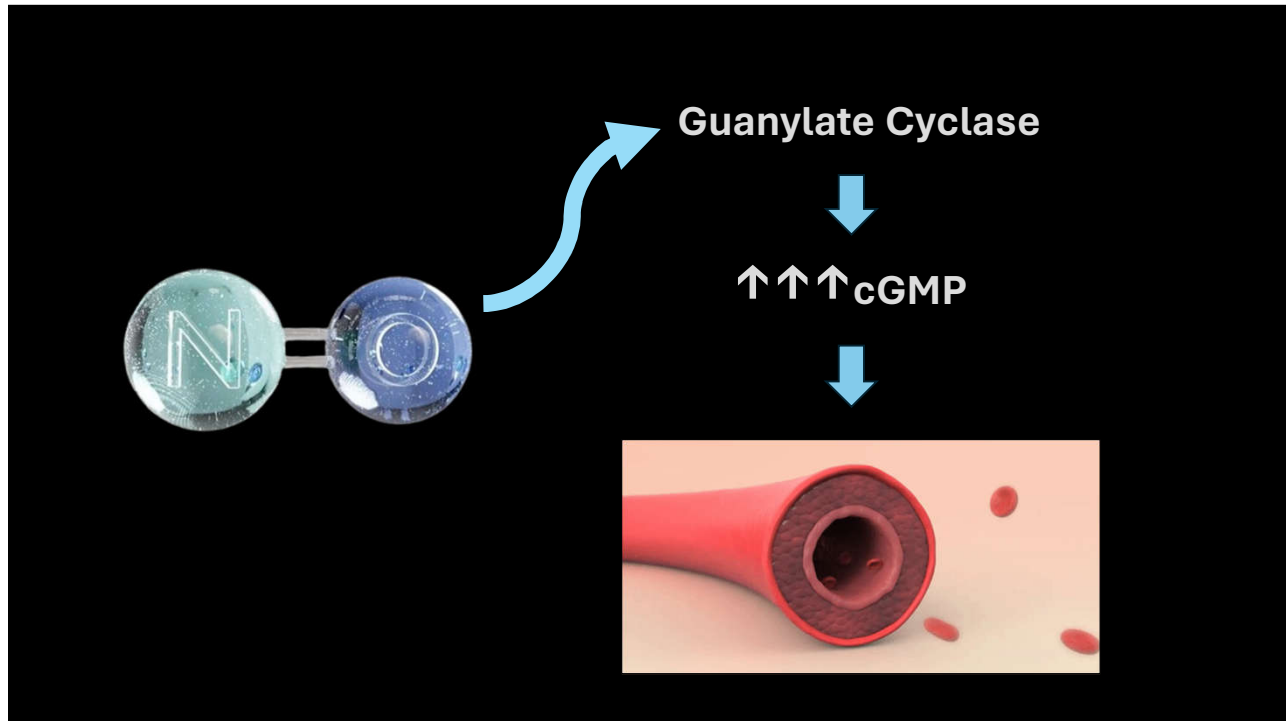
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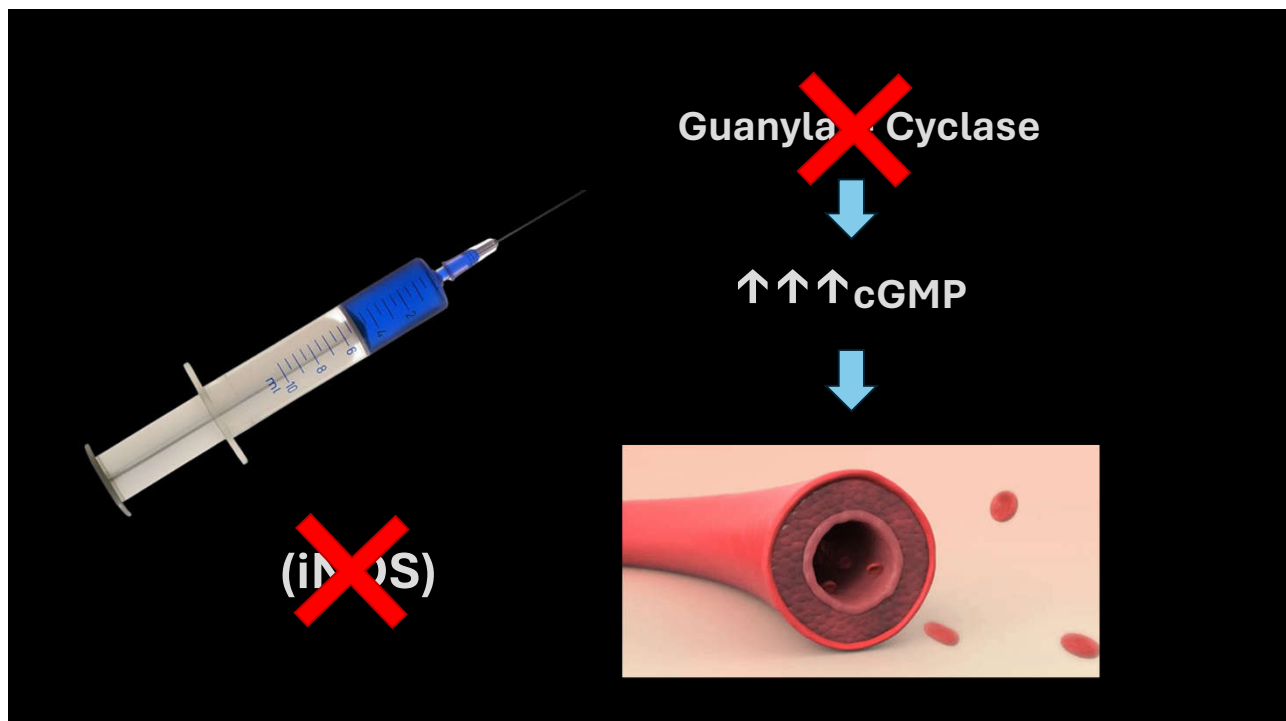
17



18



19



20



Improved survival in post-cardiac surgery vasoplegia syndrome

Levin et al, Ann Thorac Surg 2004
Hosseinian et al, Anesth Analg 2016

21



Few prospective studies in septic shock

Decreased vasopressor needs without mortality difference

Kirov et al, Crit Care Med 2001
Kwok et al, J Int Care Med 2006
Rajbanshi et al, Indian J Crit Care Med 2023

22



Ibarrá-Estrada et al. *Critical Care* (2022) 27:110
<https://doi.org/10.1186/s13054-022-44387-7>

RESEARCH **Open Access**

Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial

Miguel Ibarrá-Estrada^{1,2*}, Eduardo Kattan¹, Pavel Aguilera González², Laura Sandoval Plascencia³, Uriel Rico-Jauregui⁴, Carlos A. Gómez-Paritá⁵, Isis X. Ortiz-Macias⁶, José A. López-Pulgarín¹, Quetzalcóatl Chávez-Peña⁷, Julio C. Mijangos-Méndez⁸, Guadalupe Aguilera-Avalos¹ and Glenn Hernández^{1,4†}

Abstract
Purpose Methylene blue (MB) has been tested as a rescue therapy for patients with refractory septic shock. However, there is a lack of evidence on MB as an adjunct therapy, its optimal timing, dosing and safety profile. We aimed to assess whether early adjunctive MB can reduce time to vasopressor discontinuation in patients with septic shock.
Methods In this single-center randomized controlled trial, we assigned patients with septic shock according to Sepsis-3 criteria to MB or placebo. Primary outcome was time to vasopressor discontinuation at 28 days. Secondary outcomes included vasopressor-free days at 28 days, days on mechanical ventilator, length of stay in ICU and hospital, and mortality at 28 days.
Results Among 91 randomized patients, forty-five were assigned to MB and 46 to placebo. The MB group had a shorter time to vasopressor discontinuation (69 h [20h-59-83] vs 94 h [20h-74-141], p<0.001), one more day of vasopressor-free days at day 28 (p=0.008), a shorter ICU length of stay by 1.5 days (p=0.039) and shorter hospital length of stay by 2.7 days (p=0.027) compared to patients in the control group. Days on mechanical ventilator and mortality were similar. There were no serious adverse effects related to MB administration.
Conclusion In patients with septic shock, MB initiated within 24 h reduced time to vasopressor discontinuation and increased vasopressor-free days at 28 days. It also reduced length of stay in ICU and hospital without adverse effects. Our study supports further research regarding MB in larger randomized clinical trials.
Keywords Methylene blue, Randomized controlled trial, Septic shock, Norepinephrine, Vasopressin, Catecholamine sparing

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responders”
 ffy et al, Ann Thorac Surg 2017
 et al, BMC Anesthesiology 2022

23

Ibarrá-Estrada et al. *Critical Care* (2022) 27:110
<https://doi.org/10.1186/s13054-022-44387-7>

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Single-center, double-blind RCT

91 patients

100mg MB over 6h, daily x3d

24



Time to vasopressor dc @ 28d

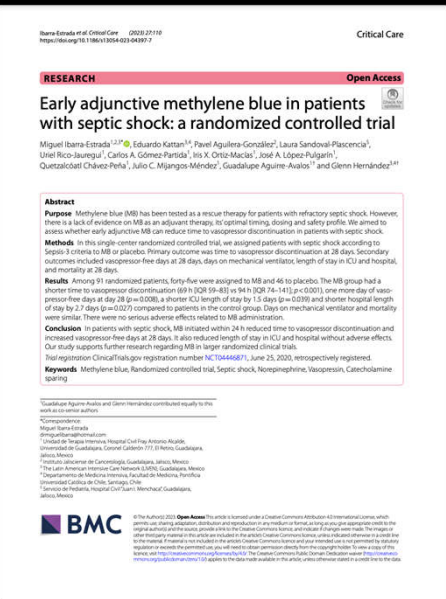
Vasopressor-free days @ 28d

Ventilator days

ICU/hospital length of stay

28d mortality

25



Shorter shock duration (69 v 94h)

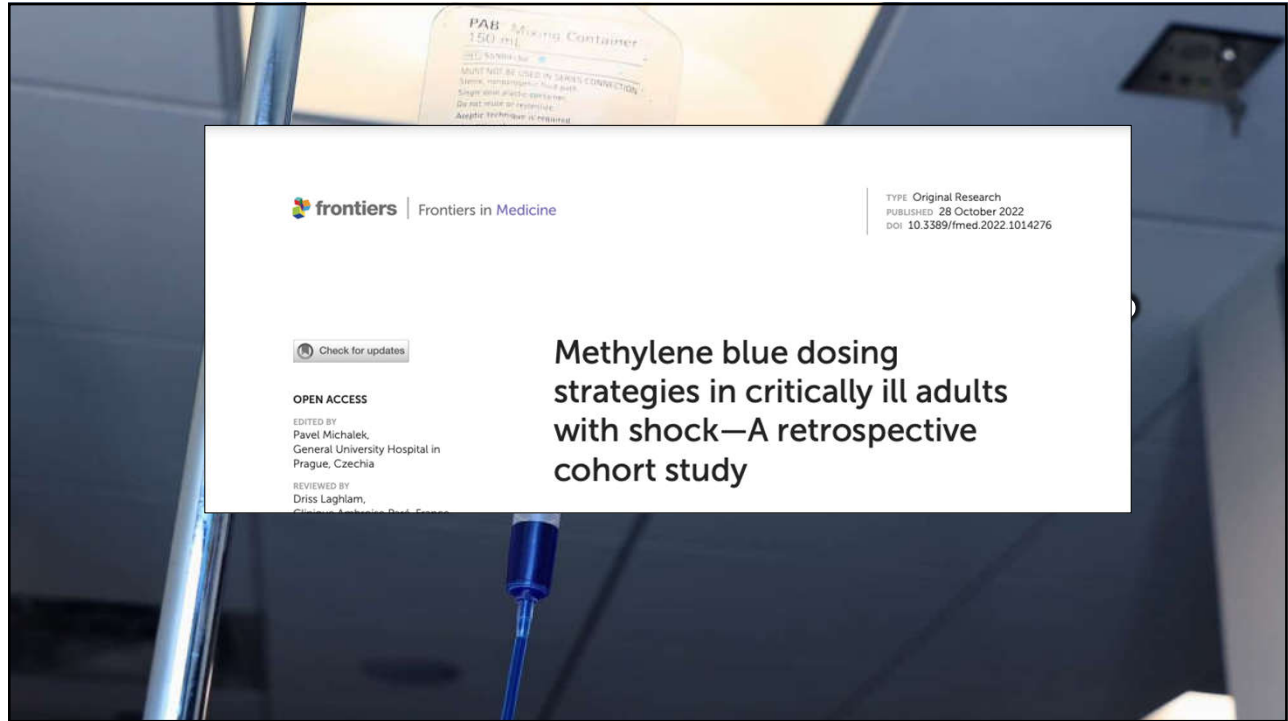
1 more vasopressor-free day

Lower cumulative fluid balance

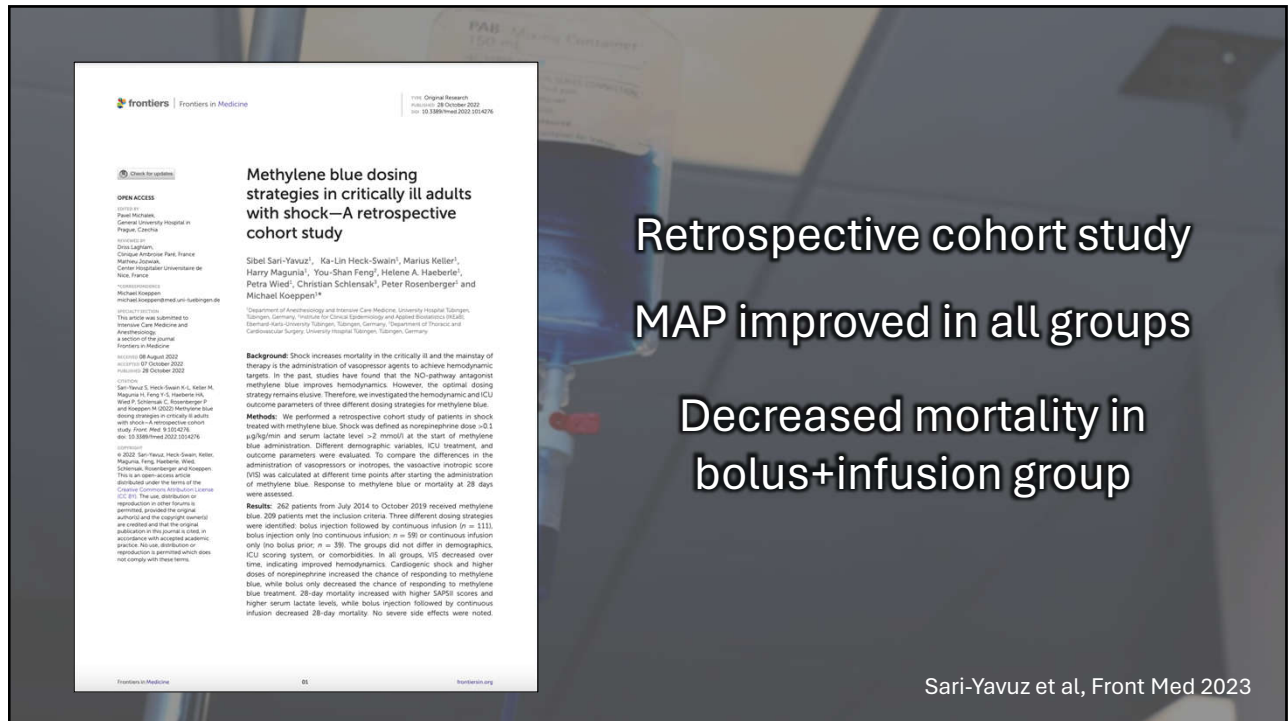
Shorter hospital/ICU LOS

No mortality difference

26



27



28



NDC 0517-0374-01
Methylene Blue
50 mg/10 mL (5 mg/mL)
Intravenous use only
Use 5% Dextrose Injection (Wheat)
Diluting
Single dose ampule – Rx only
Discard unused portion

WARNING

Avoid in combination with
serotonergic medications

Not for use in G6PD deficiency

29

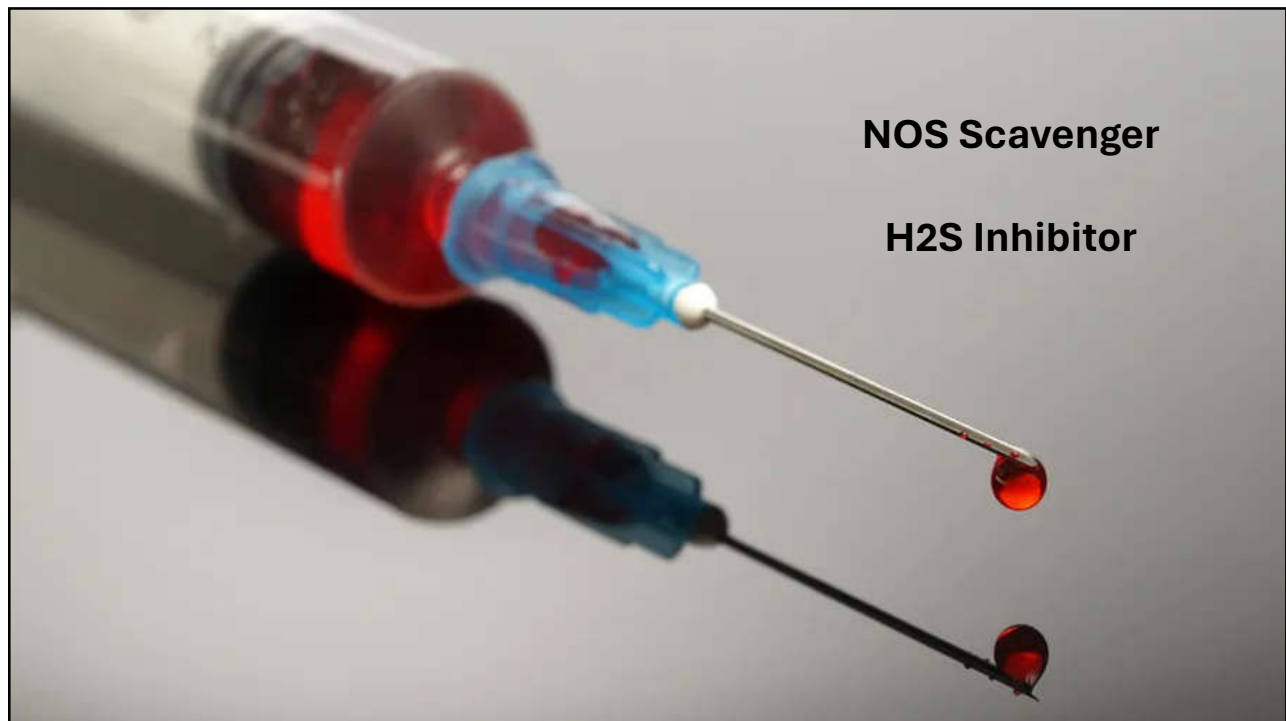


 **Methylene Blue**

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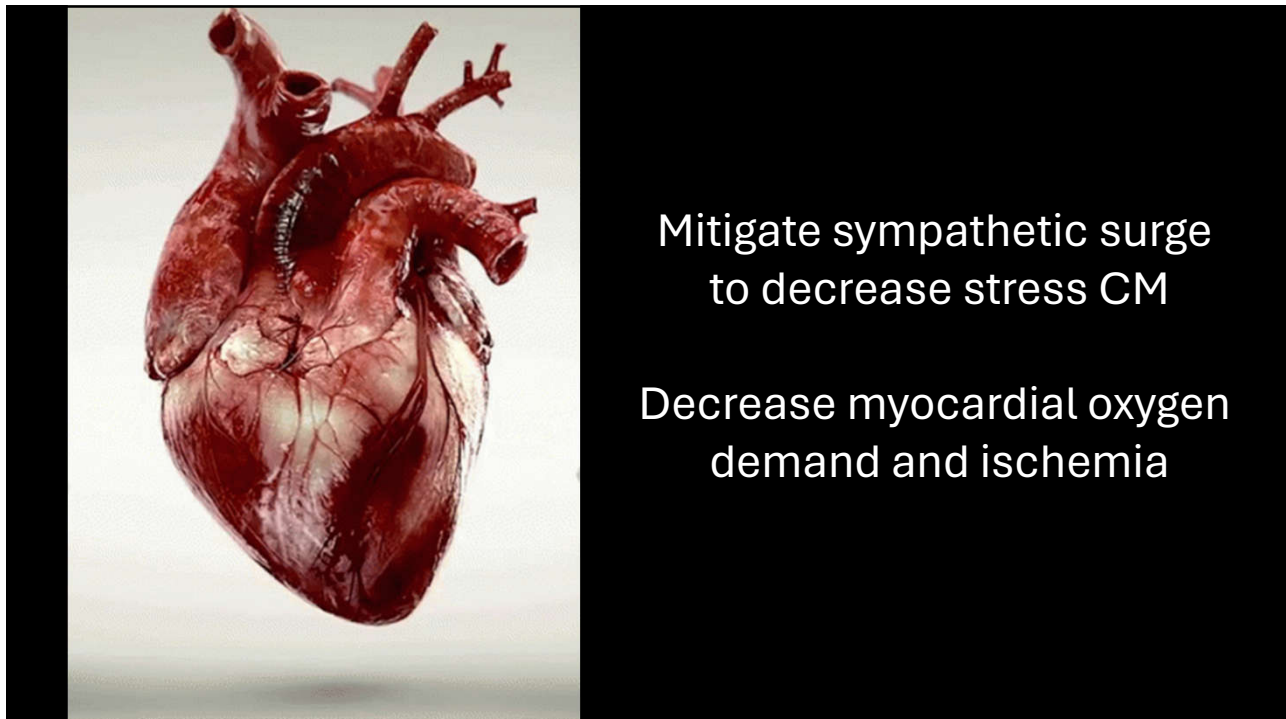
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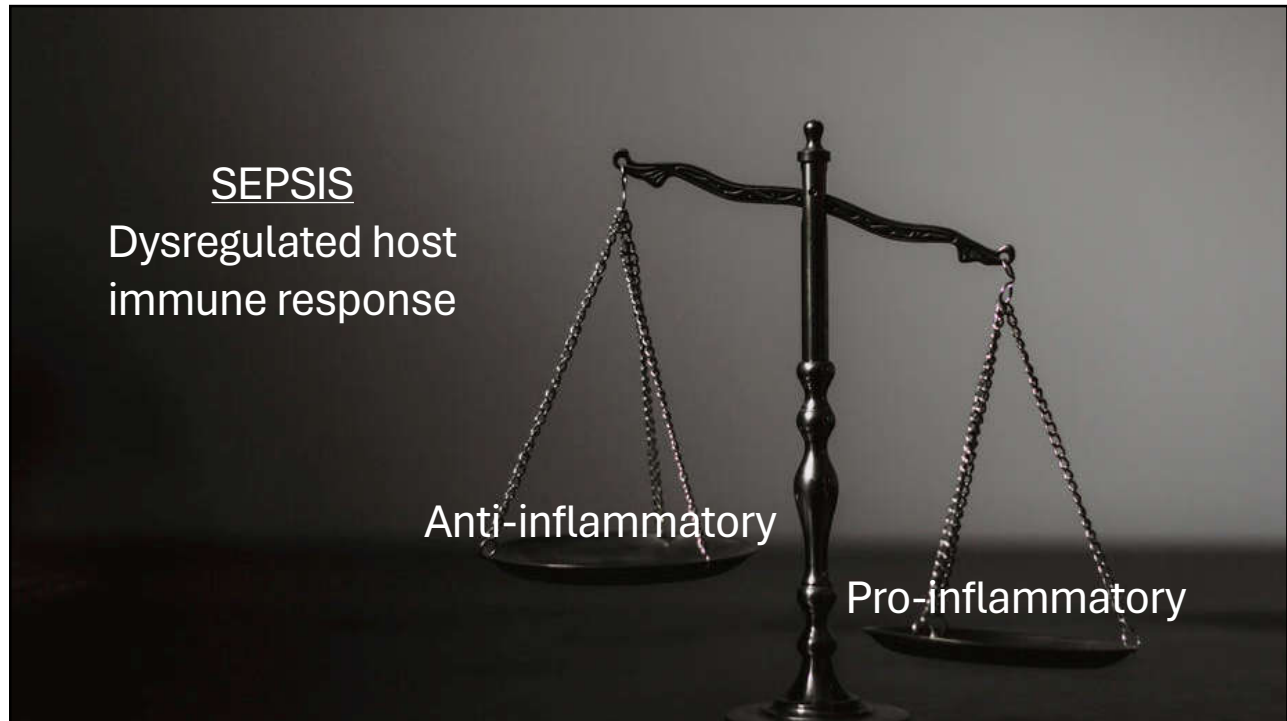
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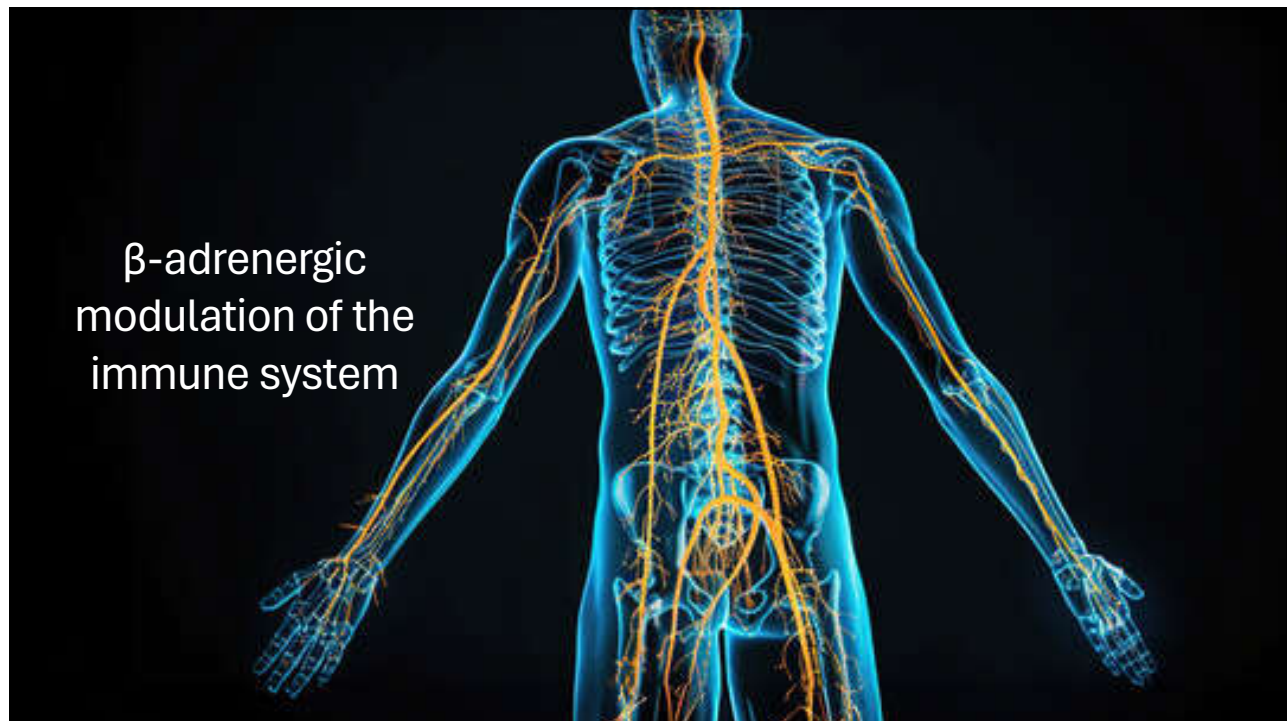
Mitigate sympathetic surge
to decrease stress CM

Decrease myocardial oxygen
demand and ischemia

34



35



36



37


↓ myocardial dysfunction

↓ inflammation & organ dysfunction

↑ survival

Suzuki et al, Crit Care Med 2005
Hagiwara et al, Shock 2009
Ackland et al, Crit Care Med 2010

38

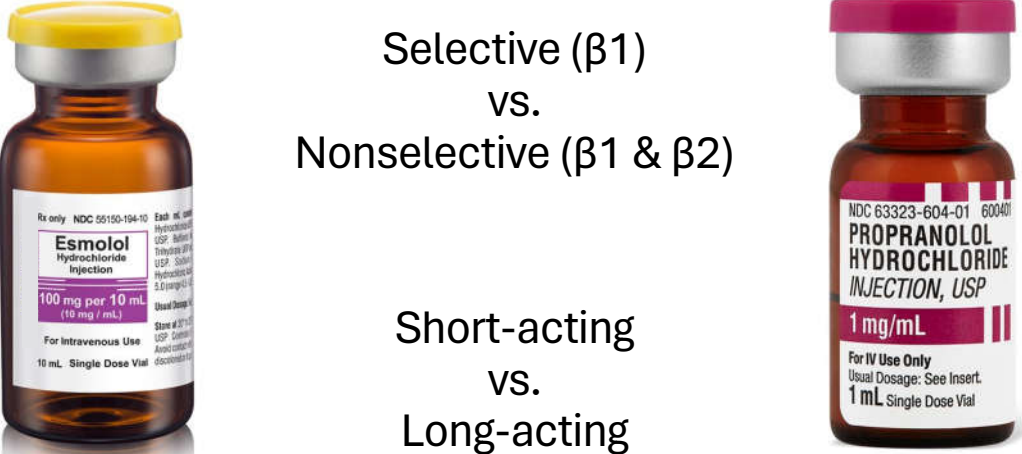


Patients on beta blockers at home
> decreased mortality

Continuing chronic oral beta-blocker
> decreased mortality

Macchia et al, Crit Care Med 2012
Tan et al, Crit Care Med 2021
Fuchs et al, Br J Anesth 2017


39



Selective (β_1)
vs.
Nonselective (β_1 & β_2)

Short-acting
vs.
Long-acting

40



Esmolol


Decreased HR & 28d mortality

Early in shock > hypotension
& decreased cardiac function

No effect on shock

Morelli et al, JAMA 2013
Levy et al, Crit Care 2021
Cocchi et al, Shock 2022

41

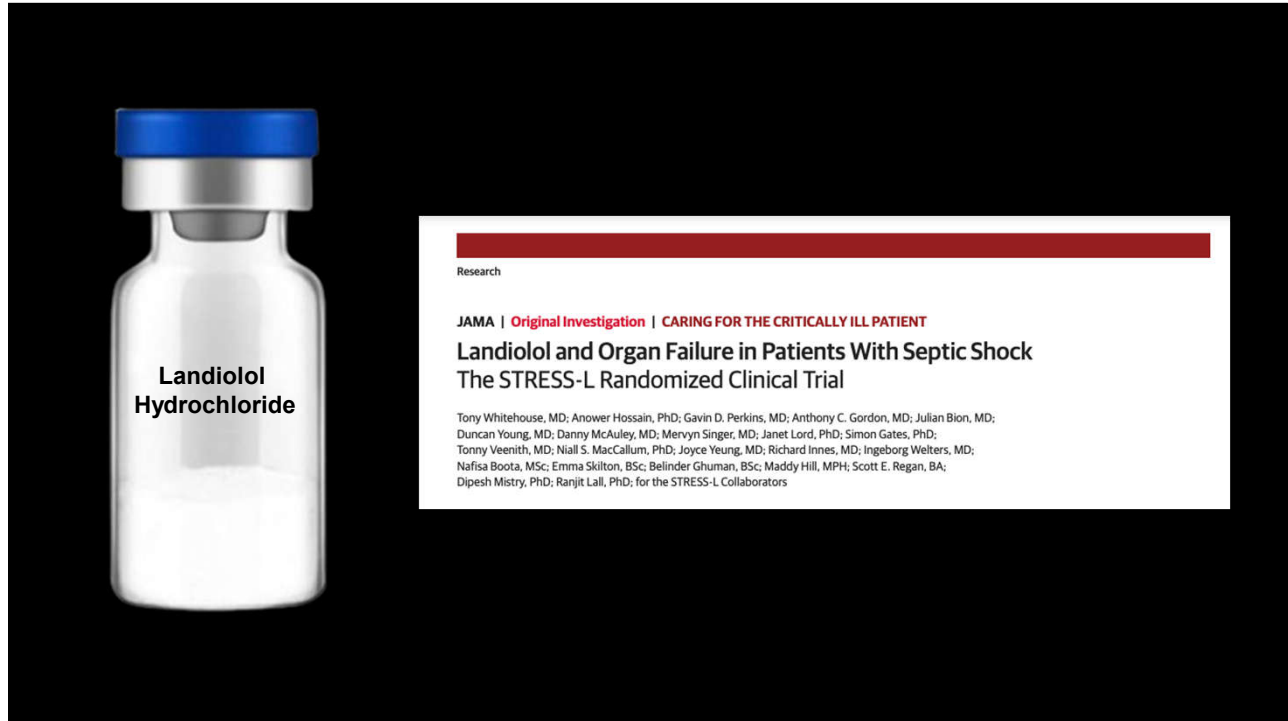


Esmolol

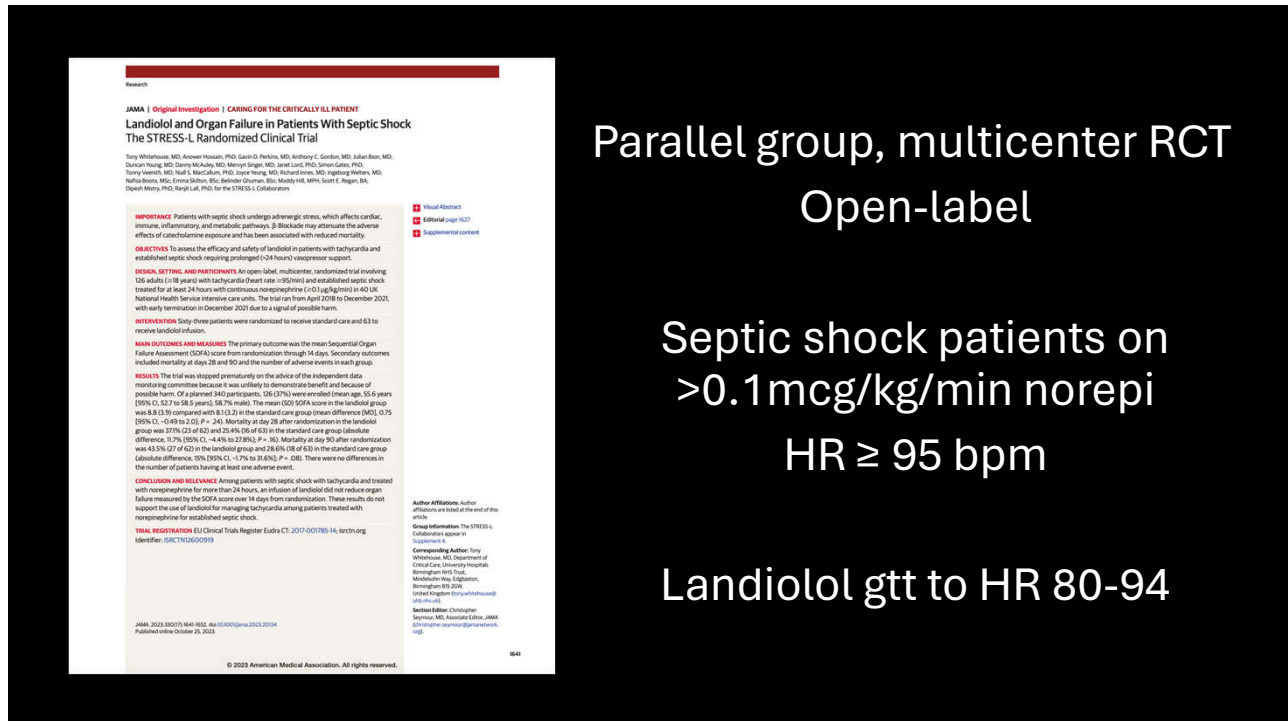
*May decrease 28d mortality, control HR,
and provide cardioprotection*

Zhang et al, Med (Baltimore) 2022

42



43



44

Mean SOFA score
28d & 90d mortality
ICU/hospital LOS
Lactate, PaO₂, PCO₂

45

Trial stopped early
No difference in SOFA score
Trend toward ↑ mortality
More adverse events

46



47

Take Homes

48



Early vasopressor initiation expedites shock control resulting in decreased organ dysfunction and possibly improved mortality.

49



Methylene blue expedites shock control when given early rather than for refractory shock. The optimal dosing strategy remains unclear.

50



Beta-blockers for septic shock are likely not one-size-fits-all and aren't yet ready for prime time.

51

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