PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

Does an orange a day keep the doctor away?

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DISCLOSURE

I have no conflicts of interest to disclose.

Learning Objectives

1. Summarize the current sepsis and septic shock treatment guidelines.
2. Evaluate the literature for ascorbic acid and hydrocortisone in septic shock.
3. Discuss recent findings of the CITRIS-ALI and VITAMINS trials.
4. Discuss the integration of current literature findings into everyday practice.

ABBREVIATIONS

ADRENAL-adjunctive glucocorticoid therapy in patients with septic shock

APROCCHSS-Activated protein C and corticosteroids for human septic shock

CITRIS-ALI- Vitamin C infusion for treatment in sepsis induced acute lung injury

HAT- Hydrocortisone, ascorbic acid, thiamine

HYPRESS- Hydrocortisone for prevention of septic shock

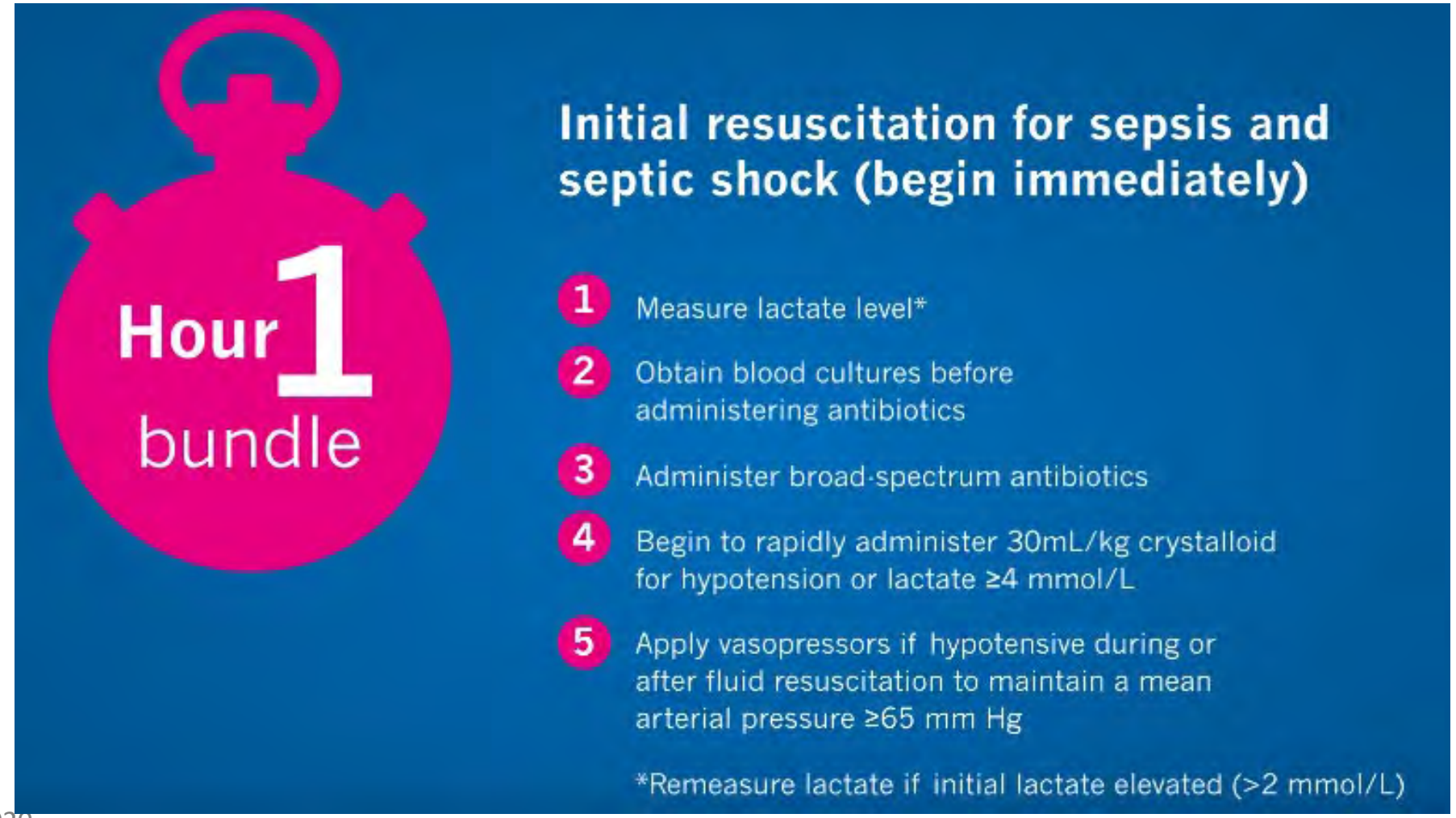
HYVCTTSS-Combined Treatment with Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock

SOFA- Sequential organ failure assessment

SIRS- Systemic inflammatory response syndrome

Sepsis & Septic Shock Treatment Guidelines

New Bundle



1.Rhodes A, et al. Crit Care Med. 2017. 45(3):304-377.

Corticosteroids In Sepsis & Septic Shock

Does your institution's sepsis protocol or order-set include the use of corticosteroids?

- ❑ Yes
- ❑ No

Cortisol and Sepsis

- Inflammatory response → activation of hypothalamic-pituitary adrenal axis
- ↑ cortisol
  - ↓ nitric oxide effects
  - Potentiates catecholamine effects
  - ↑ vasopressin synthesis
- Corticosteroid insufficiency

2. Annane D. Front Endocrinol. 2016. 7(70).

CORTICOSTEROIDS IN SEPSIS GUIDELINES

We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

1. Rhodes A, et al. Crit Care Med. 2017. 45(3):304-377.

HYPRESS TRIAL

- Enrolled 380 patients with sepsis
  - ≥ 2 SIRS criteria, proven infection, and ≥ 1 organ with new dysfunction
- IV hydrocortisone 200 mg x 5 days followed by dose tapering for total of 11 days

	IV Hydrocortisone	Placebo	P value
Septic shock 14 days	21.1%	22.9%	0.70
28 day Mortality	8.8%	8.2%	0.86
Delirium	11.2%	24.5%	0.01

3. KehD, et al. JAMA, 2016. 316(17):1775-1785

ADRENAL TRIAL

- 3658 patients with septic shock requiring vasopressors and mechanical ventilation

	IV Hydrocortisone	Placebo	P value
90 day mortality	27.9%	28.8%	0.50
Median time to shock reversal (days)	3	4	<0.001
Median time to extubation (days)	6	7	<0.001
Median ICU length of stay (days)	10	12	<0.001
Use of RRT	30.6%	32.7%	0.18

4. Venkatesh B, et al. NEJM. 2018; 378: 797-808

APROCCHSS TRIAL

- 1241 patients on hydrocortisone + fludricortisone vs placebo

	Steroids	Placebo	P value
90 day mortality	49.1	43.0	0.03
Median vasopressor free days	19	23	<0.001
Median ventilator free days(days)	4	10	0.07
Median organ failure-free days(days)	12	19	0.003
≥ 1 episode superinfection	28.4%	31.1%	0.3

5. Annane D, et al. NEJM 2018. 378:809-818

STEROIDS- TO GIVE OR NOT TO GIVE?

Pros

- ↓ duration of vasopressors
- ↓ mortality
- ↓ time to shock reversal

Cons

- ↑ infection
- ↑ blood glucose
- ↑ sodium

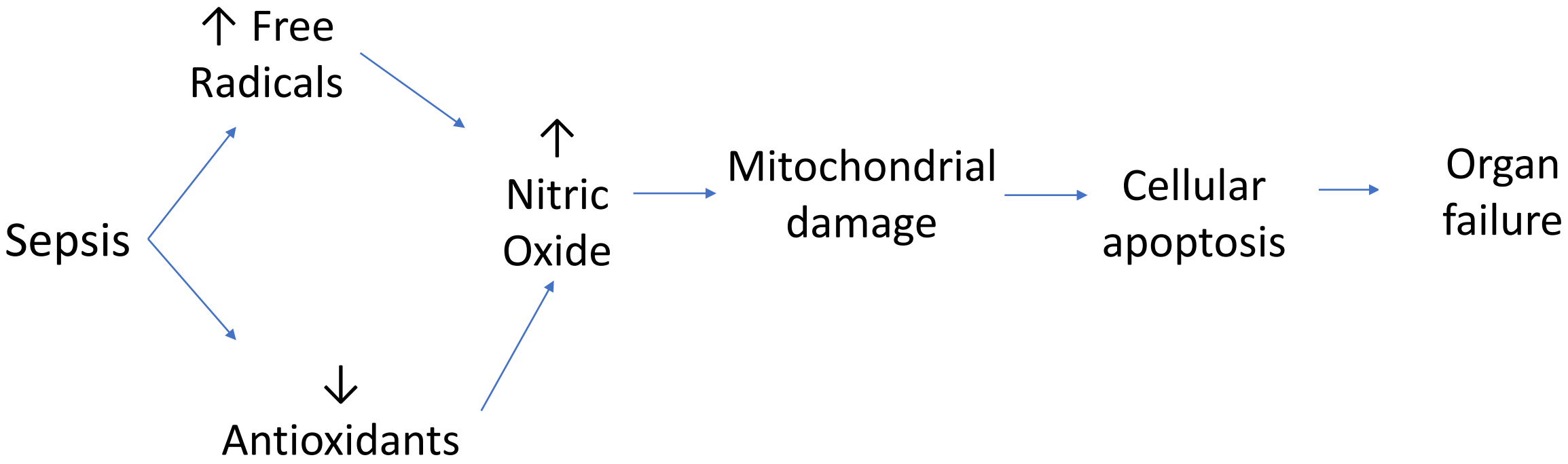
5. Annane D, et al. NEJM 2018. 378:809-818 ; 6. Sprung CL, et al. NEJM. 2008;358(2):111-124

VITAMIN C
SEPSIS & SEPTIC SHOCK

Does your institution's sepsis protocol or order-set include the use of Vitamin C?

- ❑ Yes
- ❑ No

Oxidative Stress In Sepsis



7. Mantzarlis K, et al. Oxid Med Cell Longev 23017;2017:5985209; 8.Marik PE. Pharmacol & Ther 2018; 189:63-70

What's The Harm?

- Systematic review
- 74 studies, 2801 patients
- High dose vitamin C
  - Marik's trial: 1.5 g IV q6 h
  - Median dose in this paper 22.5 g/day

9. Yanase F, et al.Crit Care Med. 2020;10.1097

WHAT'S THE HARM?

- 5 cases of oxalate nephropathy
- 5 cases of hypernatremia
- 3 cases of hemolysis in patients with G6PD deficiency
- 2 cases of glucometer error
- 1 case of kidney stones

9. Yanase F, et al.Crit Care Med. 2020;10.1097

CITRIS-ALI TRIAL

JAMA Network

QUESTION Can intravenous administration of high-dose vitamin C reduce organ failure scores and biomarkers of inflammation and vascular injury in patients with sepsis and acute respiratory distress syndrome (ARDS)?

CONCLUSION This randomized clinical trial found that in patients with sepsis and ARDS, high-dose vitamin C compared with placebo did not significantly reduce organ failure scores or improve biomarker levels.

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POPULATION

90 Men
77 Women

Adults in the intensive care unit (ICU) with sepsis and ARDS for <24 hours

Mean age: 55 years

INTERVENTION

167 Patients analyzed

84

Vitamin C
Intravenous vitamin C infusion, 50 mg/kg every 6 hours for 96 hours total

83

Placebo
Dextrose infusion every 6 hours for 96 hours total

FINDINGS

Change in mSOFA score, points (range 0-20)			
Vitamin C	3 points	Placebo	3.5 points

C-reactive protein at 168 hours, µg/mL			
Vitamin C	54.1 µg/mL	Placebo	46.1 µg/mL

Thrombomodulin at 168 hours, ng/mL			
Vitamin C	14.5 ng/mL	Placebo	13.8 ng/mL

Between-group differences were not significant:

mSOFA, **-0.10** (95% CI, -1.23 to 1.03)

C-reactive protein, **7.94 µg/mL** (95% CI, -8.2 to 24.11)

Thrombomodulin, **0.69 ng/mL** (95% CI, -2.8 to 4.2)

LOCATIONS

7
ICUs in the United States

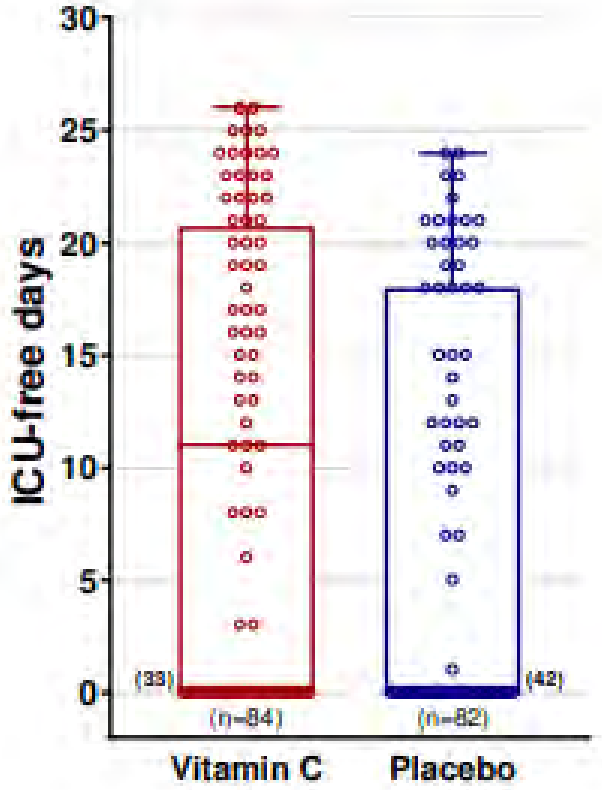
PRIMARY OUTCOME

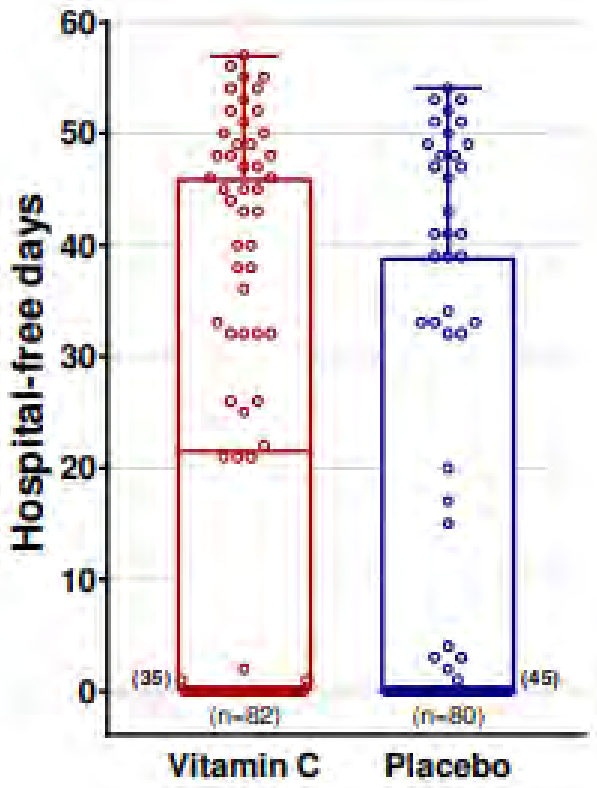
Change in organ failure assessment (mSOFA), biomarkers of inflammation (C-reactive protein), and vascular injury (thrombomodulin)

Fowler III AA, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial [published October 1, 2019]. *JAMA*. doi:10.1001/jama.2019.11825

10. Fowler III A, et al. JAMA 2019;322(13):1261-1270.

CITRIS-ALI TRIAL





10. Fowler III A, et al. JAMA 2019;322(13):1261-1270.

CITRIS-ALI TRIAL

- Higher doses of IV vitamin C
- Included intubated patients with ARDS
- Primarily a “negative” study
  - Until mortality is factored in
- Primarily a “positive” trial
  - When safety is factored in

10. Fowler III A, et al. JAMA 2019;322(13):1261-1270.

HYDROCORTISONE, VITAMIN C, THIAMINE IN SEPSIS & SEPTIC SHOCK

Does your institution's sepsis protocol or order-set include the use of Hydrocortisone, thiamine, and vitamin C?

- ❑ Yes
- ❑ No

MARIK TRIAL

- Vitamin C + Hydrocortisone + Thiamine vs. standard treatment
  - 1.5g QDS Vitamin C intravenously for 4 days or until ICU discharge
  - Hydrocortisone 50mg QDS intravenously for 7 days or until ICU discharge followed by a taper over 3 days
  - 200mg thiamine BD for 4 days or until ICU discharge

11. Marik PE, et al. Chest. 2017;151(6):1229-1238

MARIK TRIAL- OUTCOMES

Primary Outcome: Hospital mortality (vitamin C vs. standard)

- 8.5% (4 of 47) vs. 40.4% (19 of 47) $p < 0.001$

Secondary Outcomes: (Vitamin C vs standard)

- Mean duration of vasopressor therapy: 18.3 ± 9.8 hrs vs. 54.9 ± 28.4 $P<0.001$
- 72-hour delta SOFA score 4.8 ± 2.4 vs. 0.9 ± 2.7 $p<0.001$.

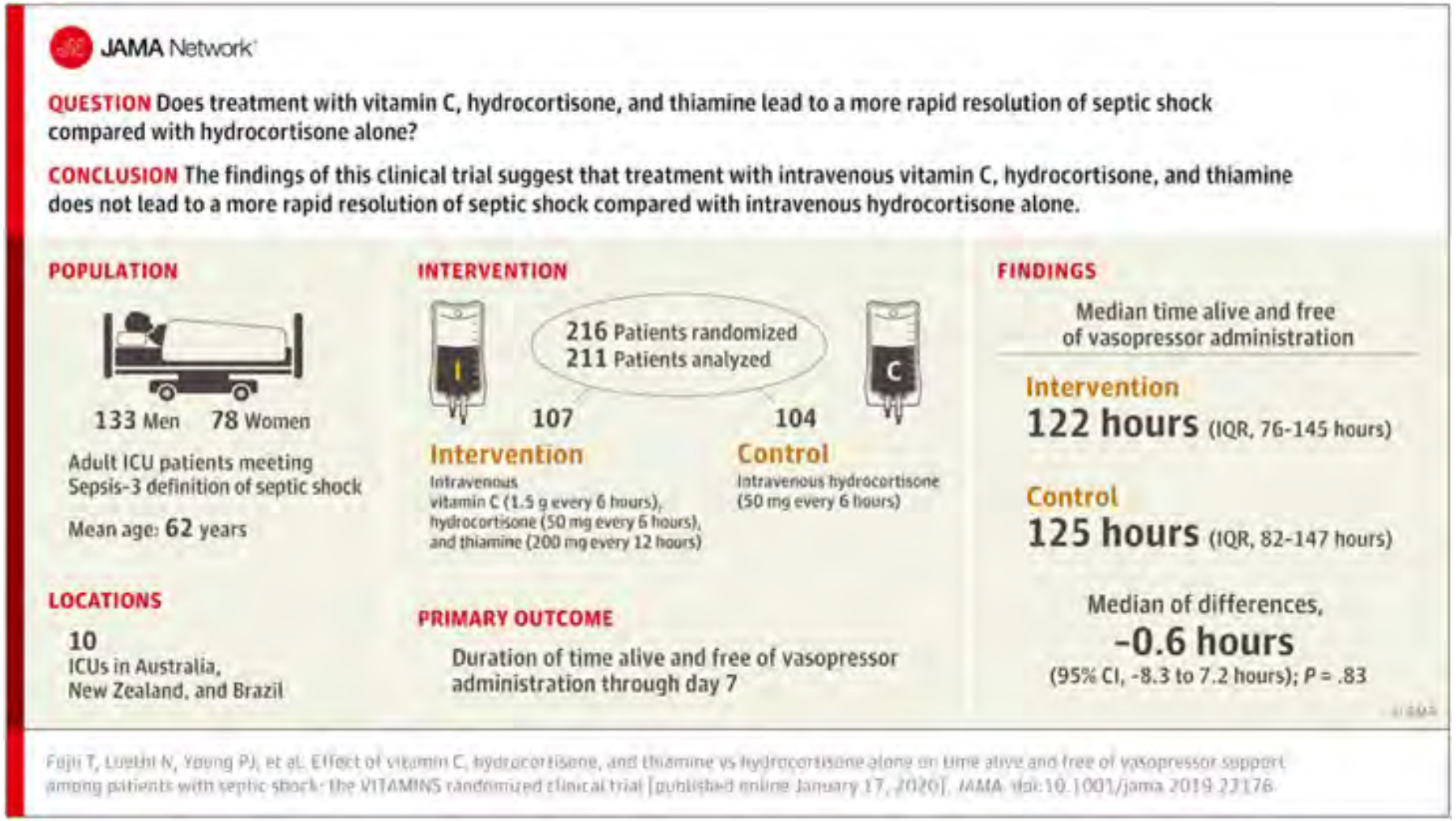
11. Marik PE, et al. Chest. 2017;151(6):1229-1238

MARIK TRIAL

- High mortality in the control group
- Multiple interventions and therefore not possible to determine which, if any, are associated with improved outcome
- The treatment and control periods were not concurrent and occurred during different seasons

11. Marik PE, et al. Chest. 2017;151(6):1229-1238

VITAMINS TRIAL



12. Fujii T, et al. JAMA, 2020;323(5):423–431

VITAMINS TRIAL

- No significant difference in the median time alive and free of vasopressors up to day 7 after randomisation between the intervention group and the control group
  - 122.1 hours [IQR, 76.3-145.4] vs. 124.6 hours [IQR, 82.1-147.0]
  - Median difference between groups, –0.6 hours [95% CI, –8.3 to 7.2]; P = 0.83

12. Fujii T, et al. JAMA, 2020;323(5):423–431

VITAMINS TRIAL

- VITAMINS trial shows that ascorbic acid and thiamine add nothing to hydrocortisone
- HAT was administered after initial resuscitation- efficacy compromised?

12. Fujii T, et al. JAMA, 2020;323(5):423–431

HYVCTTSS TRIAL

- Initial intent to enroll 140 patients
  - Final enrollment of 80

- Patients were included if they met the definition of sepsis-3 AND had a procalcitonin >2 ng/mL

- Treatment:
  - Hydrocortisone 50 mg q6 h x 7 days
  - Thiamine 200 mg q12 h x 4 days
  - Vitamin C 1.5 g q6 h x 4 days

13. Chang P, et al. Chest. 2020;158(1): 174-182

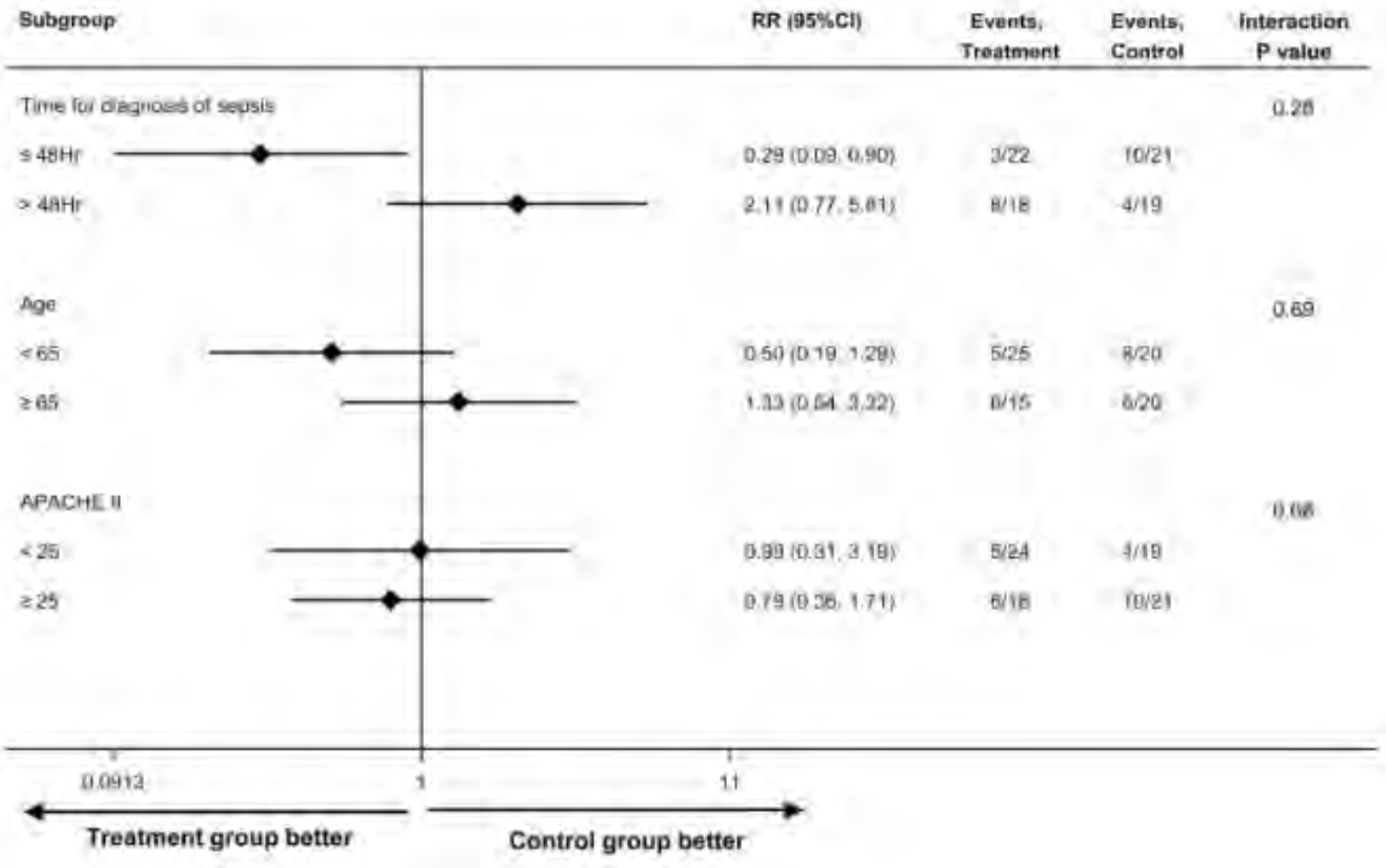
HYVCTTSS TRIAL

- Primary endpoint
  - 28 day mortality 27.5 % vs. 35% (Vitamin C vs placebo) , p =0.47

- Secondary endpoints
  - Comparable between groups for 28 day mortality, ICU length of stay, new AKI after entering ICU, procalcitonin clearance at 72 hr, lactate clearance at 72 hr and duration of mechanical ventilation
  - Duration of vasopressor 46 vs 58.5 hrs, p =0.70
  - Change in SOFA score at 72 hr 3.5 ± 3.3 vs 1.8 ± 3.0, p = 0.02

13. Chang P, et al. Chest. 2020;158(1): 174-182

HYVCTTSS TRIAL



13. Chang P, et al. Chest. 2020;158(1): 174-182

ORANGES TRIAL

Randomized to:

- Ascorbic Acid 1500 mg q6hr, thiamine 200 mg q12hr, and hydrocortisone 50 mg q6hr for a maximum of 4 days
- Placebo: saline placebo for a maximum of 4 days

14. Iglesias J, et al. CHEST. 2020;158(1):164-173

ORANGES TRIAL

- Primary outcomes
  - Resolution of shock (Time from starting blinded study medications to discontinuation of all vasopressor support)
  - Change in SOFA score (initial SOFA score minus the day 4 SOFA score)

14. Iglesias J, et al. CHEST. 2020;158(1):164-173

ORANGES TRIAL

- Secondary outcomes:
  - 28d mortality ; ICU mortality; Hospital mortality
  - Procalcitonin clearance (PCT-c) = (initial PCT - PCT at 96hrs)/initial PCT x 100
  - Hospital LOS; ICU LOS
  - Ventilator-free days
  - Acute kidney injury = ↑ in serum creatinine (SCr) >0.3mg/dL, or a level >1.5x the baseline value or initiation of RRT

14. Iglesias J, et al. CHEST. 2020;158(1):164-173

ORANGES TRIAL

- Safety:
  - Serum creatinine
  - Urine oxalate = 24-hour urine collection on day 4
  - Adverse reactions

14. Iglesias J, et al. CHEST. 2020;158(1):164-173

ORANGES TRIAL

- Primary outcomes
  - Resolution of shock (Time from starting blinded study medications to discontinuation of all vasopressor support)
    - HAT 27 ± 22hrs vs. Placebo 53 ± 58 hrs ($p < 0.001$)
  - Change in SOFA score (initial SOFA score minus the day 4 SOFA score)
    - HAT 3 vs. Placebo 2 ($p = 0.17$)

14. Iglesias J, et al. CHEST. 2020;158(1):164-173

HYDROCORTISONE, VITAMIN C, THIAMINE IN PRACTICE

HYDROCORTISONE

- Consider using when:
  - Fluids and vasopressors are not sufficient
  - Adrenal insufficiency
  - Early start is feasible?

Thiamine and Vitamin C

- Consider using in:
  - Patients with ARDS (Citris-Ali)

HYDROCORTISONE, THIAMINE, AND VITAMIN C

- Consider using
  - When the ends justify the means
  - Newer studies
    - Effects of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock (Aug 2020)
    - Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double blinded randomized, controlled study (August 2020)

REVIEW QUESTIONS

The surviving sepsis campaign guidelines includes the use of corticosteroids as part of the 1 hour bundle.

- ❑True
- ❑False

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- ❑True
- ❑False

Which of the following trials showed benefit of hydrocortisone, ascorbic acid, and thiamine in patients with ARDS and sepsis?

- ❑Oranges
- ❑HYVCTTSSS
- ❑VITAMINS
- ❑CITRIS-ALI

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- ❑Oranges
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- ❑VITAMINS
- ❑CITRIS-ALI

A 47 YOM cuts his thumb while attaching an accessory to one of his mowers. Upon their arrival at the ER, the man's temperature has reached 39.7ºC. He is flushed and ill-appearing, with a HR of 125, RR 33, and BP of 90/60 mm Hg. (His normal BP is 145/85 mm Hg.) He is initiated on noreinephrine, vasopressin, cefzolin, and lactated ringers. He is currently progressively hypotensive and has mild acute kidney injury.

Which of the following is most appropriate at this time?

- ❑Start phenylepinephrine drip
- ❑Start thiamine 10 mg PO QD
- ❑Give 150 mg IV hydrocortisone q12h
- ❑Give ascorbic acid 250 mg q8h

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6. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124
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8. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol Ther*. 2018;189:63-70.

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Session Code: