



**PHARMACY
VISION
20/20**

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Disneyland
RESORT

PEDIATRIC SEPSIS UPDATE: RECOGNITION AND MANAGEMENT

KATIE BUI, PHARM.D, ED PHARMACIST

M. TUAN TRAN, PHARM.D, ID PHARMACIST

CHOC CHILDREN'S HOSPITAL

DISCLOSURE

The authors report no financial, commercial, or industrial relationship to disclose in regards to this presentation

LEARNING OBJECTIVES – PHARMACY TECHNICIANS

- Define septic shock
- List generic and brand names of medications used in pediatric septic shock
- List dosages of medications used in pediatric septic shock
- List common side effects of medications used in pediatric septic shock

LEARNING OBJECTIVES – PHARMACISTS

- Define shock and septic shock
- Discuss guidelines and literature on pediatric sepsis
- Review pharmacological management of sepsis
- Discuss guidelines on sepsis management due to COVID19
- Discuss pharmacist's interventions to improve sepsis outcomes

SEPSIS AND SEPTIC SHOCK

SIRS: At least two of the following:

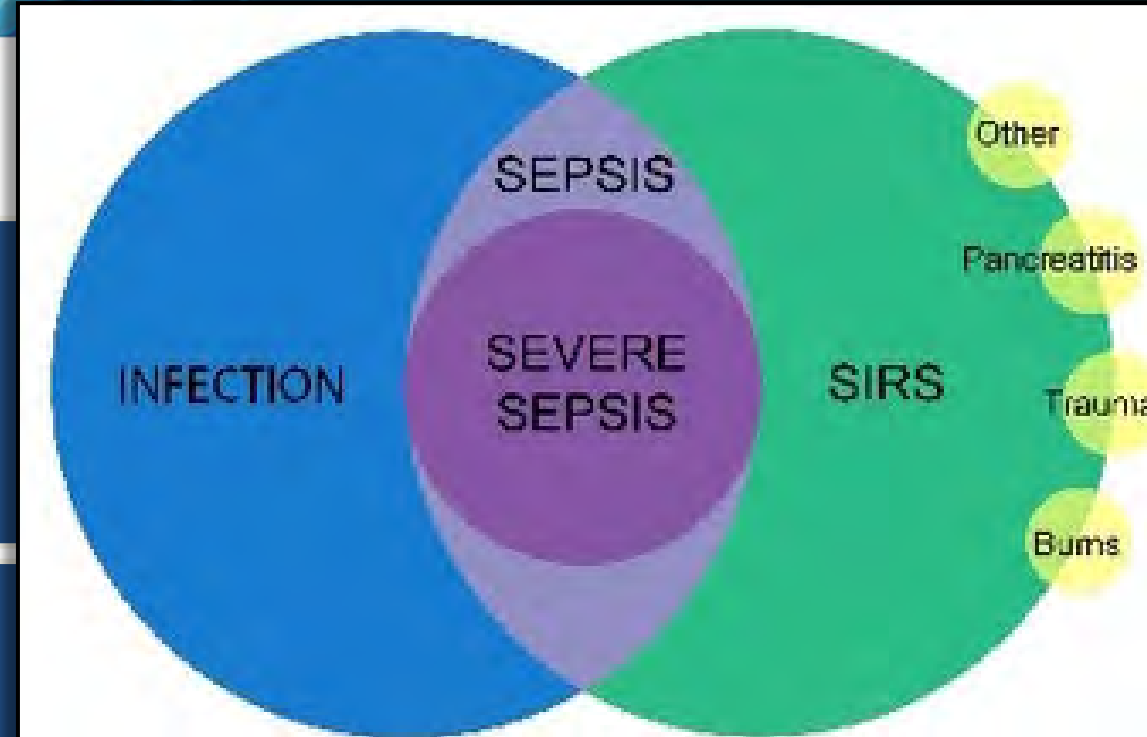
- 1) Temperature
- 2) elevated HR
- 3) Increased RR
- 4) WBC

Sepsis:

SIRS + source of infection

Septic Shock:

Severe sepsis + hypotension not reversed by fluid resuscitation



SEPSIS IN THE PEDIATRIC POPULATION

Sepsis is the #1 cause of hospital readmissions

Sepsis is #1 cause of deaths in US hospitals

- ~6800 U.S. children die each year from sepsis
- 80,000 admissions

75% are admitted to an ICU after sepsis diagnosis

Sepsis treatment accounts for at least 16% of all pediatric health care spending

- ~\$5 billion cost to hospital each year

Differences between Pediatric vs Adult Sepsis

Epidemiology	Mortality lower in pediatrics (10% vs 30%)
Pathophysiology	Myocardial dysfunction -> inotropic support
Presentation	<ul style="list-style-type: none">- Cold shock more common in pediatrics- Higher ECF to ICF ratio in pediatrics- Respiratory collapse
Recognition	<ul style="list-style-type: none">- Hypotension is a late sign -> early recognition is critical- Hypothermia more common in pediatrics

S

Shivering, fever,
clammy skin

E

Eating poorly

P

Pale or blue skin

S

Sleepy, hard to keep awake, confused

I

Infection, redness, swelling

S

Shortness of breath

Clinical Signs of Shock

Early :

- ▶ Sinus tachycardia
- ▶ Fussiness, irritability
- ▶ Delayed capillary fill (>2secs)
- ▶ Decreased BP could be early in presence of sepsis

Late :

- ▶ Bradycardia
- ▶ Altered mental status (lethargy, coma)
- ▶ Irregular breathing
- ▶ Hypotension =very late sign (Lower limit of SBP = $70 + (2 \times \text{age in years})$)
- ▶ Decreased urine output (UOP < 1ml/kg/hr)

TYPES OF SHOCK

Distributive

- Sepsis
- Anaphylaxis

Hypovolemic

- Dehydration
- Hemorrhage
- Burns

Cardiogenic

- Acute MI
- Acute decompensated HF
- Congenital heart disease

Obstructive

- Pulmonary embolism
- Pneumothorax

PEDIATRIC SEPSIS SEVERITY SCORING

Pediatric Sequential Organ Failure Assessment (pSOFA)

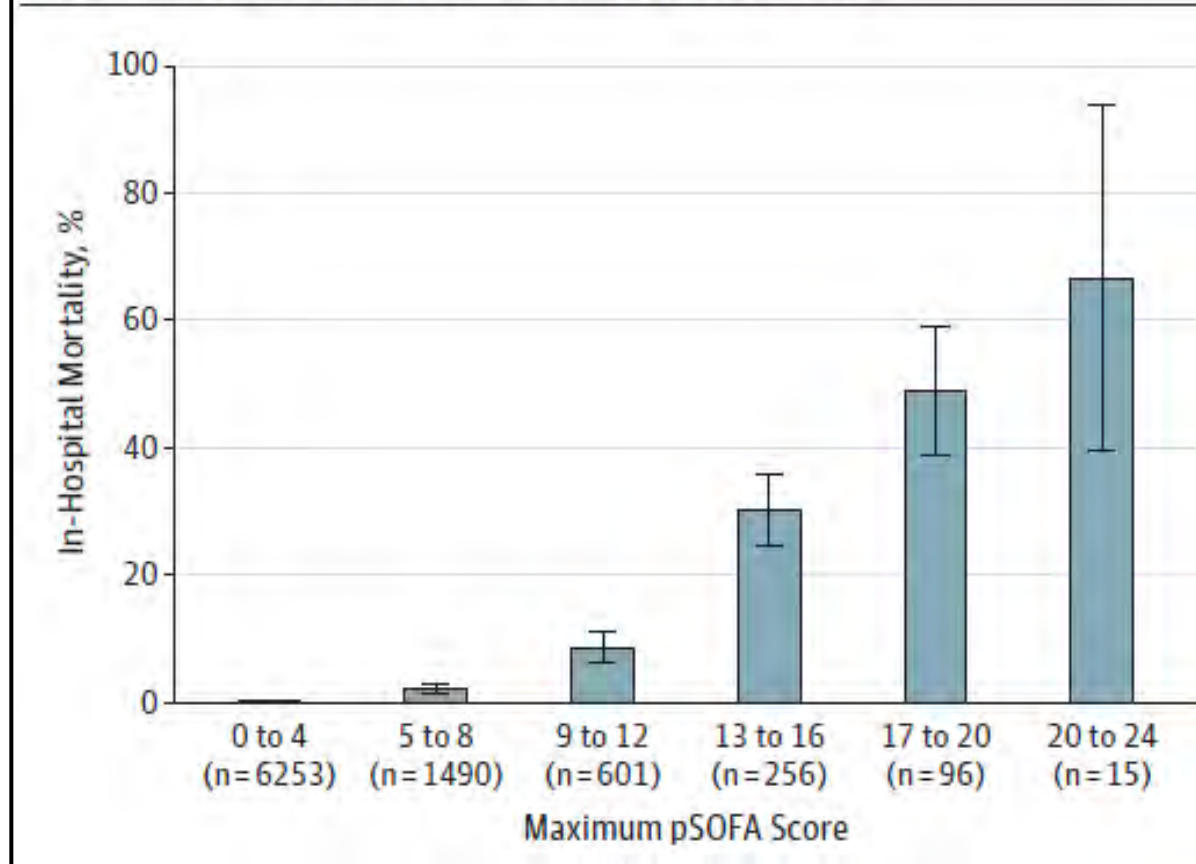
- Measures organ dysfunction and in-hospital mortality
- Age adjusted cutoffs for cardiovascular and renal systems
- Standardizes definition of sepsis across age groups
 - Better design of clinical trials
 - Improved accuracy of reported outcomes
 - Help bridge discrepancies in identifying pediatric sepsis

pSOFA

- Scoring: 0 to 4 in each of the 6 systems
- Systems assessed:
 - Respiratory
 - Coagulation
 - Hepatic
 - Cardiovascular*
 - Neurologic
 - Renal*
- Score > 8 = cut off to discriminate mortality

*age-adjusted

Figure. In-Hospital Mortality Rate Based on the Maximum Pediatric Sequential Organ Failure Assessment (pSOFA) Score



Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children

Scott L. Weiss, MD, MSCE, FCCM (Co-Vice Chair)¹; Mark J. Peters, MD, PhD (Co-Vice Chair)²;
Waleed Alhazzani, MD, MSc, FRCPC (Methodology Chair)³; Michael S. D. Agus, MD, FCCM, FAAP⁴;
Heidi R. Flori, MD, FAAP⁵; David P. Inwald, MB, BChir, FRCPCH, FFICM, PhD⁶;
Simon Nadel, MBBS, MRCP, FRCP⁶;
Luregn J. Schlapbach, FCICM, FMH-ICU, FMH-Paed, FMH-Neonatology⁷;
Robert C. Tasker, MB BS, MA, AM, MD, FRCPHC, FRCP⁴;
Andrew C. Argent, MB BCh, MMed, MD (Paediatrics)⁸; Joe Brierley, MD, MA⁹;
Joseph Carcillo, MD¹⁰; Enitan D. Carrol, MB ChB, MD, FRCPCH, DTMH¹¹;
Christopher L. Carroll, MD, MS, FCCM, FAAP¹²; Ira M. Cheifetz, MD, FCCM¹³;

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

Society of Critical Care Medicine (SCCM) recommends that hospitals have a performance improvement program

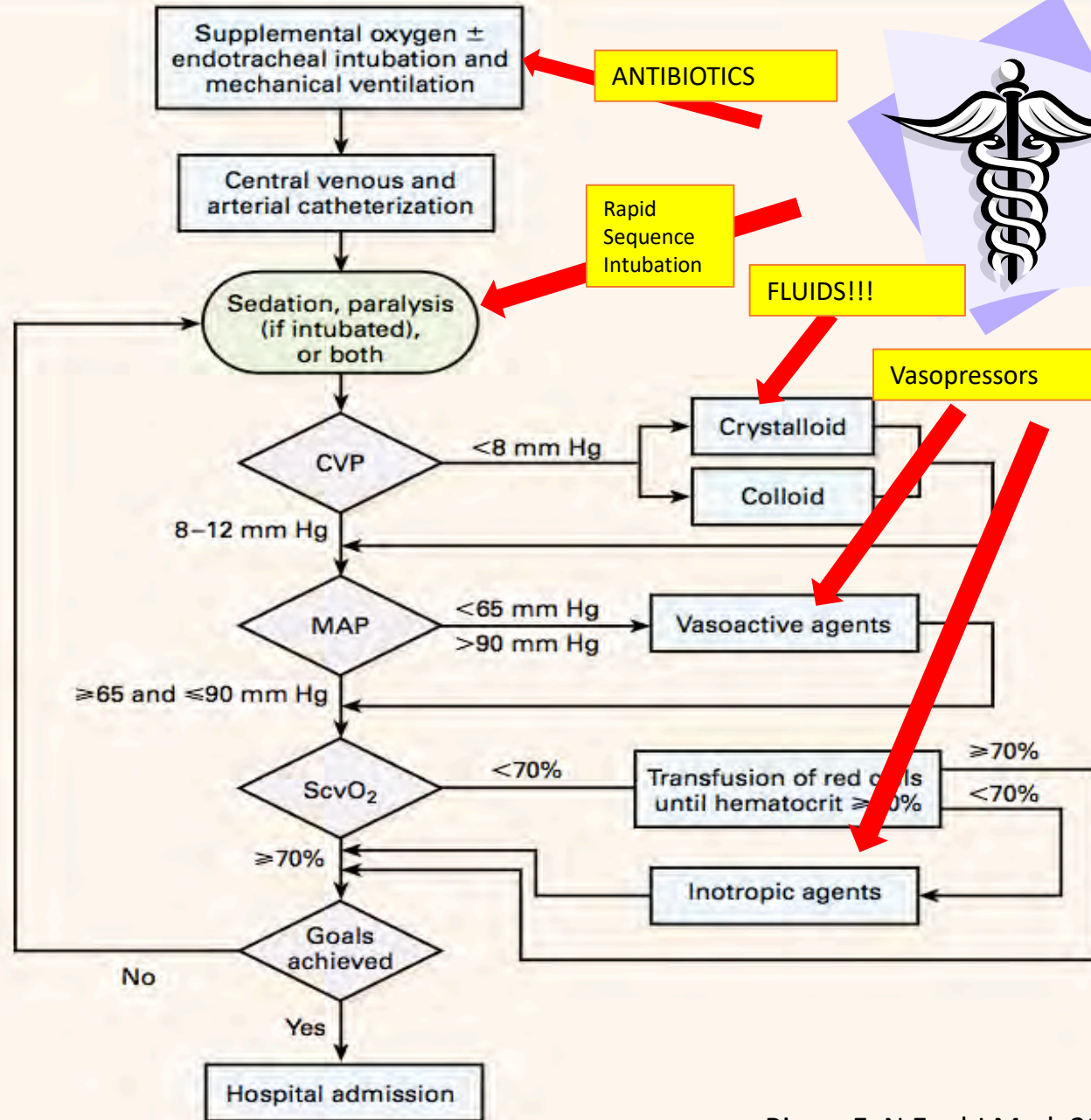
- Systemic screening for timely recognition of septic shock
- Protocol/guideline for the management of septic shock
- Initiation of antimicrobial therapy within 1 hour of recognition

TREATMENT GOALS

- Improve hemodynamic parameters and oxygen delivery
- Reverse/prevent organ hypoperfusion
- Treat underlying causes

BEST PRACTICE STATEMENT FROM SCCM

- Sepsis and septic shock are *medical emergencies* and treatment and resuscitation begin immediately → **START EARLY !!!**
 - **Initiate antibiotics within 60 min**
 - **Initiate fluid 10-20 mL/kg (up to 60 mL/kg) over the 1st hour to correct hypovolemia**
 - Restore perfusion pressure



ANTIBIOTICS

Rapid Sequence Intubation

FLUIDS!!!

Vasopressors



Rivers E. N Engl J Med. 2001.

STEPS TO IMPROVING OUTCOMES

- ***Prevention*** 
- ***Recognition***
- ***Diagnostic Evaluation***
- ***Resuscitation/Stabilization*** 
- ***De-escalation*** 
- ***Patient and Family Engagement***
- ***Optimize Performance***

Severe Sepsis Screening Form

	Axillary	Oral	Rectal
Temperature	<input type="text" value=""/>	<input type="text" value="39"/>	<input type="text" value=""/>
<input checked="" type="radio"/> Abnormal	<input type="text" value=""/>	<input type="text" value="Abnormal Oral Temperature"/>	<input type="text" value=""/>
Heart Rate	<input type="text" value="90"/>		
<input type="radio"/> Abnormal			Fever prior to ED arrival
			<input type="radio"/> Yes <input type="radio"/> No
Blood Pressure	<input type="text" value="111"/>	<input type="text" value="80"/>	
<input type="radio"/> Abnormal systolic blood pressure			
<input type="radio"/> Abnormal diastolic blood pressure			
Cap Refill & Skin Signs	<input type="radio"/> Normal <input type="radio"/> Abnormal		
Mental Status	<input type="radio"/> Normal <input type="radio"/> Abnormal		
High Risk Conditions	<input type="radio"/> No <input type="radio"/> Yes		
# of Risks	<input type="text" value="1"/>	<input type="text" value=""/>	
	<input type="radio"/> Huddle Required		
Outcome of Huddle	<input type="radio"/> Proceed with Severe Sepsis Pathway <input type="radio"/> Triage per Protocol		

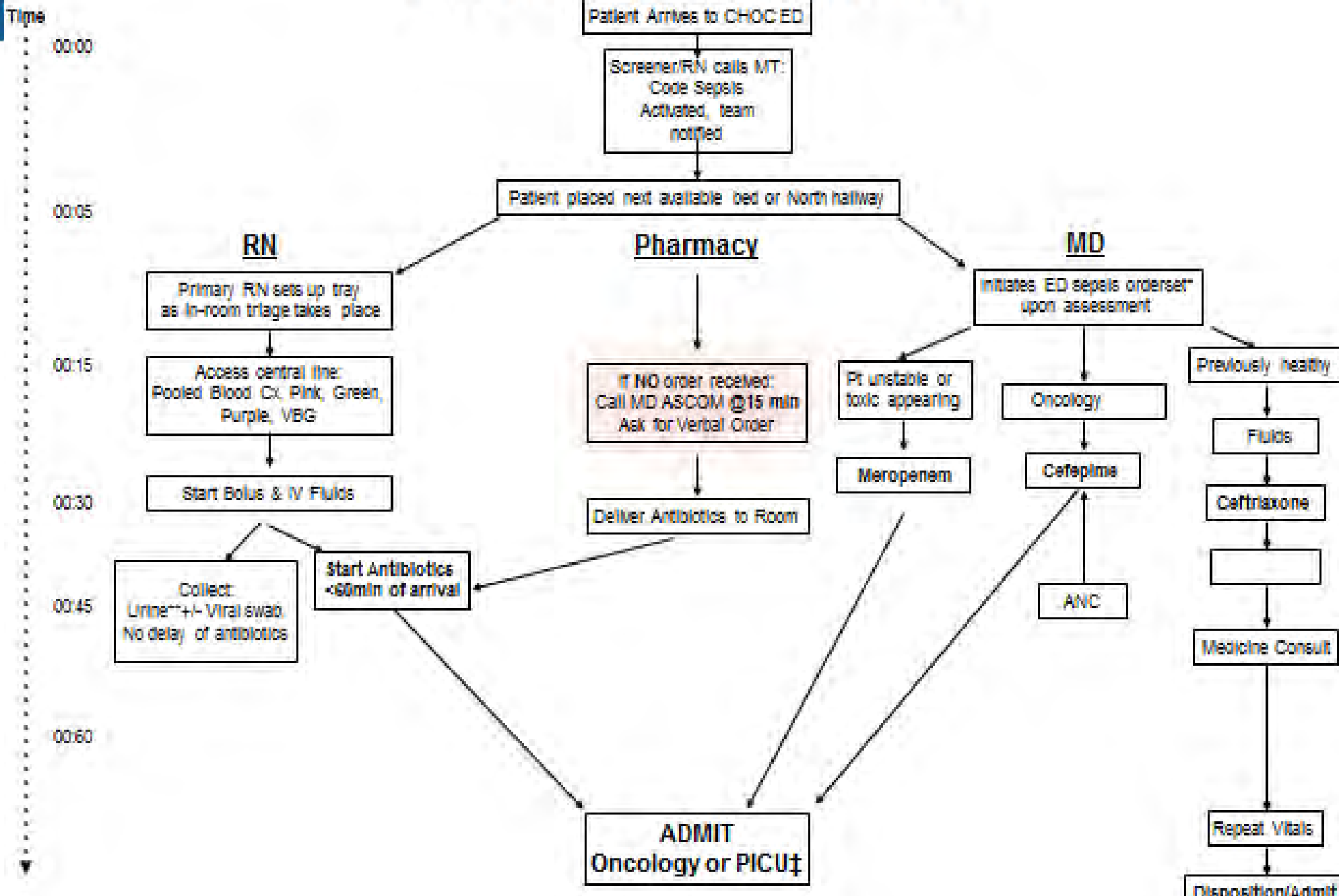
Cap Refill:
Cold shock >= 3 sec
Warm shock < 1 sec

Mental Status:
Decreased, irritable, confused, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

High Risk Conditions:
Malignancy, asplenia, bone marrow transplant, central line/catheter, solid organ transplant, severe MR/CP, immunodeficiency/immunosuppression, Tech Dependent (g-tube, trach, VP shunt)

 **Time Zero**

Code Sepsis in the ED



PHARMACY WORKFLOW

- ER pharmacist expectations:
 - Be at bedside
 - Antibiotics delivered/started within 15 minutes of order placement
- ER pharmacy technician expectations:
 - Assist pharmacist
 - Prepare antibiotic doses and bring to bedside

Screening and Huddle considerations

What's for lunch?

What are we treating?

Why didn't they give antibiotics yet?

How fast do they want that fluid?



EMPIRIC ANTIBIOTICS

- **Previously Healthy**
 - Ceftriaxone
- **Intra-abdominal**
 - Zosyn for pseudomonas and anaerobic coverage
- **Tracheitis**
 - Zosyn for pseudomonas and anaerobic coverage



EMPIRIC ANTIBIOTICS

- **Immunocompromised/Heme/Oncology**
 - Cefepime for pseudomonas coverage
- **Skin and soft tissue or Bone/Joint**
 - Cefazolin + Clindamycin or Vanco or Linezolid
- **GI/GU**
 - Meropenem for pseudomonas, ESBL, anaerobic coverage
- **Suspect MRSA or indwelling device**
 - Vancomycin load 20-30 mg/kg

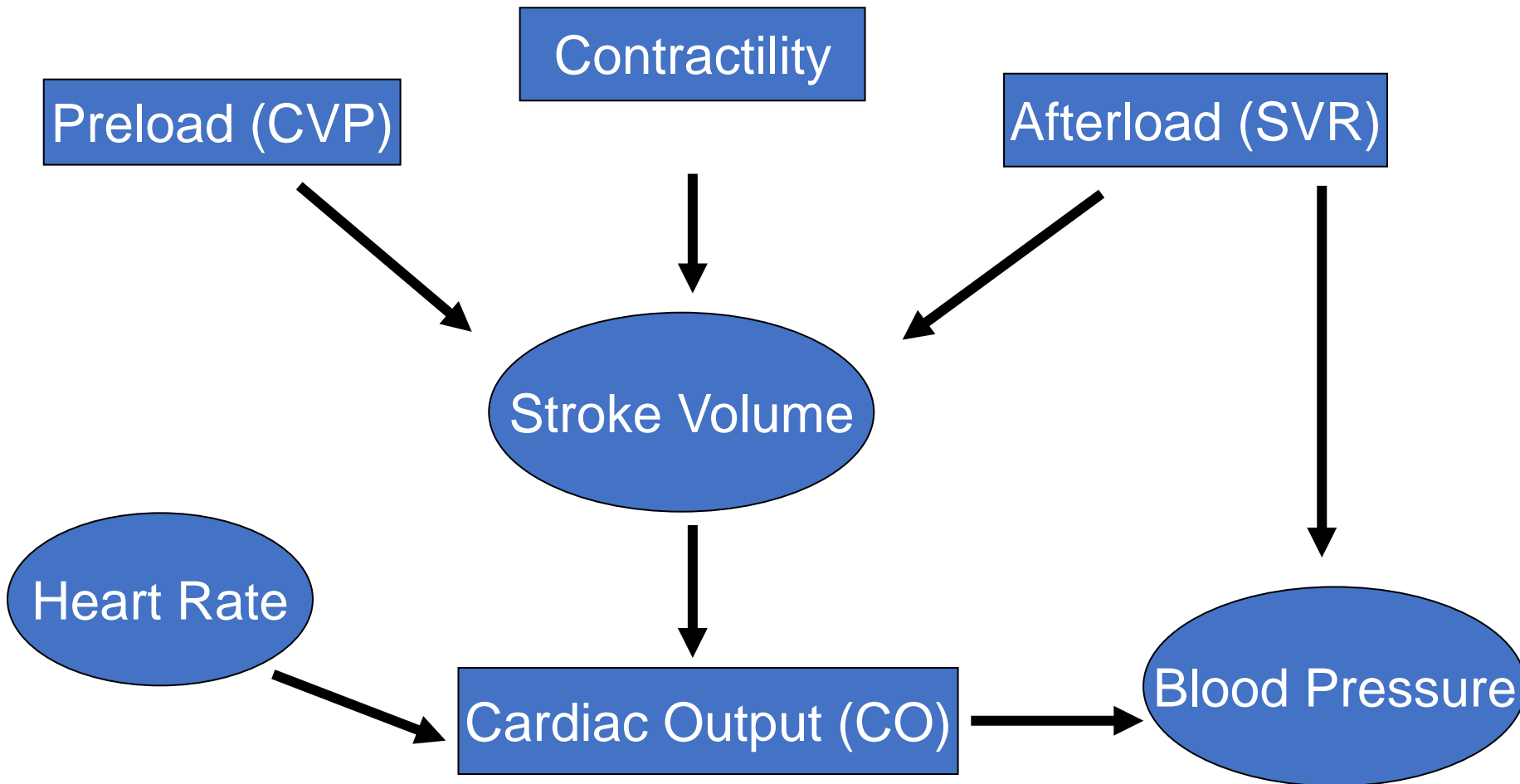


For MRSA + better GPC coverage,
toxin inhibition

DEFINITIONS

- Central Venous Pressure = CVP
 - Measures fluid status
 - Low CVP = dehydration
- Systemic Vascular Resistance = SVR
 - Cytokines release from infection causes vasodilation and leaky capillaries -> low SVR

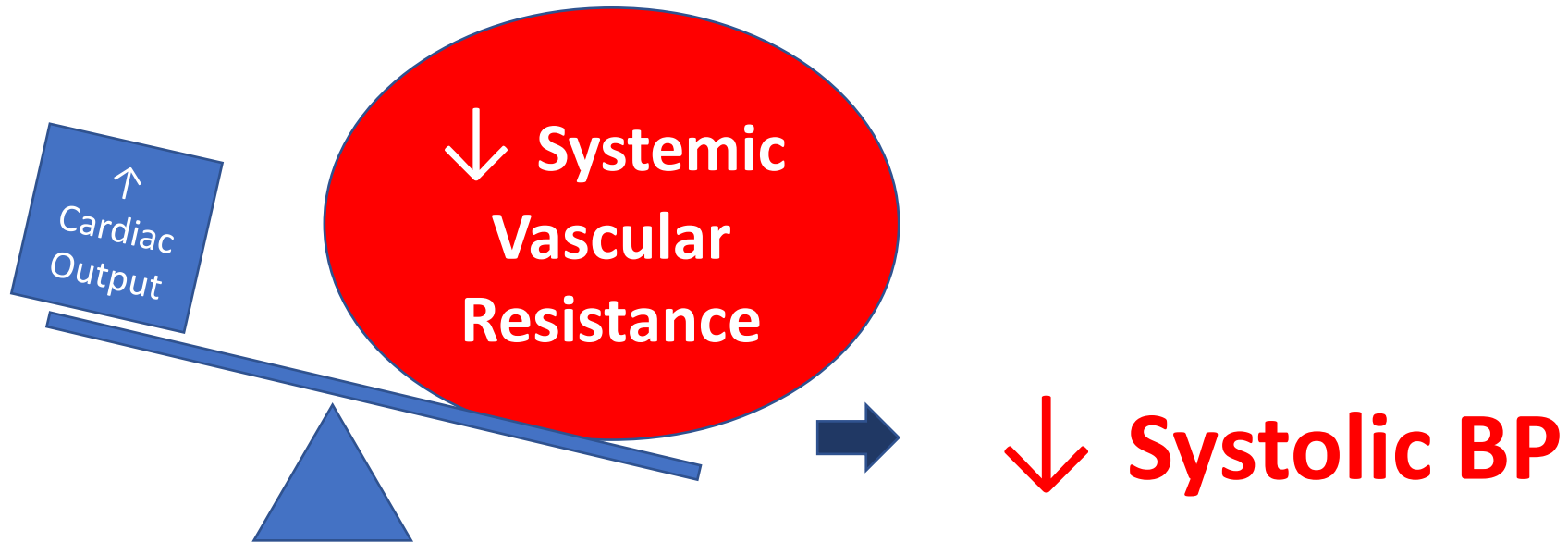
Determinants of Ventricular Function



TYPES OF SHOCK

	Hypovolemic	Cardiogenic	Septic
CVP	↓	↑	↓
CO	↓	↓	↑
SVR	↑	↑	↓

VASODILATION IS RESPONSIBLE FOR HYPOTENSION IN SEPTIC SHOCK

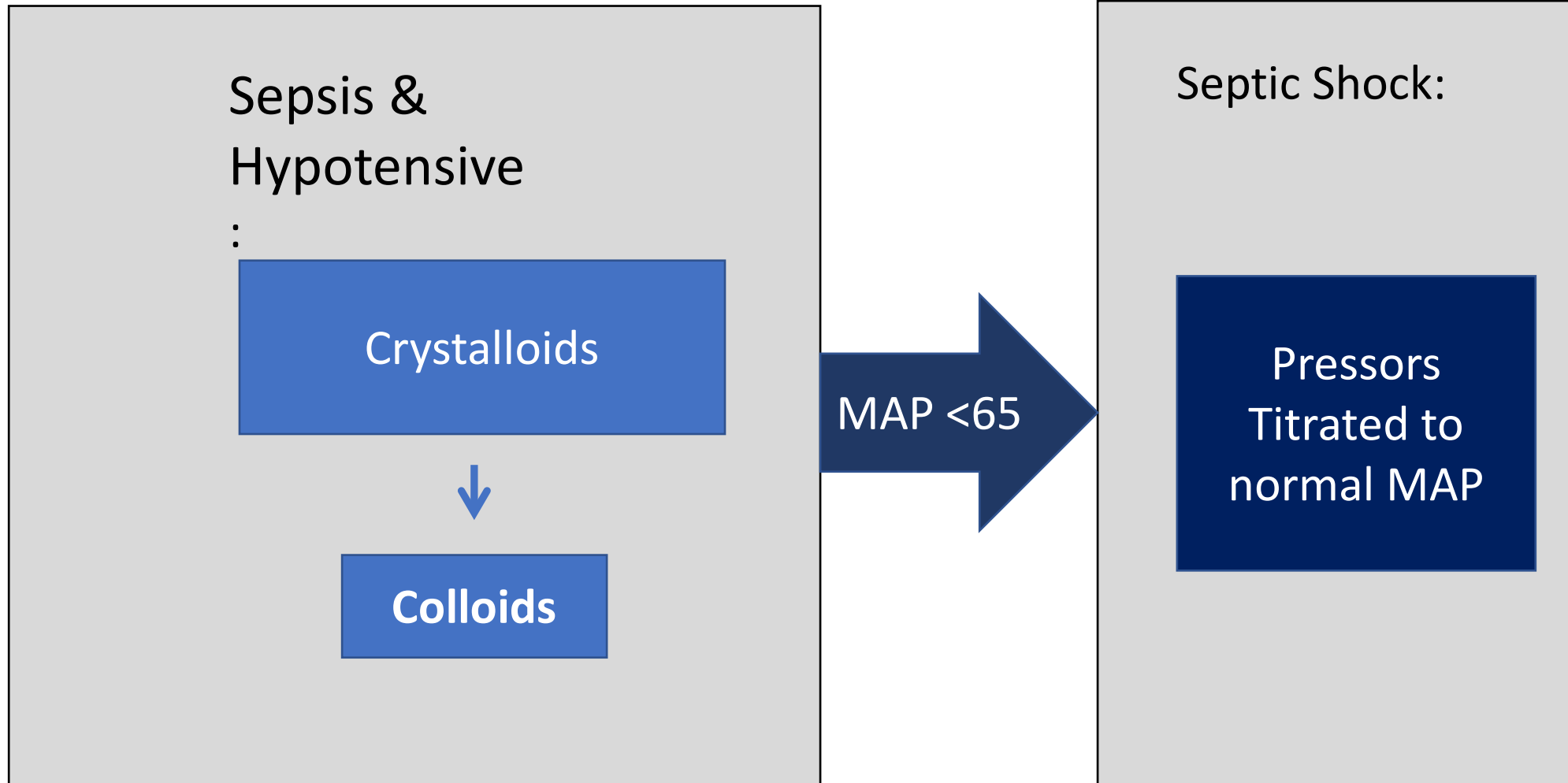


- 2 ways to increase SBP:
 1. Fluid resuscitation
 2. Vasopressors

Fluid Resuscitation

	Crystalloids	Colloids
Examples	NS, LR	Albumin
Doses	10-20 mL/kg (max 60 mL/kg)	1 gm/kg
Pros	<ul style="list-style-type: none"> Cheaper 	<ul style="list-style-type: none"> Longer duration Less volume required
Cons	<ul style="list-style-type: none"> Rapid redistribution 	<ul style="list-style-type: none"> Expensive Pulmonary edema Blood product

FLUIDS! FLUIDS! FLUIDS!



Vasopressors used in Septic Shock

	HR	CO	SVR
Norepinephrine	↑	↔ ↓	↑ ↑
Epinephrine	↑	↑	↑ ↑
Dopamine >10 mcg/kg/min	↑	↑	↑ ↑
Vasopressin	↔	↔	↑

Vasopressors used in Septic Shock

	α_1 (Constriction)	β_1 (\uparrow Contractility)	β_2 (Dilation)	V_1 (Constriction)
Norepinephrine	+++	+	-	-
Epinephrine	+++	+++	+	-
Dopamine >10 mcg/kg/min	+++	++	+	-
Vasopressin	-	-	-	+++

SCCM PEDIATRICS GUIDELINE 2020

- No recommendation for a specific first-line vasoactive agent for children with septic shock
 - Epinephrine > Dopamine
 - Norepinephrine > Dopamine
- Recommend adding vasopressin or titrate catecholamines

OTHER RECOMMENDATIONS

- Pediatric Surviving Sepsis Campaign, 2020 recommends:
 - Against IV hydrocortisone
 - IV hydrocortisone 200 mg/day, if necessary
 - Pediatric dosing: 50 mg/m²/day or 2mg/kg/day
 - Against starting insulin therapy to target BG <140 mg/dL
 - No recommendation regarding BG range to target for children
 - Against routine use of stress ulcer prophylaxis

INTUBATION FOR SEPTIC SHOCK PATIENTS

- Fentanyl/Midazolam/Vecuronium or Rocuronium for a majority of cases
- **Use with caution:** Etomidate
 - Associated with adrenal suppression due to inhibiting the conversion of cholesterol to cortisol
 - If used to preserve hemodynamic stability, give hydrocortisone 2 mg/kg before or after

SEPTIC SHOCK DUE TO COVID19

- SCCM guidelines for the management of critically ill *adults*
- Recommendations:
 - Conservative fluid strategy for acute resuscitation
 - Crystalloids >> Colloids
 - Norepinephrine as first line vasoactive agent
 - Target MAP of 60-65 mmHg
 - Low dose steroid >> No steroids

STANDARDIZATION OF DRUGS FOR COVID19 INTUBATION

CHOC ED Guideline

Pre-meds

Lidocaine 1 mg/kg

Atropine 0.02 mg/kg

Sedative

Ketamine 1.5 mg/kg

Paralytic

Rocuronium 1.2 mg/kg

Avoid etomidate for septic patients

- More time to prepare
- Minimize delays from pharmacy
- Not for head traumas, status epilepticus etc



Improving Pediatric Sepsis Outcomes

A national collaborative of children's hospitals

Multisystem Inflammatory Syndrome in Children (MIS-C)

M. Tuan Tran, ID Pharmacist
CHOC Children's Hospital

Improving Pediatric Sepsis Outcomes

A national collaborative of children's hospitals

Collaborative of 40 children's hospitals to improve fundamentals of sepsis care in pediatrics

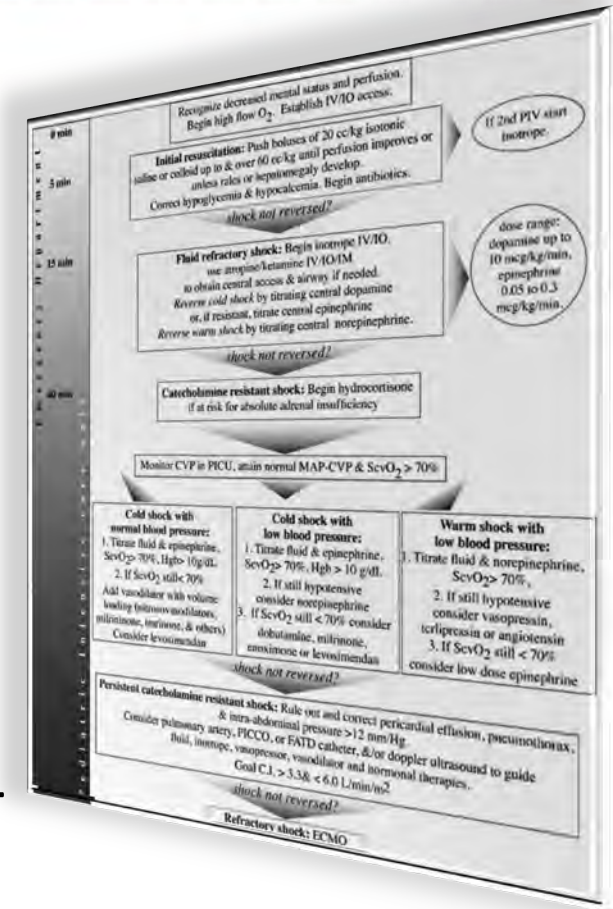
- Aim: Reduce mortality and hospital-onset severe sepsis by 75%
 - Master timely diagnosis and treatment of severe sepsis
 - Master recognition of non-severe sepsis
- No new technology, designer medications, gene therapy...
- Reliable, collaborative process, data-driven to improve outcomes, reduce cost, and advance care

Improving Pediatric Sepsis Outcomes

A national collaborative of children's hospitals

Measures

- Process: huddle activation, order-set utilization/initiation, time to 1st fluid bolus, **time to antibiotics**, time to surgical source control
- Outcome: LOS (hospital, ICU), vasoactive-free days, vent-free days, 72hr organ dysfunction



Resuscitation Bundle in Pediatric Shock Decreases Acute Kidney Injury
and Improves Outcomes

Outcomes of septic shock protocol (SSP) bundle implementation

Table II. Characteristics of the study population

Variables	PRE control group (n = 98)	POST intervention group (n = 104)	P value
Age, y	8.1 ± 5.8	7.3 ± 5.5	.31
Male, n (%)	54 (55)	53 (51)	.29
Previously healthy, n (%)	38 (39)	45 (43)	.56
PRISM score	6.6 ± 14.9	4.2 ± 12.9	.22
PELOD score	7.7 ± 16.1	10.2 ± 8.4	.16
Fluid given, mL/kg	48.7 ± 24.1	55.9 ± 15.7	.01
Time to first bolus, min	65 (29-121)	34 (24-85)	.01
Time to first antibiotic, min	141 (86-199)	54 (41-125)	.001

PRISM, Pediatric Risk of Mortality.

Time to first fluid bolus and first antibiotic is time elapsed from arrival in ED to said intervention.

Resuscitation Bundle in Pediatric Shock Decreases Acute Kidney Injury
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Outcomes of septic shock protocol (SSP) bundle implementation

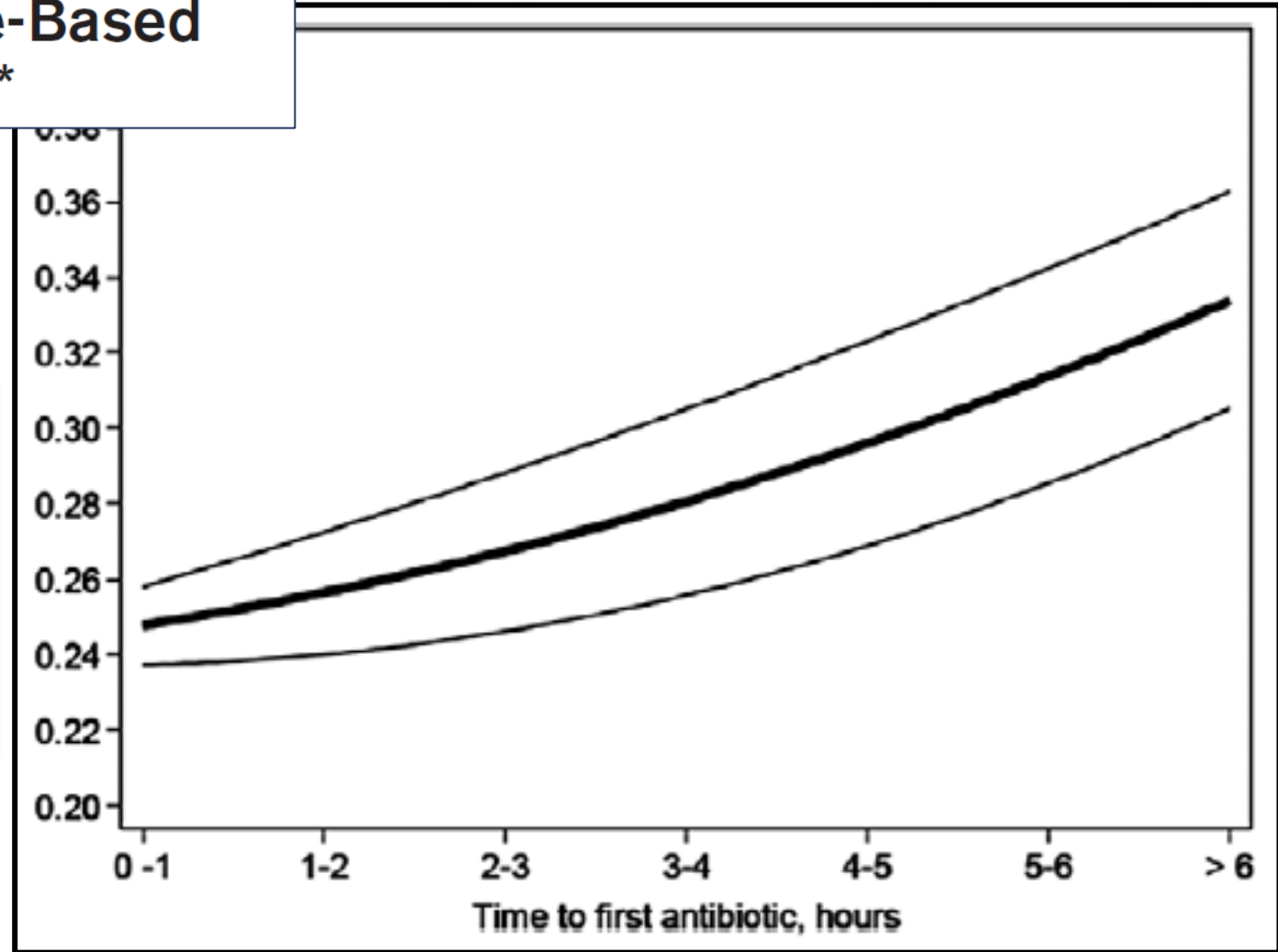
Table IV. Comparison of patient outcomes before and after institution of the SSP

Variables	PRE SSP	POST SSP	<i>P</i> value
AKI	53 (54%)	30 (29%)	<.001
Risk	32	20	
Injury	16	7	
Failure	5	3	
Severe AKI	21 (21%)	10 (9.6%)	.03
RRT	4 (4%)	0	.037
LOS, hospital, d	15.3 ± 16.9	6.3 ± 5.1	<.001
LOS, PICU, d	4.5 ± 7.6	1.9 ± 2.3	<.001
Mortality, n (%)	10 (10)	3 (3)	.037

Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*

Setting: 18K pts, 165 ICUs (US, EU, SA)

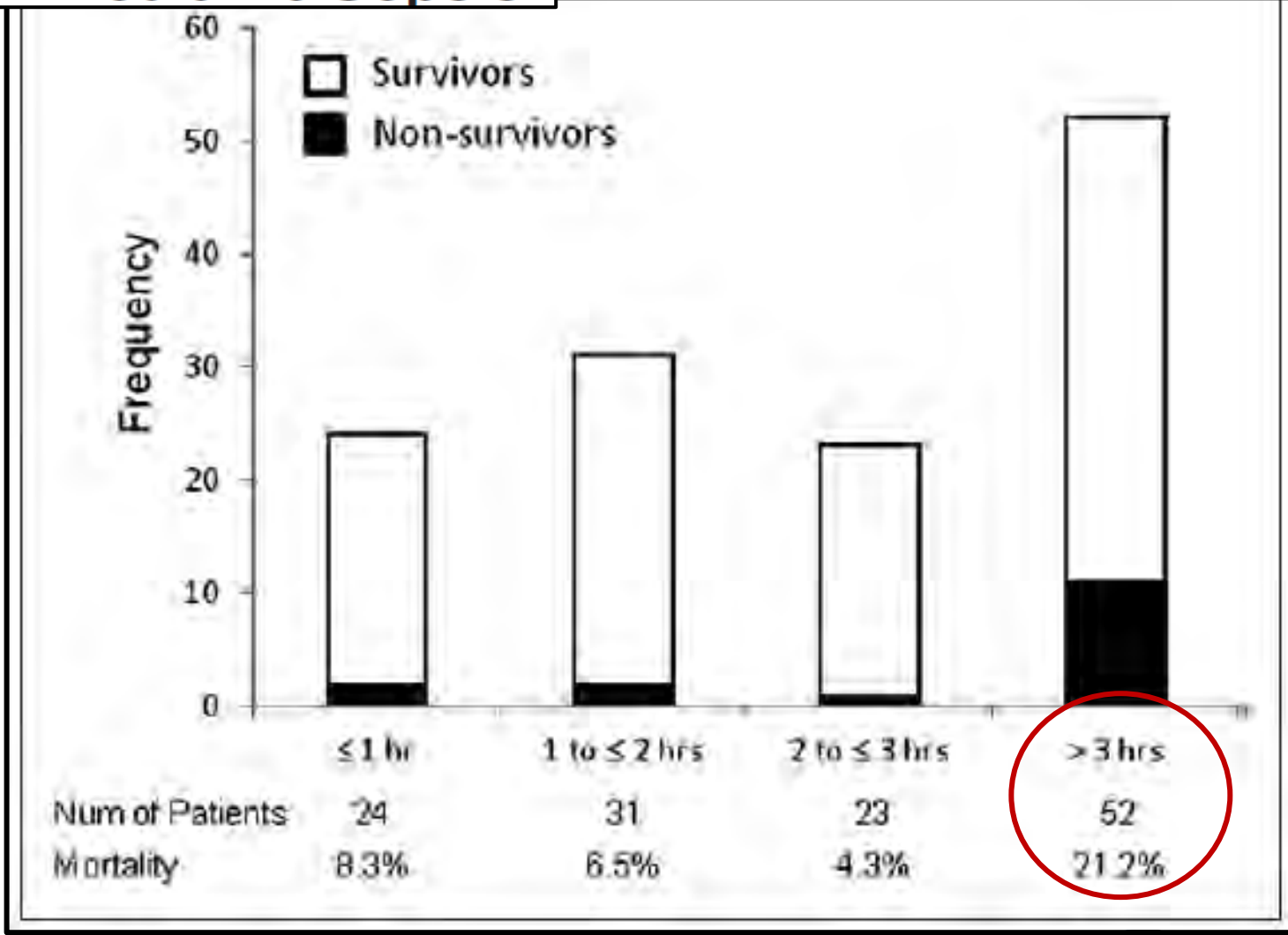
Linear increase in mortality each hour delay of ABX
(Adjusted for severity, ICU admission, geography)



Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis*

CHOP: 130pts, 79% septic shock

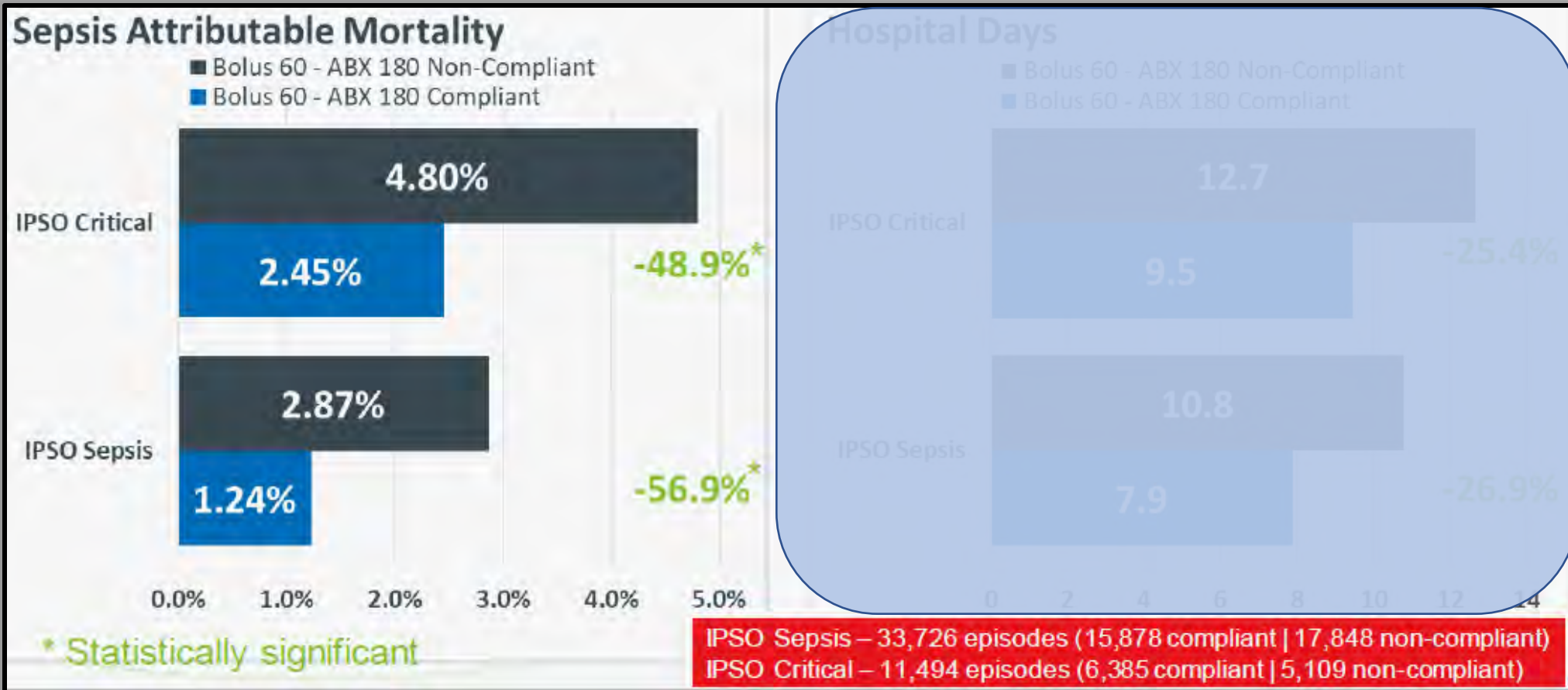
ABX delay > 3hr associated with 3.8x higher mortality (95% CI 1.06-13.8), p=0.04)
(Adjusted for Age, Sex, comorbidities, organ dysfunction, fluid bolus timing)



DOES BUNDLE COMPLIANCE LEAD TO BETTER OUTCOMES?

Bolus 60 min / ABX 180 min / Recognition*

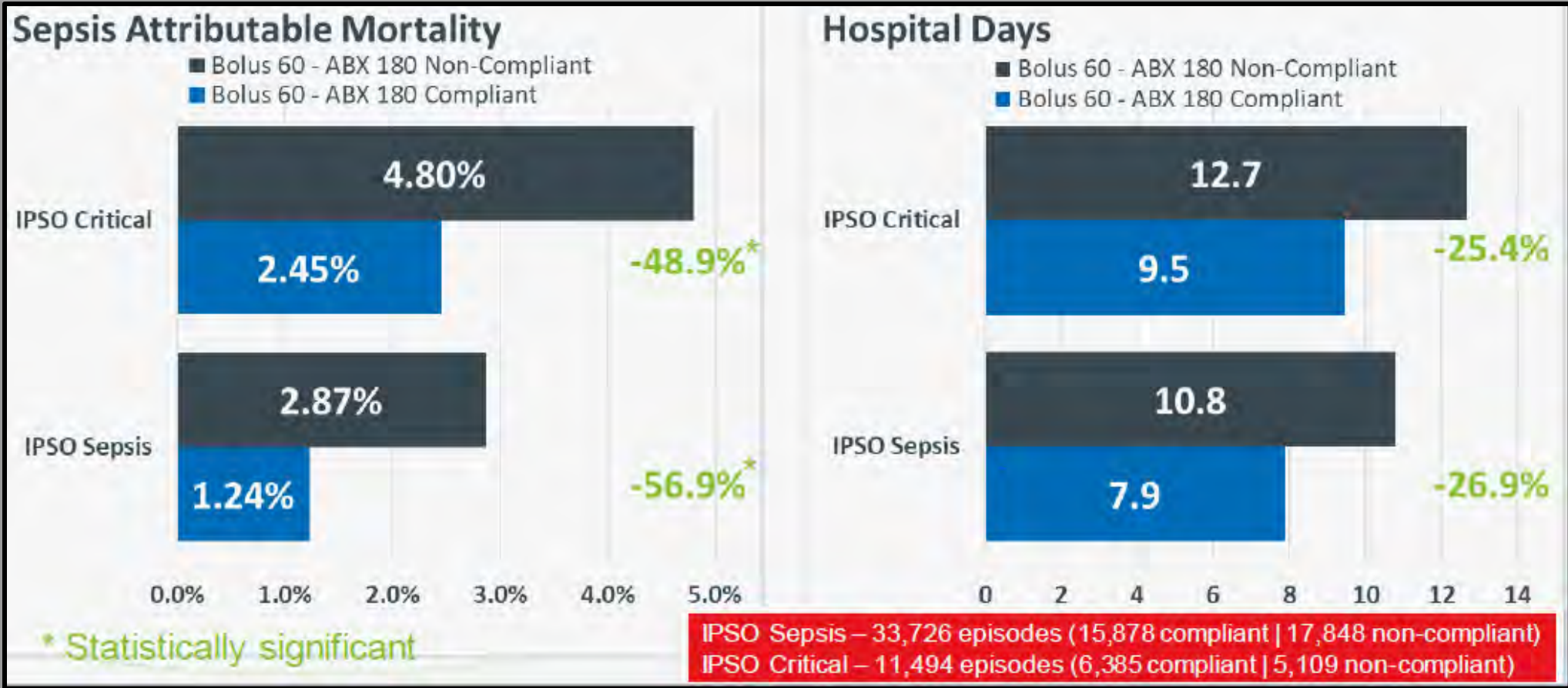
*positive screen, positive huddle or order-set use



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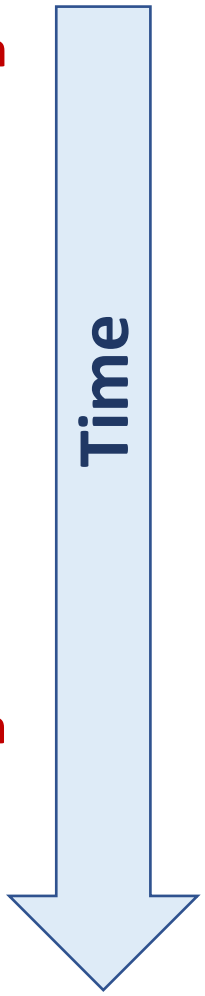
Bolus 60 min / ABX 180 min / Recognition*

*positive screen, positive huddle or order-set use



PHARMACY TEAM RESPONSIBILITIES

t= 0 min



- I. Respond to team huddle / activation**
 - Age/wt/ht, allergy, review HPI (comorbid., organ fxn, micro...etc)
- II. Prepare fluid resuscitation → 20 mL/kg NS**
- III. Anticipate, dose, prepare antibiotic**
 - Infection source
 - Ensure timely prep & admin
- IV. Dose, prepare vasopressors (Epi / NE > DA)**
 - Ensure timely prep & admin
- V. Reevaluate frequently**
- VI. Narrow & Deescalate with C&S**

t = 60 min

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

- First reported in United Kingdom in association with COVID-19
- Presentations include persistent fever, GI, mucocutaneous, elevated inflammatory markers, cardiac signs and symptoms
- Some overlap with Kawasaki disease, toxic shock syndrome and acute COVID-19
- May 14, 2020 CDC published Health advisory along with case definition

MIS-C CASE DEFINITION

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms

*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

**1 or more: CRP, ESR, procalcitonin, d-dimer, fibrinogen, ferritin, LDH, IL-6, elevated neutrophils, reduced lymphocytes, low albumin

- Some pt may fulfill full or partial criteria for Kawasaki
- Consider MIS-C in any pediatric death with SARS-CoV2 infection

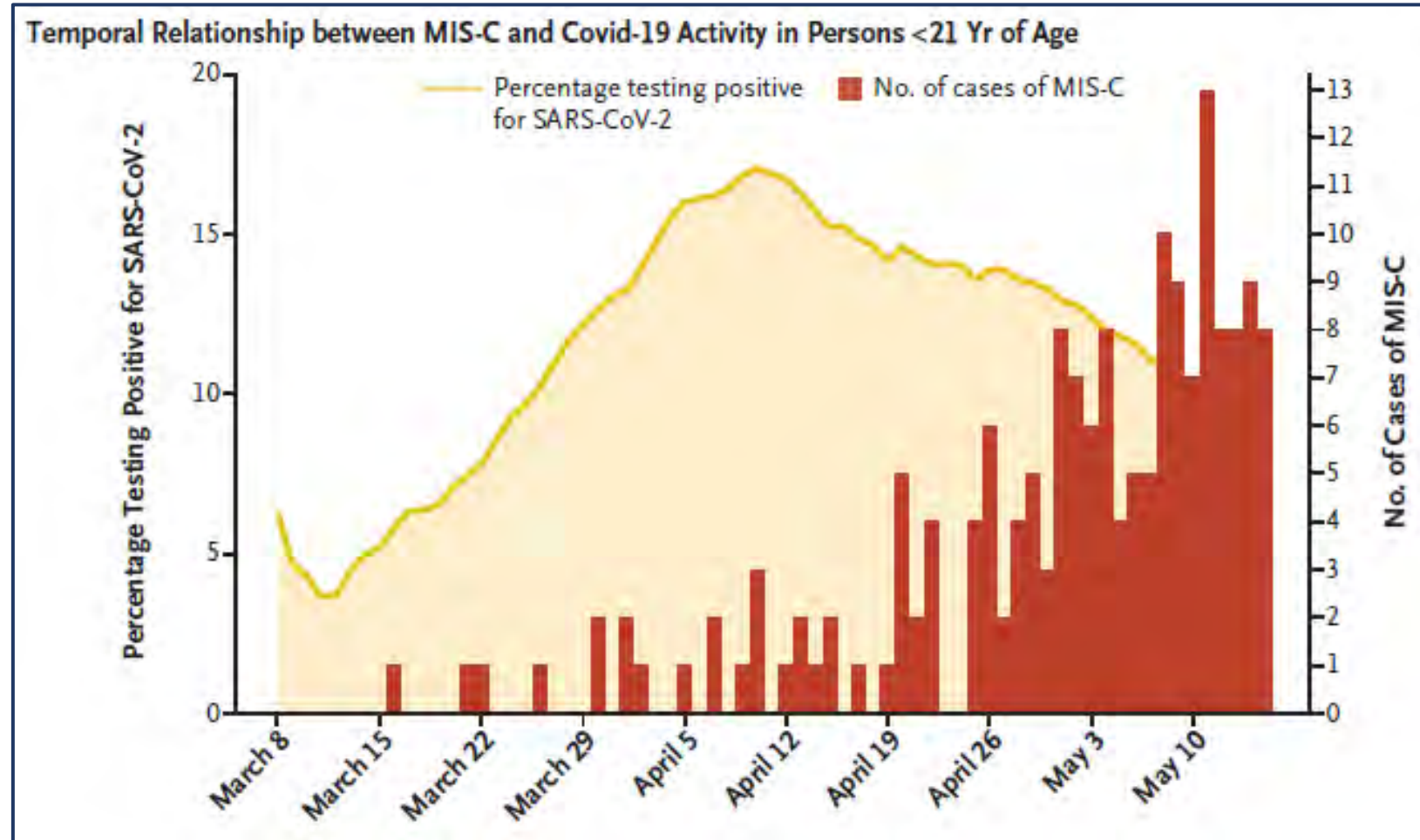
<https://www.cdc.gov/mis-c/hcp/index.html>

Centers for Disease Control and Prevention
Center for Preparedness and Response

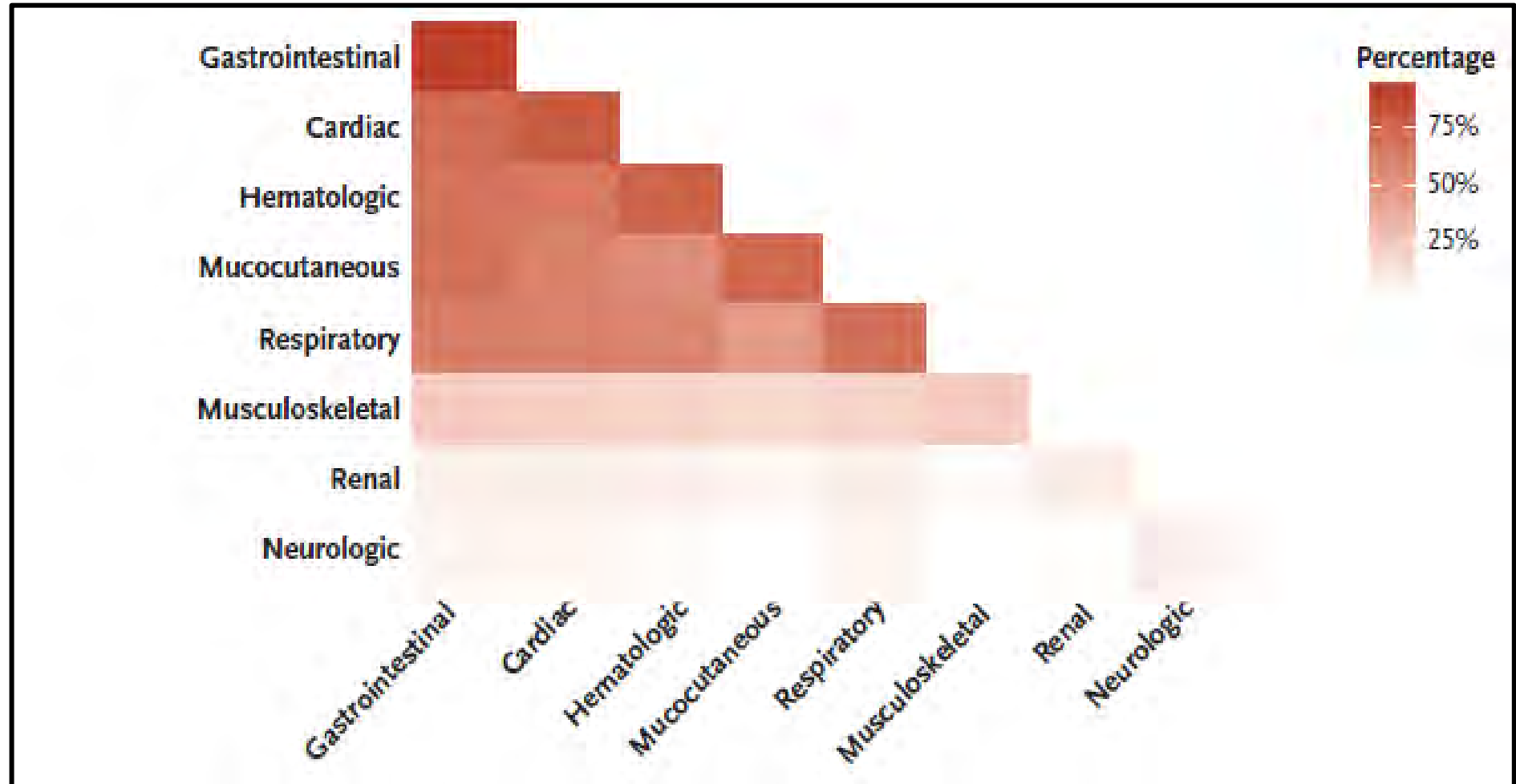


COVID-19 AND MIS-C IN THE US

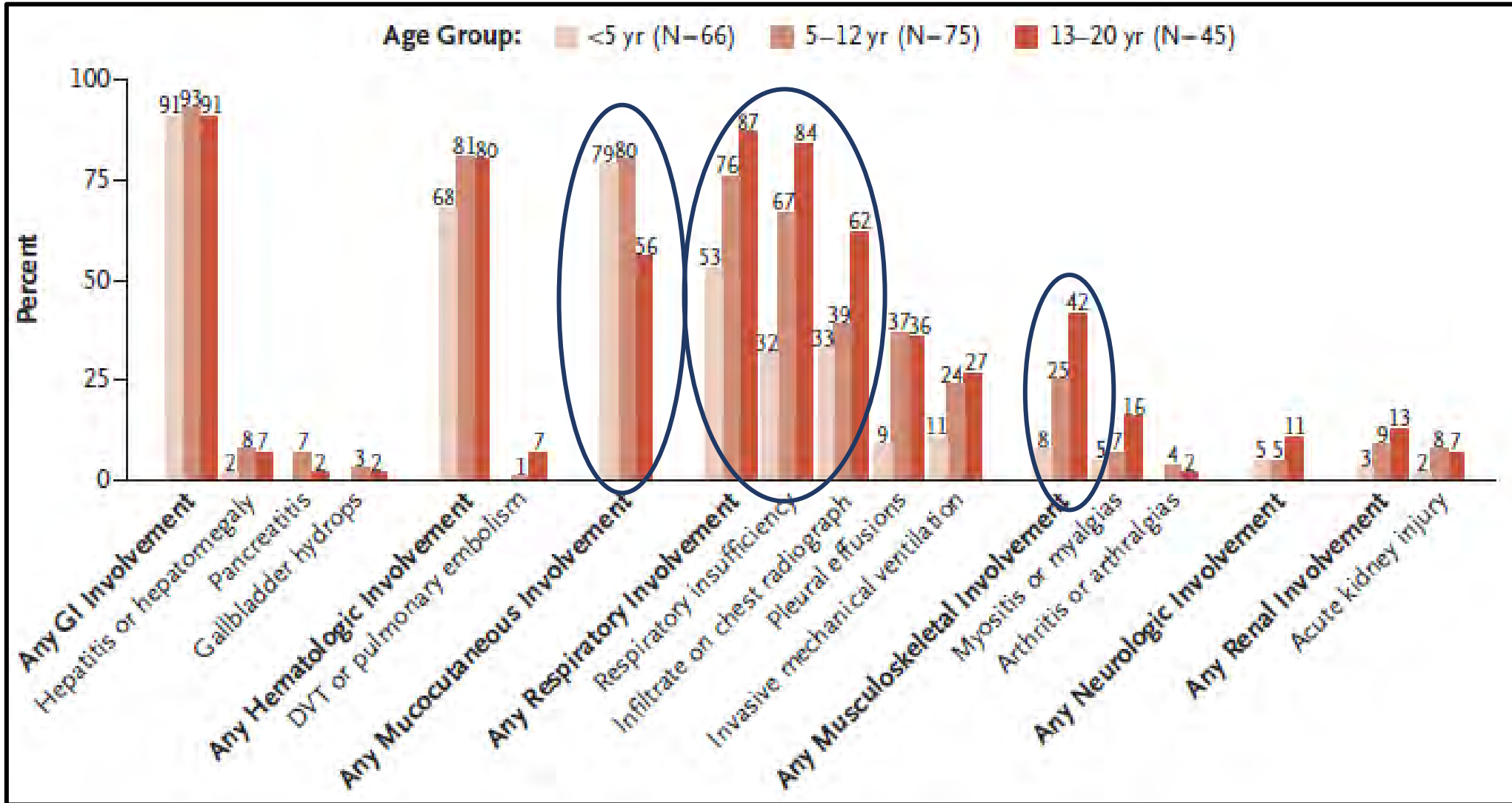
- 186 pts in 53 hospitals
- Median 8.3 yoa
- 73% prev. healthy
- 70% SARS-CoV2 or Ab+
- 80% admitted to ICU
 - 20% mech. ventilation
- 55% vasopressor support
- LOS 7d (IQR: 4-10)
- 4 (2.2%) died
 - 52 (28%) still hospitalized



MIS-C ORGAN SYSTEM INVOLVEMENT



MIS-C ORGAN SYSTEM INVOLVEMENT BY AGE



SURVEY OF MIS-C MANAGEMENT, JULY 2020

- 41 centers across the United States
- 35 with established protocols



https://emergency.cdc.gov/coca/calls/2020/callinfo_071620.asp

MIS-C CASES REPORTED TO CDC (N=342), AS OF 7/15/20

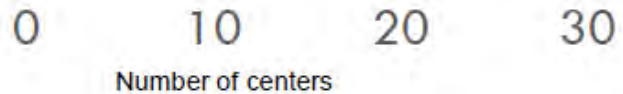
IVIG

Regardless of Severity

Severe Cases

Moderate Cases

Mild Cases



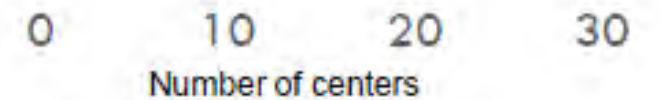
Corticosteroids

Regardless of Severity

Severe Cases

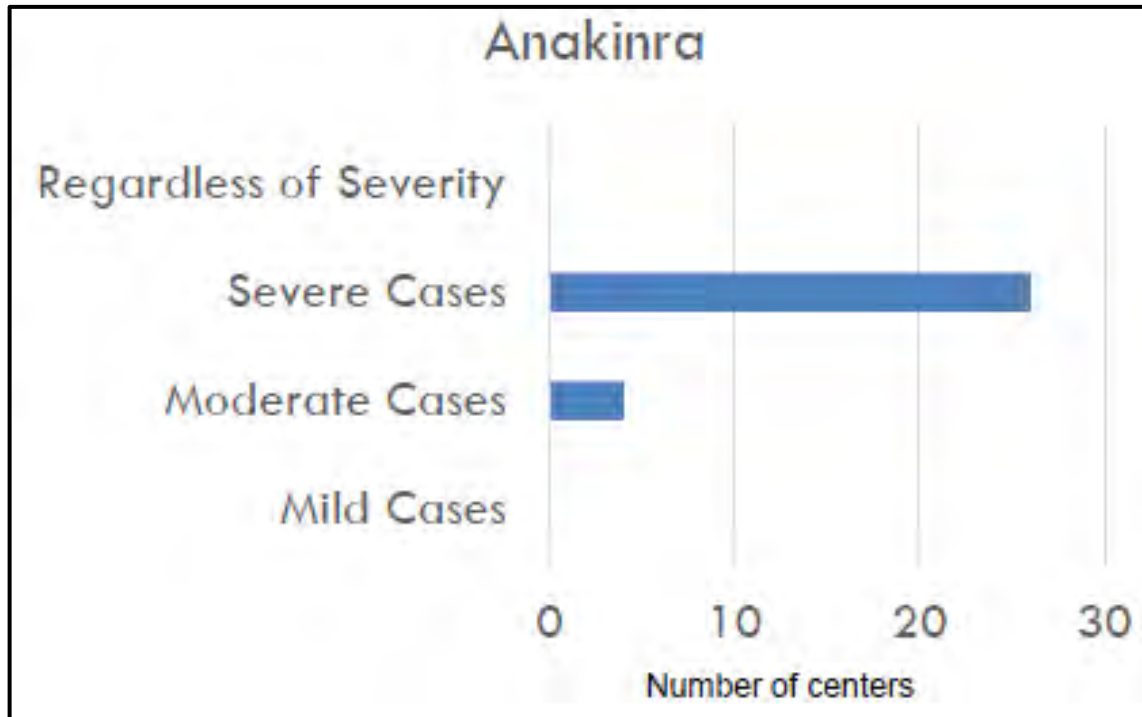
Moderate Cases

Mild Cases



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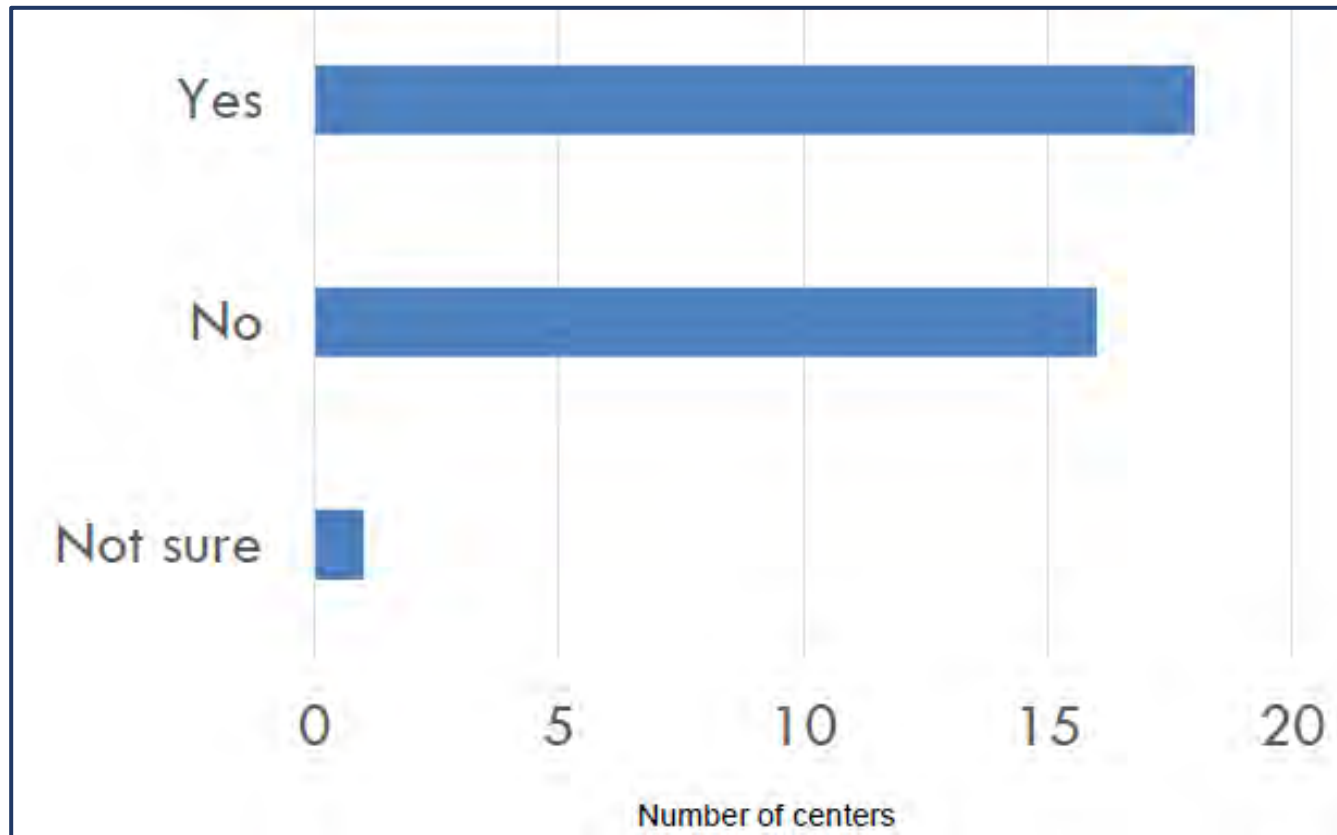


Reported by <20 centers

- Tocilizumab (11)
- Remdesivir (11)
- Warfarin (6)
- Clopidogrel (5)
- Hydroxychloroquine (1)

https://emergency.cdc.gov/coca/calls/2020/callinfo_071620.asp

FOLLOW-UP PER AHA KAWASAKI GUIDELINE ?



https://emergency.cdc.gov/coca/calls/2020/callinfo_071620.asp

MIS-C TAKE-HOME POINTS

- Evolving data, protocol continually updated, care is often individualized
- Much variation in evaluation and management
- Common theme:
 - ✓ Team approach (Rheumatology, ID, Critical Care, Hematology...)
 - ✓ IVIG and ASA are common regardless of severity
 - ✓ Steroids are common in severe cases
 - ✓ Follow-up similar to Kawasaki guideline

TEST QUESTIONS

1. The following are early signs of pediatric sepsis except:
 - a) Sinus tachycardia
 - b) Fussiness, irritability
 - c) Delayed capillary fill (>2secs)
 - d) Hypotension

2. A best practice statement from SCCM states:
 - a) Give antibiotics within 60 minutes
 - b) Give fluid 10 – 20 mL/kg (up to 60 mL/kg) over the 1st hour
 - c) Start early!!! Recognition and prevention is key!
 - d) All of the above

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TEST QUESTIONS

3. Which of the following are SCCM recommended best practices:
- a) Dopamine is the preferred vasopressor in children with septic shock
 - b) Initiate insulin therapy to target BG < 140 mg/dL in septic children
 - c) Routine stress ulcer prophylaxis are needed in septic shock children
 - d) Reevaluate antimicrobial therapy daily and de-escalate based on clinical response and microbiology results

TEST QUESTIONS

3. Which of the following are SCCM recommended best practices:
- a) Dopamine is the preferred vasopressor in children with septic shock
 - b) Initiate insulin therapy to target BG < 140 mg/dL in septic children
 - c) Routine stress ulcer prophylaxis are needed in septic shock children
 - d) **Reevaluate antimicrobial therapy daily and de-escalate based on clinical response and microbiology results**

QUESTIONS?

Katie Bui, PharmD kbui@choc.org

M. Tuan Tran, PharmD, BCPS, BCIDP mtran@choc.org

LONG LIVE CHILDHOOD



REFERENCE LIST

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2. Jordan C, Raynor N. Recognizing Pediatric Sepsis: Through the Eyes of Patients and Families. IPSO Webcast Series: April 21, 2020. Children's Hospital Association. 2020. Accessed on 5/20/2020.
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