From Current Evidences to Clinical Practices in Sepsis

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กลุ่มงานอายุรกรรม โรงพยาบาลศูนย์ขอนแก่น

Sepsis

a global burden

stop sepsis save lives

~ 27 000 000

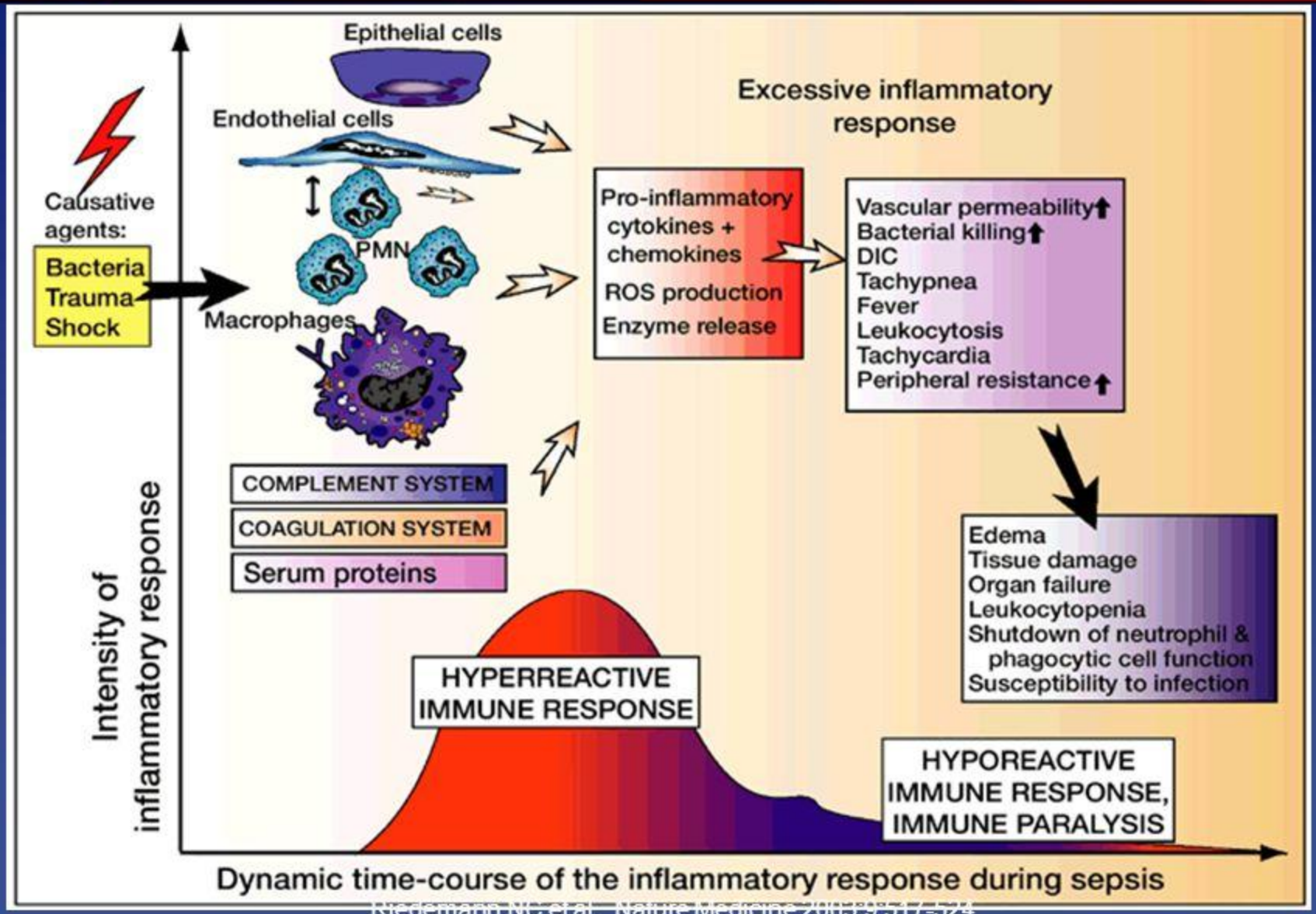
people per year develop sepsis

~ 19 000 000
people per year survive

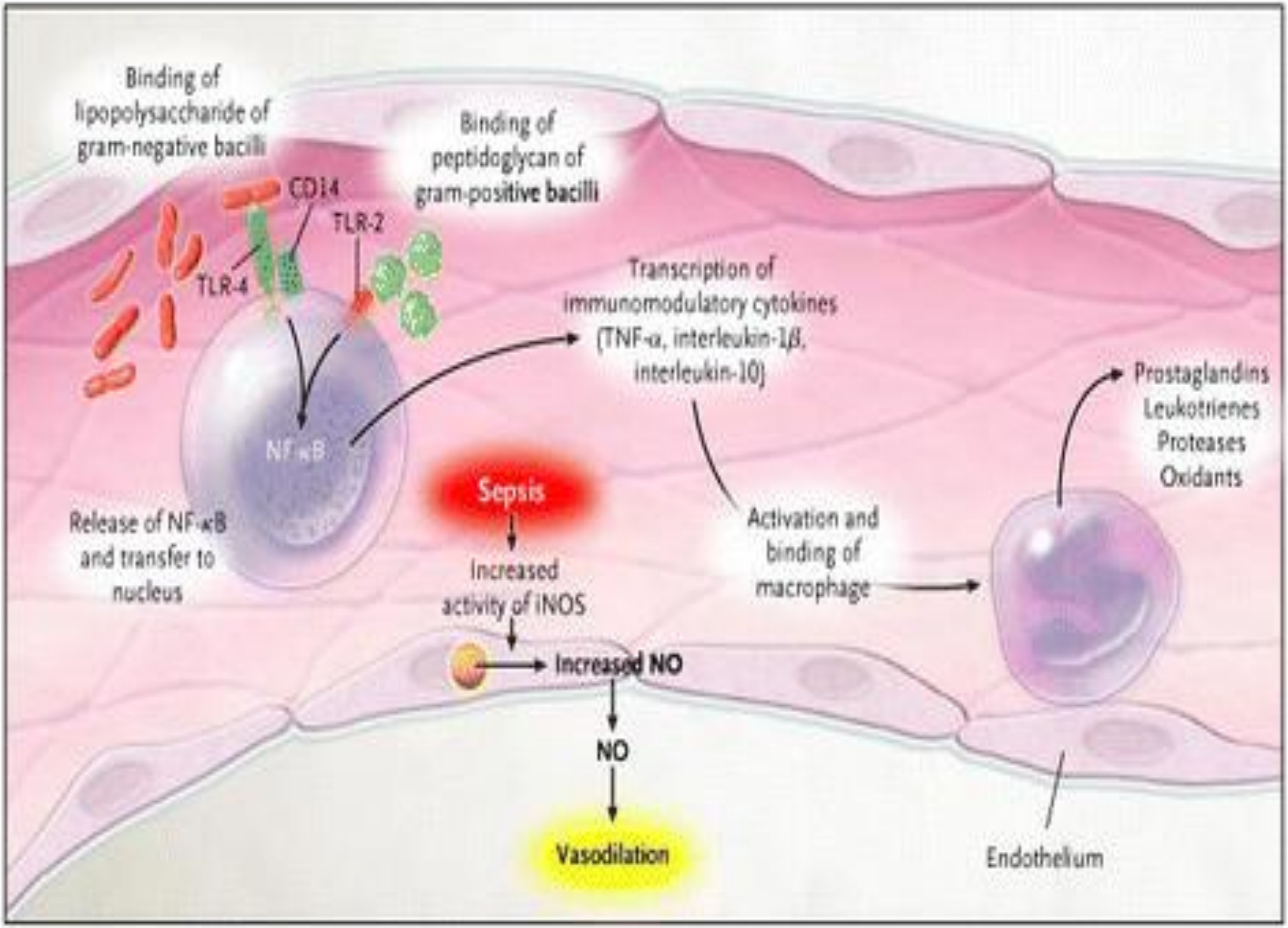
Survivors
may face lifelong complications

~ 8 000 000
people per year die

Pathophysiology of Sepsis



Riedemann NC et al. Nature Medicine 2003;9:517-524


Binding of lipopolysaccharide of gram-negative bacilli
CD14
TLR-2
TLR-4
Binding of peptidoglycan of gram-positive bacilli
Transcription of immunomodulatory cytokines (TNF-α, interleukin-1β, interleukin-10)
Prostaglandins
Leukotrienes
Proteases
Oxidants
NF-κB
Release of NF-κB and transfer to nucleus
Sepsis
Increased activity of iNOS
Activation and binding of macrophage
Increased NO
NO
Vasodilation
Endothelium

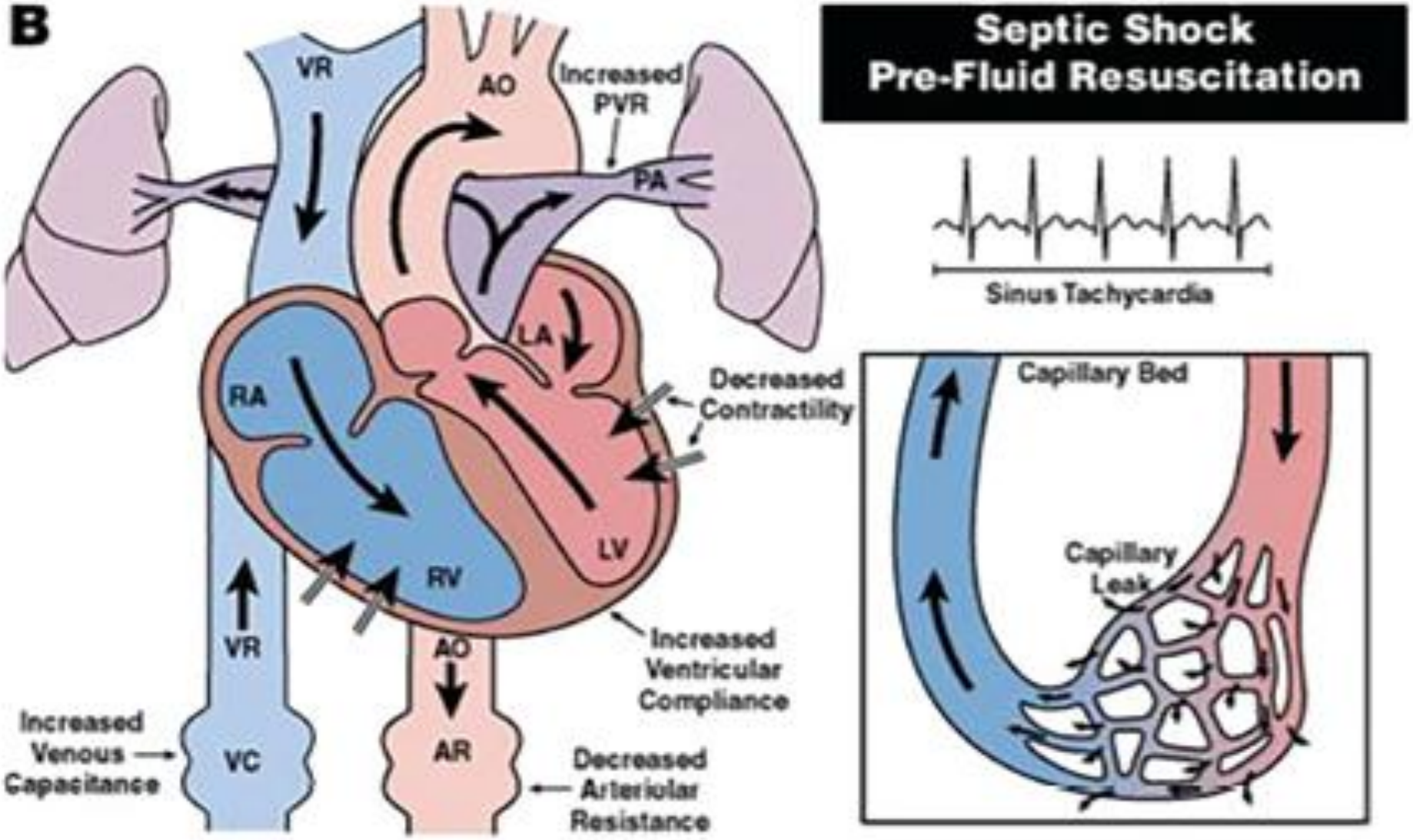
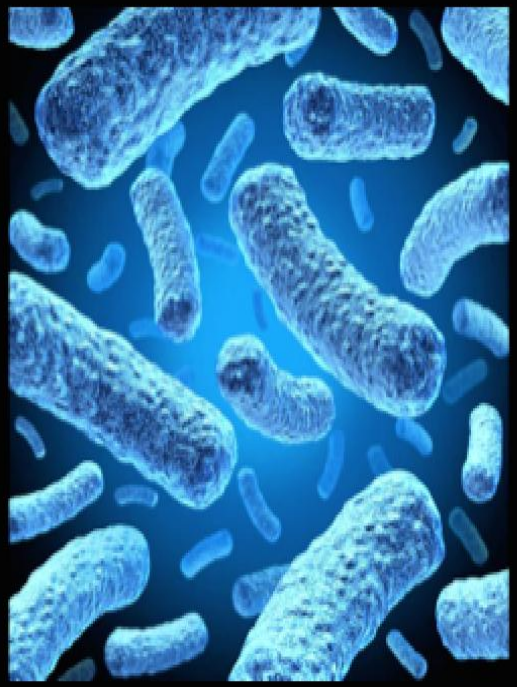


Figure 5. This cartoon shows the myriad of changes that occur with septic shock prior to fluid resuscitation and lay the groundwork for optimal therapy. Courtesy R. Phillip Dellinger, MD.

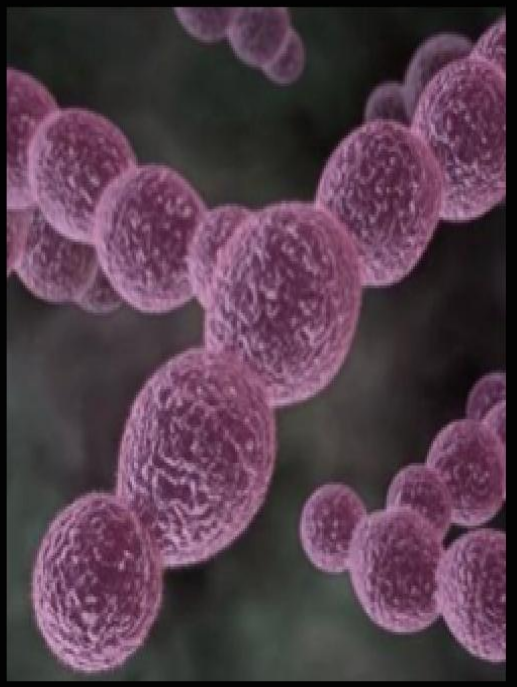
The Sepsis Trilogy

ProCESS



ARISE

ProMISe



Clinical Review & Education

The JAMA Network

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

KEY CONCEPTS OF SEPSIS

Box 2. Key Concepts of Sepsis

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.

KEY CONCEPTS OF SEPSIS (2)

- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.
- Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

NEW TERMS AND DEFINITIONS

Box 3. New Terms and Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

NEW TERMS AND DEFINITIONS (2)

- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.

NEW TERMS AND DEFINITIONS (3)

- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[8,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

HEFT EMCAST

THE THIRD INTERNATIONAL CONSENSUS DEFINITIONS FOR SEPSIS AND SEPTIC SHOCK (SEPSIS-3)

Expert international task force reviewing sepsis definitions, generating new definitions and requesting review and endorsement by international bodies

New definition of sepsis; Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

Suggest SIRS is no longer used due to low specificity
SOFA or qSOFA used

Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection

qSOFA can be used in the non-ITU setting requiring,≥2 of the following in suspected infection;
Alteration in mental status
Systolic blood pressure ≤100 mm Hg
Respiratory rate ≥22/min

Septic shock can be identified in these patients and with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation

Clinical Bottom Line
May prove more effective at identifying sepsis, needs external validation, some believe (including The Sepsis Trust) that this should not yet be implemented

Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or $PaCO_2$ <32 mm Hg (4.3 kPa)
- White blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands

From Bone et al.[9]

qSOFA


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

SEPSIS CLINICAL CRITERIA

INFECTION

+

CHANGE IN:

SEPSIS-RELATED
ORGAN
FAILURE
ASSESSMENT

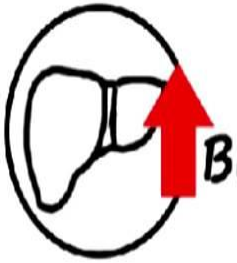
≥2

PaO_2/FiO_2

HYPOTENSION OR VASOPRESSORS

PLATELETS

GLASGOW COMA SCALE



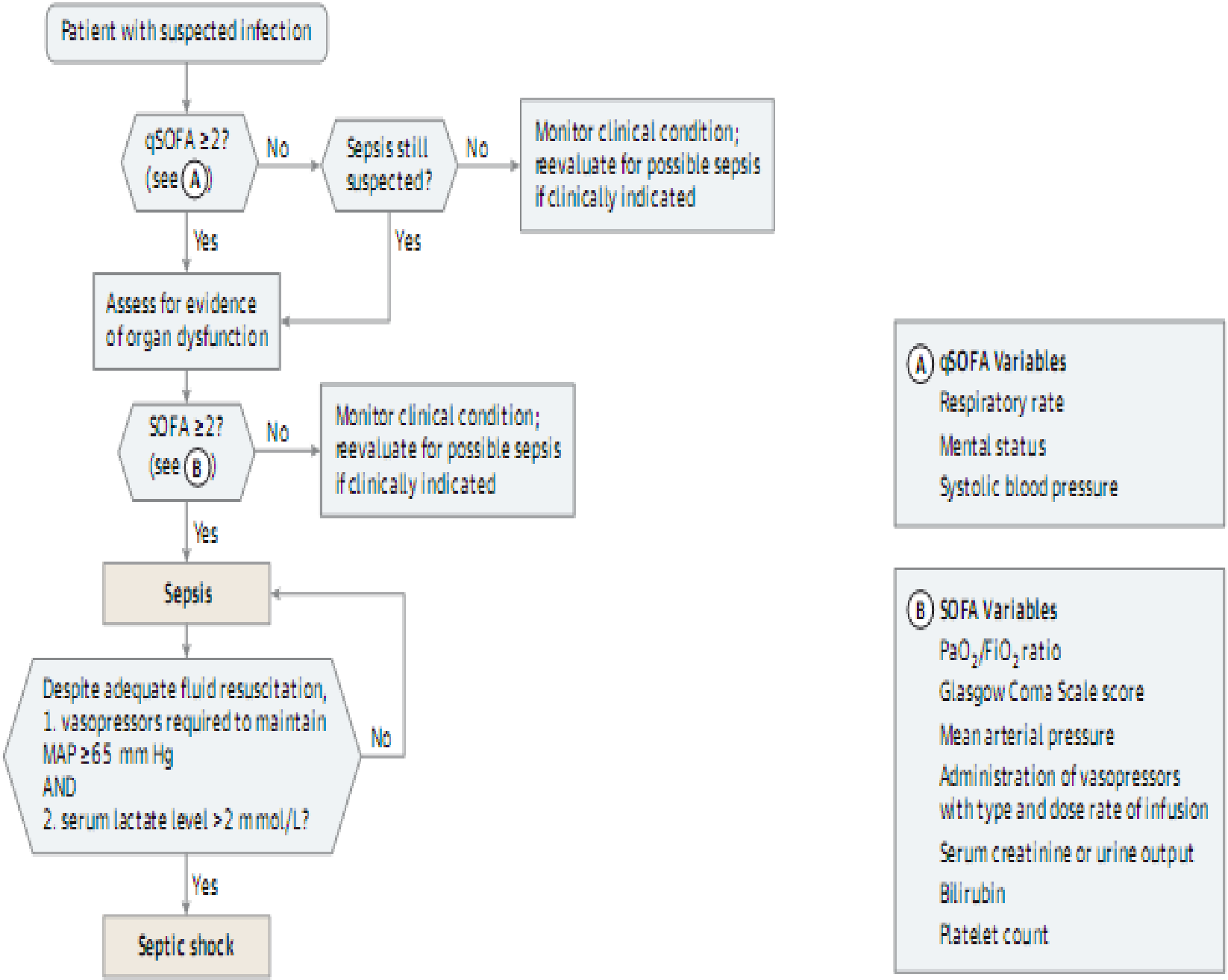
BILIRUBIN

CREATININE, OLIGURIA

Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

System	0	1	2	3	4
Respiration PaO2/FiO2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10³/uL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13 - 14	10 -12	6 - 9	<6
Renal Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) <500	>5.0 (440) <200

*Catecholamine Doses = ug/kg/min for at least 1hr


Patient with suspected infection
qSOFA ≥2? (see A)
No
Sepsis still suspected?
No
Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
Yes
Yes
Assess for evidence of organ dysfunction
SOFA ≥2? (see B)
No
Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
Yes
Sepsis
Despite adequate fluid resuscitation,
1. vasopressors required to maintain MAP ≥65 mm Hg
AND
2. serum lactate level >2 mmol/L?
No
Yes
Septic shock
A qSOFA Variables
Respiratory rate
Mental status
Systolic blood pressure
B SOFA Variables
PaO_2/FIO_2 ratio
Glasgow Coma Scale score
Mean arterial pressure
Administration of vasopressors with type and dose rate of infusion
Serum creatinine or urine output
Bilirubin
Platelet count

Surviving Sepsis Campaign Responds to Sepsis-3

March 1, 2016

Implications of the new definitions for screening and management

Step 1: Screening and management of infection

Step 2: Screening for organ dysfunction and management of sepsis

Step 3: Identification and management of initial hypotension

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

APPROACH TO TREATMENT OF SEPTIC SHOCK

1. 

IDENTIFY

Identify infection accompanied by signs of shock (such as low urine output, confusion, cool and clammy skin)

2. 

ADMINISTER

Quickly administer antibiotics, intravenous fluids, and blood tests to determine severity

3. 

ULTRASOUND

Focused ultrasound and placement of special intravenous catheters for fluids and blood pressure measurement

4. 

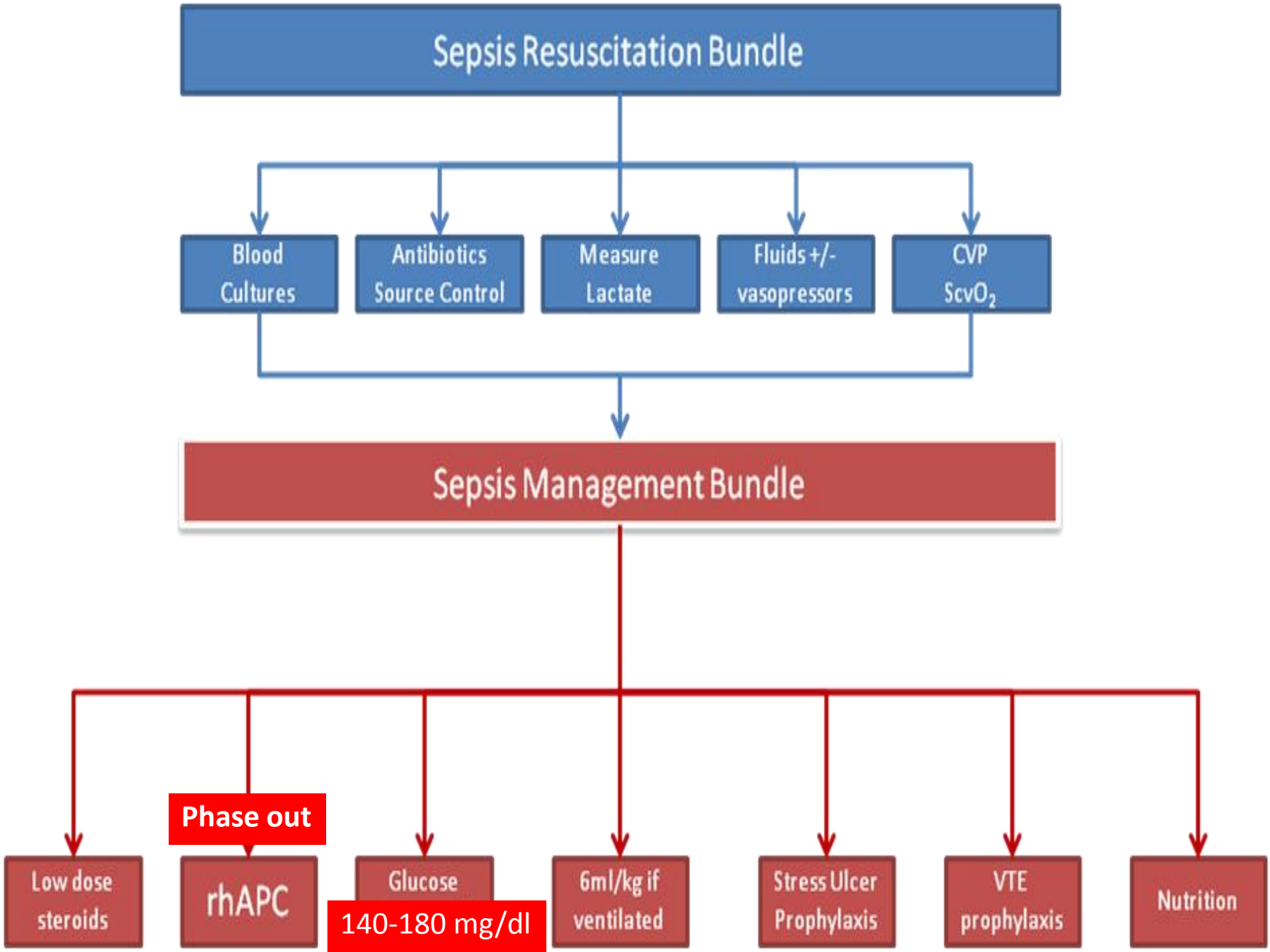
VASOACTIVE

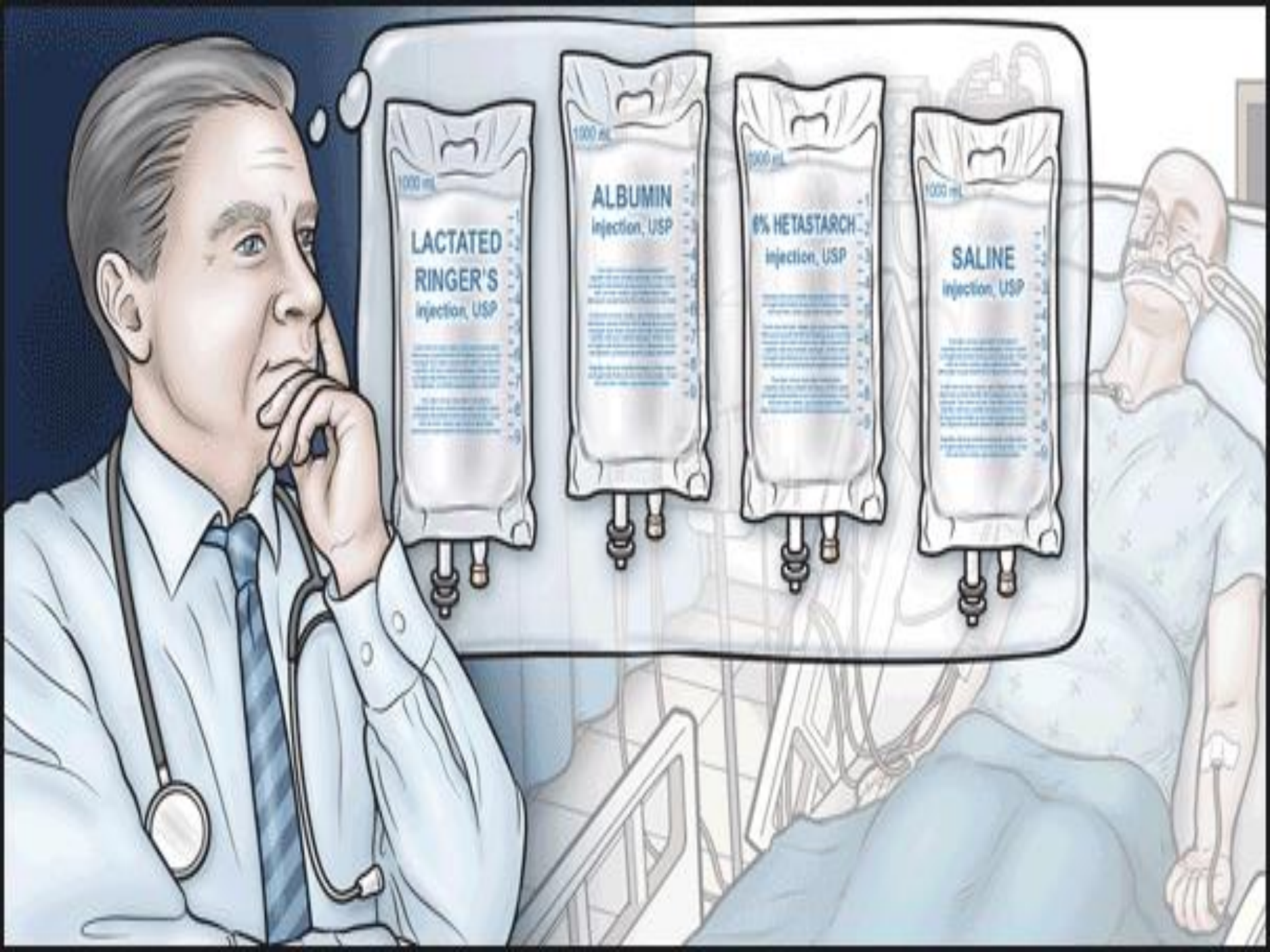
Provide vasoactive medications that support blood pressure to a normal range

5. 

REPEAT

Repeat assessments every 4 to 6 hours in intensive care


Sepsis Resuscitation Bundle
Blood Cultures
Antibiotics Source Control
Measure Lactate
Fluids +/- vasopressors
CVP
ScvO2
Sepsis Management Bundle
Low dose steroids
Phase out
rhAPC
Glucose
140-180 mg/dl
6ml/kg if ventilated
Stress Ulcer Prophylaxis
VTE prophylaxis
Nutrition


1000 mL
LACTATED RINGER'S
injection, USP
1000 mL
ALBUMIN
injection, USP
6% HETASTARCH
injection, USP
1000 mL
SALINE
injection, USP

Fluid therapy is the drug :
It can cure, it can danger.

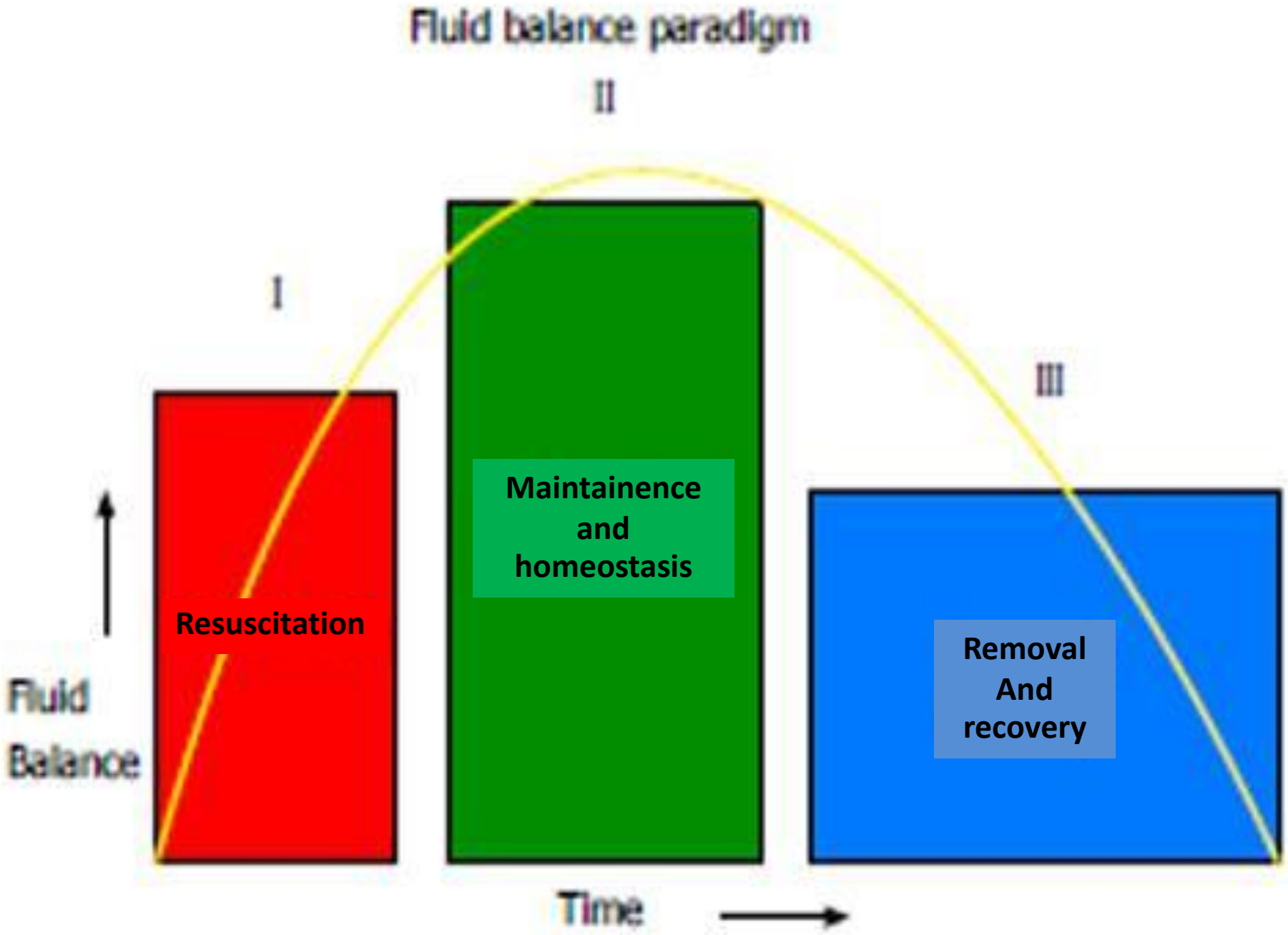
Fluid	mEq/L						pH	Osmolality
	Na	Cl	K	Ca	Mg	Buffer		mOsm/L
Plasma	141	103	4-5	5	2	Bicarb 26	7.4	289
0.9%NaCl	154	154	-	-	-	-	5.7	308
Lactated ringer's	130	109	4	3	-	Lactate 28	6.4	273
Acetated ringer's	130	108.7	4	2.7	-	Acetate 28		273.4

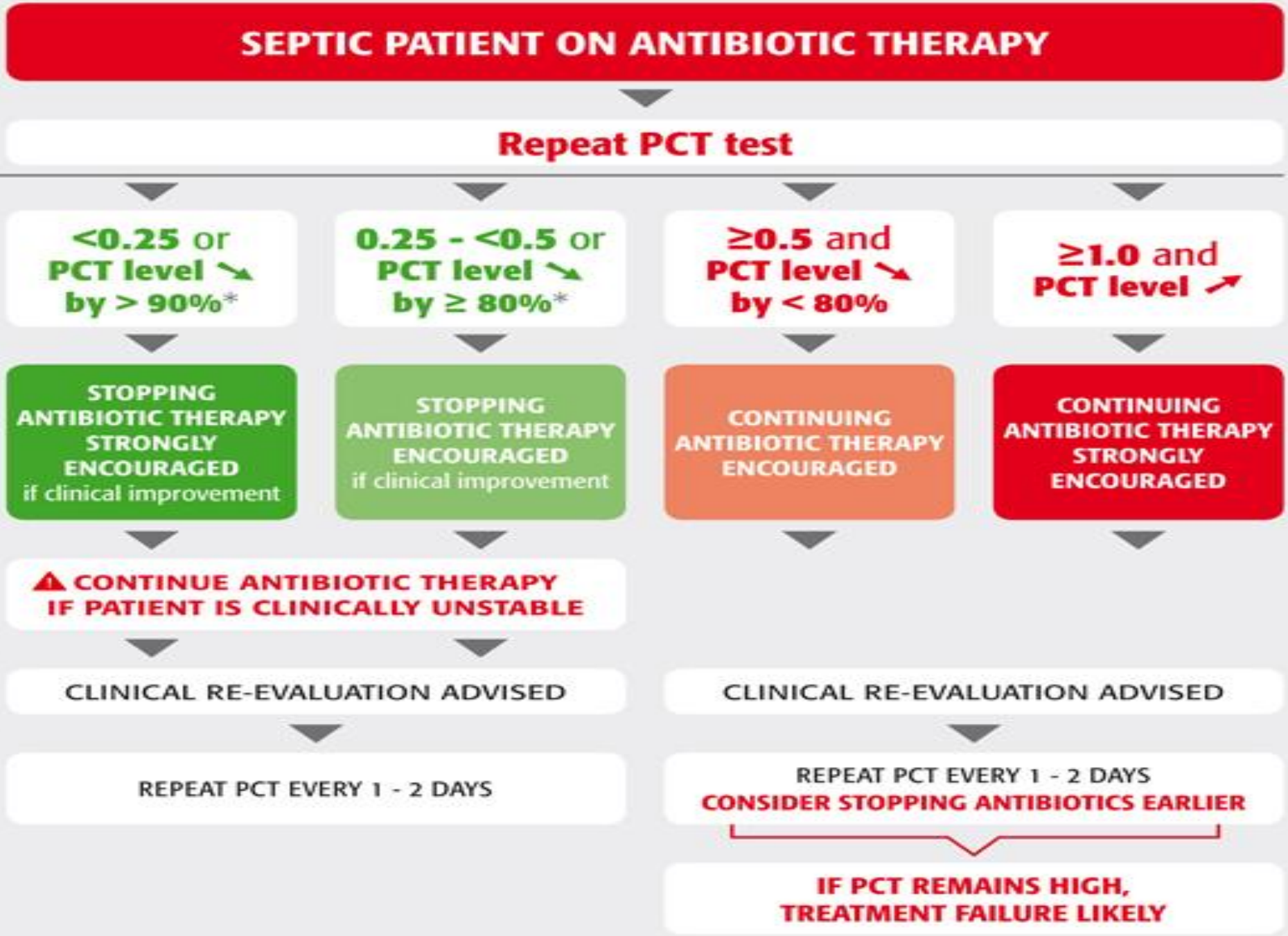
FLUID is the mainstay treatment in early phase of treatment in septic patients : Right time, Right dose, Right type.

Table 2. Supportive Therapy for Sepsis

Therapy	Details
Fluid	Use crystalloids/colloids for fluid resuscitation. Target CVP is ≥8 mmHg (≥12 mmHg in patient on mechanical ventilation). Use fluid-challenge technique while associated with hemodynamic improvement. Administer fluid challenges of 1 L crystalloids/300-500 mL colloids over 30 min (may require more rapid and larger volumes in sepsis-induced tissue hypoperfusion). Reduce rate of fluid administration if cardiac filling pressure increases without concurrent hemodynamic improvement.
Vasopressor	Maintain MAP ≥65 mmHg. Centrally administered norepinephrine and dopamine are initial vasopressors of choice. Low-dose dopamine is not effective for renal protection.
Inotropic	Use dobutamine in patients with myocardial dysfunction.
Steroid	If hydrocortisone is indicated, dosage should be ≤300 mg/day. Do not use corticosteroids to treat sepsis in the absence of shock unless warranted by patient's endocrine/corticosteroid history.

CVP: central venous pressure; MAP: mean arterial pressure; min: minute.
Source: Reference 6.


Fluid balance paradigm
II
I
III
Maintainence and homeostasis
Resuscitation
Removal And recovery
Fluid Balance
Time


SEPTIC PATIENT ON ANTIBIOTIC THERAPY
Repeat PCT test
<0.25 or PCT level ↘ by > 90%*
0.25 - <0.5 or PCT level ↘ by ≥ 80%*
≥0.5 and PCT level ↘ by < 80%
≥1.0 and PCT level ↗
STOPPING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED if clinical improvement
STOPPING ANTIBIOTIC THERAPY ENCOURAGED if clinical improvement
CONTINUING ANTIBIOTIC THERAPY ENCOURAGED
CONTINUING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
⚠ CONTINUE ANTIBIOTIC THERAPY IF PATIENT IS CLINICALLY UNSTABLE
CLINICAL RE-EVALUATION ADVISED
CLINICAL RE-EVALUATION ADVISED
REPEAT PCT EVERY 1 - 2 DAYS
REPEAT PCT EVERY 1 - 2 DAYS
CONSIDER STOPPING ANTIBIOTICS EARLIER
IF PCT REMAINS HIGH, TREATMENT FAILURE LIKELY


September
13
2016
World
Sepsis
Day

Conclusion

New SEPSIS Definitions:

#EM3
East Midlands Emergency Medicine Educational Media

SEPSIS = *'life-threatening organ dysfunction due to a dysregulated host response to infection'.*

SIRs is non-specific and therefore no longer used for Sepsis recognition
(However patients with SIRs criteria are still potentially critically unwell patients)

LOOK For: Quick SOFA score - Sepsis-related Organ Failure Assessment

Score >2 = mortality of 10%

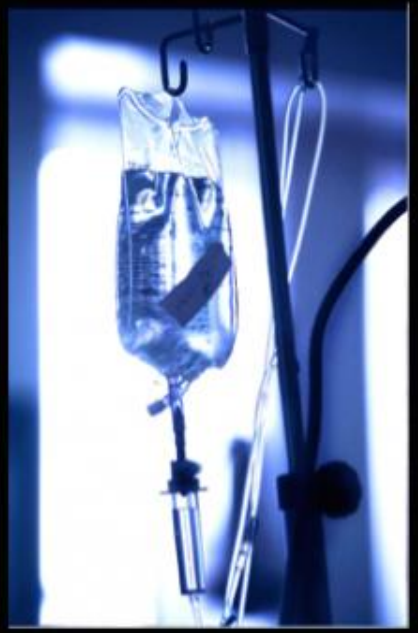
Septic shock = *'subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality'.*

1. needing vasopressors for a MAP≥ 65mmHg
2. an increase in lactate > 2 mmol/L, despite adequate fluid resuscitation.

	OLD	NEW
SEPSIS	suspected infection + SIRS	suspected infection + 2 ≥ qSOFA or rise in SOFA score by ≥ 2
SEVERE SEPSIS	sepsis + hypotension, hypoxia, elevated lactate or other lab markers of end organ dysfunction	(category removed)
SEPTIC SHOCK	sepsis + hypotension after adequate fluid resuscitation	sepsis + vasopressors + lactate > 2

EARLY

Recognition



IVF

Antibiotics