Sepsis for neurologist: SAE and pressors in neuroICU

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Introduction

72/F

Liver abscess

c septic shock s/p PCD

P/Hx

HTN

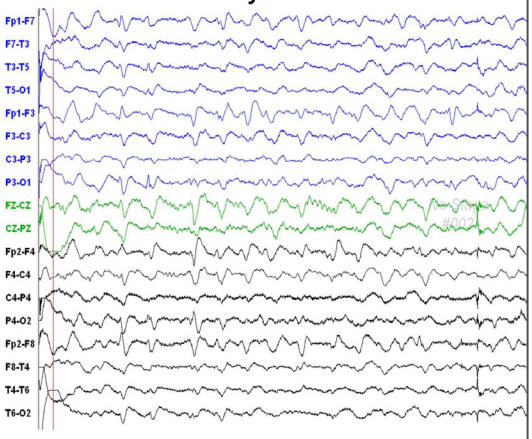
Type II DM

MI

Consultation for altered mentality

Brain image : unremarkable

CSF study : unremarkable



Introduction

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Liver abscess

c septic shock s/p PCD

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Type II DM

MI

Consultation for altered mentality

Sepsis associated encephalopathy (SAE)

Septic encephalopathy

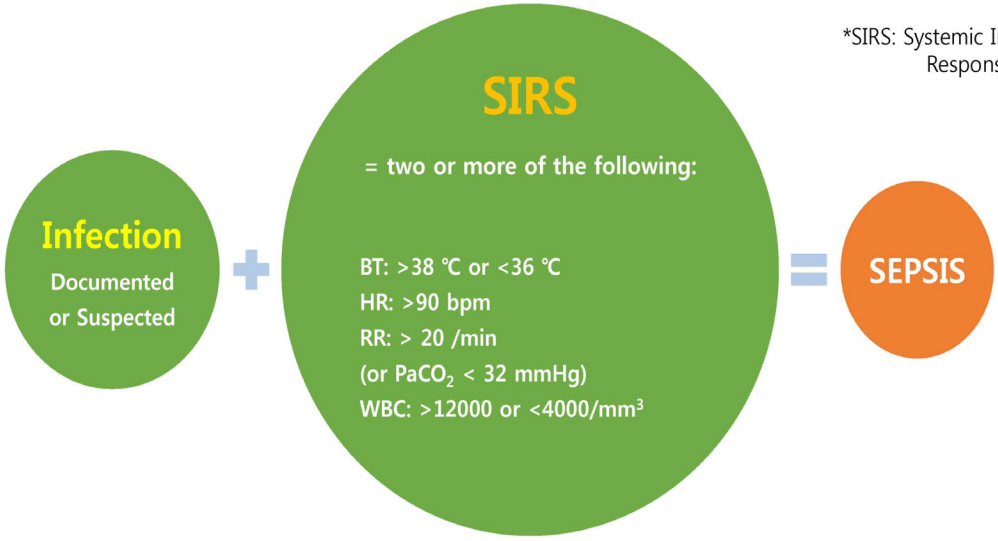
Sepsis associated delirium

Sepsis induced brain dysfunction

Definition

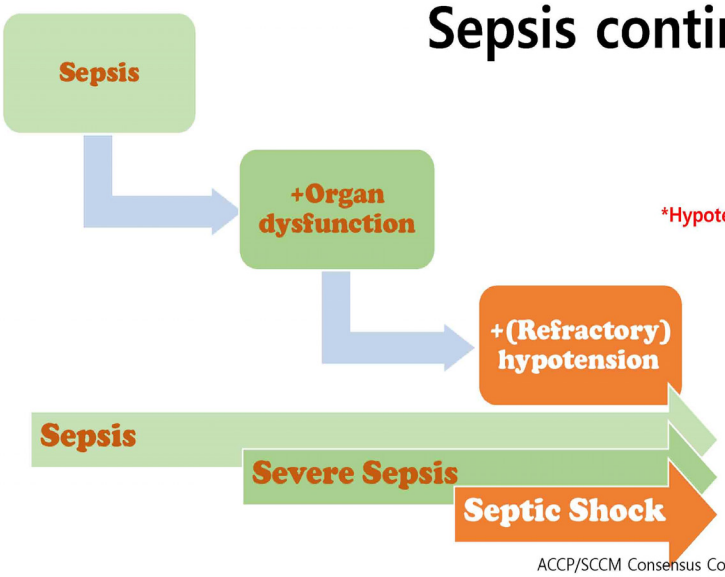
The 1991 and 2001 Definitions

*SIRS: Systemic Inflammatory Response Syndrome



ACCP/SCCM Consensus Conference: definitions for sepsis.
Bone, et al. Crit Care Med. 1992
2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.
Levy, et al. Int Care Med 2003

Definition



*Hypotension : SBP<90mmHg or MBP<70mmHg or SBP decrease>40mmHg

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Definition

Issues with the 1991 and 2001 Definitions

; ACCP/SCCM Consensus Conference: definitions for sepsis. (Bone et al. 1992)
; 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. (Levy et al. 2003)

SIRS – based

; SIRS is an appropriate response to **infection or any other stimulus that activates inflammation**.

Severe sepsis

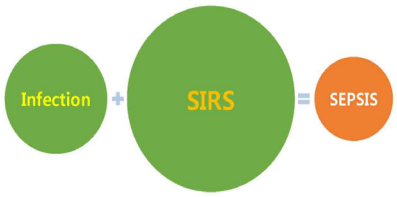
; **Confusing** – most people say "sepsis" when they mean "severe sepsis"

; Is "severe sepsis" **really needed?**

Different criteria yielding different results

; Australia – 22% (Kaukonen et al. 2014) ; Germany – 60.5% (Heublein et al. 2016) ; The Netherlands – 60% (Klein-Klouwenberg et al. 2012)

Definition



2015 Update

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection

qSOFA
- RR ≥22/min
- Altered mentation
- SBP ≤110 mmHg

SOFA
- PaO2/FiO2
- GCS
- MAP
- Vasopressors
- S.Cr or U. output
- Bilirubin
- Platelet count

So, . . . "sepsis" now = the old "severe sepsis"

qSOFA ≥2, SOFA ≥2

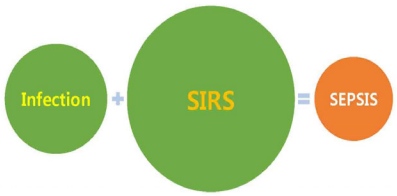
SOFA; Sequential [Sepsis-related] Organ Failure Assessment

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) **Singer, et al. JAMA. 2016**

Sequential [Sepsis-Related] Organ Failure Assessment Score

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/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 ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Definition



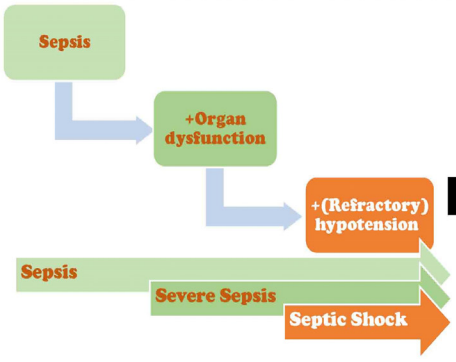
2015 Update

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection

As opposed to the "regulated host response" that characterizes the non-septic response to infection ("not simple infection")

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Singer, et al. JAMA. 2016

Definition



*Hypotension : SBP<90mmHg or
MBP<70mmHg or
SBP decrease>40mmHg

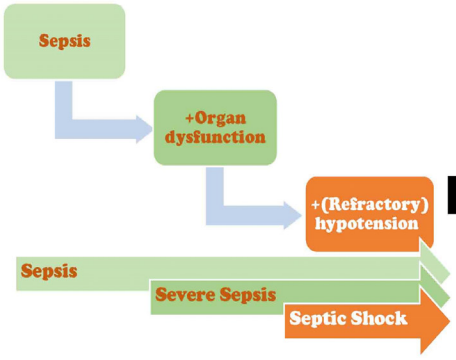
2015 Update

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

The 2001 definitions described septic shock as "a state of acute circulatory failure."

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Singer, et al. JAMA. 2016

Definition



*Hypotension : SBP<90mmHg or
MBP<70mmHg or
SBP decrease>40mmHg

"Sepsis" in place of "Severe Sepsis"

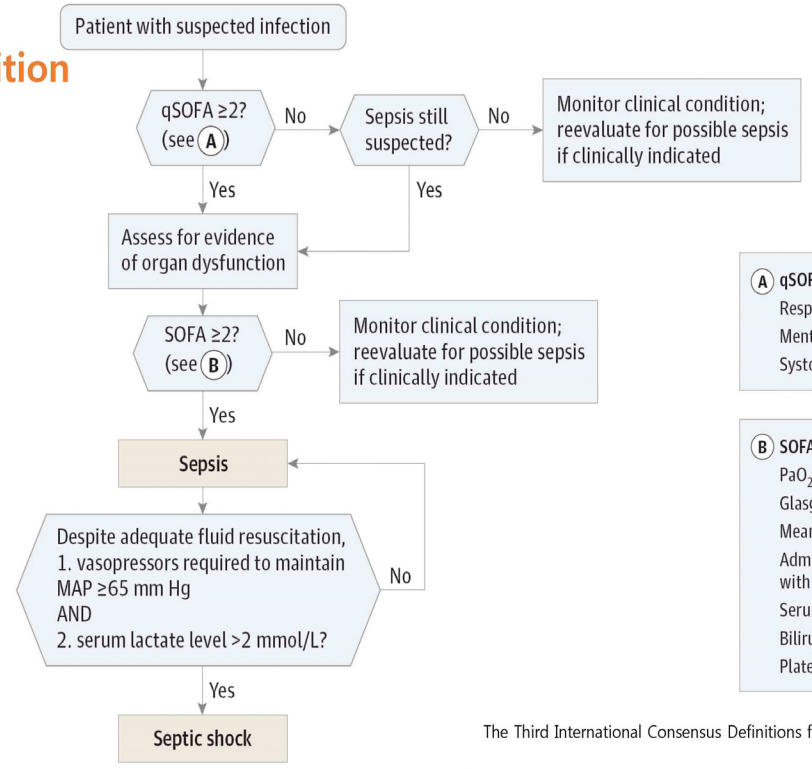
2015 Update

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

Despite adequate fluid resuscitation,
1. vasopressors required to maintain MAP ≥65 mmHg
AND
2. serum lactate level >2 mmol/L

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Singer, et al. JAMA. 2016

Definition



The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
Singer, et al. JAMA. 2016

Definition

Sepsis-associated encephalopathy

Defined by diffuse cerebral dysfunction that accompanies sepsis in the **absence** of direct CNS infection, structural abnormality or other types of encephalopathy, as detected by clinical or standard laboratory tests.

Gofton, et al. Nat. Rev. Neurol 2012

Epidemiology

✓ The most common cause of encephalopathy in the ICU

: Sepsis is the leading cause of medical illness that required ICU adm.

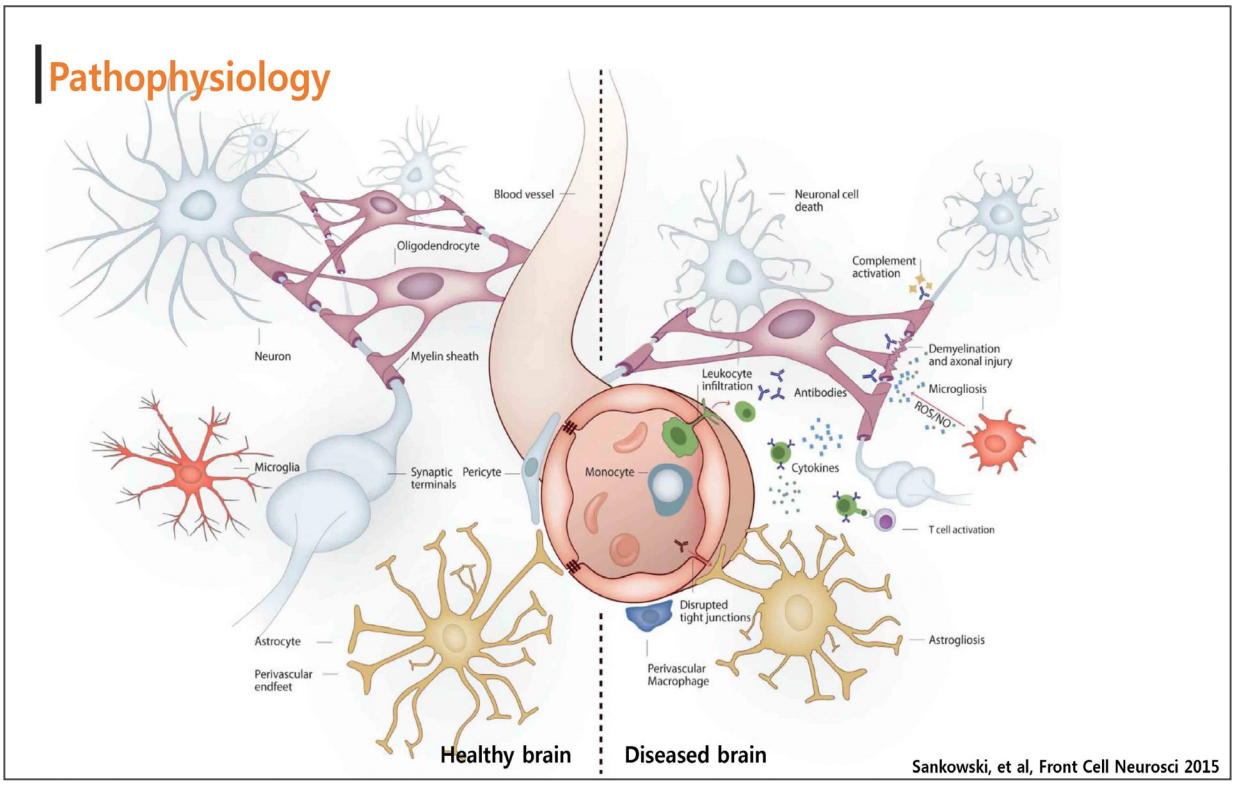
: Over half of patients with sepsis have encephalopathy.

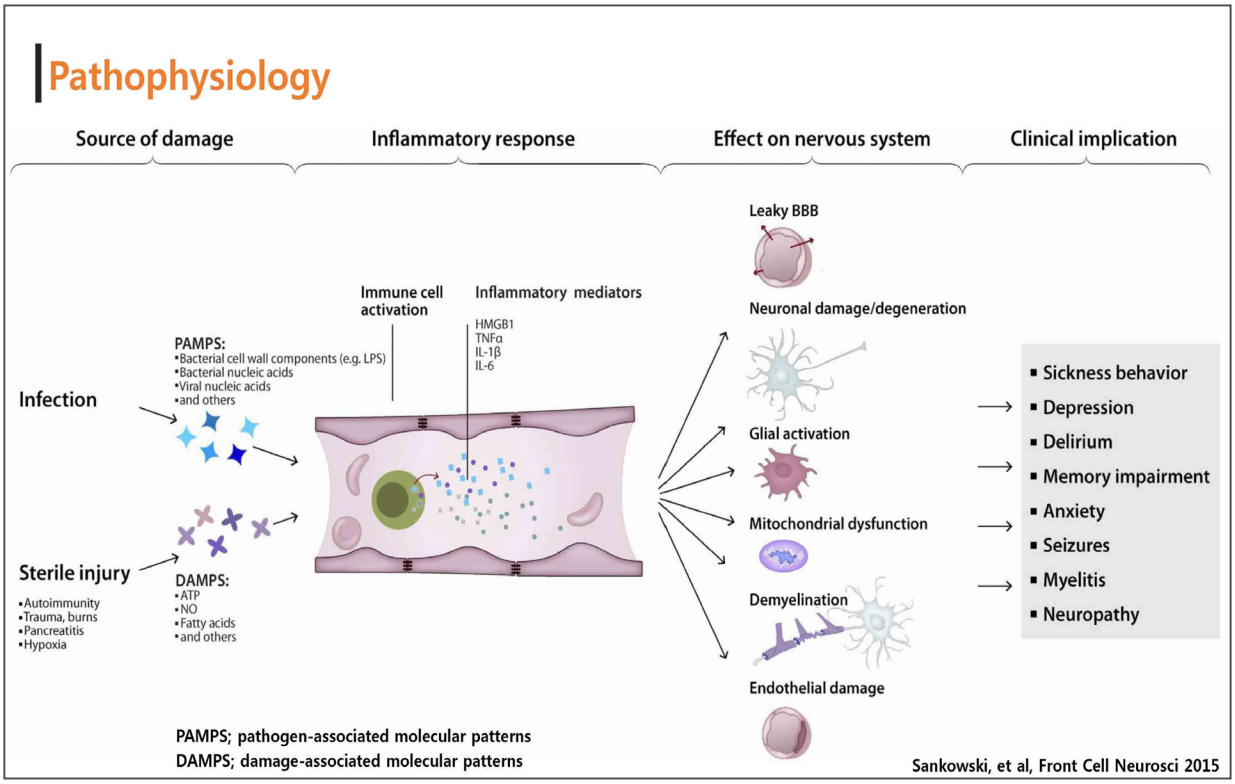
✓ Higher incidence rate in patients with bacteremia (~46%)

✓ Delirium : 20-50% of sepsis

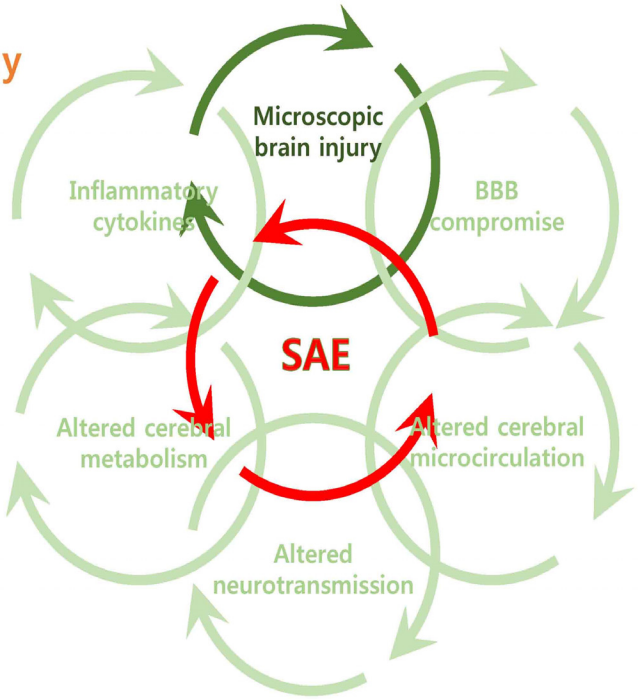
✓ High mortality : 49% in SAE vs. 26% in normal mental status

Gofton, et al. Nat. Rev. Neurol 2012
Young, et al. Clin Invest Med 1990
Bolton, et al, Ann Neurol 1993


Pathophysiology
Blood vessel
Oligodendrocyte
Neuron
Myelin sheath
Microglia
Synaptic terminals
Pericyte
Monocyte
Neuronal cell death
Complement activation
Demyelination and axonal injury
Leukocyte infiltration
Antibodies
Microgliosis
ROS/NO
Cytokines
T cell activation
Disrupted tight junctions
Perivascular Macrophage
Astrocyte
Perivascular endfeet
Astrogliosis
Healthy brain
Diseased brain
Sankowski, et al, Front Cell Neurosci 2015


Pathophysiology
Source of damage
Inflammatory response
Effect on nervous system
Clinical implication
Infection
PAMPS:
•Bacterial cell wall components (e.g. LPS)
•Bacterial nucleic acids
•Viral nucleic acids
•and others
Sterile injury
•Autoimmunity
•Trauma, burns
•Pancreatitis
•Hypoxia
DAMPS:
•ATP
•NO
•Fatty acids
•and others
Immune cell activation
Inflammatory mediators
HMGB1
TNFα
IL-1β
IL-6
Leaky BBB
Neuronal damage/degeneration
Glial activation
Mitochondrial dysfunction
Demyelination
Endothelial damage
▪ Sickness behavior
▪ Depression
▪ Delirium
▪ Memory impairment
▪ Anxiety
▪ Seizures
▪ Myelitis
▪ Neuropathy
PAMPS; pathogen-associated molecular patterns
DAMPS; damage-associated molecular patterns
Sankowski, et al, Front Cell Neurosci 2015

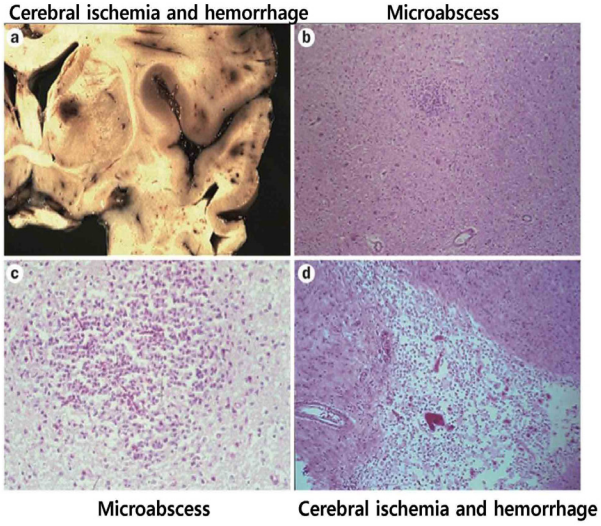
Pathophysiology

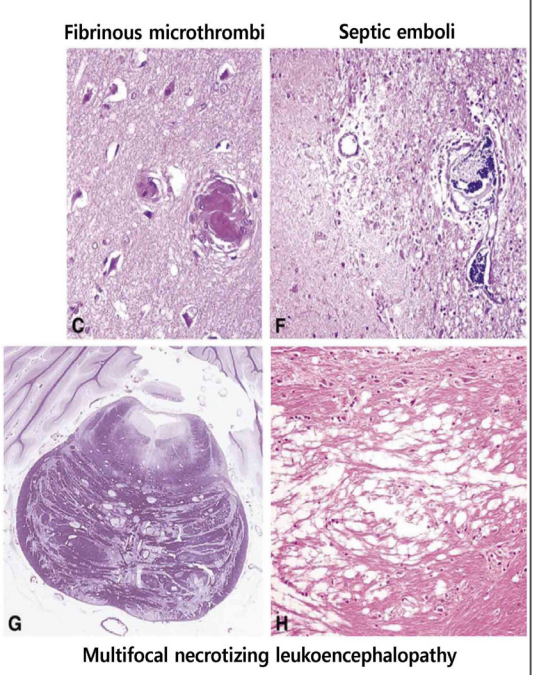


Gofton, et al. Nat. Rev. Neurol 2012

Pathophysiology

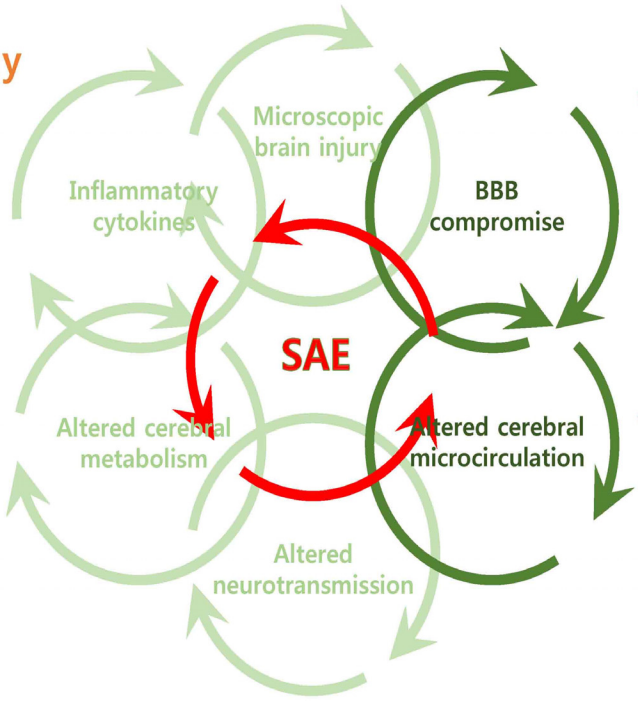
Microscopic brain injury





Gofton, et al. Nat. Rev. Neurol 2012

Pathophysiology



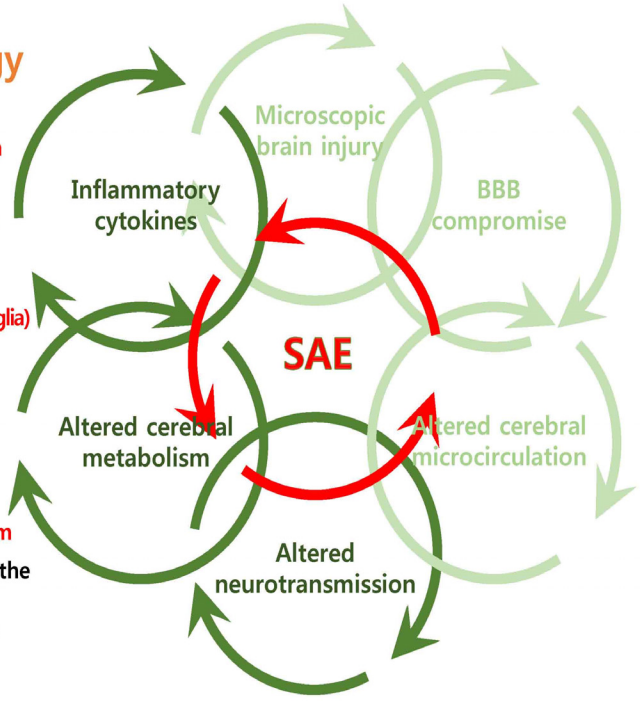
✓ ↑ permeability of the BBB in sepsis
; ↑ protein in the CSF
; astrocytic dysfunction
(from the microvasculature)

✓ Disturbances occur in cerebral autoregulation
; conflicting results
; cerebral vasoreactivity ↓
; hypoperfusion

Gofton, et al. Nat. Rev. Neurol 2012

Pathophysiology

✓ Cerebral neurotransmission
; ↑ TNF-α during sepsis
→ activate cerebral microglia
(release inflammatory mediator)
→ neurotoxic response
(↓ cholinergic inhibition of microglia)
→ delirium and SAE



✓ Altered cerebral metabolism
; oxidative stress occurs in the early stages
→ mitochondrial dysfunction
→ ATP synthesis ↓

Gofton, et al. Nat. Rev. Neurol 2012

Diagnosis

Sepsis-associated encephalopathy

Defined by diffuse cerebral dysfunction that accompanies sepsis in the absence of direct CNS infection, structural abnormality or other types of encephalopathy, as detected by clinical or standard laboratory tests.

Diagnosis of exclusion; investigate and eliminate the followings;

- ✓ **Direct CNS infection (encephalitis, meningitis, subdural empyema, cerebral abscess, etc.)**
- ✓ **Structural abnormality (stroke, septic emboli, PRES, etc.)**
- ✓ **Other types of encephalopathy (hepatic, renal, metabolic, etc.)**
- ✓ **Drug intoxication or withdrawal (alcohol, benzodiazepine, opioids, SSRI, cefepime, etc.)**
- ✓ **Non-convulsive status epilepticus**

Gofton, et al. Nat. Rev. Neurol 2012

Checklist for the evaluation of the patients with sepsis and diminished responsiveness

If Patient Has	Possible Cause	Next Steps
Bacteremia and focal deficits	Seeding of the **CNS with bacteria**; multiple embolic ± hemorrhagic **strokes**	Neuroimaging Perform TEE if: 1. Prosthetic valves 2. Prior valvular abnormality 3. S. aureus bacteremia 4. Bacteremia due to an organism known to be a common cause of infectious endocarditis, eg, Viridans streptococci
Paroxysmal or persistent a. fib and focal deficits	Cardioembolic ischemic **strokes**	Neuroimaging
Ventricular assist device, ECMO Anticoagulation or coagulopathy	Cardioembolic ischemic **strokes**; hemorrhagic **stroke**	Neuroimaging
History of epilepsy; or nystagmus, gaze deviation, or abnormal movements	**Nonconvulsive status epilepticus**	EEG

Hocker, et al. Continuum 2014

Checklist for the evaluation of the patients with sepsis and diminished responsiveness

If Patient Has	Possible Cause	Next Steps
Exposure to multiple serotonergic agents; hyperreflexia and rigidity ± dysautonomia	**Serotonin syndrome**	Discontinue serotonergic agents Control fever Consider treatment with benzodiazepines Consider treatment with cyproheptadine
Impaired renal function and cefepime use ≥3 days	**Cefepime neurotoxicity**	Replace cefepime with alternative antimicrobial and observe
Exposure to immunosuppressant; any autoimmune condition; seizures ± focal deficits	Posterior reversible encephalopathy syndrome **(PRES)**	If possible, remove immunosuppressants EEG ± AED BP control
Exposure to dopaminergic agents or DBS stimulation; history of mood disorder; rigidity ± dysautonomia	**Neuroleptic malignant syndrome** Parkinsonism-hyperpyrexia syndrome Malignant catatonia	Discontinue antidopaminergic agents, hydrate, control fever, consider treatment with dantrolene Interrogate DBS, give dopamine Benzodiazepines, electroconvulsive therapy

Hocker, et al. Continuum 2014

Diagnosis

81/F

 # Rt. psoas muscle abscess

c septic shock(MSSA) s/p PCD

 # AKI, R/O gentamicin toxicity

P/Hx

 # L5 spondylitis

 # CHF, HTN

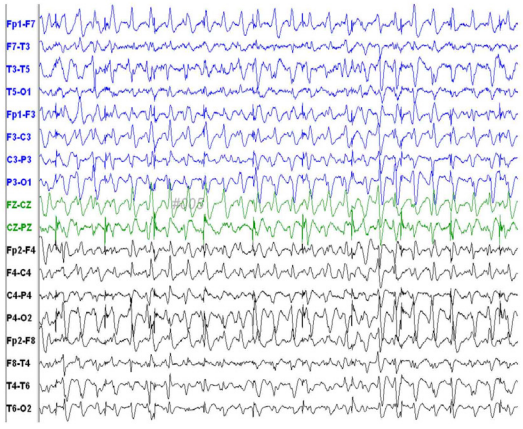
 # Panperitonitis d/t appendicitis c perforation

 # Parkinson`s disease

WBC 41400, CRP 24.6

Consultation for altered mentality

Cefepime for 2 days



Cefepime induced NCSE

Symptoms and signs of SAE

Main clinical features	Rare signs	Exceptional signs
Altered mental status (from lethargy to coma)	Asterixis	**Cranial nerve dysfunction**
Fluctuating confusional state	Myoclonus	**Lateralization**
Inappropriate behavior	Tremor	
Inattention	Seizures	
Agitation		
Delirium		
Unresponsiveness		
Coma		
Paratonic rigidity		
Peripheral nerve dysfunction		

Gofton, et al. Nat. Rev. Neurol 2012
Chelazzi, et al, Current Anaesthesia & Critical Care 2008

Symptoms and signs of SAE

Changes in cognitive or mental status that are associated with SAE can present in susceptible patients up to 36~48h before other systemic symptoms of sepsis or SIRS become apparent.

Hyperventilation can be an early feature and paratonic rigidity might be the only neurological finding, besides delirium, in early SAE.

Advanced disease is associated with critical illness polyneuropathy in 70% of cases.

Gofton, et al. Nat. Rev. Neurol 2012
Eidelman, et al. JAMA 2004

Diagnostic test

Diagnostic Testing	Findings
EEG	Theta waves
	Delta waves
	Triphasic waves
	Burst suppression
	Periodic epileptiform discharges
	Electrographic seizures
CSF analysis	Elevated protein
	Normal glucose, cell count, Gram stain, and cultures
Neuroimaging	Normal
	Ischemic strokes
	Multifocal subcortical white matter lesions

Sharshar, et al, Intensive Care Med 2007
Gofton, et al, Nat Rev Neurol 2012

Diagnostic test

EEG

- ✓ **cEEG in MICU (sepsis in 60%)**
  - **; ESZs in 10%, PED in 17%, NCSE in 67% of ESZs**
  - **; Patients with sepsis had a higher rate of ESZs or PEDs than those without sepsis (32% vs. 9%)**
  - **; ESZs or PEDs was associated with death or severe disability at hospital discharge (89% vs. 39%)**
- ✓ **Triphasic wave in 20% of patients c sepsis**
- ✓ **Bacteremia without encephalopathy ; EEG abnormality in 50%**

Changes in EEG recordings in patients with sepsis

Degree of encephalopathy	EEG findings (% of patients)				
	normal	Theta	Delta	Triphasic	Burst-suppression
None	50	38	12	0	0
Mild	0	47	53	0	0
Severe	0	10	40	20	30

Gofton, et al. Nat. Rev. Neurol 2012
Young, et al. Clin Invest Med 1992
Oddo, et al, Crit Care Med 2009

Diagnostic test

Biomarkers

✓ S 100ß, neuron-specific enolase (NSE)

→ S 100ß : reflects glial cell injury and abnormal BBB function

→ NSE : reflects neuronal injury (intraneuronal enzyme)

→ NSE was not a good biomarker for SAE compared to S 100ß.

✓ procalcitonin, IL-6, 8, amyloid-ß, glial fibrillary acidic protein (GFAP)

✓ No specific biomarkers

→ also can increase in patients with survived CA and TBI

Gofton, et al. Nat. Rev. Neurol 2012
Young, et al. Clin Invest Med 1992
Oddo, et al, Crit Care Med 2009

Treatment

✓ Early detection and treatment of delirium & SAE

; delirium - the first manifestation of sepsis

✓ Determination of the underlying cause

✓ Accurate and prompt treatment of the infection

Surviving Sepsis Campaign

✓ Avoid benzodiazepine & deep sedation

; Patients treated with dexmedetomidine had more encephalopathy-free days, shorter time on the ventilator and lower mortality than those treated with lorazepam.

; RASS 0~(–2), SAS 3~4, Ramsay sedation scale 3~5

✓ No definitive therapy exists for SAE

; magnesium, riluzole(glutamate release inhibitor), etc.

Gofton, et al. Nat. Rev. Neurol 2012
Hocker, et al. Continuum 2014
Pandharipande, et al. Crit Care 2010

Treatment

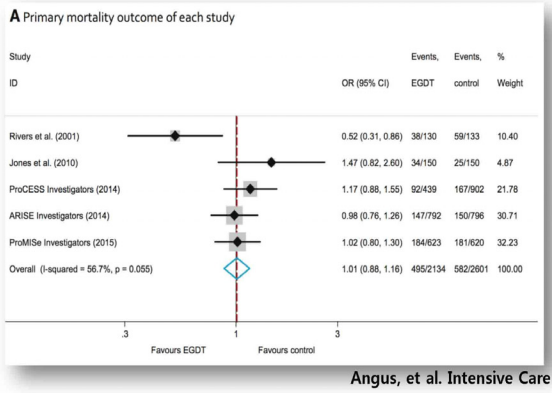
Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

2012 Recommendation for Initial Resuscitation

We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%



Angus, et al. Intensive Care Med 2015

Treatment

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

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 30ml/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 MAP ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP <65mmHg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated.

Treatment

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

Suggest albumin in addition to crystalloids for initial resuscitation and subsequent IV volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

Recommend against using hydroxyethyl starches for IV volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).

Treatment

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

Recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence)

Suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage. (weak recommendation)

Suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation)

Treatment

Surviving Sepsis Campaign

Updated Bundles in Response to New Evidence

Recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence)

Suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

Suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).

Summary

- ✓ 3rd definition of Sepsis & Septic shock
- ✓ SAE and delirium are early features of infection and might appear before other systemic features of sepsis are obvious
- ✓ SAE has a spectrum of degrees of severity, ranging from lethargy to coma
- ✓ Diagnosis relies on exclusion of primary CNS infection and other causes of encephalopathy
- ✓ Multiple mechanisms and pathophysiology
- ✓ Mortality increase with disease severity
- ✓ Early investigation and prompt treatment of underlying infection

Summary

- ✓ Recommend norepinephrine as the first-choice vasopressor
- ✓ Suggest albumin in addition to crystalloids for initial resuscitation and subsequent IV volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids
- ✓ Recommend against using hydroxyethyl starches
- ✓ Suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients
- ✓ Suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available

Thank you for your attention!

Sepsis for neurologist

; SAE and pressor in neuroICU