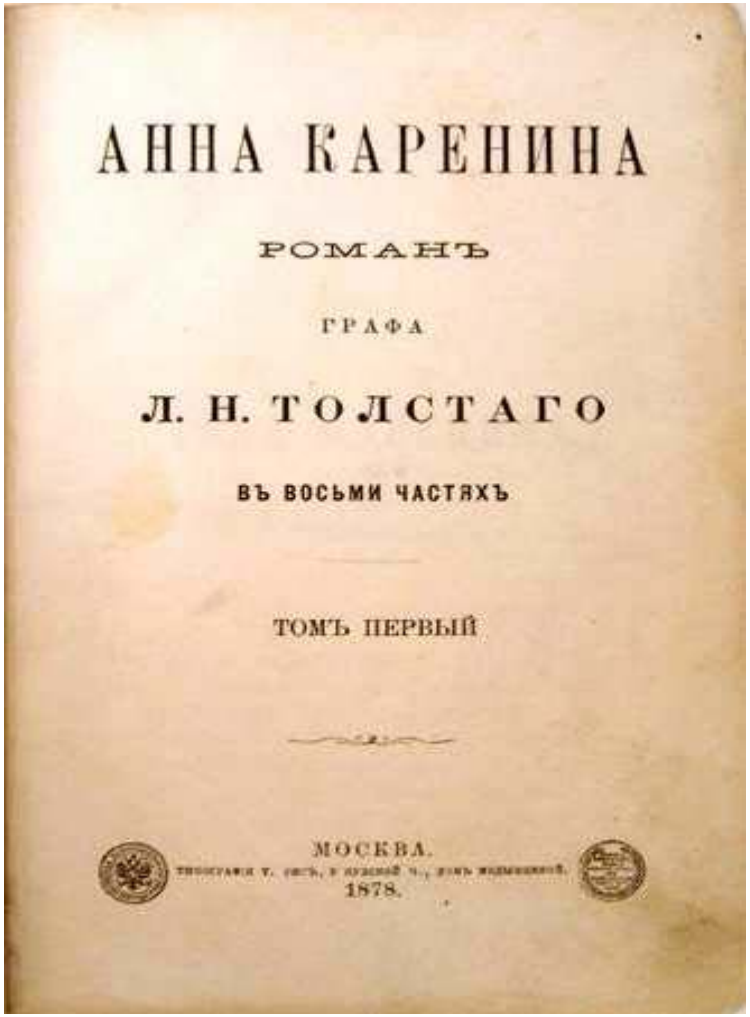
12-13 Maggio 2016
HOTEL ROYAL CONTINENTAL - Napoli

La sepsi e l'encefalo

Franco Faella


АННА КАРЕНИНА

РОМАНЪ

ГРАФА

Л. Н. ТОЛСТАГО

ВЪ ВОСЬМИ ЧАСТЯХЪ

ТОМЪ ПЕРВЫЙ

МОСКВА.
1878.

Il medico curante e i dottori dicevano trattarsi di una febbre puerperale nella quale su cento probabilità novantanove erano di morte.
Tutto il giorno ella ebbe febbre, delirio e deliquio.
A mezzanotte la malata giaceva priva di sensi e quasi senza polso.
Si aspettava la fine da un momento all'altro.

Anna Karenina
di Lev Nikolayevich Tolstoy
parte IV cap. XVII
1877

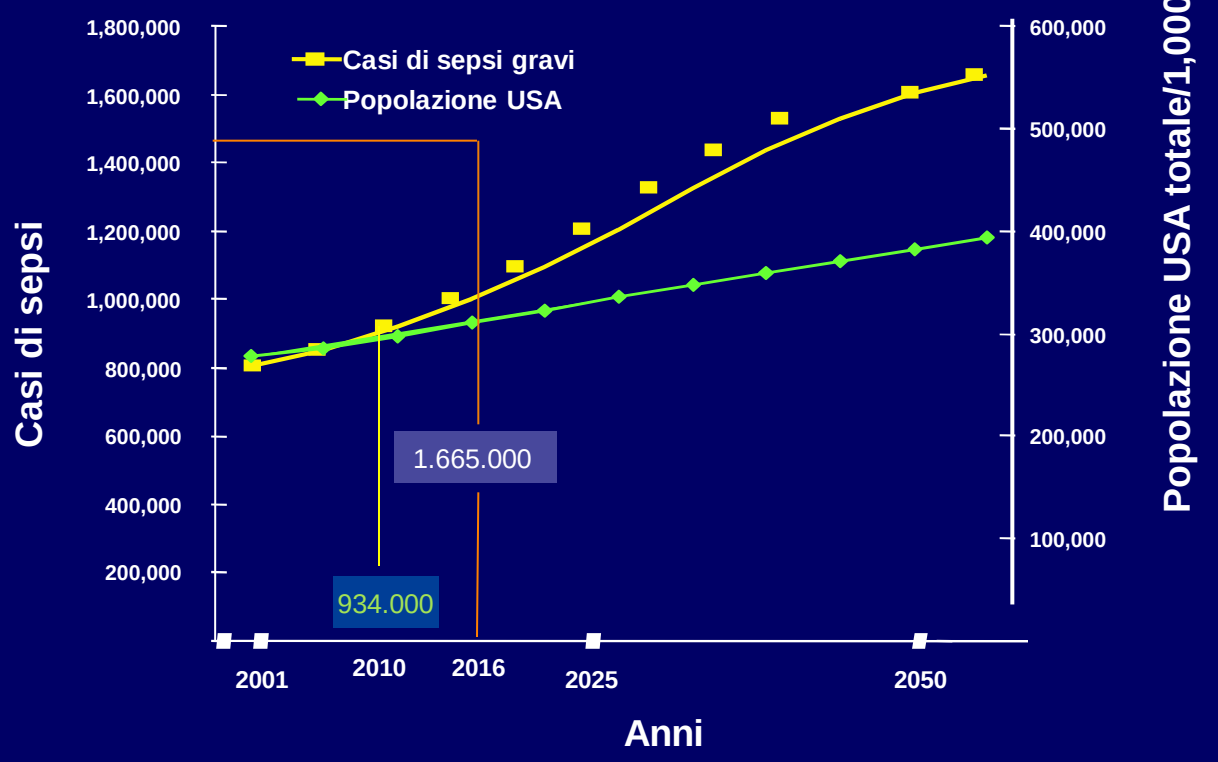
Sepsi Grave – Shock Settico

Incremento progressivo del 1.5% dei casi/anno (dati **US Census**)

1995

~750,000 casi di Sepsi Grave all'anno negli Stati Uniti*

Oggi-Domani



*Angus DC. *Crit Care Med.* 2001

- ✓ Circa 1.665.000 casi/anno negli USA (2015) con un tasso di mortalità che può raggiungere il 50%
- ✓ I casi di sepsi rappresentano circa il 75% delle patologie trattate nelle UTI
- ✓ Nelle UTI la sepsi e le sue complicanze sono la più frequente causa di elevata mortalità
- ✓ La mortalità per sepsi rimane alta nonostante i notevoli progressi in tema di diagnosi e terapia

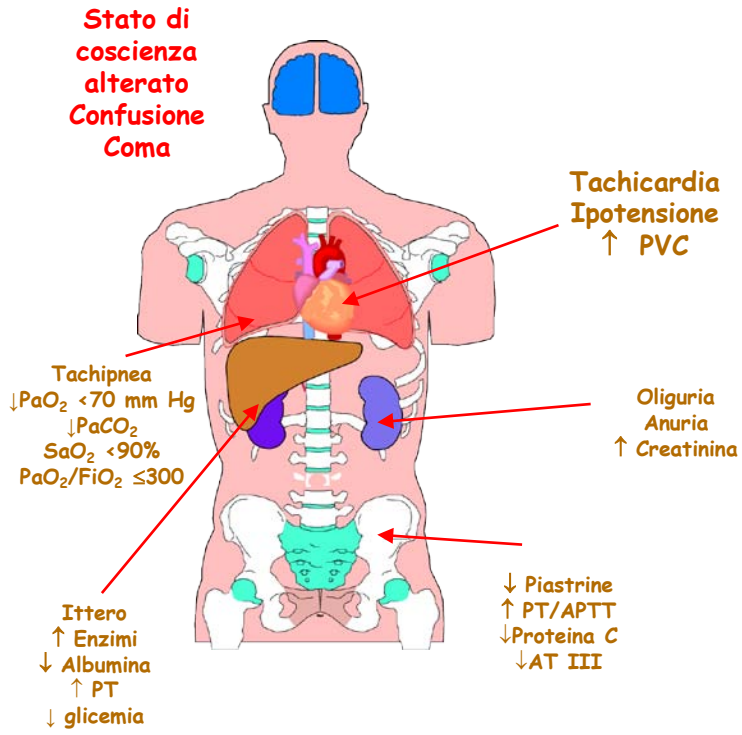
1.Vandijck D, Decruyenaere JM, Blot SI. The value of sepsis definitions in daily ICU-practice. Acta Clin Belg. 2006;61(5):220–6.

2. Vandijck DM, Reynvoet E, Blot SI, Vandecasteele E, Hoste EA. Severe infection, sepsis and acute kidney injury. Acta Clin Belg Suppl. 2007;2:332–6.

3. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA. 1997;278(3):23440.

4. Esper A, Martin GS. Is severe sepsis increasing in incidence ANDseverity? Crit Care Med. 2007;35(5):14145.

Si stima il 9-71% dei pazienti diagnosticati per sepsi presentano sintomi di *encefalopatia associata alla sepsi* (SAE)



Frontera JA.
Metabolic encephalopathies in the critical care unit.
Continuum (Minneap Minn). 2012;18(3):611–39.

Ringer TM, et al.
Neurological sequelae of sepsis: I) Septic encephalopathy.
Open Crit Care Med J. 2011;4:2-7.

Ebersoldt M, Sharshar T, Annane D.
Sepsis-associated delirium.
Intensive Care Med. 2007;33(6):941–50

Davies NW, Sharief MK, Howard RS.
Infection-associated encephalopathies:
J Neurol. 2006;253(7):833–45.

.

Sepsis-associated encephalopathy (SAE)

The syndrome is defined by diffuse cerebral dysfunction that accompanies sepsis in the absence of direct CNS infection, structural abnormality or other types of encephalopathy (for example, hepatic or renal encephalopathy)

NATURE REVIEWS | NEUROLOGY
VOLUME 8 | OCTOBER 2012 |

CRITICAL CARE MEDICINE AUGUST, 1990

Impact of encephalopathy on mortality in the sepsis syndrome

CHARLES L. SPRUNG, MD; PETER N. PEDUZZI, PHD; CLAYTON H. SHATNEY, MD; ROLAND M. H. SCHEIN, MD; MICHAEL F. WILSON, MD; JOHN N. SHEAGREN, MD; LERNER B. HINSHAW, PHD; THE VETERANS ADMINISTRATION SYSTEMIC SEPSIS COOPERATIVE STUDY GROUP*

1333 pz. con sepsi, encefalopatia in 307 casi (23%)

TABLE 1. Mortality by clinical status in patients with sepsis

Clinical Status[a]	No. Dead/No. Pts. (%)[b]	p Value
Mental Status		
Acute altered	147/302 (49)	—
Preexisting altered	158/383 (41)	—
Normal	142/549 (26)	<.000001[c]

TABLE 3. Relation between blood culture result and AAMS

Blood Culture Result	No. Patients	No. with AAMS	% AAMS
No organism	583	136	23.3[a]
Gram-negative	269	76	28.3
Gram-positive	218	55	25.2
Fungemia	13	3	23.1
Total	1083	270	24.9

In summary, alteration in mental status are common in septic patients, and are associated with significantly higher mortality.

Sintomi e segni di *SAE*

Segni e sintomi più frequenti	Segni e sintomi più rari	Segni e sintomi eccezionali
Delirio		
Agitazione		
Stato confusionale	tremore a battito d'ali	impegno nn. cranici
Disturbi comportamentali	mioclono	segni di lateralità
Disattenzione	tremori	
Convulsioni		
Coma		

Consalez C., de Gaudio A.R.*; Minerva anestesiologica* 2005

INTENSIVE CARE MEDICINE
OFFICIAL JOURNAL OF THE EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE
AND THE EUROPEAN SOCIETY OF PAEDIATRIC & NEONATAL INTENSIVE CARE

Table 4—*Independent Risk Factors for the Agitation*

Predictive Risk Factors	Odds Ratio	95% CI
Age ≥ 65 yr*	2.21	0.83–5.93
Medical cause of ICU admission*	3.04	0.85–10.54
Sepsis	2.61	1.03–6.58
Alcohol abuse	3.32	1.12–10.00
Use of sedatives in 48 h before onset of agitation	4.03	1.62–10.40
Body temperature ≥ 38°	4.52	1.80–11.49
Sodium level ≤ 134 mmol/L	4.87	1.58–14.99
Sodium level ≥ 143 mmol/L	4.95	1.95–12.54
Long-termc psychoactive drug user	5.63	1.32–23.70

*These risk factors are not significant.

Sepsis is an independant risk factors for agitation
(***Jaber S. et al – ICM - 2006***)

JAMA The Journal of the American Medical Association

Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit

E. Wesley Ely, MD, MPH; Ayumi Shintani, PhD, MPH; Brenda Truman, RN, MSN; Theodore Speroff, PhD; Sharon M. Gordon, PsyD; Frank E. Harrell, Jr, PhD; Sharon K. Inouye, MD, MPH; Gordon R. Bernard, MD; Robert S. Dittus, MD, MPH

JAMA. 2004;291(14):1753-1762. doi:10.1001/jama.291.14.1753.

Sepsis is a major cause of delirium ~ 50%

CLINICS 2011;66(10):1825-1831

REVIEW

Sepsis-associated encephalopathy: not just delirium

Fernando Godinho Zampieri,[I,II] Marcelo Park,[I,III] Fabio Santana Machado,[III] Luciano Cesar Pontes Azevedo[I,III]

***Delirium is often the first manifestation of sepsis, providing a useful diagnostic clue*.**

Delirium epidemiology in critical care (DECCA): an international study

Table 1 Demographic and clinical variables of patients according to delirium status

Variables	All patients (*n* = 497)	Delirium status[a]		*P* value
		Delirium (*n* = 75)	No delirium (*n* = 157)	
Age (years)	62 (47-74)	64 (50-77)	61 (46-74)	0. 2
Male gender, *n* (%)	261 (52.5%)	41 (54.6%)	79 (50.3%)	0.57
SAPS3 score (points)	49 (40-61)	57 (48-64)	46 (34-56)	< 0.0001
Charlson comorbidity index (points)	1 (0-3)	1 (0-3)	1 (0-3)	0.89
SOFA score (points)	4 (1-6)	4 (3-7)	3 (1-5)	0.004
Invasive mechanical ventilation, *n* (%)	191 (38.4%)	42 (56%)	36 (23%)	< 0.0001
Use of vasopressors, *n* (%)	103 (20.7%)	22 (29.3%)	21 (13.4%)	0.007
Renal replacement therapy, *n* (%)	52 (10.4%)	9 (12%)	17 (10.8%)	0.82
Main reasons for ICU admission				
Sepsis, *n* (%)	76 (15.3%)	19 (25.3%)	17 (10.8%)	0.006
Cardiovascular, *n* (%)	75 (15.3%)	10 (13.3%)	30 (18.6%)	0.35
Respiratory failure, *n* (%)	70 (11.7%)	9 (12%)	24 (15.3%)	0.55
Neurologic, *n* (%)	24 (4.8%)	12 (9.1%)	5 (3.1%)	0.004
Invasive devices				
Central venous catheter	317 (63.8%)	64 (85.3%)	85 (54.1%)	< 0.0001
Arterial catheter	158 (31.8%)	29 (38.6%)	32 (20.4%)	0.004
Urinary catheter	324 (65.1%)	62 (82.6%)	89 (56.7%)	0.0001
ICU LOS (days)	10 (4-24)	22 (11-40)	7 (4-18)	< 0.0001
ICU mortality, *n* (%)	83 (16.7%)	15 (20%)	9 (5.7%)	0.002
Hospital mortality, *n* (%)[b]	88 (19.9%)	18 (24%)	13 (8.3)	0.0017

160=**32,3**% delirium prevalenza
76=15,3% delirium+sepsis

235/**495**=**32,3%**

Salluh et al.; *Critical Care* 2010

Delirium epidemiology in critical care (DECCA): an international study

Table 1 Demographic and clinical variables of patients according to delirium status

Variables	All patients (*n* = 497)	Delirium status[a]		*P* value
		Delirium (*n* = 75)	No delirium (*n* = 157)	
Age (years)	62 (47-74)	64 (50-77)	61 (46-74)	0. 2
Male gender, *n* (%)	261 (52.5%)	41 (54.6%)	79 (50.3%)	0.57
SAPS3 score (points)	49 (40-61)	57 (48-64)	46 (34-56)	< 0.0001
Charlson comorbidity index (points)	1 (0-3)	1 (0-3)	1 (0-3)	0.89
SOFA score (points)	4 (1-6)	4 (3-7)	3 (1-5)	0.004
Invasive mechanical ventilation, *n* (%)	191 (38.4%)	42 (56%)	36 (23%)	< 0.0001
Use of vasopressors, *n* (%)	103 (20.7%)	22 (29.3%)	21 (13.4%)	0.007
Renal replacement therapy, *n* (%)	52 (10.4%)	9 (12%)	17 (10.8%)	0.82
Main reasons for ICU admission				
Sepsis, *n* (%)	76 (15.3%)	19 (25.3%)	17 (10.8%)	0.006
Cardiovascular, *n* (%)	75 (15.3%)	10 (13.3%)	30 (18.6%)	0.35
Respiratory failure, *n* (%)	70 (11.7%)	9 (12%)	24 (15.3%)	0.55
Neurologic, *n* (%)	24 (4.8%)	12 (9.1%)	5 (3.1%)	0.004
Invasive devices				
Central venous catheter	317 (63.8%)	64 (85.3%)	85 (54.1%)	< 0.0001
Arterial catheter	158 (31.8%)	29 (38.6%)	32 (20.4%)	0.004
Urinary catheter	324 (65.1%)	62 (82.6%)	89 (56.7%)	0.0001
ICU LOS (days)	10 (4-24)	22 (11-40)	7 (4-18)	< 0.0001
ICU mortality, *n* (%)	83 (16.7%)	15 (20%)	9 (5.7%)	0.002
Hospital mortality, *n* (%)[b]	88 (19.9%)	18 (24%)	13 (8.3)	0.0017

Salluh et al.; *Critical Care* 2010

Delirium epidemiology in critical care (DECCA): an international study

Table 1 Demographic and clinical variables of patients according to delirium status

Variables	All patients (*n* = 497)	Delirium status[a]		*P* value
		Delirium (*n* = 75)	No delirium (*n* = 157)	
Age (years)	62 (47-74)	64 (50-77)	61 (46-74)	0. 2
Male gender, *n* (%)	261 (52.5%)	41 (54.6%)	79 (50.3%)	0.57
SAPS3 score (points)	49 (40-61)	57 (48-64)	46 (34-56)	< 0.0001
Charlson comorbidity index (points)	1 (0-3)	1 (0-3)	1 (0-3)	0.89
SOFA score (points)	4 (1-6)	4 (3-7)	3 (1-5)	0.004
Invasive mechanical ventilation, *n* (%)	191 (38.4%)	42 (56%)	36 (23%)	< 0.0001
Use of vasopressors, *n* (%)	103 (20.7%)	22 (29.3%)	21 (13.4%)	0.007
Renal replacement therapy, *n* (%)	52 (10.4%)	9 (12%)	17 (10.8%)	0.82
Main reasons for ICU admission				
Sepsis, *n* (%)	76 (15.3%)	19 (25.3%)	17 (10.8%)	0.006
Cardiovascular, *n* (%)	75 (15.3%)	10 (13.3%)	30 (18.6%)	0.35
Respiratory failure, *n* (%)	70 (11.7%)	9 (12%)	24 (15.3%)	0.55
Neurologic, *n* (%)	24 (4.8%)	12 (9.1%)	5 (3.1%)	0.004
Invasive devices				
Central venous catheter	317 (63.8%)	64 (85.3%)	85 (54.1%)	< 0.0001
Arterial catheter	158 (31.8%)	29 (38.6%)	32 (20.4%)	0.004
Urinary catheter	324 (65.1%)	62 (82.6%)	89 (56.7%)	0.0001
ICU LOS (days)	10 (4-24)	22 (11-40)	7 (4-18)	< 0.0001
ICU mortality, *n* (%)	83 (16.7%)	15 (20%)	9 (5.7%)	0.002
Hospital mortality, *n* (%)[b]	88 (19.9%)	18 (24%)	13 (8.3)	0.0017

Salluh et al.; *Critical Care* 2010

Delirium epidemiology in critical care (DECCA): an international study

Table 1 Demographic and clinical variables of patients according to delirium status

Variables	All patients (*n* = 497)	Delirium status[a]		*P* value
		Delirium (*n* = 75)	No delirium (*n* = 157)	
Age (years)	62 (47-74)	64 (50-77)	61 (46-74)	0. 2
Male gender, *n* (%)	261 (52.5%)	41 (54.6%)	79 (50.3%)	0.57
SAPS3 score (points)	49 (40-61)	57 (48-64)	46 (34-56)	< 0.0001
Charlson comorbidity index (points)	1 (0-3)	1 (0-3)	1 (0-3)	0.89
SOFA score (points)	4 (1-6)	4 (3-7)	3 (1-5)	0.004
Invasive mechanical ventilation, *n* (%)	191 (38.4%)	42 (56%)	36 (23%)	< 0.0001
Use of vasopressors, *n* (%)	103 (20.7%)	22 (29.3%)	21 (13.4%)	0.007
Renal replacement therapy, *n* (%)	52 (10.4%)	9 (12%)	17 (10.8%)	0.82
Main reasons for ICU admission				
Sepsis, *n* (%)	76 (15.3%)	19 (25.3%)	17 (10.8%)	0.006
Cardiovascular, *n* (%)	75 (15.3%)	10 (13.3%)	30 (18.6%)	0.35
Respiratory failure, *n* (%)	70 (11.7%)	9 (12%)	24 (15.3%)	0.55
Neurologic, *n* (%)	24 (4.8%)	12 (9.1%)	5 (3.1%)	0.004
Invasive devices				
Central venous catheter	317 (63.8%)	64 (85.3%)	85 (54.1%)	< 0.0001
Arterial catheter	158 (31.8%)	29 (38.6%)	32 (20.4%)	0.004
Urinary catheter	324 (65.1%)	62 (82.6%)	89 (56.7%)	0.0001
ICU LOS (days)	10 (4-24)	22 (11-40)	7 (4-18)	< 0.0001
ICU mortality, *n* (%)	83 (16.7%)	15 (20%)	9 (5.7%)	0.002
Hospital mortality, *n* (%)[b]	88 (19.9%)	18 (24%)	13 (8.3)	0.0017

Salluh et al.; *Critical Care* 2010

Delirium epidemiology in critical care (DECCA): an international study

Table 1 Demographic and clinical variables of patients according to delirium status

Variables	All patients (*n* = 497)	Delirium status[a]		*P* value
		Delirium (*n* = 75)	No delirium (*n* = 157)	
Age (years)	62 (47-74)	64 (50-77)	61 (46-74)	0. 2
Male gender, *n* (%)	261 (52.5%)	41 (54.6%)	79 (50.3%)	0.57
SAPS3 score (points)	49 (40-61)	57 (48-64)	46 (34-56)	< 0.0001
Charlson comorbidity index (points)	1 (0-3)	1 (0-3)	1 (0-3)	0.89
SOFA score (points)	4 (1-6)	4 (3-7)	3 (1-5)	0.004
Invasive mechanical ventilation, *n* (%)	191 (38.4%)	42 (56%)	36 (23%)	< 0.0001
Use of vasopressors, *n* (%)	103 (20.7%)	22 (29.3%)	21 (13.4%)	0.007
Renal replacement therapy, *n* (%)	52 (10.4%)	9 (12%)	17 (10.8%)	0.82
Main reasons for ICU admission				
Sepsis, *n* (%)	76 (15.3%)	19 (25.3%)	17 (10.8%)	0.006
Cardiovascular, *n* (%)	75 (15.3%)	10 (13.3%)	30 (18.6%)	0.35
Respiratory failure, *n* (%)	70 (11.7%)	9 (12%)	24 (15.3%)	0.55
Neurologic, *n* (%)	24 (4.8%)	12 (9.1%)	5 (3.1%)	0.004
Invasive devices				
Central venous catheter	317 (63.8%)	64 (85.3%)	85 (54.1%)	< 0.0001
Arterial catheter	158 (31.8%)	29 (38.6%)	32 (20.4%)	0.004
Urinary catheter	324 (65.1%)	62 (82.6%)	89 (56.7%)	0.0001
ICU LOS (days)	10 (4-24)	22 (11-40)	7 (4-18)	< 0.0001
ICU mortality, *n* (%)	83 (16.7%)	15 (20%)	9 (5.7%)	0.002
Hospital mortality, *n* (%)[b]	88 (19.9%)	18 (24%)	13 (8.3)	0.0017

Salluh et al.; *Critical Care* 2010

Chin Med J 2012;125(5):828-831

Epidemiological features and risk factors of sepsis-associated encephalopathy in intensive care unit patients: 2008–2011

ZHANG Li-na, WANG Xiao-ting, AI Yu-hang, GUO Qu-lian, HUANG Li, LIU Zhi-yong and Yao Bo

232 patients
41 had SAE
17.7%

Table 1. Comparison of baseline data between two groups

Items	SAE groups	Non-SAE groups	*P* values
Age (years)	54±18	51±14	0.300
Sex (male/female, *n*)	27/14	130/61	0.854
Types of concurrent diseases (*n* (%))			
Hypertension	8 (19.5)	37 (19.4)	0.567
Diabetes	3 (7.3)	21 (11.0)	0.471
Coronary heart disease	4 (9.8)	18 (9.4)	0.573
Obstructive lung disease	3 (7.3)	11 (5.8)	0.718
Types of primary diseases (*n* (%))			
Multiple trauma	7 (17.1)	24 (12.6)	0.451
Severe pancreatitis	5 (12.3)	40 (20.9)	0.276
Severe pneumonia	6 (14.6)	15 (7.9)	0.225
Abdominal infections	14 (34.1)	53 (27.7)	0.187
Urinary tract infections	3 (7.3)	8 (4.2)	0.416
Blood diseases	1 (2.4)	7 (3.7)	0.572
Connective tissue diseases	1 (2.4)	5 (2.6)	0.713
Others	4 (9.8)	39 (20.4)	0.126
APACHE II score	22±7	17±7	0.000
GCS score	10±4	13±3	0.000

Chin Med J 2012;125(5):828-831

Epidemiological features and risk factors of sepsis-associated encephalopathy in intensive care unit patients: 2008–2011

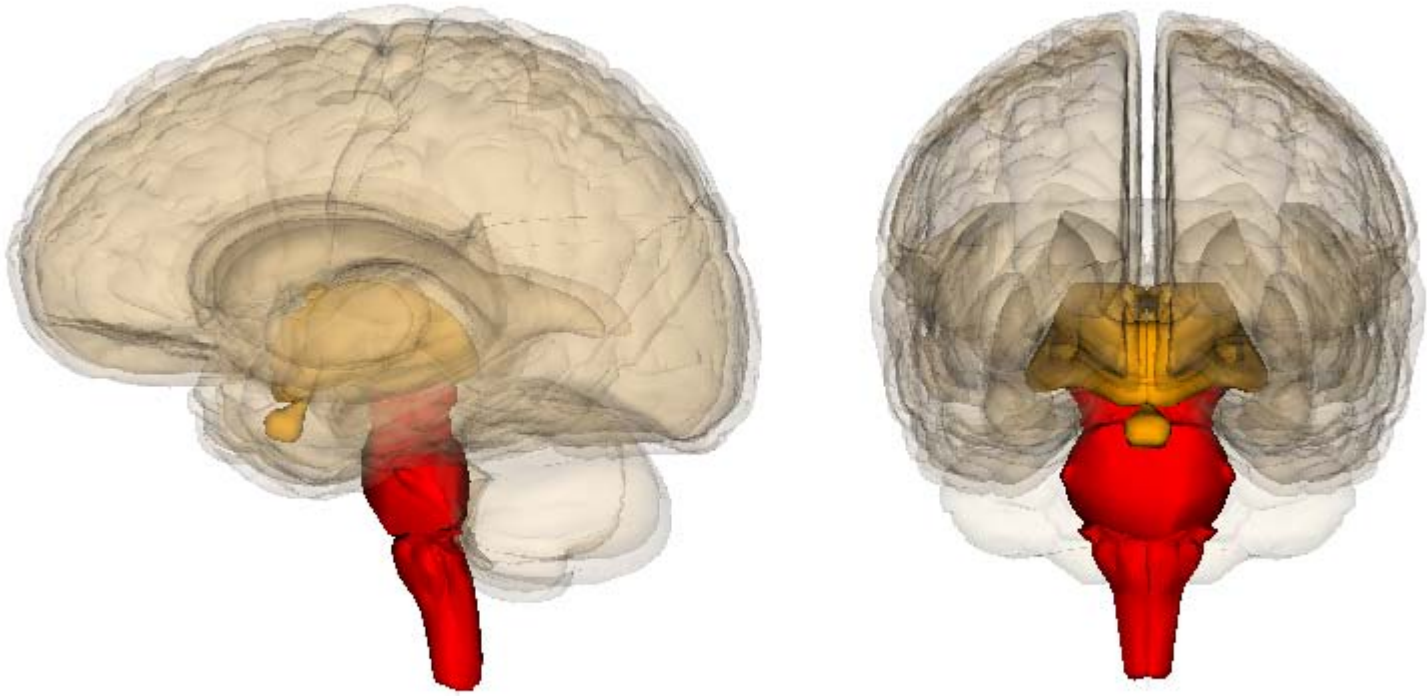
ZHANG Li-na, WANG Xiao-ting, AI Yu-hang, GUO Qu-lian, HUANG Li, LIU Zhi-yong and Yao Bo

Patients with biliary tract infections and intestinal infections caused by *Staphylococcus aureus*, *Enterococcus faecium*, *Acinetobacter* spp, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*, were more prone to develop sepsis-associated encephalopathy.

Comparison of major sites of infection and bacteriological categories between two groups (*n* (%))

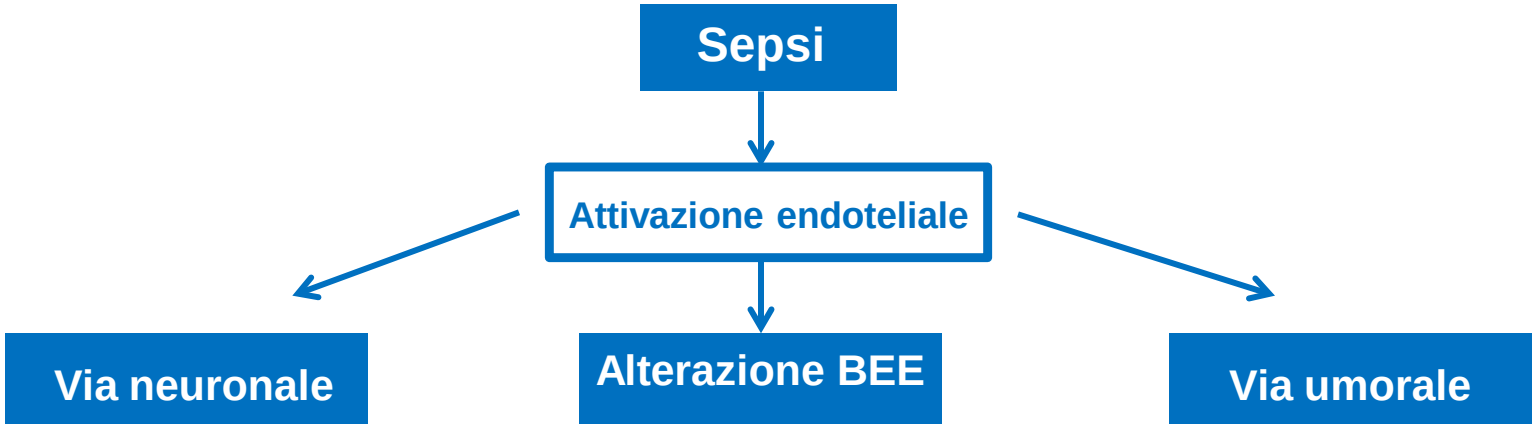
Items	SAE group	Non-SAE group	*P* values
Sites of infection			
Pulmonary infections	17 (41.46)	64 (33.51)	0.214
Biliary tract infections	10 (24.39)	24 (12.57)	0.050
Intestinal infections	18 (43.90)	52 (27.23)	0.029
Blood-borne infections	6 (14.63)	15 (7.85)	0.142
Urinary tract infections	2 (4.88)	9 (4.71)	0.610
Skin and soft tissue infections	8 (19.51)	22 (11.52)	0.131
Bacteriological categories			
Proportion of pathogen detection	29 (70.73)	85 (44.50)	0.003
E. coli	11 (26.83)	27 (14.14)	0.061
Enterobacter cloacae	2 (4.88)	9 (4.71)	0.610
Klebsiella pneumoniae	3 (7.32)	9 (4.71)	0.449
Acinetobacter *	16 (39.02)	33 (17.28)	0.005
Pseudomonas aeruginosa *	10 (24.39)	16 (8.38)	0.011
Stenotrophomonas maltophilia *	5 (12.19)	2 (1.05)	0.002
Staphylococcus aureus *	5 (12.19)	6 (3.14)	0.028
Hemolytic *Staphylococcus aureus*	1 (2.44)	4 (2.09)	0.625
Enterococcus faecalis	1 (2.44)	3 (1.57)	0.556
Enterococcus feces *	10 (24.39)	18 (9.42)	0.015
Candida	5 (12.19)	14 (7.33)	0.344
Yeast genera	3 (7.32)	7 (3.66)	0.388
Aspergillus	2 (4.88)	5 (2.62)	0.610

Sepsi → encefalopatia associata alla sepsi



"The mind has great influence over the body, and maladies often have their origin there."
Molière (1622–1673).

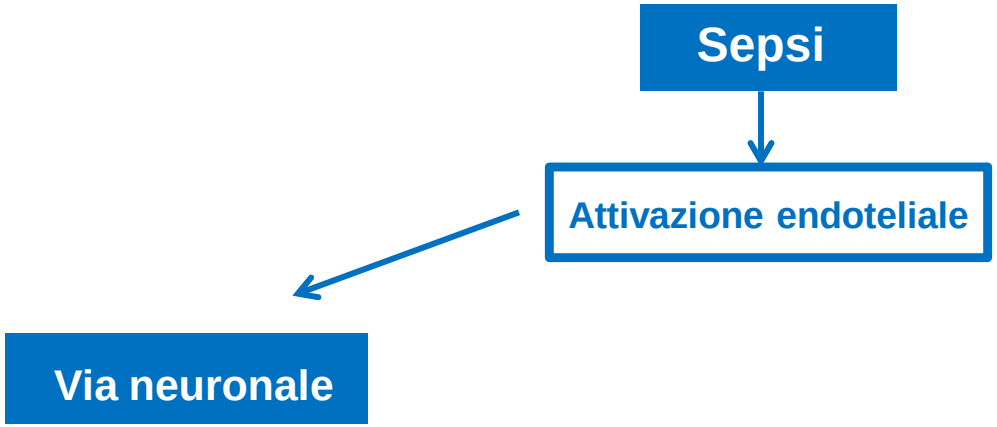
Sepsi → encefalopatia associata alla sepsi



La risposta dell'encefalo alla infezione sistemica è fisiologicamente condizionata dall'attivazione di un segnale che segue tre vie.

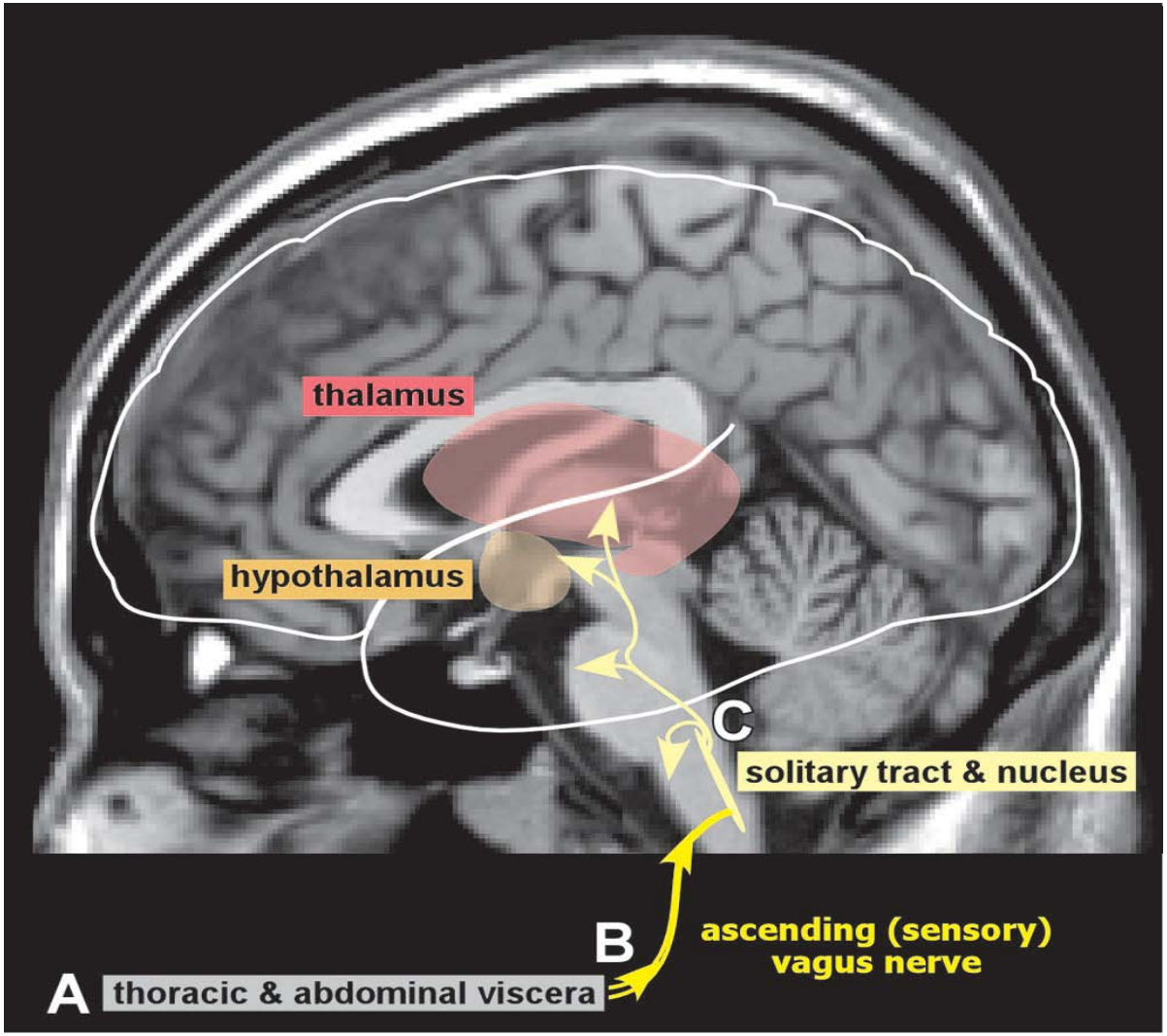
Sonneville et al. *Annals of Intensive Care* 2013

Sepsi → encefalopatia associata alla sepsi

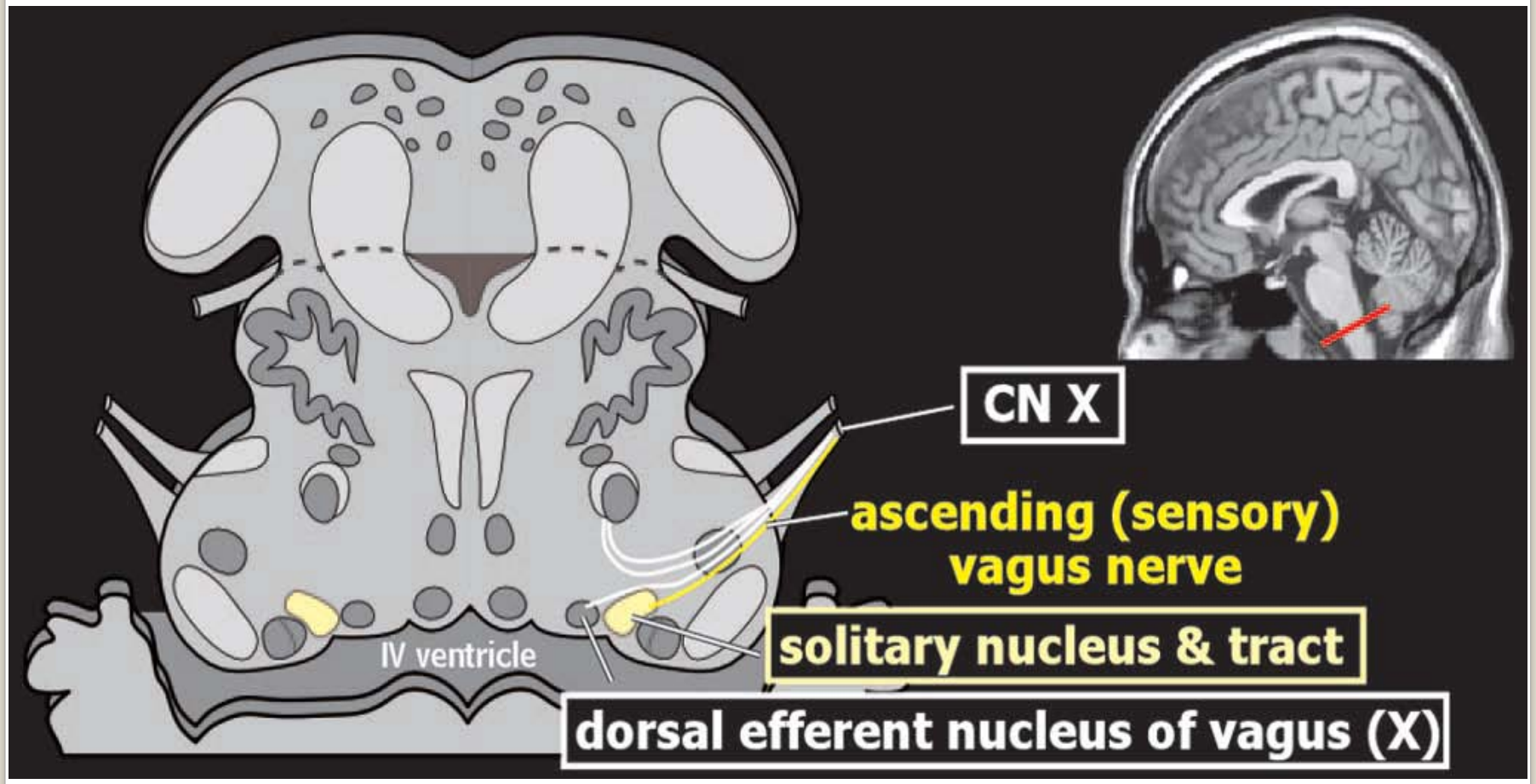


Sonneville et al. *Annals of Intensive Care* 2013

Il sistema nervoso parasimpatico gioca un ruolo importante nel segnalare la presenza di infezione

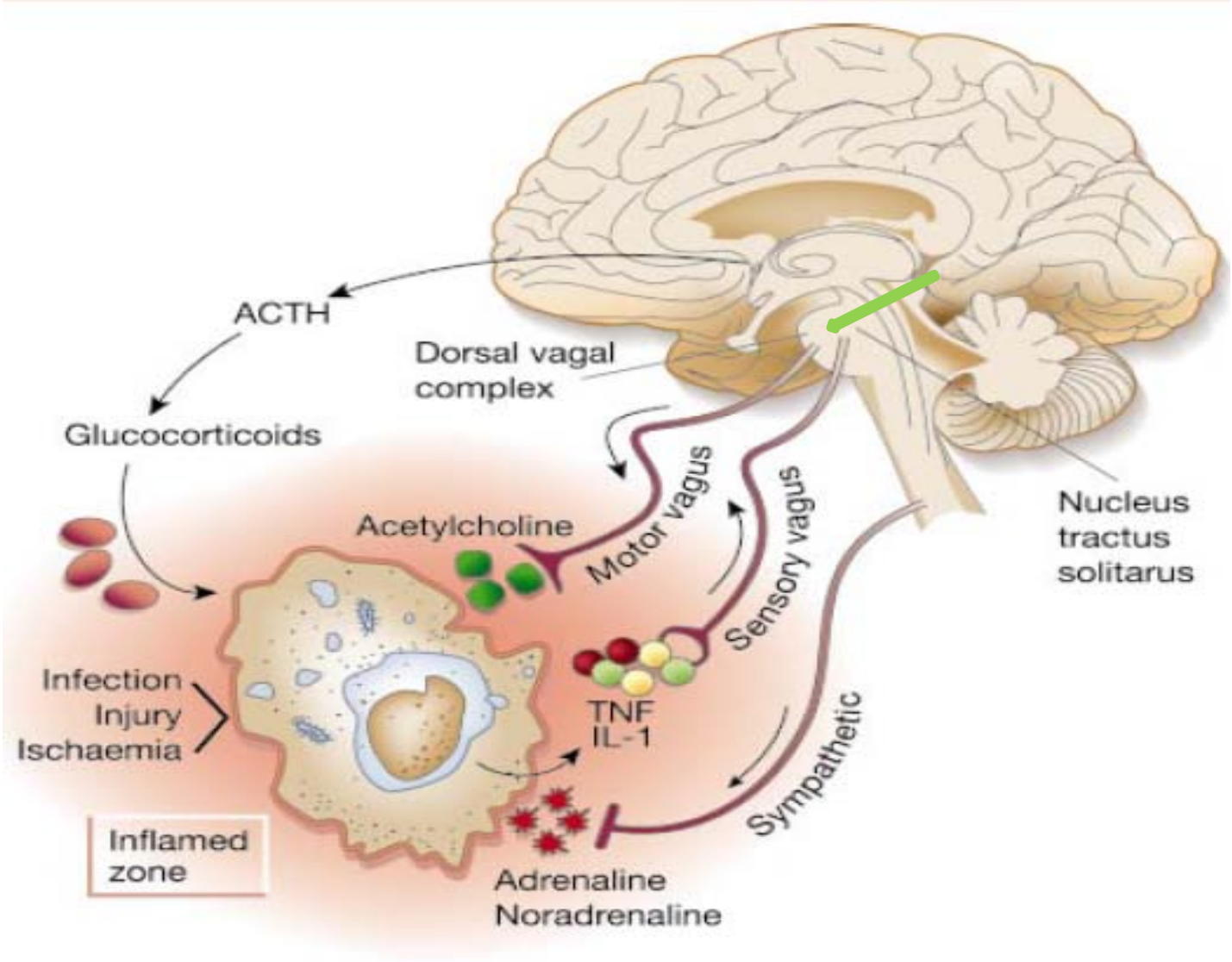


Lamar C.D. et al.; *J Neuropsychiatry Clin Neurosci*, 2011



Lamar C.D. et al.; *J Neuropsychiatry Clin Neurosci*, 2011

The *inflammatory reflex*



Tracey K.J.; NATURE 2002

Il sistema nervoso autonomo e la sepsi

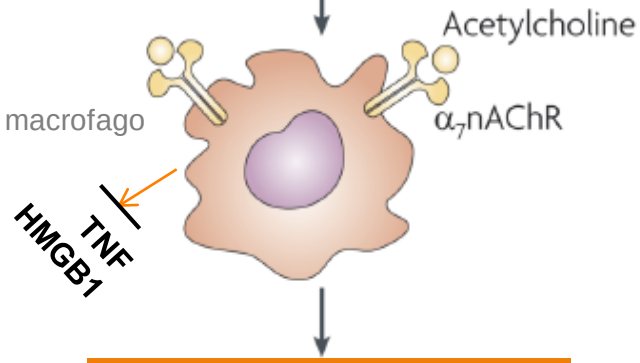
Via colinergica anti-infiammatoria

Stimolazione del nervo vago

↓

Rilascio di acetilcolina (o agonisti α_7nAChR)

↓



↓

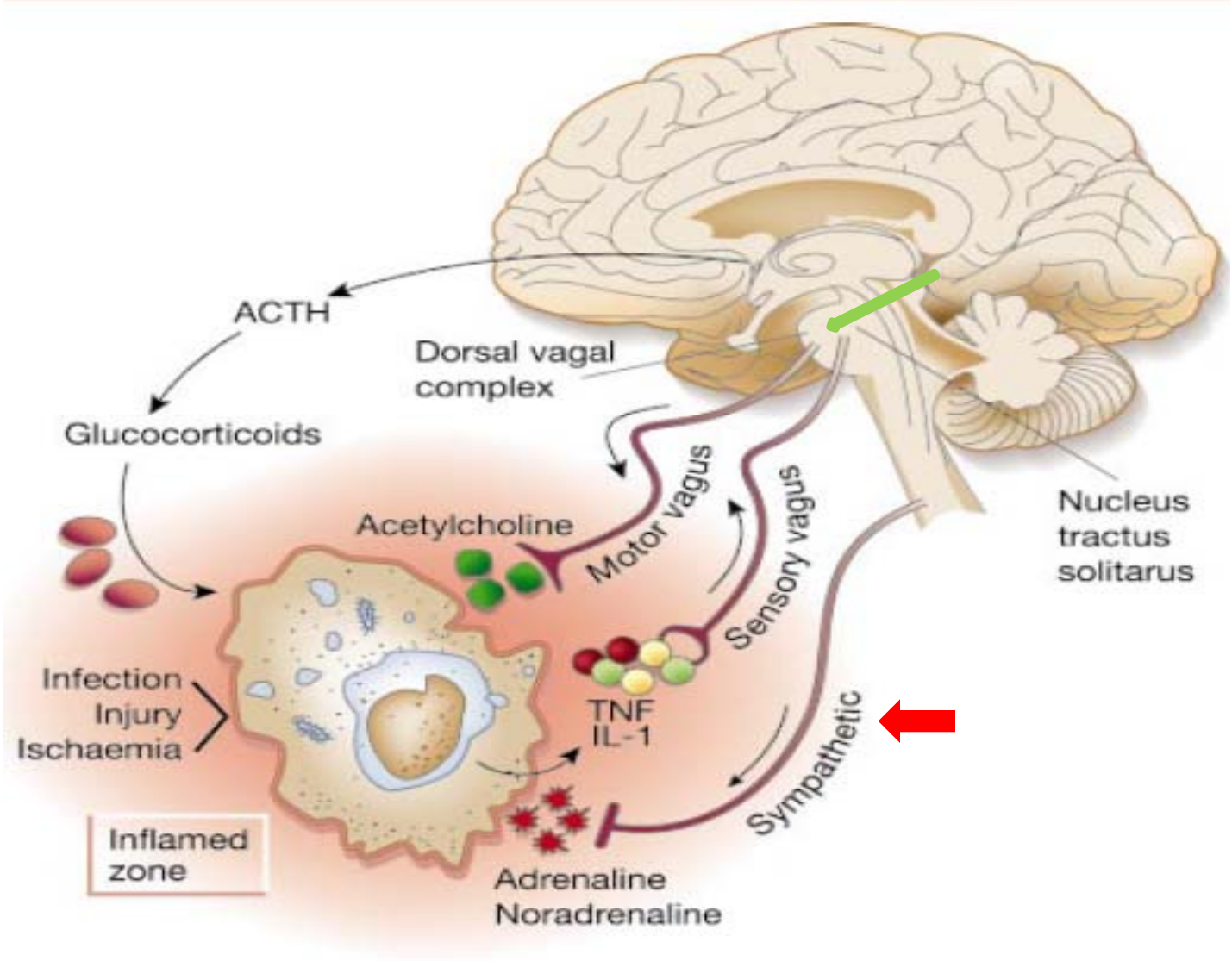
Ridotto rilascio di mediatori pro-infiammatori

↓

Risposta infiammatoria soppressa

Rittirsch D. et al.; *Nat Rev Immunol*. 2008 (modificato)

The *inflammatory reflex*



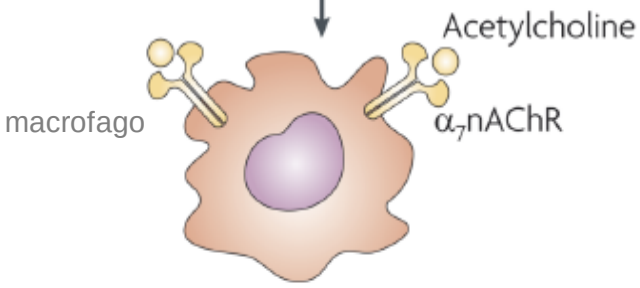
Tracey K.J.; NATURE 2002

Il sistema nervoso autonomo e la sepsi

Via colinergica anti-infiammatoria

Stimolazione del nervo vago

Rilascio di acetilcolina (o agonisti α_2nAChR)

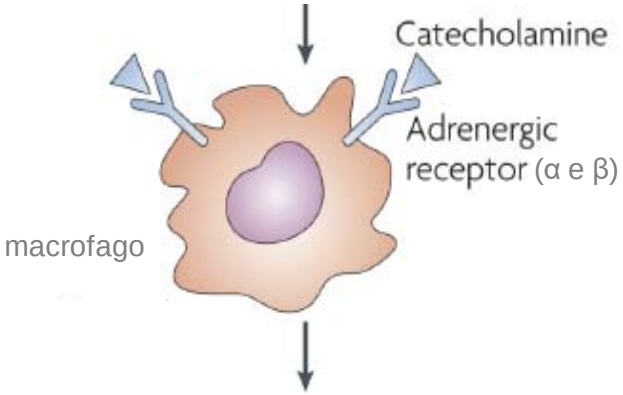


Ridotto rilascio di mediatori pro-infiammatori

Risposta infiammatoria soppressa

Via adrenergica pro-infiammatoria

Rilascio di catecolamine dalla midollare del surrene, cellule fagocitiche e linfociti



Aumentata produzione di mediatori pro-infiammatori

Amplificazione della risposta infiammatoria

Rittirsch D. et al.; *Nat Rev Immunol*. 2008 (modificato)

Sepsi → encefalopatia associata alla sepsi

Sepsi

↓

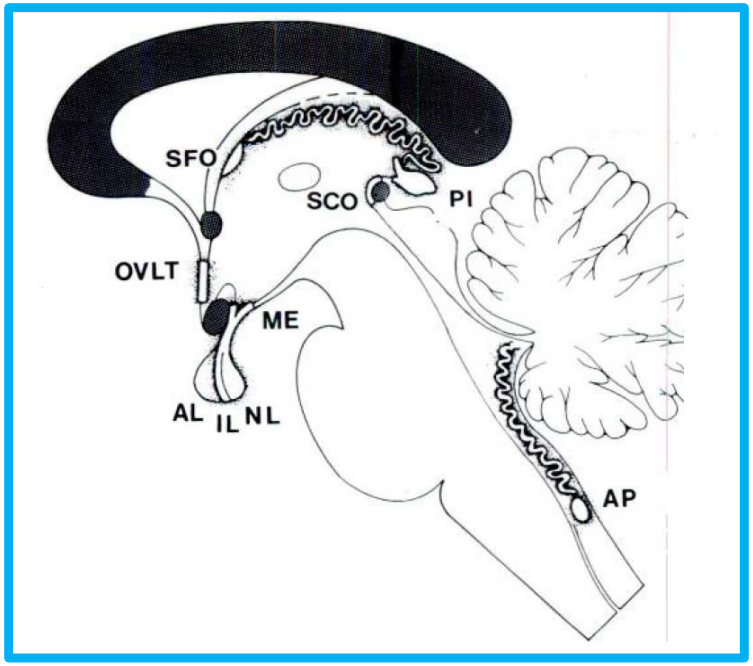
Attivazione endoteliale

↙ **Via neuronale**

↘ **Via umorale**

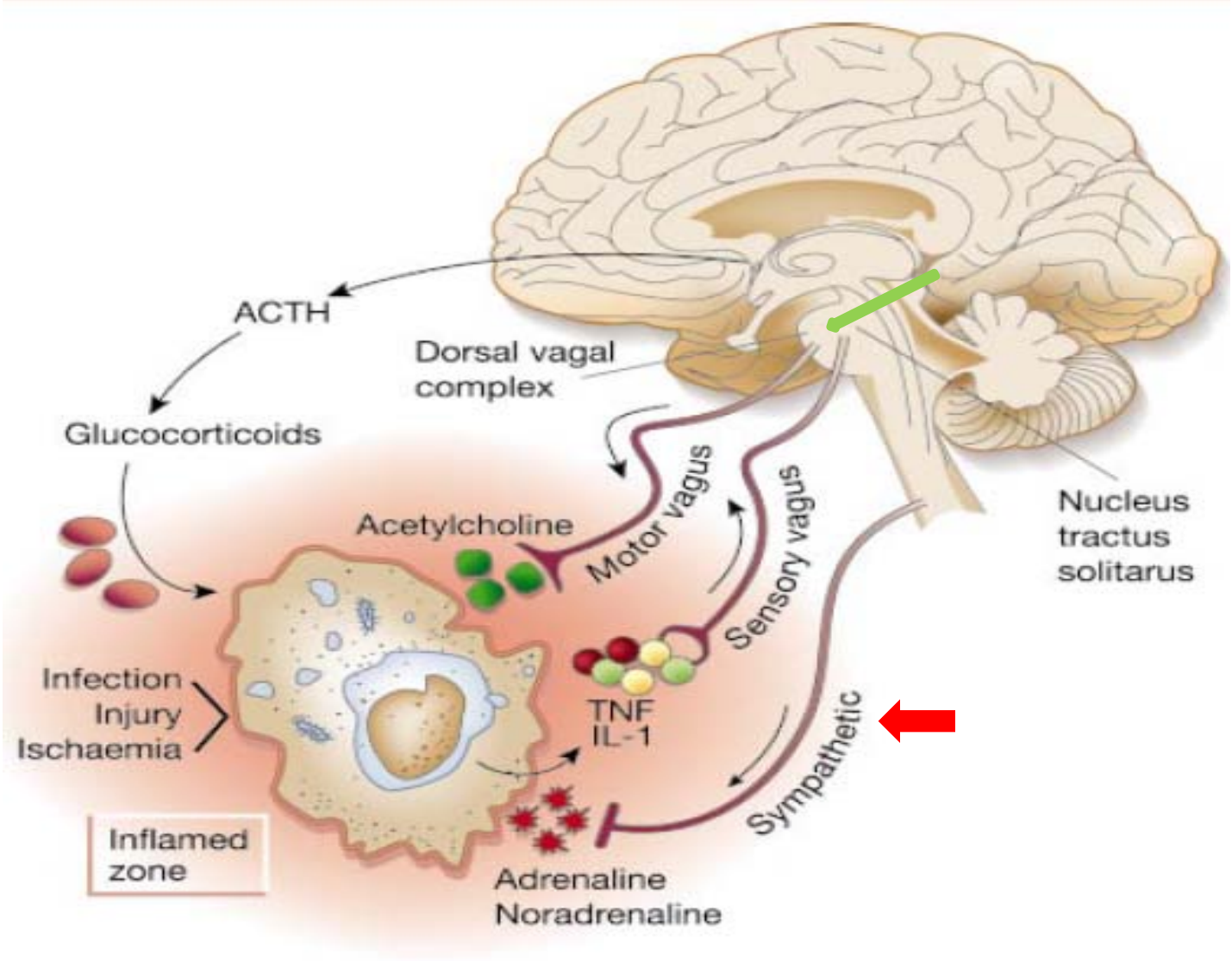
Organi circumventicolari

SF0, organo subfornicale
OVLT, organo vasculoso della *lamina terminalis*
ME, eminenza mediana
PI, epifisi
SCO, organo subcommissurale
AP, area postrema;
NL, lobo neurale dell'ipofisi



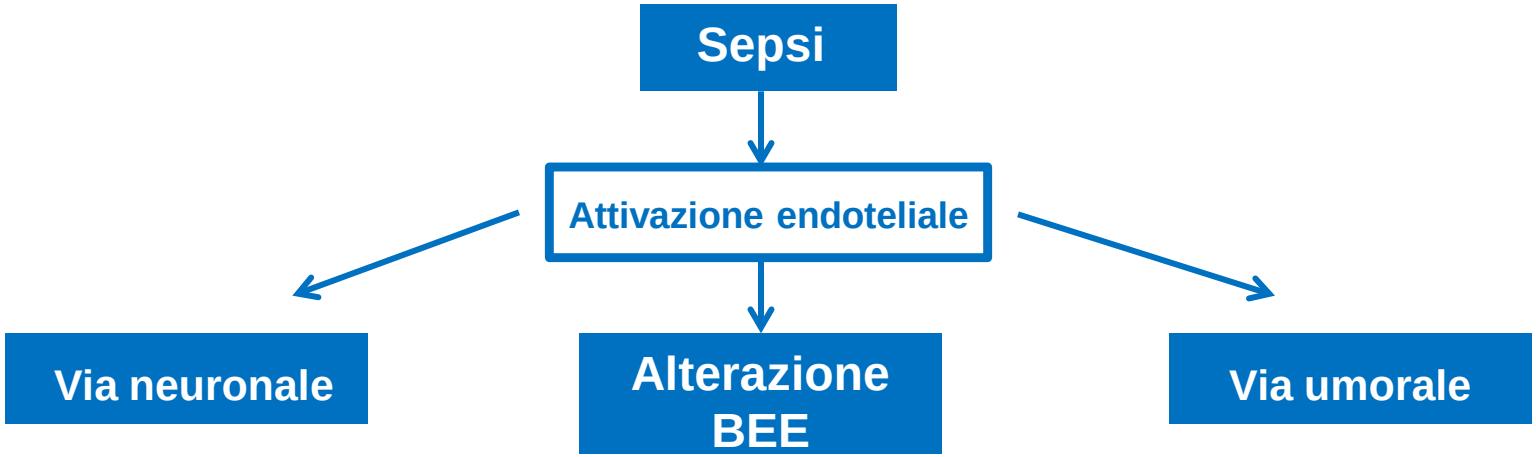
Sonneville et al. *Annals of Intensive Care* 2013

The *inflammatory reflex*



Tracey K.J.; NATURE 2002

Sepsi → encefalopatia associata alla sepsi



Per attivazione delle cellule endoteliali →rilascio mediatori (HMGB1, IL1β)

Sonneville et al. *Annals of Intensive Care* 2013

Studi recenti suggeriscono una ulteriore importanza della IL1β e *High Mobility Group Box 1* (HMGB-1) relativamente allo sviluppo del danno cerebrale nei sopravvissuti alla sepsi.

Queste citochine modulano anche *N*-methyl-D-aspartate receptors (NMDARs), recettori per il glutammato, con conseguenze negative sulle funzioni cognitive e comportamentali.

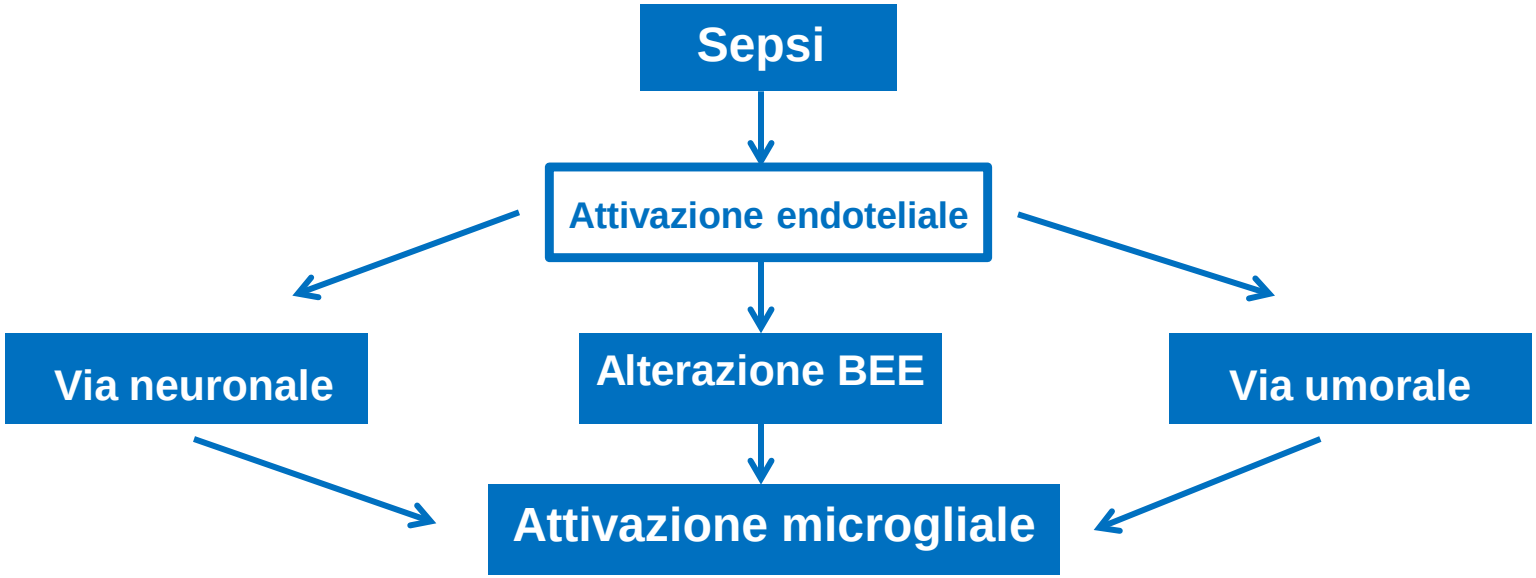
HMGB1 Mediates Cognitive Impairment in Sepsis Survivors

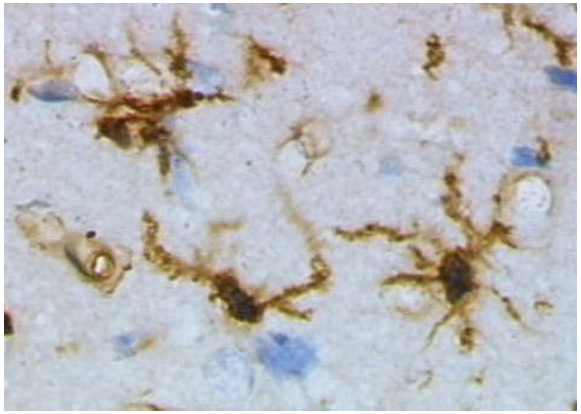
Sangeeta S Chavan,[1] Patricio T Huerta,[2*] Sergio Robbiati,[2] SI Valdes-Ferrer,[1] Mahendar Ochani,[1] Meghan Dancho,[1] Maya Frankfurt,[3] Bruce T Volpe,[4*†] Kevin J Tracey,[1†] and Betty Diamond[5†]*

Laboratories of [1]Biomedical Science, [2]Immune and Neural Networks, and [4]Functional Neuroanatomy, The Feinstein Institute for Medical Research, and [5]Center for Autoimmune and Musculoskeletal Diseases, The Feinstein Institute for Medical Research, Manhasset, New York, United States of America; and [3]Department of Science Education, Hofstra North Shore-LIJ School of Medicine, Hempstead, New York, United States of America

Molecular Medicine 2012

Sepsi → encefalopatia associata alla sepsi





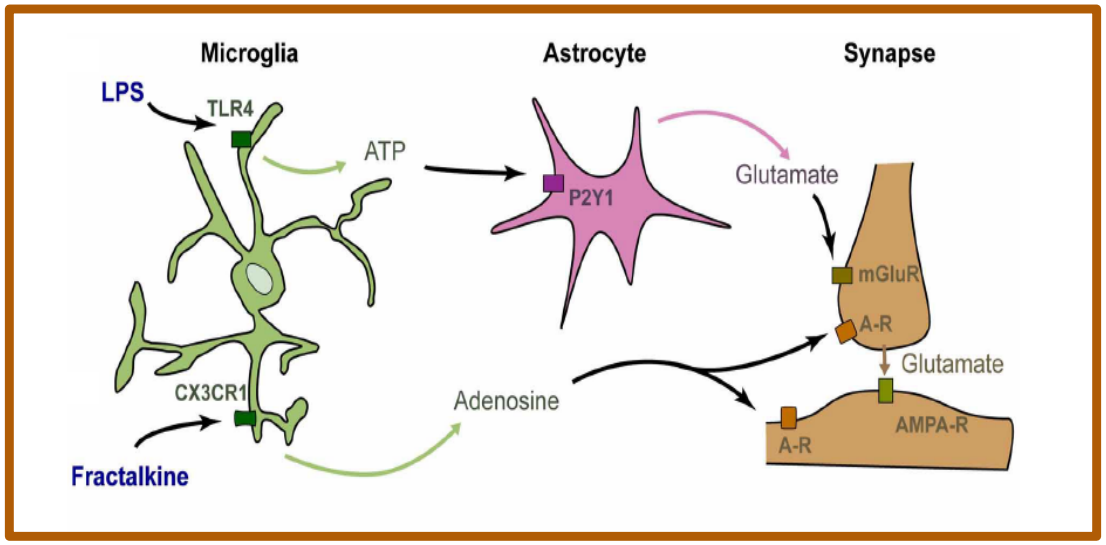
Sonneville et al. *Annals of Intensive Care* 2013

Microglia activation in sepsis: a case-control study

Afina W Lemstra*[1], Jacqueline CM Groen in't Woud[1],
Jeroen JM Hoozemans[2], Elise S van Haastert[2], Annemiek JM Rozemuller[2],
Piet Eikelenboom[1] and Willem A van Gool[1]

Journal of Neuroinflammation 2007

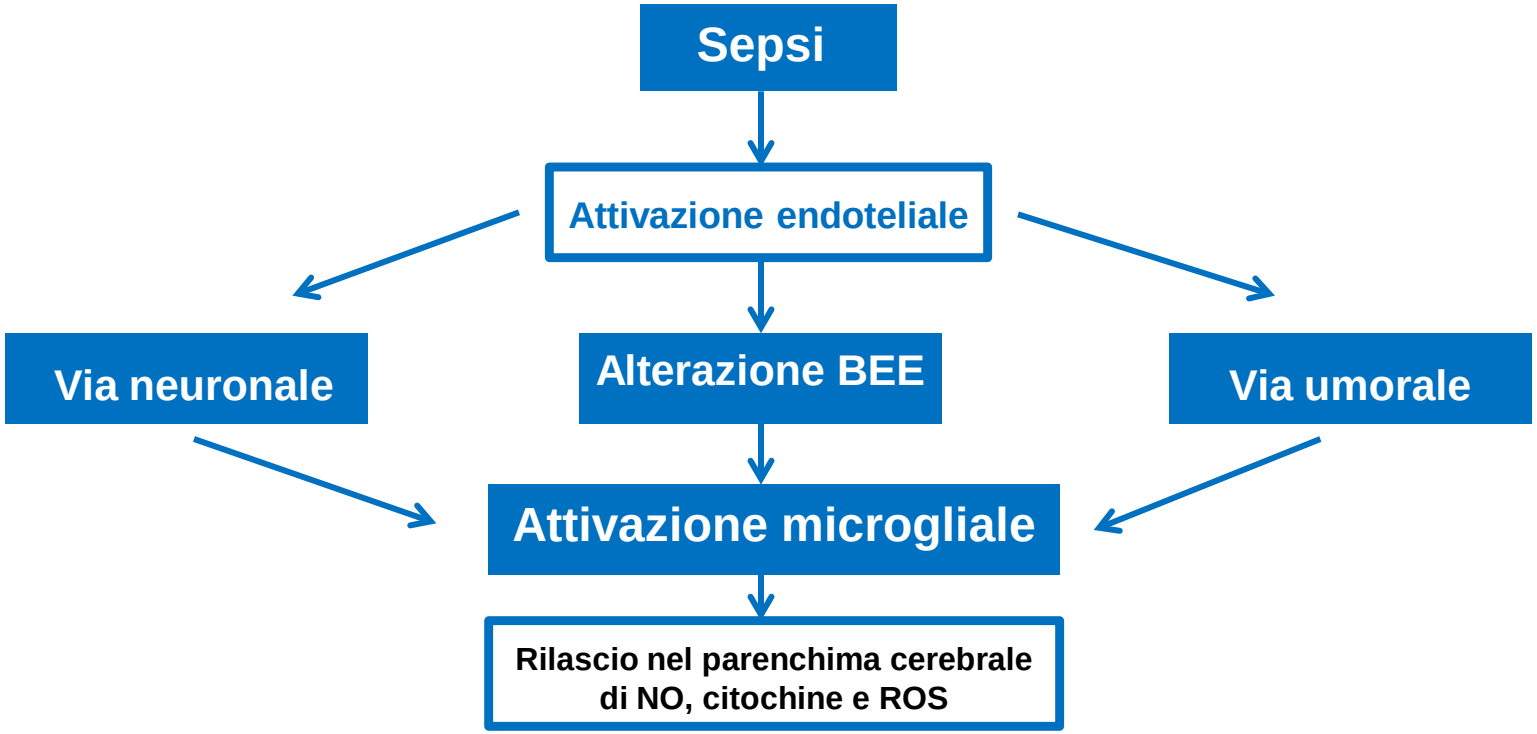
Highly active microglia may be involved in sickness behavior observed in patients with severe systemic infection



It was then demonstrated that upon LPS stimulation, microglia rapidly produce ATP, which recruits astrocytes. Astrocytes subsequently release glutamate, and this leads to <u>increased excitatory transmission</u> via a metabotropic glutamate receptor-dependent mechanism

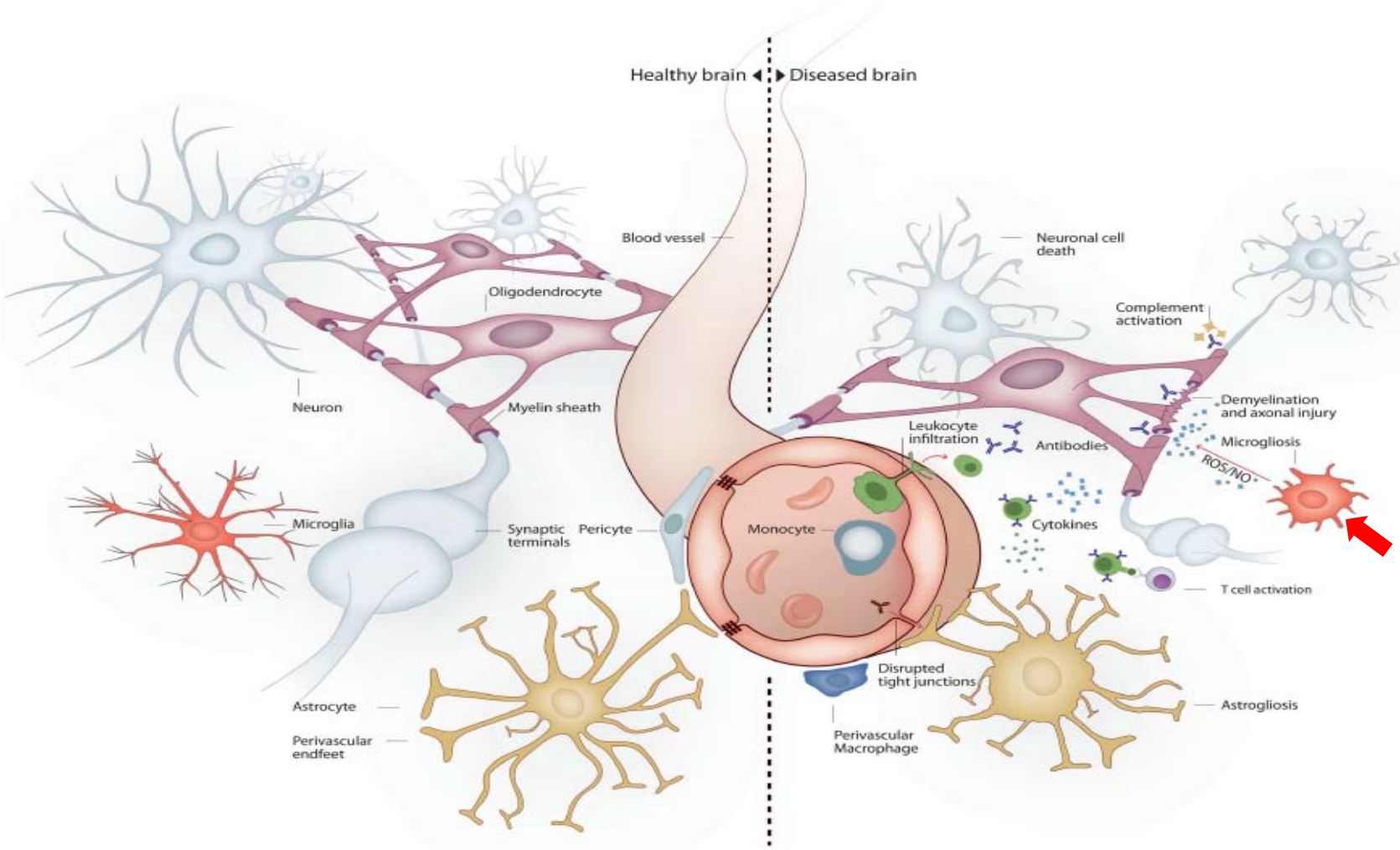
Béchade C.
Frontiers in Cellular Neuroscience
March 2013

Sepsi → encefalopatia associata alla sepsi



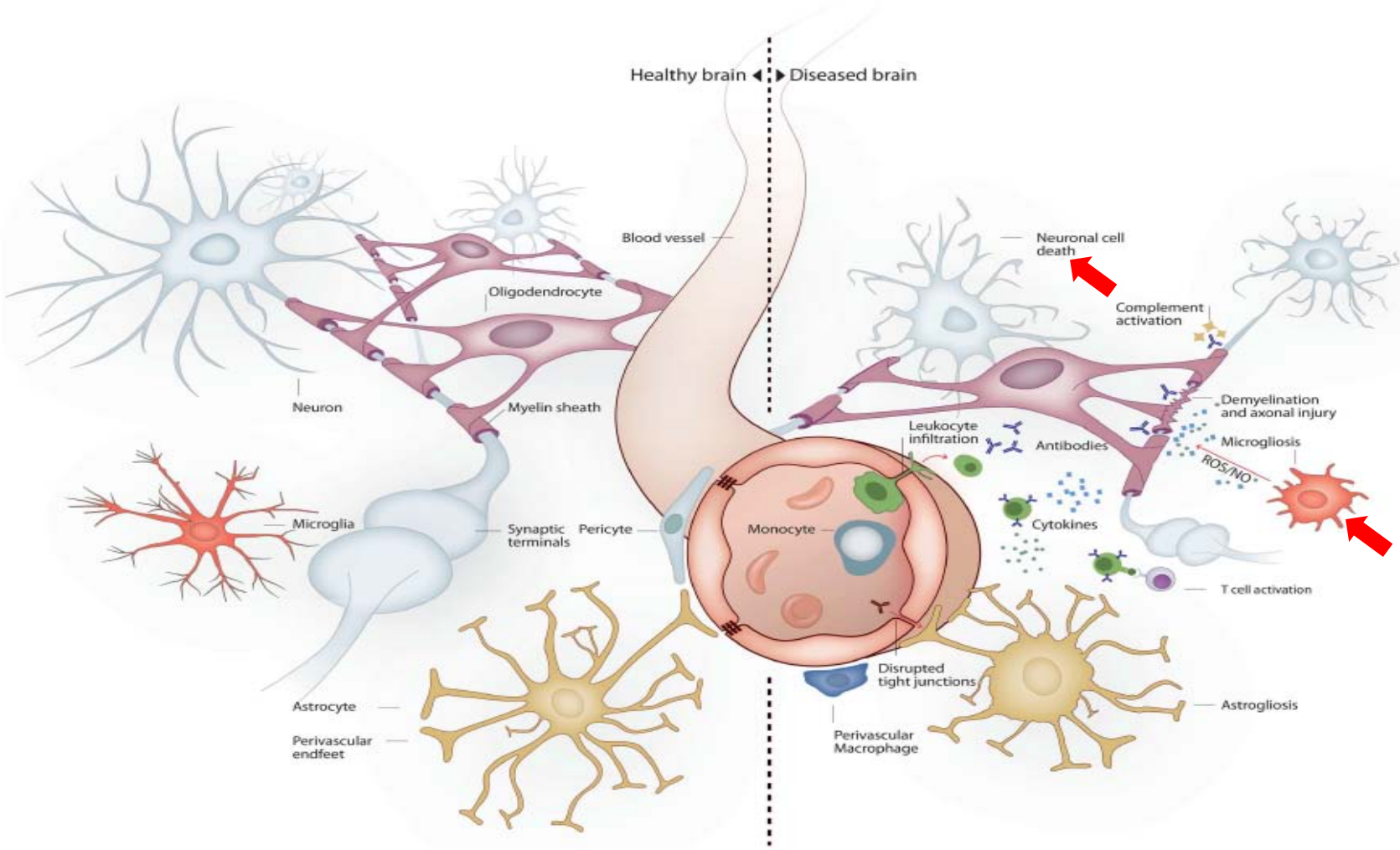
Sonneville et al. *Annals of Intensive Care* 2013

Meccanismi della sofferenza encefalica a causa della infezione sistemica



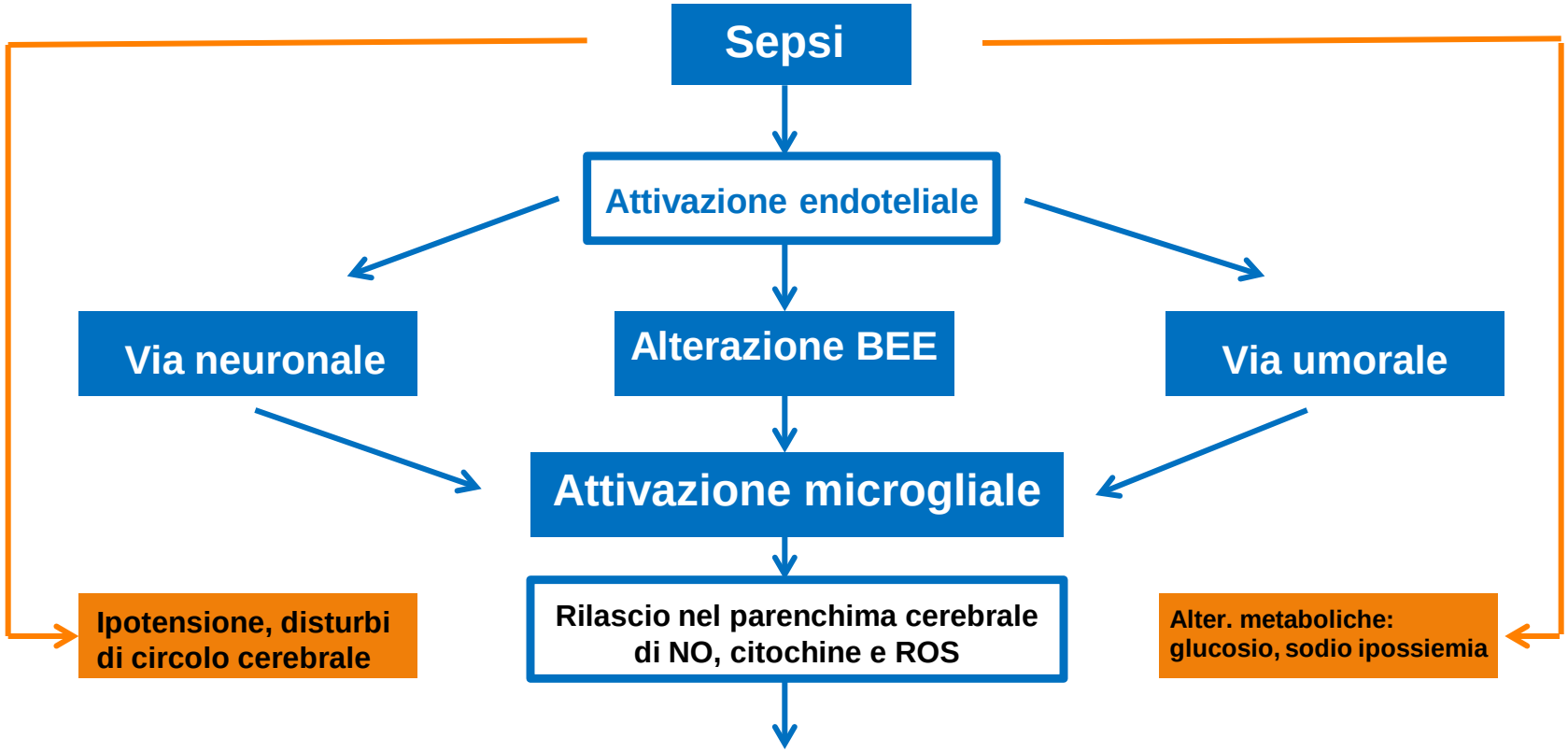
Roman Sankowski et al.; *Frontiers in Cellular Neuroscience;* February 2015

Meccanismi della sofferenza encefalica a causa della infezione sistemica



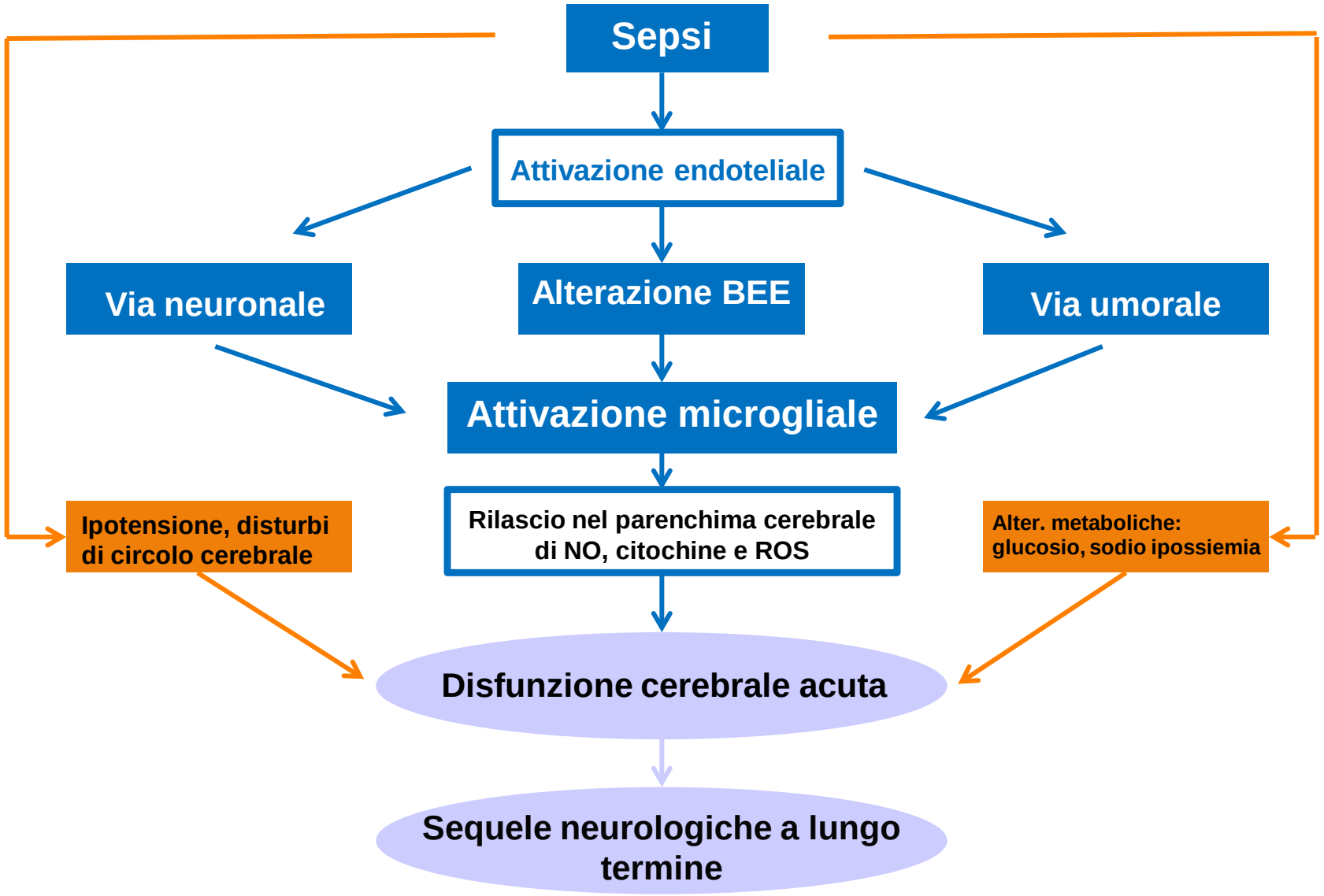
Roman Sankowski et al.; *Frontiers in Cellular Neuroscience;* February 2015

Sepsi → encefalopatia associata alla sepsi



Sonneville et al. *Annals of Intensive Care* 2013

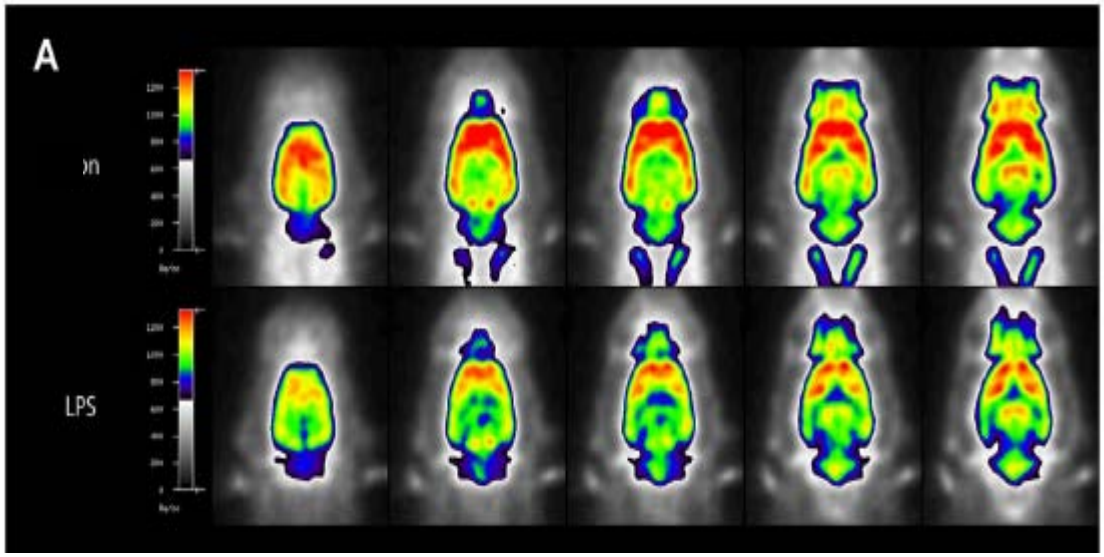
Sepsi → encefalopatia associata alla sepsi



Sonneville et al. *Annals of Intensive Care* 2013

Sepsis causes neuroinflammation and concomitant decrease of cerebral metabolism

Alexander Semmler[1], Sven Hermann[2], Florian Mormann[3], Marc Weberpals[1], Stephan A Paxian[1], Thorsten Okulla[1], Michael Schäfers[2], Markus P Kummer[1], Thomas Klockgether[1] and Michael T Heneka*[1]



L'encefalopatia sepsi-correlata è una disfunzione cerebrale grave causata dalla infiammazione sistemica in assenza di una diretta infezione dell'encefalo .

Le alterazioni del flusso ematico cerebrale sono, infatti, causate dal rilascio di molecole infiammatorie ed alterazioni metaboliche che contribuiscono alla disfunzione e morte delle cellule neuronali.

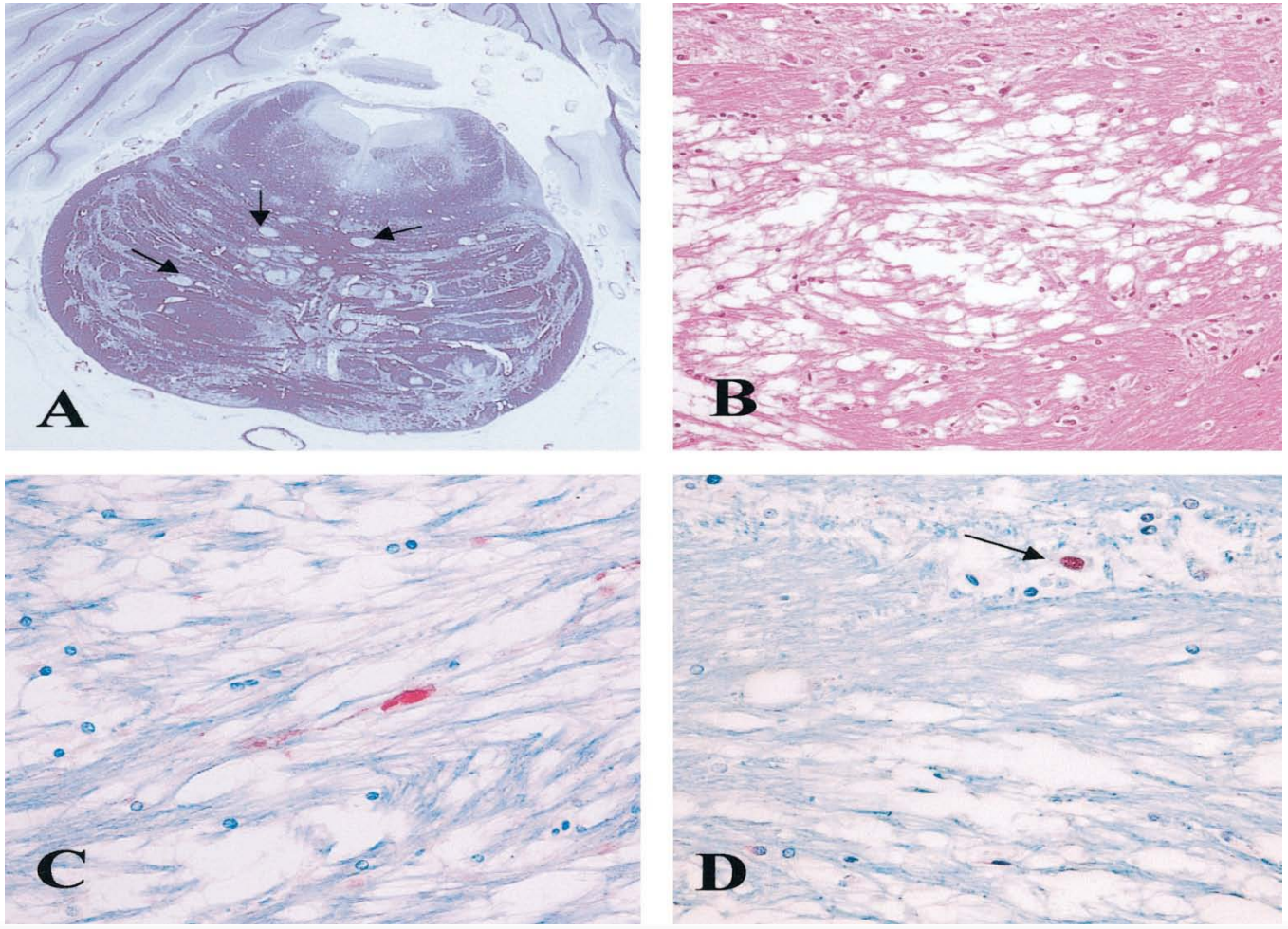
Riduzione della captazione di glucosio nella ESA : in modello animale, ratti, 5 rilevazioni di encefalo di ratto alla TC-PET con fluorodeossiglucosio, trattati in con solo veicolo (con) e con lipopolisaccaride batterico (LPS).

Differenze significative vengono evidenziate a a livello della corteccia frontale, (FC), parietale (PC) e temporale (TC).
Invece le valutazioni del nucleo caudato (NC), del talamo (THL), e dell'ippocampo (HC) non evidenziano differenze tra i due gruppi di animali.

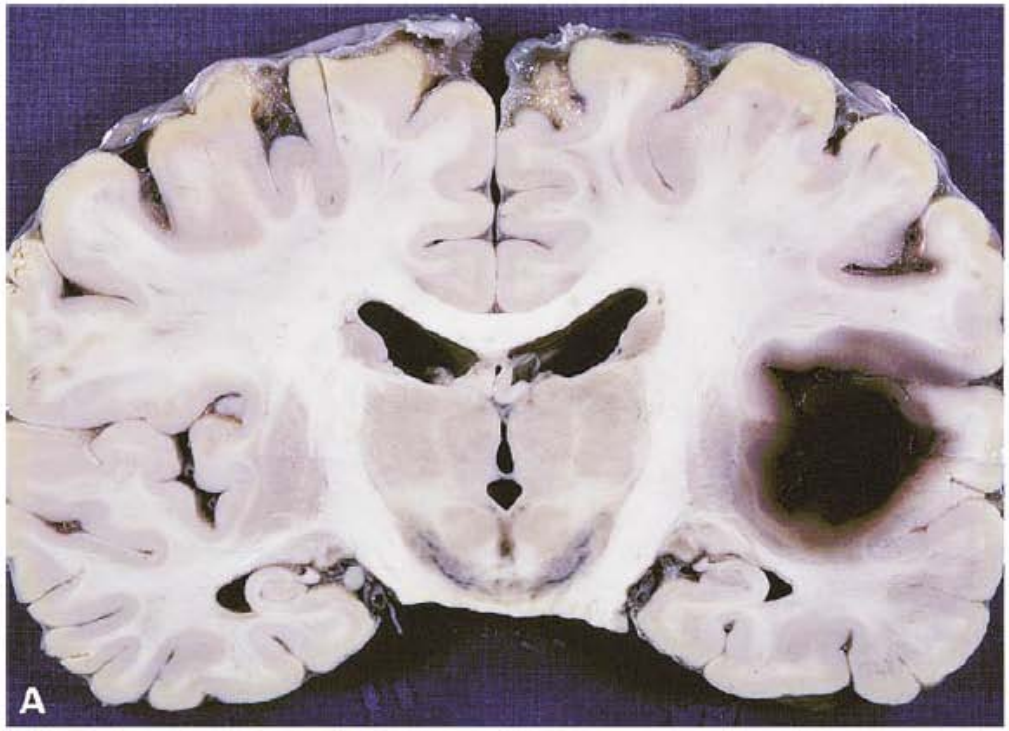
Journal of Neuroinflammation ; 2008

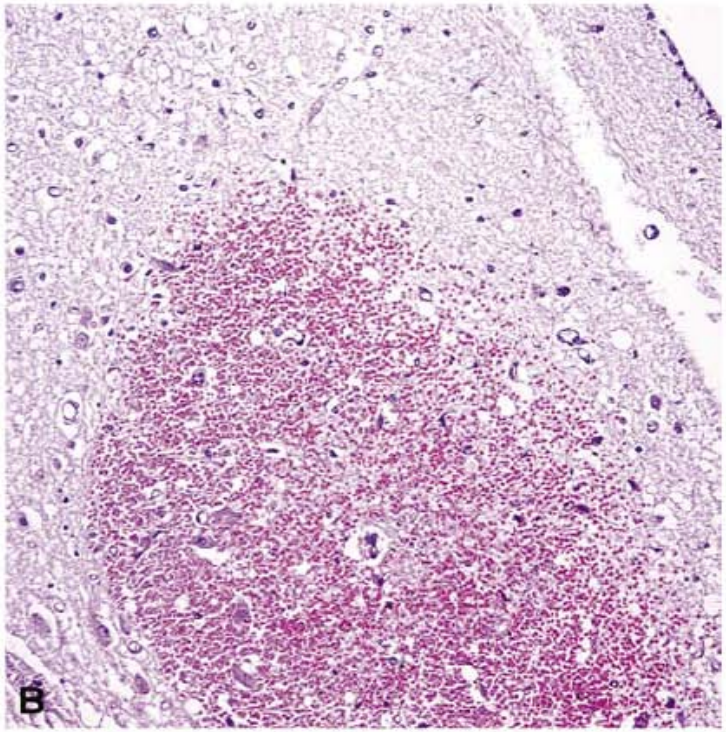
Multifocal necrotizing leukoencephalopathy in septic shock

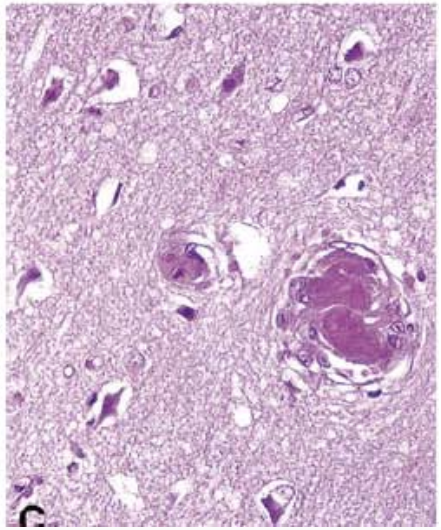
Tarek Sharshar, MD; Françoise Gray, MD; Frédéric Poron, MD; Jean Claude Raphael, MD; Philippe Gajdos, MD; Djillali Annane, MD, PhD



Sharshar T. et al.; Crit Care Med 2002





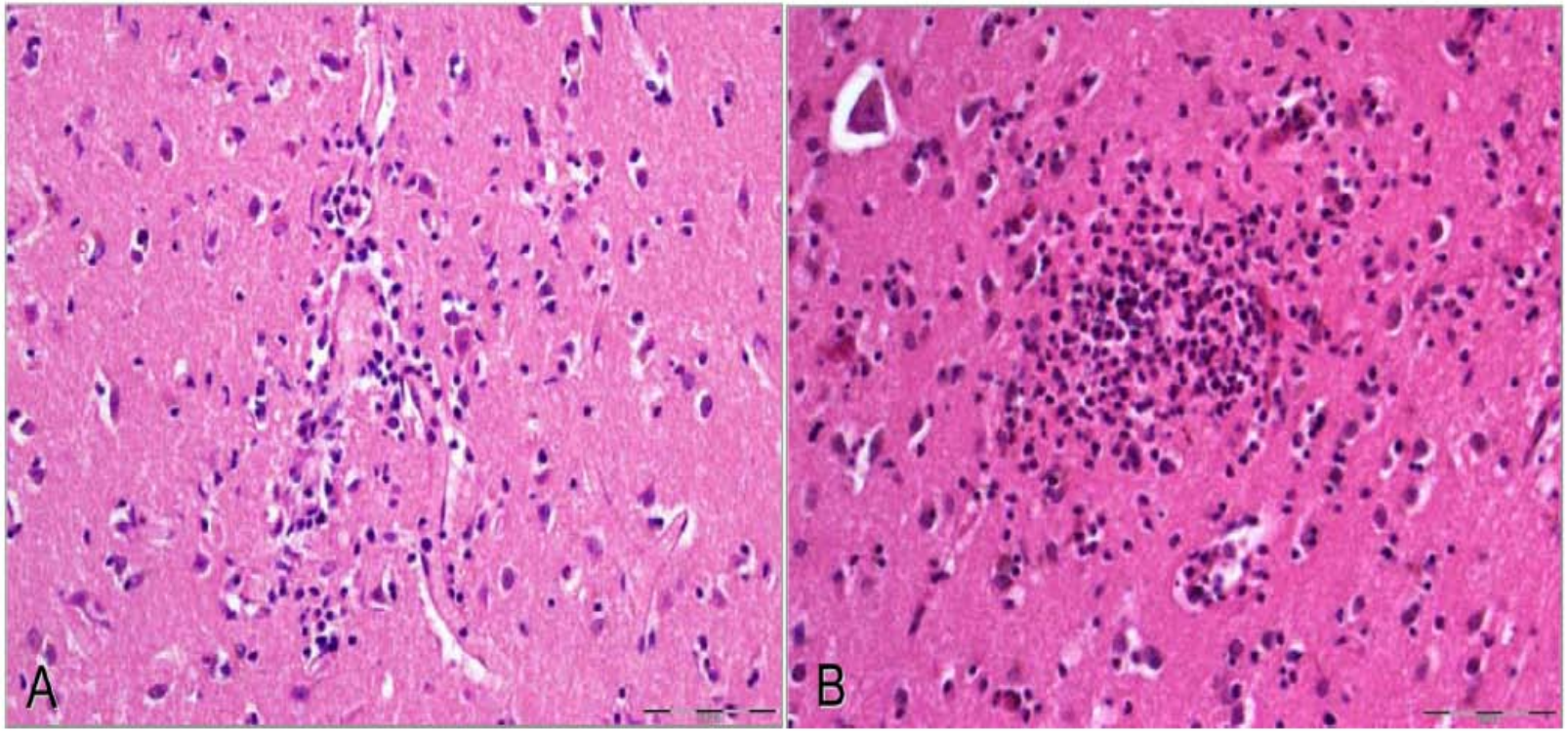


A. Estesa emorragia adiacente alla scissura silviana.

B. Piccola recente lesione emorragica petecchiale paraventricolare.

C. Microtrombo di fibrina in un caso di CID.

Tarek Sharshar et al.;*Brain Pathol 2004*



A) microglial nodule with focal accumulation of activated microglia

B) micro-abscesses that show much denser accumulation of immune cells including segmented granulocytes.

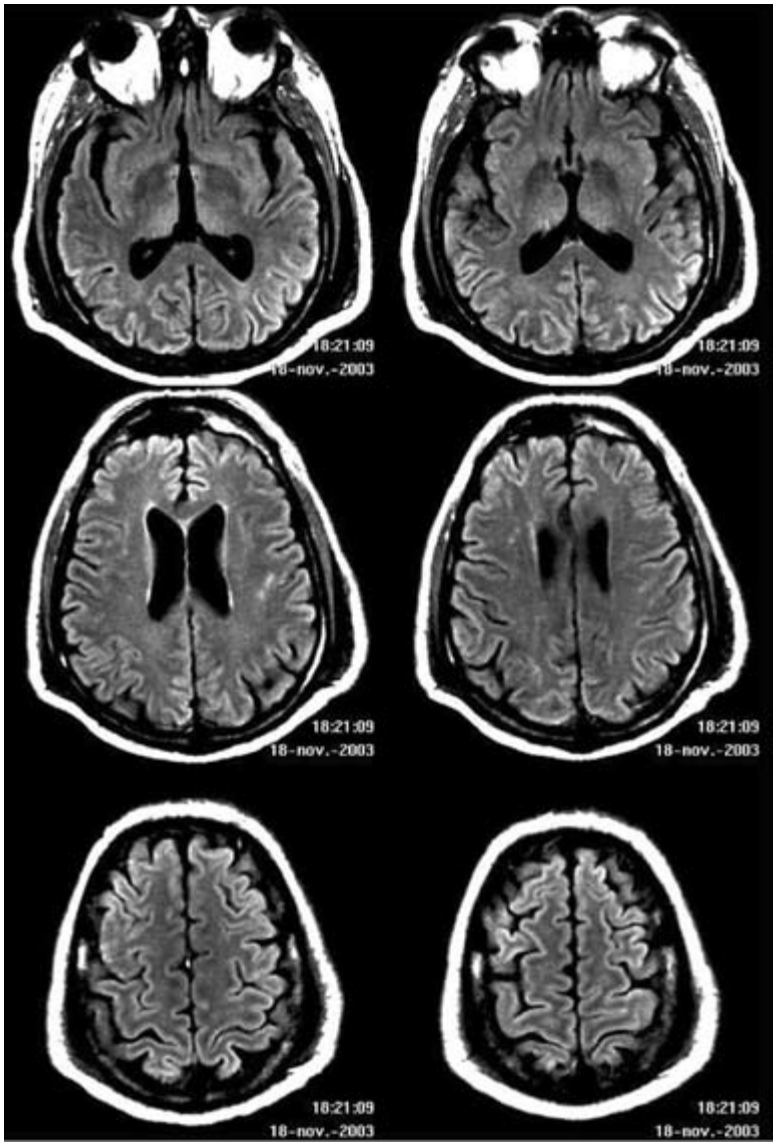
The Open Critical Care Medicine Journal, 2011, *4*, 2-7

Brain RMN patterns in sepsis

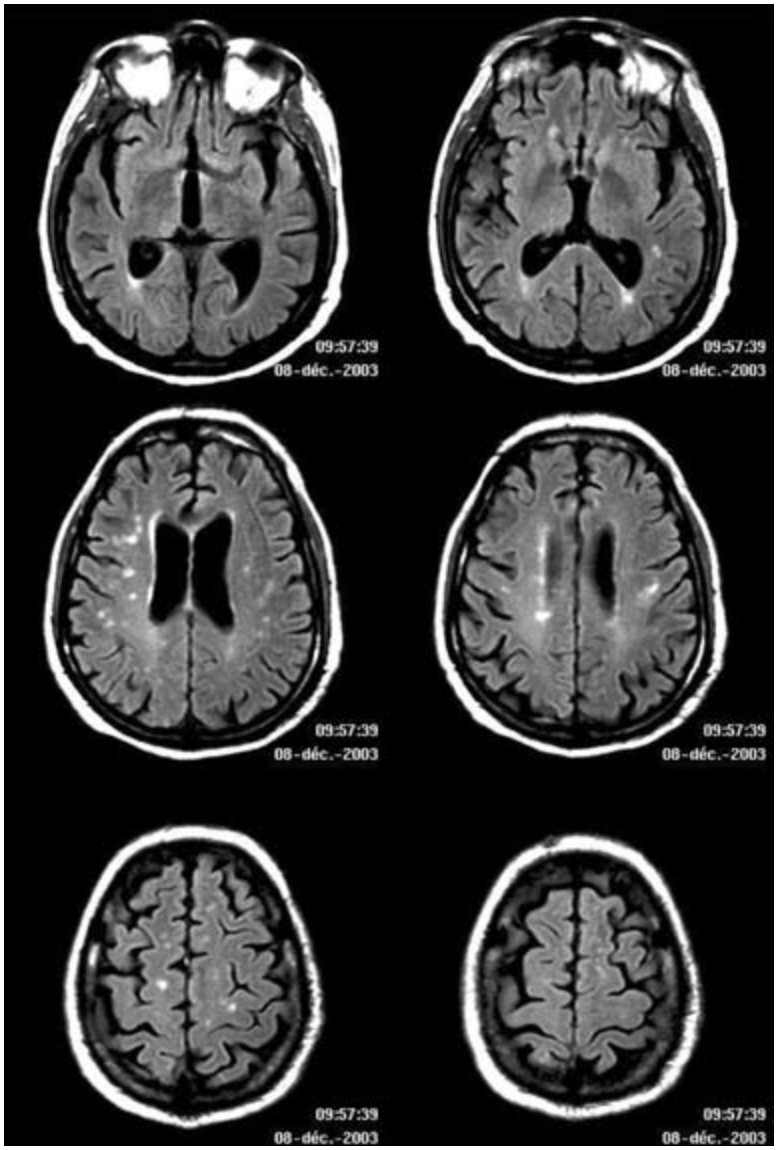
Brain MRI findings
Acute changes
Cytotoxic edema (hippocampus, cortex) ischemic lesions
Vasogenic edema
Posterior reversible encephalopathy syndrome (PRES)
Chronic changes observed in survivors
White matter disruption
Brain atrophy
(frontal cortex, hippocampus)

Sonneville et al. *Annals of Intensive Care* 2013

RM nelle fasi iniziali dello shock settico

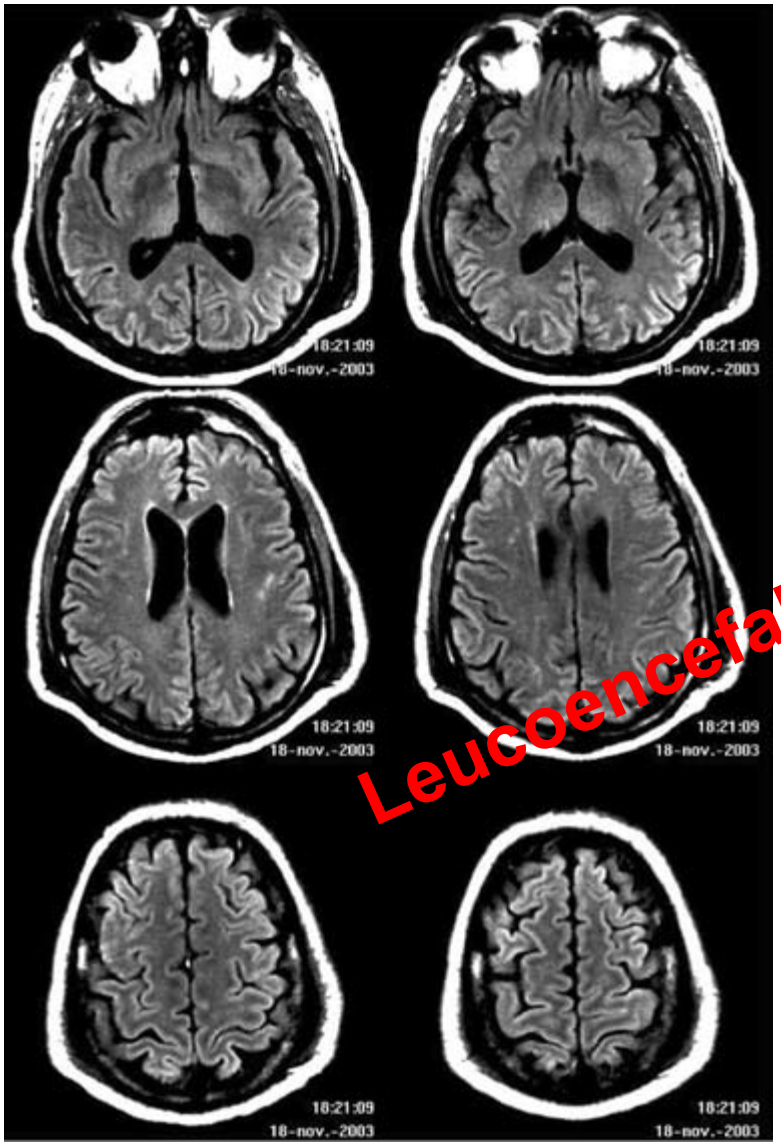


24 ore dall'inizio dello shock settico

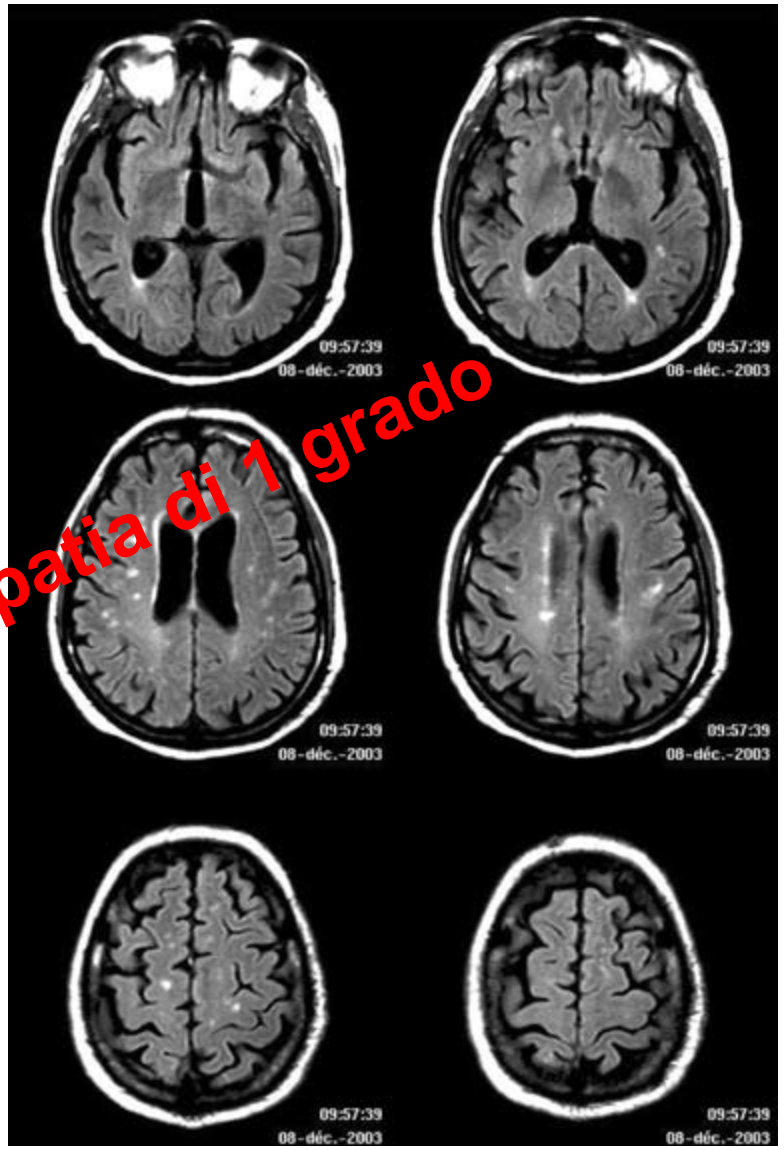


Tarek Sharshar et al.; Intensive Care Med (2007)

RM nelle fasi iniziali dello shock settico



24 ore dall'inizio dello shock settico



Leucoencefalopatia di 1 grado

Tarek Sharshar et al.; Intensive Care Med (2007)

JAMA Neurology

Magnetic Resonance Imaging Signal Hyperintensities in the Deep and Subcortical White Matter

A Comparative Study Between Stroke Patients and Normal Volunteers

Reinhold Schmidt, MD; Franz Fazekas, MD; Gertrude Kleinert, MD; Hans Offenbacher, MD; Kurt Gindl, MD; Franz Payer, MD; Wolfgang Freidl, PhD; Kurt Niederkorn, MD; Helmut Lechner, MD

Arch Neurol. 1992;49(8):825-827.

Severity of white matter lesions scored from 0 to 3, according to number and size of lesions:

grade 0 (normal);

grade 1 (punctiform)

grade 2 (patchy or confluent) and

grade 3 (diffuse)

Brain MRI respectively performed on the 3rd and 30th days after the onset of septic shock.

Seventy-nine-year-old woman with ARDS due to *Streptococcus pneumoniae*

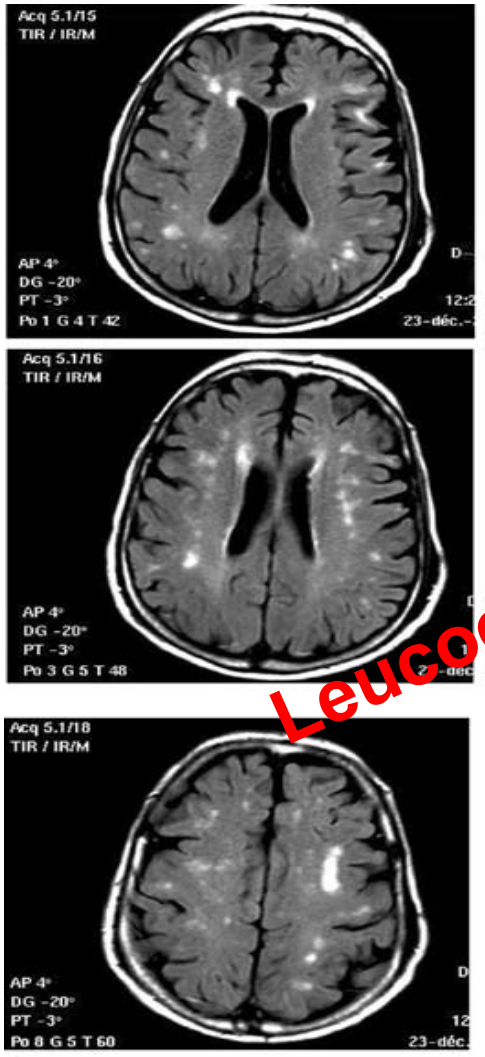


Fig. 1

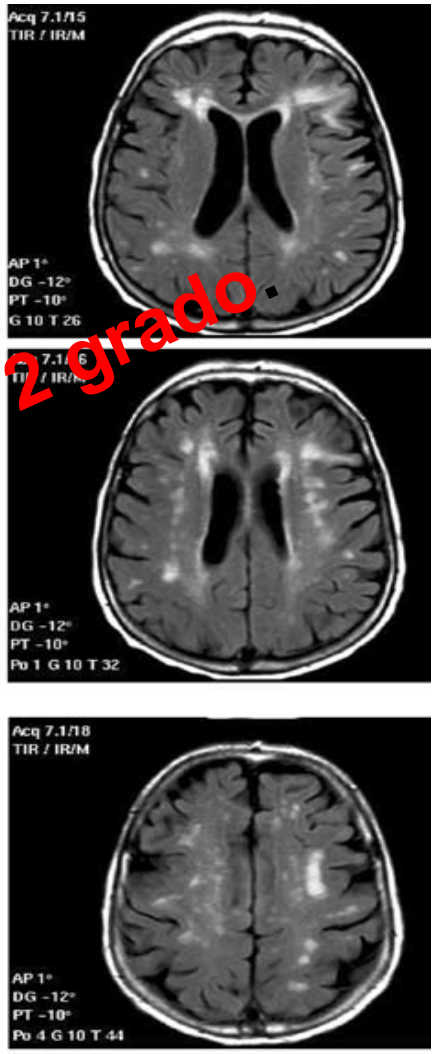


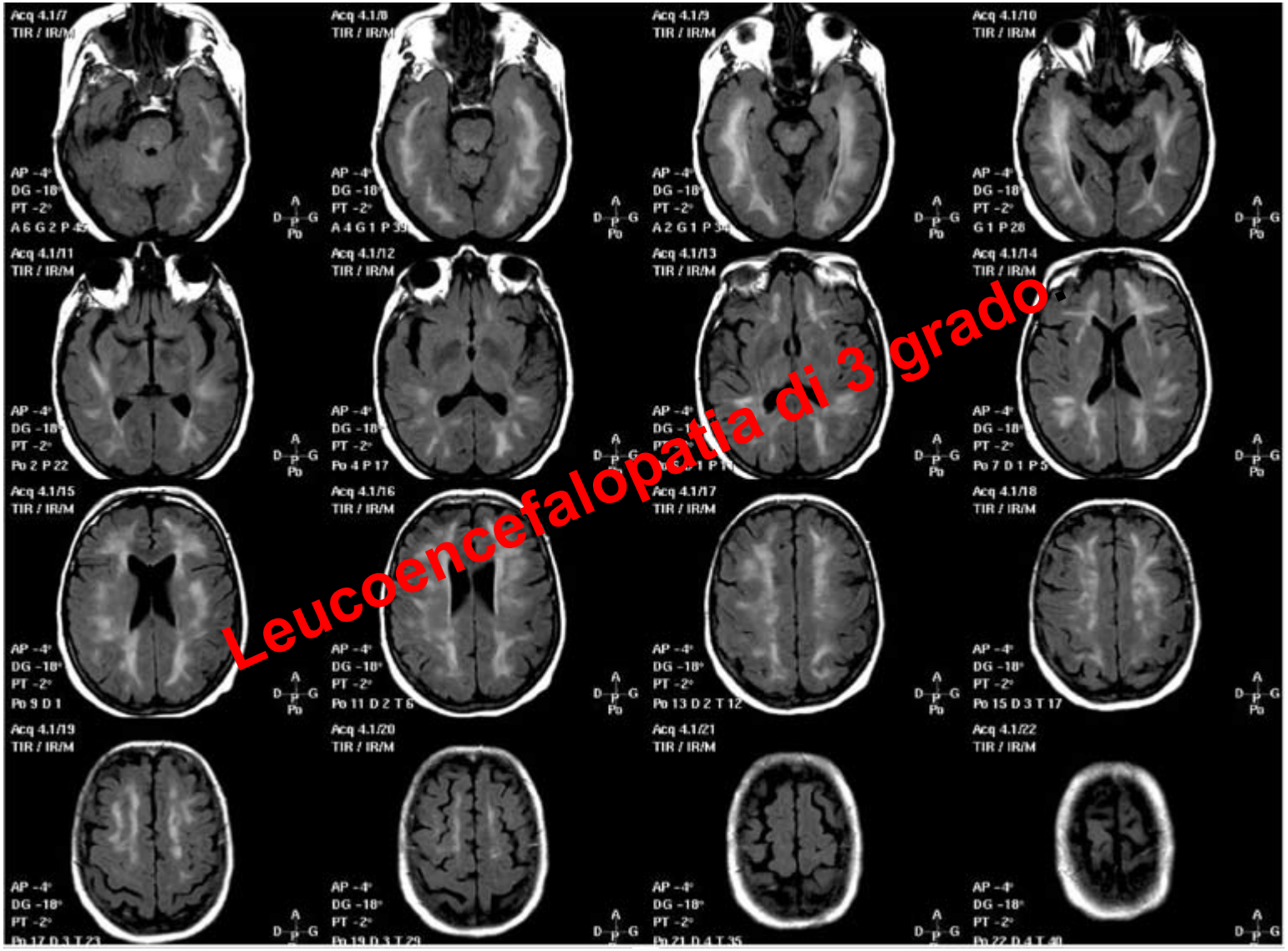
Fig. 2

Leucoencefalopatia di 2 grado.

Tarek Sharshar et al.; Intensive Care Med (2007)

MRI performed on the 4th day after the onset of septic shock

Sixty-seven-year-old woman with septicaemia due to *Pseudomonas aeruginosa*



Tarek Sharshar et al.; Intensive Care Med (2007)

Principali cause di
Posterior Reversible Encephalopathy Syndrome

COMUNI	RARE
Ipertensione arteriosa farmacoresistente Eclampsia Farmaci immunosoppressivi e citotossici Insufficienza renale acuta/cronica	Collagenopatie Lupus erimatoso sistemico Poliartrite nodosa Sindrome di Behcet Porpora trombotica trombocitopenica AIDS Porfiria acuta intermittente

Posterior Reversible Encephalopathy Syndrome in Infection, Sepsis, and Shock

W.S. Bartynski
J.F. Boardman
Z.R. Zeigler
R.K. Shadduck
J. Lister

Infezione/sepsi/shock possono essere importante causa di **PRES *encefalopatia posteriore reversibile***, particolarmente se è in causa infezione da **germi gram-positivi** .

Am J Neuroradiol 2006

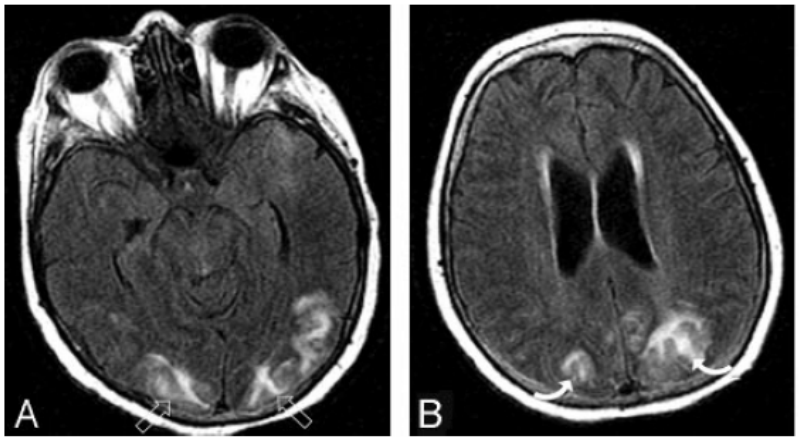
ORIGINAL RESEARCH

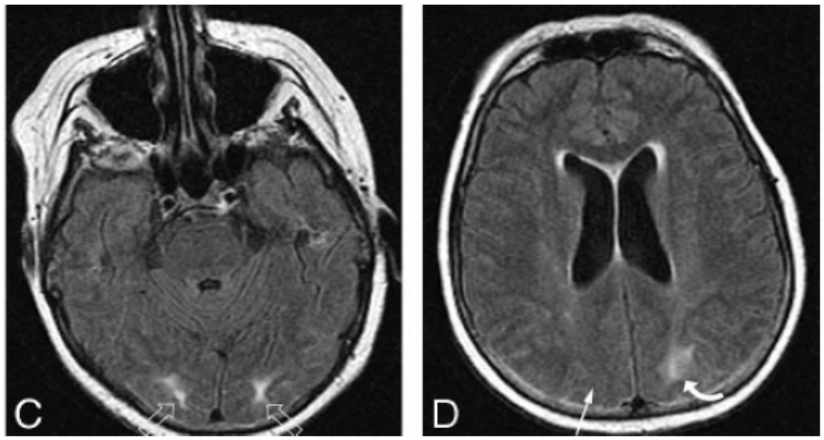
Posterior Reversible Encephalopathy Syndrome in Infection, Sepsis, and Shock

W.S. Bartynski
J.F. Boardman
Z.R. Zeigler
R.K. Shadduck
J. Lister

AJNR Am J Neuroradiol 27:2179–90 | Nov-Dec 2006 |

CONCLUSION: Infection/sepsis/shock may be an important cause of PRES, particularly in relation to infection with gram-positive organisms.





A-B, MR (FLAIR sequence) evidenzia edema vasogenico nelle regioni occipitali e parietali bilateramente tipiche di una PRES; le lesioni appartengono alla sostanza bianca, ma *distanti dai ventricoli cerebrali.*

C-D, MR (FLAIR sequence) **ad un mese** dalle precedenti ; quasi completa risoluzione dell'edema nelle regioni occipitali e parietali di sinistra ; completa risoluzione nelle aree parietali di destra.

JOURNAL OF CLINICAL NEUROPHYSIOLOGY
Wolters Kluwer Health | Lippincott Williams & Wilkins

The electroencephalogram in sepsis-associated encephalopathy.

Young GB, Bolton CF, Archibald YM, Austin TW, Wells GA.
1992 Jan;9(1):145-52.

We studied **62 patients** with positive blood cultures, patients were divided into three clinical groups:

- ✓ **the EEG *was more sensitive than our clinical criteria for encephalopathy,***
- ✓ ***showed features that were, when considered with clinical and laboratory characteristics, compatible with a potentially reversible encephalopathy,*** and
- ✓ ***had well-defined categories that correlated with percent mortality, even within a single clinical group.***

1. **non-encephalopathy (NE)**
2. **mild encephalopathy (ME),** and
3. **severe encephalopathy (SE)**

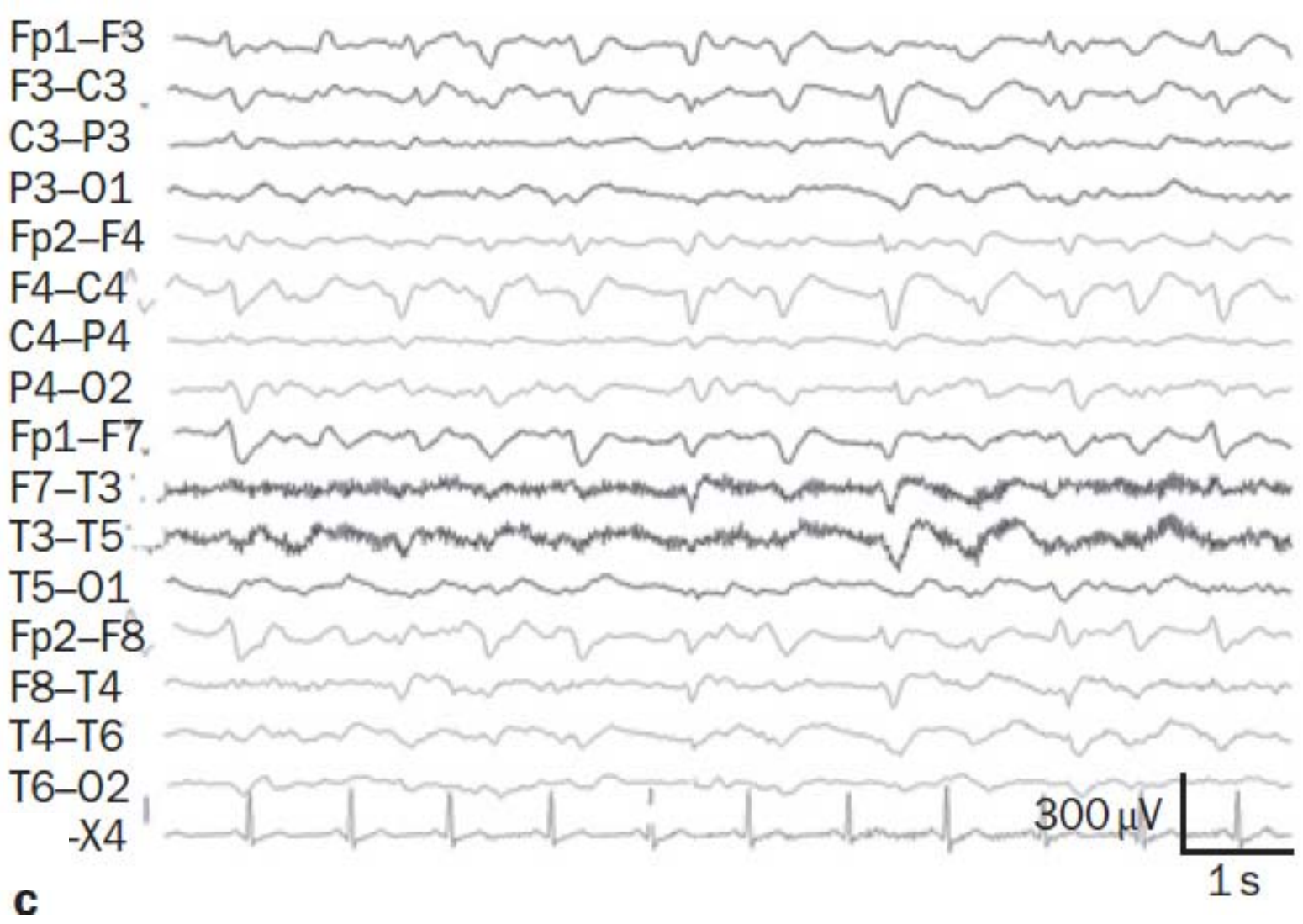
We conclude that the EEG is a sensitive index of brain function in septic encephalopathy and that it is especially useful in the intensive care monitoring of patients with sepsis.

Electroencephalographic patterns in sepsis

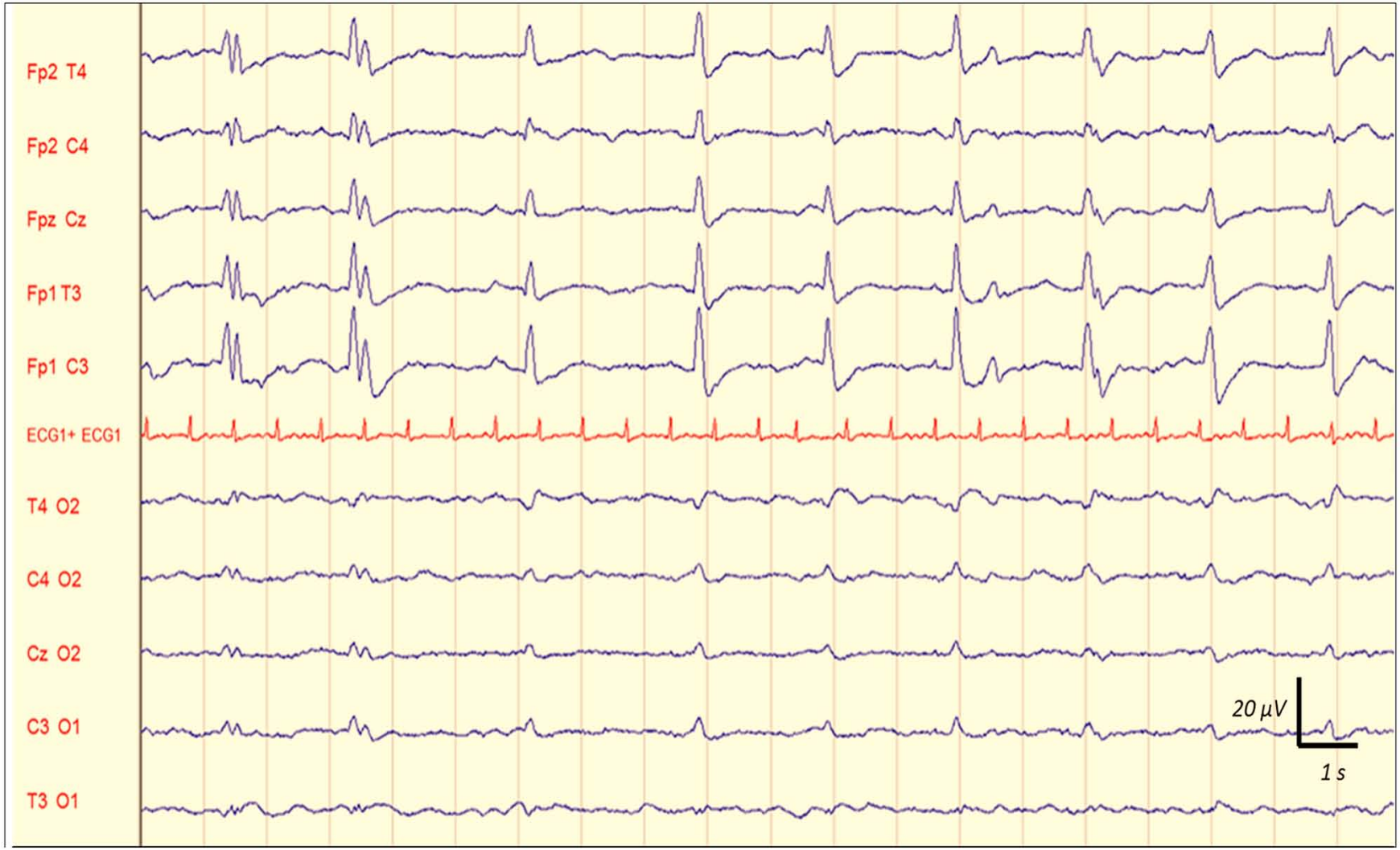
Electroencephalographic findings	Association with adverse outcome
Normal EEG	0
Theta (mild generalized slowing)	+
Delta (severe slowing)	+
Triphasic waves	+
Periodic epileptiform discharges	+
Electrographic seizures	++
Generalized suppression or burst-suppression	+++

Sonneville et al. *Annals of Intensive Care* 2013

Representative example of EEG showing teta delta e triphasic waves in a septic ICU patient.



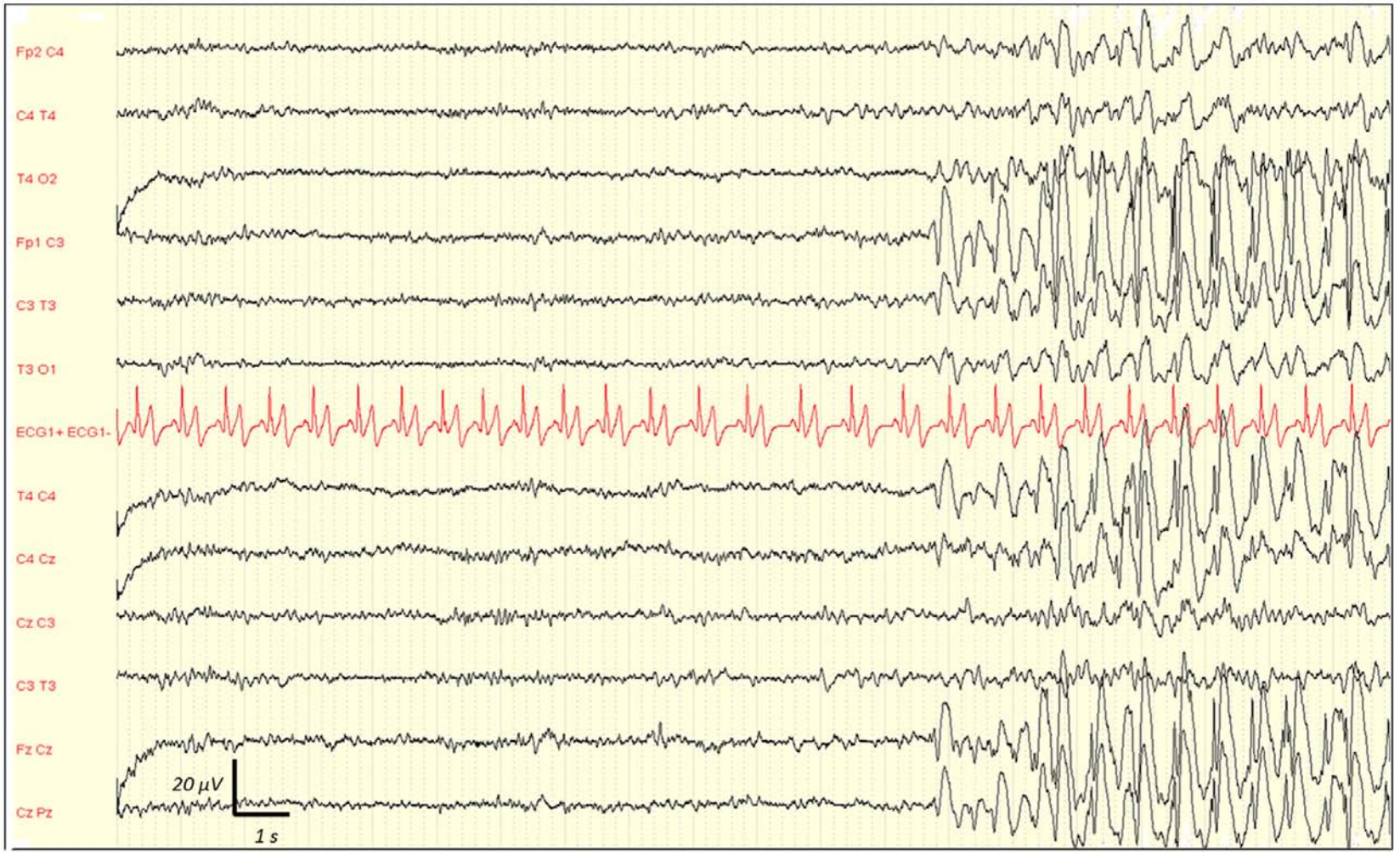
Representative example of EEG showing periodic discharges (PDs) in a septic ICU patient.



Eric Azabou et al.; PLOS ONE: October 8, 2015

Representative example of EEG showing the onset of an electrographic seizure (ESZ) in a septic ICU patient.

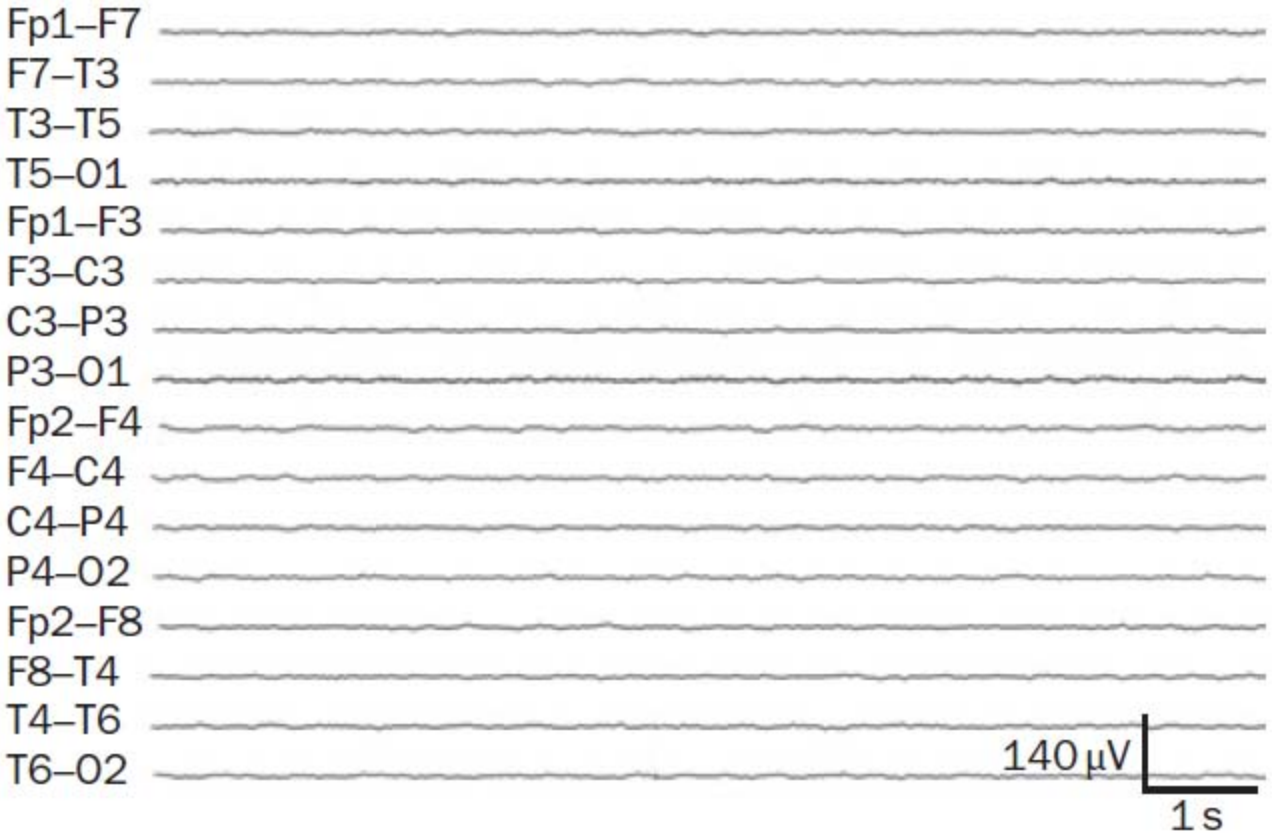
++



Eric Azabou et al.; PLOS ONE: October 8, 2015

Generalized suppression from a comatose patient

+++



Biomarkers in septic encephalopathy: a systematic review of clinical studies

Biomarcadores na encefalopatia séptica: revisão sistemática dos estudos clínicos

Paula Veriato Zenaide[1], Dimitri Gusmao-Flores[2,3]

Neuron-specific enolase (NSE)

S100 beta protein

?

Rev Bras Ter Intensiva; 2013

Biomarkers in septic encephalopathy: a systematic review of clinical studies

Biomarcadores na encefalopatia séptica: revisão sistemática dos estudos clínicos

Paula Veriato Zenaide[1], Dimitri Gusmao-Flores[2,3]

Conclusion

S100 beta and neuronspecific enolase are promising biomarkers for diagnosing and monitoring patients with septic encephalopathy, but more research is necessary.

Zenaide P.V.; *Rev Bras Ter Intensiva*; 2013

JAMA The Journal of the American Medical Association

JAMA. 2016;315(8):775-787.

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

For the Third International Consensus Definitions for Sepsis and Septic Shock

Manu Shankar-Hari, MD, MSc[1,2]; Gary S. Phillips, MAS[3]; Mitchell L. Levy, MD[4]; Christopher W. Seymour, MD, MSc[5]; Vincent X. Liu, MD, MSc[6]; Clifford S. Deutschman, MD[7,8,9]; Derek C. Angus, MD, MPh[5,10]; Gordon D. Rubenfeld, MD, MSc[11,12]; Mervyn Singer, MD, FRCP

for the Sepsis Definitions Task Force

…….septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone.

Adult patients with septic shock can be identified using the clinical criteria of *hypotension requiring vasopressor therapy to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.*

Critical Care Medicine

Society of Critical Care Medicine
The Intensive Care Professionals

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

A consensus committee of 68 international experts representing 30 international organizations

Potential strategies to reduce brain dysfunction in ICU patients

Pharmacological measures	Type of study
Reduce use of benzodiazepines and opioids	Observational studies
Perform daily sedation stops	RCT
Use dexmedetomidine (versus benzodiazepines or propofol) as sedative (Dexdor)	RCT
Pain assessment: sedation – analgesia – delirium protocol	Observational studies
Prevention of metabolic disturbances (severe hypoxemia, fever, dysnatremia(s), prolonged hyperglycemia…)	Observational studies
Nonpharmacological measures	
Sleep protocol	RCT (non-critical care setting)
Reorientation and cognitively stimulating activities	
Rehydration	
Use of eyeglasses, magnifying lenses, and hearing aids	
Avoid use of physical restraints	Observational studies
Early mobilization	RCT

RCT randomized controlled trial.

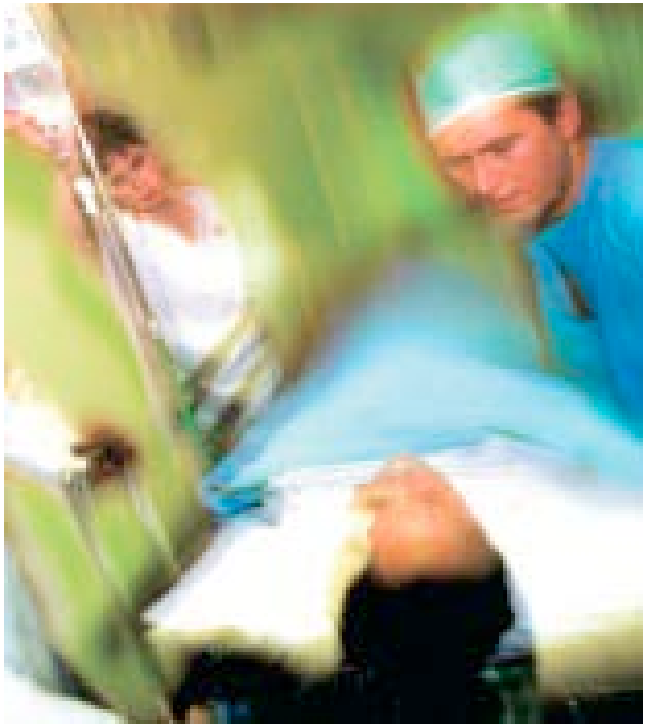
Sonneville et al. *Annals of Intensive Care* 2013

Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori*-designed analysis of the MENDS randomized controlled trial

Table 2: Outcomes of patients with and without sepsis*

	Patients with sepsis	
Outcome variable	**DEX (n = 31)**	**LZ (n = 32)**
Duration of brain organ dysfunction		
Delirium/coma-free days**	6.1 (4.3)	2.9 (3.2)
Delirium-free days†	8.1 (3.1)	6.7(2.9)
Coma-free days§	9.4 (2.9)	5.9 (4.2)
Other clinical outcomes		
MV-free days‡	15.2 (10.6)	10.1 (10.3)
ICU days	13.4 (15.1)	12.2 (9.8)
28-day mortality	16%	41%

Pandharipande *et al. Critical Care* 2010



Grazie per l'attenzione !