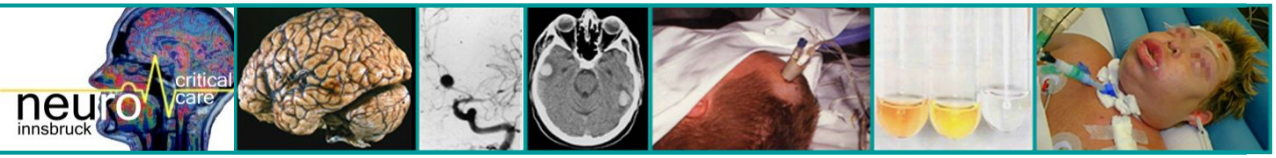

Impairment of consciousness with and without fever

Erich Schmutzhard

Department of Neurology, NICU
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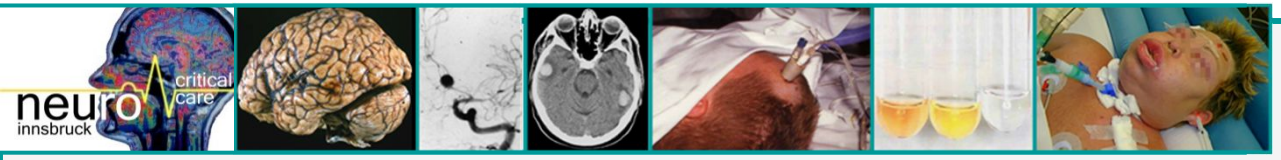
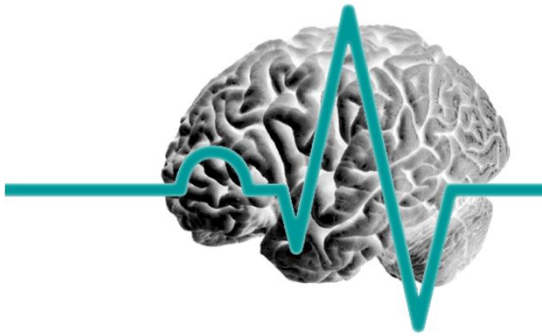
and
Bernhard-Nocht-Institute for Tropical Medicine
University Medical Centre Hamburg Eppendorf, Germany
and
Center for Global Health
Technical University Munich, Germany



Conflicts of Interest:

EAN Task Force: **Neurology in Sub-Sahara Africa**
Africa-Uninet Coordinator of the Medical University Innsbruck, Austria
ASEA Uninet Coordinator of the Medical University Innsbruck, Austria
Eurasia-Pacific Uninet Coordinator of the Medical University Innsbruck, Austria
Member of the **National Verification Committee** (NVC) for **Measles and Rubella Eradication**
(Federal Ministry for Social Affairs, Health, Care and Consumer Protection, Austria)
Member of the **National Polio-Committee**
(Federal Ministry for Social Affairs, Health, Care and Consumer Protection, Austria)
Member of **Rabies-Committee** (Federal Ministry for Social Affairs, Health, Care and Consumer Protection, Austria)
Senior Lecturer for Tropical Neurology Bernhard Nocht Institute for Tropical Medicine, Hamburg-Eppendorf, Germany
Senior Lecturer for Tropical Neurology Center for Global Health, Technical University Munich, Germany
Senior Lecturer for Tropical Neurology Medical Faculty, Universitäts-Klinikum Jena, Germany

No Conflict of Interest with respect to the topic of this lecture



Based on the most recent data in the US, which organ system accounts for the highest percentage of serious diagnostic errors in the emergency department (ED)?

A Cardiovascular	23%
B Gastrointestinal	7%
C Neurologic	**34%**
D Pulmonary	8%

According to a report published by the US Agency for Healthcare Research and Quality (AHRQ) in 2022, the top 5 organ systems with diseases linked to serious diagnostic error were neurologic (including stroke; 34%), cardiovascular (23%), pulmonary (8%), gastrointestinal (7%), and hematologic (including venous thromboembolism; 7%).

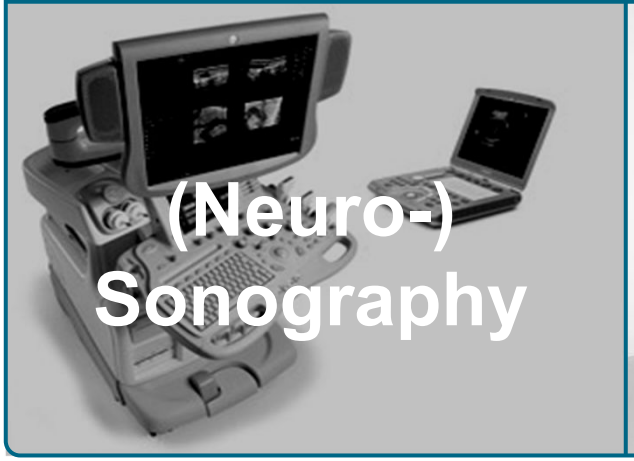
Source: Agency for Healthcare Research and Quality

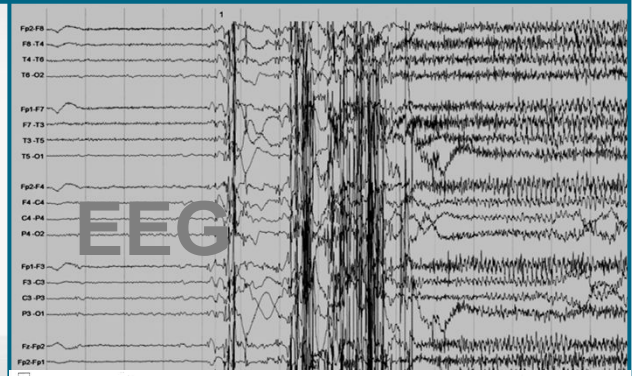
AHRQ
Agency for Healthcare Research and Quality

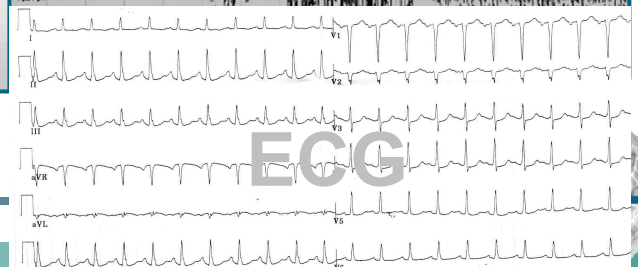
sudden onset of impairment of consciousness

➔ after **exact clinical/neurological examination AND appropriate history** (family, observers, passers-by etc): GCS, focal signs, nuchal rigidity, body temperature, seizures

➔ **stabilize the patient** and then time has come to decide ➔







What causes impaired consciousness?

The mechanism for coma or impaired consciousness involves **dysfunction of both cerebral hemispheres or dysfunction of the reticular activating system** (also known as the ascending arousal system).

Causes may be
structural or
nonstructural e.g.,
- toxic or
- metabolic disturbances.

Damage may be
focal or
diffuse.

The common causes of a sudden loss of consciousness are:

- **Accidents/trauma/traumatic brain injury**
- Drug-, alcohol overdose
- **Poisoning**
- **Metabolic derangements**, e.g. hypoglycemia etc
- **Lack of blood flow in the brain**, cardiac arrest, ventricular fibrillation, aortic dissection, abnormal heart rhythm, ventricular fibrillation, asystolia, low PB
- Severe loss of blood
- low BP
- Hyperventilation – Hypokapnia
- **Hypoventilation – Hypoxia/Anoxia, Hyperkapnia**
- **Seizure**
- **Stroke - ischemic, hemorrhagic, CSVT, SAH**
- **Infection, intracranial and systemic,** e.g. **septic shock, multi-organ malaria etc.**
- **Inflammation**

:

Clinical Diagnosis of Impairment of consciousness in adults, adolescents and children

The Glasgow Coma Scale (Graham Teasdale and Bryan Jennett, 1974)

Scoring a person's level of consciousness

This assesses 3 essential clinical features:

- **eye opening** 1 - 4
  – a score of 1 means the person doesn't open their eyes at all, and 4 means they open their eyes spontaneously
- **verbal response to a command** 1 - 5
  – 1 means no response, and 5 means a person is alert and talking
- **voluntary movements in response to a command** 1 - 6
  – 1 means no response, and 6 means a person can follow commands

A lower score indicates a more severely impaired consciousness

➔ **GCS 8 or lower means COMA**

Diagnosis - Impairment of consciousness – in infants and young children

The Blantyre Coma Scale

Eye movement

- 1 – Watches or follows
- 0 – Fails to watch or follow

Best motor response

- 2 – Localizes painful stimulus (patient's ability to remove stimuli)
- 1 – Withdraws limb from painful stimulus
- 0 – No response or inappropriate response

Best verbal response

- 2 – Cries appropriately with pain, or, if verbal, speaks
- 1 – Moan or abnormal cry with pain
- 0 – No vocal response to pain

All scores below 5 are not normal, a lower **score (2 or lower) indicates a severely impaired consciousness, i.e. COMA**

Disorders of consciousness can occur if the parts of the brain responsible for consciousness are injured or damaged.

The main causes can generally be divided into:
•traumatic brain injury
•non-traumatic brain injury
•progressive brain damage

Traumatic brain injury

Traumatic brain injury occurs when an object or outside force causes severe trauma to the brain.
This is most often caused by:
•**falls**
•**traffic accidents**
•**violent assault**

Non-traumatic brain injury

Non-traumatic brain damage is usually caused by a health condition, such as:

➔ **a condition that deprives the brain of oxygen** (without a continuous supply of oxygen, brain tissue begins to die)

➔ **a condition that directly attacks brain tissue**

Specific causes of **non-traumatic** brain injury include:

- **strokes**
- **heart attacks**
- **severe brain infections (such as meningitis, encephalitis,** brain abscess, meningovasculitis)
- **severe systemic disease affecting the brain function, e.g. septic shock**
- **drug overdoses, poisoning**
- **metabolic derangements**
- near drowning or other types of suffocation, such as smoke inhalation
- a **blood vessel rupture**, e.g. ruptured brain aneurysm, AV malformation, dissection

Progressive brain damage

In some cases, brain damage can gradually occur over time.

Examples of conditions that cause progressive brain damage include:

- Alzheimer's disease
- Parkinson's disease
- brain tumor, **space occupying lesion**, brain abscess, obstructive hydrocephalus
- **chronic CNS infection**, e.g. **CNS TB,** SSPE etc

Impaired consciousness without fever 1

Cerebral ischemia / hypoxia
- diffuse – e.g. due to cardiac arrest, drowning, strangulation, CO intox
- focal – brainstem- posterior fossa-ischemia (basilar artery occlusion), bilateral ACM ischemia

Intracranial hemorrhage
- intracerebral hemorrhage, hypertensive ICH, vascular malformations
- subrachnoid hemorrhage
- subdural, epidural hemorrhage
- sinus-, venous thrombosis

Poisoning, intoxications, withdrawal

Autoimmune-diseases

Any type of space-occupying processes
- tumors – benign, malignant
- hydrocephalus – obstructive, malresorptive

Status epilepticus, in particular non-convulsive status epilepticus

Traumatic brain injury

Septic shock

Brain death

without fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

Impaired consciousness without fever 2

Metabolic dysregulations, metabolic encephalopathies

- hypo- and hyper-, rapid shift, rapid correction

-- glycemia
-- other endocrinological disorders, e.g. adrenal - Addison-crisis
-- lactic acidosis
-- capnia
-- natremia and other electrolyte-disturbancies
-- uremia
-- hepatic failure
-- thyroidism
-- vitamin (B1, B6, B12 etc) deficiencies

-- central pontine myelinolysis (Osmotic demyelination syndrome (ODS))
-- hypothermia
-- posterior reversible encephalopathy syndrome, cerebral vasoconstriction syndrome
-- rhabdomyolysis, malignant neuroleptic syndrome

without fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

Impaired consciousness with fever 1

Cerebral ischemia / hypoxia
- diffuse – e.g. due to cardiac arrest, drowning, strangulation, CO intox
- focal – brainstem- posterior fossa-ischemia (basilar artery occlusion), bilateral ACM ischemia

Intracranial hemorrhage
- intracerebral hemorrhage, hyperten… …alformations
- subrachnoid hemorrhage
- subdural, epidural he…
- sinus-, venous…

Poisoni…

Infla…

Any …
- tumo…
- hydro… …resorptive

Status … …ticular non-convulsive status epilepticus

Traumat… …njury

Sepsis, Septic shock

each of these listed at the former 2 tables if associated with
aspiration pneumonia,
health-care-associated infection
drug induced hyperthermia,
– e.g. malignant hyperthermia

with fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

Impaired consciousness with fever 2

Systemic Infections
-- parasitic diseases
-- sepsis – septic shock, septic encephalopathy

Infections of the central nervous system
-- bacterial meningitis, meningoencephalitis
-- viral meningoencephalitis, encephalitis
-- fungal meningoencephalitis
-- brain abscess, sub-, epidural empyema
-- meningovasculitis
-- septic sinus- venous thrombosis
-- cerebral malaria with or without multiorgan malaria (P.falciparum)
-- subacute, chronic meningoencephalitis, e.g. African trypanosomiasis
-- eosinophilic meningoencephalitis (e.g. larva migrans visceralis / cerebralis)

Autoimmune encephalitides (antiNMDAR – etc,)

Secondary CNS and cerebral blood vessel affection in autoimmune diseases, e.g. systemic lupus erythematosus

Heat stroke and heat related diseases

Malignant hyperthermia, malignant neuroleptic syndrome

with fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

Sonneville *et al. Critical Care* (2023) 27:386
https://doi.org/10.1186/s13054-023-04655-8

sepsis, septic shock, or **systemic infection** with **multi-organ-** failure, -involvement

REVIEW **Open Access**

The spectrum of sepsis-associated encephalopathy: a clinical perspective

Romain Sonneville[1,2*], Sarah Benghanem[3†], Lina Jeantin[4†], Etienne de Montmollin[1,2], Marc Doman[2], Augustin Gaudemer[1,5], Michael Thy[2] and Jean-François Timsit[1,2]

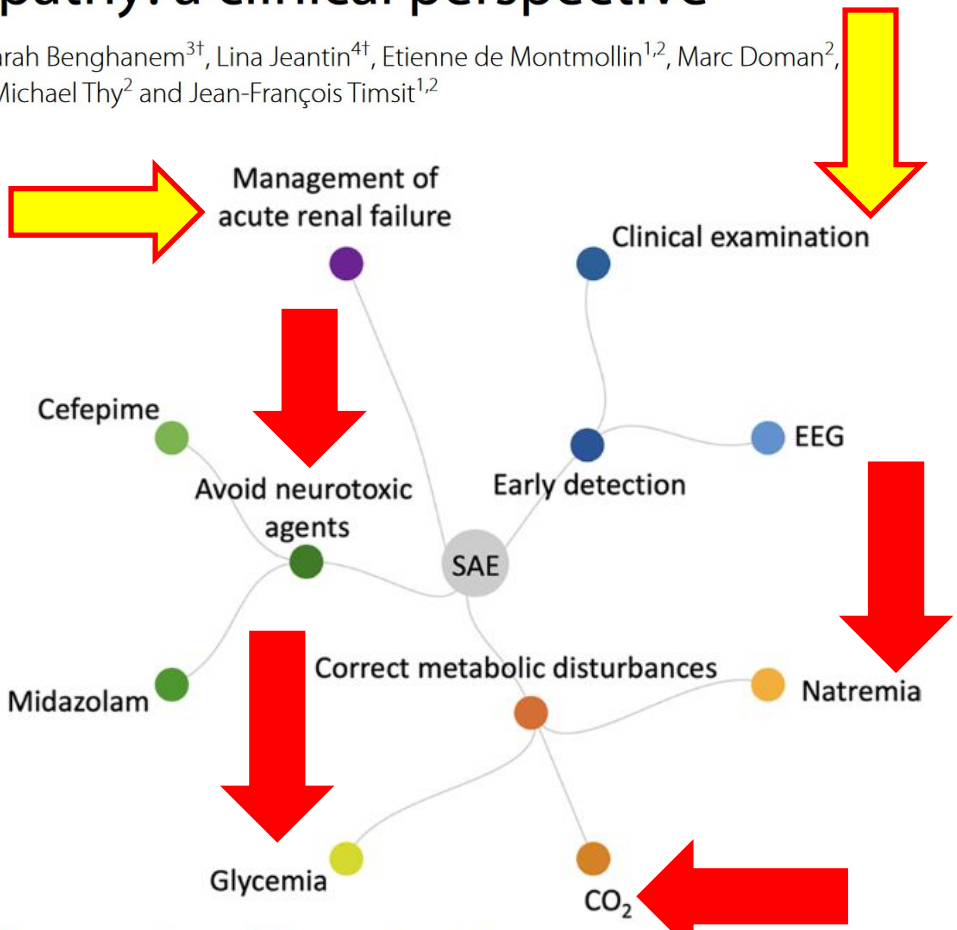


Fig. 3 A multimodal approach for the management of sepsis-associated encephalopathy. EEG Electroencephalography; SAE Sepsis-Associated Encephalopathy

Sonneville *et al. Critical Care* (2023) 27:386
https://doi.org/10.1186/s13054-023-04655-8

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Table 2 Proposed targets for control of systemic causes of secondary brain injury

Variable	Proposed target	Comments
MAP	65–80 mmHg	A higher MAP target (≥ 80mmHg) is not associated with reduced mortality [61, 63] A higher MAP target is associated with higher RASS scores during ICU stay [64]
PaO_2	80–120 mmHg	Hyperoxia is associated with increased mortality [65]
$PaCO_2$	35–45 mmHg	Hypercapnia (> 45 mmHg) is associated with an increased risk of SAE [8]
Temperature	36–38.3°C	Fever (> 38.4 °C) is associated with higher mortality [66, 67]
Natremia	135–145 mmol/L	Hypernatremia is associated with an increased risk of SAE [8]
Glycemia	5–10 mmol/L	Hypoglycemia (< 3 mmol/l) and hyperglycemia (> 10 mmol/l) are associated with an increased risk of SAE [8]
Hemoglobin	> 7g/dL	A higher transfusion threshold (> 9g/dL) is not associated with decreased mortality [68, 69]

MAP mean arterial pressure; RASS Richmond agitation sedation scale; SAE Sepsis-associated encephalopathy

Impaired consciousness with fever 2

Systemic Infections
-- parasitic diseases
-- sepsis – septic encephalopathy

Infections of the central nervous system
-- bacterial meningitis, meningoencephalitis
-- viral meningoencephalitis, encephalitis
-- fungal meningoencephalitis
-- brain abscess, sub-, epidural empyema
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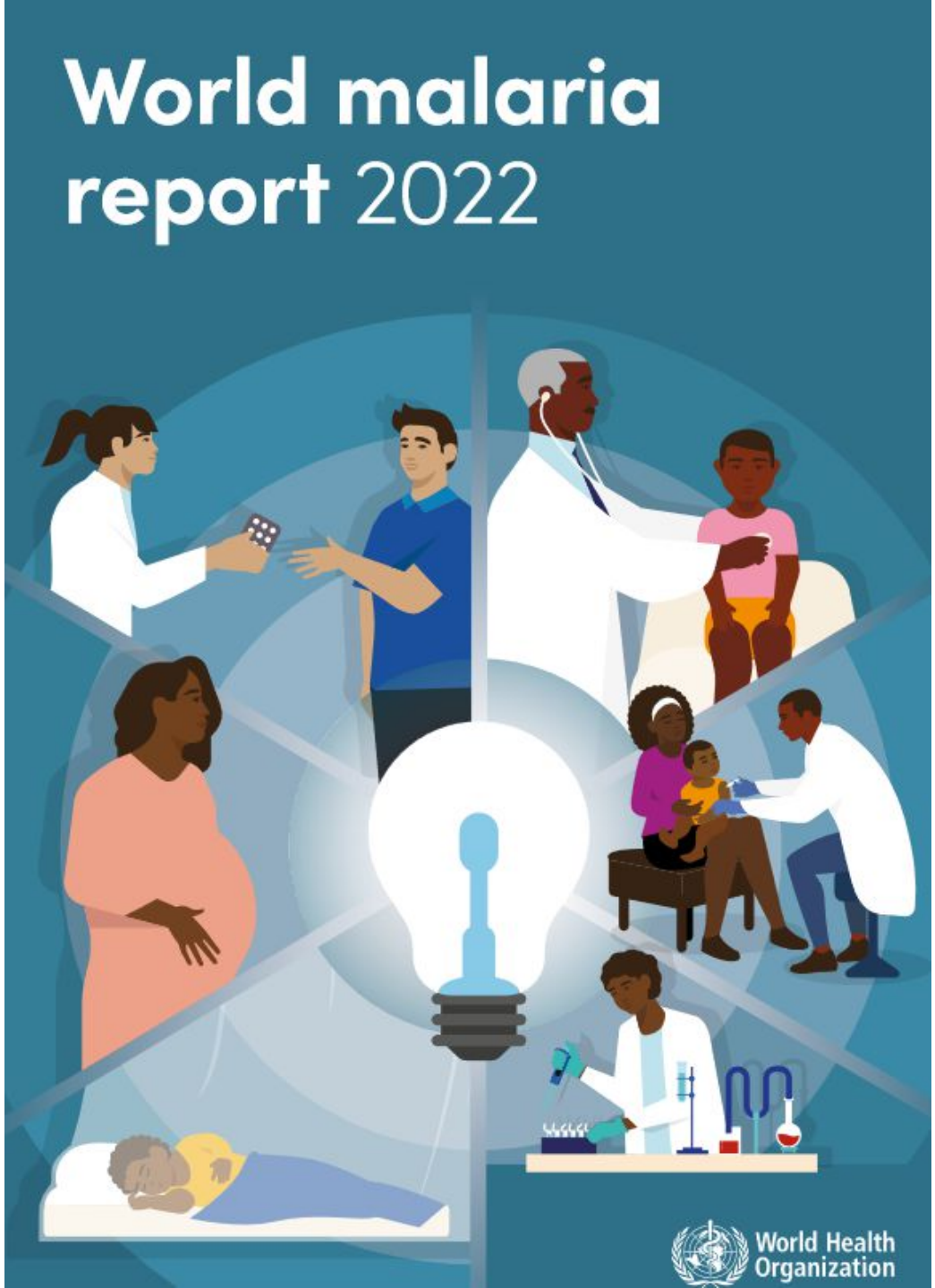
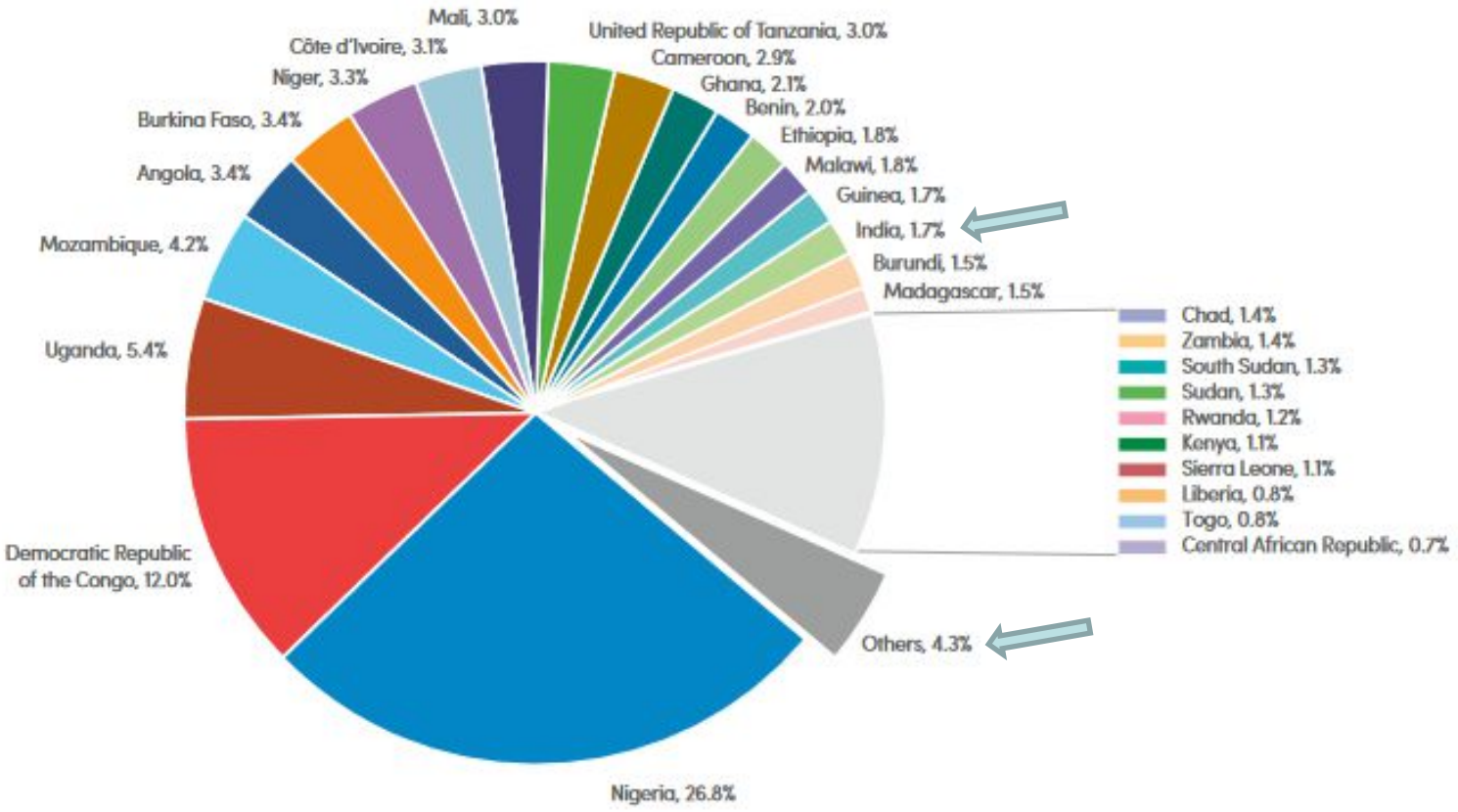
with fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

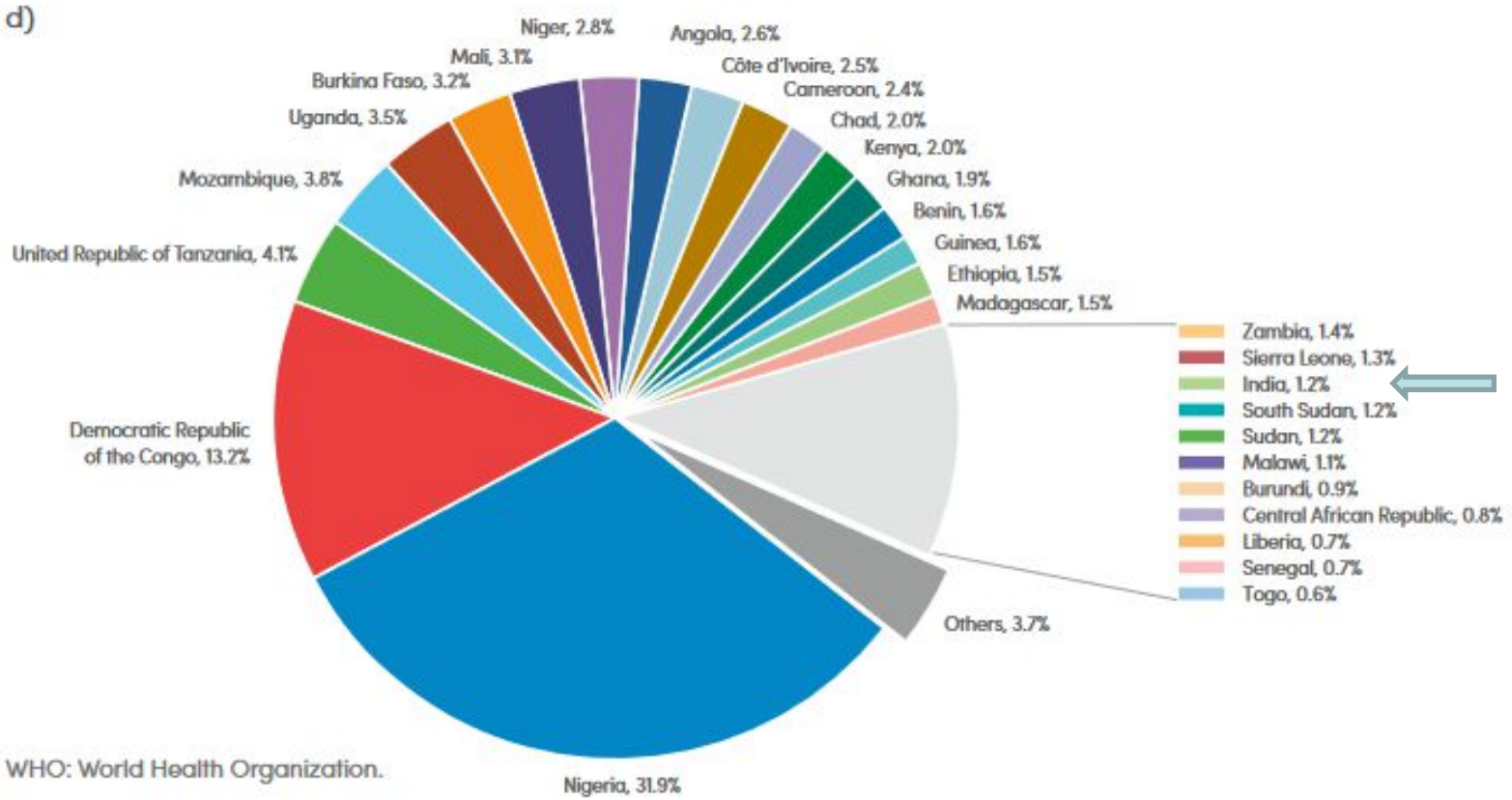
Epidemiology



c)



5 countries in SubSaharan Africa: 51,8% of all P. falciparum malaria-cases
28 countries in SubSaharan Africa: 94% of all P. falciparum malaria-cases



5 countries in SubSaharan Africa: 55,5% of all malaria P.f. deaths
28 countries in SubSaharan Africa: **95,1% of all malaria P.f. deaths**

➔In 2022, malaria caused an estimated **620 000 deaths,** mostly among **African children (<5y)**.
➔Malaria is **preventable and curable**.
➔Increased malaria prevention and control measures are dramatically **reducing** the **malaria burden** in many places, but **in 2020 and 2021 incidence is increasing.**
➔**Non-immune travellers from malaria-free areas are very vulnerable to the disease when they get infected**

World Health Organization

WHO homepage accessed 15th October 2023

>95% of all P.falciparum Malaria deaths:

Cerebral Malaria

with / without Multi-Organ-Malaria

WHO:
Diagnosis **Cerebral Malaria**:
1) History, fever
2) **Impairment of consciousness**, „severe prostration“, **epileptic seizures** , focal neurological signs and symptoms.
3) **Positive blood smear**
4) **Malaria retinopathy**

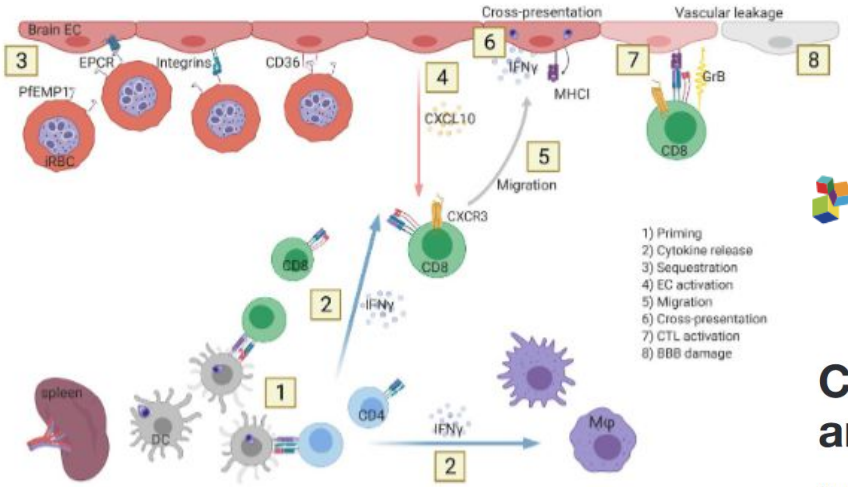
doi:10.1093/brain/awu001 Brain 2014: 137; 2119–2142 | 2119

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Cerebral malaria in children: using the retina to study the brain

Ian J. C. MacCormick,[1,2] Nicholas A. V. Beare,[2,3] Terrie E. Taylor,[5,6] Valentina Barrera,[2] Valerie A. White,[7] Paul Hiscott,[2] Malcolm E. Molyneux,[1,4,8] Baljean Dhillon[9,10] and Simon P. Harding[2,3]



1. Dendritic cells present parasite antigens to T lymphocytes in the spleen, priming CD4+ and CD8+ T as parasite-specific.
2. Primed CD4+ T helper cells produce IFNγ, thus activating the innate immune system with phagocytic macrophages (Mϕ).
3. In order to circumvent clearance in the spleen, infected red blood cells (iRBCs) bind to endothelial cells (ECs) via interaction of PfEMP1 with surface proteins CD36, endothelial protein c receptor (EPCR) and integrins αVβ.
4. Upon iRBC sequestration, ECs become activated and produce the chemokine CXCL10.
5. Parasite specific CD8+ cells express the chemokine receptor CXCR3 and migrate up the chemokine gradient to the brain.
6. IFNγ released from lymphocytes induces cross-presentation of parasite antigens by ECs, which acquire the ability to phagocytose and present parasite antigens via MHCI receptors.
7. Antigen-specific binding of CD8+ T cells evokes their cytotoxic activity (CTL).
8. Cytolytic enzymes such as Granzyme B (GrB) destroy the EC-monolayer and BBB integrity, thus leading to vascular leakage and brain oedema.

frontiers | Frontiers in Immunology

REVIEW
published: 20 April 2022
doi: 10.3389/fimmu.2022.863568

Cerebral Malaria: Current Clinical and Immunological Aspects

Karin Albrecht-Schgoer[1], Peter Lackner[2], Erich Schmutzhard[3] and Gottfried Baier[1]*

[1] Division of Translational Cell Genetics, Medical University of Innsbruck, Innsbruck, Austria, [2] Department of Neurology, Klinik Floridsdorf, Wien, Austria, [3] Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Priming
Cytokine release
Sequestration

Endotheliopathy

Endothelial Cells activation
Migration
Cross presentation

CD8+ Tcells
BBB damage

Endotheliopathy

Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

*Arjen M Dondorp, Caterina I Fanello, Ilse C E Hendriksen, Ermelinda Gomes, Amir Seni, Kajal D Chhaganlal, Kalifa Bojang, Rasaq Olaosebikan, Nkechinyere Anunobi, Kathryn Maitland, Esther Kivaya, Tsiri Agbenyega, Samuel Blay Nguah, Jennifer Evans, Samwel Gesase, Catherine Kahabuka, George Mtove, Behzad Nadjm, Jacqueline Deen, Juliet Mwanga-Amumpaire, Margaret Nansumba, Corine Karema, Noella Umulisa, Aline Uwimana, Olugbenga A Mokuolu, Olanrewaju T Adedoyin, Wahab B R Johnson, Antoinette K Tshefu, Marie A Onyamboko, Tharisara Sakulthaew, Wirichada Pan Ngum, Kamolrat Silamut, Kasia Stepniewska, Charles J Woodrow, Delia Bethell, Bridget Wills, Martina Oneko, Tim E Peto, Lorenz von Seidlein, Nicholas P J Day, Nicholas J White, for the AQUAMAT group**

Lancet 2010; 376: 1647–57

Published **Online** November 8, 2010
DOI:10.1016/S0140-6736(10)61924-1

Summary

Background Severe malaria is a major cause of childhood death and often the main reason for paediatric hospital admission in sub-Saharan Africa. Quinine is still the established treatment of choice, although evidence from Asia suggests that artesunate is associated with a lower mortality. We compared parenteral treatment with either artesunate or quinine in African children with severe malaria.

Pathophysiology of cerebral malaria:
Part of Multi-Organ-Failure
➔ **Impairment of microcirculation**
➔ **Endothelial dysfunction**
(Endotheliopathy)

Very strict recommendation: **Intensive Care Management is crucial in every patient with complicated P.falciparum** Malaria, in predominantly **cerebral malaria: neuro-critical** care management

Journal of Critical Care 43 (2018) 356–360

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Intensive care in severe malaria: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine

Dilip R. Karnad [a], Mohd Basri Mat Nor [b], Guy A. Richards [c], Tim Baker [d,e], Pravin Amin [f,*], On behalf of the Council of the World Federation of Societies of Intensive and Critical Care Medicine

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[b] *Department of Anaesthesiology and Intensive Care, School of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia*
[c] *Division of Critical Care, Charlotte Maxeke Hospital and Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa*
[d] *Department of Anaesthesia & Intensive Care, Queen Elizabeth Central Hospital, Blantyre, Malawi*
[e] *Global Health – Health Systems & Policy, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden*
[f] *Department of Critical Care Medicine, Bombay Hospital Institute of Medical Sciences, Mumbai, India*

Immediate clinical management of severe manifestations and complications of falciparum malaria

Manifestation/complication	Immediate management[a]
Coma (cerebral malaria)	CPP = MAP - ICP
Hyperpyrexia	Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.
Hypoglycaemia (blood glucose concentration of <2.2 mmol/l; <40 mg/100ml)	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.
Severe anaemia (haemoglobin <5 g/100ml or packed cell volume <15%)	Transfuse with screened fresh whole blood
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven.

Whereever NICU is available

optimize microcirculation
avoid hypotension and hypoxia
maintain CPP

endovascular cooling

avoid barbiturates

avoid hyp**o**- and hyp**er**glycemia ➔ tight control of glycemia

transfer to an ICU (in time) with invasive respiratory techniques and cardiopulmonary monitoring
avoid withdrawal of i.v. fluid!!!
early hemofiltration

Adjunctive therapies

CPP = MAP – ICP

Cerebral **P**erfusion **P**ressure (**CPP**) ➔
Elevation of **M**ean **A**rterial **P**ressure (**MAP**)
Reduction of **I**ntra**C**ranial **P**ressure (**ICP**)

A single episode of hyp**o**tension (sBP <90 mmHg for > 5min) **doubles mortality** (BTF, 2016)

➔ Fluid resuscitation ?!

➔ Catecholamines (Epinephrine, etc.) ?
– Cave: Intestine!!

In CM: avoid Hypo- and Hyperventilation, thereby avoiding Hyper- and Hypocapnia

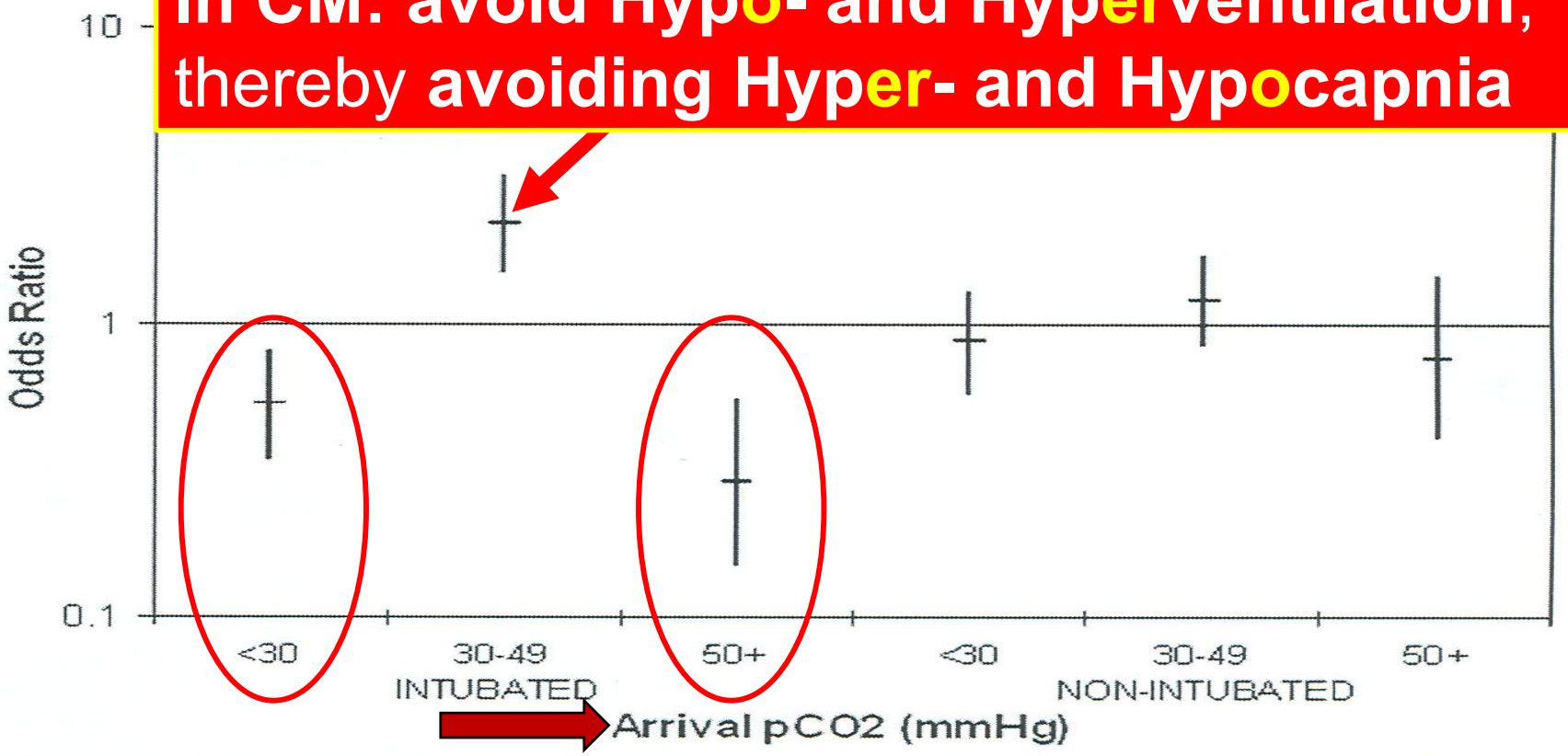


Figure 2. Adjusted odds ratio of survival and a good outcome for patients within and outside the target range for arrival P_{CO_2} (30–49 mm Hg). Odds ratios are adjusted for age, gender, mechanism of injury, year of injury, preadmission Glasgow Coma Scale, Head Abbreviated Injury Score, Injury Severity Score, preadmission hypotension, arrival P_{O_2}, and base deficit. Adjusted odds ratio of survival and good outcomes for intubated and nonintubated patients with hyperventilation (arrival P_{CO_2} values <30 mm Hg), euventilation (arrival P_{CO_2} 30–49 mm Hg), and hypoventilation (arrival P_{CO_2} ≥50 mm Hg). Intubated patients within the optimal range were compared with other intubated patients below and above this range, whereas nonintubated patients within this range were compared with other nonintubated patients outside this range.

Davis, 2006

Intensive Care Med
https://doi.org/10.1007/s00134-022-06640-1

Received: 1 October 2021 Accepted: 3 February 2022
Published online: 16 March 2022

SYSTEMATIC REVIEW

The role of acute hypercapnia on mortality and short-term physiology in patients mechanically ventilated for ARDS: a systematic review and meta-analysis

Ségolène Gendreau[1,2,3], Guillaume Geri[4,5], Tai Pham[6,7], Antoine Vieillard-Baron[4,5] and Armand Mekontso Dessap[1,2,3*]

Take-home message

We found conflicting clinical effects of hypercapnia during ARDS depending on its mechanism.

The protective effects of permissive hypercapnia seemed driven by protective ventilation while the deleterious effects of imposed hypercapnia seemed mediated by pulmonary vascular dysfunction.

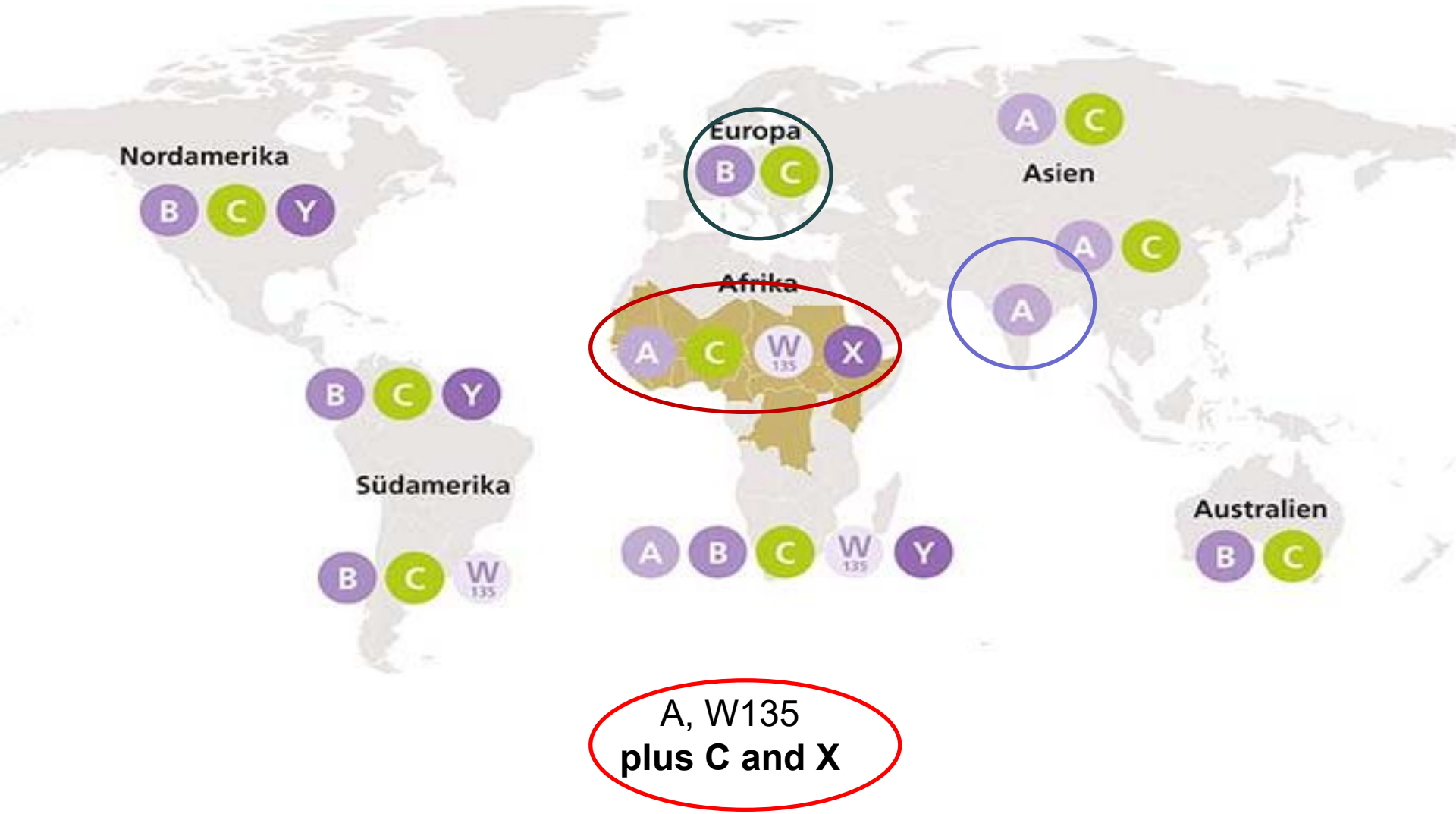
Most essential take home message if cerebral malaria is suspected

emergency blood slide and fundoscopy

Blood-gas-analysis:
pO2: never rely on pO2 alone, d.h. ohne
always and only in conjunction with **pCO2**:
➔ **Hyperkapna doubles mortality**
➔ **Hypokapnia triplicates mortality**

CAVE:
Hypoglycemia,
BUT similarly CAVE:
Hyperglycemia

➔ AVOID ALL HYPOS AND HYPERS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Journal of Infection (2008) **57**, 449—454

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Antibiotic treatment delay and outcome in acute bacterial meningitis

Rasmus Køster-Rasmussen [a,*], André Korshin [b], Christian N. Meyer [c]

in 2023: even more important:
➔ DELAY OF **APPROPRIATE** ANTIBIOTIC TREATMENT **!!**

Journal of Infection (2008) 57, 449–454

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Antibiotic treatment delay and outcome in acute bacterial meningitis

Rasmus Køster-Rasmussen [a,*], André Korshin [b], Christian N. Meyer [c]

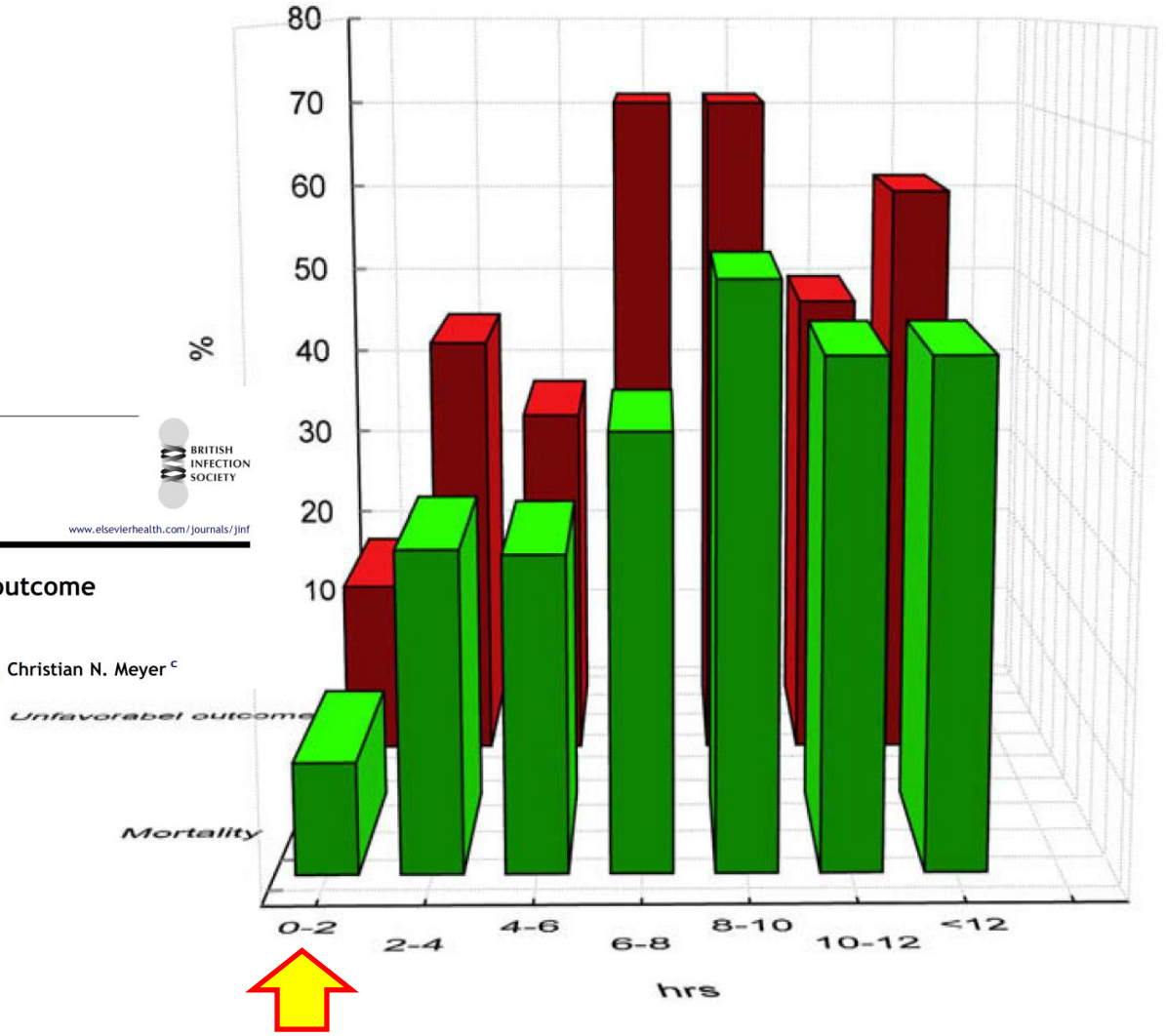
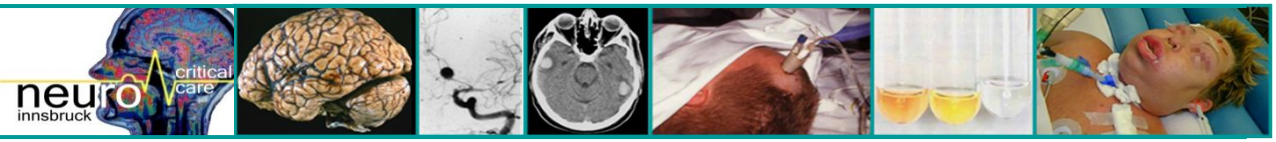
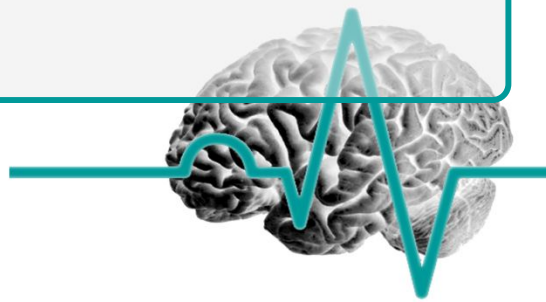


Figure 2 Rate of mortality and unfavourable outcome according to the treatment delay in time interval in acute bacterial meningitis.



VIRAL ENCEPHALITIS



Acute viral Meningoencephalitis

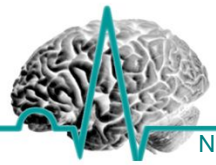
avoid neuroleptics – they might induce epileptic seizures !

- after prodromal „signs and symptoms“
  - **headache**
  - **behavioural disturbance**
  - disorientation
  - confusion
  - hallucinations
  - **somnolence/sopor/coma**
  - Focal or generalized epileptic seizures
  - focal neurology
  - **Meningism (frequently only mild)**

qualitative

impairment of consciousness

quantitative



Rabies, the most lethal virus known to man, occurs in more than 150 countries and territories. The disease is usually fatal once symptoms appear.

Dog-transmitted rabies accounts for about 99% of human rabies cases.

It is estimated that **59 000 people** die from rabies every year.

(WHO, May 2020)

World Health Organization

Accepted Manuscript

Title: Ongoing and emerging arbovirus threats in Europe

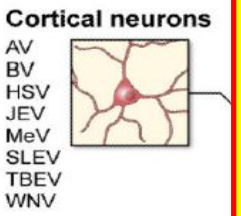
Author: Luisa Barzon

PII: S1386-6532(18)30216-6
DOI: https://doi.org/10.1016/j.jcv.2018.08.007
Reference: JCV 4044

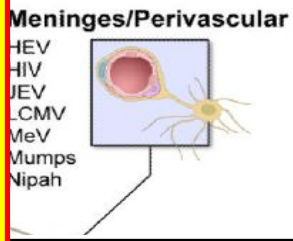
To appear in: *Journal of Clinical Virology*

Table 2. Clinical syndrome associated with arbovirus infection.

Syndromes	**Viruses**
Febrile illness	Dengue, chikungunya, O'nyong-nyong, etc.
Rash	Dengue, chikungunya, Zika, O'nyong-nyong, Sindbis virus
Arthralgia and/or myalgia	chikungunya, dengue, Crimean-Congo haemorrhagic fever, sandfly viruses, O'nyong-nyong, Sindbis virus, Ross River virus
Neurological syndrome	West Nile virus, tick-borne encephalitis, Japanese encephalitis, St. Louis encephalitis, Zika virus, Powassan virus, dengue, Toscana virus, Venezuelan and other equine encephalitis viruses, Rift Valley fever, La Crosse virus and California encephalitis virus antigenic group
Haemorrhagic syndrome	dengue, yellow fever, Crimean-Congo haemorrhagic fever, Rift Valley fever
Congenital syndrome	Zika virus



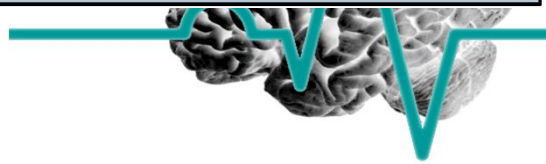
pathogenic virus and patient‘s immune-response



GHTS

- A diverse spectrum of viruses can enter the CNS, causing acute and chronic neurological disorders
- Virus-induced CNS diseases are influenced by routes of viral entry, viral tropism, and immune responses
- CNS immune reactions limit the spread of virus, but can also cause severe pathology
- Viruses can directly injure or disable cells of the CNS resulting in disease
- New animal models and therapeutic interventions are required to lessen the burden of CNS viral infections worldwide

enteroviruses, HIV, human immunodeficiency virus, HSV, herpes simplex virus, JCV, John Cunningham virus, JEV, Japanese encephalitis virus, LCMV, lymphocytic choriomeningitis virus, MeV, measles virus, Mumps, Mumps virus, Nipah, Nipah virus, PV, poliovirus, RV, rabies virus, SLEV, St. Louis encephalitis virus, TBEV, tick-borne encephalitis virus, WNV, west nile virus.



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

FOSSIL-FUEL POLLUTION AND CLIMATE CHANGE
Caren G. Solomon, M.D., M.P.H., *Editor*

Treatment and Prevention of Heat-Related Illness

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This article was published on September 28, 2022, at NEJM.org.

DOI: 10.1056/NEJMcp2210623

KEY CLINICAL POINTS

TREATMENT AND PREVENTION OF HEAT-RELATED ILLNESS

- Climate change is causing increasingly frequent and severe heat waves, resulting in increases in the incidence of heat-related illness and exacerbations of heat-sensitive conditions.
- The risk of heat-related illness is driven by heat exposure (ambient and internally generated heat from exertion), individual susceptibility (influenced by age, pregnancy status, and coexisting conditions), and sociocultural factors (including environmental racism, poverty, lack of social cohesion, lack of access to health care, and limited worker protections).
- Heat-related illnesses range from mild to life-threatening, and heat exposure exacerbates many common health conditions, including cardiac, respiratory, and kidney diseases.
- Without prompt recognition and treatment, heat stroke has high associated mortality. Treatment includes rapid cooling, rehydration, and management of potential end-organ damage.
- Heat-related illness is preventable. Clinicians have a role in identifying patients at risk, providing counseling regarding signs and symptoms, and recommending strategies for reducing risk.

Impaired consciousness without fever 1

Cerebral ischemia / hypoxia
- diffuse – e.g. due to cardiac arrest, drowning, strangulation, CO intox
- **focal – brainstem-, posterior fossa ischemia (basilar artery occlusion),** bilateral ACM ischemia

Intracranial hemorrhage
- **intracerebral hemorrhage, hypertensive ICH, vascular malformations**
- **subrachnoid hemorrhage**
- subdural, epidural hemorrhage
- sinus-, venous thrombosis

Poisoning, intoxications, withdrawal

Inflammation, autoimmune-diseases

Any type of space-occupying processes
- tumors – benign, malignant
- hydrocephalus – obstructive, malresorptive

Status epilepticus, in particular non-convulsive status epilepticus

Traumatic brain injury

Septic shock

Brain death

without fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**

Journal List > JAMA Network > PMC6515606

JAMA Neurology

View Article

JAMA Neurol. 2019 May; 76(5): 588–597.
Published online 2019 Jan 19. doi: 10.1001/jamaneurol.2019.0006

Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population

A Systematic Review and Meta-analysis

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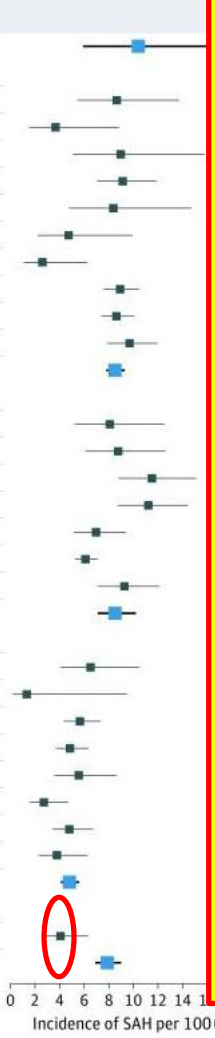
Drag image to reposition.

Total: I^2 = 99.5%			**3581**	**20108432**	**10.4 (5.9-18.5)**
Australia and New Zealand					
Australia	Anderson et al,[64] 1993	1990	18	208062	8.7 (5.5-13.7)
Australia	Islam et al,[65] 2008	1995	5	136095	3.7 (1.5-8.8)
Australia	Thrift et al,[66] 2001	1996	12	133816	9.0 (5.1-15.8)
Australia	Thrift et al,[67] 2009	1998	56	613262	9.1 (7.0-11.9)
Australia	Islam et al,[65] 2008	2000	12	143417	8.4 (4.8-14.7)
Australia	Leyden et al,[68] 2013	2010	7	148028	4.7 (2.3-9.9)
Australia	Newbury et al,[69] 2017	2010	5	192072	2.6 (1.1-6.3)
New Zealand	Bonita and Thomson,[70] 1985	1982	148	1658908	8.9 (7.6-10.5)
New Zealand	Truelsen et al,[71] 1998	1992	163	1890738	8.6 (7.4-10.1)
New Zealand	Feigin et al,[72] 2006	2002	87	897882	9.7 (7.9-12.0)
Total: I^2 = 0%			**513**	**6022280**	**8.5 (7.8-9.3)**
North America					
Mexico	Cantu-Brito et al,[73] 2010	2008	20	247665	8.1 (5.2-12.5)
United States	Brown et al,[74] 1996	1955	29	331081	8.8 (6.1-12.6)
United States	Brown et al,[74] 1996	1965	52	451611	11.5 (8.8-15.1)
United States	Brown et al,[74] 1996	1975	61	543561	11.2 (8.7-14.4)
United States	Brown et al,[74] 1996	1985	43	617554	7.0 (5.2-9.4)
United States	Longstreth et al,[75] 1993	1988	171	2800000	6.1 (5.3-7.1)
United States	Labovitz et al,[76] 2006	1995	53	571700	9.3 (7.1-12.1)
Total: I^2 = 68.9%			**429**	**5563172**	**8.5 (7.1-10.2)**
South America and Central America					
Argentina	Bahit et al,[77] 2016	2014	17	261180	6.5 (4.1-10.5)
Brazil	Minelli et al,[78] 2007	2004	1	75053	1.3 (0.2-9.5)
Brazil	Cabral et al,[79] 2009	2005	55	974094	5.7 (4.3-7.4)
Brazil	Cabral et al,[80] 2016	2012	52	1073318	4.8 (3.7-6.4)
Caribbean	Smadja et al,[81] 2001	1998	20	360000	5.6 (3.6-8.6)
Caribbean	Wolfe et al,[82] 2006	2002	13	478136	2.7 (1.6-4.7)
Chile	Alvarez et al,[83] 2010	2001	33	688824	4.8 (3.4-6.7)
Chile	Lavados et al,[84] 2005	2001	15	396311	3.8 (2.3-6.3)
Total: I^2 = 7.4%			**206**	**4306916**	**4.8 (4.1-5.6)**
Africa					
Nigeria	Okon et al,[85] 2015	2011	20	491033	4.1 (2.6-6.3)
Overall (All Continents, Including Europe) Total: I^2 = 96.6%			**8176**	**67746051**	**7.9 (6.9-9.0)**



aSAH (aneurysmatic subarachnoid hemorrhage)

Incidence:

Nigeria: 4/100.000/y

Australia: 8-9/100.000/y

South-America: 5/100.000/y

USA: 8/100.000/y

wordwide: 7-9/100-000/y

Impaired consciousness without fever 2

Metabolic dysregulations, metabolic encephalopathies

- hypo- and hyper-, rapid shift, rapid correction

-- glycemia
-- other endocrinological disorders, e.g. adrenal - Addison-crisis
-- lactic acidosis
-- capnia
-- natremia and other electrolyte-disturbancies
-- uremia
-- hepatic failure
-- thyroidism
-- vitamin (B1, B6, B12 etc) deficiencies
-- central pontine myelinolysis (Osmotic Demyelination Syndrome (ODS))
-- hypothermia
-- posterior reversible encephalopathy syndrome, cerebral vasoconstriction syndrome
-- rhabdomyolysis, malignant neuroleptic syndrome

without fever indicates: **prior** to and/or **at the time** of **acute/peracute onset** of **impairment of consciousness**