Bon usage antibiotique dans les infections communautaires graves

Cas clinique didactique

Dr Camille Legouy

GHU PARIS
PSYCHIATRIE & NEUROSCIENCES
Sainte-Anne

Madame D. 64 ans

Psoriasis

Retraitée, ancienne commerciale, de nationalité américaine, réside en France pour les vacances

Pas d'intoxication alcoolo-tabagique

Guselkumab (anticorps monoclonal anti-IL23)

Le 09/12, céphalées, photophobie, nausées-vomissements sans fièvre objectivée, reste dans sa chambre dans le noir sans consulter

11/12, appel du SMUR par le compagnon devant un syndrome confusionnel

SMUR à domicile

Hyperthermie à 40°C, PA 130/70 mmHg, FC 112 bpm

Score Glasgow 13 (Y3V4M6), raideur de nuque, photo-phonophobie,

pas de purpura, pas de signe de localisation neurologique

Que suspectez-vous?

Qu'auriez-vous fait à domicile?

Où l'emmenez-vous?

Thy et al. Annals of Intensive Care (2024) 14:15
https://doi.org/10.1186/s13613-023-01239-1

Annals of Intensive Care

RESEARCH Open Access

Impact of direct ICU admission of pneumococcal meningitis in France: a retrospective analysis of a French medico-administrative (PMSI) database

Michael Thy[1,2*], Claire Dupuis[3], Arthur Mageau[4], Bruno Mourvillier[5], Lila Bouadma[1,4], Stéphane Ruckly[4], Anne Perozziello[4], Andrey Strukov[6], Damien Van-Gysel[6], Etienne de Montmollin[1,4], Romain Sonneville[1,4] and Jean-François Timsit[1,4]

4052 patients with pneumococcal meningitis and sepsis

	2006 patients (50%) directly admitted in ICU	**2046 patients (50%) secondary admitted in ICU**
Severity	**More severe** Number of OF : 2 [2-3] SAPS II : 48 [36-63]	Less severe Number of OF : 0 [0-1] SAPS II : 44 [31-60]
In-hospital mortality	533 Deaths (27%)	567 Deaths (28%)

Direct admission in ICU associated with lower mortality* aOR = 0.67 [0.56-0.80]

***After adjustment to age, sex, comorbidities, organ failures on admission, category of the first hospital and admission from home**

Longer than 2 hours to antibiotics is associated with doubling of mortality in a multinational community-acquired bacterial meningitis cohort

Damon P. Eisen[1,2], Elizabeth Hamilton[1], Jacob Bodilsen[3], Rasmus Køster-Rasmussen[4],

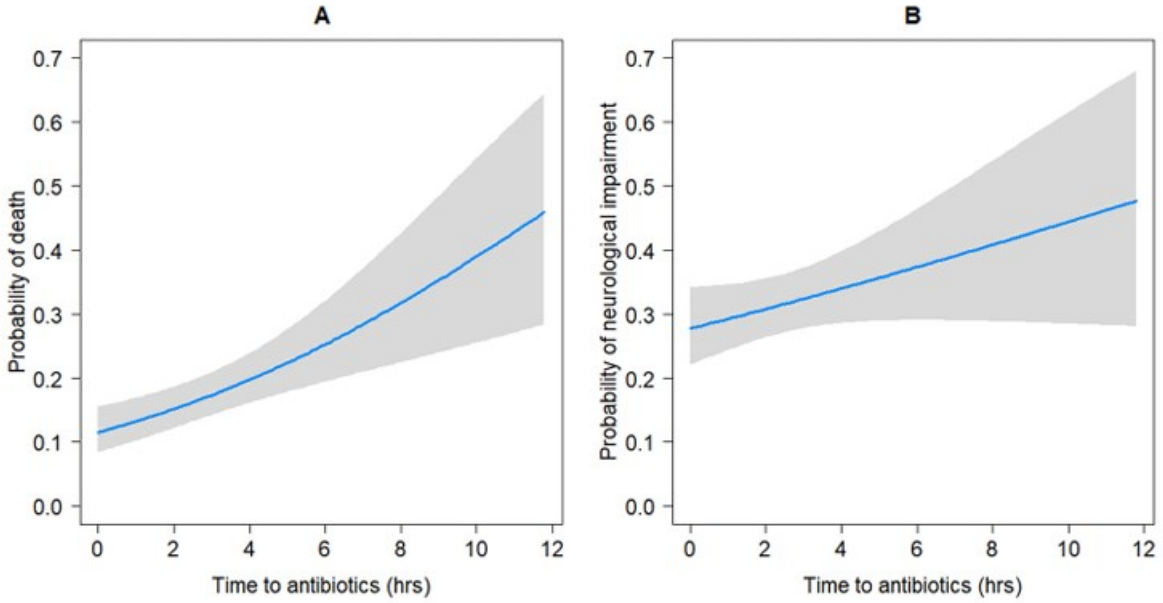


Figure 2. Probability of observing (**A**) mortality and (**B**) neurological impairment in community-acquired bacterial meningitis as a function of time to antibiotic therapy.

Antibiothérapie Cefotaxime (300 mg/kg)

Examen à l'admission en réanimation

T 39°C, 123 bpm, PA 70/40 mmHg

Aggravation neurologique rapide, crise tonico-clonique généralisée prolongée de 5 min puis GSC 5

Pupilles intermédiaires larges aréactives

Marbrures généralisées

Rivotril

IOT en séquence rapide et sédation profonde

Pose de cathéters

Prise en charge de l'état de choc

Ajout d'un antiépileptique longue durée d'action

Que faites-vous et que suspectez-vous?

Hypertension intracrânienne ?

Doppler trancrânien (IP, VTD)

Discuter osmothérapie, optimisation de la volémie,

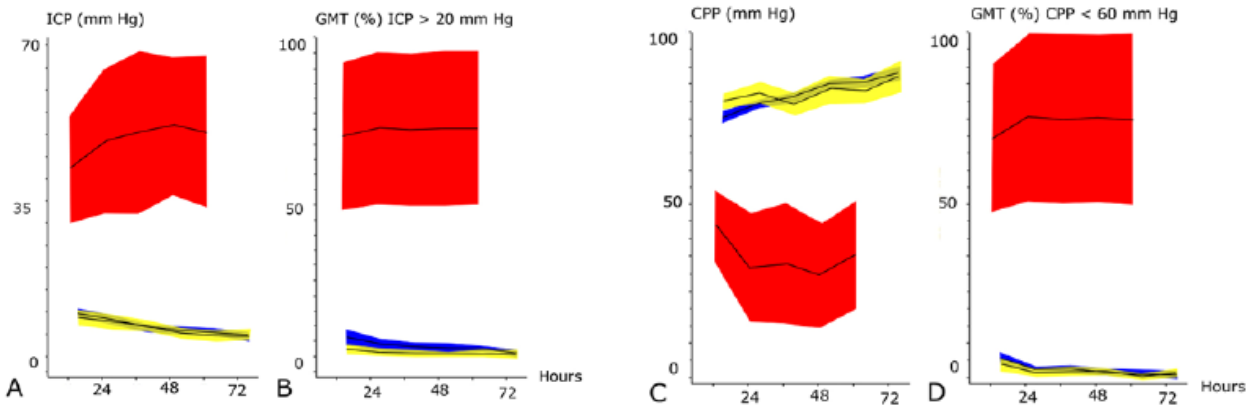
Imagerie cérébrale en urgence

Scanner cérébral: **Quel diagnostic et que faites-vous ?**

Effacement des sillons corticaux
Dédifférenciation substance blanche et substance grise
Œdème cérébral diffus

Intracranial pressure dynamics and cerebral vasomotor reactivity in community-acquired bacterial meningitis during neurointensive care

Teodor Svedung Wettervik, MD, PhD,[1] Timothy Howells, PhD,[1] Anna Ljunghill Hedberg, MD, PhD,[2] Anders Lewén, MD, PhD,[1] and Per Enblad, MD, PhD[1]



Dead Unfavorable Favorable

97 patients avec monitorage de PIC
16 (22%) patients avec PIC > 20 mmHg
21 (28%) avec PPC < 60mmHg

Stabilisation de l'HTIC sous sédations profonde, il est jugé possible de réaliser la ponction lombaire.
L'ensemble des examens vous revient:

Hb 15.6 g/dL Leuco 8.27 G/L
Pq **61** G/L TP 93% CRP 349 **PCT 37** Na 143 K 2.9 Créat 94 µmol/L Urée 12 mmol/L CPK 786 U/L
Tropo 10179 ng/L NT Pro BNP 31730 ng/L
PL + à **CG+ en diplocoque** (antigène + sur LCR) protéinorachie 5.7 glycorachie < 0.06 Leuco 370 dont 84% PNN

Au vu de son lieu de résidence habituel, modifiez-vous la prise en charge thérapeutique ?

Adjonction de vancomycine ou rifampicine

TABLE 3. Bactericidal activity of CSF (1:2 dilution) against CROi and fully CROr pneumococci

Drug(s) given	Subgroup	*n*	No. of CROi bacteria (log_{10} CFU/ml)[a] at:		*P*[b]	No. of CROr bacteria (log_{10} CFU/ml)[a] at:		*P*[b]
			2 h	6 h		2 h	6 h	
Ceftriaxone alone	CSF level, <5 mg/liter	6	5.6 ± 0.9	7.5 ± 0.6		5.2 ± 1.6	7.7 ± 0.1	
	CSF level, >5 mg/liter	5	3.3 ± 0.9	4.5 ± 2.0	<0.02	3.7 ± 0.9	5.7 ± 2.3	<0.1
	All patients	11	4.6 ± 1.7	5.8 ± 2.2		4.7 ± 1.4	6.7 ± 1.9	
Ceftriaxone plus vancomycin	All patients	10	2.9 ± 1.1	3.9 ± 2.7	<0.05	3.3 ± 1.8	4.2 ± 2.6	≤0.05
Ceftriaxone plus rifampin	All patients	10	3.2 ± 0.9	3.2 ± 1.0	<0.05	3.5 ± 0.8	3.0 ± 1.0	<0.01

[a] Initial inoculum, 10^5 organisms per ml. Values are means ± standard deviations.
[b] The first *P* value is for the ceftriaxone levels at both 2 and 6 h after administration at <5 μg/ml and at >5 μg/ml. Other *P* values compare combination therapy and ceftriaxone alone.

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h
plus risk factors for *Listeria monocytogenes*[a]	amoxicillin/ampicillin/penicillin G	penicillin G	trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis, 2017

Bactericidal Activity against Cephalosporin-Resistant Streptococcus pneumoniae in CSF of children with acute bacterial meningitis, Klugman et al, Antimicrobial agents and chemotherapy, 1995

La distribution des souches de méningites en fonction de leurs CMI de bêta-lactamines est présentée sur la Figure 27.

S. pneumoniae

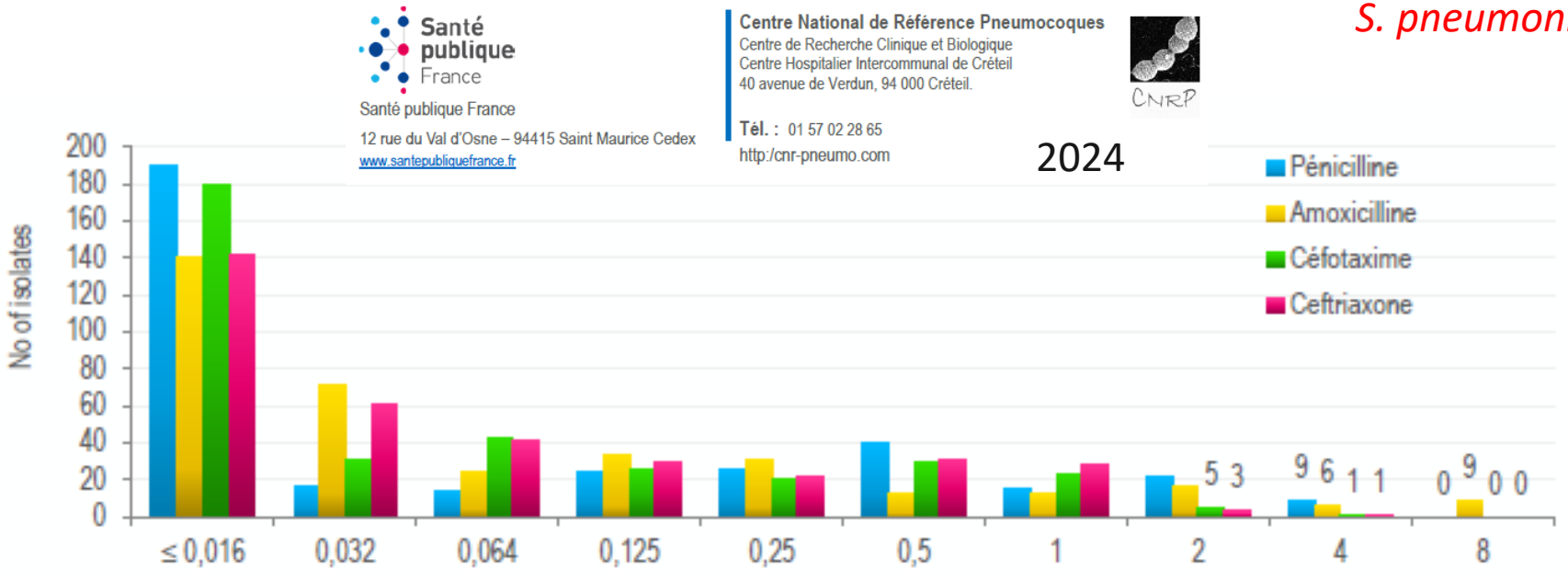


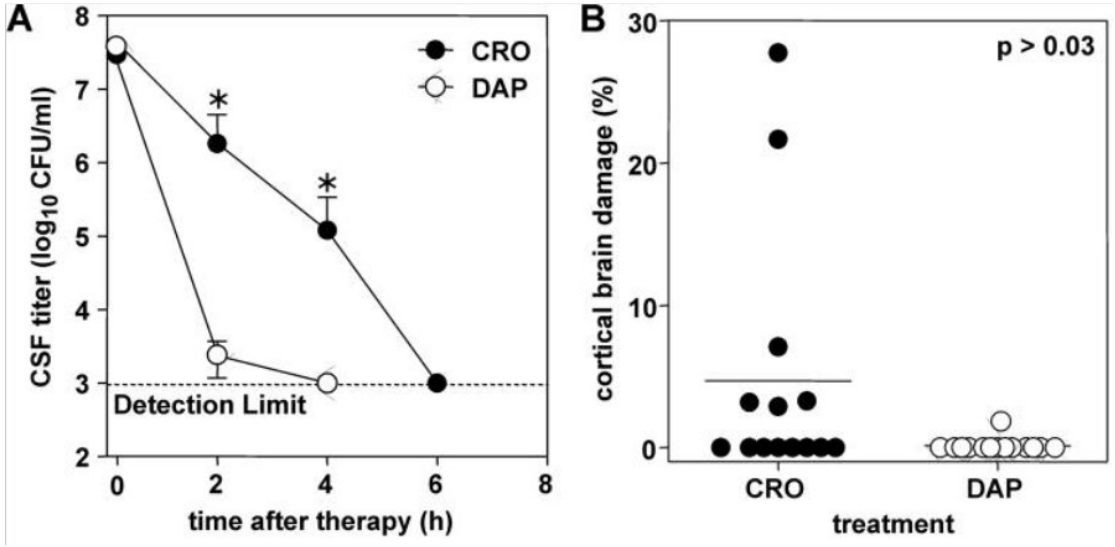
Table 2. CSF concentrations of cefotaxime according to weight-based daily dosage ($n = 40$ dosages, four missing data)

Objectif: CMI x 10

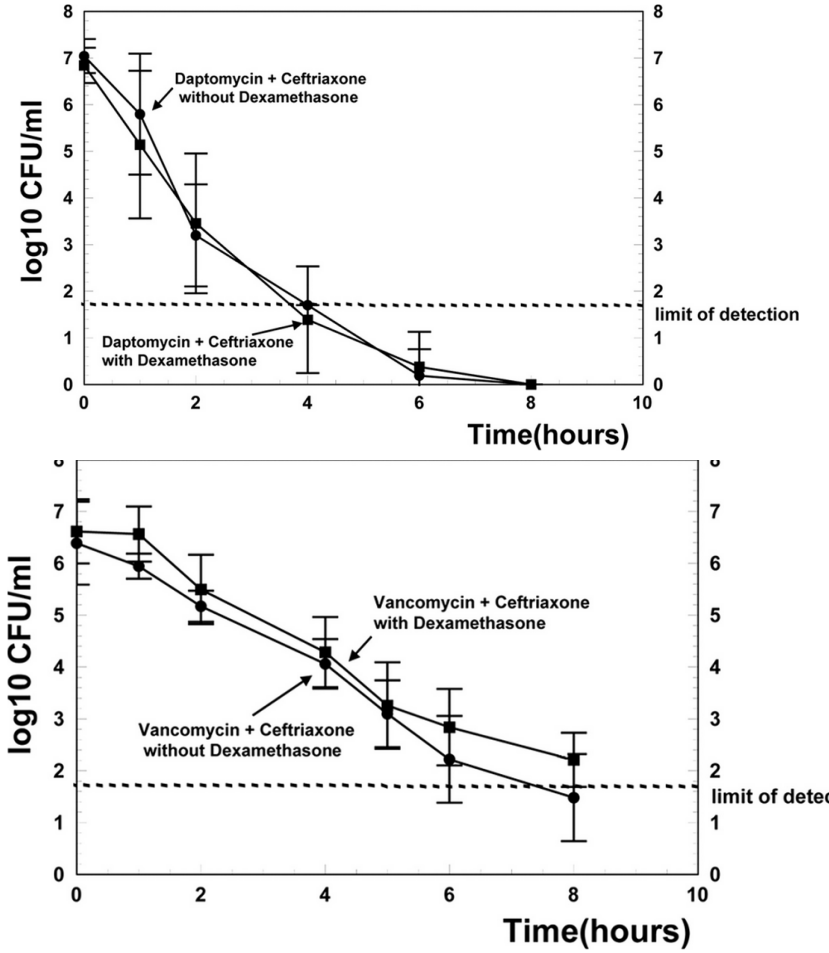
	Daily dosage (mg/kg/day)			
	<150	150–199	200–280	>280
Number of patients	6	6	11	6
Number of dosages	9	8	13	10
Time since CTX initiation (h), median	120	144	96	193
Creatinine clearance (mL/min), median	51	77.5	86.0	96.5
Creatinine clearance <30 mL/min, *n*	4 (1 md)	0	1 (2 md)	0
CSF concentration (mg/L), median (range)	7.5 (1.2–29.3)	10.3 (2.2–15.4)	5.4 (1.6–23.8)	18.3 (3.0–43.4)

Le Turnier P *et al,* CSF concentration of cefotaxime in adult patients with pneumococcal meningitis: a multicentre retrospective study, J Antimicrob chemother 2021

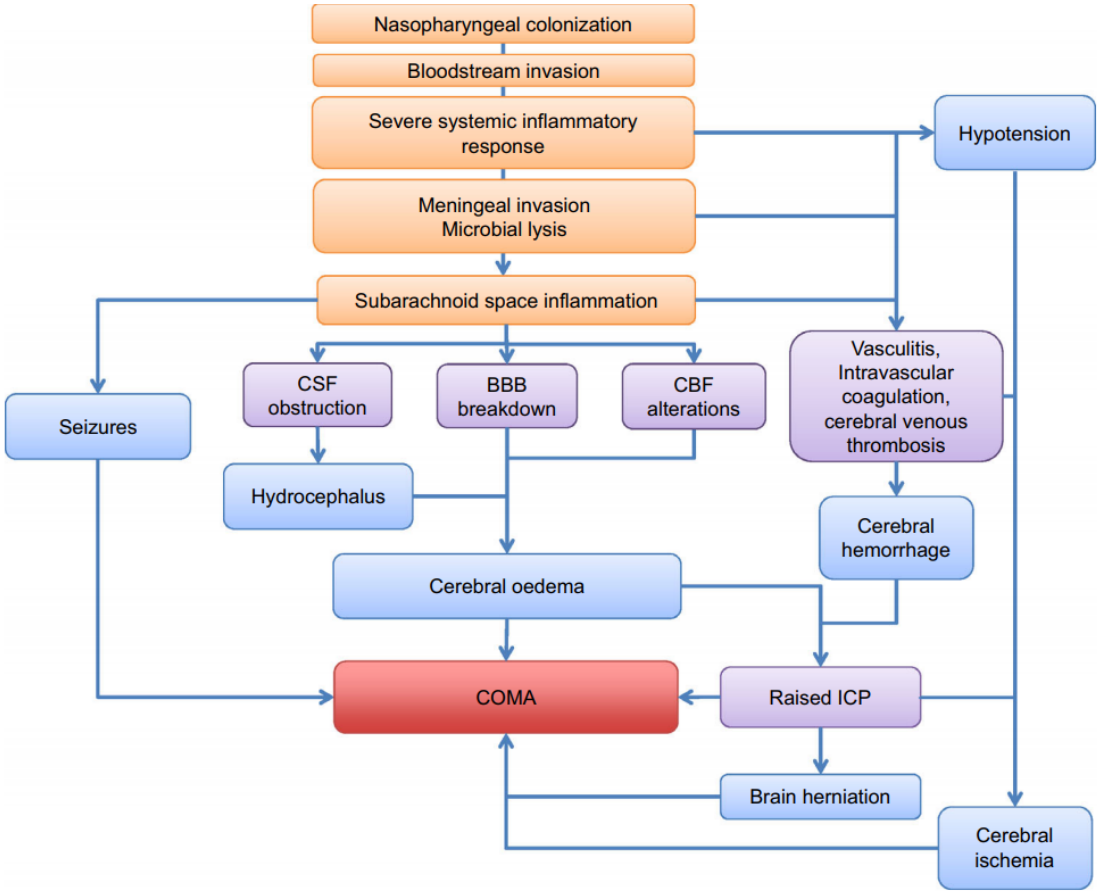
Daptomycine vs ceftriaxone chez le rat dans la méningite à pneumocoque

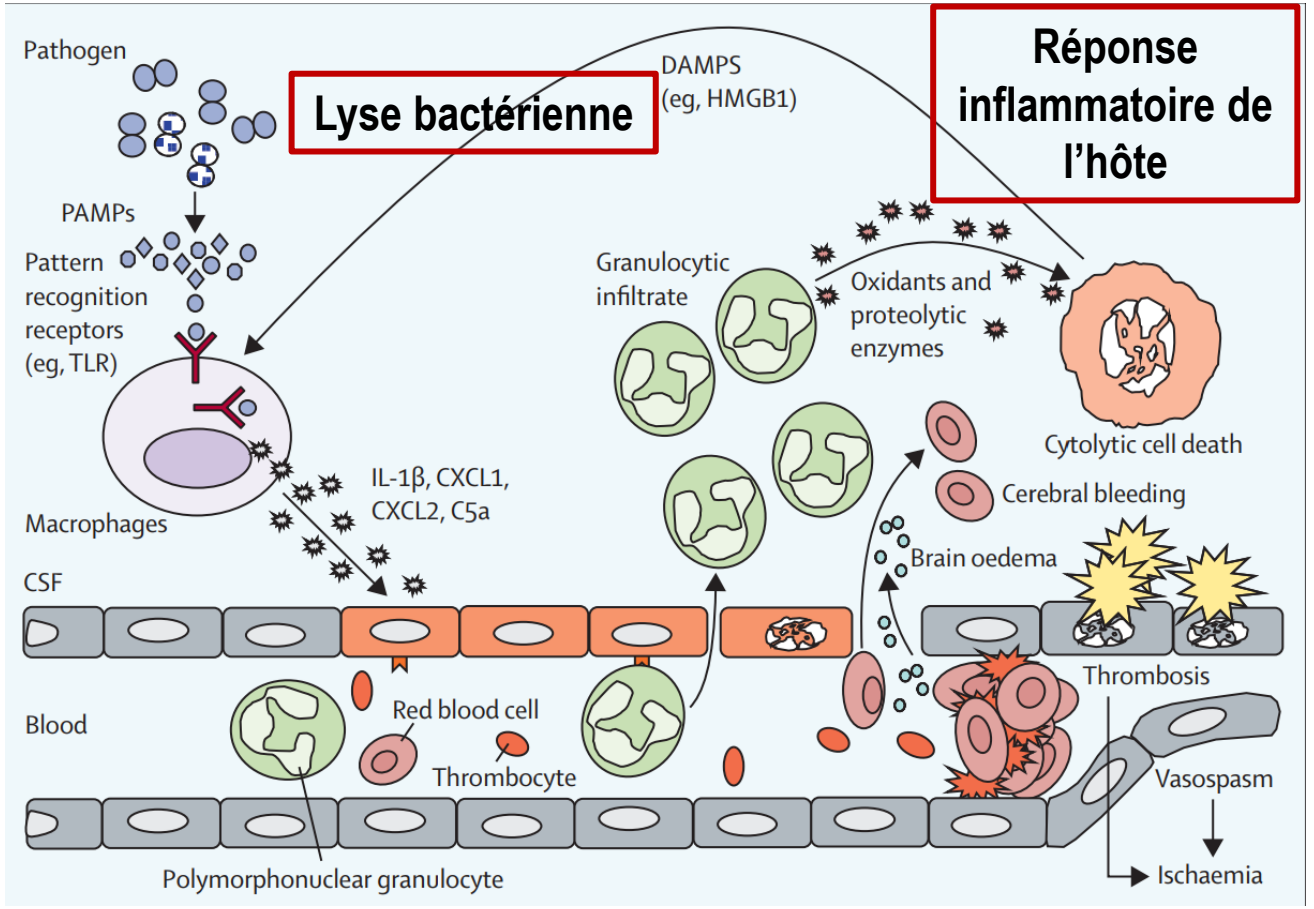


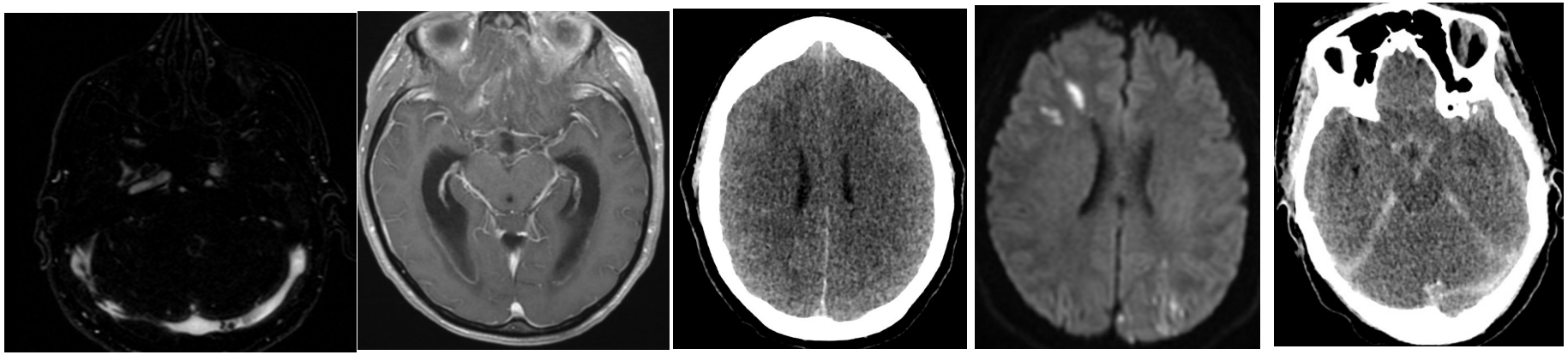
Daptomycine+ceftriaxone ± DXM vs ceftriaxone + Vancomycine ±DXM chez le lapin dans la méningite à pneumocoque



Denis Grandgirard et al, Antimicrobial Agents and chemotherapy, 2010
Egermann et al, Antimicrobial Agents and chemotherapy, 2009



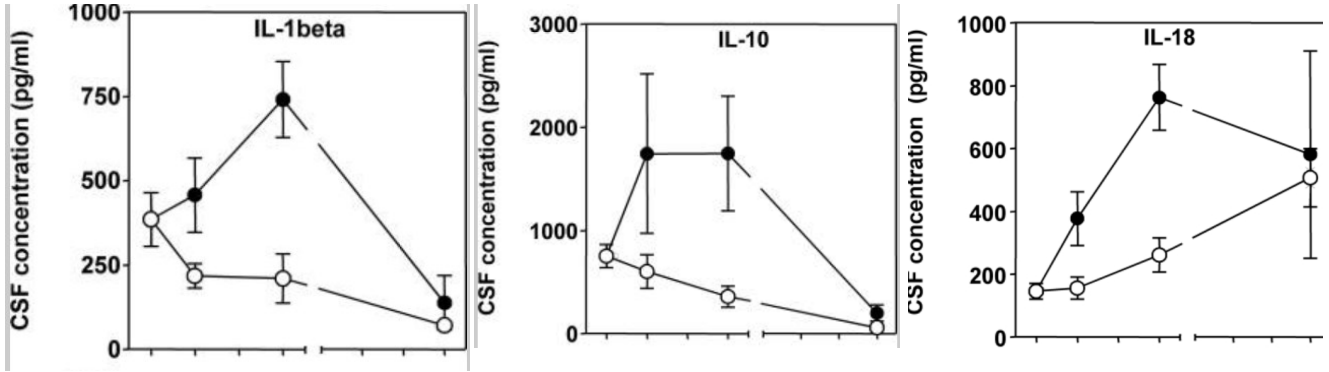


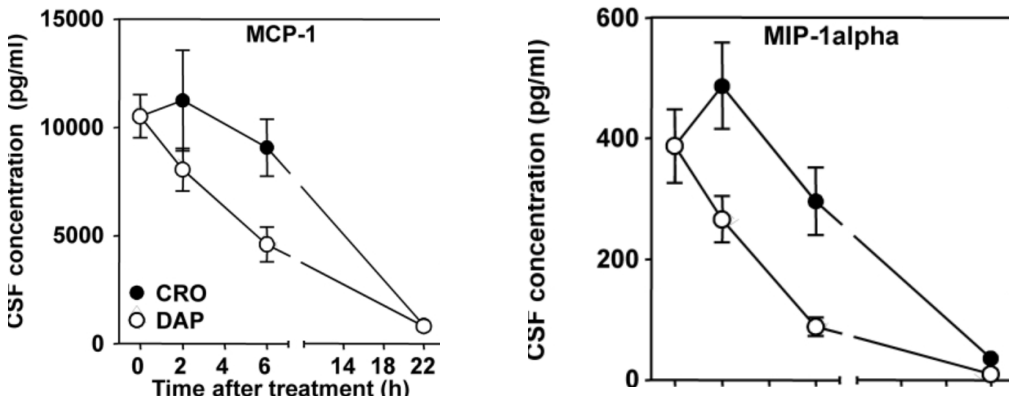


Sonneville et al, ICM 2016
Van de Beek, Lancet 2021

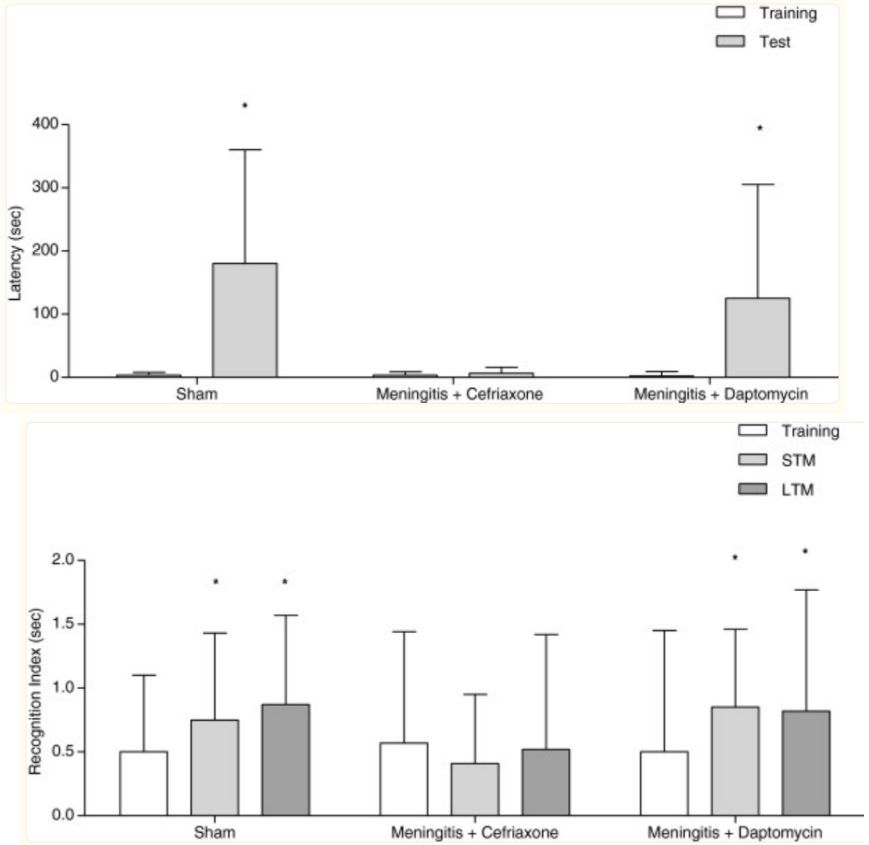
Diminution de la réaction inflammatoire pourvoyeuse de complications neurologiques ?

Daptomycine vs ceftriaxone chez le rat dans la méningite à pneumocoque
Dosage de biomarqueurs inflammatoires





Daptomycine vs ceftriaxone chez le rat dans la méningite à pneumocoque. Taches cognitives



Denis Grandgirard et al, Antimicrobial Agents and chemotherapy, 2010
Barichello et al, BMC Neurosci, 2013

Open access Protocol

BMJ Open

Addition of daptomycin for the treatment of pneumococcal meningitis: protocol for the AddaMAP study

Pascal Chavanet [1,2] Isabelle Fournel,[2,3] Abderrahmane Bourredjem,[2,3] Lionel Piroth [1] Mathieu Blot,[1] Thibault Sixt,[1] Christine Binquet [2,3]

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ AddaMAP is a multicentre single-arm phase II study assessing the safety and efficacy of a combined of non-bacteriolytic antibiotic— daptomycin—and recommended treatment for pneumococcal meningitis in adults.

⇒ Dexamethasone (10 mg) will be started, followed by daptomycin (30 min infusion of 10 mg/kg/d) and cefotaxime or ceftriaxone.

⇒ Daptomycin will be administered for 8 days if the pneumococcal meningitis is confirmed.

⇒ The diagnosis of pneumococcal meningitis will be confirmed by microbiological samples according to the French recommendations.

⇒ There is no control group in this clinical trial.

The main endpoint is the disability-free survival (defined as modified Rankin Scale mRS≤2) at day 30

Completed

Adjunction of Daptomycin for the Treatment of Pneumococcal Meningitis (AddaMAP)

ClinicalTrials.gov ID NCT03480191

Sponsor Centre Hospitalier Universitaire Dijon

Information provided by Centre Hospitalier Universitaire Dijon (Responsible Party)

Last Update Posted 2024-10-01

Prise en charge par **antibiothérapie Cefotaxime (300 mg/kg) + Dexamethasone (10 mg x 4)**. Résolution de la CIVD, contrôle de l'HTIC, diminution des sédations, instauration de levetiracetam 750X2 mg/j

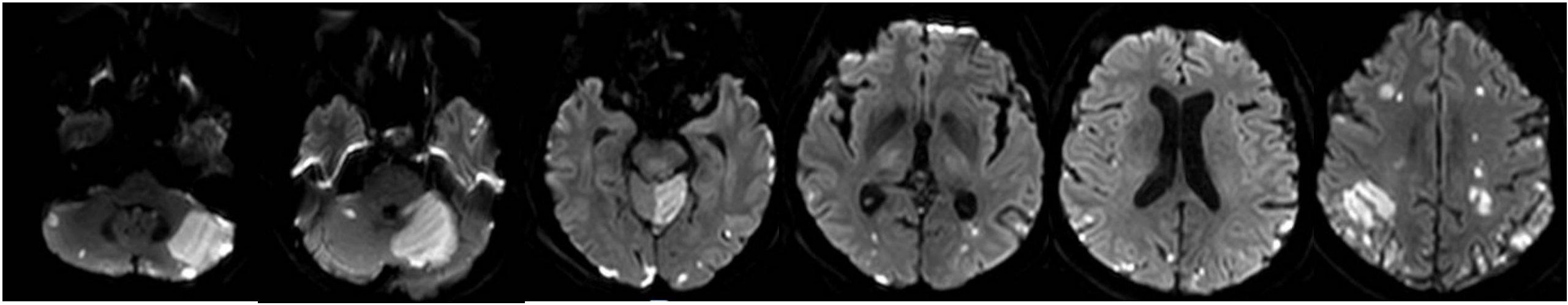
L'antibiogramme revient avec les CMI
CMI Amoxicilline **0.25 mg/l**
CMI C3G **0. 125 mg/l**

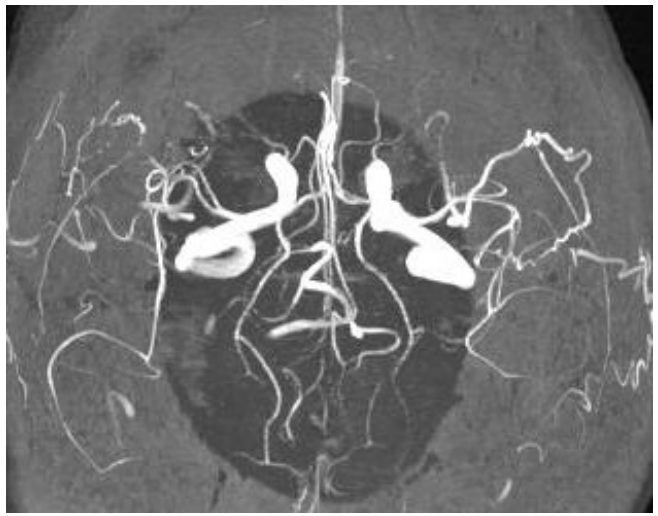
A J2 de l'arrêt des sédations et J4 du début de la prise en charge, fébrile à 38,6, persistance d'un syndrome inflammatoire biologique
Glasgow 6 (Y1V1M4) , pupilles intermédiaires réactives, réflexes du tronc cérébral présents
Syndrome pyramidal gauche avec début d'une spasticité de l'hémicorps gauche

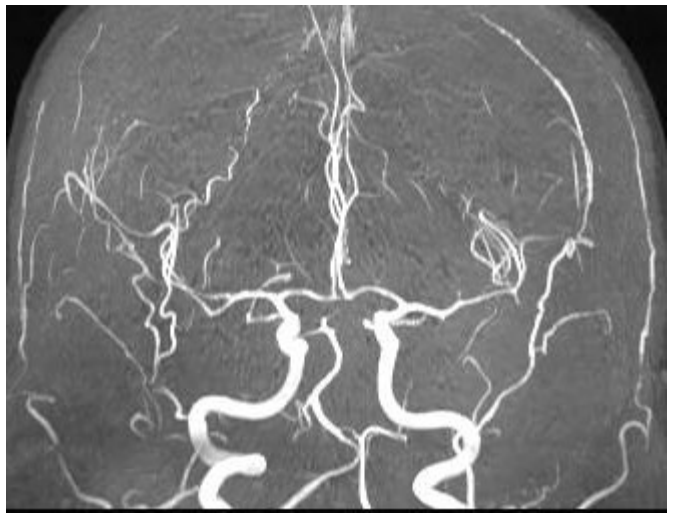
Quels examens faites-vous?

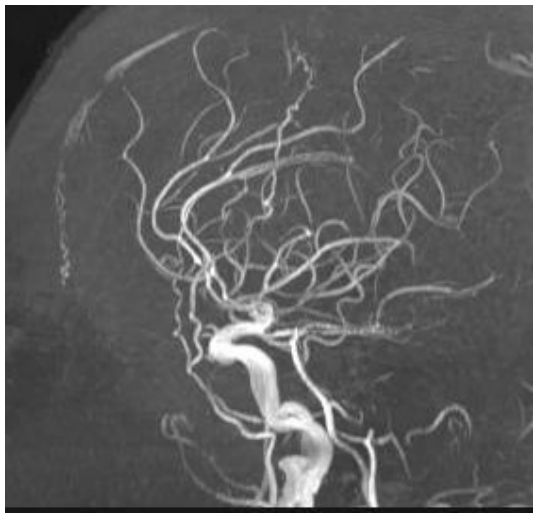
Nouvelle PL :
Leucocytes 100 dont 70 % de PNN, protéinorachie 2.7 glycorachie 2,3 mmol/l
Direct négatif
Dosage C3G:

- Sang **100 mg/L**
- **LCS : 10-20 mg/L**



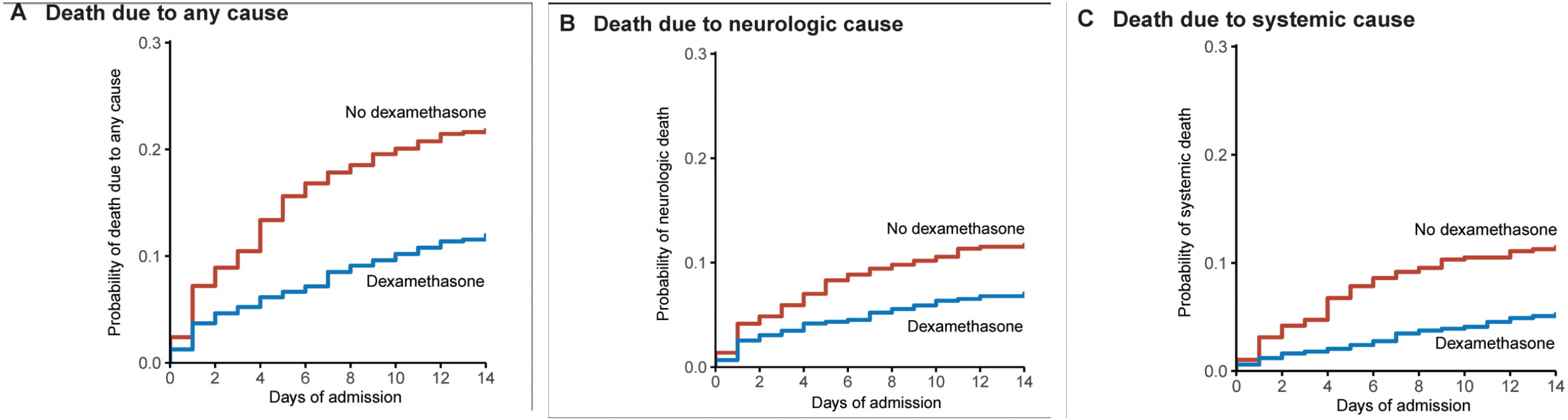






Quel est votre diagnostic et que faites-vous?

Effect of dexamethasone on survival in pneumococcal meningitis.



P values of the respective log-rank tests were all < 0.0001

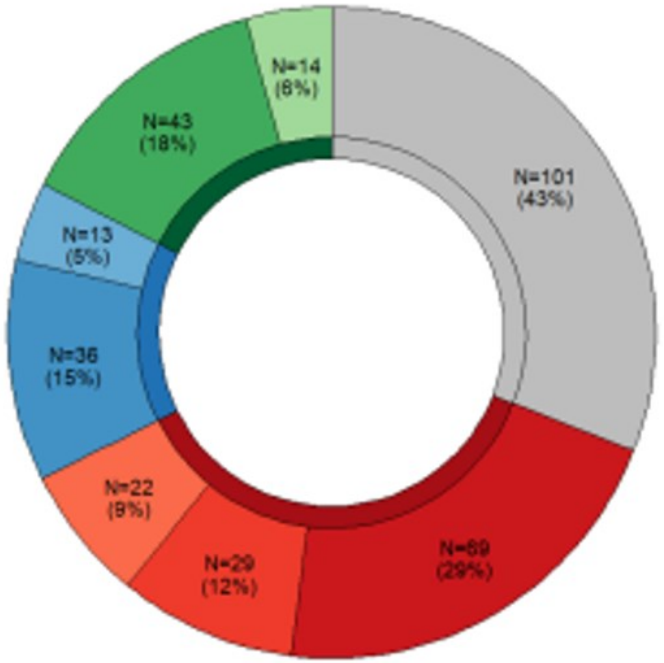
PHRC en cours de sélection « DEXALONG », Dexaméthasone 4J+ATB vs 10j + ATB

DLH Koelman et coll. Clin Infect Dis 2022

L'antibiothérapie est arrêtée après 10 jours de traitement (dose adaptée au dosages sanguins itératifs). La corticothérapie a été maintenue à doses réduites devant l'hypothèse de vascularite évoquée par l'IRM. Discussion d'une décroissance hebdomadaire de la dexaméthasone après plus de 12 jours.

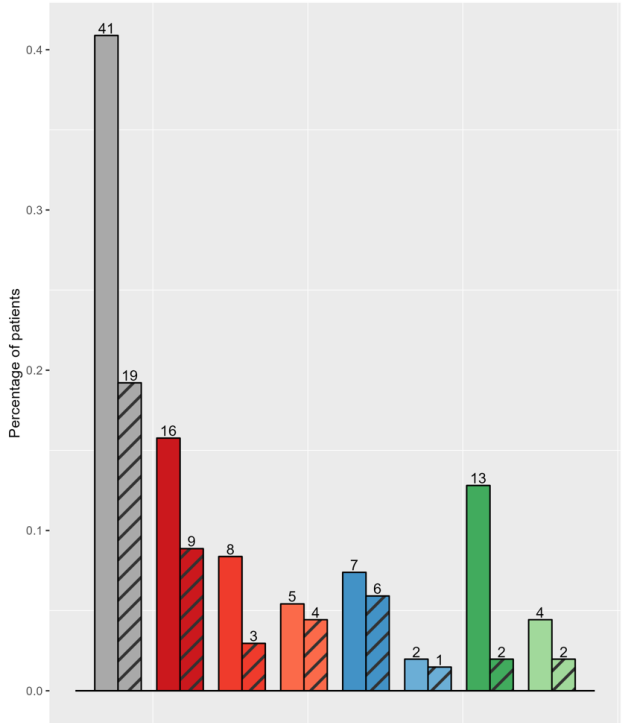
Nouvelle IRM cérébrale avant la diminution de la corticothérapie:

Devant l'extension des lésions cérébrales, décision d'un arrêt des thérapeutiques actives conduisant au décès…



Intracranial complication

- No intracranial complication
- Vascular complication
  - Ischemic lesion
  - Intracranial Hemorrhage
  - Cerebral venous thrombosis
- Infectious complication
  - Ventriculitis
  - Abcess/Empyema
- Other complication
  - Diffuse cerebral oedema
  - Hydrocephalus



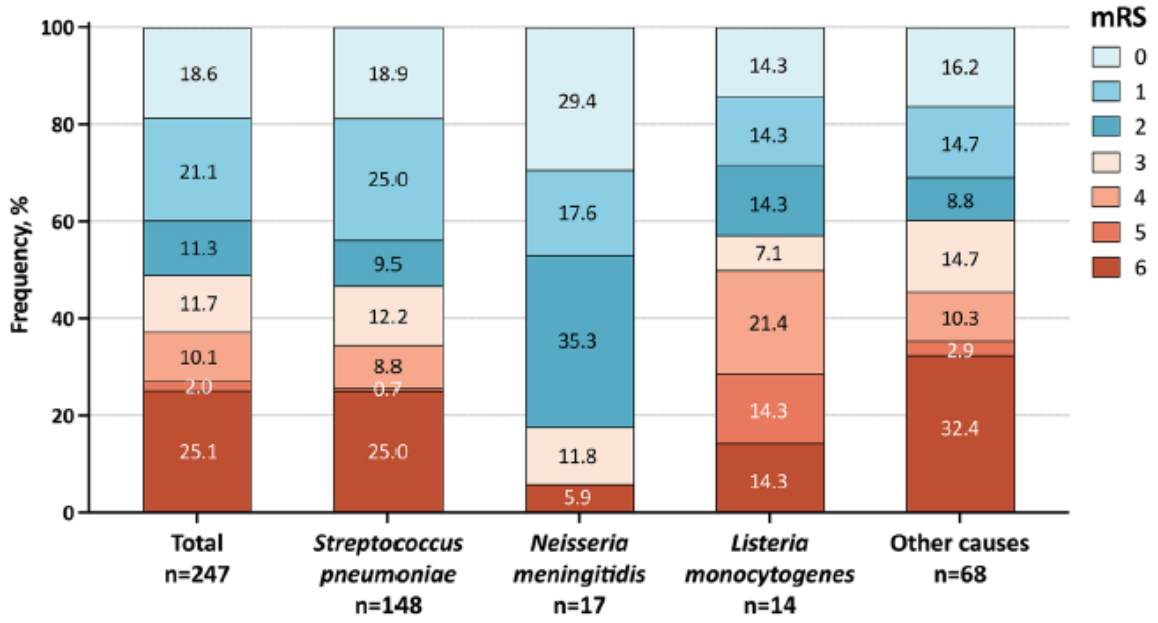
Occurrence of intracranial complications according to time of corticoid withdrawal

Univariate analysis and multivariate analysis comparing PM without CV and with CV in patients with lumbar puncture.

Variables	N	Univariate analysis (N = 168) OR [95% CI]	p value	Multivariate analysis (N = 133)** aOR [95% CI]	p value
Age for 5 units *	167	0.93 [0.84–1.03]	0.17		
Immunosuppression $	168	0.98 [0.46–2.08]	0.96		
Prior NSAID intake *	168	3.54 [1.36–9.20]	<0.01	3.28 [0.98–10.94]	0.05
Time to admission [>48 h vs ≤ 48 h) *	158	2.72 [1.19–6.22]	0.02	3.44 [1.14–10.32]	0.03
Glasgow Coma score at admission ≤ 8	163	1.28 [0.84–2.54]	0.43		
Septic shock *	162	1.72 [0.88–3.39]	0.11		
CRP (mg/L) for 50 units *	159	1.26 [1.09–1.47]	<0.01	1.19 [0.99–1.44]	0.06
Adequate antibiotic therapy *	164	2.90 [0.63–13.39]	0.17		
Adjunctive dexamethasone	163	1.60 [0.73–3.48]	0.24		
Neurological focal sign at admission *	161	1.68 [0.85–3.33]	0.14	1.72 [0.72–4.12]	0.20
CSF protein level (g/L) (>4.40 vs <=4.40) *	145	4.03 [1.63–9.96]	0.0025	4.50 [1.54–13.18]	0.006
Glycorrhachia (mmol/L)	145	0.72 [0.52–1.01]	0.0539		

Legouy et al, AIC, 2024
Artiaga, Infect Dis Now, 2023

B. Bacterial meningitis



In-hospital outcome (modified Rankin score)	
Death (6)	90/533 (16.9)
Major disability (5)	14/410 (3.4)
Moderately severe disability (4)	27/410 (6.6)
Moderate disability (3)	40/410 (9.8)
Mild disability (2)	54/410 (13.2)
Low disability (1)	107/410 (26.1)
No disability (0)	168/410 (41.0)
Unfavourable outcome[a] (mRS ≥ 2)	225/500 (45.0)

A 12 mois, 16,5 % de pronostic défavorable

Sonneville et al, Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study, ICM, 2023
Community-acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort, Tubiana, CMI 2020

Mortalité reste élevées malgré la généralisation des pratiques standardisées

Urgence à la PL, à l'antibiothérapie et à la dexaméthasone

Rechercher les **complications intracrâniennes** (vasculaires +++)

Ayez l'imagerie cérébrale facile

Pronostic fonctionnel encore sombre même à distance avec séquelles neurologiques

Grande nécessité de nouvelles pistes thérapeutiques pour améliorer le pronostic++

doi:10.1093/brain/awz222 BRAIN 2019: 142; 3325–3337 | 3325

BRAIN
A JOURNAL OF NEUROLOGY
2019

UPDATE

Targeting the complement system in bacterial meningitis

Diederik L.H. Koelman, Matthijs C. Brouwer and Diederik van de Beek

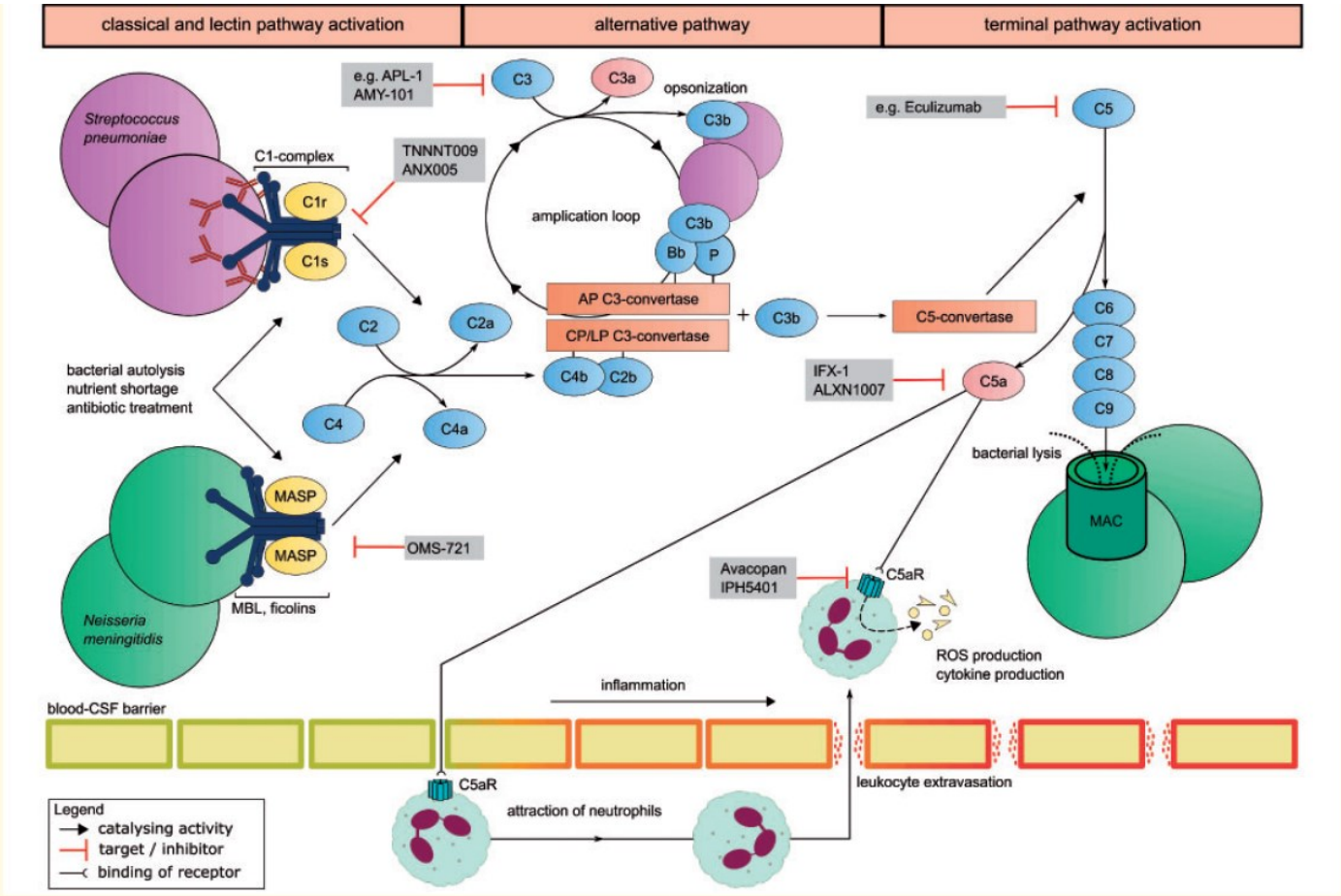


Figure 1 Complement system and therapeutic targets in bacterial meningitis. The complement system is activated via multiple

International Journal of
Molecular Sciences
2023
MDPI

Review

Blood–Brain Barrier Integrity Damage in Bacterial Meningitis: The Underlying Link, Mechanisms, and Therapeutic Targets

Ruicheng Yang [1,2], Jundan Wang [1,2], Fen Wang [1,2], Huipeng Zhang [1,2], Chen Tan [1,2,3,4], Huanchun Chen [1,2,3,4] and Xiangru Wang [1,2,3,4,*]

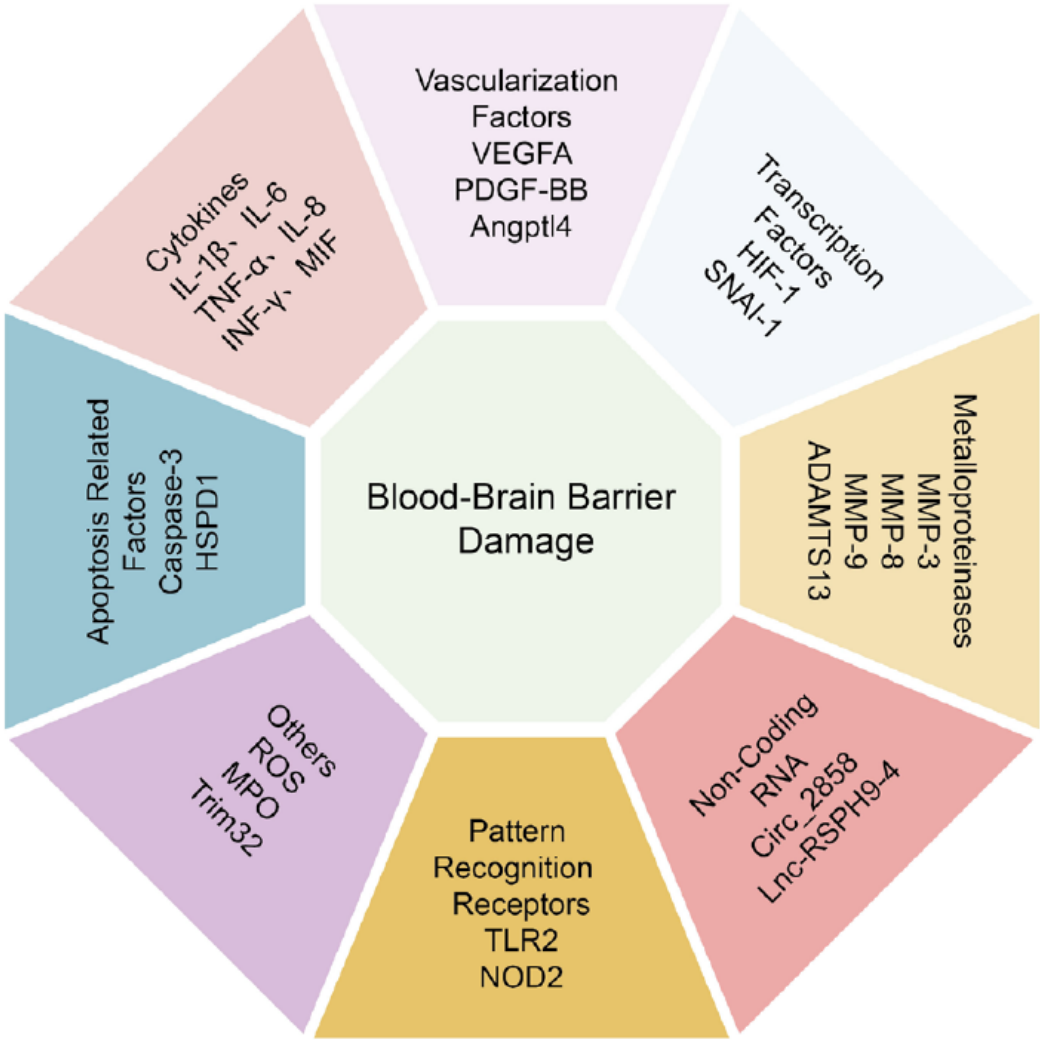
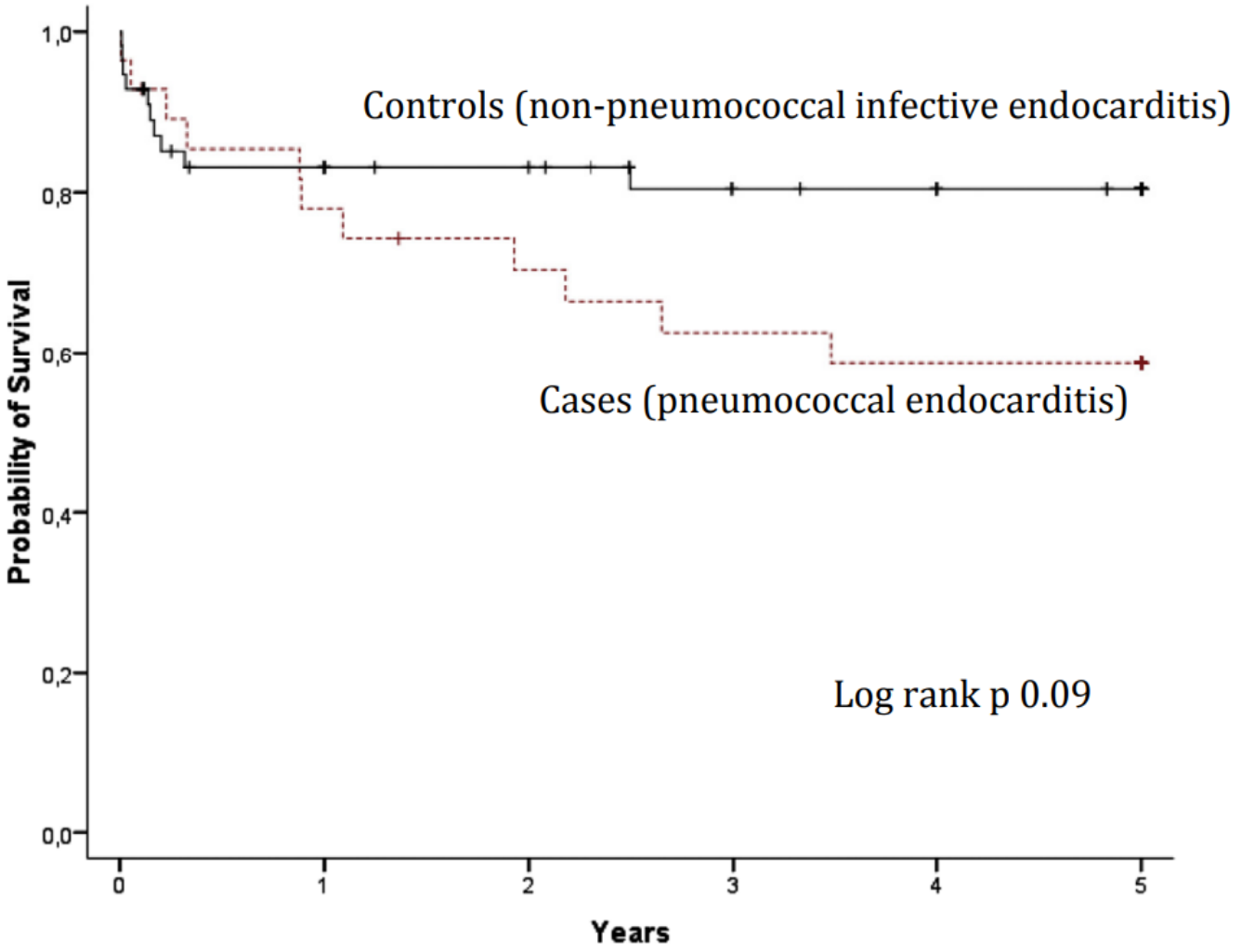


Table 3. Complications during the Clinical Course and Outcomes in Adults with Bacterial Meningitis.*

Complications	Frequency (%)
Systemic complications	
Cardiorespiratory failure	29
Hyponatremia	26
Disseminated intravascular coagulation	8
Arthritis	2–6
Endocarditis/myocarditis	<1

TABLE 1. Comparison of pneumococcal endocarditis (cases), and non-pneumococcal infective endocarditis (controls[a])

Characteristics	Pneumococcal endocarditis (*n* = 28)	Endocarditis due to other bacteria (*n* = 56)	p value
Baseline			
Age (years), mean ± SD	59.1 ± 15.3	60.9 ± 15.3	NS
Male gender, *n* (%)	19 (67.8)	40 (71.4)	NS
Alcoholism, *n* (%)	11 (39.3)	6 (10.7)	<0.01
Smoking, *n* (%)	17 (60.7)	12 (21.4)	< 0.01
Previously known valvular disease, *n* (%)	5 (17.9)	22 (39.3)	0.047
Valve(s) involved, *n* (%)			
Aortic	19 (70.4)	35 (62.5)	NS
Mitral	10 (37.0)	28 (50.0)	NS
Tricuspid	3 (11.1)	2 (3.6)	NS
Pulmonary	1 (3.7)	0 (0)	NS
Two or more valves	4 (14.8)	9 (16.1)	NS
Peri-valvular abscess	8 (34.8)	17 (30.4)	NS
Cardiac surgery, *n* (%)	18 (64.3)	31 (55.4)	NS
Time from symptoms onset to surgery, days ± SD	14.1 ± 18.2	69.0 ± 61.1	<0.001
Time from admission to surgery, days ± SD	13.3 ± 17.1	34.3 ± 43.0	0.02
Complications, *n* (%)			
Shock	15 (53.6)	13 (23.2)	<0.01
Heart failure[b]	18 (64.3)	13 (23.2)	<0.01
Embolism	5 (17.9)	16 (28.6)	NS
Meningitis	8 (28.6)	3 (5.4)	<0.01
In-hospital mortality	2 (7.1)	7 (12.5)	NS
5-year mortality	11 (39.3)	10 (17.9)	NS



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