AP-HP. Nord
Université
de Paris

Hôpital Bichat
Claude-Bernard
AP-HP

Méningites et Encéphalites
Que faire des recommandations ?

Pr Romain Sonneville - Dr Yousra Kherabi

BUA dans les infections communautaires graves

Vendredi 6 Juin 2025

INFECTIODPC

Spilf
Société de Pathologie Infectieuse de Langue Française

De quoi allons-nous parler ?

- Méningite bactérienne
- Encéphalite d’allure ‘virale’
- Méningite tuberculeuse
- Méningite à cryptocoque

De quoi allons-nous parler ?

- **Méningite bactérienne**
- Encéphalite d’allure ‘virale’
- Méningite tuberculeuse
- Méningite à cryptocoque

Vignette clinique 1

- Homme 40 ans
- ATCD: 0, alcool occasionnel
- Histoire récente : fièvre, céphalées depuis 3 jours….
- Retrouvé somnolent au domicile par sa femme

- Au SAU :
  - Température 39.1°C   GCS = 13
  - Pas de syndrome méningé
  - Pas de signe neurologique focal

  - PA 130/80 mmHg, FC 110/mn
  - FR 20, SpO2 99% en air ambiant

***Recommandations* SPILF 2017**
Grade A : Toute dysfonction aiguë du SNC associée à de la fièvre doit faire évoquer une méningo-encéphalite infectieuse

Y

Conduite à tenir à l’arrivée: laquelle de ces propositions est juste?

A. Vous débutez un traitement antibiotique avant toute chose

B. Vous réalisez une ponction lombaire (PL) d’emblée

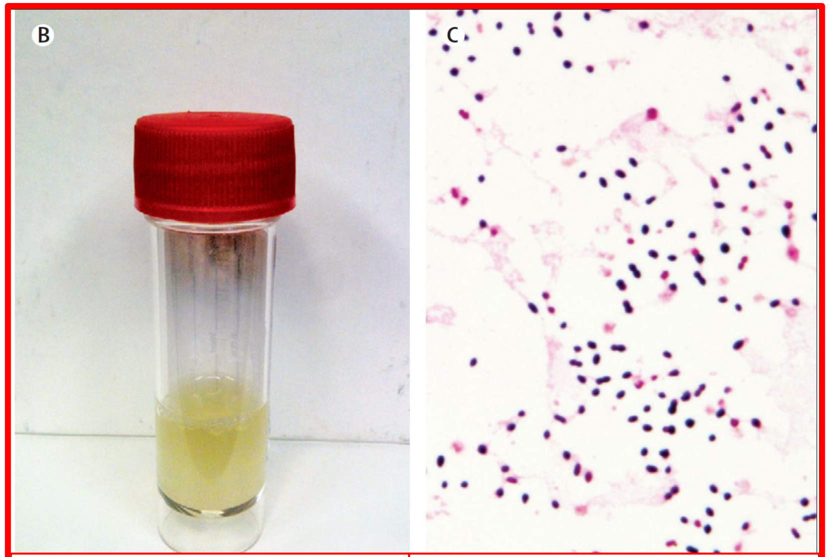
C. Vous réalisez une imagerie cérébrale puis une PL

D. Vous laissez le patient en surveillance simple car l’absence de syndrome méningé clinique rend le diagnostic de méningite bactérienne peu probable

Vignette clinique

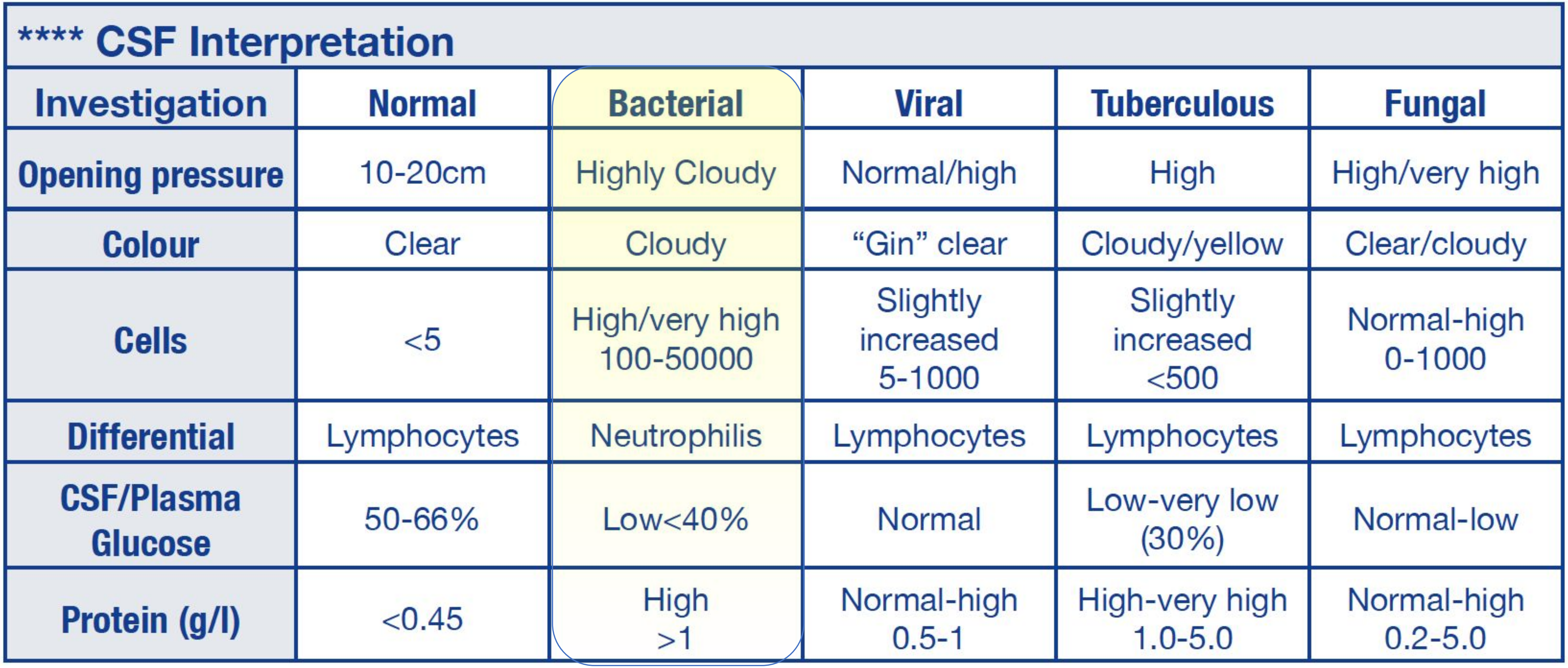
Y

- PL : pression ouverture élevée (> 20 cm H_2O)
- Traitement initial, débuté dès la constatation d'un LCS trouble:
  - Dexamethasone 10 mg x 4 / j IVD
  - Cefotaxime 4g puis 4 g x 4 / j IVL



LCR trouble | Gram

R



**** CSF Interpretation

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
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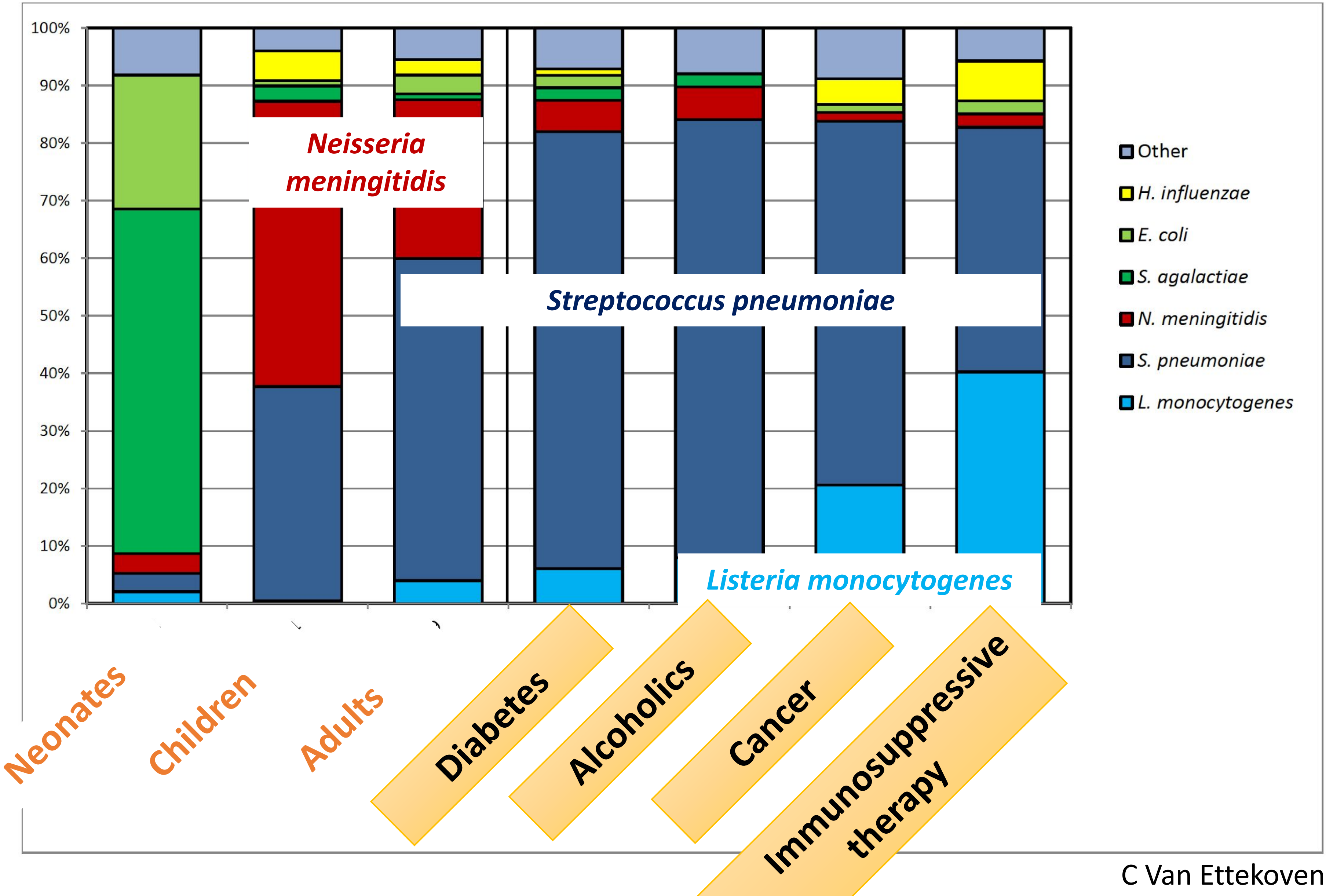
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

T. Solomon, UK guidelines for management of encephalitis, 2012

Bactéries les plus fréquentes



C Van Ettekoven, Clin Microbiology and infection 2018

R

ORIGINAL ARTICLE

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. L. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

Grade A recommendation

In patients with bacterial meningitis, **classic clinical characteristics may be absent**.

Bacterial meningitis should not be ruled out solely on the absence of classic symptoms.

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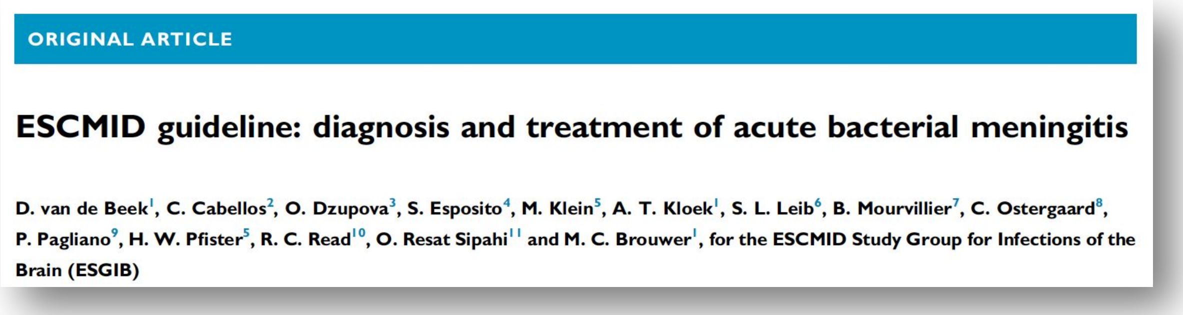
AND INFECTIOUS DISEASES

ESCMID guideline 2015 : diagnosis and treatment of acute bacterial meningitis



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R

Grade A recommendation

It is strongly recommended to perform **cranial imaging before LP** in patients with:

- focal neurologic deficits (excluding cranial nerve palsies)
- new-onset seizures
- severely altered mental status (GCS < 10)
- severely immunocompromised state

In patients lacking these characteristics, cranial imaging is NOT recommended.

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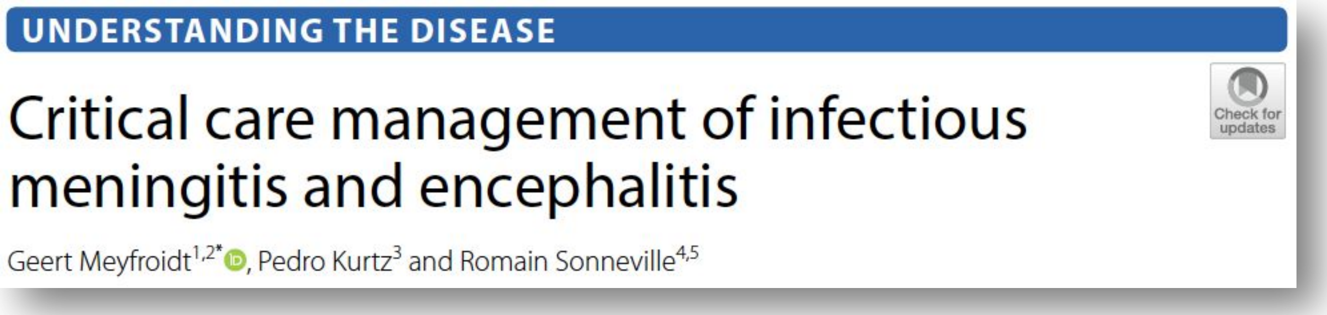

UNDERSTANDING THE DISEASE

Critical care management of infectious meningitis and encephalitis

Geert Meyfroidt[1,2*], Pedro Kurtz[3] and Romain Sonneville[4,5]

R

1 hour

1
- **Blood cultures**
- **Lumbar puncture** (unless contraindicated)

2
- **Antibiotic therapy**
- Adjunctive **dexamethasone**

3
- Early **ICU admission ?**

Intensive Care Medicine 2019

ORIGINAL ARTICLE

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D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. L. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

R

Grade A recommendation

It is strongly recommended to start antibiotic therapy **as soon as possible** in acute bacterial meningitis patients.

The time period until antibiotics are **administered should not exceed 1 hour.**

Whenever lumbar puncture is delayed (e.g. cranial CT), **empirical treatment should be started immediately** based on clinical suspicion, even if the diagnosis has not been established.

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESCMID guideline 2015 : diagnosis and treatment of acute bacterial meningitis

Antibiothérapies probabilistes pour les méningites présumées bactériennes

R

- **Cefotaxime** : 200 mg/kg/day IV (intermittent infusion, 4 doses) for all patients

- **In countries where the prevalence of cephalosporin-R pneumococcus is > 1%, add** :
  - **Vancomycin** : 30 mg/kg IV bolus followed by continuous infusion 45-60 mg/kg/day

  or
  - **Rifampicin** : 600 mg / day IV (intermittent infusion)

- **if risk factor(s) for *Listeria monocyotgenes*** is present, add :

  (Age > 50 years, alcoholism, cancer, immunosuppressive therapy…)
  - **Amoxicillin** : 200 mg/kg/day IV (intermittent infusion, 4 doses)

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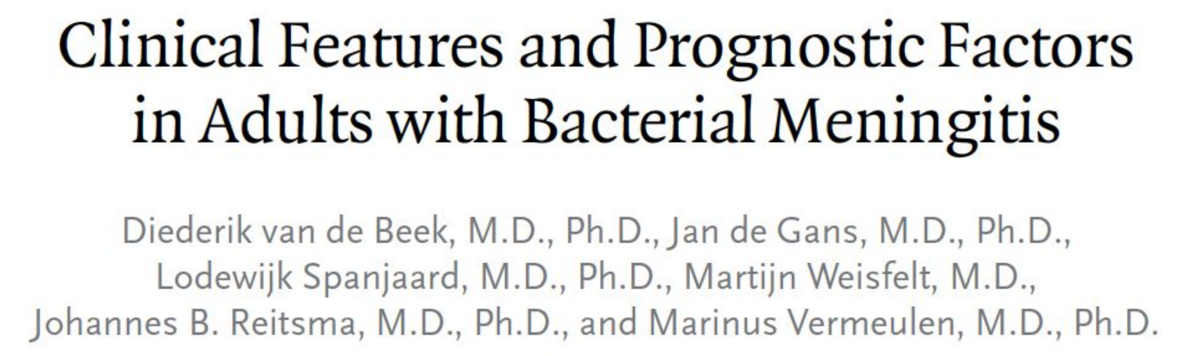
ESCMID guideline 2015 : diagnosis and treatment of acute bacterial meningitis



Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis

Diederik van de Beek, M.D., Ph.D., Jan de Gans, M.D., Ph.D.,
Lodewijk Spanjaard, M.D., Ph.D., Martijn Weisfelt, M.D.,
Johannes B. Reitsma, M.D., Ph.D., and Marinus Vermeulen, M.D., Ph.D.

R

- **Gram's staining** of **cerebrospinal fluid** revealed the microorganism in 524 of 652 episodes (sensitivity, 80 percent; specificity, 97 percent).

- The yield of **Gram's staining** was **similar in patients who had previously received antimicrobial therapy and those who had not.**

- **Positive blood cultures** were observed in **404 / 611 (66%) patients**

New Eng J Med 2004

A propos des corticoïdes: laquelle (ou lesquelles) de ces propositions est (sont) juste(s)?

A. Ils sont indiqués dans les méningites bactériennes

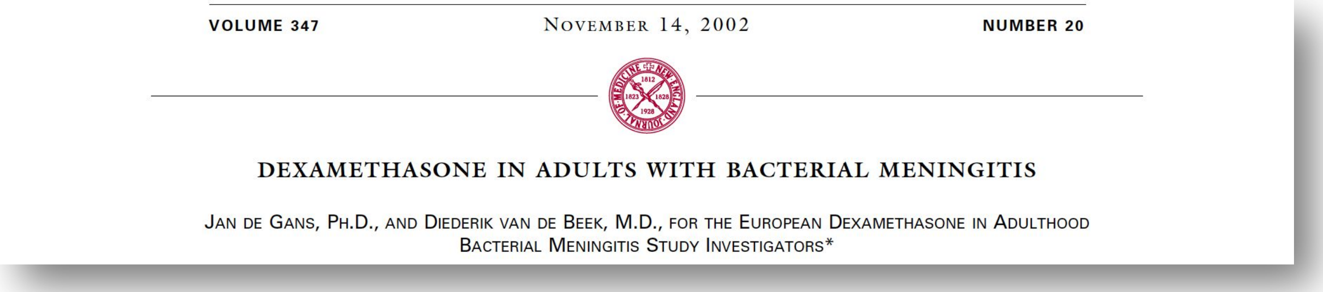
B. Ils réduisent la mortalité des méningites à méningocoque

C. Ils réduisent la mortalité des méningites à pneumocoque

D. Ils sont associés à une réduction des séquelles neurosensorielles

E. La durée de traitement standard chez l’adulte est de 8 jours

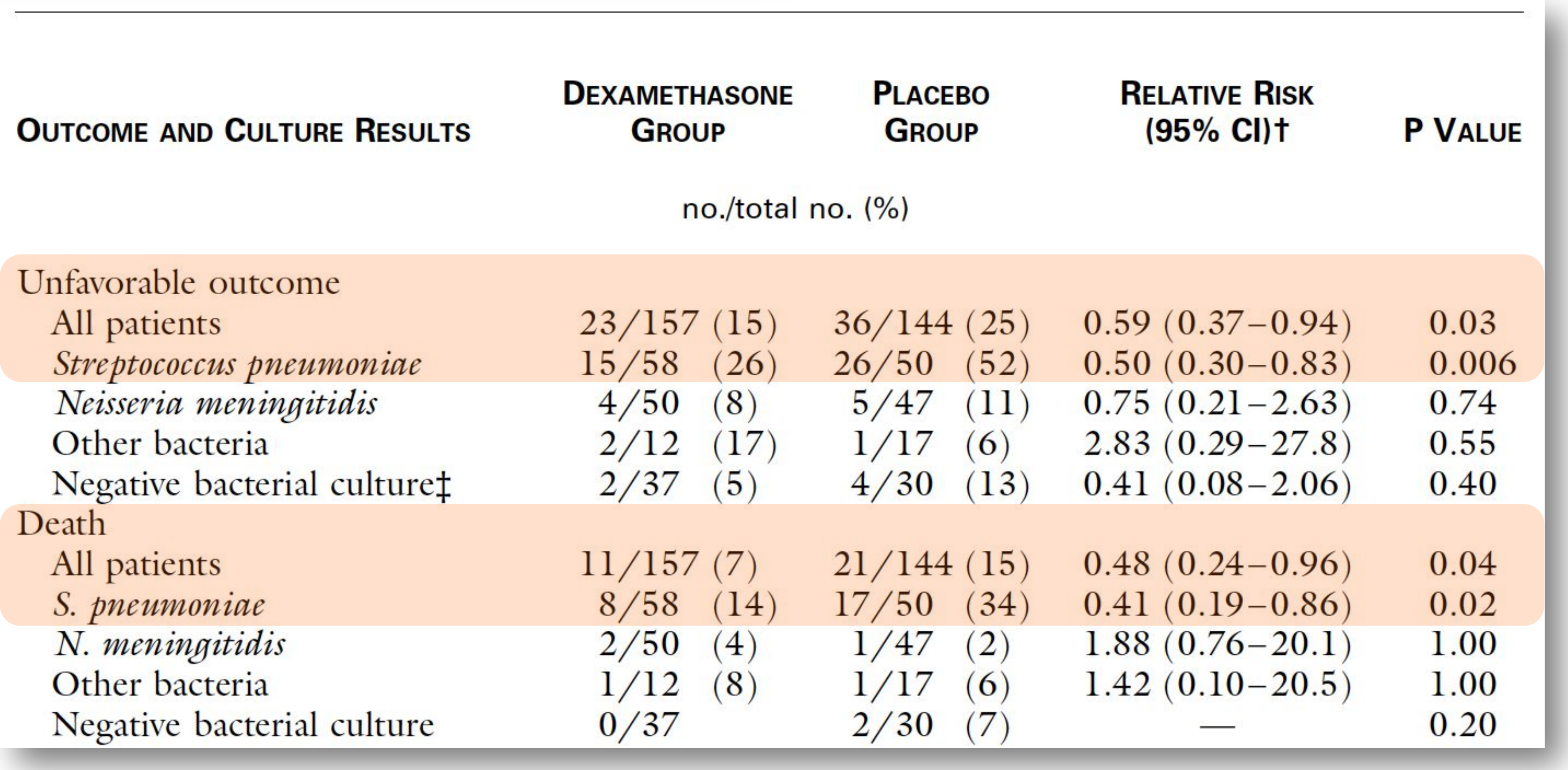
R



VOLUME 347 NOVEMBER 14, 2002 NUMBER 20

DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

JAN DE GANS, PH.D., AND DIEDERIK VAN DE BEEK, M.D., FOR THE EUROPEAN DEXAMETHASONE IN ADULTHOOD BACTERIAL MENINGITIS STUDY INVESTIGATORS*



OUTCOME AND CULTURE RESULTS	DEXAMETHASONE GROUP	PLACEBO GROUP	RELATIVE RISK (95% CI)†	P VALUE
	no./total no. (%)			
Unfavorable outcome				
All patients	23/157 (15)	36/144 (25)	0.59 (0.37–0.94)	0.03
Streptococcus pneumoniae	15/58 (26)	26/50 (52)	0.50 (0.30–0.83)	0.006
Neisseria meningitidis	4/50 (8)	5/47 (11)	0.75 (0.21–2.63)	0.74
Other bacteria	2/12 (17)	1/17 (6)	2.83 (0.29–27.8)	0.55
Negative bacterial culture‡	2/37 (5)	4/30 (13)	0.41 (0.08–2.06)	0.40
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20

New Eng J Med 2002

R

Corticosteroids for acute bacterial meningitis

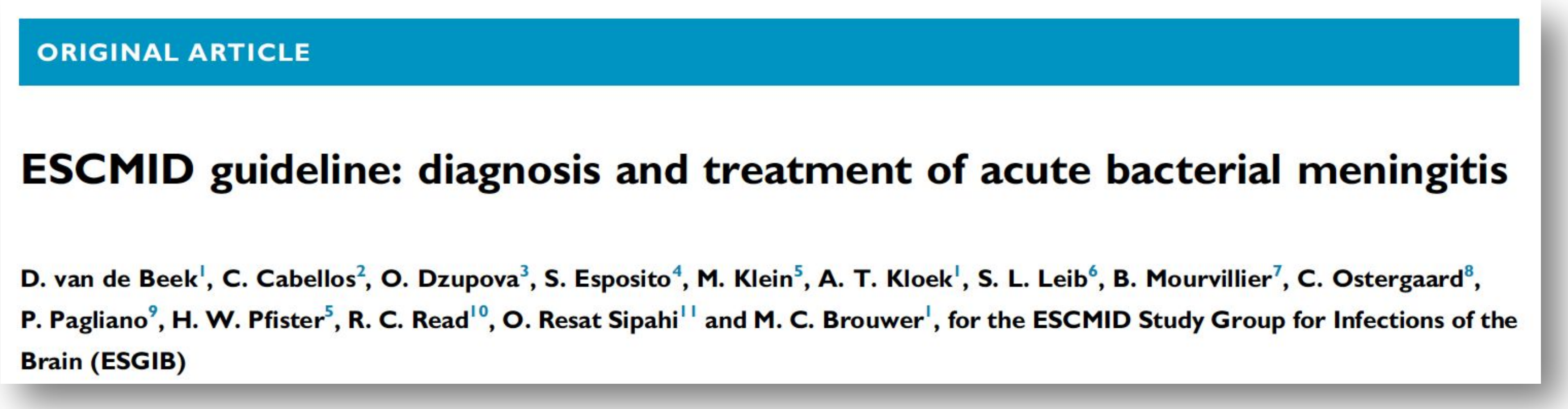
	RR	**95% CI**
Mortality*	0.90	0.80-1.01
Mortality in adults**	0.74	0.53-1.05
Mortality in patients with *S. pneumomiae* meningitis	0.84	0.72-0.98
Hearing loss	0.74	0.63-0.87
Neurological sequelae	0.83	0.69-1.00

* p= 0.07, ** p= 0.09

There was no beneficial effect of corticosteroid therapy in low-income countries.

THE COCHRANE
COLLABORATION®

Brouwer MC et al. Cochrane Database Syst Review 2015



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R

Grade A recommendations

Empiric treatment with dexamethasone is strongly recommended for all adults

(10 mg q6h for 4 days) with acute bacterial meningitis in the setting of high income countries

Treatment with dexamethasone is **strongly recommended to be initiated with the first dose of antibiotic treatment.**

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EUROPEAN SOCIETY
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AND INFECTIOUS DISEASES

ESCMID guideline 2015 : diagnosis and treatment of acute bacterial meningitis

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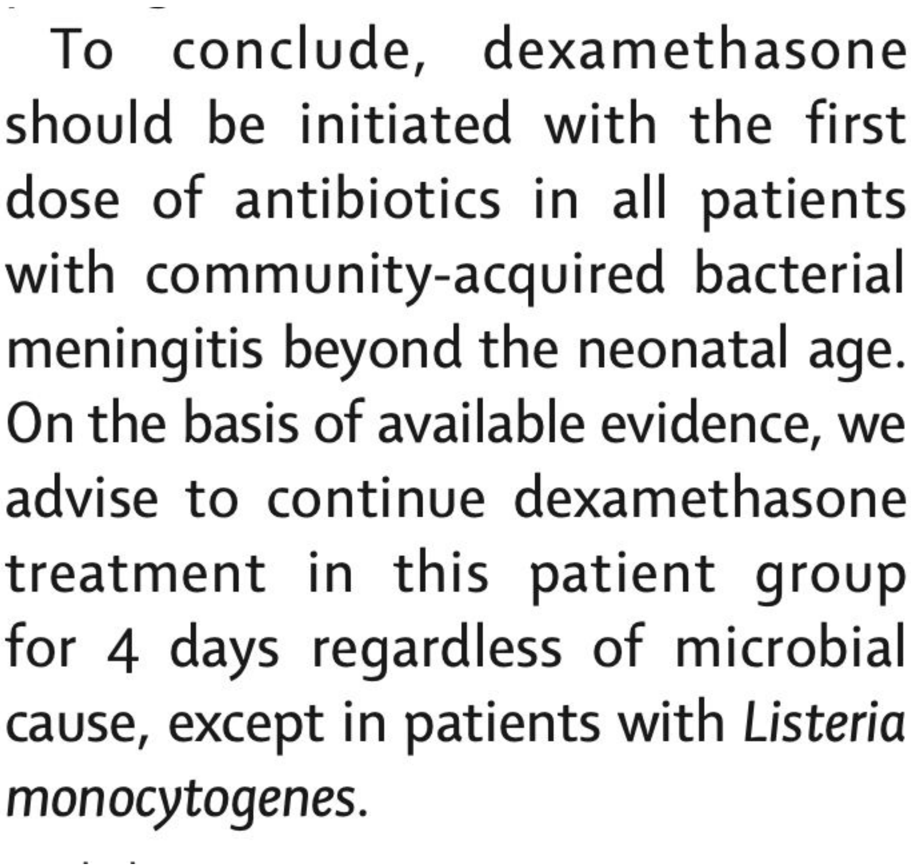
CORRESPONDENCE · Volume 399, Issue 10326, P718, February 19, 2022

Steroid use in non-pneumococcal and non-*Haemophilus* bacterial meningitis – Authors' reply



To conclude, dexamethasone should be initiated with the first dose of antibiotics in all patients with community-acquired bacterial meningitis beyond the neonatal age. On the basis of available evidence, we advise to continue dexamethasone treatment in this patient group for 4 days regardless of microbial cause, except in patients with *Listeria monocytogenes*.

Van de Beek et al. The Lancet 2022

R

Méningite - take home messages

- Au SAU / en réa souvent, pas la séquence idéale PL puis ATB

  L'URGENCE est à l'antibiothérapie < 1 heure

- Dexaméthasone avec la première dose d'antibiotique

  En 2025, pour toute méningite bactérienne… sauf *Listeria*

De quoi allons-nous parler ?

- Méningite bactérienne
- **Encéphalite d’allure ‘virale’**
- Méningite tuberculeuse
- Méningite à cryptocoque

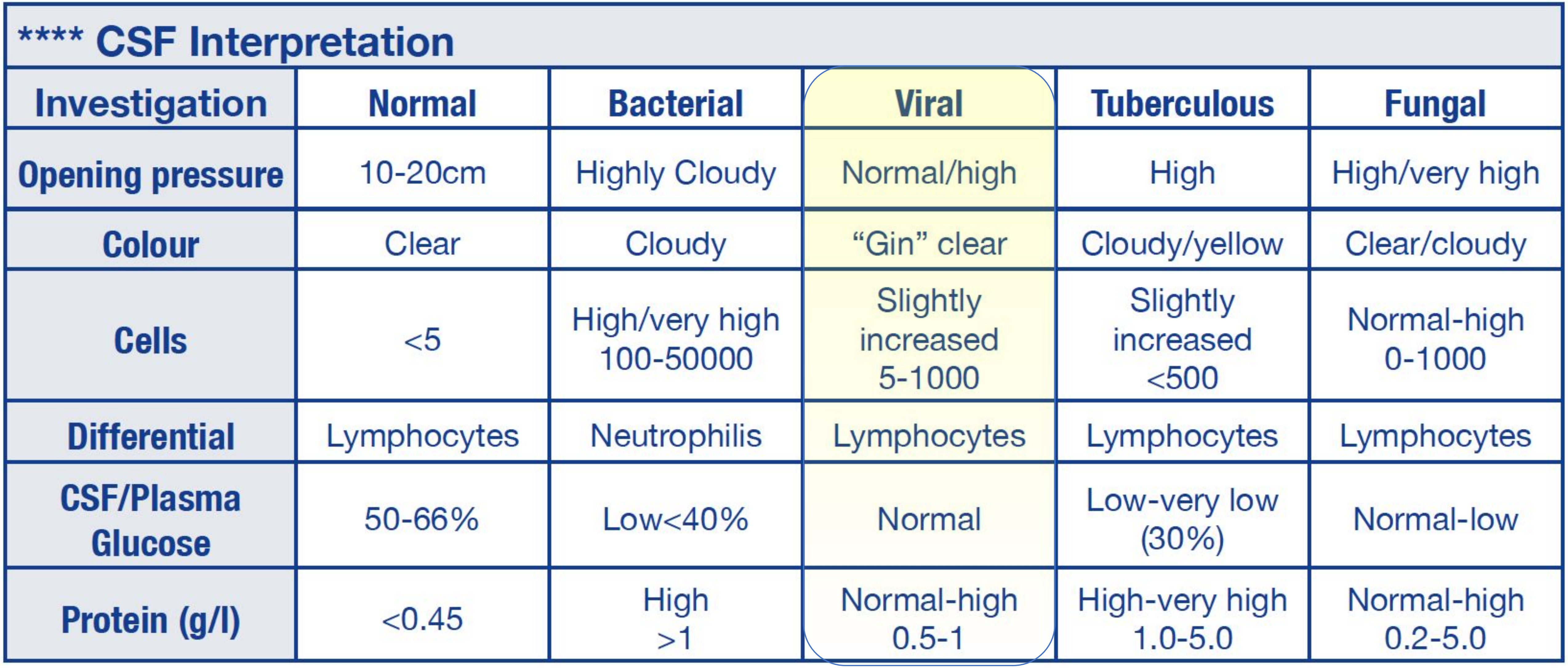
Y

Vignette clinique 2

H 27 ans, confusion, Fièvre 38.7° C
PL : 80 éléments / mm^3, 90% lymphocytes, prot 0.8g/l, glycorachie 4 mmol/l

Quelle est votre attitude thérapeutique ?

R



**** CSF Interpretation

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	“Gin” clear	Cloudy/yellow	Clear/cloudy
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CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
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T. Solomon, UK guidelines for management of encephalitis, 2012

Recommandations **SPILF 2017**

Grade A : en l’absence d’orientation étiologique, **le traitement initial** associe :

Aciclovir : 10mg/kg/8h IVL (dans les 6h suivant admission)
ET
Amoxicilline : 200 mg/kg/24h IVL en perfusion continue

Adapter les posologies à la fonction rénale

Réévaluer à 48 heures +++
(cultures bactériennes, PCR HSV, VZV, enterovirus)

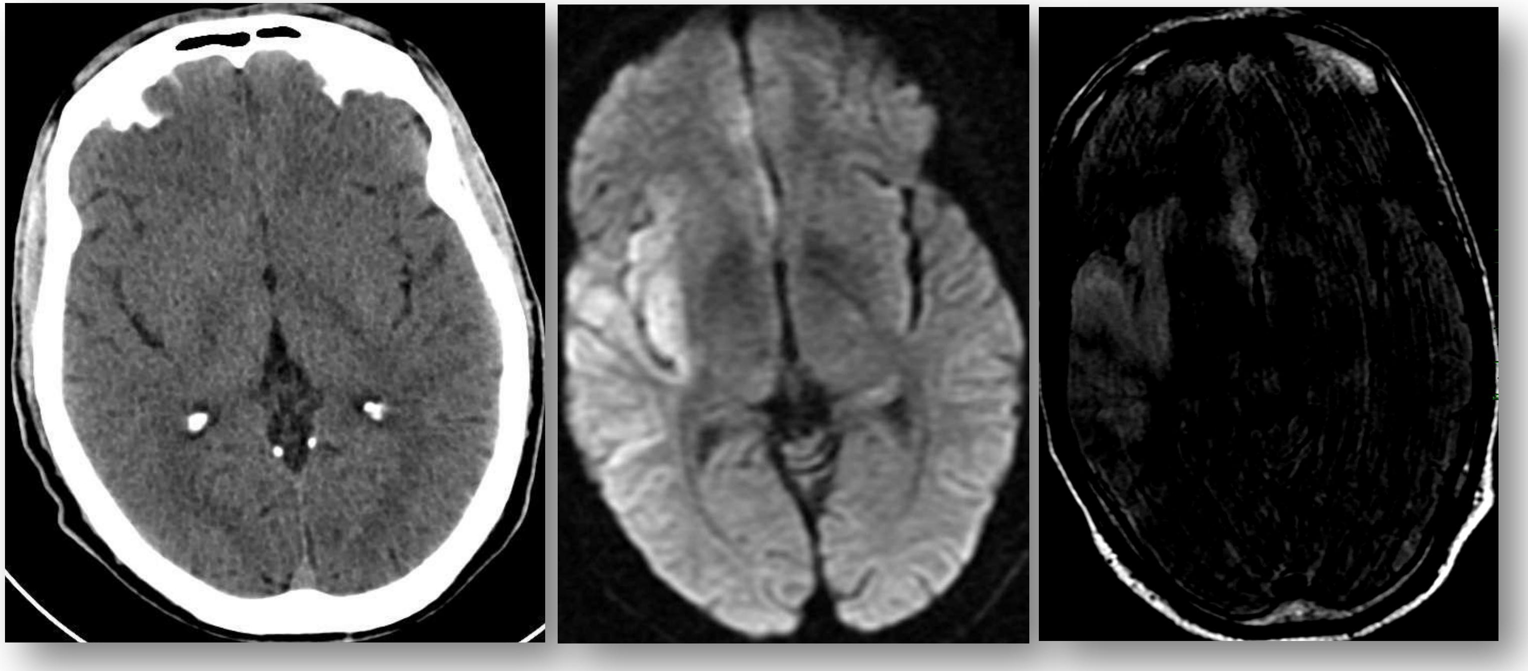
R

R

***Recommandations* SPILF 2017**
Grade A : si elle est possible, **l’IRM cérébrale** est l’imagerie à réaliser **en première intention (Diffusion, FLAIR, T2*, T1 gadolinium)**

H 27 ans, confusion, Fièvre 38.7° C
PL : 80 éléments / mm^3, 90% lymphocytes, prot 0.8g/l, glycorachie 4 mmol/l

Aciclovir IV 10mg/kg/8h IVL



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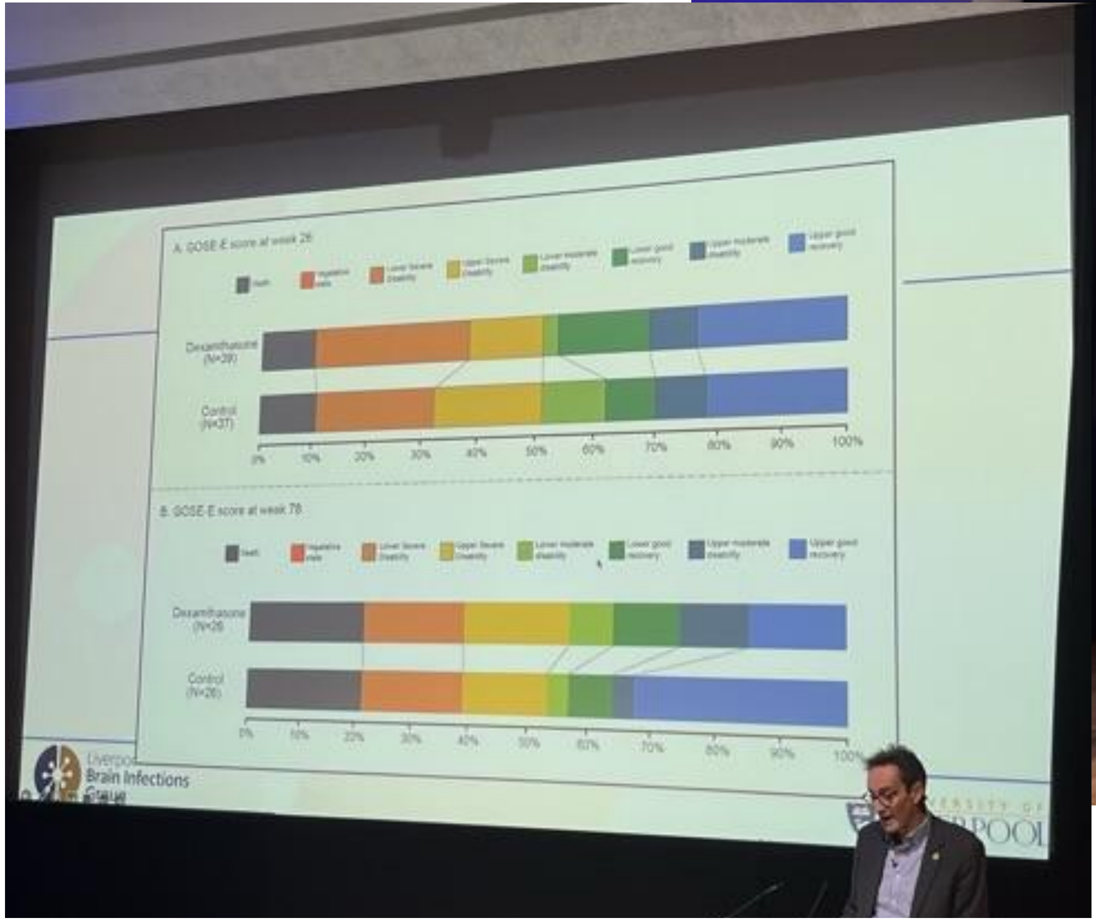
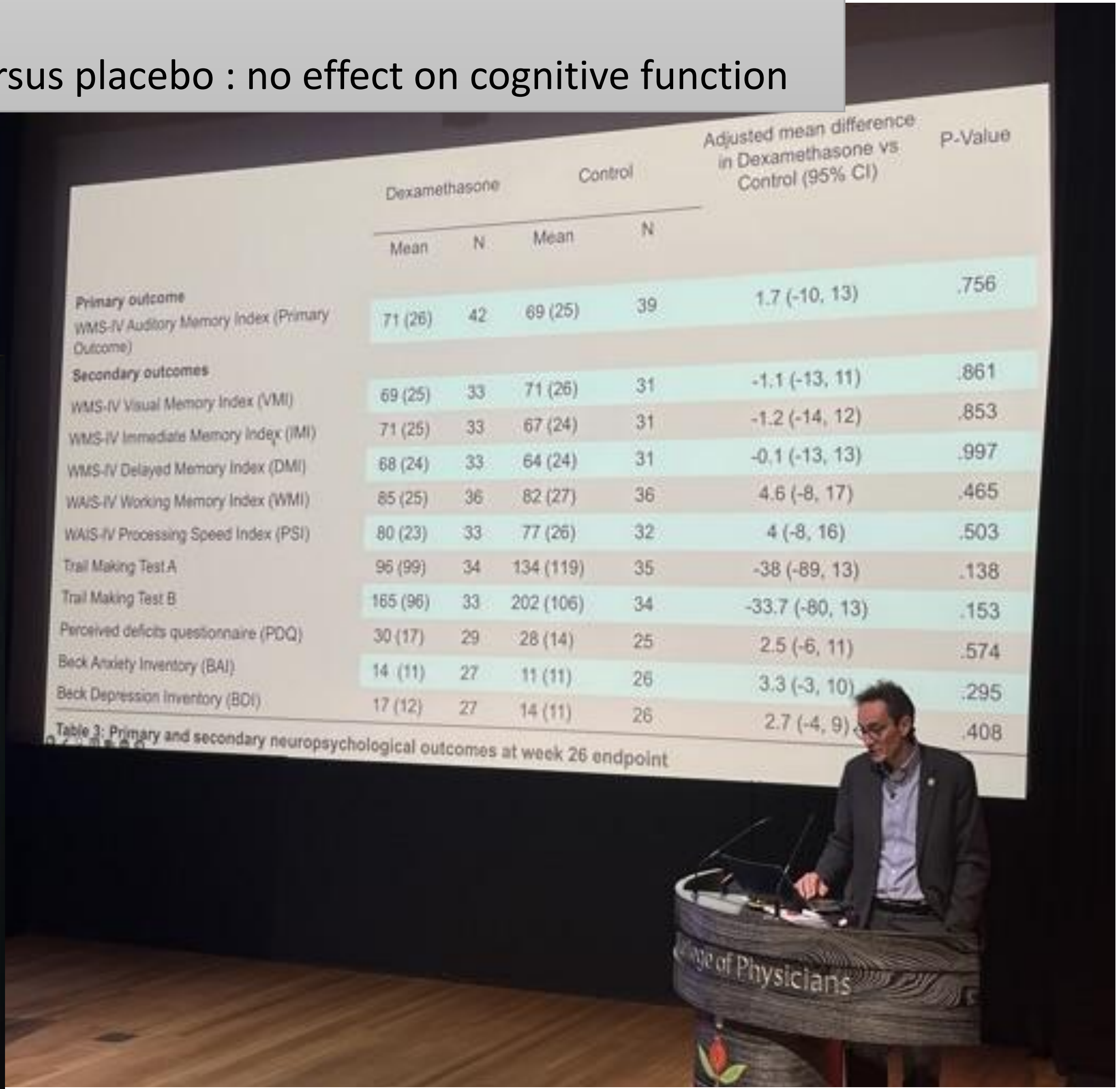
DEXENCEPH
HSV Encephalitis
DXM 10 mg x 4 / j versus placebo : no effect on cognitive function

Encephalitis International
The brain inflammation charity





	Dexamethasone		Control		Adjusted mean difference in Dexamethasone vs Control (95% CI)	P-Value
	Mean	N	Mean	N		
Primary outcome						
WMS-IV Auditory Memory Index (Primary Outcome)	71 (26)	42	69 (25)	39	1.7 (-10, 13)	.756
Secondary outcomes						
WMS-IV Visual Memory Index (VMI)	69 (25)	33	71 (26)	31	-1.1 (-13, 11)	.861
WMS-IV Immediate Memory Index (IMI)	71 (25)	33	67 (24)	31	-1.2 (-14, 12)	.853
WMS-IV Delayed Memory Index (DMI)	68 (24)	33	64 (24)	31	-0.1 (-13, 13)	.997
WAIS-IV Working Memory Index (WMI)	85 (25)	36	82 (27)	36	4.6 (-8, 17)	.465
WAIS-IV Processing Speed Index (PSI)	80 (23)	33	77 (26)	32	4 (-8, 16)	.503
Trail Making Test A	96 (99)	34	134 (119)	35	-38 (-89, 13)	.138
Trail Making Test B	165 (96)	33	202 (106)	34	-33.7 (-80, 13)	.153
Perceived deficits questionnaire (PDQ)	30 (17)	29	28 (14)	25	2.5 (-6, 11)	.574
Beck Anxiety Inventory (BAI)	14 (11)	27	11 (11)	26	3.3 (-3, 10)	.295
Beck Depression Inventory (BDI)	17 (12)	27	14 (11)	26	2.7 (-4, 9)	.408

Table 3: Primary and secondary neuropsychological outcomes at week 26 endpoint

Dans quelques jours …

EAN-ESCMID guidelines on the diagnosis and management of encephalitis in adults caused by infection

VZV : 15 mg/kg/8h → 10 mg/kg/8h

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R

Encéphalite virale - take home messages

- Importance de l’imagerie ++
- CTC et HSV : on attend les résultats définitifs de DEXENCEPH
- Les nouvelles recommandations ESCMID arrivent : baisse de la posologie pour VZV, pas de nouveauté sur la CTC

De quoi allons-nous parler ?

- Méningite bactérienne
- Encéphalite d’allure ‘virale’
- **Méningite tuberculeuse**
- Méningite à cryptocoque

Vignette clinique 3

R

Madame M. 49 ans consulte aux Urgences pour céphalées intenses depuis 8 jours

ATCD :

Infection par le VIH en rupture de suivi

Dernier bilan immuno-virologique 11/2024 : 80 CD4 CV 5 log

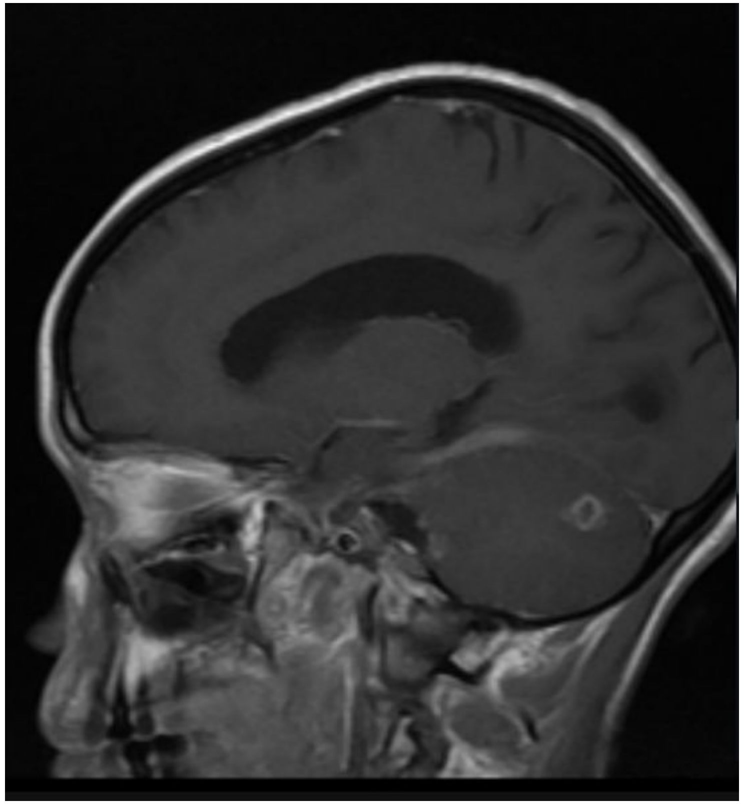
Cliniquement :

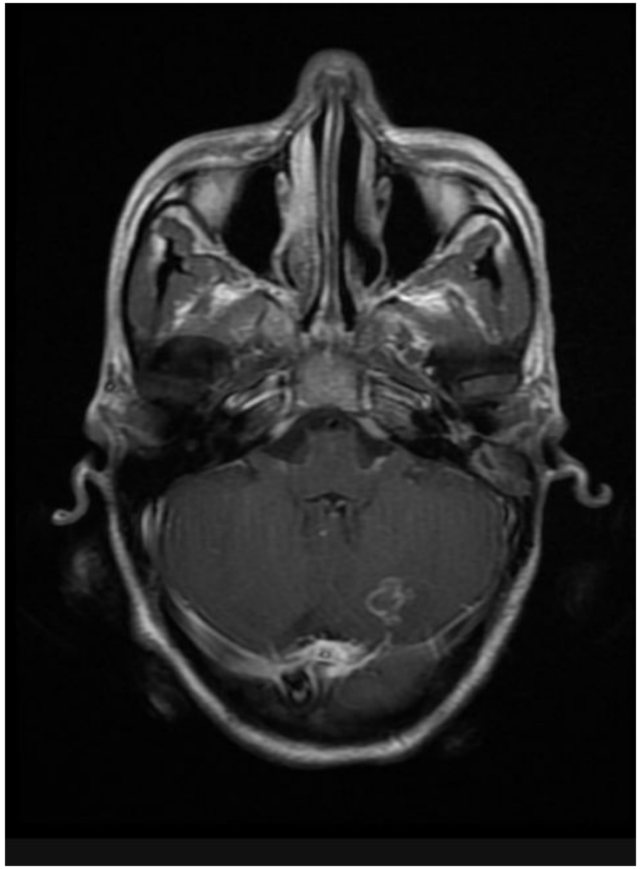
T°38.7 GCS 14

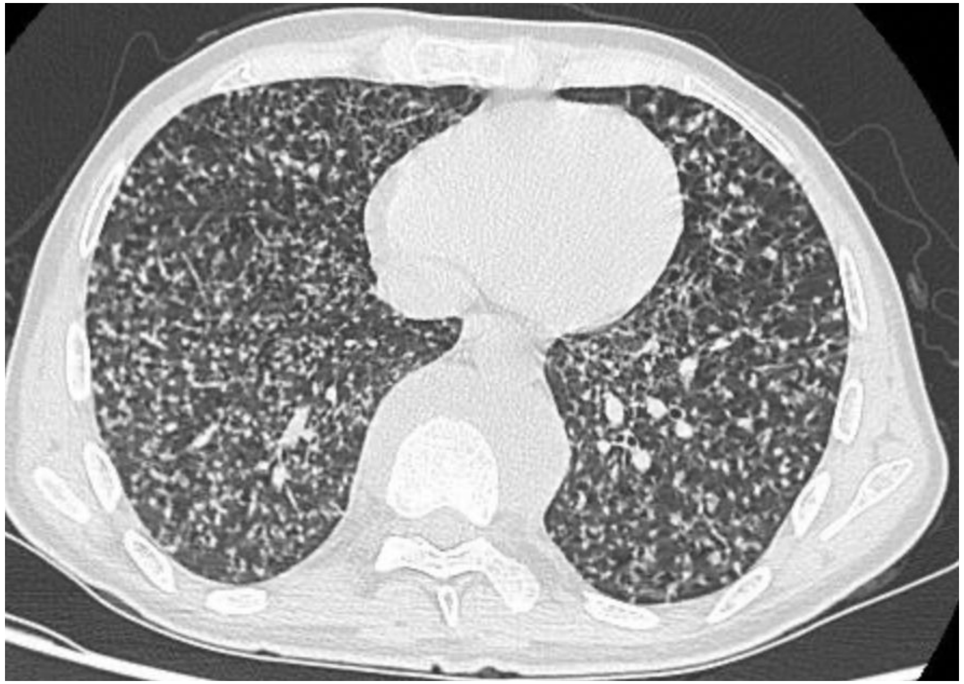
PA 113/71 mmHg - Fc 94 bpm - FR 23/min - SpO2 96% en AA

PL : 57 élements (91% lymphocytes), 0 hématies, protéinorachie 1.8 g/L, glycorachie 1,9 mmol/L (glycémie : 4,9 mmol/L)

R







Leptoméningite base du crâne
Plusieurs lésions nodulaires cérébelleuses
Miliaire tuberculeuse pulmonaire : BK crachat + à 1 BAAR/lame

R

Quel traitement instaurez-vous ?

A) Quadrithérapie RMP INH PZA EMB per os posologie standard

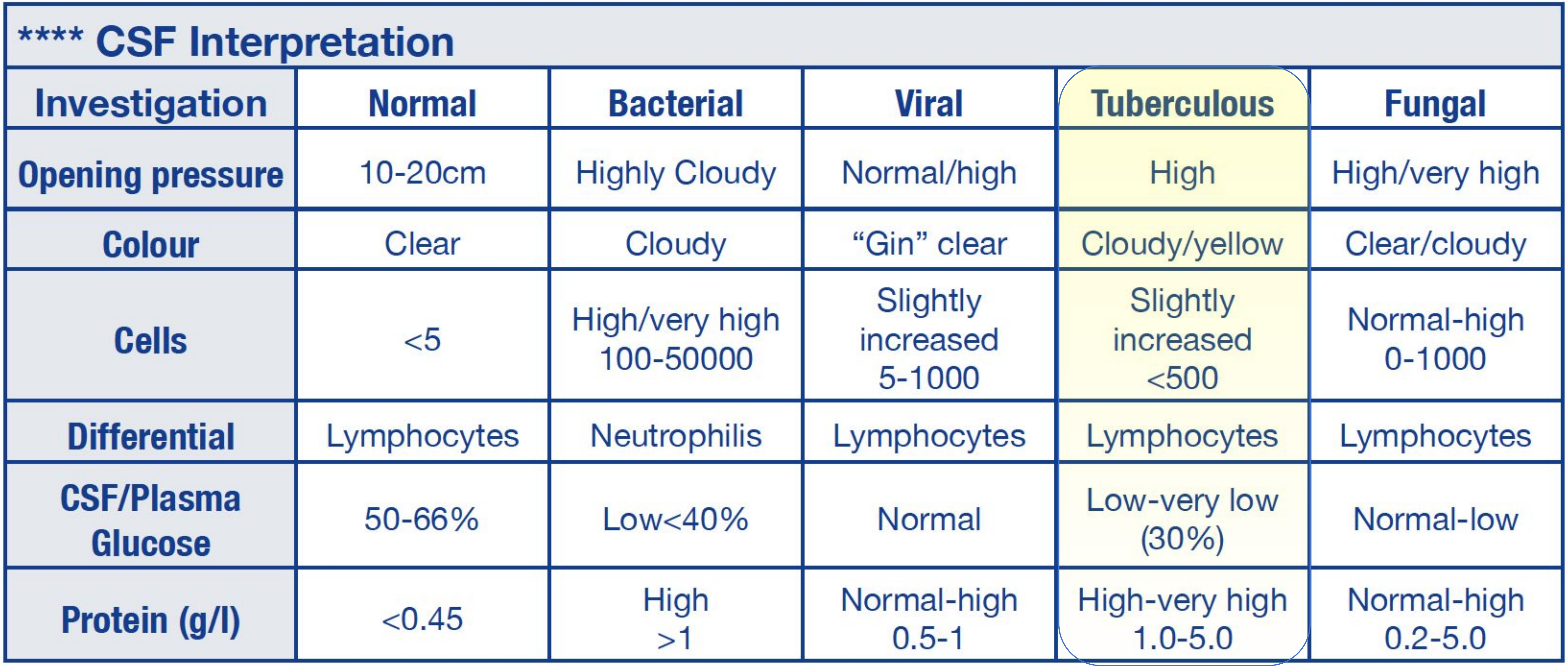
B) Quadrithérapie RMP INH PZA EMB IV posologie standard

C) Quadrithérapie RMP INH PZA EMB per os posologie élevée RMP

D) Quadrithérapie RMP INH PZA EMB per os posologie élevée INH

E) Corticothérapie systémique

Y



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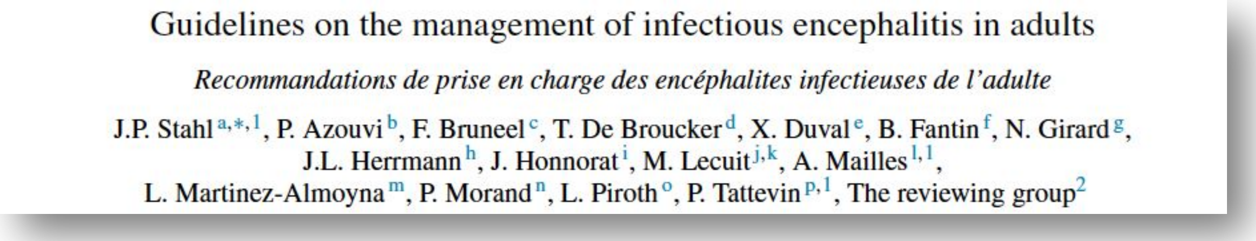
T. Solomon, UK guidelines for management of encephalitis, 2012

TUER LE BK

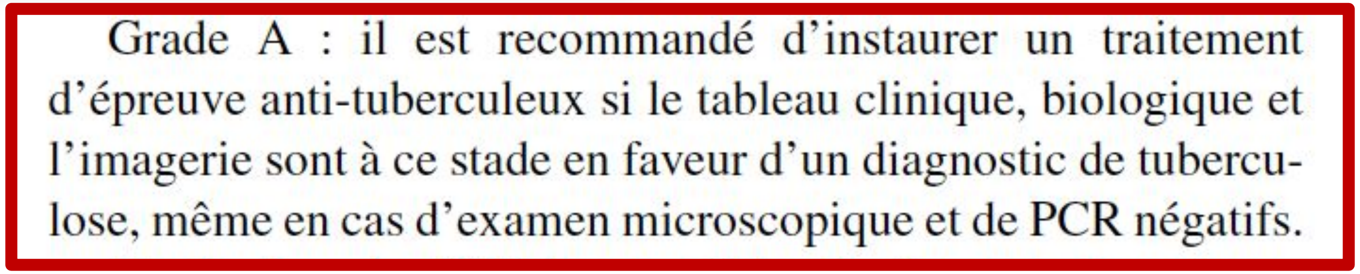


Guidelines on the management of infectious encephalitis in adults

Recommandations de prise en charge des encéphalites infectieuses de l'adulte

J.P. Stahl[a,*,1], P. Azouvi[b], F. Bruneel[c], T. De Broucker[d], X. Duval[e], B. Fantin[f], N. Girard[g],
J.L. Herrmann[h], J. Honnorat[i], M. Lecuit[j,k], A. Mailles[l,1],
L. Martinez-Almoyna[m], P. Morand[n], L. Piroth[o], P. Tattevin[p,1], The reviewing group[2]

Y



Grade A : il est recommandé d'instaurer un traitement d'épreuve anti-tuberculeux si le tableau clinique, biologique et l'imagerie sont à ce stade en faveur d'un diagnostic de tuberculose, même en cas d'examen microscopique et de PCR négatifs.

Une histoire différente en soins intensifs :

Les molécules ne se valent pas toutes

Ttt antituberculeux initial:

- ✓ Jusqu'aux résultats de l'antibiogramme
  - **Isoniazide (I) (5mg/kg/j)**
  - **Rifampicine (R) (10 mg/kg/j)**
  - **Pyrazinamide (P) (30 mg/kg/j sans dépasser 2 g)**
  - **Ethambutol (E) (20 mg/kg/j)**
- ✓ Arrêt de l'éthambutol si souche sensible à l'isoniazide
- ✓ Durée initiale de 2 mois
- ✓ Puis **bithérapie par IR pour une durée totale de 12 mois**

SPILF 2017

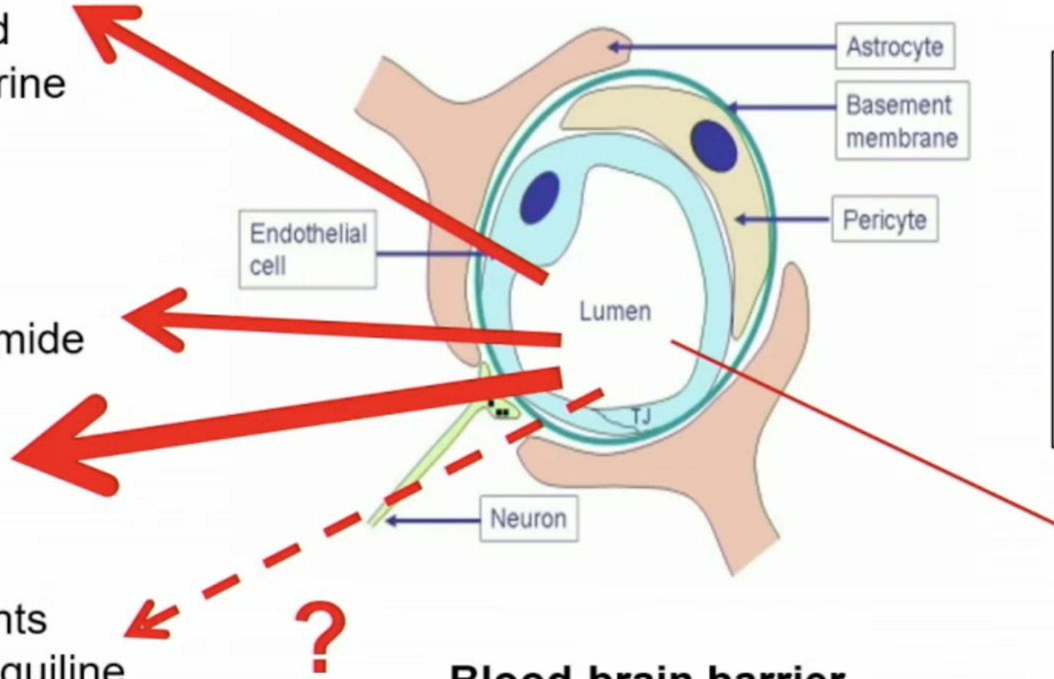
BHE : tous les anti-BK ne se valent pas

Levofloxacin
Moxifloxacin
Linezolid
Cycloserine

INH
Ethionamide

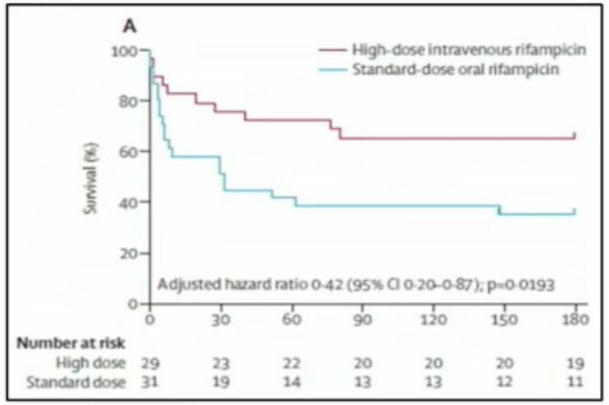
PZA

New agents
e.g. bedaquiline
Pretomanid


Astrocyte
Basement membrane
Pericyte
Endothelial cell
Lumen
TJ
Neuron
?

Blood-brain barrier

Ruslami et al LID 2013



Number at risk							
High dose	29	23	22	20	20	20	19
Standard dose	31	19	14	13	13	12	11

Rifampicin
Ethambutol
Streptomycin
Amikacin

Slide : GE Thwaites ESCMID Global 2025

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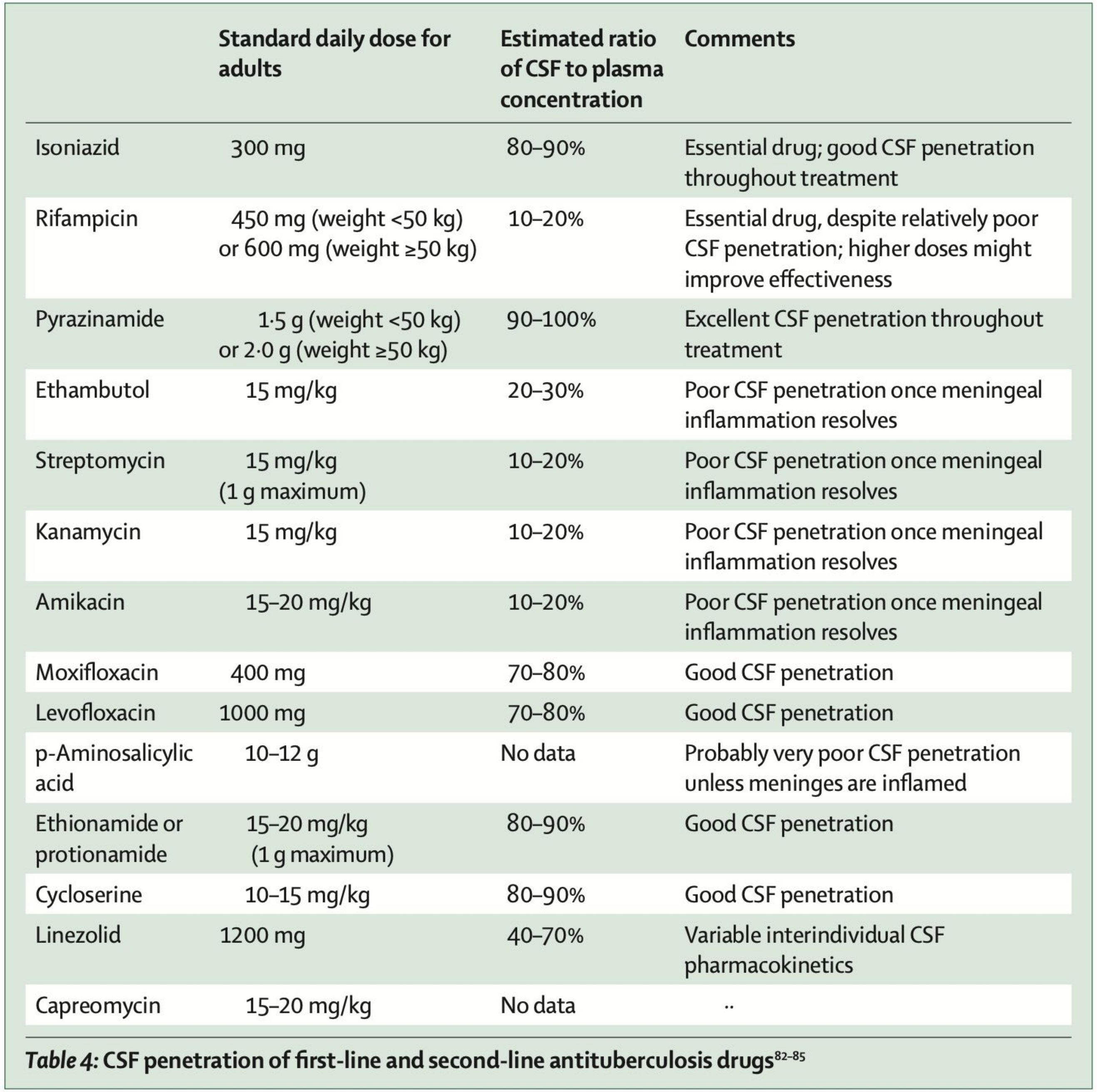

	Standard daily dose for adults	Estimated ratio of CSF to plasma concentration	Comments
Isoniazid	300 mg	80–90%	Essential drug; good CSF penetration throughout treatment
Rifampicin	450 mg (weight <50 kg) or 600 mg (weight ≥50 kg)	10–20%	Essential drug, despite relatively poor CSF penetration; higher doses might improve effectiveness
Pyrazinamide	1·5 g (weight <50 kg) or 2·0 g (weight ≥50 kg)	90–100%	Excellent CSF penetration throughout treatment
Ethambutol	15 mg/kg	20–30%	Poor CSF penetration once meningeal inflammation resolves
Streptomycin	15 mg/kg (1 g maximum)	10–20%	Poor CSF penetration once meningeal inflammation resolves
Kanamycin	15 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Amikacin	15–20 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Moxifloxacin	400 mg	70–80%	Good CSF penetration
Levofloxacin	1000 mg	70–80%	Good CSF penetration
p-Aminosalicylic acid	10–12 g	No data	Probably very poor CSF penetration unless meninges are inflamed
Ethionamide or protionamide	15–20 mg/kg (1 g maximum)	80–90%	Good CSF penetration
Cycloserine	10–15 mg/kg	80–90%	Good CSF penetration
Linezolid	1200 mg	40–70%	Variable interindividual CSF pharmacokinetics
Capreomycin	15–20 mg/kg	No data	..

Table 4: **CSF penetration of first-line and second-line antituberculosis drugs**[82–85]

Thwaites et al. Lancet Neurol 2013

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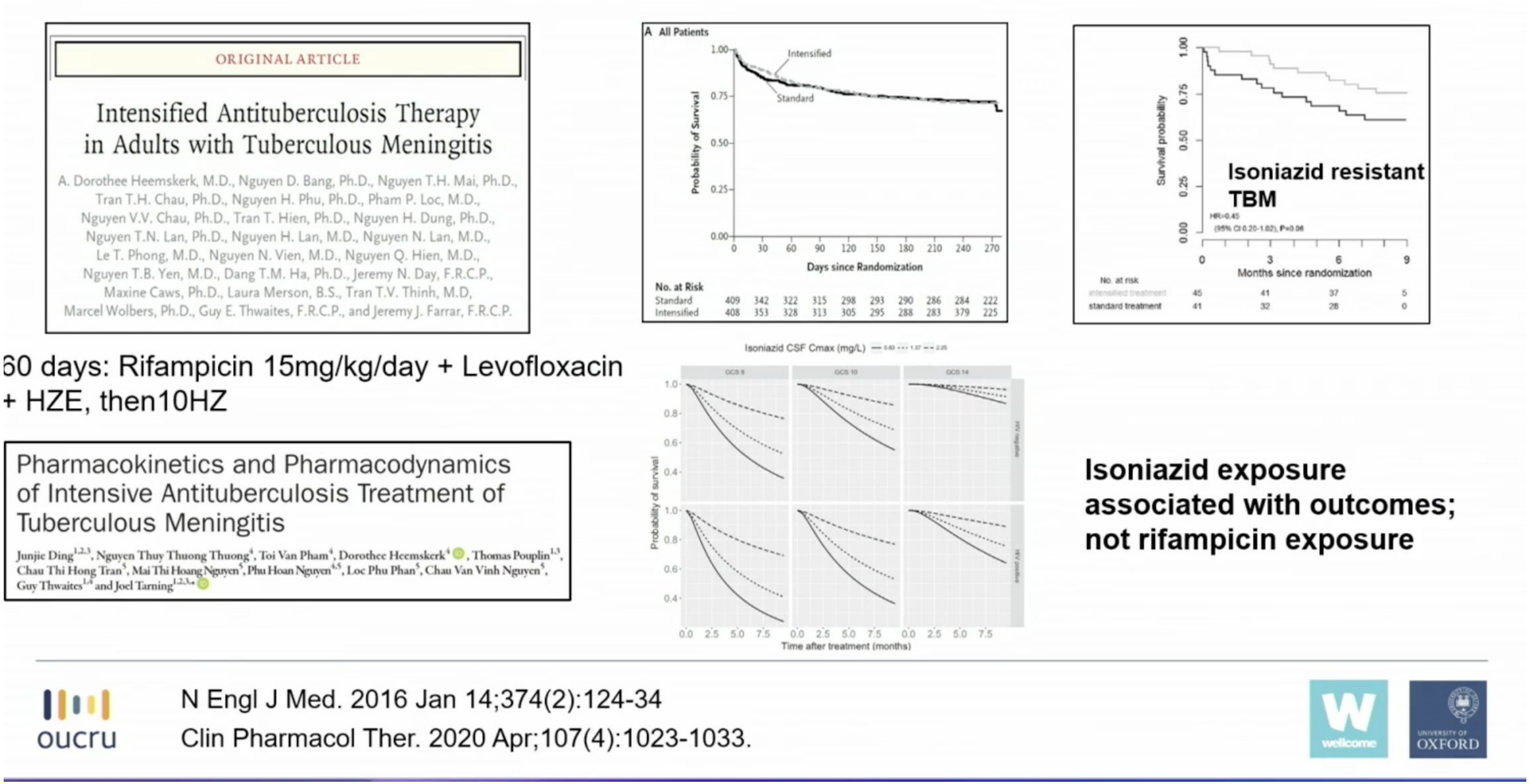
Augmenter la dose d’INH : pourquoi pas ?



ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

A. Dorothee Heemskerk, M.D., Nguyen D. Bang, Ph.D., Nguyen T.H. Mai, Ph.D.,
Tran T.H. Chau, Ph.D., Nguyen H. Phu, Ph.D., Pham P. Loc, M.D.,
Nguyen V.V. Chau, Ph.D., Tran T. Hien, Ph.D., Nguyen H. Dung, Ph.D.,
Nguyen T.N. Lan, Ph.D., Nguyen H. Lan, M.D., Nguyen N. Lan, M.D.,
Le T. Phong, M.D., Nguyen N. Vien, M.D., Nguyen Q. Hien, M.D.,
Nguyen T.B. Yen, M.D., Dang T.M. Ha, Ph.D., Jeremy N. Day, F.R.C.P.,
Maxine Caws, Ph.D., Laura Merson, B.S., Tran T.V. Thinh, M.D,
Marcel Wolbers, Ph.D., Guy E. Thwaites, F.R.C.P., and Jeremy J. Farrar, F.R.C.P.

A All Patients
1.00
0.75
0.50
0.25
0.00
Probability of Survival
Intensified
Standard
0
30
60
90
120
150
180
210
240
270
Days since Randomization

No. at Risk										
Standard	409	342	322	315	298	293	290	286	284	222
Intensified	408	353	328	313	305	295	288	283	379	225

Survival probability
1.00
0.75
0.50
0.25
0.00
HR=0.45
(95% CI 0.20-1.02), P=0.06
0
3
6
9
Months since randomization

Isoniazid resistant TBM

No. at risk				
intensified treatment	45	41	37	5
standard treatment	41	32	28	0

60 days: Rifampicin 15mg/kg/day + Levofloxacin + HZE, then10HZ

Isoniazid CSF Cmax (mg/L)
0.83
1.37
2.25
GCS 8
GCS 10
GCS 14
HIV negative
HIV positive
Probability of survival
1.0
0.8
0.6
0.4
0.0
2.5
5.0
7.5
Time after treatment (months)

Pharmacokinetics and Pharmacodynamics of Intensive Antituberculosis Treatment of Tuberculous Meningitis

Junjie Ding[1,2,3], Nguyen Thuy Thuong Thuong[4], Toi Van Pham[4], Dorothee Heemskerk[4], Thomas Pouplin[1,3], Chau Thi Hong Tran[5], Mai Thi Hoang Nguyen[5], Phu Hoan Nguyen[4,5], Loc Phu Phan[5], Chau Van Vinh Nguyen[5], Guy Thwaites[1,4] and Joel Tarning[1,2,3,*]

Isoniazid exposure associated with outcomes; not rifampicin exposure

oucru

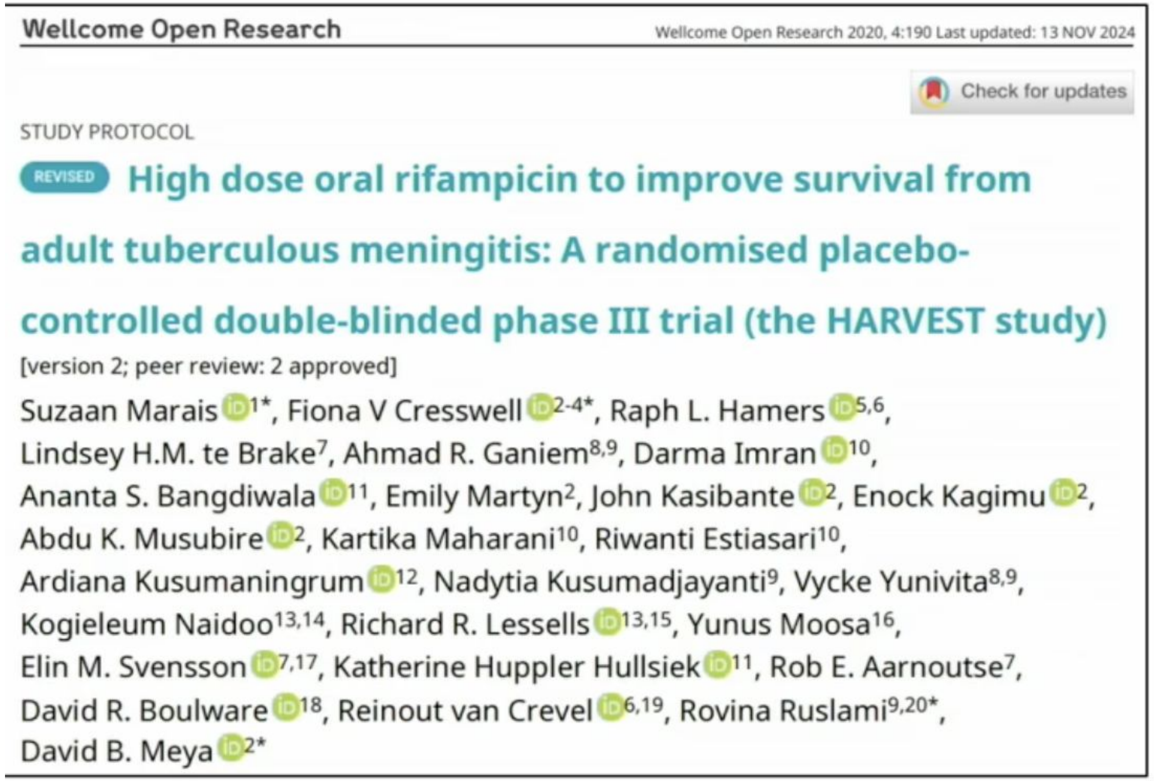
N Engl J Med. 2016 Jan 14;374(2):124-34
Clin Pharmacol Ther. 2020 Apr;107(4):1023-1033.

wellcome

UNIVERSITY OF OXFORD

Slide : GE Thwaites ESCMID Global 2025

Augmenter la dose de RMP : plutôt non



Wellcome Open Research Wellcome Open Research 2020, 4:190 Last updated: 13 NOV 2024

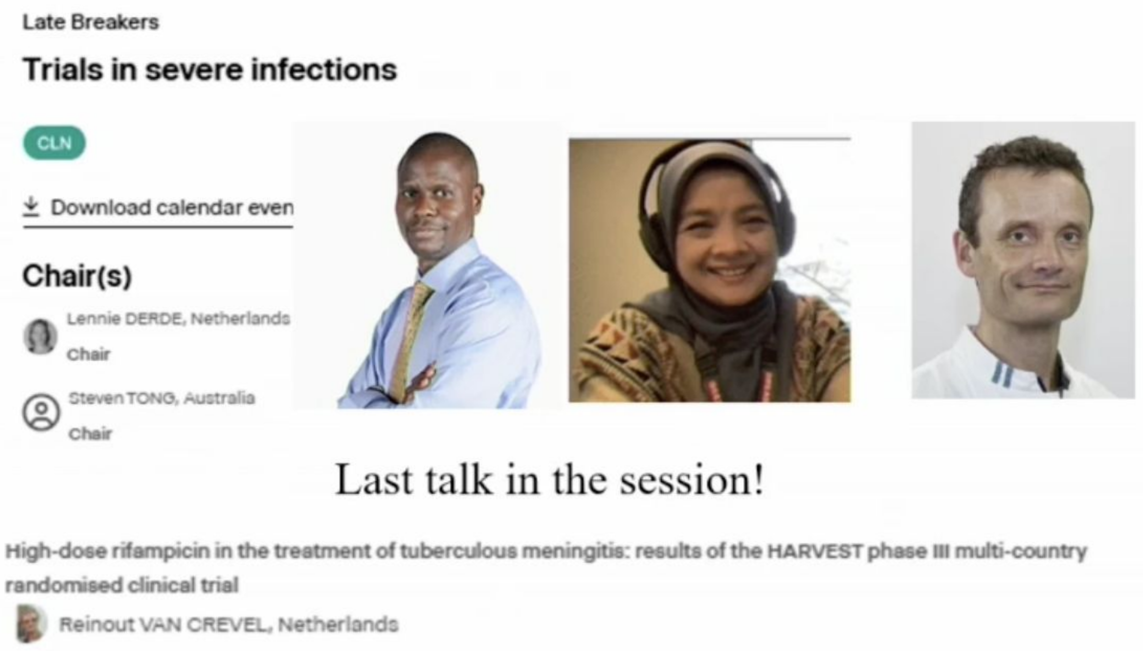
Check for updates

STUDY PROTOCOL

REVISED **High dose oral rifampicin to improve survival from adult tuberculous meningitis: A randomised placebo-controlled double-blinded phase III trial (the HARVEST study)**

[version 2; peer review: 2 approved]

Suzaan Marais[1]*, Fiona V Cresswell[2-4]*, Raph L. Hamers[5,6], Lindsey H.M. te Brake[7], Ahmad R. Ganiem[8,9], Darma Imran[10], Ananta S. Bangdiwala[11], Emily Martyn[2], John Kasibante[2], Enock Kagimu[2], Abdu K. Musubire[2], Kartika Maharani[10], Riwanti Estiasari[10], Ardiana Kusumaningrum[12], Nadytia Kusumadjayanti[9], Vycke Yunivita[8,9], Kogieleum Naidoo[13,14], Richard R. Lessells[13,15], Yunus Moosa[16], Elin M. Svensson[7,17], Katherine Huppler Hullsiek[11], Rob E. Aarnoutse[7], David R. Boulware[18], Reinout van Crevel[6,19], Rovina Ruslami[9,20]*, David B. Meya[2]*



Late Breakers

Trials in severe infections

Chair(s)

Lennie DERDE, Netherlands
Chair

Steven TONG, Australia
Chair

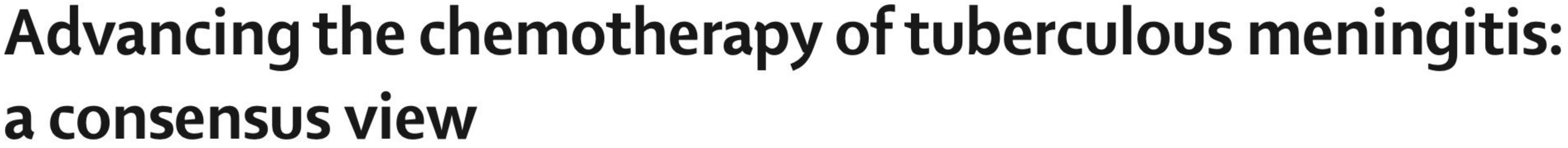
Last talk in the session!

High-dose rifampicin in the treatment of tuberculous meningitis: results of the HARVEST phase III multi-country randomised clinical trial

Reinout VAN CREVEL, Netherlands

Slide : ESCMID Global 2025

Prendre en compte plusieurs dimensions



Advancing the chemotherapy of tuberculous meningitis: a consensus view

Pondérer le choix des antibiotiques par un score combiné associant :

- Activité bactéricide
- Efficacité clinique prouvée dans essais contrôlés
- Concentration dans le LCS
- Tolérance
- Interaction médicamenteuse
- Facilité d’accès (prix, voie d’administration, réglementation etc.)

Wasserman et al. LID 2025

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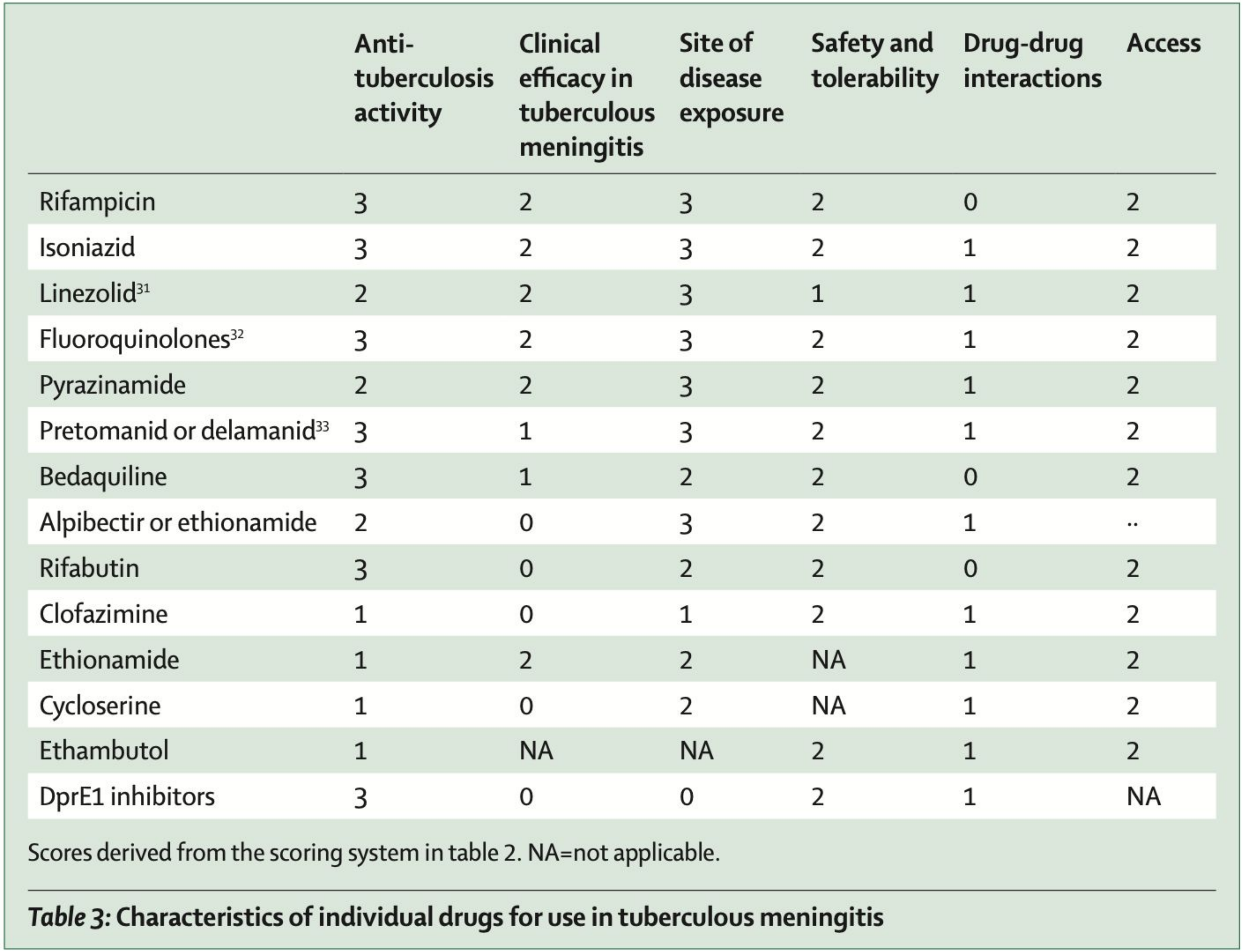

	Anti-tuberculosis activity	Clinical efficacy in tuberculous meningitis	Site of disease exposure	Safety and tolerability	Drug-drug interactions	Access
Rifampicin	3	2	3	2	0	2
Isoniazid	3	2	3	2	1	2
Linezolid[31]	2	2	3	1	1	2
Fluoroquinolones[32]	3	2	3	2	1	2
Pyrazinamide	2	2	3	2	1	2
Pretomanid or delamanid[33]	3	1	3	2	1	2
Bedaquiline	3	1	2	2	0	2
Alpibectir or ethionamide	2	0	3	2	1	..
Rifabutin	3	0	2	2	0	2
Clofazimine	1	0	1	2	1	2
Ethionamide	1	2	2	NA	1	2
Cycloserine	1	0	2	NA	1	2
Ethambutol	1	NA	NA	2	1	2
DprE1 inhibitors	3	0	0	2	1	NA

Scores derived from the scoring system in table 2. NA=not applicable.

***Table 3:* Characteristics of individual drugs for use in tuberculous meningitis**

Wasserman et al. LID 2025

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High-dose rifampicin

1. RFqZL
2. RFqZAlpE

Rifamycin-free

3. BPaMZ (SimpliciTB regimen)
4. BPaLM (TB-PRACTECAL)
5. BPaOS (tested in pan-tuberculosis trial)

Bedaquiline plus rifabutin

6. BZMRb (superior to RHZE in mice)
7. BPaORb } (Modified BPaOS regimen)
8. BPaAlpERb }

Drug scores

🟩 ≥12 🟧 9–11 🟨 <9 🟥 Not currently manufactured

		Rifamycin	Isoniazid	Pyrazinamide	Fluoroquinolone	Bedaquiline	Oxazolidinone	Nitroimidazole	AlpE	DprE1
1	RFqZL	🟩 R		🟩	🟩		🟧 L		🟥	
2	RFqZAlpE	🟩 R		🟩	🟩					
3	BPaMZ		🟩	🟩		🟧		🟧 Pa		
4	BPaLM				🟩	🟧	🟧 L	🟧 Pa		
5	BPaOS					🟧	🟨 S	🟧 Pa		🟥
6	BZMRb	🟧 Rb		🟩	🟩	🟧				
7	BPaORb	🟧 Rb				🟧		🟧 Pa		🟥
8	BPaAlpERb	🟧 Rb				🟧		🟧 Pa	🟥	

Wasserman et al. LID 2025

REDUIRE L’INFLAMMATION

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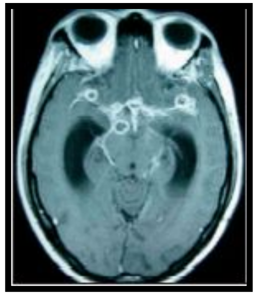
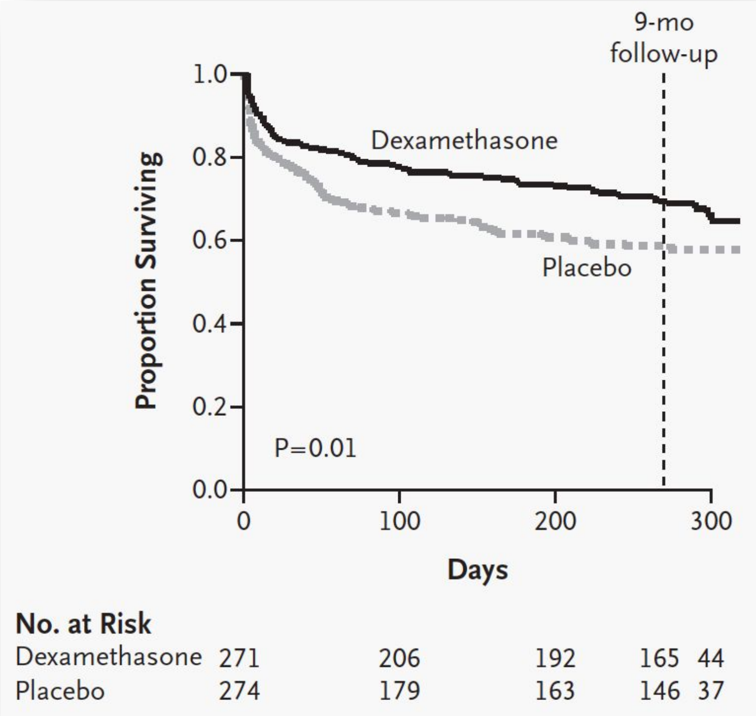
Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

The NEW ENGLAND JOURNAL of MEDICINE





No. at Risk

	0	100	200	270	300
Dexamethasone	271	206	192	165	44
Placebo	274	179	163	146	37

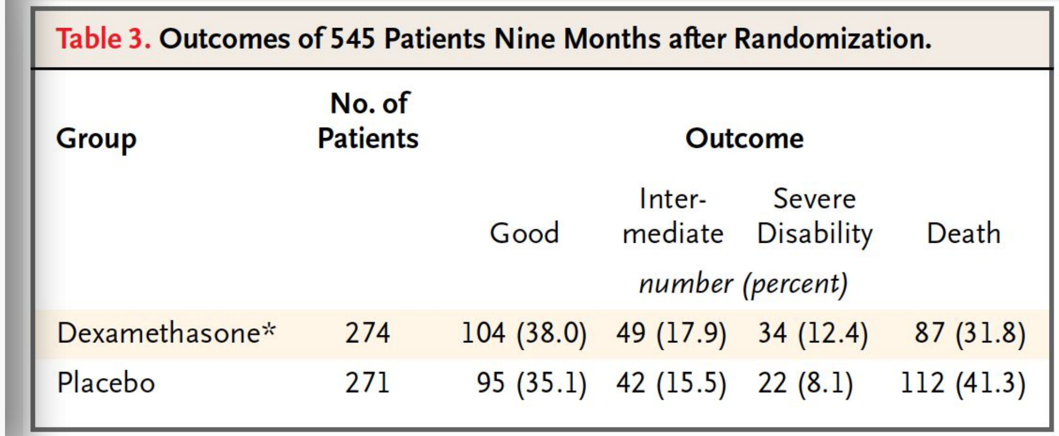
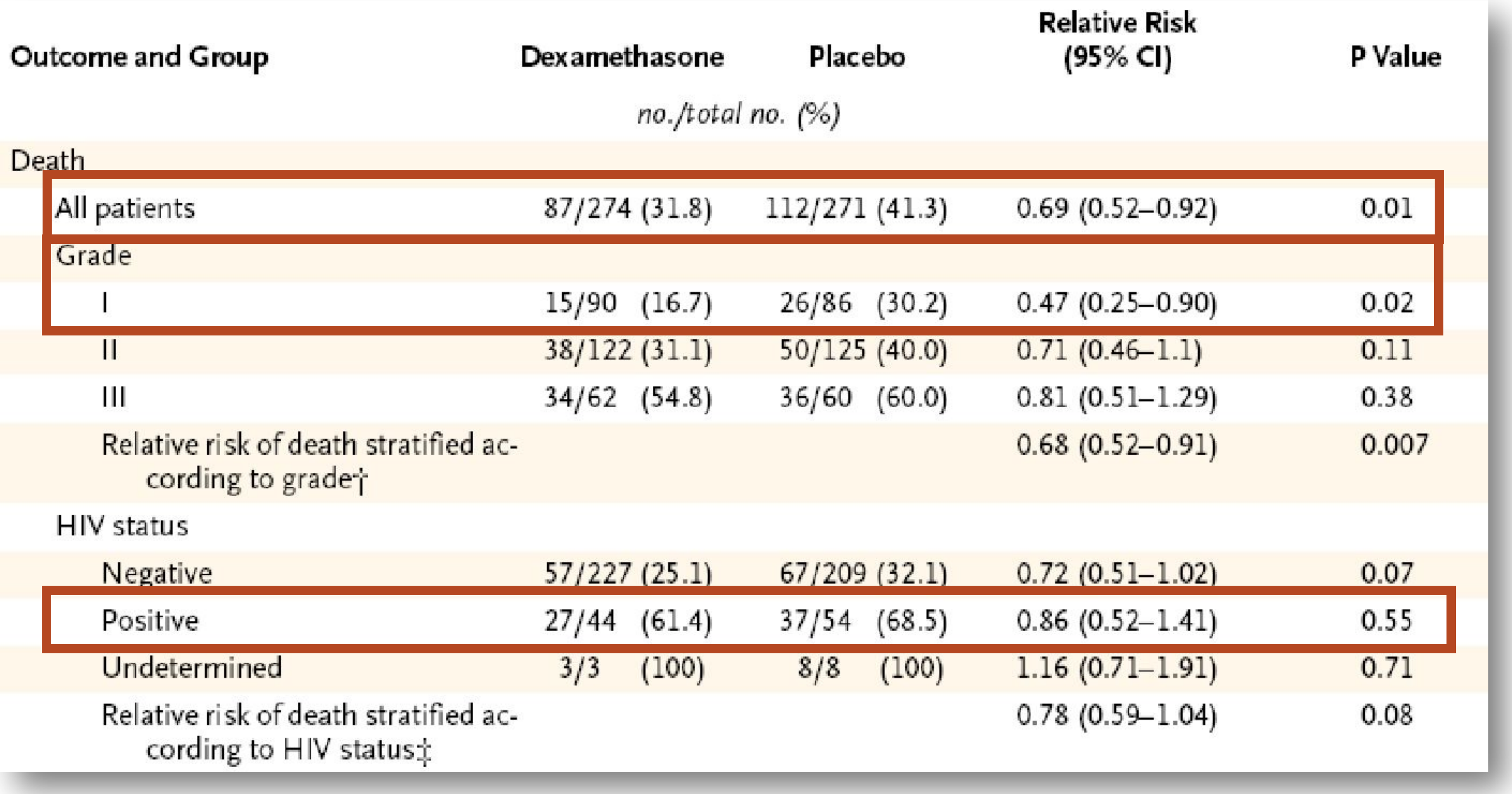


Table 3. Outcomes of 545 Patients Nine Months after Randomization.

Group	No. of Patients	Outcome			
		Good	Inter-mediate	Severe Disability	Death
		number (percent)			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

Guy E. Thwaites, N Engl J Med 2004

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults



Outcome and Group	Dexamethasone	Placebo	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Death				
All patients	87/274 (31.8)	112/271 (41.3)	0.69 (0.52–0.92)	0.01
Grade				
I	15/90 (16.7)	26/86 (30.2)	0.47 (0.25–0.90)	0.02
II	38/122 (31.1)	50/125 (40.0)	0.71 (0.46–1.1)	0.11
III	34/62 (54.8)	36/60 (60.0)	0.81 (0.51–1.29)	0.38
Relative risk of death stratified according to grade†			0.68 (0.52–0.91)	0.007
HIV status				
Negative	57/227 (25.1)	67/209 (32.1)	0.72 (0.51–1.02)	0.07
Positive	27/44 (61.4)	37/54 (68.5)	0.86 (0.52–1.41)	0.55
Undetermined	3/3 (100)	8/8 (100)	1.16 (0.71–1.91)	0.71
Relative risk of death stratified according to HIV status‡			0.78 (0.59–1.04)	0.08

Guy E. Thwaites, N Engl J Med 2004

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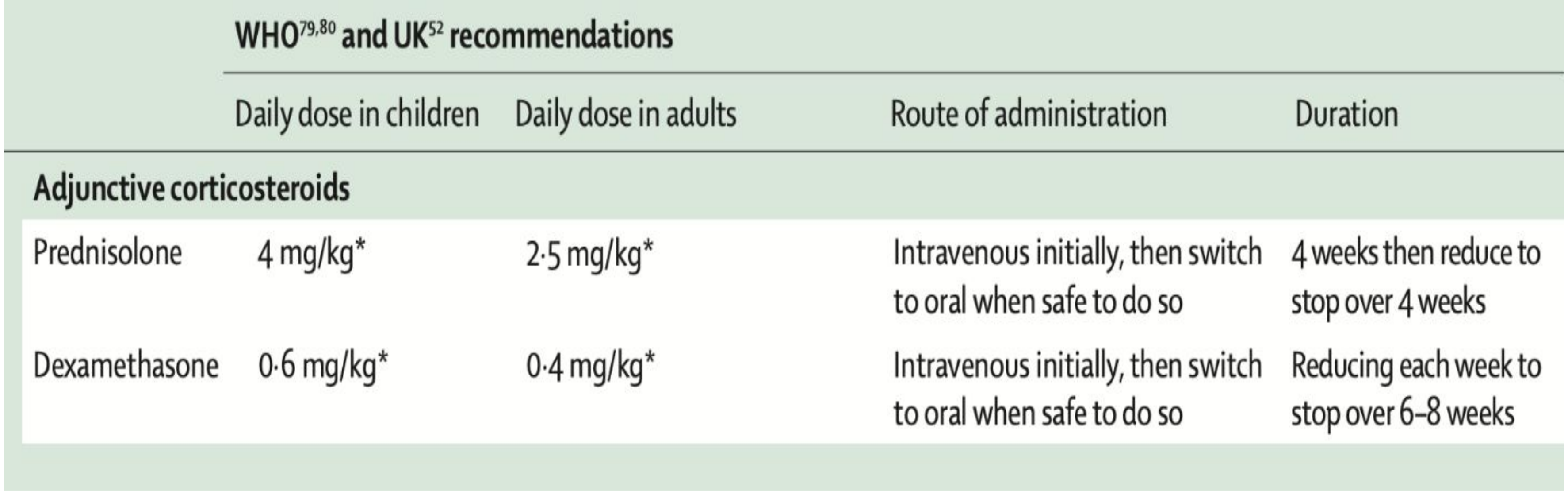
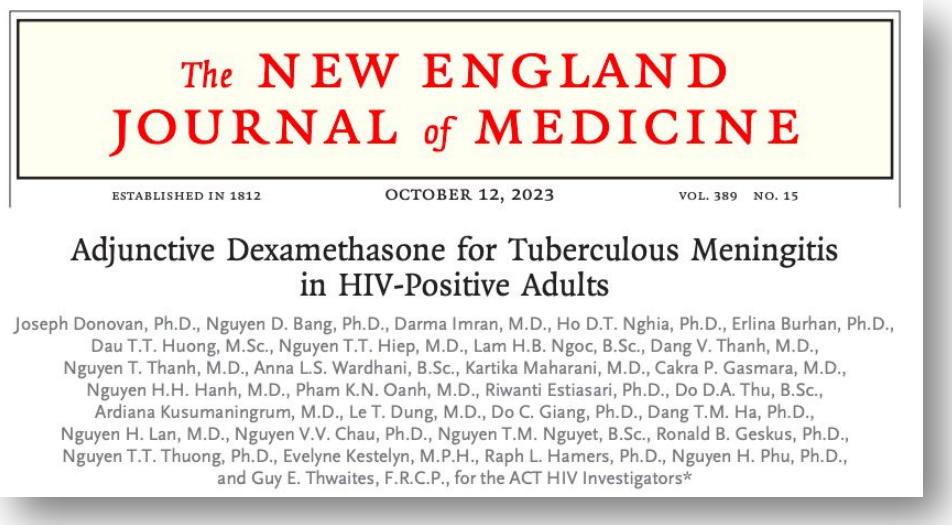
Quel protocole ?



	WHO[79,80] and UK[52] recommendations			
	Daily dose in children	Daily dose in adults	Route of administration	Duration
Adjunctive corticosteroids				
Prednisolone	4 mg/kg*	2·5 mg/kg*	Intravenous initially, then switch to oral when safe to do so	4 weeks then reduce to stop over 4 weeks
Dexamethasone	0·6 mg/kg*	0·4 mg/kg*	Intravenous initially, then switch to oral when safe to do so	Reducing each week to stop over 6–8 weeks

Thwaites et al. Lancet Neurol 2013



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2023 VOL. 389 NO. 15

Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D., Dau T.T. Huong, M.Sc., Nguyen T.T. Hiep, M.D., Lam H.B. Ngoc, B.Sc., Dang V. Thanh, M.D., Nguyen T. Thanh, M.D., Anna L.S. Wardhani, B.Sc., Kartika Maharani, M.D., Cakra P. Gasmara, M.D., Nguyen H.H. Hanh, M.D., Pham K.N. Oanh, M.D., Riwanti Estiasari, Ph.D., Do D.A. Thu, B.Sc., Ardiana Kusumaningrum, M.D., Le T. Dung, M.D., Do C. Giang, Ph.D., Dang T.M. Ha, Ph.D., Nguyen H. Lan, M.D., Nguyen V.V. Chau, Ph.D., Nguyen T.M. Nguyet, B.Sc., Ronald B. Geskus, Ph.D., Nguyen T.T. Thuong, Ph.D., Evelyne Kestelyn, M.P.H., Raph L. Hamers, Ph.D., Nguyen H. Phu, Ph.D., and Guy E. Thwaites, F.R.C.P., for the ACT HIV Investigators*

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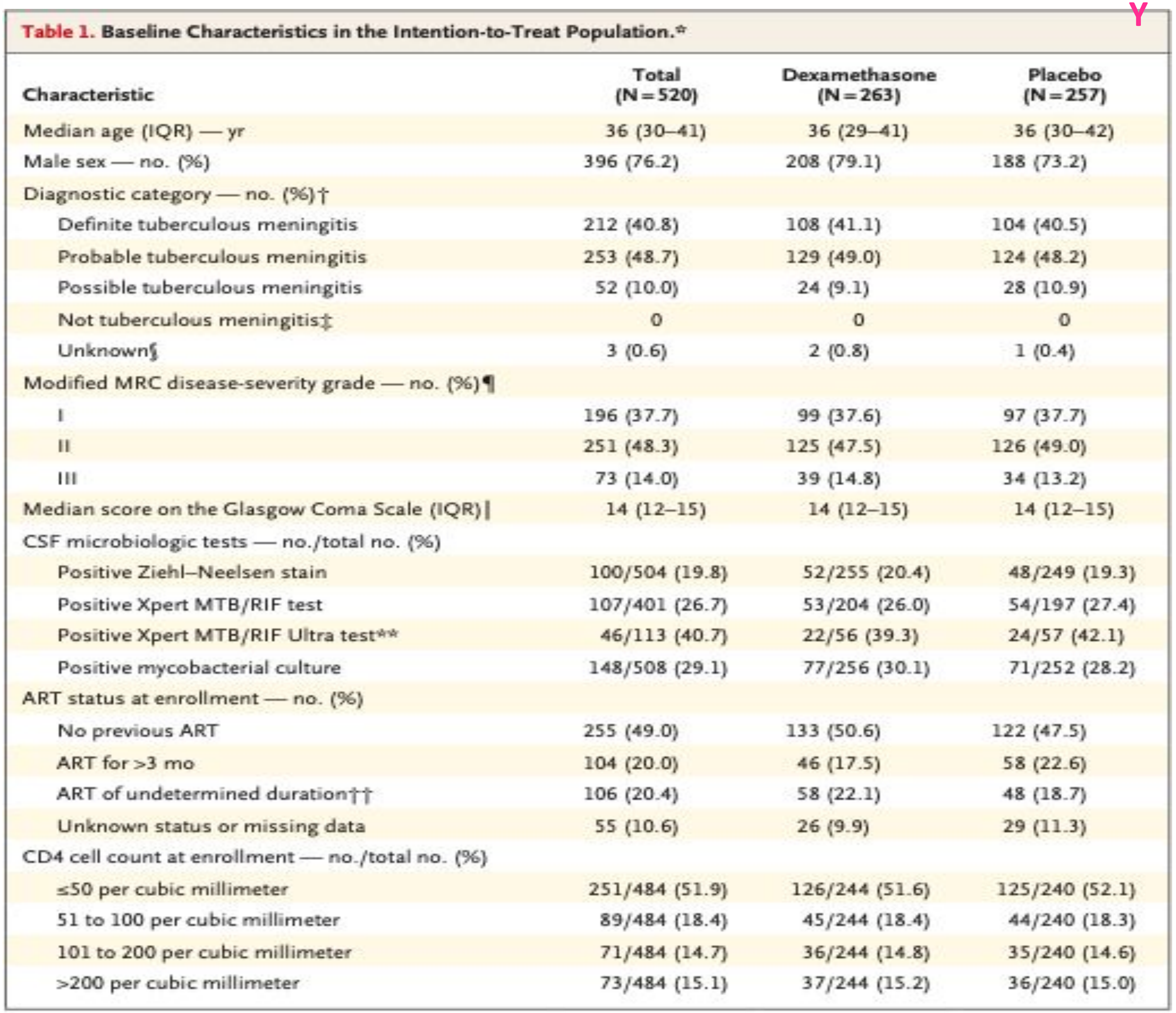


Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Total (N=520)	Dexamethasone (N=263)	Placebo (N=257)
Median age (IQR) — yr	36 (30–41)	36 (29–41)	36 (30–42)
Male sex — no. (%)	396 (76.2)	208 (79.1)	188 (73.2)
Diagnostic category — no. (%)†			
Definite tuberculous meningitis	212 (40.8)	108 (41.1)	104 (40.5)
Probable tuberculous meningitis	253 (48.7)	129 (49.0)	124 (48.2)
Possible tuberculous meningitis	52 (10.0)	24 (9.1)	28 (10.9)
Not tuberculous meningitis‡	0	0	0
Unknown§	3 (0.6)	2 (0.8)	1 (0.4)
Modified MRC disease-severity grade — no. (%)¶			
I	196 (37.7)	99 (37.6)	97 (37.7)
II	251 (48.3)	125 (47.5)	126 (49.0)
III	73 (14.0)	39 (14.8)	34 (13.2)
Median score on the Glasgow Coma Scale (IQR)‖	14 (12–15)	14 (12–15)	14 (12–15)
CSF microbiologic tests — no./total no. (%)			
Positive Ziehl–Neelsen stain	100/504 (19.8)	52/255 (20.4)	48/249 (19.3)
Positive Xpert MTB/RIF test	107/401 (26.7)	53/204 (26.0)	54/197 (27.4)
Positive Xpert MTB/RIF Ultra test**	46/113 (40.7)	22/56 (39.3)	24/57 (42.1)
Positive mycobacterial culture	148/508 (29.1)	77/256 (30.1)	71/252 (28.2)
ART status at enrollment — no. (%)			
No previous ART	255 (49.0)	133 (50.6)	122 (47.5)
ART for >3 mo	104 (20.0)	46 (17.5)	58 (22.6)
ART of undetermined duration††	106 (20.4)	58 (22.1)	48 (18.7)
Unknown status or missing data	55 (10.6)	26 (9.9)	29 (11.3)
CD4 cell count at enrollment — no./total no. (%)			
≤50 per cubic millimeter	251/484 (51.9)	126/244 (51.6)	125/240 (52.1)
51 to 100 per cubic millimeter	89/484 (18.4)	45/244 (18.4)	44/240 (18.3)
101 to 200 per cubic millimeter	71/484 (14.7)	36/244 (14.8)	35/240 (14.6)
>200 per cubic millimeter	73/484 (15.1)	37/244 (15.2)	36/240 (15.0)

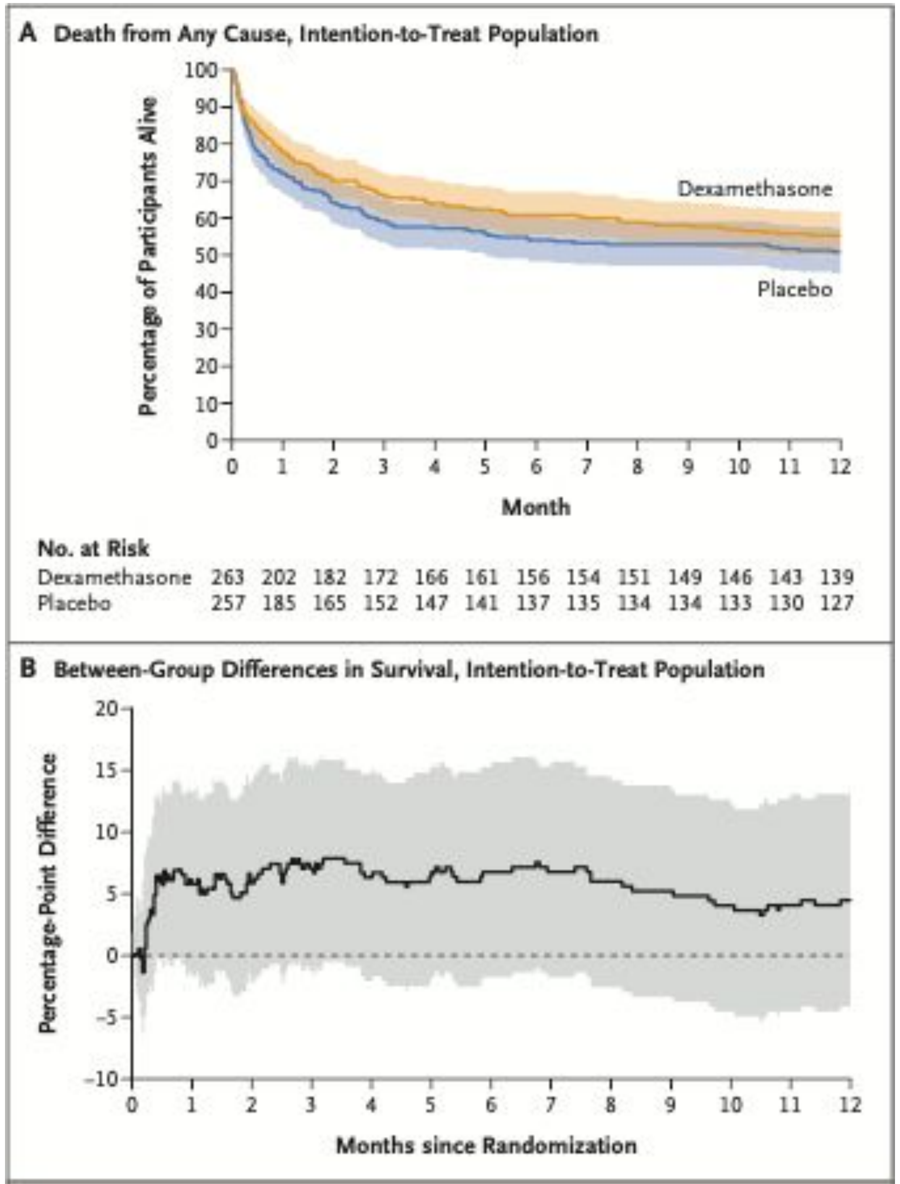


Figure 2. Death from Any Cause during 12 Months after Randomization.

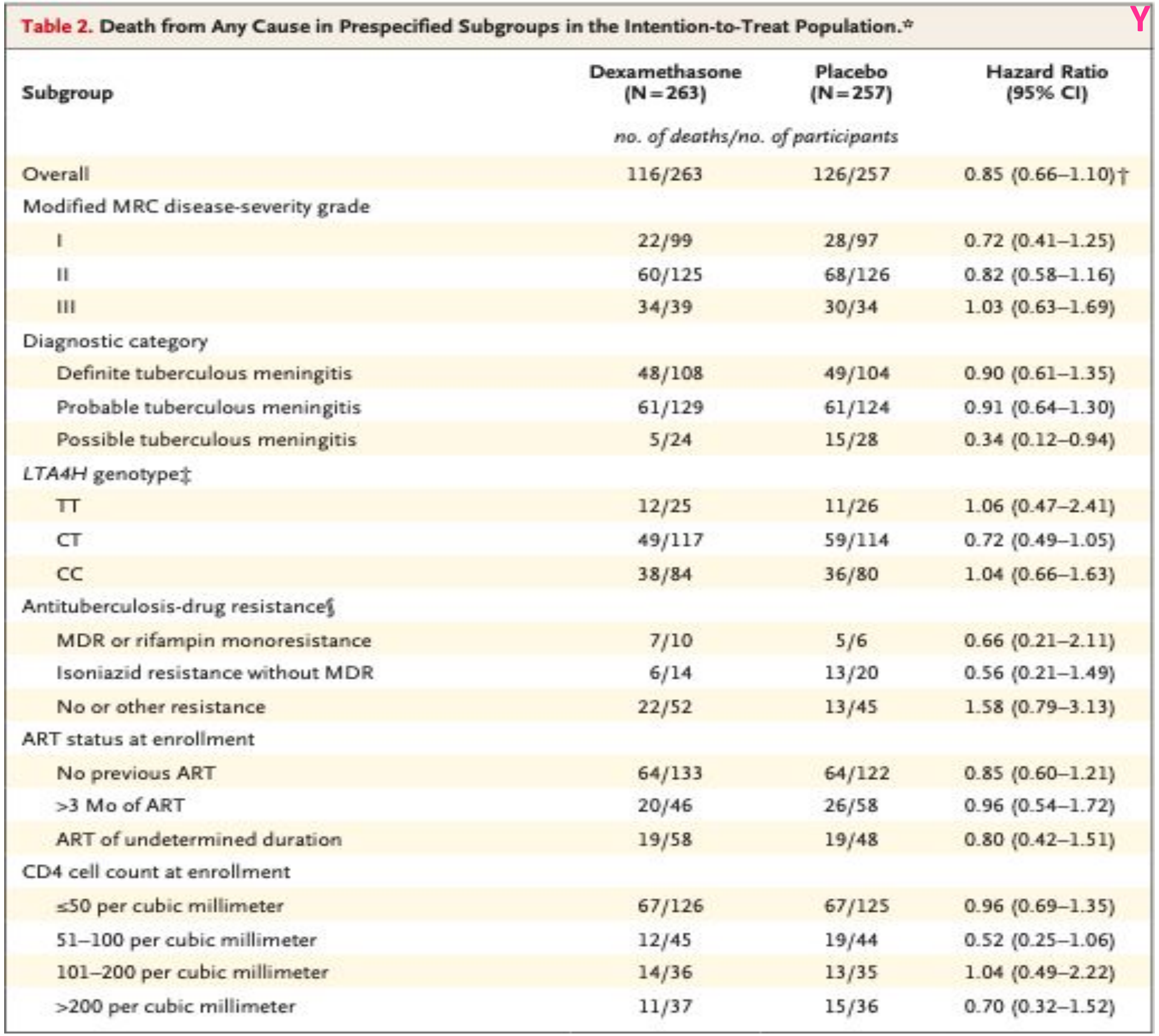
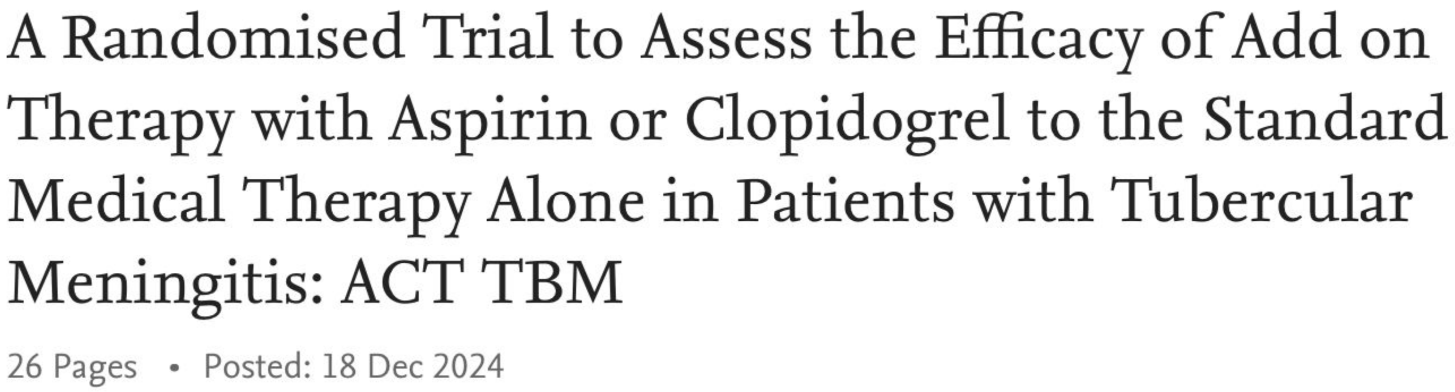


Table 2. Death from Any Cause in Prespecified Subgroups in the Intention-to-Treat Population.*

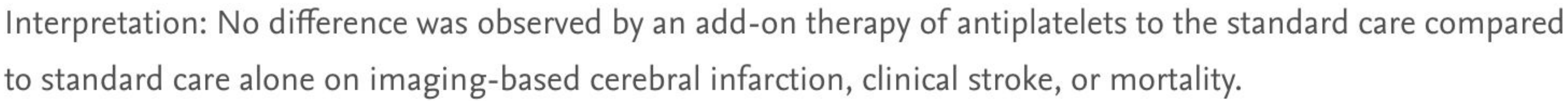
Subgroup	Dexamethasone (N=263)	Placebo (N=257)	Hazard Ratio (95% CI)
	no. of deaths/no. of participants		
Overall	116/263	126/257	0.85 (0.66–1.10)†
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
LTA4H genotype‡			
TT	12/25	11/26	1.06 (0.47–2.41)
CT	49/117	59/114	0.72 (0.49–1.05)
CC	38/84	36/80	1.04 (0.66–1.63)
Antituberculosis-drug resistance§			
MDR or rifampin monoresistance	7/10	5/6	0.66 (0.21–2.11)
Isoniazid resistance without MDR	6/14	13/20	0.56 (0.21–1.49)
No or other resistance	22/52	13/45	1.58 (0.79–3.13)
ART status at enrollment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 Mo of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrollment			
≤50 per cubic millimeter	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimeter	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimeter	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimeter	11/37	15/36	0.70 (0.32–1.52)

Aspirine ou clopidogrel : plutôt non



A Randomised Trial to Assess the Efficacy of Add on Therapy with Aspirin or Clopidogrel to the Standard Medical Therapy Alone in Patients with Tubercular Meningitis: ACT TBM

26 Pages • Posted: 18 Dec 2024



Interpretation: No difference was observed by an add-on therapy of antiplatelets to the standard care compared to standard care alone on imaging-based cerebral infarction, clinical stroke, or mortality.

Bhatia et al. preprint 2024

Méningite TB - take home messages

- TBM : 50 % de mortalité dans le monde, 100 cas par an en France
- Performances insuffisantes des outils diagnostiques actuels : combiner les tests + gros volumes de LCS
- IREP - durée 12 mois
  Doses, administration, combinaisons : incertains, essais en cours
- CTC : Réduction de la mortalité chez le non VIH seulement
  En cours d'évaluation : aspirine, anti TNF alpha
- Nouvelles recommandations SPILF 2025 à surveiller

De quoi allons-nous parler ?

- Méningite bactérienne
- Encéphalite d’allure ‘virale’
- Méningite tuberculeuse
- **Méningite à cryptocoque**

Vignette clinique 4

R

Madame C. 42 ans consulte aux Urgences pour céphalées intenses depuis 8 jours

ATCD :

Infection par le VIH en rupture de suivi

Bilan immuno-virologique fait en ville par médecin généraliste 05/2025 : 0 CD4 CV 6 log

Cliniquement :

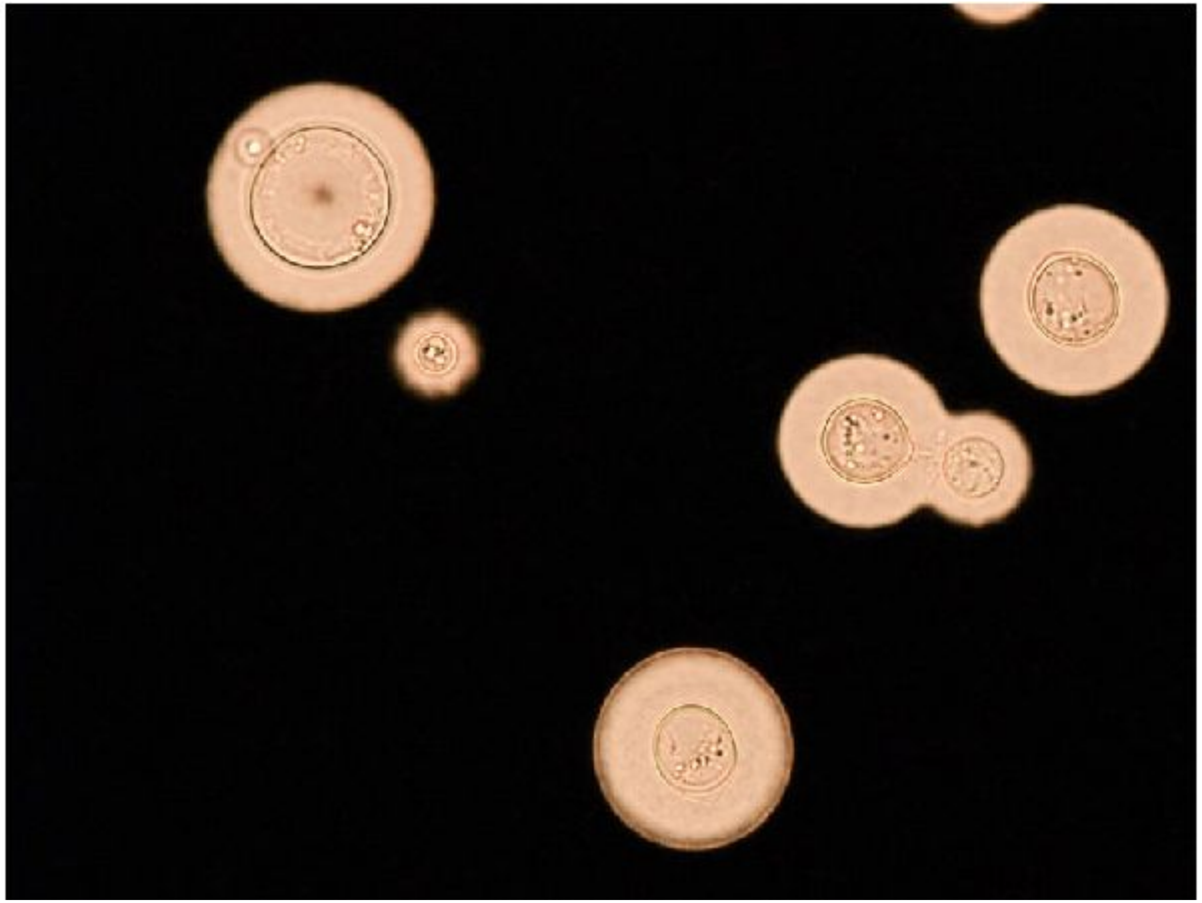
T°39 GCS 14

PA 113/71 mmHg - Fc 94 bpm - FR 23/min - SpO2 96% en AA

PL : 177 élements (93% lymphocytes), 0 hématies, protéinorachie 2.8 g/L, glycorachie 2.4 mmol/L (glycémie : 4,1 mmol/L)

Vignette clinique 4

Appel du laboratoire :



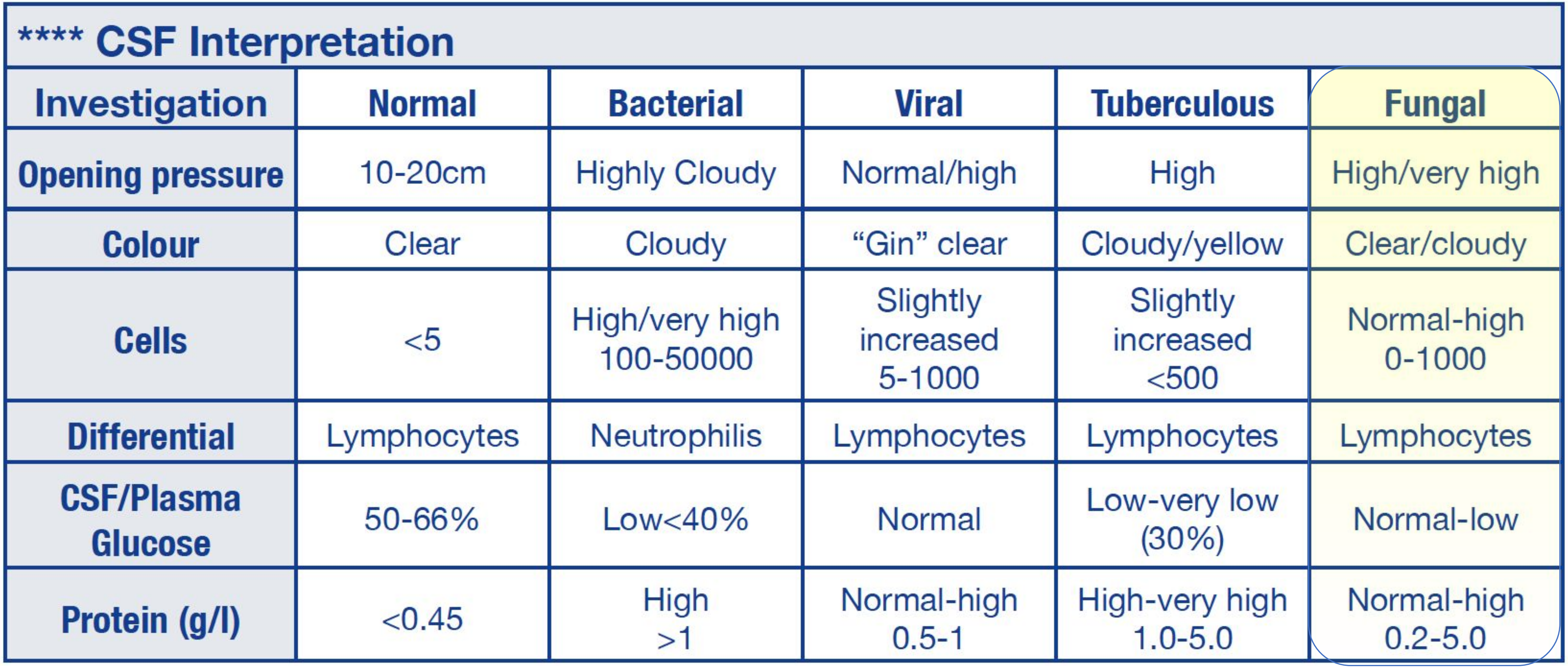
Vignette clinique 4

Quel élément pronostic majeur vous manque-t-il quant aux résultats de la PL ?

Rappel des informations données:

PL : 177 élements (93% lymphocytes), 0 hématies, protéinorachie 2.8 g/L, glycorachie 2.4 mmol/L (glycémie : 4,1 mmol/L)

Y



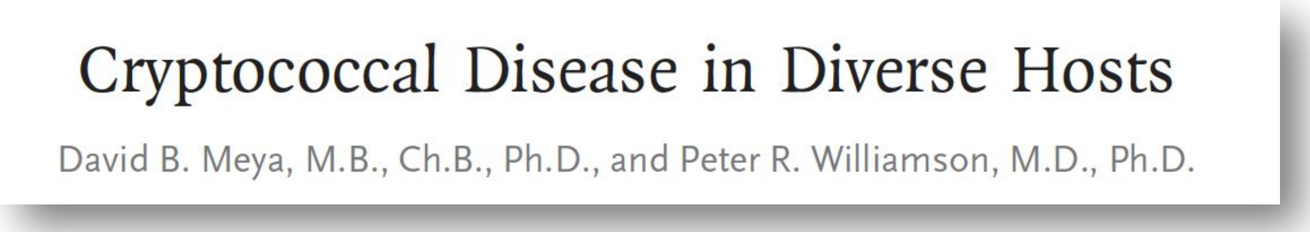
**** CSF Interpretation

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	“Gin” clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophilis	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

T. Solomon, UK guidelines for management of encephalitis, 2012

Méningite à cryptocoque en 2025

- FDR principal : déficit en immunité CELLULAIRE (HIV +++)
- 1ere cause de méningite de l'adulte en Afrique
- 20% des morts chez les PVVIH (Rajasingham LID 2022)
- Mortalité = 40% à S10
- Handicap = 70 % (Molloy NEJM 2018)



Cryptococcal Disease in Diverse Hosts

David B. Meya, M.B., Ch.B., Ph.D., and Peter R. Williamson, M.D., Ph.D.

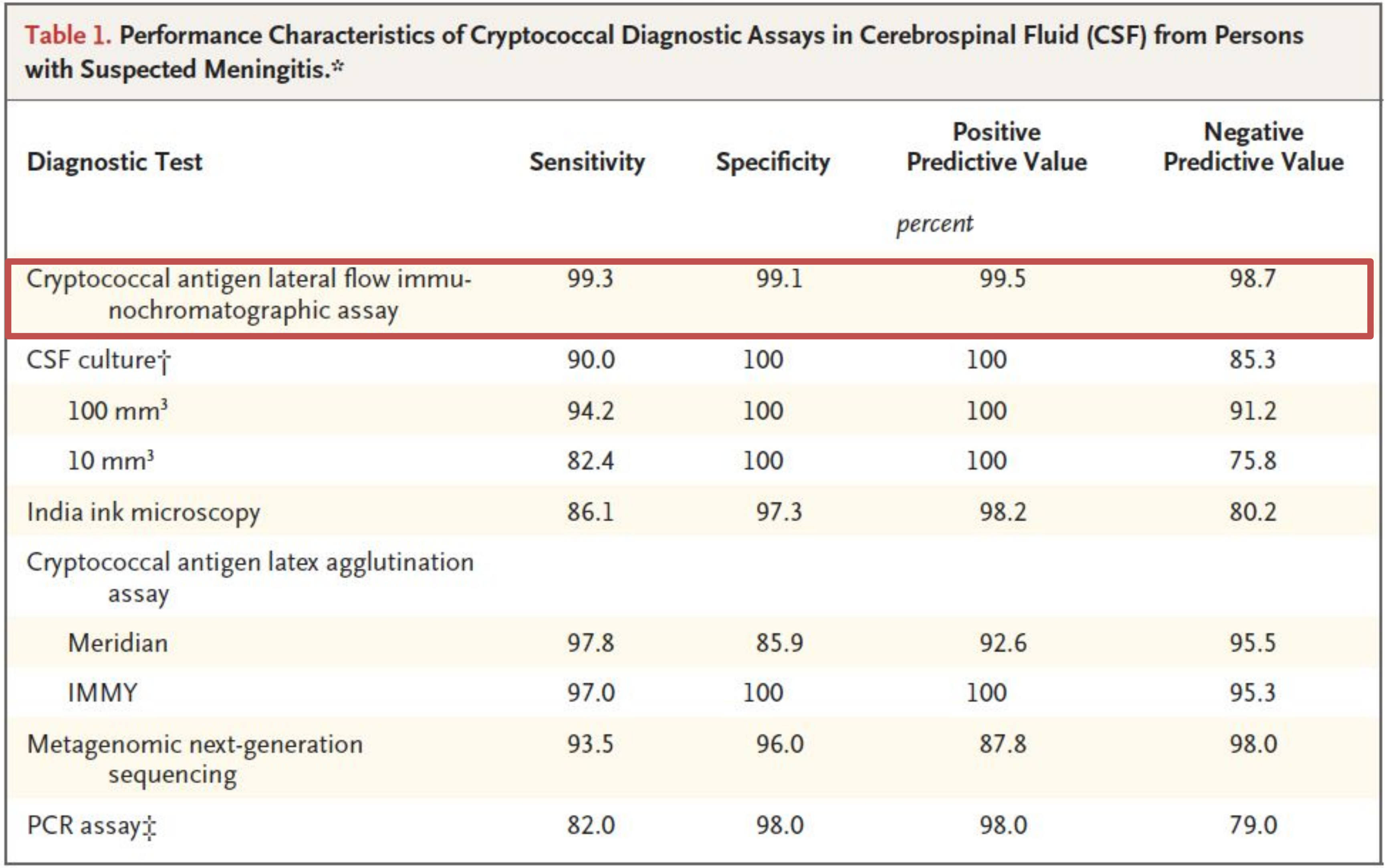
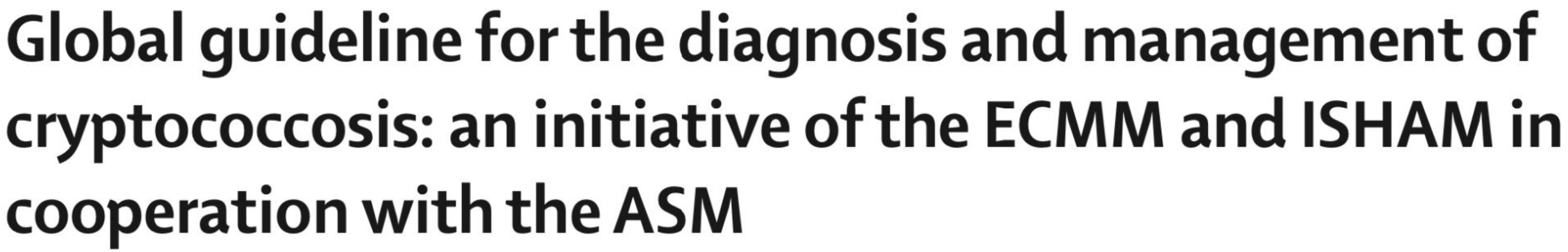


Table 1. **Performance Characteristics of Cryptococcal Diagnostic Assays in Cerebrospinal Fluid (CSF) from Persons with Suspected Meningitis.***

Diagnostic Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
		percent		
Cryptococcal antigen lateral flow immunochromatographic assay	99.3	99.1	99.5	98.7
CSF culture†	90.0	100	100	85.3
100 mm³	94.2	100	100	91.2
10 mm³	82.4	100	100	75.8
India ink microscopy	86.1	97.3	98.2	80.2
Cryptococcal antigen latex agglutination assay				
Meridian	97.8	85.9	92.6	95.5
IMMY	97.0	100	100	95.3
Metagenomic next-generation sequencing	93.5	96.0	87.8	98.0
PCR assay‡	82.0	98.0	98.0	79.0

New Eng J Med 2024

Pression intra-crânienne



Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM

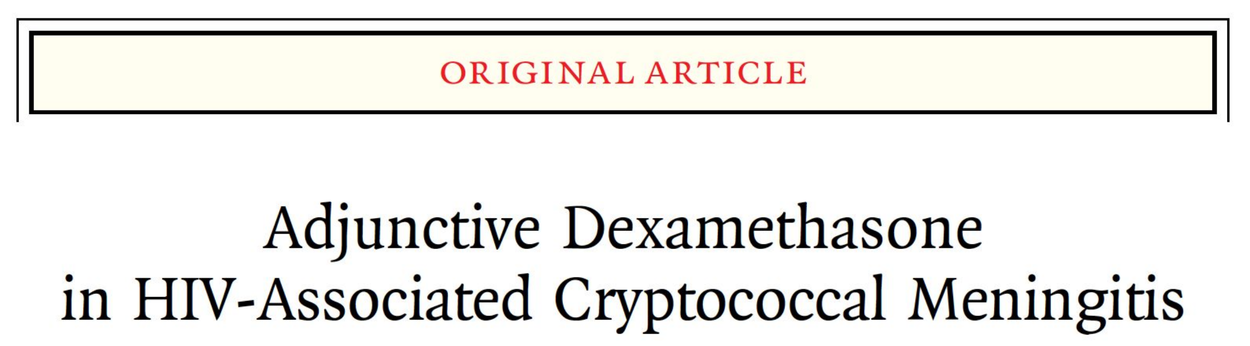
Mesurer la **pression d'ouverture** à chaque ponction lombaire.

Si normale: refaire **ponction la première semaine (à J2/J3** ou à **J7)**

Si ≥20 cmH_2O : **ponctions quotidiennes** (20–30 mL) pour ↓ ≤20 cmH_2O ou 50 %.

Si persistante : envisager **dérivation chirurgicale**

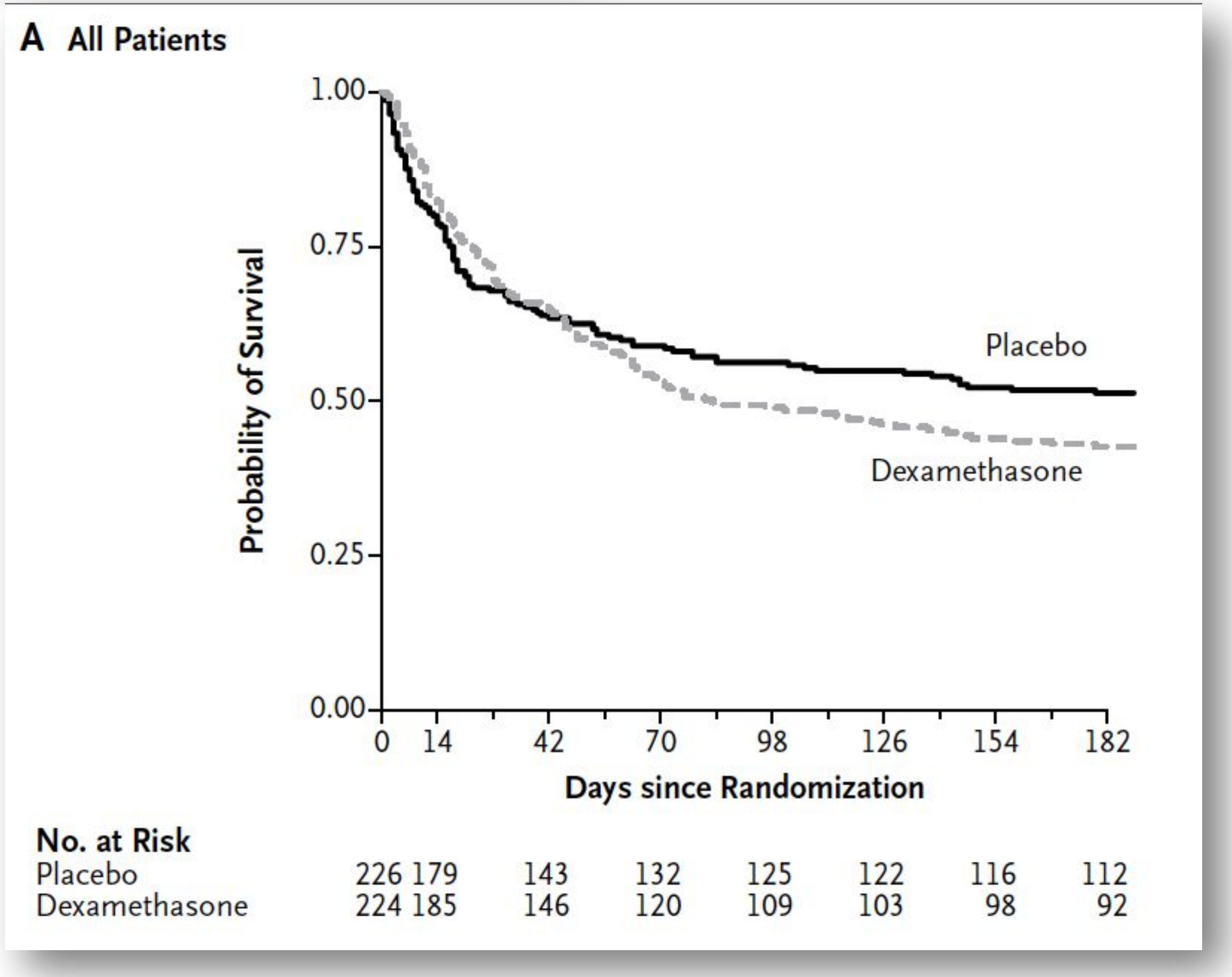
Chung et al. Lancet ID 2024



ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

Y



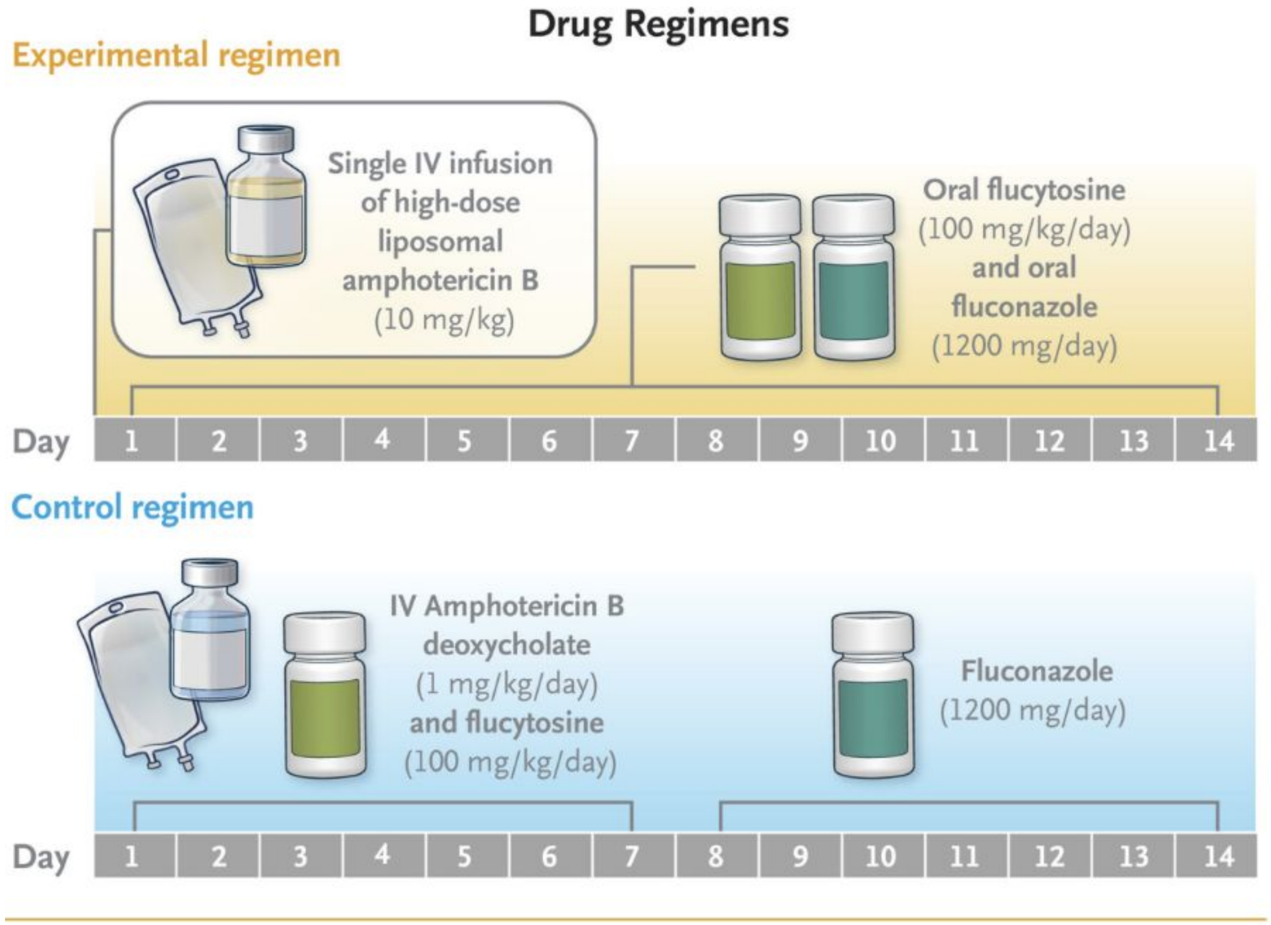
No. at Risk

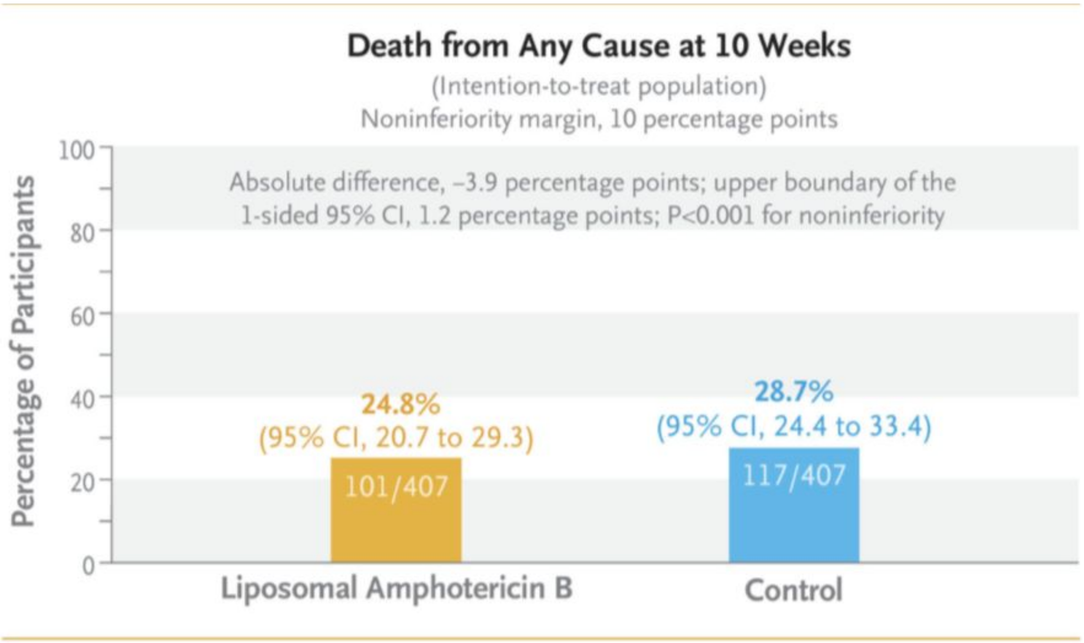
	0	14	42	70	98	126	154	182
Placebo	226	179	143	132	125	122	116	112
Dexamethasone	224	185	146	120	109	103	98	92

New Eng J Med 2016

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

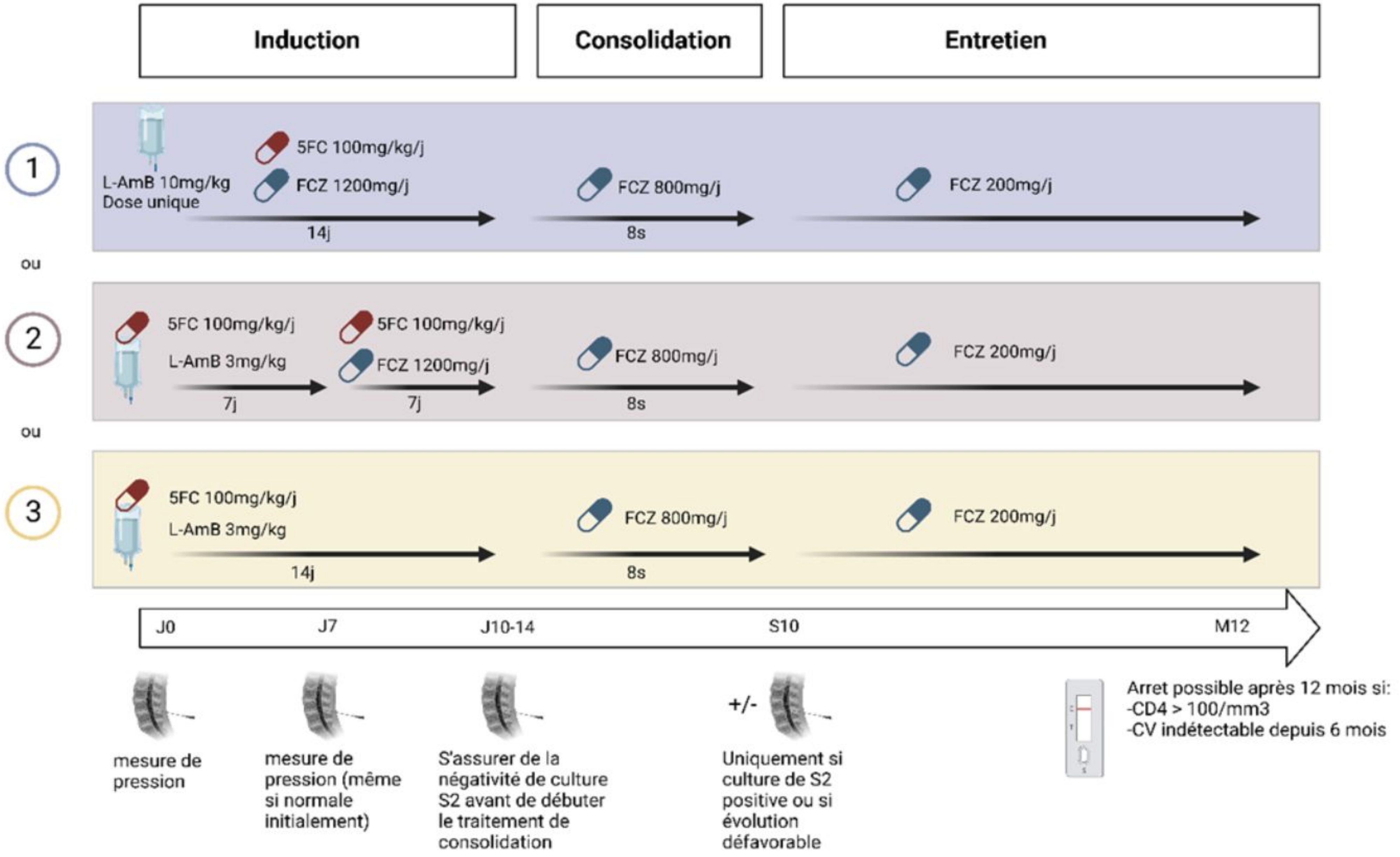
Jarvis JN et al. DOI: 10.1056/NEJMoa2111904


Drug Regimens
Experimental regimen
Single IV infusion of high-dose liposomal amphotericin B (10 mg/kg)
Oral flucytosine (100 mg/kg/day) and oral fluconazole (1200 mg/day)
Day
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Control regimen
IV Amphotericin B deoxycholate (1 mg/kg/day) and flucytosine (100 mg/kg/day)
Fluconazole (1200 mg/day)
Day
1 2 3 4 5 6 7 8 9 10 11 12 13 14



Jarvis et al. New Eng J Med 2022

Y



	Induction	Consolidation	Entretien
1	L-AmB 10mg/kg Dose unique 5FC 100mg/kg/j FCZ 1200mg/j 14j	FCZ 800mg/j 8s	FCZ 200mg/j
ou			
2	5FC 100mg/kg/j L-AmB 3mg/kg 7j 5FC 100mg/kg/j FCZ 1200mg/j 7j	FCZ 800mg/j 8s	FCZ 200mg/j
ou			
3	5FC 100mg/kg/j L-AmB 3mg/kg 14j	FCZ 800mg/j 8s	FCZ 200mg/j

J0 J7 J10-14 S10 M12

J0 : mesure de pression

J7 : mesure de pression (même si normale initialement)

J10-14 : S'assurer de la négativité de culture S2 avant de débuter le traitement de consolidation

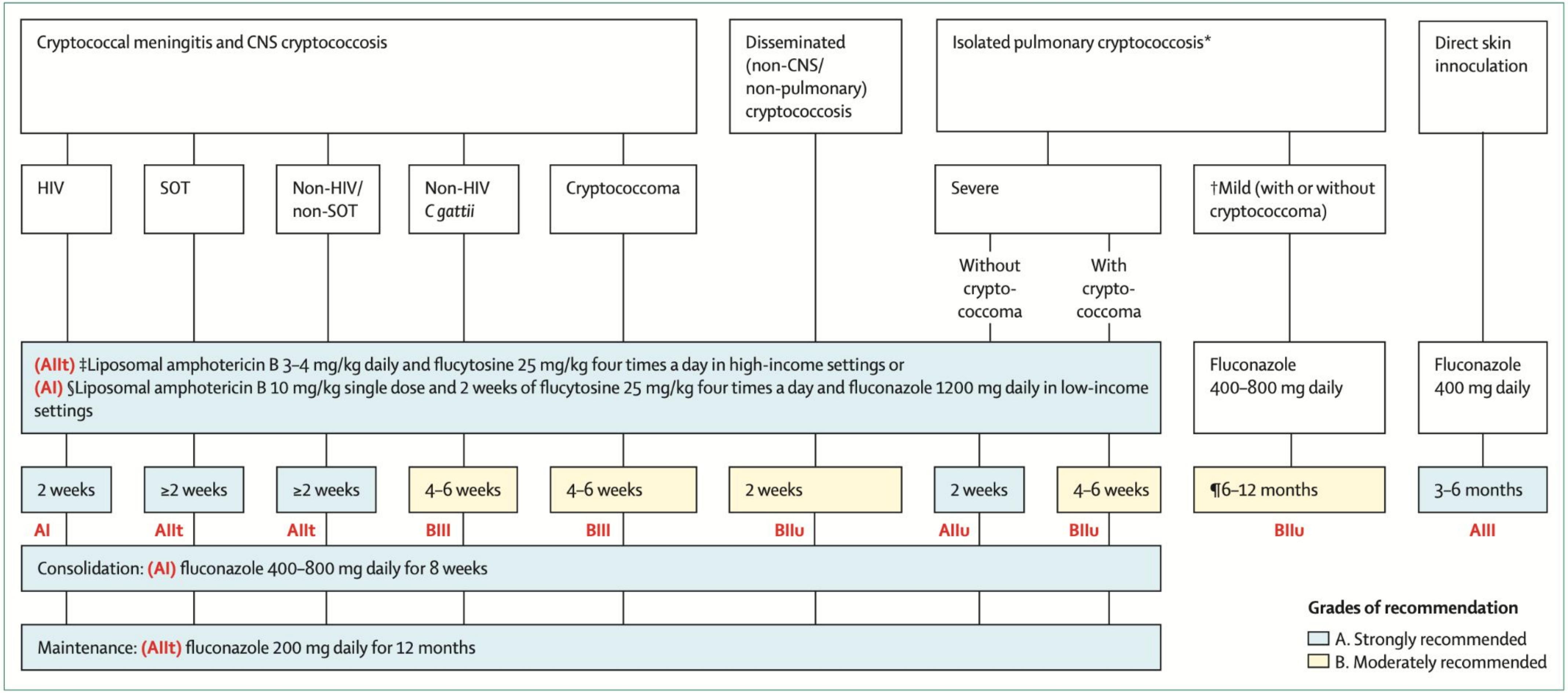
S10 : +/- Uniquement si culture de S2 positive ou si évolution défavorable

M12 : Arret possible après 12 mois si:
-CD4 > 100/mm3
-CV indétectable depuis 6 mois

5FC, flucytosine ; CrAg, antigène cryptococcique ; FCZ, fluconazole ; L-AmB, amphotéricine B liposomale

HAS 2024

Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM



Cryptococcal meningitis and CNS cryptococcosis

- HIV
- SOT
- Non-HIV/ non-SOT
- Non-HIV *C gattii*
- Cryptococcoma

Disseminated (non-CNS/ non-pulmonary) cryptococcosis

Isolated pulmonary cryptococcosis*

- Severe
  - Without cryptococcoma
  - With cryptococcoma
- †Mild (with or without cryptococcoma)

Direct skin innoculation

(AIIt) ‡Liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day in high-income settings or
(AI) §Liposomal amphotericin B 10 mg/kg single dose and 2 weeks of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily in low-income settings

Fluconazole 400–800 mg daily

Fluconazole 400 mg daily

HIV	SOT	Non-HIV/ non-SOT	Non-HIV *C gattii*	Cryptococcoma	Disseminated	Severe without cryptococcoma	Severe with cryptococcoma	Mild	Direct skin innoculation
2 weeks	≥2 weeks	≥2 weeks	4–6 weeks	4–6 weeks	2 weeks	2 weeks	4–6 weeks	¶6–12 months	3–6 months
AI	AIIt	AIIt	BIII	BIII	BIIu	AIIu	BIIu	BIIu	AIII

Consolidation: **(AI)** fluconazole 400–800 mg daily for 8 weeks

Maintenance: **(AIIt)** fluconazole 200 mg daily for 12 months

Grades of recommendation

🟦 A. Strongly recommended
🟨 B. Moderately recommended

Chung et al. Lancet ID 2024

Méningite crypto - take home messages

- HIV mais pas que (transplanté d’organe solide ++)
- Attention à la pression intracrânienne
- Régime single dose Ampho B maintenant recommandé
- Attention aux effets indésirables (rénaux réduits avec ampho B SD)
- Hors soin d’urgence : traitement long
  consolidation et entretien

RCP neuro-infectiologique depuis 2020

- RCP mensuelle le 3^{e} vendredi du mois
  LA PROCHAINE LE 20 JUIN 2025
- En présentiel à Bichat et en distanciel
- Neurologues (Delafontaine, Bichat), neuro-radiologues (FOR, Bichat), réanimateurs, infectiologues… et vous !
- Cas d'infection avérée ou suspectée du SNC

Rejoignez la mailing list
en flashant ce QR code

MERCI DE VOTRE ATTENTION

Méningite à *Listeria* et corticostéroides

- Effet plutôt délétère : étude de cohorte prospective française MONALISA (Charlier et al. The Lancet 2017)

252 neurolistérioses, mortalité à 48% chez ceux recevant de la DXM vs 27%

- Bénéfice : étude de cohorte prospective néerlandaise (Brouwer et al. The Lancet eClinicalMedicine 2023) --> 162 neurolistérioses, effet favorable sur le Glasgow Outcome scale ET sur mortalité

TBM et PL déplétive

Hydrocéphalie : complique jusqu’à 86 % des TBM (Chiang LID 2014)

Le plus souvent communicante

Peu de littérature sur interêt PL déplétive

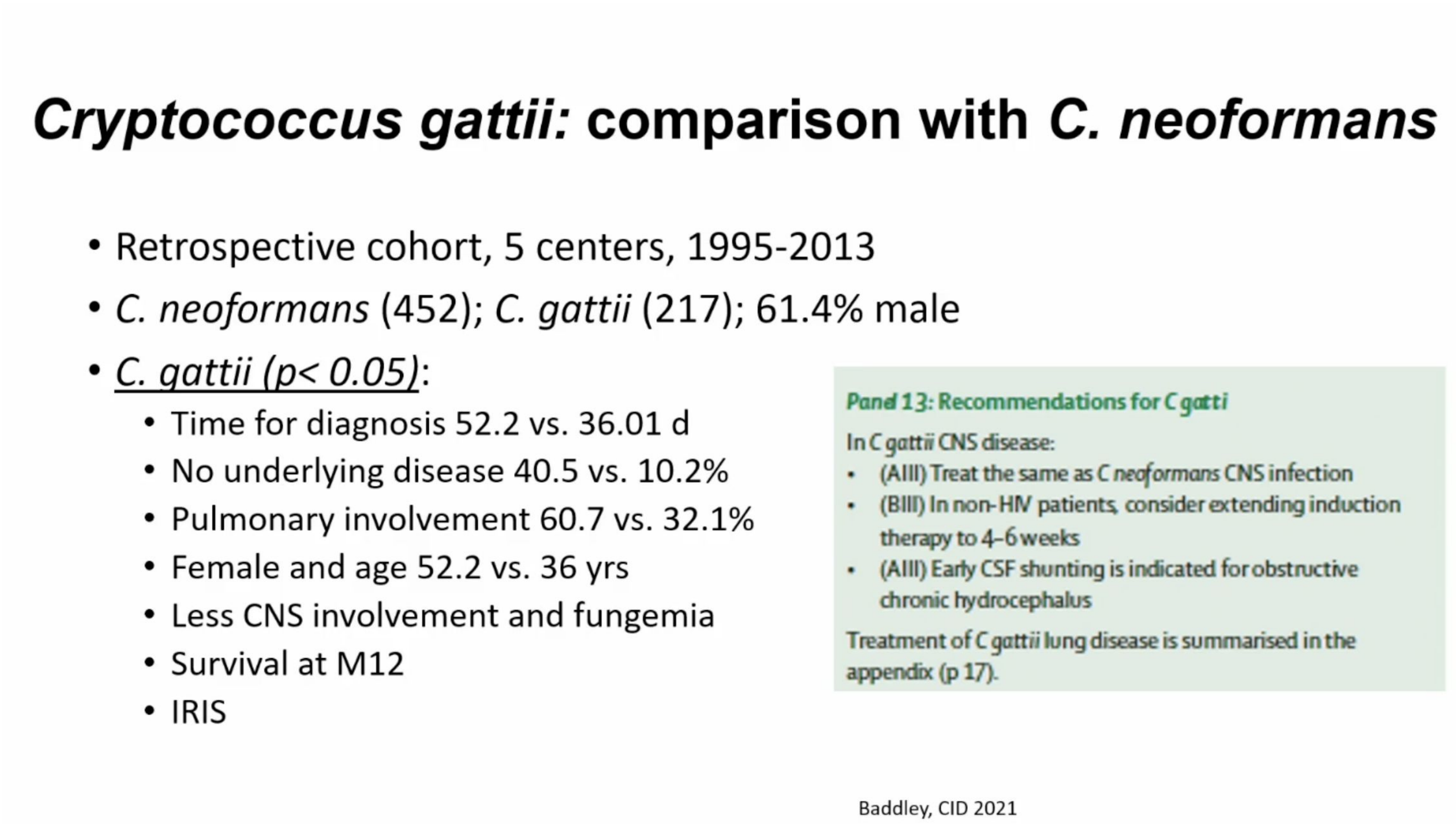
Dans la crypto : argument aussi de la baisse de la charge fongique =/= TBM

Quelques équipes l’ont fait : Neuro CH de St Denis (Lampros et al. ID now 2025)

Cryptococcose chez le transplanté :

Tardif (mois/années après la SOT)
Les plus à risque : coeur et intestin grèle
Pas de RCT avec les SOT spécifiquement : extrapolé depuis le VIH

The use of lipid-formulations in SOT recipients with CNS cryptococcosis was independently associated with reduced mortality compared with amphotericin B.



Cryptococcus gattii: comparison with *C. neoformans*

- Retrospective cohort, 5 centers, 1995-2013
- *C. neoformans* (452); *C. gattii* (217); 61.4% male
- *C. gattii (p< 0.05)*:
  - Time for diagnosis 52.2 vs. 36.01 d
  - No underlying disease 40.5 vs. 10.2%
  - Pulmonary involvement 60.7 vs. 32.1%
  - Female and age 52.2 vs. 36 yrs
  - Less CNS involvement and fungemia
  - Survival at M12
  - IRIS

Panel 13: Recommendations for *C gatti*

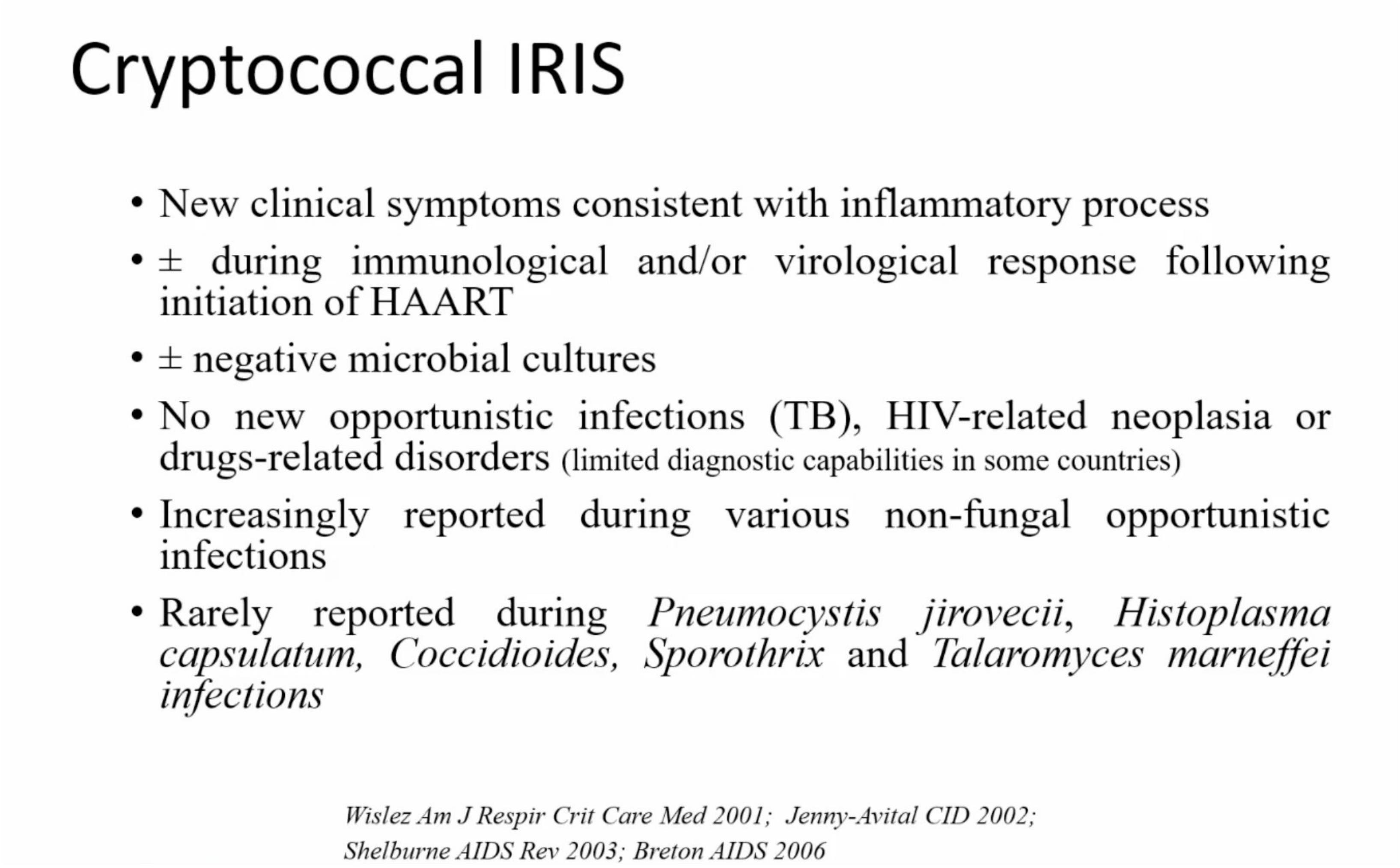
In *C gattii* CNS disease:

- (AIII) Treat the same as *C neoformans* CNS infection
- (BIII) In non-HIV patients, consider extending induction therapy to 4–6 weeks
- (AIII) Early CSF shunting is indicated for obstructive chronic hydrocephalus

Treatment of *C gattii* lung disease is summarised in the appendix (p 17).

Baddley, CID 2021

Slide from Prof. Lortholary



Cryptococcal IRIS

- New clinical symptoms consistent with inflammatory process
- ± during immunological and/or virological response following initiation of HAART
- ± negative microbial cultures
- No new opportunistic infections (TB), HIV-related neoplasia or drugs-related disorders (limited diagnostic capabilities in some countries)
- Increasingly reported during various non-fungal opportunistic infections
- Rarely reported during *Pneumocystis jirovecii*, *Histoplasma capsulatum, Coccidioides, Sporothrix* and *Talaromyces marneffei infections*

Wislez Am J Respir Crit Care Med 2001; Jenny-Avital CID 2002;
Shelburne AIDS Rev 2003; Breton AIDS 2006

Slide from Prof. Lortholary

C-IRIS

C-IRIS has been described in people with HIV usually between 2 weeks and 3 months after commencement of ART. Patients develop exaggerated symptoms and signs or atypical inflammation, reminiscent of a paradoxical recurrence,[126,127] but C-IRIS can also occur in the setting of immune recovery or withdrawal of immunosuppressants. It has also been observed in seemingly immunocompetent individuals, including in *C gattii* infections, as a post-infectious inflammatory immune response syndrome (PIIRS).[90,128] There is no diagnostic biomarker for C-IRIS. It is diagnosed by diagnosis of exclusion (figure 2).

There have been no therapeutic trials in C-IRIS. Management strategies include therapeutic lumbar puncture and symptomatic therapies. In severe C-IRIS, corticosteroids are commonly used to dampen inflammation, although their efficacy has not been rigorously examined in clinical trials. In steroid-refractory C-IRIS, there are case reports on the use of tumour necrosis factor-α blockers, such as adalimumab[129–132] or thalidomide,[133–135] with mixed success. Corticosteroids can also be beneficial in PIIRS (panel 12; appendix p 76).[136]

Early Adjunctive Steroids ?

Yes

Acute Bacterial Meningitis

De Gans, New Eng J Med 2002

(Reduced mortality and disability)

Tuberculous Meningitis

Thwaites, New Eng J Med 2004

(Reduced mortality)

Donovan, New Eng J Med 2023

(HIV+ patients ?)

Maybe ?

Viral (HSV) Encephalitis

T Solomon, DEXENCEPH trial…

(Improved cognitive function ?)

Listeria monocytogenes meningitis

Brouwer, eClinical Med 2023

(Reduced mortality and disability)

No

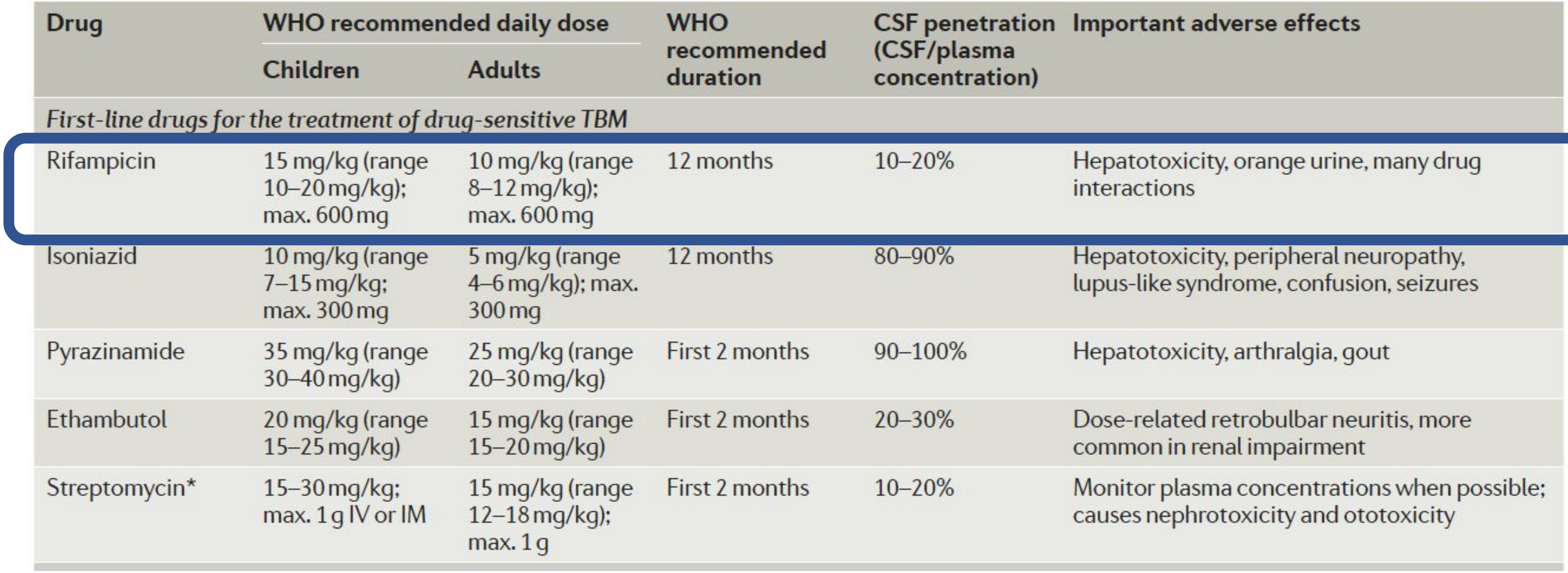
Cryptococcal Meningitis

Beardsley, New Eng J Med 2016

(More disability, more adverse events)

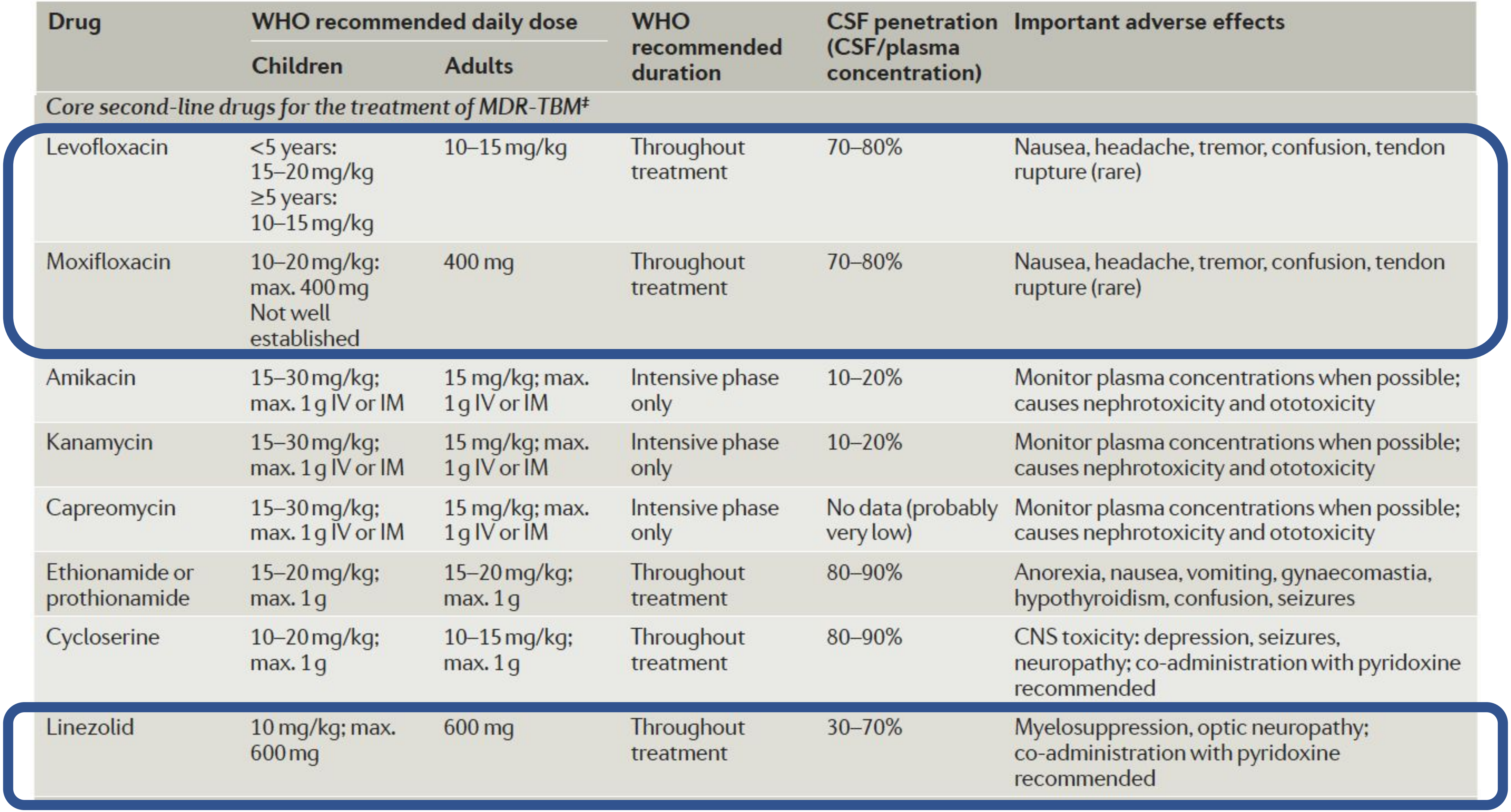
INFECTIONS OF THE CNS

Tuberculous meningitis



Drug	WHO recommended daily dose		WHO recommended duration	CSF penetration (CSF/plasma concentration)	Important adverse effects
	Children	Adults			
First-line drugs for the treatment of drug-sensitive TBM					
Rifampicin	15 mg/kg (range 10–20 mg/kg); max. 600 mg	10 mg/kg (range 8–12 mg/kg); max. 600 mg	12 months	10–20%	Hepatotoxicity, orange urine, many drug interactions
Isoniazid	10 mg/kg (range 7–15 mg/kg; max. 300 mg	5 mg/kg (range 4–6 mg/kg); max. 300 mg	12 months	80–90%	Hepatotoxicity, peripheral neuropathy, lupus-like syndrome, confusion, seizures
Pyrazinamide	35 mg/kg (range 30–40 mg/kg)	25 mg/kg (range 20–30 mg/kg)	First 2 months	90–100%	Hepatotoxicity, arthralgia, gout
Ethambutol	20 mg/kg (range 15–25 mg/kg)	15 mg/kg (range 15–20 mg/kg)	First 2 months	20–30%	Dose-related retrobulbar neuritis, more common in renal impairment
Streptomycin*	15–30 mg/kg; max. 1 g IV or IM	15 mg/kg (range 12–18 mg/kg); max. 1 g	First 2 months	10–20%	Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity

RJ Wilkinson, Nature Reviews Neurology 2017

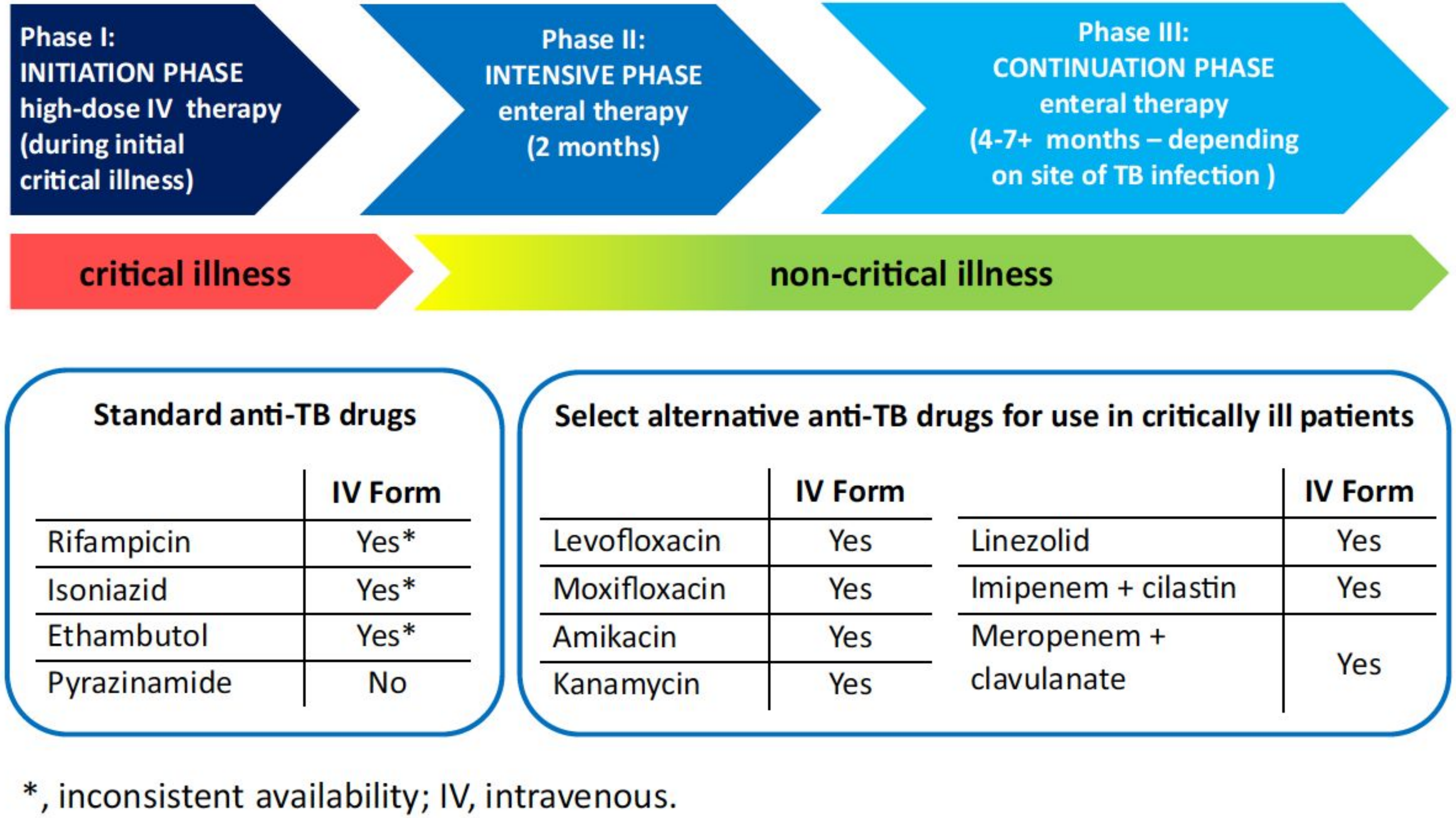


Drug	WHO recommended daily dose		WHO recommended duration	CSF penetration (CSF/plasma concentration)	Important adverse effects
	Children	Adults			
Core second-line drugs for the treatment of MDR-TBM‡					
Levofloxacin	<5 years: 15–20 mg/kg ≥5 years: 10–15 mg/kg	10–15 mg/kg	Throughout treatment	70–80%	Nausea, headache, tremor, confusion, tendon rupture (rare)
Moxifloxacin	10–20 mg/kg: max. 400 mg Not well established	400 mg	Throughout treatment	70–80%	Nausea, headache, tremor, confusion, tendon rupture (rare)
Amikacin	15–30 mg/kg; max. 1 g IV or IM	15 mg/kg; max. 1 g IV or IM	Intensive phase only	10–20%	Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity
Kanamycin	15–30 mg/kg; max. 1 g IV or IM	15 mg/kg; max. 1 g IV or IM	Intensive phase only	10–20%	Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity
Capreomycin	15–30 mg/kg; max. 1 g IV or IM	15 mg/kg; max. 1 g IV or IM	Intensive phase only	No data (probably very low)	Monitor plasma concentrations when possible; causes nephrotoxicity and ototoxicity
Ethionamide or prothionamide	15–20 mg/kg; max. 1 g	15–20 mg/kg; max. 1 g	Throughout treatment	80–90%	Anorexia, nausea, vomiting, gynaecomastia, hypothyroidism, confusion, seizures
Cycloserine	10–20 mg/kg; max. 1 g	10–15 mg/kg; max. 1 g	Throughout treatment	80–90%	CNS toxicity: depression, seizures, neuropathy; co-administration with pyridoxine recommended
Linezolid	10 mg/kg; max. 600 mg	600 mg	Throughout treatment	30–70%	Myelosuppression, optic neuropathy; co-administration with pyridoxine recommended

RJ Wilkinson, Nature Reviews Neurology 2017

current concepts in anti-tuberculosis treatment in the critically ill patient

Mervyn Mer[1], Alimuddin Zumla[2] and Martin W. Dünser[3*]



Phase I:
INITIATION PHASE
high-dose IV therapy
(during initial critical illness)

Phase II:
INTENSIVE PHASE
enteral therapy
(2 months)

Phase III:
CONTINUATION PHASE
enteral therapy
(4-7+ months – depending on site of TB infection)

critical illness

non-critical illness

Standard anti-TB drugs

	IV Form
Rifampicin	Yes*
Isoniazid	Yes*
Ethambutol	Yes*
Pyrazinamide	No

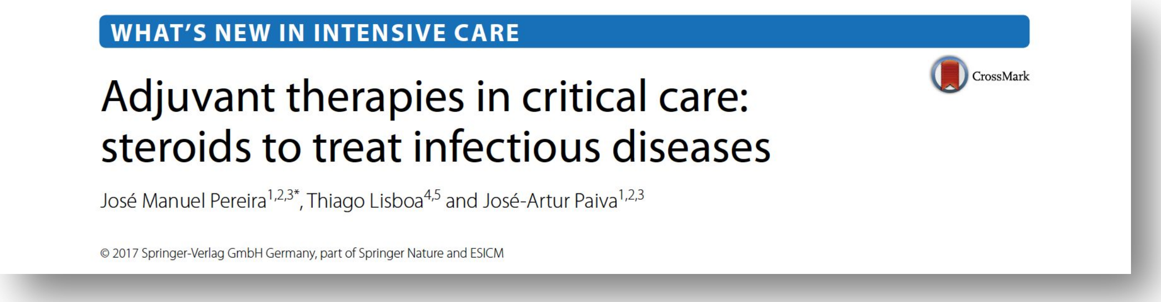
Select alternative anti-TB drugs for use in critically ill patients

	IV Form		IV Form
Levofloxacin	Yes	Linezolid	Yes
Moxifloxacin	Yes	Imipenem + cilastin	Yes
Amikacin	Yes	Meropenem + clavulanate	Yes
Kanamycin	Yes		

*, inconsistent availability; IV, intravenous.

Fig. 1 Potential novel approach to anti-TB treatment in critically ill patients consisting of three (instead of two) phases of therapy. Asterisk indicates inconsistent availability. *IV* intravenous

Intensive Care Medicine 2018


WHAT'S NEW IN INTENSIVE CARE

Adjuvant therapies in critical care: steroids to treat infectious diseases

José Manuel Pereira[1,2,3*], Thiago Lisboa[4,5] and José-Artur Paiva[1,2,3]

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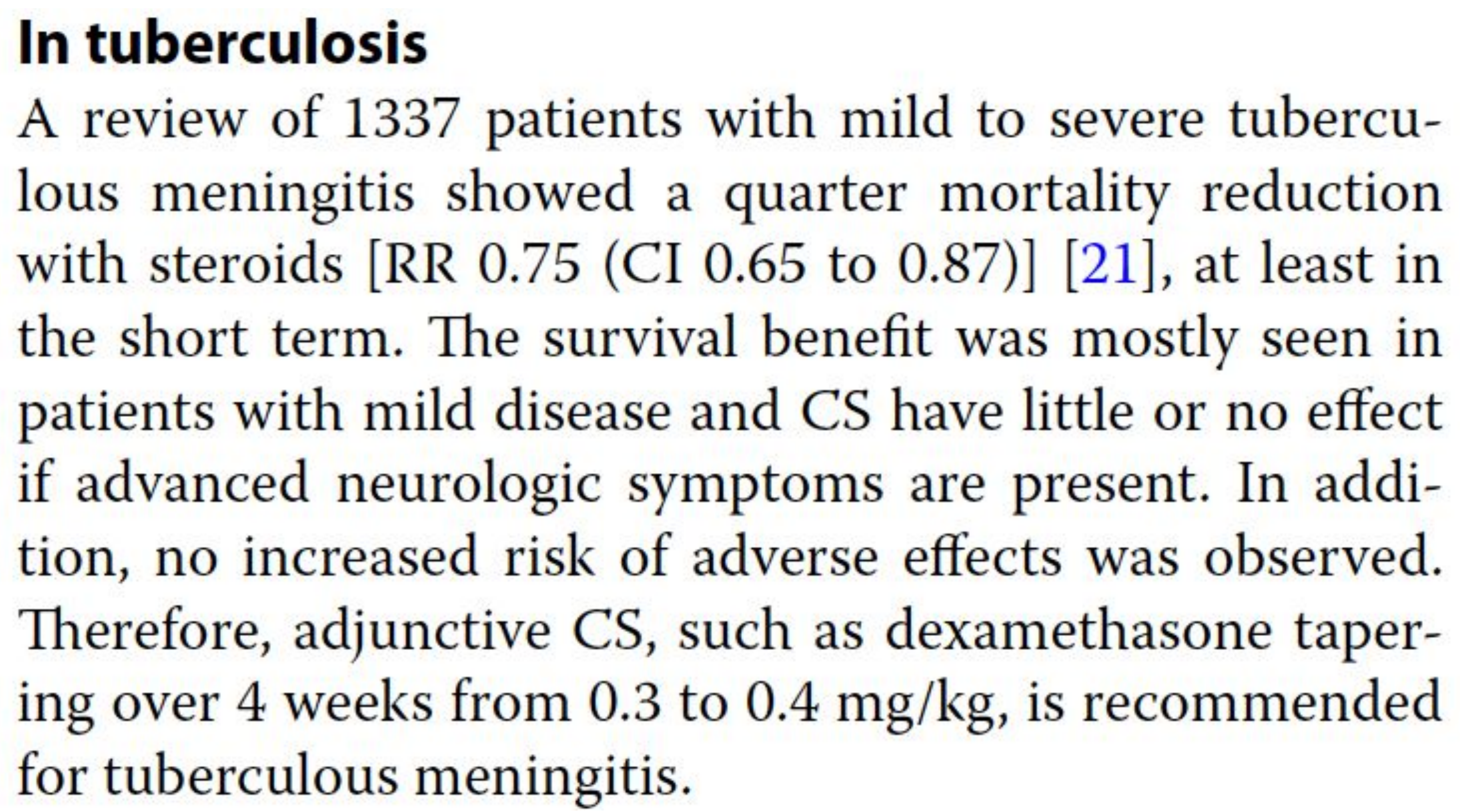
In tuberculosis

A review of 1337 patients with mild to severe tuberculous meningitis showed a quarter mortality reduction with steroids [RR 0.75 (CI 0.65 to 0.87)] [21], at least in the short term. The survival benefit was mostly seen in patients with mild disease and CS have little or no effect if advanced neurologic symptoms are present. In addition, no increased risk of adverse effects was observed. Therefore, adjunctive CS, such as dexamethasone tapering over 4 weeks from 0.3 to 0.4 mg/kg, is recommended for tuberculous meningitis.

Intensive Care Medicine 2018