

Difficultés diagnostiques et thérapeutiques de la tuberculose du système nerveux



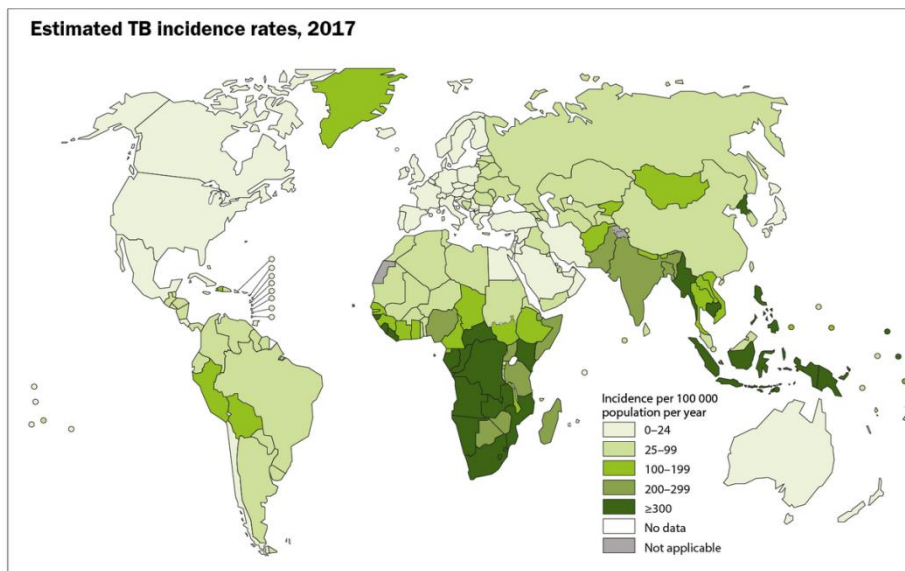
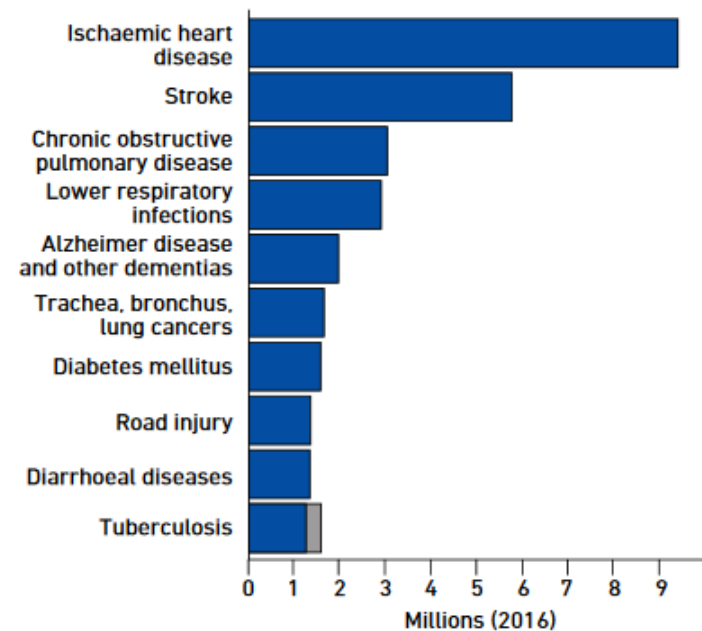
Frédéric Méchai
Service maladies infectieuses, CHU
Avicenne
Paris, 10 Oct 2019

Généralités

La tuberculose dans le monde en 2017

- **1^{ère} cause de décès par maladie infectieuse** à travers le monde
- **Incidence estimée: 10 millions de personnes/an**
- **Mortalité estimée: 1,3 millions (HIV-) + 300 000 personnes VIH+**

Top causes of death worldwide in 2016.^{a,b}
Deaths from TB among HIV-positive people are shown in grey.



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2018*. WHO, 2018.

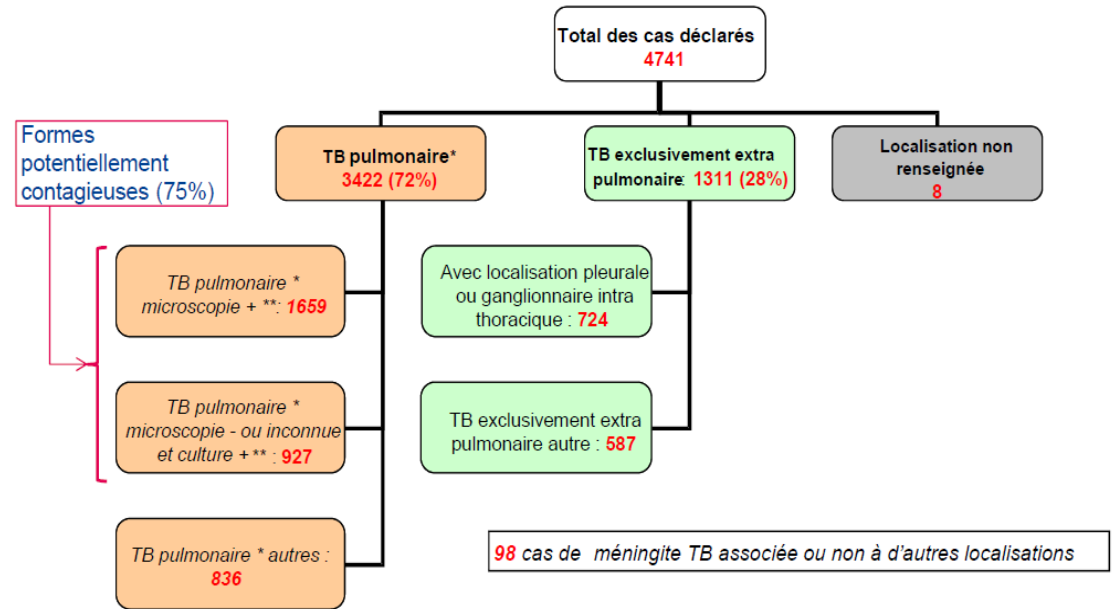
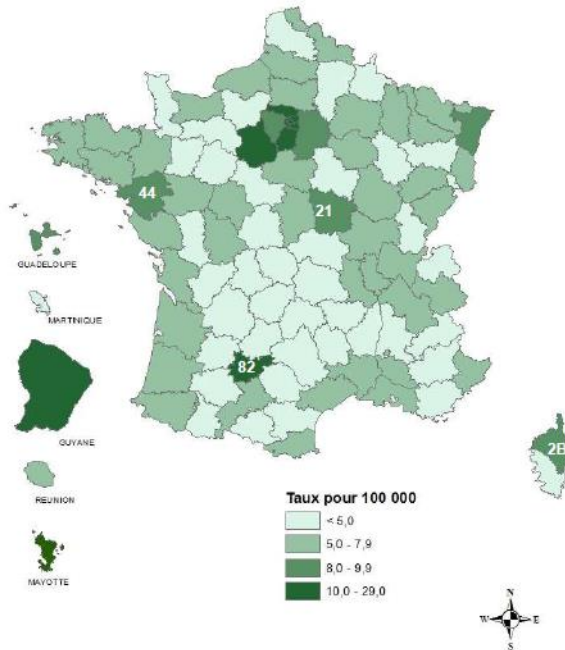


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Incidences en France en 2014 par département

Formes cliniques, France 2015

Taux pour 100 000



* avec ou sans localisation extra-pulmonaire; ** sur prélèvement respiratoire

Source: Santé publique France, déclaration obligatoire de tuberculose

Tuberculose neuro-méningée

- 1% de tous les cas de tuberculoses
- 5% des TB extra pulmonaires
- Localisation avec morbi-mortalité la plus importante (50% des patients)
- Outils diagnostiques et thérapeutiques à améliorer...

Diagnostic

Diagnostic: clinique

- **Signes cliniques les plus discriminants**

	Children ³⁷	Children and adults ^{38,40}	Adults ^{39,41-43}
History and examination	Duration of symptoms >6 days; optic atrophy; abnormal movements; focal neurological deficit	Duration of symptoms >5 days; Glasgow coma score <15 or focal neurological deficit	Duration of symptoms ≥6 days; age <36 years; rural dwelling; focal neurological deficit; fever*; neck stiffness*; coma*
CSF findings	Neutrophils <50% of total white cells	Clear appearance; white cell count >1.00×10 ⁹ /L; lymphocytes >30% of total white cells; protein >1.0 g/L; ratio of CSF to plasma glucose <0.5	Clear appearance; white cell count <0.75×10 ⁹ /L; neutrophils <90% of total white cells; ratio of CSF to serum glucose ≤0.2; lymphocytes >0.20×10 ⁹ /L; low CSF pressure*; raised leucocyte numbers*
Other findings	Blood white cell count <15×10 ⁹ /L; if HIV infected, CD4 cell count <200 per μL; negative cryptococcal antigen test

Thwaites GE, Lancet Neurol 2013

- **Scores de prédiction clinique:**
performances variables selon
les populations étudiées

Thwaites GE et al, Lancet 2002

Panel: The Vietnam diagnostic rule³⁹

Entry criteria

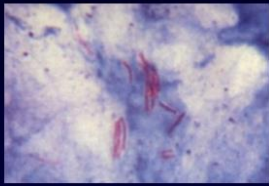
- Adult (age >15 years) with meningitis and ratio of CSF to plasma glucose <0.5

Clinical features and scores

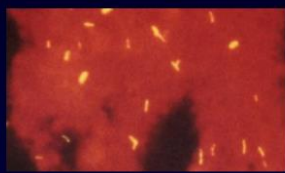
- Age ≥36 years (score +2)
- Age <36 years (score 0)
- Blood white cell count ≥15×10⁹/L (score +4)
- Blood white cell count <15×10⁹/L (score 0)
- History of illness ≥6 days (score -5)
- History of illness <6 days (score 0)
- CSF white cell count ≥0.75×10⁹/L (score +3)
- CSF white cell count <0.75×10⁹/L (score 0)
- CSF neutrophils ≥90% of total white cells (score +4)
- CSF neutrophils <90% of total white cells (score 0)

Interpretation

- Total score ≤4 = tuberculous meningitis
- Total score >4 = alternative diagnosis



Coloration de Ziehl x 1000



Coloration auramine x 400

Biologie



- **Diagnostic difficile:** infection pauci-bacillaire (LCS)
- **Outils disponibles dans le LCS:** examen microscopique, culture BK, biologie moléculaire, ADA
- **Examen microscopique:** rapide mais Se faible (10 à 20%)
- **Culture + sensible (60-70%)** mais longue (≥ 2 semaines)
- **GeneXpert MTB/RIF:** rapide, $Se \approx 60\%$, $Sp \approx 100\%$

Thwaites GE et al, Lancet neurol 2013
Donovan j et al, Lancet neurol 2019

Improving the microbiological diagnosis of tuberculous meningitis: A prospective, international, multicentre comparison of conventional and modified Ziehl–Neelsen stain, GeneXpert, and culture of cerebrospinal fluid

A. Dorothee Heemskerk^{a,b,1,2}, Joseph Donovan^{a,b,1,*}, Do Dang Anh Thu^a, Suzaan Marais^{c,d}, Lidya Chaidir^e, Vu Thi Mong Dung^a, Chad M. Centner^f, Vu Thi Ngoc Ha^a, Jessi Annisa^e, Sofiati Dian^{e,g}, Louise Bovijn^c, Nguyen Thi Hoang Mai^{a,h}, Nguyen Hoan Phu^{a,h}, Nguyen Van Vinh Chau^{a,h}, Ahmad Rizal Ganiem^e, Cao Thao Van^a, Ronald B. Geskus^{a,b}, Nguyen Thuy Thuong Thuong^{a,b}, Rovina Ruslami^e, Graeme Meintjes^c, Reinout van Crevel^{b,g}, Robert J. Wilkinson^{c,i,j}, Guy E. Thwaites^{a,b}

• Méthodes

- Etude prospective (Vietnam, Indonésie, Afrique du Sud)
- 618 adultes suspects de TB méningée (2015-2016)
 - ✓ Rentabilité tests diagnostiques vs. diagnostic clinique & vs. culture
 - ✓ Facteurs prédictifs de TB documentée

	CZN (N = 612)	MZN with cytospin (N = 605)	MZN without cytospin (N = 604)	culture (N = 602)	Xpert (N = 610)
Positive tests in TBM	129/380	129/374	116/375	119/374	95/379
Sensitivity (%) (95% CI)	33.9 (29.4–38.8%)	34.5 (29.9–39.4%)	30.9 (26.5–35.8%)	31.8 (27.3–36.7%)	25.1 (21.0–29.7%)
Specificity (%)	100	100	99.6	100	100

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1. Volume LCS (+30% par mL supplémentaire)
2. Hypoglycorachie
3. Lactatorachie



Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study



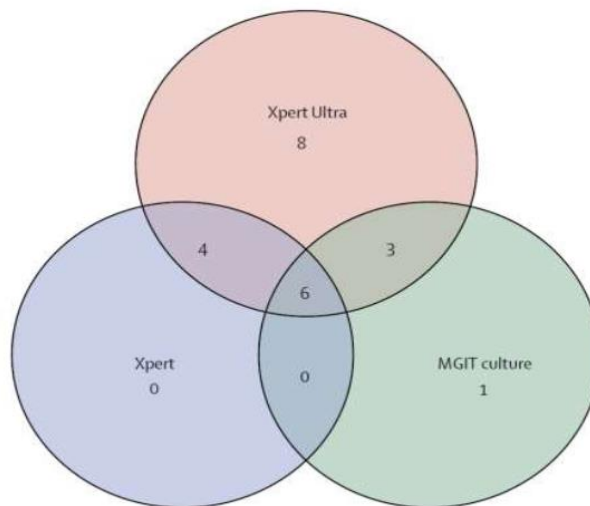
Nathan C Bahr, Edwin Nuwagira, Emily E Evans, Fiona V Cresswell, Philip V Bystrom, Adolf Byamukama, Sarah C Bridge, Ananta S Bangdiwala, David B Meya, Claudia M Denking, Conrad Muzoora, David R Boulware, on behalf of the ASTRO-CM Trial Team

Quelles sont les performances diagnostiques de la PCR Xpert Ultra dans le LCS ?

Prospectif monocentrique (Ouganda)

129 patients HIV+ suspects de méningite

PCR Xpert Ultra, Xpert standard, culture (MGIT), encre de Chine, cyto, Ziehl, FilmArray Meningitis/encephalitis (6 ml = 100 gouttes)



107 participants negative for tuberculosis

Test	Sensibilité ¹
Culture	43%
Xpert Standard	43%
Xpert Ultra	70%

¹Calculée à partir de la définition consensuelle (Marais et al, 2010)

Diagnostic test accuracy of adenosine deaminase for tuberculous meningitis: A systematic review and meta-analysis



Ali Pormohammad ^{a,*}, Seyed-Mohammad Riahi ^{b,c},
Mohammad Javad Nasiri ^a, Fatemeh Fallah ^a,
Mohammad Aghazadeh ^d, Farahnoosh Doustdar ^a,
Ramin Pouriran ^e

Journal of Infection 2017

- Dosage *Adénosine Déaminase* intéressant pour les pleurésies tuberculeuses
- *Méta-analyse*: performances de ce test dans le LCS pour le diagnostic de TBM
- 20 études: Se 89%, Sp 91%

Radiologie

- **Signes radiologiques évocateurs:**

- exsudats base du crâne
- infarctus
- tuberculomes
- hydrocéphalie

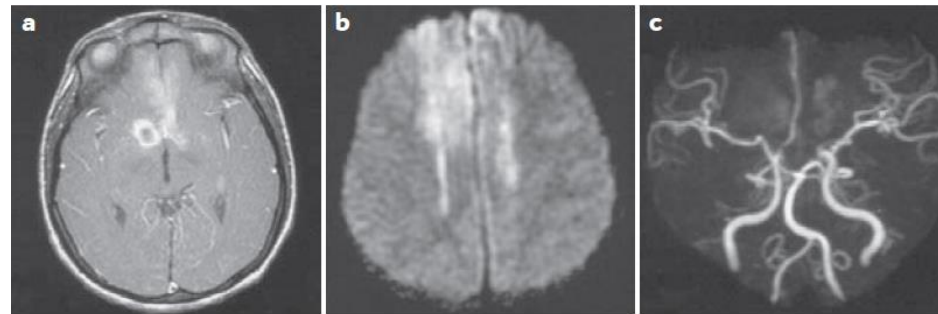


Figure 2 | **MRI scans from a patient with stage II tuberculous meningitis.** The patient had presented with fever for 15 days and altered sensorium for 1 day. **a** | Granuloma in T1 contrast axial section. **b** | Anterior cerebral artery territory infarction in diffusion-weighted sequence. **c** | Narrowing right anterior cerebral artery and occlusion of left anterior communicating artery.

- Association de ces signes intéressante mais performances diagnostiques mal connues
- Absence possible stade précoce

Traitement

Antibiotiques

	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 drugs⁸²⁻⁸⁵

Nau R et al, J Antimicrob Chemother 1992
Donald PR et al, Tuberculosis 2010
Thwaites GE, Lancet Infect Dis 2013

Randomized Pharmacokinetic and Pharmacodynamic Comparison of Fluoroquinolones for Tuberculous Meningitis^{†‡}

Guy E. Thwaites,^{1,2*} Sujata M. Bhavnani,³ Tran Thi Hong Chau,⁴ Jeffrey P. Hammel,³
M. Estée Török,⁵ Scott A. Van Wart,³ Pham Phuong Mai,⁴ Daniel K. Reynolds,³
Maxine Caws,² Nguyen Thi Dung,⁴ Tran Tinh Hien,⁴ Robert Kulawy,³
Jeremy Farrar,² and Paul G. Ambrose³

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis

A. Dorothee Heemskerck, M.D., Nguyen D. Bang, Ph.D., Nguyen T.H. Mai, Ph.D.,

N Engl J Med 2016

- **Place des fluoroquinolones** (efficacité, bonne diffusion LCS)
- **Optimisation Rifampicine:** fortes doses (>15mg/kg/j), voie IV, modèle TB pulmonaire (>35mg/kg/j, bonne tolérance)

Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami*, A Rizal Ganiem*, Sofjati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Barm, Rob E Aarnoutse, Reinout van Crevel

Summary

Background Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed *Lancet Infect Dis* 2013; 13: 27-35

Wellcome Open Research

Wellcome Open Research 2018, 3:83 Last updated: 15 MAY 2019



STUDY PROTOCOL

High dose oral and intravenous rifampicin for improved survival from adult tuberculous meningitis: a phase II open-label randomised controlled trial (the RifT study) [version 1; peer review: 2 approved]

Fiona V. Cresswell ^{1,2}, Kenneth Ssebambulidde ², Daniel Grint ³, Lindsey te Brake⁴, Abdul Musabire², Rachel R. Atherton ², Lillian Tugume², Conrad Muzoora⁵, Robert Lukande⁶, Mohammed Lamorde², Rob Aarnoutse⁴, David Meya^{2,7}, David R. Boulware ^{2,7*}, Alison M. Elliott ^{1,8*}

Traitements dirigés contre l'hôte

- Réduction mortalité avec corticoïdes

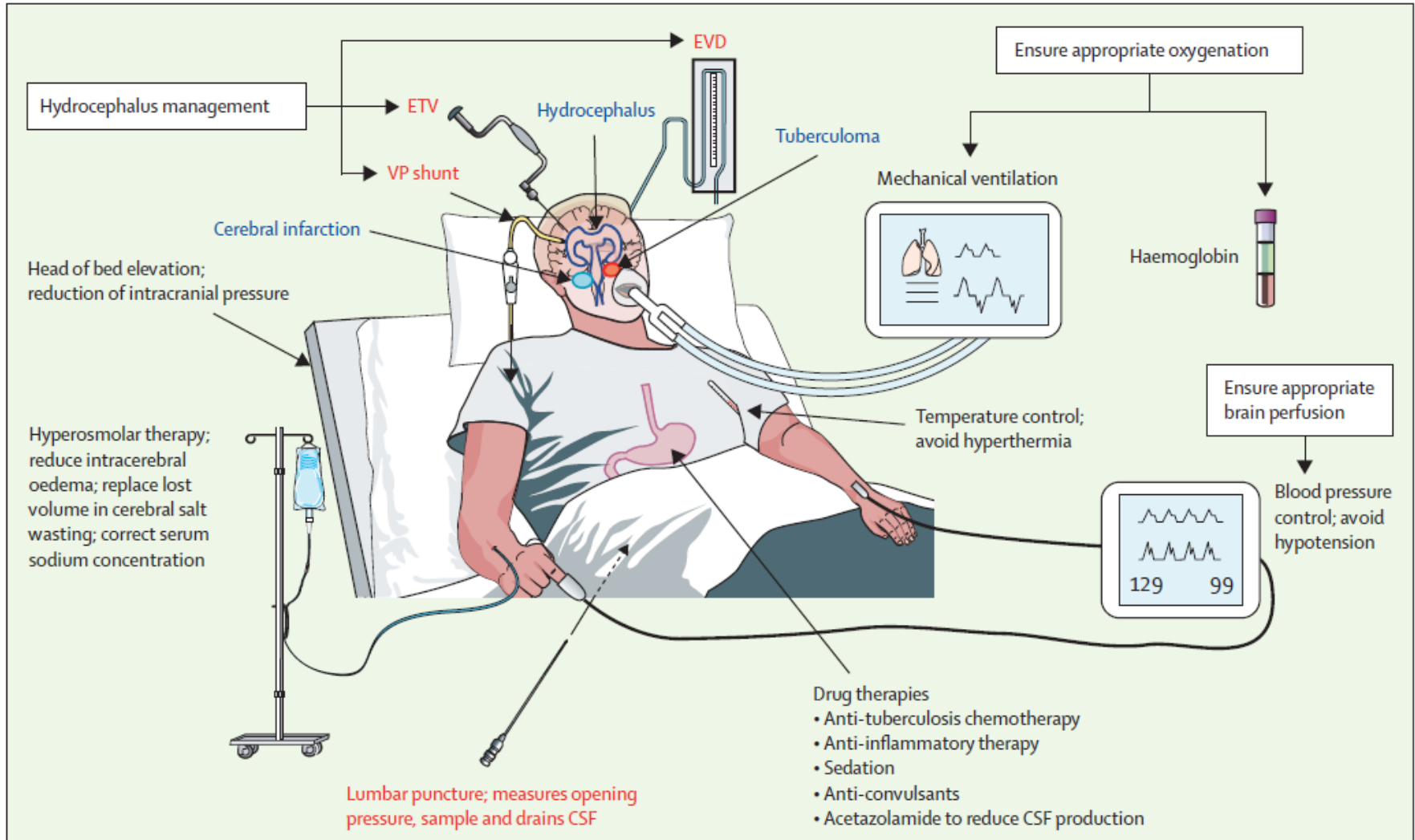
Thwaites GE, N Engl J Med 2004

- Bénéfice chez le patient VIH+: incertain (études en cours)
- Doses, mode d'administration, prednisolone ou dexaméthasone.... : incertain

Prasad K et al, Cochrane database Syst Rev 2016

- Bénéfice aspirine, thalidomide, Anti-TNF α , INF γ ... : incertain

Traitement de support



Conclusion

- **TBM:** maladie grave avec morbi-mortalité importante
- **Diagnostic:** performances insuffisantes des outils actuels. Se insuffisante pour éliminer le diagnostic de TBM. Nécessité de *combiner ces tests et volumes LCS importants*.
- **Traitement:** place de fortes doses de rifampicine, des quinolones, de la corticothérapie...