Infections graves "communautaires" du système nerveux central

Réflexions sur la prise en charge initiale

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JNI Juin 2010

Beaucoup d' infections possibles!

Méningite bactérienne

Collection intra-crânienne

Complications d'une endocardite

Méningite tuberculeuse

Encéphalite virale

Encéphalite non virale/non infectieuse

Encéphalopathie du sepsis

Une démarche clinique initiale

1. L'histoire: aiguë, subaiguë, voyages, exposition animaux…
2. Vérifier l'absence d'immunodépression
3. Syndrome méningé, signes de localisation ?
4. Profondeur du coma
5. Porte d'entrée ORL ?
6. Signes extra-neurologiques (peau, poumons, souffle cardiaque…) ?

Méningites bactériennes

1. Mortalité: 26% *(Méta-analyse sur 2029 patients: van de Beck D et al. Lancet Neurology 2010)*
2. ≥ 1 séquelle majeure: risque médian : 12,8%

   (IQR: 7,2-21%)

   - *S. pneumoniae*: 24,7% (16,2-35,3)
   - *N. meningitidis*: 7,2% (4,3-11,2)

(Méta-analyse sur 132 études: Edmond K et al. Lancet Infect Dis 2010)

Méningites bactériennes

- Une relation plutôt claire entre le délai d'administration des antibiotiques et le pronostic (4 articles)
- Une stratégie diagnostique bien codifiée (CC SPILF 2008, revues d'experts)

Conséquences négatives sur le diagnostic microbiologique ?

- Une simplification de l'antibiothérapie initiale (CC SPILF 2008) liée à l'évolution des résistances
- Un débat toujours ouvert sur les corticoïdes (IDSA 2004, CC SPILF 2008, 2 méta-analyses contradictoires!)

Antibiotic timing: clinical data

Relation

1. Adverse outcome according to inoculum[1] and delay of CSF sterilization[2]
2. Early antibiotic therapy and outcome:
   - Prehospital antibiotics for meningococcal infections[3-5]
   - Septic shock[5]
3. Outcome and door to antibiotic time

[1]Feldman WE NEJM 1977, [2] Lebel MH et al. Pediatrics 1989, [3]Strang JR et al BMJ 1992, [4]Cartwright K et al BMJ 1992, [5]Harnden A et al BMJ 2006, [5] Kumar A CCM2006

Table 2. Multivariate analysis of baseline factors at intensive care unit admission associated with 3-month mortality

156 ICU adults with *S. pneumoniae* meningitis

Variable	Odds Ratio	95% Confidence Interval	*p* Value
SAPS II[a]	1.12	1.072–1.153	.002
Penicillin-nonsusceptible *Streptococcus pneumoniae*	6.83	2.94–20.8	$<10^{-4}$
Interval >3 hrs between hospital admission and antibiotic treatment	14.12	3.93–50.9	$<10^{-4}$
CSF leukocyte count $>10^3/\mu L$	0.30	0.10–0.944	.04

Table 4. Multivariate analysis of baseline factors at intensive care unit admission associated with 3-month adverse events

Variable	Odds Ratio	95% Confidence Interval	*p* Value
SAPS II[a]	1.06	1.04–1.09	$<10^{-4}$
Penicillin-nonsusceptible *Streptococcus pneumoniae*	2.58	1.13–5.9	.02
Interval >3 hrs between hospital admission and antibiotic treatment	2.84	1.10–5.6	.03
CSF leukocyte count $>10^3/\mu L$	0.37	0.16–0.83	.02

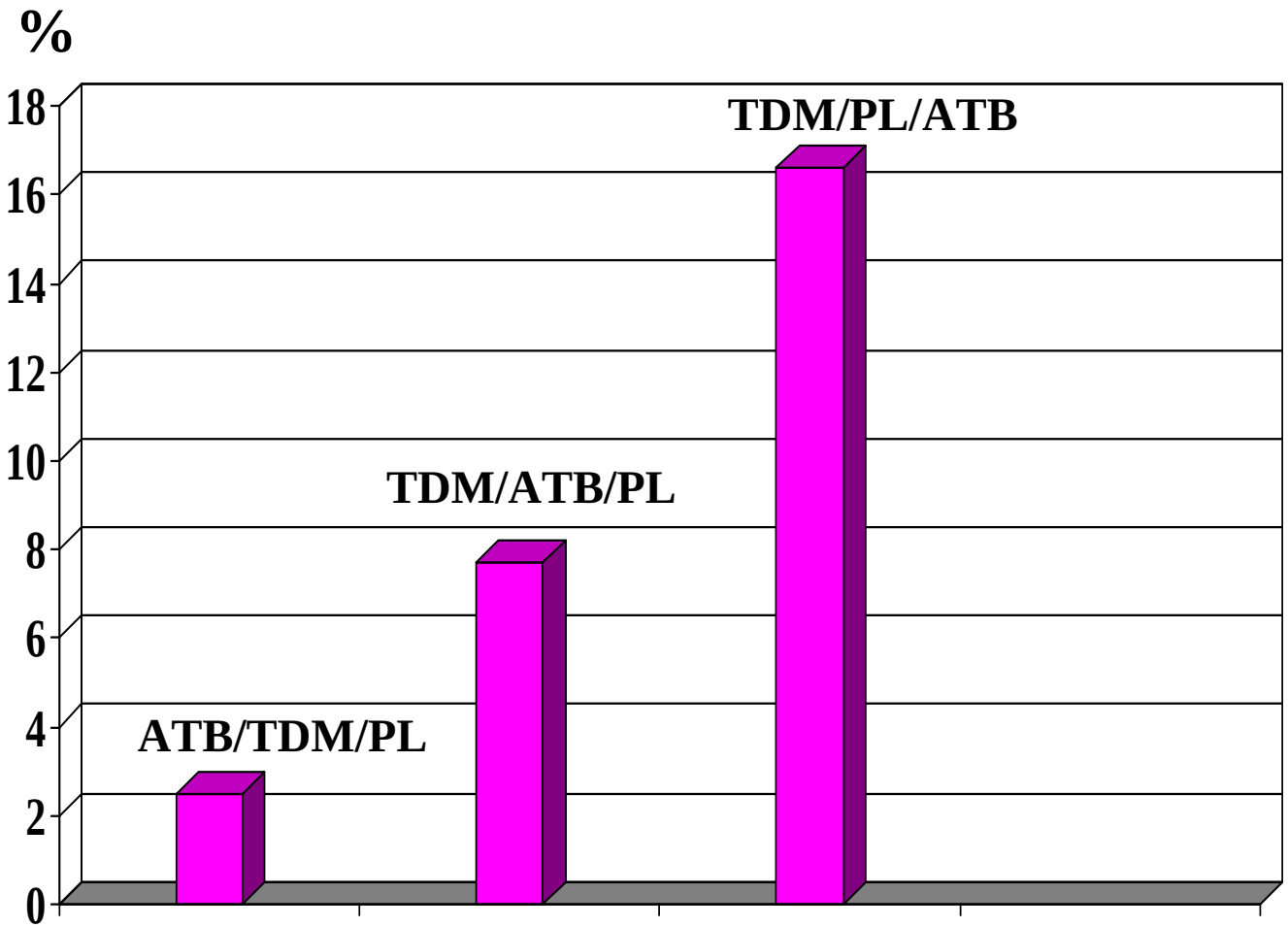
Auburtin M et al. Crit Care Med 2006; 34: 2758

Les seules indications à la réalisation d'une imagerie cérébrale avant PL chez un patient suspect de méningite bactérienne sont :

1. Les signes de localisation neurologiques tels qu'ils peuvent apparaître lors d'un examen complet utilisant par exemple les items 2 à 11 du score NIHSS
2. Les troubles de vigilance mesurés par un score de Glasgow ≤ 11
3. Les crises épileptiques récentes ou en cours, focales ou généralisées après l'âge de 5 ans, seulement si hémi-corporelles avant cet âge.

Conférence de consensus SPILF novembre 2008

MB: mortalité et séquences



Proulx et al. QJM 2005

At the ED or ICU admission

Situation A

- Meningeal syndrome
- Impaired consciousness

without focal neurological nor seizures

↓

1 BC and LP

↓

CSF: cloudy : immediate ATB

Situation B

- Impaired consciousness + focal neurological/seizures
- Immunocompromised status

↓

1: BC 2: ATB

3: CT-scan 4: LP

Conséquences négatives sur le diagnostic microbiologique ?

	PL < 4 h après 1ère dose ATB	PL > 4h après 1ère dose ATB
	n = 11	n = 71
Cultures LCR+	8 (73%)	8 (11%)

P < 0,001

Menezes MB et al. Emrg Med J 2010

Hémocultures positives: 50-60% des méningites bactériennes

La PCR est l'avenir du diagnostic microbiologique des méningites bactériennes

- 37 patients : méningite à *S. pneunoniae* ou *N. meningitidis*
PCR temps-réel: Se: 87% (NM)/100% (SP) van Gastel E et al. *Eur J Clin Microbiol Infect Dis 2007*
- 35 patients: méningite bactérienne: PCR Se 77% *Deutch S et al. Scand J Infect Dis 2008*
- 36 patients : méningite à *S. pneunoniae* ou *N. meningitidis*
PCR: Se: 100% (NM)/95% (SP) *Boving MK et al. JCM 2009*
- 32 patients : méningite bactérienne: PCR Se: 93% *Rafi W et al. J Emerg Med 2010*

La PCR : avenir du diagnostic microbiologique des méningites bactériennes

	Test	Sensitivity	Specificity
N. meningitidis (*n*=23)	PCR *ctrA*	20/23 (87%)	45/47 (96%)
	Gram stain	6/22 (27%)	46/46 (100%)
	Culture	4/23 (17%)	47/47 (100%)
S. pneumoniae (*n*=14)	PCR *ply*	14/14 (100%)	56/56 (100%)
	Gram stain	8/13 (62%)	55/55 (100%)
	Culture	5/14 (36%)	56/56 (100%)

van Gastel E et al. Eur J Clin Microbiol Infect Dis 2007

Traitement initial des méningites bactériennes

Examen direct positif	Molécule	Dosage
Suspicion de pneumocoque	Cefotaxime Ou Ceftriaxone	300 mg/kg/j soit en 4 inj soit perfusion continue avec dose de charge de 50 mg/kg sur 1 h° 100 mg/kg/j en 2 injections
Suspicion de méningocoque	Cefotaxime Ou Ceftriaxone	200 mg/kg/j soit en 4 inj soit perfusion continue avec dose de charge de 50 mg/kg sur 1 h° 75 mg/kg/j en 2 injections
Suspicion de listériose	Amoxicilline + Gentamicine	200 mg/kg/j soit en 4 injections 3 à 5 mg/kg/j en dose unique journalière

Conférence de consensus SPILF novembre 2008

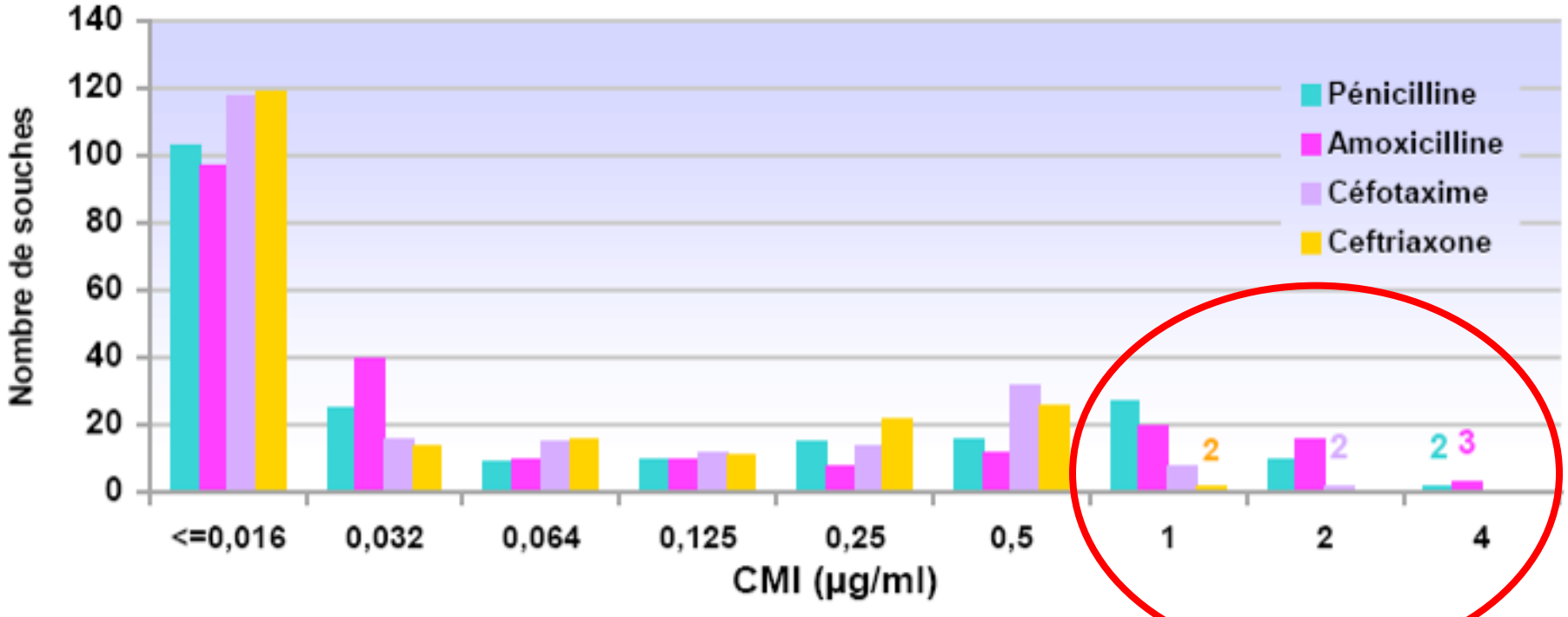


Figure 7 – Distribution des souches *S. pneumoniae* isolées de méningites chez l'adulte (n=217) en fonction des CMI de pénicilline, amoxicilline, céfotaxime et ceftriaxone [17].

E. Varon, Centre National de Référence des Pneumocoques, 2008

Steroids in adults with acute bacterial meningitis: a systematic review

Diederik van de Beek, Jan de Gans, Peter McIntyre, and Kameshwar Prasad

THE LANCET Infectious Diseases Vol 4 March 2004

Table 2. Meta-analysis of the effect of steroids on mortality in adults with bacterial meningitis

	Mortality rate (%)		Relative risk	95% CI
	Dexamethasone	Placebo		
Bennett[13]	16/38 (42)	22/47 (47)	0·9	0·56–1·46
Girgis[15]	5/68 (7)	18/79 (23)	0·3	0·13–0·82
Bhaumik[16]	1/14 (7)	3/16 (19)	0·3	0·04–3·36
Thomas[17]	3/31 (10)	5/29 (17)	0·6	0·15–2·14
De Gans[7]	11/157 (7)	21/144 (15)	0·4	0·24–0·96
Meta-analysis	36/308 (12)	69/315 (22)	0·6*	0·40–0·81

*p=0·002

Table 3. Meta-analysis of the effect of steroids on neurological sequelae in adults with bacterial meningitis

	Rate neurological sequelae (%)		Relative risk	95% CI
	Dexamethasone	Placebo		
Bennett[13]	NS	NS	..	..
Girgis[15]	NS	NS	..	..
Bhaumik[16]	3/13 (23)	2/13 (15)	1·5	0·30–7·55
Thomas[17]	5/28 (18)	9/24 (38)	0·5	0·18–1·23
De Gans[7]	18/143 (13)	24/119 (20)	0·6	0·36–1·09
Meta-analysis	26/184 (14)	35/156 (22)	0·6*	0·40–1·00

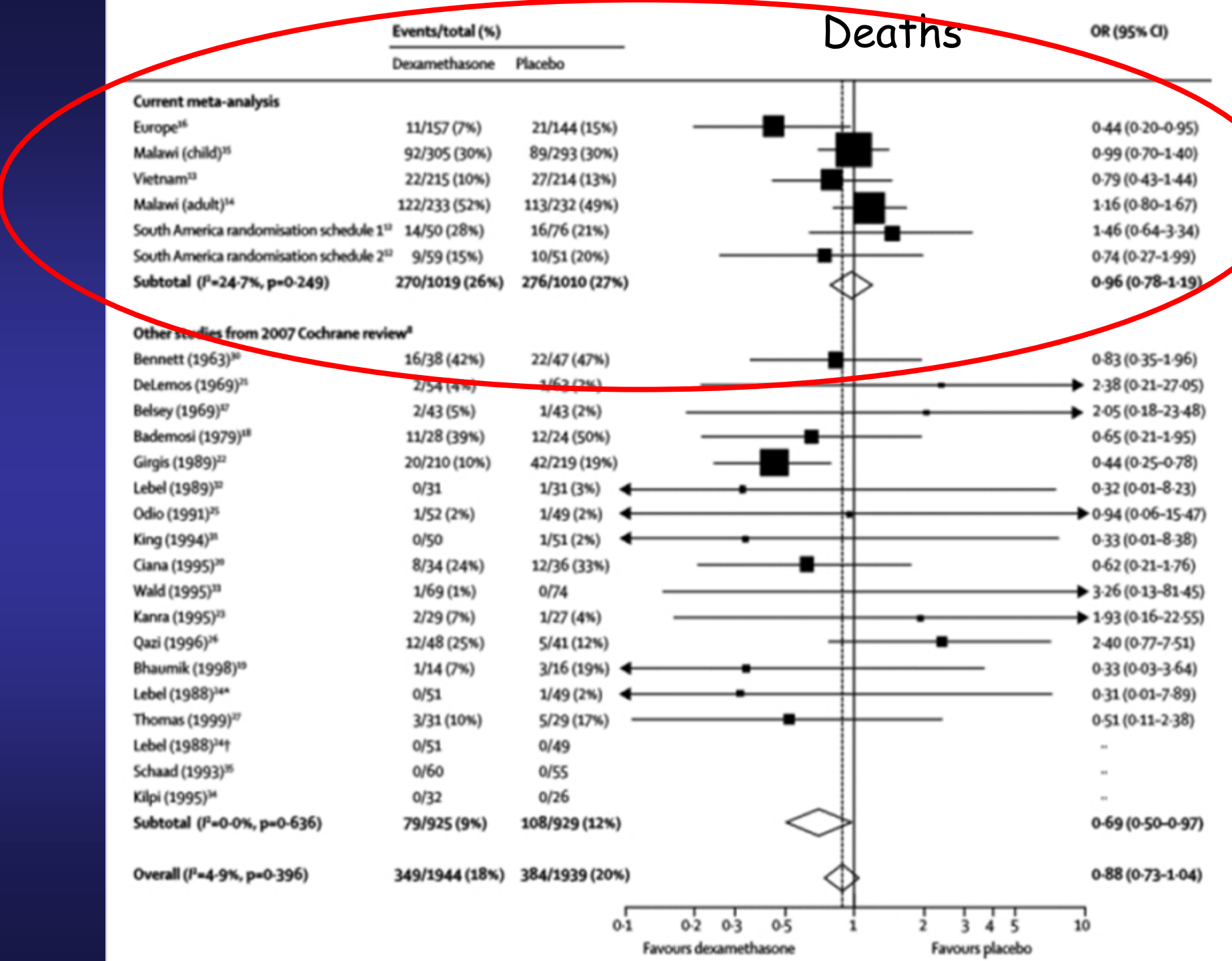
*p=0·05. NS=not stated.

Published as: *Lancet Neurol*. 2010 March ; 9(3): 254–263.

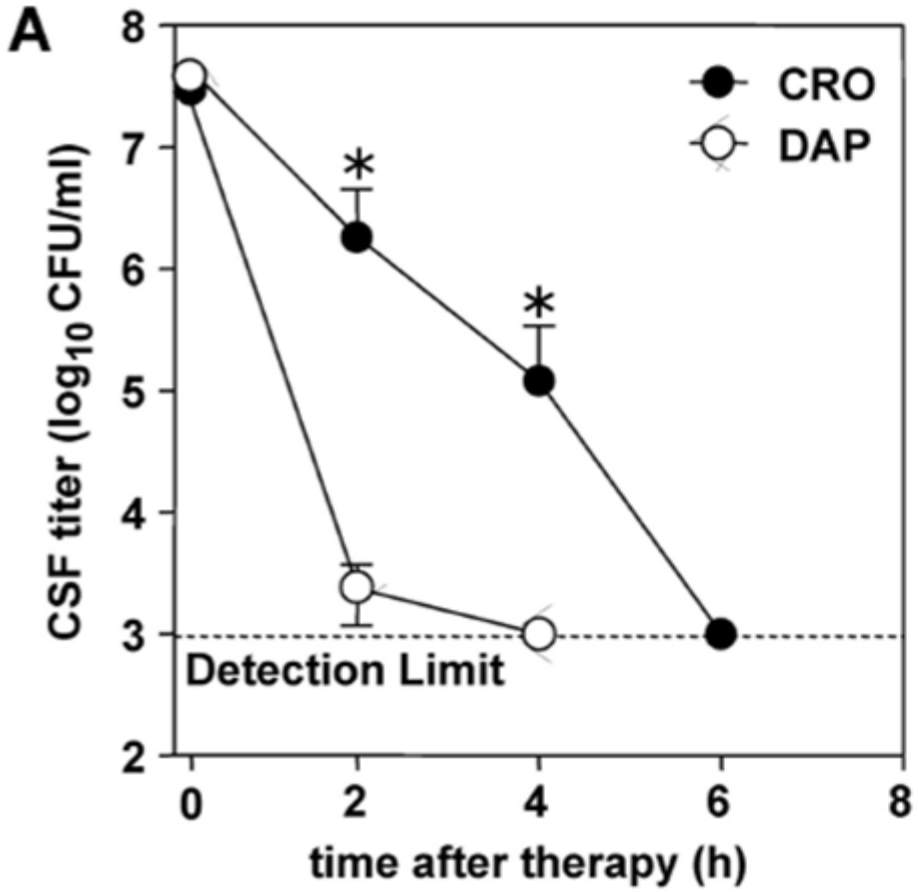
Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data

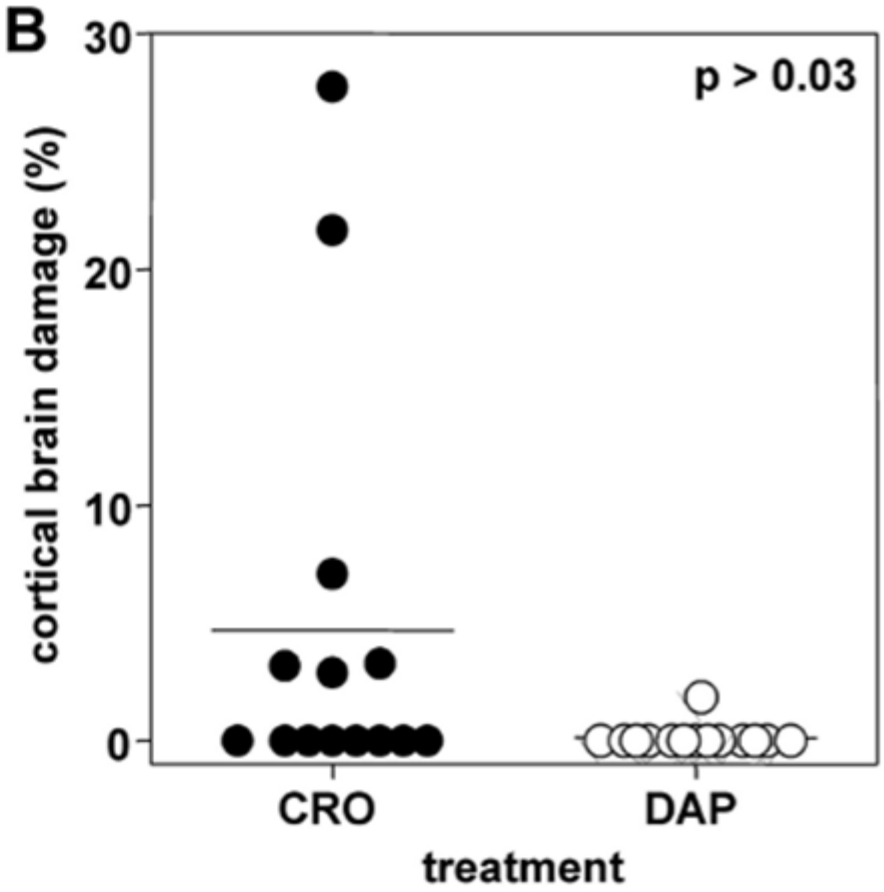
Diederik van de Beek[a], **Jeremy J Farrar**[d,e,h,*], **Jan de Gans**[a], **Nguyen Thi Hoang Mai**[d], **Elizabeth M Molyneux**[f], **Heikki Peltola**[g], **Tim E Peto**[j], **Irmeli Roine**[k], **Mathew Scarborough**[l], **Constance Schultsz**[b,e], **Guy E Thwaites**[l], **Phung Quoc Tuan**[d,e], and **AH Zwinderman**[c]

Deaths


Events/total (%)
Dexamethasone
Placebo
OR (95% CI)
Current meta-analysis
Europe[16] 11/157 (7%) 21/144 (15%) 0·44 (0·20–0·95)
Malawi (child)[15] 92/305 (30%) 89/293 (30%) 0·99 (0·70–1·40)
Vietnam[13] 22/215 (10%) 27/214 (13%) 0·79 (0·43–1·44)
Malawi (adult)[14] 122/233 (52%) 113/232 (49%) 1·16 (0·80–1·67)
South America randomisation schedule 1[12] 14/50 (28%) 16/76 (21%) 1·46 (0·64–3·34)
South America randomisation schedule 2[12] 9/59 (15%) 10/51 (20%) 0·74 (0·27–1·99)
Subtotal (I²=24·7%, p=0·249) 270/1019 (26%) 276/1010 (27%) 0·96 (0·78–1·19)
Other studies from 2007 Cochrane review[8]
Bennett (1963)[30] 16/38 (42%) 22/47 (47%) 0·83 (0·35–1·96)
DeLemos (1969)[31] 2/54 (4%) 1/53 (2%) 2·38 (0·21–27·05)
Belsey (1969)[17] 2/43 (5%) 1/43 (2%) 2·05 (0·18–23·48)
Bademosi (1979)[18] 11/28 (39%) 12/24 (50%) 0·65 (0·21–1·95)
Girgis (1989)[22] 20/210 (10%) 42/219 (19%) 0·44 (0·25–0·78)
Lebel (1989)[32] 0/31 1/31 (3%) 0·32 (0·01–8·23)
Odio (1991)[25] 1/52 (2%) 1/49 (2%) 0·94 (0·06–15·47)
King (1994)[33] 0/50 1/51 (2%) 0·33 (0·01–8·38)
Ciana (1995)[20] 8/34 (24%) 12/36 (33%) 0·62 (0·21–1·76)
Wald (1995)[33] 1/69 (1%) 0/74 3·26 (0·13–81·45)
Kanra (1995)[23] 2/29 (7%) 1/27 (4%) 1·93 (0·16–22·55)
Qazi (1996)[26] 12/48 (25%) 5/41 (12%) 2·40 (0·77–7·51)
Bhaumik (1998)[19] 1/14 (7%) 3/16 (19%) 0·33 (0·03–3·64)
Lebel (1988)[24a] 0/51 1/49 (2%) 0·31 (0·01–7·89)
Thomas (1999)[27] 3/31 (10%) 5/29 (17%) 0·51 (0·11–2·38)
Lebel (1988)[24†] 0/51 0/49 ..
Schaad (1993)[35] 0/60 0/55 ..
Kilpi (1995)[34] 0/32 0/26 ..
Subtotal (I²=0·0%, p=0·636) 79/925 (9%) 108/929 (12%) 0·69 (0·50–0·97)
Overall (I²=4·9%, p=0·396) 349/1944 (18%) 384/1939 (20%) 0·88 (0·73–1·04)
0·1 0·2 0·3 0·5 1 2 3 4 5 10
Favours dexamethasone
Favours placebo

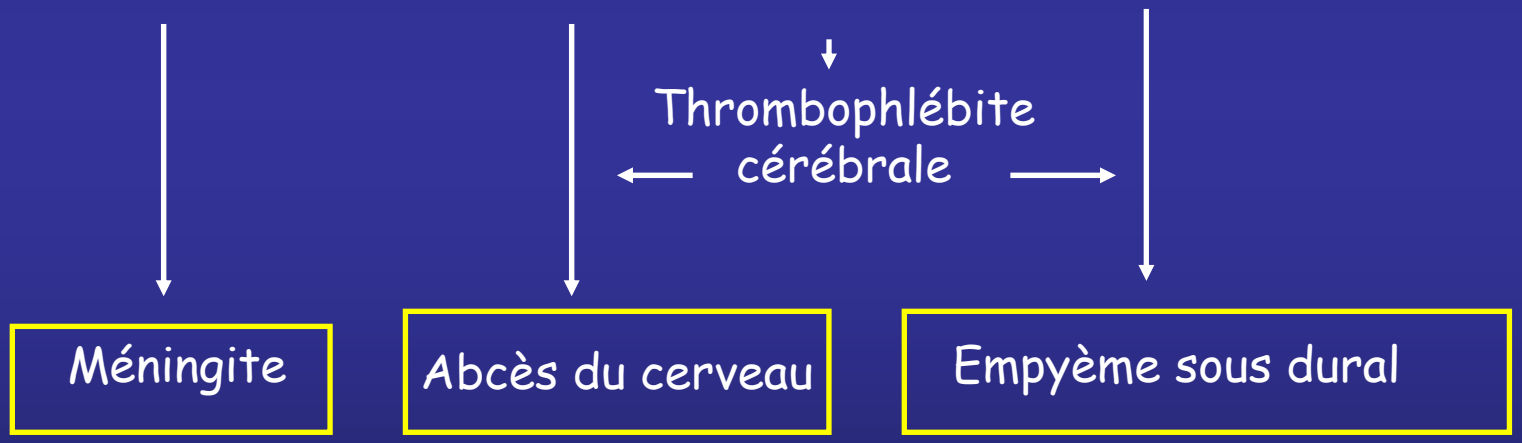
Attenuation of Cerebrospinal Fluid Inflammation by the Nonbacteriolytic Antibiotic Daptomycin versus That by Ceftriaxone in Experimental Pneumococcal Meningitis[▽]

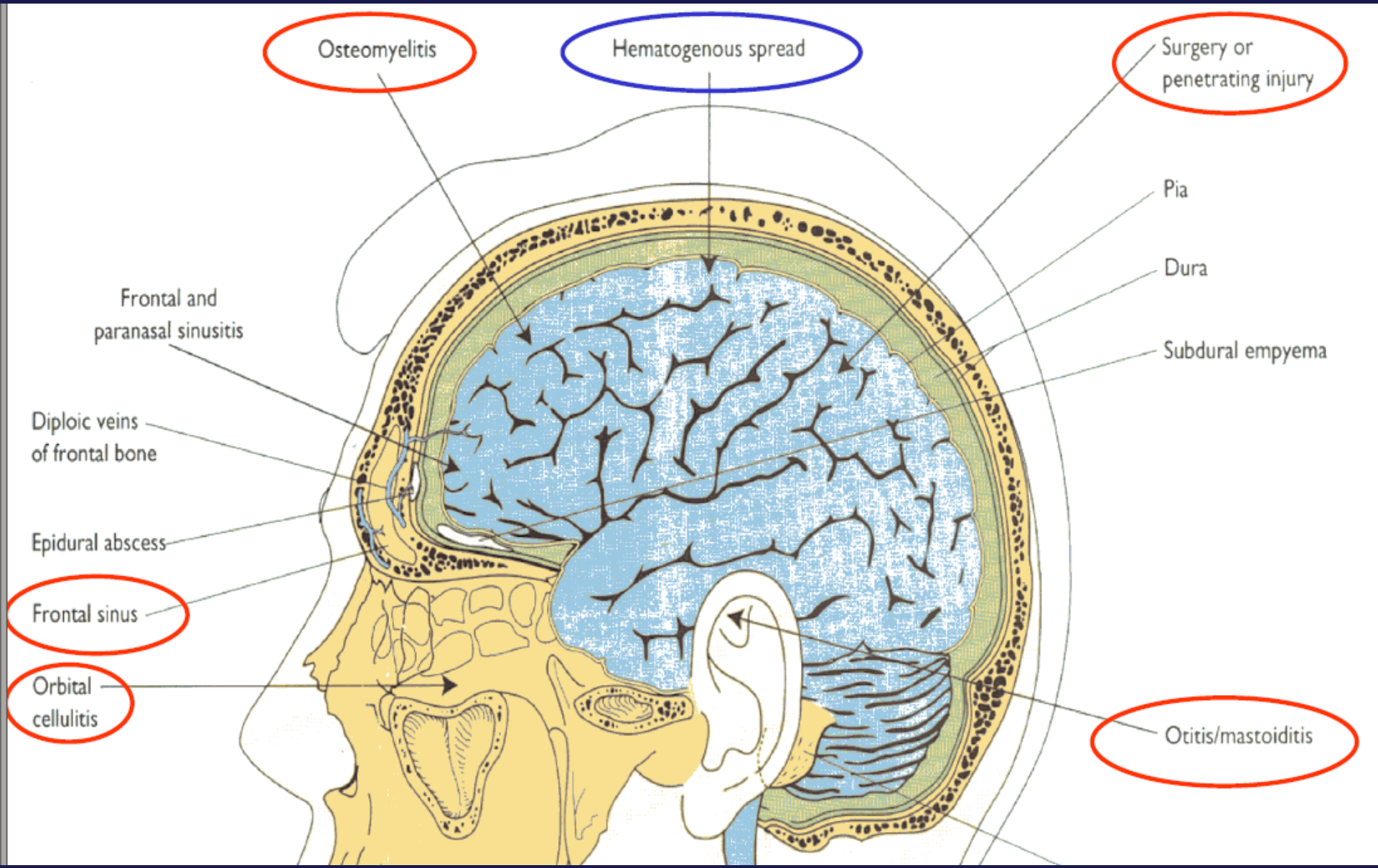




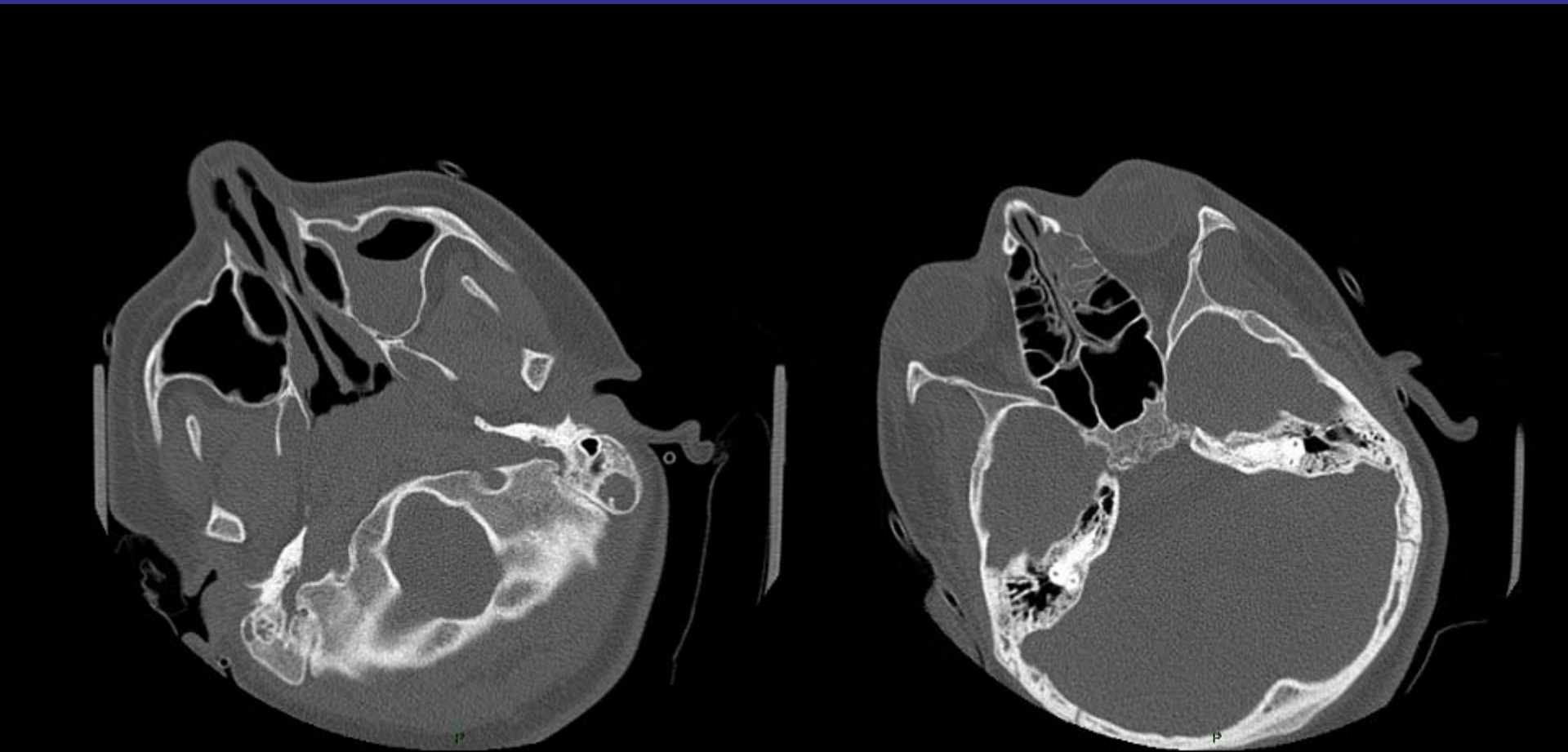
Grandgirard d et al. AAC 2010: 1323

Infection ORL et infection du SNC

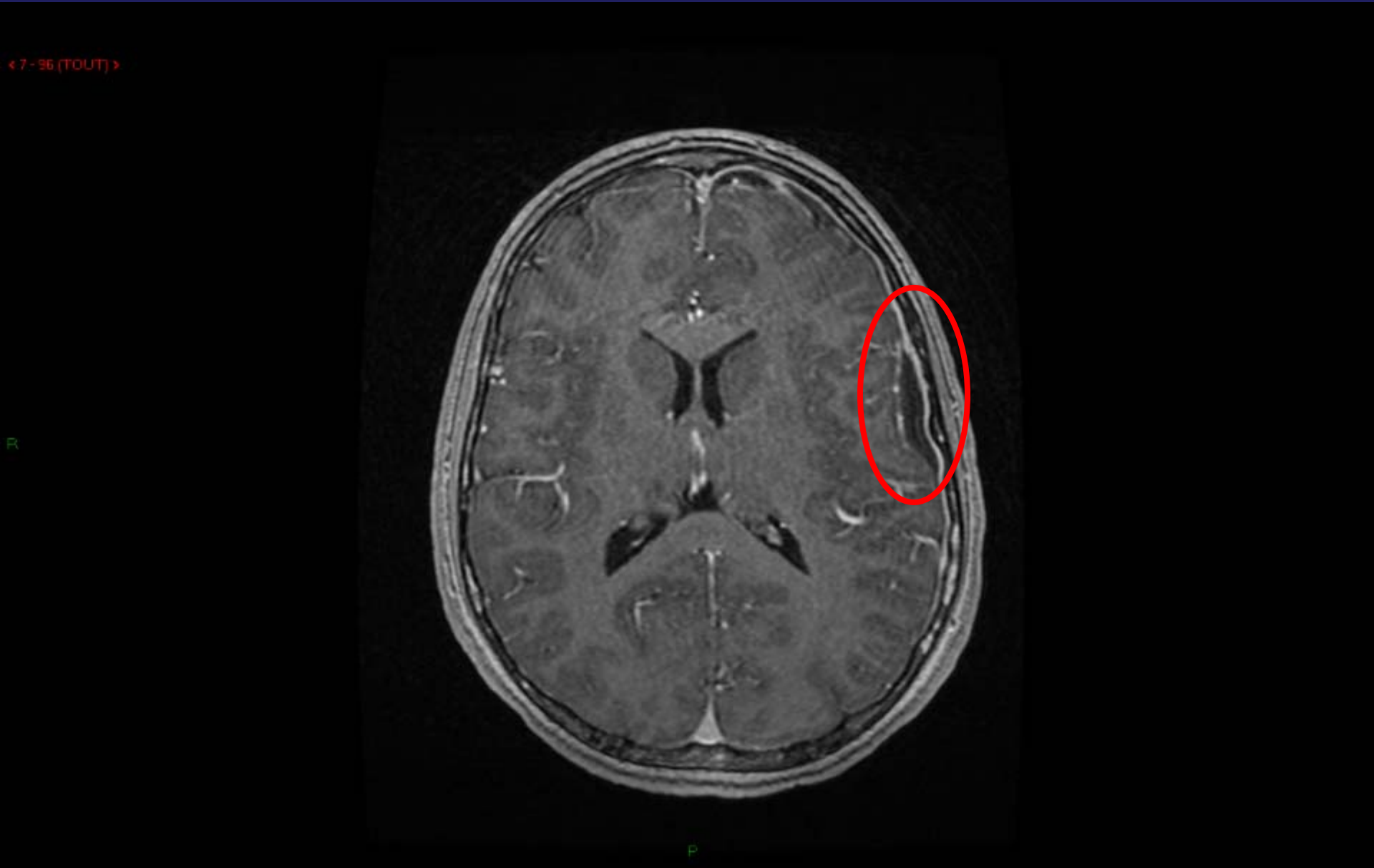



Osteomyelitis
Hematogenous spread
Surgery or penetrating injury
Pia
Dura
Subdural empyema
Frontal and paranasal sinusitis
Diploic veins of frontal bone
Epidural abscess
Frontal sinus
Orbital cellulitis
Otitis/mastoiditis

Garçon de 13 ans : Syndrome méningé fébrile, signes généraux, ptosis de l'œil gauche avec œdème palpébral, méningite puriforme, TDM sans injection: normale



IRM



Empyeme sous dural

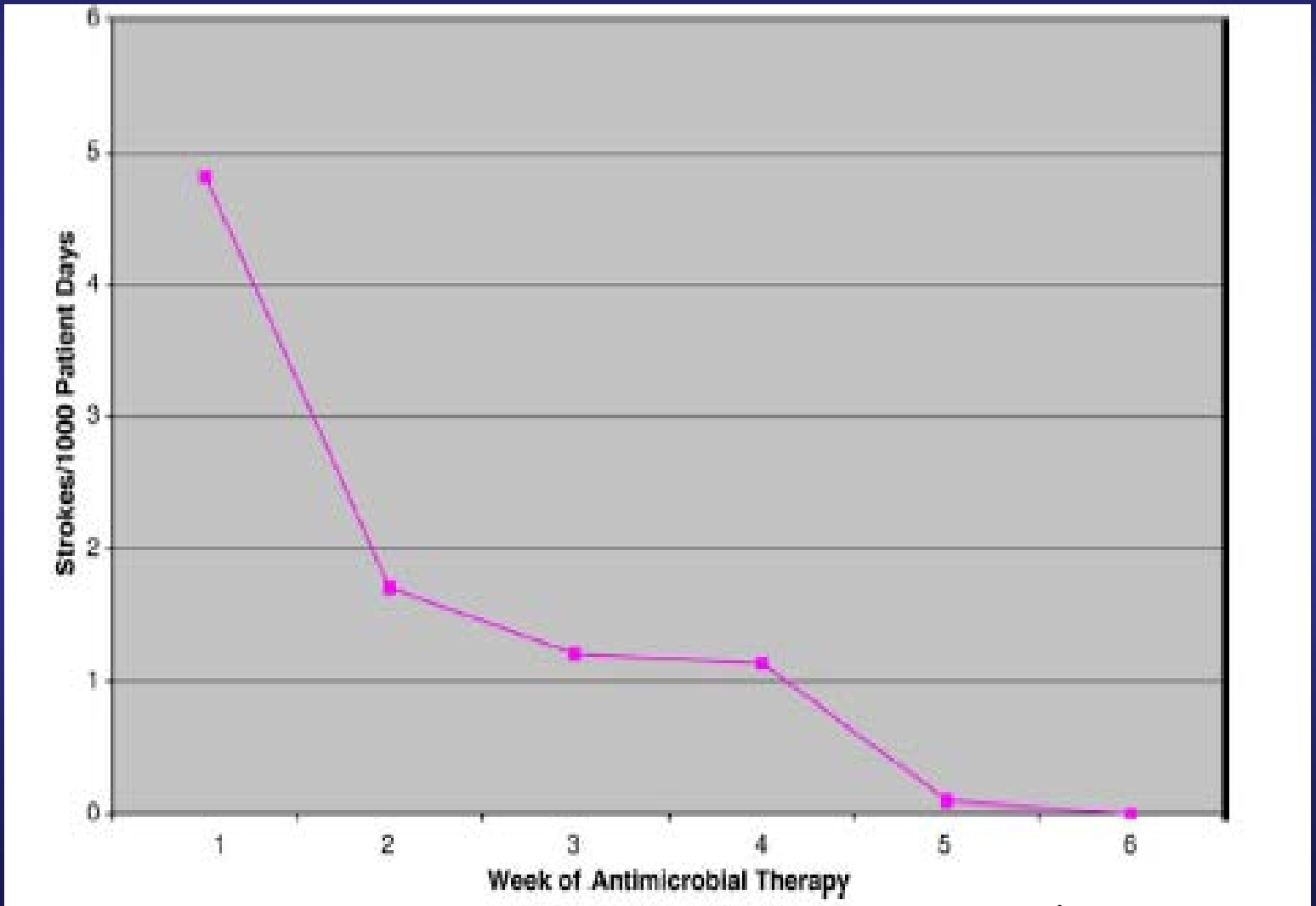
Ne pas rater le diagnostic !

- Le plus souvent complique une infection ORL
- Toujours associé avec une thrombophlébite
- Rôle de l'IRM (attention aux empyèmes iso-denses en TDM)
- Germes: streptocoques, anaérobies (+/- *S. aureus*)
- Traitement: antibiotiques **et** chirurgie

Complications neurologiques des endocardites: 6 points clés

- Cause fréquente d'admission en réanimation des EI
- Précoces, le plus souvent avant l'antibiothérapie
- Fréquemment associées avec *S. aureus*
- Complique le recours à la chirurgie cardiaque
- Peuvent nécessiter une prise en charge spécifique
- Pronostic médiocre

Stroke incidence in IE after antibiotic therapy



Stroke rate after initiation of antimicrobial therapy.

Dickerman et al AHJ 2007

Endocardite à évoquer

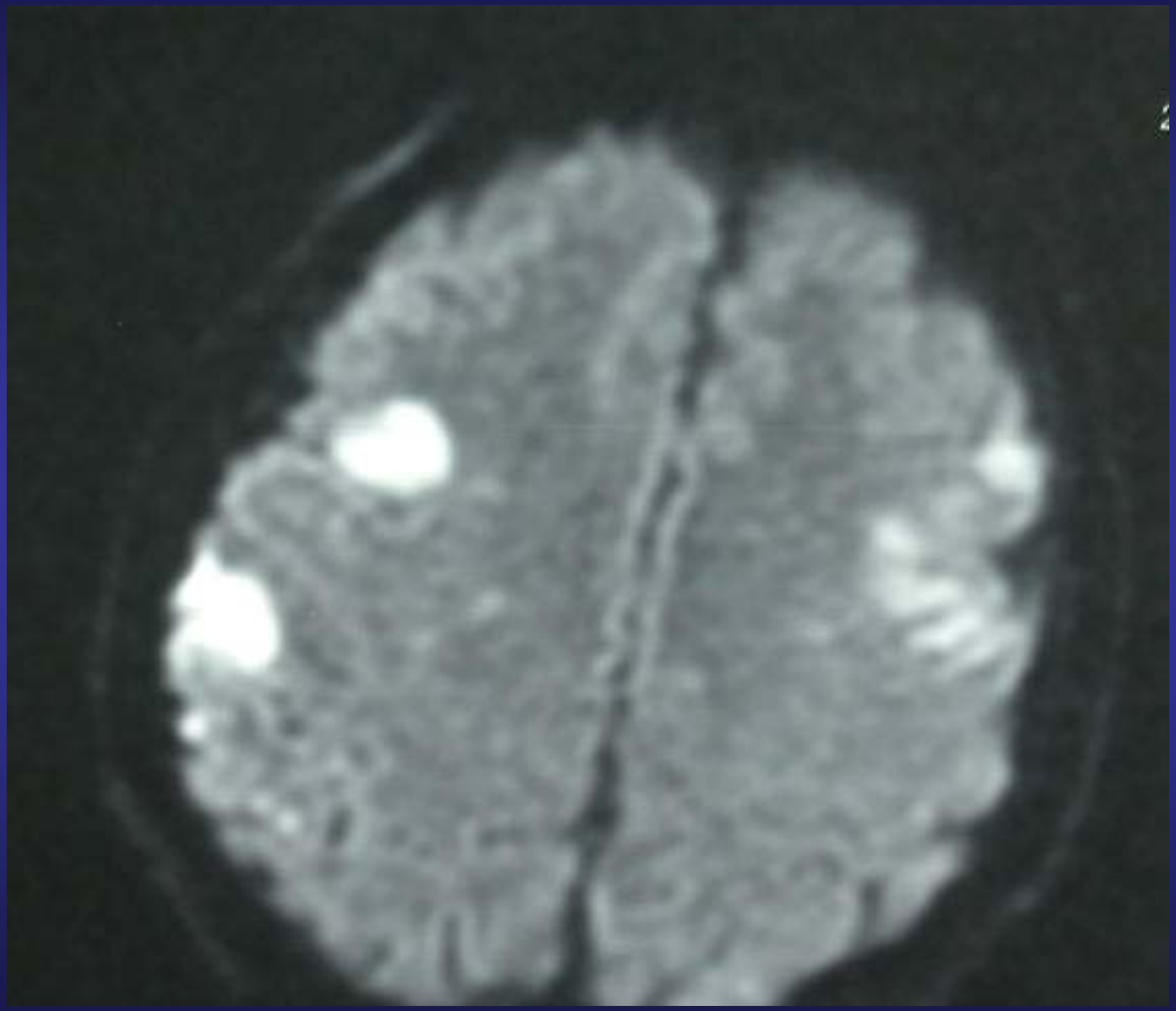
- Accident neurologique ischémique fébrile
- Accident neurologique hémorragique fébrile
- Méningite à *S. aureus*
- Abcès du cerveau

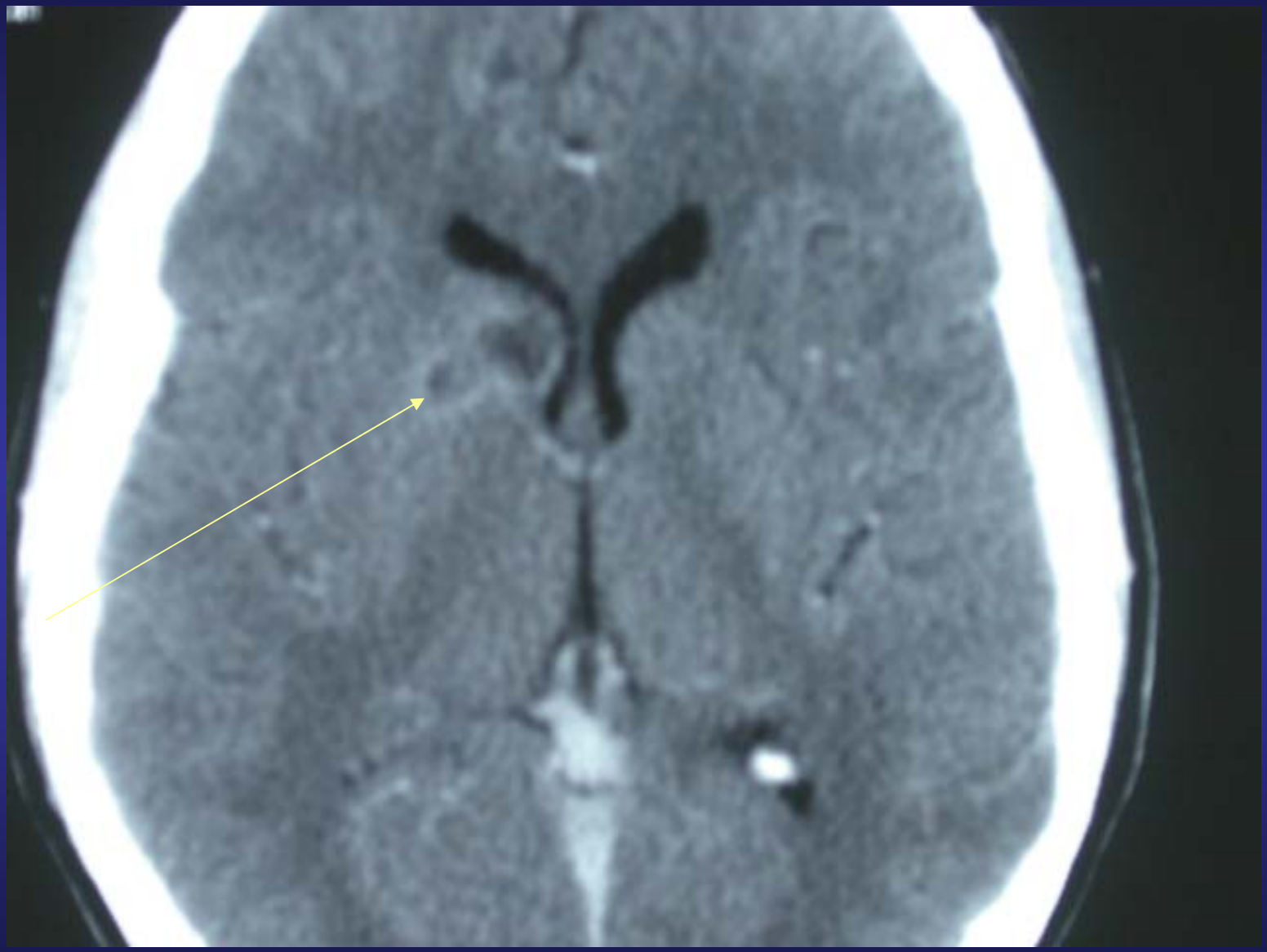
Complications neurologiques des endocardites (198 patients*/236 complications)

Complications	n
Ischémie	79
Hémorragie	53
Meningite	41
Abcès du cerveau	14
Anévrysme mycotique	10
Encéphalopathie	39

*En réanimation

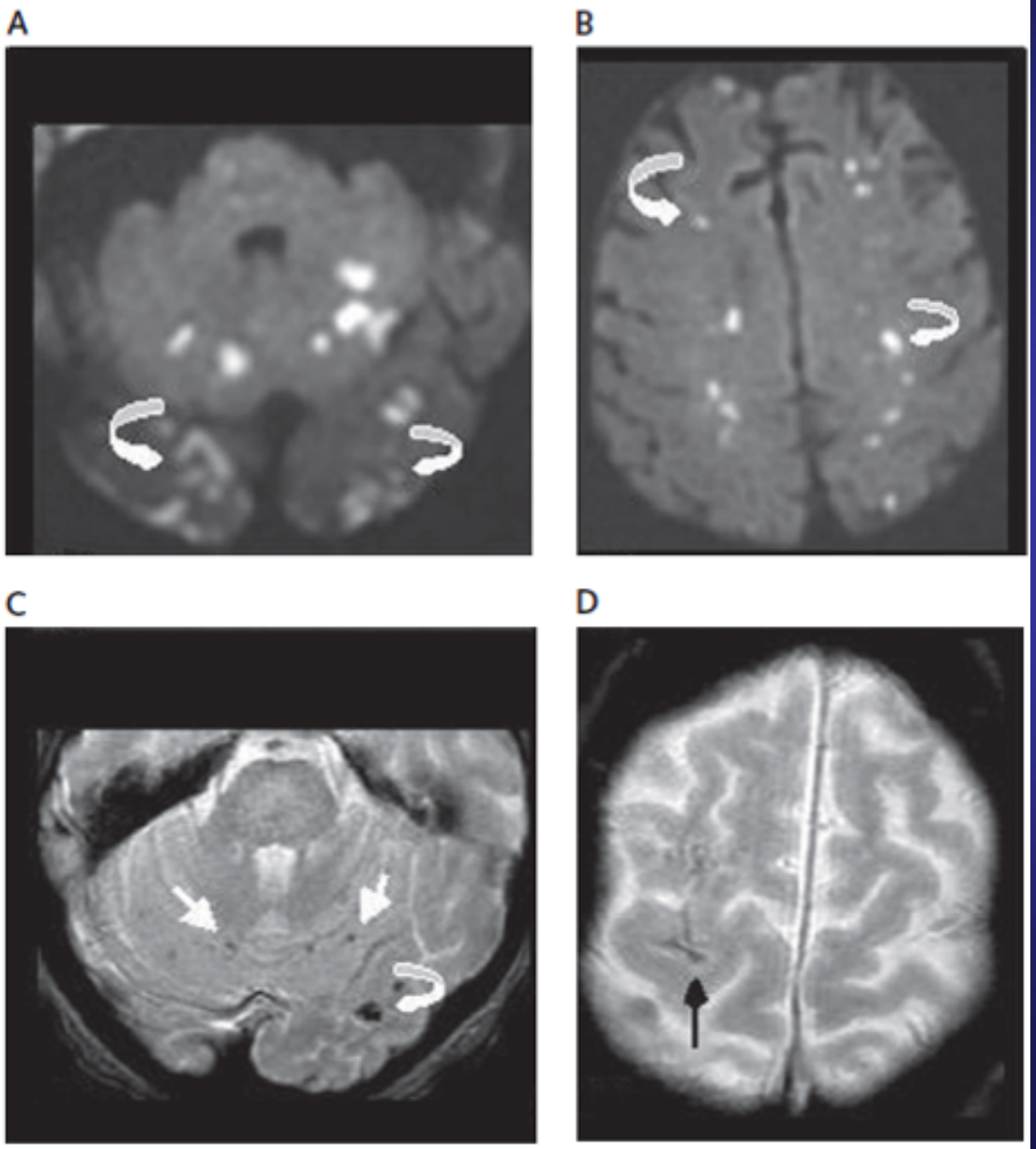
Sonneville R et al. soumis





19/08/2004

Figure 2. Infarcts and microhemorrhages.



Duval X et al. Ann Intern Med 2010

Acute encephalitis management a challenge

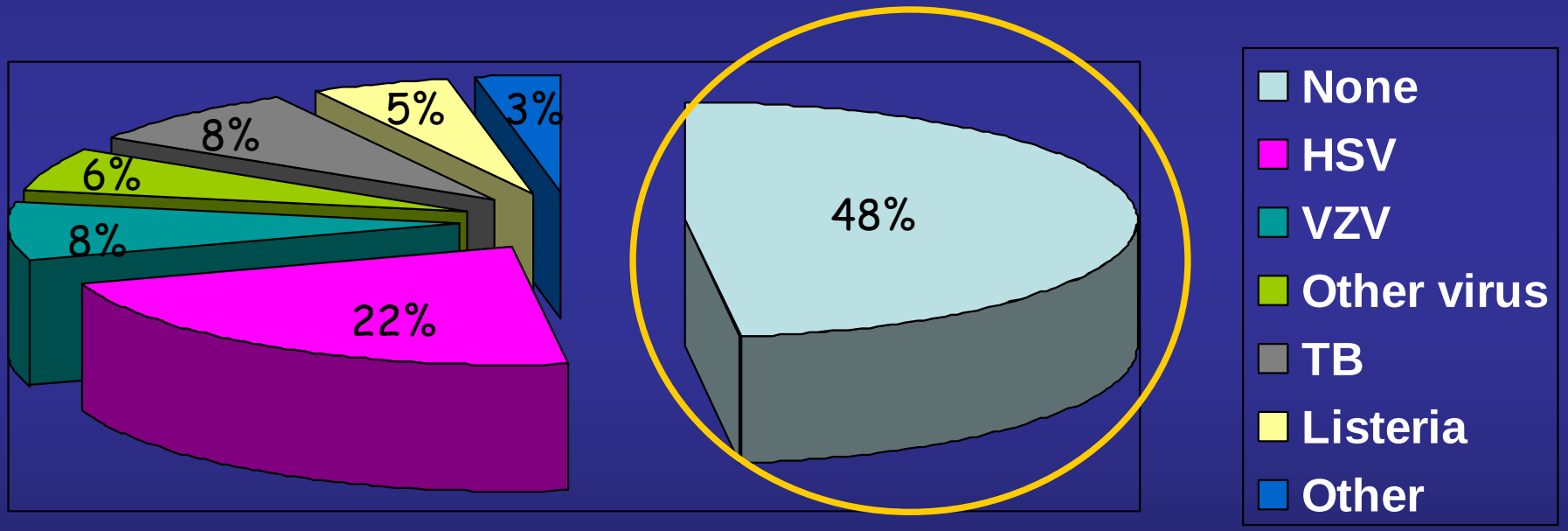
- « An inflammatory process of the brain in association with clinical evidence of neurologic dysfunction »*
- Wide variety of pathogens (virus, bacteria, fungi, parasites)
- Many cases without an identified etiology
- Infectious or post-infectious ?
- Noninfectious CNS diseases may mimic viral encephalitis
- Specific antiviral therapy mostly limited to herpesviruses.

* IDSA 2008

Les étapes clés pour un diagnostic

- Connaître les diagnostics les plus fréquents
- Conditions épidémiologiques (voyages, contacts animaux…)
- Mode de début, durée d'évolution
- Nature de l'atteinte neurologique: clinique et surtout données de l'imagerie (TDM et IRM+++)
- Anomalies du LCR
- Signes extra-neurologiques
- Outils microbiologiques (PCR, sérologies)
- Rarement la biopsie cérébrale

Causes of encephalitis



French National Encephalitis Project

CID 2009

The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America

63 recommendations

Allan R. Tunkel,[1] Carol A. Glaser,[2] Karen C. Bloch,[3] James J. Sejvar,[4] Christina M. Marra,[5] Karen L. Roos,[6] Barry J. Hartman,[7] Sheldon L. Kaplan,[8] W. Michael Scheld,[9] and Richard J. Whitley[10]

[1]Monmouth Medical Center, Long Branch, New Jersey; [2]California Department of Health Services, Richmond; [3]Vanderbilt University School of Medicine, Nashville, Tennessee; [4]Centers for Disease Control and Prevention, Atlanta, Georgia; [5]University of Washington School of Medicine, Seattle; [6]Indiana University School of Medicine, Indianapolis; [7]Weill Cornell Medical Center, New York, New York; [8]Baylor College of Medicine, Houston, Texas; [9]University of Virginia School of Medicine, Charlottesville; and [10]University of Alabama at Birmingham

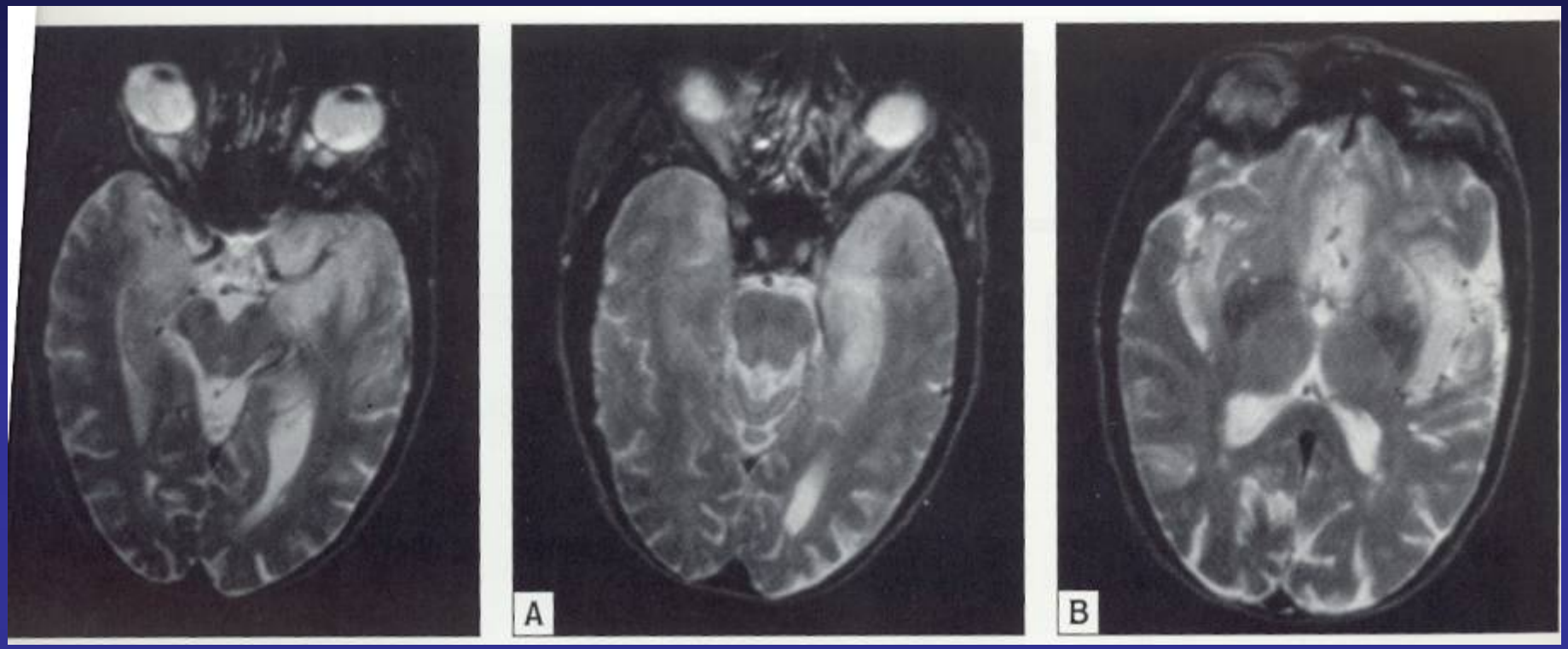
CID 2008; 47: 303

Selected recommendations

N°11: " MRI is the most sensitive neuroimaging test to evaluate patients with encephalitis" (A-I).

Magnetic resonance imaging

- MRI is more sensitive and specific (vs. CT)
- Diffusion-weighted/FLAIR imaging is superior to conventional MRI for the detection of early signal abnormalities (HSV, enterovirus, West-Nile)
- Some characteristics neuroimaging pattern have been observed in patients with encephalitis caused by specific agents (HSV, flavivirus, enterovirus)
- ADEM

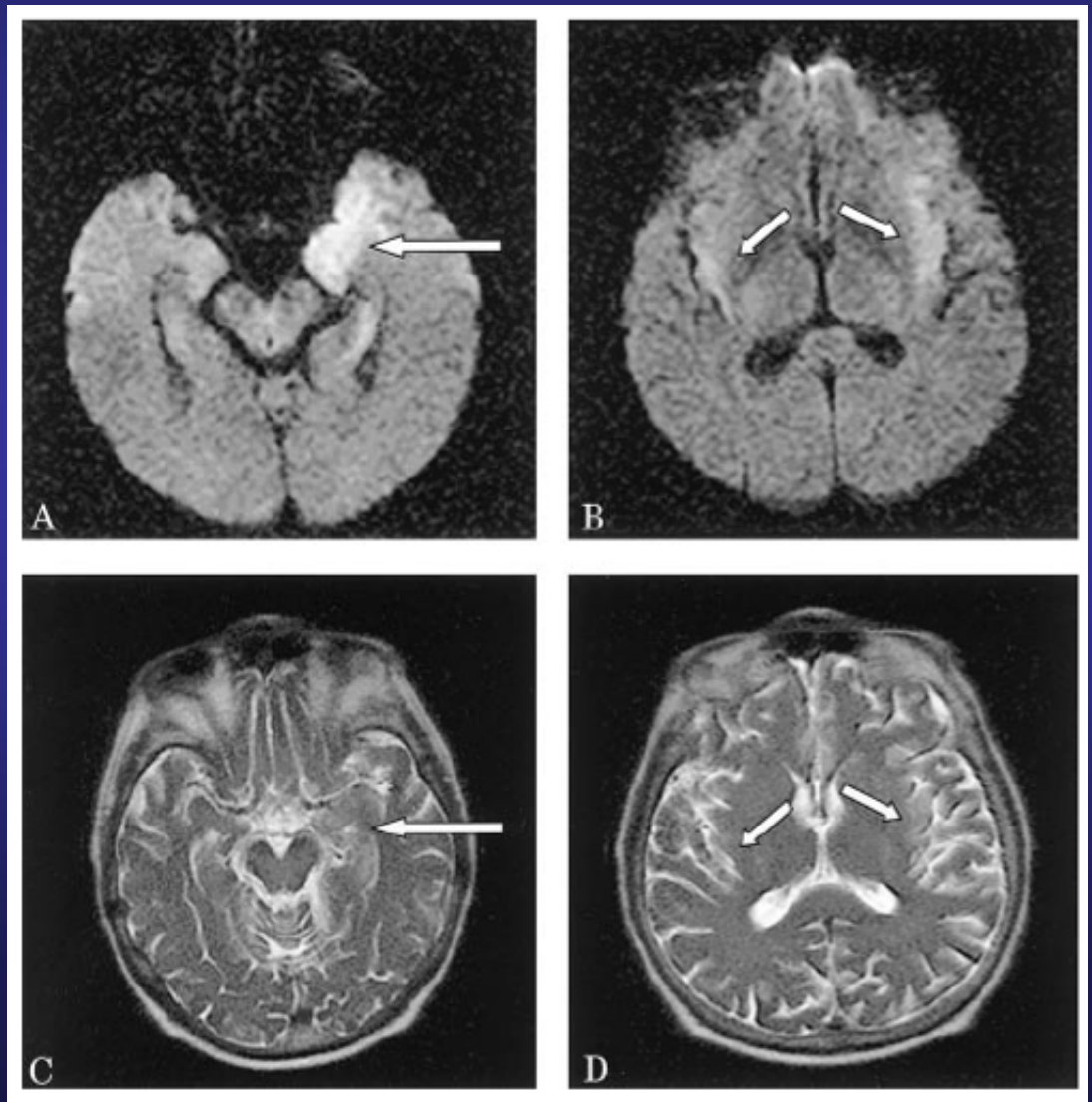


Herpes simplex encephalitis

Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis

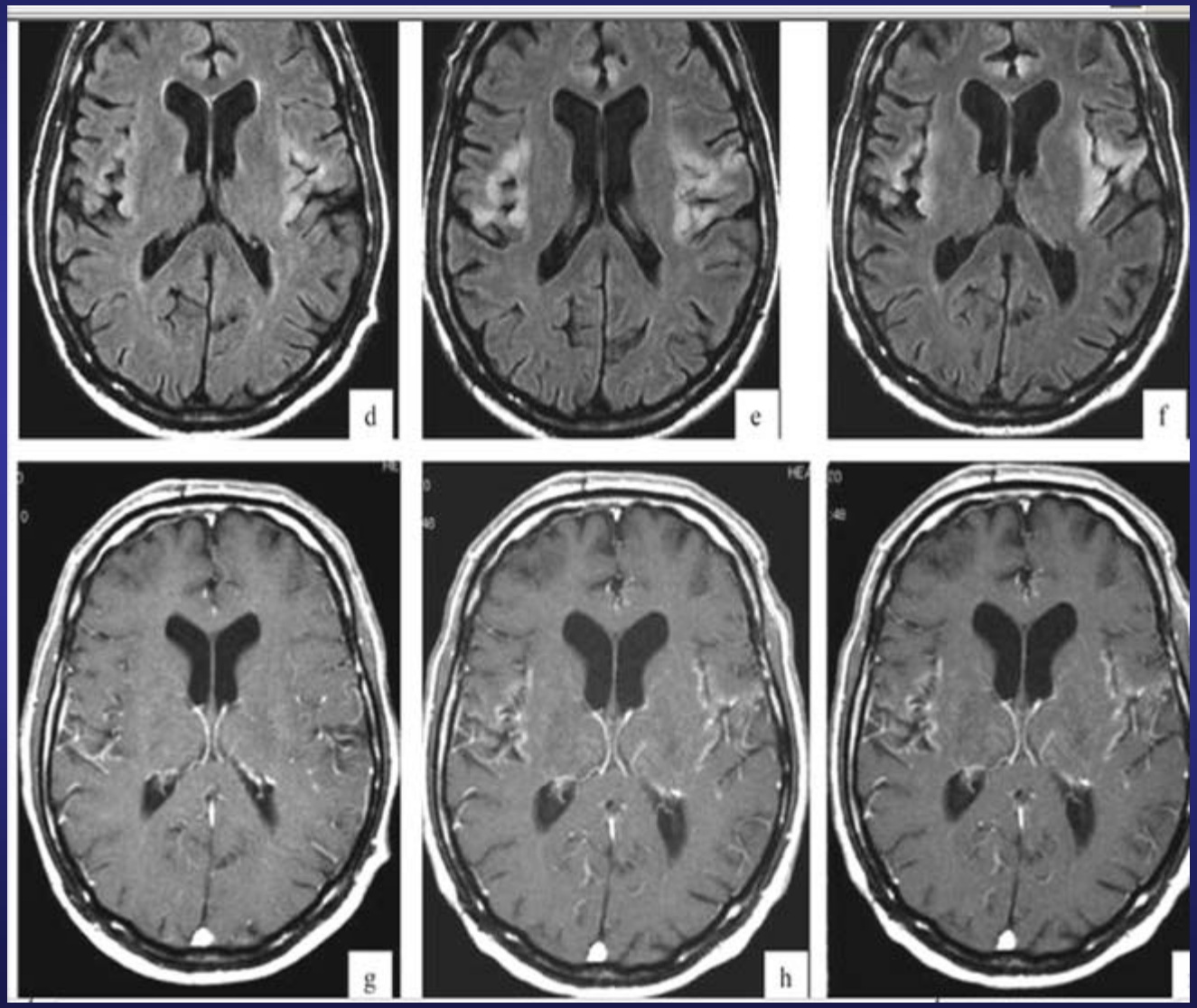
Kenneth McCabe, MD; Ken Tyler, MD, FAAN; and Jody Tanabe, MD

Neurology 2003



HSV1 encephalitis: Flair

40h D9 D19



Kuker W. Neuroradiology 2004

Selected recommendations

N°21: "Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnosis (A-III)"

N°24: Herpes simplex virus: ACV is recommended (A-I)

HSV1 encephalitis: adverse outcome at 6-month: 84 adults

Variables	OR	CI95%	p
SAPS 2 > 27	3,7	1,3-10,6	0,014
Admission-ACV > 2 days	3,1	1,1-9,1	0,037

Raschilas F et al. Clin Infect Dis 2002;35: 254

Multivariate analysis of factors associated with late initiation of ACV

- 184 adults, médian age: 60 y (17-91), males: 55%
- ACV delay > 1 day after hospital admission : 68 (37%)

Variables	OR	CI95%
Knaus ≥ 3	4,1	1,5-11,7
Chronic alcohol consumption	3,4	1,3-8,9
CSF leucocytes < 10/mm3	2,5	0,7-5,8
Time to CT/MRI after hospital admission > 1 d	8,4	3,9-18

Poissy J et al. CMI 2008

Selected recommendations

N°21: "Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnosis (A-III)"

N°24: "Herpes simplex virus: ACV is recommended (A-I)"

- Dosage: 10mg/kg/8h; 20mg/kg/8h in neonates could be better. Adults ???

- Duration: 14-21 days

PCR et encéphalites

17. Nucleic acid amplification tests (such as PCR) should be performed on CSF specimens to identify certain etiologic agents in patients with encephalitis (table 5) (A-III). Although a positive test result is helpful in diagnosing infection caused by a specific pathogen, a negative result cannot be used as definitive evidence against the diagnosis.

PCR sur sites extra-neurologiques

voies respiratoires, urines, peau….

PCR HSV

	Biopsie ⊕	Biopsie -
PCR ⊕	53	3
PCR -	**1**	**44**

Se: 98%, Sp: 94%, VPPP: 95%, VPN: 98%

Lakeman et al. JID 1995

Impact de la PCR rapide (3h) entérovirus (EV)

442 patients

↓

69 méningites à EV (53 enfants, 16 adultes)

↓

Arrêt des antibiotiques: 50-60%

Arrêt de l'acyclovir (EV+/HSV-): 62%

Archimbaud C et al. J Med Virol 2009; 81

PCR HSV1: faux négatifs précoces

Age (ans)	1er signes – PL1 (Jours)	PCR1	PCR2	PL1-PL2 (Jours)
10	3	-	+	4
37	2	-	+	7
78	1	-	+	4

Weil *et al.* CID 2002; 34: 1154-1157

PCR HSV initiale négative

- Un certain nombre d'observations rapportées *(Akhan Infection 2001, Weil CID 2002, Mc Cabe Neurology 2003, De Tiege X CID 2003, Tyler HERPES 2004, Boivin HERPES 2004, Kennedy J Neurol 2005, Whitley Antiviral Res 2006, Espy Clin Microbiol Rev 2006, Kimberlin HERPES 2007)*

- Le plus souvent LCR précoce /1ers signes neurologiques ou LCR peu inflammatoire.

- 8 PCR initiales (avant J3) négatives sur 33 enfants

- Association avec < 10 GB/^{mm3} et protéinorachie normale

De Tiège X et al. CID 2003

Selected recommendations

N°17: " In patients with encephalitis who have a negative herpes simplex PCR result, consideration should be given to repeating the test 3-7 days later in those with a compatible clinical syndrome or temporal lobe localization on neuroimaging (B-III). In this instance, a negative CSF PCR result may allow discontinuation of aciclovir therapy"

IDSA , CID 2008; 47: 303

Ann Neurol. 2010 Jun;67(6):830-3.
Acyclovir resistance in herpes simplex encephalitis.
Schulte EC et al.

Abstract
…We report the case of a 27-year-old, immunocompetent woman with acyclovir-resistant herpes simplex encephalitis. Although she had not been treated before, herpes simplex virus type 1 DNA from the cerebrospinal fluid showed a non-synonymous mutation in the thymidine kinase gene, which is likely to have caused resistance to acyclovir. Herpes simplex encephalitis resolved after treatment with foscarnet. To our knowledge, this is the first report of acyclovir-resistant herpes simplex virus encephalitis in an immunocompetent, previously therapy-naive adult

Selected recommendations

Do not miss ADEM !

N°3: In patients with encephalitis and a history of recent infectious illness or vaccination, the diagnosis of ADEM should be considered (B-III).

N°63: ADEM: high-dose corticosteroids are recommended (B-III); alternatives include plasma exchange (B-III) and IV Ig (C-III)

ADEM in 20 adult patients

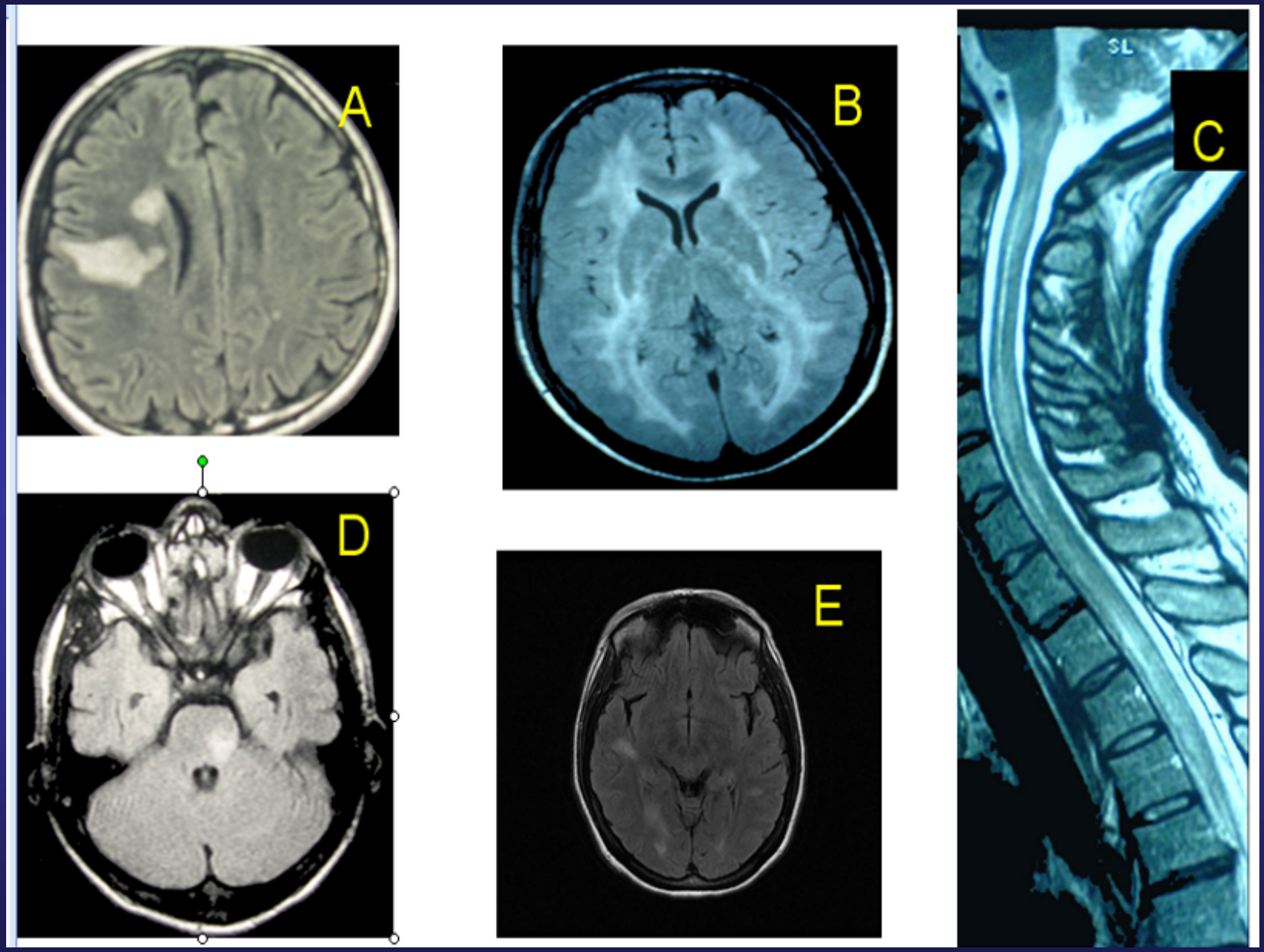
Parameter	n
Age, y	37 (27-51)
Female n (%)	11 (55)
Preceding infectious disease	14 (70)
Latency period, days	8 (6-14)
Temperature, °C	39 (38-39)
GCS	7 (4-13)
Mechanical ventilation, n (%)	14 (70)
Seizures	6 (30)
Motor deficit	17 (85)
Spinal cord symptoms	11 (55)

Sonneville R et al. ICM 2008;34:528

ADEM in 20 adult patients

CSF cells, n/mm^3	90 (60–378)
CSF predominance of neutrophils, *n* (%)	5 (25)
CSF protein, g/l	1.3 (0.5–1.9)

Sonneville R et al. ICM 2008;34:528


A
B
C
D
E

ADEM in 20 adult patients

Time between ICU admission and steroid administration, days	3 (1–9)
Steroid dose, g	10 (6–10)
IVIg, *n* (%)	6 (30)
Duration of MV, days	26 (10–36)
Length of ICU stay, days	19 (13–36)

Sonneville R et al. ICM 2008;34:528

Infectons graves du système nerveux central

- Une démarche clinique rigoureuse
- Suivie par une stratégie initiale de diagnostic et de traitement permettant de situer la place respective et la séquences des examens, notamment radiologiques
- Des performances accrues de l'imagerie et de la biologie moléculaire
- Un pronostic encore médiocre