Consultation from Surgical & Orthopedic Department

นาวาอากาศเอก ธนาสนธิ์ ธรรมกุล

หน่วยโรคติดเชื้อ กองอายุรกรรม

โรงพยาบาลภูมิพลอดุลยเดช

Post-neurosurgical Meningitis (PNM)

- Meningitis occurs
  - After craniectomy, craniotomy (0.3-8.6 %)
  - Following the insertion of
    - Internal ventricular catheters (4-17 %); Operative incidence usually < 4 %
    - External ventricular catheters (0-22 %); 10.6 per 1000 catheter-days (95% CI, 8.3–13)
    - Lumbar catheters (0.8-7 %)

- The reported rates of PNM vary, depending on
  - Neurosurgical procedure, Indications for surgery
  - Underlying medical conditions
  - Local implementation of infection-control measures
  - Definition : surveillance definitions*, and (varieties of) clinical definitions

Clin Infect Dis 2017;64(6):e34–e65.
Clin Microbio Infect 2017;23(9):e621-e628.

Meningitis after Neurosurgery or Head trauma

- Difficult to establish diagnosis
  - Surgery and trauma can induce CSF abnormalities
  - May have fever for reasons unrelated to infection (eg, central fever, drug fever, thrombophlebitis, or chemical meningitis after posterior fossa surgery)
  - The widely used CDC criteria for the diagnosis of meningitis are not applicable to patients with PNM
- Risk factors associated with post-craniotomy meningitis
  - Use of CSF drain
  - CSF leak
  - Perioperative steroid use

Clin Infect Dis 2017;64(6):e34–e65.
J Neurosurg 2015(5); 122:1113–1119.

Clinical Signs, Symptoms

- The classic meningitis triad of fever, neck stiffness, and altered mental status or headache has a sensitivity of just 40-50% for health care-associated CNS infections
  - Routine use of treatments to minimize fever, swelling, and injury
  - Infections with indolent or low virulence organisms, which elicit less meningeal inflammation and symptoms
- Clinical signs are less obvious in patients with infected shunts
  - Commonly present with vague, nonspecific complaints such as malaise, lethargy, or headache without meningeal signs
- Patients who have undergone neurosurgery
  - Quite ill to begin with, often febrile, neurologically compromised, have multiple potential sources of infections, and multiple non-infectious conditions that can cause fever, decreased level of consciousness and CSF pleocytosis

J Clin Microbiol 2018;56(11):e00861-18.
Clin Microbio Infect 2017;23(9):e621-e628.

Diagnosis of PMN

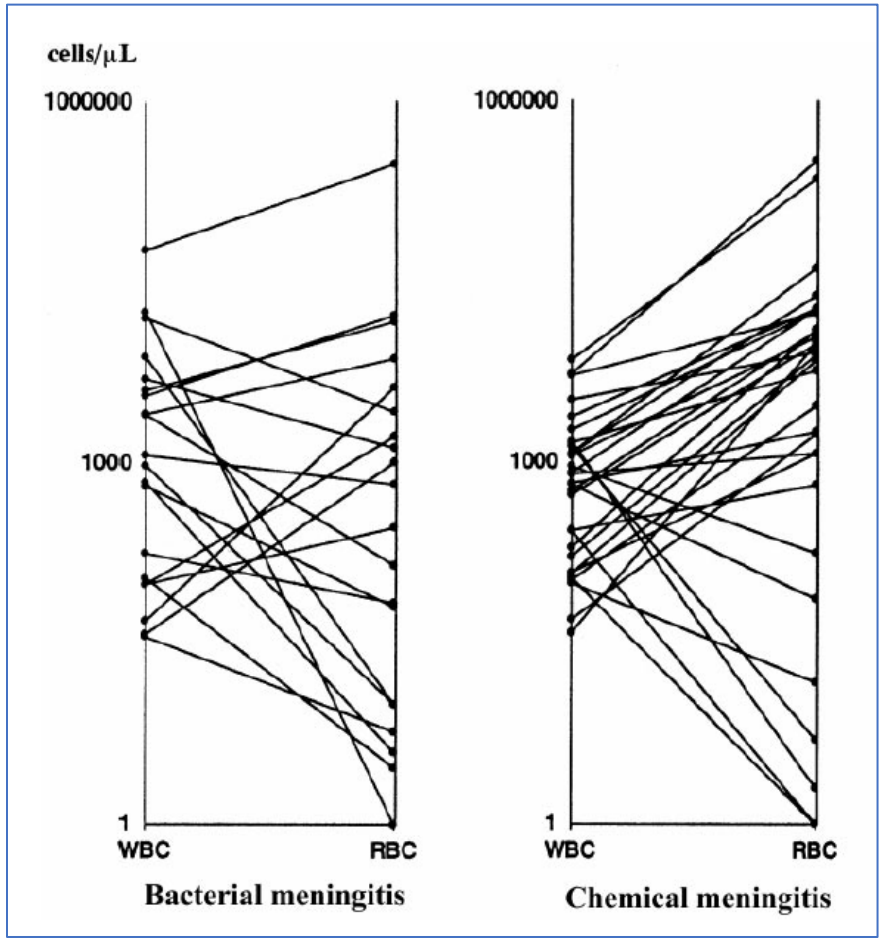
- **Classical CSF findings** including WBC and neutrophil counts, protein levels and hypoglycorrhachia are not helpful
- Increase in the CSF leukocyte count with serial sampling is suggestive of infection

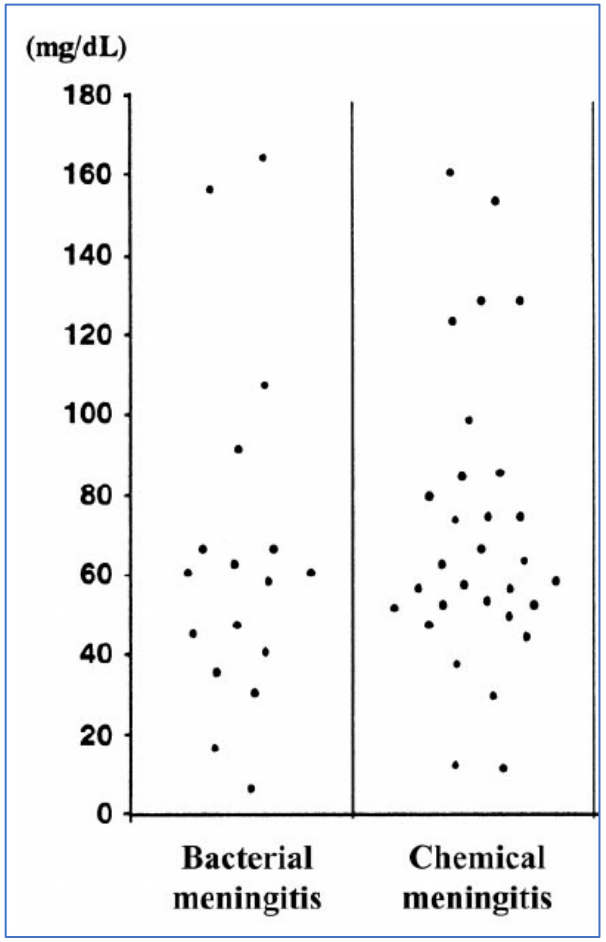
Table 2. Biological findings in CSF samples from patients with bacterial or aseptic postoperative meningitis.

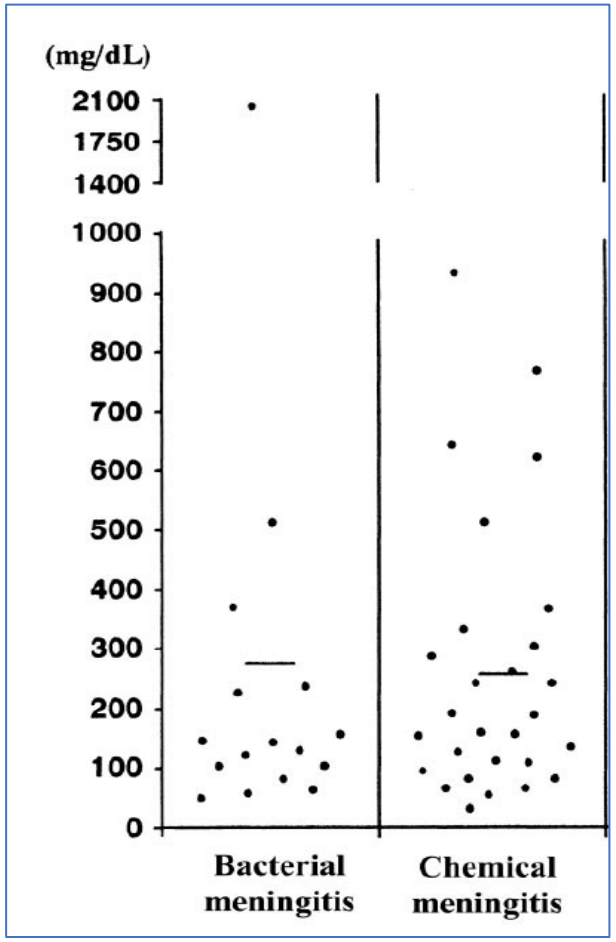
Biological variable	Patients with bacterial meningitis (n = 21)	Patients with aseptic meningitis (n = 54)
Leukocyte count, mean leukocytes/mm^3 (range)	1560 (200–4500)	1511 (180–4200)
Erythrocyte count, mean erythrocytes/mm^3 (range)	2430 (20–8500)	2100 (15–6050)
Glycorrachia, mean mmol/L (range)	1.1 (0–3.8)	1.8 (0–7.3)
Proteinorrachia, mean g/L (range)	4.7 (1.6–1.7)	3.2 (1.2–12.5)

Clin Infect Dis 2007; 44(12):1555–1559.
J Clin Microbiol 2018;56(11):e00861-18.

Characterization of Chemical Meningitis after Neurological Surgery







Clin Infect Dis 2001; 32(2):179–185.

Microbiologic Testing

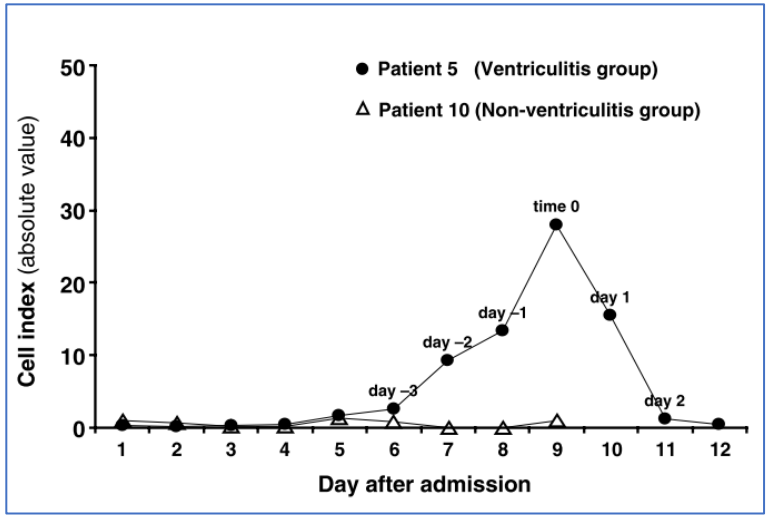
- 20% of patients with health care associated ventriculitis and meningitis had a positive CSF Gram stain
- CSF culture can be negative in 23% to 78% of patients with health care- and device-associated CNS infection
- Increase in the proportion of positive CSF cultures and clinically significant *Propionibacterium* spp. infections with the addition of anaerobic culture (solid media or broth) and prolonged incubation of broth media (10 to 14 days)

J Clin Microbiol 2018;56(11):e00861-18.

Proposed Parameter for Diagnosis of PMN

CSF Cell Index

$$\frac{\text{CSF WBCs/RBCs}}{\text{Blood WBCs/RBCs}} > 5$$



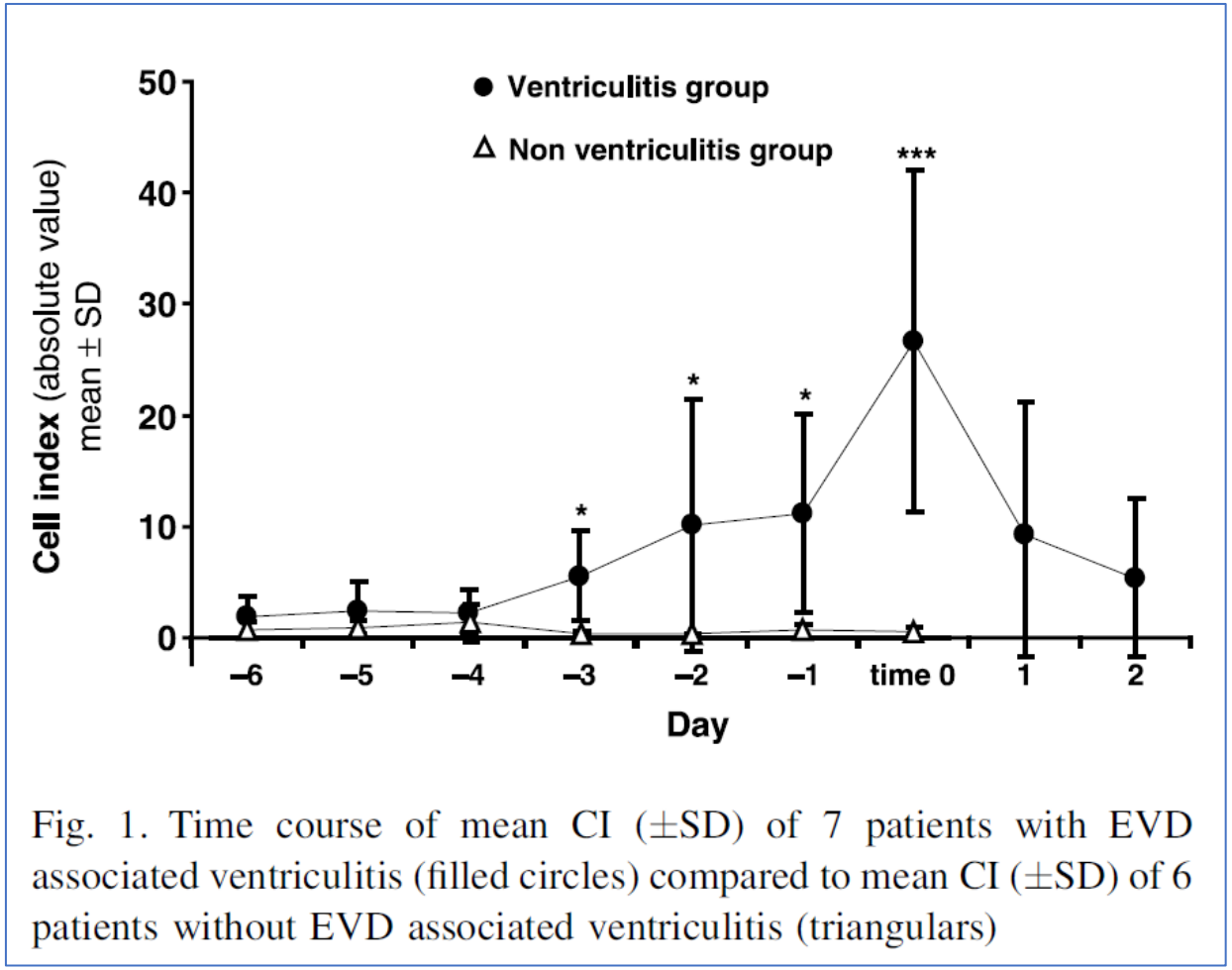


Fig. 1. Time course of mean CI (±SD) of 7 patients with EVD associated ventriculitis (filled circles) compared to mean CI (±SD) of 6 patients without EVD associated ventriculitis (triangulars)

Acta Neurochir (Wien) 2004; 146(5): 477–481.

Proposed Parameter for Diagnosis of PMN

CSF lactate

- Originates from anaerobic glycolysis inside bacteria and ischemic brain tissue caused by bacterial infection
- A relatively large body of evidence supports the use of CSF lactate (with a cutoff level of>4 mmol/L) as indicative of bacterial infection

The AUC_{-ROC} values, cut-off values and according sensitivities, specificities and Youden indices of blood examinations, CSF lactate and algorithms to diagnose PBM.

Examinations	PBM Diagnosis Accuracy AUC_{-ROC} (CI 95%)	Cut-off values	Sensitivity (%)	Specificity (%)	Youden index
Blood WBC Counts (bWBC, 10^9/L)	0.607 (0.581-0.633)	>13.85	67.15	50.23	0.1738
Blood Neutrophil Proportions (bNeut%, %)	0.538 (0.511-0.564)	>81.1	83.82	26.38	0.1020
Blood Platelet Counts (bPLT, 10^9/L)	0.680 (0.655-0.704)	>247	71.48	56.11	0.2759
Blood Sodium Concentration (bNa, mmol/L)	0.668 (0.643-0.692)	<134	64.8	60.02	0.2482
CSF Lactate Level (cLact, mmol/L)	0.891 (0.852-0.922)	>3.6	76.36	87.79	0.6476
Algorithm 1 (Z-Blood)	0.760 (0.737-0.782)	>0.181	64.00	78.00	0.4200
Algorithm 2 (Z-cLact)	0.921 (0.887-0.948)	>−0.336	86.67	85.47	0.7213

The diagnostic accuracy of each examination was evaluated based on the AUC_{-ROC} value. The diagnostic accuracy was classified as follows: 0.90 to 1.00 AUC_{-ROC} value = excellent, 0.80 to 0.89 = good, 0.70 to 0.79 = fair, 0.60 to 0.69 = poor and 0.50 to 0.59 = failure.

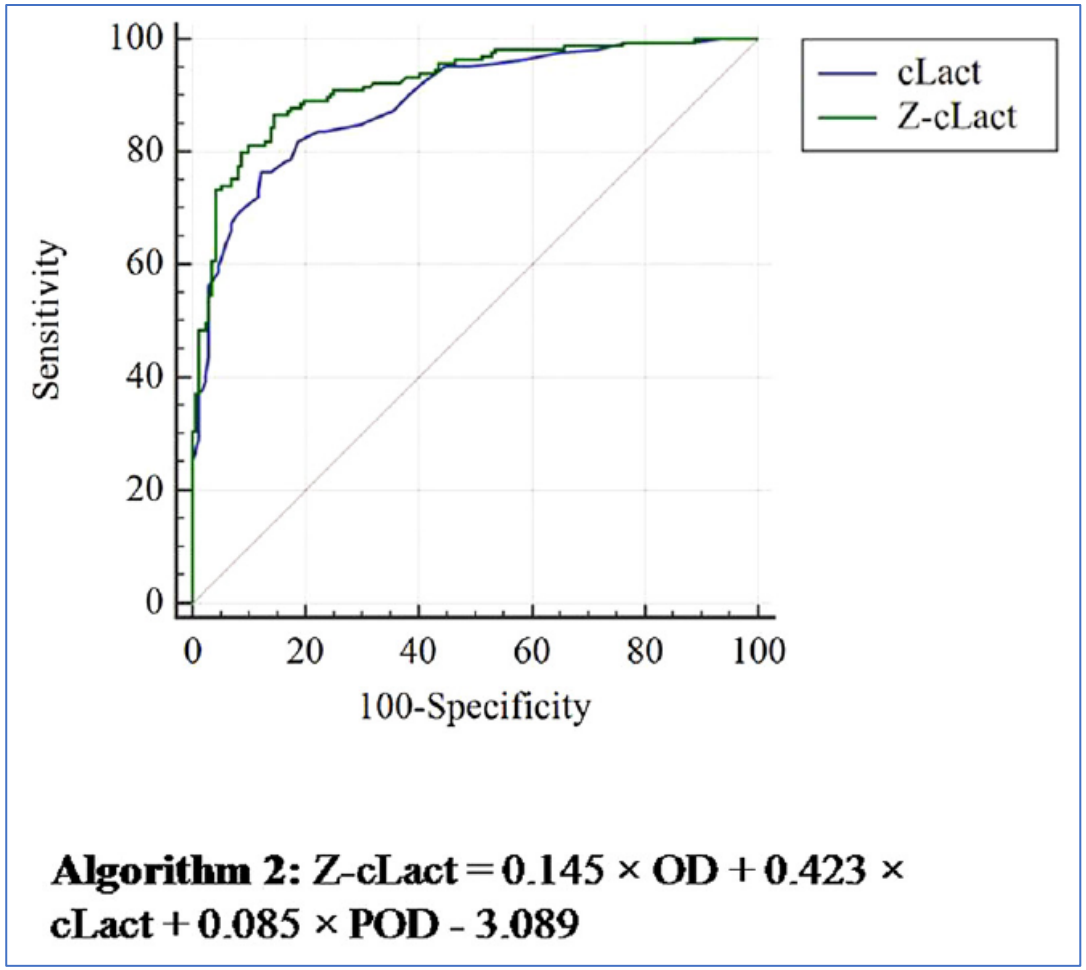
Clin Microbio Infect 2017;23(9):e621-e628.

International Journal of Infectious Diseases 2017;59(1): 50–54.

Proposed Parameter for Diagnosis of PMN

CSF lactate

- The CSF lactate level achieved rather high diagnostic accuracy (AUC-ROC = 0.891; CI 95%, 0.852-0.922)
- When the variables of patient age, operation duration, surgical diagnosis and postoperative days were integrated, the diagnostic accuracy of CSF lactate level was significantly improved with an AUC-ROC value = 0.921 (CI 95%, 0.887-0.948)



International Journal of Infectious Diseases 2017;59(1): 50–54.

ORIGINAL ARTICLE

Cerebrospinal Fluid Lactate as an Indicator for Post-Neurosurgical Bacterial Meningitis

Rebai Lotfi[1], Boussaidi Ines[2], Daghmouri M Aziz[3], Badri Mohamed[4]

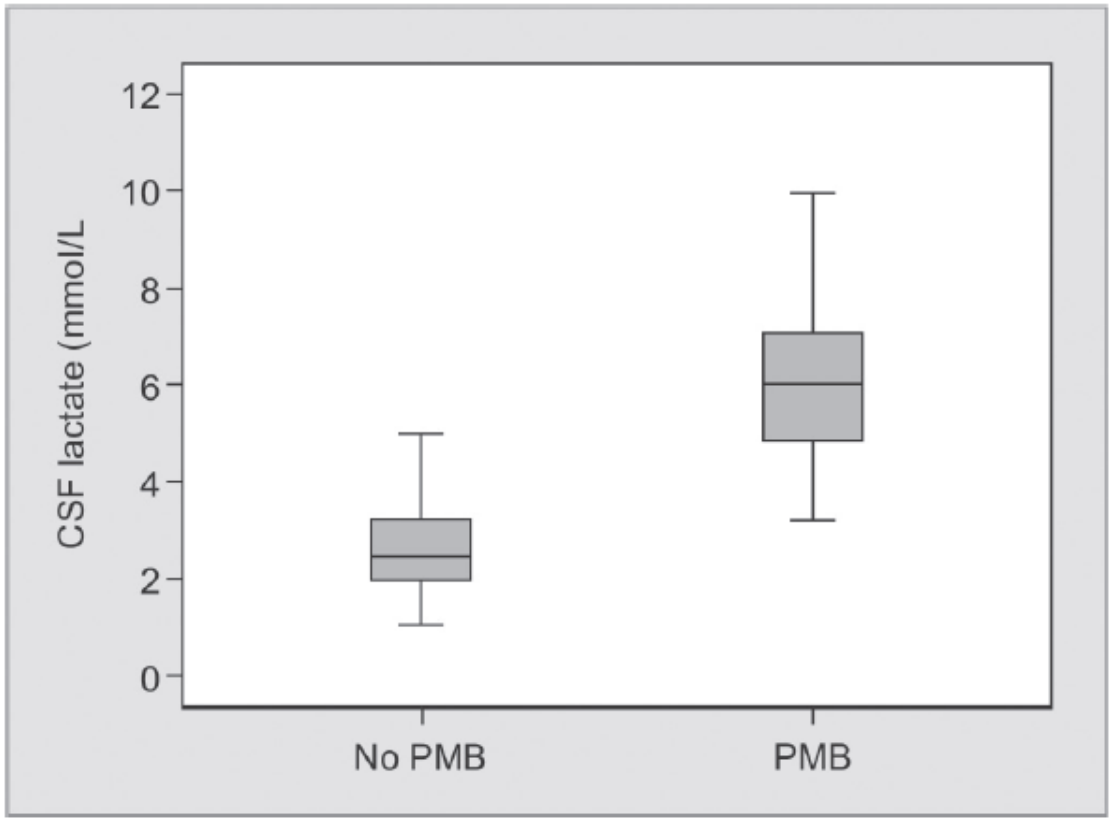


Fig. 1: CSF lactate values for PBM and no PBM groups showing significant difference (Mann-Whitney, p < 0.001)

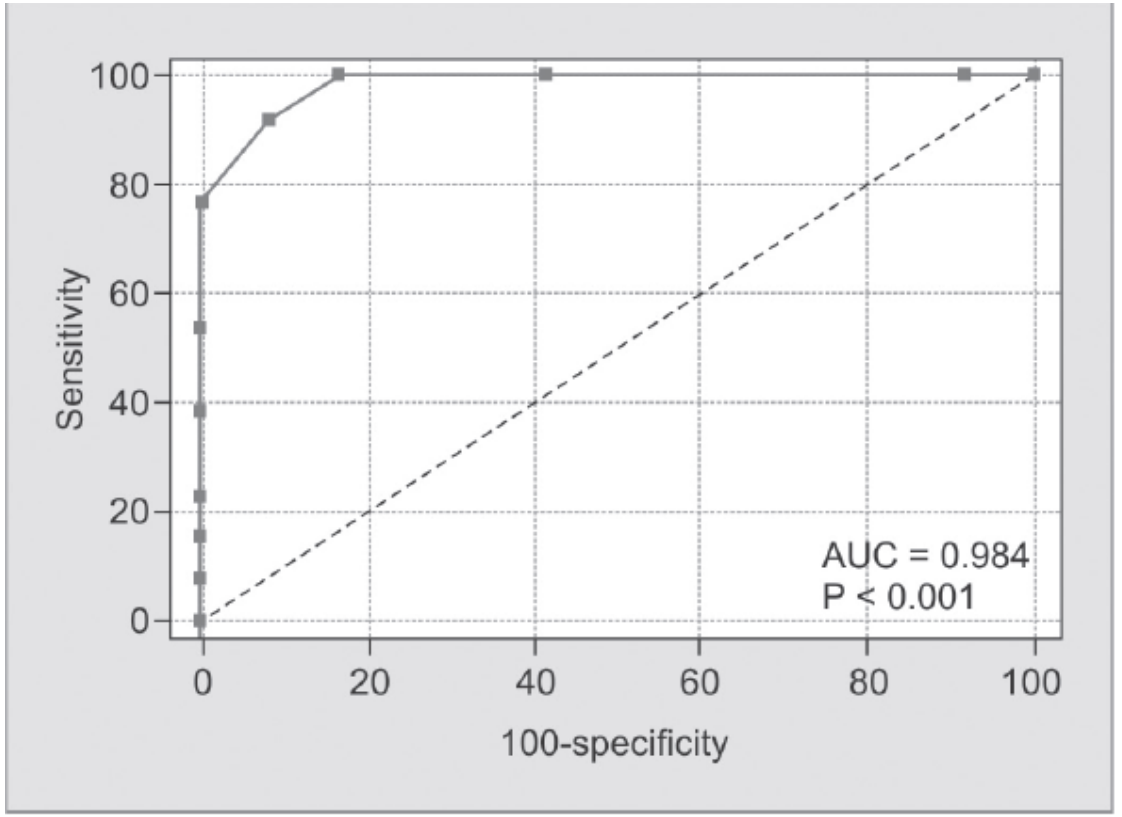


Fig. 2: ROC curve analysis for CSF lactates

Indian J Crit Care Med. 2019 Mar; 23(3): 127–130.

Proposed Parameter for Diagnosis of PMN

Procalcitonin

Received: 9 March 2016 | Revised: 6 June 2016 | Accepted: 27 June 2016

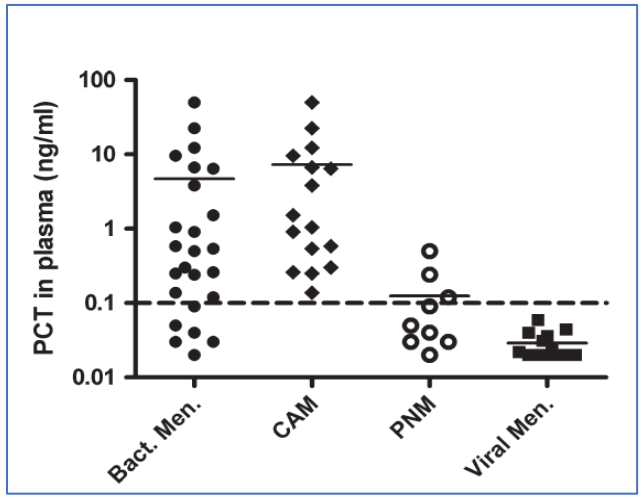
DOI: 10.1002/brb3.545

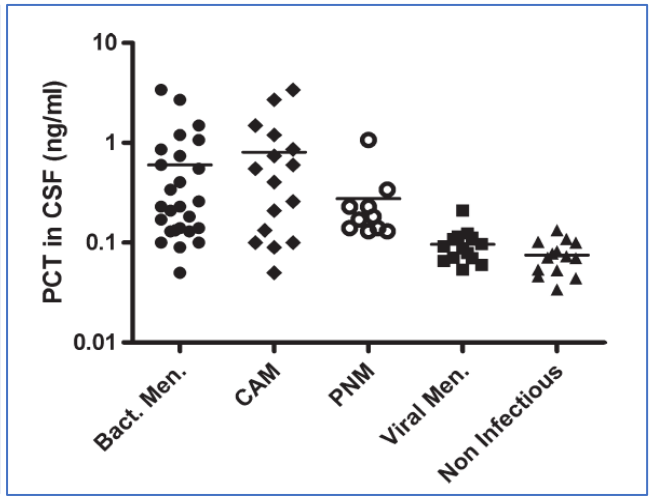
ORIGINAL RESEARCH

WILEY Brain and Behavior Open Access

Procalcitonin in cerebrospinal fluid in meningitis: a prospective diagnostic study

Imanda M. E. Alons[1*] | Rolf J. Verheul[2*] | Irma Kuipers[2] | Korné Jellema[1] | Marieke J. H. Wermer[3] | Ale Algra[4,5,6] | Gabriëlle Ponjee[2]





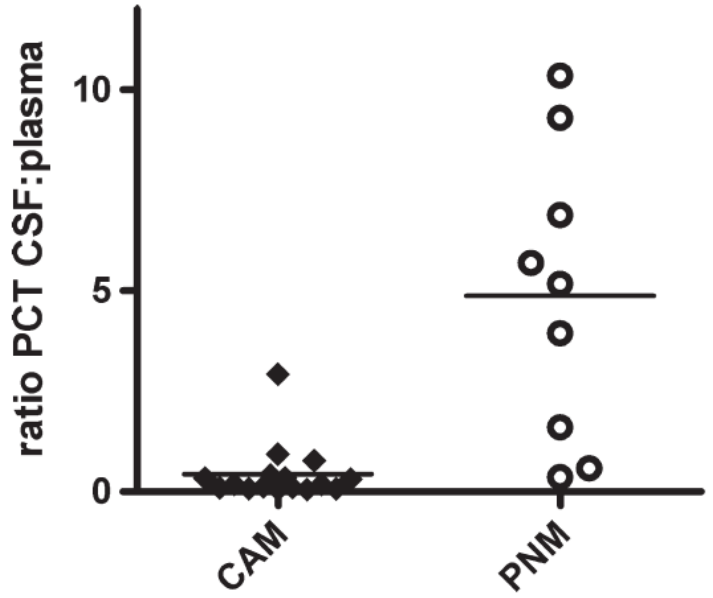


FIGURE 3 Scatter plots of procalcitonin plasma: cerebrospinal fluid ratio. Horizontal bar represents the mean value of a group, logarithmic scale

The median PCT CSF: plasma ratio was 5.18 in postneurosurgical and 0.18 in community-acquired meningitis (IQR 4.69 vs. 0.28)

Results of cell counts, glucose, protein and PCT in CSF and PCT in plasma

	Bacterial meningitis (*n* = 26)	CAM (*n* = 16)	PNM (*n* = 10)	Viral meningitis (*n* = 14)	Non-infectious (*n* = 14)
CSF leukocyte count × 10^6 per liter ave	5,998	7,551	3,514	267	1
Polynuclear cells × 10^6 per liter ave	5,589	7,428	2,832	28	0.1
Mononuclear cells × 10^6 per liter ave	616	576	677	239	0.7
Erythrocytes × 10^6 per liter ave	23,649	12,892	408,597	180	287
CSF glucose mmol L^{-1} ave	1.6	1.0	2.6	3.5	3.4
CSF protein g L^{-1} ave	3.3	3.9	2.4	1	0.4
PCT in CSF ng mL^{-1} Average (95% CI)	0.61 (0.29–0.90)	0.81 (0.31–1.31)	0.29 (0.10–0.45)	0.10 (0.08–0.12)	0.08 (0.05–0.09)
PCT in plasma ng mL^{-1} Median (IQR)	0.5 (4.36)	1.28 (6.82)	0.05 (0.08)	0.02 (0.02)	–
PCT ratio CSF:plasma Median (IQR)	0.86 (2.79)	0.18 (0.27)	5.18 (4.69)	3.00 (1.38)	–
Mean difference PCT in CSF versus non infectious (95% CI)	0.74 ng mL^{-1} (0.20–1.28)	0.73 ng mL^{-1} (0.20–1.27)	0.21 ng mL^{-1} (0.05–0.37)	0.30 ng mL^{-1} (−0.001 to 0.05)	–
Mean difference PCT in CSF versus Viral meningitis (95% CI)	0.73 ng mL^{-1} (0.19–1.27)	0.71 ng mL^{-1} (0.18–1.25)	0.18 ng mL^{-1} (0.02–0.34)	–	–

CAM, community-acquired meningitis; PNM, postneurosurgical meningitis; CSF, cerebrospinal fluid; PCT, procalcitonin.

Brain and Behavior 2016; 6: e00545

Proposed Parameter for Diagnosis of PMN

Multiplex PCR (SeptiFast) compared to traditional culture

- Sensitivity of 80.1 %
- Specificity of 97.6 %
- Positive predictive value (PPV) of 94.4 %
- Negative predictive value (NPV) of 90.9 %

Parameter	Results
CSF^+/SF^+, *n* (%)	17 (27.4)
CSF^-/SF^+, *n* (%)	1 (1.6)
CSF^+/SF^-, *n* (%)	4 (6.4)
CSF^-/SF^-, *n* (%)	40 (64.5)
CSF^+, *n* (%)	21 (34.0)
SF^+, *n* (%)	18 (29.0)
Concordance (%)	91.1
Sensitivity[a] (%)	80.1
Specificity[a] (%)	97.6
Positive predictive value[a] (%)	94.4
Negative predictive value[a] (%)	90.9
AUC[b] (95 % CI) for IL-6 and SF	0.90 (0.83–0.98)
AUC[b] (95 % CI) for IL-6 and CSF culture	0.70 (0.46–0.80)
AUC[b] (95 % CI) for lactate and SF	0.77 (0.63–0.93)
AUC[b] (95 % CI) for lactate and CSF culture	0.65 (0.50–0.80)

Diagnostic performance of CSF culture and SeptiFast in 62 CSF samples from 42 neurosurgical ICU patients with external ventricular drainage

Infection 2014; 42(4):621–627.

Microorganism	Number of isolates (*n*)			Duration of diagnostic procedures for pathogen detection in CSF			
	CSF^+/SF^+	CSF^-/SF^+	CSF^+/SF^-	Same-day result (within 8 h) by SF (yes/no)	Mean time-to-positivity of BACTEC bottles (h)	Mean time for Gram staining (h)	Mean time for species identification (h)
Staphylococcus aureus	2	0	0	One yes, one no	12.5	20.5	42.5
Coagulase-negative Staphylococci	10	1	3[a]	Yes	22.0	28.7	51.2
Escherichia coli	1	0	0	Yes	6.1	20.5	56.0
Klebsiella pneumoniae	2	0	0	Yes	40.0	46.0	70.0
Enterobacter cloacae	1	0	0	Yes	4.5	5.0	26.0
Serratia marcescens	1	0	0	Yes	15.0	21.0	42.0
Corynebacterium spp.	0	0	1	Yes	51.3	52.0	96
Total	17	1	4	In 17/18 (94 %) cases, SF results were obtained on the same day	21.6	27.7	54.8

BACTEC blood culture bottles, as described in text and Table 2

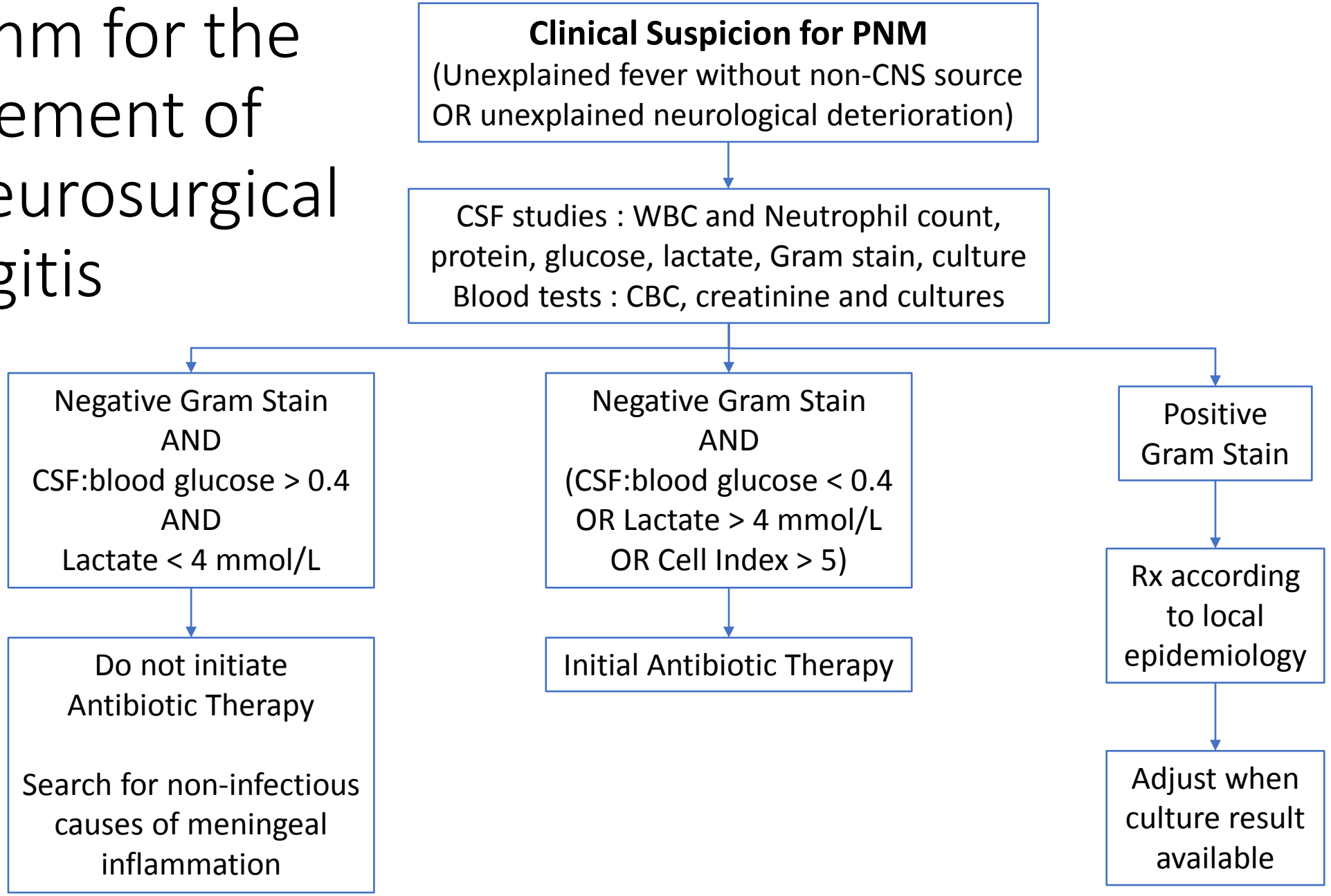
[a] The time to-positivity for these three samples was 72, 28 and 22 h, respectively

IDSA recommendation

- An elevated CSF lactate or an elevated CSF procalcitonin, or the combination of both, may be useful in the diagnosis of healthcare-associated bacterial ventriculitis and meningitis (weak, moderate).
- An elevated serum procalcitonin may be useful in differentiating between CSF abnormalities due to surgery or intracranial hemorrhage from those due to bacterial infection (weak, low).
- Nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low).

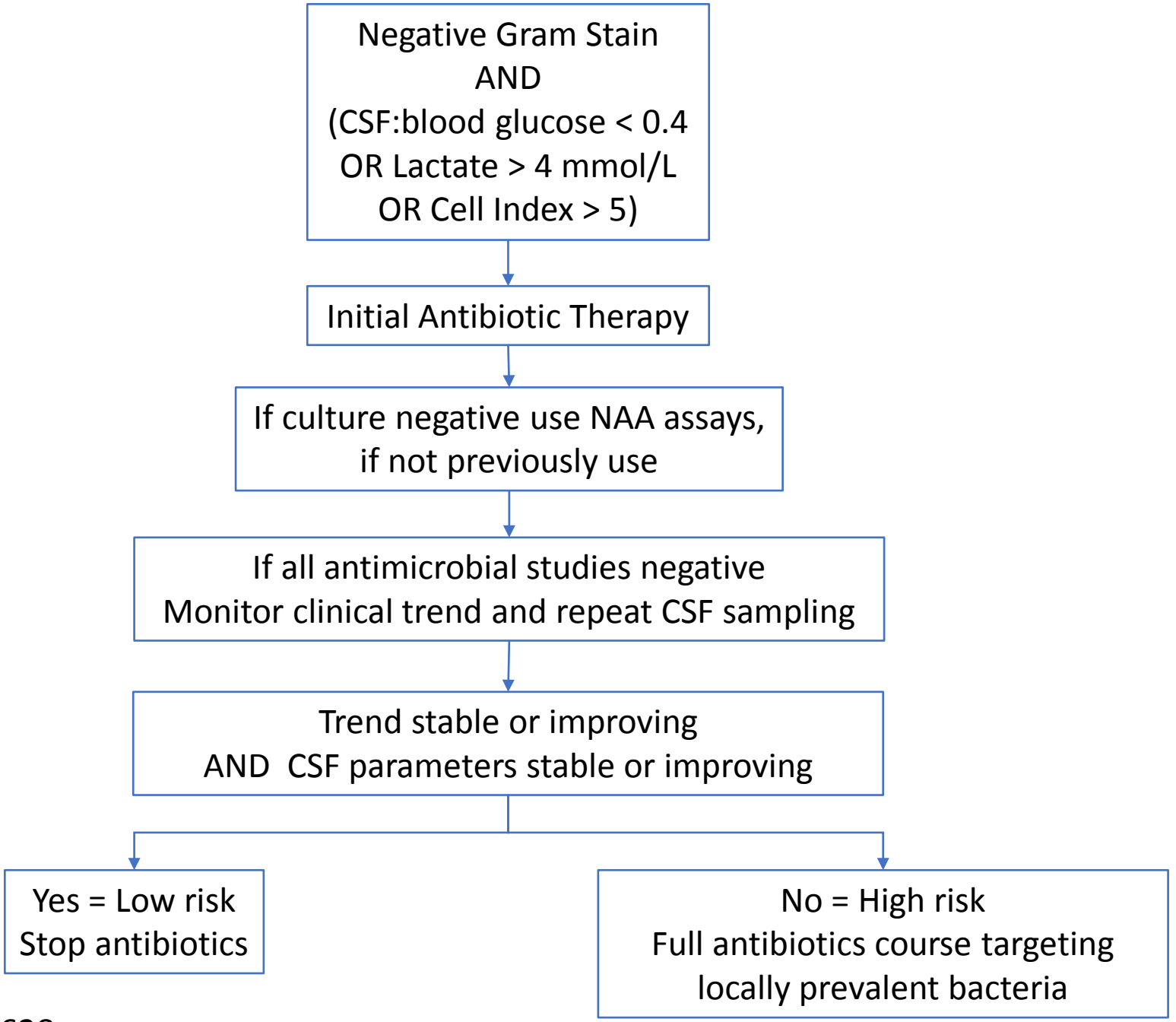
Clin Infect Dis 2017;64(6):e34–e65.

Algorithm for the management of Post-neurosurgical Meningitis



Clin Microbio Infect 2017;23(9):e621-e628.

Algorithm for the management of Post-neurosurgical Meningitis (Con't)



Clin Microbio Infect 2017;23(9):e621-e628.

Treatment of PNM

- Empiric treatment :
  - Vancomycin for coverage of staphylococci and *P. acnes*
  - *Plus* either an antipseudomonal cephalosporin or an antipseudomonal carbapenem for coverage of aerobic GNB
  - *Plus* colistin in a setting of high-prevalence of nosocomial infections caused by carbapenem-resistant *A. baumannii* and other GNB
- Initial treatment should be directed by Gram-stain smear
  - Withholding either vancomycin or the Gram-negative coverage if bacteria are observed

Clin Microbio Infect 2017;23(9):e621-e628.

Recommended Antimicrobial Therapy in Patients With Healthcare-Associated Ventriculitis and Meningitis

Microorganism	Standard Therapy	Alternative Therapies
Staphylococci[a]		
Methicillin sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin resistant	Vancomycin	Daptomycin, trimethoprim-sulfamethoxazole, or linezolid
Propionibacterium acnes	Penicillin G	Third-generation cephalosporin,[b] vancomycin, daptomycin, or linezolid
Streptococcus pneumoniae		
Penicillin MIC ≤0.06 μg/mL	Penicillin G	Third-generation cephalosporin[b]
Penicillin MIC ≥0.12 μg/mL		
Cefotaxime or ceftriaxone MIC <1.0 μg/mL	Third-generation cephalosporin[b]	Cefepime or meropenem
Cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin plus a third-generation cephalosporin[b,c]	Moxifloxacin[d]
Pseudomonas aeruginosa	Cefepime, ceftazidime, or meropenem	Aztreonam or ciprofloxacin
Haemophilus influenzae		
β-lactamase negative	Ampicillin	Third-generation cephalosporin,[b] cefepime, or a fluoroquinolone
β-lactamase positive	Third-generation cephalosporin[b]	Cefepime, aztreonam, or a fluoroquinolone
Extended spectrum β-lactamase-producing gram-negative bacilli	Meropenem	Cefepime or a fluoroquinolone
Acinetobacter baumannii	Meropenem	Colistin (usually formulated as colistimethate sodium)[e] or polymyxin B[e]
Other Enterobacteriaceae[f]	Third-generation cephalosporin[b]	Meropenem, aztreonam, trimethoprim-sulfamethoxazole, or ciprofloxacin
Candida species[g]	Lipid formulation of amphotericin B ± flucytosine	Fluconazole or voriconazole
Aspergillus species	Voriconazole	Lipid formulation of amphotericin B or posaconazole

Intrathecal administration of antimicrobials

- Compared 23 patients who received systemic and IT/IV therapy with 27 matched controls who received only systemic therapy
  - Patients who received IT/IV combined with systemic antibiotics had lower mortality than matched controls (OR 0.19; 95% CI 0.03-0.99)
  - Most had meningitis caused by carbapenem-resistant GNB

Clin Microbiol Infect 2016;22(1):66-70.

- We reserve intrathecal therapy for documented carbapenem-resistant GNB PNM, using an aminoglycoside preferentially, and vancomycin for persistent methicillin-resistant S. aureus PNM

Clin Microbio Infect 2017;23(9):e621-e628.

Recommended Dosages of Antimicrobial Agents Administered by the Intraventricular Route

Antimicrobial Agent	Daily Intraventricular Dose
Amikacin	5–50 mg[a]
Amphotericin B deoxycholate[b]	0.01–0.5 mg in 2 mL of 5% dextrose in water
Colistin (formulated as colistimethate sodium)	10 mg
Daptomycin	2–5 mg[c]
Gentamicin	1–8 mg[d,e,f]
Polymyxin B	5 mg[g]
Quinupristin/dalfopristin	2–5 mg
Tobramycin	5–20 mg
Vancomycin	5–20 mg[e,f,h]

There are no specific data that define the exact dose of intraventricular antimicrobial agents that should be used in cerebrospinal fluid (CSF) shunt and drain infections. Given the smaller CSF volume in infants (approximately 50 mL) compared to adults (approximately 125–150 mL), doses in infants should probably be decreased at least 60% or more compared to adults.

[a]The usual intraventricular dose is 30 mg daily.

[b]Not usually necessary but may be needed if removal of the device is too risky or the patient has not responded to systemic antifungal therapy.

[c]One study used 10 mg every day for 2 days and then 10 mg every 48 hours. Another study used 5 mg or 10 mg every 72 hours. Data are based on isolated case reports.

[d]Dose is 4–8 mg in adults; 1–2 mg in children.

[e]Dosage recommendations in adults based on ventricle size/volume as follows:

- Slit ventricles: 5 mg vancomycin and 2 mg gentamicin
- Normal size: 10 mg vancomycin and 3 mg gentamicin
- Enlarged ventricles: 15–20 mg vancomycin and 4–5 mg gentamicin.

[f]Recommendations for frequency of administration based on external ventricular drain output over 24 hours as follows:

- <50 mL/24 hours: every third day
- 50–100 mL/24 hours: every second day
- 100–150 mL/24 hours: once daily
- 150–200 mL/24 hours: increase the dosage by 5 mg of vancomycin and 1 mg of gentamicin and give once daily
- 200–250 mL/24 hours: increase the dosage by 10 mg of vancomycin and 2 mg of gentamicin and give once daily.

[g]Dose is 2 mg/day in children.

[h]Most studies used a 10-mg or 20-mg dose.

Clin Infect Dis 2017;64(6):e34–e65.

Antibiotic prophylaxis for the prevention of meningitis in basilar skull fractures

- Evaluated 5 RCTs
- No significant differences between antibiotic prophylaxis groups and control groups in terms of
  - reduction of the frequency of meningitis
  - all-cause mortality
  - Meningitis-related mortality
  - Need for surgical correction in patients with CSF leakage
- Currently available evidence from RCTs does not support prophylactic antibiotic use in patients with basilar skull fractures, whether there is evidence of CSF leakage or not

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004884.pub4/epdf/abstract

Role for Prophylactic Antimicrobial Therapy in Patients with Cerebrospinal Fluid Leak?

- In patients with basilar skull fractures and a CSF leak, prophylactic antimicrobial agents are not recommended (strong, moderate).
- In patients with basilar skull fractures and a prolonged CSF leakage (>7 days), an attempt to repair the leak is recommended (strong, low).
- In patients with basilar skull fractures and a CSF leak, pneumococcal vaccination is recommended (strong, moderate).

Clin Infect Dis 2017;64(6):e34–e65.

Is Asymptomatic Bacteriuria a Risk Factor for Prosthetic Joint Infection?

- 2497 patients : 12.1% (303 of 2497) ASB
- Overall PJI rate = 1.7%
  - Infection rate higher in the ASB group

    ASB group 4.3% vs non-ASB group 1.4% (OR 3.23; 95% CI, 1.67–6.27; P = .001)
- PJI in the ASB group
  - No difference in PJI rate between treated (3.9%) and untreated (4.7%) patients
  - Significantly higher proportion of PJI due to GNB than the non-ASB group, but these did not correlate to isolates from urine cultures

Clinical Infectious Diseases 2014;59(1):41–7.

Table 7. Comparison Between Treated and Untreated Patients With Asymptomatic Bacteriuria

Characteristic	Patients, No. (%)[a]		
	Treated ASB (n = 154)	Untreated ASB (n = 149)	*P* Value
PJI	6 (3.9)	7 (4.7)	.78
Age, mean (range), y	71.6 (23–90)	70.1 (36–90)	.06
Female sex	139 (90.3)	118 (79.2)	.01
Knee location	82 (53.2)	80 (53.7)	>.99
Comorbid condition			
Obesity (BMI ≥ 30 kg/m^2)[b]	61 (45.9)	66 (48.2)	.72
Diabetes[c]	4 (18.2)	19 (19.8)	>.99
ASA score ≥3[d]	27 (24.3)	34 (26.0)	.88
Postoperative UTI	1 (0.6)	4 (2.7)	.21

IDSA Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria 2019

Should Patients Undergoing Elective Nonurological Surgery Be Screened and Treated for ASB?

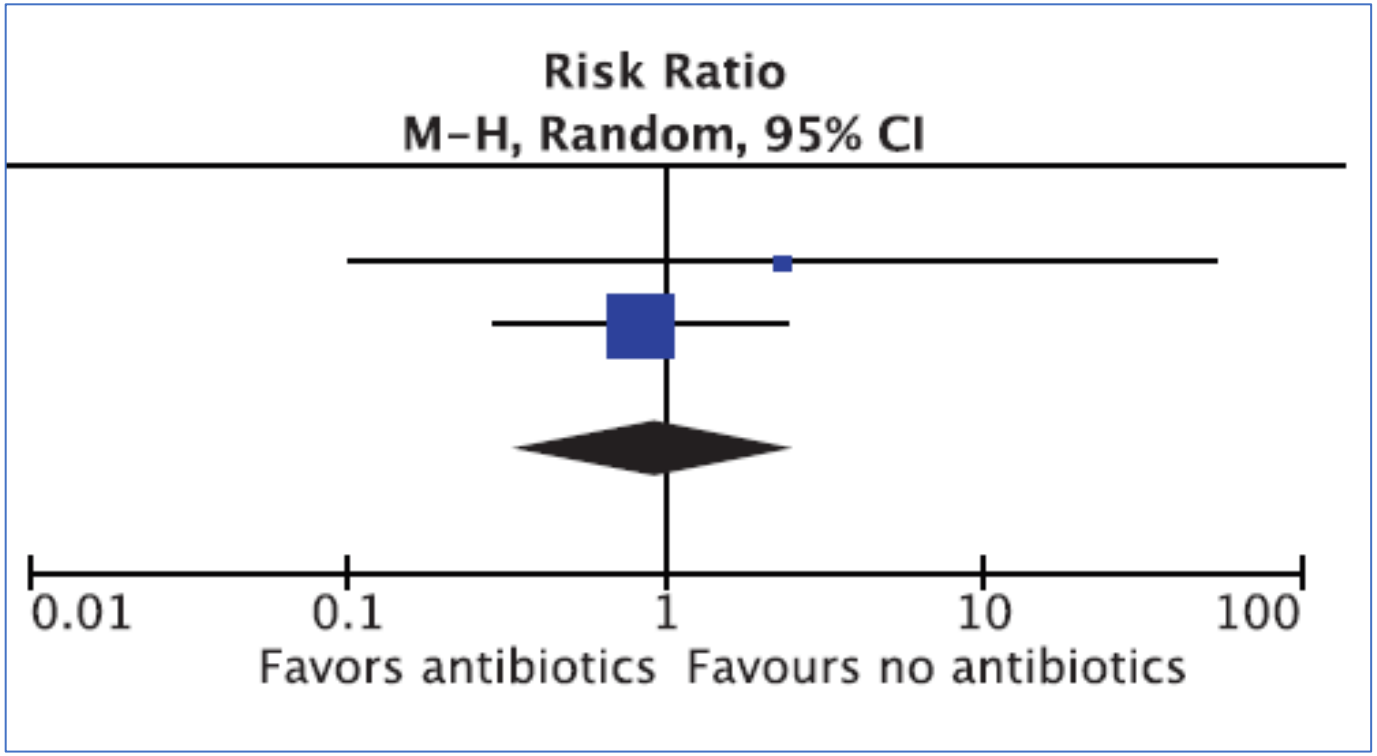
- In patients undergoing elective nonurologic surgery, we recommend against screening for or treating ASB

  (*strong recommendation, low-quality evidence*)

Clin Infect Dis 2019;68(10):e83–75.

Antimicrobial therapy for patients with ASB undergoing nonurologic surgery

- 3 studies combined
- Screened 3167 preoperative patients for ASB
- 403 (12.7%) had ASB
- Approximately half of the patients received antimicrobials targeting the ASB



Risk of prosthetic joint infection in patients treated vs not treated for asymptomatic bacteriuria in patients undergoing orthopedic surgery

Clin Infect Dis 2019;68(10):e83–75.

Management of Asymptomatic Bacteriuria, Urinary Catheters and Symptomatic UTI in Patients Undergoing Surgery for Joint Replacement

A Position Paper of the Expert Group 'Infection' of *swiss orthopaedics*

- Asymptomatic bacteriuria, urine discolouration, odd smell or positive nitrite sediments are not an indication for antimicrobial treatment
- Antimicrobial treatment of asymptomatic bacteriuria does not prevent periprosthetic joint infection, but is associated with adverse events, costs and antibiotic resistance development
- Urine analyses or urine cultures in asymptomatic patients undergoing orthopaedic implants should be avoided
- Indwelling urinary catheters are the most frequent reason for healthcare-associated urinary tract infections and should be avoided or removed as soon as possible

J. Bone Joint Infect. 2017; 2(3): 154-159