

Zapalenie opon mózgowo-rdzeniowych - trudności diagnostyczne



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Zapalenie opon mózgowo-rdzeniowych (ZOMR)

- 0,25-0,32/1000 noworodków; 1,2/1000 VLBW
- Wczesne - do 72h (*Streptococcus agalactiae*: ≤ 7 dni),
 - w ok. 10-30 % noworodków z bakteremią
 - w 72% GBs lub *E.coli* (USA 2006-2009)
- Późne- > 6 dni (w ok. 5% noworodków z późną bakteremią)
G+ (*Staphylococcus haemolyticus*, *S. epidermalis*, *Ennerococcus*, *Listeria monocytogenes*) – w 4%

ZOMR - objawy

- Zaburzenia termoregulacji- 60%
- Objawy neurologiczne: tkliwość – 60%, letarg, obniżone napięcie mięśniowe, drżenia kończyn, drgawki – 20-50%, pulsujące, napięte ciemię – 25%, sztywność karku – 15%
- Problemy z jedzeniem, wymioty – 50%
- Zaburzenia oddechowe – 33 – 50% (bezdechy – 10-30%)

ZOMR - diagnostyka

1. Badania diagnostyczne jak przy sepsie:

- Morfologia +rozmaz
- CRP, PCT, IL 6
- Posiew krwi, moczu (> 6 dnia)

2. PMR:

- Badanie ogólne
- Posiew
- PCR,
- mleczany, IgG, albuminy, cytokiny...

(pobrany zbyt wcześnie wynik może być prawidłowy → powtórzyć po 1-2 dobach)

PMR - WBC

> 20-30/ μ l – wskazuje na zapalenie opon, ale...

- ZOMR nawet przy braku ↑cytozy
- W 1-2 dniu życia WBC nawet do 90/ μ l przy braku zapalenia
- W 7 dniu życia: WBC 19/ μ l – 95 centyl
WBC 14/ μ l – 90 centyl

Age	Mean WBC/mm³ (range or 95th percentile)	ANC/mm³ or percent PMNs (range)	Mean protein (mg/dL) (range or ±SD)	Mean glucose (mg/dL) (range or ±SD)
Term neonates evaluated in the nursery setting				
0 to 24 hours (n = 135)*[1]	5 (0 to 90)	3/mm ³ (0 to 70)	63 (32 to 240)	51 (32 to 78)
0 to 10 days (n = 87) ¶[2]	8.2 (0 to 32)	61.3 percent	90 (20 to 170)	52 (34 to 119)
Term neonates evaluated in the emergency department setting △				
0 to 28 days (n = 3467)[3]	5.5 (95th percentile: 16)	2 percent (IQR: 0 to 5)	69.9 (±25.7)	45.7 (±8.0)
Preterm very low birth weight (<1500 g) neonates				
0 to 7 days (n = 88)[4]	7 (0 to 30)	NR	144 (51 to 270)	50.4 (11 to 138)
0 to 28 days (n = 45)[5]	5 (0 to 44)	8 percent (0 to 66)	148 (54 to 370)	67 (33 to 217)

Bacterial meningitis in the neonate: Clinical features and diagnosis. UpToDate 2019

[1] Naidoo BT, S Afr Med J, 1968.

[2] Sarff LD et al., J Pediatr, 1976

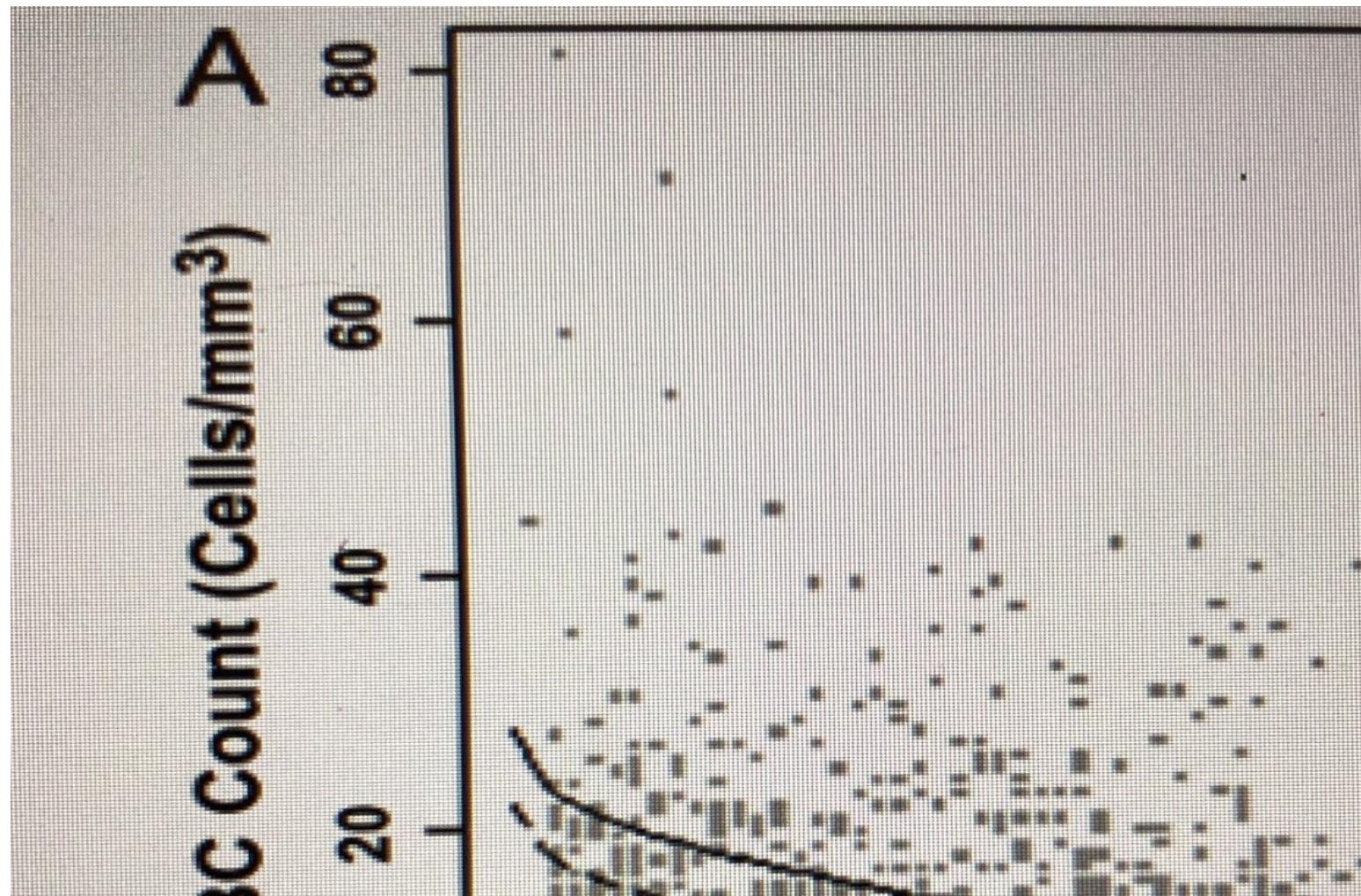
[3] Thompson J et al., Pediatr Crit Care Med., 2008

[4] Rodriguez AF, J Pediatr, 1990

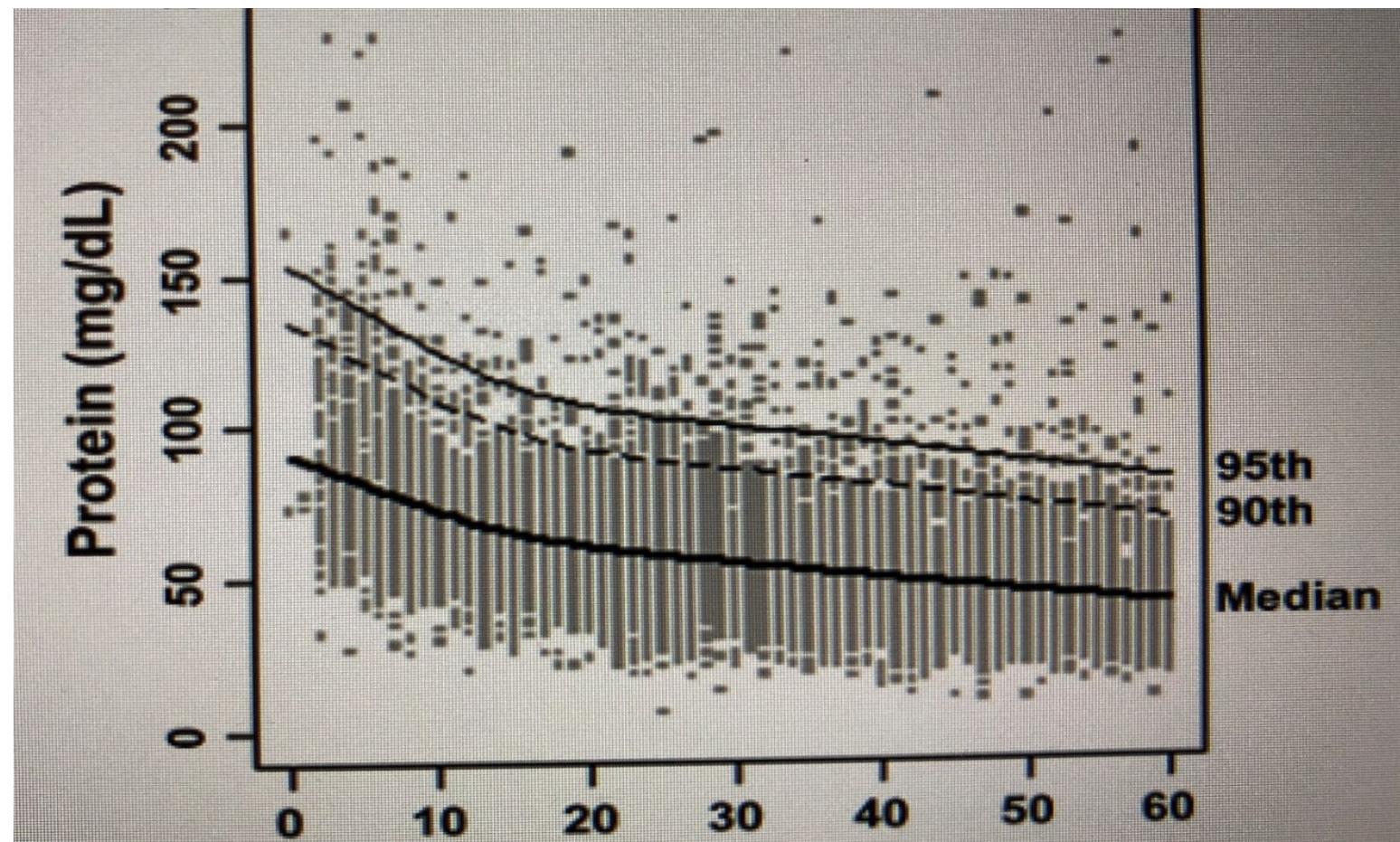
TABLE 1 CSF Normative Values by Age Among All Infants and in the Subset of Infants Who Had Negative CSF Enterovirus Test Results

Parameter	All		Negative for CSF Enterovirus	
	0–28 d	29–60 d	0–28 d	29–60 d
CSF WBC count, cells/mm ³ , n	3467	4029	480	563
Mean (SD)	5.5 (6.0)	3.6 (4.3)	6.3 (6.9)	4.6 (6.0)
Median	4	2	4	3
90th percentile	12	8	15	11
95th percentile	16	11	22	16
Upper bound	15	9	48	11
CSF protein concentration, mg/dL, n	3551	4187	499	608
Mean (SD)	69.9 (25.7)	53.2 (21.2)	68.2 (25.7)	53.7 (22.7)
Median	66	49	64	49
90th percentile	102	79	100	80
95th percentile	118	91	121	93
Upper bound	127	99	121	102
CSF glucose concentration, mg/dL, n	3556	4205	499	613
Mean (SD)	45.7 (8.0)	48.1 (8.0)	45.6 (8.3)	48.2 (7.5)
Median	45	47	45	48
10th percentile	37	39	37	39
5th percentile	35	37	34	37
Lower bound	25	27	25	28

Thomson J et al. Cerebrospinal Fluid Reference Values for Young Infants Undergoing Lumbar Puncture. Pediatrics. 2018



Thomson J et al. Cerebrospinal Fluid Reference Values for Young Infants Undergoing Lumbar Puncture. Pediatrics. 2018



*Thomson J et al. Cerebrospinal Fluid Reference Values for Young Infants
Undergoing Lumbar Puncture. Pediatrics. 2018*

2802 patients underwent lumbar puncture
(2000.01-2017.12)

972 Excluded

431 with negative cerebrospinal
fluid culture result

315 Traumatic lumbar puncture

203 Patients with an onset
age older than 28 days

23 Patients with severe
neurological disease history
or ventricular drain



1830 patients (**105** bacterial meningitis patients
and **1725** non bacterial meningitis patients)

Cerebrospinal fluid parameters in non-bacterial meningitis neonates

Parameter	Quantile				
	5th	25th	50th	75th	95th
White blood cells ($10^6/L$)	0	0	2	5	11
Protein (mg/L)	325	555	747	1000	1536
Glucose (mmol/L)	2.0	2.0	3.0	3.0	4.0
Lactate dehydrogenase (U/L)	20	35	56	192	295
Chloride (mmol/L)	108	116	119	122	127

Diagnostic efficacies of cerebrospinal fluid parameters estimated using receiver operating curves in bacterial meningitis neonates.

CSF parameters	Cutoff values	AUC	95% CI	Specificity	Sensitivity	LLR+	LLR-a
1. White blood cells ($10^6/L$)	19.5	0.982	(0.964, 1.000)	0.987	0.951	74.72	0.05
2. Protein (mg/L)	1299.5	0.874	(0.825, 0.922)	0.906	0.775	8.21	0.25
3. Glucose (mmol/L)	1.95	0.865	(0.818, 0.913)	0.982	0.663	36.05	0.34
4. Lactate dehydrogenase (U/L)	271.5	0.760	(0.678, 0.837)	0.909	0.531	5.80	0.52
5. Chloride (mmol/L)	115.5	0.579	(0.512, 0.645)	0.754	0.426	1.73	0.76
Combined parameters 1+2+3+4	-1.7032	0.978	(0.947, 1.000)	0.997	0.951	336.41	0.05
Combined parameters 1+2+3	-2.8547	0.980	(0.959, 1.000)	0.990	0.958	97.75	0.04
Combined parameters 1+2	-2.8012	0.979	(0.956, 1.000)	0.991	0.960	101.14	0.04

PMR- dehydrogenaza mleczanowa

LDH w PMR:

- zdrowe noworodki (1-4 tydzień): $50,5 \pm 6$ U/L
niemowlęta (5-8 tydzień): $33,5 \pm 5,5$ U/L
- BZOMR: 944,5 U/L (n=31, wiek 0-18 lat)
- Aseptyczne ZOMR: 49,8 U/L (n=65, wiek 0-18 lat)
- ↓↓↓ stężenia po 1-2 dniach skutecznego leczenia
(np. 426 U/L → 206 U/L; 264 U/L → 71 U/L po 1 dniu leczenia BZOMR)

Nussinovitch M et al. Am J Perinatol, 2002;19.

Nussinovitch M et al. Translational Research, 2009;154

Korekcja cytozy w PMR

- 20 319 PMR; dzieci \leq 60 dnia życia
- 14% (2880) PMR z domieszką krwi:
RBC \geq 10 000/mm³; \rightarrow 1,1% (33) ZOMR
- ZOMR: bakterie w posiewie PMR
- Pleocytoza PMR: \leq 28 dnia życia - \geq 20/mm³
 $29\text{-}60$ dnia życia - \geq 10/mm³
- Korekcja WBC w PMR: 1000 RBC \rightarrow (- 1 WBC) PMR

T.W. Lyons et al. Ann Emerg Med. 2017

Korekcja cytozy w PMR

- PMR („skrwawiony”): WBC 46/mm³ (17-128),
RBC 43 050/mm³ (19 050- 114 397)
- Po korekcji WBC: 45% PMR u dzieci ≤28 dnia życia i 48% między 29 i 60 dniem życia nie spełniało kryterium podwyższonej cytozy
- ZOMR: 26 noworodków ≤28 dnia życia i 7 między 29 i 60 dniem życia
- ≤28 dnia życia: 4 PMR bez podwyższonej cytozy bez korekcji i 6 PMR po korekcji (10/26!)
- między 29 i 60 dniem życia: 1 PMR bez podwyższonej cytozy po korekcji

T.W. Lyons et al. Ann Emerg Med. 2017

Korekcja białka w PMR

2 646 niemowląt \leq 60 dnia życia
z traumatyczną PL (RBC \geq 10.000/ μ l)

- 31 (1.2%) – bakteryjne ZOMR
- Na każde 1 000 erytrocytów w 1 μ l PMR →
 \uparrow białka o 1.1 mg/dL
- Korekcja → \downarrow czułość (74,2 → 61,3)
 \uparrow swoistość (26,4 → 56,4)
 \uparrow AUC (0,5 → 0,59)

Lyons T. et al. Pediatr Infect Dis J. 2017; 36

PMR

- Zanieczyszczenie krwią – skrzepy krwi w PMR
- Preparat barwiony PMR →
 - erytrofagi – krwawienie 2-3 dni wstecz
 - komórki żerne – wylew 2-3 miesiące temu
 - bakterie w granulocytach – obniżona zdolność bakteriobójcza

Table 2. Levels of Blood and CSF Parameters.

Variable	3-90 dzień życia	Meningitis, median (IQR) (n = 99)
Blood parameters		
TLC, $\times 10^9/L^a$		15.6 (8.2-17.6)
Hemoglobin, g/dL ^a		16.2 (14.2-19.3)
Platelet count, $\times 10^9/L^a$		178 (42-345)
CRP >8 mg/dL, n (%) ^b		84 (84.8)
Serum PCT, ng/mL ^a		0.46 (0.37-0.632)
Serum lactate, mmol/L ^a		1.5 (1.3-1.5)
CSF parameters		
RBC count, $\times 10^5/mm^3^a$		1.3 (0.7-1.71)
Uncorrected TLC, cells/mm $^3^a$		1383 (481-4505)

Nazir M et al, J of Child Neurology, 2018

Table 3. CSF Predictors of Patients With Meningitis.^a

Predictor	Crude OR (95% CI) ^a	P value	Adjusted OR (95% CI) ^a	P value
Uncorrected TLC >430 cells/mm ³	1.1 (0.7-2.2)	.46	1.32 (0.6-3.6)	.52
Corrected TLC >350 cells/mm ³	2.1 (1.2-3.9)	.062	1.5 (1-2.1)	.30
PCT >0.33 ng/mL	3.56 (2.1-6.2)	.001	3.11 (1.9-5.8)	.02
Lactate >2.2 mmol/L	9.2 (5.4-16.8)	<.001	4.31 (2.3-7.8)	<.001
CSF-serum lactate ratio >1.2	10.2 (5.8-17.8)	<.001	4.85 (2.7-8.1)	<.001

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio; PCT, procalcitonin; TLC, total leukocyte count.

^aCutoff points of laboratory tests were calculated as the maximum (sensitivity + specificity - 1) using receiver operating characteristic curve analysis.

^bOdds ratio from logistic regression model.

Table 4. Comparison of Diagnostic Efficiency of Various CSF Parameters Studied.

	Uncorrected TLC, cells/mm ³	Corrected TLC, cells/mm ³	PCT, ng/mL	Lactate, mmol/L	CSF-serum lactate ratio
AUC	0.870	0.906	0.939	0.964	0.985
95% CI	0.798-0.943	0.850-0.962	0.891-0.986	0.945-0.984	0.964-0.989
Threshold value	430	350	0.33	2.2	1.2
Sensitivity	0.848	0.909	0.848	0.939	0.909
Specificity	0.804	0.824	0.980	0.863	1.00
PPV	0.737	0.769	0.966	0.816	1.00
NPV	0.891	0.933	0.909	0.957	0.944
+LR, -LR	4.327, 0.188	5.152, 0.110	43.27, 0.155	6.844, 0.070	15.65, 0.091
Accuracy	0.821	0.857	0.929	0.893	0.964

Table 2. Levels of CSF parameters

Variable	<i>≤ 28 dzień życia</i>	Meningitis (n=75)	No meningitis (n=93)	P-value
PCT, ng ml ⁻¹ , median (IQR)		0.47 (0.38–0.88)	0.26 (0.21–0.28)	< 0.001
TLC (cells per mm ³), median (IQR)		50 (20–575)	8 (5–28)	< 0.001
Neutrophil count (cells per mm ³), median (IQR)		24 (10–259)	3 (0–5)	< 0.001
Protein (mg dl ⁻¹), median (IQR)		121 (100–140)	77 (58–98)	< 0.001
Sugar (mg dl ⁻¹), median (IQR)		23 (20.5–34)	66 (57–88)	< 0.001
CSF: serum sugar ratio, median (IQR)		0.25 (0.19–0.31)	0.69 (0.59–0.81)	< 0.001

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; PCT, procalcitonin; TLC, total leukocyte count.

Table 3. Diagnostic value of the various parameters studied

	PCT (ng ml ⁻¹)	TLC per mm ³	Neutrophil per mm ³	Protein (mg dl ⁻¹)	Sugar (mg dl ⁻¹)	CSF:serum ratio
AUC	0.926	0.965	0.961	0.874	0.946	0.920
95% CI	0.887–0.964	0.956–0.974	0.94–0.983	0.825–0.923	0.914–0.978	0.955–0.992
Optimal cut-off	0.33	5	5	102	45	0.4
Sensitivity	0.92	0.987	0.933	0.72	968	0.903
Specificity	0.871	0.871	0.914	0.87	0.853	0.920
PPV	0.852	0.86	0.897	0.82	0.891	0.933
NPV	0.931	0.988	0.944	0.794	0.955	0.885
+LR, -LR	7.13, 0.092	7.65, 0.015	10.85, 0.073	5.59, 0.321	6.59, 0.038	11.29, 0.105
Accuracy	0.893	0.923	0.923	0.804	0.917	0.911

Abbreviations: AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; LR, likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; TLC, total leukocyte count.

Age since conception				
	<40 weeks (11 infants, n=15)		40–43 weeks (30 infants, n=55)	
CSF parameter	Mean ± SD	Range	Mean ± SD	Range
White blood cells ($\times 10^6/l$)	7±5	2–20	6±5	0–20
Polymorpho-nuclear ($\times 10^6/l$)	3±2	1–6	3±3	0–12
Mononuclear ($\times 10^6/l$)	4±5	0–18	4±3	0–10
Red blood cells ($\times 10^6/l$)	695±395	3–3600	1788±700	0–3432
Glucose (mmol/l)	3±0.4	2.3–3.7	3.3±0.8	2.5–7.1
Protein (mg/l)	1160±306	634–1729	816±235	449–1652
Albumin (mg/l)	837±202	561–1120	530±192	254–1233

PMR – indeks albumin

Indeks albumin (Q Alb): Alb w PMR/Alb w sur.

- Q Alb < 20 → norma lub zakażenie wirusowe
- Q Alb > 20 → zakażenie bakteryjne

PMR - cytokiny

- Wiek ok. 6 m-cy, ZOMR- n=8, kontrola- n=30
 - IL 23 \geq 8 pg/ml \rightarrow AUC 0,9698
 - Korelacja (+) z cytozą i stężeniem białka w PMR

Srinivasan L et al. PlosOne, 2018; 2

- Model zwierzęcy (świnie), ZOMR *Streptococcus pneumoniae*
 - IL6, IL8, IL17: \uparrow we krwi i PMR do 3 dni $\rightarrow \downarrow$ poniżej stężeń w grupie kontrolnej

Sun Y et al. Inflammation, 2018; 41

PMR, cytokiny, niedotlenienie

Cytokine	Patients		Control		<i>pa</i>
	Number of samples	Value (pg/mL)	Number of samples	Value (pg/mL)	
IL-1β					
CSF	11	0.00 (0.00-0.00)	3b	0.05 (0.00-0.94)	0.1703
serum	7	0.5 (0.03-2.05)	8	0.05 (0.00-0.29)	0.0721
IL-6					
CSF	25	7.10 (3.38-21.54)	11	7.00 (2.46-10.69)	0.3963
serum	27	25.99 (10.72-108.81)	11	15.09 (3.42-15.81)	0.0408
IL-18					
CSF	12	0.00 (0.00-0.00)	7	0.00 (0.00-0.00)	0.7732
serum	12	111.13 (1.35-574.44)	5	10.07 (4.16-114.31)	0.4421
TNF-α					
CSF	15	18.62 (15.56-20.43)	3b	16.20 (16.05-18.32)	0.4975
serum	16	21.67 (18.72-38.51)	5	16.05 (15.05-17.90)	0.0219

Table 1. Baseline characteristics in 232 term neonates with bacterial meningitis by prognosis (poor or good outcome*) and predictor for the poor outcome.

	Good outcome* (n = 167)	Poor outcome* (n = 65)	P value	Multivariate logistic regression analysis	
				OR (95% CI)	P value
Sex, male(n)	59(35.3%)	29(44.6%)	0.19		
Birth weight <2500g(n)	7(4.2%)	3(4.6%)	1.00		
Delivery mode, C-Section (n)	59(35.3%)	33(50.8%)	0.03	1.84 (0.67–5.08)	0.24
Age at onset(days)	29 (12.5%) ZOMR wczesny	13.5(7.8)	11.7(7.3)	0.10	
Hospital stay(days)	28.0(12.4)	30.3(18.2)	0.07		
Clinical symptoms and signs					
Fever(n)	139(83.2%)	56(86.2%)	0.59		
Apnea (n)	4(2.4%)	12(18.5%)	<0.001	3.12(0.33–29.72)	0.32
Drowsiness(n)	40(24.0%)	39(60.0%)	<0.001	1.35(0.46–4.00)	0.58
Poor feeding(n)	40(24.0%)	47(72.3%)	<0.001	3.83(1.22–12.05)	0.02
Vomiting(n)	7(4.2%)	7(10.8%)	0.07		
Jaundice(n)	73(43.7%)	18(27.7%)	0.03	0.40(0.13–1.23)	0.11
Seizures (n)	24(14.4%)	13(20.0%)	0.29		
Bulging fontanelle(n)	5(3%)	8(12.3%)	0.01	1.81(0.26–12.65)	0.55
Irritability(n)	10(6%)	18(27.7%)	<0.001	1.22(0.31–4.77)	0.78
Hepatosplenomegaly(n)	8(4.8%)	4(6.2%)	0.74		
Sepsis(n)	74(44.3%)	21(32.3%)	0.10		
Pneumonia(n)	61(36.5%)	41(63.1%)	<0.001	3.37(1.15–9.84)	0.03
Impetigo neonatorum(n)	2(1.2%)	3(4.6%)	0.14		
Diarrhea(n)	28(16.8%)	2(3.1%)	0.005	0.31(0.04–2.45)	0.27
Blood parameters					
White blood cell($\times 10^9/L$)	16.7(6.5)	15.3(6.5)	0.15		
Hemoglobin(g/L)	142.0(29.5)	125.3(29.2)	<0.001	0.62(0.37–1.04)	0.07
Platelet($\times 10^9/L$)	298.3(113.2)	274.9(159.0)	0.28		
Thrombocytocrit (%)	0.47(0.19)	0.55(0.49)	0.11		
Mean platelet volume(fl)	10.5(1.3)	11.5(1.5)	<0.001	1.62(0.92–2.84)	0.10
Platelet distribution width(%)	12.5(2.1)	13.4(2.2)	0.004	1.08(0.63–1.86)	0.77
C-reaction protein >8mg/L (n)	111(66.5)	56(83.6)	<0.001	1.45(0.53–3.95)	0.47
CSF parameters					
Procalcitonin $\geq 0.05\mu\text{g/L}$ (n)	117(70.1%)	62(95.4%)	<0.001	2.37(0.64–8.78)	0.20
WBCs ($\times 10^6/\text{L}$)					
Mean \pm SD	212.8(351.2)	886.0(2700.4)	0.15		
<100	96(57.5%)	31(47.7%)	0.39		
100–1000	60(35.9%)	28(43.1%)			
>1000	11(6.6%)	6(9.2%)			
CSF polykaryocyte (%)	55.6(20.5)	52.2(20.0)	0.09		
CSF glucose(mmol/L)	2.3(1.1)	1.9(1.5)	<0.001	0.90(0.61–1.33)	0.58
CSF protein(mg/L)	1387.0(781.6)	2549.2(1019.7)	<0.001	4.07(2.33–7.11)	<0.001

Data are n (%) or mean (SD)

CSF = cerebrospinal fluid; WBC = white blood cell.

*The prognosis outcome was defined by clinical status on hospital discharge or at a postnatal age about 2.5 to 3 months. Using Glasgow Outcome Scale (GOS): 1 death, 2 persistent vegetative state, 3 severe disability, 4 moderate disability, 5 good recovery; GOS = 1–4: poor outcome, GOS = 5: good outcome.

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Prediction of unfavorable outcome (GOS < 5)

	bacterial meningitis		viral meningo-encephalitis		leptomeningeal metastases	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
<u>WBC</u>	0.999 (0.999-1.000)	<u>0.061</u>	0.998 (0.992-1.003)	<u>0.551</u>	0.998 (0.996-1.000)	0.147
GluR	0.664 (0.193-2.282)	0.516	0.166 (0.003-8.677)	0.374	0.023 (0.000-21.15)	0.280
protein	0.999 (0.998-1.000)	0.560	1.006 (0.989-1.023)	0.460	1.000 (0.998-1.002)	0.841
Qalb	1.002 (0.991-1.013)	0.674	1.067 (0.988-1.152)	0.095	1.002 (0.986-1.019)	0.761
IgM-index	0.927 (0.178-4.818)	0.929	14.71 (1.020-212.0)	0.048	0.800 (0.028-22.20)	0.896
IgA-index	1.902 (0.190-19.02)	0.584	655.4 (2.56-167554)	0.022	0.751 (0.015-37.38)	0.886
IgG-index	111.1 (1.876-6587)	0.024	539.8 (3.605-80821)	0.014	1.371 (0.097-19.20)	0.815
Multivariate Model						
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
age	1.004 (0.974-1.034)	0.801	1.015 (0.965-1.069)	0.565	0.970 (0.882-1.067)	0.529
Qalb	0.995 (0.981-1.009)	0.547	1.084 (0.993-1.184)	0.071	1.000 (0.984-1.017)	0.680
IgG-index	182.1 (1.6-20143)	0.030	767.6 (3.5-167197)	0.016	1.3 (0.114-15.806)	0.816

PMR, IgG

- 480 PMR, dorośli:

90 – bakteryjne ZOMR, 117 – wirusowe ZOMR,

36 – przerzuty nowotworowe do opony miękkiej

- **IgG-index (IgG PMR/sur.) ≥ 0.75** – niezależny marker wskazujący na niepomyśle następstwa ZOMR – GOS <5 (w oparciu o skalę Glasgow)

Lackner *et al.* *BMC Infectious Diseases* 2010, **10**:202