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Performance of biomarkers in the diagnosis of neonatal bacterial infection at the Centre Hospitalier Universitaire de Brazzaville

[1]Jeanne Gambomi Kibah, [1 ,2] Koumou Fylla Onanga, [2] Arnaud Franck K. Moukobolo1, [2] Rod Christopod Ibara1, [1,3] Nanikaly Moyen, [1, 4] Etienne Mokondjimobé, [1, 5]Gaston Bowassa Ekouya

Contact details of the authors:
1Faculté des Sciences de la Santé, Université Marien Ngouabi, Brazzaville, Congo.
2 Biochemistry Laboratory, Centre Hospitalier Universitaire, Brazzaville, Congo
3 Service Bactériologie- Immunologie-Virologie CHU, Brazzaville, Congo
4Lomo University of research, Kinshasa, DRC
5Neonatology Department, University Hospital Centre, Brazzaville, Congo

Jeanne Gambomi Kibah
Email. jkgambomi@gmail.com

Koumou Fylla Onanga
Email. Mrs fylla@gmail.com

Arnaud Franck K. Moukobolo
Email. mfranckarnaud1@gmail.com

Rod Christopod Ibara
Email. rodobande@gmail.com
Nanikaly Moyen
Email. Mimimoyen@yahoo.fr
Gaston Bowassa Ekouya
Email. ekouyaBG@gmail.com

Etienne Mokondjimobé
Email. Mbot@yahoo.fr
Corresponding author : ***Jeanne Gambomi Kibah*** *: jkgambomi@gmail.com*

ABSTRACT
Context.
Methods.
Results.
Conclusion.
Key words:

Abstract

Introduction: *Neonatal bacterial infection (NBI) is a public health problem. The high mortality associated with this disease and the difficulties of diagnosis increase the need to study biomarkers to enable rapid management of infected neonates. The aim of this study was to evaluate the performance of procalcitonin, interleukin-6 and C-reactive protein in the diagnosis of neonatal bacterial infection at Brazzaville University Hospital.*

Patients, Materials and Methods: This was a cross-sectional analytical study conducted in the Neonatology, Bacteriology and Biochemistry departments of the Brazzaville University Hospital Centre between April and September 2023. The study population consisted of 118 neonates aged 0 to 28 days with suspected neonatal infection. We carried out a triple survey: epidemiological (age, sex, weight), clinical (clinical signs of infection) and biological (C-reactive protein, procalcitonin, interleukin-6, blood count and blood culture). To assess the biomarkers, we calculated performance indicators. The significance threshold was 0.05.

Results: *Of the 118 neonates included, the diagnosis of neonatal bacterial infection was confirmed in 79 (66.9%). The infection was early in 47 cases (59.5%). The most common germs were gram-negative bacilli*

(83.5%), with Klebsiella (31.6%) topping the list. Of the infected newborns, 58 (73.4%) had a low birth weight and 47 (59.5%) were male. Respiratory distress was the most common clinical sign 65 (82.3%). C-reactive protein, procalcitonin, interleukin-6 and blood cultures were positive in 70.1%, 46.6%, 78.0% and 66.94% of cases respectively. The performance criteria studied are evolving in the opposite direction. The sensitivities of C-reactive protein, procalcitonin and interleukin-6 were 74.4%, 65.8% and 77.2% respectively, while the specificities of these biomarkers were 39.5%, 92.3% and 20.5% respectively. Only procalcitonin was associated with neonatal bacterial infection (p = 0.001) after logistic regression.

Conclusion: *Procalcitonin was the only biomarker with high specificity and positive and negative predictive values. Procalcitonin can therefore be used alone to diagnose neonatal bacterial infections.*

Key words*: Biomarkers, diagnosis, neonatal bacterial infection*

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I. Introduction

Biomarkers are molecules that make it possible to verify the risk of the appearance of a disease, the presence of a disease, the evolution of a disease or the effects of a treatment (Jeanne Garric, 2010). Neonatal infection (NNI) is a clinical syndrome of bacteremia characterized by clinical signs and symptoms occurring in a newborn between 0 and 28 days of age. NINs are divided into two categories: early infections diagnosed between D0 and D3 and late neonatal infections that occur between D4 and D28 [Glusko 2017]. Neonatal infection contributes substantially to neonatal morbidity and mortality and is a major public health challenge worldwide. According to the World Health Organization (WHO), every year more than 2.6 million newborns die within 28 days of birth. Infections are considered the leading cause of neonatal death (35%), followed by deaths resulting from premature delivery (28%), complications related to childbirth (24%) and asphyxia (23%) [WHO 2020]. The developing world pays the heaviest price, particularly in sub-Saharan Africa and South-East Asia [Zelalem 2020]. In the Democratic Republic of Congo, the incidence of neonatal infection

was 31.4% [Nyenga 2021]. A study in Cameroon found that 54.9% of deaths were related to neonatal infection [Danielle Christiane 2015]. In Burkina Faso, the authors identified 23.5% of neonatal infections [Kisito Nagalo 2022]. In Congo-Brazzaville, Ekouya et al found an early diagnosis of bacterial NCI in 22.3% [Ekouya 2013]. This raises the problem of appropriate management of these infections. Until now, the diagnostic standard for neonatal sepsis has been blood culture (Mohammad Yousef, 2017). Unfortunately, however, the sensitivity of blood culture can be affected by exposure to antibiotics prior to delivery or by handling and the excessive length of time taken for analyses (24 h to 7 days). Accurate diagnosis is essential if probabilistic antibiotic therapy is not to be introduced. Several compounds have recently been evaluated for the treatment of certain pathologies in newborns. Among the molecules studied, procalcitonin (PCT) and interleukin-6 (IL6) were considered promising (Mohammad Yousef, 2017). Hence this work, which aims to evaluate the performance of procalcitonin, interleukin-6 and C-reactive protein in the diagnosis of neonatal bacterial infection in newborns at Brazzaville University Hospital.

II. Methodology

This was an analytical cross-sectional study with prospective data collection from April to September 2023. Newborns with suspected bacterial infection were included. Not all neonates on treatment were included in the study. Selection was exhaustive and consecutive. A total of 118 neonates meeting the above criteria were included in the study. We carried out a triple survey: epidemiological (age, sex, weight), clinical (clinical signs of infection) and biological (C-reactive protein, procalcitonin, interleukin-6, blood count and blood culture).

Blood cultures were taken before antibiotics were administered. Blood culture results were used to stratify neonates into two groups: blood culture positive (early and late infection) and blood culture negative (no infection). Both groups were sampled for biological markers.

Blood samples were collected in appropriate tubes (dry tubes for procalcitonin and C-reactive protein; EDTA tube for blood count and interleukin-6). After the CBC was performed, the dry tube and EDTA tube were centrifuged at 3,000 rpm for minutes to obtain serum and plasma respectively.

The samples were aliquoted and stored at -80°C. Procalcitonin levels were measured using a VIDAS® (BioMérieux, France) enzyme-linked fluorescent assay (ELFA). Interleukin-6 levels were measured using a COBAS® E411 (Roche Diagnostics, Germany) by the electro-chimiluminescence (ECLIA) method. CRP was measured immunoturbidimetrically using a KENZA 240 TX (Biolabo, France). Blood counts were determined using a Mindray automatic haematology analyser (Mindray, China).

Statistical analysis was performed using SPSS version 25.0 software. The Student's t test was used for associations between qualitative and quantitative variables. The Fischer Chi-square test was used for two

qualitative variables. To assess biomarkers, we calculated performance indicators: specificity, sensitivity, positive predictive value and negative predictive value. The significance threshold was set at $p<0.05$.

III. Results

Of the 118 neonates included, the diagnosis of neonatal infection was confirmed in 79 (66.94%). The infection was considered to be early in 47 cases (59.50%) and late in 32 newborns (40.50%) (table 1). Low birth weight (89 (75.4%)) and respiratory distress (98 (83.1%)) were the most common socio-demographic and clinical signs (table 2 and table 3). Newborn biomarkers are shown in Table 4. The p value is significant for procalcitonin (p= 0.001) and CRP (p= 0.02) table 5. Logistic regression only procalcitonin is related to neonatal bacterial infection (p= 0,0001) table 6. The performance indicators for our biomarkers are shown in table 7. This study showed that the sensitivities of procalcitonin C-reactive protein and interleukin-6 were 74.4% and 65.8%, 77.2% respectively, and that the specificities of these biomarkers were 39.5% and 92.3%, 20.5% respectively.

Table 1: Distribution of germs isolated according to neonatal period (N = 79).

Gram	Germs	Early IUI (< 4)	Late IUI (≥ 4)	Total
Gram bacilli -	Acinetobacter	2 (4.3%)	0 (00%)	2 (2.5%)
	Citrobacter	2 (4.3%)	1 (3.1%)	3 (3.8%)
	E.coli	3 (6.4%)	4 (12.5%)	7 (8.9%)
	Enterobacter	5 (10.6%)	6 (18.8%)	11 (13.8%)
	Klebsiella	17 (36.2%)	8 (25.0%)	25 (31.6%)
	Pantoea	2 (4.3%)	5 (15.6%)	7 (8.9%)
	Pseudomonas	1 (2.1%)	0 (00%)	1 (1.3%)
	Raoultella	4 (8.5%)	3 (9.4%)	7 (8.9%)
	Seratia	3 (6.4%)	0 (00%)	3 (3.8%)
Total		**39 (49.4%)**	**27 (34.2%)**	**66 (83.5%)**
Gram + cocci	Staphylococcus aureus	2 (4.3%)	2 (6.3%)	4 (5.1%)
	Staphylococcus epidermidis	6 (12.8%)	3 (9.4%)	9 (11.4%)
Total		**8 (10.2%)**	**5 (6.3%)**	**13 (16.5%)**
Total germs		**47 (59.5%)**	**32 (40.5%)**	**79 (100%)**

Table 2: Socio-demographic characteristics of newborns (N=79)

Variables	Bacterial infection	
	n	%
Age range (days)		
<4	47	**59,5**
≥4	32	40,5
Sex		
Female	32	40.5
Male	47	**59.5**
Weight (g)		
<2500	58	**73,4**
≥2500	21	26,6

Grammes : g
Sex ratio: 1.36
Median age of newborns: 2 (1 ; 5) days vs 3 (2 ; 4) Days
Median weight of newborns: 2015 (1520 ; 2400) g vs 1800 (1500 ; 2520) g

Tableau 3 : Caractéristiques cliniques des nouveau-nés (N=79)

Variables	Infection bactérienne	
	n	%
Détresse respiratoire		
Oui	33	**84,6**
Non	6	15,4
Succion		
Moins vigoureuse	27	**69,2**
Vigoureuse	12	30,8
Activité spontanée		
Diminuée	23	**59**
Rigoureux	16	41
Réanimation		
Oui	15	38,5
Non	24	61,5
Fièvre		
Oui	6	15,4
Non	33	84,6
Ictère		
Oui	15	38,5
Non	24	61,5
Distension abdominale		
Oui	2	5,1
Non	37	94,9
Diarrhée vomissements		
Oui	0	0
Non	39	100
Conjonctivite purulente		
Oui	1	2,6
Non	38	97,4

Table 4. Biomarkers of neonatal infection (N=118)

	NIN		Early infection		Late infection		
	n	%	n	%	n	%	P value
Protein-C reactive							**0.02**
Normal	36	29.9	28	37.8	8	18.1	
High	82	70.1	46	62.1	36	81.1	
Procalcitonin							**0.0001**
Normal	63	53.4	22	29.7	41	93.1	
High	55	46,6	52	70,2	3	6,8	
Interleukin-6							**0,89**
Normal	26	22,0	16	21,6	10	22.7	
High	92	78.0	92	78,0	34	77.3	
Haemoglobin							**0.18**
Normal	55	46.6	38	51.4	17	38.6	
Low	63	53.4	36	48.6	27	61.4	
White blood cells							**0.54**
Normal	66	55.9	43	58.1	23	52.3	
Low	52	44.1	31	41.9	21	47.7	
Platelets							**0.10**
Normal	49	41.5	35	47.3	14	31.8	
Low	69	58.5	39	52.7	30	68.2	

NIN=neonatal infection

Table 5. Bivariate analysis in neonatal infection (N=118)

Biomarkers	**Bacterial infection**					
	Yes		**No**		**OR [IC95%]**	**P-value**
	n	**%**	**n**	**%**		
Protein-C reactive						**0.08**
High	59	74.7	23	58.9	2.05 [0.90-4.64]	
Normal	20	25.3	16	41.0	1*	
Procalcitonin						**0.0001**
High	52	65.8	3	7.7	23.1 [6.51-81.6]	
Normal	**27**	34.2	36	92.3	**1***	

Interleukin-6						**6 0.78**
High	61	77.2	31	79.5	0.87 [0.34-2.23]	
Normal	18	22.8	8	20.5	**1***	
Haemoglobin						**0.47**
Low	44	55.7	19	48.7	0.75 [0.34-1.63]	
Normal	35	44.3	20	51.3	**1***	
White blood cells						**0.47**
Low	33	41.8	19	48.7	0.75 [0.34-1.63]	
Normal	46	58.2	20	51.3	1*	
Platelets						**0.75**
Low	47	59.5	22	56.4	1.13 [0.52-2.46]	
Normal	32	40.5	17	43.6	**1***	

Table 6. Multivariate analysis of neonatal infection (N= 118)

Biomarkers	ORa	[95% CI]	P-value
Prorein-C reactive	1.246	[0.40 - 3.80]	0.699
Procalcitonin	55,819	[10,9 - 284,0]	**0,0001**
Interleukin-6	0,376	[0,12 -1,21]	0.101
Haemoglobin	2,142	[0,76 - 6,04]	0,15
White blood cells	0,828	[0,30 -2,29]	0,716
Platelets	0,428	[0,14 - 1,29]	0,131

Table 7. Se, Sp, PPV, NPV of biomarkers in neonatal infection (N=118)

	Infection		**Not Infection**		**Indicators**			
	n	**%**	**n**	**%**	**Se**	**Sp**	**VPP**	**VPN**
Protein-Creactive					74,7**%**	39.5**%**	72,0%	42,9%
Normal	20	25,3%	16	41,0%				
High	59	74,7%	23	58,9%%				
Procalcitonin					65,8%	**92,3**	**94,5**	**57,1%**
Normal	27	34,2%	36	2,3%				
High	52	65,8%	3	7,7%				
Interleukin-6					**77,2%**	20,5%	66,3%	30,8%
Normal	18	22,8%	8	20,5%				
High	61	77,2%	31	79,5%				
Haemoglobin					55,7%	51,3%	69,8%	36,4%
Normal	35	44,3%	20	51,3%				
High	44	55,7%	19	48,7%				
White blood cells					41,8%	51,3%	63,5%	30,3%
Normal	46	58,2%	20	51,3%				
Low	33	41,8%	19	48,7%				
Platelets					59,5%	43,6%	68,1%	34,7%
Normal	32	40,5%	17	43,6%				
Low	47	59,5%	22	56,4%				

Se: sensitivity; Sp: specificity; NPV: negative predictive value; PPV: positive predictive value

IV. Discussion

As the study was prospective, most of the data were well documented.

Germs causing neonatal infection

Neonatal bacterial infection remains the most frequent reason for hospitalisation 79 (66.94%). These results corroborate those of Kemeze et al in Cameroon (96.8%) (Sandrine Kemeze; 2016). This high hospital frequency can be explained by the fact that Brazzaville University Hospital receives patients from all the health facilities in the city and the surrounding area. Most of these newborns are evacuated by unsuitable means of transport, and are therefore susceptible to infection during transport.

Early neonatal infection was the most common (59.5%). Several studies have reported high rates of early neonatal infection (Danielle Christiane et al. 2015; Andreas Chiabi et al. 2011). This most often reflects vertical transmission from mother to child before or during delivery (Oliver Walker et al, 2019). In contrast, Vergano et al in Nigeria found a predominance of NIN in the late neonatal period (Vergnano S et al; 2005).

In our study, the bacteriological profile was dominated by Klebsiella (31.6%). Chiabi et al in Cameroon and Jaballah et al in Tunisia found 28.6% and 22.7% respectively (Jaballah et al 2006 ; Andreas Chiabi et al; 2011). However, Eyesus et al in Ethiopia found a predominance of Staphylococcus aureus (40.8%) (Eyesus et al; 2017).

Socio-demographic characteristics of newborns

Male newborns were the most infected in 59.5% of cases, i.e. a sex ratio of 1.36. Our results are comparable to those found by Kemeze C et al in Cameroon who found 62% with a sex ratio of 1.63 (Shah GS 2006). Several studies report that males were more exposed to neonatal infection. However, Mulongo et al in the Democratic Republic of Congo found a predominance of females (52.9%) with a sex ratio of 0.89 (Mulongo M; 2015).

Eighty-nine (75.4%) were born with low birth weight (< 2500 grams). Manta et al in India and Nyenga et al in the Democratic Republic of Congo found (52.5%) (60%) (Jajoo et al, 2015; Nyenga A; 2021). Low birth weight can be linked to either intrauterine growth retardation or prematurity. In fact, on the one hand, newborns with intra-uterine growth retardation and those born prematurely present a risk of developing a bacterial infection due to a deficit in immune defences. On the other hand, weight failure and prematurity may be the consequence of infectious aggression of the foetus (Roberto R. et al, 2007). In contrast, Minko et al 2018 obtained 51% normal weights.

Clinical characteristics of newborns

The clinical expression of neonatal infection in newborns is highly variable and non-specific. Several clinical presentations were reported in our series, with the most common symptoms being respiratory distress (74.6%), less vigorous sucking (66.9%) and decreased spontaneous activity (61.0%). As in our series, Minko et al 2018 in Gabon reported respiratory distress in 22% of cases. In contrast, Nyenga et al in the Democratic Republic of Congo (Nyenga A; 2021). Glusko-charl et al in France (Glusko-Charleta, et al; 2017) found respectively (41.36%); (42.4%) fever as the most frequent symptom and Chemsi et al in Morocco (Chemsi M; 2015) noted neurological disorders in 49.5% of cases. The clinical polymorphism of neonatal infection is described in the literature (Andi L; 2027). This makes clinical diagnosis imprecise and would explain the sometimes abusive indications of antimicrobials in neonatal patients, particularly in regions where paraclinical support is either absent or not accessible.

Biomarkers

We found that only procalcitonin was associated with neonatal bacterial infection ($p = 0.001$). Our results corroborate those of Adouani et al ($p = 0.026$), which proves that procalcitonin has a very good diagnostic value for distinguishing bacterial infection from other infections (viral, parasitic and mycotic) (Adouani et al 2021).

In our study, procalcitonin was the only biomarker with higher specificity (92.3%), positive predictive value (95.5%) and negative predictive value (57.1%) than the other proteins of the acute phase of inflammation. However, interleukin-6 had a slightly higher sensitivity (77.2%) than procalcitonin (65.8%). Our results are comparable to those of Ahmed, Rashwan et al in Egypt (Ahmed Ali; 2019; Adouani et al 2021). However, Gueye et al in Senegal and Adouani et al Algeria reported that procalcitonin was more sensitive but less specific than interleukin-6 (Gueye C et al; 2021, Adouani et al 2021).

V. Conclusion

Neonatal infection remains a major problem in daily clinical practice. Its clinical and sociodemographic presentation is dominated respectively by respiratory distress and low birth weight. The bacterial ecology is dominated by Gram-negative bacilli, in this case Klebsiella. In our study, procalcitonin is the only biomarker associated with neonatal infection and has a higher specificity and positive and negative predictive value than the other proteins of the acute phase of inflammation. Procalcitonin can therefore be used alone to diagnose neonatal bacterial infections.

Conflicts of interest

No actual or potential conflicts of interest

Authors' contributions

All authors undertook the data collection, statistical analysis and drafting of the manuscript. All have read and approved the final version.

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