Definitions of SIRS and sepsis in correlation with early and late onset neonatal sepsis

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Abstract

Objective. To examine the applicability of the 2002 International Pediatric Sepsis Consensus Conference definitions of the systemic inflammatory response syndrome (SIRS) and sepsis to term and preterm newborns in the diagnosis of early (EOS) and late onset sepsis (LOS).

Methods. Retrospective cohort study including 1) all newborns with hospitalization within the first 72 hours of life and 2) infants with episodes of suspected LOS at a tertiary care neonatal intensive care unit between 2004 and 2008, and correlating the definitions of SIRS and sepsis with culture proven and clinical EOS and LOS.

Results. Association with EOS: Among term newborns SIRS and sepsis definitions applied to 62 and 39/245 newborns (25% and 16%, respectively) and to 5/13 cases of culture proven EOS (38%) and 34/66 cases of clinical EOS (52%), respectively. Among preterm newborns SIRS and sepsis definitions applied to 202 and 124/505 newborns (40% and 25%, respectively) and to 17/24 cases of culture proven EOS (71%) and 107/160 cases of clinical EOS (67%), respectively. Sensitivity of SIRS and sepsis definitions was higher in preterm compared to term newborns in case of culture proven and clinical EOS ($p=.047$ and $p=0.03$, respectively).

Association with LOS: SIRS and sepsis definitions applied to 5/5 episodes of culture proven LOS (100%) and to 4/9 episodes of clinical LOS (44%) in newborns who were term at onset of sepsis (corrected gestational age) and to 14/19 episodes of culture proven LOS (74%) and 24/28 episodes of clinical LOS (86%) in preterm newborns.

Conclusion. The definitions of SIRS and sepsis correlated well with LOS but poorly with EOS, where nearly two thirds of term and one quarter of preterm newborns would have been missed. Postnatal age rather than gestational age had a positive influence on the correlation.

Keywords: Systemic inflammatory response syndrome, bacterial infections, preterm and term newborns, neonatal sepsis

Introduction

Diagnosis of bacterial sepsis remains a difficult task for neonatologists, since clinical signs are often non-specific and may be indistinguishable from those occurring in non-infectious conditions [1]. Blood cultures as the gold standard in bacterial bloodstream infection diagnosis are of limited sensitivity [2] and even agreement of specialists in hindsight adjudication of episodes of suspected infection is of questionable reliability [3].

These diagnostic difficulties in finding appropriate and reliable sepsis criteria for the classification of newborns remains in all clinical trials. A recent review of criteria used for the classification of neonatal sepsis found a high disparity with exact specification in only a quarter of studies [4]. This inconsistency makes comparisons difficult and meta-analysis questionable.

In 2002 the International Pediatric Sepsis Consensus Conference was held with the aim to create clear definitions for the systemic inflammatory response syndrome (SIRS) and different stages of sepsis for children adaptable to different age groups, ranging from term neonates to adolescents. The definitions should help researchers by creating standardized entry criteria for clinical trials and, thus, making studies comparable [5] following the

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successful and quickly applied definitions for adults from the American College of Chest Physicians/Society of Critical Care Medicine published in 1992 [6,7]. However, to our knowledge, there exist no studies addressing their applicability in newborns.

The aim of this study was therefore to examine the applicability of the 2002 International Pediatric Sepsis Consensus Conference definitions of “SIRS” and “sepsis” for term and preterm newborns in the diagnosis of early onset sepsis (EOS) and of late onset sepsis (LOS).

Materials and methods

Study design

This is a retrospective study based on chart and database review taking place at the neonatal intensive care unit of the Pediatric Department of the Medical University of Graz, a tertiary care center with a catchment area of about 8000 births per year. Data were collected from 2004 to 2008 by analyzing medical reports, case histories and the electronic patient filing system (“MEDOCS”), which includes perinatal data and detailed results of all clinical examinations done during hospitalization. Examinations were done every two to four hours; heart, respiratory rate, and peripheral oxygen saturation were recorded continuously. Regarding data quality all clinical, perinatal and laboratory data were cross-checked.

Inclusion criteria were either hospitalization within the first 24 hours of life or one or more episodes of suspected LOS with documentation of laboratory and clinical data in order to classify newborns regarding EOS and LOS criteria and the criteria of SIRS and sepsis according to the pediatric consensus conference [5]. Regarding LOS only newborns with continuous hospitalization from birth to onset of LOS were included. Exclusion criteria were missing or incomplete data necessary for the definitions of SIRS, sepsis, EOS, and LOS.

Unit policies regarding sepsis work-up algorithms and antibiotic treatment remained unchanged during the study period.

Definitions of EOS and LOS

EOS and LOS were divided in culture proven and clinical. Culture proven EOS and LOS were defined as positive culture from blood, cerebrospinal fluid, or

tracheal aspirate in clinically suspected sepsis within and following the first 72 hours of life, respectively. Blood cultures were drawn from every patient with suspected infection from a peripheral vein or, if available, from a central venous catheter at the time of catheter insertion before starting antibiotic treatment. Liquor cultures were obtained from every patient with suspected meningitis. Cultures of tracheal aspirates were obtained from every intubated patient with suspected sepsis. Cultures positive for coagulase negative staphylococci and cultures from tracheal aspirates were regarded as true sepsis only with one or more abnormal laboratory markers (white blood cell count and absolute neutrophil count with age-adapted cut-off values [8], C-reactive protein >8 mg/L, immature to total neutrophil ratio >0.2). Other bacteria recovered in cultures were considered to be pathogenic unless they were normal skin or upper respiratory flora. Clinical EOS was defined as presence of three or more out of five clinical signs of sepsis (a) respiratory symptoms (apnea, tachypnea, retractions, cyanosis, respiratory distress); b) cardiocirculatory symptoms (tachy- or bradycardia, arterial hypotonia); c) neurological symptoms (lethargy, irritability, seizures); d) hypo- or hyperthermia (core temperature >38.5 °C or <36.0 °C); e) poor skin color or prolonged capillary refilling time >2 seconds) with either maternal risk factors (preterm rupture of membranes (>18 hours in term newborns), chorioamnionitis, and fever during labour) or a positive laboratory sepsis screen with two or more out of four laboratory parameters positive (see above) [9–11]. Regarding EOS a control group was formed by all remaining sepsis negative newborns hospitalized within the first 24 hours of life during the study period. Regarding LOS no control group was formed.

Definitions of SIRS and sepsis

SIRS and sepsis were defined according to the actual definitions published by Goldstein et al. [5] determined at the 2002 International Pediatric Sepsis Consensus Conference. SIRS was diagnosed when at least two of the following four criteria were positive (a or b obligatory): a) core temperature >38.5 °C or <36.0 °C; b) white blood cell count elevated or decreased (8), or >10% immature neutrophils; c) tachycardia >180/min or bradycardia <100/min over a >0.5 hour period without external stimulus or drug therapy; d) tachypnea >60/min or mechanical ventilation for an acute process. Sepsis was defined as SIRS in the presence of or as a result of proven or suspected infection.

Patients fulfilling criteria for SIRS and sepsis were considered being positive in both categories.

Statistical analysis

Statistical analysis was done with SPSS version 17 (SPSS Inc., 2008, Chicago, USA) and Microsoft Excel 2007 (Microsoft Corporation, 2007, Redmond, USA). Incidence rates of SIRS, sepsis, and EOS were calculated as well as sensitivity, specificity, positive and negative predictive value with 95% confidence intervals of both definitions and of the single diagnostic criteria of SIRS (see above) in predicting culture proven and clinical EOS in term and preterm newborns. Sensitivity with 95% confidence interval of the consensus definitions and of the single diagnostic criteria of SIRS (see above) in predicting culture proven and clinical LOS were calculated in different groups of corrected gestational age at onset of LOS. Proportions were compared by chi-square test; correlations for not normally distributed variables were calculated using Mann-Whitney test or Spearman's correlation coefficient. Statistical significance was set at $p < 0.05$.

Results

Correlation with EOS

Among 863 newborns hospitalized within the first 24 hours of life, 113 were excluded because of

incomplete clinical or laboratory information. Thus, the study population included 750 newborns with a median gestational age of 34 weeks and a median birth weight of 2150 grams. 245 newborns (33%) were term and 505 (67%) were preterm born. Perinatal data are presented in detail in table 1.

Blood culture proven EOS was diagnosed in 37 newborns (5%). Group B Streptococci were the most frequently isolated pathogens followed by Ureaplasma urealyticum and Escherichia coli (see table 2). 226 newborns had clinical sepsis (30%) and 487 newborns were EOS negative (65%).

Among term newborns the definitions of SIRS and sepsis were fulfilled in 62/245 and 39/245 infants (25% and 16%, respectively), five of them had culture proven EOS (38% of all 13 cases of culture proven EOS) and 34 had clinical EOS (52% of all 66 cases of clinical EOS). EOS negative newborns fulfilled SIRS definition in 23/166 (14%) cases.

Among preterm newborns the definitions of SIRS and sepsis were fulfilled in 202/505 and 124/505 infants (40% and 25%, respectively), 17 of them had culture proven EOS (71% of all 24 cases of culture proven EOS) and 107 had clinical EOS (67% of all 160 cases of clinical EOS). EOS negative newborns fulfilled SIRS definition in 78/321 (24%) cases.

Sensitivity of the definitions of SIRS and sepsis in predicting culture proven and clinical EOS were higher in preterm compared to term newborns ($p = 0.047$ and $p = 0.03$). Newborns positive for SIRS and sepsis definitions had significantly lower gestational age and lower birth weight ($p < 0.001$).

Table 1
Clinical data of study patients*

	Early onset sepsis			Late onset sepsis	
	Culture proven	Clinical	Negative	Culture proven	Clinical
Study population/Episodes	37 (100)	226 (100)	487 (100)	24 (100)	37 (100)
Birth weight in grams	2051 (674-4185)	2144 (400-4480)	2284 (500-5300)	750 (100-2970)	940 (450-4185)
Gestational age at birth/Corrected gestational age at onset of LOS in weeks	33 (23-41)	34 (23-43)	34 (23-42)	31.5 (25-64)	32 (27-59)
Gestational age <28 weeks	10 (27)	30 (13)	27 (6)	4 (17)	2 (5)
Gestational age 28-32 weeks	7 (19)	68 (30)	136 (28)	9 (38)	19 (51)
Gestational age 33-37 weeks	7 (19)	62 (27)	158 (32)	6 (25)	7 (19)
Gestational age >37 weeks	13 (35)	66 (29)	166 (34)	5 (21)	9 (24)
Sex (male:female)	19:18 (51:49)	138:88 (61:39)	246:241 (51:49)	16:8 (67:33)	27:10 (73:27)
Small for gestational age	1 (3)	15 (7)	52 (11)		
Positive maternal risk factors**	14 (38)	87 (38)	105 (22)		
Onset (day of life)				19.5 (6-178)	22 (5-142)

*Data are presented as median (range) or number (%).

**Premature rupture of membranes, intra-amniotic infection or fever during labor.

Table 2

Organisms isolated from infants from blood, cerebrospinal fluid and/or tracheal aspirate and correlation with the definitions of SIRS and sepsis*
(summarized due to identical results)

Early onset sepsis Pathogen	n (%)	SIRS/Sepsis
Group B Streptococci	20 (54)	12 (60)
Ureaplasma urealyticum	8 (22)	4 (50)
Escherichia coli	4 (11)	3 (75)
Enterococcus faecalis	2 (5)	1 (50)
Staphylococcus aureus	1 (3)	0 (0)
Chlamydia trachomatis	1 (3)	1 (100)
Klebsiella pneumoniae	1 (3)	1 (100)
All	37 (100)	22 (59)
Late onset sepsis Pathogen	n (%)	SIRS/Sepsis
Coagulase negative staphylococci	11 (38)	9 (82)
Enterococcus faecalis	6 (21)	4 (67)
Enterococcus faecium	2 (7)	1 (50)
Candida albicans	2 (7)	2 (100)
Klebsiella pneumoniae	2 (7)	2 (100)
Staphylococcus aureus	1 (3)	1 (100)
Ureaplasma urealyticum	1 (3)	1 (100)
Stenotrophomonas maltophilia	1 (3)	1 (100)
Citrobacter divergens	1 (3)	1 (100)
Enterobacter cloacae	1 (3)	1 (100)
Chlamydia trachomatis	1 (3)	0 (0)
All	29 (100)	23 (79)
Multiple pathogens	5 (21)	4 (80)

*Data are presented as number (n) and percentage (%).

Abbreviations: SIRS, systemic inflammatory response syndrome.

Correlation with LOS

During the study period 54 newborns had a total of 69 episodes of suspected LOS. Eight episodes were excluded because of missing clinical or laboratory data. Thus the study population included 48 newborns with 61 episodes of LOS. The median gestational age was 27 weeks and the median birth weight was 940 grams. In 14 episodes the corrected gestational age at onset was ≥ 37 weeks (23%). Further clinical data are presented in table 1.

Coagulase negative staphylococci were the most frequently isolated pathogens followed by enterococci. In 5 episodes cultures yielded growth of 2 different pathogens (see table 2).

Among newborns who were term at onset of LOS the definitions of SIRS and sepsis were fulfilled in 5/5 episodes of culture proven LOS (100%) and in 4/9 episodes of clinical LOS (44%, see table 3).

Among newborns who were preterm at onset of LOS the definitions of SIRS and sepsis were fulfilled

in 14/19 episodes of culture proven LOS (74%) and in 24/28 episodes of clinical LOS (86%, see table 3).

Sensitivity of the definitions of SIRS and sepsis in predicting clinical EOS was higher in newborns who were preterm at onset of clinical LOS ($p=0.012$).

Discussion

Clinical criteria for defining sepsis should be sensitive enough to identify most patients with the syndrome while minimally sacrificing inevitable specificity [12]. In this study, analyzing for the first time the applicability of the 2002 International Pediatric Sepsis Consensus Conference definitions of SIRS and sepsis [5] in the newborn, 79% of culture proven LOS episodes, but only 59% of culture proven EOS episodes fulfilled the criteria for the systemic inflammatory response. Unexpectedly, by utilizing the definition of sepsis nearly two thirds of term but only one quarter of preterm newborns would have been missed in the diagnosis of culture proven EOS.

Table 3

Sensitivity, specificity, positive and negative predictive value (95% confidence interval) of the definitions of SIRS and sepsis, and of the single diagnostic criteria of SIRS definition in the diagnosis of culture proven and clinical EOS (13/245 and 66/245 term and 24/505 and 160/505 preterm newborns, respectively) and culture proven and clinical LOS (5and 9 episodes in newborns term at onset and 19 and 28 episodes in newborns preterm at onset).

Culture proven EOS		SIRS	Sepsis	Fever/hypothermia	WBC elevated or depressed	Respiratory symptoms	Tachy- or bradycardia
Term or preterm at birth							
Term	Sensitivity	38 (14-68)	38 (14-68)	38 (14-68)	15 (2-45)	92 (64-100)	54 (25-81)
	Specificity	86 (80-91)	93 (88-97)	95 (91-98)	85 (77-90)	42 (34-49)	94 (89-97)
	PPV	18 (6-37)	31 (11-59)	38 (14-68)	8 (1-27)	11 (6-18)	41 (18-67)
	NPV	95 (90-98)	95 (91-98)	95 (91-98)	92 (85-96)	99 (92-100)	96 (92-99)
Preterm	Sensitivity	71 (49-87)	71 (49-87)	33 (16-55)	58 (37-78)	100 (86-100)	54 (33-74)
	Specificity	76 (71-80)	85 (81-89)	96 (93-98)	73 (67-78)	25 (20-30)	89 (85-92)
	PPV	18 (11-27)	27 (16-39)	36 (17-59)	14 (8-23)	9 (6-13)	27 (15-42)
	NPV	97 (94-99)	98 (95-99)	95 (92-97)	96 (92-98)	100 (95-100)	96 (93-98)
Clinical EOS							
Term or preterm at birth		SIRS	Sepsis	Fever/hypothermia	WBC elevated or depressed	Respiratory symptoms	Tachy- or bradycardia
Term	Sensitivity	52 (39-64)	52 (39-64)	35 (24-48)	35 (24-48)	98 (92-100)	45 (33-58)
	Specificity	86 (80-91)	93 (88-97)	95 (91-98)	85 (77-90)	42 (34-49)	94 (89-97)
	PPV	60 (46-72)	76 (60-87)	74 (55-88)	51 (36-66)	40 (33-48)	75 (59-87)
	NPV	82 (75-87)	83 (77-88)	79 (72-84)	74 (67-81)	99 (92-100)	81 (75-87)
Preterm	Sensitivity	67 (59-74)	67 (59-74)	38 (31-46)	51 (43-59)	100 (98-100)	69 (61-76)
	Specificity	76 (71-80)	85 (81-89)	96 (93-98)	73 (67-78)	25 (20-30)	89 (85-92)
	PPV	58 (50-65)	69 (62-77)	81 (71-89)	49 (41-57)	40 (35-45)	76 (68-83)
	NPV	82 (77-86)	84 (79-88)	76 (71-80)	75 (69-79)	100 (95-100)	85 (81-89)
Culture proven LOS							
Term or preterm at onset of LOS		SIRS	Sepsis	Fever/hypothermia	WBC elevated or depressed	Respiratory symptoms	Tachy- or bradycardia
Term	Sensitivity	100 (48-100)	100 (48-100)	80 (28-100)	100 (48-100)	60 (15-100)	40 (5-100)
	Specificity	74 (49-100)	74 (49-100)	58 (33-100)	50 (25-100)	100 (82-100)	53 (29-100)
Clinical LOS							
Term or preterm at onset of LOS		SIRS	Sepsis	Fever/hypothermia	WBC elevated or depressed	Respiratory symptoms	Tachy- or bradycardia
Term	Sensitivity	44 (14-79)	44 (14-79)	78 (40-97)	44 (14-79)	56 (21-86)	33 (7-70)
	Specificity	86 (67-96)	86 (67-96)	44 (25-65)	74 (54-89)	96 (82-100)	79 (59-92)

Abbreviations: SIRS, systemic inflammatory response syndrome; EOS, early onset sepsis; LOS, late onset sepsis; PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cell count.

We are aware of the fact that the definitions were created for the use in different age groups, from term newborns to adolescents, but not in preterm newborns. Nevertheless we have chosen to include them but to separate the results. In fact, studies on septic newborns frequently include infants of a broader range of gestational age – term, near-term, and/or preterm newborns. Therefore a sepsis definition which can be applied only to a part of patients is hindering and makes the planning and organization of a study more difficult. Unexpectedly, the definitions of SIRS and sepsis applied more frequently to preterm compared to term newborns in case of EOS. In fact, nearly two thirds of term but only one quarter of preterm newborns would have been missed in the diagnosis of culture proven EOS. Rather than gestational age the postnatal age seemed to improve the number of correctly classified septic infants.

In contrast to the adult definitions the pediatric consensus conference based the definition of SIRS on temperature or leukocyte abnormalities and specified that diagnosis should not simply rely on heart and respiratory rate are elevated [5]. Both are sensitive but not specific tools in diagnosis of early onset infections [13,14,15], thus explaining the low sensitivity of the definition of SIRS missing many cases of EOS. Preterm newborns seemed to be more likely to react in an overwhelming systemic reaction to a bacterial invasion compared to term infants and thus to fulfill criteria for systemic inflammatory response. The definition of sepsis is always dependent on the presence of SIRS and therefore of limited sensitivity especially in term newborns. In contrast, temperature and white blood cell count abnormalities both had a higher sensitivity in the diagnosis of LOS compared to EOS ($p=0.04$ and 0.06 , respectively) resulting in a better correlation with SIRS and sepsis definitions.

Certain limitations of the study should be noted. As a retrospective study, evidence based medicine level is definitely lower compared to prospective analyses, even though data collection was done carefully. All data were collected from one tertiary care unit, thus the results should only be extrapolated with regard to center-specific characteristics. A standard sepsis definition for newborns does not exist at the moment, so the consensus definitions were tested against the current gold standard for trials and studies, positive blood culture. However, this is known to lack sensitivity [16] and obtaining cultures from neonates can be difficult as sample volumes are small and a substantial number are contaminated or negative

[17–18]. As a result the number of culture positive newborns is limited and the true infection rate is probably underestimated. Therefore we chose to include a clinical definition of EOS in combination with defined risk factors and elevated values of inflammatory markers. However, in both groups definitions of SIRS and sepsis were of surprisingly low sensitivity in detecting bacterial infections.

In this study we have chosen to not address the correlation of EOS and LOS to the definitions of severe sepsis and septic shock. These definitions concentrate on illness severity and their correlation with culture proven infections is only secondary to presence of SIRS and thus sepsis.

While in this study the consensus definitions applied well to episodes of LOS, correlation with EOS was not sufficient. In the early postnatal period the variety of clinical signs that a septic infant may present limits the applicability of a narrow sepsis definition such as the pediatric consensus conference definition. In this period a combination of a broader range of clinical signs with risk factors and inflammatory markers including CRP may be more appropriate. In a recent analysis Modi et al [13], found that three clinical signs were the best predictor for a positive blood culture and stated that the use of clearly defined clinical criteria leads to additional opportunities for capturing the incidence of culture negative bloodstream infection or for quantifying bloodstream infections without cultures. Sepsis criteria should be elaborated similarly in observational studies, including multivariate analysis and calculations of likelihood ratios for clinical signs and risk factors [15]. A clear definition of clinical sepsis adapted for the newborn infant is of general interest [2,19], and an evidence based definition of neonatal sepsis might improve standardization of further clinical trials and thus make studies more comparable.

Conclusions

In conclusion the definitions of SIRS and sepsis correlated insufficiently with the diagnosis of culture proven and clinical EOS, especially in term newborns. In this age group they showed low sensitivity and low predictive value. In contrast the definitions applied to 77% of culture proven and clinical LOS. Postnatal rather than gestational age seemed to positively influence the correlation.

References

- [1] Kurlat I, Stoll BJ, McGowan JE. Time to positivity for detection of bacteremia in neonates. *J Clin Microbiol* 1989; 27: 1068–71.
- [2] Haque KN. Defining common infections in children and neonates. *J Hosp Infect* 2007; 65(suppl): 2110–4.
- [3] Fischer JE, Seifarth FG, Baenziger O, Fanconi S, Nadal D. Hindsight judgement on ambiguous episodes of suspected infection in critically ill children: poor consensus amongst experts? *Eur J Pediatr* 2003; 162: 840–3.
- [4] Reyna-Figueroa J, Yuri-Toala E, Ortiz-Ibarra FJ, Rodríguez-Ramírez E, Limón-Rojas AE. Disparity in the criteria for including patients with neonatal sepsis in scientific medical studies. Are we swimming in a sea without limits? *An Pediatr (Barc)* 2006; 65: 536–40 (in Spanish).
- [5] Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6: 2–8.
- [6] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864–74.
- [7] Trzeciak S, Zanotti-Cavazzoni S, Parillo JE, Dellinger RP. Inclusion criteria for clinical trials in sepsis: did the American College of Chest Physicians/Society of critical care medicine consensus conference definitions of sepsis have an impact? *Chest* 2005; 127: 242–5.
- [8] Letsky EA. Haematological values in the newborn. In: Rennie JM, Robertson NRC, editors. *Textbook of neonatology* 3rd ed. Edinburgh: Churchill Livingstone; 1999, p. 1399.
- [9] Resch B, Gusenleitner W, Müller WD. Procalcitonin and interleukin-6 in the diagnosis of early-onset sepsis of the neonate. *Acta Paediatr* 2003; 92: 243–5.
- [10] Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. *Pediatrics* 1980; 65: 1036–41.
- [11] Gerdes JS, Polin RA. Sepsis screen in neonates with evaluation of plasma fibronectin. *Pediatr Infect Dis J* 1987; 6: 443–6.
- [12] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. SCCM/ESICM/ACCP/ATS/SIS: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2003; 29: 530–8.
- [13] Modi N, Doré CJ, Saraswatula A, Richards M, Bamford KB, Coello R, et al. A case definition for national and international neonatal bloodstream infection surveillance. *Arch Dis Child Fetal Neonatal* 2009; 94: F8–12.
- [14] Ng PC. Diagnostic markers of infection in neonates. *Arch Dis Child Fetal Neonatal* 2004; 89: F229–35.
- [15] Mishra UK, Jacobs SE, Doyle LW, Garland SM. Newer approaches to the diagnosis of early onset neonatal sepsis. *Arch Dis Child Fetal Neonatal* 2006; 91: F208–12.
- [16] Volante E, Moretti S, Pisani F, Bevilacqua G. Early diagnosis of bacterial infection in the neonate. *J Matern Fetal Neonatal Med* 2004; 16(suppl): 213–6.
- [17] Paisley JW, Lauer BA. Pediatric blood cultures. *Clin Lab Med* 1994; 14: 17–30.
- [18] Escobar GJ. What have we learned from observational studies on neonatal sepsis? *Pediatr Crit Care Med* 2005; 6 (suppl): S138–45.
- [19] Arnon S, Litmanovitz I. Diagnostic tests in neonatal sepsis. *Curr Opin Infect Dis* 2008; 21: 223–7.