

Supplemental Materials for Article: A Systematic Review and Meta-Analysis of the Diagnostic Ability of CRP, ESR, WBC, and PCT in Detecting Neonatal Sepsis and Pneumonia

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Supplemental Table 1. Description of articles assessing the test characteristics of biomarkers for the diagnosis of neonatal sepsis.

Citation	Study Location	Study Design	Study Country	Patient Age Range	Study Population	Biomarker(s)	Gold Standard	Inclusion Criteria	Exclusion Criteria	QUADAS-2 Score
Abdalla EOE, et al. <i>Cogent Medicine</i> . 2017. ¹	NICU	Prospective cohort	Sudan	0-72 hours	49	CRP, PCT	Blood culture	-Full term infants with risk factors for early-onset neonatal infection including GBS infection during pregnancy, membrane rupture before onset of uterine contractions, prolonged premature rupture of membranes >18 hours, offensive odor of amniotic fluid -Infants who developed clinical features of infection within 72 hours of birth including hypothermia/hyperthermia, irritability, lethargy, apnea, and bradycardia	-Infants started on antibiotics before admission -Infants with major congenital anomalies, proven inborn errors of metabolism or hypoxic ischemic encephalopathy -Infants whose parents refused consent	Level 2
Abdollahi A, et al. <i>Mediterr J Hematol Infect Dis</i> . 2012. ²	NICU	Cross Sectional	Iran, Islamic Rep.	0-12 hours	95	CRP, PCT	Blood culture (for "proven early-onset sepsis") or clinical signs of sepsis* and positive sepsis screen or maternal risk factor (for "clinical early-onset sepsis)	-12 hours old or younger -Clinical signs of sepsis -Maternal risk factor for sepsis	-Congenital malformations -TORCH infection	Level 3
Aboud MI, et al. <i>Iran J Med Sci</i> . 2010. ³	NICU	Prospective Cohort	Syrian Arab Republic	1-30 days	47	CRP, PCT, WBC	Blood culture	-Admission to NICU with bacteremia evaluation	-Congenital malformations -Exchange transfusion for neonatal hyperbilirubinemia -Death during follow up	Level 2
Adib M, et al. <i>Iran J Basic Med Sci</i> . 2012. ⁴	NICU	Cross Sectional	Iran, Islamic Rep.	1 hour-30 days	87	CRP, PCT	Blood culture	-Maternal risk factor such as fever, prolonged rupture of amniotic membrane >24 hours -Low birth weight (<2500 grams) -Signs and symptoms of sepsis: feeding intolerance, lethargy, temperature instability, apnea, respiratory distress, poor perfusion, seizures, tachypnea, bradycardia, abdominal distension or vomits -Premature birth (<37 weeks)	Not specified	Level 2
Ahmed E, et al. <i>Pak J Med Sci</i> . 2017. ⁵	NICU	Prospective Cohort	Pakistan	1-12 days	135	CRP	Blood culture	-Suspected sepsis (presence of unexplained fever or hypothermia, irritability, poor or no feeding, lethargy, respiratory dysfunction	-Birth weight <1.5 kg -Birth asphyxia -Already taking any antibiotic treatment	Level 1

								(e.g. apnea or tachypnea), cardiovascular dysfunction (e.g. intermittent tachycardia or bradycardia and cold peripheries), presence of maternal risk factors (foul smelling vaginal discharge, rupture of membranes for >18 hours, history of fever in prenatal or post-natal period)		
Ahmed Z, et al. <i>J Coll Physicians Surg Pak.</i> 2005. ⁶	NICU	Cross Sectional	Pakistan	1-30 days	200	CRP, ESR, WBC	Blood culture	-Non-specific sign and symptom of sepsis or focal signs of infection	-Congenital malformations -Birth asphyxia -Inborn errors of metabolism -Jaundice -GA <33 weeks -Respiratory distress due to surfactant deficiency	Level 1
Akhmaltdinov a L, et al. <i>Int J Inflam.</i> 2021. ⁷	NICU	Cross sectional	Kazhakstan	0-4 days	57	CRP	Blood culture	-criterion for determining a case of sepsis was a positive blood culture -control group consisted of children who received treatment in the intensive care unit with negative blood cultures and unconfirmed infectious complications	-born to HIV-positive mothers -receiving therapy with high doses of glucocorticosteroids -primary immunodeficiency state -blood loss -severe malformations -acute hemolytic disease of the newborn	Level 2
Al-Zahrani AK, et al. <i>J Infect in Dev Ctries.</i> 2015. ⁸	NICU	Retrospective cohort	Saudi Arabia	1-30 days	100	CRP, PCT	Blood culture	-Neonates clinically suspected to have sepsis which included respiratory manifestations such as apnea or tachypnea (respiratory rate over 70 breaths per minute in preterm and over 60 breaths per minute in term neonates), nasal flaring, retractions, cyanosis or respiratory distress, bradycardia (heart rate less than 100 beats per minute in preterm and less than 80 bpm in term neonates), or tachycardia (the upper threshold of heart rate based on age: 1-2 days, > 159 bpm; 3-6 days, > 166 bpm), hypotonia or seizures, poor skin color, and irritability or lethargy	-Neonates suspected to have congenital malformations and/or laboratory confirmed TORCH infections	Level 3
Ali AM, et al. <i>Egypt J of Immunol.</i> 2008. ⁹	NICU	Prospective Cohort	Egypt, Arab Rep.	1-7 days	69	CRP, PCT	Blood culture	-Controls (healthy infants) -Signs of sepsis (i.e. tachypnea, grunting, apnea, cyanosis, pallor, hypotension, tachycardia, bradycardia, rejection of food, abdominal distension, hepatomegaly, lethargy,	-Infants born to mothers with gestational diabetes	Level 3

								convulsions, anemia)		
Alkan Ozdemir S, et al. <i>J Clin Lab Anal.</i> 2018. ¹⁰	NICU	Prospective cohort	Turkey	3-35 days	127	CRP	Blood culture	-All neonates consecutively admitted	-Neonates with congenital anomalies, congenital infections, born to mothers with clinical chorioamnionitis, or those who had early-onset neonatal sepsis, perinatal asphyxia, or intrauterine growth restriction	Level 1
Aminullah A, et al. <i>Med J Indones.</i> 2001. ¹¹	NICU	Prospective Cohort	United States	1-7 days	220	CRP, ESR, WBC	Blood culture	-Suspected sepsis (history of prematurity, prolonged rupture of membranes, maternal fever, chorioamnionitis, or maternal colonization with group B strep)	-Incomplete data	Level 1
Amponsah SK, et al. <i>Pan Afr Med J.</i> 2017. ¹²	NICU	Cross Sectional	Ghana	1-12 hours	62	CRP, PCT	Blood culture	-Maternal risk factors (prolonged rupture of amniotic membrane >18 hrs, chorioamnionitis) -Neonatal risk factors (low birth weight and premature birth) -Clinical symptoms (feeding intolerance, lethargy, temperature instability, tachypnea, bradycardia, tachycardia, abdominal distension or vomiting) -Presumptive diagnosis of sepsis by admitting physician	-Meconium aspiration -Perinatal asphyxia -Neonates who required resuscitation for any reason	Level 2
Anwer SK, et al. <i>J Pak Med Assoc.</i> 2000. ¹³	NICU	Retrospective cohort	Pakistan	12 hours-20 days	50	CRP, WBC	Blood culture	-Inborn infants with prematurity (< 36 weeks), low birth weight, birth asphyxia, home delivery, instrumentation. -Infants with feeding problem, lethargy, temperature instability, respiratory distress, irritability (including convulsions), abdominal distention, and apnea or cyanotic spells	Surgical cases	Level 2
Arnon S, et al. <i>Biol Neonate.</i> 2005. ¹⁴	NICU	Prospective cohort study	Israel	5-36 days	116	CRP	Blood culture	-Clinical sepsis diagnosed by one or more signs of infection and two laboratory signs suggestive of sepsis (increasing incidence of apnea and/or bradycardia of more than 30% from the previous day, hypotension, respiratory dysfunction, muscular hypotonia, lethargy and fever or hypothermia -Biochemical variables suggestive of sepsis (acidosis (pH < 7.25); hyperglycemia (glucose > 160 mg%); thrombocytopenia (< 150 x 10 ⁹ /l); neutropenia (< 1.5 x 10 ⁹ /l) and a ratio of immature to total neutrophils (I/T ratio)	Not specified	Level 2

								exceeding 0.2)		
Ayazi P, et al. <i>Le Infezioni in Medicina</i> . 2014. ¹⁵	Not Specified	Prospective cohort	Iran, Islamic Rep.	“Infant”, age not specified	83	CRP	Culture (blood, cerebrospinal fluid, urine) or clinical signs of sepsis with two or more of the following: WBC <4000 or >10000 per mm ³ , band cells to total neutrophil ration > 0.2 and a positive acute phase reactant test	-More than three of the following symptoms: maternal risk factors such as maternal fever, alcohol consumption, premature rupture of membranes (more than 24 hours), chorioamnionitis, and maternal urinary tract infection; neonatal risk factors such as low birth weight (less than 2500 g) and premature birth (less than 37 weeks); anorexia, lethargy, temperature instability (fever and hypothermia), jaundice, apnea, respiratory distress, tachycardia (>180/ min), tachypnea (>60/min), cyanosis, and vomiting	Not specified	Level 3
Ballot DE, et al. <i>S Afr Med J</i> . 2004. ¹⁶	NICU	Prospective Cohort	South Africa	“Infant”, age not specified	183	PCT	Blood culture	-All neonates undergoing sepsis evaluation; evaluation for sepsis was done at the discretion of the attending physician for a variety of reasons including maternal risk factors for sepsis (e.g. prolonged rupture of membranes, chorioamnionitis, maternal pyrexia, maternal urinary tract infection, foul-smelling liquor) and signs of neonatal sepsis (e.g. temperature instability, lethargy, feeding intolerance, seizures, ongoing respiratory distress, irritability, blood glucose abnormalities, hypotension, poor perfusion, acidosis)	-Incomplete data (missing blood culture results, no PCT obtained) -Contaminated blood cultures	Level 1
Beltempo M, et al. <i>BMC Pediatr</i> . 2018. ¹⁷	NICU	Retrospective Cohort	Canada	3-28 days	416	CRP, WBC	Blood culture	-Increased apnea episodes -Temperature instability -Feeding intolerance -Lethargy -Hypotonia	-Known contaminants such as <i>Corynebacterium</i> and unidentified organisms	Level 1
Benitz WE, et al. <i>Pediatrics</i> . 1998. ¹⁸	NICU	Prospective cohort	United States of America	1-118 days	987	CRP	Blood culture	-Neonates who were treated for sepsis due to intrapartum fever, chorioamnionitis, prolonged rupture of membranes, premature preterm rupture of membranes, premature onset of labor, preterm labor refractory to tocolysis, fetal tachycardia, meconium staining of amniotic fluid) and neonatal clinical signs ⁵	-Infants > 44 weeks post-conceptual age	Level 1

Berger C, et al. <i>Eur J Pediatr.</i> 1995. ¹⁹	NICU	Prospective Cohort	Switzerland	0-6 weeks	195	CRP, WBC	Blood culture	-Any neonate with suspected sepsis	-Possible viral infection -Post-operative	Level 1
Blommendahl J, et al. <i>Scand J Infect Dis.</i> 2002. ²⁰	Inpatient	Prospective Cohort	Finland	Not stated, "neonates"	169	CRP, PCT	Blood culture	-Children whom the attending physician suspected of having an infection based on clinical symptoms such as tachypnoea, respiratory distress, apnoea, irritability, grunting, lethargy, tachycardia, bradycardia, retractions, convulsions, temperature instability, gastrointestinal disturbances and hypotony -All very premature babies (birth before 32 completed weeks of gestation)	-All neonates who had received antibiotic treatment, including maternal antibiotic treatment	Level 3
Bohnhorst B, et al. <i>Acta Paediatr.</i> 2012. ²¹	NICU	Prospective Cohort	Germany	Preterm and newborn infants after DOL 4	170	CRP, PCT	Blood culture, urine culture, CSF culture, CXR for pneumonia, NEC confirmed with pathogen cultured from abdominal puncture fluid or intraoperative swabs	-All preterm and newborn infants treated in NICU from January 2006 to June 2009 who were clinically suspected to have an infection from the 4th day of life	-Discharge/transfer <4 th day of life -Death <4 th day of life -Patients with sepsis transferred -Incomplete/neglected blood-taking	Level 3
Boo NY, et al. <i>Singapore Med J.</i> 2008. ²²	NICU	Prospective Cohort	Malaysia	"Infant", age not specified	43	CRP, PCT	Blood culture	-Infants admitted to NICU with signs suggestive of sepsis -Infants who developed signs of sepsis while in the ward	-Infants on antibiotics -Infants who developed signs of sepsis within 72 hours of discontinuation of antibiotics	Level 4
Boskabadi H, et al. <i>Iran J Pediatr.</i> 2010. ²³	NICU	Prospective Cohort	Iran, Islamic Rep.	Neonates > 72 hours of life	93	CRP	Blood culture or clinical sepsis	-Positive clinical signs of sepsis -Positive blood or cerebrospinal fluid culture	-Congenital malformations -Congenital infections associated with the TORCH complex -Lack of parental consent	Level 4
Broner CW, et al. <i>Clin Pediatr.</i> 1990. ²⁴	Emergency Department, Clinics	Prospective cohort	United States of America	0-56 days	52	CRP, ESR, WBC	Blood culture	-Infants with rectal temperature ≥ 38.1 °C	-Not specified	Level 4
Buck C, et al. <i>Pediatrics.</i> 1994. ²⁵	NICU	Prospective cohort	Germany	0-3.5 days	222	CRP	Blood culture and clinical sepsis	-Newborns admitted to the regular and intermediate-care wards -Newborns suspected of having infection during their hospital stay were included -Newborns with the presumptive diagnosis of sepsis/neonatal	-Incorrect or incomplete blood sampling	Level 4

								infection		
Bunduki GK, et al. <i>BMC Res Notes</i> . 2020. ²⁶	Inpatient	Cross sectional	Democratic Republic of Congo	0-30 days	228	CRP	Blood culture	-Neonates admitted a three hospitals in Butembo/Eastern DRC between September to November 2018 with suspected sepsis according to International Paediatric Sepsis Consensus (IPSC) criteria	-Neonates diagnosed with sepsis but who died immediately or upon arrival at the health facility and blood samples were not yet taken were excluded -Neonates with a congenital malformation or dysmorphic features, those diagnosed with malaria parasitemia, those from HIV-positive mother, those under antibiotic therapy, and those above 30 days of life were also excluded	Level 1
Chacha F, et al. <i>BMC Pediatrics</i> . 2014. ²⁷	NICU	Prospective Cohort	Tanzania	Not specified	305	CRP, WBC	Blood culture	-All neonates with clinical suspicion of neonatal sepsis according to WHO criteria admitted to NICU	-History of use of antibiotics before enrolment for more than 72 hours -Body weight less than 1 kilogram	Level 1
Chen CJ, et al. <i>J Chin Med Assoc</i> . 2009. ²⁸	Inpatient	Prospective cohort	China	0-3 months	135	CRP, WBC	Blood culture, chest radiograph, urine culture, CSF culture	-Infants admitted with fever >38C	-Infants born before 36 weeks of gestation -Infants with congenital heart disease, bronchopulmonary dysplasia, chronic lung disease, immunodeficiency, chromosome anomalies, or congenital gastrointestinal tract anomalies -Infants with hyperbilirubinemia and those who exhibited an antenatal setup for sepsis (i.e. premature rupture of membranes, maternal fever, or peripartum antibiotics)	Level 3
Chiesa C, et al. <i>Clin Chem</i> . 2003. ²⁹	NICU	Prospective Cohort	Italy	0- 49 hours	134	CRP, PCT	Blood culture	-Consecutively enrolled critically ill newborns over a 6-month period in 2 maternity hospitals	-Preadmission deaths -Lethal abnormalities -Babies whose cord blood was not sampled for all three study markers	Level 2
Choo YK, et al. <i>Korean J Pediatr</i> . 2012. ³⁰	NICU	Prospective Cohort	Korea, Rep.	0-30 days	23	CRP, WBC	Blood culture	-Neonates born at >/=30 weeks gestation and admitted to NICU from May to August 2010 with clinical signs of sepsis	Not specified	Level 2
Coggins SA, et al. <i>PLoS One</i> . 2013. ³¹	NICU	Prospective cohort	United States of America	not stated	363	CRP	Blood culture	-All inborn preterm infants weighing at least 1500 grams with negative blood cultures -All patients admitted with positive blood cultures	-Neonates with congenital anomalies or surgery performed within the first 3 postnatal days -Non-viable infants or infants who did not survive past the first 48 hours post-partum -patients no longer hospitalized 48 hours after birth -patients who did not have at least one time-correlated set of CRP and neutrophil data	Level 1
Değirmenciog̈ lu H, et al.	NICU	Prospective Cohort	Turkey	4-60 days	55	CRP	Blood culture	-Born ≤32 weeks gestational age -4 to 60 days postnatal age	-Major congenital and/or chromosomal anomalies.	Level 2

<i>BMC Infect Dis.</i> 2019. ³²								-Gram-positive and/or negative bacteria detected in blood culture		
Deshpande SS, et al. <i>J Clin Diag Res.</i> 2021. ³³	NICU	Prospective Cohort	India	0-28 days	104	CRP	Blood culture	-neonates admitted with clinical suspicion of sepsis	-neonates with hyaline membrane disease, transient tachypnea of newborn or hypoxia induced encephalopathy	Level 3
Distefano G, et al. <i>Acta Paediatr.</i> 2004. ³⁴	NICU	Prospective Cohort	Italy	0-10 days	35	CRP, PCT	Blood culture	-Premature infants (gestational age <37 weeks) with clinical findings (respiratory distress, apnoea, circulatory instability, poor capillary refill, hypothermia, tachycardia, tachypnoea, hypoxaemia, oliguria) -Hematological findings (leucocyte count) of infection -Positive blood cultures were included in the study group -Matched preterm babies with no clinical or haematological signs of infection and negative blood cultures were enrolled as controls	-Neonates born of mothers receiving antibiotics before or during delivery -Babies suffering birth trauma	Level 2
Doellner H, et al. <i>J Pediatr.</i> 1998. ³⁵	NICU	Prospective Cohort	Norway	0-7 days	122	CRP, WBC	Blood culture and clinical sepsis	- The study included 241 neonates consecutively admitted to the neonatal intensive care unit at the University Hospital of Trondheim during an 11-month period in 1993.	NA	Level 1
Du WX, et al. <i>Clin Chim Acta.</i> 2016. ³⁶	Inpatient (all patients were neonates)	Prospective Cohort	China	0-72 hours	157	CRP, PCT, WBC	Blood culture	-Preterm and term neonates with suspicion of an early-onset (within 72 h after birth) infection	-Major congenital malformations -Confirmed intrauterine viral infection -Lack of parental consent	Level 3
Duhan A, et al. <i>J Krishna Inst Med Sci Univ.</i> 2016. ³⁷	NICU	Prospective cohort	India	Not specified	128	CRP, WBC	Blood culture	-Clinical suspicion of sepsis based on clinical features including feeding problems, lethargy, respiratory distress, irritability, convulsions, abdominal distention, recurrent attacks of apnea, or cyanotic spells, vomiting, poor cry, and tachypnoea -major perinatal risk factors were prematurity, low birth weight, birth asphyxia, home delivery, caesarean section, and meconium aspiration -63 normal neonates from immunization clinic were studied	-Contaminated cultures, prior antibiotic exposure, major congenital abnormalities, inborn errors of metabolism, and hemolytic jaundice	Level 2

								for comparison		
Edgar JDM, et al. <i>Clin Sci (London)</i> . 1994. ³⁸	NICU	Prospective Cohort	United Kingdom	Not specified	60	CRP	Blood culture	-Suspected of having infection	Not specified	Level 2
El Sehmawy AA, et al. <i>Infect Drug Resist</i> . 2021. ³⁹	NICU	Case control	Egypt, Arab Rep.	1-3 days	60	CRP, PCT	Blood culture	-	-	Level 5
Forest JC, et al. <i>Clin Biochem</i> . 1986. ⁴⁰	NICU	Retrospective cohort	Canada	Not specified	127	CRP	Blood culture	-Neonates admitted with 26-40 weeks gestation and birth weight from 703-4000 grams	-Not specified	Level 2
Franz AR, et al. <i>Pediatr Infect Dis J</i> . 1999. ⁴¹	NICU	Prospective Cohort	Germany	0-11 days	162	CRP, PCT	Blood culture, clinical sepsis	Infants suspected of having bacterial infection (BI) or admitted on DOL1 with maternal history of amniotic infection-	-Umbilical artery pH <7.00 -Trisomy 21 -Incomplete data collection.	Level 2
Franz AR, et al. <i>Acta Paediatr</i> . 2001. ⁴²	NICU	Prospective cohort	Germany	0-72 hours	70	CRP	Blood culture	-Neonates clinically suspected to have sepsis based on one clinical sign suggesting bacterial infection including pallor, greyish skin color, poor perfusion (capillary refill >2 seconds) and arterial hypotension, tachypnea (>60 breaths/minute), dyspnea (grunting, nasal flaring, retractions), apnea, inspiratory oxygen fraction (FiO ₂) > 0.21, and respiratory insufficiency, and muscular hypotonia or hypertonia, hyperexcitability, irritability, and lethargy -maternal history of amniotic infection rupture of membranes before the onset of labor, rupture of membranes >18 hours before delivery, foul-smelling amniotic fluid, ineffective tocolysis before 35 weeks of gestation, fetal tachycardia (baseline >160 beats/minute) and maternal rectal temperature >38.5C	-Chromosomal anomalies, meconium aspiration, or umbilical artery pH < 7.0, transferred to other hospitals	Level 2
Frerot A. et al. <i>Eur J Clin Microbiol and Infect Dis</i> . 2019. ⁴³	NICU	Prospective cohort	France	Birth	186	Cord blood PCT	Definite sepsis: positive blood or cerebrospinal fluid culture. Probable sepsis: WBC < 5000/mm ³ or s ≥ 21,000/mm ³ ,	-All preterm neonates born between 24 weeks and 27 weeks and 6 days with cord blood PCT lab testing	-Excluded patients with insufficient umbilical cord blood sample volume	Level 2

							CRP > 10 mg/dL, and clinical signs of sepsis, antibiotic treatment > 72 hours			
Gajdos V, et al. <i>Arch Pediatr.</i> 2005. ⁴⁴	Emergency Department	Prospective cohort	France	6-92 days	315	CRP	Blood, urine and CSF culture	-Not specified	-Not specified	Level 2
Gao C, et al. <i>BMC Infect Dis.</i> 2021. ⁴⁵	NICU	Cross sectional	China	0-28 days	142	CRP	Blood culture	-age <28 days and routine blood examinations,	-infants who had incomplete information or discontinued therapy	Level 3
Gupta SK, et al. <i>Indian Pediatr.</i> 1989. ⁴⁶	Inpatient	Prospective cohort	India	0 hours – not specified	150	CRP	Clinical sepsis (not defined)	-Neonates born at the hospital or admitted with clinical evidence of septicemia	-Not specified	Level 4
Habib A, et al. <i>J Coll Physicians Surg Pak.</i> 2021. ⁴⁷	NICU	Cross-sectional	Pakistan	1-29 days	171	PCT	Blood culture	-criteria of suspected neonatal sepsis included any two: temperature >38.5°C or <36°C, increased heart rate above two standard deviations of normal for age, respiratory rate greater than two standard deviations of normal for age, TLC increased or decreased for age or >10% immature neutrophils in peripheral blood	-on antibiotics before blood culture -congenital disorder -evidence of respiratory distress syndrome on chest x-ray -inborn errors of metabolism	Level 2
Hagag AA, et al. <i>Infect Disord Drug Targets.</i> 2021. ⁴⁸	NICU	Case control	Egypt, Arab Rep.	0-28 days	80	CRP	Clinical sepsis	-full-term neonates with high probable sepsis	-Preterm or low birth weight neonates -multiple congenital anomalies, chromosomal abnormalities, hypoxic-ischemic encephalopathy, infant of diabetic mother and neonates with abnormal thyroid function screening	Level 2
Hagag A, et al. <i>Infect Disord Drug Targets.</i> 2020. ⁴⁹	NICU	Prospective cohort	Egypt, Arab Rep.	Not specified	80	CRP	Blood culture or clinical sepsis	-Any full-term neonate presented with high probable sepsis	-Preterm or low birth weight neonates and those with multiple congenital anomalies, chromosomal abnormalities, hypoxic-ischemic encephalopathy, infant of diabetic mother and neonates with abnormal thyroid function screening	Level 4
Hashem HE, et al. <i>Int J Microbiol.</i> 2020. ⁵⁰	NICU	Prospective cohort	Egypt, Arab Rep.	Not specified	235	CRP	Blood culture	-For sepsis patient's identification and selection, neonates had presumed one or more infection risk factors, in addition to at least 2 clinical and 2 laboratory criteria: (1) respiratory compromise: respiratory rate >60 breaths per minute, or cessation of	-Patients who had confirmed intrauterine viral infection (toxoplasmosis, rubella, cytomegalovirus, syphilis, and herpes), patients with long-standing hospitalization (admitted for more than one-month duration), and those neonates who had recently undergone	Level 4

								respiration for ≥ 20 seconds, occurring at a rate of ≥ 2 times per hour, or pulse oximeter readings of $\leq 85\%$; (2) cardiovascular compromise: heart rate < 100 beats per minute, pallor, or hypotension; (3) metabolic changes: hypothermia (rectal temperature $< 36^\circ\text{C}$), a body temperature of $> 38^\circ\text{C}$, feeding intolerance (increased gastric residuals $> 50\%$ of milk volume in ≥ 2 feedings within 24 hours), glucose instability (blood glucose level < 45 mg/dL or > 125 mg/dL), or metabolic acidosis ($\text{pH} < 7.25$); or (4) neurologic changes: lethargy or decreased activity, whereas laboratory criteria were white blood cell (WBC) count < 5 or $> 20 \times 10^9/\text{L}$, immature to total neutrophil (I : T) ratio > 0.2 , platelet count $< 100 \times 10^9/\text{L}$, and $\text{CRP} > 10$ mg/L	surgical intervention were excluded from the study.	
Hashem HE, <i>Dis Markers</i> . 2021. ⁵¹	NICU	Case control	Egypt, Arab Rep.	0-28 days	184	CRP	Blood culture	-neonates with presumed one or more infection risk factors in addition to at least 2 clinical and 2 laboratory criteria: "(1) respiratory rate > 60 breaths per minute or cessation of respiration for ≥ 20 seconds, occurring at a rate of ≥ 2 times per hour, or pulse oximeter readings of $\leq 85\%$; (2) heart rate of < 100 beats per minute, pallor, or hypotension; (3) hypothermia (rectal temperature of $< 36^\circ\text{C}$), a body temperature of $> 38^\circ\text{C}$, feeding intolerance (increased gastric residuals of $> 50\%$ of milk volume in ≥ 2 feedings within 24 hours), glucose instability (blood glucose level of < 45 mg/dL or > 125 mg/dL), or metabolic acidosis ($\text{pH} < 7.25$); or (4) lethargy or decreased activity, whereas laboratory criteria were white blood cell (WBC) count < 5 or $> 20 \times 10^9$ cells/L, immature to total neutrophil (I : T) ratio > 0.2 , platelet count $< 100 \times 10^9/\text{L}$, and	-recently undergone surgical interventions (within the last 15 days) -patients admitted for more than one month -neonates who had confirmed intrauterine viral infection (toxoplasmosis, rubella, and Cytomegalovirus)	Level 2

								CRP>10mg/L. ⁵²		
Hassan HR, et al. <i>J Clin Neonatol.</i> 2016. ⁵²	NICU	Prospective cohort	India	0-72 hours	100	CRP, ESR, WBC	Blood culture	-Neonates with sepsis risk factors including as prematurity, low birth weight, birth asphyxia, foul-smelling liquor, unclear per vaginal examination before delivery, prolonged rupture of membranes, and prolonged labor	-Neonates already receiving antibiotics	Level 2
Hisamuddin E, et al. <i>Pak J Med Sci.</i> 2015. ⁵³	NICU	Prospective cohort	Pakistan	0-28 days	147	CRP	Blood culture	-All neonates having suspected neonatal sepsis defined by clinic pathological features of perinatal risk factors including maternal pyrexia (within 1 week prenatal and/or 48 hours postnatal), prolonged rupture of membranes (18 hours), foul smelling vaginal discharge or/and maternal urinary tract infection diagnosed in last month -Neonates having unexplained hypothermia/hyperthermia, lethargy, irritability, poor feeding or milk intolerance, respiratory dysfunction evidenced by apnea (>10 sec.), tachypnoea (>60 breaths/minute), cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradycardia (<100 beat/min).	-Neonates with birth asphyxia and very low birth weight	Level 3
Ipek IO, et al. <i>J Matern Fetal Neonatal Med.</i> 2010. ⁵⁴	NICU	Prospective Cohort	Turkey	2-26 days	97	CRP	Blood culture or clinical sepsis	-Term newborns hospitalized for 'rule out sepsis' to NICU with clinical signs and symptoms suggesting sepsis and two abnormalities in lab findings	-Use of antibiotics by the newborn or the mother (shortly before delivery) -Maternal hypertension -Meconium in amniotic fluid -Asphyxia -Congenital abnormality	Level 3
Jacquot A, et al. <i>Arch Dis Child Fetal Neonatal Ed.</i> 2009. ⁵⁵	NICU	Prospective cohort	France	0-72 hours	73	CRP, PCT	Clinical sepsis	-All newborn infants with clinical suspicion of LOS (after 72 h of life) who were hospitalized in a NICU (Croix-Rousse Hospital, Lyon, France) were enrolled.	- Newborn infants under antibiotic treatment, with severe congenital malformation or requiring neo- natal surgery, or diagnosed with necrotizing enterocolitis were excluded.	Level 4
Jaswal RS, et al. <i>Indian Pediatr.</i> 2003. ⁵⁶	Not Specified	Prospective cohort	India	0 day-1 month	50	CRP	Blood culture	-Birth weight > 1500g with suspected septicemia based on sepsis score defined as 3 or more of the following: refusal to feed, abdominal distention, vomiting, lethargy, jaundice, poor cry, seizures, diarrhea, apnea,	-Neonates that had undergone surgery -Neonates with suspected meningitis	Level 3

								tachypnea, poor capillary refill, hypothermia, fever and umbilical discharge.		
Karabulut B, et al. <i>Fetal Pediatr Pathol.</i> 2020. ⁵⁷	NICU	Retrospective cohort	Turkey	12-24 hours	159	CRP, ESR, PCT, WBC	Blood culture	-Neonates who were appropriate for gestational age and diagnosed with early-onset sepsis.	-Neonates < 37 weeks or > 42 weeks gestation, small for gestational age, intrauterine growth restriction, perinatal asphyxia, congenital abnormality, chromosomal abnormality, preeclampsia, lack of data	Level 1
Kaur S, et al. <i>Int J Pediatr.</i> 2021. ⁵⁸	NICU	Prospective cohort	India	0-7 days	60	CRP	Blood culture	-clinical symptoms and signs of suspected neonatal sepsis/high-risk factors for developing sepsis	-received antibiotics previously	Level 3
Khair KB, et al. <i>Mymensingh Med J.</i> 2012. ⁵⁹	NICU	Prospective Cohort	Bangladesh	0-28 days	100	CRP, WBC	Blood culture	-Newborns with clinically suspected neonatal sepsis in the NICU between April 2009 and March 2010	-Neonates who were critically ill -Severe jaundice due to blood group incompatibilities	Level 4
Khan F. <i>J Coll Physicians Surg Pak.</i> 2019. ⁶⁰	NICU	Cross sectional	Pakistan	0-28 days	385	CRP	Blood culture	- Inclusion criteria were neonates from 0 to 28 days of life having clinical features suggestive of NS and willingness of parents to participate in the study	- Excluded patients were those who were advised antibiotics (for any reason) 24 hours before admission to neonatal unit, those positive blood cultures which showed contamination and unwillingness of parents to participate in study.	Level 2
Khashabi J, et al. <i>Iran J Med Sci.</i> 2004. ⁶¹	NICU	Prospective cohort	Iran, Islamic Rep.	0-13 days	110	CRP	Blood culture	-Newborns with suspected clinical sepsis defined by signs and symptoms suggestive of clinical sepsis including unexplained unstable temperature (hypo- and hyperthermia), lethargy, irritability, poor feeding or milk intolerance, vomiting, abdominal distension, bloody stool, respiratory dysfunction evidenced by apnea, tachypnea (>60 breaths/min); cardiovascular dysfunction such as persistent tachycardia (>160 beat/min) or bradycardia (<100 beat/min), seizure, sclerema -biochemical and hematological parameters including persistent acidosis, unexplained hypo- and hyperglycemia, thrombocytopenia, leukopenia or leukocytosis	-Newborns who had undergone mechanical ventilation, surgical operation, exchange transfusion, or were resuscitated before admission -Newborns with metabolic aberrations, chromosomal abnormalities, and who had received parenteral antibiotic therapy before admission, birth weight less than 2,000gm	Level 1
Kiser C, et al.	NICU	Retrospective	United	Birth	554	CRP	Blood culture	-All neonates of gestational age	-None	Level 1

<i>Pediatrics</i> . 2014. ⁶²		cohort	States of America					≥35 weeks exposed to chorioamnionitis and admitted to level III NICU.		
Kocabas E, et al. <i>Turk J Pediatr</i> . 2007. ⁶³	NICU and outpatient department	Prospective Cohort	Turkey	1-30 days	55	CRP, PCT	Blood culture	-Consecutive neonates admitted with a suspected clinical sepsis and hospitalized -Consecutive healthy neonates who had no signs of infection but were hospitalized for perinatal risk factors -Consecutive healthy neonates without infectious risk factors admitted to well-baby outpatient clinics	-Newborns started on antibiotic treatment -Newborns with a history of maternal antibiotic administration	Level 2
Koksal N, et al. <i>Turk J Pediatr</i> . 2007. ⁶⁴	NICU	Prospective Cohort	Turkey	0-30 days	67	CRP, PCT	Clinical criteria (including culture)	-Infants with clinical (Temperature instability, apnea, need for supplemented oxygen, need for ventilation, tachycardia/bradycardia, hypotension, feeding intolerance, abdominal distension, necrotizing enterocolitis) or laboratory findings of neonatal sepsis -Infants who had no signs of clinical and laboratory infection were included as the control group	-Administration of antibiotic therapy during admission -Lack of parental consent -Newborns who died during follow-up -Newborns who had exchange transfusion for neonatal hyperbilirubinemia	Level 5
Kordek A, et al. <i>Postepy Hig Med Dosw (Online)</i> . 2014. ⁶⁵	NICU	Prospective cohort study	Poland	5-50 days	140	CRP, PCT, WBC	Blood culture	-Clinically evidenced sepsis after three days of life. -All cases fulfilled the Centers for Disease Control and Prevention (CDC) criteria for nosocomial infection.	NA	Level 3
Koskenvuo et al. <i>Eur J Clin Microbiol Infect Dis</i> . 2003. ⁶⁶	NICU	Retrospective cohort	Finland	0-84 hours	22	CRP, PCT	Blood culture	-Neonates admitted with clinical signs of infection	-Not specified	Level 3
Krishna BV, et al. <i>Indian J Pathol Microbiol</i> . 2000. ⁶⁷	NICU	Prospective cohort	India	0-28 days	57	CRP	Blood culture	-Neonates clinically suspected to have sepsis not otherwise specified	-None listed	Level 2
Kumar D, et al. <i>Int J Pharm Clin Res</i> . 2021. ⁶⁸	NICU	Prospective cohort	India	0-6 days	80	CRP	Blood culture	-age <7 days of life, inborn or outborn with suspected sepsis and with high risk factors (antenatal, natal, postnatal)	-age >7 days of life -septic shock patients or rapidly deteriorating clinical condition	Level 3
Kumar R, et al. <i>East Afr Med J</i> . 2010. ⁶⁹	NICU	Cross sectional	Kenya	1-55 days	212	CRP	Blood culture	-All neonates admitted to KNH Newborn Unit during the study period with suspected sepsis	-Neonates whose parents/guardians declined to give consent and those with history of meconium aspiration,	Level 1

								based on perinatal risk factors or suspicious clinical findings were recruited before first-line or change over to second-line were initiated.	perinatal asphyxia, tissue injury and severe hepatocellular involvement were excluded.	
Kumar S, et al. <i>Int J Pharma Clin Res.</i> 2022. ⁷⁰	NICU	Prospective Cohort	India	0-28 days	61	CRP	Blood culture	All neonates (<28 days) presenting with symptoms and signs of sepsis like poor feeding, lethargy, tachypnea, hypothermia, convulsion, etc. were included in the study.	All newborns with neonatal hyperbilirubinemia due to causes other than sepsis like physiological jaundice, Rh, ABO incompatibility, TTN, MAS without clinical or laboratory suspicion of sepsis were excluded from the study.	Level 3
Lam HS, et al. <i>Neonatology.</i> 2011. ⁷¹	NICU	Prospective Cohort	Hong Kong	0-30 days	310	CRP	Blood culture	-All infants admitted to NICU at Prince of Wales Hospital who presented with symptoms suggestive of intra-abdominal sepsis or surgical abdomen or -Infants who required full sepsis screening and antibiotic treatment or -Infants referred for pediatric surgical assessment	-Chromosomal abnormalities -Lethal congenital malformations -Family history of immunodeficiencies	Level 1
Lopez Sastre JB, et al. <i>BMC Pediatr.</i> 2007. ⁷²	NICU	Prospective Cohort	Spain	0-48 hours	238	PCT	Clinical criteria (including culture)	-All consecutive neonates admitted to participating hospital within 48 HOL who had blood samples available for timed PCT measurement according to three postnatal periods: shortly after birth, within 12-24 h of life, and within 36-48 h of age	-Infants born to mothers with gestational diabetes -Refusal of parental consent for blood sampling	Level 4
Lubis BM. <i>Int Med J.</i> 2021. ⁷³	NICU	Cross sectional	Indonesia	0-28 days	65	PCT	Blood culture	-age <28 days admitted to perinatology ward and they were not suspected or proven with immunodeficiency, hematological disorder, or receiving immunomodulator drugs	-suspected or proven with immunodeficiency -hematological disorder -receiving immunomodulator drugs	Level 4
Mannan MA, et al. <i>Mymensingh Med J.</i> 2010. ⁷⁴	NICU	Prospective cohort	Bangladesh	0-28 days	150	CRP, WBC	Blood culture (42/100 were pre-treated)	-Newborns with one clinical feature (respiratory distress, poor feeding, lethargy, hypothermia, abdominal distention, sclerema, convulsion) AND one major or two minor risk factors (major risk factors were rupture of membranes > 24 hours, chorioamnionitis, maternal fever >100.4, Fetal HR >160) (minor risk factors: rupture of membranes >12 hours, maternal WBC >15,000, low Apgar, preterm labor, low birth weight, foul	-Newborns with any congenital abnormality	Level 3

								lochia, maternal colonization)		
Manucha V, et al. <i>J Paediatr Child Health</i> . 2002. ⁷⁵	NICU	Prospective cohort	India	0-3 days	150	CRP	Blood culture	-Neonates clinically suspected to have sepsis based on abnormal fetal and maternal clinical findings “as described in standard textbooks of neonatology”	-None listed	Level 3
Mathers NJ, et al. <i>Eur J Pediatr</i> . 1987. ⁷⁶	NICU	Prospective cohort	Germany	0-27 days	245	CRP	Blood culture	-Consecutive admissions to the NICU	-Focal bacterial source (skin or UTI or gastrointestinal)	Level 1
Milcent K, et al. <i>JAMA Pediatr</i> . 2016. ⁷⁷	Emergency Department	Prospective Cohort	France	7-90 days	2047	CRP, PCT	-Blood, CSF, urine, stool culture (SBI) -IBI defined as positive blood or CSF culture	Infants older than 7 days and younger than 91 days with temperatures of 38°C or higher at home or on admission	-antibiotics in previous 48 hours -major comorbidities (immune deficiency, congenital abnormality, chronic disease) -parental consent or data collection could not be obtained	Level 1
Misra PK, et al. <i>Indian Pediatr</i> . 1989. ⁷⁸	NICU	Prospective cohort	India	0-7 days	83	ESR, WBC	Blood culture	-Clinical manifestation of sepsis fever, hypothermia, poor suck, lethargy, sclerema	None listed	Level 5
Mkony MF, et al. <i>BMC Pediatrics</i> . 2014. ⁷⁹	NICU	Prospective cohort	Tanzania	0-28 days	208	CRP	Blood culture	-WHO clinical criteria history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate ≥ 60 breaths per minute, severe chest indrawing, axillary temperature $\geq 37.5^\circ\text{C}$, axillary temperature $\leq 35.5^\circ\text{C}$, bulging anterior fontanelle, signs of infection on the skin with pus spots and umbilicus pus spots	-Unwillingness of the parent or guardian to participate in the study -Very sick neonates in decompensated state and requiring resuscitation -Neonates with severe congenital malformation	Level 1
Mondal SK, et al. <i>Int J Appl Basic Med Res</i> . 2012. ⁸⁰	NICU	Prospective cohort	India	0-30 days	102	CRP, ESR, WBC	Blood culture	-Clinical history, signs, symptoms, and presence of predisposing factors in mothers and neonates for sepsis. ¹	-None listed	Level 3
Monsef A, et al. <i>Iran J Pediatr</i> . 2012. ⁸¹	NICU	Cross sectional	Iran, Islamic Rep.	Not specified	49	PCT	Blood culture	-Newborns with clinical and laboratory findings in favor of bacterial infection (before antibiotic therapy) and a positive blood, CSF, or urine culture	-Newborns with prior antibiotic therapy, expired infants, exchange transfusion, direct or hemolytic hyperbilirubinemia	Level 2
Morad EA, et al. <i>Int J Microbiol</i> . 2020. ⁸²	NICU	Cross sectional	Egypt, Arab Rep.	1-16 days	50	CRP, PCT	Blood culture	- Any neonate (up to age 28 days) with signs or symptoms of suspected sepsis at the time of admission or who developed sepsis in the hospital during the study period was enrolled in this study. The suggestive clinical manifestation included respiratory distress, apnea, pallor, poor feeding, hypotension, shock,	- Any neonate with apparent major congenital anomalies, Apgar score less than seven, or on antibiotics therapy before the start of the study was excluded.	Level 2

								instability of the temperature, lethargy, irritability, and increased oxygen requirement, besides abnormal laboratory findings as abnormal leukocyte count, increased I/T (immature to total neutrophil) ratio, and decreased platelet count.		
Nakamura H, et al. <i>Acta Paediatr Jpn.</i> 1989. ⁸³	NICU	Prospective cohort	Japan	0-100 days	90	CRP	Blood culture	-Infants admitted to NICU who were clinically suspected to have bacterial infection	-Not specified	Level 2
Ng PC, et al. <i>Pediatr Res.</i> 2002. ⁸⁴	NICU	Prospective Cohort	Hong Kong	0 days-1 year	90	CRP	Blood culture	-Birth weight <1500g -Postnatal age >72h -Symptoms suggestive of systemic infection and requiring full sepsis evaluation and antibiotic treatment -Parental consent	-Baby of diabetic mother	Level 2
Ng PC, et al. <i>Arch Dis Child Fetal Neonatal Ed.</i> 1997. ⁸⁵	NICU	Prospective Cohort	Hong Kong	72 hours	101	CRP	Blood culture	- Preterm infants with (a) birth weight < 1500 g, (b) postnatal age > 72 hours, (c) sign and symptoms suggestive of systemic infection and requiring full sepsis evaluation and antibiotic treatment, and (c) parental consent, in the neonatal unit at Prince of Wales Hospital, Hong Kong were eligible for enrollment into the study.	- Patients who were already on parenteral antibiotic treatment at the time of sepsis evaluation, or had severe congenital or chromosomal abnormalities, were excluded.	Level 4
Numbenjapon N, et al. <i>J Med Assoc Thai.</i> 2015. ⁸⁶	NICU	Prospective cohort	Thailand	Day of life 0	98	CRP	Blood culture	-All neonates with birth weight > 1500 grams who were diagnosed as clinical sepsis defined as a neonate who had at least one of the following conditions: 1) maternal fever that required antibiotic treatment, 2) maternal prolonged rupture of membranes >24 hours, 3) purulent gastric content that contained more than 10 white blood cells per high power field, 4) fetal distress in utero, 5) clinical manifestation of sepsis including lethargy, irritability, poor feeding, core temperature higher than 37.5°C, tachycardia or bradycardia, respiratory distress, apnea, vomiting, hepatosplenomegaly, hypotonia, convulsion, poor skin	-Neonates who were intubated, had umbilical or central line catheterization, diagnosed with conditions requiring prolonged antibiotic treatment (e.g. meningitis, arthritis, and osteomyelitis)	Level 5

								color and prolonged capillary refill		
Nupponen I, et al. <i>Pediatrics</i> . 2001. ⁸⁷	NICU	Prospective Cohort	Finland	0-48 hours	47	CRP	Blood culture; clinical criteria	-The series consisted of 39 neonates, with a gestational age of 29 to 41 weeks, who were treated in the neonatal unit for suspected infection. Inclusion criteria were the presence of at least 1 clinical sign suggesting infection at the age of 0 to 48 hours, and a blood sample for bacterial culture having been requested by the clinician. - 12 healthy term neonates w/physiologic hyperbilirubinemia not requiring PTX and with normal CRP served as controls	-Plasma IL-8 concentration or neutrophil CD11b expression value missing.	Level 3
Ohlin A, et al. <i>Acta Paediatr</i> . 2010. ⁸⁸	NICU	Prospective cohort	Sweden	0-28 days	393	CRP	Blood culture	-All neonates who had clinical signs of infection and subsequent blood culture and sepsis treatment with IV antibiotics as determined by treating neonatologist	-Not stated	Level 1
Omar J, et al. <i>Malays J Med Sci</i> . 2019. ⁸⁹	ICU	Prospective cohort	Malaysia	24-120 hours	60	PCT	Blood culture	-Suspected neonatal sepsis due to either preterm ruptured of membrane or prolonged ruptured of membrane, maternal infection, chorioamnionitis, group B streptococcus colonization, or signs of fetal distress during labor. -Neonates with feeding intolerance, lethargy or tachypnea, poor perfusion, seizures, respiratory distress, bradycardia, abdominal distention, or vomiting	-All neonates whose parents refused to consent	Level 2
Pastor Peidró JA, et al. <i>An Pediatr</i> . 2007. ⁹⁰	NICU	Prospective cohort	Spain	1 hour-30 days	113	PCT	Blood culture	-All newborns whose clinical history contained at least one risk factor for infection including bacteriuria during pregnancy, >18 hours of membrane rupture, and mothers received incomplete prophylactic antibiotics	-Not specified	Level 2
Peakman M, et al. <i>Arch Dis Child</i> . 1992. ⁹¹	NICU	Prospective Cohort	United Kingdom	1-73 days	56	WBC	Blood, CSF, urine culture	- babies admitted to NICU - either suspected of infection or controls (infants not suspected of infection but with blood taken for management purposes)	Not specified	Level 2
Philip AGS, et al. <i>Pediatrics</i> . 1980. ⁹²	NICU	Prospective Cohort	United States of America	0-7 days	376	CRP, WBC, ESR	Blood, CSF, urine culture	Any baby suspected on clinical grounds of having sepsis or meningitis in the first week after	Not specified	Level 1

								birth was included in the study.		
Pynn JM, et al. <i>Pediatr Res.</i> 2015. ⁹³	NICU	Prospective cohort	United States	>72 hours	139	CRP	Blood culture	- The eligible infants were of any GA and BW, inborn or outborn, who underwent one or more evaluations for late-onset sepsis.	- The infants on antibiotics at the time of sepsis evaluation were excluded.	Level 1
Rashwan NI, et al. <i>Pediatr Neonatol.</i> 2019. ⁹⁴	NICU	Prospective Cohort	Egypt, Arab Rep.	Not specified (presumably 0-30 days based on enrollment of "neonates")	168	CRP, PCT	Blood culture	-Neonates recruited from the NICU who exhibited clinical signs and symptoms of sepsis (respiratory distress, apnea, oxygen dependence, feeding intolerance, poor feeding, hypotension, shock, poor peripheral perfusion, tachycardia, lethargy, temperature instability, seizures, altered mental status, skin mottling and unexplained acidosis)	-Clearly apparent malformations -Prematurity -Apgar score less than seven -On antibiotics treatment before the start of the study	Level 1
Resch B, et al. <i>Acta Paediatr.</i> 2003. ⁹⁵	NICU	Prospective Cohort	Austria	0-12 hours	68	CRP, PCT	Blood culture; clinical criteria	-Positive clinical signs of sepsis and/or a history of factors associated with increased risk for infection	-Congenital malformations -Congenital infections associated with the TORCH complex -Refusal of parental consent	Level 2
Rohsiswatmo R, et al. <i>J Neonatal Perinatal Med.</i> 2020. ⁹⁶	NICU	Cross sectional	Indonesia	3-64 days	52	CRP, PCT, WBC	Blood culture	-Neonates >72 hours of age, at least one risk factor of LONS, and a predicted LONS score of >7 -Risk factors of LONS: low birth weight, prolonged parenteral nutrition, central intravenous access, and presence of morbidities (persistent ductus arteriosus, necrotizing enterocolitis, or hypoxic-ischemic encephalopathy)	-Multiple congenital anomalies or syndromes, history of surgery, or birth weight <1,000 grams	Level 2
Russell GAB, et al. <i>Arch Dis Child.</i> 1992. ⁹⁷	NICU	Prospective cohort	United Kingdom	Not specified	172	CRP	Blood culture	-All neonates admitted with either suspected infection or management of prematurity, low birth weight, respiratory distress syndrome, and asphyxia neonatorum	-Not stated	Level 2
Saboohi E, et al. <i>Pak J Med Sci.</i> 2019. ⁹⁸	NICU	Prospective cohort	Pakistan	0-7 days	85	CRP	Blood culture	-Neonates admitted to the NICU with presumed sepsis based on clinical suspicion not otherwise specified	-None listed	Level 3
Sakha K, et al. <i>Pak J Biol Sci.</i> 2008. ⁹⁹	NICU	Retrospective cohort	Iran, Islamic Rep.	0-28 days	117	CRP, PCT	Blood culture	-Neonates with suspected sepsis (proven sepsis who had positive blood culture and suspected sepsis who had negative blood culture but had positive CRP and either	-All neonates with congenital anomalies, gestational age <34 weeks, suspected hemorrhage, and neonates delivered with asphyxia.	Level 3

								neutropenia or thrombocytopenia and positive chest x-ray)		
Saleeh A, et al. <i>J Clin Neonatol.</i> 2020. ¹⁰⁰	NICU	Cross sectional	Egypt, Arab Rep.	0-8 days	55	CRP	Clinical sepsis	-Preterm and full-term neonates with both sexes, diagnosed with neonatal sepsis based on clinical and laboratory results. -We used clinical (temperature instability, respiratory rate >60 breaths/min plus grunting or desaturations, heart rate 180 beats/min or 100 beats/min, lethargy/altered mental status, glucose intolerance (plasma glucose >10 mmol/l) and feed intolerance) and laboratory criteria (thrombocytopenia, leukopenia, leukocytosis, CRP >10 mg/l or 2 standard deviation above normal value, immature neutrophils >10%, immature: total neutrophil ratio >0.2) plus positive blood cultures for diagnosis of neonatal sepsis.	-We excluded neonates with central nervous system malformations, birth asphyxia, and intracranial hemorrhages.	Level 4
Salzer HR, et al. <i>Acta Obstet Gynecol Scand.</i> 1987. ¹⁰¹	Not specified	Prospective cohort	Austria	Birth	25	CRP	Blood culture	-Infants whose mothers presented either with premature rupture of membranes alone, with PROM complicated by fever or without PROM but foul-smelling amniotic fluid and amnionitis (confirmed by histologic examination)	-Not stated	Level 3
Schmidt BK, et al. <i>Ped Infect Dis J.</i> 1987. ¹⁰²	NICU	Prospective cohort	Canada	4-48 days	297	CRP	Blood culture	-All neonates who underwent evaluation for suspected infection	-Not stated	Level 3
Seibert K, et al. <i>J Paediatr Child Health.</i> 1990. ¹⁰³	Not specified	Prospective cohort	Australia	0-3 days	125	CRP	Blood culture	-Neonates suspected of perinatally acquired infection, consisted of infants born at a gestational age of 31 weeks or less who were studied after birth.	-None listed	Level 3
Sharma A, et al. <i>Indian J Pediatr.</i> 1993. ¹⁰⁴	NICU	Prospective cohort	India	0-30 days	50	CRP, ESR	Blood culture	-Neonates with suspected sepsis with no obvious focus of infection	-None listed	Level 3
Shaw CK, et al. <i>East J Med.</i> 2012. ¹⁰⁵	NICU	Retrospective Cohort	Nepal	0-30 days	183	CRP	Blood culture or cerebrospinal fluid culture	-Neonates who presented with signs and symptoms of septicemia	Not specified	Level 3
Sonawane VB, et al. <i>J</i>	Inpatient	Prospective cohort	India	0-28 days	108	CRP, ESR, WBC	Blood culture	-Neonate with clinical suspicion of sepsis or with a positive	-None listed	Level 3

<i>Nepal Paediatr Soc.</i> 2014. ¹⁰⁶								"Neonatal sepsis score"		
Sorsa A. <i>Open Microbiol J.</i> 2018. ¹⁰⁷	NICU	Prospective Cohort	Ethiopia	0-28 days	303	CRP, WBC	Blood culture	-Clinical dx of sepsis (≥ 2 of low birth weight (<2500 grams) or prematurity (<37 weeks of gestation), presence maternal febrile illness within 2 weeks prior to delivery, foul smelling and/or meconium stained amniotic liquid, suspected chorioamnionitis, rupture of membranes >18 hours, prolonged labor >24 hrs, perinatal asphyxia (Apgar score <4 at 1 minute), clinical signs of sepsis)	Neonate whose mother available was not to give consent and interview.	Level 3
Squire EN, Jr., et al. <i>Pediatr Infect Dis J.</i> 1982. ¹⁰⁸	NICU	Prospective Cohort	United States of America	0-30 days	123	CRP, ESR, WBC	Culture (blood, CSF, urine, tracheal aspirate, peritoneal fluid, and middle ear fluid)	-All newborns placed on antibiotics for presumptive bacterial infection	-Prior prophylactic antibiotics treatment -Incomplete data	Level 3
Stein M, et al. <i>Clin Pediatr.</i> 2015. ¹⁰⁹	Emergency Department	Prospective Cohort	Israel	3 days-3 months	112	CRP, PCT, WBC	Blood, urine, CSF culture	-All children who were evaluated for suspected SBI for symptoms including body temperature $\geq 38.0C$ or $\leq 35.7C$, vomiting, restlessness, drowsiness, poor appetite, pathologic jaundice, respiratory distress, or apnea	-Patients with underlying conditions -Previous antibiotic treatment -Immune deficiency -Neonates with history of prematurity (born prior to 37 gestational weeks)	Level 2
Steinberger E, et al. <i>Scan J Clin Lab Invest.</i> 2014. ¹¹⁰	NICU	Retrospective Cohort	Austria	"Neonates", age not specified	218	CRP, PCT	Blood culture; clinical criteria	-Prematurity (<37 weeks of gestation) -Suspected infection -Inborn birth	-Death during the first 3 days of life -Severe malformation -Missing values of PCT, IL6 or CRP -Unavailable information for the diagnosis of EOS	Level 2
Sucilathangam G, et al. <i>J Clin Diagn Res.</i> 2012. ¹¹¹	NICU	Prospective Cohort	India	0-24 days	50	CRP, ESR, PCT, WBC	Blood culture	-Neonates with signs suggestive of sepsis not otherwise specified	-Neonates who were on antibiotics previously -Neonates who had birth asphyxia, aspiration syndromes, inborn errors of metabolism, and congenital anomalies	Level 3
Tessema B, et al. <i>Diagnostics (Basel).</i> 2020. ¹¹²	Not specified	Cross sectional	Germany	0-28 days	739	CRP	Blood culture	- Sepsis-suspected neonates were retrospectively classified as proven sepsis, clinical sepsis, or controls based on C-reactive protein (CRP) and blood culture results. Proven sepsis was defined as CRP > 10 mg/L in at least one of the five serial measurements and positive blood culture. Clinical sepsis was defined as	- Neonates with positive blood cultures for coagulase negative staphylococci (CoNS) organisms and CRP < 10 mg/L in all five serial measurements were considered as potential contamination and excluded from our analysis.	Level 3

								CRP > 10 mg/L in at least one of the five serial measurements and negative blood culture. No sepsis (control) was defined as neonates suspected for sepsis, with negative blood culture, CRP < 10 mg/L in all five serial measurements, and neonates who had not started antibiotics treatment before blood collection.		
Magudumana MO, et al. <i>J Trop Pediatr.</i> 2000. ¹¹³	NICU	Prospective cohort	South Africa	0-30 days	255	CRP	Blood culture	-All neonates who were investigated for suspected sepsis based on respiratory distress, apnea/bradycardia, lethargy, irritability, seizures, temperature instability, increasing vent requirements, hypotension, poor peripheral circulation, abdominal distention, and feeding intolerance	-Problem with specimen (e.g., insufficient sample, specimen lost) -Lack of parental consent	Level 3
Panda SK, et al. <i>Cureus.</i> 2021. ¹¹⁴	NICU	Retrospective cohort	India	"neonates"	93	CRP	Blood culture	Not included	Not included	Level 5
Puello Avila AC, et al. <i>Rev Chilena Infectol.</i> 2021. ¹¹⁵	NICU	Cross sectional	Colombia	"neonates"	198	CRP	Blood culture	-neonates evaluated for sepsis	-born in another hospital, serious medical problems, low birth weight	Level 4
Salah A, et al. <i>BMC Infect Dis.</i> 2021. ¹¹⁶	NICU	Cross sectional	Yemen	0-72 hours	199	CRP, WBC	Blood culture	-admitted for 72 hours or more	-congenital anomalies and hemolytic jaundice	Level 2
Shivasharana B, et al. <i>Eur J Molecular Clin Med.</i> 2022. ¹¹⁷	NICU	Prospective cohort	India	Not listed	128	PCT	Blood culture and clinical sepsis	-at least 3 symptoms and signs of late onset sepsis	-babies with clinical features of sepsis before 72 hours of life -HIE stage III -neonate with surgical problem -babies with life threatening congenital anomalies -extramural babies	Level 3
Takassi OE, et al. <i>Arch Pediatr.</i> 2022. ¹¹⁸	NICU	Case control	France	0-3 days	50	CRP, PCT	Blood culture	-born alive at <37 weeks of gestational age with suspected neonatal bacterial infection during the first 3 days of life were included in the study	-	Level 2
Tunç T, et al. <i>J Neonatal Perinatal Med.</i> 2020. ¹¹⁹	NICU	Prospective cohort study	Turkey	0-72 hours	130	CRP	Blood culture	-Preterm and term newborns being followed-up in the NICUs with the suspicion of sepsis -Presenting with non-specific findings of sepsis including apnea, needing supplemental oxygen or mechanical ventilation	-Patients with congenital abnormalities	Level 3

								hypotension, bradycardia or tachycardia, temperature instability, feeding intolerance, abdominal distension, and necrotizing enterocolitis		
Turner D, et al. <i>Acta Paediatr.</i> 2006. ¹²⁰	NICU	Prospective Cohort	Israel	3-66 days	85	CRP, PCT	Confirmed sepsis: positive blood, CSF or urine culture/radiologically proven pneumonia/cellulitis and clinical signs of infection. Clinical sepsis: clinical signs of infection	-Preterm infants (< 36 weeks) admitted to NICU -Sepsis workup during admission	-No parental consent	Level 4
Utkarshni SJ, et al. <i>Int J Curr Res Med Sci.</i> 2018 ¹²¹	NICU	Prospective cohort	India	4-28 days	50	CRP, PCT	Blood culture	- Any neonate with signs and symptoms suggestive for sepsis or who developed signs of sepsis while in the ward in 4-28 days of life.	- The exclusion criteria for this study was administration of antibiotic therapy prior to admission, neonates with birth asphyxia, aspiration syndromes, laboratory findings, suggestive of inborn errors or metabolism and in neonates with any congenital anomalies.	Level 3
Varsha, et al. <i>Indian J Pathol Microbiol.</i> 2003. ¹²²	NICU	Prospective Cohort	India	"Neonates", age not specified	150	CRP, WBC	Blood culture	-Admitted to nursery with clinically suspected sepsis -Term, appropriate for gestational age, apparently healthy neonates recruited as controls	-Pregnancy induced hypertension -Birth asphyxia	Level 2
Vazzalwar R, et al. <i>J Perinatol.</i> 2005. ¹²³	NICU	Prospective Cohort	United States of America	"Neonates", age not specified	51	CRP, PCT	Blood, cerebrospinal, or urine culture	-<37 weeks gestation at birth -Birth weight ≤1500 g -No antibiotic therapy for the previous 48 hours	-Lethal congenital anomalies	Level 3
Velasco R, et al. <i>Pediatr Infect Dis J.</i> 2015. ¹²⁴	Emergency Department	Prospective cohort	Spain	0-90 days	766	CRP, PCT, WBC	Blood and/or CSF culture	-Neonates <90 days old presenting with fever without a source to the pediatric emergency department who had CRP, WBC count, urine dipstick, urine and blood culture performed	-No collection or urine or blood by sterile method -No WBC or CRP values determined -Patients in whom the history and/or the physical examination suggested the source of the fever -Afebrile patients at arrival who had not any measured temperature >38°C at home -Parental refusal to participate -No phone contact to follow-up 1 month after the study	Level 2
Verboon-Maciolek MA, et al. <i>Pediatric</i>	Multiple	Prospective Cohort	Netherlands	0-60 days	92	CRP, PCT	Culture (blood, CSF), PCR	-Two or more of the following clinical symptoms: fever or temperature instability,	Not specified	Level 3

Research. 2006. ¹²⁵								respiratory distress, poor peripheral circulation, irritability, lethargy, apnea, tachycardia, hypotension, poor feeding, abdominal distention, and diarrhea -Controls were infants without signs of infection who were admitted to the NICU		
Wagle S, et al. <i>J Paediatr Child Health</i> . 1994. ¹²⁶	NICU	Prospective Cohort	Australia	Age not specified	309	CRP, WBC	Culture (blood, cerebrospinal fluid, urine)	-All babies born <30 weeks GA admitted to the NICU between Jan to Dec 1990 in the state of Western Australia	Not specified	Level 2
Waterfield T, et al. <i>BMC Pediatr</i> . 2018. ¹²⁷	Emergency Department	Prospective Cohort	United Kingdom	0-90 days	126	CRP, PCT	Blood, CSF culture	-Any child under 90 days of age presenting with signs or symptoms suggestive of possible bacterial infection	Not specified	Level 1
Weirich E, et al. <i>J Pediatr</i> . 1998. ¹²⁸	NICU	Prospective cohort	United States of America	0-1 day	106	CRP	Blood, CSF, and urine cultures (bacterial or viral)	-All neonates born >28 weeks gestation admitted on the first day of life with perceived risk for infection, per attending pediatrician in accordance with NICU guidelines, either because of maternal intrapartum risk factors or infant symptoms	-Neonates with noninfectious diagnoses that accounted for symptoms	Level 3
Wen N, et al. <i>Int J Clin Exp Med</i> . 2019. ¹²⁹	NICU	Prospective cohort	China	1-28 days	92	CRP, PCT	Clinical "established by the Chinese Medical Association Pediatrics Branch"	-Patients admitted to the neonatology department from January to February 2018 were included	-Simultaneous infection with other blood disorders, autoimmune diseases, malignant tumor complications, and patients who were unwilling or unable to cooperate with the study and follow-up	Level 4
West BA, et al. <i>Antimicrob Resist Infect Control</i> . 2012. ¹³⁰	NICU	Prospective cohort	Nigeria	"neonates"	420	CRP	Blood culture	-Neonates with clinical suspicion or risk factors for sepsis	-Neonates of mothers who had intrapartum antibiotics within 1 week of delivery -Neonates with prior antibiotic therapy for present illness	Level 2
Woelker JU, et al. <i>Pediatr Emerg Care</i> . 2012. ¹³¹	Emergency Department	Prospective Cohort	United States of America	2-60 days	155	PCT, WBC	Serious bacterial infection was defined as positive blood or CSF culture, bacterial pathogen in stool, or as a positive urine culture with greater than 50,000 colony-	-Infants presenting to the pediatric ED with a rectal temperature of 38-C or higher (recorded at home, in a physician's office, or in the pediatric ED) who appeared generally well	-Beyond study age -No recorded temperature -Temperature less than threshold -Pretreatment with antibiotics	Level 1

							forming units/mL of a single pathogen or 10,000 to 49,000 colony-forming units/mL with positive urinalysis (UA)			
Ye Q, et al. <i>Pediatr Res.</i> 2017. ¹³²	Multiple	Prospective Cohort	China	0-30 days	840	CRP	Blood culture	-positive blood culture and compatible clinical features, (respiratory distress, cyanosis, poor perfusion, lethargy, poor feeding, apnea, and bradycardia) -Neonatal patients with jaundice or enterovirus infection and healthy newborns were matched for age, body weight, and gender and recruited as controls	Not specified	Level 3
Yu R, et al. <i>J Int Med Res.</i> 2020. ¹³³	NICU	Prospective cohort	China	0-28 days	47	PCT	Blood culture	-admitted neonates with clinically suspected sepsis -criteria for sepsis included: 1) symptoms of infection, including an unstable temperature, apnea, or decrease in heart rate; and 2) positive for at least two of the following experimental tests: total white blood cell count <5 10 ⁶ /L or >20 10 ⁶ /L, immature-to-total neutrophil ratio 0.16, platelet count 100 10 ⁶ /L, CRP levels ≥6 mg/L, and PCT levels 0.5 ng/mL.		Level 3
Zhou B, et al. <i>Exp Ther Med.</i> 2016. ¹³⁴	NICU	Prospective cohort	China	day of life 0	200	CRP	Blood culture	-Neonates with premature rupture of membranes, amnionitis, meconium stained amniotic fluid, birthweight <2,500 grams, preterm infants (<37 weeks), resuscitation required in the labor room, mother having temperature of >38C, urinary tract infection in the mother	-Neonates born to mothers who had received antenatal antibiotic therapy <48 hours prior to delivery -Neonates with major congenital anomalies	Level 2

Supplemental Table 2. Test characteristics of erythrocyte sedimentation rate (ESR) in the diagnosis of neonatal sepsis.

ESR Cut Point (mm/hour), ≥	Sensitivity (95% CI)	Specificity (95% CI)	Youden's Index	Area Under Receiver Operating Characteristic Curve	Reference Standard(s)	Total Patients, n	Disease, n ^a	Studies, n	I ²
<i>All Included Studies</i>									
15	0.30 (0.19, 0.44)	0.81 (0.26, 0.98)	0.11	0.36 (0.17, 0.85)	Blood culture	599	125	3	29.7-30.3%

^aDefined as positive for disease using reference standard.

Supplemental Table 3. Test characteristics of white blood cell (WBC) count in the diagnosis of neonatal sepsis

WBC Level (cells/mm ³), ≥	Sensitivity (95% CI)	Specificity (95% CI)	Youden's Index	Area Under Receiver Operating Characteristic Curve	Reference Standard(s)	Total Patients, n	Disease, n ^a	Studies, n	I ²
<i>All Included Studies</i>									
5,000	0.30 (0.21, 0.41)	0.87 (0.83, 0.91)	0.17	0.75 (0.47, 0.86)	Blood culture	1,850	509	11	5.3%
<i>High Income Countries Only</i>									

5,000	0.35 (0.21, 0.52)	0.86 (0.79, 0.91)	0.21	0.73 (0.37, 0.87)	Blood culture	1,280	292	5	8.1-8.2%
15,000	0.34 (0.20, 0.52)	0.74 (0.52, 0.88)	0.08	0.50 (0.30, 0.77)	Blood culture	973	79	3	0%
<i>Low Income Countries Only</i>									
5,000	0.26 (0.14, 0.43)	0.89 (0.82, 0.94)	0.15	0.76 (0.38, 0.89)	Blood culture	570	217	6	3.4%
20,000	0.40 (0.15, 0.70)	0.87 (0.73, 0.95)	0.27	0.78 (0.38, 0.88)	Blood culture	610	192	3	1.1%

^aDefined as positive for disease using reference standard.

Appendix 1. Search terms used to identify potential articles reporting the results of studies evaluating test characteristics of selected biomarkers.

PubMed

((((((((((Procalcitonin[mesh] OR Procalcitonin[tiab] OR Calcitonin[mesh] OR "Calcitonin Precursor Polypeptide"[tiab] OR "Calcitonin 1"[tiab] OR "Calcitonin Related Polypeptide Alpha"[tiab] OR "Pro-Calcitonin"[tiab]))) OR (("C-Reactive Protein"[mesh] OR "C Reactive Protein"[tiab] OR CRP[tiab])) OR (("Blood Sedimentation"[mesh] OR "Blood Sedimentation"[tiab] OR "Erythrocyte Sedimentation"[tiab] OR ESR[tiab]))) AND (((("Radiography, Thoracic"[mesh] OR "chest x ray"[tiab] OR "chest x rays"[tiab] OR CXR[tiab] OR "thoracic radiography"[tiab] OR "thoracic radiographies"[tiab] OR "chest radiography"[tiab] OR "chest radiographies"[tiab] OR "thoracic x ray"[tiab] OR "thoracic x rays"[tiab])) OR (("Bacteriological Techniques"[mesh] OR culture[tiab] OR cultures[tiab] OR cultured[tiab])) OR (("clinical impression"[tiab] OR "clinical impressions"[tiab] OR "clinical gestalt"[tiab] OR "clinical presentation"[tiab] OR "clinical presentations"[tiab] OR "clinical feature"[tiab] OR "clinical features"[tiab] OR "clinical finding"[tiab] OR "clinical findings"[tiab]))) AND (((((((adolescent[mesh] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR teen[tiab] OR teens[tiab] OR teenager[tiab] OR teenagers[tiab] OR youth[tiab] OR youths[tiab])) OR ((child[mesh] OR child[tiab] OR children[tiab])) OR ((child, preschool"[mesh] OR toddler[tiab] OR toddlers[tiab])) OR ((infant[mesh] OR infants[tiab] OR infant[tiab] OR baby[tiab] OR babies[tiab])) OR ((infant, newborn"[mesh] OR newborn[tiab] OR newborns[tiab] OR neonate[tiab] OR neonates[tiab])) OR ((pediatrics[mesh] OR pediatrics[tiab] OR pediatric[tiab]))) NOT "case reports"[Publication Type]

EMBASE

('procalcitonin'/exp OR procalcitonin:ab,ti OR 'calcitonin'/exp OR 'calcitonin':ab,ti OR 'calcitonin precursor polypeptide':ab,ti OR 'calcitonin 1':ab,ti OR 'calcitonin related polypeptide alpha':ab,ti OR 'pro-calcitonin':ab,ti OR 'c reactive protein'/exp OR 'c reactive protein' OR 'c reactive protein':ab,ti OR crp:ab,ti OR 'erythrocyte sedimentation rate'/exp OR 'erythrocyte sedimentation rate' OR 'blood sedimentation':ab,ti OR 'erythrocyte sedimentation':ab,ti OR esr:ab,ti) AND ('thorax radiography'/exp OR 'chest x ray':ab,ti OR 'chest x rays':ab,ti OR cxr:ab,ti OR 'thoracic radiography':ab,ti OR 'thoracic radiographies':ab,ti OR 'chest radiography':ab,ti OR 'chest radiographies':ab,ti OR 'thoracic x ray':ab,ti OR 'thoracic x rays':ab,ti OR 'bacterium culture'/exp OR culture:ab,ti OR cultures:ab,ti OR cultured:ab,ti) AND ('adolescent'/exp OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR teen:ab,ti OR teens:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR youth:ab,ti OR youths:ab,ti OR 'child'/exp OR child:ab,ti OR children:ab,ti OR 'preschool child'/exp OR 'school child'/exp OR toddler:ab,ti OR toddlers:ab,ti OR 'infant'/exp OR 'baby'/exp OR infants:ab,ti OR infant:ab,ti OR baby:ab,ti OR babies:ab,ti OR 'newborn'/exp OR newborn:ab,ti OR newborns:ab,ti OR neonate:ab,ti OR neonates:ab,ti OR 'pediatrics'/exp OR pediatrics:ab,ti OR pediatric:ab,ti) NOT 'case report'/de

CINAHL

(DE 'Calcitonin' OR AB 'procalcitonin' OR AB 'calcitonin'/exp OR AB 'calcitonin' OR AB 'calcitonin precurs' OR AB 'polypeptide' OR AB 'calcitonin 1' OR AB 'calcitonin related polypeptide alpha' OR AB 'pro-calcitonin' OR DE 'C-Reactive Protein' OR AB 'c reactive protein' OR AB 'c reactive protein' OR AB 'crp' OR DE 'Blood Sedimentation' OR AB 'erythrocyte sedimentation rate' OR AB 'blood sedimentation' OR AB 'erythrocyte sedimentation' OR AB 'esr') AND (DE 'Radiography, Thoracic' OR AB 'chest x ray' OR AB 'chest x rays' OR AB 'cxr' OR AB 'thoracic radiography' OR AB 'thoracic radiographies' OR AB 'chest radiography' OR AB 'chest radiographies' OR AB 'thoracic x ray' OR AB 'thoracic x rays' OR DE Microbial Culture and Sensitivity Tests' OR AB 'culture' OR AB 'cultures' OR AB 'cultured') AND (DE 'adolescence' OR AB 'adolescent' OR AB 'adolescents' OR AB 'adolescence' OR AB 'teen' OR AB 'teens' OR AB 'teenager' OR AB 'teenagers' OR AB 'youth' OR AB 'youths' OR DE 'child' OR AB 'child' OR AB 'children' OR DE 'child, preschool' OR AB 'toddler' OR AB 'toddlers' OR DE 'infant' OR AB 'infants' OR AB 'infant' OR AB 'baby' OR AB 'babies' OR AB 'newborn' OR AB 'newborns' OR AB 'neonate' OR AB 'neonates' OR DE 'pediatrics' OR AB 'pediatrics' OR AB 'pediatric')

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