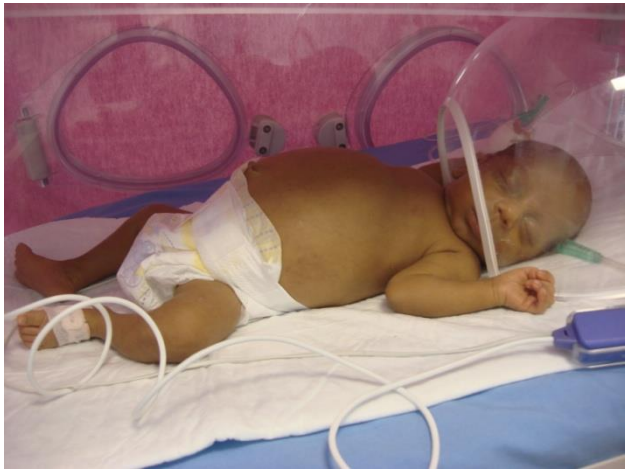


Yenidoğan sepsisi

Tanı ve Tedavi

Prof.Dr.Rahmi Örs

NE Ü Meram Tıp Fakültesi

Neonatoloji Bilim Dalı

NEONATAL MORTALITY RATES, 2010

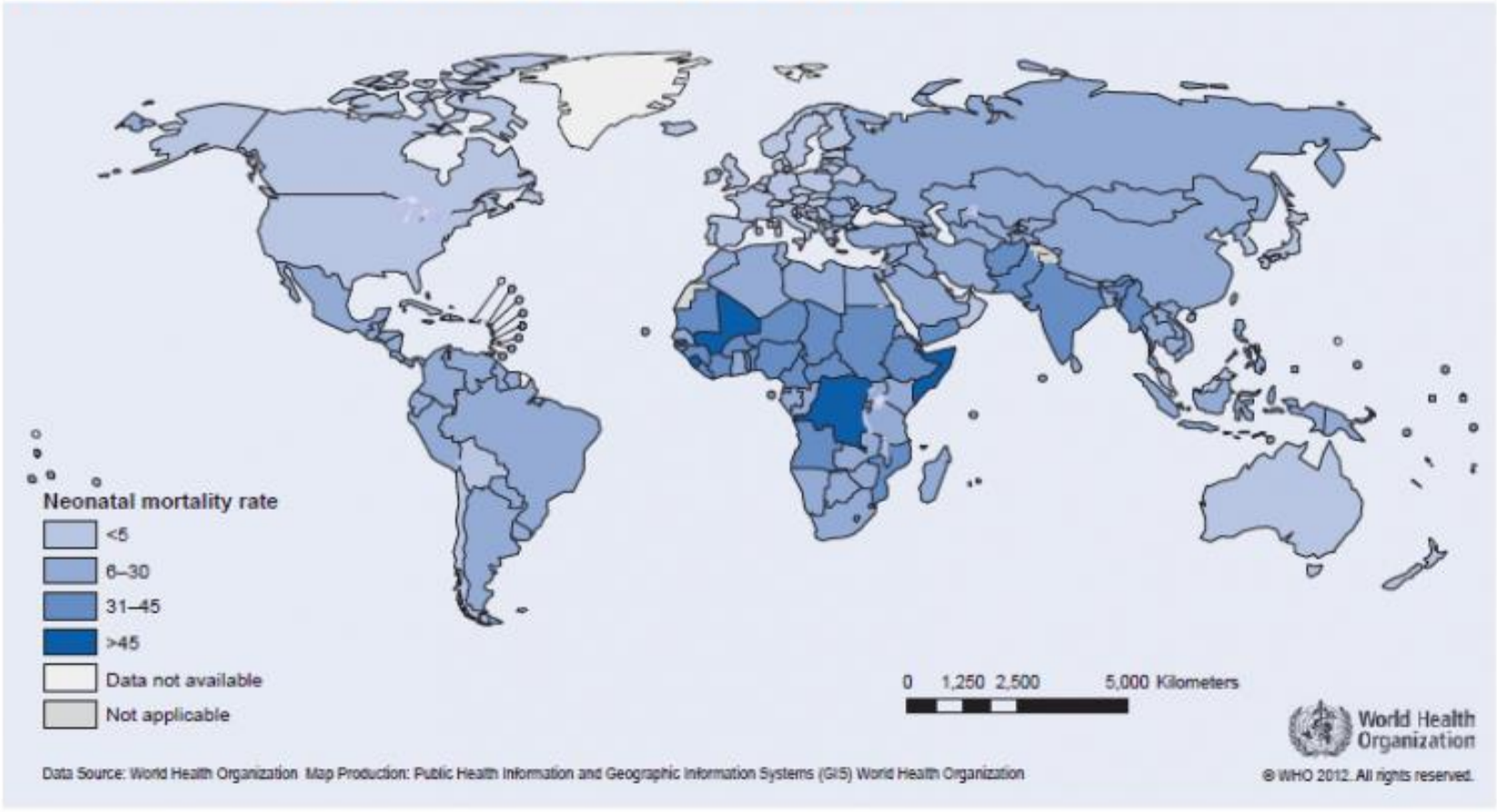
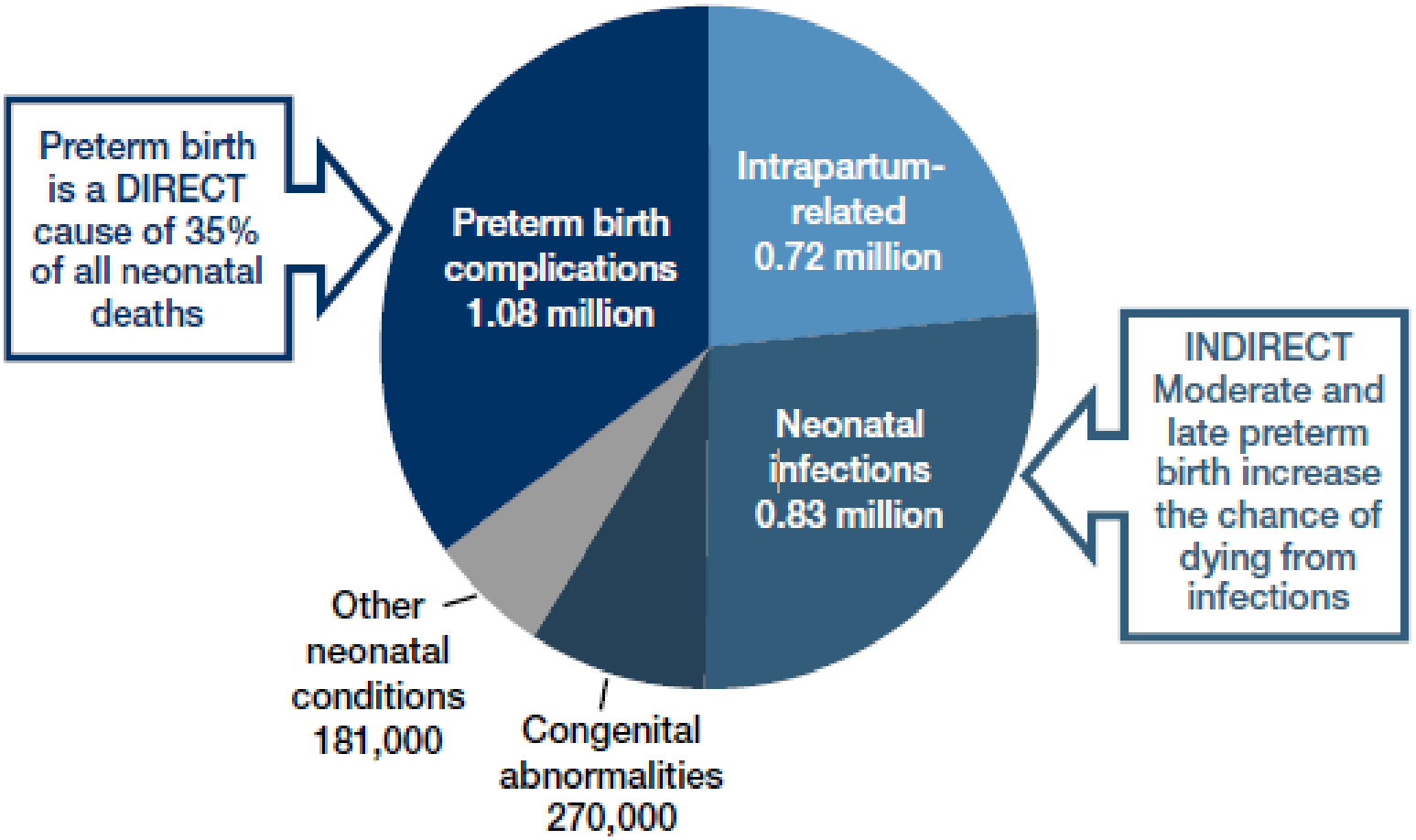


Figure 2.1: Estimated distribution of causes of 3.1 million neonatal deaths in 193 countries in 2010



Preterm birth is a risk factor for neonatal and postneonatal deaths
At least 50% of all neonatal deaths are preterm

Source: Updated from Lawn et al., 2005, using data from 2010 published in Liu Let al., 2012.

Neonatal Sepsis

- Yenidoğan ölümlerinde bütün dünyada önemli bir neden
- Erken tanı ve hedefe yönelik tedavi önemli

- ÇDDA'lı bebeklerin > %20 geç sepsis
- Kuşkulu sepsis
  - YYBU'lerinde en sık tanılardan biri
  - Sepsisi taklit eden, sepsis riskini artıran klinik durumlar
  - Sağlıklı gözüken bir bebeği uzun süre tedavi
- Aciliyet
  - Erken tanı ve tedavi başlama kritik
  - Tedavi gerektirmeyecek vakaları tanımak
  - Başlayınca tedaviyi kesme zorluğu
  - Gereksiz tedavi dirençli mikroorganizmalarla enfeksiyon riskini artırır
- Anneden ayrılma, hastanede yatışın riskleri

Stoll B, Hansen N, Fanaroff A, et al. Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. *Pediatrics. 2002;110:285-291.*

Clark R, Bloom B, Spitzer A, et al. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics. 2006;117:67-74.*

Box 6-1 Differential Diagnosis: Clinical Signs Associated With Neonatal Sepsis and Some Noninfectious Conditions

Respiratory Distress (Apnea, Cyanosis, Costal and Sternal Retraction, Rales, Grunting, Diminished Breath Sounds, Tachypnea)

Transient tachypnea of the newborn
Respiratory distress syndrome
Atelectasis
Aspiration pneumonia, including meconium aspiration
Pneumothorax
Pneumomediastinum
Central nervous system disease: hypoxia, hemorrhage
Congenital abnormalities, including tracheoesophageal fistula, choanal atresia, diaphragmatic hernia, hypoplastic lungs
Congenital heart disease
Cardiac arrhythmia
Hypothermia (neonatal cold injury)
Hypoglycemia
Neonatal drug withdrawal syndrome
Medication error with inhaled epinephrine

Temperature Abnormality (Hyperthermia or Hypothermia)

Altered environmental temperature
Disturbance of central nervous system thermoregulatory mechanism, including anoxia, hemorrhage, kernicterus
Hyperthyroidism or hypothyroidism
Neonatal drug withdrawal syndrome
Dehydration
Congenital adrenal hyperplasia
Vaccine reaction

Jaundice

Breast milk jaundice
Blood group incompatibility
Red cell hemolysis, including blood group incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency
Resorption of blood from closed space hemorrhage
Gastrointestinal obstruction, including pyloric stenosis
Extrahepatic or intrahepatic biliary tract obstruction
Inborn errors of metabolism, including galactosemia, glycogen storage disease type IV, tyrosinemia, disorders of lipid metabolism, peroxisomal disorders, defective bile acid synthesis (trihydroxycoprostanic acidemia)
Hereditary diseases, including cystic fibrosis, α1-antitrypsin deficiency, bile excretory defects (Dubin-Johnson, Rotor, Byler, Aagenaes syndrome)
Hypothyroidism
Prolonged parenteral hyperalimentation

Hepatomegaly

Red cell hemolysis, including blood group incompatibility, G6PD deficiency
Infant of a diabetic mother
Inborn errors of metabolism, including galactosemia, glycogen storage disease, organic acidemias, urea cycle disorders, hereditary fructose intolerance, peroxisomal disorders
Biliary atresia
Congestive heart failure
Benign liver tumors, including hemangioma, hamartoma
Malignant liver tumors, including hepatoblastoma, metastatic neuroblastoma, congenital leukemia

Gastrointestinal Abnormalities (Anorexia, Regurgitation, Vomiting, Diarrhea, Abdominal Distention)

Gastrointestinal allergy
Overfeeding, aerophagia
Intestinal obstruction (intraluminal or extrinsic)
Necrotizing enterocolitis
Hypokalemia
Hypercalcemia or hypocalcemia
Hypoglycemia
Inborn errors of metabolism, including galactosemia, urea cycle disorders, organic acidemias
Ileus secondary to pneumonia
Congenital adrenal hyperplasia
Gastric perforation
Neonatal drug withdrawal syndrome

Lethargy

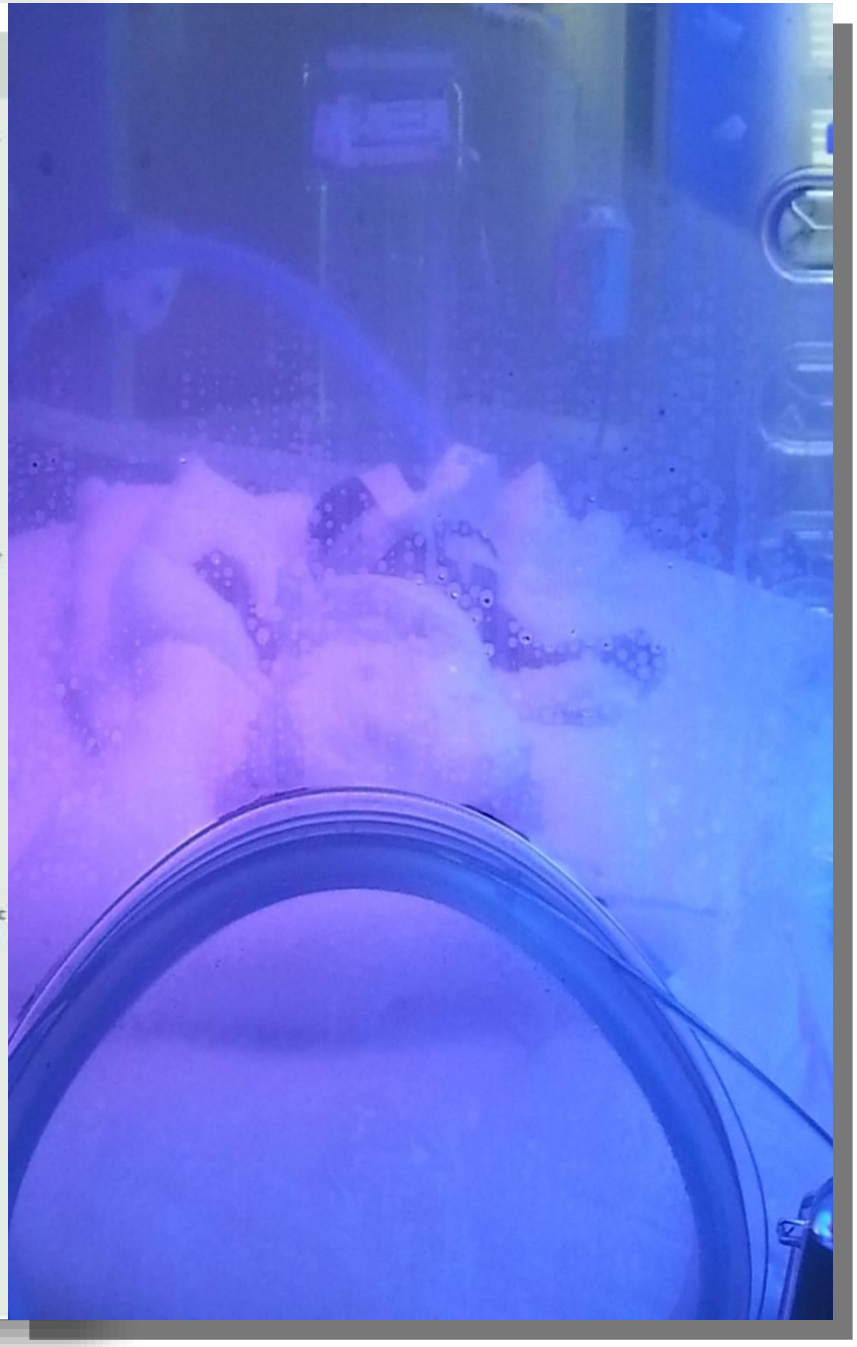
Central nervous system disease, including hemorrhage, hypoxia, or subdural effusion
Congenital heart disease
Neonatal drug withdrawal syndrome
Hypoglycemia
Hypercalcemia
Familial dysautonomia

Seizure Activity (Tremors, Hyperactivity, Muscular Twitching)

Hypoxia
Intracranial hemorrhage or kernicterus
Congenital central nervous system malformations
Neonatal drug withdrawal syndrome
Hypoglycemia
Hypocalcemia
Hyponatremia, hypernatremia
Hypomagnesemia
Inborn errors of metabolism, including urea cycle disorders, organic acidemias, galactosemia, glycogen storage disease, peroxisomal disorders
Pyridoxine deficiency

Petechiae, Purpura, and Vesiculopustular Lesions

Birth trauma
Blood group incompatibility
Neonatal isoimmune thrombocytopenia
Maternal idiopathic thrombocytopenic purpura
Maternal lupus erythematosus
Drugs administered to mother
Giant hemangioma (Kasabach-Merritt syndrome)
Thrombocytopenia with absent radii (TAR) syndrome
Disseminated intravascular coagulopathy
Coagulation factor deficiencies
Congenital leukemia
Child abuse
Cutaneous histiocytosis



- Kardiyak
  - Konjenital
    - Hipoplastik sol kalp sendromu
    - Diğer yapısal defektler
    - PPHN (persistan pulmoner hipertansiyon)
  - Kazanılmış
    - Miyokardit
    - Hipovolemik veya kardiyojenik şok
    - PPHN
- Hematolojik
  - Neonatal purpura fulminans
  - İmmün mediated trombositopeni
  - İmmün mediated nötropeni
  - Ciddi anemi
  - Malignansi (konjenital lösemi)
  - Herediter pıhtılaşma bozuklukları
- GİS
  - Nekrotizan enterokolit
  - Spontan GİS perforasyon
  - Yapısal anomaliler

- Metabolik
  - Hipoglisemi
  - Doğumsal metabolizma hatalıkları: Organik asidemi, laktik asidozlar, üre siklus bozuklukları
  - Adrenal bozukluklar: Adrenal hemoraji, adrenal yetmezlik, konjenital adrenal hiperplazi
- Nörolojik
  - İntrakraniyal hemoraji: Spontan veya istismar
  - Hipoksik iskemik ensefalopati
  - Konvülziyonlar
  - İnfantil botulizm
- Solunum
  - Respiratuar distress sendromu
  - Yenidoğanın geçici takipnesi
  - Aspirasyon pnömonisi: Amniyotik sıvı, mekonyum veya mide içeriği aspirasyonu
  - Akciğer hipoplazisi
  - Trakeoözefajial fistül

- ÇDDA'lı bebeklerin > %20 geç sepsis
- Kuşkulu sepsis
  - YYBU'lerinde en sık tanılardan biri
  - Sepsisi taklit eden, sepsis riskini artıran klinik durumlar
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  - Erken tanı ve tedavi başlama kritik
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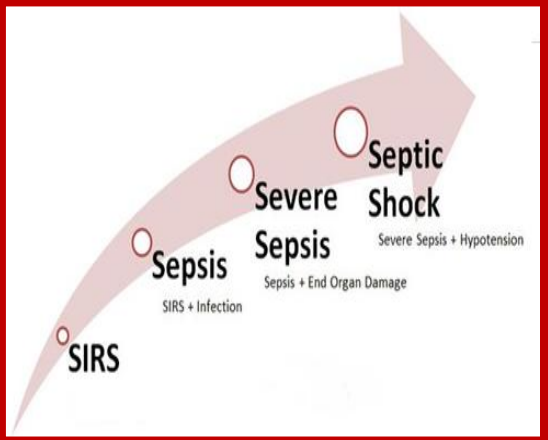
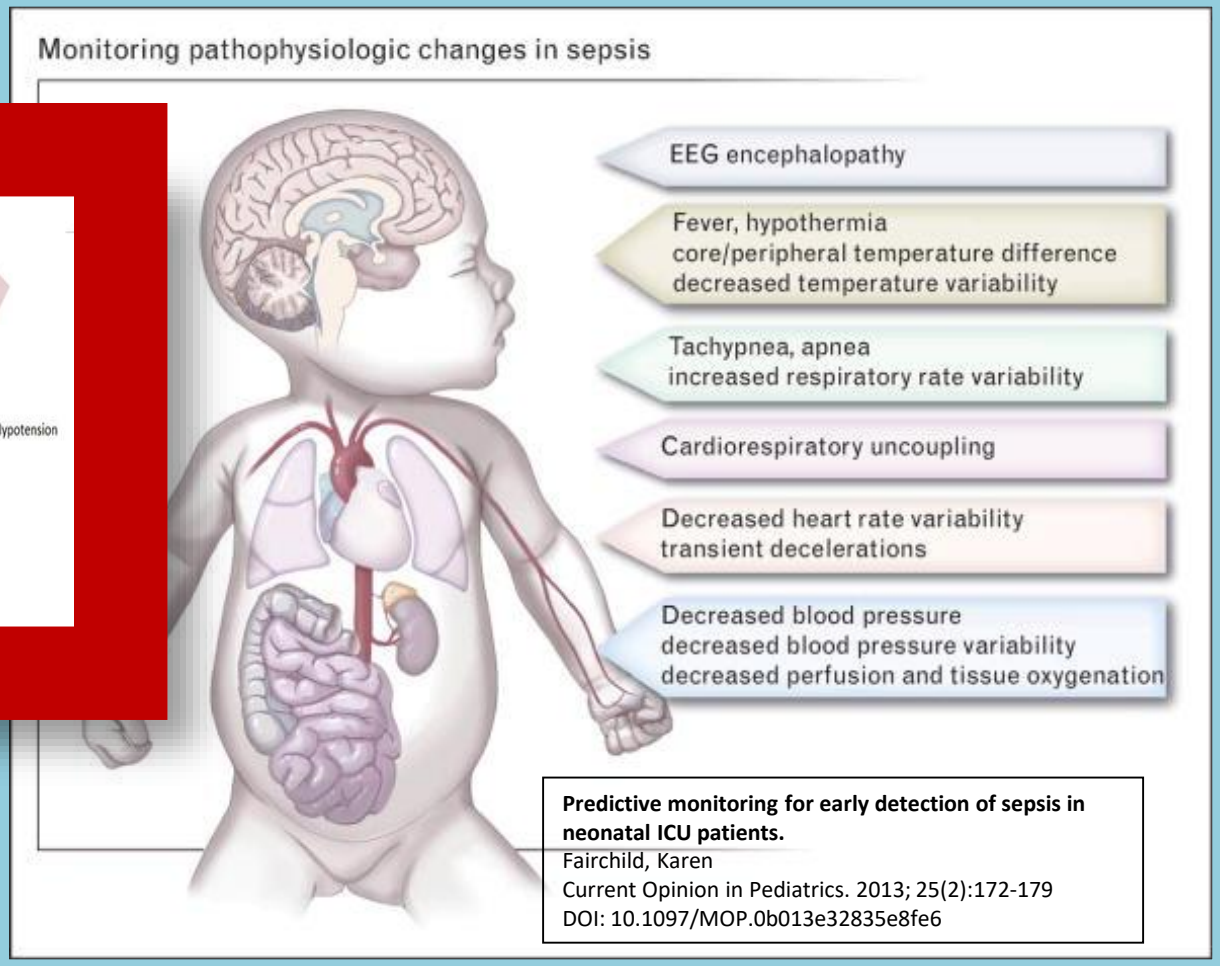
Riskli bebek grupları

- Sıklık: 1000 canlı doğumda 1-5
- Term erkeklerde iki kat daha fazla
- Prematüre ve DDA bebeklerde 3-10 kat fazla
  - Maternal genital trakt infeksiyonu prematüreliğin önemli nedeni
  - İntraamniyotik infeksiyon sıklığı fazla
  - İmmün disfonksiyon daha belirgin
  - Uzamış hospitalizasyon, invazif işlemler, intübasyon vs
- Çoğul gebelik
- Maternal koriyoamniyonitis
  - İntrapartum ateş(>38), maternal lökositoz(>18000/mm3), uterin hassasiyet
  - Histolojik koriyoamniyonitis gebelik haftası ile ters orantılı
- Konjenital immün defektler
- Asplenia
- Galaktozemi (E.Koli)
- Malformasyonlar (obstrüktif üropati)
- Erken membran rüptürü: 18 saatten uzun
- Nozokomiyal infeksiyon:
  - Tanım?
    - 3 günden sonra oluşan
    - Hastaneden kazanılan
  - Risk grupları
    - Prematüre, LBW, invazif işler, entübasyon, şant, deri ve müköz membran bütünlüğünde bozulma, geniş spektrumlu antibiyotik kullanımı, uzun süre hasatnede kalma



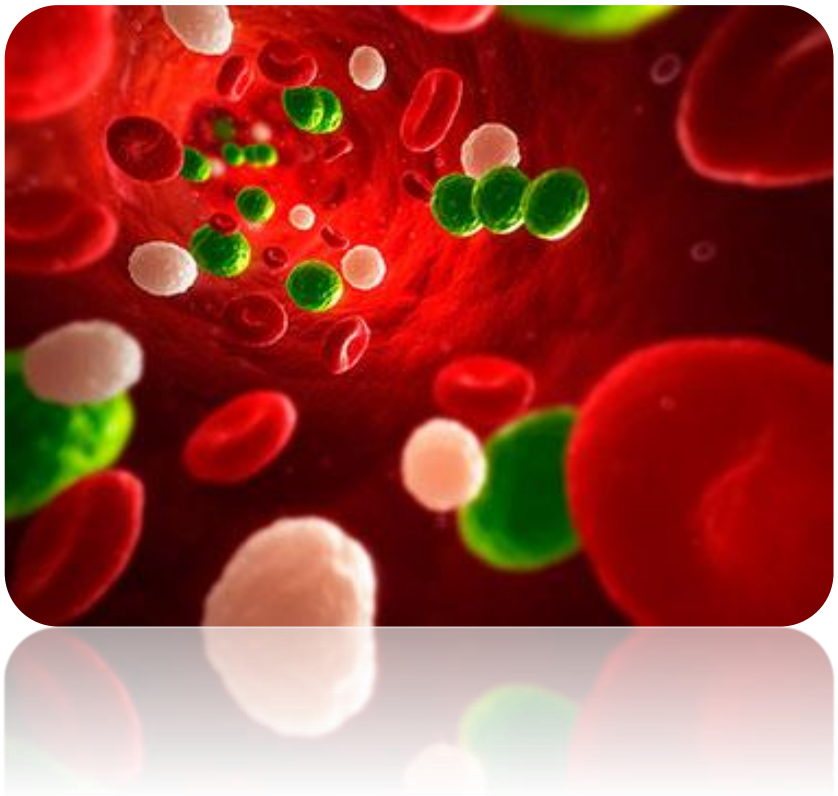


Predictive monitoring for early detection of sepsis in neonatal ICU patients.
Fairchild, Karen
Current Opinion in Pediatrics. 2013; 25(2):172-179
DOI: 10.1097/MOP.0b013e32835e8fe6

Wolters Kluwer Health | OvidSP

Dalgic N, Ergenekon E, Koc E, et al. NOSEP and clinical scores for nosocomial sepsis in a neonatal intensive care unit. *J Trop Pediatr. 2006;52:226-227.*
Griffin MP, Lake DE, Bissonette EA, et al. Heart rate characteristics: Novel physiomarkers to predict neonatal infection and death. *Pediatrics. 2005; 116: 1070-1074.*

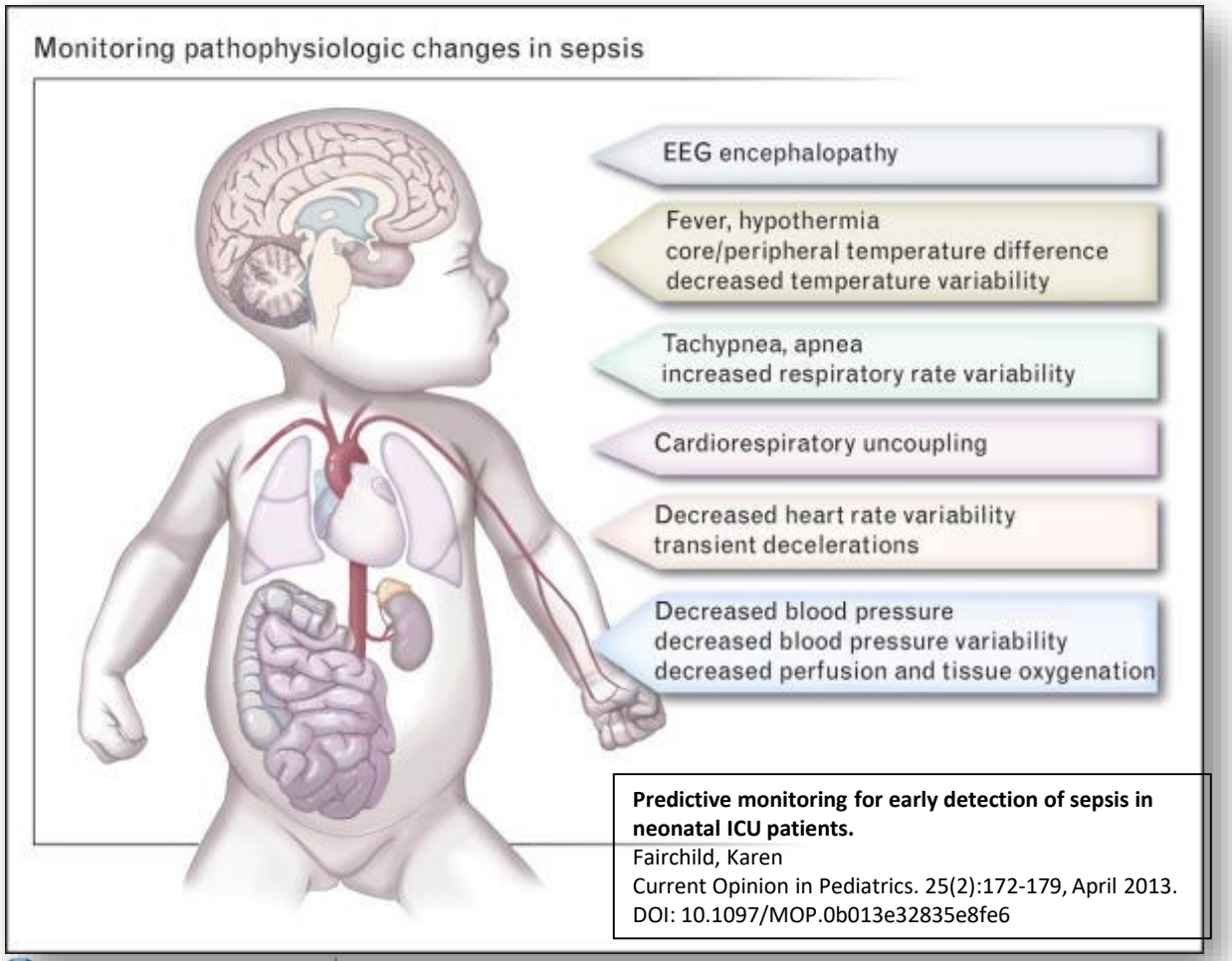
Sepsis: İnfeksiyonla oluşan SIRS tablosu



- Yenidoğanlarda SIRS
  - Isı düzensizliği (<35 veya >38.5)
  - Respiratuar disfonksiyon(hipoksemi, ARDS, gaz değişiminde bozulma)
  - Kardiyak disfonksiyon(taşikardi, kapiller doluş zamanında uzama, hipotansiyon)
  - Perfüzyon anormallikleri (oligüri, metabolik asidoz)
    - Vasküler permeabilitede artma, kapiller kaçak, pulmoner ve periferik ödem
    - Multisistem organ yetmezliği ve ölüm

Ateş

- 37.5 üzerinde cilt ısısı
- Enfeksiyon dışı nedenler
  - Çevre ısısı
  - Küvöz ve oda ısısı
  - Dehidratasyon
  - SSS bozuklukları
  - Hipertiroidi
  - Familyal disotonomi
  - Ektodermal displazi
- Bir saatten uzun süren ateş
- Hipotermi veya ısı düzensizliği özellikle prematürelerde enfeksiyonla daha uyumlu



Predictive monitoring for early detection of sepsis in neonatal ICU patients.
Fairchild, Karen
Current Opinion in Pediatrics. 25(2):172-179, April 2013.
DOI: 10.1097/MOP.0b013e32835e8fe6

Hipotermi (Prematüre)
Hipertermi (Termlerde)
Kalp atımında değişiklikler
Skorlama sistemleri

Dalgic N, Ergenekon E, Koc E, et al. NOSEP and clinical scores for nosocomial sepsis in a neonatal intensive care unit. ***J Trop Pediatr. 2006;52:226-227.***
Griffin MP, Lake DE, Bissonette EA, et al. Heart rate characteristics: Novel physiomarkers to predict neonatal infection and death. ***Pediatrics. 2005; 116: 1070-1074.***

Klinik olarak önceden kestirmek?

Erken sepsis için

- İntrapartum fetal taşikardi
- Mekonyumla boyalı amniyotik sıvı
- Düşük Apgar skoru
  - 5.dakika ≥ 6 ise 36 kat risk fazla

Escobar GJ, Li DK, Armstrong MA, Gardner MN, Folck BF, Verdi JE, Xiong B, Bergen R. Neonatal sepsis workups in infants>/=2000 grams at birth: A population-based study. Pediatrics. 2000;106(2 Pt 1):256.
Soman M, Green B, Daling J. Risk factors for early neonatal sepsis. Am J Epidemiol. 1985;121(5):712

Klinik olarak önceden kestirmek?

Geç sepsis için

- 48 saatten fazla hastanede kalan
  - 1295 kuşkulu sepsis
  - 934 laboratuar olarak doğrulanmış sepsis

- Tüm yenidoğanlar için
  - Letarji
  - Solukluk/ciltte beneklenme
- DDA bebekler için
  - Apne
  - Bradikardi
  - Doku perfüzyonunda bozulma
- Güçlü bulgular, ancak rehberlik edebilir
- Sınırlı tanısal değeri var

Verstraete EH, Blot K, Mahieu L, Vogelaers D, Blot S. Prediction Models for Neonatal Health Care-Associated Sepsis: A Meta-analysis. Pediatrics. 2015 Apr;135(4):e1002-e1014. Epub 2015 Mar 9

Clinical findings in neonatal sepsis

Finding	Frequency*
Hyperthermia	+++
Respiratory distress	+++
Tachycardia	+++
Lethargy	++
Poor feeding	++
Apnea	++
Bradycardia	++
Poor perfusion / hypotension	++
Vomiting	++
Jaundice	++
Hepatomegaly	++
Cyanosis	+
Hypothermia	+
Irritability	+
Seizures	+
Abdominal distension	+
Diarrhea	+

* +++: commonly associated (≥50 percent of cases); ++: frequently associated (25 to 50 percent); +: occasionally associated (<25 percent).

References:
Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Infectious Diseases of the Fetus and Newborn Infant, 7th ed, Remington JS, et al (Eds), Elsevier Saunders, Philadelphia 2010. p.244.
Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 2011; 127:817.

Töllner sepsis skorlama sistemi

Puan	0	1	2	3
Deri renginde değişiklik	yok	-	orta	belirgin*
Periferik dolaşım bozukluğu	yok	-	bozuk	belirgin
Hipotoni	yok	orta	belirgin	-
Bradikardi	yok	var	-	-
Apne	yok	var	-	-
Respiratuar distress	yok	var	-	-
Hepatomegali	yok	>4cm	-	-
GİS bulgusu	yok	var	-	-
Lökosit sayısı	yok	lökositoz	-	lökopeni
Sola kayma	yok	-	orta	belirgin
Trombositopeni	yok	-	var	-
Metabolik asidoz	yok	>7.2	<7.2	-

**4 puan verilir.*

10 puan üzeri olası sepsis; 5-10 puan sepsis şüphesi ;
0-4 puan sepsis şüphesi yok

- İyi emmiyor
- İyi görünmüyor
- İyi solumuyor

EMR'li bebeklerde sepsis skorlaması

Puan	0	1	2
Gebelik haftası	>37	34-37	<34
APGAR skoru	>7	5-7	<5
Annede korioamnionit veya bebekte midede lökosit	yok	var	
EMR süresi (gün)*	-	1	2

**Rüptür sonrası geçen her gün için 1 puan verilir.*

3 ve üzeri sepsis

Neonatal sepsis için erken uyarı skoru (NEWS)

- Erişkinlerde kullanılan erken uyarı skoru sisteminin yenidoğanlarda da benzer sonucu vermesi beklenir.

NEONATAL EARLY WARNING SCORE (NEWS)

C Flannigan[1], M Hogan[2]
[1]Paediatrics, Antrim Area Hospital, Antrim, Northern Ireland
[2]Neonatology, Craigavon Area Hospital, Portadown, Northern Ireland

A PILOT STUDY VALIDATING THE USE OF A NEONATAL EARLY WARNING SCORE

K. Nowlan, M. Soliman, R. Mathur, S. Jaiswal

Paediatrics, Frimley Park Hospital NHS Foundation Trust, Frimley, UK

Background: A Neonatal Early Warning Score (NEWS) is currently not used consistently, and screening for sepsis can be a subjective decision. NEWS may help to alert clinicians as to which infants are sick or at risk of impending illness.

Aims: To demonstrate usefulness of NEWS signs and consequent actions in confirmed and suspected cases of neonatal sepsis.

Methods: A retrospective analysis of infants with either a positive blood culture or who received antibiotics with negative blood culture from July 2007 to June 2009. A 'traffic light' NEWS proforma was designed based on colour coded alert signs & symptoms according to severity. Data from the NEWS proforma was collated in Excel and analysed using simple statistical methods and percentage calculations.

Results: 15 case notes in the positive blood culture group were reviewed; 23 case notes in the antibiotic treatment group were reviewed. This gave a total of 38 case notes.

58% infants had one or more 'red alert' signs and were transferred to SCBU

47% infants had one or more 'amber alert' signs and had a senior review

39% infants had one or more 'green alert' signs and had a review within one hour

Some of the babies had more than 1 alert.

Conclusions: This NEWS would have highlighted all the infants with confirmed or suspected sepsis. Given the majority of junior trainees with relative inexperience it is helpful to have a validated proforma.

Pediatric Research **(2011) 70, 701-701;doi:10.1038/pr.2011.926**

Neonatal Early Warning Score (NEWS)

NEWS Score	Action
0	Continue
1	Inform doctor
≥ 2	Request urgent review

0	1	2	Call 6000
white	yellow	amber	red

When this chart should be used

1. PROM >24hrs
2. Maternal GBS colonisation
3. Paediatric concerns
4. Midwifery concerns

Date											
Time											
Respiratory Rate	> 80										
	71-80										
	61-70										
	51-60										
	41-50										
	31-40										
	20-30										
	< 20										
SAO_2	>92%										
	88-91%										
	<88%										
Temp °C	> 38.0										
	37.4 – 38.0										
	36.0 – 37.3										
	35.6-36.0										
	< 35.6										
Heart Rate	>220										
	200-219										
	180-199										
	160-179										
	140-159										
	120-139										
	100-119										
	80-99										
	<80										
Conscious Level	Alert										
	Irritable/lethargic/ jittery/poor feeding										
	Unresponsive to all stimuli										
Capillary Refill Time	>3										
	2-3										
	<2										
BM	>2.6										
	1.6-2.5										
	<1.5										

NHS Trust

NEWBORN EARLY WARNING

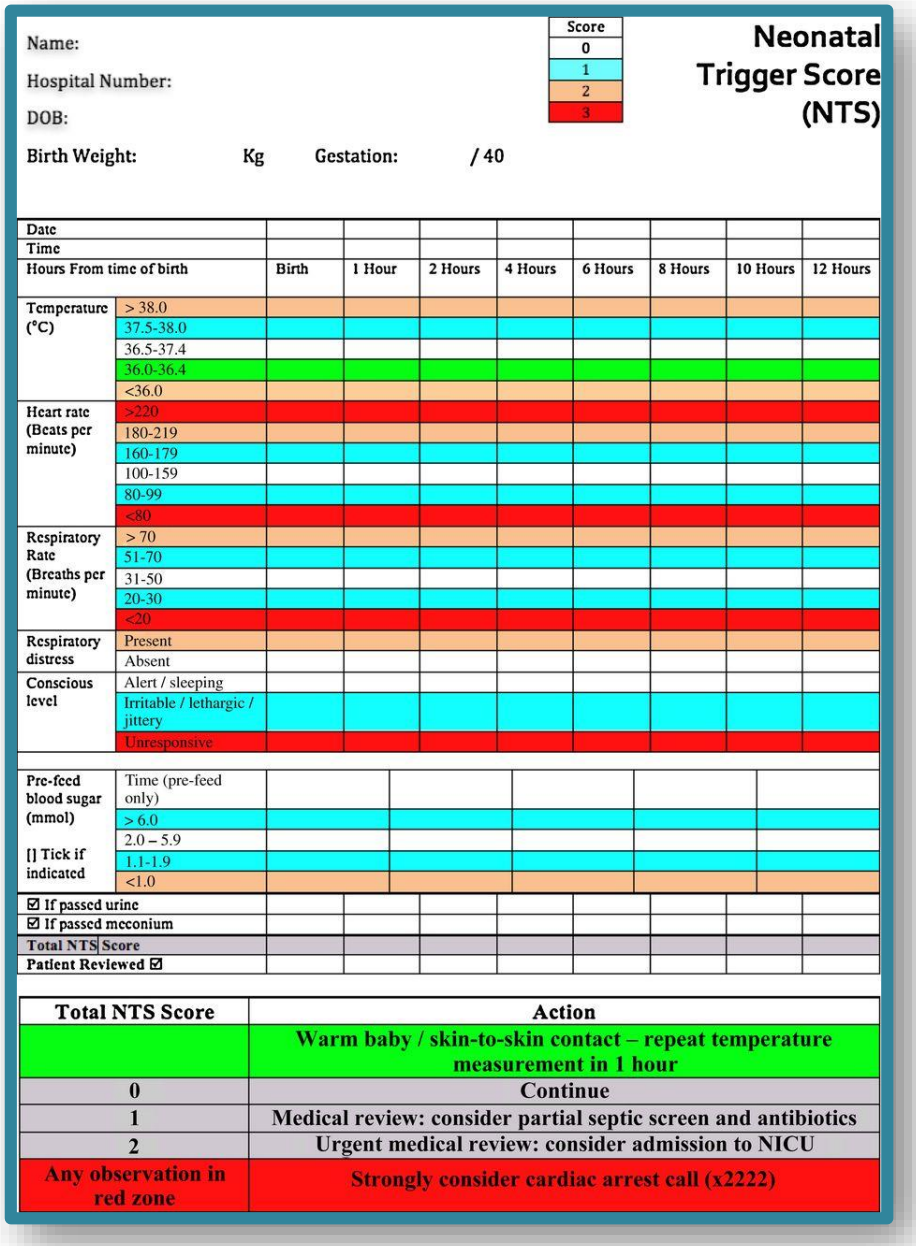
OBSERVATION CHART FOR NEWBORN INFANTS

First Name
Hospital No.
NHS Number
D.O.B.
Affix patient label here

DATE																								
TIME																								
TEMP	39.0																							
	38.0																							
	37.0																							
	36.0																							
	35.0																							
RESPIRATION	85																							
	80																							
	75																							
	70																							
	65																							
	60																							
	55																							
	50																							
	45																							
	40																							
	35																							
	30																							
	25																							
	20																							
GRUNTING																								
HEART RATE	200																							
	190																							
	180																							
	170																							
	160																							
	150																							
	140																							
	130																							
	120																							
	110																							
	100																							
	90																							
	80																							
	70																							
	60																							
COLOUR (SpO_2)	PINK (>94%)																							
	90-94%																							
	DUSKY/BLUE (<90%)																							
NEURO	ACTIVE/WAKES TO FEED																							
	JITTERY/IRRITABLE																							
	FLOPPY/DIFF TO ROUSE																							
	SEIZURES																							
SCORE	RED																							
	AMBER																							

RESPONSE		
	ALL OBSERVATIONS IN WHITE	CONTINUE OBERVATIONS 4 HOURLY OR AS REQUESTED.
	ONE IN AMBER	CONTACT SHO/ANNP/SENIOR MIDWIFE. VERBAL MANAGEMENT PLAN OR REVIEW. REPEAT OBSERVATIONS IN 30 MINUTES.
	TWO IN AMBER OR **ONE** IN RED	**IMMEDIATE REVIEW**

Neonatal trigger skorlama ve gözlem kartı.



Name:

Hospital Number:

DOB:

Birth Weight: Kg Gestation: / 40

Score
0
1
2
3

Neonatal Trigger Score (NTS)

Date									
Time									
Hours From time of birth		Birth	1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours
Temperature (°C)	> 38.0								
	37.5-38.0								
	36.5-37.4								
	36.0-36.4								
	<36.0								
Heart rate (Beats per minute)	>220								
	180-219								
	160-179								
	100-159								
	80-99								
	<80								
Respiratory Rate (Breaths per minute)	> 70								
	51-70								
	31-50								
	20-30								
	<20								
Respiratory distress	Present								
	Absent								
Conscious level	Alert / sleeping								
	Irritable / lethargic / jittery								
	Unresponsive								

Pre-feed blood sugar (mmol) [] Tick if indicated	Time (pre-feed only)						
	> 6.0						
	2.0 – 5.9						
	1.1-1.9						
	<1.0						
☑ If passed urine							
☑ If passed meconium							
Total NTS Score							
Patient Reviewed ☑							

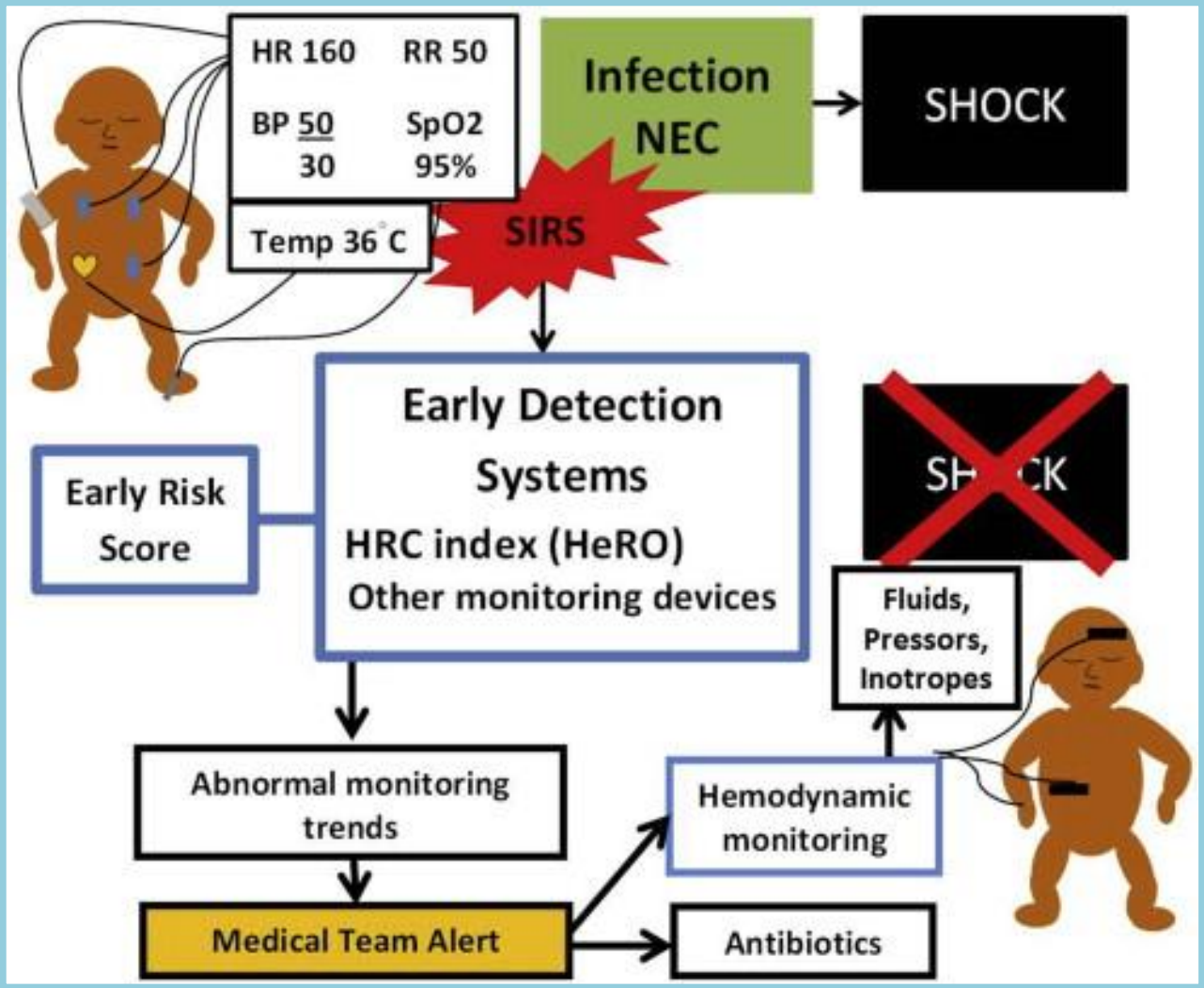
Total NTS Score	Action
	Warm baby / skin-to-skin contact – repeat temperature measurement in 1 hour
0	Continue
1	Medical review: consider partial septic screen and antibiotics
2	Urgent medical review: consider admission to NICU
Any observation in red zone	Strongly consider cardiac arrest call (x2222)

ADC

Harriet Holme et al. Arch Dis Child 2013;98:A3-A5

Harriet Holme et al. Pediatrics 2013;131:e837-e842

PEDIATRICS



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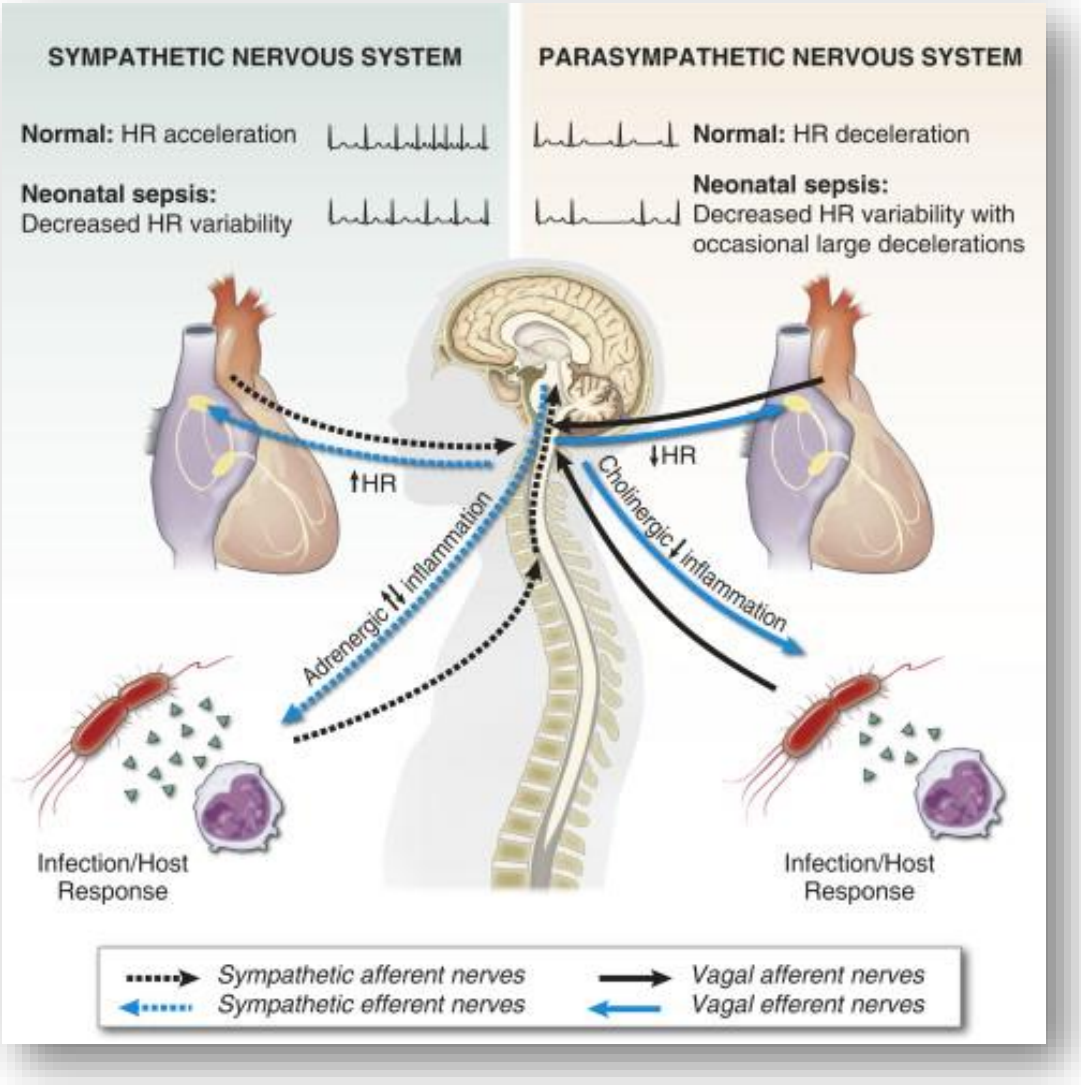

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0031-3998/03/5306-0920
PEDIATRIC RESEARCH

Vol. 53, No. 6, 2003
Printed in U.S.A.

Abnormal Heart Rate Characteristics Preceding Neonatal Sepsis and Sepsis-Like Illness

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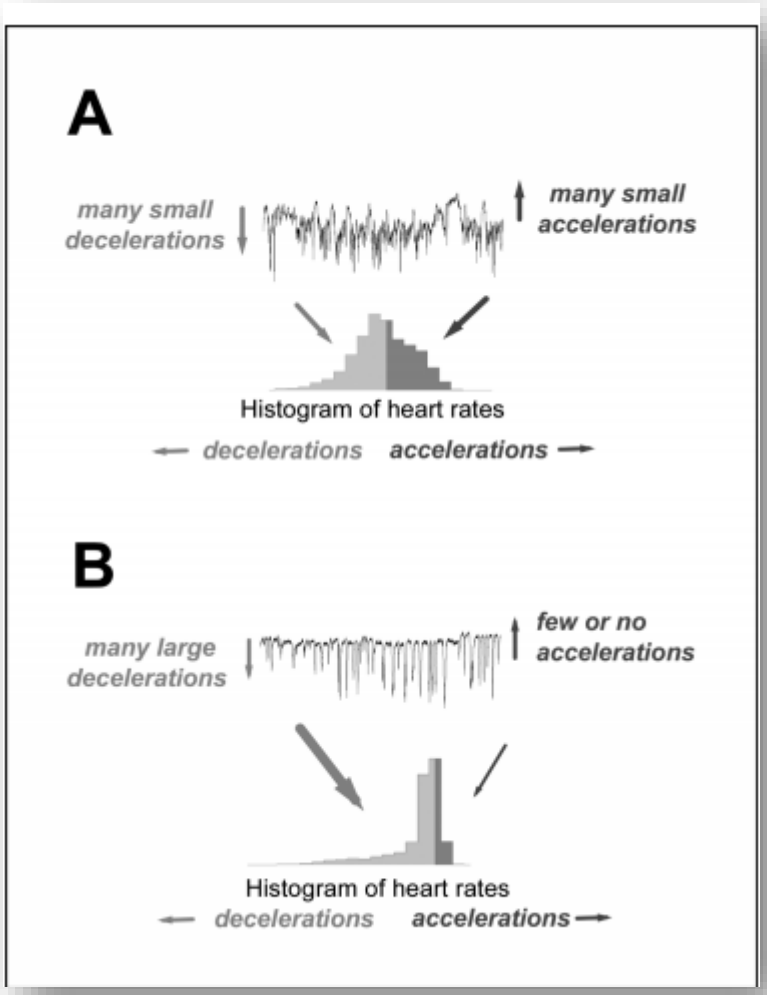
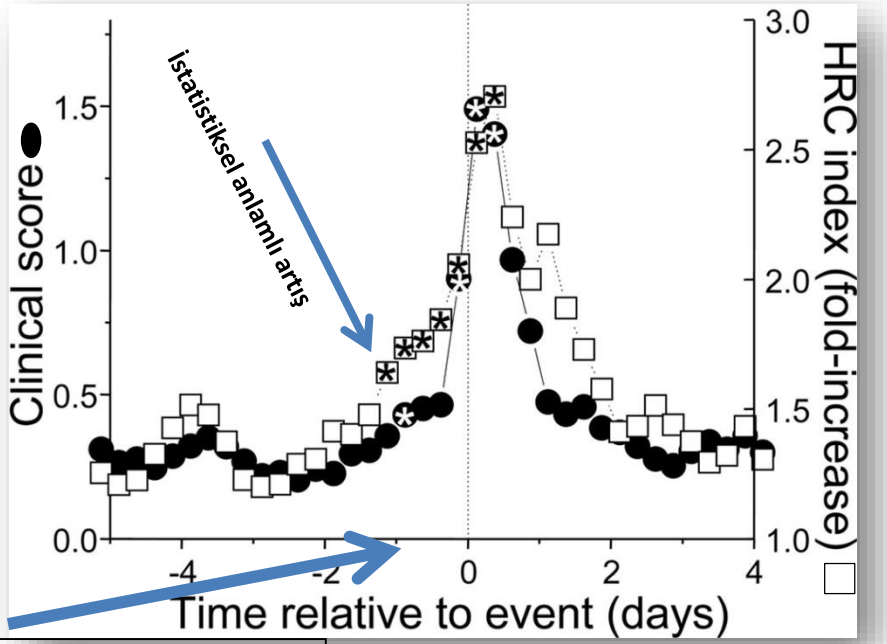
ABSTRACT

Late-onset neonatal sepsis is a significant cause of morbidity and mortality, and early detection could prove beneficial. Previously, we found that abnormal heart rate characteristics (HRC) of reduced variability and transient decelerations occurred early in the course of neonatal sepsis and sepsis-like illness in infants in a single neonatal intensive care unit (NICU). We hypothesized that this finding can be generalized to other NICUs. We prospectively collected clinical data and continuously measured RR intervals in all infants in two NICUs who stayed for >7 d. We defined episodes of sepsis and sepsis-like illness as acute clinical deteriorations that prompted physicians to obtain blood cultures and start antibiotics. A predictive statistical model yielding an HRC index was developed on a derivation cohort of 316 neonates in the University of Virginia NICU and then applied to the validation cohort of 317 neonates in the Wake Forest University NICU. In the derivation cohort, there were 155 episodes of sepsis and sepsis-like illness in 101 infants, and in the validation cohort, there were 118 episodes in 93 infants. In the validation cohort, the HRC index *1*) showed highly significant association with impending sepsis and sepsis-like illness (receiver operator characteristic area 0.75, $p < 0.001$) and *2*) added significantly to the demographic information of birth weight, gestational age, and days of postnatal age in predicting sepsis and sepsis-like illness ($p < 0.001$). Continuous HRC monitoring is a generally valid and potentially useful noninvasive tool in the early diagnosis of neonatal sepsis and sepsis-like illness. (***Pediatr Res*** **53: 920–926, 2003)**

Abbreviations

BW, birth weight
GA, gestational age
HRC, heart rate characteristics
HRV, heart rate variability
NICU, neonatal intensive care unit
ROC, receiver operating characteristic
SampEn, sample entropy
UVA, University of Virginia
WFU, Wake Forest University





24 saat öncesinden belirgin

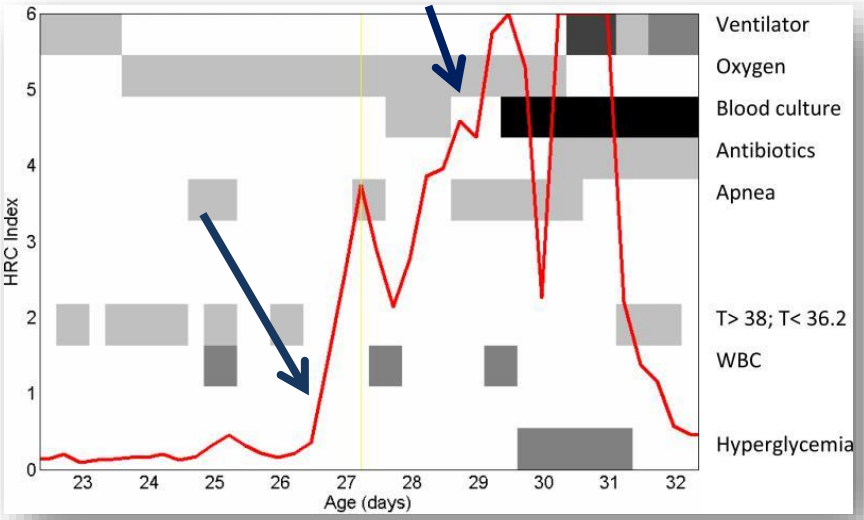
Signs	Points
Feeding intolerance (feedings held for greater than 24 hours) in an infant who had been tolerating advancing or full feeds for three days	2
Severe apnea requiring positive pressure ventilation	2
50% increase in number of apneic episodes over a 24 hour period in an infant who had been extubated and stable for three days	2
Immature/total neutrophil (I:T) ratio greater than 0.2	2
Increase in ventilatory support and F_iO_2 by 25% from baseline	1
Lethargy or hypotonia	1
Temperature instability (>38°C or < 36.2°C); two episodes within an eight hour period	1
Hyperglycemia (>180 mg/dL)	1
Abnormal white blood cell count (>25,000 or < 5,000)	1

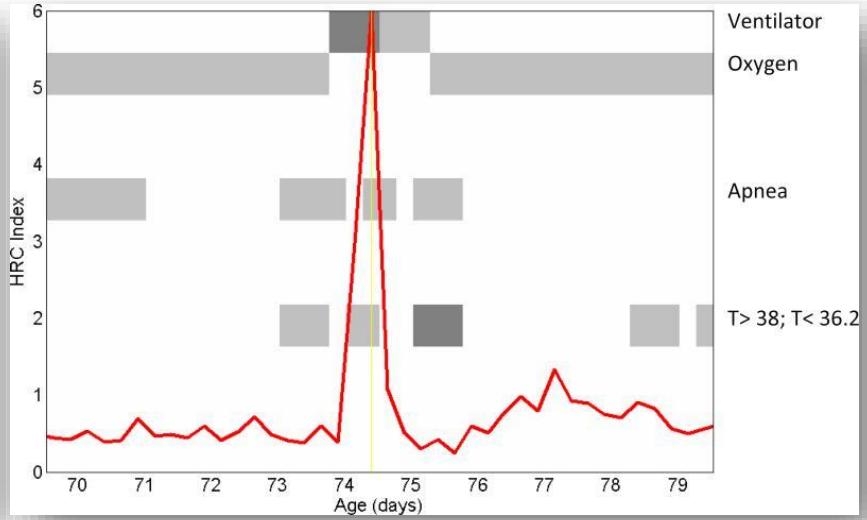
Griffin MP, et al. Heart rate characteristics and clinical signs in neonatal sepsis. Pediatr Res.2007;61(2):222–7

26 haftalık bebek 27.günde apne ve lökositoz; kültür negatif

29.günde alınan kültürde KNS/ 30.günde entübasyon

26 haftalık bebek 74.günde ROP cerrahisi





Griffin MP, et al. Heart rate characteristics and clinical signs in neonatal sepsis. Pediatr Res.2007;61(2):222–7

Pediatric RESEARCH

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PEDIATRIC RESEARCH | CLINICAL INVESTIGATION

Septicemia mortality reduction in neonates in a heart rate characteristics monitoring trial

Karen D. Fairchild, Robert L. Schelonka, David A. Kaufman, Waldemar A. Carlo, John Kattwinkel, Peter J. Porcelli, Cristina T. Navarrete, Eduardo Bancalari, Judy L. Aschner, M. Whit Walker, Jose A. Perez, Charles Palmer, Douglas E. Lake, T. Michael O'Shea & J. Randall Moorman

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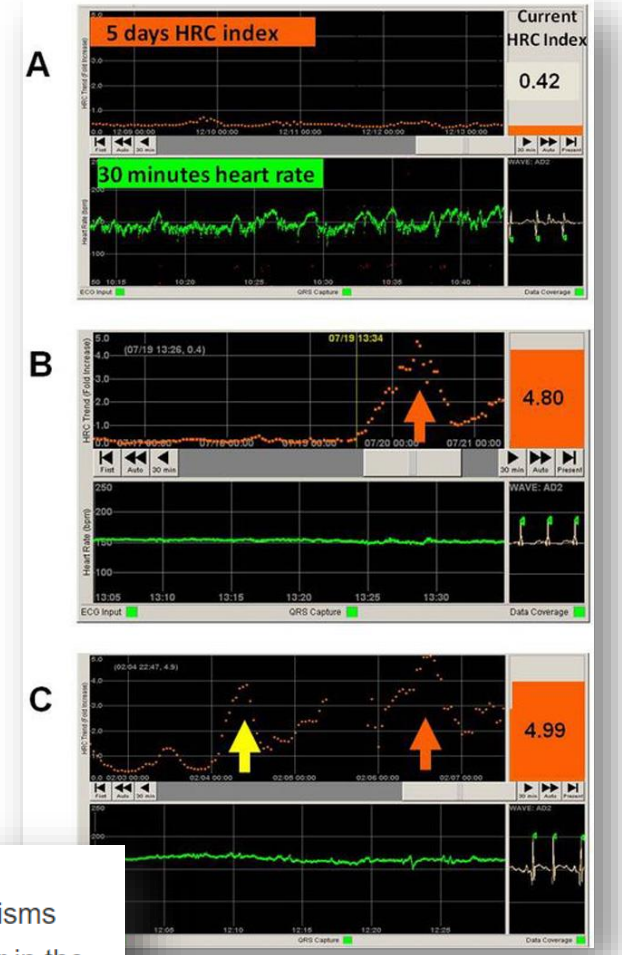
Pediatric Research (2013) **74**, 570–575 | doi:10.1038/pr.2013.136

Received 21 December 2012 | Accepted 29 March 2013

Accepted article preview online 13 August 2013 | Advance online publication 25 September 2013



Results:

LOS was diagnosed 974 times in 700 patients, and the incidence and distribution of organisms were similar in HRC display and nondisplay groups. Mortality within 30 d of LOS was lower in the HRC display as compared with the nondisplay group (11.8 vs. 19.6%; relative risk: 0.61; 95% confidence interval: 0.43, 0.87; $P < 0.01$), but mortality reduction was not statistically significant for patients without LOS. There were fewer large, abrupt increases in the HRC index in the days leading up to LOS diagnosis in infants whose HRC index was displayed.

Conclusion:

Continuous HRC monitoring is associated with a lower septicemia-associated mortality in VLBW infants, possibly due to diagnosis earlier in the course of illness.

Erken başlangıçlı sepsis

- Yaşamın ilk 3 günü içinde
- Fulminan seyirli
- Multisistemik enfeksiyon
- Genellikle vertikal geçiş
- Mortalite yüksek

- **Geç başlangıçlı sepsis**
  - Yaşamın 4. gününden sonra
  - Sinsi başlangıçlı
  - Vertikal ve horizontal geçiş
  - Menenjit sıklıkla
- **Çok geç başlangıçlı sepsis**
  - 3 aydan sonra ortaya çıkar
  - Sıklıkla çok düşük doğum ağırlıklı bebekler
  - Uzun süreli girişimlere maruz kalan bebekler

Yenidoğanın Erken ve Geç Sepsisi

	Erken	Geç
Ort. başlama yaşı	Genellikle 3 günden küçük	4.-28 gün
Prematürite	Yüksek	Seyrek
Obstetrik riskler	Artmış koloniz., amnionit	Seyrek
Klinik görünüm	Solunum sık. pnömoni şok	Ateş, MSS Bul, Fokal Bul.
Menenjit	%30	%75
Diğer sistemler	Nadir	Piyelonefrit osteomiyelit Septik artrit, Sellülit
Patojenler	GBS, E Coli Listeria Klepsiella Enterokok	GBS, E.Coli, Listeria, Herpes, Streptokok
Tedavi	Ampisillin+Gentamisin	Sefotaksim+Amikasin
Mortalite	%30-50	%10-20

Sepsisde laboratuar tanı

- İnfeksiyon kanıtı
  - Kültür (kan, BOS, idrar ve diğer örnekler)
    - Klinik sepsis
    - İdrar için kataterle veya suprapubik aspirasyon
  - Mikroorganizmanın doku ve sıvıda gösterilmesi
    - İlk gün gastrik aspirat annede amniyonit
    - ET sekresyon veya aspiratın boyanması
  - Antijenin gösterilmesi (idrar, BOS)
  - Anne ve/veya neonatal seroloji (sifiliz, toxoplazmozis)
  - Plasentanın incelenmesi
  - Otopsi

Kan kültürü neden çok yardımcı değil?

- Alınan kanın çok az olması
  - 1 ml örnek. 0,5 ml yeterli olmayabiliyor
- Zor üreyen mikroorganizmalar
  - Mikroorganizmalar düşük koloni sayısına sahip
  - Kontaminasyon, kolonizasyon
- Annenin aldığı antibiyotikler
- Kesin sonuçlar için 24-72 saat beklenmesi

Polin R& Committee on Fetus and Newborn. Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2012;129:1006–1015

Sepsisde laboratuar tanı-2

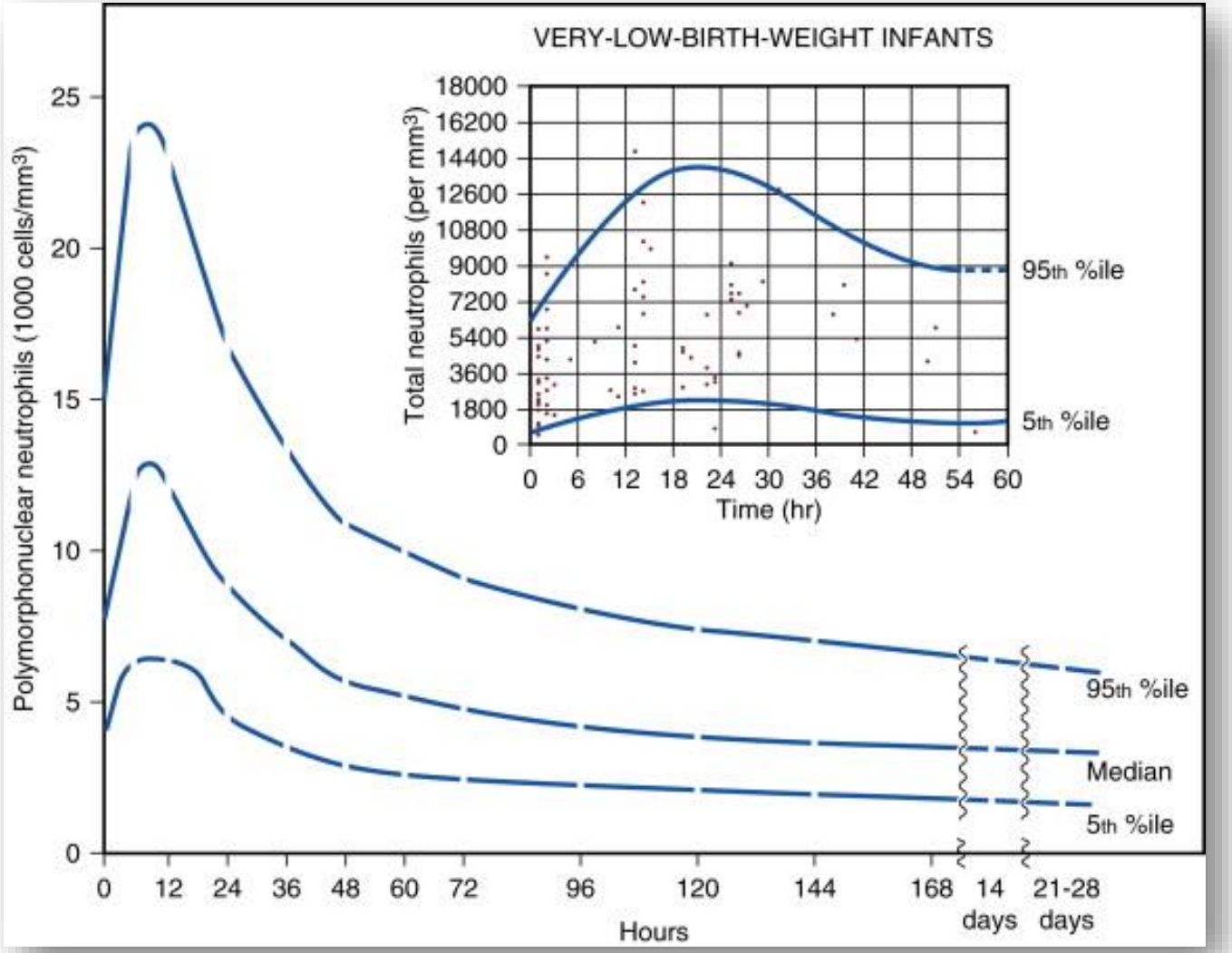
- İnflamasyon kanıtı
  - Lökosit sayısı
    - 30000/mm3 üzeri veya 5000/mm3 altı
      - » Nötropeni hipertansiyon, asfiksi
      - » 12 saat sonra tekrarlanmalıdır
  - Lökosit formülü ve I/T oranının 0.2 üzerinde olması
  - Trombositopeni: <150 bin/mm3
  - Akut faz reaktanları
    - ESR
    - CRP
  - Sitokinler
    - IL-6
  - BOS'da veya steril sıvılarda pleositoz
  - DİK tablosu

Sepsisde laboratuar tanı-3

– Multiorgan sistem hastalığı kanıtı
  - Metabolik asidoz: pH, pCO2
  - Pulmoner fonksiyon: pO2, pCO2
  - PA Akciğer grafisi
  - Renal fonksiyon: BUN; kreatinin
  - Hepatik fonksiyon: Bilirübin, AST, ALT, amonyak, PT, PTT
  - Kemik iliği fonksiyonu: Nötropeni, anemi, trombositopeni

Beyaz küre, formül, I/T oranı

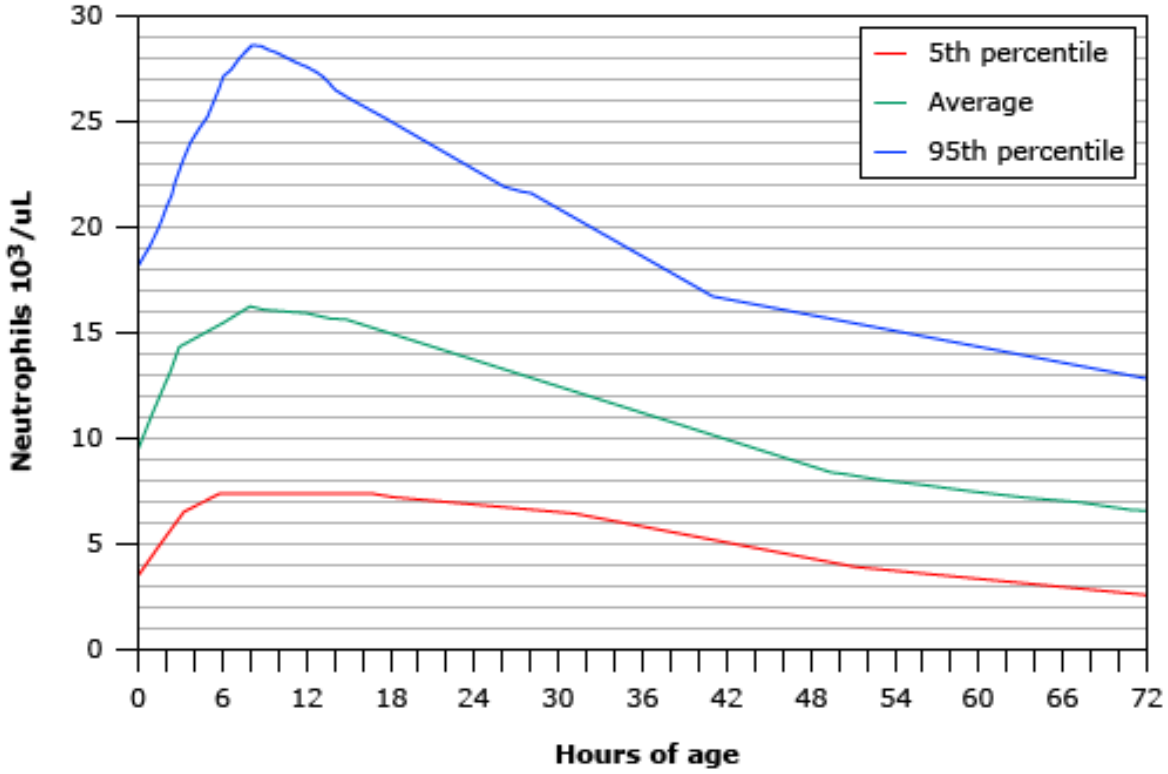
- BK ES'te başlangıçta yarısından fazlasında normal
- Yaşa göre değerler yorumlanmalı
- Formül lökosit
  - Lenfositlerde artma konj.sifiliz, boğmaca
  - Monositlerde artma konj.sifiliz, perinatal listeriozis
  - Sepsisten iyileşme döneminde ve ABO uyuşmazlığında
  - Eozinofili prematürelerde
    - DDA, immatürite,TPN, transfüzyon, sepsis,pozitif nitrojen dengesi, nutrisyonel durumda düzelmeyle ilişkili
  - Bazofil sayısı eozinofildeki dalgalanmayı takip eder
- Toksik granüller, toksik vakuoller, Döhle cisimcikleri



Total neutrophil counts in normal term infants and in very-low-birth-weight infants (inset). (The data are for term infants and align well with those from most14,24,27 but not all other sources. The data for the inset are from Mouzinho and colleagues and align well with other studies.)

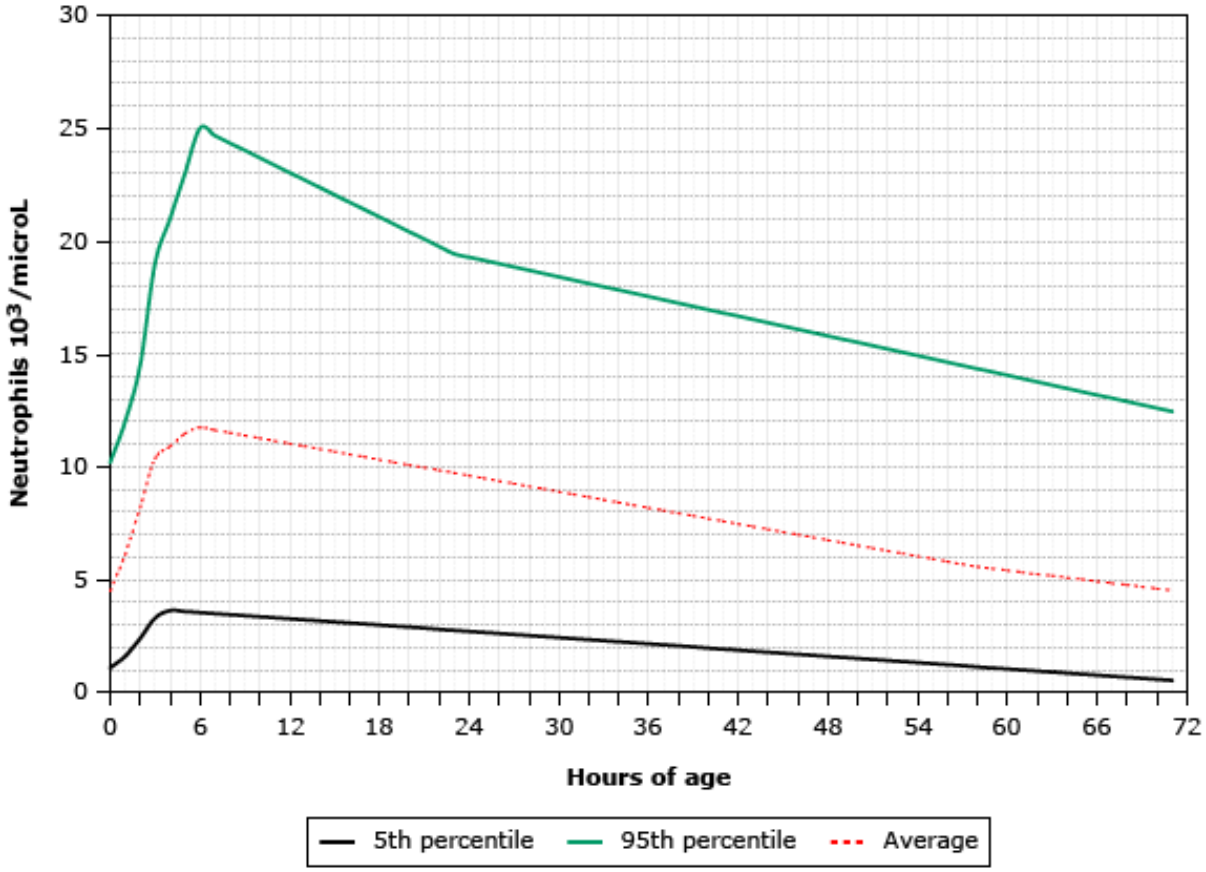
Laboratory Aids for Diagnosis of Neonatal Sepsis
Weinberg, Geoffrey A., Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant, 36, 1132-1146

Range of neutrophil count for newborn infants born with a gestational age >36 weeks during the first 72 hours of life



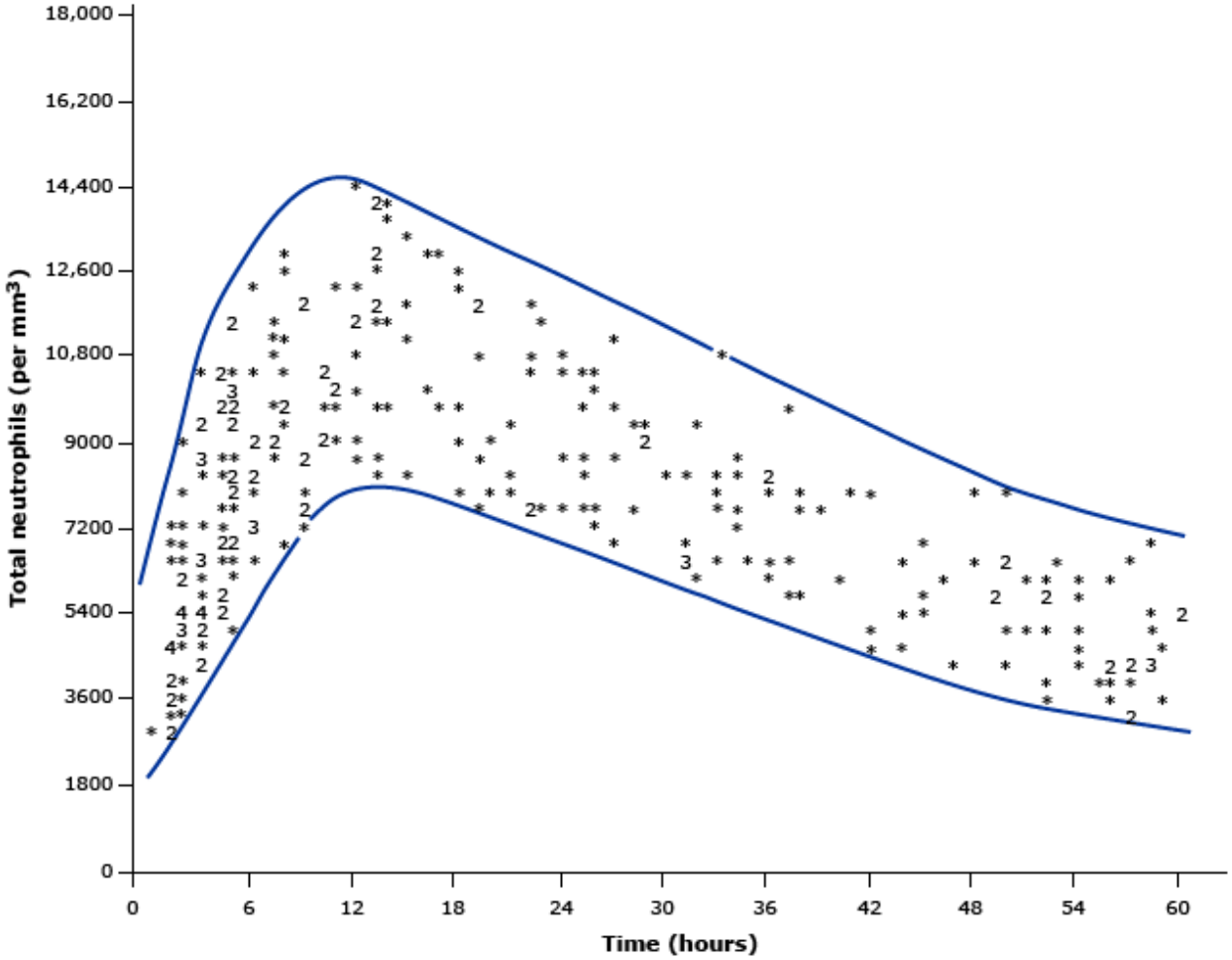
Neutrophils per microL of blood during the first 72 hours after the birth of term and near-term (>36 weeks of gestation) neonates. A total of 12,149 values were obtained for the analysis. The 5th percentile, the mean, and the 95th percentile values are shown.

Normal range of neutrophil count for newborn infants with a gestational age between 28 and 36 weeks during the first 72 hours of life



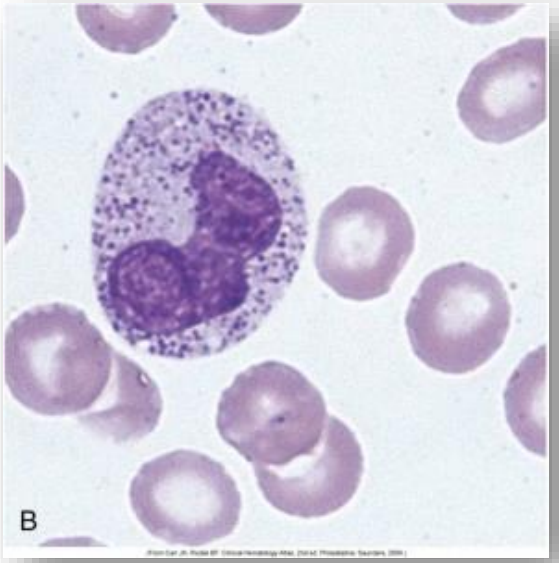
Neutrophils per microL of blood during the first 72 hours after the birth of 28- to 36-week gestation preterm neonates. A total of 8896 values were obtained for the analysis. The 5th percentile, the mean, and the 95th percentile values are shown.

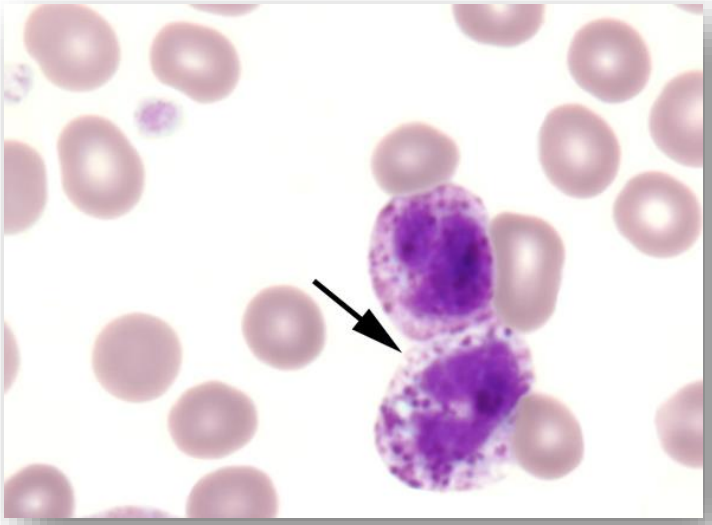
Normal neutrophil count for healthy neonates from the Manroe study

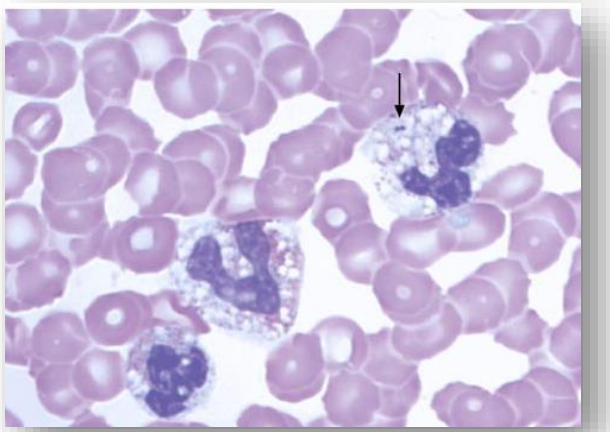


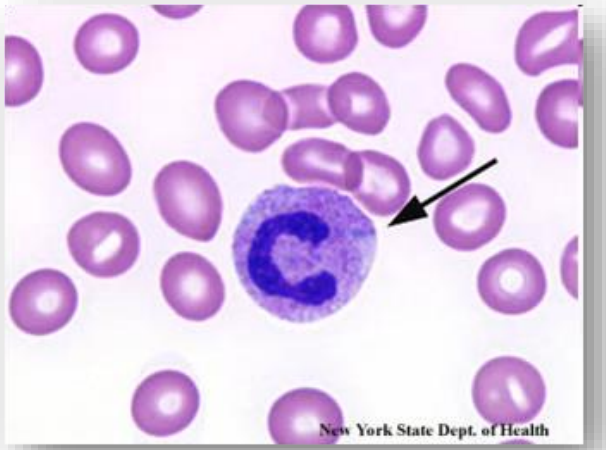
The total neutrophil count reference range in the first 60 hours of life. Stars represent single values; numbers represent the number of values at the same point. Heavy lines represent the envelope bounding these data.

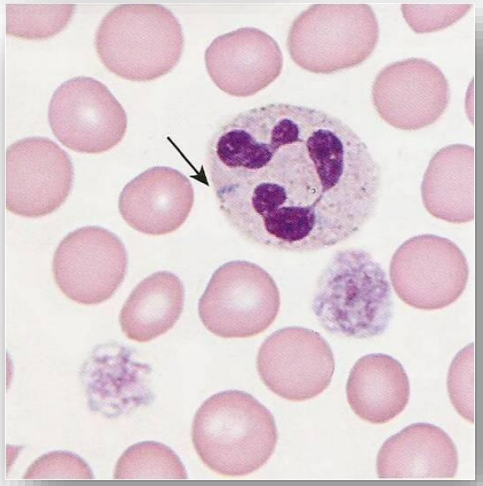
Reproduced from: Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr 1979; 95:89. Illustration used with the permission of Elsevier Inc. All rights reserved.



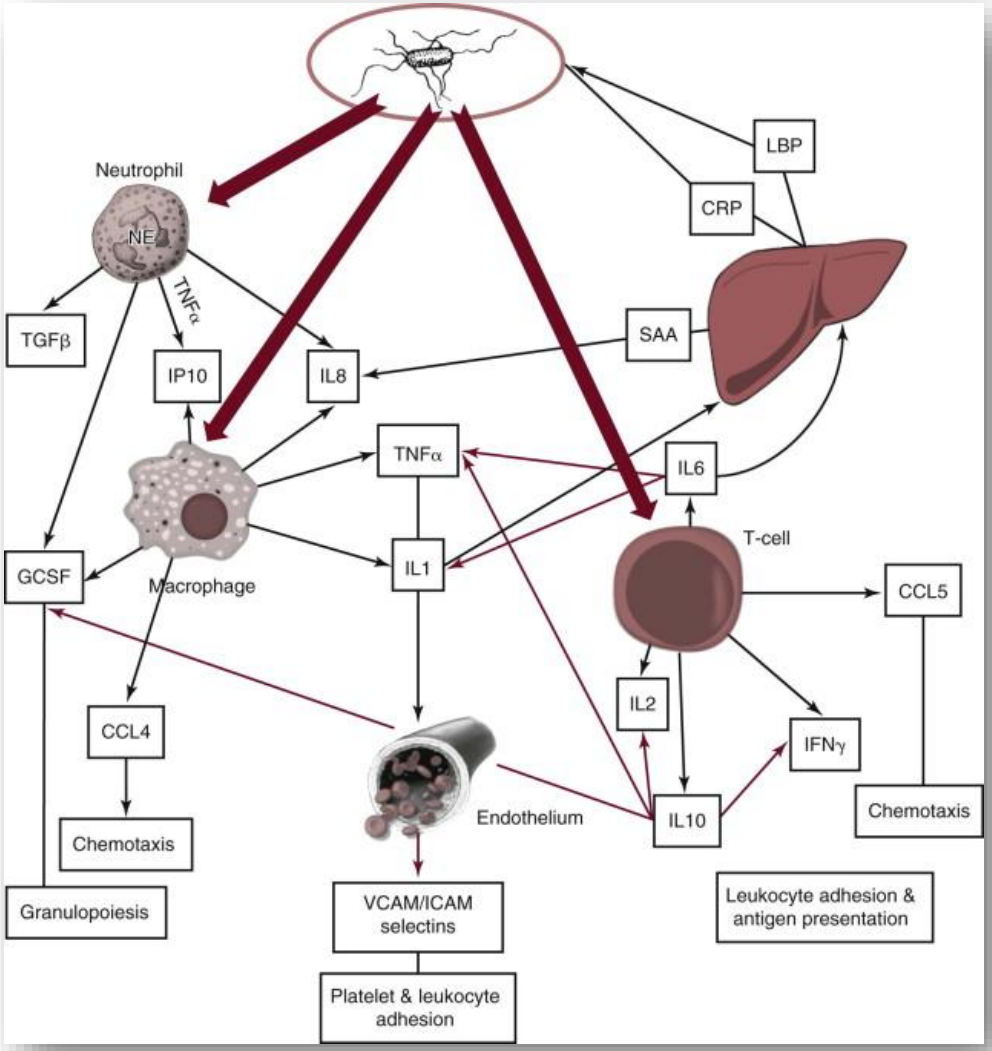








PPV %50



Nader B. The Use of Biomarkers for Detection of Early- and Late-Onset Neonatal Sepsis. Hematology, Immunology and Infectious Disease: Neonatology Questions and Controversies, 2nd ed (eds.Ohls RK, Maheshwari A), Elsevier-Saunders, Chapter 18, 303-315

Erken ve geç başlangıçlı sepsiste biyobelirteçlerin doğruluğu

Biomarker	Sensitivity	Specificity	PPV	NPV
Cytokines				
IL-6[7,8]	67-89	89-96	84-95	72-91
Umbilical cord IL-6[9]	87-90	93	93	93-100
GCSF >200 pg/mL[17]	95	73	40	99
TNF[15]	83.3	80.6		
Chemokines				
CCL4 >140 pg/mL[18]	92	40		98
IL-8[5]	80-91	76-100	70-74	91-95
Free IL-8[21]	97			99
Urine IL-8 >75 pg/mg Cr[22]	92			
IP-10 >1250 pg/mL[23]	93	89		
Cell Surface Markers				
CD64	64-97	72-96	64-88	84-98
CD11b[24]				
Neutrophils	100	56		
Monocytes	86	94		
Acute Phase Proteins				
CRP[7]	60-82	93-96	95-100	75-87
SAA[25]	96	95	85	99
Procalcitonin[26]	82-100	87-100	86-98	93-100
IαIp[27]	89.5	99	95	98
Combination Biomarkers				
IL-6/IL-10/CCL5[13]	100	97	85	100
IL-6 and/or CRP[5]	93	88-96	86-95	95
IL-8 and/or CRP[5]	80	87	68	93

CCL4, C-C motif ligand-4; *CCL5*, C-C motif ligand-5; *Cr*, creatinine; *CRP*, C-reactive protein; *GCSF*, granulocyte colony-stimulating factor; *IαIp*, inter-alpha inhibitor protein; *IL*, interleukin;

Bishara N. The Use of Biomarkers for Detection of Early- and Late-Onset Neonatal Sepsis. Hematology, Immunology and Infectious Disease: Neonatology Questions and Controversies,2nd ed (eds.Ohls RK, Maheshwari A), Elsevier-Saunders, p.305.

Akut faz proteinleri

- Biyokimyasal ve fonksiyonel farklı 30 protein
  - Başlıca hepatositlerde; genelde artma [albüminde azalma, negatif AFP)
- C-reaktif protein (CRP)
- Prokalsitonin (PCT)
- Serum amiloid A (SAA)

Örs R, İşlek M, Taştekin A, Kızıltunç A, İnandı T. Diagnostic accuracy of IL-8, IL-1b, CRP and platelet count in neonatal sepsis. Pediatr Res 2002; 52(5):133A.

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Annagür A, Altunhan H, Örs R, Mehmetoğlu İ. Procalcitonin Level at 24 Hours of Age May be Predictive for Transient Tachypnea of the Newborn. Arch Dis Child 2012 97: A338.

Ertuğrul S, Annagür A, Kurban S, Altunhan H, Ors R. Comparison of urinary neutrophil gelatinase-associated lipocalin, C-reactive protein and procalcitonin in the diagnosis of late onset sepsis in preterm newborns. J Matern Fetal Neonatal Med 2013 Mar;26(4):430-3.

CRP

- Non spesifik bir AFP
- Yarı ömrü 19 saat
- Klinik olarak başlangıçta yüksek değil
- Akut dönemde logaritmik artar
- %90 duyarlı ancak nonspesifik

Mishra UK, Jacobs SE, Doyle LW, et al. Newer approaches to the diagnosis of early onset neonatal sepsis. Arch Dis Child Fetal Neonatal Ed. 2006;91:F208-F212.

CRP

- Geç sepsiste tedaviyi izlemede
- Seri ölçümler sepsisi dışlamak için
- 48 saat boyunca normal seyrederse tedaviyi kesmeye yardımcı olabilir
- CRP fungal sepsis de de yüksek
  - İzlem ve tedaviyi sonlandırmada yararlı
- Cerrahi ile, aşılamayı takiben, perinatal asfiksi, mekonyum aspirasyonu,IVH, annede ateş, gastroşizisde de yüksek
- SAA ve PCT CRP'den daha iyi gözüküyor
- Yaygın kullanım tüm dünyada CRP

Polin RA. The "ins and outs" of neonatal sepsis. *J Pediatr. 2003;143:3-4*

Örs R, Özkan B, Ceviz N, Aktaş E, Olgun H. Is the persistence of elevated serum C-reactive protein a predictive marker in the diagnosis of systemic candidiasis in premature newborns? Pediatr Res 1999; 45: (6) 891-891.

Oguz SS, Sipahi E, Dilmen U. C-reactive protein and interleukin-6 responses for differentiating fungal and bacterial aetiology in late onset neonatal sepsis. *Mycoses. 2011;54:212-216.*

Serum amiloid A (SAA)

- CRP’den daha erken yükselir, daha fazla yükselir ve daha çabuk normale döner.
- Erken fazda daha iyi
- SAA ile CRP karşılaştırıldığında; daha duyarlı (%96 vs. %30), özgüllük benzer (%95 vs. %98), pozitif prediktif değeri (%85 vs. %78), ve negatif prediktif değer (%99 vs. %83)

Arnon S, Litmanovitz I, Regev RH, et al. Serum amyloid A: An early and accurate marker of neonatal early-onset sepsis. *J Perinatol. 2007;27:297-302.*

Prokalsitonin (PCT)

- Daha çok bakteriyel kaynaklı
- İlk günlerde cut-off değerler?
- İlk 2 günde fizyolojik artış
- Perinatal asfiksi, preeklampsi, intrakraniyal kanama da artabilir
- Geç sepsis de CRP'den daha iyi

Altunhan H, Annagür A, Örs R, Mehmetoğlu İ. Procalcitonin measurement at 24 hours of age may be helpful in promt diagnosis of early-onset neonatal sepsis. Int J Infect Dis 2011; 15: e854-e858.
Annagür A, Altunhan H, Örs R, Mehmetoğlu İ. Procalcitonin Level at 24 Hours of Age May be Predictive for Transient Tachypnea of the Newborn. Arch Dis Child 2012 97: A338.
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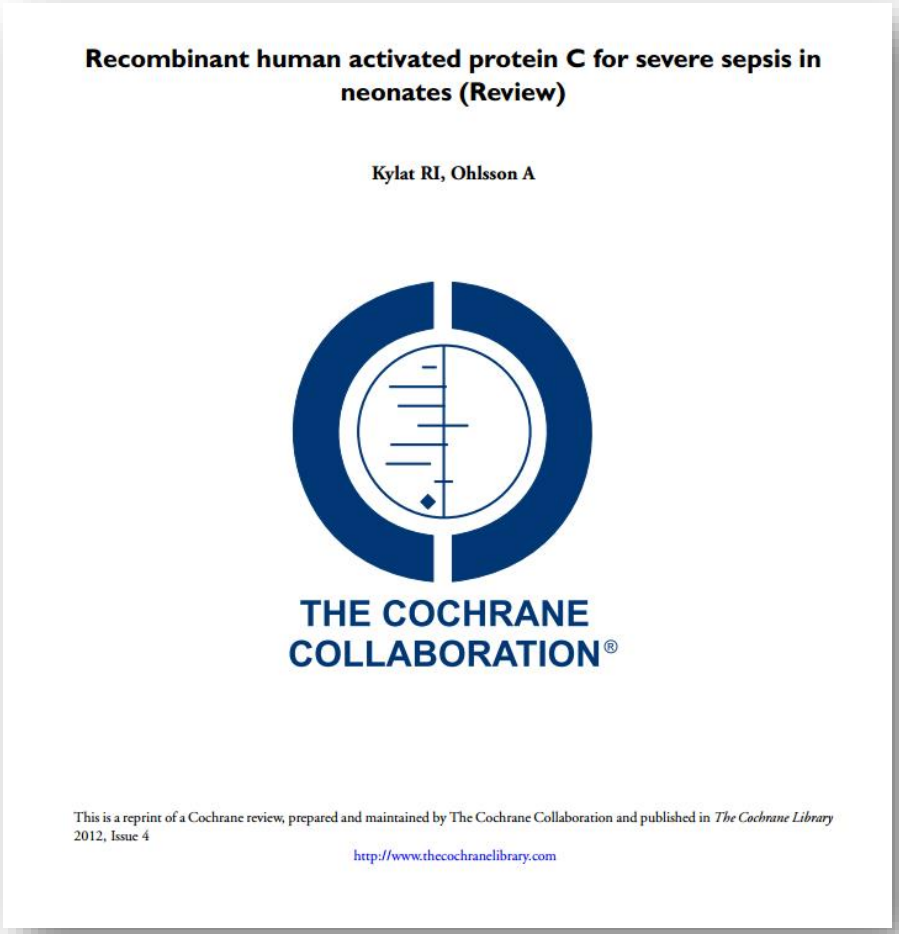
Tedavi

- Antibiyoterapi
  - Ampirik:
    - Ampisilin veya Penisilin + Genta veya Sefotaksim
    - Nozokomiyal üniteye göre:Vankomisin, Meropenem, Tazobaktam
    - Nekrotik deri bulguları Psödomonas ..piperasilin, tikarsilin, karbenisilin, seftazidim+ aminoglikozid
    - Antifungal: flukonazol, amfoterisin B
  - Spesifik
    - GBS: penisilin Anaerob: Klindamisin; Metranidazol
    - Listeria: Ampisilin
  - Süre 1 hafta-10 gün
    - Gram negatif: 14 gün
    - GBS menenjit 14-21 gün

Tedavi

- Sürekli monitorizasyon
- Yeterli oksijenizasyon
  - Ventilatör desteği: sepsis, pnömoni, ARDS, PH
- Sıvı tedavisi
- İnotropik ajanlar
- Elektrolit ve glukoz düzeyi
- Kortikosteroid: Adrenal yetmezlik varsa
- Hiperbilirübinemi… kernikterus riski artar
- Nöbetlerin kontrolü
- Total parenteral beslenme ile destekleme gerekebilir
- DİK: TDP, trombosit süspansiyonu veya taze kan verilmesi
- Nötropenik hastalarda GM-CSF veya G-CSF
- Granülosit transfüzyonu(?)
- Taze kan değişimi(?)
- IVIG (IgM'den zengin)
- Pentoksifilin



Authors' conclusions

Despite the scientific rationale for its use, there is insufficient data to use rhAPC for the management of severe sepsis in newborn infants. Due to the results among adults with lack of efficacy, an increase in bleeding and resulting withdrawal of rhAPC from the market, neonates should not be treated with rhAPC and further trials should not be conducted.

Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates (Review)

Pammi M, Haque KN

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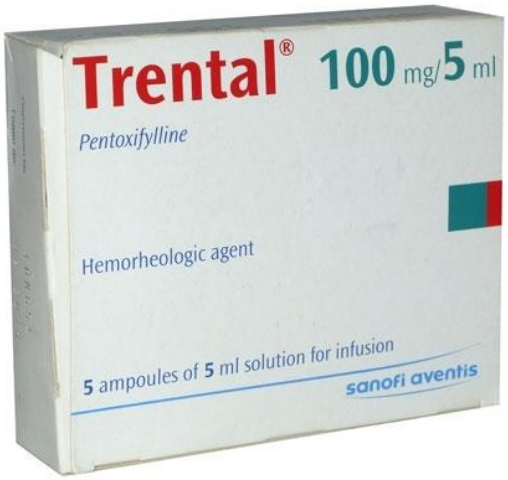

We found low-quality evidence that pentoxifylline in combination with antibiotics decreases deaths and duration of hospital stay in newborn sepsis. Pentoxifylline treatment did not affect lung, eye, or brain injury as a result of sepsis (very low-quality evidence). We identified no adverse effects due to pentoxifylline. There were no completed studies looking at pentoxifylline treatment in NEC. We need better-quality evidence on the use of pentoxifylline in the treatment of sepsis or NEC in the newborn.

Authors' conclusions

Low-quality evidence from six small studies suggests that pentoxifylline therapy as an adjunct to antibiotics in neonatal sepsis decreases mortality without any adverse effects. We encourage researchers to undertake large, well-designed multicentre trials to confirm or refute the effectiveness of pentoxifylline in reducing mortality and morbidity in neonates with sepsis or NEC.

Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock (Review)

Alejandria MM, Lansang MAD, Dans LF, Mantaring III JB

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 9

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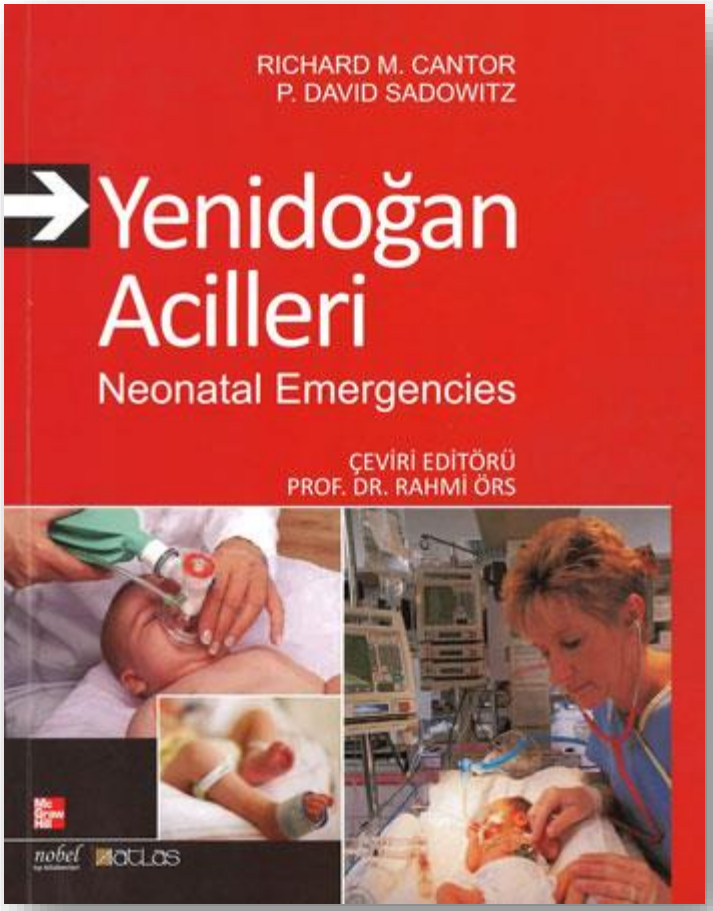
Authors' conclusions

Polyclonal IVIG reduced mortality among adults with sepsis but this benefit was not seen in trials with low risk of bias. Among neonates with sepsis, there is sufficient evidence that standard polyclonal IVIG, as adjunctive therapy, does not reduce mortality based on the inclusion of the large polyclonal IVIG trial on neonates. For Ig-M enriched IVIG, the trials on neonates and adults were small and the totality of the evidence is still insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IVIGs remains experimental.



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