

Early Diagnosis of Neonatal Sepsis

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Immunologic Basis for Neonatal Sepsis

Phagocytic immunity

proliferation and pool ↓

adherence, migration, chemotaxis, phagocytosis ↓

Cell-mediated immunity

T-cell naiv

cytokine production

Humoral immunity

T-cell help for B-cell differentiation ↓

complement ↓

Characteristics of an Ideal Laboratory Test

early

high sensitivity / specificity

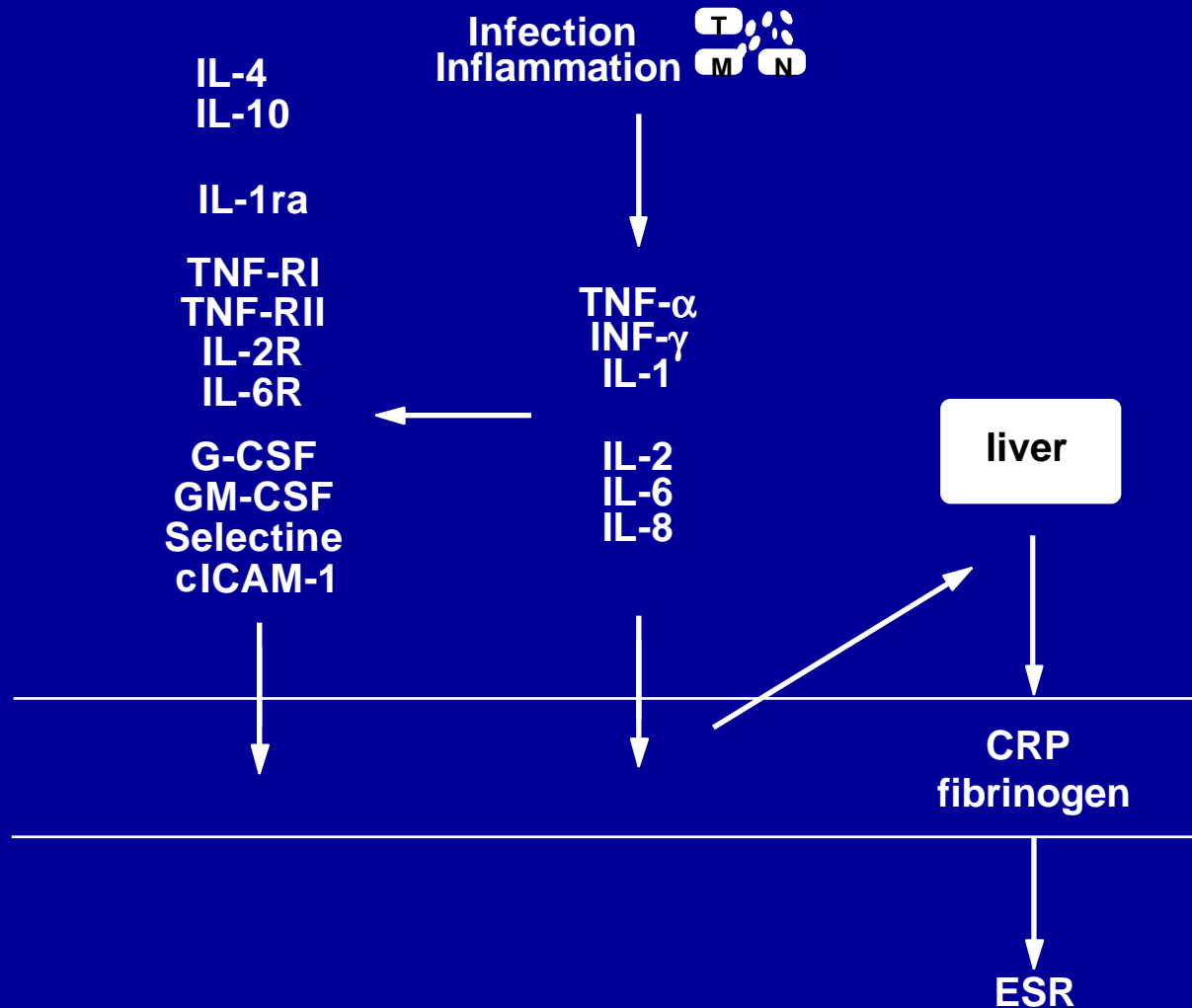
rapidly available

small volume

stable

cheap

Immunoreaction in Sepsis



Tests Available

cultures

traditional clinical chemistry

clinical signs

cytokines

Blood Culture

sensitivity: 82%

specificity: 96%

Squire 1979

1-10 bacteria / ml blood during sepsis

Fischer 1974

Liquor Culture

<u>study</u>	<u># pts.</u>	<u>LP</u>	<u>BC neg.</u>	<u>kontam. LP</u>
1	11.035		0	8
2		3423	0	35
3	10 years	284	0	5
4		238	0	
5		1712	1	4
6	1 year	522	1	6
7			4	
8	169.849		≤ 4	
9		2800	< 3	
10	67.500		~ 7	

Urine Culture

incidence: 1/146 bzw. 1/188
DiGeromimo 1992; Visser 1979

sensitivity: 0-90%
Becker 1993

latex agglutination test GBS:
sensitivity 43-84%
false positive 30%
Williamson 1995; Greenberg 1995; Palmer 1996

White Cell Count

<u>study</u>	<u>cut off</u>	<u>sensitivity</u>	<u>specificity</u>
1	<5000	22	98
2	<5000	46	94
3	<5000 oder >20000	18	76
4	<5000 oder >20000	58	86
5	>20000	78	57

Voora 1982; Philip 1984; Peakman 1992; Philip 1982; Luttkus 1993, Jackson 2004

IT-Ratio

<u>study</u>	<u>cut off</u>	<u>sensitivity</u>	<u>specificity</u>
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1	$\geq 0,2$	86	68
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2	$\geq 0,2$	18	96
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Krediet 1992; DaSilva 1994

CRP

<u>blood taken</u>	<u>sensitivity [%]</u>	<u>specificity [%]</u>
on admission	22	97
after 10-14h	44	94
after 22-26h	61-84	94-96

Mathers 1987, Ng 1997

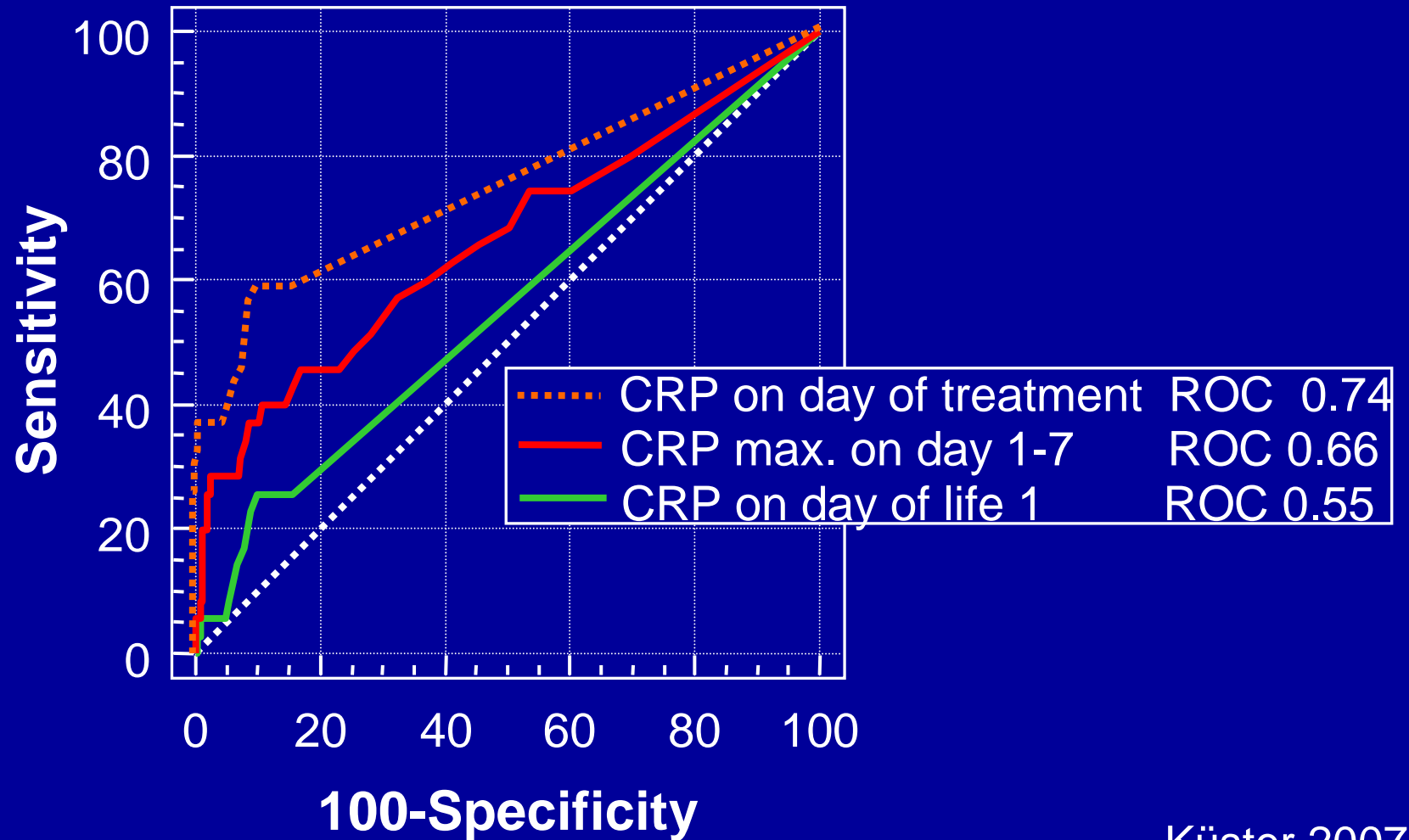
Frequency of Antibiotic Treatment

in full-term newborns during first week of life

	<u>Küster</u> <u>1996</u>	<u>Alistar 2000</u> <u>1997/8</u>
Number of full-term newborns	1532	7348
Observation	30 %	25 %
Antibiotic treatment	3,0 %	5,6 %
because of clinical symptoms	2,5 %	2,8 %
CRP	0,6 %	2,8 %
risk factors	0,3 %	2,9 %

CRP

Sensitivity and Specificity



100-Specificity

Küster unpublished

Küster 2007

Clinical Score

for early onset sepsis in full-term infants

Lung	tachypnea, nasal flaring
	FiO ₂ > 0.21 more than 24h
	mechanical ventilation
Circulation	capillary refill time >2c
	greyish skin color
	temperature instability
ABC	apnoea, bradycardia, cyanosis
Neurology	weak suck, high-pitched cry, lethargy, sensitive to touch, hyperexcitability

Score positive if >1 of maximal 8

Küster unpublished

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Clinical Score

for late onset sepsis in VLBW infants

Circulation	Capillary refill time >2"
Lung	FiO₂ increases >20% *
	MAP increases >3 cm H₂O *
	2x bradycardia or apnoea or stimulation *
Nutrition	Daily oral nutrition decreases >20% *
Laboratory unspecific	Thrombocytopenia <150.000/μl
	Base excess <-7 mmol/L
	Blood glucose change >50% *
Laboratory specific	CRP >10 mg/L
	I/T Ratio >0,15

* in comparison to the previous day

Score positive if >1 of maximal 5

Küster unpublished

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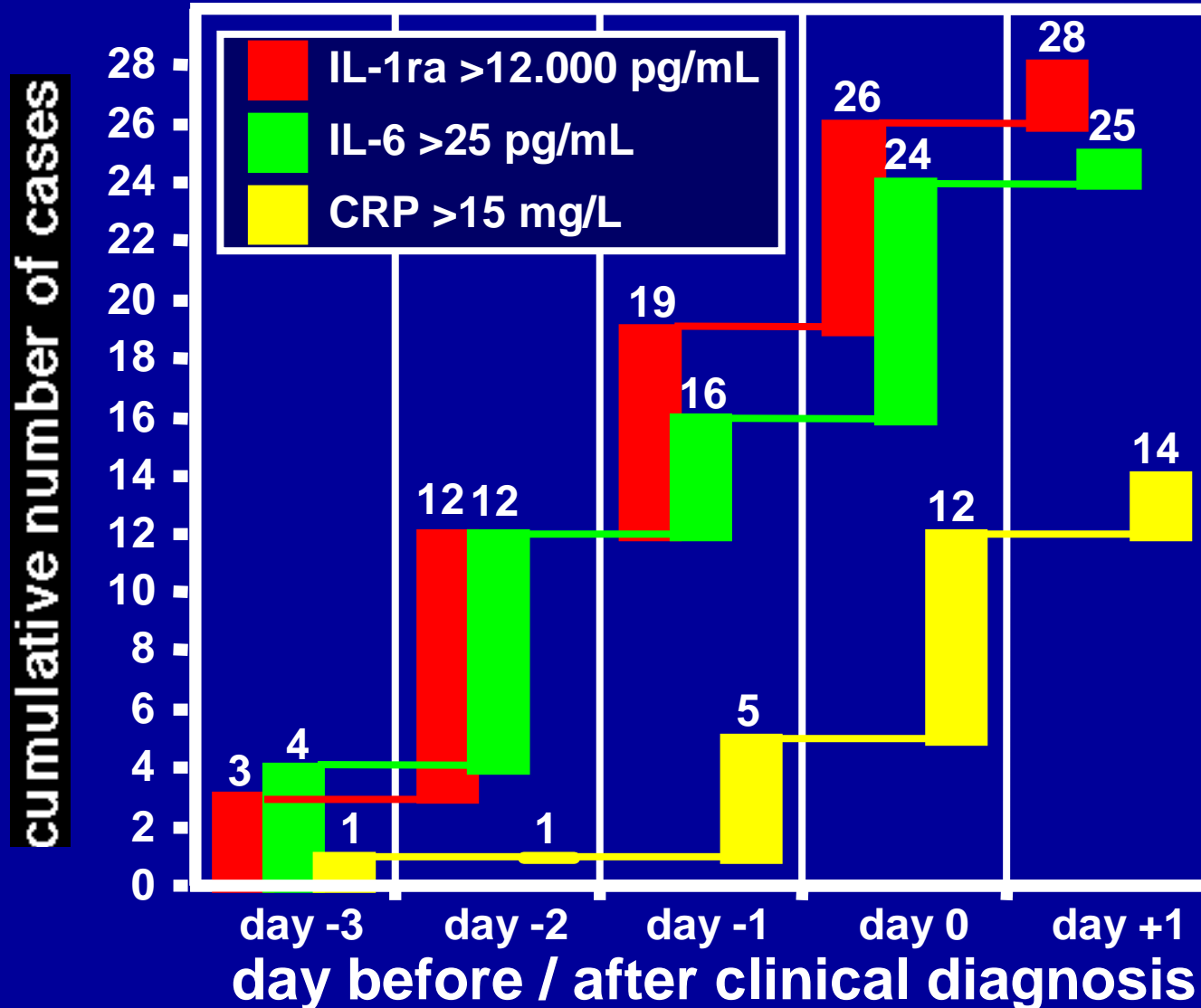
Interleukines

<u>parameter</u>		<u>sensitivity</u>	<u>specificity</u>
CRP	>12	60	96
IL-8	>300	91	93
IL-6	> 31	89	91
IL-6	>100	87	93
G-CSF	>500	81	92
TNFα	> 13-17	75-82	86-88
IL-1β	> 1-10	82-83	68-86
sICAM-1	>400	64	68
E-selectin	>174	64	89

Lehrnbecher 1996, Küster 1998, Panero 1997, Ng 1997,
Berner 1998, Bhartia 2000, Nupponen 2001, Franz 2004

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IL-1ra, IL-6, CRP: Elevated Values



Küster Lancet 1998

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Future

PTT, D-Dimer, ATIII, Protein C

sTREM-1 (Triggering receptor expressed on myeloid cells 1) ROC 0.97

Gibot 2004, 2005

LPB (Lipoprotein binding protein) ROC 0.89

Pavcnik 2004, Behrend 2004

SAA (Serum amyloid A)

Arnon 2004, 2005

CD11b

Weirich 1998, Nupponen 2001

CD64, CD69, G-CSF, lysed cell IL-8 (CD25, CD45RO, CD45RA, HLA-DR, L-selectin)

NG 2002, Ng 2004, Horisberger 2004, Orlikowsky 2004, Turunen 2005,

Anti-inflammatory response (IL-4, IL-10, TGF- β , IP-10, MIG, MCP-1, RANTES)

Cytokine ratios: IL-10/TNF α or IL-6/IL-10

NG 1997

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Summary

blood culture
liquor culture
urine culture
peripheral swabs
leukocyte count
differential smear
CRP
PCT
interleukines
clinical signs

low sensitivity
in EOS if blood culture positive
in EOS not useful
?
not useful
usually not useful
after 24-48 h, not in preterm
not useful
if available (flow cytometry)
circulation, neurology

Consequence

full-term newborns within the first days of life:

- asymptomatic without risk factors
- asymptomatic with risk factors
observe, no diagnostic, CRP after 24-48h?
- symptomatic
sufficient blood-culture, swabs?
no urine, no LP if blood-culture negative?
IL-6 or -8, after 24-48h: CRP and evaluation

preterm infant within the first days of life:

IL-6 or -8, cultures, antibiotics, evaluation p 48h

late onset sepsis:

IL-6 or -8, cultures, urine, LP, antibiotics, evaluation p 48h

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