

Infections in the Neonatal Intensive Care Unit – Novel Approaches to Prevention, Diagnosis and Treatment

Univ. Prof. Dr. Angelika Berger
MedUniWien

The high amount of antibiotic use, in combination with the low grade of colonisation of neonates at the time of their admissions, turns the NICU into an environment where antibiotic policy is likely to have a pronounced effect on the resistance problem.

DeMan, Lancet 2000



An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker

- 2 identical NICUs, different empirical antibiotic regimens
- NICU B: PenG/Tobramycin EOS
 Flucloxacillin/Tobra LOS
- NICU A: Ampicillin/Cefotaxim EOS
 Flucloxacillin/Cefotaxim LOS
- After 6 months regimen change
- Weekly surveillance cultures (rectal and pharyngeal swabs)

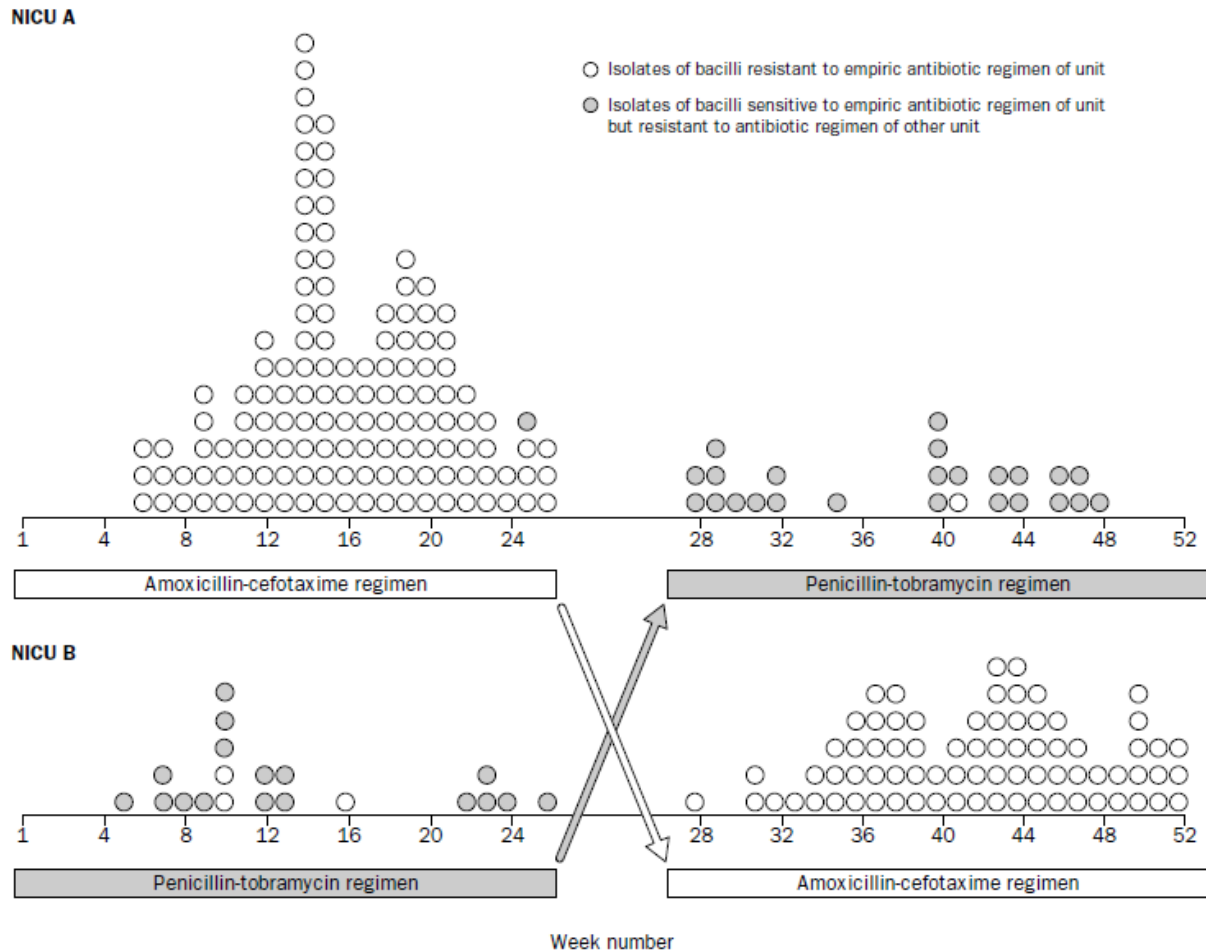
An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker

- 436 admission (218 each)
- Colonization of babies with pathogens resistant to empiric antibiotic regimen
 - 3 patients in NICU B
 - 41 patients in NICU A ($p < 0.001$)
- RR for colonization with resistant pathogens was 18 times higher in NICU A
- Predominant Gram-neg. pathogen in NICU B: *E. coli*, in NICU A: *E. cloacae*
- Same pattern after exchange of empiric regimen

An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker



Unnatural selection: reducing antibiotic resistance in neonatal units

D Isaacs

- Which antibiotics to use?
 - Narrow better than broad
 - No empiric use of 3rd gen cephalosporins (selection pressure)
 - Resistant aminoglycoside – change to another aminoglycoside
- Good microbiology essential (BacTec od. BactAlert)
- Never use prophylactic antibiotics (no matter whether mechanically ventilated, central venous catheter, drains, etc.)
- Stop antibiotics if blood cultures remain negative after 36–48hours

Unnatural selection: reducing antibiotic resistance in neonatal units

D Isaacs

- 10 crucial points to reduce antibiotic resistance in the NICU
- Always take cultures of blood (+ urine) before starting AB
- **Use the narrowest spectrum AB possible, almost always a penicillin and an AG**
- **Do not start treatment with a 3rd gen cephalosporin or carbapenem**
- Develop local and national AB policies to restrict the use of expensive, broad spectrum AB
- Trust the microbiology laboratory: rely on the blood culture results
- Do not believe that abnormal results for a non-specific test (e.g.CRP) means that the baby is definitely septic
- **If blood cultures are negative at 48h, it is almost always safe and appropriate to stop AB**
- Do not to use AB for long periods
- **Treat sepsis, but not colonisation – do not use prophylactic antibiotics**
- **Do your best to prevent nosocomial infection, by reinforcing infection control, particularly hand washing**

Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study

Joseph B Cantey, Phillip S Wozniak, Jessica E Pruszynski, Pablo J Sánchez

Overuse of AB associated with sepsis, NEC and death in neonates –
Antimicrobial stewardship project in a level 3 NICU

All antibiotic use in NICU patients monitored and analyzed

Intervention period:

- Empirical AB discontinued after 48h in electronic medical record
- Duration of therapy for pneumonia 5 days
- Duration of therapy for culture–negative sepsis 5 days

Statistically significant 27% reduction in AB use ($p < 0.0001$)

No difference in safety outcomes (re–institution of AB within 14d after discontinuation, LOS, NEC, death)

⇒ Effective AB stewardship efforts can help to prevent adverse outcomes

Principles and Strategies of Antimicrobial Stewardship in the Neonatal Intensive Care Unit

Sameer J. Patel, MD^a and Lisa Saiman, MD, MPH^{b,c}

„Get Smart Campaign“ – antimicrobial stewardship initiative for acute care settings of CDC

Get Smart Principles	Examples
Accurately identify patients who need antibiotic therapy	Obtain two blood cultures for evaluation of late onset sepsis prior to starting antibiotics
Utilize local and regional antibiograms	Avoid use of meropenem for empiric treatment of suspected late onset sepsis if rates of multi-drug resistant gram-negative bacilli are low.
Avoid therapy with overlapping activity	Avoid simultaneous use of metronidazole and meropenem to treat necrotizing enterocolitis.
Give the right dose and interval of drug	Target vancomycin trough to 15–20 mg/L to treat pneumonia caused by MRSA.
Review culture results and adjust antibiotics	Review microbiology results at transitions of care (e.g. sign out, weekend cross-coverage) and narrow antibiotic coverage promptly.
Monitor for toxicity and adjust therapy accordingly	Adjust antibiotic dose for patients with deteriorating renal function.
Stop therapy promptly if indicated by culture results	Discontinue antibiotics after 48 hours if blood cultures are negative and ongoing infection is not suspected.

Principles and Strategies of Antimicrobial Stewardship in the Neonatal Intensive Care Unit

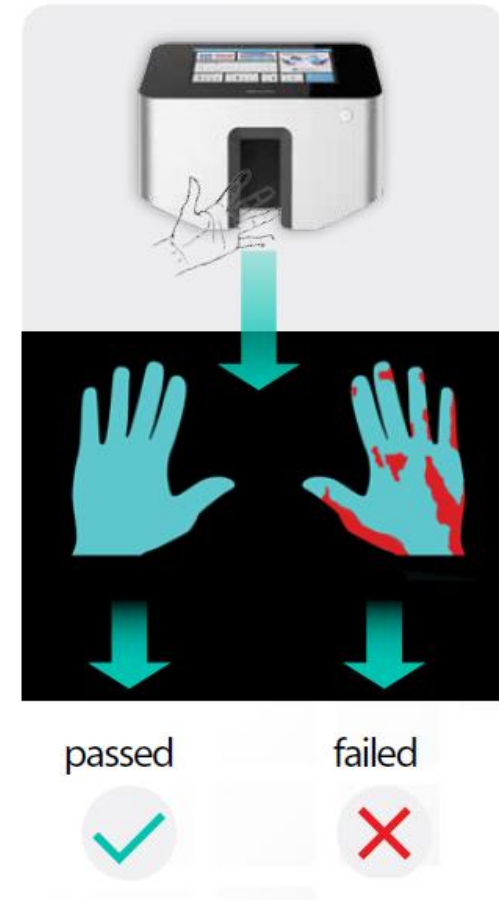
Sameer J. Patel, MD^a and Lisa Saiman, MD, MPH^{b,c}

Examples of antimicrobial stewardship strategies

Strategy	Examples
Prescriber audit and feedback	Review of microbiology results and patient record by antimicrobial stewardship team within 48 – 72 hours of initial approval of vancomycin with recommendation to continue, change or discontinue antibiotics
Formulary restriction and prior authorization	Require prior authorization from the antimicrobial stewardship team prior to the use of meropenem
Education	Provide lecture series about stewardship principles and antibiotic options for the treatment of gram-negative pathogens.
Guidelines and clinical pathways	Develop consensus guidelines for the duration of treatment of presumed ‘culture-negative’ sepsis
Antimicrobial order forms	Use automatic stop orders to provide the correct duration of perioperative prophylaxis
Dose Optimization	Target vancomycin trough levels between 15–20 mg/L for treatment of persistent MRSA bacteremia.
Computer surveillance and decision support	Automated alerts for redundant antibiotic combinations

Recommendations to prevent nosocomial infections in NICUs

- Hand hygiene
- Minimizing use of devices (lines, tubes, ..)
- Antiseptic and antimicrobial impregnated catheters
- Meticulous catheter care (use of central-line insertion and maintenance bundles)
- Education programmes
- Adequate nurse staffing
- Participation in surveillance programs, feedback of surveillance data
- Fluconazole, lactoferrin, probiotics



Fluconazole to prevent fungal infections in NICUs

- Prophylactic systemic fluconazole reduces invasive fungal infections in very low birth weight infants
- No effect on overall mortality rates, no long-term neurodevelopmental outcome data available
- 3mg/kg twice weekly safe and effective in ELBWI
- No adverse events (except 1 fatal case of anaphylaxis reported 2014)
- No effect on resistance pattern so far – ??
- Implemented in NICUs in Vienna in 2007 after 2 fatal cases of early-onset Candida sepsis in two extremely low birthweight infants
- Given routinely to all premies $\leq 27+6$ wks GA, 3mg/kg twice weekly for 6 wks or until on full enteral feeds

Lactoferrin

- Glycoprotein with anti-infective properties (innate immune defense), family of transferrins
- Great homology between bovine and human lactoferrin
- Main whey protein in human milk, high concentration in colostrum
- Anti-inflammatory, anti-oxidativ
- Inhibition of cytokine production (TNF α , IL-1 β , IL-6) – „Anti-endotoxin“
- Reduces production of free oxygen radicals

Pammi and Abrams. Cochrane Database Syst Rev. 2017

Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants



- Six RCTs
- Oral lactoferrin supplementation decreased late-onset sepsis (RR 0.59, 95% CI 0.4–0.87, NNT17) and NEC stage II or greater (RR 0.40, 95% CI 0.18–0.86, NNT 25)
- Oral lactoferrin plus probiotics decreased late-onset sepsis (RR 0.27, 95% CI 0.12–0.6, NNT 8) and NEC stage II or greater (RR 0.04, 9% CI 0.00–0.62, NNT 20)

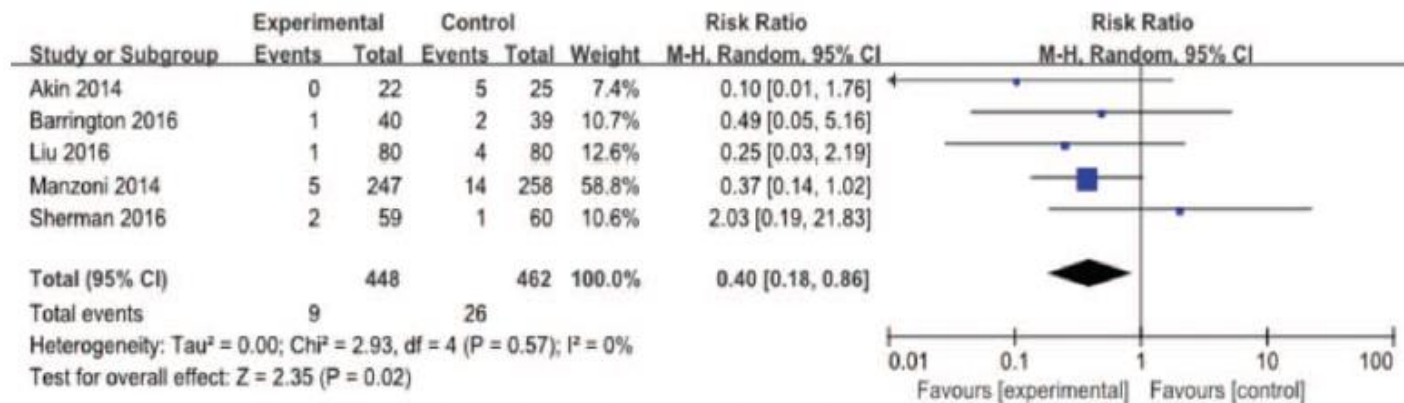
⇒ ...oral lactoferrin with or without probiotics decreases late-onset sepsis and NEC stage II or greater in preterm infants without adverse effects.....

Data of more than 6000 patients awaited from ongoing trials

He et al. 2018

Prophylactic lactoferrin for preventing late-onset sepsis and necrotizing enterocolitis in preterm infants. A PRISMA-compliant systematic review and meta-analysis

9 trials included



Outcome necrotizing enterocolitis

He et al. 2018

Prophylactic lactoferrin for preventing late-onset sepsis and necrotizing enterocolitis in preterm infants. A PRISMA-compliant systematic review and meta-analysis

Outcome late-onset sepsis

⇒ Lactoferrin supplementation in preterm neonates is safe without adverse effects

⇒ Prophylactic supplementation of lactoferrin could significantly reduce the incidence of NEC and LOS in preterm neonates

⇒ Trend of decreased infection-related mortality

⇒ Trend of reduction of time to full enteral feeding and duration of hospitalization

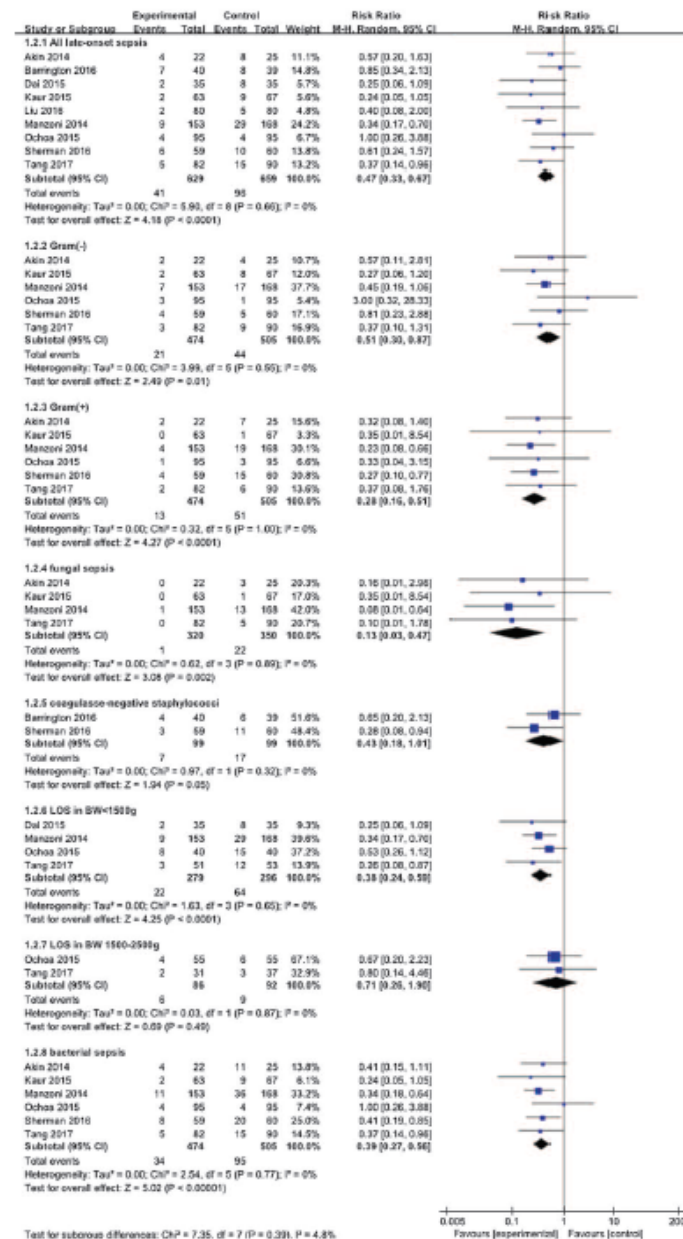


Figure 5. Outcome 1.2: Effect of lactoferrin on late-onset sepsis in preterm neonates.

AlFaleh and Anabress. Cochrane Database Syst Rev. 2014

Probiotics for prevention of necrotizing enterocolitis in preterm infants

- 24 RCTs
- Probiotics significantly reduced the incidence of severe NEC (stage II or more) (RR 0.43, 95% CI 0.33–0.56)
- Probiotics significantly reduced mortality (RR 0.65, 95% CI 0.52–0.81)
- Probiotics preparations containing either lactobacillus alone or in combination with bifidobacterium were found to be effective

⇒ ...enteral supplementation of probiotics prevents severe NEC and all cause mortality in preterm infants.....our updated review strongly supports a change in practice.....

Case 1

History

Grav 1, Para 1, CS at 23+6 wks GA after PPROM at 20+6 wks, mother on ampicillin since 7 days, laboratory parameters of mother negative. Infant bradycardic, respiratory insufficiency – intubation in delivery room – ad NICU

Course Day 1

High ventilatory setting, HMD IV – 2x surfactant on day 1 (f65/min, PIP28mmHg, PEEP 7mmHg, FiO2 $\geq$ 0.6)

Hemodynamic depression, PH – Hydrocortison, Milrinon, Noradrenalin

Laboratory

CRP 0,4 I:T ratio 0.25, thrombocytes 180.000/ μ l, leukocytes 22.000/ μ l, IL-8 no result (technical problems in lab) – Start with ampicillin/gentamicin

Case 1

What is most likely diagnosis?

- A: Severe HMD due to extreme prematurity
- B: Pulmonary hypertonus due to lung hypoplasia
- C: Congenital sepsis
- D: Iatrogenic problem – inadequate ventilatory setting and respiratory support due to inexperienced young doctor on duty

Case 1

Subsequent course

- Day 2 in the evening: Phone-call from Microbiology Department – growth of Gram-negative rods in blood culture of day 1 of life

Any change in antibiotics?



Case 1

What is most likely diagnosis?

- A: Stay on ampicillin/gentamicin since most bacteria expected in case of early-onset sepsis are covered with this combination
- B: Change to ampicillin/cefotaxim since you want to have a better CNS penetration of antibiotics
- C: Change to piperacillin/gentamicin since you want to cover ampicillin-resistant *E. coli*
- D: Change to meropenem/gentamicin since this infant is so ill and you are suspecting multi-resistant gram-negative bacteria

Case 1

Subsequent course

- Change of antibiotics to piperacillin/gentamicin
- Laboratory Day 3:
CRP 17mg/dl, I:T ratio 0.3, IL-8 120pg/ml, thrombocytes 20.000/ μ l, leukocytes 7000/ μ l
- Laboratory Day 4:
CRP 7mg/dl, I:T ratio 0.2, IL-8 70pg/ml, thrombocytes 72.000/ μ l (after transfusion), leukocytes 7.000/ μ l
- Day 8.: Extubation – Infantflow, FiO₂ 0.3

Case 1

Most likely final diagnosis?

- A: Congenital sepsis with GBS
- B: Congenital sepsis with ESBL Klebsiella spp.
- C: Congenital sepsis with ampicillin-resistant E.coli
- D: No idea – thank´s heaven the baby is better now

Case 1

Most likely final diagnosis?

- A: Congenital sepsis with GBS
- B: Congenital sepsis with ESBL Klebsiella spp.
- C: **Congenital sepsis with ampicillin-resistant E.coli**
- D: No idea – thank´s heaven the baby is better now

Case 1

Most likely final diagnosis?

TABLE 3. RATES OF EARLY-ONSET SEPSIS AND ASSOCIATED PATHOGENS IN 1991–1993 AND 1998–2000.*

EARLY-ONSET SEPSIS	1991–1993		1998–2000	
	NO. INFECTED/ TOTAL NO.	RATE/ 1000 LIVE-BORN VLBW INFANTS	NO. INFECTED/ TOTAL NO.	RATE/ 1000 LIVE-BORN VLBW INFANTS
Any	147/7606	19.3	84/5447	15.4
Gram-positive	83/7606	10.9	31/5447	5.7†
Group B streptococci	45/7606	5.9	9/5447	1.7‡
Gram-negative	63/7606	8.3	51/5447	9.4
<i>Escherichia coli</i>	24/7606	3.2	37/5447	6.8§
Fungus	1/7606	0.1	2/5447	0.4

*Data from the period from 1991 to 1993 are from Stoll et al.¹ P=0.007 for the change in the distribution of pathogens between the two periods; there was no significant change in the overall rate of sepsis. Very-low-birth-weight (VLBW) infants are defined as infants weighing between 401 and 1500 g. When the three centers that were not included in the earlier birth cohort are excluded from the analysis, the rates of group B streptococci and *E. coli* in the recent birth cohort are 2.1 per 1000 live-born very-low-birth-weight infants and 7.3 per 1000 live-born very-low-birth-weight infants, respectively, and the changes remain significant (P=0.003).

†P=0.002 for the comparison with the earlier period.

‡P<0.001 for the comparison with the earlier period.

§P=0.004 for the comparison with the earlier period.

- *E. coli* most common pathogen in EOS in VLBWI
- Increased incidence of ampicillin-resistant *E. coli* reported in preterm infants, particularly VLBWI

Case 1

Subsequent course

- Day 4: IVH II in cranial US
- Day 5: IVH IV left side cranial US
- Subsequent clinical course uncomplicated except for posthemorrhagic ventricular dilation – external ventricular drainage – VP-shunt
- Outcome: right-sided spastic hemiplegia and moderate mental retardation at age 2

⇒ IVH – frequent complication of congenital sepsis in extremely premature infants

Case 1



Neonatal sepsis – Outcome

Increased neonatal mortality and morbidity

- Mortality ↑ (30% EOS, 5–50% LOS)
- RDS, CLD
- Prolonged hospitalisation (30% increase after LOS in VLBWI)
- Intraventricular hemorrhage (32% after EOS in VLBWI)
- Periventricular leukomalacia (21% after EOS in VLBWI)
- Neurodevelopmental impairment (30–400% increased risk)
- Cerebral palsy

Neurologic follow–

Case 2

History

Grav 1, Para 1, uncomplicated pregnancy, delivery by cesarean section at maternal request at 38+0 wks GA, uncomplicated postnatal adaptation – ad well-baby nursery

Clinical course day 1

6 hours pp peripheral cyanosis, prolonged recap-time, oxygen saturation 79% – ad incubator – information of neonatologist on duty

What is the most likely diagnosis?

Case 2

What is the most likely diagnosis?

- A: Transposition of great vessels
- B: Congenital sepsis with GBS
- C: Inborn error of metabolism
- D: Wet lung after cesarean section

Case 2

Subsequent course Day 1

- Transfer to NICU – RDS, increasing oxygen demand
- At age 8 hours intubation and mechanical ventilation
- Laboratory parameters:
CRP 0mg/dl, I:T ratio 0.1, thrombocytes 280.000/ μ l, leucocytes 18.000/ μ l, IL-6 65pg/ml
- Echo: pulmonary hypertension, PDA with bi-directional shunt, no complex cardiac defect

Do you start with antibiotics? Which ones?

Case 2

Subsequent course

- Day 2: telephone call Clinical Microbiology Department – growth of gram-positive cocci in blood culture of day 1
- Laboratory parameters:
CRP 11mg/dl, I:T ratio 0.4, IL-6 380pg/ml, thrombocytes 220.000/ μ l, leukocytes 17.000/ μ l
- Deterioration of respiratory situation – FiO₂ 0.8 to 1.0, after surfactant (2x) only short recovery
- Echo: pulmonary hypertonus, PDA with right–left shunting
– start with NO

What next? Change of antibiotics?

Case 2

What next?

- A: Change of antibiotics from ampicillin/genta to carbapenem/genta because of increasing laboratory parameters of infection
- B: Change of antibiotics from ampicillin/genta to vancomycin/genta to cover potentially resistant gram-positive pathogens
- C: Ampicillin/genta, in addition immunoglobulins due to severe course of sepsis
- D: Ampicillin/genta, in addition pentoxifylline due to severe course of sepsis

Immunoglobulins for sepsis in neonates

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Neonatal Sepsis
with Intravenous Immune Globulin

The INIS Collaborative Group*

Cochrane Database Syst Rev 2013

Intravenous immunoglobulin for suspected or proven infection in neonates. Ohlsson, Lacy

Results of the INIS trial – 3493 infants – no reduction in death or major disability at 2 years of age

⇒ Routine administration of IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended

Immunoglobulins for sepsis in neonates

Cochrane Database Syst Rev 2015

Intravenous immunoglobulin for suspected or proven infection in neonates. Ohlsson, Lacy

- The undisputable results of the INIS trial, which enrolled 3493 infants, and our meta-analyses (n = 3973) showed **no reduction in mortality during hospital stay, or death or major disability at two years of age** in infants with suspected or proven infection.
- Although based on a small sample size (n = 266), this update provides additional evidence that **IgM-enriched IVIG does not significantly reduce mortality during hospital stay** in infants with suspected infection.
- Routine administration of IVIG or IgM-enriched IVIG to prevent mortality in infants with suspected or proven neonatal infection is **not recommended**.
- **No further research is recommended.**



Pentoxifylline (Trental®) for sepsis and NEC in neonates

- Xanthinderivate, phosphodiesterase inhibitor, immunomodulatory effects
- Reduces TNFa and IL-6 levels, improves organ perfusion
- 2 studies Lauterbach et al. 1996, 1999 (107 premies with culture-positive sepsis): significant reduction of mortality (OR 0.14, CI 0.03–0.76, $p=0.04$, NNT 6)

Cochrane Review 2015: Pentoxifylline for sepsis and NEC

⇒ PTX as adjunct to antibiotics in neonatal sepsis decreases mortality without any adverse effects...

Shabaan et al. PIDJ 2015

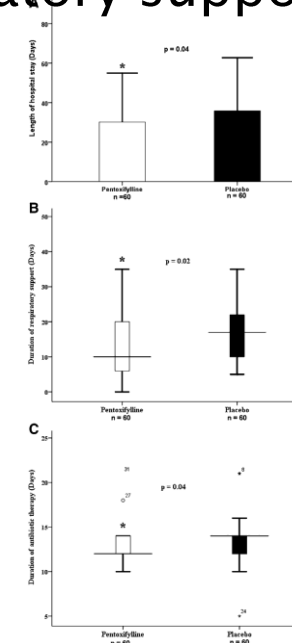
Pentoxifylline therapy for late-onset sepsis in preterm infants: a randomized controlled trial.

- no effect on mortality
- significantly lower cytokine levels
- less need for vasopressors, lower incidence of metabolic acidosis, DIC and thrombocytopenia
- Significantly shorter LOS, duration of respiratory support and duration of AB

TABLE 3. Laboratory and Clinical Outcomes of the Studied Groups

	Pentoxifylline Group (n = 60)	Placebo Group (n = 60)	P Value
Serum TNF- α after intervention (pg/mL)	56.8 (45–78)	85.5 (53–182)	0.006
Serum CRP after intervention (mg/L)	40.6 $\pm$ 26.3	61.2 $\pm$ 30.7	0.007
Need for vasopressors after intervention	4 (7%)	16 (26%)	0.01
Disseminated intravascular coagulopathy	8 (13%)	21 (36%)	0.03
Thrombocytopenia after intervention	12 (20%)	27 (46%)	0.02
Metabolic acidosis after intervention	8 (13%)	22 (36%)	0.03
Oliguria after intervention	20 (33%)	16 (26%)	0.39

Data are expressed as mean $\pm$ SD, median (interquartile range) or number (%).



Adjuvant treatment for sepsis and NEC

Treatment	Indication	Dosage
Pentoxiphyllin (Trental®)	•<u>Severe sepsis</u> (defined as sepsis with severe inflammation plus failure of at least on organ system, e.g. leuco- and/or thrombocytopenia, IL-8 >500pg/μl, respiratory failure, hemodynamic instability, KCA, metabolic acidosis) •<u>NEC</u> (radiologically and clinically confirmed plus systemic inflammation, e.g. leuco- and/or thrombocytopenia, IL-8 >500pg/μl)	5mg/kg/h infusion for 6 h/d 5-6 consecutive days
G-CSF (Neupogen®)	Sepsis and NEC with severe neutropenia (Neutrophils < 1500/μl)	10μg/kg/d (10μg=1Mio Units, 1ml = 30 Mio Units) Infuse over 1h
Immunoglobulin (Pentaglobin®)	No positive effect in INIS study proven for IgG preparation. No large prospective data with IgM preparations available in preterm infants. ⇒ Case-to-case indication in individual cases (e.g. repetitive severe infections, suspected immunodeficiency)	3-5ml/kg/d 3 consecutive days Infuse over 3h

Case 2

Subsequent course

- Stabilisation with ampicillin/gentamicin and pentoxiphylline on day 4, extubation day 8, discharge home on day 17
- Normal neurodevelopmental outcome at age 2 years

⇒ Sepsis with Group B Streptococcus

Case 2

Most common pathogens in neonatal sepsis

- GBS most common pathogen in EOS overall
 - E. coli most common pathogen in EOS in preterm infants
 - GBS most common pathogen in EOS in term infants
- Mortality 16% for EOS overall
 - 30% (GBS) and 38% (E. coli) in preterm infants
 - 2% (GBS) and 10% (E. coli) in term infants

Case 3

History

Premie 28+4 wks GA, IUGR (pre-eclampsia of mother), birth weight 640g, uncomplicated course until week 4, small PDA, almost on full enteral feeds, current weight: 880g

At age 5 weeks

- Sudden onset of increased apnea and bradycardia, step-up in respiratory support from oxygen cannula to CPAP
- Abdominal distension, green (bilious) gastric residues
- Instability of temperature, baby „tired, sleepy“

Case 3

Most likely diagnosis?

- A Early-stage necrotizing enterocolitis
- B Symptomatic PDA
- C Nosocomial sepsis with gastrointestinal involvement
- D Severe anemia of prematurity

Case 3

Next steps

- Sepsis screen + blood culture: CRP 2.6mg/dL, leukocytes 18.000/ μ l, thrombocytes 290.000/ μ L, I/T-ratio 0.45, IL-8 180pg/ml, hematocrit 24%
- X-Ray lung and abdomen: lung o.B., distended loops of small bowel, questionable thickened bowel walls, no free air or pneumatosis
- Cranial US: no bleeding
- ECHO: PDA closed

Case 3

What next?

- A Start pip/taz+AG, TPN, call for pediatric surgeon for suspected NEC
- B Give blood transfusion since anemia is most likely reason for clinical deterioration
- C Give coffein bolus, start with doxapram, wait for blood culture results
- D Start vancomycin/gentamicin for suspected LOS, reduce enteral feeding

Case 3

Subsequent course

- Clinical condition improves with vanco/genta and bolus of caffeine, still distending abdomen, no resistance, no pressure pain, still bilious gastric residues, no spontaneous stool
- Laboratory parameters next day: CRP 4,0mg/dL, leukocytes 16.000/ μ l, thrombocytes 270.000/ μ l, I/T-ratio 0.2, IL-8 80pg/ml
- Telefon call from Microbiology Department: Growth of Gram-positive cocci in blood culture

Case 3

What next?

- A No change in management
- B Stop gentamicin – go on with vancomycin mono
- C Stop gentamicin – go on with vancomycin mono and remove silastic catheter due to positive blood culture
- D Switch to pip/taz + genta since pediatric surgeon suspects early NEC

Case 3

Day 3 of infectious episode

- Blood culture result: Growth of CONS, Staphylococcus haemolyticus, in vitro susceptible to vancomycin
- Further clinical improvement
- After 6 days of treatment discontinuation of vancomycin due to negative laboratory parameters of infection

2 days after discontinuation of antibiotics

- Again increase in apnea and bradycardia, need to switch to CPAP again
- Laboratory parameter: CRP 3mg/dl, I:T ratio 0.25, IL-8 180pg/ml

What next? Start with antibiotics? Which ones?

Case 3

Next step?

- A Start with vanco/genta after taking a blood culture
- B Start with vancomycin/meropenem after taking a blood culture
- C Remove silastic catheter and start with vancomycin/genta after taking a blood culture
- D Remove silastic catheter and start with linezolid/meropenem after taking a blood culture

Case 3

The second blood culture still grows *S. hämolyticus*, in vitro susceptible to vancomycin. After start with vancomycin the clinical situation improves again.

How long do you treat this time?

- A 5 days
- B 7 days
- C 10 days
- D 3 weeks

Case 3

The repeat blood culture two days after start with vancomycin treatment remains negative – discontinuation of treatment after 10 days – baby remains well

What was the problem?

S. hämolyticus needs longer treatment than other CONS – min 10 days

Repeat blood culture and remove silastic catheter in case of repeat positive culture

Sometimes switch to linezolid necessary (intermediate susceptibility to vancomycin)

Early removal versus expectant management of central venous catheters in neonates with bloodstream infection

Vasudevan et al.

BACKGROUND

Uncertainty about management of newborn infants with bloodstream infection and CVC in place

CVC may act as a nidus for infecting organisms and early removal may improve outcome

CVC provides secure vascular access to deliver nutrition and medications – early removal might be harmful

MAIN RESULTS

We did not identify any eligible randomised controlled trials

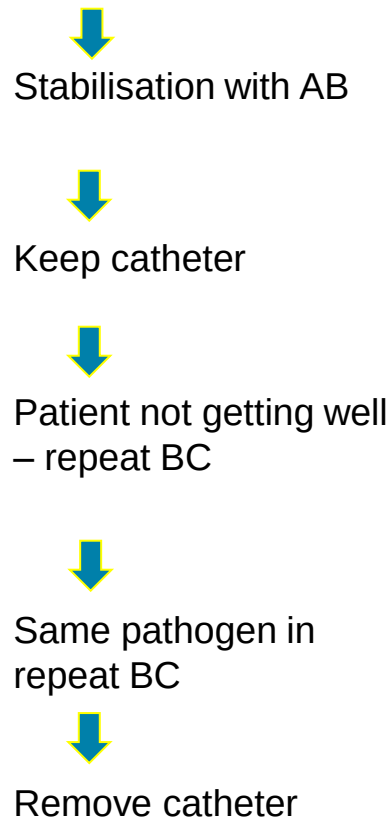
AUTHORS' CONCLUSIONS

There are no trial data to guide practice regarding early removal versus expectant management of CVCs in newborn infants with bloodstream infections

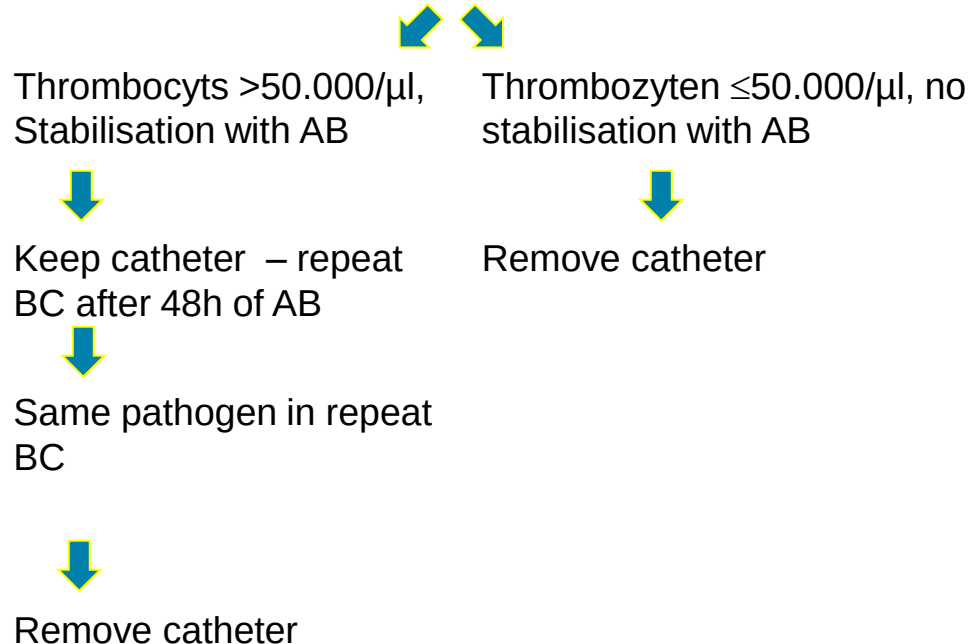
Positive Blood culture plus CVC

(CVC can not be removed easily)

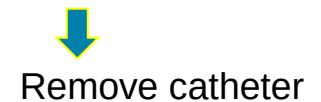
CONS



Other Gram-pos or Gram-neg. pathogens



Fungi



Treatment of neonatal sepsis

Antibiotics for early and late neonatal sepsis

Cochrane Reviews

- 2004 „Antibiotic regimens for suspected early neonatal sepsis“
- 2005 „Antibiotic regimens for suspected late onset sepsis in newborn infants“

⇒ No evidence from randomised trials to suggest that any antibiotic regimen may be better than any other – more studies needed to resolve this issue

Treatment of neonatal sepsis

- Prompt treatment reduces mortality of early neonatal sepsis ⇒ start early already at sepsis suspicion (e.g. ampicillin plus gentamicin), stop after 48hrs if cultures and laboratory parameters remain negative
- You need to know blood–culture isolates of your ward in order to establish an empirical regimen for nosocomial sepsis (e.g. vancomycin plus gentamicin)
- Change antibiotics according to antibiogram – use AB with narrowest spectrum possible
- Short treatment – 5 days for culture–negative sepsis, 5–7 days for CONS sepsis, longer for Gram–negative sepsis
- Discontinue antibiotics after 48hrs in case of negative culture and laboratory results

Neonatal sepsis - Management

Condition	Therapy	Additional considerations
Empiric management		
Early-onset sepsis	Ampicillin + AG: 10d in case of bacteremia, 14d for GBS and uncomplicated meningitis, extend to 21d for complicated infections	Consider a 3rd gen cephalosporin or carbapenem for meningitis. Tailor therapy to pathogen Discontinue therapy if pathogen not isolated!
Late-onset sepsis	Vancomycin + AG: duration dependent on pathogen and site	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. AG-based regimen preferred to cephalosporin given reduced risk of resistance. Discontinue therapy if pathogen not isolated!
Non-antimicrobial strategies		
Recombinant G-CSF Recombinant GM-CSF	Enhance neutrophil number and function, no improvement in survival when administered as therapy	Insufficient evidence to support clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections
IVIG	Augments AB-dependent cytotoxicity and improves neutrophilic function,	No evidence that IVIG reduces death in neonatal sepsis from 10 RCTs
Prevention strategies		
IAP	Administration of penG or ampicillin 4h prior to parturition	Successfully reduces rates of EOS due to GBS. No effect on LOS GBS
Fluconazole prophylaxis	Administration of high-risk preterm infants (<1500g, <28wks)	Most beneficial in NICUs with high baseline rates of invasive candidiasis
BLF supplementation	BLF is human milk glycoprotein with role in innate immune response	BLF supplementation reduces incidence of first LOS in VLBWI

Case 4

History

- Premie 26+2 wks GA, mild RDS after birth, 12d CPAP, then nasal cannula
- On full enteral feeds after 14 days, uneventful course
- Transfer to intermediate care unit after 21 days
- Discharge scheduled at 36 wks corrected age – mother admitted to mother–child–unit 3 days prior to discharge, on this day standard vaccinations given
- The next day the baby starts with apnea and bradycardia, tachy/dyspnea, nasal flaring, sternal retractions

Case 4



Case 4

What is the most likely diagnosis?

- A Late-onset nosocomial sepsis
- B Side effect of vaccination, commonly seen in preterm infants
- C Nosocomial pneumonia
- D Viral respiratory tract infection

Case 4

Subsequent course

- Laboratory parameters: CRP 0.9, I:T ratio 0.15, leukocytes 16.000/ μ l, thrombocytes 240.000/ μ l, IL-8 120pg/ml, blood and urine ad microbiology for culture, respiratory secretion ad microbiology and virology
- X-ray: no distinct infiltration, diffuse opacity
- Clinically the baby deteriorates – increasing oxygen demand – CPAP – tachy/dyspnea – nasal secretion – transfer to NICU
- Day 3 of infectious episode: nasal secretion PCR positive for RSV

Case 4

What now?

- Give palivizumab 15mg/kg to patient, no antibiotics
- Give palivizumab to patient, add intravenous amoxicillin/clavulanate
- Amoxicillin/clavulanate – no palivizumab
- Give ribavirin inhalation to patient, add intravenous AB

Case 4

What about the other patients on the NICU?

- No palivizumab to any other NICU patient
- Palivizumab to all other NICU patients, independent of GA
- Palivizumab to all preterm infants < 28 wks GA
- Palivizumab to patients with BPD or cardiac defect
- Palivizumab to all preterm infants < 28 wks GA plus all infants with BPD or cardiac defect

RSV outbreaks in NICUs

Reference	Location	No RSV pos infants	No of deaths	Palivizumab	Patients with palivizumab	No of RSV pos after Palivizumab
Salcedo et al 2000	Spain	4	0	yes	All infants	0
Cox et al. 2001	UK	7	1	yes	High-risk infants*	1
Kilani et al. 2002	Saudi Arabia	8	1	yes	All infants	0
Heerens et al. 2002	USA	9	2	no		
Abdesso et al. 2004	Portugal	3	0	no		
Abadesso et al. 2004	Portugal	3+5	1	yes	All infants	0
Halasa et al. 2005	USA	9	0	yes	All infants	0
Kurz et al. 2007	Austria	1	0	yes	All infants	0
Dizdar et al 2010	Turkey	13	5	yes	All infants	2
O'Connell et al 2011	Ireland	4	0	yes	All infants	0
Alan et al. 2012	Turkey	3	0	yes	High-risk infants* ⁴	0

Palivizumab to control outbreaks

- CDC: no recommendation can be made (unsolved issue)
- Spanish Neonatal Society: palivizumab prophylaxis suggested for preterm infants and newborns with CHD during NICU outbreaks
- Turkish Neonatal Society: RSV prophylaxis for premature infants in NICU recommended if at least 3 RSV-positive patients present in NICU

Case 4

Subsequent course

- You gave palivizumab to the index case and all other patients in the NICU (term and preterm infants), no antibiotics
- Laboratory parameters of infection stay negative/low (maximum CRP 1.5mg/dl, maximum I:T ratio 0.22)
- Baby on CPAP for 6 days, maximum FiO₂ 0.4
- After 8 days re-transfer to IMC, still on nasal cannula
- Discharge home after another 14 days, baby still PCR positive for RSV at discharge

Does this patient need subsequent palivizumab dosages during RSV season?

Incidence and implications of unrecognized viral respiratory tract infections in premature infants during their birth hospitalization.

Bennett et al., J Pediatr 2012

- Prospective surveillance of premies < 32 weeks GA in 2 NICUs
- 708 specimens tested from 50 patients over 52 week period
- Multiplex PCR: influenza, RSV, parainfluenza, coronavirus, rhinovirus, enterovirus, adenovirus, hMPV
- 66 positive results – 26/50 (52%) positive at least once during hospital stay
- Patients asymptomatic or minimally symptomatic at time of positive PCR result, however, longer hospital stay and more severe respiratory morbidity

Incidence and implications of unrecognized viral respiratory tract infections in premature infants during their birth hospitalization.

Bennett et al., J Pediatr 2012

Infected vs
uninfected infants
had longer length
of stay and
respiratory support

Clinical Comparison of virus-infected and uninfected infants.

Clinical Characteristics	Infected N=26	Infection-free N=24	P-value
Gestational Age (mean)	28.0 weeks	29.4 weeks	0.10
Birth Weight (mean)	1213 gm	1441 gm	0.30
Average Length of Stay	70 days	35 days	0.002 *
Average duration of Intubation	19 days	5 days	0.03 *
Supplemental oxygen	N = 19 (73%)	N = 9 (38%)	0.02 *
Average duration of oxygen use	51 days	13 days	0.002 *
BPD (O ₂ at 36 wks)	N = 12 (46%)	N = 5 (21%)	0.05 *
Clinical Events			
Apnea	0.19	0.38	0.0015 *
Bradycardia	1.37	1.32	0.74
Desaturation	7.09	3.90	<0.0001 *
Clinical deteriorations	38	8	<0.0001 *

*
p ≤ 0.05 calculated by unpaired t-test

Nosocomial transmission of respiratory syncytial virus in neonatal intensive care and intermediate care units. Berger et al. PIDJ 2010

- Prospective epidemiologic survey
- Nasopharyngeal swabs taken twice weekly from patients, staff and parents during RSV season 2007/08
- Of 1002 samples, only 4 positive (2 from a patient, 2 from staff)
- No nosocomial transmission
- 1 patient (preterm 26 weeks) died



Nosocomial rhinovirus infection in preterm infants. Steiner, Berger PIDJ 2012

- Prospective screening during 2011 in 2 NICUs (22 beds) and 2 nIMCUs (24 beds) at clinical suspicion of viral infection (cough, nasal congestion, otherwise unexplained respiratory deterioration)
- RT-PCR for panel of respiratory viruses (rhino, adeno, hMPV, RSV, influenza)
- Positive cases followed twice weekly until 2 negative test results or discharge home

Nosocomial rhinovirus infection in preterm infants. Steiner, Berger PIDJ 2012

- 455 infants, 106 infection screens, 17 positive (16%)
- 1 hMPV, 16 HRV
- Median birthweight 865g, median days of life: 71 days
- Duration of clinical symptoms: median 13d (range 6–37d)
- Duration of HRV–RNA shedding: median 15d (range 5–44d), 5 still positive at discharge
- 12/16 increase in respiratory support* during infection
- 3 cases mechanical ventilation due to respiratory failure

*increased oxygen demand, step up in ventilation mode

TABLE 1. Baseline Data and Clinical Characteristics of the 16 Preterm Infants With Human Rhinovirus Infection

Pt/Sex	GA (wk)	BW (g)	Month of Diagnosis/ Ward	Age at Onset (d)	Clinical Signs & Symptoms	Ventilation Mode, Oxygen Demand (%) Before Infection	Ventilation Mode, Oxygen Demand (%) After Infection	CRP at Onset (mg/dL)	IL-8 at Onset (pg/mL)	CRP/IL-8 Elevation During Infection	Duration of Symptoms (d)/ Duration Viral Shedding (d)	Comorbidities*
1/F	32 + 4	1256	April/IMCU	60	Rr, cough, apnea, increased WOB	O ₂ -insuffl., 25%	nCPAP, 50%	0.5	31.4	No	33/27	Suspected syndrome
2/M	25 + 0	570	July/IMCU	119	Rr, apnea	No support, 21%	O ₂ -insuffl., 30%	0.1	23.3	No	14/14	
3/F	24 + 1	630	April/IMCU	89	Rr, increased WOB	No support, 21%	O ₂ -insuffl., 25%	0	33.9	No	24/26 [†]	
4/M	33 + 0	1335	April/IMCU	110	Rr, cough, increased WOB	No support, 21%	No support, 21%	0.8	58.9	No	37/44	
5/M	23 + 6	770	April/IMCU	83	Rr, cough, increased WOB	O ₂ -insuffl., 25%	Mechanical ventilation, 30%	0.8	n.d.	Yes (CRP 18.8) [‡]	24/32	Intestinal perforation
6/F	31 + 6	2450	July/IMCU	43	Rr, cough, increased WOB	O ₂ -insuffl., 25%	nCPAP, 50%	0.2	82.7	No [‡]	24/27	Neuromuscular disorder
7/M	33 + 6	2210	May/ICU	169	Rr, cough, apnea	nCPAP, 21%	nCPAP, 21%	0.3	17.6	No	11/12	Spina bifida
8/F	26 + 5	460	May/ICU	82	Rr, increased WOB	O ₂ -insuffl., 23%	O ₂ -insuffl., 23%	0.3	47.4	No [‡]	6/5	
9/F	24 + 1	605	April/IMCU	83	Rr, apnea, increased WOB	No support, 21%	nCPAP, 25%	0.6	24.5	No	8/13 [†]	
10/F	26 + 0	830	April/IMCU	59	Rr, increased WOB	O ₂ -insuffl., 21%	O ₂ -insuffl., 25%	0.6	45.4	No	10/8 [†]	
11/M	29 + 2	1260	July/IMCU	53	Rr, cough, apnea, increased WOB	No support, 21%	O ₂ -insuffl., 40%	1	n.d.	No	12/15	Esophageal atresia
12/F	27 + 6	900	April/ICU	50	Rr, increased WOB	O ₂ -insuffl., 30%	Mechanical ventilation, 40%	2	45.6	Yes (CRP 13.6) [‡]	15/22	Giant thoracic lymphangioma
13/M	27 + 6	1165	April/IMCU	38	Rr	No support, 21%	No support, 21%	0.1	11.6	No	9/26 [†]	Liver tumor
14/F	26 + 4	740	July/IMCU	46	Rr, increased WOB	No support, 21%	O ₂ -insuffl., 21%	0.1	20.8	No	6/6	
15/F	25 + 3	422	Nov/ICU	123	Rr, increased WOB	nCPAP, 40%	Mechanical ventilation, 63%	7.9	536	Yes (IL-8 1121) [‡]	Expired/11	Suspected metabolic dis.
16/F	36 + 1	2200	Dec/IMCU	54	Rr, apnea, increased WOB	No support, 21%	Mechanical ventilation, 21%	0.1	42	No [‡]	9/n.a.	Severe perinatal asphyxia

Case 5

History

Premie 25+3 wks GA, congenital sepsis with E. coli, mechanically ventilated for whole of 2 weeks, complicated respiratory course (2x re-intubation), nosocomial sepsis with CONS in 3rd week of life, treatment with vanco for 5 days, currently baby stabil on CPAP, FiO₂ around 0.4, silastic catheter since day of life 2, current weight: 817g

Day 23

- Nurse reports increase in apnea and bradycardia, pale skin colour and temperatur instability
- You order coffeinbolus – no improvement – increasing oxygen demand up to FiO₂ 0.6

Case 5

On clinical examination the baby does not appear „septic“, you manipulate on CPAP prongs resulting in reduction to FiO2 0.55 – what next?

- A No further action required – deterioration is consequence of young, inexperienced nurse
- B Start with vanco/genta after blood culture (CONS sepsis most likely)
- C Sepsis work-up inclusive of blood culture and laboratory signs of infection– no antibiotics until lab results are available
- D Start with pip/taz/genta after blood culture (early NEC most likely)

Case 5

Sepsis work-up

- CRP 1.1 mg/dL, leukocytes 14.000/ μ l, thrombocytes 260.000/ μ l, I/T-ratio 0.24, Interleukin-8 98 pg/ml, hematocrit 25%
- X-ray: lung ok, abdomen slight dilation of intestinal loops, otherwise ok
- Urine: leukocytes negativ, nitrit negativ
- Clinical exam: pale skin colour, slight dilation of abdomen, otherwise nothing abnormal detected

What next?

Case 5

What next?

- a) No antibiotics because of inconclusive laboratory test results, you order blood for transfusion
- b) Start with vanco/genta and removal of silastic catheter (CONS sepsis most likely diagnosis), order blood for transfusion
- c) No action required – wait and see (hopefully the nurse of the next shift will be more experienced)
- d) Start vancomycin/meropenem since this is 3rd infectious episode and you do not want to risk re-intubation in this baby

Case 5

Subsequent course

- After start with vanco/genta and infusion of RBC the baby's condition improves over night, still FiO₂ 0.45, some apnea/bradycardia
- Second transfusion of RBC after 24h
- Laboratory 48hrs after start with antibiotics: CRP 0.6 mg/dL, leukocytes 13.000/μl, thrombocytes 240.000/μl, I/T-ratio 0.1, interleukin-8 88 pg/ml, hematokrit 38%, blood culture still negative
- Further improvement of clinical condition, FiO₂ 0.4, some apnea/bradycardia

Case 5

What next?

- A Continue vancomycin + gentamicin since baby has improved with this treatment
- B Stop antibiotics after 48hrs since clinical situation improved, blood culture still negative, laboratory parameters negative
- C Wait for one more day on antibiotics, check laboratory signs of infection again after 24hrs and stop antibiotics if still negative – you do not want to risk deterioration in this baby
- D Stop gentamicin, continue with vancomycin for whole of 5 days (CONS often need longer than 48hrs to grow in culture)

Case 5

You stop antibiotics after 48hrs, baby's condition remains stable, FiO₂ slowly decreasing to 0.3–0.35, some apnea/bradycardia – diagnosis?

Increase in apnea/bradycardia due to anemia of prematurity, no infection

⇒ It is almost always safe to discontinue antibiotics after 48hrs if blood culture and lab parameters remain negative

Case 6

History

- Premie 23+6 wks GA, birthweight 520g, LISA, stable on CPAP for 12days, then intubation with increasing oxygen demand and respiratory exhaustion, ventilated for 4 days, extubation, re-intubation after 12hrs, ventilated for another 4 days, extubation, CPAP FiO₂ around 0.4
- Complicated enteral nutrition, recurrent bilious gastric residues, baby still not on full enteral feeds, repetitive episodes of suspected NEC, no proven NEC episode
- Silastic catheter since day 2 of life (21 days)
- St.p. nosocomial sepsis (Staph epi – vanco 7d), antibiotics for whole of 9 days (including 48hrs ampicillin/genta after birth), fluconazole prophylaxis 3mg/kg twice weekly since birth

Case 6

Subsequent course

- Day 24: increase in apnea/bradycardia, pale skin, dyspnea, increasing oxygen demand on CPAP up to 60%, hemodynamically stable, no KCA
- Sepsis work-up: blood culture, urine culture, CRP 2.2mg/dl, I:T ratio 0.28, thrombocytes 120.000/ μ l, leukocytes 18.000/ μ l, IL-6 192pg/ml
- X-ray lung: no distinct infiltration, global hazy appearance, PIE (interstitial emphysema) both sides, picture of „BPD“, pneumonia cannot be excluded
- Clinical exam: pale skin, retractions/dyspnea, distended abdomen, no resistance

Case 6

What next? Most likely diagnosis?

- A Suspected nosocomial sepsis – start with vanco/genta
- B Suspected nosocomial pneumonia (increasing oxygen demand, dyspnea, inconclusive X-ray) – start with piperacillin/gentamicin
- C Suspected nosocomial pneumonia – start with meropenem/gentamicin
- D Suspected nosocomial sepsis – start with vanco/meropenem since 2nd episode of infection

Case 6

Subsequent course

- After start with piperacillin/gentamicin for suspected pneumonia there is respiratory deterioration within next 12 hours, intubation, conventional MV – high ventilatory settings, PIP 28mmHg, FiO₂ 0.5–0.7, yellowish tracheal secretion – ad microbiology for culture
- X-ray lungs: patchy opacities on both sides, no pneumothorax
- Baby hemodynamically stable, no KCA

Case 6

Any change in management?

- A No, baby is stable, waiting for results of cultures (blood, urine, TS)
- B Yes, switch to HFOV to prevent further damage of premature lung, no change in antibiotics until culture results are available
- C Yes, change antibiotics to meropenem/linezolid, since pneumonia very likely and no improvement with piperacillin/genta
- D Yes, change of antibiotics to meropenem/linezolid/amphotericinB since fungal pneumonia cannot be ruled out

Case 6

Subsequent course

- You didn't change management lately – baby still stable but high ventilatory support 36 hours later
- Telefon call from Microbiology Department: growth of *Candida albicans* in urine culture, blood culture and TS negative

What next?

Case 6

What next?

- A Continue pip/genta, increase fluconazole from prophylactic dosage (3mg/kg twice weekly) to therapeutic (15mg/kg once daily)
- B Same as A plus removal of all intravenous catheters, insertion of two new peripheral lines
- C Continue pip/genta, add amphotericin B, remove intravenous lines
- D Stop pip/genta, start fluconazole in therapeutic dosage, removal of intravenous lines
- E Stop pip/genta, start micafungin, remove intravenous lines

Case 6

Subsequent course

- After switch to micafungin significant clinical improvement
- TS after 3 days of micafungin treatment negative, no growth of bacteria or fungi, urine culture also negative
- After 5 days of micafungin treatment the baby can be extubated – CPAP with FiO₂ 0.35–0.45
- After 14d of micafungin treatment and repeat negative cultures of TS treatment is discontinued

Case 6

Diagnosis

- Nosocomial pneumonia with *Candida albicans*
- *Candida albicans* in vitro susceptible to fluconazole and amphotericin B – often no clinical eradication of fungi in extremely preterm infants
- Treatment with amphotericin B an option, echinocandins good alternative (Caspofungin, Micafungin) – highly effective, few side effects
- Perhaps higher mortality with liposomal amphotericin B compared to conventional amphotericin B

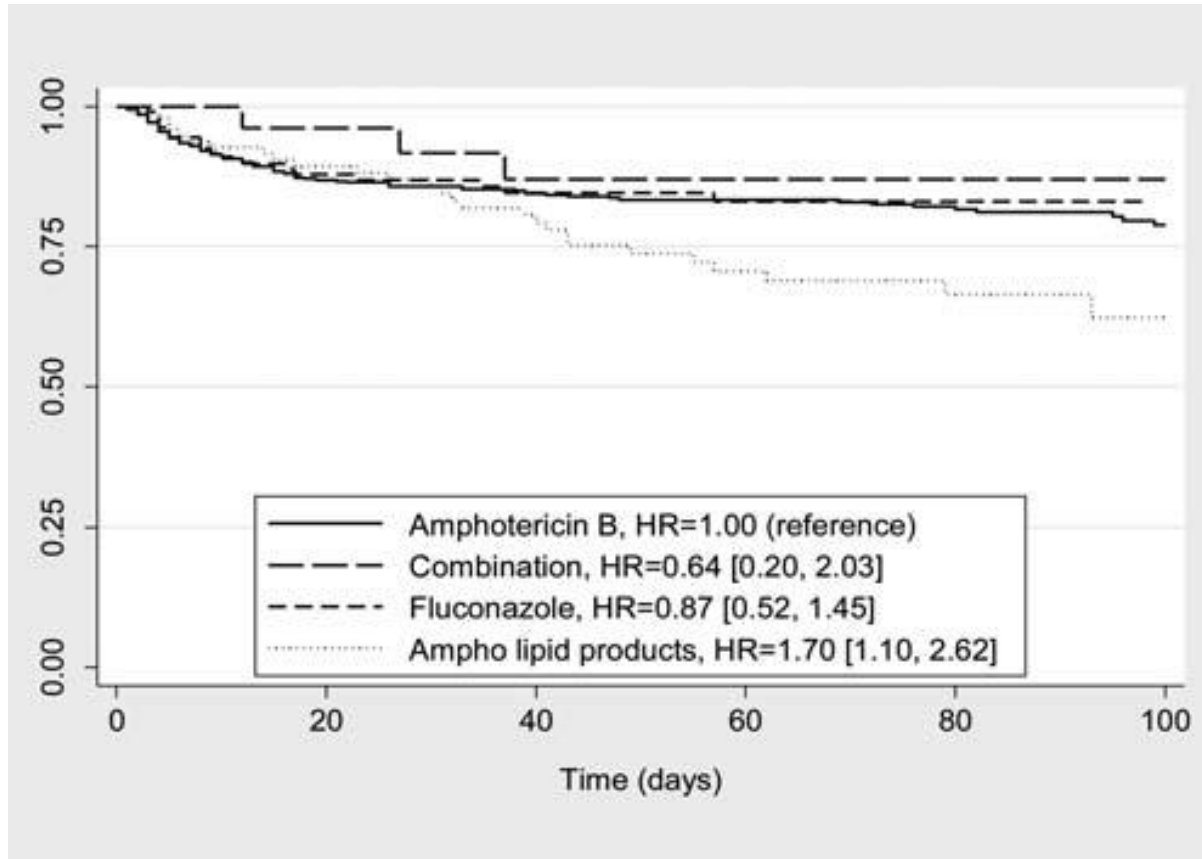
Candida species in NICUs

Candida spp	Percentage	Fluconazole resistance
Candida albicans	58%	No
Candida parapsilosis	34%	No
Candida tropicalis	4%	Possible
Candida glabrata	2%	Yes, often (> 20%)
Candida lusitaniae	2%	Possible
Candida krusei	0,2%	Yes, always

Mortality rate of candida sepsis in premies

Birthweight	Mortality rate
Very low birthweight (<1500g)	28–32%
Extremely low birthweight (<1000g)	37–40%

AmphoB lipid formulations higher mortality in the NICU?



Infants treated with amphotericin B lipid products had higher mortality than infants treated with either amphotericin B deoxycholate or fluconazole

Removal of catheter imperative

TABLE 3 Adjusted Logistic Regression Analysis for NDI or Death
Related to Timing of Catheter Removal (*N* = 189)

Variable ^a	No.	Proportion With NDI/Death, %	OR	95% CI	<i>P</i>
Catheter removal					
Early	57	59.65	Reference		
Late	132	78.79	2.69	1.25–5.79	.01
Gestational age					
≥25 wk	83	60.24	Reference		
<25 wk	106	83.02	3.91	1.85–8.29	<.001
Gender					
Female	94	67.02	Reference		
Male	95	78.95	2.30	1.09–4.84	.03

NDI was defined as any one of the following: moderate or severe cerebral palsy, Bayley MDI of <70, Bayley PDI of <70, blindness (no useful vision in either eye), or deafness (hearing aids in both ears). These numbers differ from those in Table 4 because of the proportions of children who completed follow-up evaluations. Data were adjusted for center as outlined in "Methods."

^a Variables evaluated but not entered into the model during forward selection (*P* < .05) included birth weight, race, days with peripherally inserted central catheter, age at first enteral feeding, days of mechanical ventilation, PDA, IVH, H₂ receptor blockers, days with central venous line, days of parenteral alimentation, and *Candida* species.

Early removal of catheter reduces mortality and adverse neurodevelopmental outcome of fungal sepsis in ELBW infants!

Empiric antifungal treatment

Azole prophylaxis and/or critically ill

- Micafungin (10 mg/kg/d) or
- Conventional amphotericin B (1 mg/kg/d)

No Azole prophylaxis and not critically ill

- 1. Choice:
Fluconazol (25 mg/kg loading, 12–15 mg/kg/d in 1 ED)
- 2. Choice:
Micafungin (10 mg/kg/d in 1 ED) or conventional amphotericin B (1 mg/kg/d)

Take home message

Candida infections in the NICU

- Often treated, rarely diagnosed...
- Remove/replace all intravenous lines – Candida has high affinity to catheter surfaces, produces biofilms – Increased mortality and morbidity with late vs. early catheter removal reported
- High mortality up to 40% in ELBW infants
- Treat 14d after last positive culture
- Prophylactic fluconazole reduces incidence of invasive Candida infections in VLBWI – no effect on mortality proven