RESEARCH PAPER | Medical Science | Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

Intrahospital Infections Prophylaxis in the Premature Newborn

KEYWORDS: sepsis, enterocholitis, retinopathy, dysplasia

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ABSTRACT *Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection within the first 4 weeks of life. We performed o retrospective study over 2 years (01.01.2011-31.12.2012) in the Neonatology Clinic, "Louis Turcanu" Children's Emergency Hospital Timisoara, gathering 76 premature newborns (4.7%), selected from a total of 1617 neonates, according to history, clinical, epidemiological and biological findings. The disease had a prevalence of 4.7 %, and high mortality 19,7%, even under specific antimicrobial therapy. Microbian flora involved was represented by gram negative bacilli (81.35%), staphylococci (13.55%) and candida (5.08%). There is a statistically significant correlation between neonatal sepsis and ulcero necrotic enterocolitis (2.63%), premature retinopathy (52.6%), intraventricular haemorrhage (59.2%), bronchopulmonary dysplasia (3.94%) and death (19,7%). Neonate infection prophylaxis, especially in the current public health care system, needs involvement of an ensemble of both medical and social strategies, implementing postnatal care regarding the health of both mother and newborn.*

Preterm babies have a three to tenfold higher infection incidence than term newborns with normal birthweight. Neonatal sepsis remains among the primary causes of death, even in developed countries.

Introduction: sepsis and septic shock persists as a challenge for neonatologist and pediatrician, notwithstanding modern treatment and resuscitation techniques and strategies. Depending on the age at the debut, septicemia can be devided in: a) early-onset neonatal septicemia or maternal-fetal infection, starting in the first 3 days of life; usually a fulminant multisystemic infection, aquired by vertical transfer from the mother; b) late-onset neonatal septicemia or postnatal infection, starting after the first 3 days of life; can have acute or insidioous beginning, occurs especially in preterm infants in Neonatal Intensive Care Units (NICU). Vary late-onset neonatal sepsis has also been recognized, debuting after the first 3 months of life, affecting low birthweight infants. (1)

Aim: Analysis of risk factors, etiology, diagnostic methods, treatment response, intrahospital neonatal infection prophylaxis in a lot of preterm newborns admittedin the Neonatology Clinic, "Louis Turcanu" Children's Emergency Hospital Timisoara.

Material and methods:
The study was performed retrospectively over 2 years (01.01.2011-31.12.2012) in the Neonatology Clinic, "Louis Turcanu" Children's Emergency Hospital Timisoara, gathering 76 premature newborns, selected on history, clinical, epidemiological and biological criteria. Out of 1617 newborns 165 were preterm, 76 of them developing neonatal sespsis.

The infants were divided in 2 groups:

Group I: 59 neonates with early-onset neonatal septicemia (EOS), with debut in the first 3 days of life (77.63%)

Group II: 17 neonates with late-onset neonatal septicemia (LOS), with debut after the first 3 days of life (22.36%)

The study protocol for each newborn included:
- risk factors of sepsis: gestational age, obstetrical manoevers, invasive procedures during birth, history of spontaneous and provoked abortion, history of newborn with streptococcal infection, maternal infections, premature rupture of membranes, way the birth was given, socio-economicstatus of the mother
- clinical exam performed dayly, in order to identify specific signs
- sugestive paraclinical investigations and evaluation of diagnostic value over studied groups: HLG, glicemia, CRP, procalcitonin
- implementation of a therapeutic conduct and evaluation of treatment on the studied group
- anatomo-pathological exam of the deceased newborns

Results and discussions:
Early infections had been reduced significantly once intrapartum antibiotics were introduced. The incidence of nosocomial infections remains constant due to health care and intensive care procedures provided to the ill preterm newborn. While new reports in developed countries demonstrate the incidence of neonatal sepsis varying between 1 to 5 in every 1000 live newborns, other studies in developing countries return sepsis rates varying from 49 to 170 in every 1000 live newborns. The medical literature reveals that sepsis incidence among LBW infants with prolonged hospitalization increased dramatically to 300 cases in 1000 LBW infants – 25% in our study.

Risk factors for EOS:
Gestational age
Infection (not only colonization) is possible, because defence mechanisms against infection are not fully developed in preterm newborns.

It has been determined that newborns below 29 weeks of gestation may develop EOS aproximately 20 times more frequent than term infants, and 30-50% of LBW and ELBW preterm babies may die from EOS. By contrast, the incidence of materno-fetal infections among newborns over 34 weeks of gestation is 0.4 to 0.6 cases in 1000 births, with 0-3% associated mortality. (2) In our study group, preterm infants over 34 weeks of gestation registered 1.2% EOS incidence, with 2.6 % mortality.

Maternal infection
Among studied cases 36% of pregnant women presented

Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

infections. Most frequent were urinary and genital infections (cervicovaginitis and endometritis)

- Urinary infection had a 6% incidence
  Correlation between urinary tract infection and materno-fetal infection was more accurate as the urinary infection was more severe or treated more superficially (not treated or not fully treated).
- Secondary bacteriemia is a possible explanation, the newborn being infected by transplacental transfer.
- Genital infections (cervicovaginitis and endometritis)
  The pathogenes infected the newborn by either ascendant route, after membrane rupture, or contiguity, during the passing through the pelvigenital canal.
- Fever over 39°C during labour or the first hours after birth is a major risk factor for materno-fetal infections (38.9%).
- Maternal colonization with pathogens
  The pathogens on the women's vagina wall can infect the newborn during birth, either by contiguity or by inhaling the vaginal secretions.
- Although the medical literature mentions the group B streptococcus as a frequent pathogen for materno-fetal infections, no babies presented positive cultures for the germ in out lot.
- Prolonged time between rupture of membranes and beginning of birth.
- The longer the period between rupture of membranes and beginning of birth, the higher the risk for infection. Two thirds of infected newborns' mothers had ruptured membranes over 24 hours prior to birth.
- Invasive procedures during pregnancy: amniocentesis, fetal transfusions, cervical cerclage (2.6%)
  Birth method: C-section (60%)
- Neonatal infection is more frequent in males (61%)
  The higher sespsis incidence in male infants is mentioned throughout the medical literature, probably due to defects of an immunomodulator X-linked gene, but there is no actual explanation for this phenomenon.

Risk factors for LOS:
Prematurity
This was the leading risk factor involved in LOS (97,5%). The most frequent prematurity causes are:

- immaturity of the defence systems against infection of the preterm newborn
- frequent contact with the health care personel in maternity wards
- the use of invasive health care techniques (perfusions, catheters, gavage probes)

Long hospitalization
Hospital microbial flora is a permanent threat for newborns, due to high susceptibility towards infection.

Severe diseases of the neonate (hyaline membrane disease, pulmonary atelectasis) represent an important risk factor for neonatal infection because these children present poor ventilated regions and vascular disorders that require invasive techniquea (mechanically assisted ventilation, perfusions, catheters). Extended contact with intrahospital microbial flora favours the debut in pulmonary infections.

Superficial infections of the neonate: piodermitis, omphalitis, impetigo, contiguity solutions in the skin (intravenous fluids, central/peripheral catheters) (3) Contamination is possible in the same infant through contact with different parts of the body or by horizontal dissemination between babies.

Extended treatment with wide spectrum antibiotics are also involved in nosocomial infections.

Clinical manifestations:
Sugestive simptomatology for neonatal sepsis (table 1):

Clinical signs	manifestations	Percent
Thermoregulation disorders	Hypotermia, hypertermia	25%
Behavioural disorders	Lethargy, irritability, spontaneous groaning	88%
Cutaneous alterations	Acrocianosis, pallor, marmorated skin, purpura, edema, scleral edema, abscesses	55-65%
Respiratory disorders	Respiratory distress, apnea with cyanosis, tachypnea	55-60%
Cardio-vascular disorders	Early septic shock, Refractory septic shock Hypotenssion - TA < percentila 5 Systolic blood pressure < 2 DS	65% 12% 10%
Digestive disorders	Bowel distension, digestive intolerance, hepatomegaly	46%
Neurological disorders	Lethargy, irritability, seizures, abnormal eye movements, hypotonia, hypertonia, abolition of archaic reflexes	35%

Table 1: Neonatal sepsis: clinical signs

- Depending on the result of blood cultures, we distributed the neonatal infection in four groups:
- Sepsis with germs identified in blood culture, associated with clinical and biological context, 13 cases (17,1%).
- Asymptomatic bacteriemia, without clinical or biological context, but with risk factors for neonate sepsis, 9 cases (11,8 %).
- Sepsis without identified germs in blood cultures, but with marked clinical and biological context (suspicion of sepsis), 14 cases (18,4%).
- Sepsis with germs identified in septic focuses, with existent clinical and biological characteristics, but with negative blood cultures, and at least two positive cultures from septic focuses that can communicate one with the other only through hematogenous routes, 37 cases (48,68%).

Etiology:
Concerning the etiologic spectrum of positive blood cultures, the results were as follows (in accordance with microbian flora in maternal and nosocomial infections):

- **gram negativi bacilli**, 48 cases (81,35%), Pseudomonas aeruginosa – 22 cases, Serratia marcescens – 15 cazuri, Klebsiella pneumoniae – 7 cases, Enterobacter – 2 cases, Escherichia coli – 2 cases
- **staphylococcus species**, 8 cases (13,55%)
- **Candida albicans**, 3 cases (5,08 %), in neonates with birthweight < 1500 g

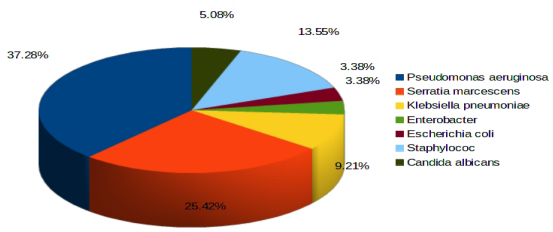
Data in medical literature mentions the highest percentage for nosocomial infections to be Datele din literatura citeaza in infectia nosocomiala cele mai mari procente pentru Coagulazo negative Stafilococcus (CoNS) and Enterobacteriaceae. In our study the most frequent germs in nosocomial infections were S. epidermidis and Enterobacteriaceae.

CoNS presents low pathogenity in immunocompetent hosts, the newborns being susceptible to invasive procedures infections with CoNS. The first step of pathogenicity is the adhesion of the bacteria to the skin, mucous membrane or insertion of artificial devices like intravascular catheters, CNS shunts, often used in preterm infants. The most frequent staphilococcus involved in nosocomial infections is S. epidermidis (6 cases = 10,16 %) and S. aureus (2 cases = 3.38 %). Another risk factor signoficant for CoNS infection is perfusion with intravenous lipids, that provide a growth medium for these microorganisms. (4)

Gram negative bacilli
Although some studies demonstrated maternal milk and de-

Volume : 3 | Issue : 12 | Dec 2013 | ISSN - 2249-555X

vices used for its collection are sources for colonization with gram negative bacilli and invasive diseases (5), our lot did not registers such cases.



Graphic 1: Microbian flora incidence in neonatal septicemia

Igieno-dietetic treatment
Includes special environments for newborns, oxygenotherapy and enteral/parenteral nutrition.

Antibiotic therapy
Empiric antibiotic therapy in the asymptomatic newborn that presents risk factors for sepsis was performed associating a beta-lactamine (Ampicillin) and an aminoglycoside (Gentamicin). This combinationwas used in 5 preterm infants (6.57%). The decision on the empiric treatment must be based on a series of factors: moment and circumstances the ilness appears, most frequent microorganisms, susceptibility profile of these microorganisms, the site of the supposed infection and the safety of the antibiotic.

Empiric antibiotic therapy in the symptomatic was performed associating a cephalosporin (Cefotaxime, Ceftazidime) with an aminoglycoside (Gentamicine, Amikacine); used in 60 (78.94%) newborns.

Targeted antibiotic therapy
Considering the most frequent flora in our department was gram negative bacilli, we used most seldom cephalosporins associated with aminoglycosides, then carbapenems (Imipenem – 30% of cases, Meropenem – 50% of cases), Vancomicina (10 cases (13.15%) 5 with positive cultures with Staphylococcus sensitive to Vancomicin (6.57%)), antimicotics (sepsis with Candida was rare (5.08%), due to the use of Fluconazol or Caspofungin in all children with antibiotic therapy extended beyond 10 days).

Antimicrobian therapy was administered for at least 14 days, extended to 3 weeks in case of severe sepsis and to 6 weeks in sepsis associated with: osteitis, arthritis.

Current medical practice and excesive use of wide spectrum antibiotics contributed to the selection of multiresistent microorganisms, also due in part to multiple risk factors and in part to preterm immunodeficiency.

Emergence of multi drug resistant organisms (MDRO) is a worrying perspective**. *Meticilino-resistent Staphylococcus aureus*** (MRSA) is an important in nosocomial pathogen we met in 6 cases (7.89%).

Though adequate antimicrobian therapy is crucial, supporting treatment is equally important: treatment of sepstic shock, clotting disorders, intrainfectious acute anemia, metabolic acidosis, immunoglobulin therapy.

Immunoglobulin therapy
Intravenous treatment with immunoglobulins (IGIV) in neonates with sepsis is controversial.

In our lot, the use of nonspecific IGIV, together with antibiotic therapy was performed in pacients with high degree of severity if hemodynamic disorders and acido-basic disorders (80%), though the evolution of these neonates was similar to babies treated without IGIV, a fact demonstrated in studies performed in developed countries.

A cochrane metaanalysis on preventive nonspecific IVIG administration from 19 randomized controlled studies studii randomizate controlate in preterm or LBW infants established that the use of IVIG has a decrease by 3% of sepsis and by 4% of any other severe infection, with one or more episodes, but it was not associated with decrease in other important effects: sepsis, necrotizing enterocolitis, intraventricular haemorrhage, hospitalization time. But most importantly, administering IVIG had no significant effect on mortality, infectious or of any other origin. (7)

Prophylactic treatment
EOS prophylaxis
Early sepsis prophylaxis was done by carefully monitoring of pregnant women, avoidance of premature deliveries, periodic performance of cultures (urine culture, cervix culture), and correct treatment with antibiotics of any infection during pregnancy. In our study out of the 76 neonates with neonatal sepsis, in 52 cases (68%) the pregnancy was dispensarized, with gynecologic check-ups and cultures following recommendations. Current research in developed countries aim towards steady decrease of neonatal sepsis, developing maternal vaccines against pathogens like Streptococcus agalactiae (group B Streptococcus). In our country antibiotic prophylaxis is performed with Peniciline G or Ampicilline.

LOS prophylaxis
- early enteral nutrition: maternal milk blocks development of ulcero-necrotizing enterocolitis
- reducing invasive procedures
- immunoprophylaxis with immunoglobulines and vaccines: studies in developed countries assessed that prophylactic use of IGIV did not reduce the incidence of nosocomial infections, morbidity and mortality in preterm newborns (6)
- cyclic monitoring of microbian cultures: periodic peripheral cultures to track down early nosocomial infections.

Sepsis and pneumonia represent the second cause of mortality among preterm infants: the medical literatures quotes 26-30% (Lawn et al, 2005). Our study registered higher mortality in EOS (25%), 14% being ELBW, (35% in medical literature).

There are significant correlations between neonatal sepsis and ulcero-necrotizing enterocolitis (2.63%), preterm retinopathy (52,6%), intraventricular haemorrhage (59.2%), broncho-pulmonary dysplasia (3.94%), death (20%).

Conclusions:
1) **Sepsis** is one of the major morbidity and mortality causes in the neonatal period.
2) **Risk factors** linked to early-onset sepsis were: urinary infection (6,5%), fever during labour (38,9%), early membrane rupture (78%).
3) **Septic shock** was often seen among the studied cases. Early septic shock, manifested by peripheral circulation disturbances, arterial hypotension, tachycardia, causeless changes in blood pressure, was encountered in 65% of the cases. Late septic shock manifested through acute renal failure, scleredema, clotting disturbances (thrombocytopenia, CID) was seen in a smaller proportion 18% (CID, 4%)
4) **Etiological spectrum of blood cultures** was dominated by the presence of gram negative germs (81.3%). In early sepsis E.coli was involved most often, while in late sepsis there were klebsiella, proteus and pathogen staphylococcus.
5) **Candida infection** was rare among the studied cases due to due to the prophylactic use of fluconazole in all the children with broad-spectrum antibiotic therapy exceed-

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ing 14 days.

6) Current medical practice and **excesive use of wide spectrum antibiotics** contributed to the selection of multiresistent microorganisms, also due in part to multiple risk factors and in part to preterm immunodeficiency.

7) **Treatment with intravenous immunoglobulins** did not have the expected effects; the drug named Endobulin was however used, administered in a dose of 400 mg/kg body weight/day, repeated after 7 days.

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