

Postoperative sepsis in infants below 6 months of age

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Background: Sepsis is a threatening postoperative complication especially in small infants. Regarding the advances in perinatal medicine, its incidence is unknown to date. We aimed to investigate the incidence, risk factors, laboratory findings and outcome of postoperative sepsis in infants younger than 6 months old.

Methods: We examined postoperative sepsis in babies below 6 months of age during a 4-year period at a tertiary pediatric institution.

Results: The rate of postoperative sepsis was 6.9%. Laparotomy with enterotomy, thoracotomy and diaphragmatic hernia repair ($P<0.05$, respectively) as well as low postnatal age and long operation time ($P<0.001$, respectively) were correlated with the incidence of sepsis. Significant independent predictors for the development of sepsis were the presence of a central venous catheter and perioperative antibiotic treatment ($P<0.001$, respectively). Coagulase negative *Staphylococci* were the major infecting organism associated with postoperative sepsis, accounting for 53% of monomicrobial infections. Complete blood counts with differential were not different between infants with sepsis and controls, who had undergone the same surgical procedures. Outcome was favorable in all cases; however, the length of hospital stay was significantly longer in sepsis patients ($P<0.05$).

Conclusions: Postoperative sepsis syndrome is a frequent complication in infants below 6 months of age and causes significant prolongation of hospital stay. Adequate prevention and therapeutic strategies warrant further prospective investigations.

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Introduction

Postoperative sepsis is a major problem in surgical practice. The morbidity and mortality of postoperative sepsis have been reported to be particularly high in neonates.^[1-4] Reports on general pediatric surgery date back to the 1970s and 1980s, but more recent series focus on complications in special fields such as neonatal heart or liver surgery.^[5] Regarding the advances made in perinatal medicine, it might be suggested that on the one hand the morbidity and mortality of postoperative sepsis are lower to date.^[6] On the other hand, the incidence of postoperative complications in this patient group might also be increasing due to improved survival of conditions formerly causing early death.

Sepsis is defined as a general reaction to a pathogenetic microorganism or its products.^[7] Following the 2005 International Consensus Conference on Definitions for Pediatric Sepsis, its diagnosis can be made on the basis of different clinical and laboratory findings with either temperature or leukocyte abnormalities.^[7] Ruling out sepsis remains a major challenge to physicians as generalized unspecific reaction can not be clearly differentiated from a specific reaction to an invading microorganism, especially in the postoperative situation in small children.

Routine laboratory parameters such as C-reactive protein (CRP) or differential blood counts are barely helpful since they are regularly altered following surgery. Therefore, in order to avoid postoperative complications, empirical antibiotic therapy is commonly performed. But there is large heterogeneity in the use of perioperative antibiotics. Their application might enhance selection of otherwise less harmful germs and predispose to superinfection. Besides, antibiotic prophylaxis might produce resistance to antibiotics and colonization with gram-negative germs.

The present study was undertaken to retrospectively investigate the incidence, risk factors, laboratory

findings and outcome of postoperative sepsis in infants below 6 months of age at a single tertiary institution.

Methods

In 2001 and 2002 we evaluated all charts of operated infants below 6 months of age at the Inselspital, Bern, for morbidity rate and risk factor analysis of postoperative sepsis. For the assessment of laboratory parameters and microbial cultures, we assessed the respective data from all patients with postoperative sepsis from 2001 until 2004. Inclusion criteria were surgery performed in the operation theater under general anesthesia and patient age below 6 months postnatally. Excluded were patients who had undergone diagnostic and therapeutic interventions without skin incision, operations for infectious diseases (necrotizing enterocolitis, intestinal perforation, and abscess evacuation), actual treatment for neonatal sepsis, or more than one surgical procedure within 5 days.

Sepsis was defined according to the criteria of the International Consensus Conference on Definitions for Pediatric Sepsis.^[7] Patients were classified as having sepsis when there was systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infections. SIRS was assumed in the presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: body temperature $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; tachycardia >2 standard deviations (SD) above normal for age in the absence of external stimuli; tachypnea, defined as a mean respiratory rate $>2\text{SD}$ above normal for age or mechanical ventilation for an acute process not related to neuromuscular disease or receipt of anesthesia; white blood cell count abnormalities (0 day to 1 week: $>34 \times 10^9/\text{L}$; 1 week to 1 month: >19.5 or $<5 \times 10^9/\text{L}$; 1 month to 6 months: >17.5 or $<5 \times 10^9/\text{L}$; for all ages: $>10\%$ immature neutrophils).^[7]

The following parameters were recorded: birth weight (BW), gestational age (GA), gender, Apgar score, mode of delivery (caesarean-section versus vaginal delivery), perinatal complications, duration of preoperative and total hospital stay, type of surgical treatment, length of surgery, presence of a central venous catheter (CVC), perioperative antibiotic prophylaxis and growth of bacterial culture.

Because of the diversity of surgical interventions, the procedures were classified as to their contamination potential (Table 1). In infants with sepsis and in the three procedure groups with the highest risk for sepsis (control group), complete blood cell counts with differential and CRP levels were recorded. In sepsis patients, we recorded laboratory parameters on the

day of initial symptoms. In addition, the laboratory parameters taken before and after initial laboratory evaluation for sepsis were recorded. Since the mean duration from operation to symptoms of sepsis was 9 ± 5 days, the parameters in the control group were recorded on postoperative day 9 ± 1 , as well as those taken before and afterwards.

Hematological parameters were evaluated using a Coulter Counter (Celldyn 3500 R, Abbott, IL, USA). Plasma CRP concentrations were quantitated by a latex photometric assay (Hitachi 917, Boehringer Mannheim, Germany).

Statistical analysis was performed using SPSS[®] version 15. Stepwise multivariate logistic regression analysis was used to identify independent factors associated with the occurrence of postoperative sepsis. Associations between variables were determined using Pearson's product-moment correlation coefficient. Differences between the two groups were assessed using Student's *t* test in case of equivalent variation and normal distribution of values. Otherwise, the Mann-Whitney *U* Test was performed. Ordinal data were assessed using the Chi-square test and Fisher's exact test. Changes of laboratory parameters within groups with time were assessed using analysis for repeated measurements. Data were presented as means \pm SD unless otherwise specified. $P < 0.05$ was considered statistically significant.

Results

A total of 36 infants with postoperative sepsis were included in this study, among them 18 were recruited from 2001-2002 (6.9%, $n=260$), and the other 18 were from 2003-2004.

Postnatal age at surgery was significantly lower and operation time was significantly longer in infants with sepsis as compared to those without ($P < 0.001$, respectively). The rate of postoperative use of CVC was significantly higher in infants with sepsis (72%) as compared to those without (8%) ($P < 0.001$) (Table 2).

Patients undergoing laparotomy with enterotomy, thoracotomy or diaphragmatic hernia repair had a higher risk for postoperative infection with a rate of sepsis of 20%, 50% and 100%, respectively (Table 1). However, the three surgical treatments were not independent predictors for the development of postoperative sepsis according to multivariate stepwise regression analysis ($P > 0.05$), despite the presence of a central venous line ($r=2.9$, $P < 0.001$) and perioperative antibiotic treatment ($r=3.2$, $P < 0.001$).

There were no differences in the laboratory parameters between patients with sepsis and those

undergoing comparable procedures (Table 3). In some patients with sepsis, leucocyte count was abnormal.

Table 1. Number of patients per type of surgical procedure with postoperative sepsis during 2001-2002

Surgical procedures	No sepsis n (%)	Sepsis n (%)	P
Hernia repair	95 (100)	-	ns
Laparotomy without enterotomy	12 (92)	1 (8)	ns
Laparotomy with enterotomy	33 (80)	8 (20)	<0.05
Myelocele repair	6 (100)	-	ns
Retroperitoneal intervention	4 (100)	-	ns
Thoracotomy	5 (50)	5 (50)	<0.05
Urogenital correction	11 (100)	-	ns
Plastic surgery with osteotomy	14 (93)	1 (7)	ns
Orthopedic intervention	41 (98)	1 (2)	ns
Gastroschisis closure	1 (100)	-	ns
Diaphragmatic hernia repair	-	2 (100)	<0.05
Craniotomy with meningeal incision	20 (100)	-	ns

Differences between groups are considered significant at $P < 0.05$. ns: not significant.

Table 2. Basic cohort data during the observation period 2001-2002

Parameters	No sepsis	Sepsis	P
Number of patients (n)	242	18	-
Gestational age (wk)	38.2±0.2	38.8±0.7	ns
Birth weight (kg)	2.98±0.02	3.02±0.17	ns
Birth weight percentile (%)	42±2	43±7	ns
Sex (% male)	69%	70%	ns
Postnatal age (d)	69±3	27±9	<0.001
Duration of hospital stay (d)	13±21	49±41	<0.001
Operation time (min)	82±4	126±12	<0.001
Central venous catheter (%)	8%	72%	<0.001

Values are mean±SD. Differences between groups are considered significant at $P < 0.05$. ns: not significant.

Table 3. Laboratory parameters in patients with sepsis and in controls during 2001-2004

Parameters	Sepsis (n)			Control (n)		
	1	2	3	1	2	3
Leukocyte count (G/L)	14±6 (30)	15±7 (33)	15±9 (31)	13±5 (38)	14±4 (16)	15±5 (18)
Immature neutrophils (%)	5±7 (25)	16±4 (31)	9±9 (28)	3±3 (17)	4±4 (5)	3±3 (7)
Platelet count (G/L)	305±180 (26)	369±169 (29)	388±215 (25)	321±171 (18)	455±186 (8)	372±43 (4)
C-reactive protein (mg/dl)	35±33 (26)	63±55 (29)	72±71 (25)	-	-	-

1: before sepsis (sepsis) or before the postoperative day 9 (controls); 2: when sepsis was diagnosed (sepsis) or on postoperative day 9±1 (controls); 3: at the first follow-up evaluation following the diagnosis of sepsis or after postoperative day 9.

Table 4. Pathogens causing postoperative sepsis in infants below 6 months of age during 2001-2004

Parameters	Source of culture					Total
	Blood	Blood & tip of CVC	Tip of CVC	Wound/peritoneum	Others	
Coagulase negative <i>Staphylococci</i>	5	6	3	-	-	14
<i>Staphylococcus aureus</i>	2	-	-	2	-	4
<i>Streptococcus pneumoniae</i>	-	-	-	-	2	2
Gram negative	2	1	1	-	2	6
Total (%)	9 (35%)	7 (27%)	4 (15%)	2 (8%)	4 (15%)	26 (100%)

CVC: central venous catheter.

But group allocation was not necessarily based on leucocyte counts in any patient since there were other sepsis criteria.^[7] No significant changes of laboratory parameters over time could be observed in the two groups. However, patients with sepsis had a trend towards a higher number of immature leucocytes as compared to previous postoperative parameters, follow-up parameters or patients without sepsis ($P > 0.05$, respectively).

In 5 patients, culture results were not obtained due to technical reasons. In one patient, cultures remained sterile. In the remaining 30 patients, bacterial growth was positive for blood (9 patients), catheter tip (4), blood and catheter tip (7), catheter tip and pleural effusion (1), catheter tip and tracheobronchial secretion (TBS) (1), TBS (2), pleural effusion (1), TBS and pleural effusion (1), urine (1), peritoneal swab (1), wound swab (1), wound and peritoneal swab (1) (Table 4). Polymicrobial growth was found in 4 cases. Gram-positive bacteria caused 20 (77%) of the monomicrobial infections: 14 isolates (53%) were coagulase negative *Staphylococci* (*CoNS*), 4 (15%) were *Staphylococcus aureus*, and 2 (8%) were *Streptococcus pneumoniae*. Gram-negative bacteria caused 6 (23%) of monomicrobial infections: 2 isolates (8%) were *Escherichia coli*, 2 (8%) were *Enterococcus* species, 1 (4%) was *Enterobacter* species, and 1 (4%) was *Serratia liquefaciens*.

Outcome was favorable following antibiotic treatment and withdrawal of central lines if present. None of the children with sepsis died during hospital treatment. However, the length of hospital stay was significantly correlated with the occurrence of sepsis as confirmed by regression analysis ($r = 3.6$, $P < 0.001$).

Discussion

The first aim of this study was to explore the incidence of postoperative sepsis in infants below 6 months of age. The overall morbidity of postoperative sepsis was about 6.9% in this study, which is comparable to that in neonates operated on in the 1980s reported by Madden et al.^[8] and in infants from birth to 8 years undergoing sternotomy for heart or lung surgery between 1995 and 2003 by Shah et al.^[5] In addition, the rate of sepsis for 20% we found following laparotomy with enterotomy is comparable to that reported during the 1970s and 1980s.^[3] There are few reports of large series on the incidence of postoperative sepsis in infants and newborns. The present study and others are based on single European and North American institution's retrospective investigations and may not fully represent the neonatal populations in the western world. One may nonetheless speculate that the rate of postoperative sepsis has not changed in the past two or three decades. The spectrum of operations however may have changed since more premature and low birth weight infants can undergo surgery nowadays.

The second purpose of this study was to identify risk factors associated with postoperative sepsis. In contrast to the report by Madden et al.,^[8] we found that perioperative antibiotic prophylaxis does not prevent postoperative infection. Inversely perioperative antibiotic treatment was an independent predictor for sepsis. This phenomenon seems to be paradoxical at the first glance, but Adam and Gross^[1] have already described infections and death due to sepsis despite adequate antibiotic prophylaxis and therapy in postoperative neonates. Possible explanations might be on the one hand that the choice to perform antibiotic prophylaxis represents the extent and degree of possible surgical contamination. On the other hand the neonate, especially following surgery, can be considered an immunocompromised host and therefore susceptible to invading microorganisms. Inadequate antibiotic prophylaxis might thus predispose to superinfection with subsequent bacterial invasion. *CoNS* are usually resistant to ampicillin and variably resistant to amikacin and gentamicin, the most commonly used antibiotics for perioperative prophylaxis in neonates. There is no consensus on optimal antibiotic regimen for neonates or small infants undergoing surgery and practice patterns vary considerably.^[9] However, the elevated frequency of postoperative sepsis and the absence of institutional regimens for antibiotic prophylaxis indicate the need of prospective investigations in this field.

Our results confirm that CVCs are a major risk factor and that *CoNS* are the major infecting organisms associated with postoperative sepsis in infants below 6 months of age.^[8,10]

In contrast to the previous reports,^[1,3] the microorganisms cultured in the present study did not have an enteric predominance. We believe that the correlation between perioperative antibiotic treatment and later sepsis reflects the attitudes of the treating physicians towards a large and possibly non-sterile surgical intervention other than a possible pathophysiological link in between. Furthermore the postoperative conditions of the child, e.g., short bowel, gastroschisis or other situations that do not allow for feeding might also have an impact on the decision whether to insert CVC.

In 6 patients, *CoNS* were cultured from the catheter tip simultaneously with its culture from blood, and in 8 patients they were from either the CVC tip or blood culture. Besides bacterial growth in blood and catheter tip cultures, bacterial growth from other sources was found frequently. These cultures were all taken simultaneously to the occurrence of SIRS, and isolated bacteria were presumably responsible for sepsis. However, in the 8 patients without a second positive culture, either from blood or from the catheter tip, as well as in the patients with bacterial growth from sites other than blood or catheter tip, we can not definitely distinguish between coincidental sepsis arising from other foci and catheter-related infection. A hindrance in comparability of studies on catheter-related infection is the lack of a unique definition. Chien et al.^[10] required only one positive blood culture, whereas the National Institute of Child Health and Human Development Neonatal Research Network (NICHD) more rigorously required two positive blood cultures.^[11] Simultaneous blood cultures drawn through the CVC and peripheral vein, as well as catheter tip cultures in case of removal of the CVC might furthermore help to confirm the diagnosis of CVC related blood stream infection.^[12]

In the present study, the laboratory data at the onset of symptoms showed no significant changes compared with parameters before disease onset, at septic workup and in the follow-up evaluation. In addition, we found no differences between the septic patients and controls at the time points. We conclude that standard laboratory parameters are barely helpful in clinical decision-making. This conclusion is in line with other reports on the usefulness of routine laboratory parameters.^[13,14] More modern parameters as procalcitonin, IL-6 or thrombelastography may be helpful in the judgment of a potentially septic infant in the postoperative period,^[15,16] but currently no single test fulfills the criteria of an ideal diagnostic test. However, the comparison of laboratory data we made between sepsis and control patients has some important limitations. First, due to the heterogeneity of sepsis patients with large variances in gestational age, postnatal age,

surgical trauma and others, we did not succeed in defining a perfectly matched control group for the factors possibly influencing the occurrence of sepsis. Second, the retrospective study design is affected by potential sources of bias which may possibly lead to impaired reproducibility of result. In addition, even in a prospective study with narrow inclusion criteria, it is often difficult to clearly differentiate septic from non-septic patients since there is so far no gold standard for the diagnosis of sepsis.^[17]

Unlike a high mortality rate of septic infants from the 1970s and 1980s, none of our patients died during hospitalization.^[1,3] As reported, we found a prolongation of hospital stay in patients with sepsis.^[5,14] The dramatic decrease of mortality might be due to the well-trained professional staff in modern tertiary centers and high awareness of the risk of infection in neonates and small children. But in consideration of the retrospective study design, the reasons for the decrease of mortality and the prolonged hospital stay remain speculative. We assume that the retrospective study design has obvious limitations. In the present study, prophylactic antibiotic therapy was at the discretion of the treating physician and not dictated by a protocol, the antibiotic treatment regimens were not uniform. Therefore, the conclusions on perioperative antibiotic prophylaxis from the present study need to be considered with caution. Taken into consideration the personal and financial consequences of postoperative infections in neonates, the prophylaxis, recognition and treatment of this complication in a potentially increasing population warrants further exploration in multicenter prospective trials.

We conclude that postoperative sepsis syndrome is still a common complication in infants below 6 months of age. Groups of low and high risk can be defined on the basis of the child's age, type and duration of surgery, and the necessity to place a CVC. In contrast to the 1980s, the mortality following postoperative sepsis is negligible, but the prolongation in the length of hospital stay is significant. Routine laboratory results within normal ranges can not rule out postoperative sepsis. Prospective larger trials may be warranted to develop prophylactic regimens and specific laboratory tools for prevention and early recognition of postoperative sepsis in infancy.

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Contributors: Kessler U proposed the study and wrote the first draft. Ebnetter M analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. Berger S is the guarantor.

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