



Epidemiology of Sepsis in Neonates: Microbiological Profile and Antibiotic Susceptibility

Yenidoğan Sepsis Epidemiyolojisi: Etken Dağılımı ve Antibiyotik Duyarlılıkları

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Abstract

Objective: Continuous surveillance is important to be informed on local epidemiology and cover organisms likely to cause sepsis in empirical therapy. We aimed to determine the characteristics of neonates with sepsis and etiological organisms in a single center.

Material and Methods: This retrospective study included neonates admitted at level I-III units (NICU) in Kanuni Sultan Suleyman Training and Research Hospital during a one-year period (January 1st, 2010 to December 31st, 2010). The characteristics of neonates diagnosed as sepsis were compared to those without sepsis in order to determine risk factors. The distribution and resistance pattern of pathogens causing sepsis during 2010 were identified and compared with those of the previous years.

Results: Among the 4703 patients treated in our NICU, 292 (6.2%) were diagnosed as culture proven sepsis [96 early-onset sepsis (EOS), 196 late-onset sepsis (LOS)]. Mean birth weight was 2304 ± 1066.9 g (640-5250 g) and mean gestational age was 36 ± 4.2 weeks (24-40 weeks). Preterm babies were infected four times more frequently than babies born at term [OR, 3.96 (95% CI, 3.10-5.06, p= 0.001)]. Presence of central venous catheter, ventilation support, total parenteral nutrition, and prolonged hospitalization were other risk factors for sepsis development. Mortality from EOS was higher than that from LOS (19.8% vs. 4.1%, p= 0.001). Coagulase negative staphylococci (CoNS) were the most commonly isolated pathogens in blood cultures of term neonates. Gram-negative bacilli [*Klebsiella pneumoniae* (18.4%), other GNB (27%)] were more common in preterm babies than term neonates. Resistance to penicillin and ampicillin were high in gram-positive bacteria. Ampicillin,

Öz

Giriş: Sepsiste, lokal epidemiyolojinin bilinmesi ve ampirik tedavide etken olabilecek mikroorganizmaların kapsanması amacıyla devamlı sürveyans önemlidir. Bu çalışmada bir merkezde, sepsisli yenidoğanların özelliklerinin ve etken mikroorganizmaların belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışma Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Yenidoğan Yoğun Bakım Ünitesi (YDYBÜ) Düzey I-III'te bir yılda (1 Ocak 2010-31 Aralık 2010) yatırılan yenidoğanları kapsamaktadır. Risk faktörlerinin belirlenebilmesi için sepsis tanısı alan yenidoğanların özellikleri sepsis olmayanlar ile karşılaştırıldı. 2010 yılında sepsise neden olan etkenlerin dağılımı ve antibiyotik dirençleri önceki yıllar ile karşılaştırıldı.

Bulgular: YDYBÜ'de tedavi edilen 4703 hastanın 292 (%6.2)'si kültürle ispatlanmış sepsis [96 erken sepsis (EOS), 196 geç sepsis (LOS)] tanısı aldı. Ortalama doğum ağırlığı 2304 ± 1066.9 g (640-5250 g) ve ortalama gebelik haftası 36 ± 4.2 hafta (24-40 hafta) idi. Enfeksiyon gelişimi preterm bebeklerde, term bebeklere kıyasla 4 kat daha fazla bulundu [OR, 3.96 (%95 GA, 3.10-5.06; p= 0.001)]. Santral venöz kateter varlığı, mekanik ventilasyon desteği, total parenteral beslenme ve hastanede uzun süreli yatış diğer risk faktörleri idi. EOS'da mortalite LOS'a göre daha yüksek bulundu (%19.8 ve %4.1, p= 0.001). Term bebeklerin kan kültürlerinde en sık üreyen patojen koagülaz negatif stafylokok (KNS)'tu. Pretermelerde gram-negatif bakteriler (GNB) [*Klebsiella pneumoniae* %18.4 ve diğer gram-negatifler %27] term bebeklere göre daha sık olarak etken olmuştur. Gram-pozitif bakterilerde penisilin ve ampisilin direnci yüksekti.

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gentamicin, cefotaxime, and carbapenem resistances in GNB were 63%, 36%, 33%, and 7.5%, respectively.

Conclusion: Prematurity is a major risk factor for sepsis. During the years of 1997, 2005, 2007, and 2010, CoNS remained the most frequent pathogen. The relative proportion of gram-negative bacilli is substantial in preterm babies. Carbapenem resistance in GNB is worth consideration.

Keywords: Neonate, prematurity, early-onset sepsis, late-onset sepsis, antibiotic resistance

Introduction

Sepsis constitutes the 3rd common cause of death in neonates globally (1). World Health Organization (WHO) has reported that each year 4 million neonatal deaths occur and infections are among the leading causes of neonatal deaths (2). Knowledge on the incidence of neonatal infections is important for planning preventive and intervention strategies and for comparisons within and between countries. In developed countries, the incidence of neonatal sepsis is 1-10 over 1000 live births (3,4). In developing countries, the incidence may even reach to 170 over 1000 live births when clinical sepsis cases are included (5,6).

Organisms causing neonatal sepsis may vary geographically. Group B streptococcus (GBS) is the most common cause of early-onset sepsis (EOS) while coagulase-negative staphylococci (CoNS) cover over 50% of late-onset sepsis (LOS) in Western countries (3,4). Limited data is available for community-acquired infections from middle and low income countries. Most EOS is due to *Klebsiella* spp., *Escherichia coli*, other gram-negative enteric bacilli; and *Staphylococcus aureus*, GBS, *Streptococcus pneumoniae*, and non-typhoidal *Salmonella* spp. are among the most common pathogens in babies after seven days of age (5). A multicenter study from Turkey revealed that the most frequent microorganisms grown in blood cultures were *Klebsiella* spp. (seven centers), *Serratia* spp. (three centers), and CoNS spp. (three centers) (6).

In this study, we aimed to evaluate the incidence and risk factors of microbiologically confirmed sepsis at a sentinel neonatal unit in Istanbul, Turkey. We also compared the distribution and resistance pattern of pathogens in neonatal sepsis with those of the previous years to help assess empiric management.

Materials and Methods

Setting and Subjects

Our hospital is a referral center where 17-19 thousand babies are born annually and 4500-5000 newborns are treated at neonatology level I-III units. Both inborn and out born neonates (babies delivered in other hospitals and transferred to the study center) with clinical sepsis and at least one confir-

GNB'lerde ampicilin, gentamisin, sefotaksim ve karbapenem direnci sırasıyla %63, %36, %33 ve %7.5 bulundu.

Sonuç: Prematürite sepsis gelişimi için önemli bir risk faktörüdür. 1997, 2005, 2007 ve 2010 yıllarının tümünde KNS en sık etken olarak görülmektedir. GNB'lerin kısmi oranı preterm bebeklerde önemli yer tutmaktadır. Gram-negatif bakterilerde karbapenem direnci dikkate değerdir.

Anahtar Kelimeler: Yenidoğan, prematürite, erken sepsis, geç sepsis, antibiyotik direnci

matory blood culture were included into the study. Data were collected from January 1st 2010 to December 31st 2010. Information regarding sex, birth weight, gestational age, premature rupture of membranes (PROM), catheter insertion, ventilation support, exchange transfusion, home delivery, and duration of hospitalization were noted. Risk factors for the development of sepsis were analyzed.

Definitions

Töllner sepsis score was used to identify neonates with clinical sepsis (7). Presence of toxic appearance or high clinical index of suspicion for sepsis, a single axillary temperature reading of $> 38.5^{\circ}\text{C}$ or $< 36.0^{\circ}\text{C}$ or two consecutive temperature readings of 38.1°C or higher, non-palpable or weak pulse, seizures in the absence of a clear neurological cause or a full fontanel, sclerema, petechiae or cyanosis of skin or mucosae, hypotonia, bradycardia, apnea, hepatomegaly, respiratory distress, leukocytes $< 5000/\text{mm}^3$ or $> 25.000/\text{mm}^3$, thrombocytopenia ($< 100.000/\text{mm}^3$), metabolic acidosis were accepted as features of sepsis (8). Neonatal sepsis was classified as EOS if it occurred within the first week of life and LOS if it occurred after the first week until the end of the neonatal period. Preterm birth referred to a delivery that occurred before 37 weeks of gestation (9). PROM referred to membrane rupture before the onset of uterine contractions (10). Preterm PROM (PPROM) was defined as PROM before 37+0 weeks of gestation. Pneumonia was defined by using a combination of imaging, clinical and laboratory criteria (11).

Microbiological Methods

Blood samples were incubated in Bactec 9240 system (Becton Dickinson, USA) for up to 7 days. The microorganisms isolated were identified by the API 20 NE system (bioMerieux, France). Susceptibility of the organisms to antimicrobial agents was done by using (Kirby-Bauer) disk-diffusion method on Mueller-Hinton agar, according to the guidelines of Clinical Laboratory Standards Institute (CLSI).

Statistical Methods

The results were analyzed by arithmetic mean and standard deviation. SPSS 16 pocket program (IBM, Chicago, USA) was used for statistical analysis.

The study was approved by the local Ethics Board.

Results

Demographic Characteristics

Between January 2010-December 2010, 4703 neonates were hospitalized due to various clinical problems. Of these, 292 patients (61.6% male) were diagnosed with sepsis. Mean (SD) birth weight was 2304 (1066.9) g (range: 640-5250 g) and mean (SD) gestational age was 36 (4.2) weeks (range: 24-40 weeks). 42.1% of the babies were delivered by normal spontaneous delivery.

Associated Factors for Development of Sepsis

Low gestational age, central venous catheter insertion, and mechanical ventilation were the most common risk factors for sepsis. 9.5% of the neonates with positive maternal genitourinary cultures developed sepsis (Table 1). Preterm premature

rupture of membranes (PPROM) was reported in 8.9% of the patients with sepsis.

Comparison of EOS and LOS

There were 96 episodes of EOS and 196 episodes of LOS. Sixty-eight (70.8%) patients with EOS and 112 (57.1%) patients with LOS were preterm ($p < 0.05$). Pneumonia was more frequent in patients with EOS than LOS (47.9% vs. 10%, $p < 0.05$). Meningitis was more common in patients with LOS than EOS (14% vs. 2%, $p < 0.05$) (Table 2).

Etiological Organisms

CoNS (49.8%) were the most frequently isolated pathogens followed by *Klebsiella pneumoniae* (12.3%), other gram-negative bacilli (GNB) (19%) (e.g. *Serratia* spp., *Pseudomonas* spp., *Enterobacter* spp., *Achromobacter xylosoxidans*), *S. aureus* (9.5%), GBS

Table 1. Risk factors for sepsis development

Characteristic	Sepsis positive	Sepsis negative	p	OR (95% CI)
Number of neonates hospitalized	292	n= 4411		
Prematurity; n (%)	180 (61.6)	1273 (28.9)	^a 0.001**	3.962 (3.102-5.060)
GA > 32 weeks	92 (31.5)	921 (20.8)	^a 0.001**	2.503 (1.823-3.436)
GA < 32 weeks	88 (30.1)	352 (7.9)		
Central venous catheter; n (%)	73 (25.0)	308 (7.0)	^a 0.001**	4.440 (3.326-5.929)
Exchange transfusion; n (%)	8 (2.7)	35 (0.8)	^b 0.004**	3.522 (1.619-7.663)
Mechanical ventilation; n (%)	78 (26.7)	368 (8.3)	^a 0.001**	4.004 (3.025-5.300)
Prolonged hospitalization (> 14 days); n (%)	144 (49.3)	684 (15.5)	^a 0.001**	5.302 (4.156-6.763)
PROM; n (%)	30 (10.2)	352 (7.9)	^a 0.165	1.320 (0.891-1.956)
TPN; n (%)	165 (56.5)	1303 (29.5)	^a 0.001**	3.099 (2.437-3.940)
Home delivery; n (%)	5 (1.7)	44 (1.0)	^b 0.228	1.729 (0.680-4.394)
Maternal colonization (except PROM); n (%)	6 (2.1)	58 (1.3)	^b 0.289	1.575 (0.674-3.680)

GA: Gestational age, PROM: Premature rupture of membranes, TPN: Total parenteral nutrition, OR: Odds ratio.
^aPearson chi-square test, ^bFisher's Exact test, * $p < 0.05$, ** $p < 0.01$.

Table 2. Comparative characteristics of patients with early-onset sepsis (EOS) and late-onset sepsis (LOS)

Characteristic	EOS (n= 96) n (%)	LOS (n= 196) n (%)	p
Prematurity	68 (70.8)	112 (57.1)	^a 0.024*
Early membrane rupture	18 (18.8)	12 (6.1)	^a 0.001**
Prolonged hospitalization (> 14 days)	48 (50.0)	96 (49.0)	^a 0.870
Mechanical ventilation	21 (21.9)	57 (29.1)	^a 0.191
Central venous catheter	16 (16.7)	35 (17.9)	^a 0.801
Total parenteral nutrition	57 (59.4)	108 (55.1)	^a 0.489
Home septic delivery	4 (4.2)	1 (0.5)	^b 0.042*
Exchange transfusion	6 (6.3)	2 (1.0)	^b 0.017*
Meningitis	2 (2.1)	28 (14.3)	^a 0.001**
Pneumonia	46 (47.9)	20 (10.2)	^a 0.001**
Mortality	19 (19.8)	8 (4.1)	^a 0.001**

^aPearson chi-square test, ^bFisher's Exact test, * $p < 0.05$, ** $p < 0.01$.

(2.7%), and *Candida* spp. [*C. albicans* (2%), *C. parapsilosis* (1.3%)]. Most common organisms detected in maternal cultures were GBS and *E. coli*. Preterm neonates were more frequently infected with *K. pneumoniae* and other GNB (18.4% and 27%, respectively) than term neonates (3.8% and 1.8%) (Figure 1,2).

Antibiotic Susceptibility Pattern

Gram-positive bacteria (GPB): GPB showed high resistance to penicillin and ampicillin (96% and 76.5% respectively). Vancomycin resistance was detected in 6% of GPB (all resistant isolates were *Enterococcus* spp.) (Figure 3).

Gram-negative bacteria (GNB): Ampicillin, gentamicin, cefotaxime, and carbapenem resistances in GNB were 63%, 36%, 33%, and 7.5%, respectively (Figure 4).

Mortality

Mortality (directly or probably due to sepsis) from EOS and LOS were 19.8% and 4.1%, respectively. Preterm babies showed increased mortality rate in comparison to term newborns (12.8% vs. 3.4%, $p < 0.05$).

Discussion

Advances in neonatology increased the survival rate of risky newborns. Nevertheless, supportive treatment beginning from delivery and invasive interventions expose the newborn to increased risk for sepsis (12-14). Most high-income settings use standardized, computerized reporting systems to track infection rates at individual institutions, and at regional and national level. In contrast, in developing countries, the

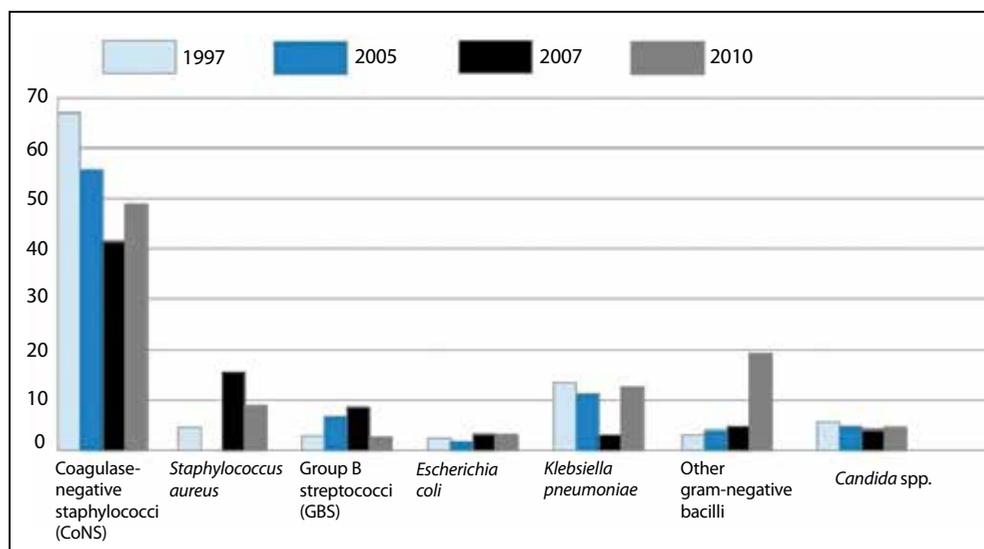


Figure 1. Microbiological profile in positive blood cultures from neonates with sepsis according to years.

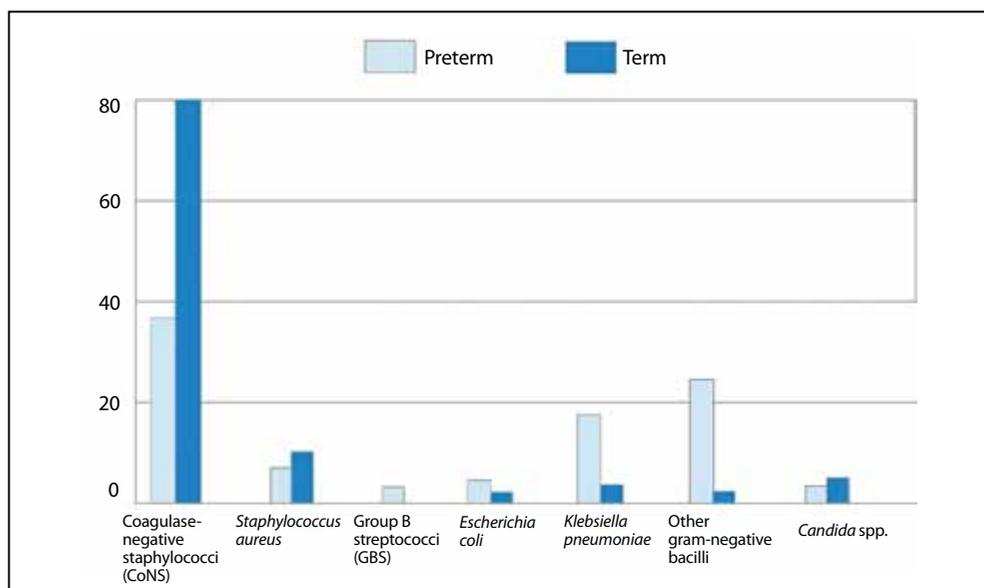


Figure 2. Comparison of pathogens causing sepsis in term and preterm neonates with sepsis.

reliability of reported infection rate depends on factors such as definitions, case ascertainment, population selection, culturing practices, and the reliability of microbiology laboratory (15). Neonatal nosocomial infection rates are reported in the range of 6 to 9 infections/1000 patient days in high-income settings. In developing countries, these rates are much higher (15–62 infections/1000 patient days) (16,17). Culture-proven sepsis frequency was 6.2% in all of the infants admitted to Kanuni Sultan Suleyman Training and Research Hospital neonatology units in 2010. Previous reports show that nosocomial sepsis incidence varies in the range of 2.1 to 17% in Turkey (6).

Lower gestational age, presence of central venous catheters, mechanical ventilation, and prolonged hospital stay were the most commonly associated factors for sepsis in this study.

Among 379 babies with gestational age less than 32 weeks, 88 (23%) developed sepsis. In Bangladesh, home delivery (60%) was commonly reported in neonates with sepsis. EOS and prematurity were also common and 7% of the patients had maternal infection (18). A baby with EOS is colonized with the same organism implying that colonization of the fetus' mucosal surfaces commonly precedes bacteremia. If the mother's birth canal is colonized with potentially virulent organisms (e.g. methicillin resistant *S. aureus*, *Salmonella*, *Pseudomonas*), a baby colonized prenatally may develop sepsis. Very recently, Esposito et al. have reported that genetic variability could play a role in sepsis in preterm neonates by influencing susceptibility to and the severity of the disease, as well as the risk of having disease due to specific pathogens (19).

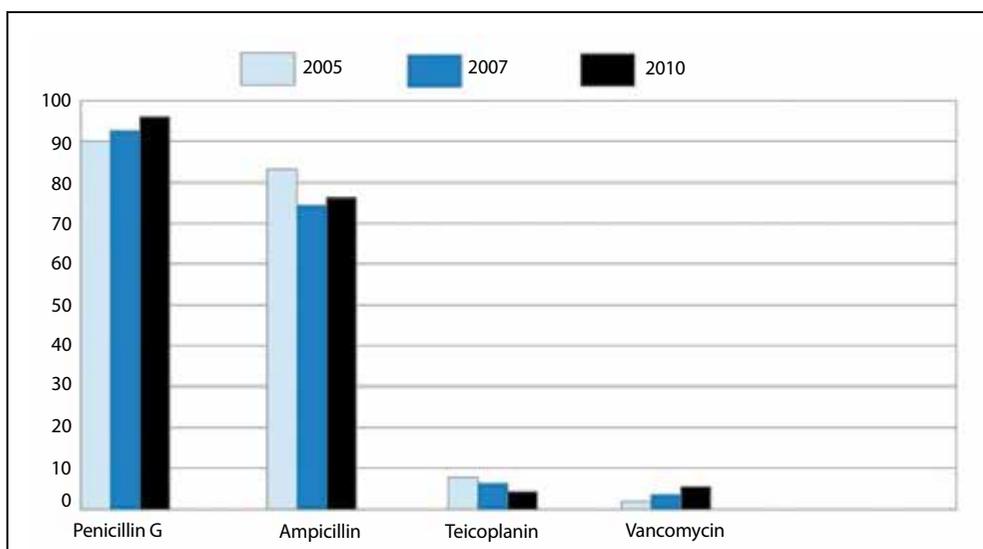


Figure 3. Comparative percentage of resistance to the tested antimicrobial agents among gram-positive isolates.

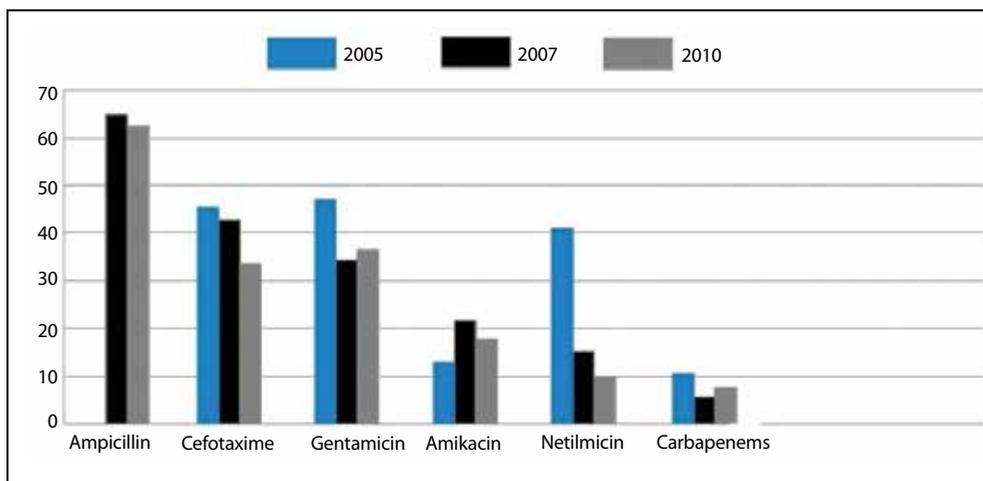


Figure 4. Comparative percentage of resistance to the tested antimicrobial agents among Gram-negative isolates.

The causative organisms of LOS are different from those of EOS. However, a recent study from India has showed that this distinction is getting blurred (20). We identified CoNS (49.8%) as the most common pathogens in neonatal sepsis. CoNS remained the most frequent pathogen identified in blood cultures from 1997-2010. GBS was a rare pathogen (3%) as previously reported in Turkey (21). CoNS are known pathogens for LOS and central line associated blood stream infection (CLABSI), as well as common blood culture contaminants. The Centers for Disease Control and Prevention (CDC) defines skin contaminants (e.g. CoNS) as pathogens if the same organism is cultured from 2 or more blood cultures drawn on separate occasions and the patient has at least 1 of the following signs or symptoms (fever, chills, or hypotension) plus signs and symptoms and positive laboratory results are not related to an infection at another site (22). Freeman et al. have commented that physicians are more likely to consider a positive blood culture a true infection, irrespective of the organism, if obtained from a VLBW infant (23). Unfortunately, contamination of neonatal samples is common, and interpretation of culture results such as *Staphylococcus epidermidis* still relies on clinical judgment (24).

In developing countries *Klebsiella* spp., *E. coli*, and *S. aureus* are reported as major causes of infections in the first week of life (5). In a recent study evaluating young infants with community acquired sepsis, probable or definite pathogens have been identified in 10.6% of the newborns 0-6 days of age (44/424) and in 10.9% of the infants 7-59 days of age (39/358). *S. aureus* was the most commonly isolated species (36/83, 43.4%) followed by various species of GNB (39/83, 46.9%; *Acinetobacter* spp., *E. coli* and *Klebsiella* spp. were the most common organisms) (25). We observed an increase in GNB bacilli other than *Klebsiella* spp. and *E. coli* in 2010. This increase may be partly explained by *A. xylosoxidans* outbreak in our NICU, which was described in detail in a previous report (26).

Reports of multi-resistant bacteria causing neonatal sepsis in developing countries are increasing (5,18,27). Globally, gram-negative infections are increasing and drug resistance is steadily rising. In a review of 10 studies, 72% of *E. coli* was resistant to ampicillin, 78% to cotrimoxazole and 19% resistant to third generation cephalosporins (28). *Klebsiella* species were almost 100% resistant to ampicillin, 45% to cotrimoxazole, and 66% to third generation cephalosporins. A subsequent study from India reported that over 80% of GNB causing EOS exhibited multi-drug resistance to ampicillin, third generation cephalosporins and gentamicin indicating that these multi-resistant organisms circulate widely in the community (20). Hamer et al. reported that resistance to second and third generation cephalosporins was present in more than half of isolates causing neonatal bacteremia and 44% of the gram-negative isolates

were gentamicin-resistant (25). Of note is the increasing prevalence of *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) in Africa. Among 717 blood stream infection episodes, gram-negative pathogens predominated (65%), followed by gram-positives (31%) and fungi (4%) (29). Given the rapidly evolving resistance profiles and emerging antibiotic resistance mechanisms, our study is important to provide knowledge for Turkey. Ampicillin, gentamicin, cefotaxime, and carbapenem resistances in GNB were 63%, 36%, 33%, and 7.5% respectively. Resistances of GNB to gentamicin, cefotaxime, and carbapenems are decreased in 2010 in comparison to 2005. Judicious use of antibiotics may have led to this result.

Conclusion

CoNS-related bacteremia is the leading cause of sepsis especially among term neonates and LOS. The relative proportion of gram-negative infection is substantial in preterm babies. The observed increase in percentage of other GNB during 2010 is worth consideration and should be monitored.

Ethics Committee Approval: The study was approved by the local Ethics Board.

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - EA, SK; Design - OT; Supervision - SK; Materials - OT; Data Collection and/or Processing - EA, OT; Analysis and/or Interpretation - OT; Literature Review - OT; Writing - OT, SK; Critical Review - All of authors.

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