**TITLE PAGE**

**Title: Epidemiology of Infections and Antimicrobial Use in Greek Neonatal Units**

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**Abstract**

**OBJECTIVE:** to describe the epidemiology of neonatal infections and of antimicrobial use in Greek Neonatal Units (NNUs) in order to develop national, evidence-based guidelines on empiric antimicrobial use for neonatal sepsis in Greece.

**DESIGN:** Retrospective analysis of prospectively collected infection surveillance data from 2012 to 2015, together with a Point Prevalence Survey (PPS) on antimicrobial use and the collection of data on local empiric antimicrobial policies.

**SETTING:** 16 NNUs in Greece participating in the neonIN infection surveillance network

**PATIENTS:** Newborns in participating NNUs who had a positive blood, cerebrospinal fluid or urine culture and were treated with at least 5 days of antibiotics.

**RESULTS:** 459 episodes were recorded in 418 infants. The overall incidence of infection was 50/1000 NNU-admissions. The majority of episodes were Late-Onset Sepsis (LOS) (413, 90%). *Coagulase-negative Staphylococci* (CoNS) (80%) were the most common Gram-positive organisms causing LOS and *Klebsiella spp* (39%) the most common Gram-negative. Nearly half (45%) of the *Klebsiella spp* were resistant to at least one aminoglycoside. The PPS revealed that 196 of 484 (40%) neonates were on antimicrobials. The survey revealed wide variation in empiric antimicrobial policies for LOS.

**CONCLUSIONS:** This is the largest collection of data on the epidemiology of neonatal infections in Greece and on neonatal antimicrobial use. It provides the background for the development of national evidence-based guidelines. Continuous surveillance, the introduction of antimicrobial stewardship interventions and evidence-based guidelines are urgently required.

**KEYWORDS:** epidemiology, neonatal infections, Greece, antimicrobial use

**MAIN TEXT**

**INTRODUCTION**

 Infection is a major cause of neonatal morbidity and mortality, particularly among premature and low birth weight neonates. Data on the pathogens causing infections in the Neonatal Units (NNUs) in Greece are limited [[1-7](#_ENREF_1)] and the emergence of multi-drug resistant organisms (MDRO) [[7](#_ENREF_7), [8](#_ENREF_8)] makes the establishment of a national surveillance system a high priority [[9](#_ENREF_9)]. NeonIN is an international neonatal infection surveillance network, established in the UK in 2004, which captures data on neonatal infections and antibiotic resistance patterns (<http://www.neonin.org.uk/>)[[10](#_ENREF_10)]. From January 2012, Greek NNUs joined this network with the objective of describing the epidemiology of neonatal sepsis in Greece and subsequently to implement changes in clinical practice, inform policies and improve quality of care.

 In addition, as Greece is known to be among the highest antibiotic consumers in Europe[[11](#_ENREF_11)], we aimed to understand the current use of antibiotics in order to design relevant and effective antimicrobial stewardship interventions [[12](#_ENREF_12)]. The Antibiotic Resistance and Prescribing in European Children (ARPEC) project has revealed high rates and broad-spectrum antibiotic prescriptions in hospitalised children in Greece[[13](#_ENREF_13)]. In general, little is known about antibiotic prescribing in NNUs, a setting where unnecessary or inappropriate antibiotic administration is a particular concern [[13](#_ENREF_13), [14](#_ENREF_14)] because of its association with necrotising enterocolitis, invasive candidiasis, late onset sepsis and death [[15-19](#_ENREF_15)], as well as with alteration of the gastrointestinal microbiome [[20](#_ENREF_20)].

 The present study has two components. The first is a description of the epidemiology of neonatal sepsis in Greek NNUs and the second, an analysis of current patterns of antimicrobial use. Our main aim is the development of national, evidence-based guidelines on empiric antimicrobial use for neonatal sepsis in Greece.

**METHODS**

**1. Epidemiology of Neonatal Infections in Greece**

 Data were prospectively collected from the Greek neonIN NNUs from January 1st 2012 to December 31st 2015. There were no exclusion criteria in terms of population coverage, hospital size and academic characteristics. Of note, community acquired neonatal infections are not recorded in neonIN. An episode of neonatal infection was defined as a positive culture collected from a normally sterile site [blood, cerebrospinal fluid (CSF) and urine (obtained in a sterile manner)] for which clinicians prescribed at least 5 days of antimicrobials. Early-onset sepsis (EOS) was defined as occurring within 48 hours of birth and late onset sepsis (LOS) as an infection occurring thereafter. A standardized neonIN proforma was completed by the clinician for each positive culture. This included the infant’s demographics, clinical information and microbiological data, as well as the antibiotic susceptibility profile of the isolate. Antimicrobial susceptibility data were analysed against a pre-defined list of commonly used empiric antimicrobial combinations (for EOS benzylpenicillin/gentamicin or amoxicillin/cefotaxime whereas for LOS flucloxacillin/gentamicin or amoxicillin/cefotaxime or piperacillin-tazobactam/gentamicin or meropenem ). Organisms were deemed ‘susceptible’ if susceptible to at least one of the antibiotics in the combination and ‘resistant’ if resistant to all the constituent antibiotics individually. Anonymised data were transferred onto the web-based neonIN database (www.neonin.org.uk).

**2. Antimicrobial Use & Policies in Greek NNUs**

The Point Prevalence Surveys (PPS) on antibiotic prescribing were conducted simultaneously in the participating NNUs on specific dates in three consecutive months (July, August and September 2015) and included all neonates present on the wards at 8:00 am and receiving antibiotics. Demographics, clinical data, information on the prescribed antibiotics as well as the local antimicrobial policies of each NNU were recorded in standardized forms derived from the neonIN and the ARPEC study [[13](#_ENREF_13)](Supplementary files 1 and 2).

**Statistical Analysis:** Data on the epidemiology were analysed on STATA 14, by the neonIN team at St George’s University of London. Data on antimicrobial use were analysed using SPSS 20 for Microsoft Windows.

**Ethical approval:** The neonIN database received ethics approval from the London-Surrey Borders Research Ethics Committee in April 2005 (05/Q0806/34) and this was extended in December 2013 (05/Q0806/34+5) for a period of five years. Each participating NNU in Greece received separate approval from the local ethics committee.

**RESULTS**

**1. Epidemiology of neonatal infections in Greece**

**Infection Incidence and Patients Characteristics**

Data were collected from 16 NNUs, representing 55% of all Greek NNUs. Fifteen NNUs were Level 3 (Neonatal Intensive Care Units) and 1 was Level 2 (Local Neonatal Units)[[21](#_ENREF_21), [22](#_ENREF_22)]. Overall, 459 infection episodes were recorded from 418 neonates. The incidence of EOS and LOS was 4.6 and 45.4 per 1000 NNU-admissions respectively. Table 1 shows the clinical characteristics of the study population overall and in babies <1500gr.

***Table 1: Clinical Characteristics of Infection Episodes***

**Pathogens and antimicrobial resistance**

Gram-positive (GP) bacteria represented 41% of all pathogens, Gram-negative (GN) 49%, and fungi 10%. Pathogen distribution in EOS and LOS is detailed in Table 2. Figure 1 shows the pathogen distribution by gestational age. The susceptibility of EOS pathogens to the combination of benzylpenicillin/gentamicin, ampicillin/ gentamicin and ampicillin/cefotaxime was 80%, 80% and 74.2% respectively. In LOS cases the susceptibility to the combinations of flucloxacillin/gentamicin, ampicillin/cefotaxime, piperacillin/tazobactam/gentamicin was 62.4%, 67.5% and 75.7%, respectively. The susceptibility of LOS pathogens to meropenem was 89%. Nearly half (45%) of the *Klebsiella spp* were resistant to at least one aminoglycoside (either gentamicin or amikacin), 34% to at least one third-generation cephalosporin and 3% to a least one carbapenem. *Enterobacter spp* showed 14% resistance to at least one aminoglycoside, 65% to at least one third-generation cephalosporin and 33% to at least one carbapenem. The resistance profile of *E.coli* was 8% to at least one aminoglycoside (either gentamicin or amikacin) and 16% to at least one third-generation cephalosporin.

***Table 2: Pathogen distribution for EOS and LOS in Greek NNUs***

**2. Antimicrobial Point Prevalence Survey (PPS) and Antimicrobial Guidelines (Local Protocols)**

Data on the PPS are shown in Table 3 and on the Antimicrobial Guidelines (Local Protocols) in Table 4. The most common reasons for antibiotic prescribing in the PPS were: sepsis (52.6%), prophylaxis for newborn risk factors (27%), lower respiratory tract infection (11%) and prophylaxis for maternal risk factors (9.4%). The majority of neonates (85%) were being treated for EOS, with a combination of ampicillin and an aminoglycoside. In cases of LOS sepsis the two most frequent antibiotic combinations were: meropenem with a glycopeptide followed by piperacillin/tazobactam with a glycopeptide.

***Table 3: Antimicrobial Point Prevalence Survey***

***Table 4: Antimicrobial Guidelines in Greek NNUs***

**DISCUSSION**

These are the first nationally representative data on the epidemiology of neonatal sepsis in Greece which, when combined with the patterns of current antimicrobial use, will aid the development of evidence-based guidelines.

In comparison with epidemiological data from the UK and other countries our population has a higher birth weight and gestational-age at birth [[10](#_ENREF_10), [23](#_ENREF_23), [24](#_ENREF_24)], although overall the incidence of neonatal sepsis is similar to that reported from the UK neonIN units over the same time period [[23](#_ENREF_23)]. In EOS, with the exclusion of CoNS, Group B streptococcus (GBS) was the predominant pathogen. The incidence of GBS infection is significantly lower compared to the neonIN UK NNUs[[23](#_ENREF_23)] which might be due to differences in GBS colonisation rates in pregnancy and / or the molecular characteristics of the isolates[[25](#_ENREF_25)] [[26](#_ENREF_26)]. In addition, although no official national guidance exists on GBS screening in pregnant women, anecdotally, the majority of obstetricians in Greece follow the US Centers for Disease Control (CDC) recommendations and undertake swab-based screening [[27](#_ENREF_27)]. In contrast, the UK follows a risk based strategy [[28](#_ENREF_28)].

In the case of LOS, there was a wide range of responsible pathogens, with surprisingly high rates of GN pathogens, unusually so for a resource-rich country [[29](#_ENREF_29)]. However, countries in Southern Europe appear to have more GN infections among LOS when compared to those in Northern Europe[[30](#_ENREF_30)].The pathogen distribution is also different with *Klebsiella spp* being the commonest, as compared with *E.coli* in the UK[[10](#_ENREF_10), [23](#_ENREF_23)]. A concerning feature of the GN pathogens is the high rates of antimicrobial resistance to aminoglycosides and third generation cephalosporins. The explanations for these findings is likely to be multifactorial and may include the higher rates of broad-spectrum antibiotics use [[31](#_ENREF_31)], the lack of standardised infection control policies, and, the low nurse-to-patient ratios observed in Greek NNUs[[32-34](#_ENREF_32)].

In the second part of this study (PPS), we demonstrated that 40% of inpatients were on antibiotics, in keeping with the previously reported figure of 45% for Greece from the ARPEC project in 2011 [[13](#_ENREF_13)]. This is higher than the overall figure from the 2012 ARPEC neonatal PPS [[31](#_ENREF_31)] of 30%. The commonest antibiotic combination used for EOS was an aminoglycoside with ampicillin in West and South Europe, Latin and North America and Asia versus an aminoglycoside and benzylpenicillin in North Europe, Australia and Africa[[31](#_ENREF_31)]. Our results are similar to those reported from other countries in South Europe. With respect to the use of carbapenems, our higher percentages resemble more those described in Asian NNUs. As for the indications for antibiotic use, our results were in accordance with the ARPEC PPS with sepsis and empirical versus targeted treatment being the more common reasons.

 There are currently no national antimicrobial guidelines for neonatal sepsis in Greece, and as we have shown that institutional protocols for empiric antimicrobial cover vary significantly. This variation is not an unexpected finding as it has been previously reported [[35-37](#_ENREF_35)] and could be partially explained by local epidemiology and antimicrobial susceptibility patterns but might also reflect the absence of national guidelines. The development of guidelines could be assisted by the findings of our study on both epidemiology and antimicrobial use. In particular, for EOS the combination of ampicillin or benzylpenicillin with an aminoglycoside appears to be a reasonable first line choice. Given the relatively low incidence of neonatal listeriosis the use of benzylpenicillin and gentamicin might be preferred to ampicillin and gentamicin as there is no evidence that ampicillin is superior. For LOS, however, the situation is more complicated when considering the existing variations of both pathogens and resistance patterns between NNUs. Although, the current resistance profile of GNs makes empiric coverage with carbapenems seem appropriate, this will undoubtedly exacerbate the development of carbapenem resistance. A suitable alternative may be the combination of piperacillin/tazobactam with gentamicin which provides slightly lower coverage than meropenem but covers the most important pathogens well, and also ensures that meropenem use can be reserved for those where it is needed. Another issue is the widely used empiric coverage with vancomycin for suspected CoNS LOS. In one US study, a vancomycin restriction policy did not adversely affected short-term patient safety [[38](#_ENREF_38)] and in another, no survival benefit of a policy of empirical vancomycin therapy over delayed vancomycin therapy for CoNS bacteremias was shown[[39](#_ENREF_39)]. We propose that vancomycin use should not be empirical but based on the results of relevant cultures.

As thisstudy was a pragmatic one, there are a number of limitations includingthe use of voluntary reporting of infection episodes. In addition, we acknowledge that the burden of CoNS bacteremia is likely to be over-estimated (especially as a cause of EOS) as some of the recorded CoNS cases are likely to be contaminants, although a standard surveillance definition for clinical significance was used[[40](#_ENREF_40)]. With regards to antimicrobial utilization, we acknowledge that we do not provide data on antimicrobial duration and on the appropriateness of the given treatment.

 In conclusion, we anticipate that the interpretation of these data on epidemiology and patterns of antimicrobial use will assist in the development of evidence-based national guidelines on the management of neonatal sepsis. Moreover, continuous surveillance at a national level will facilitate a better understanding of the disease and antibiotic resistance burden and monitor the impact of new approaches to prevent and treat these important infections. Introduction of antimicrobial stewardship interventions based on evidence-based guidelines and local epidemiology patterns are urgently required in Greece.

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**What is already known on this topic**

* Data on the pathogens causing neonatal infections in Greece are limited and the emergence of multi-drug resistant pathogens is an important public health concern.
* The neonatal infection surveillance network (neonIN) monitors the epidemiology of neonatal infections in Europe.

**What this study adds**

* This is the largest collection of data on the epidemiology of neonatal infections in Greece as well as on the use of antimicrobials in neonatal units.
* These data will assist in the development of national evidence-based guidelines on the management of neonatal sepsis in Greece.

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**Figure 1: Pathogen Distribution by Day of Onset**

**Table 1: Clinical Characteristics of Infection Episodes**

|  |  |  |
| --- | --- | --- |
| Clinical Characteristics | Overall |  < 1500gr |
| Number of infection episodes  | 459  | 166 (36.2%) |
| Male sex, n (%) | 281 (63.4%)  | 97 (58.8%) |
| Gestational age at birth (weeks)a | 33.5 (29-38)  | 28 (26-30) |
| Birth weight (grams)a | 1910 (1176-3030)  | 1020 (820-1220) |
| Postnatal age (days)a | 13 (7-27)  | 13 (7-27) |
| Central line in-situ, n (%) | 107 (23.3%)  | 59 (35.5%) |
| Treated for meningitis, n (%) | 72 (15.7%)  | 31 (18.7%) |
|  C-reactive protein (mg/dL)a(maximum CRP at or within 48h of obtaining positive culture) | 27.5 (7.3-87.8)  | 20.2 (5-79) |
|  Pathogen isolated from blood culture, n (%) | 363 (79.1%)  | 146 (88%) |
|  EOS episodes (<48h) | 46 (10.0%)  | 17 (10.2%) |

aData are presented as median (IQR)

**Table 2: Pathogen distribution for EOS and LOS in Greek NNUs**

|  |  |  |
| --- | --- | --- |
|  | EOS n (%) | LOS n (%) |
| Pathogens | **46 (10%)** | **413 (90%)** |
| Gram positive (GP) | 28 (60.9%) | 162 (39.2%) |
| Most common GP pathogen  | *CoNS* (8, 28.6%) | *CoNS* (130, 80.3%) |
| GP pathogens (CoNS excluded) | *GBS* (6, 30.0%)*Enterococcus spp* (4, 20%)*Streptococcus spp* (5, 25%)*Listeria* (3, 15%)*Diphtheroids* (2, 10%) | *Enterococcus spp* (22, 68.7%)(*VRE****a*** 14%)*Bacillus spp* (4, 12.5%)*S. aureus (all MSSA**b)*(2, 6.2%)*GBS* (1, 3.1%)*Streptococcus spp* (3, 9.3%) |
| Gram negative (GN) | 17 (37.0%) | 207 (50.1%) |
|  GN pathogens | *E.coli* (8, 47.1%)*Klebsiella spp* (2, 11.7%)*S. maltophilia* (2, 11.7%)*Acinetobacter spp* (1,5.8%)*Haemophilus spp* (1, 5.8%)*Proteus spp* (1, 5.8%)*Citrobacter spp* (1, 5.8%)*Enterobacter spp* (1, 5.8%) | *Klebsiella spp* (80, 38.7%)*E.coli* (54, 26%)*Enterobacter* *spp* (33, 16%)*Serratia spp* (16, 7%)*Pseudomonas* (8, 3.8%)*Acinetobacter* spp (8, 3.8%)*Citrobacter spp* (4, 1.9%)*Proteus spp* (2, 1%)*Haemophilus spp* (1, 0.5%)*S. maltophilia* (1, 0.5%) |
| Fungi | 1 (2.1%) | 44 (10.7%) |
| Most common fungi  | - | *Candida parapsilosis* (23, 52.3%) |

*a VRE = Vancomycin-Resistant Enterococcus, bMSSA = Methicillin-Susceptible Staphyloccus Aureus*

**Table 3: Antimicrobial Point Prevalence Survey**

|  |  |
| --- | --- |
| Number of participating NNUs | 11 |
| Patients on antibiotics, n (%) | 196/484 (40.5%) |
| Male sex, n (%) | 119/196 (60.7%) |
| Gestational Age (weeks)a  | 35 (32-38) |
| Birth Weight (grams)a  | 2240 (1557-2990) |
| Postnatal age (days)a | 8 (4-18) |
| On respiratory support, n (%) | 79/196 (40.3%) |
| On empiric antibioticsb, n (%) | 165/196 (84.1%) |
| Most frequent indication for antibiotic prescribing, n (%) | Suspected sepsis, 103/196 (52.6%) |

*aData are presented as Median (IQR)*

*b Empirical treatment = antibiotics prescribed according to local guidelines, targeted treatment = antibiotics prescribed according to microbiological culture and antibiotic susceptibility results*

**Table 4: Antimicrobial Guidelines in Greek NNUs**

|  |  |  |
| --- | --- | --- |
|  | Empiric Antimicrobial Policies | N (%)  |
| Early Onset Sepsis | Ampicillin + Gentamicin Benzylpenicillin + Gentamicin Ampicillin + AmikacinCefotaxime (second line option) | 9 (73)2 (18)1 (9)7 (64)  |
| Late Onset Sepsis | Piperacillin/tazobactam + TeicoplaninCefotaxime + GlycopeptideMeropenem + VancomycinPiperacillin/tazobactam + AmikacinCefepime + VancomycinFlucloxacillin + Gentamicin  | 3 (27)3 (27)2 (18)1 (9)1 (9)1 (9) |
| Antifungal Prophylaxisa | Fluconazole IV Nystatin PO No prophylaxis No policy  | 6 (54)2 (18)2 (18)1 (9) |

a *where recommended, antifungal prophylaxis is for all babies <1000 gr*