

Management of Early Onset Neonatal Sepsis: comparative study of ampicillin vs penicillin G in combination with gentamicin

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Abstract

Background: Both AMP and PEN combinations with GEN are in use in the empirical treatment of EOS but have never been compared head to head. In a prospective, two center open label cross over cohort study we aimed to compare the clinical effectiveness of AMP and PEN combined with GEN in the empirical treatment of EOS.

Methods: All neonates admitted to two 3rd level NICUs within the first 72 hours of life needing empirical antibiotic (AB) treatment were included if different regimen had not been administered for more than 24 hours and meningitis, NEC or resistant bacteria requiring a different AB regimen were not suspected. During the first period AMP was used in one and PEN in another unit. After recruiting half of pre-calculated sample size AB regimens were switched. Clinical effectiveness was evaluated by composite end-point of need for change of AB regimen within 72 hours and/or 7 day mortality.

Results: The incidence of proven EOS in this study was 4.9%. Among neonates receiving AMP (n=142) or PEN (n=141) the change of AB regimen within 72 hours (10/142 vs. 10/141; OR 1.0; 95% CI 0.4-2.5), 7 day mortality (11/142 vs. 14/141; OR 0.7; 95% CI 0.3-1.6) and the composite endpoint (20/142 vs. 20/141; OR 0.9; 95% CI 0.5-1.8) occurred at similar rates. Total NICU mortality of infants born before 26th week of gestation was lower in AMP vs. PEN group (6/24 vs. 13/21 OR 0.2; 95% CI 0.06-0.7). AMP regimen was associated with lower rate of *S. epidermidis* late onset sepsis than PEN (2.3 vs. 7.8 per 1000 patient days RR 0.30; 95% CI 0.11-0.82).

Conclusions: In empiric treatment of EOS AMP and PEN both combined with GEN have equal efficacy in all but extremely premature infants but the use of AMP may reduce late onset sepsis caused by *S. epidermidis*.

Introduction

Study hypothesis

AMP and PEN in combination with gentamicin have similar efficacy in empirical treatment of EOS.

AMP and PEN in combination with gentamicin are the most widely recommended and used regimens in the empirical treatment of neonatal EOS. Their efficacy against major Gram-positive pathogens of EOS (like GBS, *L. monocytogenes*) is similar

but

AMP has wider spectrum with better coverage of Gram-negative microorganisms like *E. coli* and...

... the incidence of *E. coli* EOS is increasing, especially among premature neonates

... AMP resistance is increasing among *E. coli* strains

... AMP is associated with the spread of ESBL-positive *K. pneumoniae* strains in NICU environment

Abbreviations

AB – antibiotics
AMP – ampicillin
PEN – penicillin
GEN – gentamicin
EOS – early onset neonatal sepsis
LOS – late onset neonatal sepsis
NEC – necrotising enterocolitis

Methods

Study design: two-center prospective open label cluster-randomized study

Inclusion criteria:

- (1) admission to NICU within the first 72 hours of life
- (2) need for early empiric AB for EOS or risk factors of infection according to the CDC criteria
- (3) not transferred within the following 24 hours.

Exclusion criteria:

- (1) prior administration of a different AB regimen for more than 24 hours
- (2) presence of suspected or proven meningitis, NEC, peritonitis, severe sepsis or septic shock with isolation of microorganisms resistant to the study regimen in maternal urinary tract or birth canal
- (3) other situations where the treating physician considered a different antibiotic regimen necessary.

Primary outcome: need for change of empirical AB regimen within 72 h and/or death within 7 days

Sample size calculation

Assumptions: (1) 10% of neonates receiving early empirical AB need change of AB regimen within 72 h; (2) treatment arms are equivalent if the difference in primary outcome does not exceed 10%

Accepting a two-sided type I error rate of ≤ 0.05 and a power of 80% both treatment arms were to enroll at least 140 patients.

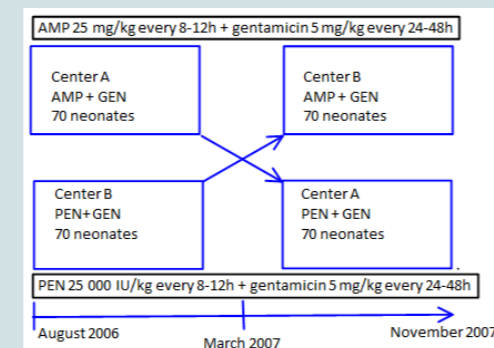
The study was approved by the Ethics Committee of Tartu University

Informed consent was considered not necessary for the following reasons:

- (1) there were no procedures that were conducted for study purposes only
- (2) prospective consent was unfeasible and retrospective consent would have carried high risk of introducing a systematic bias
- (3) before initiating the study in both units PEN and AMP in combination with gentamicin were routinely cycled for the empiric AB therapy of EOS

Statistical analysis: for comparisons between groups hierarchical models appropriate for cluster-randomised cross-over design incorporating the effect of study center and treatment period were used

Study outline

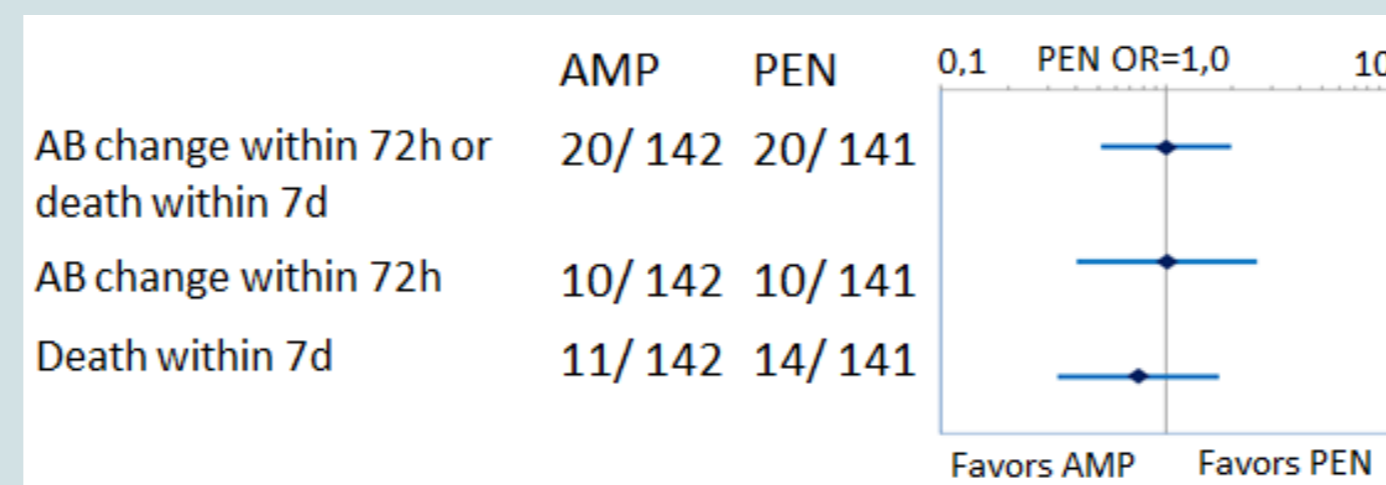


Situations pre-specified to require change of AB regimen

- (1) suspicion of meningitis or abdominal infection/NEC
- (2) isolation of bacteria resistant to the empiric AB regimen from maternal urinary tract/birth canal of a neonate with signs and symptoms of sepsis
- (3) isolation of bacteria resistant to the empiric AB regimen from a neonate with signs and symptoms of sepsis
- (4) no improvement or deterioration of clinical findings
- (5) suspicion of nosocomial infection
- (6) other situations where treating physician considered change of AB regimen necessary

Primary outcome

OR of composite primary outcome and its separate components with point estimate and 95% CI



Discussion

A surrogate not validated marker was chosen as primary endpoint because the most appropriate endpoints like culture proven EOS or EOS related mortality are rare. In this study the incidence rate of EOS in a high risk population was 4.9% with a case fatality rate of 28.6%. The study that would have had mortality of EOS as a primary endpoint would need to enroll more than 6893 neonates per study arm to show equivalence, defined as not more than 0.5% difference in mortality between the two treatment regimens with a power of 80%. We believe that both components of the selected surrogate composite endpoint describe adequately the efficacy of the antibiotic regimen since clinical status of septic neonates deteriorates rapidly with inadequate treatment and the all cause mortality within the first seven days is the most conservative approach. The time limit of 72 hours was chosen as a widely accepted limit between EOS and LOS, likely to include most EOS-related and exclude most LOS-associated decisions. AMP combination appeared to offer some protection against *S. epidermidis*-caused LOS, more obvious among infants with birth weight above 1000 g, and was associated with lower need for late AB therapy than PEN combination. It is believed that due to production of beta-lactamases *S. epidermidis* becomes resistant to PEN and AMP. In vitro studies have shown that MIC values of CONS including *S. epidermidis* are relatively low. We tested 100 randomly chosen colonizing strains of *S. epidermidis* and all proved to be resistant to AMP at MIC of 2 µg/ml. The median of MIC for these strains was 4 µg/ml remaining well below the clinically achievable serum concentration in neonates.

Results

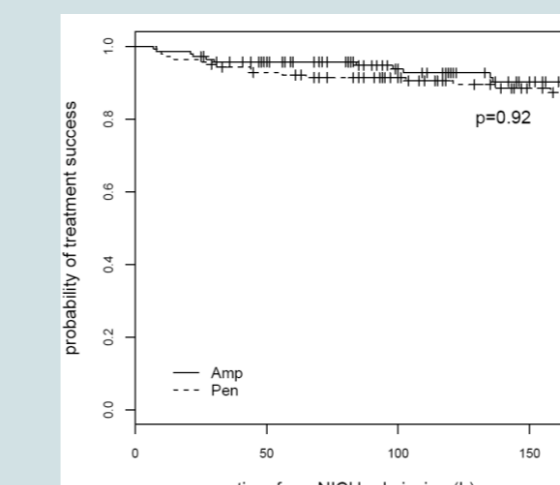
283 of 465 neonates admitted to units A and B throughout the study period fulfilled the inclusion criteria. 29 neonates were excluded as needing AB treatment other than the study regimen:

- 18 required perioperative AB prophylaxis with cefazolin
- 4 had suspected NEC and/or peritonitis and received metronidazole, ampicillin-sulbactam and/or piperacillin-tazobactam
- 3 received third generation cephalosporins for suspected Gram-negative EOS or meningitis and one for severe renal failure
- 1 neonate received antifungal treatment for systemic candidiasis
- 2 neonates accidentally received penicillin G for suspected group B streptococcal sepsis during the AMP period.

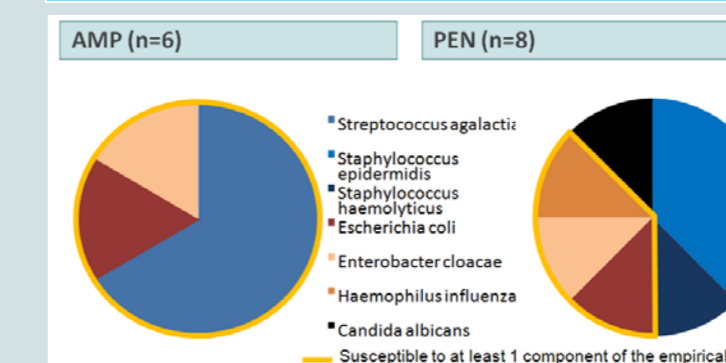
Demographic variables

	AMP (n=142)	PEN (n=141)	P-value/OR (95% CI)
Gestational age – weeks			
Mean (SD)	31.2 (5.1)	31.5 (5.1)	0.723
>36 weeks – n (%)	29 (20)	28 (20)	1.04 (0.58-1.85)
>28 weeks – n (%)	41 (29)	34 (24)	1.30 (0.76-2.25)
<26 weeks – n (%)	24 (17)	21 (15)	1.18 (0.61-2.29)
Birth weight – g; median (quartiles)	1467 (920-2553)	1500 (960-2343)	0.795
<1501g – n (%)	73 (51.4)	72 (51.1)	1.02 (0.63-1.63)
<751g – n (%)	19 (13)	15 (11)	1.30 (0.63-2.67)
M/F sex – n	78/64	85/56	0.80 (0.50-1.29)
Mean Apgar score at 5 min	6.6 ± 1.5	6.3 ± 1.6	0.076
Ventilated – n (%)	99 (70)	116 (82)	0.44 (0.24-0.81)
Surfactant – n (%)	81 (56)	88 (62)	0.79 (0.49-1.29)
Cesarean section – n (%)	77 (54)	80 (57)	0.88 (0.55-1.40)
Multiple pregnancies – n (%)	34 (24)	24 (17)	0.62 (0.34-1.12)
Chorionamnionitis – n (%)	21 (15)	30 (21)	0.64 (0.35-1.19)
PROM >16 h – n (%)	25 (18)	28 (20)	0.86 (0.46-1.62)
Prenatal glyocorticoids	86 (61)	71 (50)	1.51 (0.95-2.43)
Maternal antibiotic therapy – n (%)			
during pregnancy	38 (27)	27 (19)	1.55 (0.88-2.72)
during delivery	51	46	1.16 (0.66-2.03)

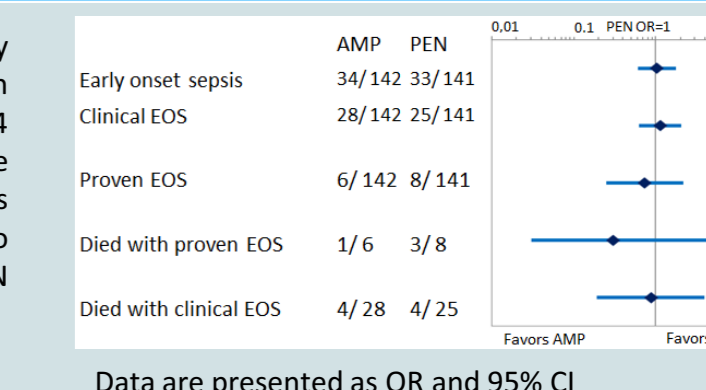
Kaplan-Meier curve of the reverse treatment failure rate



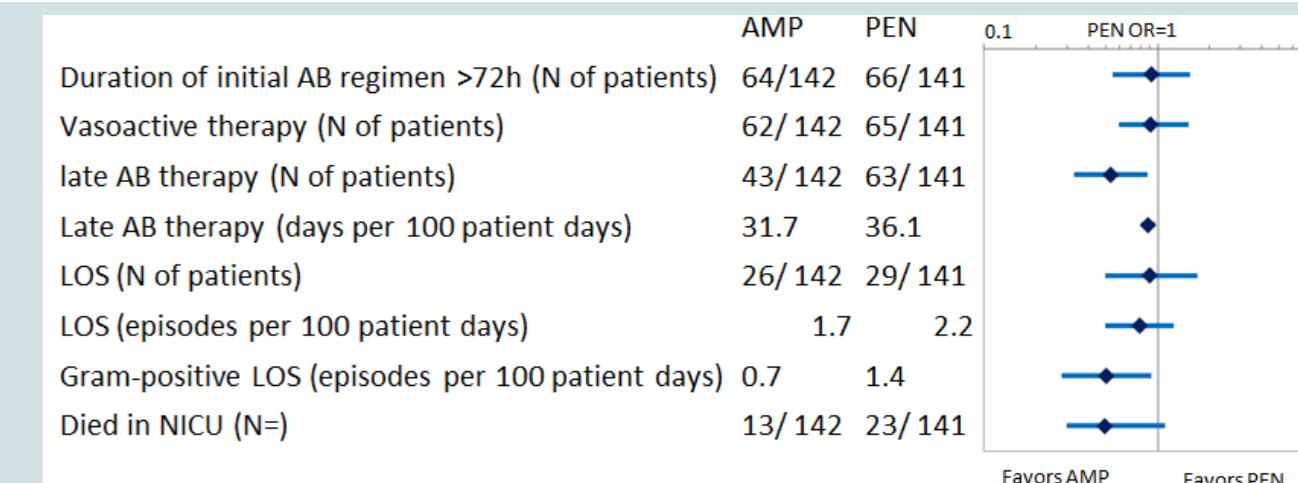
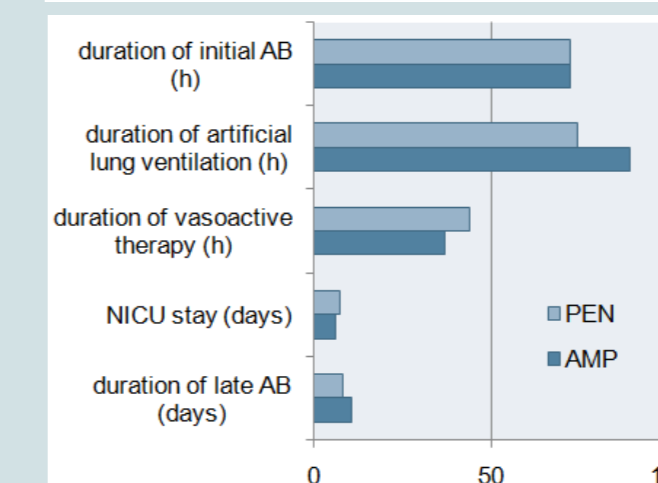
EOS: bacterial etiology and outcome



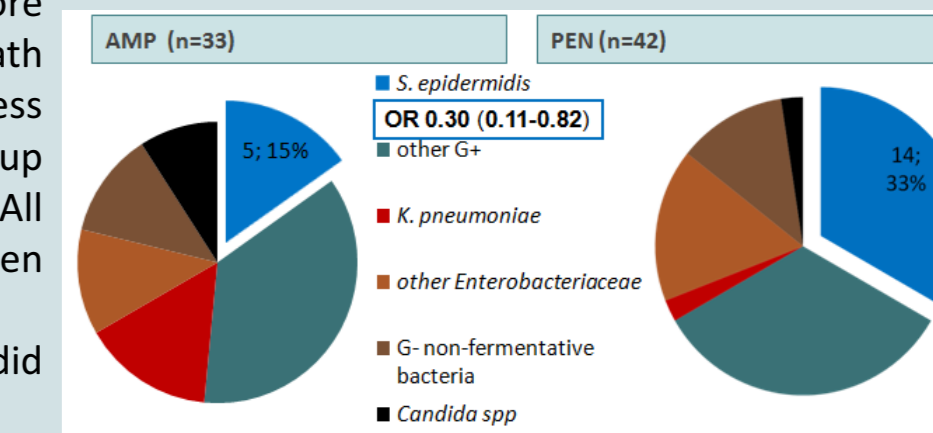
S. epidermidis strains with no mortality were responsible for the difference in susceptibility to empirical AB. Of all 14 strains susceptibility to at least one component was documented in 9 strains for both empiric AB regimens and to both components in 4 and 6 in the PEN and AMP groups, respectively.



Secondary outcome and bacterial etiology of LOS



Bacterial etiology of LOS



Conclusions

In the empiric treatment of EOS AMP and PEN combined with GEN are equally effective in terms of need for early change of empirical AB regimen and early neonatal mortality.

AMP containing regimen may be associated with lower rate of LOS due to *S. epidermidis* and lower need of late AB therapy than that containing PEN.