

Comparative Effectiveness and Safety of Empiric Ampicillin plus Gentamicin or Empiric Piperacillin-Tazobactam in the Neonatal Intensive Care Unit

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Abstract

Background. This study was designed to assess piperacillin tazobactam (PT) as an alternative to ampicillin and gentamicin (AG) in neonates with suspected systemic infection.

Methods. A retrospective, unmatched population of AG (2007-2009) and PT (2009-2012) exposed infants were evaluated for initial effectiveness, adverse events, and subsequent morbidities or mortality. Data included gestational age, birth weight, sex, Apgar score, length of hospital stay, glomerular filtration rate for days 1 and 2, duration on mechanical ventilation, duration on oxygen therapy, incidence of sepsis (blood or cerebrospinal fluid culture positive), incidence of ventilator associated pneumonia, and incidence of necrotizing enterocolitis. All positive blood cultures during the study period were reviewed. Data about specific microorganisms and sensitivity to antibiotics were collected.

Results. No significant differences in demographics or initial Apgar scores were noted. There were no significant differences in systemic rash or diaper rash. PT was associated with higher glomerular filtration rate on day two. Four infants had early onset sepsis with ampicillin resistant *E. coli*. One of these, in the PT group, had intermediate sensitivity to gentamicin as well.

Conclusion. Use of PT as the initial empiric antibiotic was not associated with increased adverse outcomes. The challenge of ampicillin resistant *Escherichia coli* should encourage others to consider this change.

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Introduction

The most common antibiotic combination used for therapy of presumed early-onset neonatal sepsis is ampicillin and gentamicin (AG), based upon the rationale that the majority of bacterial pathogens are sensitive to this combination. The most prevalent gram positive organism is Group B *Streptococcus*, although this organism has been in decline coinciding with increased intrapartum ampicillin.¹⁻⁴ The most frequent gram negative bacteria are *Escherichia coli*, followed by

Haemophilus influenzae and *Citrobacter* species.

There are many concerns regarding the use of AG. The recommended dose is potentially insufficient to treat *Listeria meningitis*.^{5,6} Antenatal exposure and prolonged postnatal ampicillin exposure increase the risk of necrotizing enterocolitis (NEC).^{1-4,7-9} In addition, ampicillin increases bleeding times through a direct effect on platelets.¹ However, the most important concerns are ototoxic and renal toxic effects of gentamicin, gentamicin resistance in late

onset infection and emergence of ampicillin and gentamicin resistant *E. coli*. Given the lack of controlled experiences, the use of PT in infants less than two months is not included in the package insert.

Due to these concerns, our institution changed from AG to piperacillin-tazobactam (PT) for routine empiric coverage of suspected early onset of sepsis. The impact of PT was monitored in our very low birth weight (VLBW) infants. Results showed no increase in major morbidities or significant adverse events. PT was associated with a transient increase in glomerular filtration rate during exposure and decreases in NEC and diaper rash when compared with AG.¹ Therefore, a study was designed to assess whether PT was associated with altered outcomes in infants with greater than 1500 grams birth weight.

Methods

A retrospective unmatched, cohort study was conducted to compare effectiveness and safety following the change from AG to PT at the Wesley Medical Center (WMC) Neonatal Intensive Care Unit (NICU). WMC switched from AG to PT in January 2010.

An unmatched comparison of AG exposed infants with PT exposed infants was conducted in the populations from two years prior (2007-2009) and three years after (2009-2012) the change in antibiotic policy. Cohorts were evaluated for effectiveness, congenital infection, adverse events, subsequent morbidities and mortality. During these two periods, there were no changes in the indications for initiation of antibiotic coverage. Data were collected from inborn infants with the birth weight greater than 1500 grams, who had suspected systemic

infection and were receiving AG (12/20/2007-12/31/2009) or PT (12/20/2009-12/31/2012). Patients with Methacillin Resistant *Staphylococcus Aureus* colonization were excluded from the study.

Study data included gestational age, birth weight, sex, Apgar score, length of hospital stay, glomerular filtration rate (GFR) for days 1 and 2, duration on mechanical ventilation, duration on oxygen therapy, incidence of sepsis (blood or cerebrospinal fluid culture positive), incidence of ventilator associated pneumonia (clinical and radiographical change), and incidence of NEC (clinical and radiographic changes). All positive blood cultures in the study period were reviewed. Data about specific microorganisms and sensitivity to antibiotics were reviewed and collected.

Statistical methods included Mann-Whitney U-test, t-test and analysis of variance (ANOVA) for nominal and continuous variables. Chi-square analysis was used for categorical variables. Descriptive statistics were stratified by group.

Results

A total of 1682 patients were identified, 653 exposed to AG and 1029 exposed to PT. No significant differences in demographics or initial Apgar scores were noted (Table 1). There were no significant differences in systemic or diaper rash. PT was associated with higher GFR on day 2. Four infants had early onset sepsis with ampicillin resistant *E. coli* (3AG/1PT). One of these, in the PT group, had intermediate sensitivity to gentamicin as well. One additional PT infant had *Haemophilus influenzae* sepsis at birth which was sensitive to ampicillin.

Table 1. Demographics and Apgar Scores

Variable	AG	PT	Test Statistic
N	653	1029	
Birth Weight - 25 th , 50 th , 75 th percentile	1.88, 2.20, 2.70	1.93, 2.24, 2.72	U=1.29, p=0.20
Gestational Age - 25 th , 50 th , 75 th percentile	32, 34, 35.5	33, 34, 35	U=1.32, p=0.19
Male - N (%)	356 (55%)	590 (57%)	X2(1)=1.29, p=0.26
Caesarian - N (%)	348 (53%)	565 (55%)	X2(1)=0.38, p=0.54
Apgar <7 at 1 minute - N (%)	232 (36%)	357 (35%)	X2(1)=0.10, p=0.75
Apgar <7 at 5 minutes - N (%)	66 (10%)	107 (10%)	X2(1)=0.04, p=0.85
GFR day 1 - 25 th , 50 th , 75 th percentile	13.86, 16.02, 18.45	14.49, 16.56, 18.9	U=2.692, p=0.007
GFR day 2 - 25 th , 50 th , 75 th percentile	11.34, 13.55, 15.48	12.57, 15.12, 17.82	U=6.612, p<0.001
Mortality - N (%)	7 (1%)	12 (1%)	X2(1)=0.03, p=0.86
NEC - N (%)	4 (0.6%)	4 (0.4%)	X2(1)=0.42, p=0.52

Discussion

PT as an empiric choice for suspected neonatal sepsis was not associated with any adverse outcome and can be used successfully as a monotherapy. Patients receiving AG had a lower GFR, consistent with our previous study in which this was transient and not sustained.¹ We did not abstract GFR beyond the exposure period. There are some limitations to this study. It is a retrospective, unmatched comparison study, and as such cannot be used to assert causation. However, in our previous study,¹ matching did not alter

results; therefore, we determined it was necessary for the present study. The current challenge of ampicillin resistant *E. coli* should encourage others to consider this change.

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