NON-INTERVENTIONAL STUDY REPORT

ABSTRACT

Title: Safety and Effectiveness of Piperacillin/Tazobactam (Zosyn®) for the Treatment of Pediatric Hospital Acquired Pneumonia (HAP) in the United States: A Retrospective Cohort Study

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Rationale and Background

Piperacillin/tazobactam (P/T) (Zosyn®) is an injectable broad spectrum antibacterial agent first approved by the Food and Drug Administration (FDA) in 1993. The safety and effectiveness of P/T for the treatment of HAP among pediatric patients has not been formally studied in either comparative non-interventional (NI) studies or randomized controlled-trials. This NI study was designed to assess the safety and effectiveness of P/T in pediatric patients with HAP.

The study was designated as a Post-Authorization Safety Study (PASS) and was a commitment to the US FDA.

Research Question and Objectives

Primary Objective: To estimate the risk of serious adverse events including mortality, among pediatric patients with HAP in the US treated with P/T as compared to other HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin).

Specifically, to evaluate serious adverse events (referred to as "serious events"):

- Among pediatric patients with HAP who received at least one dose of P/T at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours ("HAP dosing") to those who received at least one dose of a comparator HAP appropriate antibiotic at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients.

- Among pediatric patients with HAP who received at least one dose of P/T ("Any dosing") to patients who received at least one dose of a Comparator HAP appropriate antibiotic.

Secondary Objective: To evaluate effectiveness of the antibiotic therapy (using a binary treatment outcome of "patient clinically improved" or "did not improve") in pediatric patients with HAP in the US by comparing P/T to Comparator HAP appropriate antibiotic therapies.

Specifically, to estimate the proportion of patients classified into the binary treatment outcome related to effectiveness:

- Among pediatric patients with HAP who received P/T at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours (HAP dosing).

- Among pediatric patients with HAP who received a Comparator HAP appropriate antibiotic at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients (HAP dosing).

Study Endpoints: The primary study endpoint was the development of serious adverse events, referred to as "serious events" within 40 days of treatment initiation. A serious event was defined as *"any untoward medical occurrence documented in a physician's daily progress note in patients taking P/T or Comparator HAP appropriate antibiotics that results in death, is life-threatening, requires prolongation of hospitalization, or results in persistent or significant disability/incapacity*". All cause-mortality rate at 30-days after initiation of treatment for HAP was estimated by treatment group as well.

The secondary study endpoint was the effectiveness of the antibiotic therapy categorized into the binary outcome: patient "clinically improved" or 'did not improve" from HAP diagnosis within 14 days of treatment initiation. This secondary outcome was determined by trained research personnel that performed review of the daily medical records from the day of HAP therapy initiation until completion of follow-up.

Methods

Study Design: This was a retrospective cohort study of pediatric patients receiving antibiotics for the indication of HAP at multiple pediatric hospitals across the US admitted between January 01, 2003 and June 30, 2016. Pediatric patients receiving P/T were included in the exposed group and those receiving Comparator HAP appropriate antibiotics in the Comparator group (i.e., unexposed to P/T), as follows:

P/T Groups

- **P/T HAP Dosing Group:** Pediatric patients who received at least one dose of P/T at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours as the first antibiotic administered for the treatment of HAP. This "P/T HAP dosing group" was considered as the primary P/T exposed group.

- **P/T Any Dosing Group:** Pediatric patients who received at least one dose of P/T at any dose as the first antibiotic administered for the treatment of HAP.

Comparator Groups

The following are the three comparator groups:

- **Comparator HAP Dosing Group:** Pediatric patients who received at least one dose of one of the comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime or ciprofloxacin), at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for the treatment of HAP. This group was considered as the "primary comparator group".

- **Comparator Any Dosing Group:** Pediatric patients who received at least one dose of one of the Comparator HAP appropriate antibiotics at "Any dose" as the first antibiotic administered for the treatment of HAP.

- **Comparator subset: carbapenems HAP Dosing Group:** Pediatric patients who received at least one dose of a carbapenem at a dose consistent with the product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for the treatment of HAP[1]. This was used for the subgroup analysis.

Study Population and Setting: Pediatric patients aged 2 months to <18 years initiated on antibiotics for the indication of HAP constituted the study population. The pediatric patients with potential HAP diagnosis were initially identified from the Pediatric Health Information System (PHIS), an administrative database that collects patient-level data from pediatric hospitals across the US, and then confirmed as receiving antibiotics for the indication of HAP through review of individual patient medical charts at the participating sites.

Index Date and Follow Up: The index date was the "date of initiation of HAP treatment" and all study patients were followed up from the index date, as follows:

- For all serious events except all-cause mortality, completion of 40 days after the first dose of P/T or Comparator antibiotics, or discharge from the hospital (or death), whichever occurs first (after which time all surviving patients were considered censored).

[1] Similar to P/T, carbapenems are broad spectrum antibiotics that are commonly used in patients with serious hospital-acquired infections (i.e., clinical condition/severity of P/T treated patients and carbapenems treated patients is expected to be similar), and therefore this group provided an additional/ more focused Comparator group to P/T (i.e., subgroup analysis). The carbapenem medications of interest in this study included meropenem and imipenem.

- For all-cause mortality, a period of 30-days after the first dose of P/T or Comparator antibiotics (at which time all surviving patients were considered censored), and,

- For assessment of the treatment effectiveness outcome, 14 days from initiation of HAP therapy.

Variables (Exposure, Outcomes and Potential Confounders): Detailed data from medical charts were collected for all study patients:

- Exposures: Data on P/T and Comparator HAP antibiotics including the duration of use using start and stop dates.

- Outcomes: Data on serious events, including mortality, and data pertaining to treatment outcomes related to effectiveness.

- Potential confounders: Data on covariates/potential confounders including demographic (e.g., age, sex, race) and clinical characteristics (e.g., duration of hospitalization, concomitant medications, ventilator support, laboratory data pre- and post-HAP diagnosis).

Data Source and Patients Selection: The study data were obtained from the PHIS database and patients' medical charts. Step-I included electronically querying the PHIS database with the screening inclusion/exclusion criteria to identify "potential" HAP patients. Subsequently, trained research personnel reviewed the medical chart of each patient identified from the PHIS database screening to "confirm" the diagnosis of HAP (Step –II). After confirmation of HAP diagnosis, the research personnel proceeded with a detailed chart review and data abstraction. If HAP was not confirmed by initial chart review, no further data abstraction was performed.

Study Size and Statistical Analysis: The target sample size was 450 patients: 150 in the P/T and 300 in the Comparator groups. Descriptive statistics were performed to describe patient demographic and clinical characteristics by the treatment group.

Crude incidence rate (per 100 person-days) of all serious events (i.e., sum of first occurrence of all individual events) and all-cause mortality rate were compared between P/T HAP dosing and Comparator HAP dosing groups (and separately for Comparator subset: carbapenems).

Comparative analyses of all incident serious events between P/T HAP dosing and Comparator HAP dosing groups were conducted using an inverse probability weighted informed Poisson regression models with an offset for person-time at risk and a robust variance estimate. The weights were obtained from propensity score models used to predict the probability of receiving a specific HAP antibiotic (P/T or Comparator) conditional on observed demographic and clinical characteristics including age, duration (days) of hospitalization/intensive care unit (ICU) admission, ventilator support, intubation performed prior to HAP diagnosis, and a respiratory co-morbid condition. Two adjusted Poisson

regression models were developed; both models were weighted, but one model adjusted for participating site and the other model did not. Comparative analyses of all incident serious events between "P/T HAP dosing group" and the Comparator subset- "carbapenems HAP dosing group", were also conducted using the same approach described above.

Sensitivity analyses using Negative binomial models with the same approach, described above, were conducted as there were concerns that the assumption of the Poisson modeling may be violated due to the potential rarity of outcomes. Adjusted incidence rate ratios (IRR) with corresponding 95% confidence intervals (CI) were reported from the Poisson (and Negative binomial) regression models. Additional subgroup analysis (e.g., by age and sex) and sensitivity analysis by duration of HAP therapy (e.g., 2 days of therapy, 5 days of therapy) were also conducted to better understand the data and assess the risk in patients' subgroups.

For treatment effectiveness outcome, counts and proportions (%) were calculated of patients categorized as "clinically improved" or "did not improve". Two inverse probability-weighted adjusted logistic regression models were developed to evaluate the effect of P/T HAP dosing on the treatment effectiveness outcome compared with the Comparator HAP dosing group. One model adjusted for participating site and the other model did not. In addition, comparative analyses of treatment effectiveness outcome between P/T HAP dosing and Comparator subset: carbapenems HAP dosing groups were conducted using the same approach described above. Adjusted odds ratios (OR) and associated 95% CI's were reported for each model. Further, sensitivity analysis to evaluate the effect of duration of HAP therapy (e.g., 2 days of therapy, 5 days of therapy) on the effectiveness outcome was also conducted.

Analysis Data Sets: All patients meeting the study eligibility criteria were included and divided into two analysis data sets:

- Primary Analysis Set included patients who received at least one dose of P/T at a dose 80-100 mg/kg piperacillin/ 10-12.5mg/kg tazobactam every 6 hours as the first antibiotic administered for treatment of HAP, OR received at least one dose of one of the Comparator HAP appropriate antibiotics at a dose consistent with the respective product label indicated for moderate to severe infections in pediatric patients as the first antibiotic administered for treatment of HAP. Recognizing that there could be modest rounding when calculating medication doses, a dose within 10% of the dose range for both P/T and Comparator antibiotics was considered to meet the definition of the HAP dosing and subsequently included in this analysis set.

- Full Analysis Set (i.e., Secondary analysis population) included all enrolled pediatric patients with HAP who received at least one dose of P/T or one of the Comparator HAP appropriate antibiotics at "Any dose" as the first antibiotic administered for treatment of HAP.

Results

A total of 19 PHIS affiliated hospitals were considered for inclusion in the study; 11 sites were invited, and 7 sites agreed to participate in the study. Of 1,899 patients initially identified from the seven participating sites with a presumed diagnosis of HAP in the PHIS database (Step-I), 412 patients were confirmed with HAP upon review of their medical charts (Step-II) and were included in the study (141 patients in the P/T and 271 patients in the Comparator groups). Of these 412, 407 (98.8%) patients received HAP dosing: 141 patients in the P/T and 266 patients in the Comparator groups. Median (IQR) follow up time for 141 patients in the P/T group was 15 days (8-31) days and for 266 patients in the Comparator patients was 18.5 days (10-38 days).

Patients in the P/T and Comparator HAP dosing groups were comparable with regard to the distribution of sex and race—about half of the patients were White and >55% were male in both groups. The crude incidence rate (per 100 person-days) of all serious events was 1.27 (95% CI: 0.84-1.70) in the P/T HAP dosing group, 1.02 (95% CI: 0.76-1.28) in the Comparator HAP dosing group, and 1.59 (95% CI: 0.91-2.26) in the Comparator subset: carbapenems HAP dosing group.

Both adjusted Poisson regression models showed no increased risk of having all serious events (i.e., sum of first occurrence of all individual events) with P/T HAP dosing group compared to the Comparator HAP dosing group (adjusted IRR for model without participating site: 1.21, 95% CI: (0.63, 2.30), p=0.57 and adjusted IRR for model with participating site: 0.80 (95% CI: 0.30, 2.12, p=0.65). Also, no association was found when compared with the Comparator subset: carbapenems in separate models adjusting for the same covariates (adjusted IRR for model without participating site: 0.76, 95% CI: (0.32, 1.78), p=0.53 and adjusted IRR for model with participating site: 0.95 (95% CI: 0.35, 2.62, p=0.93)). Also, no increased risk of having the all serious events was shown when P/T Any dosing group was compared with the Comparator Any dosing group.

Furthermore, the results of the sensitivity analyses using the Negative binomial regression models were consistent with the Poisson models and showed that treatment with P/T HAP dosing group was not associated with an increased risk of all serious events compared to the Comparator HAP dosing group in multivariable analyses using the same propensity score weights as described above (adjusted IRR for model without participating site: 1.07, 95% CI: 0.53-2.16; p=0.86, and adjusted IRR for model with participating site: 0.92, 95% CI: 0.29-2.90; p=0.89). Findings from subgroups and sensitivity analyses were also consistent with the results of the main regression analyses.

A small number of deaths were observed in both treatment groups. All-cause mortality rate within 30 days of HAP treatment initiation was 3.57 % (5/140) in the P/T HAP dosing group, 4.53 % (12/265) in the Comparator HAP dosing group, and 9.09% (5/55) in the Comparator subset: carbapenems HAP dosing group.

A comparable proportion of patients in both treatment groups were categorized as clinically improved at or before 14 days from the start of HAP therapy: 90.78% in the P/T HAP dosing

and 91.73% in the Comparator HAP dosing groups. Neither of the two adjusted logistic regression models found a significant association between P/T HAP dosing and treatment effectiveness outcome (adjusted OR for model without participating site: 1.45, 95% CI: 0.65-3.27; p=0.37, and adjusted OR for model with participating site: 1.23, 95% CI: 0.39-3.85; p=0.72). Additionally, no significant association was noted with various durations of P/T HAP dosing and treatment effectiveness outcome in sensitivity analyses that used the same adjusted logistic regression models approach described above .

Discussion

To our awareness, this was the first study conducted to characterize the safety of P/T in pediatric patients (aged 2 months to < 18 years) with HAP by comparing P/T with other HAP appropriate antibiotics. Overall, the rates of all serious events and all-cause mortality was comparable between the P/T and Comparator HAP dosing groups and no significant difference was observed in the adjusted comparative analysis of the treatment groups. Furthermore, a comparable proportion of patients in both treatment groups were categorized as clinically improved within 14 days from the start of HAP therapy.

The strengths of the study include the large number of pediatric HAP patients (n=412) included from multiple hospitals across the US, and collection of detailed real world data on safety and effectiveness of P/T and Comparator HAP antibiotics from routine clinical practices. Additionally, the study employed robust statistical analyses to investigate the primary and secondary objectives.

While it was attempted to control for major confounders in the regression analyses, given that the study utilized retrospective data from medical records, chances of residual and unmeasured confounders cannot be ruled out and caution must therefore be applied in the interpretation of the results. Estimates of serious events in pediatric patients treated for HAP are not available in the published literature for comparison. It is possible that the rates of serious events might be underestimated in both groups given that the study procedures were designed to capture serious events that were documented in the daily progress notes of the physician of record (POR). This approach was chosen because it was expected that due to the severity of the underlying illness, every patient would have a progress note on each day and thus this data source would be consistent for all enrolled patients. Notably, if a serious event occurred but was not documented in the progress note it would have been missed. However, it is expected that most serious events (unlike non-serious adverse events) would have been recorded in the daily progress notes and would therefore have been captured. Furthermore, because this study procedure was dependent on daily progress notes consistently present for each enrolled patient that it is expected that any missed serious events would be *non-differential* to the study treatment groups. This assumption of *non-differential* documentation of serious events between the two treatment groups is in part supported by the comparable all-cause mortality rates, which is a well-defined 'hard endpoint', observed in the two groups. Ultimately, the conclusion from the analyses was that the incidence of serious events is comparable between the two groups (and also comparable with the Comparator subset: carbapenems group).

The treatment effectiveness outcome was based on determination by trained research personnel who systematically performed review of daily charts for each enrolled patient. Based on the reviews of the medical record, the research personnel designated the patient's treatment outcome as "clinically improved" or "did not improve". It was planned to have a study physician(s), blinded to treatment group, confirm the research personnel's outcome designation by reviewing progress notes from the POR that specifically documented whether the patient improved or did not improve after starting their HAP therapy. However, a substantial proportion of patients (42.6% patients in the P/T and 50% in the Comparator group) did not have a progress note within 14 days of HAP treatment initiation in which the POR specifically indicated either that the patient had improved or did not improve from their HAP diagnosis. For those patients, it was necessary for the trained research personnel to make an independent decision regarding clinical status at the time of performing the on-site/remote comprehensive chart review. In the absence of a specific progress note documenting clinical improvement or lack thereof, it was not possible to capture the entirety of the chart/patient's clinical status for future study physician confirmation. Research personnel consulted with study physicians on as-needed basis and assigned designation of treatment effectiveness into the binary categories, as instructed; however, misclassification of the outcome might have occurred in some patients due to the lack of clear documentation in a substantial proportion of medical charts pertaining to the treatment effectiveness outcome within 14 days of treatment initiation. While this was a limitation, it should be noted that this study was primarily designed to assess the safety of P/T in the treatment of pediatric HAP and the assessment of treatment effectiveness was a secondary endpoint. As suggested by the FDA, copies of a sample (approximately 5%) of de-identified daily progress notes with documentation pertaining to safety risks/serious events, treatment effectiveness, and also complete charts are being submitted as examples.

Overall, this study suggests that the rate of serious events and all-cause mortality in patients treated with P/T is comparable with Comparator HAP antibiotics. However, it is important to carefully weigh the risk of serious events and the benefits of the P/T HAP dosing when prescribing to pediatric patients with HAP.

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