NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

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

Compound Name:	Piperacillin/Tazobactam (Zosyn®)
Study Number:	B2361001 (Formerly 0910K2-4015)
Version and Date:	[Amendment-IV: September 21, 2017] [Amendment-III: November 01, 2016] [Amendment-II: December 18, 2014] [Amendment-I: September 18, 2012] [Final: October 13, 2009]
EU PAS #	8352

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LIST OF ABBREVIATIONS

AE	Adverse Events
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAP	Community Acquired Pneumonia
CBC	Complete Blood Count
CHOP	Children Hospital of Philadelphia
CI	Confidence Interval
CNS	Central Nervous Systems
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRAs	Clinical Research Associates
CRNs	Clinical Research Nurses
e-HRD	Electronic Health Related Databases
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HAP	Hospital Acquired Pneumonia
IAI	Intra Abdominal Infections
ICD	International Classification of Diseases
IEA	International Epidemiological Association
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LFTs	Liver Function Tests
NCHS	National Center for Health Statistics
NDI	National Death Index
OR	Odds Ratio

PHIS	Pediatric Hospital Information System
PhRMA	Pharmaceutical Research and Manufacturers Association
P/T	Piperacillin/Tazobactam
IRR	Incidence Rate Ratio
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
TBD	To Be Determined

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
Original Protocol	October 13, 2009	Not applicable	Not applicable	Not applicable	Not applicable
Amendment I	September 18, 2012	Substantial	2.0 Study objectives 3.0 Methods including: 3.3 Identification and selection of pediatric patients with HAP 3.4 Index date and follow up 3.5 Definition of P/T exposed and comparator groups 3.6 Data collection including: 3.6.2.1 Serious events 3.6.2.2 Treatment outcomes related to effectiveness 3.7 Data collection procedure 3.9 Pilot study 7.0 Statistical analysis 8.0 Strengths and limitations	Refer to the following for details: • Pfizer's response to "FDA's No Agreement Letter" received December 4, 2009 and request for a Type A Meeting dated October 7, 2011, and the Briefing Document for the meeting • Minutes for the meeting with the FDA (teleconference dated March 26, 2012)	Protocol was amended to address FDA's concern detailed in the FDA's Special Protocol Assessment "No Agreement letter" (adequacy of retrospective data to evaluate safety and effectiveness, low sample size/ attempt to obtain data on 150 patients) and following recommendations during the teleconference on March 26, 2012

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
			9.0 Anticipated timeline Case Report Form (CRF)		
Amendment II	December 18, 2014	Substantial	3.3.1 Step-I: PHIS database screening 3.6.3 Data on covariates 4.0 Adverse event reporting 9.0 Anticipated study timeline CRF	The protocol was amended to incorporate changes based on the findings of the pilot study. In addition, the following sections were also updated: • Section 3.3.1 'Step-I: PHIS database screening': The following was added to further clarify patient inclusion/exclusion criteria: "In case of more than one HAP admissions for a patient during the study period, the first admission will be counted (i.e., subsequent admissions will be excluded)" • Section 4.0 'Adverse event reporting': New safety language/protocol was adopted	The pilot study was conducted, as planned, to identify potential issues in the full study methodology/processes and to test the adequacy of the CRF to collect the required data. The 'Adverse event reporting' section was updated to comply with new pharmacovigilance regulations, which intends to enhance the reporting of adverse events in the study
Amendment III	November 01, 2016	Substantial	3.3.1 Step-I PHIS database screening	Inclusion criterion "Hospital admission between January 1, 2003 and June 30, 2013" was changed to "Hospital admission between January 1,	PHIS screening criterion for patient inclusion was extended from June 30, 2013 to June 30, 2016 to maximize patient enrollment in an attempt to

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
				2003 and June 30, 2016"	meet the required study sample size
Amendment IV	September 21, 2017	Administrative	3.7 Data Collection Procedure	The protocol is being amended to allow study data abstraction from medical records 1) by the local site staff (nurses, research associates or physicians), and 2) remotely in sites with capability of remotely accessing the electronic medical records	This changes in data collection procedure are being made to include additional sites in the study in order to achieve the target sample size

1.0 BACKGROUND AND RATIONALE

Pneumonia is the second most common hospital acquired infection in children and adults. [1] Hospital acquired pneumonia (HAP) can result from a variety of Gram positive or Gram negative organisms. [1, 2] Appropriate antibiotic therapy for these infections is imperative to reduce subsequent morbidity and mortality. [1, 3, 4, 5]

Piperacillin/tazobactam (P/T) (Zosyn®) is an injectable antibacterial combination medication consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium for intravenous administration. P/T was first approved by the Food and Drug Administration (FDA) in 1993. Currently, P/T is approved for several adult indications in the US, including:

- Appendicitis (complicated by rupture or abscess),
- Uncomplicated and complicated skin and skin structure infections,
- Postpartum endometritis or pelvic inflammatory disease,
- Community-acquired pneumonia (CAP) (moderate severity only), and
- Nosocomial pneumonia (moderate to severe).

Although not approved for use in children by the FDA P/T is being utilized by pediatric clinicians to treat HAP in children. The safety and effectiveness of P/T in the treatment of HAP among pediatric patients has not been formally studied in interventional studies including randomized controlled trials (RCTs) or in observational studies. We hypothesize that P/T will have similar safety profile and effectiveness to that of other current antibiotic therapies for HAP in children i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin (hereafter referred to as “comparator HAP appropriate antibiotics”).

Based on a previously attempted RCT in children with pneumonia, the prospective recruitment of pediatric patients with pneumonia is challenging and likely will ultimately result in inadequate recruitment even over an extended period of time. [6] Therefore, it is not feasible to conduct an RCT or a prospective observational study to evaluate the safety and effectiveness of P/T. In the interim it is likely that pediatricians will continue to administer P/T to children with HAP.

A retrospective cohort study is proposed to study the safety profile and effectiveness of P/T in pediatric patients treated for HAP. The proposed retrospective study design offers certain advantages to evaluate the safety and effectiveness of P/T. First, it evaluates the treatment of pediatric HAP in a real-world setting, which offers broad generalizability of study findings. Second, a retrospective study can be completed in less time compared to a prospective study.

This proposed retrospective cohort study evaluating the safety and effectiveness of P/T in pediatric patients with HAP is a post-approval commitment to the FDA. As such, this study is a Post-Authorization Safety Study (PASS).

2.0 STUDY OBJECTIVES

2.1 Primary objective

To estimate the risk of serious events including mortality within 30 days of treatment initiation (as defined in section 3.6.2.1) among pediatric patients with HAP in the US, comparing P/T to comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin).

Specific objectives

Compare the incidence of serious events:

- Among US pediatric patients with HAP who received at least one dose of P/T 80-100 mg/kg every 6 hours 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 US pediatric patients with HAP who received at least one dose of P/T (any dose) to patients who received at least one dose of a comparator HAP appropriate antibiotic (any dose).

2.2 Secondary objective

To evaluate effectiveness of the antibiotic therapy (using binary treatment outcome "patient clinically improved" or patient clinically did not improve" as described in section 3.6.2.2) in pediatric patients with HAP in the US, comparing P/T to comparator HAP appropriate antibiotic therapies.

Specific objectives

Estimate the proportion of patients classified into binary treatment outcome related to effectiveness:

- Among US pediatric patients with HAP who received P/T at dose 80-100 mg/kg every 6 hours.

- Among US 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.

3.0 METHODS

3.1 Study design

We will conduct a cohort study of pediatric patients treated for HAP at multiple pediatric hospitals across the US. Children with HAP receiving P/T will be included in the "exposed" group and those receiving comparator HAP appropriate antibiotics in the "comparator" (i.e., unexposed) group (as described in section 3.5).

3.2 Study population and data source

Children diagnosed with HAP constitute the study population. The potential pediatric patients with HAP will be 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 HAP via patient medical chart review.

The PHIS database is a comprehensive pediatric database containing clinical and financial details of more than six million pediatric patients from 43 children hospitals across the US. The PHIS member hospitals represent most of the major metropolitan areas nationwide, with only one children's hospital representing each city. Updated quarterly, data are available for PHIS member institutions on every inpatient since January 1, 2003. The member institutions can access PHIS data via a virtual private network or modem. There are two levels of data within the PHIS database. **Level 1** data contain patient identification, demographics, dates of admission and discharge, physician profiles, clinical classification and primary discharge diagnosis and primary procedure codes coded in International Classification of Diseases-9-Clinical Modification (ICD-9-CM). **Level 2** data contain detailed information about the patient encounter including up to 40 ICD-9-CM discharge diagnosis and procedure codes and specific financial/ utilization data i.e., medical supply, laboratory, radiology/imaging, and clinical services. However, the PHIS database does not contain information on daily patient physical exams, medication doses and daily physician impression and management plans.

The PHIS member hospitals have access to the multi-center database (the Peer database) and their hospital-specific database. All aforementioned data are contained in the Peer and hospital-specific databases.

3.3 Identification and selection of pediatric patients with HAP

There is no specific ICD-9 code for HAP. Therefore, we will follow a two-step process to identify pediatric patients diagnosed and treated for HAP. As described below, Step 1 will consist of screening the PHIS database for potentially eligible patients, and Step 2 will consist of medical chart review to confirm that study inclusion/exclusion criteria are met (hereafter referred to as "confirmation of HAP diagnosis") before inclusion in the final study cohort.

3.3.1 Step-I: PHIS database screening

During the first step, the PHIS database will be screened to identify patients with a presumed diagnosis of HAP with the inclusion criteria, as follows (Figure 1):

- Hospital admission between January 1, 2003 and June 30, 2016,
- Aged between 2 months and 18 years at the time of hospital admission,
- Presence of at least one discharge ICD-9-CM code consistent with bacterial pneumonia (Table 1), and
- Received at least 1 dose of P/T or comparator HAP appropriate antibiotic during the hospitalization.

The following patients will be excluded during the PHIS database screening (Figure 1):

- Patients who have received an antibiotic(s) consistent with treatment of CAP (i.e., 2nd or 3rd Generation cephalosporins, ampicillin/amoxicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam, azithromycin, clindamycin, or penicillin) during the first two days of hospitalization,
- Patients with a diagnosis of cystic fibrosis based on ICD-9 CM codes (Table 2); these patients will be excluded because they are frequently admitted for cystic fibrosis pulmonary exacerbations and receive similar antibiotic therapy but likely do not have HAP,
- Patients who were started on two HAP appropriate antibiotics simultaneously (within one day). These patients will be excluded because they will likely to be clinically different than patients started on monotherapy,
- Patients who received P/T or comparator antibiotics for other infection(s) prior to the diagnosis of HAP, or,
- Patients with missing pharmacy data in PHIS.

As noted in section 3.2, the PHIS database does not contain information on daily patient physical exams, medication doses and daily physician impression and management plans. Therefore, the review of patient medical charts is required to confirm the diagnosis of HAP. Once a patient is confirmed as HAP, the medical chart review will continue in order to obtain information on the administered doses of P/T and comparator HAP appropriate antibiotics, and to document the onset of serious events and treatment outcomes related to effectiveness with HAP therapy.

3.3.2 Step-II: Review of patient medical chart

A review of the medical chart for each of the potential cases of HAP identified from the PHIS database screening will be performed to systematically confirm the diagnosis of HAP, as follows (Figure 2):

- Confirmation of an absence of a diagnosis of CAP in the physician of record's documentation at any time in the first two days of hospitalization,
- Confirmation of pneumonia diagnosis in daily progress notes anytime after the first two days of hospitalization,
- Confirmation of receipt of P/T or comparator HAP appropriate antibiotic(s) administered within one day of the pneumonia diagnosis,
- Confirmation that patient did not receive two HAP appropriate antibiotics simultaneously (within one day), and
- Confirmation that patient did not receive P/T or comparator antibiotics for other infection(s) prior to the diagnosis of HAP.

Once the diagnosis of HAP is confirmed, a detailed chart abstraction will be performed to gather data on exposure to P/T and comparator HAP appropriate antibiotic(s), data on serious events including mortality and treatment outcomes related to effectiveness of the antibiotic therapy, and other relevant data.

3.4 Index date and follow up

The index date will be the "date of initiation of HAP treatment. The follow-up time for a patient outcome, which measures the person-time at risk, is defined as the time interval from the index date until one of the following:

- For the outcome of all cause mortality, a period of 30 days after the first dose of P/T or comparator antibiotics (at which time all surviving patients will be considered censored), and,
- For all other serious events, completion of 28 days after the last dose of P/T or comparator antibiotics, or discharge from the hospital (or death), whichever occurs first (after which time all surviving patients will be considered censored).

3.5 Definitions of P/T exposed and comparator groups

Owing to the wide range of pathogenic bacteria, the empiric therapeutic options for HAP are often broad. In adults, monotherapy is suggested, however, if concern exists for *Pseudomonas*

aeruginosa as the pathogen then therapy with two antipseudomonal agents from different antibiotic classes is recommended.[1] Formal guidelines for pediatric patients with HAP do not exist. Typical clinical pediatric practice frequently results in the administration of a single agent with Gram negative activity (including anti-pseudomonal coverage) such as P/T, ceftazidime, cefepime, ticarcillin/clavulanate, carbapenem, or ciprofloxacin (i.e., monotherapy for HAP).

Preliminary data extracted from PHIS (Table 3) supports the notion that typically only one of the aforementioned HAP appropriate antibiotic agents are initiated in pediatric patients, as only a minority of patients were started on two HAP appropriate antibiotics on the same day. These few patients started on two HAP appropriate antibiotics simultaneously will be excluded as they are expected to be clinically distinct from patients started on only one of the a priori defined HAP antibiotic agents. Operationally, patients started on two HAP appropriate antibiotics will be considered as those administered two HAP appropriate antibiotics "within 1 day of starting HAP therapy".

Although not a common practice, it is conceivable that some clinicians may have initiated other antibiotics simultaneous to the initiation of the P/T or comparator HAP appropriate antibiotic for broader Gram positive coverage (i.e., vancomycin) or broader Gram negative coverage (i.e., aminoglycoside). Therefore, patients who received vancomycin and/or aminoglycoside will be included in the study.

3.5.1 P/T exposed groups

P/T Group (HAP Dosing):

Children who received at least one dose of P/T 80-100 mg/kg as the first antibiotic administered for treatment of HAP will be included in this group. *This will be the primary exposed group.*

P/T Group (Any Dosing):

Children with HAP who received at least one dose of P/T (any dose) as the first antibiotic administered for treatment of HAP will be included in this group.

3.5.2 Comparator groups

Comparator Group (HAP Dosing):

Children with HAP 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 treatment of HAP will be included in this group. *This will be the primary comparator group.*

Comparator Group (Any Dosing):

Children with HAP who received at least one dose of one of the comparator HAP appropriate antibiotics (i.e., ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime or ciprofloxacin) (any dose) as the first antibiotic administered for treatment of HAP will be included in this group.

Comparator Group (Carbapenems):

Children with HAP 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 treatment of HAP will be included in this group.

The two Comparator groups (i.e., HAP Dosing and Any dosing) will include patients who were started on one of the five comparator HAP appropriate antibiotics from different antibiotic classes (two cephalosporins, an anti-pseudomonal penicillin, a fluoroquinolone or a carbapenem) with varying safety/adverse event and effectiveness profiles. The third comparator group (Carbapenems) will only include patients who were administered a carbapenem as the first antibiotic administered for treatment of HAP, and therefore provide an additional/ more focused comparator group to P/T. 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).

3.5.3 Dose of P/T and comparator HAP appropriate antibiotic(s)

P/T dose

As noted in section 1.0, P/T is not currently approved for the treatment of pediatric HAP. Therefore, it is likely that prescribing dose and frequency of P/T in children with HAP will vary by hospital. Currently P/T is approved for use in pediatric patients ≥ 2 months of age for the treatment of intra-abdominal infections (IAI) at a dose of 240/30 to 300/37.5 mg/kg/kg divided and administered every 8 hours.[7] However, adult data suggest that higher and more frequent dosing is necessary when *Pseudomonas aeruginosa* is a concern such as in nosocomial pneumonia.[8] Therefore, in the setting of pediatric HAP it is expected that P/T will have been prescribed at higher and more frequent dosing regimens than what is recommended for IAI.

Patients receiving P/T 80 to100 mg/kg every 6 hours for the piperacillin component up to the maximum of 4gm every 6 hours for the piperacillin component will be included in the P/T Group (HAP dosing). However, data on patients receiving P/T other than 80-100 mg/kg range (any P/T dosing) will also be collected. Further, recognizing that there could be modest rounding when calculating medication doses, a dose within 10% of the 80-100 mg/kg range will be considered within the range.

Comparator HAP appropriate antibiotics dosing

There are currently no available dosing recommendations for any of the comparator medications that are specific to the treatment of HAP in pediatric patients. However, it is likely that most clinicians will consider HAP as a moderate to severe infection and will dose antibiotic treatments accordingly. We will use pediatric dosing included in the respective product label for moderate to severe infections, which are summarized in Table 4. Similar to the P/T group, a dose within 10% of the respective product label dosing will be considered within the range. Further, data on patients receiving comparator antibiotic(s) at a dose other than the respective product label(s) indicated for moderate to severe infections in pediatric patients (i.e., any comparator dosing) will also be collected.

3.6 Data collection

The following patient-level data will be collected from the PHIS database and patient medical charts.

3.6.1 Exposure data

The following data on P/T and comparator HAP appropriate antibiotics will be collected from each patient's medical chart:

- Dose/frequency
- Duration of use (using the start and stop dates)

In addition to dose/frequency and duration of antibiotic use, the data on changes or additions of antibiotics will also be collected.

3.6.2 Outcome data

The data on serious events and treatment outcomes related to effectiveness will be collected directly from each patient's medical chart.

3.6.2.1 Serious events

The primary study outcome is the development of "serious events". A serious event is defined as any untoward medical occurrence 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.

Medical and scientific judgment will be exercised in determining whether an event is an important medical event and can be classified as a serious event. A serious event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one

of the other outcomes listed in the definition above, the important medical event will be documented as a serious event.

The following serious events in pediatric HAP patients treated with P/T or comparator HAP appropriate antibiotics (irrespective of 'causal' relationship to therapy) have been reported in clinical studies and post-marketing data, and will be specifically focused upon:

- Central nervous systems (CNS)/neurologic: seizure
- Gastrointestinal: cholestatic jaundice, hepatotoxicity, hepatitis
- Hematologic: hemolytic anemia, thrombocytosis, agranulocytosis, pancytopenia
- Immune: anaphylactic/anaphylactoid reactions (including shock)
- Infection: sepsis, super-infections, *C. difficile* infection
- Skin and appendages: erythema multiforme, Stevens-Johnson Syndrome
- Renal: interstitial nephritis, renal failure

The Clinical Research Nurses (CRNs), performing chart reviews for this study, will collect all untoward medical events documented in the daily progress notes of the physician of record/problem list or impression section of the chart from the day of initiation of P/T or comparator HAP appropriate antibiotics through the duration of hospitalization or 28 days after the last dose of the HAP antibiotic(s), whichever comes first. The CRNs will also collect AE onset date, which will correspond to the date of the progress note, and supporting laboratory and radiological data, if available. Physician documentation/notes on the possibility of 'causal relationship' between the administered antibiotic(s) for HAP treatment and the untoward medical event(s) will also be noted in the case report form (CRF) (Appendix-I), when available. In addition, data on pre-existing conditions (i.e., prior to the diagnosis of HAP) which worsen during HAP treatment will also be collected.

Subsequently, the abstracted data on untoward medical events from each chart will be reviewed by the study physician who will be blinded to the antibiotic that each patient received for HAP to determine whether the event meets the above definition of serious event.

Ascertainment of mortality at 30 days after initiation of HAP treatment

An attempt will be made to ascertain vital status at 30-day after initiation of treatment for HAP for all patients. The vital status at 30-day after initiation of treatment for HAP may not be available in charts for patients who stayed in hospital less than 30 days after initiation of HAP treatment. The following sequential approach will be used to determine vital status at 30-day after initiation of HAP treatment:

- Query the PHIS database and/or review the patient's medical chart to determine whether the patient had a clinic visit or readmission at some point 30 days after initiation of treatment for HAP.

  If no readmission or clinic visit was found then:

- Query the National Death Index (NDI) for a matching record. NDI is a central computerized index of death record information compiled from computer files submitted to the National Center for Health Statistics (NCHS) by each state's vital statistics office. Information on patients' name and date of birth or social security number is needed in order to search for a 'matching record' in the NDI. The study database will contain information on patient's personal identifiers including first and last name and date of birth. After IRB approval is obtained at the patient's local institution, available personal identifiers of patients with unknown 30-day vital status will be submitted to the NCHS, with a request to search the NDI for a matching record. In case of a matching record (i.e., patient's death), the 'date of death' from the NDI report will be used to ascertain the vital status of the patient at 30 days after initiation of HAP treatment.

3.6.2.2 Treatment outcomes related to effectiveness

Unblinded CRN review of charts
The secondary study outcome is the effectiveness of the antibiotic therapy. In addition to collecting daily pertinent laboratory, radiographic and co-morbid condition data, the clinical research nurses (CRNs) will also review daily progress notes of the treating physician (up to 14 days of HAP treatment initiation) to assess whether the patient is considered by the treating physician to be 'clinically improved' or 'clinically did not improve,' and record one of these two outcomes in the CRF.

Blinded physician review of CRF/abstracted data
Subsequently, a study physician who will be blinded to the antibiotic that each patient received for HAP will review abstracted data (which will include CRN assessment of effectiveness outcomes based on treating physician's notes and other relevant data e.g., x-rays, laboratory data) to confirm the effectiveness of the therapy as 'clinically improved' or 'clinically did not improve.'

3.6.3 Data on covariates

In addition to the data on exposure and outcome, the data on covariates and potential confounders will be collected.

The following data will be collected from the PHIS database for <u>all patients</u> with a potential diagnosis of HAP:

- Age
- Gender
- Race
- Hospital admission number
- Discharge identification number
- Encrypted patient record number
- Date of admission and discharge (duration of hospitalization)

- Daily medications administered during hospitalization *(Note: Dosage information is not available in PHIS)*, and
- Clinical diagnoses based on ICD-9-CM discharge codes.

The following data will be collected from medical charts, if available, only for patients with a confirmed diagnosis of HAP:

- Pre-existing medical conditions as reported in the physician of record's admission notes by medical system (e.g., CNS, cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological etc),
- Daily problem list/physician impressions
- Laboratory results (e.g., CBC, metabolic panels, LFTs)
- Imaging results (e.g., chest radiography)
- Dosage and duration of use (i.e., #of days) for P/T and comparator HAP appropriate antibiotics administered during the study period. Comprehensive list and duration of use of all other enteral, intravenous, and inhaled medications
- Use of mechanical ventilator
- Admission to ICU
- Endotracheal intubation
- Tracheostomy
- Outpatient clinic visit or readmission after 30 days of initiation of HAP treatment, if available *(This information will be used to assess vital status at 30 days of initiation of HAP treatment).*

3.7 Data collection procedure

Once a hospital has agreed to participate in the study and obtained approval from the IRB and hospital administration (if applicable), the PHIS database will be queried with the screening inclusion/exclusion criteria (Step-I) to identify potential HAP patients in the respective hospital. The data on potential HAP patients will be downloaded at the principal study center, Children's Hospital of Philadelphia (CHOP), PA.

Subsequently, trained study personnel (CRNs, Clinical Research Associates (CRAs) or physicians) will perform a review of the medical chart of each patient identified from the PHIS database screening to confirm the diagnosis of HAP as described in section 3.3.2 (Step-II).

After confirming the diagnosis of HAP, the study personnel will proceed with a detailed chart review and data abstraction. If HAP is not confirmed by initial chart review, no further data abstraction will be performed. CHOP study personnel will travel to each participating institution in order to perform chart abstraction. However, for hospitals with capability of remotely accessing the electronic medical record (EMR), virtual chart review and data abstraction will be performed from within CHOP. For sites that do not allow outside personnel to access medical

records in person or remotely, site-specific personnel will be trained to complete data abstraction by the CHOP study personnel.

Depending on IRB approvals, we will perform chart reviews from hospitals with the highest number of potential HAP patients receiving P/T in descending order until the data on at least 150 patients who received at least one dose of P/T and 300 patients with HAP who received at least one dose of comparator HAP appropriate antibiotics are collected (see section 7.2 Historical counts of potential HAP patients in PHIS database). The PHIS hospitals will be enrolled in the study on a rolling basis. Once a hospital is enrolled, all patients with a potential diagnosis of HAP identified from the PHIS database screening during the study period will have their chart reviewed by the study personnel

As requested by the FDA, de-identified copies of a random sample of approximately 5% of the medical charts of HAP patients included in this study will be submitted to the FDA with the final study report. The approval to process de-identified copies of a patient chart at each institution will be contingent upon local IRBs approval. For patient charts from hospitals that are unable to approve this process, a second trained person will perform a repeat data abstraction for 5% of the patients to compare to the primary abstracted data. In case of discrepancies in the abstracted data points in the two CRFs, each reviewer will revisit the charts to determine the reason for discrepancies and agree on the appropriate information to be recorded in the database prior to lockdown. The two completed original CRFs (as replacement to copies of patient medical charts) will be submitted to the FDA with the final study report.

The study personnel will undergo formal training by the PI on how to confirm the diagnosis of HAP and perform detailed chart abstraction. The PI will implement measures such as random validation/ QC check of the completed CRFs to ensure that the abstracted data are reliable and valid, and prevent/minimize variations in data abstraction among study personnel.

3.8 Quality control

The investigators will follow CHOP's Standard Operating Procedures (SOPs) for medical research throughout the conduct of this study. The data collected from various hospitals will be periodically checked for consistency by the study manager.

3.9 Pilot study

A pilot study in a small number of patients (10-15) from the hospital of the PI (or another participating hospital depending on the IRB approval) will be conducted to identify issues, if any, in the study processes (e.g., evaluate inclusion/exclusion criteria on PHIS database to identify potential HAP patients, chart review to confirm the diagnosis of HAP) and test the draft CRFs (e.g., whether the content and format of the draft CRFs is appropriate to collect the study data or if changes are necessary). The methodology (i.e., study design, population, data source, inclusion/exclusion criteria and data collection method) in the pilot will be identical to those

intended for the actual study. Lessons learned from the pilot will be incorporated to improve the study processes and CRFs.

4.0 ADVERSE EVENT REPORTING

This study uses patient-level electronic health related databases (e-HRD), in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual.

This study protocol requires review of the patient medical chart and/or narrative/verbatim fields in the dataset. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the defined dataset (defined per the patient population and study period specified in the protocol).

The data collection process involves collecting drug-related effects in individuals. The reviewer may identify a serious adverse event (SAE) with explicit attribution to a Pfizer drug via patient chart and/or narrative /verbatim field review (and with an identifiable reporter). Such SAEs must be reported to Pfizer or its representative for submission to regulatory authorities. Explicit attribution is not inferred by a temporal relationship between drug administration and an SAE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the SAE.

DEFINITION OF AN ADVERSE EVENT

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter “pediatric formulas”]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;

- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

SERIOUS ADVERSE EVENTS

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event many not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If there is a written notation in the medical chart/narrative field indicating that a physician attributed a serious adverse event to a Pfizer drug, the reviewer will complete a Non-Interventional Study Adverse Event Report Form within 24 hours of identification of the event and submit it to Pfizer Safety.

5.0 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical

Sciences (CIOMS), FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and EMA European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

5.1 Institutional Review Board Approval

Approvals from each hospital's IRB and administration (when applicable) will be sought before proceeding with chart abstraction on any potential HAP patients.

5.2 Human Subject Involvement

This study will abstract existing data (i.e., PHIS and medical chart data) after appropriate IRB approvals. All abstracted data will be maintained in password protected files located on password protected research network drives. There will be no direct interaction with any patients or their families. Therefore, approval of exemption of informed consent or assent from individual patients will be requested from each participating institutions IRB.

5.3 Potential Risks

There is no direct risk to patients in this retrospective study. One potential (indirect) risk is the loss of confidentiality of personal data imparted by participating in any research study where the patient's identifying information is collected. We will institute strict procedures to maintain confidentiality of the study data. Each subject in the study will be assigned a unique identifier (a study number that is distinct from the patient's medical record number) to be used on the CRF. A master list will be used to link the study number to the medical record number and any personally identifiable information of each patient. Only the project staff will have access to this information. Once the data from PHIS screening and chart abstraction are obtained and merged, all personally identifiable patient information will be removed from the data. The database will contain the study number only and will be kept in a password-protected research network drive, which is backed up and only accessible by approved CHOP study personnel.

6.0 DATA MANAGEMENT

There will be one final analytic dataset containing data from both PHIS screening and patient charts from all hospitals that will participate in the study. The data on potential HAP patients from PHIS screening will be downloaded into Microsoft Excel at CHOP. The data abstracted from patient charts using CRF will be entered into an electronic database. The two datasets will be merged using an assigned study ID number.

All analyses will be conducted on appropriately de-identified data. Data management and statistical analyses will be conducted using SAS (SAS Institute, Cary, NC) and STATA (College Station, TX). The final dataset will be maintained at the principal study center, CHOP.

7.0 STATISTICAL ANALYSIS

7.1. Sample Size and Precision of Estimate

This study is not intended to test specific hypotheses but rather to estimate the rate of serious events and proportion of patients classified into binary treatment outcomes related to effectiveness for various antibiotic agents in the treatment of pediatric HAP. We plan to collect data from at least 150 children with a diagnosis of HAP who received at least one dose of P/T and 300 children with HAP who received one dose of comparator HAP appropriate antibiotic(s).

95% confidence intervals (CIs) around the rates of serious events in the P/T and comparator groups, and rate ratios (RRs) for serious events (P/T vs. comparator) will be estimated. The target sample size of 150 P/T patients and 300 comparator patients permits estimation of the rate and RR with the following CI widths, tabulated for underlying serious event rates ranging from 2% to 10%:

Rate (%) of serious event*	Width of 95% CI for Rate in P/T Group	Width of 95% CI for RR (P/T vs. comparator)
2	5.7	3.9
4	7.3	2.2
6	8.4	1.7
8	9.5	1.4
10	10.3	1.2

*Serious event rate within 28 days after the last dose of HAP treatment, assumed equal rate in both groups.

For example, assuming an underlying serous event rate of 2%, the width of the 95% CI for the serious event rate in the P/T group with 150 patients will be 5.7, and the width of the 95% CI for the RR (P/T vs. comparator) will be 3.9.

7.2. Historical counts of potential HAP patients in PHIS database

A query of the PHIS database identified 2138 patient admissions between 2003 and 2009 with a presumed diagnosis of HAP, among them at least 629 were initially treated with at least 1 day of P/T and 1439 with one of the five comparator HAP appropriate antibiotics (Figure 3). These potential HAP patients were identified from 40 PHIS hospitals. Given the operational challenges in hospital enrollment, it will be extremely difficult to include all 40 PHIS hospitals in this study. The PHIS data suggest that inclusion of the 20 PHIS hospitals with the highest number of potential HAP patients will result in identification of 568 patients that initially received at least one day of P/T and 791 patients that initially received at least one day of comparator HAP appropriate antibiotics (Table 5).

7.3. Statistical Methods

Detailed methodology for summarization and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), separate from the protocol.

Descriptive Statistics

Descriptive statistics will be performed to describe patient characteristics such as age, sex, race/ethnicity, geographical location, length of hospital stay, presence of co-morbid conditions at the time of hospital admission, concomitant medication use and ventilator support in the P/T exposed and comparator groups. Categorical variables will be presented as frequencies and percents. Continuous variables will be summarized by mean with standard error, standard deviation, median, interquartile range, minimum, and maximum. Figures and box plots will be used to supplement the descriptive statistics when appropriate.

Safety Outcomes

Below are the safety outcomes of interest for this study. All serious events will be coded into standardized terms.

- All incident serious events overall (i.e., sum of all individual incident events)
- All incident serious events by body system (e.g., Gastrointestinal/hepatic: hepatotoxicity, hepatitis etc)
- All incident serious events individually
- All cause mortality

For each of the serious events outcomes, one or more events that occur during the follow-up time (as described in section 3.4 Index date and follow up) will be counted for each patient.
Each outcome will be analyzed using a Poisson model with an offset for person-time at risk and robust variance estimate. The model will include potential confounders at baseline, such as:

- Age groups (e.g., 2 months to 1 year, 1-5 years, etc.);

- Gender;
- Race/ethnicity;
- Co-morbid conditions at the time of HAP diagnosis;
- Study center.

Results will be presented by group (P/T, comparator) for the:

- Total number of events,
- Cumulative person-time at risk,
- Model adjusted event rate per 1,000 person years with corresponding 95% CI, and
- Model adjusted incidence rate ratio (IRR) with corresponding 95% CI.

Comparisons of interest will be those which are displayed in the table below:

Statistical Comparisons of Interest		
P/T Group		**Comparator Group**
P/T (HAP dosing)	versus *Primary comparison*	Comparator (HAP dosing)
P/T (Any dosing)	versus	Comparator (Any dosing)
P/T (HAP dosing)	versus	Comparator (Carbapenems)

Results will also be computed for select groups for the primary comparison only (e.g. age groups (e.g., 2 months to 1 year, 1-5 years, etc) gender (i.e., male, female), race (e.g., White, Black, Asian etc), duration of HAP treatment (e.g., <1 day, 1 day, 2 days etc.).

Effectiveness Outcomes

Counts and percentages of HAP patients categorized as "clinically improved" or " clinically did not improve" (as described in section 3.6.2.2) will be calculated.

The binary outcome will be analyzed using a logistic regression model for the primary comparison only, with the same model terms as specified above for the Poisson model for serious events. Results will be presented by group (P/T, comparator) with counts and percentages for each outcome, model adjusted odds ratio (OR), and associated 95% CI for the OR.

Results will also be computed for select groups for the primary comparison only (e.g. age groups (e.g., 2 months to 1 year, 1-5 years, etc) gender (i.e., male, female), race (e.g., White, Black, Asian etc), duration of HAP treatment (e.g., <1 day, 1 day, 2 days etc.).

8.0 STRENGTHS AND LIMITATIONS

Strengths:

- **Use of real world data:** This study will use the data from a real-world setting collected from multiple pediatric institutions across the US. We expect to observe pediatric HAP patients treated with a range of antibiotic dosing regimens.

- **Generalizability of findings**: External validity or generalizability is defined as the degree to which the findings/inference drawn from the study extends beyond the study sample. We believe that a study conducted in a usual care setting using real-world data will have greater generalizability than a RCT. Further, this study has been designed to evaluate a cohort of pediatric patients treated for HAP from multiple children's hospitals across the US. The multi-site approach will result in a study population from various regions across the country. Therefore, it is expected that the results of this study will be generalizable to the treatment of pediatric HAP across the US.

- **Availability of study results:** By using data that have already been recorded (i.e., existing data), compared to a RCT (or any prospective design), this retrospective study will likely be completed sooner, and in turn, will hasten the availability of P/T safety and effectiveness data to health care professionals and patients.

Potential limitations:

- **Confounding by indication:** Confounding by indication may take place if the decision to initiate or to stop an antibiotic was influenced by the clinical status of the patient. This is of particular concern for broad spectrum antibiotics such as P/T or the carbapenems as physicians may be more inclined to start such agents if a patient is more ill appearing. This would falsely result in an association of the broad spectrum antibiotics with worse outcomes. Although complete control of this confounding is unlikely, the adjustment in multivariate analysis for the presence of co-morbid conditions and for the clinical status of the patient at the initiation of the HAP antibiotic will reduce this confounding effect. Additionally, comparison of P/T patients with only patients treated with a carbapenem will help to assess the effect of this confounding.

- **Selection bias:** In a cohort study, selection bias occurs when the choice of exposed and unexposed subjects is somehow related to the outcome of interest. A retrospective cohort study is particularly subject to this bias since the choice of subjects happens after the exposure and outcome of interest have taken place. However, selection bias for this study will be unlikely because the data in PHIS were collected in real time without knowledge of this study's outcomes of interest. The determination of exposure status for each subject will be based on claim records for the antibiotics administered. The claim records are recorded in

the PHIS database at the time of each hospital admission. Further, the data on exposure status will be extracted without simultaneous knowledge of serious events or patient treatment outcome status.

- **Misclassification bias:** Misclassification bias occurs when study subjects are classified incorrectly according to exposure or outcome status. Data on each patient's antibiotic exposures are only subject to misclassification secondary to dependence on data from the PHIS database. We are less concerned about misclassification since determination of antibiotic exposure is dependent on billing documentation, which should be complete in the database and represents medications actually administered to the patient. Furthermore, if some of the billing is not complete we have no reason to believe that this would be *differential* in nature between the P/T exposed and comparator groups.

  The ability to accurately classify serious events and treatment outcomes related to effectiveness for each patient will be dependent on the documentation made in the daily physician notes. We expect inter- and intra-hospital variations in the completeness of physician documentation/progress notes. Incomplete or poor documentation may result in under reporting of serious events in some patients. It is not possible to account for the potential under reporting of prior physician documentation. However, there is no reason to believe that this will occur *differentially* between the P/T exposed and comparator groups.

- **Confounding by study center:** This study is designed to include patients from multiple pediatric hospitals across the US making the analysis susceptible to confounding by study center. This type of confounding is possible since the outcomes and the exposures can both be associated with the hospital. Hypothetically, if one hospital systematically prescribes a specific antibiotic and has a higher mortality rate in HAP patients than other institutions, then it could be very difficult to distinguish the effect of the study center from the exposure. Adjustment for this confounding will be attempted by including a variable "study center" in the multivariate regression model.

- **Availability of vital status of patients after 30 days of initiation of HAP treatment**: As described in section 3.6.2.1, NDI data will be queried to determine vital status at 30 day for patients who stayed in hospitals less than 30 days after initiation of HAP treatment. Variation in IRB practices may prohibit our ability to query NDI using personal identifiers without prior consent of patients. Therefore it is possible that the vital status at 30 days after initiation of HAP treatment may not be known for some patients.

9.0 ANTICIPATED STUDY TIMELINE

The estimated completion time of this retrospective cohort study is approximately 5 years from approval of the protocol. It will take approximately 1 year to recruit hospitals, obtain IRB approvals and develop study database structure, 1 year for the pilot study and updating the protocol, draft CRF and database based on lessons learned from the pilot, if required, 2 years for

data collection/compilation, 6 months for data cleaning/verification, and 6 months for statistical analyses and the study report development.

The final study report is expected in the third quarter of 2018. The updates on the progress of the study will be provided to the FDA annually.

REFERENCE

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Figure 1. Step I: PHIS database screening to identify patients with potential HAP

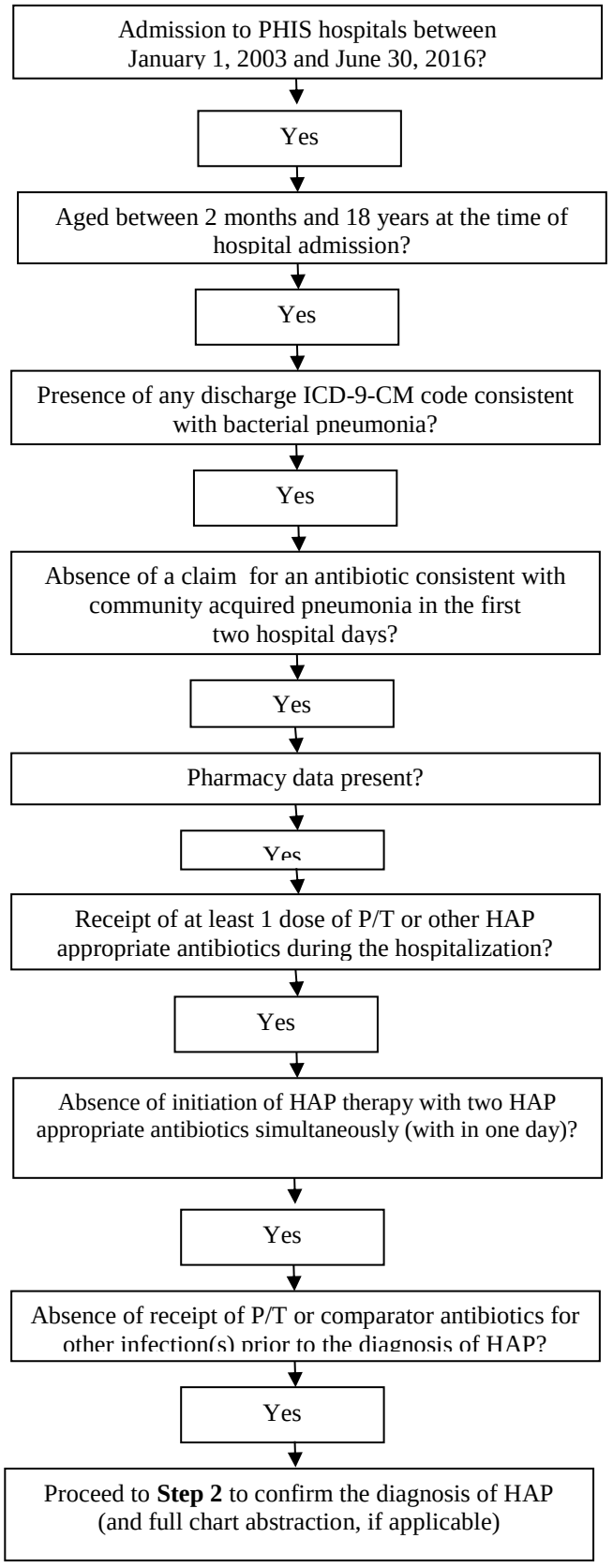
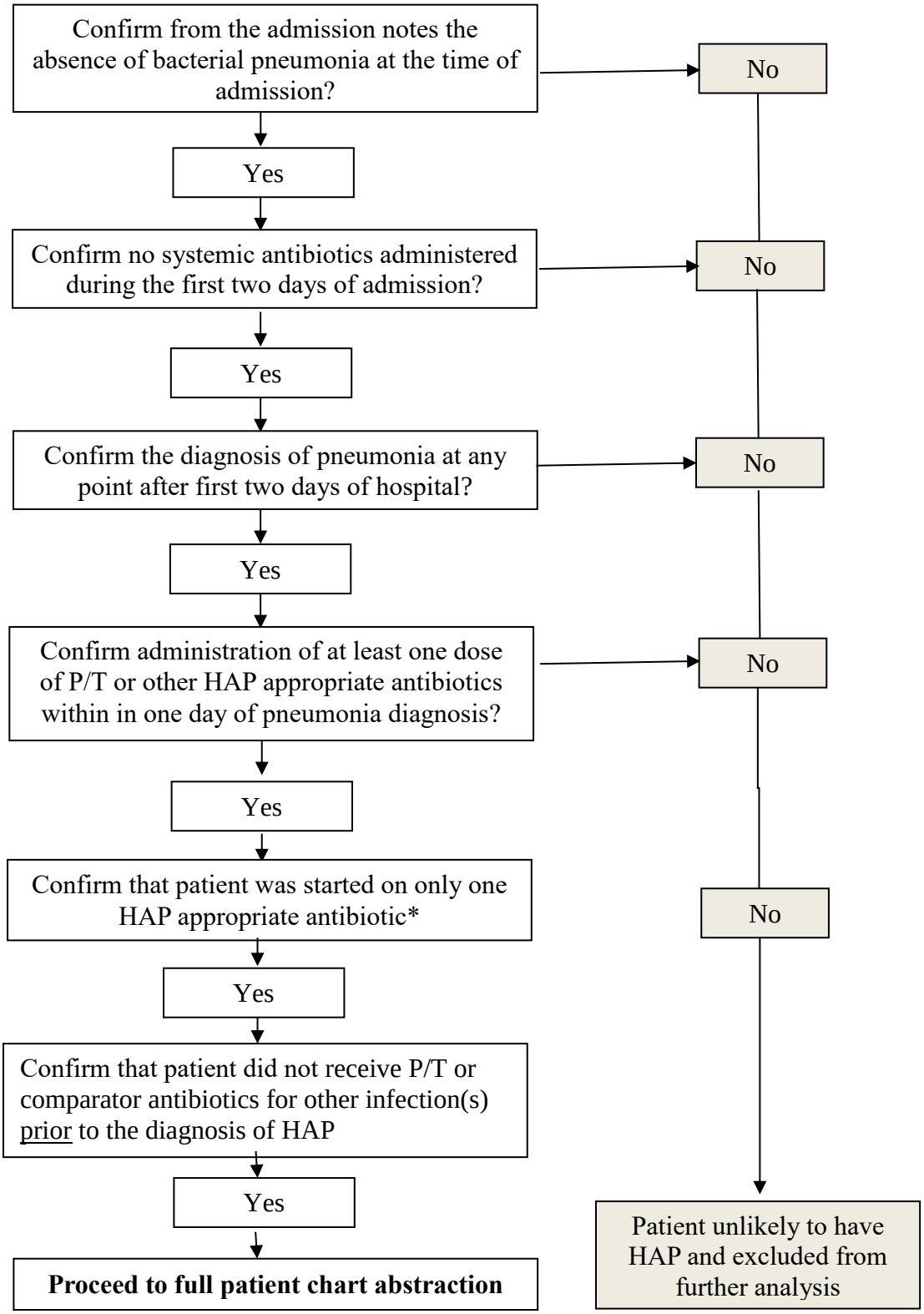


Figure 2. Step II: Initial chart review to confirm the diagnosis of HAP



*HAP patients started on two HAP appropriate antibiotics will be excluded because they are likely to be clinically different than patients started on monotherapy

Table 1. ICD9-CM codes for bacterial pneumonia

Code	Description
Bacterial pneumonia codes	
481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia] Lobar pneumonia, organism unspecified
482.0	Pneumonia due to Klebsiella pneumonia
482.1	Pneumonia due to *Pseudomonas*
482.2	Pneumonia due to Hemophilus influenzae [H. influenzae]
482.30	Pneumonia due to Streptococcus, unspecified
482.31	Pneumonia due to Streptococcus, Group A
482.32	Pneumonia due to Streptococcus, Group B
482.39	Pneumonia due to Streptococcus , Other Streptococcus
482.40	Pneumonia due to *Staphylococcus*, unspecified
482.41	Pneumonia due to *Staphylococcus* aureus
482.49	Other *Staphylococcus* pneumonia
482.81	Pneumonia due to Anaerobes, Gram-negative anaerobes Bacteroides (melaninogenicus)
482.82	Pneumonia due to *Escherichia coli*
003.22	Salmonella pneumonia
482.83	Pneumonia due to other gram-negative bacteria Gram-negative pneumonia NOS Proteus *Serratia marcescens* Excludes: gram-negative anaerobes (482.81) Legionnaires' disease (482.84)
482.89	Pneumonia due to Other specified bacteria
482.9	Bacterial pneumonia unspecified
Other pneumonia (bacterial only)	
483.8	Pneumonia due to Other specified organism
485	Bronchopneumonia, organism unspecified Bronchopneumonia: hemorrhagic terminal Pleurobronchopneumonia Pneumonia: lobular Segmental
486	Pneumonia, organism unspecified Excludes: hypostatic or passive pneumonia (514) influenza with pneumonia, any form (487.0) inhalation or aspiration pneumonia due to foreign materials (507.0-507.8) pneumonitis due to fumes and vapors (506.0

Table 2. ICD 9 codes for cystic fibrosis

ICD-9-Code	Description
277.0	Cystic Fibrosis
277.00	Cystic Fibrosis without mention of meconium ileus
277.01	Cystic Fibrosis with meconium ileus
277.02	Cystic Fibrosis with pulmonary manifestations
277.03	Cystic Fibrosis with gastrointestinal manifestations
277.09	Cystic Fibrosis with other manifestations

Table 3. Number of patients by receipt of antibiotic and year admitted to 40 PHIS hospitals across the US (2003-2009)

Year	Piperacillin/Tazobactam	Ticarcillin-Clavulanate	Carbapenems	Ceftazidime	Cefepime	Ciprofloxacin	Two Antibiotics*
2003	55	14	21	65	40	19	5
2004	72	25	34	74	44	20	9
2005	75	26	27	97	49	21	9
2006	60	24	28	87	50	16	6
2007	97	17	48	84	81	22	11
2008	151	12	55	74	75	20	14
2009	119	8	43	60	41	18	16
Total	**629**	**126**	**256**	**541**	**380**	**136**	**70**

*Two of the six antibiotics were initiated on the same day

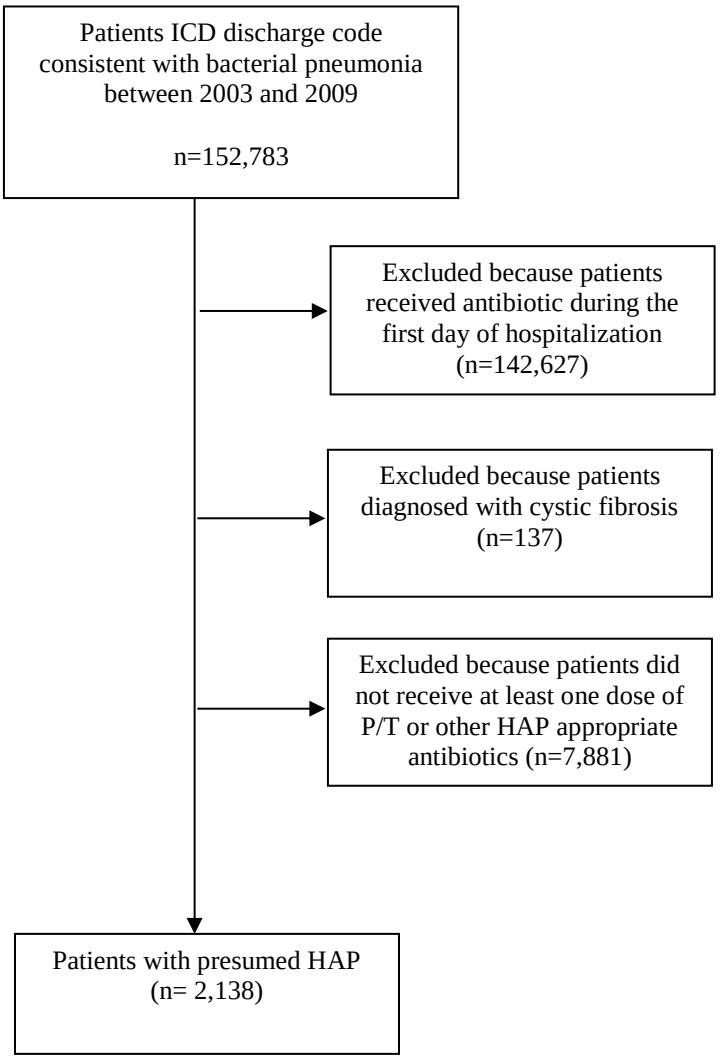
Table 4. Recommended dosing regimens for comparator HAP appropriate antibiotics for the treatment of moderate to severe infections in children (source: Package Insert of listed products)

Comparator Antibiotic	Age Range	Recommended Dose	Maximum Daily Dose
Ticarcillin/clavulanate	< 3 months ≥3 months Children > 60 kg	300 mg/kg/day ÷ Q 8 hours 200-300mg/kg/day ÷ Q 4-6 hours 3 grams/dose Q4-6 hours	24 grams
Imipenem	< 3 months ≥3 months Adults	100mg/kg/day ÷ Q 6 hours 60-100 mg/kg/day ÷ Q 6 hours 2-4 grams/day ÷ Q 6 hours	4 grams
Meropenem	< 3 months ≥3 months Adults	60 mg/kg/day ÷ Q 8 hours 60-120 mg/kg/day ÷ Q 8 hours 1-2 grams/dose Q 8 hours	6 grams
Ceftazidime	> 1 month to ≤ 12 years of age > 12 years of age	100-150 mg/kg/day ÷ Q 8 hours 1-2 grams/dose Q 8 hours	6 grams
Cefepime	≥2 months Children > 40 kg	50 mg/kg/dose Q 8-12 hours 2 grams/dose Q 8-12 hours	6 grams
Ciprofloxacin (Oral)	All Children	20-30 mg/kg/day ÷ Q 12 hours	1.5 grams
Ciprofloxacin (IV)	All Children	20-30 mg/kg/day ÷ Q 12 hours	800 milligrams

Table 5. The 20 PHIS hospitals with the most pediatric patients with potential HAP treated with P/T or comparator HAP appropriate antibiotics between 2003 and 2009

PHIS Hospital	Piperacillin/ Tazobactam (P/T)	Ticarcillin/ Clavulanate	Carbapenems	Ceftazidime	Cefepime	Ciprofloxacin
1	96	0	28	18	57	19
2	69	1	6	15	11	3
3	65	0	12	0	1	3
4	50	0	4	4	1	4
5	47	1	6	8	7	3
6	29	5	2	18	3	2
7	28	0	8	5	1	9
8	19	0	4	14	0	2
9	18	0	2	15	4	2
10	18	5	29	8	15	3
11	18	1	7	4	29	4
12	17	1	8	13	10	0
13	16	0	19	2	14	1
14	15	30	2	85	0	10
15	14	0	31	31	5	12
16	11	0	9	15	0	0
17	10	0	2	0	23	3
18	10	0	2	0	9	0
19	9	2	8	5	1	0
20	9	0	5	16	1	3
Total 2003-2009	**568**	**46**	**194**	**276**	**192**	**83**

Figure 3. Historical count of potential HAP patients in the PHIS hospitals between 2003 and 2009



10.0 APPENDIX-I: DRAFT CASE REPORT FORM (CRF)

CASE REPORT FORM

This case report form is a draft representation of a web-based remote data entry system. This form will not actually be used for data collection but rather represents the data elements to be collected. All data are abstracted from the chart and entered directly into the web-based database. There is no paper data collection form.

Research Assistant ID	|___|___|___|___|
Date of Chart Abstraction (mm/dd/yyyy)	|___|___| - |___|___| - |___|___|___|___|
Patient PHIS ID	|___|___|___|___|
Patient Hospital ID	|___|___|___|___|
Encrypted Medical Record Number	|___|___|___|___|

SECTION 1: PATIENT IDENTIFICATION DATA

This section includes data on patient personal identifiers and hospital admission and discharge dates

1.1 Date of birth (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

1.2 Date of hospital admission (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

1.3 Date of discharge (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

1.4 Sex |___|

1 = Male
2 = Female
9 = Unknown

1.5 Race |___|

1 = White
2 = Black
3 = Latino
4 = Asian
5 = Other (specify: _____)
9 = Unknown

1.6 Ethnicity |___|

1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Other (specify: _____)

9 = Unknown

SECTION 2: CONFIRMATION OF HAP DIAGNOSIS

Information collected in this section will be used to confirm the diagnosis of HAP

2.1 Was diagnosis of bacterial pneumonia present in the physician of record's documentation at any time in the first two days of hospitalization? |___|

1 = Yes **(If 'Yes' then do not go further and exclude this patient)**
2 = No

2.2 Was pneumonia diagnosed by a physician within two days of hospital admission? |___|

1 = Yes **(If 'Yes' then do not go further and exclude this patient)**
2 = No

2.2a If Yes, date of pneumonia diagnosis (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|
99-99-9999= if unknown

2.3 Was the patient started on one of the HAP appropriate antibiotics (listed below in 2.3a) within one day of the pneumonia diagnosis? |___|

1 = Yes
2 = No **(If 'No' then do not go further and exclude this patient)**

2.3a If Yes, which HAP appropriate antibiotic (s) was started?

1 = Piperacillin/Tazobactam |___|
2 = Ticarcillin/Clavulanate |___|
3 = Ceftazidime |___|
4 = Cefepime |___|
5 = Imipenem |___|
6 = Meropenem |___|
7 = Ciprofloxacin |___|

If response to the question 2.3 is "Yes" then please move forward and perform the detailed chart abstraction

SECTION 3: HOSPITAL ADMISSION DATA

This section includes data at the time of hospitalization

3.1 Weight |__ __.__kg|
|__ __.__lb| *(if in lb)*

3.2 Height |__ __ __.__cm|
|__ __.__ft& inches|
(if in ft& inches*)*

3.3 Indication for hospital admission |___|

1 = Respiratory Infection
2 = Non-respiratory infection
3 = Non-infectious reason
4 = Other (Specify: _____)
9 = Unknown

3.4 Where was the patient admitted from? |___|

1 = Home
2 = Chronic care facility
3 = Another hospital
4 = Inpatient rehabilitation center
5 = Other (Specify: _____)
9 = Unknown

3.5 Prior to this admission, was patient hospitalized within the past 30 days? |___|

1 = Yes
2 = No
9 = Unknown

3.6 Did patient have a tracheostomy prior to admission? |___|

1 = Yes
2 = No
9 = Unknown

3.7 Was the patient ventilator dependent prior to this admission? |___|

1 = Yes
2 = No
9 = Unknown

3.8 What type of unit was patient initially sent to on this admission? |___|___|

1 = Gen Peds floor
2 = PICU
3 = CICU
4 = NICU
5 = Oncology
6 = Step down unit
7 = Adolescent
8 = Other (Specify: _____)
9 = Unknown

SECTION 3-A: PREVIOUS MEDICAL HISTORY

This section includes data about previous medical history as documented in the hospital admission notes

Medical System (check all that apply)	Specific co-morbidity
Neurologic/CNS O Brain & spinal cord malformations O Mental retardation O Central nervous system degeneration and disease O Infantile cerebral palsy O Epilepsy O Muscular dystrophies and myopathies O Multiple sclerosis Other (specify):_____	
Cardiovascular O Heart and great vessel malformations O Cardiomyopathies O Conduction disorders and dysrhythmias Other (specify):_____	
Respiratory O Respiratory malformations O Chronic respiratory disease Other (specify):_____	
Renal O Congenital anomalies O Chronic renal failure Other (specify):_____	
Gastrointestinal O Congenital anomalies O Chronic liver disease and cirrhosis O Inflammatory bowel disease Other (specify):_____	
Hematological and immunodeficiency O Sickle cell disease O Hereditary anemias O Hereditary/Primary immunodeficiency O Human immunodeficiency virus disease Other (specify):_____	
Metabolic O Amino acid metabolism O Carbohydrate metabolism O Lipid metabolism O Storage disorders O Other metabolic disorders O Diabetes mellitus type 1 Other (specify): _____	
Other congenital or metabolic defect O Chromosomal anomalies O Bone and joint anomalies O Diaphragm and abdominal wall Other congenital anomalies:(specify): _____	
O **Malignancy** (specify): _____	
Rheumatologic or Autoimmune illness O Lupus O Rheumatoid or juvenile rheumatoid arthritis	

O Ankylosing spondylitis Other autoimmune illness:(specify): _____	
Other (specify:_____)	

SECTION 4: SELECTED HOSPITALIZATION DATA PRIOR TO THE DIAGNOSIS OF HAP

This section includes selected hospitalization data prior to the diagnosis of HAP

4.1 Did the patient require ICU admission during hospitalization prior to the diagnosis of HAP? |___|

1 = Yes
2 = No
9 = Unknown

4.1a If yes: Date of ICU admit (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|
Date of ICU discharge (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

4.2 Did the patient require a tracheostomy prior to the diagnosis of HAP? |___|

1 = Yes
2 = No
9 = Unknown

4.2a If yes: date of the procedure (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

4.3 Did the patient require endotracheal intubation prior to the diagnosis of HAP??

1 = Yes
2 = No
9 = Unknown

4.3a If yes: Date of intubation: |___|___| - |___|___| - |___|___|___|___|
Date of extubation: |___|___| - |___|___| - |___|___|___|___|

4.4 Did the patient require ventilator support during hospitalization prior to the diagnosis of HAP? |___|

1 = Yes
2 = No
9 = Unknown

4.4a If yes: Mechanical ventilation support started (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|
Mechanical ventilation stopped (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

Laboratory data prior to the diagnosis of HAP
(Note: Include the last record prior to the diagnosis of HAP in case of multiple records)

4.5 Complete blood count (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

Results:

White blood cell count (THOU/ul) |___|___| . |___|
Band forms: |___|___| (%)
Neutrophils (/ul) |___|___|___|___|___|
Hemoglobin (Hgb) (g/dl) |___|___| . |___|

4.6 Blood chemistry (date) |___|___| - |___|___| - |___|___|___|___|

Results:

Sodium (mmol/L) |___|___|___|
BUN (mg/dL) |___|___|
Creatinine (mg/dl) |___|___| . |___|
Albumin (g/dl) |___|___| . |___|
ALT (U/L) |___|___|___|___|
AST (U/L) |___|___|___|___|
Bilirubin (mg/dl) |___|___| . |___|
GGT (U/L) |___|___| . |___|
Glucose |___|___| . |___|
Amylase |___|___| . |___|
Lipase |___|___| . |___|
Glucose (mg/dl) |___|___|
CO_2 |___|___|
Calcium(mg/dl) |___|___|
Chloride (mEq/L) |___|___|

4. 7 Medication data up to 7 days prior to the diagnosis of HAP*

Please complete the table (template) below to collect the medication data

Day of hospitalization (prior to the diagnosis of HAP)	**Medications (Antibiotics and other)**	**Dose (total mg)**	**Frequency**
1 day prior to HAP diagnosis Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
2 days prior to HAP diagnosis Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
3 days prior to HAP diagnosis** Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
4 days prior to HAP diagnosis** Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
5 days prior to HAP diagnosis** Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
6 days prior to HAP diagnosis** Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
7 days prior to HAP diagnosis ** Date |___|___| - |___|___| - |___|___|___|___|	1._____ 2._____ 3._____		
*Medication data for seven days prior to the HAP diagnosis will be obtained. If the patient was admitted for fewer than 7 days prior to HAP diagnosis, medication data from admission note will be included, if available. ** Patient may not be hospitalized.			

SECTION 5: DATA ON THE DIAGNOSIS OF HOSPITAL ACQUIRED PNEUMONIA(HAP)

This section includes data on the diagnosis of HAP

5.1 Was HAP diagnosed by a physician during this hospitalization? |___|

1 = Yes
2 = No
9 = Unknown

5.1a If yes, date of HAP diagnosis (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

5.2 Where was patient located at time of HAP diagnosis? |___|___|

1 = Gen Peds floor
2 = PICU
3 = CICU
4 = NICU
5 = Oncology
6 = Step down unit
7 = Adolescent
8 = Other (Specify: _____)
9 = Unknown

5.3 Was a respiratory or sputum culture obtained within 24 hours of starting HAP antibiotic(s)? |___|

1 = Yes
1 = No
9 = Unknown

5.3a If yes, were any organisms identified? |___|

1 = Yes
2 = No
9 = Unknown

5.3b If yes, which organisms were identified? (check all that apply)

0 = Normal respiratory flora |___|___|
1 = *Pseudomonas* spp. |___|___|
2 = *Stapyhlococcus aureus* |___|___|
9 = Other (_____)
9 = Unknown |___|___|

5.4 Check off any other defined bacterial co-infections at the time of HAP diagnosis:

1 = None |___|
2 = Meningitis/encephalitis |___|
3 = Sinusitis |___|
4 = Bone/joint infection |___|
5 = Endocarditis/pericarditis |___|
6 = Abdominal infection |___|
7 = Pyelonephritis/UTI |___|
8 = Pre-existing pneumonia |___|
9 = Other (Specify: _____)

SECTION 6: RADIOLOGY AND LABORATORY DATA RELATED TO HAP

This section includes radiology and laboratory data related to the diagnosis and treatment of HAP from the day of HAP diagnosis through the date of discharge or 28 days after the last dose of P/T or other HAP appropriate antibiotic(s), whichever comes first

(Note: Additional copies (as needed) of this section will be provided to CRNs to collect multiple values of radiology and laboratory data)

6.1 Chest x-ray (date) |___|___| - |___|___| - |___|___|___|___|

6.1a Results of CXR (list all that apply)

1 = Not done
2 = stable/no acute change |___|
3 = New infiltrate(s)
4 = Effusion/empyema |___|
5 = Other (_____)
9=Unknown |___|

6.2 Complete blood count (date) |___|___| - |___|___| - |___|___|___|___|

6.2a Results:

White blood cell count (THOU/ul) |___|___| . |___|

Band forms: |___|___| (%)

Neutrophils (/ul) |___|___|___|___|___|

Hemoglobin (Hgb) (g/dl) |___|___| . |___|

6.3 Blood chemistry (date) |___|___| - |___|___| - |___|___|___|___|

6.3a Results:

Sodium (mmol/L) |___|___|___|
BUN (mg/dL) |___|___|
Creatinine (mg/dl) |___|___| . |___|
Albumin (g/dl) |___|___| . |___|
ALT (U/L) |___|___|___|___|
AST (U/L) |___|___|___|___|
Bilirubin (mg/dl) |___|___| . |___|
GGT (U/L) |___|___| . |___|
Glucose
Amylase |___|___| . |___|
Lipase |___|___| . |___|
Glucose (mg/dl) |___|___|
CO_2 |___|___|

Calcium(mg/dl) |___|___|
Chloride (mEq/L)

SECTION 7: DAILY ANTIBIOTICS AND OTHER MEDICATIONS USED AFTER THE DIAGNOSIS OF HAP

This section includes data on daily antibiotics and other medication use from the day of HAP diagnosis through the date of discharge or 28 days after the last dose of P/T or comparator HAP appropriate antibiotic(s), whichever comes first

(Note: CRNs will use the below table (template) to collect data on antibiotic(s) and other medications administered. (The list includes frequently used inpatient antibiotics in addition to P/T or comparator HAP appropriate antibiotics)

1 = Not Applicable
2 = Amikacin
3 = Amoxicillin
4 = Amoxicillin/clavulanate
5 = Ampicillin
6 = Ampicillin/sulbactam
7 = Azithromycin
8 = Aztreonam
9 = Cefazolin
10 = Cefepime
11 = Cefotetan
12 = Cefoxitin
13 = Ceftazidime
14 = Ceftriaxone
15 = Chloramphenicol
16 = Clarithromycin
17 = Clindamycin
18 = Doxycycline
19 = Erythromycin
20 = Gentamicin
21 = Imipenem
22 = Meropenem
23 = Metronidazole (flagyl)
24 = Mezlocillin
25 = Nafcillin
26 = Netilmicin
27 = Nitrofurantoin
28 = Penicillin
29 = Piperacillin
30 = Piperacillin/tazobactam
31 = Ticarcillin
32 = Ticarcillin/clavulanate
33 = TMP-SMX (bactrim)
34 = Tobramycin
35 = Vancomycin
36 = Ciprofloxacin
37 = Levofloxacin
38 = Imipenem/Cilastatin
39 = Linezolid
40 = Cefotaxime
41 = Other: specify:_____
42 = Other: specify:_____
43 = Other: specify:_____
44 = Other: specify:_____

Day of HAP diagnosis	Antibiotic(s) & other medications	Dose (total mg)	Frequency
Day 0* Date |___|___| - |___|___| - |___|___|___|___|	|___|___| |___|___| |___|___|		
Day 1 Date |___|___| - |___|___| - |___|___|___|___|	|___|___| |___|___| |___|___|		
Day 2 Date |___|___| - |___|___| - |___|___|___|___|	|___|___| |___|___| |___|___|		
...	|___|___| |___|___| |___|___|		
Day 27 Date |___|___| - |___|___| - |___|___|___|___|	|___|___| |___|___| |___|___|		
Day 28** Date |___|___| - |___|___| - |___|___|___|___|	|___|___| |___|___| |___|___|		

*Diagnosis of HAP and initiation of antibiotics for HAP);
** Date of discharge or 28 days after the last dose of P/T or comparator HAP appropriate antibiotic(s), whichever comes first

SECTION 8: ADDITIONAL HOSPITALIZATION DATA AFTER THE DIAGNOSIS OF HAP

This section includes additional hospitalization data after the diagnosis of HAP

8.1 Did the patient require ICU admission during the hospitalization after the diagnosis of HAP? |___|
1 = Yes
2 = No
9 = Unknown

8.1a If yes: Date of ICU admit (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|
Date of ICU discharge (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

8.2 Did the patient require a tracheostomy after the diagnosis of HAP? |___|
1 = Yes
2 = No
9 = Unknown

8.2a If yes: date of the procedure (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

8.3 Did the patient require endotracheal intubation after the diagnosis of HAP?
1 = Yes
2 = No
9 = Unknown

8.3a If yes: Date of intubation: |___|___| - |___|___| - |___|___|___|___|
Date of extubation: |___|___| - |___|___| - |___|___|___|___|

8.4 Did the patient require ventilator support during hospitalization after the diagnosis of HAP? |___|
1 = Yes
2 = No
9 = Unknown

8.4a If yes: Mechanical ventilation support started (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|
Mechanical ventilation out (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

8.5 Did the patient die within 30 days of first day of the study medication?

|___|
1 = Yes (document the date of death)
2 = No
9 = Unknown (prompt to query the National Death Index to find out if the patient died within the 30-day of HAP treatment initiation)

8.5a Date of death (mm/dd/yyyy) |___|___| - |___|___| - |___|___|___|___|

8.5b Cause of death as documented in the chart:_____

SECTION 9: DAILY LOG OF NEW MEDICAL CONDITIONS

This section includes data on all untoward medical events from initiation of P/T or comparator HAP appropriate antibiotics through the date of discharge or 28 days after the last dose of P/T or comparator HAP appropriate antibiotic(s), whichever comes first

Day _____ of HAP treatment initiation Date |___|___| - |___|___| - |___|___|___|___|

Documented untoward medical events	Physician documentation implies relatedness to HAP antibiotics [Indicate the name(s)]	Supporting Lab/clinical Data	Supporting radiographic data	Physician documentation that event(s) result in untoward condition e.g., death, prolongation of hospitalization, persistent disability etc
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				
Untoward event:(specify):_____				

SECTION 10: DATA ON EFFECTIVENESS OF HAP THERAPY & TIME OF DISCHARGE

This section includes data on effectiveness of HAP therapy and time of discharge

10.1 Did the physician document outcome/ progress of HAP therapy within 14 days of treatment initiation? |___|

1 = Yes
2 = No
9 = Unknown

If yes, please indicate dates when the physician documented outcome/progress of HAP therapy (up to 14 days of HAP treatment initiation):

10.1a Dates of documentation (mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|
10.1b Dates of documentation (mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|
10.1c Dates of documentation (mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|
10.1d Dates of documentation (mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|
10.1e Dates of documentation (mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|

Note: Please make copies of the relevant physician notes (documented on the above dates) for adjudication of treatment outcome

10.2 Assessment of HAP therapy (based on the physician's daily progress notes) within 14 days of HAP treatment initiation:

Patient clinically improved: |___|
Patient clinically did not improve: |___|

10.3 Where was the patient discharged to? | ____ |

1 = Home
2 = Chronic care facility
3 = Another hospital
4 = Inpatient rehabilitation center
5 = Still in the hospital at 30 days after HAP diagnosis
6 = other (Specify: _____)
9 = Unknown

10.3a Date of discharge(mm/dd/yyyyy) |___|___| - |___|___| - |___|___|___|___|

End of chart review and data abstraction