NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-World Study of Ceftazidime-Avibactam to Characterize the Usage in Clinical Practice
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Date	12 April 2022
Active substance	ceftazidime-avibactam, ACT: J01DD52
Medicinal product	Zavicefta® (ceftazidime-avibactam)
Research question and objectives	The main objective of this observational study is to describe the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice in China.
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2. LIST OF ABBREVIATIONS

Abbreviation	Term
A-aDo_2	alveolar-arterial oxygen gradient
ABG	arterial blood gas
AE	adverse event
AEM	adverse event monitoring
AIDS	Acquired Immunodeficiency Syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation II
APS	Total Acute Physiology Score
CAI	community-acquired infection
CARSS	China Antimicrobial Resistance Surveillance System
CE	clinically evaluable
CHINET	China Antimicrobial Surveillance Network
CI	confidence interval
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
CP	carbapenemase-producing
CRE	carbapenem-resistant *Enterobacteriaceae*
CRF	case report form
CRO	contract research organization
CRPA	carbapenemase-producing *Pseudomonas aeruginosa*
CRKP	carbapenem-resistant *Klebsiella pneumoniae*
CSA	clinical study agreement
CT	computed tomography
DCT	data collection tool
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCS	Glasgow Coma Scale
HA	hospital-acquired
HAI	hospital-acquired infection
HAP	hospital-acquired pneumonia
HCAI	healthcare-associated infection
HCO_3	bicarbonate
IAI	intra-abdominal infection
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LOS	length of stay
LTO	Limited Treatment Options

Abbreviation	Term
MIC	minimum inhibitory concentration
MDR	multi-drug resistant
MDR-GNB	Multidrug-resistant gram-negative bacilli
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mmHg	millimeter of mercury
MRI	magnetic resonance imaging
NI	non-interventional
NIS	non-interventional study
NP	nosocomial pneumonia
PaO_2	partial pressure of oxygen
PV	pharmacovigilance
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
VAP	ventilator-associated pneumonia
WHO	World Health Organization
XDR-GNB	Extensively drug-resistant gram-negative bacilli

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

- Real-World Study of Ceftazidime-Avibactam to Characterize the Usage in Clinical Practice

- Protocol Amendment 3, 12 April 2022

- Author: PPD , PharmD, PPD Pfizer, China; PPD MD PhD, PPD Pfizer, China; PPD MSc PPD Pfizer, China; PPD MD MSc PPD Pfizer, NYHQ.

Rationale and background

Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB) and extensively drug-resistant gram-negative bacilli (XDR-GNB) can be difficult to treat and are associated with high morbidity, mortality, and increased medical burden. This constitutes a serious threat to public health that there is an urgent need of new antibiotic agents with activity against MDR-GNB. Considering the limited cases studied in the clinical trials and the increasing post-approval use of ceftazidime-avibactam in clinical settings, it is necessary to understand the real-world use of ceftazidime-avibactam focusing on treatment of XDR-GNB infection, with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) as the most frequently reported pathogen.

Research Question and Objectives

The main objective of this observational study is to describe the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice in China.

Study design

This observational study will enroll approximately 450 in-patients among approximately 20 clinical research centers. Medical information and microbiological outcomes from hospitalized patients treated with ≥1 dose of ceftazidime-avibactam will be collected. The recruitment will last for approximately 6 months or until recruitment target is met. Medical information will be collected from the patients' medical records. Patients will be followed from the first dose of ceftazidime-avibactam until death, withdraw of the study,60 days following hospital discharge, whichever comes first. The clinical outcomes and microbiological outcomes will be evaluated at: 7 days, 14 days, 21 days, 30 days, 60 days, and end of treatment (EOT) after the first dose of ceftazidime-avibactam, if patients are not discharged prior to the next upcoming timepoint.

Population

Hospitalized patients treated with ≥1 dose of ceftazidime-avibactam at approximately 20 China clinical research centers.

Variables

- Exposure: ceftazidime-avibactam
- Key outcomes: clinical outcomes, microbiological outcomes, length of hospital stay, readmission, deaths and healthcare resource utilization
- Key covariates: Patient demographics, indications, baseline characteristics, infection source (hospital/ community) and history of antibiotic(s) exposure

Data sources

The study data source will be medical records from the participating clinical research centers. The microbiology isolates from enrolled patients, obtained through routine procedures (eg, centrifugation and purification) at the local lab of participating clinical research centers, will be stored and transported to a central lab, when available, following standard procedure. At the central lab, the pathogen identification and the sensitivity testing to common antibiotic drugs will be confirmed. Genotype characterization of carbapenem-resistant organisms will be performed. Central lab results will be collected for epidemiology purpose only and will not be sent back to participating clinical research centers. Transfer of microbiology isolates to the central lab will be done following local laws, regulations and Institutional Review Board/ Independent Ethics Committee (IRB/IEC) recommendations.

Study size

The study will enroll approximately 450 in-patients treated with ceftazidime-avibactam.

Data analysis

Patient demographics, baseline characteristics, clinical outcomes, microbiological outcomes, readmission rate, mortality rate, history of antiobiotic(s) treatment, and healthcare resource utilization will be summarized for hospitalized patients receiving ceftazidime-avibactam treatment. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP).

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1 Protocol V2.0	22 December 2021	Research methods; Management and reporting of adverse events; Annex	Minor change in Study design; Definitions of variables; Data abstraction schedule; Specify Safety reporting requirement for different data source	1. To describe more detail on study design and data abstraction instruction. 2. To update the safety reporting language to align with updated standard process. 3. To adhere to Pfizer internal versioning policy.
Amendment 2 Protocol V3.0	30 January 2022	Milestone; Research methods; Annex	Change in inclusion criteria; Definitions of setting; Recalculate study size; Definitions of analysis sets; Data abstraction schedule;	1. To include patients with at least one dose of CAZ-AVI 2. To update the setting with more details. 3. Due to the change of inclusion criteria, the study size was re-estimated and the title of data abstraction schedule was also updated. 4. To clarify the analysis sets based on updated population.
Protocol Amendment 3	12 April 2022	• Study title • Section 7 • Section 8 • Section 9 and 9.1.1 • Section 9.2 • Section 9.3 • Section 9.7.2, 9.7.3 • Section 13 • Annex	• Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document. In addition, changes have been made to section heading numbers, table cross-references, and reference listing where necessary, due to amendments detailed in this document. • Title: study title has been revised to better describe the purpose of the study • Rationale and background: the rationale and background section has been streamlined. • Research question and objectives: the description of primary and secondary objectives have been refined with no major changes. Recurrence due to the same infection within 30 days after treatment completion has been removed from the secondary objectives considering the local practice feasibility. Corresponding endpoints and estimands have been revised to reflect the changes made in study objectives and to specify the evaluation timepoints. • Study design: remove 'cured' from patient's follow-up period to be consistent with the primary objective of the study. Description of study design has been refined with no major changes. • Setting: the setting sections has been refined and replaced the term 'sites' to 'clinical research centers'. • Variables: data collection on Sequential Organ Failure Assessment (SOFA) has been added and the operational definition of Acute Physiology and Chronic Health Evaluation II (APACHE II) has been revised according to local clinical practice feasibility. APACHE II score is more difficult to obtain at standard clinical practice, thus included the collection of SOFA score to better evaluate disease severity of enrolled patients. • Source of infection: definition of hospital-acquired infection (HAI) and community-acquired infection (CAI) have been revised, and the description of healthcare-associated infection (HCAI) has been removed based on local clinical practice consideration. • Analysis of the primary and secondary endpoint: analysis on recurrence rate of index infection within 30 days after treatment completion has been removed, and the analysis on length of mechanical ventilation has been added to be consistent with the changes made in study objectives. Minor editorial changes have been made in other description of analysis of the primary endpoints with no major changes. • Annex 6: SOFA score has been added to the annex to reflect the changes made in variable section.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 July 2022
End of data collection	28 February 2023 or later, if the sample size is not reached
Interim report 1	once the clinical outcomes at end of treatment (EOT) are collected for 200 patients in the case report form (CRF)
Final study report	30 September 2023

7. RATIONALE AND BACKGROUND

With extensive use of carbapenems, the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP strains are increasing. The 2014-2019 antimicrobial resistance surveillance report issued by China Antimicrobial Resistance Surveillance System (CARSS) pointed out that the detection rate of CRKP continued to increase from 6.4% in 2014 to 10.9% in 2019.[1] According to China Antimicrobial Surveillance Network (CHINET) 2020 data, the resistance rates of *Klebsiella pneumoniae* to imipenem and meropenem increased from 3.0% and 2.9% in 2005 to 23.2% and 24.2% in 2020, respectively.[2]

Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB and extensively drug-resistant gram-negative bacilli (XDR-GNB can be difficult to treat and are associated with high morbidity, mortality, and increased medical burden. This constitutes a serious threat to public health that there is an urgent need of new antibiotic agents with activity against MDR-GNB. According to a retrospective analysis among patients with intra-abdominal infections (cIAI) in China, *Escherichia coli* (34.5%) and *Klebsiella pneumoniae* (21.2%) were the leading pathogens in patients with hospital-acquired (HA) cIAI. Most carbapenem-resistant *Enterobacteriaceae* (CRE) isolates carried bla_{KPC} (80.9%), followed by bla_{NMD} (19.1%).[3] Studies in China demonstrated a HA-cIAI rate of 3.22%-5.22% and a hospital-acquired pneumonia (HAP) rate of 1.76% to 1.94%.[4-5] HAP has been associated with multidrug-resistant gram-negative bacterial infection among patients in intensive care units or receiving mechanical ventilation.[6] Inadequate empiric antibiotic therapy has been considered by several epidemiological studies as one of the risk factors of in-hospital deaths, and the failure of initial empiric antibiotic therapy was associated with higher morbidity, mortality, and increased medical burden. [7-11]

Carbapenems have been used as the last resort treatment for gram-negative bacteria causing infections. The ever increasing number of infections caused by CRE and carbapenem-resistant pseudomonas aeruginosa (CRPA) posed a major therapeutic challenge that there is an urgent need of novel antibiotics agents with activity against MDR-GNB. [12-13] Zavicefta® (ceftazidime-avibactam), which inhibits the activities of Ambler classes A and C β-lactamase (including the *Klebsiella pneumoniae* carbapenemase, KPC), was approved in China on 21 May 2019 for the treatment of cIAI, HAP/ventilator-associated pneumonia (VAP), and infections with limited options caused by *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa* in adult patients. [14] Zavicefta® is a unique combination of ceftazidime and the novel β-lactamase inhibitor avibactam. Ceftazidime exerts its antibacterial effect by binding to penicillin-binding proteins, thereby inhibiting peptidoglycan crosslinking during cell wall syntheses, leading to bacterial cell lysis and death.

Ceftazidime-avibactam efficacy have been assessed in Phase II trials and in non-inferiority Phase III trials. Ceftazidime-avibactam plus metronidazole was compared to meropenem in patients with cIAI, results demonstrated that ceftazidime-avibactam was non-inferior for clinical cure rate for IAI; Ceftazidime-avibactam was compared to meropenem in patients with HAP including VAP, results showed that ceftazidime-avibactam was non-inferior for

clinical cure rate. [15-18] Ceftazidime-avibactam in vitro activity against CRE has been shown. Previous studies have reported that ceftazidime-avibactam has higher clinical success in CRKP infections, including urinary tract infections, pneumonia, and bloodstream infections. However, there is limited evidence of ceftazidime-avibactam in efficacy in central nervous system infections that future studies are needed. [19-25] Results from 7 Phase II and Phase III clinical trials among 2024 adult patients treated with ceftazidime-avibactam showed that most common adverse reactions occurring in ≥5% of patients were positive Coombs direct tests, nausea, and diarrhea. Nausea and diarrhea were usually mild or moderate in intensity.[14]

Considering the limited cases studied in clinical trials and the increasing post-approval use of ceftazidime-avibactam in clinical settings, it is necessary to understand the real-world use pattern and effectiveness of ceftazidime-avibactam in clinical practice. This study further collects the isolates from enrolled patients to understand the distribution, antimicrobial susceptibility pattern, and genotype characteristics of carbapenem-resistant organisms. Findings from this study can provide the basis on ceftazidime-avibactam treatment of XDR-GNB infection, including CRE, in clinical practice.

8. RESEARCH QUESTION AND OBJECTIVES

The main objective of this observational study is to describe the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice in China.

The primary objectives of this study are to:

- Describe the clinical outcomes of patients (i.e., treatment success, failure, or indeterminate) at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at end of treatment (EOT) (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.
- Describe the microbiological outcomes of patients at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.
- Describe the real-world usageof ceftazidime-avibactam at clinical practice, including patient baseline characteristics, type of infection, source of infection, etc.
- Describe the microbiological features of isolated strains at baseline, including pathogen identification, distribution, susceptibility of ceftazidime-avibactam and other common antibiotic drugs including carbapenem-resistant organisms, and genotype characteristics of carbapenem-resistant organisms.

The secondary objectives of this study are to:

- Describe the antibiotic treatment administered to the enrolled patients, including the dosage, frequency, duration (start and end dates) of ceftazidime-avibactam, and combination medications with ceftazidime-avibactam.
- Describe the in-hospital length of stay (LOS), LOS in ICU and healthcare resource utilization in patients treated with ceftazidime-avibactam.
- Describe the readmission rate due to the recurrence of infection happened in the same location 30 and 60 days after discharge.
- Determine the in-hospital all-cause mortality.

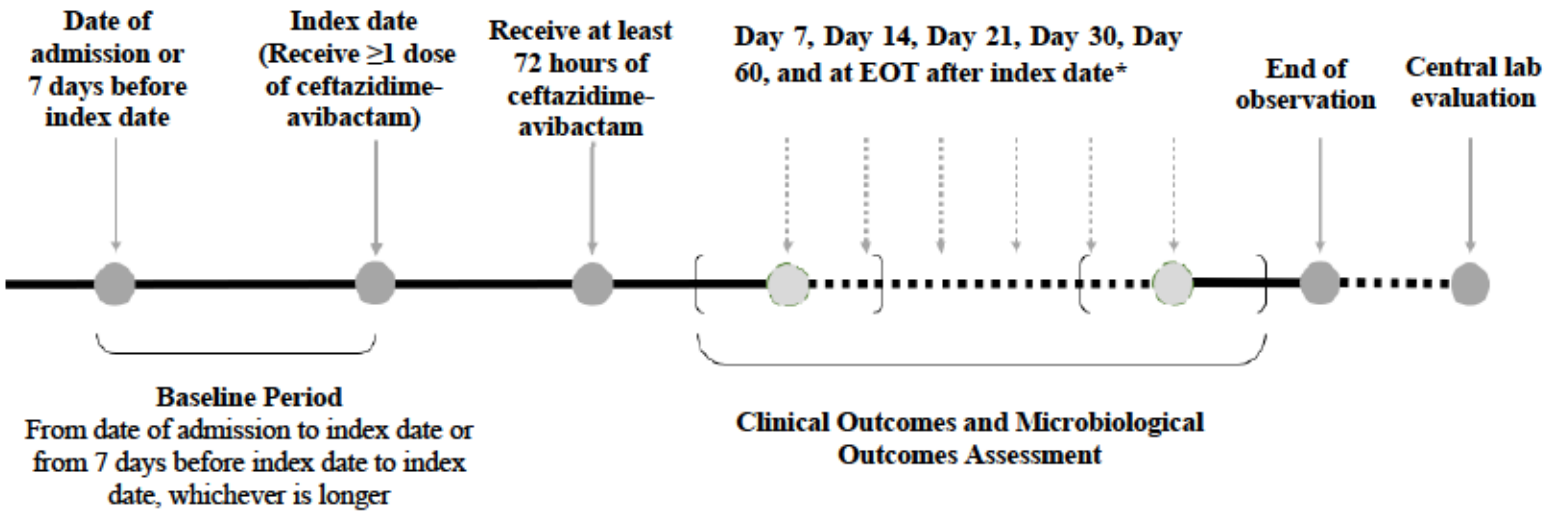
9. RESEARCH METHODS

9.1. Study design

This is a multicenter, observational study aiming to examine the real-world usage, effectiveness and microbiological features of ceftazidime-avibactam in clinical practice at approximately 20 clinical research centers in China. Approximately 450 hospitalized patients receiving ≥1 dose of ceftazidime-avibactam from 01 July 2022 to 31 December 2022 will be enrolled. The recruitment will last for approximately 6 months or until recruitment target is met. Eligible patients are adult patients who have been treated with ≥1 dose of ceftazidime-avibactam during hospitalization. Each patient will be only included in the study once.

Medical information will be collected from the patients' medical records. Patients will be followed from the first dose of ceftazidime-avibactam until death, withdraw of the study, 60 days following hospital discharge, whichever comes first. The clinical outcomes and microbiological outcomes will be evaluated at: 7 days, 14 days, 21 days, 30 days, 60 days, and EOT after the first dose of ceftazidime-avibactam, if patients are not discharged prior to the next upcoming timepoint. The clinical and microbiological outcomes will be assessed by the investigator and recorded in case report form (CRF).

The study data collection and assessment schedule are described in Figure 1. All assessments described in this non-interventional protocol are part of China clinical practice or treatment guidelines.



* Outcomes will be evaluated at each timepoint if patients are not discharged prior to the next upcoming timepoint. Three days identification window will be applied before and after each time points.

Figure 1 Study design

9.1.1. Endpoints and estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Describe the clinical outcomes of patients (i.e., treatment success, failure, or indeterminate) at Day 7 (± 3 days), Day 14 (± 3 days), Day 21(± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.	• Clinical outcome	• The clinical success rate at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.
Describe the microbiological outcomes of patients at Day 7 (± 3 days), Day 14 (± 3 days), Day 21 (± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam treatment initiation, if patients are not discharged prior to the next upcoming timepoint.	• Microbiological outcome	• The microbiological success rate at Day 7 (± 3 days), Day 14 (± 3 days), Day 21(± 3 days), Day 30 (± 3 days), Day 60 (± 3 days), and at EOT (± 3 days) after ceftazidime-avibactam initiation, if patients are not discharged prior to the next upcoming timepoint.
Describe the real-world usage of ceftazidime-avibactam at clinical practice, including patient baseline characteristics, type of infection, source of infection, etc.	• • Baseline characteristics • Indication • Source of infection	• The number and percentage of patients by demographic characteristics, indication, type and source of infection.
Describe the microbiological features of isolated strains, including pathogen identification, distribution, susceptibility of ceftazidime-avibactam and other common antibiotic drugs including carbapenem-resistant organisms, and genotype characteristics of carbapenem-resistant organisms.	At baseline: • Pathogen identification • Drug susceptibility • Genotype and type of enzyme	• The number and percentage of isolated strains. • Susceptibility and resistance rate of ceftazidime-avibactam and other common antibiotic drugs • The number and percentage of carbapenem-resistant organisms
Secondary:	**Secondary:**	**Secondary:**

Describe the antibiotic treatment administrated to the enrolled patients, including the dosage, frequency, duration of ceftazidime-avibactam, and combination medications with ceftazidime-avibactam	• Dose • Frequency • Duration of expose (start and end dates) • Combination therapy	• The number and percentage of patients treated in different dose and frequency of ceftazidime-avibactam. • The descriptive statistics on the duration of exposure to ceftazidime-avibactam. • The number and percentage of patients receiving combination therapy with ceftazidime-avibactam. • The number and percentage of patients in each combination therapy with ceftazidime-avibactam.
Describe the in-hospital LOS, LOS in ICU and healthcare resource utilization in patients treated with ceftazidime-avibactam.	• LOS • LOS in ICU • Admission diagnosis • Discharge diagnosis • Concomitant procedures • Mechanical ventilation	• Descriptive statistics of LOS and ICU LOS. • The number and percentage of patients by different admission and discharge diagnosis. • The number and percentage of patients with invasive procedures, source of infection management, dialysis, surgery, etc • Length of mechanical ventilation
Describe the readmission rate due to the recurrence of infection happened in the same location 30 and 60 days after discharge.	• Readmission	• The percentage of patients with any readmission due to recurrence of infection happened in the same location within 30 and 60 days after discharge.
Determine the in-hospital all-cause mortality.	• Death	• The percentage of patients treated by ceftazidime-avibactam died during hospitalization.

9.2. Setting

Patients will be enrolled from approximately 20 clinical research centers in China. Clinical research centers will be evaluated and then selected based on the capability of conducting the study.

Investigators will start eligibility screening and recruitment from adult patients who received ceftazidime-avibactam treatment. Patients who provide written informed consent and who fulfill the eligibility criteria will be enrolled in the study. Eligibility criteria for patient enrollment in the study have been summarized in Section 9.2.1 and Section 9.2.2. Patients participating in clinical trials are excluded from this study because protocol-driven activities may be outside of normal practice and could confound effectiveness assessments. Each patient will be only included in the study once.

The index hospitalization will be defined as patients' first hospitalization met the eligible criteria.

The index date will be defined as the date of patients initiated ⩾1 dose of ceftazidime-avibactam treatment during the index hospitalization.

The enrollment period is from 01 July 2022 to 31 December 2022 or later if the sample size is not reached. Patients who initiated treatment with ≥1 dose of ceftazidime-avibactam during enrollment period will be enrolled.

The data collection period is from 01 July 2022 to 28 February 2023 or later if the sample size is not reached, patient's information will be filled in CRF during data collection period.

The baseline period will be defined as from date of admission to index date or from 7 days before index date to index date, whichever is longer. When patients have multiple records for variables of interest during the baseline period, the one closest to the index date will be selected.

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Initiate ≥1 dose of ceftazidime-avibactam during hospitalization.
2. Aged ≥ 18 years old at the time of the informed consent signature.
3. Provide signed informed consent.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Are enrolled in any clinical trial, including enrollment in non-interventional studies.
2. Pregnant women.

9.2.3. Study population

Hospitalized patients treated with ≥1 dose of ceftazidime-avibactam at approximately 20 China clinical research centers.

9.2.4. Medical information collection

Patient medical information will be collected as recorded in patient's medical record (e.g., patient information, baseline characteristics [disease characteristics and risk factors], infection status and exposure variables).

9.2.5. Baseline assessment

The baseline assessment of this study is the last assessment before the start of ceftazidime-avibactam treatment.

9.2.6. Medical record review

Investigators will record the study data in CRF based on the medical record of the enrolled patient. The investigators will assess the clinical outcome and microbiological outcome and record on CRF.

9.2.7. Central lab assessment

The microbiology isolates from enrolled patients, obtained through routine procedures (e.g., centrifugation and purification) at the local lab of participating clinical research centers, will be stored and transported to a central lab, when available, following standard procedure. At the central lab, the pathogen identification and the susceptibility testing to common antibiotic drugs will be confirmed. Genotype characterization of carbapenem-resistant organisms will be performed. Central lab results will be collected for epidemiology purpose only and will not be sent back to participating clinical research centers. Transfer of microbiology isolates to the central lab will be done following local laws, regulations and Institutional Review Board/ Independent Ethics Committee (IRB/IEC) recommendations.

- Strain identification

The central lab will use mass spectrometry or other methods to re-identify CRE and CRPA strains.

- Drug susceptibility test

According to the latest version of the Clinical and Laboratory Standards Institute (CLSI) document, the central lab uses the broth micro-dilution method to determine the minimum inhibitory concentration (MIC) of the CRE and CRPA strain against clinically commonly used antibacterial drugs, including at least the following drugs: amikacin, ceftazidime, meropenem, colistin, tigecycline, ceftazidime-avibactam and ciprofloxacin etc.

- Strain gene and carbapenemase test

The central lab will use molecular biology method to detect carbapenemase genes (including bla_{KPC}, bla_{NDM}, bla_{IPM}, bla_{VIM} and bla_{OXA-48}, etc).

The data generated by those testing will be included in the final analyses report for the study.

9.2.8. Data collection date

This study will collect at least 280 patients with clinical outcome and 220 patients with microbiological outcome for the calculation of clinical success rate and microbiological success rate. The sample size calculation is detailed in Section 9.4.

If there are not enough number of patients with clinical and microbiological outcome collected before the planned data collection end date, the data collection end data will be postponed to enroll more patients.

If the required number of patients with clinical and microbiological outcome can be collected before the planned data collection end date, the end date will be moved forward. If the total number of patients does not reach 450, the end date will be set to a date when at least 450 patients can be enrolled.

9.3. Variables

Table 1 shows the list of exposures, outcomes, and other variables to be collected including risk factors, comorbidities, combination medications and concomitant procedures. The details on data abstraction schedule are provided in ANNEX 8.

Table 1. List of variables and definitions

Variable	Role	Operational definition
Informed consent	Required for participation	Signed informed consent form submitted to study personnel.
Age	Baseline characteristic	As recorded in medical record. Age at ICF sign-off.
Sex	Baseline characteristic	As recorded in medical record.
Ward of admission	Baseline characteristic	As recorded in medical record
Employment	Baseline characteristic	As recorded in medical record.
Height, weight	Baseline characteristic	Height and weight as recorded in medical record.
Alcohol consumption	Baseline characteristic	Alcohol consumption as recorded in medical record.
Smoking	Baseline characteristic	Smoking frequency as recorded in medical record.
Comorbidity	Baseline characteristic	Assessed the baseline by investigator. See Section 9.3.1.
Recent hospitalization	Baseline characteristic	Within 90 days prior to date of admission for the current hospitalization, date of admission and discharge, reason for hospitalization.
History of antibiotic exposure	Baseline characteristic	Antibiotic(s) used within 90 days prior to date of admission for the current hospitalization.
Recent healthcare procedure	Baseline characteristic	Within the 30 days before ceftazidime-avibactam initiation.
Pre-treatment disease severity (APACHE II, SOFA, Pitt Bacteremia Score, or other prognostic assessment)	Baseline characteristic	Measured at time of receiving 1st dose of ceftazidime-avibactam treatment. For ICU patients, record the APACHE II and SOFA score; for patients admitted to other wards, APCHE II and SOFA are recorded as available. See Section 9.3.2 for APACHE II and SOFA score. See Section 9.3.3 for Pitt Bacteremia Score. See ANNEX 6 for SOFA score.
Admission diagnosis	Baseline characteristic	Diagnosis at the start of the hospitalization as recorded in medical record.
Source of infection	Baseline characteristic / sub-group identifier	As recorded in medical record. See Section 9.3.4.
Indication for ceftazidime-avibactam	Baseline characteristic / sub-group identifier	Site of infection (organ) and type of infection; date of diagnosis. See Section 9.3.5.

Table 1. List of variables and definitions

Variable	Role	Operational definition
Pre-treatment microbiology sample	Baseline characteristic	Microbiological culture(s) of current infection before ceftazidime-avibactam initiation (sample date(s), sample site(s)).
Pre-treatment microbiology results	Baseline characteristic / sub-group identifier	Results from microbiological culture (method of testing, identified pathogen(s), susceptibility, MDR) before ceftazidime-avibactam initiation. See Section 9.3.6.
Prior antibiotic therapy	Baseline characteristic	Antibiotic(s) used for current infection before ceftazidime-avibactam initiation. Dates of administration, dose(s), frequency, duration, route of administration, reason of treatment discontinuation, empiric or definitive therapy (See Section 9.3.7).
Ceftazidime-avibactam	Exposure	Dates of administration, dose(s), frequency, duration, reason of treatment discontinuation, empiric or definitive therapy (See Section 9.3.7).
Combination antibiotic therapy	Exposure /sub-group identifier	Name(s) of antibiotic(s) used concurrently with ceftazidime-avibactam, dates of administration, dose(s), frequency, duration, route of administration, empiric or definitive therapy (See Section 9.3.7).
Microbiology sample after treatment initiation	Outcome	Microbiological culture(s) after ceftazidime-avibactam initiation (sample date, sample site).
Microbiology results after treatment initiation	Outcome	Results from microbiological culture after treatment initiation (method of testing, identified pathogen(s), susceptibility, MDR).
Discharge diagnosis	Outcome	Diagnosis when discharge.
Clinical outcome	Outcome	Success, failure, and indeterminate. See Section 9.3.8.
Microbiological outcome	Outcome	Success, failure, emergent infections and unevaluable. See Section 9.3.8.
Death (all-cause mortality) during hospitalization	Outcome	Death during hospitalization after start of ceftazidime-avibactam treatment. Date and all-cause death will be collected.
Length of hospital stay	Outcome	Date(s) of hospital admission, date(s) of hospital discharge.
Admission date	Outcome	As recorded in medical record.
Discharge date	Outcome	As recorded in medical record.
Length of ICU stay	Outcome	Date(s) of ICU admission, date(s) of ICU discharge.
ICU admission date	Outcome	As recorded in medical record.
ICU discharge date	Outcome	As recorded in medical record.
Hospital readmission	Outcome	Hospital readmission for the recurrence of infection happened in the same location 30 and 60 days after discharge; reason for readmission, date of readmission.

Table 1. List of variables and definitions

Variable	Role	Operational definition
Healthcare resource utilization	Outcome	Detailed list of therapeutic and diagnostic procedures (mechanical ventilation, dialysis, computed tomography [CT], magnetic resonance imaging [MRI], invasive procedures, other) and dates of procedures.
Hospital ward	Outcome	All wards attended, ward of admission, ward of diagnosis (surgical, medical, oncology, hematology, infectious disease, ICU, other).
Physician specialty	Site characteristic	Medical specialty of the treating physician (e.g., infectious disease, surgical).

9.3.1. Deyo-Charlson Comorbidity Index

Comorbidity related information will be collected from the medical records for the patients (e.g., solid tumor [yes/no], blood system disorders, diabetes, hypertension, chronic obstructive pulmonary disease, renal insufficiency, etc.). Deyo-Charlson Comorbidity Index will be used to quantify comorbidity, assessed by the investigator. Details of Deyo-Charlson Comorbidity Index calculation are provided in ANNEX 4.

9.3.2. APACHE II score and SOFA score

For ICU patients, APACHE II and SOFA score will be collected as per ICU routine practice. For patients admitted to ward other than ICU for whom APCHE II and SOFA score are not present in the medical records, it will not be calculated for this study. Details of APACHE II score and SOFA score calculation are provided in ANNEX 5 and ANNEX 6.

9.3.3. Pitt Bacteremia Score

The disease severity will also be quantified by Pitt Bacteremia Score. The information will be collected from medical records of patients. Details of Pitt Bacteremia Score calculation are provided in ANNEX 7.

9.3.4. Source of infection

Hospital-acquired infection (HAI): are nosocomially acquired infections that are typically not present or might not be incubating at the time of admission. These infections are usually acquired after hospitalization and manifest 48 hours after hospital admission. [25]

Community-acquired infection (CAI): are infections that are contracted outside of a hospital or might be incubating at the time of admission,diagnosed within 48 hours of hospital admission without any previous health care encounter. [25]

9.3.5. Indication

Indications includes:

- cIAI: a clinical diagnosis of IAI (i.e., peritonitis, intraperitoneal abscess, liver abscess, pancreatic abscess, appendicitis, diverticulitis, gastric or duodenal ulcers, cholangitis, cholecystitis) and evidence of involvement of more than 1 organ, causing peritonitis and requiring both surgical and antibiotic therapy (beyond 24 hours regimen), as registered in the medical record or record. Hospital-acquired cIAI will be defined as cIAI that develops at least 48 hours after hospital admission. Healthcare-associated cIAI will be defined as cIAI that occurs while receiving treatment for other conditions in a healthcare facility (e.g., nursing home, long-term care, hemodialysis clinic, hospital) within 3 months prior to the inpatient admission or during the inpatient admission.[26]
- HAP/VAP: a clinical diagnosis of pneumonia and evidence of nosocomial origin as registered in the medical record. HAP is defined as pneumonia that occurs at least 48 hours after hospital admission; VAP is defined as pneumonia that occurs at least 48 hours after endotracheal intubation or tracheostomy.
- Limited Treatment Options (LTO) indication: any infection with limited treatment options, based upon clinical or microbiological evidence.

The site of infection refers to the original organ of the infection (e.g., appendix, bladder, kidney, large intestine, lungs, liver, gallbladder, pancreas, peritoneum small intestine, stomach, urethra, other).

9.3.6. Microbiological test result

Pathogen susceptibility: susceptibility information will be collected for the isolated pathogens (e.g., aminoglycosides, β-lactams, carbapenems, cephalosporins, glycopeptides, macrolides, oxazolidinones, penicillins, β-lactamase inhibitors, quinolones, tetracyclines, other). Sensitivity to each antibiotic (susceptible, intermediate, resistant) will be collected. For CRE strains, the corresponding enzyme type and genotype monitoring results from local lab will also be collected.

Multidrug-resistance: The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories, excluding antibiotic classes to which the pathogen is intrinsically resistant.[27]

Carbapenem resistance is define as isolates resistant to any of the carbapenems of imipenem, meropenem, ertapenem, or doripenem.

9.3.7. Empiric therapy and definitive therapy

The empiric or definitive usage of ceftazidime-avibactam will be recorded by investigators based on clinical practice and medical records. Empiric therapy will be defined as therapy employed prior to release of microbiological test results (pathogen identified), whereas definitive therapy will be defined as therapy given after release of microbiological test results (pathogen identified).

9.3.8. Clinical and microbiological outcome evaluation

The evaluation criteria of clinical and microbiological outcome is described in ANNEX 3.

9.4. Data sources

The study data source will be medical records from the clinical research centres and microbiological result from the central lab.

The information from medical record will be recorded by the investigator in electronic CRF (eCRF). Variables and data abstracted from medical record are described in Table 1.

Pre-treatment microbiology sample and result, and post-treatment microbiology sample and result will be collected from laboratory records when available, and microbiological outcome and the failure reason.

The microbiological outcome and the failure reason will be obtained from central lab investigator assessment.

9.5. Study size

Sample size for this study was calculated with the goal of maximizing precision (confidence interval [CI]) when estimating clinical and microbiological treatment success. 450 eligible patients will be enrolled.

Clinical Success Assumptions:

- Considering all data lost due to all kinds of reasons, 62.5% of eligible patients are assessable for clinical outcome (success or failure).
- 65% of the assessable patients experience clinical treatment success.

Microbiological Success Assumptions:

- Considering all data lost due to all kinds of reasons, 50% of eligible patients are assessable for microbiological outcome.
- 75% of the assessable patients experience microbiological success.

Table 2 displays the precision of each estimate (95% CI), for different rate of clinical and microbiological success and sample sizes ranging from 200 to 350 evaluable patients. Assuming clinical success rate is 65% and 280 patients (about 62.5% of 450 patients) are evaluable after enrolling 450 eligible patients, the precision of clinical success rate is 59.4% and 70.6%, i.e., the width of 95% CI is 11.2%. Assuming microbiological success rate is 75% and 220 patients (about 50% of 450 patients) are evaluable after enrolling 450 eligible patients, the precision of microbiological success rate is 69.3% and 80.7%, i.e., the width of 95% CI is 11.4%.

Table 2. Precision of the estimate (95% CI) for different clinical and microbiological success rates and number of evaluable patients

Number of Evaluable Patients	Clinical and Microbiological Success Rate (%)				
	60	65	70	75	80
200	(53.2, 66.8)	(58.4, 71.6)	(63.6, 76.4)	(69.0, 81.0)	(74.5, 85.5)
220	(53.5, 66.5)	(58.7, 71.3)	(63.9, 76.1)	**(69.3, 80.7)**	(74.7, 85.3)
240	(53.8, 66.2)	(59.0, 71.0)	(64.2, 75.8)	(69.5, 80.5)	(74.9, 85.1)
260	(54.0, 66.0)	(59.2, 70.8)	(64.4, 75.6)	(69.7, 80.3)	(75.1, 84.9)
280	(54.3, 65.7)	**(59.4, 70.6)**	(64.6, 75.4)	(69.9, 80.1)	(75.3, 84.7)
300	(54.5, 65.5)	(59.6, 70.4)	(64.8, 75.2)	(70.1, 79.9)	(75.5, 84.5)
320	(54.6, 65.4)	(59.8, 70.2)	(65.0, 75.0)	(70.3, 79.4)	(75.6, 84.4)
350	(54.9, 65.1)	(60.0, 70.0)	(65.2, 74.8)	(70.5, 79.5)	(75.8, 84.2)

9.6. Data management

Detailed data management requirement and tools are documented in the Data Management Plan.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidance.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRFs may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRFs, and for which the CRFs will stand as the source document.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Analysis sets

- Full Analysis Set (FAS):

  The FAS will include all enrolled patients. The enrolled patients should meet the criteria in Section 9.2.1 and Section 9.2.2.

- Clinically Evaluable (CE) Analysis Set:

The CE set will include all patients from the FAS with at least 72 hours use of ceftazidime-avibactam and at least 1 non-missing clinical evaluation outcome.

- Microbiologically Evaluable (ME) Analysis Set:

  The ME set will include all patients from the FAS with at least 72 hours use of ceftazidime-avibactam and at least 1 non-missing microbiological evaluation outcome.

9.7.2. Analysis of the primary endpoint

The clinical outcome will be summarized in CE Analysis Set.

The microbiological outcome and its subcategory will be summarized overall and by pathogenin ME Analysis Set Analysis Set. The microbiological outcome will also be summarized based on the evaluation by site investigator and the central lab, respectively.

The microbiological failure reason will be summarized in ME Analysis Set.

Indication, type of infection, site of infection and source of infection for the initial ceftazidime-avibactam will be summarized in the FAS.

The identified pathogen, susceptibility, genotype and type of enzyme at baseline will be summarized in FAS.

9.7.3. Analysis of the secondary endpoint

Secondary endpoints will be summarized in both FAS and CE Analysis Set.

Summarize the dose and frequency, of ceftazidime-avibactam. Summarize the combination therapy with ceftazidime-avibactam by therapy name.

The LOS and ICU LOS will be summarized using descriptive statistics.

The admission diagnosis, discharge diagnosis and baseline diagnosis at initiating ceftazidime-avibactam will be summarized.

The concomitant procedures will be summarized by preferred term defined by Medical Dictionary for Regulatory Activities (MedDRA).

The length of mechanical ventilation will be summarized using descriptive statistics.

The rate of readmission due to recurrence of infection happened in the same location 30 and 60 days after discharge will be summarized.

The mortality in hospital will be summarized.

9.7.4. Analysis of the covariates

All covariates will be summarized using descriptive statistics.

9.8. Quality control

The investigator must permit study related monitoring, audits, IRB/IEC review, and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, and all applicable regulatory requirements.

Monitoring details describing strategy, including definition of study critical data items and processes, methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on site monitoring), are provided in the Data Management Plan, and Monitoring and Data Quality Oversight Plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The investigator(s) will notify the sponsor or its agents immediately of any findings about the quality of the study.

9.9. Limitations of the research methods

There are some limitations in this study. First of all, because data will be collected via medical record, it is likely that some of the requested information will be missing, incomplete, or inaccurate. Safeguards against missing and inaccurate data will be employed throughout the research process, which include choosing qualified sites, ensuring primary variables of interest that are routinely collected, using validated eCRFs and CRF completion guideline, when appropriate.

Secondly, it is possible that this study will have a selection bias. For example, patients treated in selected tertiary hospitals in our study may likely to have more severe diseases and received better supportive care compared to those who attend smaller tertiary care facilities or lower level care facilities. These may limit the generalizability of study results to represent the use of ceftazidime-avibactam in China. Therefore, our study results will be interpreted within study setting context. Also, baseline characteristics of enrolled patients in the study will be summarized and compared to other studies to evaluate the potential effects.

Finally, outcome misclassification may occur in this study. Patients will be followed for 30 and 60 days after hospital discharge. It will be difficult to distinguish patients who were lost to follow-up from those who were readmitted at a different healthcare facility. This may result in an underestimate of some outcomes.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons regarding the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

The informed consent/assent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient or his or her legally acceptable representative, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. The investigator will retain the original of each patient's signed consent/assent document.

10.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with

the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical conduct of the study

The 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 described in Guidelines for Good Pharmacoepidemiology Practices, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR–International Society for Pharmacoepidemiology (ISPE) Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences, European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

11.1. Safety reporting for primary data collection

Data from central lab assessment will be primary data collection. Reporting of safety event identified during central lab assessment will follow the instructions below.

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious adverse events (AEs) (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	All

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to ceftazidime-avibactam**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of ceftazidime-avibactam or the time of the patient's informed consent if s/he is being treated with ceftazidime-avibactam at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during

this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to ceftazidime-avibactam, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each non-serious AE. For AEs with a causal relationship to ceftazidime-avibactam, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that ceftazidime-avibactam caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether ceftazidime-avibactam caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that ceftazidime-avibactam did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- 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.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE 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 (see below for circumstances that do not constitute AEs);
- 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 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 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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization;

however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) ceftazidime-avibactam, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed ceftazidime-avibactam (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to ceftazidime-avibactam prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with ceftazidime-avibactam, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to ceftazidime-avibactam in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).
- The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE
- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
- An identifiable reporter;

- A suspect product;
- The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11.2. Safety reporting for secondary data collection structured data analysis

Structured data from site medical records will be secondary data collection. The structured data do not contain individual-level verbatim data. Reporting requirement of safety event for structured data in site medical records will follow the instructions below.

This study involves data that exist as structured data by the time of investigator start input data from medical record into CRF.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.3. Safety reporting for secondary data collection requires human review of unstructured data

Unstructured Data from site medical records will be reviewed by investigators. Reporting requirement of safety event when reviewing unstructured data in site medical records will follow the instructions below.

REQUIREMENTS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans,

X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) AEM Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors"*.

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11.4. Single reference safety document

The product label of Zavicefta® (ceftazidime-avibactam) approved in China will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

13. REFERENCES

1. China Antimicrobial Resistance Surveillance System. Antimicrobial resistance of bacteria: surveillance report from China Antimicrobial Resistance Surveillance System in 2014-2019. Chin J Infect Control. 2021;20(1):15-31.
2. China Antimicrobial Surveillance Network. (2020). Distribution of major strains from the 251135 isolates from hospital. Available from: http://www.chinets.com/Data/AntibioticDrugFast. Accessed on: 2 July 2021.
3. Liu J, Zhang L, Pan J, et al. Risk Factors and Molecular Epidemiology of Complicated Intra-Abdominal Infections With Carbapenem-Resistant Enterobacteriaceae: A Multicenter Study in China. J Infect Dis. 2020;221(Suppl 2):S156-S63.
4. Wu A, Wen X, Li C, et al. China national point prevalence survey on healthcare-associated infection and antimicrobial use in 2012. Chinese Journal of Infection Control. 2014;13:8-15.
5. Ren N, Wen X, Wu A. Study on the changing trends in national nosocomial infection transection investigation results. Chinese Journal of Infection Control. 2007;6:16-8.
6. Fish DN, Piscitelli SC, Danziger LH. Development of resistance during antimicrobial therapy: a review of antibiotic classes and patient characteristics in 173 studies. Pharmacotherapy. 1995;15(3):279-91.
7. Sanchez Garcia M. Early antibiotic treatment failure. Int J Antimicrob Agents. 2009;34 Suppl 3:S14-9.
8. Giske CG, Monnet DL, Cars O, et al. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother. 2008;52(3):813-21.
9. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA. 2003;289(7):885-8.
10. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005;18(4):657-86.
11. Perez F, Hujer AM, Hujer KM, et al. Global challenge of multidrug-resistant Acinetobacter baumannii. Antimicrob Agents Chemother. 2007;51(10):3471-84.
12. Perez F, El Chakhtoura NG, Papp-Wallace KM, et al. Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply "precision medicine" to antimicrobial chemotherapy? Expert Opin Pharmacother. 2016;17(6):761-81.
13. Wong D, van Duin D. Novel Beta-Lactamase Inhibitors: Unlocking Their Potential in Therapy. Drugs. 2017;77(6):615-28.
14. Zavicefta (ceftazidime-avibactam). LLD avibactam sodium ceftazidime pentahydrate - Zavicefta - CHN - Simplified (CHN); 17 August 2020, Operations Support Group, Ringaskiddy, County Cork, Ireland: Pfizer Ireland Pharmaceuticals. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=14473. Accessed on: 25 May 2021.

15. Lucasti C, Popescu I, Ramesh MK, et al. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. J Antimicrob Chemother. 2013;68(5):1183-92.
16. Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin. 2012;28(12):1921-31.
17. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis. 2016;62(11):1380-89.
18. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018;18(3):285-95.
19. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
20. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137(10):791-7.
21. Cardoso T, Ribeiro O, Aragao I, et al. The impact of healthcare-associated infection on mortality: failure in clinical recognition is related with inadequate antibiotic therapy. PLoS One. 2013;8(3):e58418.
22. Chow AW, Evans GA, Nathens AB, et al. Canadian practice guidelines for surgical intra-abdominal infections. Can J Infect Dis Med Microbiol. 2010;21(1):11-37.
23. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.
24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-9.
25. Henderson H, Luterbach CL, Cober E, et al. The Pitt Bacteremia Score Predicts Mortality in Nonbacteremic Infections. Clin Infect Dis. 2020;70(9):1826-33.
26. Chow AW, Evans GA, Nathens AB, et al. Canadian practice guidelines for surgical intra-abdominal infections. Can J Infect Dis Med Microbiol. 2010;21(1):11-37.
27. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. CRITERIA FOR EVALUATION OF CLINICAL AND MICROBIOLOGICAL OUTCOME

Evaluation	Outcome	Subcategory	Criteria
Clinical Evaluation	Success	Cure	Resolution of all signs and symptoms of infection such that no further antimicrobial therapy is necessary. Discontinuation of the antibiotic therapy is considered a treatment success.
	Failure	Failure	Inadequate response to ceftazidime-avibactam therapy or resistant, worsening, or new recurrent signs and symptoms at the end of ceftazidime-avibactam therapy. This may include the addition of other antibiotic therapies(except bacteria or carbapenamases that are outside the treatment spectrum of ceftazidime-avibactam) after 4 days of treatment, discontinuation of ceftazidime-avibactam without clinical cure (e.g., AE, insufficient effect), or readmission to a hospital with same infection within 60 days of the initial hospital discharge date.
	Indeterminate	Indeterminate	There is not enough information to conclude whether the antibiotic regimen containing ceftazidime-avibactam was a clinical failure or a success.
Microbiological Evaluation	Success	Eradication	Absence of causative pathogen from appropriately obtained specimens at the site of infection.
		Presumed Eradication	Repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.
		Colonization	Detection of pathogen from the site of infection during therapy without need for antimicrobial treatment or a superinfection with a microbiological agent outside the treatment spectrum of ceftazidime-avibactam (G+/fungi).
	Failure	Not Eradicated	Detection of pathogen from the site of infection after completion of therapy.
		Presumed Not Eradicated	Absence of appropriate material for culture or absence of results of control microbiological tests coupled with lack of clinical improvement after a pathogen was initially isolated.
	Emergent Infections	Superinfection	Detection of a new pathogen from the site of infection during therapy with need for additional antimicrobial treatment.
		New Infection	Detection of a new pathogen from the site of infection after therapy with need for additional antimicrobial treatment.

Evaluation	Outcome	Subcategory	Criteria
	Unevaluable	Unevaluable	Patients without cultures or evident pathogens from the presumed site of infection.

ANNEX 4. DEYO-CHARLSON COMORBIDITY INDEX

ANNEX 5. APACHE II

Total APACHE II Score = sum of (A. Total Acute Physiology Score (APS), B. Age, and C. Chronic Health Score).

A. APACHE II Score Form

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE +4	+3	+2	+1	0	LOW ABNORMAL RANGE +1	+2	+3	+4
1. Temperature – rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2. Mean arterial pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
3. Heart rate (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
4. Respiratory rate (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
5. Oxygenation A-aDO_2 or PaO_2 (mmHg)									
a) FiO_2 ≥0.5: record A-aDO_2	≥500	350-499	200-349		<200				
b) FiO_2 <0.5: record only PaO_2					>70	61-70		55-60	<55
6. Arterial pH - If no ABGs record Serum use HCO_3 below	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
7. Serum Sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
8. Serum Potassium (mmol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9. Serum Creatinine (mg/dL) Double point score for acute renal failure	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10. Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
11. White Blood Count (/mm^3) (in 1.000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
12. Glasgow Coma Scale (Score = 15 minus actual GCS)									
A. APS				**Sum of the 12 individual points=**					
□ Serum HCO_3 (venous-mmol/L) (Not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

Abbreviations: A-aDO_2 = alveolar-arterial oxygen gradient, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, ABG = arterial blood gas, HCO_3 = bicarbonate, GCS = Glasgow Coma Scale

B. Age Score

AGE (years)	Score
≤ 44	0
45 – 54	2
55 – 64	3
65 – 74	5
≥ 75	6

C. Chronic Health Score

If a patient has a history of severe organ system insufficiency or is immunocompromised, assign points as follows:

a. For nonoperative or emergency postoperative patients — 5 points
b. For elective postoperative patients — 2 points]

Definitions

Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV — Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.

RENAL: receiving chronic dialysis.

IMMUNOCOMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

ANNEX 6. SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE*

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3\ \mu L^{-1}$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg dL^{-1} ($\mu mol\ L^{-1}$)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a]
Central Nervous System (CNS)					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg dL^{-1} ($\mu mol\ L^{-1}$)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL per day				<500	<200

FIO_2: fraction of inspired oxygen; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen.
[a]Catecholamine doses are given as $\mu g\ kg^{-1}\ min^{-1}$ for at least 1 h.
[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

*Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (sepsis-3) .JAMA 315:801-810, 2016.

ANNEX 7. PITT BACTEREMIA SCORE

The Pitt bacteremia score is widely used in infectious disease research as a severity of acute illness index. It ranges from 0 to 14 points, with a score ≥4 commonly used as an indicator of critical illness and increased risk of death. [40]

Pitt bacteremia score assessing severity of illness (1998 version)

Fever (oral)	
<=35°C	2 points
36°C	1 point
36.1-38.9°C	0 points
39°C	1 point
>=40°C	2 points
Hypotension (a) Acute hypotensive event drop in systolic >30 mmHg and diastolic >20 mmHg; or (b) Requirement for intravenous pressor agents; or (c) Systolic blood pressure <90 mmHg	2 points
Mechanical ventilation	2 points
Cardiac arrest	4 points
Mental status: alert	0 point
Disoriented	1 point
Stuporous	2 points
Comatose	4 points

*All parameters graded within 2 days prior to or on the day of first positive blood culture. Take the highest score during that time.
Critically ill defined as accumulation of greater or equal to 4 points from the above categories.

ANNEX 8. DATA ABSTRACTION SCHEDULE

Time of visit	Baseline (from date of admission to index date or from 7 days before index date to index date)	Index date (Receive ≥1 dose of ceftazidime-avibactam)	Day 7, Day 14, Day 21, Day 30, Day 60, and at EOT after index date	Discharge from index hospitalization	Day 30 and Day 60 after discharge	End of observation	Central lab evaluation
Informed consent		×					
Demographic characteristics (Age, Sex, Employment, Height, weight, etc)	×						
Medical history (Alcohol consumption, Smoking, Comorbidity, etc)	×						
Admission diagnosis	×						
Pre-treatment disease severity	×						

Time of visit	Baseline (from date of admission to index date or from 7 days before index date to index date)	Index date (Receive ≥1 dose of ceftazidime-avibactam)	Day 7, Day 14, Day 21, Day 30, Day 60, and at EOT after index date	Discharge from index hospitalization	Day 30 and Day 60 after discharge	End of observation	Central lab evaluation
Source of infection	×	×					
Ceftazidime-avibactam treatment information (e.g., dosage, frequency, etc.)		×	×				
Indication for ceftazidime-avibactam	×	×					
Microbiology sample after treatment initiation		×	×				×
Microbiology results after treatment initiation		×	×				×

Time of visit	Baseline (from date of admission to index date or from 7 days before index date to index date)	Index date (Receive ≥1 dose of ceftazidime-avibactam)	Day 7, Day 14, Day 21, Day 30, Day 60, and at EOT after index date	Discharge from index hospitalization	Day 30 and Day 60 after discharge	End of observation	Central lab evaluation
Discharge diagnosis				×			
Readmission					×		
Clinical outcome			×				
Microbiologic outcome			×				×