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Can Pharmacovigilance Data Represent a Potential Tool for Early Detection of the Antibiotic Resistance Phenomenon?

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Abstract: Background: Antibiotic resistance represents a growing concern. A new strategy developed to treat severe infections is represented by ceftazidime/avibactam (CZA/AVI). Despite the promising activities against more pathogens, continuous monitoring is required to identify potential antibiotic resistance in clinical practice settings. Therefore, real-world data from pharmacovigilance databases can help to better define the safety profile. Methods: We analyzed all Individual Case Safety Reports (ICSRs) collected in the EudraVigilance database focusing on ICSRs with at least one adverse event (AE) potentially suggestive of drug resistance (DR) and drug ineffectiveness (DI). Results: A total of 654 ICSRs related to CZA/AVI were retrieved from EudraVigilance, of which N = 378 (57.8%) were related to male and N = 230 (35.1%) to adult patients. A total of 80.2% of all AEs were serious but with a positive outcome. Overall, we found N = 129 (19.7%) cases of potential DR or DI after CZA/AVI administration. The majority of CZA/AVI-induced DR or DI occurred in adult male patients. The most frequently reported AEs were "drug ineffective" and "pathogen resistance". Lastly, CZA/AVI was mostly used for the treatment of "Klebsiella infection" and "Pneumonia". Conclusions: The present study showed how pharmacovigilance could play a key role in generating evidence about the safety profile of CZA/AVI. Further studies are warranted.

Keywords: ceftazidime–avibactam; antibiotic resistance; drug resistance; drug ineffectiveness; safety monitoring

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1. Introduction

Nowadays, antibiotic drugs provide the most significant public health benefit in terms of direct therapeutic effect on patients and especially for infectious disease prophylaxis in communities [1,2]. Most antibiotics now employed in clinical settings have a broad spectrum to treat illnesses caused by both Gram-positive and Gram-negative bacterial infections. Unfortunately, the inappropriate use of that essential therapeutic tool has led to the development and spread of bacterial resistance [3]. Antibiotic resistance is a natural evolutionary process accelerated by the selection pressure of antibiotics on sensitive bacteria, leading to the growth and expansion of resistant bacteria, if present [4]. Moreover,

once a strain of resistant bacteria emerges, the resistance can be acquired by other bacteria through a variety of processes, resulting in multi-resistant strains. At the molecular level, resistance mechanisms are generally due to gene mutations that lead to modification of the antibiotic action target, inactivation of the drug by enzymatic biotransformation or reduction of its intracellular accumulation [5]. Currently, of particular concern is the rate of resistance occurring in many Gram-negative pathogens, especially those that produce β-lactamase; i.e., enzymes that hydrolyze β-lactam antibiotics [6]. Indeed, despite the initial demonstrated efficacy of third-generation cephalosporins against these types of bacteria, the increasing prevalence of β-lactamase production as a mechanism of resistance has greatly reduced their usefulness, due to inactivation [7,8]. Therefore, one of the main strategies used to restore the effectiveness of β-lactam antibiotics against these organisms is to use β-lactamase inhibitory molecules to avoid hydrolyzing the antibiotic. In this regard, an efficient strategy consists of the use of innovative β-lactam/β-lactamase inhibitor combinations such as ceftolozane–tazobactam, ceftazidime–avibactam, imipenem–relebactam and meropenem–vaborbactam [9]. Among all the associations mentioned, ceftazidime–avibactam (CZA/AVI) represents the first authorized combination of a third-generation cephalosporin (ceftazidime), with a non-β-lactam β-lactamase inhibitor of new generation (avibactam) [10]. Following binding to penicillin-binding proteins, ceftazidime inhibits the synthesis of the bacterial peptidoglycan cell wall and leads to cell death. In parallel, avibactam acts by forming a covalent adduct, stable to hydrolysis, with a wide variety of enzymes, including both class A and class C β-lactamase (Figure 1) [11]. This combination is an optimal therapeutic option against multi-drug-resistant bacteria, because ceftazidime has the broadest Extended-Spectrum Beta-Lactamase (ESBL) profile, over common antibiotics in its class. Whereas some third- and fourth-generation cephalosporins are hydrolyzed by ESBL, ceftazidime is not. Moreover, avibactam is more potent compared to tazobactam (older generation of β-lactamase inhibitor) and it has a spectrum of action including carbapenemases [12,13]. Finally, this pharmacological association sets itself apart in that both components share similar pharmacokinetic properties, including distribution volume, renal elimination and half-life. This is important because the half-life of avibactam is long enough to protect ceftazidime from degradation, giving it more time to work in the body [14–16]. Based on a large number of randomized controlled studies, CZA/AVI received marketing authorization from the European Medicines Agency (EMA) on June 23, 2016, for the treatment of adult and pediatric patients aged 3 months and older affected by complicated intra-abdominal infections (cIAIs), complicated urinary tract infections (cUTI) and hospital-acquired pneumonia (HAP) [17,18]. As for all medicines, the Marketing Holder has submitted a Risk Management Plan (RMP) to ensure effective monitoring of the safety of CZA/AVI in the post-marketing contest. According to the RMP, additional efficacy and safety data are usually retrieved from ongoing studies and post-marketing reports, and they will be reviewed on a regular basis by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC). In this scenario, although CZA/AVI has a favorable risk–benefit profile, it is the only β-lactam/β-lactamase inhibitor combination that presents the bacterial resistance development as an important potential risk in the RMP, other than meropenem–vaborbactam [19]. However, evidence about this potentially important risk is still scant. Considering that CZA/AVI was approved earlier than meropenem–vaborbactam and its use is growing in clinical practice, continuous monitoring of the safety profile is required also to stem the phenomenon of bacterial resistance and in turn minimize the incidence of adverse events (AEs) related to it. In this context, literature data have highlighted the potential role of pharmacovigilance as a source of data of the new methodological approaches to monitoring antimicrobial stewardship programs [20–22]. Therefore, the present pharmacovigilance study aims to perform a descriptive analysis of spontaneously suspected adverse reactions (ADRs) potentially suggestive of drug resistance (DR) or drug ineffectiveness (DI), reported for CZA/AVI, based on spontaneous reports from EudraVigilance (EV), the European database of pharmacovigilance. Specifically, DR refers to the

ability of a microorganism to withstand the effects of a medication that once effectively treated it; in particular, antibiotic resistance is often caused by mechanisms such as enzyme production that degrades the drug, changes in drug target sites, or reduced permeability to the drug [23]. Moreover, DI is defined as the failure to achieve the desired therapeutic effect, regardless of the presence of resistant pathogens; this can occur due to incorrect drug selection, inappropriate dosing, poor patient adherence, or other clinical factors [24]. In this context, Individual Case Safety Reports (ICSRs) of suspected ADRs remain an important source of post-marketing safety information providing data to support recommendations on how to best evaluate these cases.

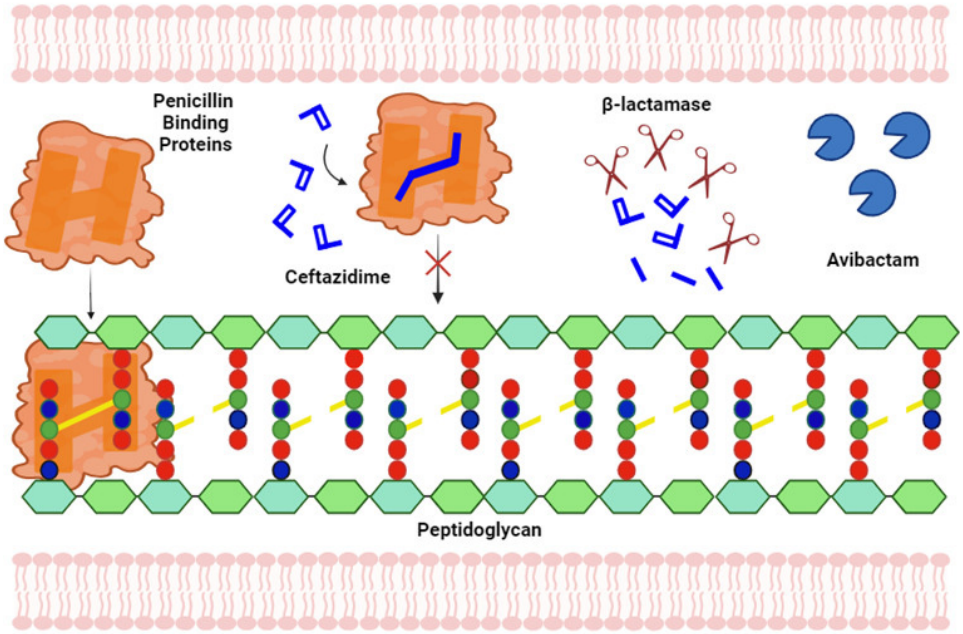

Figure 1. Mechanism of action of ceftazidime/avibactam.

2. Results

During the study period, a total of N = 654 ICSRs reporting CZA/AVI as suspect were retrieved from the EudraVigilance ADR report website. Among these ICSRs, N = 378 (57.8%) were related to male patients and N = 230 (35.2%) to adults (18–64 years of age). All ICSRs were spontaneous (N = 654; 100.0%). More than 80.0% of ICSRs were issued by a healthcare professional (N = 563; 86.1%) and the majority occurred in the European Economic Area (EEA) (N = 331; 50.6%). Almost all ICSRs included the combination of CZA/AVI without other suspected drugs (N = 464; 70.9%); no concomitant drugs were reported (Table 1). The mean number of events reported in each ICSR was 2.2 (±1.99), for a total of 1467 AEs. Since each ICSR could describe more than one suspected ADR, the total number of analyzed events was higher than the overall ICSRs.

As reported in Figure 2, from 2016 and until 2023, a continuous positive trend in ICSR reporting was observed, with a peak recorded in 2022; it should be specified that data relating to 2023 are incomplete (updated 11 September 2023).

Of all ICSRs, 80.2% were classified as serious. Considering the reported seriousness criteria, "Other medically important condition" (N = 539; 45.8%) and "Caused or prolonged the hospitalization" (N = 344; 29.2%) were the more commonly selected. For the majority of AEs, the outcome was not reported (N = 697; 47.5%) and was "Recovered/Resolved" for 21.0% of ICSRs, "Recovering/Resolving" for 14.0% of ICSRs, "Fatal" for 11.3% of ICSRs, "Not Recovered/Not Resolved" for 5.9% ICSR, and "Recovered/Resolved With Sequelae" for 0.3% of ICSRs. Looking at the overall events with a related reported duration, the mean length of events was 9.02 (±16.04) days (Table 2).

Table 1. Demographic characteristics of Individual Case Safety Reports (ICSRs) involving ceftazidime–avibactam reported in the EudraVigilance spontaneous reporting system from 24 June 2016 to 11 September 2023.

	All ICSRs [a] 654 (%)
Sex	
Male	378 (57.8)
Female	213 (32.6)
Not Specified	63 (9.6)
Age group	
Pediatrics (<18 Years)	30 (4.6)
Adult (18–64 Years)	230 (35.2)
Elderly (65–85 Years)	211 (32.2)
Very Elderly (>85 Years)	48 (7.3)
Not Specified	135 (20.7)
Primary source qualification	
Healthcare Professional	563 (86.1)
Non-Healthcare Professional	91 (13.9)
Primary source country for regulatory purposes	
European Economic Area	331 (50.6)
Non-European Economic Area	323 (49.4)
Report Type	
Spontaneous	654 (100.0)
Non-Spontaneous	0 (-)
Adverse Events	
Total Number	1467
Mean AE [b] per ICSR (±SD) [c]	2.2 (±1.99)
Suspected drug(s) other than ceftazidime/avibactam	
0	464 (70.9)
1	83 (12.7)
2	49 (7.5)
3	19 (2.9)
4	14 (2.1)
≥5	25 (3.9)

[a] ICSRs = Individual Case Safety Reports; [b] AE = Adverse Event; [c] SD = Standard Deviation.

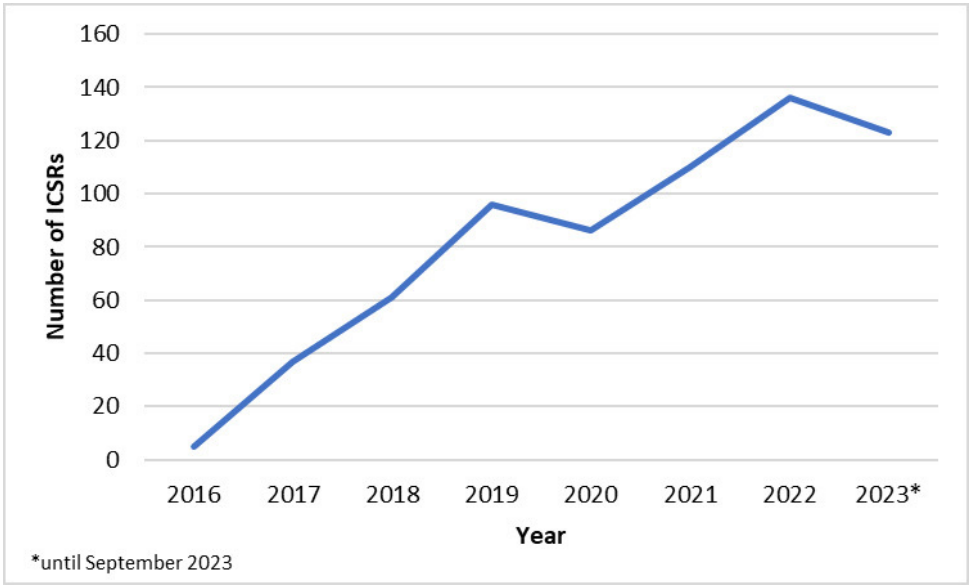

Figure 2. Distribution of Individual Case Safety Reports (ICSRs) having ceftazidime/avibactam as a suspect drug by year (June 2016–September 2023).

Table 2. Characteristics of Adverse Events (AEs).

	Number of AE [a] 1467 (%)
Seriousness	
Not Serious	291 (19.8)
Serious	1176 (80.2)
Seriousness Criteria	
Other Medically Important Condition	539 (45.8)
Caused/Prolonged Hospitalisation	344 (29.2)
Results in Death	207 (17.6)
Life Threatening	74 (6.3)
Disabling	12 (1.1)
Congenital Anomaly	0 (-)
Outcome [b]	
Recovered/Resolved	308 (21.0)
Recovering/Resolving	205 (14.0)
Fatal	166 (11.3)
Not Recovered/Not Resolved	87 (5.9)
Recovered/Resolved With Sequelae	4 (0.3)
Unknown	697 (47.5)
Adverse Event Duration, Days, Mean (±SD) [c]	9.02(16.4)

[a] AEs = Adverse Events. The total number of reported AEs is different from the total number of analyzed ICSRs and this apparent discrepancy is explained by the fact that one ICSR could report more than one adverse event; [b] in cases of more than one event/outcome, the worst outcome was considered; [c] SD = Standard Deviation.

Reported AEs are coded using PTs and corresponding System Organ Class (SOC), according to MedDRA terminology (Table 3). The most common SOC was "General disorders and administration site conditions" (N = 232; 15.8%), followed by "Infections and infestations" (N = 188; 12.8%), "Investigations" (N = 185; 12.6%), "Nervous system disorders" (N = 143; 9.7%), "Injury, poisoning and procedural complications" (N = 138; 9.4%), "Skin and subcutaneous tissue disorders" (N = 130; 8.9%), "Blood and lymphatic system disorders" (N = 77; 5.2%), "Renal and urinary disorders" (N = 77; 5.2%), "Hepatobiliary disorders" (N = 57; 3.9%) and "Gastrointestinal disorders" (N = 54; 3.7%). As shown in Table 3, the most frequently reported PTs for each above-mentioned SOC were "Drug ineffective", "Pathogen resistance", "Platelet count decreased", "Encephalopathy", "Off label use", "Rash", "Thrombocytopenia", "Acute kidney injury", "Hepatic function abnormal", and "Diarrhoea".

Table 3. Distribution of Preferred Terms (PTs) belonging to the top 10 System Organ Classes (SOCs).

System Organ Classes and Preferred Terms		**N. of Adverse Events (%) ***
General disorders and administration site conditions	N = 232	
Drug ineffective	44	(19.0)
Drug resistance	27	(11.6)
Pyrexia	22	(9.5)
Death	20	(8.6)
Condition aggravated	19	(8.2)
Multiple organ dysfunction syndrome	13	(5.6)
Treatment failure	8	(3.4)
Infections and infestations	N = 188	
Pathogen resistance	45	(23.9)
Septic shock	14	(7.4)
Pneumonia	9	(4.8)
Sepsis	9	(4.8)
Klebsiella infection	9	(4.8)
Pseudomonas infection	6	(3.2)

Table 3. *Cont.*

System Organ Classes and Preferred Terms		N. of Adverse Events (%) *
Investigations	N = 185	
Platelet count decreased	31	(16.8)
Blood creatinine increased	15	(8.1)
Blood bilirubin increased	8	(4.3)
Alanine aminotransferase increased	6	(3.2)
White blood cell count decreased	6	(3.2)
Nervous system disorders	N = 143	
Encephalopathy	21	(14.7)
Seizure	18	(12.6)
Coma	10	(7.0)
Depressed level of consciousness	10	(7.0)
Myoclonus	8	(5.6)
Epilepsy	6	(4.2)
Tremor	6	(4.2)
Altered state of consciousness	6	(4.2)
Injury, poisoning and procedural complications	N = 138	
Off label use	71	(51.4)
Product use issue	22	(15.9)
Product use in unapproved indication	12	(8.7)
Skin and subcutaneous tissue disorders	N = 130	
Rash	30	(23.1)
Erythema	17	(13.1)
Pruritus	14	(10.8)
Rash maculo-papular	11	(8.5)
Rash erythematous	8	(6.2)
Urticaria	8	(6.2)
Rash pruritic	4	(3.1)
Drug eruption	4	(3.1)
Blood and lymphatic system disorders	N = 77	
Thrombocytopenia	21	(27.3)
Eosinophilia	11	(14.3)
Neutropenia	8	(10.4)
Anaemia	6	(7.8)
Haemolytic anaemia	5	(6.5)
Agranulocytosis	4	(5.2)
Myelosuppression	4	(5.2)
Leukopenia	3	(3.9)
Renal and urinary disorders	N = 77	
Acute kidney injury	22	(28.6)
Renal failure	17	(22.1)
Renal impairment	17	(22.1)
Hepatobiliary disorders	N = 57	
Hepatic function abnormal	11	(19.3)
Drug-induced liver injury	9	(15.8)
Cholestasis	9	(15.8)
Hepatic cytolysis	7	(12.3)
Jaundice	3	(5.3)
Hepatocellular injury	3	(5.3)
Mixed liver injury	3	(5.3)
Liver injury	3	(5.3)
Hepatitis	2	(3.5)
Hepatic failure	2	(3.5)

Table 3. *Cont.*

System Organ Classes and Preferred Terms		N. of Adverse Events (%) *
Gastrointestinal disorders	N = 54	
Diarrhoea	14	(25.9)
Melaena	5	(9.3)
Gastrointestinal haemorrhage	4	(7.4)
Dysbiosis	4	(7.4)
Nausea	3	(5.6)
Vomiting	3	(5.6)
Ascites	2	(3.7)
Rectal haemorrhage	2	(3.7)
Pancreatitis acute	2	(3.7)
Faeces discoloured	2	(3.7)
Haematemesis	2	(3.7)

* All Preferred Terms (PTs) that represented at least 3% of all events were reported in the table.

Regarding the distribution of ICSRs by therapeutic indications, CZA/AVI was mostly used for the treatment of "Pneumonia" (N = 125; 8.7%), followed by "Klebsiella infection" (N = 86; 6.0%) and "Infection" (N = 68; 4.8%), in line with the approved indications. Lastly, in N = 227 ICSRs (15.9%), the therapeutic indication was not reported. Based on the N = 255 ICSRs with a known length of therapy, the median duration of CZA/AVI treatment was 8 days (interquartile range—IQR: 4–14).

Drug Resistance and Drug Ineffectiveness

With regard to ICSRs with PT potentially suggestive of DR and DI, we performed the following additional analysis. Overall, 129 out of 654 ICSRs (19.7%) were suggestive of events of interest; in particular, N = 69 potential cases of DR (53.5%) and N = 54 of DI (41.9%); N = 6 (4.6%) ICSRs reported both PT related to DR and DI. As shown in Table 4, most ICSRs were reported for males (51.1%) and adult patients (18–64 years of age) (N = 49; 38.0%). The outcome was not reported for N = 83 ICSRs (64.4%), whereas for N = 11 (8.5%) ICSRs, that was classified as "Recovered/Resolved", and N = 6 (4.6%) "Recovering/Resolving". Twenty-nine ICSRs (22.5%) reported a fatal outcome. Overall, those ICSRs (N = 129) reported a total of 336 AEs (mean AE 4; ±2.66), of which N = 77 related to DR and N = 62 to DI (Table 4).

Table 4. Characteristics of Individual Case Safety Reports (ICSRs) potentially suggestive of drug resistance (DR) or drug ineffectiveness (DI) reported in the EudraVigilance database (June 2016–September 2023).

	All ICSRs [a] N= 129 (%)	ICSRs DR [b] N = 69 (%)	ICSRs DI [c] N = 54 (%)	ICSRs DR/DI N = 6 (%)
Gender				
Male	66 (51.1)	28 (40.6)	33 (61.1)	5 (83.3)
Female	37 (28.7)	19 (27.5)	17 (31.5)	1 (16.7)
Not Specified	26 (20.2)	22 (31.9)	4 (7.4)	0 (-)
Age group				
Pediatrics (<18 Years)	5 (3.9)	1 (1.4)	4 (7.4)	0 (-)
Adult (18–64 Years)	49 (38.0)	23 (33.4)	23 (42.6)	3 (50.0)
Elderly (65–85 Years)	28 (21.7)	16 (23.2)	10 (18.5)	2 (33.3)
Very Elderly (>85 Years)	4 (3.1)	1 (1.4)	3 (5.5)	0 (-)
Not Specified	43 (33.3)	28 (40.6)	14 (26.0)	1 (16.7)

Table 4. *Cont.*

	All ICSRs [a] N= 129 (%)	ICSRs DR [b] N = 69 (%)	ICSRs DI [c] N = 54 (%)	ICSRs DR/DI N = 6 (%)
Outcome [d]				
Recovered/Resolved	11 (8.5)	5 (7.2)	5 (9.3)	1 (16.7)
Recovering/Resolving	6 (4.6)	4 (5.8)	2 (3.7)	0 (-)
Fatal	29 (22.5)	7 (10.1)	21 (38.9)	1 (16.7)
Not Recovered/Not Resolved	0 (-)	0 (-)	0 (-)	0 (-)
Recovered/Resolved With Sequelae	0 (-)	0 (-)	0 (-)	0 (-)
Unknown	83 (64.4)	53 (76.9)	26 (48.1)	4 (66.6)

[a] ICSRs = Individual Case Safety Reports; [b] DR = Drug resistance; [c] DI = Drug ineffectiveness; [d] in case of more than one event/outcome, the worst outcome was considered.

Looking at the distribution of PTs potentially suggestive of DR or DI, a specific PT was more commonly reported than others. In this regard, "Drug ineffective" (N = 47; 34.0%) was the most frequently reported PT followed by "Pathogen resistance" (N = 44; 32.0%), "Drug resistance" (N = 26; 19.0%), "Treatment failure" (N = 8; 6.0%), "Multiple-drug resistance" (N = 6; 4.0%), "Therapy non-responder" (N = 2; 2.0%), "Therapeutic product effect incomplete" (N = 2; 2.0%), and "Therapeutic product ineffective" (N = 1; 1.0%) (Insert Figure 3A).

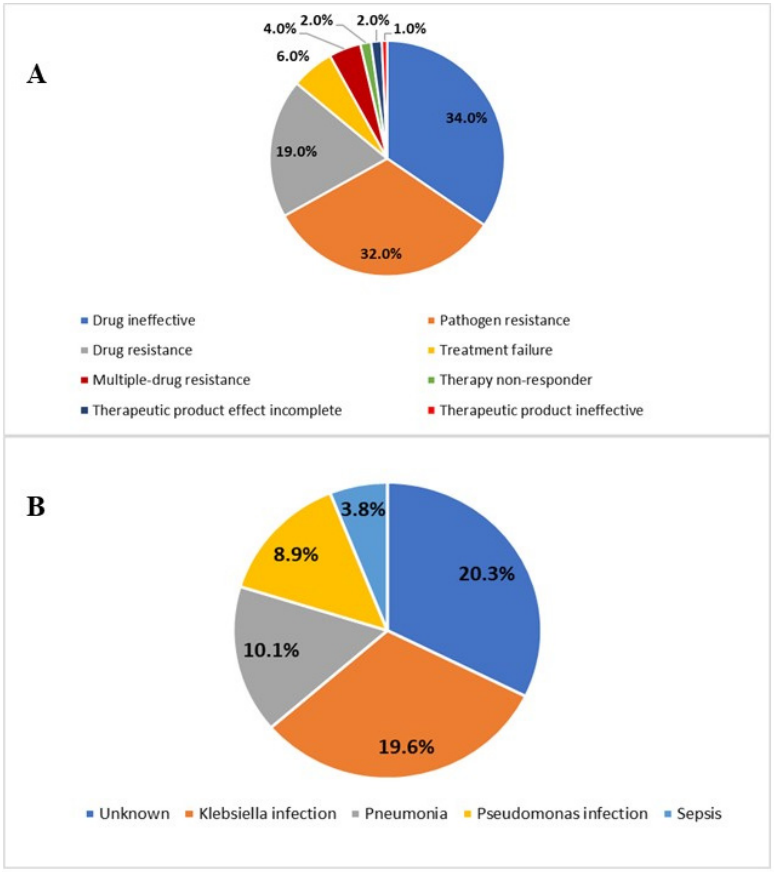

Figure 3. Panel (**A**): Distribution of Preferred Terms (PTs) potentially suggestive of drug resistance (DR) or drug ineffective (DI). Panel (**B**): Therapeutic indications were reported in ceftazidime/avibactam-related ICSRs related to drug resistance (DR) and drug ineffective (DI). The PTs "therapeutic product effect decreased", "decreased activity", "drug ineffective for unapproved indication", and "therapeutic response decreased" are not shown in Figure 3A as they were not reported. Therapeutic indications with a prevalence lower than 3.0% are not included in Figure 3B.

Lastly, considering that each ICSR could report more than one therapeutic indication, the total number of therapeutic indications was 158. As shown in Figure 3B (Insert Figure 3B), "Klebsiella infection" was the therapeutic indication more frequently reported (N = 31; 19.6%), followed by "Pneumonia" (N = 16; 10.1%), "Pseudomonas infection" (N = 14; 8.9%), and "Sepsi" (N = 6; 3.8%). In 32 (20.3%) cases, the information about the therapeutic indication for CZA-AVI prescription was not reported (Figure 3B).

3. Discussion

Nowadays, antimicrobial resistance is a major public health problem. The main cause lies in antibiotic inappropriate use, often associated with self-medication, that gives rise to their gradual loss of efficacy. This emergence becomes even more worrisome when we consider that it also involves a second- or third-line therapeutic alternative, resulting in reduced treatment options in cases of multi-resistant infections.

Research in the field of pharmacology is progressing quickly; however, it stands still in terms of the discovery of new antibiotic molecules. In fact, few molecules have recently been introduced commercially, which is a clinically serious issue because it is estimated that over 35,000 people die every year as a direct result of an infection due to antibiotic-resistant bacteria [25]. Recently, to counter the growing phenomenon, the European Commission proposed to modernize the pharmaceutical sector with a "One Health" patient-centric approach. One of the highlights is the strengthened surveillance of antibiotic resistance [26]. In this context, pharmacovigilance studies could be a valuable and helpful tool to monitor and detect the occurrence of therapeutic failures related to potential antimicrobial resistance in the real clinical practice, considering their impact in terms of AEs on the patient. The present study, specifically, exploits the potentiality of spontaneous reports to evaluate the safety profile ofCZA/AVI, a new β-lactam/β-lactamase inhibitor combination, for which an important potential risk of bacterial resistance development has already been reported in RMP [18].

Therefore, through a descriptive analysis of all ICSRs retrieved in the EudraVigilance database, our study focuses on ICSRs potentially related to DR or DI. The rationale is based on evidence that early detection on trends in suspected resistance allows for faster response from the scientific society, including prescribers, to optimize CZA/AVI use. During the study period, from June 2016 to September 2023, a total of 654 ICSRs reported to CZA/AVI as a suspected drug were retrieved from EudraVigilance, of which 57.8% were related to male and to adult patients with an age range of 18–64 years. The majority of ICSRs were reported by healthcare professionals (86.1%) and 50.1% of theme occurred in the European Economic Area (EEA). Regarding the sex distribution, literature data underlines that female patients have a higher frequency of reporting suspected AEs; this could be attributed to the higher consumption of medicines among women but is also owing to distinct gender-related pharmacokinetic or pharmacodynamic susceptibility and differences in psychosocial, behavioral, or cultural aspects [27–30]. Moreover, it should be highlighted that there are gender disparities in the prescription of antibiotics and, as a result, in adverse events. In particular, women are more likely than men to obtain prescriptions for antibiotics, and patients between the ages of 16 and 54 showed the largest gender disparity [31,32]. However, in apparent contrast with preliminary and general data described above but in line with other pharmacovigilance studies on CZA/AVI, our data were mainly of male and adult patients [33,34]. Also, the greater involvement of healthcare professionals as reporters is consistent with findings from previous studies suggesting the higher involvement of that stakeholder in pharmacovigilance activities as requested by the new pharmacovigilance legislation that came into force in July 2012 [35–39]. Our results showed an increase in ICSR reporting from 2016 until 2022. This trend is probably related to the growing utilization of the novel β-lactam/β-lactamase inhibitor CZA/AVI. Indeed, since the approval of CZA/AVI in 2016, an increase of almost 20-fold over 3 years in the normal clinical practice has been recorded [40]. Our study described that the majority of reported AEs were serious and also in this case, that result could be related to the higher propensity of clinicians for re-

porting serious AEs instead of not serious ones [37,41]. Furthermore, the occurrence of AEs classified as serious following the administration of CZA/AVI is very common, as already observed in previous pharmacovigilance studies [33,42]. Our results showed that "off label use" (51.4%), "acute kidney injury" (28.6%), "thrombocytopenia" (27.3%), and "diarrhoea" (25.9%) were the most frequently reported AEs, in line with the CZA/AVI 's Summary of Product Characteristics (SmPC). Unfortunately, with the minimum data accessibility, it is not possible to ascertain between off-label use for indications, or age, or using a dosage, or dosage form (including route of administration). However, analyzing ICSRs with available information on therapeutic indication, our analysis highlighted that "Pneumonia", "Klebsiella infection", and "Infection" were the most commonly reported indications. These data are not surprising if we consider that CZA/AVI is mainly indicated for the treatment of intra-abdominal infection, urinary tract infection, infections due to aerobic Gram-negative organisms (such as Klebsiella) and hospital-acquired pneumonia, as already reported in its SmPC [11,43]. One of the most concerning issues related to CZA/AVI treatment is the occurrence of antibiotic resistance whose mechanism would be due to β-lactamase-related mutations [44]. Therefore, our study focused on the analysis of ICSRs with at least one PT potentially suggestive of drug resistance and drug ineffectiveness. Given the recent approval of CZA/AVI, to date, we have identified N = 129 ICSRs, and specifically N = 139 PTs, suggestive of DR/DI. In line with our results, in the study conducted by Shields a colleagues, important warnings emerged regarding the emergence of resistance to CZA/AVI in 8% (3/37) of cases, including 30% of microbiological failures [45]. Furthermore, Santavecchi and colleagues performed a multicenter, retrospective case series, up to July 2019 [46]. Specifically, cases of drug resistance have been observed during therapy with CZA/AVI in 20% of patients treated for 50 and 13 days, respectively. Therefore, based on available evidence, it is clear that after years of clinical application, the development of antibiotic resistance is possible. In reference to pharmacovigilance databases, as reported in the guideline on good pharmacovigilance practices (GVP—Module VI.B.6.4), reports of therapeutic ineffectiveness, with no suspected adverse reactions, can be presented as ICSRs when the suspected drugs are used in urgent situations or for the treatment of life-threatening illnesses. Clinical judgement is obviously required. For example, in the case of antibiotics used in a life-threatening infection, a report of therapeutic ineffectiveness should be submitted when it appears to be due to the development of a new resistant bacteria (previously considered as susceptible), but not when the use of the drug was not appropriate for the infective agent. Furthermore, the ICSRs related to lack of therapeutic efficacy for medicines used in urgent situations or for the treatment of life-threatening illnesses (with no suspected adverse reaction) needed to be presented as serious [37]. Therefore, considering what is reported, a relevant number of ICSRs on DR or DI should be considered as indicating potential increased antibiotic resistance related to CZA/AVI association [47]. More recent studies, indeed, support that bacterial resistance to CZA/AVI has been emerging and present a positive trend [48]. Several factors may contribute to the occurrence of these AEs reported for CZA/AVI, such as undertreatment as a result of inadequate length of therapy. In that regard, indeed, as reported in the CZA/AVI's SmPC, regardless of clinical indication, 5–14 days of treatment is recommended. Moreover, it cannot be ruled out that also severity of illness as well as inappropriate use of the antibiotic could contribute to our results [18,49]. According to the AWaRe (Access, Watch, Reserve) classification of antibiotics (developed by the World Health Organization to encourage sparing use of antibiotics) CZA/AVI is included in the "Reserve" group, which comprises antibiotics to reserve for treatment of infections due to multi-drug-resistant organisms [50]. One of the most troubling issues is the misuse of "Reserve" group antibiotics (where CZA/AVI is present), considering that they represent "last land" options [51]. Therefore, there is urgent need to optimize the clinical use of antibiotics, especially for CZA/AVI, to slow the spread of resistance, and to mitigate its impact with the development of novel effective treatments. In that regard, a joint intervention could be extremely important conducted by regulatory authorities together with scientific associations, to re-educate patients about the appropriate and safe

use of antibiotics [52]. On the other hand, pharmacovigilance studies could represent one of the most important multidisciplinary approaches used for surveillance and warning about antibiotic resistance.

4. Materials and Methods

4.1. Study Design and Data Source

We performed a retrospective analysis of spontaneous reports submitted to the European Pharmacovigilance database EudraVigilance aiming to evaluate potential cases of drug resistance or drug ineffectiveness related to CZA/AVI until September 2023.

Data on Individual Case Safety Reports (ICSRs) with CZA/AVI as the suspected drug were retrieved from the website of suspected adverse drug reactions (ADRs) (www.adrreports.eu) of the European pharmacovigilance database EudraVigilance (EV) for the period June 2016 (gateway date) to September 2023 (accessed on 11 September 2023). EudraVigilance, managed by EMA, is a system for managing and analyzing information on suspected adverse reactions to both medicines or vaccines which have been approved or are being studied in clinical studies in the European Economic Area (EEA). The EV collected all ICSRs reported by a healthcare professional or a non-healthcare professional (e.g., a citizen or other professional figure) to a European Union national competent authority or a marketing authorization holder. These data are publicly available for transparency through the EMA website www.adrreports.eu (accessed on 11 September 2023).

4.2. Selection of Individual Case Safety Reports with Line Listing

By using the line listing function of EudraVigilance, all ICSRs reporting CZA/AVI, the suspected drugs were selected. A suspect drug is one that is thought to have caused the adverse drug reactions or a side-effect in a patient, while a concomitant drug is one which a patient is using to treat another medical condition. A subgroup analysis was performed to identify ICSRs that suggested a potential drug resistance (DR) or drug ineffectiveness (DI). We used the Medical Dictionary for Regulatory Activities (MedDRA®) (version 23.1). In a unique Excel file, we shared the information of all selected ICSRs. To identify the ICSRs related to potential "drug resistance" and "drug ineffectiveness", based on a protocol that has been published in the literature, we selected all ICSRs which reported the following Preferred Terms (PTs): "pathogen resistance", "drug resistance", "multiple drug resistance" (DR identifiers), "therapeutic product effect decreased", "therapeutic product effect incomplete", "decreased activity", "drug ineffective for unapproved indication", "therapeutic product ineffective", "therapeutic response decreased", "treatment failure", "therapy non-responder", and "drug ineffective" (DI identifiers) [13]. ICSRs were identified based on the presence of at least one PT.

4.3. Descriptive Analysis

A descriptive analysis of information on patient characteristics (age and sex), AEs (outcome, duration, and seriousness), therapeutic indication, primary source qualification, primary source country for regulatory purposes, number of suspected drugs (classified as 1, 2, 3, 4, or $\geq$5) other than CZA/AVI, and number of concomitant drugs was performed. Numbers 1, 2, 3, 4, or $\geq$5 were the numbers of suspected drugs reported in each ICSRs. Number 0 was attributed when no other suspected drug was reported.

The duration of therapy (reported in days) was retrieved from each ICSR, where available. The seriousness was classified in accordance with the International Council on Harmonization E2D guidelines [53]. A case is defined as "serious" if it is life threatening, results in death, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, determines a congenital anomaly/birth defect, or results in some other clinically important conditions [54]. If additional criteria were reported for each suspected ADR, the most serious was classified. The outcome of suspected ADR was classified as "Recovered/Resolved", "Recovering/Resolving", "Recovered/Resolved with Sequelae", "Not Recovered/Not Resolved", "Fatal", and "Unknown". If an ICSR reported

two or more AEs with different outcome for each one, the result with the lowest level of resolution was used for classification. ICSRs were classified as fatal if death was observed. A subgroup analysis was performed for ICSRs with at least one of the PTs mentioned above. All data analyses were carried out using Excel (Excel, Microsoft 365 office).

4.4. Ethical Consideration

Due to data-protection restrictions, the recovered data contained non-identifiable patient information, and the free text narrative from the ICSRs was not available, so no ethical review board permission was required.

5. Conclusions

During the study period from June 2016 to September 2023, a total of 654 Individual Case Safety Reports (ICSRs) were retrieved, predominantly involving male and adult patients. The majority of ICSRs were serious, reflecting the propensity of clinicians to report severe AEs. Commonly reported AEs included "off-label use", "acute kidney injury", "thrombocytopenia", and "diarrhea", aligning with the drug's Summary of Product Characteristics. Notably, the analysis focused on 129 ICSRs suggestive of DR or DI, indicating potential instances of antibiotic resistance development. This raises concerns about the effectiveness of CZA/AVI over time. Undertreatment also due to AEs may pose a significant risk to patients to develop bacterial resistance, as it limits treatment options and can lead to prolonged illness or even fatal outcomes [36]. Considering that antimicrobial resistance is a multifaceted challenge, addressing it requires a holistic approach. The increase in reported AEs and potential resistance to CZA/AVI underscores the urgency of developing new antibiotic molecules and implementing stringent antibiotic stewardship programs. The "One Health" approach advocated by the European Commission emphasizes the interconnectedness of human and animal health, the environment, and the need for collaborative efforts to combat antimicrobial resistance [15]. In conclusion, pharmacovigilance studies provide valuable insights into the safety and effectiveness of antibiotics, contributing to early detection on a suspected trend in antibiotic resistance. Pharmacovigilance supports the need for ongoing monitoring and proactive measures to address emerging challenges such as antimicrobial resistance. The integration of AEs and the potential for undertreatment or misuse underscores the critical role of healthcare professionals, researchers, and policymakers in safeguarding public health. Future strategies including rigorous follow-up of patients and environments where CZA/AVI may be dismissed due to adverse reaction should be implemented to understand the role of these events in antimicrobial resistance genesis.

6. Strengths and Limitations

This pharmacovigilance study has strengths and limitations. First of all, the EudraVigilance database represents a valuable and inexpensive tool for the collection and analysis of drug safety data. At the same time, EudraVigilance is useful for quantifying and controlling the use of antibiotics and, indirectly, evaluating and monitoring the trend of the antibiotic resistance phenomenon. In addition, the spontaneous reporting system allows the identification of specific AEs, which cannot be detected during the pre-marketing phase, including rare and serious ones. However, it is known that the spontaneous reporting system suffers from unavoidable limitations mainly related to underreporting and the poor quality and lack of evaluable information reported in each ICSR. Therefore, it is possible that important information, such as encoding of drug resistance or drug ineffectiveness, was not listed in the ICSRs included in our analysis. Furthermore, we cannot rule out the possibility of other confounding variables contributing to the occurrence of drug resistance or drug ineffectiveness. Finally, the coding of adverse events according to MedDRA may be influenced by subjective choices, which are not necessarily correct.

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