

Kounis syndrome due to antibiotics: A global overview from pharmacovigilance databases



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ABSTRACT

Background: Kounis syndrome (KS) is characterized by concurrent presence of anaphylactic and cardiac components. Available evidence suggests that antibiotics are frequently associated to KS. We therefore analyzed KS cases associated with antibiotics use from the two largest pharmacovigilance databases.

Methods: Two pharmacovigilance databases, EudraVigilance and Vigilyze, were searched for cases reporting the adverse reaction “Kounis Syndrome” with antibiotics as suspected active substance. We analyzed the period from December 1st, 2001 to February 16th, 2016. For the most reported active substance, proportional reporting ratio (PRR) was calculated.

Results: A total of 10 cases of KS associated with antibiotic use were retrieved from EudraVigilance database. Mean patients' age was 58.2 years and 70% were male. The most frequently reported suspected antibiotic was the combination amoxicillin/clavulanic acid (four cases). Vigilyze database reported 13 KS cases associated to antibiotics. Mean age was 56 years and 61% of patients were male. The most frequently reported antibiotic was again the combination amoxicillin/clavulanic acid (five cases). Seven duplicate cases were identified, leaving a total of 16 cases of KS, with six of them associated to amoxicillin/clavulanic acid use. The PRR value for amoxicillin/clavulanic acid against other kinds of antibiotics was 2.62 considering EudraVigilance data and 1.61 considering Vigilyze data.

Conclusions: This analysis provided a complete picture of the cases of KS associated with antibiotic use and identified a possible association between amoxicillin/clavulanic acid and KS. Since the number of cases is low, especially considering its wide use, further analyses are needed to confirm the association.

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1. Introduction

Kounis syndrome (KS) is a recently described disease characterized by the concurrent presence of anaphylactic and cardiac components [1]. Following an allergic stimulus, the activation of mast cells leads to histamine, leukotrienes and serotonin release [2]. In severe cases, these mediators can trigger a massive hemodynamic response with generalized vasodilatation leading to allergic or anaphylactic shock. In KS, inflammatory mediators cause a spastic contraction of coronary smooth muscle cells [3]. Mast cells [4], eosinophils and lymphocytes [5] are usually found in histological reports. However, the exact pathophysiological mechanism underlying this syndrome remains unclear. The syndrome usually manifests clinically with typical cardiac ischemic signs and symptoms such as chest pain, electrocardiographic alterations in ST segment or T waves, or atrioventricular block and other arrhythmias. Cases of myocardial infarction (MI) with elevation of myocardial necrosis

biomarkers have also been observed [6]. Clinical findings suggestive of an allergic or hypersensitivity reaction, such as hypotension, pruritus or dyspnea, complete the typical presentation of the syndrome [1]. This syndrome might also result in death, usually by complications of MI [7].

Kounis syndrome can occur in elderly as well as in pediatric age [8,9]. There is currently no consensus on the best treatment of KS [10] and therapy is directed on one side to reduce the inflammatory cascade and allergic reaction by administration of corticosteroids and antihistamines and on the other side to manage the acute coronary syndrome [6]. The use of adrenaline is debated since it is the drug of choice in the case of severe allergic reactions [11,12] but have well-known side effects which may worsen a ventricular function already compromised by ischemia [10,13,14]. However, it has been frequently given to patient with KS and should be considered as treatment of the most severe cases [15].

Potentially, any kind of medication can trigger severe allergic reactions and multiple agents were associated with KS, although antibiotics are the most frequently involved drugs [16,17]. Insect bites [18–20] and drug-eluting stents [21,22] have also been associated with KS.

Actual incidence of KS is yet to be determined. However, despite the rarity of KS, there is an increasing awareness of physicians on this

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specific event, in particular when KS occurs following the use of medicines. We recently reported a large case series of pharmacovigilance-reported cases of KS [23] that confirmed that antibiotics are among the drugs most frequently associated with KS. Therefore, aim of our study was to identify and describe KS cases associated to antibiotic administration by searching two large pharmacovigilance databases, and to analyze causing drugs, clinical presentation of KS, and treatment undertaken to manage the syndrome.

2. Methods

Two pharmacovigilance databases, EudraVigilance and Vigilyze, were searched. The EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse drug reactions (ADR) during the development and the marketing authorization of medicinal products in the European Economic Area (EEA). The first operating version was launched in December 2001. Vigilyze is the global World Health Organization database for Individual Case Safety Reports (ICSRs) spontaneously collected since 1968, and includes data from over 100 countries (including U.S. and Europe). It is managed by the Uppsala Monitoring Centre on behalf of the World Health Organization.

We collected all cases that reported the ADR “Kounis Syndrome”, preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) [24], associated to the antibiotics when these were considered suspected active substance by the reporter. A case by case analysis was conducted from three expert investigators who carefully excluded all reports already published in scientific literature and duplicated cases from both databases. Antibiotics were included based on anatomical therapeutic chemical (ATC) classification “J01–antibacterials for systemic use”. We investigated cases reported between December 1st, 2001 and February 16th, 2016.

The following variables were extracted from the identified reports: geographic region, year of ADR occurrence, age, sex, type of ADR, time to ADR onset, seriousness and clinical outcome, suspected causative drug, concomitant drugs and their therapeutic indications, route of administration, type of reporter. Also the narrative of the cases was analyzed if available; thus, an in-depth analysis aimed at identifying underlying risk factors, features of symptomatology, clinical procedures to confirm the diagnosis of KS, and actions undertaken to manage the event, was performed.

The proportional reporting ratio (PRR) was calculated taking into account the cases of KS associated with amoxicillin/clavulanic acid, the substance most frequently associated with KS among antibiotics, for the period 2001–2016. The PRR summarizes the strength of the association between an ADR and a drug and it is applicable with a minimum of three cases. It compares the frequency of a particular ADR (in individuals taking a specific drug) with the frequency with which the same adverse event occurs in patients taking all other drugs. We computed PRR as described by Evans et al. [25] (Supplementary Appendix). To calculate PRR, we considered all reports of KS available from databases (comprehensive of literature cases) for amoxicillin/clavulanic acid, for other active substances and for antibiotics involved in KS (amoxicillin, amoxicillin/clavulanic acid and its salts, ceftriaxone, piperacillin/tazobactam, cefazolin, levofloxacin, metronidazole). In particular, we calculated PRR also comparing cases of ADRs associated with amoxicillin/clavulanic acid both versus cases of ADRs associated with all other drugs and versus cases of ADRs associated with all other antibiotics. Of note, due to organization of the pharmacovigilance databases and the large number of cases reported, it was very difficult to identify and exclude duplicate and previously published cases of KS and other adverse reactions to antibiotics and all the other drugs. Therefore, for consistency purposes, we decided not to exclude duplicate and already published KS cases, in order to not introduce a bias in the PRR calculation. As a result, PRR was calculated including all cases of KS registered in the databases, including duplicate and previously published cases.

Ninety-five percent confidence interval (95% CI), chi-squared and standard deviation were also calculated.

After identification of all cases, we cross-checked the data from the two databases in order to identify and delete duplicated cases. Duplicated cases were identified following in-depth analysis of the data on geographic area, age, gender, described ADR and suspected drug. Also the data on seriousness and the outcome more described than others were reported.

The causality assessment was performed on the cases KS and amoxicillin/clavulanic acid using the Naranjo algorithm [26] for standardized case causality assessment. Causality assessment, as performed by three expert operators, allowed to evaluate and classify causal relationship between drug intake and onset of adverse drug reaction as definite, possible, probable or doubtful.

3. Results

3.1. EudraVigilance cases

In the considered period, 10 cases of KS associated to antibiotic use were retrieved (Table 1). The first two spontaneous reports were registered in 2012, followed by four cases reported in 2014 and further four in 2015.

Table 1

Spontaneous reports of Kounis Syndrome retrieved in EudraVigilance and Vigilyze.

	EudraVigilance (N)	Vigilyze (N)
Geographic region		
US	0	2
Europe	10	11
Sex		
Male	7	9
Female	3	4
Not specified	0	0
Age groups		
1–17 years	1	1
18–65 years	6	8
65 + years	3	4
Active substance		
Amoxicillin/clavulanic acid	4	5
Amoxicillin	2	3
Piperacillin/tazobactam	2	2
Others (levofloxacin, metronidazole, cefazolin, ceftriaxone)	2	3
Seriousness		
Caused/prolonged hospitalization	2	4
Death	0	0
Life threatening	3	3
Life threatening, caused/prolonged hospitalization	3	4
Not available	1	2
Outcome		
Fatal	0	0
Not recovered/not resolved	0	0
Recovering/resolving/resolved/resolved with sequelae	10	11
Unknown	0	2
TOT cases	10	13

These ten cases occurred in France (3 cases), Liechtenstein (2 cases), Italy (2 cases), Turkey, Spain and the Netherlands (1 case each). All ten cases were reported by health care professionals. Mean age was 58 years old (range 14–99) and males were 70% (seven cases). All cases were reported from healthcare professionals. The most frequently reported suspected active substances were the combination amoxicillin/clavulanic acid (4 cases) followed by amoxicillin (2), piperacillin/tazobactam (2), ceftriaxone (1) and cefazolin (1).

In three cases an antibiotic monotherapy was described: amoxicillin, piperacillin/tazobactam and ceftriaxone. Concomitant medications were reported in 7 seven cases and ranged from two to five drugs. Narratives of the cases described the following concomitant drugs: paracetamol (1 case); propofol, cisatracurium, sufentanil (1 case); gliclazide, paracetamol, sitagliptin, simvastatin, hydroxyzine (1 case); lactic acid bacteria (1); acetylsalicylic acid, atorvastatin (1 case); acetylsalicylic acid, clopidogrel, diltiazem hydrochloride, ramipril, atorvastatin (1 case); perindopril (1 case).

Information about indication for antibiotic therapy was available for nine cases. Kounis syndrome developed in two patients receiving antibiotic as prophylaxis before surgical procedures, in two patients receiving antibiotics for treatment of erysipelas, in two patient receiving antibiotics for dental care and in one patient each who was receiving antibiotics for sore throat, for prevention (not otherwise specified) and for automedication for cough.

The route of administration was reported in nine cases: intravenous administration in five cases and oral administration in four cases.

Kounis syndrome was confirmed by electrocardiograms (2 cases) and laboratory examinations (5 cases), including triptase (2 cases), eosinophiles count (1 case) and troponin (3 cases) samplings. Prick test for amoxicillin was performed in one patient and had positive results.

Three patients had a history of hypersensitivity (3 cases) and three patients had a history of cardiovascular disease (myocardial ischaemia, peripheral arterial occlusive disease; aortic valve insufficiency, hypertension; myocardial ischaemia, respectively).

Other clinical conditions of the patients referred in the medical history included: a previous surgical procedures (in 2 cases); food and seasonal allergy (in 1 case); malignant neoplasm, surgery; erysipelas, herpes labialis, lymphadenopathy.

All cases were considered serious by the reporters. Based on seriousness criteria for ADR, a total of three patients required hospitalization. In three cases ADR was severe enough to be reported as life threatening event. For three patients were described both hospitalization that life threatening conditions. In one case it was reported that the reaction resulted serious enough to affect also other medically important condition not further specified. A severe anaphylactic reaction was reported in four cases, and myocardial infarction occurred in two cases, with KS in 10 cases ADR was described as resolved/recovered in the outcome section of the reporting form.

Time from first antibiotic administration to manifestation of KS was variable. For one case the time was not obtainable. In seven cases corresponded to less than 1 day; in five of these cases KS occurred in less than 20 min, showing that KS could be triggered even by a single drug dose administration. The two KS cases associated with the use of piperacillin/tazobactam occurred after 5 days and after 3 months, respectively.

The actions most frequently undertaken to manage KS were “drug withdrawal” in all cases, administration of epinephrine (in three cases), and administration of corticosteroids (1 case), antihistaminic drugs (1 case), salbutamol (1 case), and oxygen (1 case). In remaining cases the actions were not described. In three cases coronary angiography was performed.

Considering only EudraVigilance data for amoxicillin/clavulanic acid versus all drugs, we calculated a PRR = 69.63 (95% CI = 54.83 to 88.43) with a chi-squared of 4538.79 (SD = 0.12) (Table 2a). Considering amoxicillin/clavulanic acid versus all antibiotics, we obtained a PRR = 2.62 (95% CI = 1.96 to 3.51), with chi-squared = 44.74 (SD = 0.14) (Table 2a).

3.2. Vigilyze cases

In the study period we found a total of 13 KS reports (Table 1): six in 2014, five in 2015, and one case in 2011 and 2012, respectively. These were reported from different countries: France (3 cases), United States (2), Italy (2), Switzerland (2), Netherlands (2), Turkey (1) and Spain (1). Reports were mostly issued by hospital physician (n = 8 [61%]). Males were 61% and the age ranged from 18 to 65 years with a mean age of 56.

The most frequently reported suspected antibiotic was the combination amoxicillin/clavulanic acid (five cases, corresponding to 38%). Amoxicillin alone was reported in two cases (15%) and piperacillin/

tazobactam in other two (15%). Ceftriaxone and cefazolin were reported in association to one case each. In the further two cases the suspected active substances were amoxicillin/epinephrine and levofloxacin/metronidazole, respectively.

The route of administration was reported in 11 cases: six reported an oral administration and five an intravenous administration.

The therapeutic indication for antibiotics were: prevention/prophylaxis (2 cases), erysipelas (2 cases), periodontal abscess (1 case), respiratory infection (1 case), systemic inflammatory response syndrome (1 case), and sore throat (1 case).

Finally, in 1 case amoxicillin/epinephrine reported as suspected was used for the treatment of anaphylactic shock. In four cases the indication for antibiotic treatment was not reported.

Concomitant drugs received from the patients were reported in eight narratives of the cases: paracetamol (1); gliclazide, hydroxyzine, simvastatin, sitagliptin (1); lactic acid bacteria (1); propofol, cisatracurium, sufentanil (1); piperacillin/tazobactam (1); acetylsalicylic acid, clopidogrel, ramipril, diltiazem (1); acetylsalicylic acid, atorvastatin (1) and perindopril (1).

In four cases the allergic reaction was serious enough to be reported as an anaphylactic reaction together with KS; in one of these cases MI also reported. Severity of ADR was reported as follow: in seven cases it was described as life threatening and in eight cases caused or prolonged a hospitalization. In two cases severity of reaction was not specified.

The outcome of the ADR was described as recovering/resolved/resolved with sequelae in 11 cases; while in two cases the outcome is unknown. Reports were mostly issued by hospital physician (N = 8 [61%]).

Time from drug administration to KS manifestation was less than 1 day in most of the circumstances (nine cases), while was unspecified for four cases. Considering only Vigilyze data for amoxicillin/clavulanic acid versus all drugs, we calculated a PRR = 32.61 (95% CI = 23.97 to 44.36) with a chi-squared of 1243.2 (SD = 0.16) (Table 2b). Considering amoxicillin/clavulanic acid versus all antibiotics, we obtained a PRR = 1.61 (95% CI = 1.15 to 2.26), with chi-square = 7.75 (SD = 0.17) (Table 2b).

3.3. Eudravigilance and Vigilyze

After cross-check of data from the two databases (age, gender, geographic area), we identified seven duplicated reports (three for amoxicillin/clavulanic acid and four for other antibiotics), leaving a total of 16 cases of KS associated with antibiotic administration (Fig. 1). In consideration to seriousness in the same number of cases (3) were respectively described: life threatening, hospitalization, or both. The outcome was mainly resulted as resolution of ADR. For amoxicillin/clavulanic acid, the three duplicate cases were: a Turkish case involving a 14-years-old male

Table 2a
Proportional reporting ratio – Data and results from EudraVigilance database.

Amoxicillin/clavulanic acid vs all drugs			
Cases of KS with amox/clav		Cases with amox/clav	
83		25,333	
Cases of KS with all drugs		Cases with all drugs	
433		7,464,040	
PRR	95% CI	CHI ²	Standard deviation
69.63	54.83–88.43	4,538.79	0.12
Amoxicillin/clavulanic acid vs all antibiotics			
Cases of KS with amox/clav		Cases with amox/clav	
83		25,333	
Cases of KS with antibiotics*		Cases with antibiotics	
180		102,791	
PRR	95% CI	CHI ²	Standard deviation
2.62	1.96–3.51	44.74	0.15

Amox/clav: amoxicillin/clavulanic acid; CI: confidence interval; KS: Kounis syndrome; PRR: proportional reporting ratio

* antibiotics involved in KS (amoxicillin, amoxicillin/clavulanic, ceftriaxone, piperacillin/tazobactam, cefazolin, levofloxacin, metronidazole)

Table 2b
Proportional reporting ratio – data and results from Vigilyze.

Amoxicillin/clavulanic acid vs all drugs			
Cases of KS with amox/clav		Cases with amox/clav	
48		70,192	
Cases of KS with all drugs		Cases with all drugs	
310		12,565,490	
PRR	95% CI	CHI ²	Standard deviation
32.61	23.97–44.36	1243.2	0.16
Amoxicillin/clavulanic acid vs all antibiotics			
Cases of KS with amox/clav		Cases with amox/clav	
48		70,192	
Cases of KS with antibiotics		Cases with antibiotics	
158		329,318	
PRR	95% CI	CHI ²	Standard deviation
1.61	1.15–2.26	7.75	0.17

*Antibiotics involved in KS (amoxicillin, amoxicillin/clavulanic, ceftriaxone, piperacillin/tazobactam, cefazolin, levofloxacin, metronidazole)

Amox/clav: amoxicillin/clavulanic acid; CI: confidence interval; KS: Kounis syndrome; PRR: proportional reporting ratio

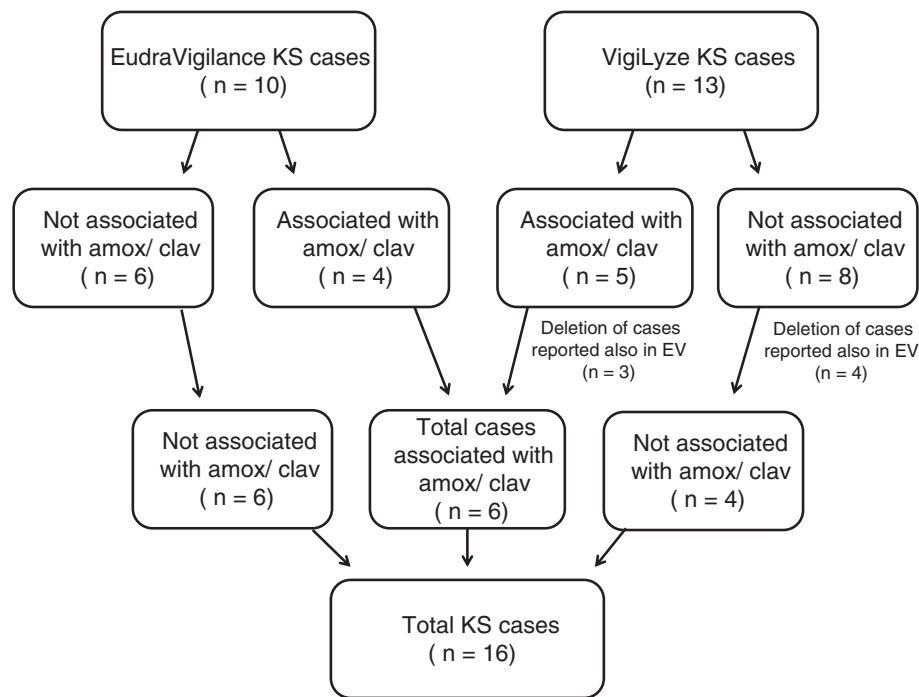


Fig. 1. Number of cases of Kounis syndrome identified in the two databases, before and after removal of duplicate cases. Amox/clav: amoxicillin/clavulanic acid; EV: EudraVigilance; KS: Kounis syndrome.

patient; a French case involving a 56-years-old patient; a Dutch case involving a male, 57-years-old patient. Therefore the total of reported KS cases associated with amoxicillin/clavulanic acid after exclusion of duplicate cases was six (previously corresponding to 4 in EV and 5 in Vigilize). In the majority of these cases, was described hospitalization with the resolution of the ADR (4 cases). Causality assessment through Naranjo algorithm classified one case as probable and five cases as possible (Table 3).

4. Discussion

In our study, the analysis of spontaneous reports from the two pharmacovigilance databases EudraVigilance and Vigilize allowed to identify the largest case series on KS associated with antibiotic use ever published and to identify a potential causal association between use of amoxicillin/clavulanic acid and occurrence of KS based on PRR values. Our study included also a statistical evaluation with quantitative method and causality assessment on the most reported antibiotic, amoxicillin/clavulanic acid.

In our case series, we identified a total of 16 cases of KS associated with antibiotics administration, six of which associated with amoxicillin/clavulanic acid administration. The largest cases series published so far on KS for all drugs included 51 cases and antibiotics resulted among the most frequent reported drugs associated with KS [23]. To the best

of our knowledge, the only case series specifically investigating the association between antibiotics administration and KS included a total of three patients, two of which received amoxicillin/clavulanic acid and one amoxicillin alone [16]. In addition, an association between amoxicillin/clavulanic acid administration and KS has been reported in several case reports. Biteker and colleagues [8,27], described two cases of KS in a 13-year-old and an 11-year-old boy occurred after they received oral amoxicillin/clavulanic acid. Both patients had ST segment elevation of ECG, regional wall motion abnormalities on echocardiography, elevated cardiac biomarkers, but normal coronary arteries at angiography. Both patients were treated with anti-histamines and steroids, and were discharged after few days with complete regression of signs and symptoms [8,27]. Tavil and colleagues reported a case of 61-year-old man with history of ischemic heart disease who developed cardiac ischemic and allergic symptoms 10 min after ingestion of 1000 mg amoxicillin/clavulanic acid [28]. He also had ST segment elevation on ECG and elevation of troponin T and Creatine kinase-MB fraction. Coronary angiography revealed absence of new lesions, and the patient was treated with oral antihistamines. He was discharged few days later after regression of signs and symptoms [28]. An additional case was reported from Viana-Tejedor and colleagues in 2011 [29]. They reported a case of a 64-year-old man with history of food allergy and coronary artery disease. Five years before, he underwent PCI for myocardial infarction and received two drug-eluting stents in the left anterior descending (LAD) artery. He received amoxicillin for shortness of breath, and immediately developed severe dyspnea, rash and urticaria. By arrival in Emergency Department, he also had chest pain which he reported similar to that from his previous MI. In this case, thrombotic occlusion of first diagonal branch of LAD was found [29]. Ralapanawa and Kularatne described the case of a 74-year-old man who developed signs and symptoms of anaphylactic shock together with chest pain associated to ST segment elevation on ECG. He was treated with steroids, anti-histamines, epinephrine, heparin, dual antiplatelet therapy, metoprolol and atorvastatin. Of note, he refused to undergo coronary angiography and was discharged after resolution of signs and symptoms [30]. Finally, Bezgin and colleagues reported a case of 29-year-old man who developed dyspnea and chest pain after receiving intra-muscular ampicillin/sulbactam and oral amoxicillin/clavulanic

Table 3
Causality assessment with Naranjo algorithm for the cases referred amoxicillin/clavulanic acid as suspected drug.

Geographic area	Age	Active substance	Causality assessment
TK	14 M	Amoxicillin/clavulanic acid	Probable
NL	82 M	Amoxicillin/clavulanic acid	Possible
NL	57 M	Amoxicillin/clavulanic acid	Possible
FR	56 M	Amoxicillin/clavulanic acid	Possible
IT	54 M	Amoxicillin/clavulanic acid	Possible
IT	55 M	Amoxicillin/clavulanic acid	Possible

acid [31]. ECG showed ST segment elevation, and the patient was treated with morphine, steroids and anti-histamines. He had normal coronary arteries and was discharged with regression of signs and symptoms [31]. Other antibiotics which have been associated to KS cases are cefuroxime [32], clarytromycin [33], ampicillin/sulbactam, ampicillin alone [31], and parenteral penicillin [34]. Our study confirmed that amoxicillin/clavulanic acid is among the most frequently involved antibiotics, representing the 37% of retrieved cases. Nevertheless, several molecules may be involved, with the vast majority of antibiotics being β -lactams. Actually, in only one case KS developed following administration of a non- β -lactams antibiotic (a combination of levofloxacin and metronidazole). Our data therefore confirm that β -lactams are the antibiotic class more frequently associated with allergic and hypersensitivity reactions [35].

Compared with previously published literature, we confirmed that occurrence of KS following antibiotic administration is usually rapid, but can also occur several days later. The only two cases of late presentation (more than 1 day after antibiotic administration) were associated with piperacillin/tazobactam administration. Interestingly, in one of these cases KS was reported to occur 3 months after antibiotic administration, suggesting that KS may not necessarily be an immediate and acute reaction. However, in the specific case, it also possible that other unidentified agents led to development of KS.

In contrast to previously published cases and case series, only in a minority of cases identified by a positive ECG or elevated cardiac biomarkers were reported. This might be a consequence of the lack of specific diagnostic criterion for KS, which is a clinical diagnosis. Although diagnosis of KS can be supported by ECG findings and laboratory analysis, but is largely based on history and clinical examination [36]. Histopathological examination may also be of help, but is difficult to obtain [36]. Furthermore, clinical presentation of KS is variable, and three types of this syndrome has been described [6,37]. However, information provided by reporters in the analyzed databases were insufficient to determine the type of KS occurred.

As in previously reported cases, treatment included anti-histamines and corticosteroids, and in several cases epinephrine was also administered. Interestingly, we identified one case in which epinephrine was reported as a drug suspected of causing KS together with amoxicillin. This is somewhat surprising, as epinephrine is commonly administered to treat allergic reactions. However, administration of catecholamines may be associated with cardiac ischemia. A possible explanation is that epinephrine was administered to treat an allergic reaction, and ischemic symptoms subsequently developed. Unfortunately, the reporter did not specify the time of administration of epinephrine with respect to ischemic symptoms, and, due to the organization of the Vigilyze database, it was not possible to retrieve this information.

History of allergy and cardiac disease were frequently reported and these conditions could be risk factors to the occurrence of this ADR.

The in-depth case analysis identified the occurrence in the perioperative period in many cases. This high incidence of perioperative KS might be due to the relatively frequent use of antibiotics in the perioperative period. However, it may also be a manifestation of the increase in the risk of occurrence of cardiovascular events after a surgical intervention [38]. Information provided by reporters in the two databases were however insufficient to establish precise timing of occurrence of KS with respect to surgical procedures.

Our study confirmed that KS may have a relevant clinical and prognostic impact, as MI occurred in three cases, in six developments of KS led to hospitalization or caused a prolonged hospital length of stay. These data are consistent with those reported in the largest case series, which described at least three cases of lethal KS out of 51 identified [23]. We chose to conduct a specific study on antibiotics and the occurrence of KS due to the widespread use of these drugs and well-known association between antibiotics and anaphylactic reactions [39]. Furthermore, antibiotics are among the drugs most frequently reported to be associated with KS [23]. As of today, there are no specific studies which

specifically investigate, either in-vitro or in-vivo, the mechanism of coronary spasm induced by antibiotics. However, we can hypothesize that the mechanism is similar to other allergic reactions. An allergen is recognized by IgE immunoglobulin and trigger mast cells degranulation. Mediators released by mast cells include histamine, tryptase and other enzymes, and several cytokines and other biologically active peptides. Histamine itself can cause vasoconstriction, while proteases released by mast cells can lead to activation of matrix metalloproteinases, which can induce coronary plaque erosion and rupture. Other mediators such as leukotrienes, thromboxane and platelet-activating factor have been involved in pathogenesis of myocardial ischemia [36].

Considering the number of patients receiving these antibiotics, the number of identified cases in our study is rather low. Interestingly, however, all retrieved cases were reported after 2012. This likely reflects increased awareness of KS and it is possible that the number of reported cases will increase in the next years. Furthermore, with increased awareness of this rare condition, it is also possible that both diagnostic accuracy and understanding of the pathophysiology of the syndrome will improve.

We used European database and the international database that allowed us to access to a large source of data. In particular, we considered useful to obtain PRR values with two methods, one that provided a comparison with all drugs, used as denominator, and another one more specific for rare syndrome considering as denominator only antibiotics known to involve in the occurrence of KS, based on our search. Taking into consideration all drugs we noted also a large confidence interval. Moreover, the outcome of the PRR for rare ADR [40] is more likely to be influenced by the amount of reports and therefore cannot be considered really significant. When we considered as denominator a total number of cases for antibiotics, PRR value remains significant, although the lower CI limit is just above 1.

4.1. Limitations

The analysis of database resulted into different results (i.e. 10 cases and 13 cases for antibiotics) and this could be explained by the different policies established by participating countries to the implementation of these databases (i.e. timelines, typology of reports sent in the database), differences in database management, and different criteria used to define ADRs.

Another limitation of our study is that all identified cases were spontaneously reported using pre-specified forms. Therefore, completeness and correctness of our data depends on accuracy of the reporter. The spontaneous reports often contained few information and the unavailability of data from all cases do not allow the complete evaluation of the association between the occurrence of KS and the use of the involved antibiotics. The evaluation to establish suspected and concomitant drug in the ADR occurrence was conducted by the reporters and subsequently validated. We adhered strictly to what reported in the spontaneous reports not modifying the evaluation already conducted, also because we had no access to full medical records with confidential data of the patients, but only on the information provided by the reporter and based on the reporting form.

An important limitation of the two searched databases is that they do not provide definite diagnostic criterion for KS (which is a clinical diagnosis), and they do not allow distinction between the different types of KS described in literature [6,36]. Therefore, mis-reports of misdiagnoses cannot be excluded.

From the two databases it is not possible to extrapolate easily data for all active substances excluding literature and duplicated cases for PRR calculation, therefore, PRR calculation was performed including also duplicate and already published cases.

Furthermore, when calculating the PRR for Kounis syndrome of amoxicillin/clavulanic acid vs all antibiotics using data from Vigilyze database, we obtained a PRR value of 1.61, which was not enough to generate the signal [25].

4.2. Conclusions

The specific analysis on association between antibiotics and KS provides an updated vision on the cases of KS associated with antibiotic use from two global pharmacovigilance databases. The overall number of cases identified is low, but is increasing in this last years, reflecting increased awareness of KS by physicians. Beta-lactam antibiotics are the most frequently reported causative drugs. Although a causal relation “amoxicillin/clavulanic acid and KS” cannot be ruled out considering the value of disproportionality measure, the number of cases is low, especially considering its wide use. Further analyses are needed to confirm this association.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.09.066>.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Disclosures

All of the Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No

information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data

According to WHO policy and UMC Guidelines, ICSRs sent from the WHO PIDM member countries to VigiBase are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). As the controller of the Data, the user shall be

liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

- (i) regarding the source of the information
- (ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
- (iii) that the information does not represent the opinion of the World Health Organization.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

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APPENDIX 2

Kounis syndrome due to antibiotics: a global overview from pharmacovigilance databases

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Calculation of Proportional Reporting Ratio (PRR) page 2

Supplementary References page 3

CALCULATION OF PROPORTIONAL REPORTING RATIO (PRR)

Proportional Reporting Ratio (PRR) is calculated as follows, according to Evans et al. [1]:

$$1) [a/(a+c)] / [b/(b+d)]$$

where a , b , c and d presented in 1) are defined according to the following 2×2 table:

	Drug of interest	All other drugs in database
Reaction(s) of interest	a	b
All other reactions	c	d

SUPPLEMENTARY REFERENCES

- [1] S.J. Evans, P. C. Waller, S. Davis, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiol. Drug. Saf.* 10 (2001) 483-6. doi: 10.1002/pds.677