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ARTICLE

Antibiotics-related adverse events in the infectious diseases department of a French teaching hospital: a prospective study

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Abstract Antibiotics are a significant cause of adverse events (AE), but few studies have focused on prescriptions in hospitalized patients. In infectious diseases departments, the high frequency and diversity of antibiotics prescribed makes AE post-marketing monitoring easier. The aim of our study was to assess the incidence and type of AE in the infectious diseases department of a French teaching tertiary-care hospital. The main characteristics of each hospitalization, including all antibiotics prescribed and any significant AE were recorded prospectively in the medical dashboard of the department. We included all patients having suffered an AE due to systemic antibiotics between January 2008 and March 2011. Among the 3963 hospitalized patients, 2682 (68 %) received an antibiotic and 151/2682 (5.6 %) suffered an AE. Fifty-two (34 %) AE were gastrointestinal disorders, 32 (21 %) dermatological, 20 (13 %) hepatobiliary, 16 (11 %) renal and urinary disorders, 13 (9 %) neurological and 11 (7 %) blood disorders. Rifampin, fosfomycin, cotrimoxazole and linezolid were the leading causes of AE. Sixty-two percent of the antibiotics causing an AE were stopped and 38 % were continued (including 11 % with a dose modification). Patients suffering from AE had an increased length of stay (18 vs 10 days, $P<0.001$). Our data could help choosing the safest antibiotic when several options are possible.

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Introduction

According to the World Health Organization, an adverse event is an injury related to medical management, in contrast to a complication of a disease [1]. Adverse events (AE) may be preventable (caused by an error) or non-preventable. Antimicrobials in conjunction with central nervous system agents, insulins, oral hypoglycemic agents, hematologic agents, cardiovascular agents and antineoplastic agents are among the most frequent causes of adverse drug events [2–4]. Post-marketing monitoring of drugs related AE is essential in order to detect rare events, or events in patients with multiple co-morbid conditions, who are often not included in randomized controlled trials. In hospitals, the high frequency and diversity of antibiotics prescribed makes antibiotics' adverse events (AAE) post-marketing monitoring easier, in particular in an infectious diseases (ID) department. Such monitoring is also possible in the outpatient setting [5], but the profile of patients, classes of antibiotics prescribed, doses and route of administration are different, and biological monitoring is uncommon. Few data are available in the literature regarding AAE. In Europe, two Italian studies have been published on this topic [6, 7] but none has focused on AAE in an ID department to the best of our knowledge. Gholami et al. [8] and Sun et al. [9] have reported an AAE incidence of 8 % and 24 % in an ID department among 460 patients in Iran and 299 patients in Taiwan, respectively. Anti-tuberculosis agents, antifungals, carbapenems and glycopeptides were reported as the leading causes of AAE among these hospitalized patients [8, 9], whereas for outpatient prescriptions penicillins, cephalosporins, cotrimoxazole and clindamycin were the most frequently involved in patients presenting to US emergency departments [5]. Such

studies are essential to enable clinicians to choose the less toxic drugs, bearing in mind the high cost of AAE [10]. The aim of our prospective study was to assess the incidence and type of AAE in the ID Department of a French teaching tertiary-care hospital.

Material and methods

This prospective observational study was conducted over a 38-month period (from January 2008 to March 2011 inclusive) in the 34-bed ID department in Nice University Hospital (France). Mean antibiotic use in defined daily doses (DDD) [11] in 2009–2010 in this department was 5,626 DDD/1,000 patient-days compared to 421 DDD/1,000 patient-days for the whole hospital at the same period. A pharmacovigilance specialist visited the ward once weekly systematically, and was available on request for advice at all times. The medical dashboard of our ward recorded prospectively the main characteristics of each hospitalization including all antibiotics prescribed and the occurrence of any significant adverse event, as judged by the infectious diseases physician in charge of the patient [12]. Main goals for this dashboard are real-time evaluation of medical practices and follow-up of internal guideline observance. Based on available software (Statview version 4.5), using defined parameters consensually chosen by the medical team which are systematically included in the report of hospitalization, our database has been prospectively informed since 2005. The secondary use of our medical database is observational researches. We included in our study all hospitalized patients having suffered an adverse event due to systemic antibiotics. Muco-cutaneous candidiasis episodes and catheter-induced thrombosis were excluded, since they are respectively a non-specific adverse event of all antibiotics and a device-related infection. We collected the following data regarding these AAE episodes, using the prospective database and a review of medical records: HIV status of the patient, type and grade of the AAE using the common terminology criteria for adverse events (CTCAE) version 4.0 [13], written advice of a pharmacologist regarding the AAE, impact of the AAE on the antibiotic course and on hospitalization. The length of stay was considered as increased when the review of the medical record revealed a delayed discharge of the patient because of the time necessary to control the AAE by either a symptomatic treatment or a dosage/drug modification. Incidence of AAE for the main antibiotics involved was calculated using two different denominators: (1) the total number of treatment courses for the drug during the 38-month period of study and (2) the mean DDD/1,000 patient-days for the drug in 2009 and 2010 (to take into account dose and duration). We also assessed if the AAE was preventable, a preventable AAE being defined as an inappropriate prescription or an administration error taking the current guidelines as a reference (e.g. an excessive dose in regard to the age of the patient, his/her renal clearance or liver function). Percentages were calculated for the categorical variables and means for continuous variables. The univariate analysis used the chi-square test for categorical variables, or Fisher's exact test when needed (sample size <5), and *t*-test to compare means. Data were analysed using SPSS software, version 18 (SPSS Inc., Chicago). All reported p-values were two-tailed, and a p-value <0.05 was considered to be significant.

Results

Among the 3,963 patients hospitalized during the study period, 2,378 (60 %) were men, 396 (10 %) were HIV positive and the mean age was 60±20 years. Types of infections leading to hospitalization are presented in Table 1, with 471 (14.2 %) of these infections being healthcare-acquired. Systemic antibiotics were prescribed in 2,682 (68 %) patients and 151/2,682 (5.6 %) suffered an AAE. Twelve (8 %) AAE were preventable. AAE were reviewed by the pharmacovigilance specialist in 38 (25 %) cases, more frequently when the AAE was severe. Drugs involved are presented in Table 2.

Organs affected by the AAE with distribution of severity grade are presented in Fig. 1, and the organs affected by the antibiotics most frequently responsible for the AAE are presented in Table 3. There were two *Clostridium difficile*

Table 1 Infections presented by the 3,313 patients during the 38-month study period

Site of infection	*n* (%)	Health-care acquired (%)	Mean duration of hospitalization (days)
Lung	801 (24.1)	1.5	8.8
Bone and/or joint	561 (17)	50.9	13.3
Urinary tract	503 (15.2)	9.7	8.7
Skin	414 (12.5)	12.3	8.9
Central nervous system	227 (6.9)	6.6	10.8
Abdominal	206 (6.3)	4.4	8.6
Cardiovascular	153 (4.6)	32.7	13.4
Ear–nose–throat	116 (3.5)	0.9	7.6
Bacteremia	89 (2.7)	10.1	12.8
Fever of viral origin	79 (2.4)	0	7
Tuberculosis[a]	65 (2)	0	21.5
Malaria	62 (1.9)	0	3.4
Other infections	37 (1.1)	5.4	6.5

650/3963 (16.4 %) patients were hospitalized for non-infectious motives

[a] Tuberculosis: 44 pulmonary, ten lymphadenitis, four osteomyelitis, four abdominal, one pericarditis, one urogenital and one meningoencephalitis

Table 2 Antibiotics responsible for the 151 adverse events

Antibiotic	Adverse event		Severity grade				
	n	%	1 (n)	2 (n)	3 (n)	4 (n)	5 (n)
Rifampin	33	21.8	4	27	2		
Beta-lactams	27	17.8	1	18	7	1	
Fluoroquinolones	20	13.2		8	9	2	1
Cotrimoxazole	18	11.9	1	9	7	1	
Vancomycin	10	6.6	2	3	4	1	
Association of antibiotics[a]	7	4.6		4	3		
Association of antimycobacterial agents[a]	6	3.9	1	4	1		
Linezolid	6	3.9		3	2	1	
Clindamycin	6	3.9		2	4		
Macrolides	5	3.3		3	1	1	
Fosfomycin (IV)	5	3.3		2	3		
Fusidic acid	3	1.9		1	1	1	
Aminoglycosides	2	1.3		1	1		
Pyrazinamide	2	1.3	1			1	
Colistin	1	0.6			1		
Total	151	100	10	85	46	9	1

[a] Associations of antibiotics or antimycobacterial agents refer to an adverse event that could not be attributed to only one drug

associated diarrheas (severity grade 2 and 3), one of whom was a recurrence. They represented 3.8 % of the gastrointestinal AAE, both occurred under antibiotic association prescribed for prosthetic joint infections: benzathine cloxacillin with levofloxacin and ceftazidime with ciprofloxacin. There were only two allergic reactions of type 1 immediate hypersensitivity revealed by a generalized urticarial eruption due to pyrazinamide and amoxicillin. The only AAE that led to death (grade 5) was a toxic epidermal necrolysis related to ciprofloxacin. AAE incidence for the main drugs involved was calculated using two denominators (antibiotic courses and DDD) and results are presented in Table 4. Management of the AAE induced a prolongation of hospitalization in 74 (50 %) cases. Patients suffering from AAE had an increased length of stay (18 vs 10 days, *t*-test, $P<0.001$, $N=2{,}682$). Sixty-two percent of the antibiotics causing an AAE were stopped and 38 % were continued, including 11 % with a dose modification. AAE were more frequent in patients with bone and joint infections (11 % vs 4 %, $\chi^2=34$, $P< 0.001$, $N=2{,}682$) and healthcare-acquired infections (11 % vs 4 %, $\chi^2=32$, $P<.0.001$, $N=2{,}682$). There was no significant association between AAE and HIV status.

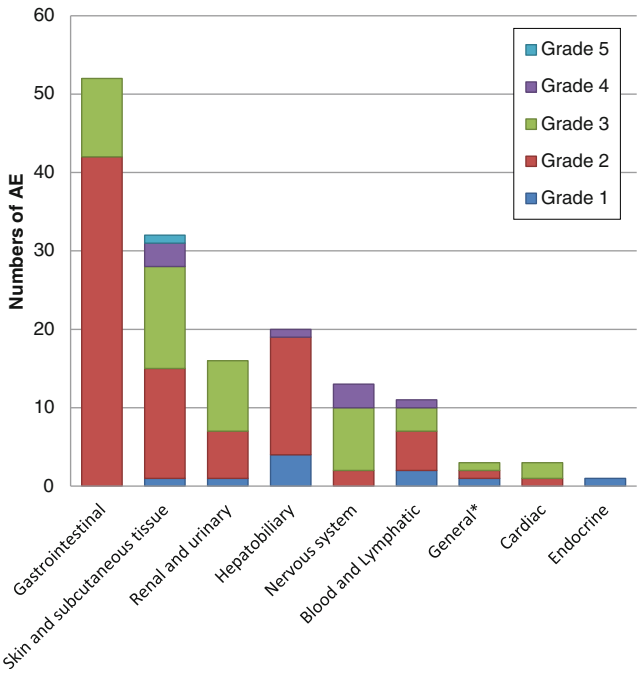

Fig. 1 Organs affected by the adverse events (AE) with distribution of severity grade. *General disorder refers to iatrogenic fever

Discussion

Our prospective study conducted over a 38-month period in an ID department showed a 5.6 % incidence rate for antibiotics-related AE. Rifampin, fosfomycin, cotrimoxazole and linezolid were the leading causes of AAE. Among the organ systems affected, gastro-intestinal and skin were the most frequently affected (55 %), followed by liver and kidney disorders (13 % and 11 %, respectively).

Our large prospective study was conducted in an ID department, with a wide variety of different antibiotics, sometimes prescribed using high doses and long durations of therapy in infective endocarditis or prosthesis-related joint infections. ID specialists were highly knowledgeable regarding AAE, with

Table 3 Organs affected by the antibiotics responsible for adverse events (AE)

	Number of AE	Number of prescriptions	Gastrointestinal	Skinand subcutaneous	Renal and urinary	Hepatobiliary	Nervous system	Blood and Lymphatic	Cardiac	General	Endocrine
Rifampin	33	317	14	2		13		4			
Beta-lactams	27	1938	14	8		1	3			1	
Fluoroquinolones	20	794	3	4	1	2	7	2	1		
Cotrimoxazole	18	198	5	4	6			1		2	
Vancomycin	10	135	1	3	4		1	1			
Association of antibiotics[a]	7	1731	5		1		1				
Association of antimycobacterial agents[a]	6	65	4	1							1
Linezolid	6	80	2	2			1	1			
Clindamycin	6	235	3	2							
Macrolides	5	159	1	2		1		1			
Fosfomycin (IV)	5	52		2	1				2		
Fusidic acid	3	65		1		1		1			
Aminoglycosides	2	311			2						
Pyrazinamide	2	57		1		1					

Color code: frequency of AE occurrence for each antibiotic, < 0.5 % white; 0.5–2 % yellow; 2–5 % red

[a] Associations of antibiotics or antimycobacterial agents refer to an adverse event that could not be attributed to only one drug

the help of a pharmacovigilance specialist. Few studies have compared the incidence of AAE between classes of antibiotic agents in hospitalized patients [6–9]. Our observations offer useful information to clinical physicians prescribing antibiotic agents.

This study however presents some limitations. First, although our data describe clinically relevant drug-related adverse events that warranted medical attention and were worth mentioning in the medical report, we could not account for unreported events and events identified in other health care settings, such as offices of physicians when the patient was discharged. Second, we could not describe AAE at the individual antibiotic level. Last, the setting of an ID department in a tertiary care center may appear as too specialized but it can also help to highlight AAE occurring despite adequate prescription.

Because of differences in study design, data collection, and definition of AAE, the diversity of drugs used, and the heterogeneity of the investigated populations, the reported prevalence of AAE in the inpatient setting varies greatly in the literature, from 3 % to 24 %, the highest rates being reported in ID departments: 2.8 % in two Italian pulmonology departments [7], 8.2 % in an Iranian ID department [8], 4 % in one Italian hospital [6] and 24 % in one ID department in Taiwan [9].

Ten percent of all rifampin courses were complicated by an adverse event in our study, of grade 2 (moderate) severity in 82 % of cases. The usual dose in France is 20 mg/kg/day (except for tuberculosis), and these high doses may account for the high frequency of hepatobiliary disorders (4 % of all rifampin courses, compared to less than 2 % in the literature

Table 4 Incidence of antibiotics-related adverse events (AE)

Antibiotic	Number of AE	Antimicrobial courses	AE incidence[a]	DDD/1000 patient-days	AE incidence[b]
Rifampin	33	317	10.4 %	NA	–
Fosfomycin	5	52	9.6 %	37	13.5
Cotrimoxazole	18	198	9.1 %	846	2.1
Linezolid	6	80	7.5 %	61	9.8
Vancomycin	10	135	7.4 %	80	12.5
Fusidic acid	3	65	4.6 %	48	6.25
Macrolides	5	159	3.1 %	160	3.1
Clindamycin	6	235	2.6 %	168	3.6
Fluoroquinolones	20	794	2.5 %	568	3.5
Beta-lactams	27	1938	1.4 %	3,467	0.8
Aminoglycosides	2	311	0.6 %	191	1

[a] Number of AE divided by the total number of antimicrobial courses over the study period for the drug

[b] (Number of AE divided by the mean DDD/1000 patient-days for 2009–2010) x 100

NA data non available

[14]), since liver toxicity appears to be dose-related [14]. Blood AAE occurred in 1.3 % of cases with three cytopenias and one international normalized ration disequilibrium during anticoagulant therapy.

AAE were observed in 9 % of cotrimoxazole courses, mainly kidney (3 %) and skin (2 %) disorders. Among the six kidney AAE, there were four hyperkaliemias and two renal insufficiencies, four were severe (grade 3) and four led to discontinuation of treatment. Fraser et al. reported 11.2 % of acute kidney injury with cotrimoxazole in a specific middle-aged population treated for a minimum of six days [15], while Antoniou et al. identified cotrimoxazole treatment as a major risk of hospitalization for hyperkaliemia in elderly patients receiving spironolactone [16]. Two of the four skin reactions were of severity grade≥3 associated to cotrimoxazole discontinuation. Hematotoxicity occurred in only one patient with a neutropenia of grade 2 managed with dosage decrease. Our results are in accordance with the literature, since the prevalence of skin and blood disorders related to cotrimoxazole and leading to hospitalization were reported to be very low (0.06 % and 0.03 %, respectively) [17].

Vancomycin courses were complicated by an AAE in 7 % of cases, which affected mainly skin (2 %) and kidney (3 %) organ systems.

An AAE occurred in nearly 8 % of linezolid courses, affecting mainly skin, gastrointestinal tract, nervous system and hemic system. Linezolid was commonly used to treat bone and joint infections as well as multi-resistant tuberculosis in our unit, for long durations of treatment, and this may explain this high incidence. This observation emphasizes the risks associated with an off-label use—incidence, severity or type of AE may vary and the prescriber remains the only responsible party.

Fluoroquinolones were quite rarely responsible for AAE (2.5 %), with a very wide range of organs affected, but with the highest rate of grade 3 (severe) AAE. The nervous system was the most frequently affected organ by fluoroquinolones with five confusions, one seizure and one dizziness and this is in accordance with the literature [9]. The severity grades of those nervous system AAE, always≥3 (dizziness excluded) and the age of the patients (mean, 79 years) are noteworthy and should lead to high caution regarding the dosage prescribed in elderly patients associated with a specific neurologic clinical monitoring.

The AAE incidence rates of clindamycin (2.6 %) and fluoroquinolones (2.5 %) were similar. No *C. difficile* associated diarrhea occurred with clindamycin in our department. This antibiotic does not seem to deserve its bad reputation regarding its safety profile, and similar findings were also noted by Sun et al. [9].

Surprisingly only two *C. difficile*-associated diarrheas occurred with antibiotic regimens containing both fluoroquinolones and beta-lactams. This result may be linked to the limitation of our study previously mentioned, i.e. such AAE can occur after discharge of the patient [18] and even if those AAE were treated by our physicians in the outpatient setting the dashboard would not record it. Another explanation could be the non standardized but frequent use in our ward of probiotics, especially for antibiotic associations, which is known to reduce the incidence of *C. difficile*-associated diarrhea [19].

Beta-lactams were responsible for AAE in 1.4 % of the cases, with mainly skin and gastro-intestinal disorders, as expected. AAE related to aminoglycosides were rare (two cases only), probably because, infective endocarditis aside, the duration of prescription was usually short in our department (less than three days) as well as compliance with the dosing guidelines and therapeutic drug monitoring were common practice in our ID department.

HIV status was not associated with the occurrence of an AAE in our study, even though HIV patients have been reported to be more susceptible to AAE in the literature [20–22]. During the last decade hospitalization causes of HIV-infected patients have, with the help of highly active antiretroviral therapy, significantly changed [23–25], e.g. hospitalizations for non infectious comorbidities or community-acquired infections are more frequent. Thus, the safety profile of antimicrobials used in those patients has also changed, especially for pulmonary infections [26], and may explain our results.

In conclusion, hospital-based monitoring of AAE is a good method with which to detect known and unknown links between drug exposure and adverse events. These data cannot be used in isolation to dictate the decision as to whether to prescribe antibiotics or to determine optimal antibiotic selection for individual patients. However, they can be used by clinicians to help assess the validity of their perceptions of the safety profile of various antibiotic classes. These population-based findings are also important, because adverse event data from spontaneous reports cannot provide population rates, and safety data from clinical trials largely reflect adverse events among a small number of highly selected persons.

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