

## Adverse drug events in hospitalized patients in Brazil: Integrative literature review

Eventos adversos em pacientes hospitalizados no Brasil: Revisão integrativa da literatura

Eventos adversos por fármacos em pacientes hospitalizados en Brasil: Revisión integradora de la literatura

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### Abstract

**Objective:** Analyzing studies related to Adverse Drug Events (ADE) in hospitalized patients in Brazil. **Method:** integrative review, for which the National Library of Medicine (PubMed), Biblioteca Virtual de Saúde (BVS), Repository of the Fundação Oswaldo Cruz (FIOCRUZ) and Capes Journals databases were selected for searching the studies primary, with the descriptors: Patient Safety, Drug-related side effects and adverse reactions, Patient harm, Hospitalization, Inpatients. **Results:** Twenty articles were identified, 50% (10) were from the southeast region of Brazil. Regarding the methodology adopted to identify the ADEs, 70% (14) used the retrospective data review. The trackers were used in 5 (25%) articles, 3 of which used the triggers proposed by the Institute for Healthcare Improvement, and the other 2 the trackers used were proposed by the researchers themselves. The number of adverse drug reactions ranged from 12 to 96, while the occurrence of AE ranged from 4 to 122. In one study 50% (41) of participants had at least one adverse drug event. **Conclusion:** There is great variability in scientific production in Brazil, and in the occurrence of Adverse Drug Events as well. There is a need for strategies to identify these events and create strategies to promote patient safety.

**Keywords:** Drug-related side effects and adverse reactions; Pharmacovigilance; Quality indicators, Health care.

### Resumo

**Objetivo:** Analisar estudos relacionados a Eventos Adversos a Medicamento (EAM) em pacientes hospitalizados no Brasil. **Método:** revisão integrativa, para a qual foram selecionadas as bases de dados da Biblioteca Nacional de Medicina (PubMed), Biblioteca Virtual em Saúde (BVS), Repositório da Fundação Oswaldo Cruz (FIOCRUZ) e Periódicos Capes para a busca dos estudos primários, com os descritores: Patient Safety, Drug-related side effects and adverse reactions, Patient harm, Hospitalization, Inpatients. **Resultados:** Foram identificados 20 artigos, 50% (10) da região sudeste do Brasil. Em relação à metodologia adotada para identificar os ADEs, 70% (14) utilizaram a revisão retrospectiva dos dados. Os rastreadores foram utilizados em 5 (25%) artigos, dos quais 3 utilizaram os gatilhos propostos pelo Institute for Healthcare Improvement e os outros 2 os rastreadores utilizados foram propostos pelos próprios pesquisadores. O número de reações adversas a medicamentos variou de 12 a 96, enquanto a ocorrência de EA variou de 4 a 122. Em um estudo, 50% (41) dos participantes tiveram pelo menos um evento adverso a medicamentos. **Conclusão:** Há grande variabilidade na produção científica no Brasil, bem como na ocorrência de Eventos Adversos a Medicamentos. São necessárias estratégias para identificar esses eventos e criar estratégias para promover a segurança do paciente.

**Palavras-chave:** Efeitos colaterais e reações adversas relacionados a medicamentos; Farmacovigilância; Indicadores de qualidade em assistência à saúde.

### Resumen

**Objetivo:** Analizar estudios relacionados con Eventos Adversos a Medicamentos (AME) en pacientes hospitalizados en Brasil. **Método:** revisión integradora, para lo cual se seleccionaron las bases de datos de la Biblioteca Nacional de Medicina (PubMed), Biblioteca Virtual en Salud (BVS), Repositorio de la Fundación Oswaldo Cruz (FIOCRUZ) y Revistas Capes para la búsqueda de estudios primarios, con los descriptores : Patient Safety, Drug-related side effects and adverse reactions, Patient harm, Hospitalization, Inpatients.. **Resultados:** Se identificaron veinte artículos, 50% (10) de la región sureste de Brasil. En cuanto a la metodología adoptada para identificar las EAM, el 70% (14) utilizó la revisión retrospectiva de los datos. Los rastreadores se utilizaron en 5 (25%) artículos, de los cuales 3 utilizaron los activadores propuestos por el Instituto para la Mejora de la Salud y los otros 2 seguidores utilizados fueron propuestos por los propios investigadores. El número de reacciones adversas a medicamentos varió de 12 a 96, mientras que la aparición de EA varió de 4 a 122. En un estudio, el 50% (41) de los participantes tuvo al menos un evento adverso de medicamentos. **Conclusión:** Existe una gran variabilidad en la producción científica en Brasil, así como en la ocurrencia de Eventos Adversos a los Medicamentos. Se necesitan estrategias para identificar estos eventos y crear estrategias para promover la seguridad del paciente.

**Palabras clave:** Efectos colaterales y reacciones adversas relacionados con medicamentos; Farmacovigilancia; Indicadores de calidad de la atención de salud.

## 1. Introduction

Patient safety, according to the World Health Organization (WHO), is one of the quality attributes of health services. According to WHO (2009), it aims to “reduce the risk of unnecessary harm associated with healthcare to the minimum acceptable”.

According to the Institute of Medicine (IOM) (2000) and the National Health Surveillance Agency (2013), the term “patient safety” started to be discussed internationally with the launch of the report “To Err is Human” prepared by the Institute of Medicine (IOM), which found, through a retrospective analysis of medical records of patients admitted to hospitals in New York, Utah and Colorado, that about 100,000 people die each year in the United States due to ADEs.

WHO (2002) and Mendes, Martins, Rozenfeld and Travassos (2009), state that Adverse Events (AE) can be defined as any incident that results in unintentional damage resulting from care, unrelated to the patient's natural course of illness. Thus, Adverse Drug Events (AME) are among the three most common causes of AS. AEs include Adverse Drug Reactions (ADRs), defined as any harmful or unwanted effects after drug administration in doses commonly used by humans for the prophylaxis, diagnosis or treatment of a disease.

Vicent (2010) ensures that in the United States, at least one medication error occurs each day in each patient. These errors, although almost predictable, can trigger events. Thus, hospitalized patients are particularly susceptible to the occurrence of AMI.

The study by Kimelblatt et al. (1988) indicated the occurrence of ADEs in 10 to 20% of all hospitalized patients. Classen found that 2.3% of hospitalized patients had their clinical condition aggravated by ADEs and 3.5% of these led to death. In these studies, it is possible to identify the increase in hospital stay and, consequently, the cost of treatment by 174%. Also concluded that 50% of expenditures could be avoided by DE prevention measures (Classen, Pestotnick, Evans, Lloyd & Burke, 1997). The studies by Venulet & Ham (1996), Nunes (2000) and Brasil (2013) indicate that in Brazil, between 2006 and 2013, the report of the Health Surveillance Notification System (NOTIVISA) showed a total of 103,887 EA, 38,730 were ADEs and of these, 14.8% to 59% could be avoided.

According to WHO (2002), among the methods of identifying AMI, are voluntary notification (passive search) and intensive monitoring (active search).

As explained by Dolores-Menendez et al. (2019), Spontaneous Notification is a low cost method, in which professionals and / or patients spontaneously report the occurrence of AE. The main limitation of this methodology is

underreporting.

In the active search, AE is identified through a retrospective and / or prospective review of the patient's medical record based on criteria previously defined by the institution. This method is more effective in identifying AE, but it requires time, human and financial resources to be well employed. In addition, the effectiveness of the method, when performed retrospectively, depends on the quality of the professionals' records, which also becomes a limiting factor (WHO, 2002; Griffin & Resar, 2009; Classen et al, 2011).

Therefore, identifying and knowing the occurrence of ADRs and ADEs are requirements to make health services more secure and financially healthy. Therefore, this review aims to analyze studies related to Adverse Drug Events (AME) in hospitalized patients in Brazil.

## 2. Methods

Also based on studies by Haukland, Plessen, Nieder and Vonen (2017). This work is an integrative review based on the research question: "How is the identification of ADRs made and what is the profile of AS in hospitalized patients in Brazil?". This was delimited by the PICO strategy (acronym for Patient, Intervention, Comparison, Results). The steps taken in preparing the study were: elaboration of the research question, sampling or search in the literature of primary studies, data extraction, evaluation of primary studies, interpretation of results, presentation of the review.

The primary studies were searched from July to August 2019, in the following databases: National Library of Medicine of the National Institutes of Health (PubMed), Virtual Health Library (VLH / BVS), Repositório da Fundação Oswaldo Cruz (FIOCRUZ) and Capes Journals.

The controlled descriptors selected in the Health Sciences Descriptors (HSD) of the Virtual Health Library (VLH / BVS) and HSD in PubMed were "Patient Safety, Side Effects and Adverse Reactions Related to Medicines, Patient Damage, Hospitalization, Inpatients " (in English). The descriptors were combined using the Boolean operators, which obtained the following searches: "patient safety AND side effects and adverse reactions related to drugs and damage to the patient and hospital and inpatients", "patient safety AND related side effects and adverse reactions to medicines ". OR damage to the patient AND Hospitalization OR Inpatients ".

The inclusion criteria were articles whose main and / or secondary objective was to identify ADRs and / or ADEs in hospitalized patients. Regarding the period, we selected the articles published in the last five years (2014 to 2019). The search was conducted in Portuguese, Spanish and English. The exclusion criteria were: studies carried out in emergency rooms and outpatient services in hospitals, case reports and studies that did not differentiate the types of adverse events.

The choice of articles was divided into three stages:

- 1) Search for articles using descriptors in the databases, filtering the period of 5 years.
- 2) Reading of titles and abstracts by two independent reviewers who decided to include or exclude the article. In case of disagreement, a third reviewer was invited.
- 3) Reading of the articles in full by the reviewers, in order to identify whether the article answered the proposed question.

Were identified 194 articles in the four databases. After applying the criteria, 174 articles were excluded, for the following reasons: Duplicates (17), Secondary Studies and / or Case Report (8), Other Countries (6), Does not Answer the Proposed Question (116) and Studies in Outpatients (27). Thus, 20 articles were qualified for this review.

## 3. Results

The information extracted from the primary studies included in the review is shown in Table 1.

**Table 1** - Information extracted from the primary studies.

Nº	Title	Autor Ano	Language Place	Population Sample	Objective	Method	Gender	Length of stay	Age	Nº of ADE	Nº of ADR	Main Drugs	Risk factors
1	Factors associated with drug interactions in elderly hospitalized in high complexity hospital.	Veloso, Figueiredo, Barroso, Nascimento & Reis (2019)	Portuguese Minas Gerais	237 seniors	Determine the frequency of possible drug interactions (PID) in hospitalized elderly and associated factors.	Retrospective analysis of medical records. Period: 1 year	120 (50,6%) male	≤ 12 days, (51,5%)	70 years	-	51 ADR 16 (6,8%) related to drug interaction	-	-
2	Incident analysis occurrence related to potentially dangerous medicines distributed in teaching hospital.	Basile, et al. (2019)	Portuguese São Paulo	786 Notifications	Analyze the reports of incidents related to potentially dangerous drugs dispensed in a teaching hospital in the interior of São Paulo.	Retrospective analysis of notifications. Period: 5 years	226 (28,72%) male and 226 (28,72%) sexo female	-	-	-	30 ADR 15,95% of notifications	Drugs That Act On: Nervous System 67 (35,63%);	-
3	Increase of 10% in the Rate of Adverse Drug Reactions for Each Drug Administered in Hospitalized Patients.	Ribeiro, Motta, Marcondes-Fonseca, Kalil-Filho & Giavina-Bianchi (2018)	English São Paulo	472 patients	Assess risk factors, incidence and severity of adverse drug reactions in inpatients	Prospective analysis of medical records, patients hospitalized for more than 48 hours. Duration: 3 years Causality: Naranjo Algorithm	239 (51,5%) female.	16,8 days	57,5 years ( ± 19,9)	-	94 ADR in 75 patients (16%)	Antibiotics (21.2%) Opioids (13.8%) Iodinated contrast media (10.6%)	Chronic renal failure; Prolonged length of stay; Higher number of medications on admission; For each drug introduced during hospitalization, there was a 10% increase in the adverse drug reaction rate.
4	Hospitalizations and deaths from drug poisoning and adverse reactions in Brazil: an analysis from 2000 to 2014.	Santos & Boing (2018)	Portuguese Brazil	-	Describe the tendency of mortality and hospitalizations for these diseases in Brazil, between 2000 and 2014.	Retrospective analysis of data from MIS (Mortality Information System) and SIH-SUS (SUS Hospital Information System) CID-10 Period: 4 years	-	-	-	0,4% hospital admissions proportional to 100,000 inhabitants	-	-	

5	Preventable adverse drug events in critically ill HIV patients: Is the detection of potential drug-drug interactions a useful tool?	Ramos, Japiassu, Bozza & Guaraldo (2018)	English Rio de Janeiro	62 patients with HIV / AIDS in the ICU	Develop a strategy to identify AE associated with drug interactions by analyzing prescriptions of critically ill patients	Retrospective analysis of medical records. Causality: Naranjo Algorithm Period: 2 years	72,6 male	13 days	37,5 years	9% of interactions resulted in 24 MI in 16 (25.8%) patients	20 ADR (83,3%)	Anticonvulsant	-
6	Risk factors associated with hypoglycemia and analysis of adverse events in intensive therapy.	Roque, Silva, Santos & Melo (2018)	Portuguese Rio de Janeiro	355 adults in ICU	Evaluate the predictive factors associated with the occurrence of severe hypoglycemia and to analyze adverse events related to insulin use and oral hypoglycemic agents in ICU patients.	Prospective analysis of medical records of ICU patients. Period: 1 year IHI adaptation Causality: Naranjo Algorithm	189 (53%) Female	Enfermaria: 9,83 days  UTI 17,5 days	60,18 years	120 events of severe hypoglycemia	-	-	Presence of liver disease; Sepsis; Occurrence of adverse events;
7	Adverse events to drugs identified in hospitalized patients in Brazil according to codes of the International Classification of Diseases (ICD-10).	Martins, Giordani, Guaraldo, Tognoni & Rozenfeld (2018)	English 2018 Brazil	55.604.537 hospital admission records	It examined the potential of applying CID-10 codes (10 <sup>th</sup> revision of the International Classification of Diseases) in a national public health system database (SIH-SUS).I	Retrospective analysis of data from SIM (Mortality Information System) and SIH-SUS (SUS Hospital Information System) CID Code Period: 4 years	-	-	-	273,440 (0.49%) were related to at least one ADE	-	-	-
8	Triggers for active surveillance of adverse drug events in newborns.	Fabretti, Brassica, Cianciarullo & Romano-Lieber (2018)	Portuguese São Paulo	125 Neonates in the Neonatal Intensive Care Unit (ICU) and Conventional Neonatal Intermediate Care Unit (UCINCo).	Verify the application and performance of triggers for adverse drug events in hospitalized newborns.	Prospective analysis of medical records of patients admitted to the ICU and neonatal ICU. Period: 7 months Own Trackers	-	-	-	115 ADE	-	-	-

9	Risk factors for death in patients with non-infectious adverse events.	Gadelha, Paixão, Prado, Viana & Amaral (2018)	English Acre	792 ICU adult patients	Identify risk factors for death in patients who have experienced non-infectious adverse events.	Retrospective analysis of medical records; Period: 1 year and 11 months	466 (58,8%) male	458 (58,3) ≤ 7 days	> 50 years	From the AE identified 94 (17.7%) Medication and blood transfusion	-	40 (43.9%) Antimicrobials 16 (17.6%) Anti or procoagulants 07 (7.7%) Sedation / Analgesia 05 (5.5%) Electrolytes	-
10	Factors associated with adverse drug reactions in older inpatients in teaching hospital.	Figueiredo, Groia, Barroso, Nascimento & Reis (2017)	English Minas Gerais	237 elderly hospitalized for more than five days.	Determine the prevalence of ADRs among elderly patients and the factors associated with their occurrence. Brazilian hospital environment.	Retrospective analysis of medical records; Own trackers Period: 1 year.	120 (50,6%) male	12 days	70 years	-	62 ADR in 50 (21.1%) of the elderly	Vancomycin (n = 5), Morphine (n = 4), Captopril (n = 4), Furosemide (n = 4).	Cardiac insufficiency Length of stay >12 days.
11	Risk factors for adverse drug reactions in pediatric inpatients: A cohort study.	Andrade, Lobo & Silva (2017)	English Sergipe	173 pediatric patients hospitalized for more than 48 hours.	Identify risk factors for adverse drug reactions (ADRs) in pediatric patients.	Prospective analysis of medical records, team and patient reports, and spontaneous reports; Naranjo's algorithm Period: 10 months	95 (54,9%) male	8 days	4,8 years	-	66 ADR in 38 (22%) patients.	Antiepileptic drugs; Use of systemic antibiotics; Use of meglumine antimoniato;	Previous history of ADR;
12	Epidemiological, clinical and evolutionary aspects of tuberculosis among elderly patients of a university hospital in Belém, Pará	Chaves (2017)	Portuguese Pará	82 elderly with tuberculosis	Evaluate the epidemiological, clinical and evolutionary aspects of tuberculosis in the elderly in a University Hospital in the city of Belém, Pará.	Retrospective analysis of medical records. Period: 4 years	Male predominance	-	69,8 years	-	77 ADR in 41 (50%) of the elderly for TB	-	-

13	Antimicrobial drug-related problems in a neonatal intensive care unit	Nunes, Xavier & Martins (2017)	Portuguese 2017 Rio Grande do Norte	85 neonates in the ICU, hospitalized for more than 24 hours.	Determine the main drug-related problems in neonates using antimicrobials.	Prospective analysis of medical records.	58,5% male	-	-	-	12 RAM represents 15.2% of identified drug related problems	Gentamicin Amikacin Cefazolin	-
14	Potentially inappropriate prescribing and the risk of adverse drug reactions in critically ill older adults.	Galli, Reis & Andrzejewski (2016)	English Paraná	185 elderly patients admitted to the ICU for more than 24 hours	Describe the prevalence and factors associated with the use of MPI and the occurrence of adverse reactions related to ADE in critical elderly.	Retrospective analysis of spontaneous notifications Period: 1 year	54,9% male.	14 days	71 years	-	49 ADRs in 33 (17.8%) patients	23 ADRs were associated with the drugs in the Beers Criterion.	-
15	Adverse events in the intensive care unit: impact on mortality and length of stay in a prospective study	Roque, Tonini & Melo (2016)	Portuguese Rio de Janeiro	355 adult patients in the ICU	Assess the occurrence of adverse events and their impact on length of stay and mortality in the intensive care unit (ICU).	Prospective analysis of medical records. IHI Trackers Naranjo's algorithm Period: 1 year	189 53,2% female	34 dias with AE  15 without AE	60,2 years	79 EAM (24,4%) em 21 (13,8%) pacientes	-	Vasoactive and sedative amines	Nº of medicines
16	Factors associated with the occurrence of adverse events in critical elderly patients	Toffoletto et al, (2016)	Portuguese São Paulo	315 elderly hospitalized for more than 24 hours in the ICU	Identify the factors related to the occurrence of adverse events in critically ill elderly patients admitted to the intensive care unit according to demographic and clinical characteristics.	Retrospective analysis of medical records Moderate and severe events only	60,6% male	10,62dias with ADE  5,06 without ADE	71,30 years	4 EAM (2,5%) do total de 183 eventos adversos	-	-	-
17	Adverse Drug Reactions in Patients Receiving Systemic Antifungal Therapy at a High-Complexity Hospital.	Souza, Santos & Reis (2016)	English Minas Gerais	183 patients who used antifungal therapy	Determine the frequency of adverse drug reactions associated with the use of systemic antifungals in patients hospitalized in a highly complex hospital.	Retrospective analysis of medical records Period: 1 year	105 (57,4%) male	-	43 years	-	96 ADRs in 53 patients (29%)	-	Diagnosis of neoplasia; Hospitalization time; Use of 13 or more medications;

18	Adverse drug events identified by triggers at a teaching hospital in Brazil.	Giordani, Rozenfeld & Martins (2014)	English Paraná	240 patients older than 15 years, hospitalized for more than 48 hours.	Evaluate the incidence of ADEs and to characterize them in terms of degree of damage, medication involved and patient symptoms in a Brazilian university hospital.	Retrospective analysis of medical records Period: 7 months IHI Trackers Causality: Naranjo's algorithm.	63,8% male	-	50,8 years	44 EAM em 35 (14,6%) pacientes	-	Anti-infectives	Length of stay; Use of 10 drugs or more;
19	Severe cutaneous reactions to drugs in the setting of a general hospital.	Grando, Schmitt & Bakos (2014)	English Rio Grande do Sul	57 patients with severe reactions	Evaluate the clinical and epidemiological aspects of serious cutaneous adverse drug reactions in a tertiary hospital in Porto Alegre, Brazil.	Retrospective analysis of medical records Period: 5 years	-	-	38,4 years	-	57 patients with skin reactions caused by medication.	Anticonvulsants Antibiotics Painkillers	-
20	Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in a hospital in Distrito Federal.	Emerick, Rodrigues, Pedrosa, Novaes & Gottems (2014)	Portugues Distrito Federal	22 patients hospitalized with SSJ and NET in the ICU and Burn Unit.	Analyze the demographic and clinical aspects of patients diagnosed with Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (NET), as well as to identify health professionals' actions for the management of adverse drug reactions (ADR) in a public hospital in the District. Federal, Brazil.	Retrospective analysis of medical records Period: 7 years	Female	-	-	-	22 patients with SSJ and NET due to medications.	Antiepileptics.	-

Source: Research Protocol (2019).



#### 4. Discussion

In this review 50% (10) of the studies came from the southeast region, from these, 20% (4) concentrated in SP. These data corroborate the reports of The Royal Society (2011) which verified spatial heterogeneity in scientific production, with a large concentration of studies in the southeast region, and listed São Paulo as the region responsible for about 20% of scientific production in Brazil.

In the methodology adopted, there was a prevalence 70% (14) of studies with retrospective review of data. According to some authors in the identification of ADEs, retrospective review of medical records is one of the most widely used methods, as well as spontaneous reporting, but they point out the retrospective methodology usually has limitations in identifying associated risk factors and determining the causality chain <sup>[38, 39,40]</sup>. In addition, Franklin's study at a surgical center in 2010 found the lack of complete data in patient records was a factor that hinder the ADEs identification, from the 207 records analyzed, 25% (51 / 207) did not have complete data and 17% (35) did not have accessible laboratory data (Franklin, Birch, Sachter & Barber, 2010).

In literature, there are variations in the identification rates of AE found through trackers (IHI or other triggers), some studies show rates of only 2%, while in others the identification rates are approximately 24% (Classen, Pestotnik, Evans, Burke & Battles, 1991; Davies, Green, Mottram & Pirmohamed, 2006). In addition to the lack of information in medical records, other factors that may interfere are the number of trackers used to identify events and the rate of change that trackers undergo when adapted to the reality of each health service (Seddon et al, 2013). There is a correlation between the event occurrence and variables such as length of stay, gender, age and presence of comorbidities. Thus, the characteristics of the studied population also directly influence the number of adverse events found (Seddon et al, 2013; Robb, Loe, Maharaj, Hamblin & Seddon, 2017; Varallo *et al*, 2017).

This information corroborates the data found in the selected articles, where studies using the IHI triggers identified 120 (Roque *et al.*, 2018) and 44 (Giordani, *et al.*, 2014) ADEs, and 79 (Roque *et al.*, 2016) ADRs. While other trackers proposed by the authors identified 115 (Fabretti *et al.*, 2018), 62 (Figueiredo *et al.*, 2017) ADEs.

There is great variability in the occurrence rates of ADES and/or ADRs within hospital services, this may be related to the fact that there is no gold standard to calculate the rate of AE, as well as the safety measures already implemented by health services where the studies were performed (Griffin & Resar, 2009).

From the 16 articles, which characterized the patients' gender, 11 (69%), had a prevalence of male hospitalization. This data is consistent with some studies in which men present characteristics that potentiate the disease, due to greater neglect of health and low use of primary and secondary care, being at greater risk of clinical decompensation (Camarano, 2002; Almeida, Mafra, Silva & Kanso, 2015).

Fifty per cent (7) of the 14 articles which identify the patients age had a mean age greater than 60 years. Among the factors that predispose the patient to ADEs, the following stand out: extremes of age, severity of the clinical condition, comorbidities and polytherapy, which would characterize geriatric patients as a risk group. The geriatric population is possibly the most medicalized group in society due to the high incidence of chronic degenerative diseases among them, and the progressive decrease in functional capacity and self-medication. In addition, during the aging process there are physiological changes interfering in pharmacokinetic (drug absorption, metabolism and excretion) and pharmacodynamic processes, which predispose this group to toxicity-related interactions, drug interactions, and adverse reactions (Silva, Ribeiro, Klein & Acurcio, 2012; Carvalho *et al.*, 2012).

Regarding the drugs that caused ADEs, we highlight the antimicrobial and central nervous system drugs. In the study by Almeida, Castro and Caldas (2011) anti-infectious drugs were also the main drugs related to ADEs. These drug classes were

related to severe skin reactions such as Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (Grando et al., 2014; Emerick *et al.*, 2014).

The risk factors associated with the occurrence of myocardial infarction were the length of stay, polytherapies and previous history of myocardial infarction. Regarding length of stay, two studies showed differences of 5 (Toffoletto *et al.*, 2016) and 15 (Roque et al., 2016) days, respectively, when comparing patients with and without ADE. These findings corroborate the results found by Briant, Ali, Lay-ye, and Davis (2004) and Rozenfeld, Giordani and Coelho (2013), where the first author identified patients that were affected by drug-related damage had their length of stay increased by 6 days, and the second author showed the time difference between the two groups. These variables seem to be interdependent, since as events increase length of stay, prolonged hospitalization is closely related to the increased risk of suffering care events and increased cost to health services.

Obviously, there are several methods for searching and identifying adverse events, despite the active search, such as the use of trackers. This kind of study had identified the largest number of adverse events, and spontaneous reporting was biased to underreport events, it should not be replaced by another active search methodology. For while active search usually mobilizes only a few authors involved in event screening, spontaneous reporting spreads the culture of harm reduction and promotion of patient safety among all participants in the care process (Sari *et al.*, 2007). Thus, health services should structure both forms of event identification (Rutberg *et al.*, 2014).

The drug-related events are the third leading cause of adverse events within health services usually due to medication errors. In the structure of services the pharmacist represents one of the best professionals to identify, correct or reduce potential risks associated with therapy (Pepe & Osório-de-Castro, 2000), but in this review only 2 studies used the pharmacist to identify ADEs. Due to his vast knowledge of medicines and therapeutics, the pharmacist is trained to act directly in the identification, detection, prevention and management of medication errors, drug interactions, and adverse reactions within the multiprofessional team (Sriram *et al.*, 2011). There are even studies that have already shown a reduction in the number of medication errors in institutions where pharmacists performed interventions with the clinical staff (Planas, 2004). In this sense, the pharmaceutical intervention, by reducing the number of adverse events, should be used to increase the quality of care and decreases hospital costs.

## 5. Conclusion

In Brazil, there is variability in the occurrence of ADEs in hospitalized patients, and because these events are associated with increased length of stay, patient damage, and increased hospital costs, health services should implement strategies for their identification. Performing analysis of each event individually in order to identify possible weaknesses in the processes within hospitals and propose corrective measures that promote patient safety are urgent. Therefore, it is essential that new studies are carried out focused on the identification and risk factors, but mainly prevention factors.

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