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Prevalence and Risk Factors of Cutaneous Adverse Antibiotic Reaction among Inpatients in Six Hospitals, Shanghai, China, 2010— June 2014

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Bachelor of Science
Fudan University
2013

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2015

Abstract

Prevalence and Risk Factors of Cutaneous Adverse Antibiotic Reaction among Inpatients in Six Hospitals, Shanghai, China, 2010— June 2014

By Chao Fu

Introduction: Adverse antibiotic reaction (AAR) is any noxious, unintended, and undesired effect of antibiotics that occurs at doses used for prevention, diagnosis, or treatment. Due to the high antibiotic usage, AAR presents a global public health threat, especially in China, where AAR cost USD $0.5 to 2 billion in 2013. Among all types of AARs, cutaneous adverse antibiotic reactions (CAARs) ranked as the most commonly occurring AAR in China. However, there have been few studies examining risk factors for CAARs.

Methods: We analyzed data from the Adverse Drug Reaction Surveillance System (ADRSS) in six hospitals in Shanghai to identify risk factors associated with CAARs.

Results: Children aged 0 – 10 years old were the most affected group. Most AARs were administrated intravenously, and the mean latency period for AARs was 1.21 days. Among all AAR-related antibiotics, cephalosporins, quinolones, and macrolides were most common, and skin and subcutaneous tissue disorders were the most common AARs, accounting for 61.7% of all cases. After controlling for age, gender, hospital, and latency time, the antibiotic used, weight of patient, administration route, and past history of AAR were found significantly associated with CAARs. So patients administered penicillins, weighing < 30 kg, administered the antibiotic orally, and who had a previous history of AAR are more likely to develop CAARs than other patients.

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Background

Introduction

Adverse drug reactions (ADRs) are defined by WHO as "any noxious, unintended, and undesired effect of a drug, that occurs at doses used for prevention, diagnosis or treatment" [1]. As a common clinical problem, ADRs cause a global burden, 4.2%-30% of hospital admissions in the USA and Canada, 5.7%-18.8% of admissions in Australia and 2.5%-10.6% of admissions in Europe were attributed to ADRs [2]. The United Status spends up to $ 30.1 billion annually on the ADRs. The number of ADRs in China has also increased from 692,904 in 2010 to 1,317,000 in 2013 [3,4]. Among all ADRs, Adverse Antibiotic Reactions (AARs) account for a great proportion. AARs are a subset of ADRs and induced by administration of antibiotics. They comprise approximately 7% of all ADRs over the world and 34.94% of all ADRs in China [5,6]. Expenditures to treat AARs in China were estimated to be $ 0.5-2 billion in 2013 [7].

Antibiotics and Adverse Reactions

Antibiotics are frequently used to treat infection. Especially in China, antibiotics are used more frequently (52.2% by outpatients and 72.4% hospital admissions received at least one type) [8,9]. Most antibiotics are safe considering their wide usage, while some may have life-threatening adverse reactions.

AARs are usually caused by three mechanisms. One is due to exaggerated response to the known pharmacological effects. The second is by immunologic reactions to the antibiotics and its metabolites. And the last is due to toxic effects of the compound or its metabolites [10].

Antibiotics can be classified into several types by their chemical structures: β-lactams, macrolides, quinolones, lincomycins, aminoglycosides, tetracyclines,

chloramphenicals and sulfonamides. And β-lactams can be divided into penicillins, cephalosporins, β-lactamase inhibitors, carbopenems and other β-lactams.

Some AARs are common with all types of antibiotics, while some AARs are seen only in specific antibiotics. Common AARs triggered by penicillin includes morbilliform rashes, fevers, arthralgias, diarrhea, nausea, vomitting and urticaria. Rare AARs such as Steven-Johnson syndrome (SJS), respiratory distress, thrombocytopenia and lymphadenopathy were also seen with penicillins [11].

Cephalosporins can cause common AARs including rash, urticaria, exanthem and pruritus. Rare AARs induced by cephalosporins were reported like Coagulation defects, acute interstitial nephritis and exfoliative dermatitis [12,13]. Quinolones may induce nausea, vomiting, rash, phototoxicity, trovafloxacin, prolongation of QTc interval, thrombophlebitis [14-17]. Among all antibiotics used in China, cephalosporins, penicillins, quinolones and β-lactamase inhibitors were top four antibiotics inducing the most AARs in 2013 [4].

Risk Factors for AARs

There are many risk factors associated with AARs, which can be summarized into three categories. The first is drug-related. Drug-related risk factors are elements related to the drug and the administration of drugs. The molecular and chemical property is one influencing factor.

Other risk factors include administration dosage, administration route, administration frequency, multi-drug interactions, and contaminating and excipient substances. Large doses of drugs and multiple drug combination treatments may increase the occurrence of AARs [18].

The second category of risks are patient-related. This type is related to the characteristics of the patient receiving antibiotics treatment. Age, gender, disease state, history of sensitivity to other drugs and genetic factors are considered important. Patients with extreme age, past history of ADR may have a higher risk of AARs. Socioeconomic factors such as race and ethnicity factors, alcohol drinking, smoking may also have an effect on the occurrence of AARs [19].

The third categories are factors related to hospitals and medical professionals. Irrational drug use, nursing care, hospital management in different hospitals may also act as risk factors associated with occurrence of AARs among hospitalized patients.

Cutaneous Adverse Antibiotic Reactions

Cutaneous Adverse Antibiotic Reactions (CAARs) are a common skin reaction classified among all AARs. It was estimated that 56.2% of AARs were CAARs in China [20]. The prevalence of CAARs was reported as 1.4 cases per 1,000 populations in 2012 [21]. Previous studies showed various risk factors for CAARs. Age was reported as significantly associated with the occurrence of CAARs in a study in Virginia [22].

A study in India reported that history of allergy and multiple drugs were found to be risk factors for CAARs, while age and gender were found to have no significant association with CAARs [23]. Another study earlier in India reported the proportion of age, sex and antibiotics were different among patients with CAARs. A study in Thailand reported that multiple underlying medical conditions, especially cerebrovascular diseases, were risk factors for serious CAARs and elderly patients were more likely to have CAARs [24]. Most studies in China focused on descriptive analyses and reported the distribution of gender, age, types of drug and types of adverse reactions among patients with CAARs. Only one study on hospitalized

patients concluded that gender, age, and duration of hospitalization were significantly associated with the occurrence of CAARs [25]. Our research focuses on patients with CAARs and estimated the association between various risk factors and occurrence of CAARs.

Methods

Study Population

China established the Adverse Drug Reaction Surveillance System (ADRSS) in 2006. All suspected ADRs among hospitalized patients were reported to clinical pharmacists for confirmation. Confirmed cases were then recoded into the ADRSS. Six hospitals in China were selected (by convenience) for this study. Four were level-3 hospitals and two were level-2[1]. ADR patient-records induced by antibiotics were selected, and data from January 2010 – June 2014 were abstracted.

Variables

Three demographic variables were collected from ADRSS: gender, age, and weight. Other variables from ADRSS included hospital, history of adverse antibiotics reaction, administration route of antibiotics, name of adverse drug reactions, starting date of administration of antibiotics, ending date of administration of antibiotics, date of AARs occurrence, date of AARs reported, and results of AARs.

Antibiotics were classified into ten groups based on chemical structure: penicillins, cephalosporins, other β-lactamas, macrolides, quinolones, lincomycins, nitromidazoles, aminoglycosides, tetracyclines and sulfonamides. Administration routes were categorized into five groups: intravenous, intramuscular, oral, ocular and transdermal. AARs were classified according to Common Terminology Criteria for

[1] Level of hospitals were ranked by China's government with three levels based on factors such as physicians, performance and bed numbers from the most sophisticated (Level Three) to least sophisticate (Level One).

Adverse Events (CTCAE, Version 4.0). CAARs referred to skin and subcutaneous tissue disorders in CTCAE (Version 4.0). Patients' age was grouped into 5-year categories. Patients' weight was categorized into 10 kg segments.

Numbers of AAR types were counted based on the classification of AAR. And duration from antibiotic administration to AAR occurrence was calculated based on the starting date of the administration of antibiotics and the date of AAR occurrence.

Data Analyses

Age, weight, gender, hospital, history of AAR, classification of antibiotic, administration route, and duration were established as independent variables, with CAAR as the dependent variable.

A multivariate logistic regression was fitted by a backward selection method applying alpha=0.05 removal criteria. Odds ratios and p-values of multivariate logistic regression were estimated by Firth's Penalized Likelihood method due to the phenomenon of separation caused by some sparse cells. Data analyses were performed with SAS v 9.4 *(SAS Institute, Cary, North Carolina)*.

Results

Adverse Antibiotic Reactions

Two thousand and three hundred (2,300) inpatients from six hospitals were administered antibiotics and experienced at least one type of AAR between January 2010 and June 2014. Among these, 1,183 (51.5%) of 2,300 were female (Table 1). Their mean age was 37.9±26.8 years and mean body weight was 47.6±20.7 kg.

Patients were categorized based on their age (5-year age groupings) and based on their weight (10 kg groupings). Those who experienced more AARs than others were children between 0 – 5 years old (17%). Among the 2,300 patients, 1972 (85.7%) received antibiotics intravenously, and 2,058 (89.5%) experienced only one type of

AAR. Only 116 patients had a prior history of AAR, accounting for 9.2% of 1,257 patients. The mean latency period of AAR was 1.21±3.08 days.

Ten antibiotics were prescribed and administrated to the 2,300 patients. Four of the 10 accounted for almost 90% of all AARs. Eight hundred and fifty-two (36.7%) patients with AAR received cephalosprins, 483 (20.8%) received quinolones, 363 (15.6%) received macrolides and 318 (13.7%) received penicillins. Sulfomides and tetracylines were associated with fewer occurrences of AAR, 4(0.2%) and 3 (0.1%), respectively.

According to Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)[26], 26 types of adverse events were defined based on the system organ. Sixteen types of adverse events were recorded among the 2,300 patients. Skin and subcutaneous tissue disorders stand out as the most common AAR with 1,431 (61.7%) cases, about three times of the second ranked type of AAR, gastrointestinal disorders, which were reported among 527 (22.7%) patients. The other types of AARs were seen less frequently among inpatients varying from one case to 203 (8.8%) cases.

Common skin and subcutaneous tissue disorders included rash, pruritus, purpura, urticaria, erythroderma, pain of skin. Common gastrointestinal disorders included diarrhea, dry mouth, nausea, stomach pain, and vomiting. General disorders and administration site conditions mainly included chills, edema face, edema limbs, facial pain, fatigue, fever, injection site reaction, non-cardiac chest pain and general pain. Nervous system disorders seen among inpatients were cognitive disturbance, dizziness, headache and tremor.

Allergic reaction and anaphylaxis were the majority of immune system disorders. Respiratory, thoracic and mediastinal disorders were mainly reported as cough.

Common cardiac disorders reported among all patients were chest pain (cardiac). Phlebitis and Superficial thrombophlebitis were two vascular disorders seen among all AAR cases. Metabolism and nutrition disorders were typically seen as anorexia, hypoglycemia. Eye disorders were mainly dry eye, eye pain. Psychiatric disorders varied from anxiety, confusion to depression. Blood and lymphatic system disorders were reported as leukopenia and hemolysis. Hematuria was the only reported renal and urinary disorders. Musculoskeletal and connective tissue disorders included back pain and bone pain. Ear pain and Tinnitus were reported ear and labyrinth disorders in the database. Upper respiratory infection was the only case reported as infection and infestations.

Cutaneous Adverse Antibiotic Reactions (CAARs)

Among all types of AARs, skin and subcutaneous tissue disorders ranked top with 1,431 cases. Gender, age group, weight group, different hospitals, history of AAR, classification of antibiotics and administration route were chosen as potential factors associated with CAARs.

In univariate analysis the following were significantly associated with CAARs: age ($p<0.001$), weight ($0<0.001$), history of AAR ($p=0.098$), classification of antibiotics ($p<0.001$), administration route ($p<0.001$), duration period from administration of antibiotics to occurrence of AAR ($p=0.034$).

In the multivariate analysis, though three factors were not found significantly associated with CAARs in univariate analysis, they were included in the multivariate logistic regression model because of potential confounding. Four factors remained in the multivariate logistic regression model with backward selection: history of AAR, classification of antibiotics, administration route, and weight group (Table 4). Multicollinearity was assessed with no obvious collinearity problems among risk

factors. Goodness of fit for this model was checked; the model fit the data well (p=0.9582).

After controlling for age, weight, history of AAR, administration route, and latency period, classification of antibiotics was found significantly associated with CAAR (p<0.001).

The risk of CAAR among patients receiving macrolides was 0.27 times that of patients receiving cephalosporins (OR=0.27; 95% CI=0.18-0.40). The risk of CAARs among patients receiving other ß-lactams (except penicillins and cephalosporins) was only 0.19 times the risk of patients administered cephalosporins (OR=0.19; 95% CI=0.06-0.58). However, the risk of CAARs among patients received penicillins was 1.83 times compared to that among patients receiving cephalosporins (OR=1.83; 95% CI=1.17-2.96). Weight group was also significantly associated with CAARs after controlling for other variables. Compared to the most common weight group from 51 kg to 60 kg, patients with less weight were more likely to have CAARs. Patients who were 0 to 10 kg were 11.92 times more likely to have CAARs compared to patients weighted between 51 to 60 kg (OR=11.92; 95% CI=3.14-45.23). Patients who were 11 to 20 kg were 2.11 times more likely to experience CAARs compared to those weighted from 51 to 60 kg (OR=2.11; 95% CI=1.39-3.20). And patients who weight between 21 – 30 kg were 2.19 times more likely to experience CAARs compared to patients who weighed between 51 – 60 kg (OR=2.19; 95% CI=1.26-3.79).

The administration route was significantly associated with CAARs (p=0.0013). Compared to patients who received antibiotics intravenously, those who received them orally were 2.23 times more likely to have CAARs (OR=2.23; 95% CI=1.53-3.26). Having a history of AAR was significantly associated with CAARs. Patients

with no previous AAR history were 0.59 times less likely to experienced CAARs comparing to those who had AAR history (OR=0.59; 95% CI=0.37-0.93).

Discussion

Conclusion

Our study found out that among all patients, children aged from 6 to 10 years old and elderly groups aged from 56 to 60 years old were the most vulnerable groups to antibiotics reactions. Cephalosporins, quinolines and macrolides ranked top three among all antibiotics causing AARs, totally accounting for over 80% of all AAR cases. Penicillins and lincomycins followed as fourth and fifth most frequent antibiotics associated with AARs. This result may not necessarily indicate that cephalosporins, quinolines and macrolides are more likely to cause AARs, because cephalosporins, penicillins and quinolones are also the antibiotics most frequently administrated to patients according to China's annual Adverse Drug Reaction Reports [27].

The most common AARs were skin and subcutaneous tissue disorders, accounting for over 60% of all AARs. The overall average latency of all AAR cases was 1.21 days, which means most cases developed symptoms shortly after administration of antibiotics. Therefore, nurses and clinical pharmacists should pay attention to the AARs especially in the early period after administration.

Due to the high frequency of occurrence of skin and subcutaneous tissue disorders, we further analyzed on cutaneous adverse reactions and identified four potential risk factors associated with CAARs. With multivariate logistic regression model, we found that antibiotic, weight, route of administration and history of AAR were four risk factors significantly associated with occurrence of CAAR, while gender, age, and latency period were not significantly related. Previous studies on Asian patients

suggested that weight, antibiotics, route of administration, history of allergy were potential risk factors [28-31]. Some studies indicated age and gender were related with CAARs [31, 32], while other studies concluded as no significant relationship [33]. Our study confirmed that antibiotics, weight, route of administration and history of AAR are risk factors, while age and gender were not found as potential risk factors. With four potential risk factors, we found that penicillins most likely caused CAARs, and other ß-lactams except penicillins and cephalosporins least likely caused CAARs. Macrolides was also found as less likely to cause CARs compared to cephalosprins and penicillins. Patients with weight from 0kg to 30kg was found much more likely to develop CAARs compared to other groups. Thus, babies and children should be paid attention when administrated with antibiotics. Patients administrated through oral and with history of AAR before were found more likely to develop CAARs.

Limitations

Our study has several limitations, especially on the data collection. Since the ADRSS database didn't include patients who received antibiotics without AARs, our analysis was conducted in the proportional morbidity method. Without data from AAR-free patients, the reliability of model may decrease. Due to lack of other relevant variables, we are not able to include their as confounders or interactions. Other relevant variables include genetic information, family history of allergy, other medications administrated to patients besides antibiotics, comorbidities, etc. Second, sparse sample size in some categories resulted in huge standard deviation for estimated odds ratio and instability of the model. Further study based on both patients with CAAR and patients without CAARs with large sample size is needed to understand risk factors of CAAR more accurately and comprehensively. In addition, we only collected inpatients from six hospitals in Level Three and Level Two in Shanghai.

These patients may be with higher socioeconomics status and education background compared to other areas in China. Thus the results may not be good representatives for all patients in China.

Recommendations

Our study suggested that cephalosporins, quinolones and macrolides caused most AARs in inpatients. When using these three types of antibiotics, nurse and physicians should pay more attention to adverse reactions. Among all adverse reactions, cutaneous adverse reactions are the most common one. Though most CAARs don't have great risk, but serious CAARs like Stevens-Johnson syndrome should be paid attention during the administration. The average time of latency period was not too long with only one to two days, indicating AARs of antibiotics appeared shortly after administration. Nursing and clinical pharmacists should pay attention especially to the first few days of administration of antibiotics. Patients who may have higher risk of developing CAARs are characterized with young babies or children, having previous history of AARs, administrated with penicillins and taking antibiotics orally. Patients with these characteristics should be paid more attention of CAARs.

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Table 1. Demographic Characteristics of Patients with Adverse Antibiotic Reactions in Six Hospitals, Shanghai, China, 2010 – June 2014

	N=2,300	
Characteristic	n	%
Gender	**2,295**	
Female	1,183	51.5
Age	**2,300**	
Mean (sd*)	37.9	26.8
0-5	390	17
6-10	209	9.1
11-15	43	1.9
16-20	57	2.5
21-25	136	5.9
26-30	179	7.8
31-35	127	5.5
36-40	102	4.4
41-45	99	4.3
46-50	111	4.8
51-55	135	5.9
56-60	170	7.4
61-65	118	5.1
66-70	98	4.3
71-75	95	4.1
76-80	84	3.7
81-85	88	3.8
86-90	47	2.0
>=91	12	0.5
Weight (kg)	**2,124**	
Mean (sd)	47.6	20.7
0-10	64	3
11-20	337	15.9
21-30	175	8.2
31-40	58	2.7
41-50	319	15
51-60	613	28.9
61-70	382	18.0
71-80	146	6.9
81-90	25	1.2
>=91	5	0.2

*SD: Standard Deviation

Table 2. Clinical Characteristics of Patients with Adverse Antibiotic Reactions in Six Hospitals, Shanghai, China, 2010 – June 2014

	N=2,300	
Characteristics	n	%
History of AAR*	**1,257**	
Yes	116	9.2
Administration route	**2,300**	
intravenous	1972	85.7
oral	315	13.7
transdermal	10	0.4
intramuscular	2	0.1
ocular	1	0.1
Number of AAR types	**2,300**	
1	2,058	89.5
2	211	9.2
3	30	1.3
4	1	0.1
Latency (days)		
Mean (sd†)	1.21	3.1

* Classification of adverse antibiotics reaction was defined by CTCAE 4.0
† Standard deviation

Table 3. Antibiotics Administered to Patients with Adverse Antibiotic Reactions in Six Hospitals, Shanghai, China, 2010 – June 2014

	N=2,300	
Antibiotic	**n**	**%**
Cephalosporins	852	36.7
Quinolones	483	20.8
Macrolides	363	15.6
Penicillins	318	13.7
Lincomycins	153	6.6
Other ß-lactams*	45	1.9
Nitromidazoles	40	1.7
Aminoglycoside	39	1.7
Sulfomides	4	0.2
Tetracyclines	3	0.1

* all ß-lactams except penicillins and cephalosporins

Table 4. Classification of Adverse Antibiotic Reactions among Patients in Six Hospitals, Shanghai, China, 2010 – June 2014

Classification*	N=2300	
	n	%
Skin and subcutaneous tissue disorders	1,431	61.7
Gastrointestinal disorders	527	22.7
General disorders and administration site conditions	203	8.8
Nervous system disorders	125	5.4
Immune system disorders	93	4
Respiratory, thoracic and mediastinal disorders	65	2.8
Cardiac disorders	61	2.6
Vascular disorders	50	2.2
Metabolism and nutrition disorders	33	1.4
Eye disorders	27	1.2
Psychiatric disorders	24	1
Blood and lymphatic system disorders	16	0.7
Renal and urinary disorders	12	0.5
Musculoskeletal and connective tissue disorders	7	0.3
Ear and labyrinth disorders	6	0.3
Infection and infestations	1	0.1
* Classification of adverse antibiotics reaction was defined by CTCAE 4.0		

Table 5. Risk Factors for Cutaneous Adverse Reaction among Patients with Adverse Antibiotics Reactions in Six Hospitals in Shanghai, China, 2010 – June 2014[*]

Risk Factor	Strata	Odds Ratio (95% CI)	P-value
Antibiotic	quinolones	0.80 (0.56-1.15)	<.001
	macrolides	**0.27 (0.18-0.40)**	
	penicillins	**1.83 (1.17-2.86)**	
	lincomycins	0.67 (0.43-1.05)	
	other ß-lactams[†]	**0.19 (0.06-0.58)**	
	nitromidazoles	1.03 (0.43-2.45)	
	aminoglycosides	0.50 (0.20-1.26)	
	sulfomides	0.05 (0.00-1.20)	
	tetracyclines	0.55 (0.05-5.84)	
	cephalosporins	-	
Weight (kg)	0-10	**11.92 (3.14-45.23)**	<.001
	11-20	**2.11 (1.39-3.20)**	
	21-30	**2.19 (1.26-3.79)**	
	31-40	0.93 (0.42-2.07)	
	41-50	1.08 (0.73-1.60)	
	61-70	0.92 (0.63-1.34)	
	71-80	0.55 (0.32-0.94)	
	81-90	2.48 (0.68-9.04)	
	≥91	0.16 (0.01-4.17)	
	51-60	-	
Route of Administration	oral	**2.23 (1.53-3.26)**	0.0013
	transdermal	1.31 (0.22-7.72)	
	intramuscular	2.29 (0.02-221.47)	
	ocular	7.27 (0.08-707.31)	
	intravenous	-	
History of AAR	no	**0.59 (0.37-0.93)**	0.0233
	yes	-	

* 1182 observations used to generate multivariate model
† all ß-lactams except penicillins and cephalosporins