



## Research Article

### DRUG ALLERGY: A COMPARATIVE AGE AND GENDER CHARACTERISTICS

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#### ABSTRACT

**Background:** The monitoring committees are possible side effects of the drugs, which are produced in several countries, register annually from 5 to 100 thousand allergic reactions through medicines, among which over 1% of the fatal outcome. Whilst 70% of all adverse reactions to the drugs are allergic and they are detected in 8-12% of patients. Along with this is revealed the incidence of individual nosological forms of allergy drug etiology, as well as their dependence on individual groups of drugs.

**Materials and methods:** The analysis was applied to 278 medical history of patients treated in the Tashkent Allergy Centre in 2008, and 269 medical history of patients was admitted to the Allergy Department of the Hospital in Tashkent in 2012. Medical history was analyzed with respect to the pharmacological group of drugs, and clinical forms of appearances of the allergic complications. The collected data were processed by the method of variation statistics.

**Results:** The vast majority of patients with allergic complications were caused by a drug (72% of patients), and the only 1/4 of the patients were develop allergic conditions two or more drugs. In 78 patients with polyvalent allergy, in 70 cases the cause was a combination of two, and in 8 – a combination of three drugs. In 2012, there was an increase in the proportion of such patients is more than 1.5 times. In 2008, the largest share of the drugs that have caused allergic complications had anti-microbial agents in every second patient. Second in importance was occupied by non-steroidal anti-inflammatory (NSAIDs) and analgesic agents who were the cause of allergic complications in almost every 4<sup>th</sup> patient. The highest proportion of patients with angioedema were taking sulfonamides and analgesics. The development of Stevens-Johnson syndrome and anaphylactic shock was the most characteristic complications from taking antibiotics.

**Conclusion:** Allergic complication, requiring hospital treatment occurred in every second patient on an antibiotic and every 4<sup>th</sup> patient on non-steroidal anti-inflammatory and analgesic drugs, and 1 in 4 allergic reactions developed in response to the reception of a combination of several drugs. The dynamics of the five-year observation showed that the increase in the proportion of polyvalent allergy with increasing the intake of antibiotics

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#### INTRODUCTION

The rapid development of pharmacology with the emergence of a large number of new drugs, along with the successful treatment of some diseases, lengthening the life expectancy of the population and improve its quality, has led to an increasing prevalence of drug allergy (Viktorov *et al.*, 2003; Grishkina and Lutkovska, 2010; Dadykina and Vertkin, 2005; A brief outline of the Federal centre for monitoring drug safety, 2010; Yu, 2010). The results of the recent pharmaco-epidemiological studies indicate that underestimation and a delayed solution side effects of medications are fraught with the development of the

most serious consequences (A brief outline of the Federal centre for monitoring drug safety, 2010). The monitoring committees are the possible side effects of drugs produced in Russia, USA, France, England and other countries, to register annually from 5 to 100 thousand allergic reactions to medicines, among which over 1% of the fatal outcome. While 70% of all adverse reactions to drugs are allergic and detected in 8-12% of patients. The prevalence of drug allergy in these countries varies widely, from 1 to 30% and higher, and depends on the type of applied medication. According to WHO, mortality from drug allergy for more than 5 times higher than the mortality from surgical interventions. Deaths occur in 1 out of 10,000 cases, allergic reactions that cause death in 0.01% of surgical and 0.1% of medical inpatients (Bush, 1995). In Uzbekistan, according to some reports, from 6 to 15% of patients undergoing the

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treatment, have noted certain side effects to the medication in 5-10% of cases are allergic reactions (Saidahmedov *et al.*, 2008). However, overall, the situation in this area still remains insufficiently clear. Based on the foregoing, we have retrospectively analyzed the medical history of patients with allergic diseases of drug etiology to determine the frequency of their occurrence, their existence depending on the intake of selected medicines.

## MATERIALS AND METHODS

The analysis was applied to 278 medical history of patients treated in the Tashkent City Allergological Centre in 2008, and 269 medical history of patients admitted to the Allergy Department of the Hospital in Tashkent city, in 2012 regarding the etiology of drug allergy. Medical history was analyzed with respect to the pharmacological group of drugs, and clinical forms of manifestations of allergic complications. The obtained data were processed by the method of variation statistics.

## RESULTS

The results of the retrospective study showed that in 2008 the vast majority of patients with allergic complications were caused by a drug (72% of patients), and the only 1/4 of the patients develop allergic conditions was two or more drugs. Moreover, of these, 78 patients with polyvalent allergy (complications of the use of several medicines), in 70 cases the cause was a combination of two, and in 8 – a combination of three drugs (Fig.1). However, in 2012, there was an increase in the proportion of such patients is more than 1.5 times.

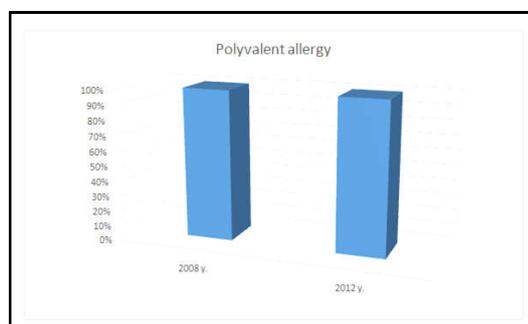


Figure 1. Dynamics of detection of polyvalent Allergy to the reception of multiple drugs

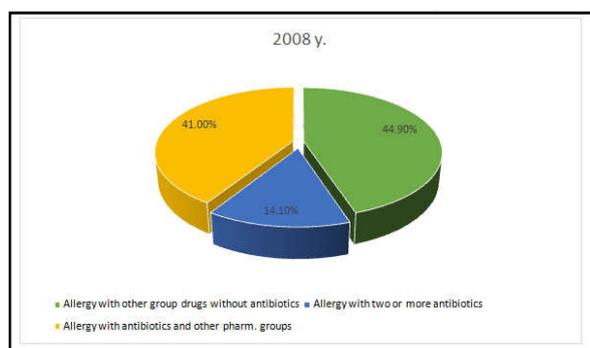


Figure 2. The frequency of detection of polyvalent Allergy caused by a combination of different groups of medicines

As can be seen from Fig. 2, the highest number of cases of allergy were observed when using combinations of antibiotics

with other drugs, including antibiotics themselves. Thus, in 2008 an allergy only when a combination of several antibiotics was observed in 14.1% of cases and in the prescription of antibiotics with drugs of other pharmacological groups are 41%. Subsequently, these indicators increased by 3% with a corresponding decrease in the proportion of allergy is caused due to combinations of drugs of different groups with the exception of antibiotics. Because the quality of urgent measures for the correction of these complications depends largely on the etiological factor, i.e. of the drug caused this complication, then we have separately analyzed the drug (monotherapy cause of allergic complications) related to different pharmacological groups (Fig. 3).

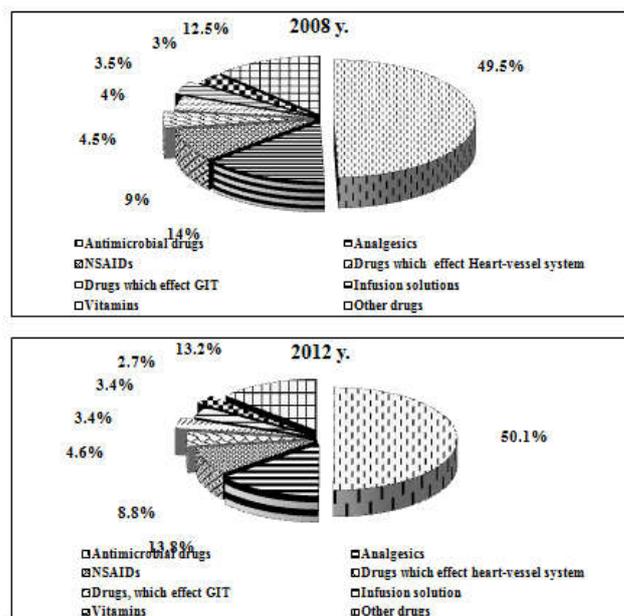


Figure 3. The frequency of detection of allergy to individual drugs

The analysis showed that in 2008 the largest share of drugs that have caused allergic complications had anti-microbial agents (every second patient). Second in importance was occupied by non-steroidal anti-inflammatory (NSAIDs) and analgesic agents who were the cause of allergic complications in almost every fourth patient. When using drugs that affect the cardiovascular system (CVS), gastrointestinal tract (GIT), vitamins, infusion solutions, etc., the development of drug Allergy was observed in approximately every fifth patient with allergies. In 2012 significant changes in the picture never happened.

Therefore, the obtained results clearly indicate that among drugs that cause allergic complications, the highest proportion of antimicrobials and analgesics. As we can see, allergic reactions to antimicrobial drugs have developed in every second patient with drug Allergy complications and it remained stable during the studied 5 years. The study of the structure of antimicrobial agents that caused allergic complications, suggests that the primary cause of Allergy are antibiotics. Structural changes of allergic reactions in relation to different groups of antibiotics revealed the following picture. As can be seen from Fig. 4, 2008 among antimicrobials were leading antibiotics, other things are most often allergic complications arose on the antibiotic cephalosporin (26,8%), then, slightly yielding to them, was situated the penicillin.

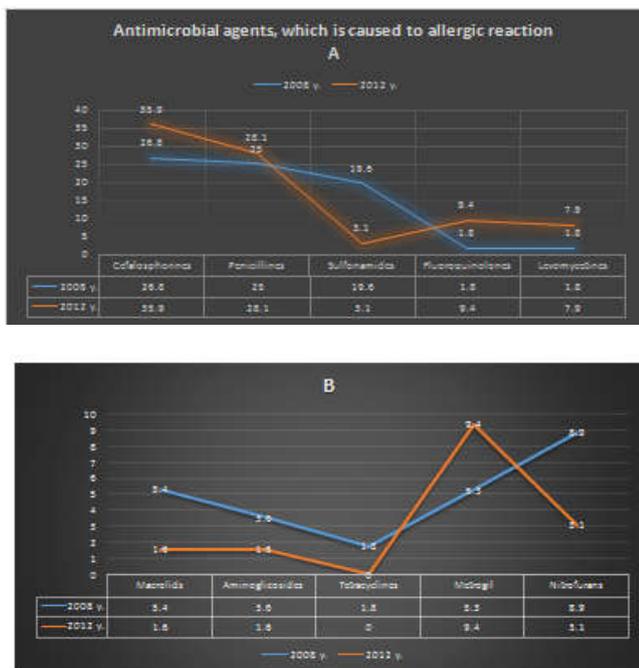


Figure 4. Dynamics of change the frequency of occurrence allergic reactions caused by individual groups of antimicrobials

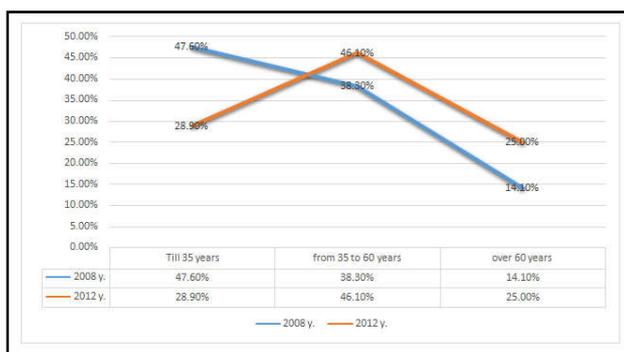


Figure 5. The dynamics of the detection of Allergy to antimicrobial agents depending on the age of patients for the period 2008-2012

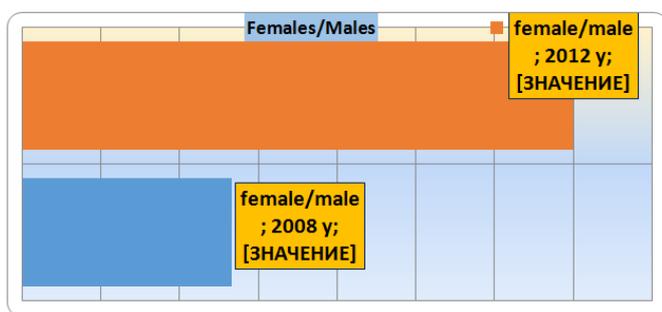


Figure 6. Dynamics of manifestations of Allergy to antimicrobial drugs depending on sex differences

Sulfa drugs were the cause of those or other allergic complications in 19.6% of cases, and, mostly, they occurred to the reception of Biseptolum and only in two cases against the use of Streptocid. Almost an order of magnitude lower was the incidence of allergic complications in response to antibiotics from the groups of fluoroquinolones and chloramphenicol (1.8%).

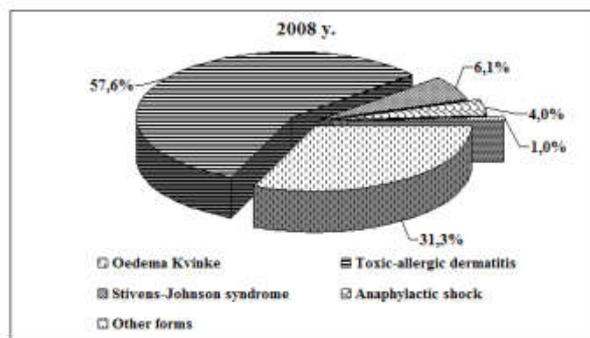


Figure 7. The ratio of clinical forms of allergic reactions to antimicrobials

Further, the correlation among antibacterial agents in their ability to cause allergic reactions has undergone some changes. Thus, the proportion of sulfa drugs began to decline and by 2012 reached the level of 3.1%, which is almost 6 times lower than five years ago. Against this background, with the exception of penicillin, there was a significant increase in the proportion of antibiotics of different groups. The most significant increases have become the antibiotics of the groups of fluoroquinolones and chloramphenicol, the share of which has increased more than 4-5 times. Still remained the leading cephalosporin antibiotics, allergic complications from which have already amounted to 1/3 of those from taking antimicrobials. Thus, in 2012 allergic complications caused by antimicrobial means, basically, was provided with antibiotics (96.9%). It is possible that this pattern reflects changes in the structure of consumption of antimicrobials.

Dynamics of changes in the age category of patients allergic to antimicrobial agents in the period 2008-2012 were shown in Figure 5. As can be seen from the presented data, in 2008, allergic complications of drug antimicrobial series had on patients at a young age, i.e. up to 35 years (47.6 per cent). Somewhat less in this regard were presented to older age groups (35 to 60 years - 38.3% and over of 14.1%). However, in subsequent years, the majority of patients allergic to antimicrobial agents ranged in age from 35 to 60 years, the share of which amounted in 2012 to 46.1 percent. At the same time, the share of patients older than 60 years averaged 1/4 (2012) part of all patients allergic to antimicrobial drugs.

As can be seen from figure 5, for the five-year period there were changes of allergic complications of antimicrobial drugs by age in the direction of "aging" patients, i.e. increasing the share of representatives of over 35 years, by reducing the share of younger individuals. In addition, patients older than 60 years of this period is almost 2 times more. Overall, by 2012 the ratio of age groups in ascending order in relation to the development of allergic reactions to antimicrobial agents were as follows: 1-2-1. Moreover, age from 35 to 60 years has become prevalent in the process. In predicting the likely risk of allergic side effects from medicines, along with the presence of a certain dependence on groups of drugs and their forms are important individual characteristics of the patient. In this regard, some interest may represent the gender of the patient. As can be seen from the data presented in Fig.6, among patients in whom the cause of allergies was anti-microbial agents, the ratio of male/female in 2008 was 1:1,33, indicating a marked predominance among patients proportion of women.

In subsequent allergies to antimicrobials has increased dramatically and has reached in 2012. up to 3.5 times more common in women compared with men. Along with the identification of the frequency of occurrence of drug allergies to antimicrobials, we determined the dynamics of changes in the proportion of certain nosological forms of Allergy etiology drug during the 5-year period. Dynamics of changes in the ratio of clinical forms of allergic reactions to antimicrobial drugs in 2008-2012 is presented in Fig.7. As can be seen from the presented data, in 2008 allergic diseases of drug etiology in most cases is manifested in the form of sharp allergy dermatitis and angioedema, which accounted for a total of 88.9 percent. In this case, the undisputed leader in this picture was secured toxic- allergic dermatitis (57.6 percent), and the proportion of angioedema was almost 2 times less.

Among other clinical forms to a certain extent prevailed syndrome Stevens-Johnson. Despite significant changes in the frequency of drug allergies in individual classes of antimicrobials during the analyzed 5-year period, significant shifts in the ratio of clinical forms of Allergy etiology drug in 2012 did not happen. Revealed only a tendency to a slight decrease in the share of allergic dermatitis due to the increase of that of angioedema. For other clinical forms were observed the twofold reduction in the development of the syndrome of Stevens-Johnson and increasing the share of other forms of allergies.

It was found that antiseptics, NSAIDs, antibiotics and analgesics most frequently contribute to the emergence of acute allergic dermatitis. And the reception sulfa drugs accompanied in equal measure by the development of acute allergic dermatitis and angioedema. The most frequent cause of development of acute allergic dermatitis and angioedema are antibiotics, mainly cephalosporin. Thus, generalised form of allergic dermatitis relatively often develops on receiving 2 or more medications. At the same time, the number of cases of the limited form of allergic dermatitis to receive 2 drugs was twice less, than in patients with the generalized form of the Allergy, patients allergic to receiving 3 drugs were rare among them. The highest proportion of patients with angioedema were when taking sulfonamides and analgesics. And the development of the syndrome of Stevens-Johnson and anaphylactic shock was the most characteristic complications from taking antibiotics. It is possible that changes in the frequency of drug allergies to sulfonamides and separate classes of antibiotics were reflected in the spectrum of the clinical forms of Allergy drug etiology.

## DISCUSSION

On the basis of retrospective analysis of case histories of patients with the drug, allergies can conclude that in most cases the Allergy arises on the admission of the same drug. In addition, 1/4 part of the patients with drug allergies cause was the combined use of medicines. In General, it became clear that in Uzbekistan the largest share among drugs that have caused allergic complications, are anti-microbial agents (in every second patient treated with one drug). The second role analgesics and, then, non-steroidal anti-inflammatory drugs (NSAIDs), which together were the cause of allergic complications in almost every fourth patient. As for other drugs that affect the cardiovascular system (CVS), gastrointestinal tract (GIT), vitamins, infusion solutions, etc., the development of drug Allergy was detected in approximately every fifth

patient with allergies to monotherapy. Moreover, in the case of Allergy to receive two or more medicines make up the largest share in the combination of antibiotics with other medicines. First of all, of course, such a pattern may reflect changes in the structure of consumption of antimicrobials. So, in 2012 allergic complications caused by antimicrobial means, basically, was provided with antibiotics (96,9%) and a drastic increase due to the fall in the share of sulfa drugs, compared to 2008, to some extent, reflect changes in the preferences of physicians in choosing medicines when prescribing them to patients. Of course, this does not exclude the presence of more allergenic properties of antibiotics and polypharmacy is becoming "fashionable" phenomenon recently.

According to studies in several countries, as Uzbekistan, among the drugs, which cause allergic reactions. The most common are antibiotics (especially beta-lactam series) – up to 55%, nonsteroidal anti-inflammatory drugs – up to 25%, sulfonamides up to 10%, local anesthetics 6%, iodine - and bromic drugs – up to 4%, vaccines and sera – to 1.5%, drugs, affecting mostly textile processes (vitamins, enzymes, and other drugs affecting the metabolism) – up to 8%, other groups of drugs to 18% (Agúndez *et al.*, 2015). Given the high clinical efficacy and low toxicity, beta-lactam antibiotics constitute the basis of modern antimicrobial therapy, occupying the main place in the treatment of patients with various bacterial infections (Macy, 2014). Beta-lactam antibiotics are classified according to their chemical structure, as penicillins, cephalosporins, monobactam, carbapenem and clavam.

Allergic reactions frequently observed with the use of penicillins (5-10%), fewer cephalosporins (2%), carbapenems and monobactams (less than 1%). So, the results of recently conducted clinical trials of cephalosporin III, phase, frequency of allergic reactions, including hypersensitivity reactions of immediate type, amounted to more than 3%(Macy, 2014; Sicherer, 2015). Penicillin allergy remains the most common, with fluctuations of 8-12% depending on the specifics of the evaluated populations. These values increase slightly among women, with increasing age and number of medications taken (Macy, 2012; Macy, 2009). However, we believe that revealed the structure of drug allergy might reflect the pattern of consumption of drugs because in several countries identified additional relationships. Thus, in the Latin America (Jares *et al.*, 2014), drug groups most often cause an allergic reaction, were NSAIDs (52.3%), beta-lactam antibiotics (13.8%) and other antibiotics (10.1 %). In predicting the likely risk of allergic side effects from drugs, along with the presence of each group of drugs and their dosage forms are important, the influence of some factors and individual characteristics of the patient. In this respect, a certain interest can represent sex and age belonging of the patient.

It was found that between the incidence of clinical forms of allergy medication and age there is a certain dependence. So, younger patients were committed to the allergy to one drug, while patients of older age groups more committed to allergies to the reception of two or more drugs. This fact is quite understandable from the standpoint that, among older age groups, due to the presence of several diseases, increases the need for taking different drugs, making the risk of side effects, including allergic, is relatively high. Identification of the indicators of allergic reactions to drugs depending on the sex of

the patients may have not only theoretical value but may be useful for the effective conducting diagnostic and therapeutic procedures. The results of our studies showed a significant prevalence of these reactions among women, but these data are difficult to compare with foreign because of their small size. Currently, the most consistent and reliable data were obtained only for some allergic diseases. Thus, the prevalence of asthma among men was revealed only for the period of childhood. Accordingly, the studies were made in Belgium, found an increase in the spread of asthma and allergic rhinitis and eczema among boys of the primary school. Among boys, older children (13-14 years), relative to girls, was more prevalent only asthma (Wieringa *et al.*, 1999). Similar data were found in crossover in England, which revealed the most frequent prevalence of allergic rhinitis among boys prepubescent age (Shamssain and Shamsian,.; Shamssain and Shamsian, 1999). One of the most productive research was done in Scotland, which included a sample of the population in 266733 people (Osman *et al.*, 2007). The spread of asthma in early childhood was significantly higher in boys, but by age 15 years this diagnosis became prevalent in girls, and these changes remained unchanged and in more mature age. Within the Global project of the European Network of Asthma and Allergy (GA<sub>2</sub>LEN), Almqvist *et al.* (Almqvist *et al.*, 2008) performed a Medline search regarding the terms: gender or sex, child, childhood or adolescence and asthma. Found that boys had a greater tendency to hoarseness and asthma than girls, but in adolescence this pattern changed in favour of female population.

Age - and sex-related pattern for allergic rhinitis was similar to that for asthma. Prevalence rates for this disease were higher in the 6 - 7 year - old boys than in girls (Wieringa *et al.*, 1999). This male dominance continued until the age of 15, and then there was a reverse sex ratio against girls and women post-pubertal age (Osman *et al.*, 2007). As a possible explanation for this, the authors suggested hormonal changes and the sex-specific differences in exposure to environmental factors. Because the scope of our study children and adolescents were not included, this circumstance may also explain our results. For drug allergies, the sex-dependent pattern is still poorly understood. These are the only ones that provide information for a large range of age (from 3 to 80 years) in the gender proportions to the broad spectrum of allergic diseases, including asthma, seasonal and sustainable allergic rhinitis, atopic and contact dermatitis, and drug allergy (Liebhart *et al.*, 2014). The results clearly show a female predominance among adult subjects suffering from allergies. A number of studies found a significant increase in documented penicillin allergy in patients who are women, relative to men (Macy and Ho, 2012; Zopf *et al.*, 2008). The study also showed that the Asian race could be better protected from allergies to penicillin, compared with Caucasian race, which is the first discovery of such racial protective capability. From the above data on the differences in the prevalence of allergy in the period of childhood and maturity, it is clear that sex hormones may play a significant role in this phenomenon although we cannot neglect the peculiarities of the style of life and work. The results of our studies showed that among allergic complications on drugs like when taking the same drug, or two or more – the highest proportion of acute allergic dermatitis and edema Kvinke. It is known that skin rashes are the most common clinical manifestations of drug allergy (Revyakina, 2010).

In this case, to skin allergic reactions are also the most commonly observed urticaria, angioneurotic edema (angioedema), and psoriasis, exudative multiform erythema, exfoliative dermatitis, eczema etc. Although most cutaneous reactions are mild and self-limiting, can cause such serious reactions, such as syndrome Steven Johnson (SJS), toxic epidermolysis (TEN), and reaction to drugs with eosinophilia and systemic symptoms (DRESS) that are associated with significant morbidity and mortality. In some strollercise cutaneous side effects of drugs are combined the term toxicodermatosis. For example, in the Dermatological Department of Hospital in Finland, to 32% of cases drug toxicodermia was presented with drug rash, in 20% of the urticaria and angioedema, in 34% of fixed toxicodermia, in 2% were polymorphic exudative erythema, in 1% syndrome Stevens-Johnson, in 1% erythrodermia, and in 3% were developed drug photosensitization (Myasnikova and Latysheva, 2004). The frequency of drug toxicodermia with medication is 3:1000, of which nearly two-thirds of cases due to penicillin, preparations containing a sulfonamide group, and blood products.

A study of the number of allergic reactions in cohorts of hospitalized patients has revealed the level of incidence vary from 1 in 1000 to 2 in 100 of the total number of hospitalized patients (Naldi, 2014). For drugs such as aminopenicillins and sulfonamides incidence of skin reactions was 3 to 5 cases out of 100 treated people. Frequency and clinical patterns of cutaneous reactions depend on the drugs used, the prevalence of specific conditions (e.g., HIV infection), and pharmacogenetic characteristics of the population, which may vary significantly among different populations worldwide. Given this terminology and features, to judge the causes of similarities or differences in the pattern of occurrence of clinical forms of drug Allergy, depending on ethnic and geographical factors is extremely difficult.

## Conclusion

Thus, in our research conducted earlier, it was shown that allergic complication, requiring hospital treatment occurred in every second patient on an antibiotic and every fourth patient on non-steroidal anti-inflammatory and analgesic drugs, and one in four allergic reactions developed in response to the reception of a combination of several drugs. The dynamics of the five-year observation showed that the increase in the proportion of polyvalent allergy by increasing the intake of antibiotics. Especially cephalosporin, a shift of the predominant indicators of the development of drug allergy in the direction of older age and women, a slight decrease in the detection of syndrome of Stevens-Johnson and toxic-allergic dermatitis due to the growth of the other more rare clinical forms.

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