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Drug Allergy in Adults at a Multidisciplinary Hospital: Prevalence Assessment Using the Global Trigger Tool

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ABSTRACT

INTRODUCTION. Allergic drug reactions in hospitalised patients limit the opportunities for rational pharmacotherapy and increase the risk of polypharmacy due to the need for managing the patient's condition and prescribing anti-allergic agents. An objective assessment of the prevalence of inpatient allergic drug reactions and a categorisation of medicinal products are critical for treatment adjustment and will lead to both a significant improvement in clinical outcomes for patients and a reduction in the financial burden for the healthcare system. The Global Trigger Tool (GTT) methodology is based on analysing medical records and capturing specific triggers, which makes GTT easily applicable in clinical practice.
AIM. This study aimed to investigate the applicability of GTT in studying the prevalence of allergic drug reactions in patients admitted to a multidisciplinary hospital.
MATERIALS AND METHODS. This study used GTT in retrospective pharmacoepidemiological analysis of medical records of patients admitted to City Clinical Hospital 24 of the Moscow City Health Department from 1 October 2022 to 1 April 2023. The study included medical records of patients treated in the internal medicine and surgery departments during the specified period and excluded those of allergology patients.
RESULTS. A total of 8,934 patients were admitted to the internal medicine and surgery departments during the analysed period. Triggers suggestive of allergic drug reactions were identified in 229 (2.6%) of their medical records. This would correspond to a prevalence of 2,563 cases per 100,000 patients. However, the analysis of prescriptions, diary cards, and clinical and laboratory findings identified only 52 (22.7%) true triggers of allergic drug reactions. In the remaining 177 (77.3%) cases, the triggers were classified as false positives, as anti-allergic agents were prescribed before or concomitantly with the suspected medicinal product, presumably, to prevent potential allergic reactions. The main groups of medicinal products suspected to cause allergic reactions were systemic antimicrobial agents (22 (40.7%) products, in particular, 14 (20.3%) beta-lactam antibiotics) and monoclonal antibodies (21 (38.9%) products).
CONCLUSIONS. The true prevalence of allergic drug reactions was 0.58%, which corresponds to 582 cases per 100,000 patients. The study demonstrated the effectiveness of the GTT in identifying allergic drug reactions in real-world clinical practice. The exclusion of false triggers, first of all, anti-allergic agents prescribed as prophylaxis, significantly reduces the bias in estimating the true prevalence of allergic drug reactions and the risk of overdiagnosis.

Keywords: Global Trigger Tool; adverse drug reactions; drug allergies; H1-histamine receptor blockers; antimicrobial agents; monoclonal antibodies

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Лекарственно-индуцированная аллергия у взрослых в многопрофильном стационаре: оценка распространенности методом глобальных триггеров

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РЕЗЮМЕ

ВВЕДЕНИЕ. Лекарственно-индуцированные аллергические реакции (ЛИАР) у госпитализированных пациентов ограничивают возможности рациональной фармакотерапии и увеличивают риск полипрагмазии в связи с необходимостью коррекции состояния пациента и назначения противоаллергических препаратов. Объективная оценка частоты ЛИАР в стационаре и структуры препаратов для коррекции назначений является актуальной задачей, решение которой позволит как достичь значимого улучшения клинических исходов пациентов, так и снизить бремя затрат системы здравоохранения. Метод глобальных триггеров основан на анализе медицинской документации и фиксировании определенных триггеров, что делает его легко применимым в клинической практике.

ЦЕЛЬ. Изучение возможности использования метода глобальных триггеров для оценки распространенности ЛИАР у пациентов многопрофильного стационара.

МАТЕРИАЛЫ И МЕТОДЫ. Ретроспективное фармакоэпидемиологическое исследование медицинской документации пациентов, госпитализированных в ГБУЗ «Городская клиническая больница № 24 Департамента здравоохранения города Москвы» в период с 01.10.2022 по 01.04.2023, с использованием метода глобальных триггеров. Критерии включения: пациенты, проходившие стационарное лечение в отделениях терапевтического и хирургического профиля в указанный период. Критерии исключения: пациенты отделения аллергологии.

РЕЗУЛЬТАТЫ. Всего за анализируемый период в отделения терапевтического и хирургического профилей поступили 8934 пациента. Триггеры ЛИАР были идентифицированы у 229 (2,6%, то есть 2563 на 100000 пациентов). Оценка листов назначений, дневников и клинико-лабораторных данных позволила выявить лишь 52 истинных триггера ЛИАР (22,7%). В оставшихся 177 случаях (77,3%) противоаллергический препарат был назначен до или одномоментно с подозреваемым лекарственным средством, предположительно с целью профилактики возможного развития аллергической реакции, что оценивали как ложный триггер. Основными группами подозреваемых препаратов явились антибактериальные средства для системного применения (22 препарата (40,7%), в частности бета-лактамные антибиотики – 14 препаратов (20,3%)), а также моноклональные антитела (21 препарат (38,9%)).

ВЫВОДЫ. Истинная частота развития ЛИАР составила 0,58% (582 на 100000 пациентов). Продемонстрированные в исследовании результаты показали эффективность применения метода глобальных триггеров для выявления случаев лекарственной аллергии в реальной клинической практике. Исключение ложных триггеров (прежде всего профилактических назначений лекарственных препаратов) уменьшает искажение реальной частоты ЛИАР и гипердиагностики данного состояния.

Ключевые слова: метод глобальных триггеров; нежелательные реакции; лекарственная аллергия; блокаторы Н1-гистаминовых рецепторов; антибактериальные препараты; моноклональные антитела

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INTRODUCTION

An adverse drug reaction (ADR) is an unintended adverse reaction associated with the use of a medicinal product (MP) and suggesting a relationship with the use of the suspected MP[1]. ADRs are most common among hospitalised patients, occurring in nearly 20% of the admissions [1]. According to estimates based on global burden of disease data from 1990 to 2019, the age-standardised mortality rate associated with ADRs will reach 1.58 (95% confidence interval: 1.33–1.80) by 2040 [2]. According to a 2024 meta-analysis, the cost of managing one ADR patient (one hospital admission) in the developed countries ranges from 6,000 to 10,000 euro [3], reflecting the high healthcare system costs in the event of ADR.

Early ADR recognition in hospital settings is a necessary element in improving pharmacotherapeutic safety. Several validated methods exist for identifying and assessing these ADRs. The spontaneous reporting method is based on voluntary reports from all participants of MP civil commerce. Spontaneous reporting method provides an ADR database created at the national level. However, this method has its limitations: reporting rates can vary significantly depending on the reporter's motivation, time available, qualifications, and interpretation of the problem significance [4]. There is also a system of active drug safety monitoring based on dynamic post-treatment follow-up. ADRs can be identified through direct patient interviews or screening of patient medical records. A disadvantage of this method is a relatively small number of patients [5]. Another active monitoring method is the Global Trigger Tool (GTT), developed at the US Institute for Healthcare Improvement (IHI). This tool includes a search for specific ADR triggers in the patient's medical record, allowing for a rapid and cost-effective assessment of the pharmacotherapeutic safety, especially important in drug-induced allergic reactions [6].

Triggers for the potential DIAR development in hospitalised patients may include abruptly discontinued or changed medication; drugs such as H1-histamine receptor blockers, epinephrine, topical steroids, intravenous glucocorticosteroids; and typical symptoms of an allergic reaction described in observation diaries.

DIARs can account for up to a third of all ADR cases in emergency departments [7]. The most common drug group causing DIARs are antibacterials [1]. Meta-analysis of 32 studies (n=1,089,675) shows the prevalence of reported DIAR cases induced by antibacterial drugs in the range from 5% to 35% [8]. Risk factors include a history of any DIAR, repeat prescription of the suspected MP, as well as parallel prescription of other certain other drug groups (e.g., angiotensin-converting enzyme inhibitors) [9], and female sex [10]. Polypharmacy also plays a significant role in the development of DIARs [11].

At the same time, DIAR overdiagnosis, in particular if caused by antibiotics, significantly limits the resources of the attending physician and contributes to antibiotic resistance due to alternative MPs included in the treatment regimens; this indicates the need for active study of the true DIAR prevalence [12].

The aim of the study is to investigate the applicability of GTT in studying the prevalence of allergic drug reactions in patients admitted to a multidisciplinary hospital.

MATERIALS AND METHODS

A retrospective pharmacoepidemiological study of the medical records from patients hospitalised at the Moscow City Clinical Hospital No. 24 from 1 October 2022 to 1 April 2023 was conducted using GTT.

We analysed medical records of inpatients who met the following inclusion criteria:

[1] Decision of the Council of the Eurasian Economic Commission dated 03.11.2016 No. 87 "On approval of the Rules of good pharmacovigilance practice of the Eurasian Economic Union".

closed and fully completed medical records (including discharge summaries) from the medical (cardiology, internal medicine, neurology) and surgical (gynaecology, general surgery, proctology, and urology) departments; a patient's hospital stay of at least 72 hours; patients aged 18 years or older; prescribed medications belong to the group of antihistamines (ATC code: R06[2]) and systemic corticosteroids (ATC code: H02[3]). Exclusion criteria: medical records of patients in the allergy department, since it is impossible to differentiate ADRs from the basic treatment of the underlying disease.

DIAR was assessed using two of the six GTT modules: Module I. Patient Care and Monitoring, as well as Module II. Medication Treatment [13]. Triggers were defined as 1) prescription of diphenhydramine, encompassing other anti-allergic agents, such as antihistamines and calcium gluconate; 2) prescription of glucocorticosteroids, as they are most often used in real-world clinical practice to relieve allergic symptoms.

During the analysed period, 8,934 patients were admitted to the study sites (departments). Medical records were analysed independently by three researchers with relevant clinical expertise and experience. DIAR triggers were identified in 229 medical records.

The average age of patients with the identified DIAR triggers in medical histories (*n*=229) was 53.2±19.5 years; 48% (*n*=111) of patients were over 60 years old *(Table 1)*.

When a trigger was detected in a prescription drug list, medical documents (diaries; interdisciplinary examination protocols by various specialists; medical and underlying disease history; laboratory and diagnostic data) were thoroughly analysed to confirm the adverse reaction, assess the harmful effect on the patient's health, and identify the DIARs. DIARs were classified by the coding rules of the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0 (March 2024)[4].

An analysis of medical records allowed us to divide all the identified triggers into two groups: true and false. False triggers included 1) prescribing anti-allergic agents to patients without allergic reaction symptoms described in their medical history (daily records: diary, interdisciplinary examination protocols by various specialists) or their laboratory signs (normal blood eosinophil count); 2) prescribing a trigger MP before or simultaneously with antibacterials, nonsteroidal anti-inflammatory MPs, general and local anaesthetics. True triggers included prescribing anti-allergic agents several hours or days after the first administration of the suspected MP, as well as prescribing medications that triggered the patient's allergic reaction, as noted in the medical records.

Study results were statistically analysed using Microsoft Excel 2019 software. Descriptive statistics was used for quantitative indicators: qualitative variables included absolute (*n*) and relative (%) values; the data were tested for normal distribution using Shapiro-Wilk test. All study variables were normally distributed, thus the mean (*M*) and standard deviation (*SD*) was calculated. The positive predictive value (PPV[5]) was also used.

RESULTS

Analysis of 8,934 case histories revealed triggers in 229 cases (2.6%, or 2,563 per 100,000 patients). The total number of identified trigger prescriptions was 254. Among the trigger medications *(Table 2)*, H1-histamine receptor antagonists prevailed (96.9%, *n*=246). Glucocorticosteroids were prescribed in 2.8% (*n*=7), calcium gluconate – in 0.4% of the cases (*n*=1). The total number of case records with true triggers presumably causing ADRs was 52 (22.7%; PPV=20.47%). In 77.3% (*n*=177) of the

[2] ATC code R06A | Antihistamines for systemic use | ATC classification of drugs 2025.
[3] ATC Code H02 | Systemic corticosteroids | ATC Classification of Drugs 2025.
[4] Medical Dictionary for Regulatory Activities – MedDRA.
[5] PPV is a statistical measure that reflects the probability of a patient with a positive test result having the investigated condition (the proportion of true positive results to all positive test results). PPV values below 50% are generally considered low; in such cases, more than half of the positive test results are false. PPV will be low when the prevalence is low (even if the test has high accuracy) and high when prevalence is high.

Table 1. Profile of patients with allergic drug reaction triggers identified in medical records (*n*=229)

Parameter	Value
Age (*M*±*SD* (min; max)), years	53.2±19.5 (18.0; 91.0)
Female sex, *n* (%)	139 (60.7)
Body mass index (*M*±*SD* (min; max)), kg/m²	27.1±6.5 (16.4; 52.0)
Inpatient treatment duration (*M*±*SD* (min; max)), days	7.5±3.7 (3.0; 35.0)
Comorbidity	
Cardiovascular diseases, *n* (%)	77 (33.6)
Kidney diseases, *n* (%)	15 (6.5)
Diabetes mellitus, *n* (%)	22 (9.6)
Liver dysfunction, *n* (%)	14 (6.1)
Cancer, *n* (%)	28 (12.2)

The table was prepared by the authors using their own data

Note. M, mean value; *SD*, standard deviation.

Table 2. List of the identified trigger medicinal products

International Non-proprietary Name (INN)	Quantity	
	n	%
H1-histamine receptor blockers (total)	246	96.9
Chloropyramine	68	26.8
Clemastine	139	54.7
Hydroxyzine	9	3.5
Cetirizine	25	9.8
Mebhydroline	5	2.0
Glucocorticoids (total)	7	2.8
Dexamethasone	2	0.8
Prednisolone	5	2.0
Other (calcium gluconate)	1	0.4

The table was prepared by the authors using their own data

cases, trigger MPs were prescribed to prevent possible allergic reactions; these triggers were defined as false *(Table 3)*.

The next study stage aimed at assessing the allergy history in the groups with true and false triggers. Analysed medical records of all patients revealed a history of drug allergy in 14% (33/229).

The average number of medications administered per patient in the true trigger group was 6.9±3.2 (min – 2; max – 15).

Analysis of the clinical picture accompanying DIAR development in the true trigger group revealed 58 ADRs (classification by MedDRA primary system organ classes): Skin and subcutaneous tissue disorders – rash, urticaria (70.7%, *n*=41), erythema (5.2%, *n*=3); General disorders and administration site conditions – itching and red skin at the injection site (18.9%, *n*=11); Immune system disorders – anaphylactoid reaction (3.4%, *n*=2); Respiratory, thoracic, and mediastinal disorders – bronchospasm (1.7%, *n*=1). The majority of identified adverse reactions (94.8%, 55/58) were non-serious (temporary injury).

After analysing the prescription drug lists of patients in the group with true triggers, a list of 130 MPs suspected of causing DIAR was compiled (mean value per patient 2.5±1.2 (1; 6)). Based on the opinions of the treating physicians, clinical pharmacologists, and consultations by allergists and immunologists, the list of MPs suspected of causing DIAR was reduced to 54 *(Table 4)*.

The main suspects in the DIAR development were two MP groups: systemic anti-

Table 3. Distribution of medical records of patents admitted to different hospital departments by false and true triggers

Department	Number of medical records			
	Total, *n*	Total patients with triggers, *n* (%)	With false triggers *n* (%)	With true triggers, *n* (%)
Gynaecology	883	16 (1.8)	11 (69)	5 (31)
General surgery	1329	7 (0.5)	5 (71)	2 (29)
Coloproctology	1473	4 (0.27)	4 (100)	0 (0)
Urology	429	144 (33.5)	139 (96)	5 (4)
Cardiology	2549	20 (0.78)	9 (45)	11 (55)
Internal medicine	1047	13 (1.24)	9 (69)	4 (31)
Neurology	1224	25 (2)	0 (0)	25 (100)
Total	8934	229 (2.6)	177 (76)	52 (24)

The table was prepared by the authors using their own data

Table 4. List of medicinal products suspected to cause allergic drug reactions in patients with true triggers identified in medical records

Medicinal products (*n*=54)	Quantity	
	n	%
Antimicrobial agents	22	40.7
Cephalosporins	11	20.3
Fluoroquinolones	5	9.2
Aminoglycosides	1	1.9
Glycopeptides	1	1.9
Carbapenems	1	1.9
Monobactams	1	1.9
Oxazolidinones	1	1.9
Penicillins	1	1.9
Monoclonal antibodies	21	38.8
Non-steroidal anti-inflammatory drugs	2	3.7
Amiodarone	1	1.9
Atorvastatin	1	1.9
Acetylcysteine	1	1.9
Iron–sugar complex	1	1.9
Oxaliplatin	1	1.9
Spironolactone	1	1.9
Fluconazole	1	1.9
Fluoxetine	1	1.9
Empagliflozin	1	1.9

The table was prepared by the authors using their own data

bacterials – 40.7% (22/54), primarily beta-lactams – 63.6% (14/22), and monoclonal antibodies – 38.9% (21/54). Due to the need to use a particular MP, in most cases, a physician had to continue therapy adding anti-allergic agents. Medication was discontinued/changed in only 7.4% of cases (4/54).

In 92.1% (163/177) of cases of false triggers, the prescription of anti-allergic agents was likely associated with the prevention of an allergic reaction while taking antibacterials, in particular from the cephalosporin group (90 cases (50.9%)) and fluoroquinolones (84 cases (47.5%)).

The average hospital stay for patients in the true trigger group was 8.5 days. More details are provided in *Table 5*.

DISCUSSION

Using GTT, we identified 2.6% (229/8,934) of inpatient medical records who could develop DIAR during hospitalisation. This is significantly lower than the DIAR rate reported in published data (15–20% for hospitalised patients) [1], but generally corresponds to the results of a study analysing GTT tool to identify ADRs: the overall ADR prevalence was 13.39%, while the proportion of allergic reactions (cutaneous ADRs) was approximately 2.4% of all patients [14].

Literature shows that DIAR risk factors include a history of DIAR, polypharmacy, and female sex [9–11, 15]. Our profile of DIAR patients resulting from exposure to true triggers is consistent with this picture [16–19]: a history of drug allergy was present in 57.7% (30/52) of cases. Female patients predominated (61.5%). Female sex is known to be a risk factor for various DIAR forms. For example, among adult female patients, the risk of penicillin allergy is 10 times higher than in males [20]. Cutaneous DIARs, including severe ones, also developed more frequently in female patients [21, 22].

In DIAR patients, the average number of MPs taken was 6.9±3.2. For more than five prescriptions, ADR risk increased sharply [23]. A prospective study conducted in Great Britain (n=218, 1-month follow-up) showed that in the group of hospitalised patients who developed ADRs, the average number of medications used by one patient was 10.5±4.6 compared with 7.8±5.1 for patients without ADRs; polypharmacy was detected in 91% of the ADR group and 73% of the non-ADR group [24]. Notably, 1 to 10% of population with drug allergies have multiple drug intolerance syndrome (intolerance to three or more structurally and pharmacologically unrelated drugs); in the context of polypharmacy, it further increases the DIAR risk [25]. A significant factor in DIAR prevention is a planned and controlled reduction in the number of MPs prescribed to the patient – deprescribing – one of the important tools for improving pharmacotherapeutic safety [26].

In the study, the average hospital stay for patients with true DIAR triggers was 8.5±4.7 days. The study [27] demonstrated a significantly longer stay (mean difference 3.98 days; 95% CI: 2.91 to 5.05 days). The greatest length of stay increased due to ADRs was observed in aged and older patients (12.4±11.0 days *vs* 7.3±6.4 days in patients without ADRs; p<0.0001) [28]. Furthermore, prolonged hospital stay is a factor contributing to increased healthcare costs. Russian researchers assessed ADR economic costs during the therapy and found that ADR correction accounts for 1 to 10% of total direct treatment costs [29].

Table 5. Profile of patients with true allergic drug reaction triggers identified in medical records (n=52)

Parameter	Value
Age (*M*±*SD* (min; max)), years	48.8±20.2 (18.0; 91.0)
Number of patients >60 years, *n* (%)	20 (38.5)
Female sex, *n* (%)	32 (61.5)
Body mass index (*M*±*SD* (min; max)), kg/m^2	26.8±6.05 (18.2; 44.0)
Body mass index >30 kg/m^2, %	27%
Inpatient treatment duration (*M*±*SD* (min; max)), days	8.5±4.7 (3.0; 35.0)
Cardiovascular diseases, *n* (%)	19 (36.5)
Kidney diseases, *n* (%)	5 (9.6)
Diabetes mellitus, *n* (%)	2 (3.8)
Liver dysfunction, *n* (%)	3 (5.8)
Cancer, *n* (%)	8 (15.4)

The table was prepared by the authors using their own data

The majority of MPs presumably causing DIARs in the study were systemic antibacterial agents (40.7%, *n*=22), particularly beta-lactam antibiotics (20.3%, *n*=14), as well as monoclonal antibodies (38.9%, *n*=21). These groups are typical DIAR triggers [8, 30]. DIAR prevalence caused by beta-lactams, particularly penicillins, is as high as 10% [9, 30]. According to the Russian National Pharmacovigilance Database (a period of 02 April 2019 – 21 June 2023), drug-induced anaphylaxis was associated with the use of beta-lactams in almost 88% of the cases [31]. Beta-lactams were identified as the cause of severe cutaneous DIARs (Stevens-Johnson syndrome, toxic epidermal necrolysis) in 61% of cases, according to an analysis of the Russian pharmacovigilance database (a period of 1 April 2019 – 31 December 2023) [32]. Current data suggest an increasing role for monoclonal antibodies in the DIAR progress. In particular, they were identified as the second most common cause of anaphylaxis in the United States (FAERS database, 1999–2019), antibacterial agents deemed as the leading cause; the increase rate in anaphylaxis reports due to monoclonal antibodies was the highest among all the classes [33]. Similarly, the highest growth rate in the specific proportion of reports among all the classes was determined for monoclonal antibodies and in the case of drug-induced severe skin allergic reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis); in 2004, there were no reports in the FAERS database, while in 2021, they accounted for 4.79% [34].

To prevent hypersensitivity reactions in a hospital setting, histamine H1- and H2-receptor blockers and glucocorticoids may be prescribed immediately before using a potential DIAR trigger. This method is used in cases of the established drug allergy that cannot be replaced with an alternative [35]. However, to prevent unjustified prescriptions and the resulting polypharmacy, clinical pharmacologists and allergists should be additionally involved.

Study limitations include: the study with a patient sample based on one health facility; a narrow timeframe, and the lack of control group without adverse reactions. Subsequent study phases are planned with an extended timeframe to obtain more data / increase the patient sample. The authors also plan to investigate the feasibility of using GTT in assessing the overall pattern of adverse reactions among hospitalised patients.

CONCLUSIONS

In a retrospective study using GTT of 8,934 medical records from a multidisciplinary hospital, DIAR triggers were identified in 2.6% of cases (2,563 per 100,000 patients). Analysis of prescription drug lists, diaries, and clinical laboratory data allowed us to exclude false triggers (preventive prescription of antiallergic agents) and identify the true DIAR prevalence: 0.58% (582 per 100,000 patients). The main groups of MPs presumably causing DIARs were systemic antibacterial agents (40.7%, in particular beta-lactam antibiotics – 20.3%) and monoclonal antibodies (38.9%).

The results demonstrated GTT effectiveness for identifying drug allergy cases in real clinical practice. Eliminating false triggers (primarily prophylactic medical prescriptions) reduces statistical distortion of the actual DIAR prevalence and overdiagnosis of this condition.

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