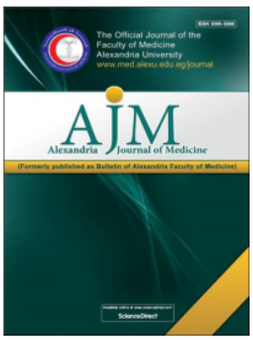

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Antimicrobials associated adverse drug reaction profiling: a four years retrospective study (Pharmacovigilance study)

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ABSTRACT

Background: All drugs profoundly modify our biological processes and may manifest as adverse drug reactions (ADRs), which are unpredictable and inevitable consequences. Antibiotics are a common cause of ADR, necessitating stopping or change of antibiotics. The incidence of ADRs increases with the number of drugs prescribed in a prescription, and antibiotics are rarely prescribed as monotherapy.

Aim: The study aimed to assess frequency, class of antibiotics, symptoms, causality, the severity of antimicrobial-associated ADRs, and see the demographic distribution.

Methods: ADRs were collected and filled in suspected ADR forms and sent *via* vigiflow to the National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI). These ADR reports, termed individual case safety reports (ICSRs), were analyzed from Jan 2016 to Dec 2019.

Results: A total of 414 (54.33%) ICSRs of 762 were identified as antimicrobial-associated. Adults in the age group 19–65 years accounted for 345 (83.09%) of ADRs. A total of 192 (46.38%) were males, and 222 (53.14%) were females. Skin and subcutaneous tissue System organ class was involved in 54% of cases. In the causality assessment, 268 (64.49%) were "probable," 123 (29.71%) were "possible," and 23 (5.56%) were "certain." On severity assessment, 256 ADRs (61.83%) were mild, 133 (32.12%) were moderate, and 25 (6.03%) were severe. A total of 54 antimicrobial agents, excluding anti-tubercular drugs, were identified, and antibacterial accounted for 268 (64.73%) ADRs, followed by antiviral 90 (21.73%), antiprotozoal agents 33 (7.97%) antimalarials anti-scabicidal, antifungal accounting for the remaining.

Conclusion: Antimicrobials play a crucial role in treating infections, and utmost vigilance during antimicrobials prescription reduces the frequency and severity of the ADRs, thereby reducing the morbidity and mortality and the pharmacoeconomic burden to the health care system. Pharmacovigilance must be boosted to ensure the safe and effective use of antibiotics and reduce the occurrence of ADRs.

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Antimicrobials; antibiotics; adverse drug reactions (ADRs); individual case safety reports (ICSRs); severity of ADRs; causality assessment

1. Introduction

Antibiotics are the most prescribed medication worldwide, and their use is constantly increasing. The World Health Organization (WHO) report on surveillance of antibiotic consumption between 2016 and 2018 shows an overall consumption ranging from 4.4 to 64.4 Defined Daily Doses (DDD) per 1000 inhabitants per day [1]. India is among the leading consumer of antibiotics, and its consumption increased from 3.2 billion DDDs in the year 2000 to 6.5 billion DDDs in 2015, amounting to a 103% rise [2]. Globally, consumption of antibiotics increased from 8.2 to 13.6 DDD per 1000 inhabitants per day from the year 2000 to 2015, amounting to a 65% rise [3]. This surge in antibiotic usage in India is attributed to increased incidence of infectious diseases, mass manufacturing of generic antibiotics that are cheaper, increased income, and availability of government health insurance schemes. Availability of antibiotics without prescription is another major issue in India; therefore, red strip labeling of packages has been made mandatory to reduce dispensing without prescription. Increased use of antibiotics is associated with an increase in antimicrobial resistance and an increased incidence of adverse drug reactions (ADRs) [4]. Adverse drug reaction (ADR), as defined by the World Health Organization (WHO), is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [5]. ADRs can occur with any class of drugs, and over half of the hospitalized patients receive at least one antibiotic during their hospital stay, of which 55.5% ADRs are definitely preventable and accounts for 20–50% of the drug expenditure in the hospitals [6]. According to a study conducted in Johns Hopkins Hospital, Maryland, between 2013 and 14, 20% of the hospitalized patients experienced at least one antibiotic-associated ADR and its frequency increase as the number of antibiotics increase [7]. The overall incidence of ADRs is 0.15% to 30% [8]. A systematic review in India reports that the median incidence of

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ADRs leading to hospitalization is 2.85% and those developed during hospitalization as 6.34% [9]. Despite drug safety studies done during clinical trials and manufacturing, diagnosing, and quantifying prescription-related ADRs remains a challenge. This is because clinical trials are limited to a few hundred to thousand patients chosen based on inclusion and exclusion criteria, unlike patients in clinical settings with various comorbidities and lifestyles. Antibiotic-associated ADRs have resulted in 43% of antibiotics withdrawal, mostly cephalosporins, and fluoroquinolones approved between 1980 and 2009 within 15 years of approval [10]. Development of ADR with an antibiotic compels the clinician to prescribe an antibiotic either of the altered spectrum or efficacy and toxicity, posing a threat to patient safety. The incidence of ADRs associated with certain antibiotics is predicted while for some it is not. For example, penicillin's most serious hypersensitivity reaction is anaphylaxis and is fatal in about 0.001% of patients; and skin rash of all types due to ampicillin occur in 9% patients [11]. However, frequency of certain ADRs is not known, and such ADRs mandate drug regulatory authorities to update drug usage information.

In line with this inkling, the WHO established the Pharmacovigilance program in 1968 for pooling data in ADRs from multiple countries. This program is coordinated at its collaborating center in Uppsala Monitoring Centre (UMC), Sweden, with more than 160 countries participating, including India [11]. Pharmacovigilance Programme of India (PvPI), maintained by the Indian Pharmacopeia Commission (IPC), functions as the National Coordination Centre (NCC) started in 2010 and became a WHO collaborating center in 2017 and is responsible for ensuring the safety of medicines used by the Indian population. India collects about 50,000 domestic ADRs yearly and shares them with the World Health Organization (WHO) Programme for International Drug Monitoring in VigiBase [WHO global database of individual case safety reports (ICSR)] through vigiflow. More than 250 ADR monitoring centers (AMC) are functioning for reporting ADRs in the Indian database. PvPI aims to enhance patient care and safety concerning the use of medicines and provide reliable information by regularly sending drug safety and therapeutic device alerts [12,13]. The AMC at our tertiary hospital contributes ICSRs to the NCC, and in addition, regularly analyzes the ADRs, deals with under-reporting issues, and sensitizes the health care workers to report any suspected ADR to reduce drug-related morbidity and mortality [14].

India is the fourth largest pharmaceutical producer globally with more than 60,000 formulations and is emerging as a clinical trial hub exposing a large population to newer drug treatments and related ADRs [15]. Therefore, it is imperative to identify antibiotic-associated ADRs as early as possible to ensure their management, formulate guidelines for adequate and appropriate consumption, and frame ADR reporting and prevention policy. However, specific antibiotic-associated ADR data from India is not available, more so from central India, necessitating more studies from regional and state AMCs. A previous study from our AMC analyzed ADRs occurring due to all medicines and reported the highest ADRs due to antimicrobial, so a need for longer duration and specific antimicrobial-associated ADR profiling was felt [14]. With this context in mind, this study was conducted to analyze the frequency, antibiotics involved, System Organ Class (SOC) affected, causality, and severity of antimicrobial-associated ADRs in a tertiary hospital of central India. Antimicrobial-associated ADRs reported from both outpatient and inpatient settings, by all routes and for all ages were included, enabling us to produce a comprehensive picture of the overall incidence and profile of ADRs.

2. Materials and methods

2.1. Data source

The study was conducted at the Department of Pharmacology, PT JNM Medical College, and associated B. R. Ambedkar hospital, Raipur, Chhattisgarh, India. It is a 1100 bedded tertiary care teaching hospital. Suspected ADR form was used to collect ADR information as per the NCC-PvPI standard operating procedure. The ADRs were sent to IPC-PvPI (Indian database) *via* vigiflow as Individual case safety reports (ICSRs). Data was extracted from the Indian Database between January 2016-December-2019 (4 years). Collection and assessment follow the procedure described by Singh *et al.* [14].

2.2. Study design

The database search comprised all the ICSRs reported from Pt JNM Medical College Raipur associated BR Ambedkar Hospital, Raipur Chhattisgarh, India. Only those suspected ADRs involving at least one antimicrobial agent with at least one dose in all age groups, by any route of administration, and both outpatient and inpatient patients, were included in the study (Figure 1). ADRs related to anti-tubercular drugs were excluded from the study as separate hospital functions to implement the National Tuberculosis Elimination Program and report the ADRs directly to the IPC-PvPI. The identification of the patients and reporters was kept confidential.

The ADR profiling was done explicitly under the following heads: demography, antimicrobial agent implicated, SOC involved [Medical Dictionary for Regulatory Activities (MedDRA Version 22.1)], as MedDRA terminology helps to standardize ADR terminology and enhance profiling [16]. The causality assessment was done using the WHO UMC causality

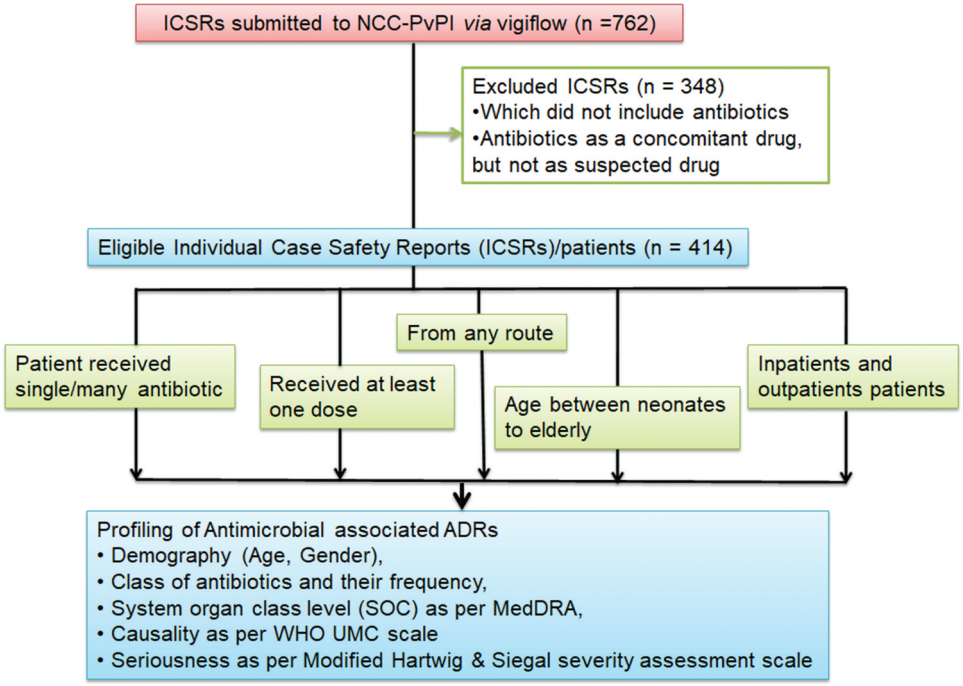

Figure 1. Flow-chart diagram for plan of study.

scale (causality assessed by the AMC causality assessment committee to avoid incongruity between assessors) [17]. Severity assessment was done by Modified Hartwig and Siegel severity assessment scale and classified as mild, moderate, or severe [18,19].

2.3. Statistical analysis

The data was incorporated in the MS-Excel sheet, and the categorical data in numbers were converted to percentages to achieve readily comparable information and quantify the difference between them.

3. Results

3.1. Demography

During the study period, a total of 414 (54.33%) antimicrobial-associated ICSRs were analyzed of 762 ICSRs. Adults in the age group 19–65 years accounted for 345 (83.33%) of ADRs, and the remaining age groups comprised only 69 (16.67%) ADRs. In addition, 222 (53.62%) ICSRs were of females, and 192 (46.38%) of males, as illustrated in Table 1.

Table 1. Analysis of demographic, and causality of adverse drug reactions (ADRs).

Parameter	No. of ADRs (n = 414)	Frequency %
Gender		
Male	192	46.38
Female	222	53.62
Age		
Neonate (below 27 days)	1	0.24
Infant (28 days to 1 yr)	3	0.73
Child (2–11 yrs)	37	8.94
Adolescent (12–18 yrs)	19	4.59
Adult (19–65 yrs)	345	83.33
Elderly (66 yrs and above)	9	2.17
Causality		
Certain	23	5.56
Probable	268	64.73
Possible	123	29.71
Unlikely	0	0
Unclassified	0	0
Unclassifiable	0	0

3.2. Drug frequency

A total of 54 antimicrobial agents were involved (Table 2) comprising: antibacterial [268 (64.73%)], antiviral [90 (21.73%)], antiprotozoal [33 (7.97%)], antileprotic and antifungal [9 each (2.17% each)], antimalarial [3 (0.72%)] and antiscabicidal [2 (0.48%)]. Anti-tubercular drugs were excluded. The cephalosporins [104 (25.12%)], antiretroviral agents [90 (21.7%)], penicillin, and its semisynthetic derivatives [78 (18.84%)] quinolones and antiprotozoal [33 (7.97%) each] were the top five offenders. Among individual antimicrobial drugs, the top five agents causing ADR were ceftriaxone [75 (18.11%)], fixed drug combination (FDC) of tenofovir/lamivudine/efavirenz (TLE) [68 (16.42%)], piperacillin tazobactam FDC and Ciprofloxacin [24 (5.79%) each], and cefixime [20 (4.83%)].

3.3. System organ class (SOC) involvement

Some ICSRs showed involvement of multiple systems in the body, so of 414 ICSRs reported, 527 SOC involvement was noted as per Medical Dictionary for Regulatory Activities (MedDRA) terminology using version 22.1 (Figure 2). “Skin and subcutaneous tissue” was involved

Table 2. Individual drug frequency reported in individual case safety reports [(ICSRs) n = 414].[a]

Antimicrobial Class Total no. of drugs (Frequency %)	Types of antimicrobial Drugs involved in different ICSRs (n = 54)	No. of Individual antimicrobials (frequency %)
Sulfonamides-12 (2.89%)	Sulfamethoxazole/Trimethoprim	11 (2.65)
	Pyrimethamine/Sulfadoxine	1 (0.24)
Quinolones-33 (7.97%)	Ciprofloxacin	24 (5.78)
	Ofloxacin	4 (0.96)
	Norfloxacin	2 (0.48)
	Levofloxacin	2(0.48)
	Moxifloxacin	1 (0.24)
Penicillins-78 (18.84%)	Penicillin	1 (0.24)
	Ampicillin	2 (0.48)
	Amoxicillin	2 (0.48)
	Amoxicillin/Clavulanic acid	49 (11.83)
	Piperacillin/Tazobactam	24 (5.79)
Cephalosporins-104 (25.12%)	Ceftriaxone	75 (18.11)
	Cefixime	20 (4.83)
	Cefpodoxime	4 (0.96)
	Cephalexin	1 (0.24)
	Cefuroxime	1 (0.24)
	Cefoperazone/Sulbactam	2 (0.48)
	Cefotaxime	1 (0.24)
Other betalactum- 7 (1.69%)	Meropenem	7 (1.69)
Tetracyclines-2 (0.48%)	Minocycline	1 (0.24)
	Doxycycline	1 (0.24)
Aminoglycoside-8 (1.93%)	Gentamicin	5 (1.20)
	Streptomycin	1 (0.24)
	Amikacin	2 (0.48)
Macrolides-10 (2.41%)	Azithromycin	8 (1.93)
	Clindamycin	1 (0.24)
	Clarithromycin	1 (0.24)
Miscellaneous antibacterials-14 (3.38%)	Vancomycin	7 (1.69)
	Linezolid	5 (1.20)
	Nitrofurantoin	2 (0.48)
Antileprotic-9 (2.17%)	Dapsone	9 (2.17)
Antifungal-9 (2.17%)	Fluconazole	3 (0.72)
	Terbinafine	1 (0.24)
	Itraconazole	3 (0.72)
	Sertaconazole	1 (0.24)
	Clotrimazole	1 (0.24)
Antiviral-90 (21.73%)	TLE	68 (16.42)
	T/TL	5 (1.20)
	ZLN	6 (1.44)
	ZL	5 (1.20)
	ZLE	3 (0.72)
	Abacavir	1 (0.24)
	Acyclovir	1 (0.24)
	Ritonavir	1 (0.24)
Antimalarials-3 (0.72%)	Artemether/Lumefantrine	2 (0.48)
	Sulfadoxine/Pyrimethamine	1 (0.24)
Antiprotozoal- 33(7.97%)	Metronidazole	16 (3.86)
	Ornidazole	2 (0.48)
	Tinidazole	2 (0.48)
	Ofloxacin/Ornidazole	7 (1.69)
	Norfloxacin/Tinidazole	5 (1.20)
	Ciprofloxacin/Tinidazole	1 (0.24)
Antiscabicidal-2 (0.48%)	Permethrin	2 (0.48)

[a]E: Efavirenz; L: Lamivudine; N: Nevirapine; T: Tenofovir; Z: Zidovudine.

in 277 (52.56%) reports, followed by "gastrointestinal disorders" [59 (11.19%) reports] and "general disorders and administrative site" [53 (10.05%) reports]. On individual SOC analysis, drugs most implicated in the SOC of skin and subcutaneous tissue (Table 3) were antiviral FDC of TLE (17.32%), ceftriaxone (12.19%), and amoxicillin-clavulanic acid (10.46%); and manifested as a maculopapular itchy rash, urticaria, and in some cases as skin exfoliation. In the SOC Gastrointestinal disorders (Table 4), the drugs most implicated were FDC of TLE (23.72%) and amoxicillin-clavulanic acid (22.03%); and manifested as vomiting, abdominal pain, oral mucositis, and diarrhea. Table 4 also shows the involvement of other SOCs and drug frequencies. Immune system disorders were reported in only seven ICSRs manifesting as anaphylaxis, and the drugs implicated were ceftriaxone, amoxicillin-clavulanic acid, and dapsone in 4, 2, and 1 case, respectively. No drugs could be assigned to SOC of endocrine disorders, neoplasm, product issues, surgical and medical conditions, and congenital disorders.

3.4. Causality

As per the "WHO UMC scale," the causality was "certain" in 23 (5.5%) ICSRs, "possible" in 123 (29.71%) ICSRSs, and "probable" in 268 (64.73%)

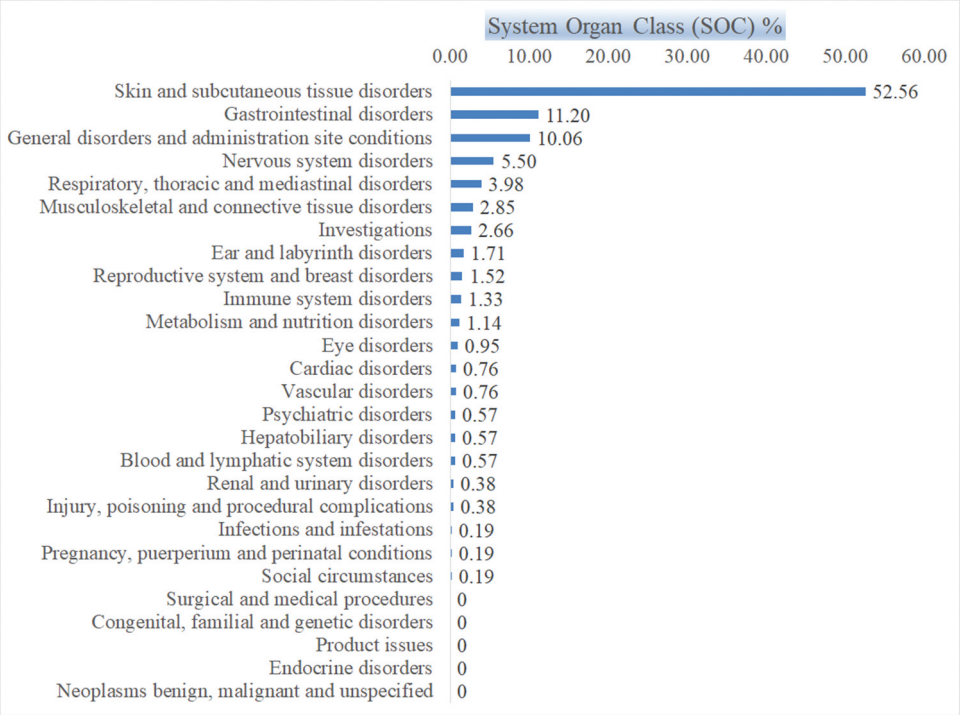

Figure 2. System organ class (SOC) involved in adverse drug reactions (ADRs).

ICSRs. No cases were assigned to "unlikely," "unclassified," and "unclassifiable" (Table 1).

3.5. Severity assessment

On severity assessment (Table 5), 61.83% ADRs were "mild" (level 1 and 2), 32.12% were "moderate" (level 3 and 4), and 6.03% were "serious" (level 4,5, and 6). Serious ADRs were most frequent with ceftriaxone, amoxicillin-clavulanic acid, and FDC of TLE. Fatal outcomes reported in four cases were suspected to be due to ceftriaxone (two cases) and FDC of TLE and dapsone (one case each).

4. Discussion

Suspected ADRs are common in both inpatient or outpatient settings and are a common cause of morbidity and mortality. The global or national frequency of antimicrobial-associated ADRs is unknown and varies across different countries and within our country. A higher occurrence of antimicrobial-associated ADR was found in this study (54.4%) compared to studies reporting a lower occurrence (17% to 20%). This could be due to variation in the type of studies, their inclusion and exclusion criteria, and settings [7,20,21]. However, one study reports a still higher frequency (62.8%) of ADR [8,22]. The higher frequency of antimicrobial-associated ADRs in this study could be due to reasons cited in various studies. India is a low-income country with an increased incidence of bacterial and non-bacterial infections, poor quality of air and associated respiratory tract infections and overcrowding, contributing to the easy spread of infections [3]. Availability of antibiotics without a prescription, non-essential prescription, easy availability of cheap/affordable generic antibiotics, and accessibility of health insurance, both public and private, adds to the problem [23]. Most antibiotic prescriptions contain concomitant medication for symptomatic relief, and these medicines might interact, leading to increase in adverse events. The increase in ADR frequency is exponential rather than linear and is 3.6% in patients receiving up to three drugs and increase to 11.1% when four or more drugs are used [24]. Hurwitz N also reports an increase in ADR frequency from 3.3% to 19.8% when the number of drugs increased from 5 or less to 6 or more [25]. Antibiotics-associated ADRs frequently affect the skin and subcutaneous tissue, the largest organ and the most visible, leading to early reporting [8]. The female preponderance in this study is consistent with other antibiotic-associated ADR studies [7,8,20]. Females are reported to be at 1.5 to 1.7 fold higher risk than males, and this could be due to pharmacokinetic and pharmacodynamic differences in gender and drug use habit, as women seek medical attention more than males for trivial problems leading to receiving more drugs [26–28].

The frequently implicated classes of antimicrobials were cephalosporins (25.12%), antiretrovirals (21.73%) followed by penicillins (18.84%). Among individual drugs, ceftriaxone (18.11%), fixed-dose combination of tenofovir/lamivudine/efavirenz [(TLE) (16.42%)], and amoxicillin-clavulanic acid (11.83%) were the top

Table 3. Antimicrobial-associated adverse drug reactions (ADRs) involved in skin and subcutaneous tissue (SOC).[a]

Class of Drugs involved in Skin and subcutaneous tissue	Individual drugs	Frequency of ADRs	Most common types of ADRs
Sulfonamides	Cotrimoxazole	9	Rash, pruritus, urticaria, Erythema multiforme
Quinolones	Ciprofloxacin	18	Angioedema, rash and pruritus
	Ofloxacin	3	Angioedema, fixed drug eruption and vomiting
	Norfloxacin	2	Skin hyperpigmentation and whiteheads, itching
	Levofloxacin	1	Itching
	Moxifloxacin	1	Rash
Penicillins	Penicillin	1	SJS
	Ampicillin	1	Erythematous skin rash
	Amoxicillin	2	Rash and skin peeling
	Amoxicillin/Clavulanic acid	29	SJS, rash, bullous eruptions, vascular purpura and diarrhea
	Piperacillin/Tazobactam	23	Eczematous rash, dermatitis, maculopapular rash, itching, angioedema
Cephalosporins	Ceftriaxone	36	Rash, maculopapular rash bullous eruptions
	Cefixime	21	Erythematous skin rash, pruritic rash, urticaria SJS
	Cefpodoxime	3	TEN, Pruritic rash, acute diarrhea
	Cefalexin	1	Rash
	Cefuroxime	1	Rash
	Cefoperazone/Sulbactum	1	Itching
	Cefotaxime	1	Lip angioedema
Other betalactum	Meropenem	7	SJS, Rash, skin peeling, bullous eruption
Aminoglycoside	Gentamicin	4	Rash, lip angioedema
	Amikacin	2	Macular rash
Macrolides	Azithromycin	3	Erythematous rash
	Clindamycin	1	Maculopapular rash
Miscellaneous antibacterials	Vancomycin	5	Erythematous rash, itching, Redman syndrome
	Linezolid	1	Pruritic rash
Antileprotic	Dapsone	5	Dapsone syndrome, Erythema nodosum, hypersensitivity reaction
Antifungal	Fluconazole	3	Erythematous rash and bullous eruptions
	Itraconazole	2	Erythematous rash and papular rash
	Sertaconazole	1	Application site itching
	Clotrimazole	1	Itching
Antiviral	Tenofovir+Lamivudine +Efavirenz	48	Maculo-papular, urticaria, itching and skin peeling
	Zidovudine+Lamivudine +Nevirapine	12	Pruritic rash, hyperpigmentation, itching and skin peeling
	Acyclovir	1	Rash
	Ritonavir	3	Rash
	Artemether/Lumefantrine	1	Rash
Antimalarials	Sulfadoxine/Pyrimethamine	1	Toxic epidermal necrolysis
	Metronidazole	4	Angioedema, urticaria and rash
Antiprotozoal	Ornidazole	3	Itching, Fixed drug eruptions, TEN
	Tinidazole	2	Rash
	Ofloxacin/Ornidazole	6	Erythema multiforme, photosensitivity, bullous eruptions, urticaria
	Norfloxacin/Tinidazole4	4	Bullous eruptions, pruritic rash
	Ciprofloxacin/Tinidazole	1	SJS
Antiscabicidal	Permethrin	2	Bullous eruptions, itching

[a]SJS: Steven Johnson syndrome; TEN: Toxic Epidermal Necrosis.

offenders. It is challenging to compare this study with other studies because of different inclusion and exclusion criteria and varied methodology. Shehab *et al.*, in their study, excluded topical antibiotics, report 19% of the visit to the emergency department due to antibiotic-associated ADRs, and allergic manifestations (78.7%) was most common; Penicillin and cephalosporin were implicated in 36.9% and 12.2% ADRs [29]. Similarly, R Kiguba *et al.* conducted their study among hospitalized patients only; the most frequent ADR was gastrointestinal symptoms (50%) followed by neurological symptoms (24%), and ceftriaxone was the most common antibiotic (43%) [20]. Hagiya H *et al.* conducted the study among hospitalized patients who received only systemic antibiotics and reported gastrointestinal, hepatobiliary, and dermatological manifestations in decreasing frequency, and piperacillin-tazobactam (20.7%) as the most frequently implicated drug [21]. Jong *et al.* report the most frequent involvement of skin and subcutaneous tissue conditions followed by gastrointestinal disorders and penicillin and quinolones (16%) followed by third generation cephalosporins (14.9%) as the most frequently implicated antibiotics [8]. Richa *et al.* conducted a similar study in India between 2010 and 2013 and reported that only 15.15% of ADRs were due to antibiotics; dermatological symptoms seen in 47.44% and gastrointestinal disorders in 39.28% reports; and ceftriaxone injections followed by azithromycin oral tablets implicated in 35.71%, and 7.39% ADRs [30]. All the above study done in the last 15 years are different; none includes all classes of antimicrobials: antibacterials, antivirals, antifungals, and antiprotozoals. However, penicillins and cephalosporins both belong to β-lactam group of antibiotics is

Table 4. Antimicrobial-associated adverse drug reactions (ADRs) involved in different system organ class (SOC).[a]

system organ class (SOC)	Antimicrobial class	Individual drugs	Frequency of ADRs	Most common types of ADRs
Gastrointestinal disorders	Quinolones	Ciprofloxacin	2	Abdominal pain, Diarrhea
		Ofloxacin	1	Vomiting
		Levofloxacin	1	Constipation
	Penicillins	Amoxicillin	1	Black tongue
		Amoxicillin/ Clavulanic acid	13	Diarrhea and vomiting
		Piperacillin/ Tazobactam	1	Vomiting
	Cephalosporins	Ceftriaxone	5	Vomiting, Abdominal pain
		Cefixime	3	Vomiting
		Cefpodoxime	1	Vomiting
		Ceftazidime	1	Abdominal cramps
	Other beta-lactums	Meropenem	2	Vomiting
	Aminoglycoside	Gentamicin	1	Vomiting
	Miscellaneous antibacterials	Linezolid	2	Vomiting
	Antileprotic	Dapsone	1	Diarrhea
	Antiviral	TLE	14	Oral ulcer, Diarhhoea and vomiting
		ZLN	1	Vomiting
		Atazanavi/Ritonavir	1	Vomiting
	Antiprotozoal	Metronidazole	5	Vomiting
		Ofloxacin/ Ornidazole	1	Lip swelling
		Norfloxacin/ Tinidazole	2	Lip swelling
General disorders and administration site conditions	Quinolones	Ciprofloxacin	3	Generalized edema, warmth sensation
	Penicillins	Amoxicillin/ Clavulanic acid	8	Shivering, rigor, generalized edema
		Piperacillin/ Tazobactam	2	Generalized edema
	Cephalosporins	Ceftriaxone	15	Rigor and shivering
		Cefixime	2	Tiredness and edema
		Cefalaxin	1	Chest tightness
		Cefoperazone/ Sulbactum	1	Swelling at injection site
	Aminoglycoside	Gentamicin	1	Rigor
	Miscellaneous	Vancomycin	1	Shivering
		Nitrofurantoin	1	Swelling at injection site
	Antiviral	TLE	7	Generalized edema, tiredness and weakness
		ZLN	4	Fatigue, rigor
	Antiprotozoal	Metronidazole	6	Chills, rigors warmth sensation
	Antiscabicidal	Permethrin	1	Itching at application site
Nervous system disorders	Quinolones	Ciprofloxacin	3	Convulsion, impaired concentration, burning sensation
		Norfloxacin	1	Lethargy
	Penicillin	Amoxicillin/ Clavulanic acid	2	Shoulder numbness and dizziness
	Cephalosporins	Ceftriaxone	7	Convulsion and dizziness
	Macrolides	Azithromycin	1	Anosmia
	Miscellaneous antibacterial	Linezolid	1	Giddiness
		Nitrofurantoin	3	Headache, dizziness, burning sensation all over body
	Antiviral	TLE	8	Headache, dizziness, loss of taste, convulsion, numbness
		Atazanavir	1	Lethargy
	Antiprotozoal	Metronidazole	2	Headache
Respiratory, thoracic and mediastinal disorders	Penicillins	Amoxicillin/ Clavulanic acid	5	Dyspnea, respiratory distress
		Piperacillin/ Tazobactam	1	Dyspnea
	Cephalosporins	Ceftriaxone	7	Dyspnea
		Ceftazidime	1	Dyspnea
		Ciprofloxacin	1	Respiratory distress
	Macrolides	Azithromycin	1	Throat irritation
	Miscellaneous antibacterial	Linezolid	1	Dyspnea
	Antiprotozoal	Metronidazole	3	Dyspnea
	Miscellaneous antibiotic	Nitrofurantoin	1	Breathing difficulty
Musculoskeletal and connective tissue disorders	Quinolones	Ciprofloxacin	1	Muscle cramps
	Penicillins	Amoxicillin/ Clavulanic acid	1	Myalgia
		Piperacillin/ Tazobactam	2	Muscle twitching
	Cephalosporins	Ceftriaxone	5	Muscle burning sensation
	Tetracycline	Minocycline	1	Systemic lupus erythromatosis
	Macrolides	Clarithromycin	2	Myalgia, arthralgia
	Antifungal	Itraconazole	2	Cervical pain and generalized myalgia
	Antiviral	TLE	1	Arthralgia

(*Continued*)

Table 4. (Continued).

system organ class (SOC)	Antimicrobial class	Individual drugs	Frequency of ADRs	Most common types of ADRs
Investigations	Sulfonamides	Cotrimoxazole	3	Raised serum creatinine
	Penicillins	Amoxicillin/ Clavulanic acid	1	Decreased oxygen saturation
	Miscellaneous antibacterial	Linezolid	1	Decreased platelet count
	Antiviral	TLE	7	Raised serum creatinine
		ZLN	1	Raised serum creatinine
		Abacavir	1	Raised serum creatinine
Ear and labyrinth disorders	Cephalosporins	Ceftriaxone	2	Vertigo
	Macrolides	Azithromycin	1	Plugged ears
	Antiviral	TLE	6	Vertigo
Reproductive system and breast disorders	Penicillins	Amoxicillin/ Clavulanic acid	2	Vaginal itching
	Cephalosporins	Ceftriaxone	1	Vaginal itching
	Macrolides	Azithromicin	1	Vaginal itching
	Antiviral	TLE	4	Gynecomastia
Immune system disorders	Penicillins	Amoxicillin/ Clavulanic acid	2	Anaphylactic reaction
	Cephalosporins	Ceftriaxone	4	Anaphylactic reaction
	Antileprotic	Dapsone	1	Anaphylactic reaction
Metabolism and nutrition disorders	Macrolides	Azithromycin	1	Anorexia
	Miscellaneous antibacterial	Linezolid	1	Anorexia
	Antiviral	TLE	3	Anorexia
		ZLN	1	Anorexia
Eye disorders	Quinolones	Ciprofloxacin	1	Stinging eyes
	Cephalosporins	Ceftriaxone	4	Diminished vision, eye bleeding, periorbital edema
Hepatobiliary disorders	Penicillins	Piperacillin/ Tazobactam	1	Hepatitis
	Antileprotic	Dapsone	1	Hepatitis
	Antimalarial	Artemether/ Lumefantrine	1	Hepatomegaly
Cardiac disorders	Cephalosporins	Ceftriaxone	1	Bradycardia
		Cefixime	2	Palpitations
	Miscellaneous	Vancomycin	1	Tachycardia
Vascular disorders	Penicillins	Amoxicillin/ Clavulanic acid	3	Hypotension, hypertension and flushing
	Cephalosporins	Ceftriaxone	1	Hypertension
Psychiatric disorders	Penicillins	Ampicillin	1	Irritable mood
	Macrolides	Azithromycin	1	Restlessness
	Antiviral	TLE	1	Insomnia
Blood and lymphatic system disorders	Cephalosporins	Ceftriaxone	1	Thrombocytopenia
	Antileprotic	Dapsone	1	Microcytic anemia
	Antiviral	ZLN	1	Hemolytic anemia
Renal and urinary disorders	Penicillins	Amoxicillin/ Clavulanic acid	1	Burning micturition
	Macrolides	Azithromycin	1	Scanty urine
Injury, poisoning and procedural complications	Quinolones	Ciprofloxacin	1	Accident
	Cephalosporins	Ceftriaxone	1	Documented hypersensitivity to administered drug
Infections and infestations	Antileprotic	Dapsone	1	Dapsone syndrome
Pregnancy, puerperium and perinatal conditions	Penicillin	Amoxiclav	1	Eclampsia
Social circumstances	Quinolones	Ciprofloxacin	1	Driving ability disturbed

[3]E: Efavirenz; L: Lamivudine; N: Nevirapine; T: Tenofovir; Z: Zidovudine.

common in all the above studies. Penicillin and its semisynthetic derivatives and cephalosporins are frequently involved in immediate hypersensitivity reactions mostly mediated by immunoglobulin E [31]. β-lactams act as haptens, cross reactivity between penicillin and cephalosporin and unknown prior exposure to penicillin in any form and frequent prescription to these drugs could be the reason for this increased ADRs [31–33].

According to the MedDRA SOC classification, ADRs involving "Skin and subcutaneous tissue" were most frequent (54.02%), followed by "gastrointestinal disorders" and "general disorders and administrative site conditions" (10.15% each). Some drugs involved more than one organ system, so we report 527 SOCs involvement for 414 ICSRs. Few system organ class involvement was not observed in this study, as shown in Figure 2, like endocrine disorders, neoplasms, congenital familial and genetic disorders, surgical and medical procedures, and product issues. The ADRs involving these SOCs often go unreported or are misallocated to other SOCs because of the difficulty in implicating a drug as its cause. Treating clinicians must possess a high suspicion index to label these effects as drug-induced. For example, glucose metabolism disorders and diabetic complications are multiaxial and can be linked to both SOC- "metabolism" and

Table 5. Severity of adverse drug reactions (ADRs) as per modified Hartwig and Siegel severity assessment scale.

Level	Modified Hartwig and Siegel Severity Assessment Scale	No of cases	Severity, Frequency (%)
Level 1	An ADR occurred but required no change in treatment with the suspected drug.	59	Mild
Level 2	An ADR required that the treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay.	197	256 (61.3)
Level 3	An ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An antidote or other treatment requirement was required. No increase in length of stay.	69	Moderate 133 (32.12)
Level 4	Any level 3 ADR which increases the length of stay by at least 1 day. OR The ADR was the reason for admission.	64	
Level 5	Any level 4 ADR which require intensive medical care.	18	Severe
Level 6	The ADR caused permanent harm to the patient.	3	25 (6.03)
Level 7	The ADR either directly or indirectly lead to the death of the patient.	4	

"nutrition disorders." So, if one had to report gatifloxacin (now withdrawn) associated dysglycemia, it can be reported in any one of the two SOC [34]. Metronidazole, sulfamethoxazole, dapsone, and isoniazid-induced pancreatitis can be attributed to either endocrine or gastrointestinal disorders SOC [35]. It is often reported as gastrointestinal SOC as the patient presents with abdominal pain, vomiting, and diarrhea. Laboratory findings of raised pancreatic enzyme and radiological investigations for confirmatory diagnosis are seldom done in the initial phase to diagnose it as drug-induced pancreatitis to label it as an endocrinal effect. Antimicrobials causing congenital disorders or teratogenicity are well documented and include sulfonamides, aminoglycosides, chloramphenicol, tetracycline, erythromycin, and vancomycin, and are usually not prescribed during pregnancy [36]. Therefore, the occurrence of ADRs in SOC congenital familial and genetic disorders is rare. The SOC product issue is focused on issues related to products rather than clinical or patient-related concepts and mostly goes unreported. Identifying neoplasms, both benign and malignant, as an adverse outcome of antibiotics or any medication requires in-depth knowledge, eliciting a detailed history, long-term follow-up, and maintaining the patient's electronic medical records, which may be possible after a few decades in India.

The WHO UMC scale was used for the causality assessment of the individual case report. "Probable" ADRs, followed by "possible" and "certain," follow the same frequency pattern reported in other studies [8,30,37]. This higher frequency of probable is ascribed to the fact that it is convenient to establish a causal time relationship of the adverse reaction with the suspected drug and exclude its occurrence due to disease or other drug and improvement on withdrawal. Reporting an ADR as "certain" is problematic because diagnostic tests specific for the adverse drug effect are usually absent, and a re-challenge is ethically unjustified [17].

Severity assessment using modified Hartwig and Siegel severity assessment scale allocates a majority of the ADRs as mild, followed by moderate and severe, which corroborates with Indian studies [6,37]; however, one study shows a preponderance of moderate severity ADRs [38]. The most offending agent in severe ADR was Ceftriaxone, and this could be due to higher ceftriaxone prescriptions in our setting. In its report on antibiotic consumption, "WHO" mentions high consumption of cephalosporins and quinolones in some countries and very high consumption of third-generation cephalosporins in all states in India [1]. Other risk factors for ceftriaxone-related ADRs include rapid intravenous injection and not eliciting the previous history of allergic reaction. It must be mentioned here that routine intradermal testing is done in most hospitals, preventing many ADRs. We report four fatalities; two with injectable ceftriaxone and one each with oral TLE and Dapsone. Ceftriaxone has been implicated for the highest number of deaths in the Iranian database also [39]. A study on ADRs due to antimicrobial agents reports TLE-based regimens accounting for 66.9% of the total ADRs but do not mention any fatal reaction [40]. We must keep in mind that antiretroviral therapy is relatively safe, and, 5–40.8% of death in patients with human immunodeficiency virus (HIV) occur within the first six months of initiating treatment and could be due to advanced clinical stage of the disease, low baseline CD4 count predisposing to infections, and poor treatment adherence [41]. Fatality reported with dapsone was diagnosed as Dapsone Hypersensitivity Syndrome (DHS) and is well known as a rare potentially fatal reaction if not recognized and managed timely [42]. The incidence of DHS is 0.5–3.6% with a mortality of 9.9%; acute clinical courses, mucosal involvement, hepatitis, older age, and low socioeconomic status of the patient account for higher risk of fatal outcome [43].

The strength of our study is its broad inclusion of all antimicrobials, including antibacterials, antivirals, antifungals, antiprotozoals, and long study duration. However, there are several limitations to our study. First, this study was conducted at a single ADR monitoring center and lacked reports from other state centers. Second, ADRs are usually reported voluntarily, and mild reactions might have gone unreported. Third, few reports contained more than one antibiotic, the clinical

manifestation of suspected adverse effect was ascribed to the antibiotic well known for the documented adverse effect with a possibility of missing out on "new signals." Fourth, our findings cannot be generalized to other hospitals in our state or country, which have a different antibiotic utilization pattern, and there is a difference in the clinician's knowledge, experience, and observational skills for reporting ADRs.

5. Conclusion

Ceftriaxone was responsible for the highest risk for antibiotic-associated ADRs, followed by a tenofovir-based TLE regimen. The most frequent clinical symptoms were of skin and subcutaneous tissue SOC, followed by gastrointestinal disorders. The causality of a majority of ADRs was probable, and the severity was mild. The national coordinating center must publish a similar study and compare it with other developed countries to find if our population is more prone to specific antibiotic-associated ADRs. Periodic analysis of antibiotic safety data will help assess the accurate burden of ADRs in terms of patient morbidity and mortality, human resources, and financial resources; and help formulate guidelines and policies to prevent or reduce the frequency and severity of ADRs, and contribute to antibiotic stewardship.

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Disclosure of potential conflicts of interest

Manju Agrawal, Preeti Singh, and Usha Joshi declare that they have no competing interests.

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