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An Ethnicity Based Assessment of Adverse Drug Reactions Due To Antibiotics –Anti microbials Usage in India

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ABSTRACT

To assess and evaluate the suspected ADRs reported among two ethnic groups with use of antibiotic (antimicrobials) medications. A prospective observational study was conducted over a period of approximately 2 years on inpatient population involving two ethnic groups ; Santhals and Chaush tribe attending Rajendra Institute of Medical Science (RIMS) situated in Ranchi, Jharkhand state, India and Axon hospital situated in Hyderabad, Telangana state, India. Non-statistical significance in odds for number of suspected ADRs for both ethnic groups (OR 0.99, 95% CI: 0.78 – 1.27). The study found no difference and events were preventable as per Schumocks and Thorontons criteria. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality, susceptibility varies with genetic make-up, age, sex, physiology, exogenous factors, and disease state as ethnic groups are more susceptible during treatment. Here Ethnic group may act as a marker for underlying genetic or environmental differences.

Key Words: Ethnicity, Adverse Drug Reactions, Antibiotics, In patients, Susceptibility

INTRODUCTION

Antibiotics or antibacterials are a type of antimicrobial used in the treatment and prevention of bacterial infection.[1,2]They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately.[3] An antimicrobial is an agent that kills microorganisms or inhibits their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against.[4]
The common Side-effects range from mild to very serious depending on the antibiotics used, the microbial organisms targeted, and the individual patient. Safety profiles of newer drugs are often not as well-established as for those that have a long history of use.[5] Adverse effects range from fever and nausea to major allergic reactions, including photo dermatitis and anaphylaxis. Common side-effects include diarrhea, resulting from disruption of the species composition in the intestinal flora, resulting, for example, in overgrowth of pathogenic bacteria, such as *Clostridium difficile*.[6] Adverse drug reactions (ADRs) due to medications use is one of the leading cause for morbidity and mortality. Incidence of ADRs accounts for 0.3% – 7% of all hospital admissions and occurs in 5% – 8% of hospitalized patients. [7] In United States, after heart disease, cancer and stroke it was found that ADRs in drug recipients are the fourth leading cause of death. [8]

There are many potential factors of variability in drug response in drug recipients which includes food and concomitant medication come under the category of extrinsic factors whereas gender, race and ethnicity, age, weight, renal or hepatic function or genetic differences that make up the expression of genes come under the category of intrinsic factors. Although ethnicity is one of the many causes for adverse drug reactions of the medication use, the extent to which it affects susceptibility to adverse reactions remains unclear. Not very new but an older example on use of angiotensin converting enzyme inhibitors where African Americans (Black patients) compared to non-Black patients have an increase susceptibility to angioedema (relative risk 3.0) and cough (relative risk 1.1)[9] and Drug-induced hypersensitivity for aminopenicillins in Caucasians. [10]

Responses to drugs can be altered by a wide variety of individual characteristics that affect the pharmacokinetics of a drug (differences in absorption, metabolism, distribution, excretion, or the presence of other drugs)or the patient's response to the drug(differences in coexisting illness, etiology of disease, or again, the presence of other drugs, etc.). In some cases these differences have been related to demographic characteristics, such as gender or race.
It is therefore important to include in drug development representation of the broad range of patients who will eventually receive the drug, including people of both genders, representatives of major racial/ethnic groups, and patients with a wide range of disease severity, concomitant illnesses, and use of concomitant treatments. Attention to potential racial and ethnic differences in response to drugs is part of a larger effort by the FDA to ensure that the safety and efficacy of drugs are adequately studied in people who represent the full range of patients who will receive them upon marketing. FDA guidelines and regulations encourage the participation of racial and ethnic groups in all phases of drug development, promote collection of race related data during research and development, and recommend analysis of the data for race effects.

According to ICH E2A guideline, "All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions" and WHO Technical Report 498 [1972] reads Adverse Drug Reaction for marketed medicinal products as "A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function". For ethnicity, ICH E5 guideline addresses the intrinsic factors associated with environment and culture that could affect the results of clinical studies and describes the concept of the "bridging study" where the new region may request to determine whether data on use of medicine from another region applicable to its population. Antibiotics and Cardiovascular class of drugs were found to be commonly involved drug classes in ADRs. [11]T-cell mediated Type I or Type IV reactions are commonly observed with the use of antibiotics especially with sulfa and beta lactam antibiotics. In India, over the counter availability, lack of knowledge and dissatisfaction among patients without antibiotic prescription are the leading causes for unrestricted use of antibiotics. However, little is known about ethical/racial differences and ADRs in people seeking antibiotics for their illness. Therefore, the present study aimed to assess and evaluate adverse drug reactions to antimicrobial use in two different ethnic groups in India, where one group was Santhals tribe and the other group was Chaush (community of Yemeni Arab). The paper uses words 'ethnic' or 'race' synonymously for ethnicity.

MATERIALS AND METHODS

Ethical Committee Approval: The study was approved by the S2J Independent ethics committee for Rajendra Institute of Medical Science (RIMS) situated in Ranchi, Jharkhand (North Indian region), India and Axon hospital situated in Hyderabad, Telangana (South Indian region), India. The study was conducted as per the Declaration of Helsinki (DoH), 2000 version on ethical standards for medical research involving human subjects.

Methodology

Study Design: A prospective observational study was conducted over a period of approximately 2 years (from October, 2010 to September, 2012).

Study Site: Rajendra Institute of Medical Science (RIMS) situated in Ranchi, Jharkhand state, India and Axon hospital situated in Hyderabad, Telangana state, India.

Patient enrolment: The Patients were enrolled for the study after obtaining Informed consent either from patients or through Legally Acceptable Representative for documentation of any suspected ADRs.

Inclusion Criteria: The in patients and patients in critical care unit (both male and female), who were prescribed or treated with antimicrobial medication, were included in the study. The patients who

belonged to Chaush community and Santhals tribe. The patients under age group of ≥ 65 and < 65 and the patients with one or two co morbid.

Exclusion Criteria: The out patients and the patients with ADR refusing hospitalization and patients not ready for Informed Consent were excluded from the study.

Plan of Work: The pharmacists with the help of treating physicians and nurses reported any of the suspected ADRs related to antibiotic use in the two ethnic groups i.e., for Santhal at RIMS hospital, Ranchi and for Chaush at AXON hospital, Hyderabad. Pharmacists identified ethnicity of patients from case sheet or through direct interview with patients/relatives.

Patient Data Collection Form: The relevant details such as clinical presentation, date of starting and stopping of event, relevant laboratory investigations, other relevant history including pre-existing diseases, suspected medication (including dose, frequency, route of administration, dates and duration of administration and indications for use), dechallenge and rechallenge data (if available) and concomitant medicines (including self-medication and herbal remedies) of inpatients were recorded on a patient data collection form if any of the suspected ADRs related to antibiotic usage were identified or reported.

Statistical Analysis: The data was collected using Causality assessment with Naranjo's algorithm [12]. Naranjo's Algorithm scale grades causality of ADRs as Definite, Probable, Possible and Unlikely. Preventibility score was determined using Schumocks and Thorontons criteria [13]. Direct comparisons of the ADRs rates between different races and age groups were performed using an online two-way contingency table calculator (http://statpages.org/ctab2x2.html). The significance level was set at $P<0.05$ as depicted in Table 6.

RESULTS

A total of 950 patients were enrolled for the study of which 466 were males and 484 were females who received antimicrobial drugs out of them 161 males and 189 females reported ADR's as illustrated in table and figure 1.On classifying patients based on age there were 553of more than 65 years and 397 patients less than 65 years of which 135 and 215 were patients reporting ADR's respectively as shown in table and figure 2. 447 patients belong to Santhals tribe while 503 patients belong to Chaush community , 164 belonging to santhals tribe and 186 patients belonging to chaush community reported ADR's as depicted in table and figure 3. Non-statistical significance in odds for number of suspected ADRs was observed between two ethnic groups (OR 0.99, 95% CI: 0.78 – 1.27). Also, non-significance in odd was observed between patients with comorbidity of two or more than two (OR 0.61, 95% CI: 0.48 – 0.79). The patients who reported ADR's with less than 2 comorbid conditions are 143 of 501and those who reported ADR's with 2 or more than 2 comorbid conditions are 207 of 499 as shown in table and figure 4.

Of the total number of patients who received antibiotics only 350 patients reported suspected ADRs in which 161 events occurred in males and 189 events occurred in females and 47 events caused prolongation of existing hospitalization which was probably related to study medications (Santhals vs Chaush; 17 vs 30).

The common adverse drug reactions reported with commonly used antibiotics during our study were stomatitis-ciprofloxacin; urticaria-doxycycline, ceftriaxone;, rashes /lesions all over the body-azithromycin, norfloxacin+ tinidazole, hydroxyl chloroquine, amikacin, larithromycin, ornidazole, ethambutol, amoxicillin, quinine, ceftriaxone, amoxicillin+cloaxacillin; swelling of lips-ceftriaxone, cotrimoxazole; maculopapular rashes-cefpodoxime, cefixime, clindamycin; anaphylaxis-crystalline penicillin; hypertension-pipercillin+tazobactum; pancytopenia –linezolid, ofloxacin,; SJS-Ciprofloxacin; disorientation-isoniazid; thrombocytosis(platelet count 9 lacs)-Amoxicillin, popular urticaria, chills and rigors and headache-Amphotericin –B; , epistaxis, pedal oedema-ciprofloxacin; metallic taste-tinidazole; blurring of vision, generalized erythema-levofloxacin, erythematous patches all over the legs, vomiting's- cefotaxime, ceftriaxone, ciprofloxacin, metronidazole; peripheral neuropathy-isoniazid;, tinnitus-quinine; visual disturbance-hydroxychloroquine, alopecia, loose stools-cefaperazone+salbactum; interstitial nephritis-rifampicin, hypokalemia-fluconazole, elevated liver enzyme-neviparine, pruritus and angiodema-cefixime, loss of appetite-nitrofurantoin; ARF-Streptomycin; headache- nitroglycerine; blurred vision-ethambutol; erythematous patches over legs-minocycline.

All the reported ADRs were preventable as per Schumocks and Thorontons criteria.with non-statistical significance of odds (OR 0.89, 95% CI: 0.69 – 1.13). Similarly, non-statistical significance in odds was observed in patients between age groups of

≤ 65 years or ≥ 65 years (OR 0.44, 95% CI: 0.35 – 0.57) .

DISCUSSION

This study is first of its kind in India to assess the relation between ethnicity and ADRs on use of antibiotics in a hospital setting involving inpatients as the study group. The study comprises of two different ethnic groups: The Santhals, who live mainly in the states of Jharkhand, West Bengal, Bihar, Odisha and Assam. They are the largest tribe in India to retain a good language (Munda) to the present day and famous Santhali culture where group dancing and singing is the most important medium to express their joy and happiness and the Chaush, a muslim community most commonly found in Telangana State in Hyderabad an area called Barkas. Arabian food is common in this community which includes famous dishes such as mandi, kabsa, harees (A sweet version of Haleem in south Arabian style), aseed (South Arabian sweet), and ghava.

In almost every clinical trial, ethnic/race information is collected generally but this information will not be reflected in efficacy or safety of the drug and many of the marketed drugs are available without ethnicity related efficacy and safety information as the importance of ethnicity is known only after drug has been approved for marketing, as data on ethnicity if provided lack concomitant genetic analysis. Therefore, there is growing need for race/ethnic/genetic studies because patient's response to drugs differs based on environment, society, genetics and other factors and information from such studies can lead to personalization of medicines to prevent the occurrence of ADRs. However, in the present study we found no difference in suspected ADRs reported between the two ethnic groups (Santhal vs Chaush) on use of antibiotics.

Many of the ADRs reported from these two ethnic groups are preventable which supports earlier study by Debellis et al., (2003) where ADRs are common and often preventable among older persons in the ambulatory clinical setting. [14] In our study, majority of the reported ADRs are probably related in similar to the study reported by Arulmani et al., (2007) where about two third events are probably related to treatment/medication. [11]

ADRs' not only cause injury and death but also affects length of hospital stay leading to an increase healthcare costs. In this study, we have not calculated the amount incurred for the treatment or numbers of days the patients were hospitalized for ADRs. An average amount of approx. 481 INR was spent for the treatment of ADR's but room rent and other domiciliary charges like nursing care etc were not included as reported by Arulmani et al (2007) and also the patients were treated in Government hospital which could the reasons for low cost incurred for treatment of ADRs. [11]Moura et al (2009) reported, each ADR presented by the patient was related to an increase of 2.38 days in the ICU. [15]

Gender plays an important role in susceptibility for ADRs. Studies have shown that females more than males are prone for ADRs. [16, 17]However, in our study even though higher number of females in both races reported ADRs due to antibiotic use but this difference was not statistically significant. Also, ADRs are commonly observed in pediatrics [18, 19]and geriatric patients, [20] no data was calculated for pediatrics population in this study and the reason was, the information regarding pediatrics population in one ethnic group (Telangana region) was incomplete. However, in both the ethnic groups more number of patients among age group ≥65 years compared to age group <65 years presented ADRs, but this difference was not statistically significant.

Limitations: Among different class of drugs, antibiotics are common cause for ADRs and Beta-lactam antibiotics pose high risk for cutaneous adverse reactions. In this paper we have not included the information regarding frequency and class of antibiotics commonly used in both the ethnic groups as the essential drug list for both the hospitals was missing.

Conclusion: The goal of rational drug treatment is to maximize benefits or the chance of benefit and to minimize harm or the risk of harm. The relative frequencies of ADRs in different populations were provided which suggested that the risk of harm may vary with ethnic group and may help the clinician present more accurate and relevant data to their patients during prescription writing. When ethnic differences in susceptibility exist, they may act as a marker for potentially important genetic or environmental factors that will be possible only through increased recruitment of individuals from different ethnic groups and when pharmaceutical companies report data on ethnicity. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality and susceptibility to ADRs varies with genetic make up, age, sex, physiology, exogenous factors, and disease state, some ethnic groups may be more susceptible to ADRs during treatment with antibiotics hence, ethnic group acts as a marker for underlying genetic or environmental differences in this susceptibility of ADRs.

Our study concludes that there is no significant difference in ADRs on antibiotic use between the two groups although the trend was higher in Chaush community. Among both the races there was high incidence of ADRs on use of antibiotics, hence educational campaigns giving information about careful use of antibiotics were more likely to make fewer demands for unnecessary antibiotics to decrease the incidence of ADRs. Finally, studies in India on ethnicity and prevalence of ADRs among different classes of drugs in both ethnic groups on use of antibiotics are warranted even though no difference in suspected ADRs were found and reported.

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Conflicts of Interest: The authors have no conflicts of interest to declare.

Table 1: Relationship between patient's characteristics and severity of ADRs based on Gender

Characteristic of patients	Number of patients	Patients with ADRs	Odd ratio	95% CI
GENDER				
Male	466	161	0.88848	(0.6920, 1.1312)
Female	484	189		

Table 2: Relationship between patient's characteristics and severity of ADRs based on Age

Characteristic of patients	Number of patients	Patients with ADRs	Odd ratio	95% CI
AGE				
≥ 65	533	135	0.4425	(0.3446, 0.5684)
< 65	397	215		

Table 3: Relationship between patient's characteristics and severity of ADRs based on Community

Characteristic of patients	Number of patients	Patients with ADRs	Odd ratio	95% CI
COMMUNITY				
Santhals tribe	447	164	0.9922	(0.7761, 1.2684)
Chaushcommunity	503	186		

Table 4 : Relationship between patient's characteristics and severity of ADRs based on Comorbid Conditions

Characteristic of patients	Number of patients	Patients with ADRs	Odd ratio	95% CI
CO-MORBID CONDITION				
Less than 2 condition	501	143	0.6161	(0.4808, 0.7896)
2 condition more than 2 condition	499	207		

Table 5: Illustrating common ADRs associated with the use of Antibiotics in the study

Drug	ADR	No.of Patients (%)
Ciprofloxacin	Stomatitis	15
Ciprofloxacin	SJS	10
Doxycycline	Urticaria	25
Ceftriaxone	Urticaria	12
Azithromycin	Rashes	10
Norfloxacin	lesions all over the body	5
Hydroxychloroquine	lesions all over the body	3
Amikacin	lesions all over the body	2
Clarithromycin	lesions all over the body	5
Ornidazole	lesions all over the body	6
Ethambutol	lesions all over the body	8
Amoxicillin	lesions all over the body	10
Quinine	lesions all over the body	11
amoxicillin+cloaxacillin	lesions all over the body	15
Ceftriaxone	swelling of lips	8
Cotrimaxazole	swelling of lips	6
Cefixime	maculopapular rashes	4
Clindamycin	maculopapular rashes	15
crystalline penicillin	Anaphylaxis	20
pipercillin+tazobactum	Hypertension	10
Linezolid	Pancytopenia	8
Ofloxacin	Pancytopenia	7
Isoniazid	Disorientation	15
Amoxicillin	Thrombocytopenia	20
amphotericin B	chills and rigors with headache	10
Ciprofloxacin	Epistaxis	12
Ciprofloxacin	pedal oedema	13
Tinidazole	metallic taste	15
Levofloxacin	blurring of vision	16
Levofloxacin	generalised erythema	18
Cefotaxime	Vomitings	13
Ceftriaxone	Vomitings	15
Ciprofloxacin	Vomitings	20
Metronidazole	Vomitings	13
Quinine	Tinnitus	10
Hydroxychloroquine	visual disturbances	8
cefaperazone + salbactum	loose stools	6
Rifampicin	interstitial nephritis	5
Fluconazole	Hypokapemia	3
Neviparine	elevated liver enzymes	10

Cefixime	pruritis and angiodema	5
Nitrofurantoin	loss of appetite	6
Streptomycin	ARF	10
Nitroglycerine	Headache	15
Ethambutol	blurred vision	13
Minocycline	erythematous patches all over the legs	12

Table 6: **Relationship between patient's characteristics and severity of ADRs with Statistical Analysis of the Data:**

Characteristic of patients	**Number of patients**	**Patients with ADRs**	**Odd ratio**	**95% CI**
Sex				
Male	466	161	0.8848	(0.6920, 1.1312)
Female	484	189		
Age				
≥ 65	553	135	0.4425	(0.3446, 0.5684)
< 65	397	215		
Santhals tribe	447	164	0.9922	(0.7761, 1.2684)
Chaush community	503	186		
Comorbid condition				
Less than 2 condition	501	143	0.6161	(0.4808, 0.7896)
2 condition more than 2 condition	449	207		

Figure 1: **Relationship between patient's characteristics and severity of ADRs based on Gender**

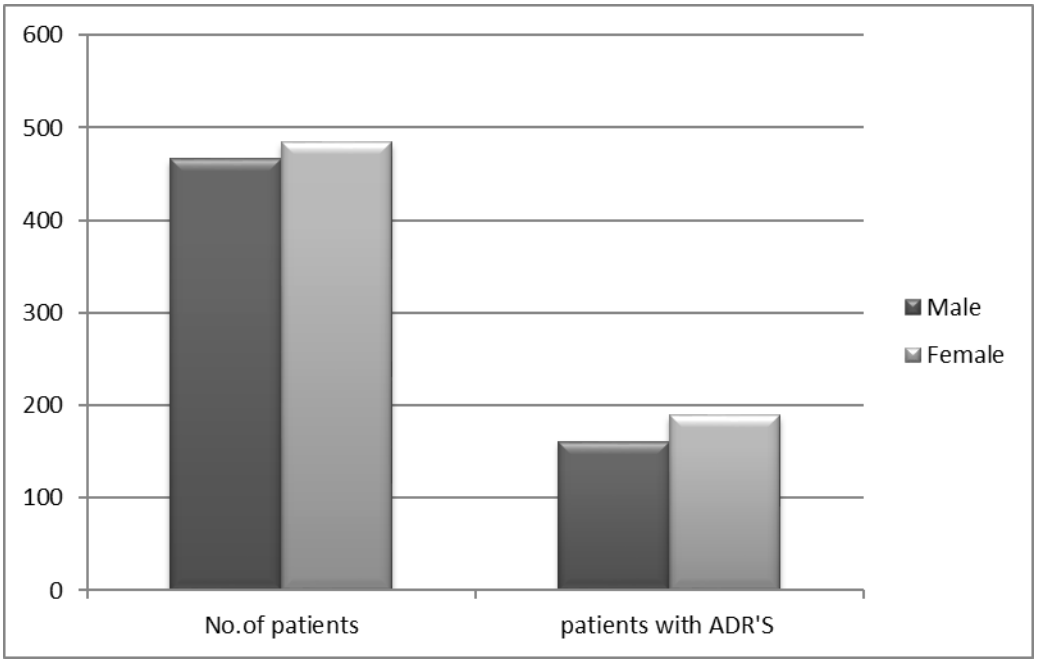


Figure 2: **Relationship between patient's characteristics and severity of ADRs based on Age**

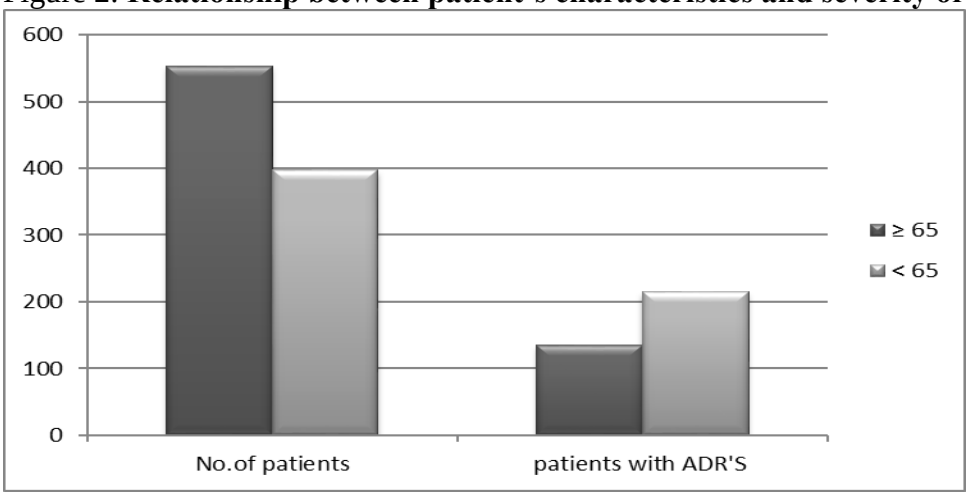


Figure 3: **Relationship between patient's characteristics and severity of ADRs based on community**

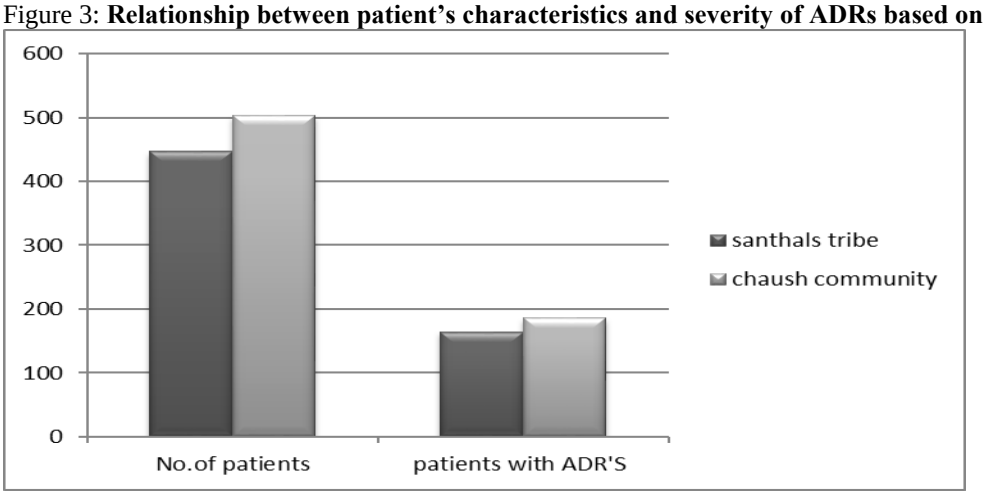


Figure 4: **Relationship between patient's characteristics and severity of ADRs based on comorbid conditions.**

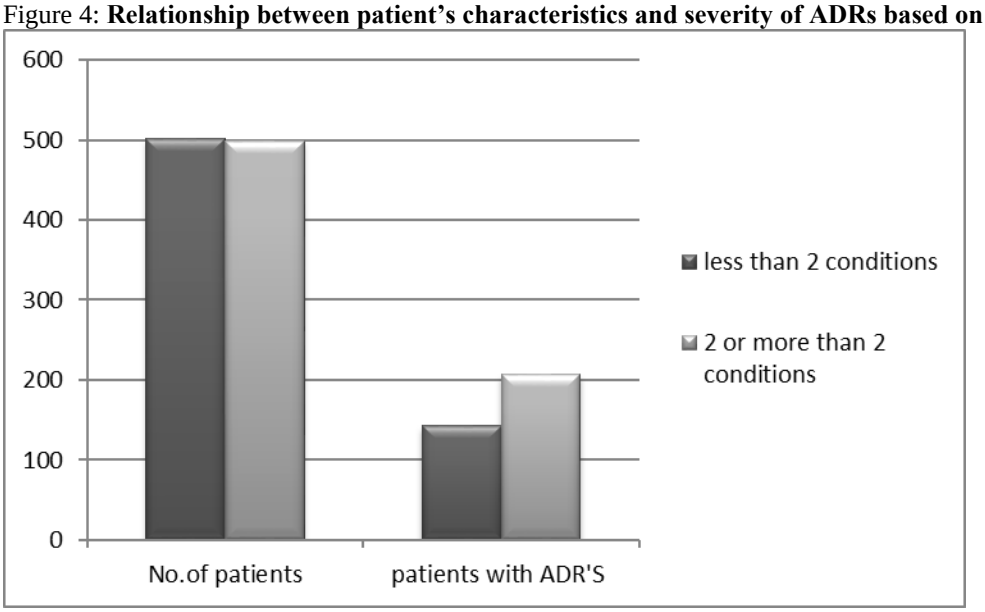
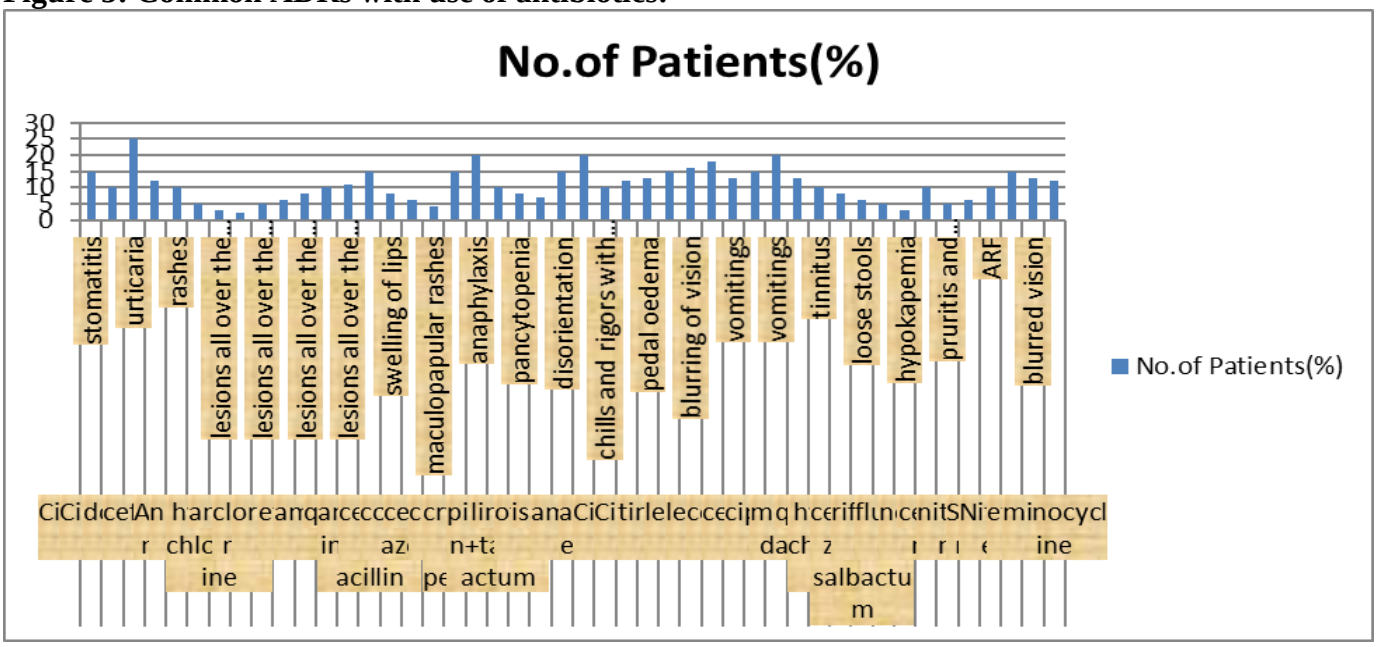


Figure 5: Common ADRs with use of antibiotics:



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