Original Research Article

ANTIMICROBIAL THERAPY: AN IMPORTANT RISK FOR ACQUIRED APLASTIC ANEMIA

ABSTRACT:

Background: Aplastic anemia although a rare hematological disorder but it is associated with poor prognosis and high mortality. It is a matter of greater public health concern for the Asian population with prevalence 3 times greater than other part of the globe. Exposures of specific drugs, chemicals and others have been connected with an AA etiology. We aimed to examine the association of antimicrobial drugs exposures with AA. **Methods:** We conducted a case-control study in Karachi, Pakistan, selecting the patients with two blood lineages depressed on bone marrow biopsy as the cases while patients without any hematological disorder as controls. For each case four age-sex matched control were enrolled. Information associated to socio-demographics and exposure to antibiotics was collected on a questionnaire during personal interview. **Results:** We identified 191 cases with an age range of 1-66 years and 696 controls. Predominant participant were male (67%), female being 33%. Antimicrobial drugs were used by 49.74% of aplastic anemia cases whereas the use was reported in 29.31% controls. Beta-lactam antibiotics, chloramphenicol, macrolides, Trimethoprim/Sulfamethoxazole, tetracycline and others were the drug categories evaluated. **Conclusion:** Antimicrobials were reported to be used more frequently in aplastic anemia cases as compared to their normal controls

KEY WORDS: Aplastic Anemia, antibiotics, chronic exposure.

INTRODUCTION:

Idiosyncratic drug-induced aplastic anemia is an undesirable reaction against few drugs due to presence of abnormal susceptibility in certain individuals [1]. It depends on multiple internal and external factors like amount of drug exposure, physical and chemical properties of drug, genetic variation of recipient for drug metabolism [2]. Drug-induced aplastic anemia has variable and insidious onset, symptoms appear from days to months after exposure of the drug, with the average time period of about 6.5 weeks [3]. Drug-induced aplastic anemia was initially reported in the 1930s, associated with arsenicals and aminopyrines [4]. Epidemiologic studies documented that certain anti-infective, non-steroidal anti-inflammatory drug, anti-thyroid, diuretics, anticonvulsants, antihistamine and other miscellaneous drug have been implicated in the incidence of aplastic anemia [5]. Among the anti-infective drugs, chloramphenicol is the most notorious drug which often has been reported as a risk factor of aplastic anemia globally. The risk of chloramphenicol associated aplastic anemia is approximately 1 in 20,000 among patients treated with chloramphenicol [7]. Chloramphenicol was reported to be attributed for 22% cases of aplastic anemia while 44% of the drug-induced cases of aplastic anemia due to its frequent use probably [8]. The time between exposure and onset of symptoms of aplastic anemia was few months. Thiazide group of diuretics and Mebendazole from the anti-helminths were also reported to cause aplastic anemia [9]. This current research was carried out to assess antimicrobial exposure as a risk factor for the development of aplastic anemia.

METHODOLOGY:

This case-control design study was executed in Karachi, Pakistan. The participants included patients accessing healthcare in different hospitals in December 2018. There were 191 cases, 696 controls selected by using StatCal of Epiinfo by using 7% exposure among control. The eligible cases had at least two of the three criteria with hypocellular bone marrow (1) hemoglobin <10gm/dl (2) platelets count 50x 109 /L (3) neutrophil count 50x 109 /L. For each case four age-sex matched control were selected from different outpatient department of hospitals (e.g.

patient with trauma, eye or ENT infection etc.) The exposure was defined as a history of antimicrobial prescription between 29-180 days. Exposure history less than one month was excluded. Information on timing, frequency and duration (including use extending back beyond 6-month period) of use was recorded. Statistical Package for the Social Sciences (SPSS) version 22 was used for data analysis. Frequency distribution for cases and controls according to their exposure status was calculated p value < 0.05.

RESULTS:

There were 191cases and 696 healthy controls 89% with age range of 1-66 years with 67% males and 33% females. Among cases 95 (49.7%) were found to be exposed to antimicrobial drugs chronically while 96 (50.3%) were found to be non-exposed. In controls 204 (29.3%) gave history of chronic use of antibiotics while no such overuse was reported by 492 (70.7%) subjects. These findings show positive associations of antimicrobial drugs with a P value 0.0001 [Table-1, Fig-1]. The history of Beta lactam Antibiotics usage was 6.81% (13) in cases and 3.59% (25) among controls, for Chloramphenicol use it was 6.81% (13)among cases and 3.74% (26)in controls, Trimethoprim/ Sulfamethoxazole were used by 13.09%(25) cases and 8.62% (60) controls, Tetracycline were used by 14 (7.31%) controls and 28(4.02%) controls, Macrolides were used by 12 (6.28%) cases and 25 (3.59%) controls whereas Other agents were used by 18(9.42%)cases 40(5.75%)[Table-2,Fig-2].

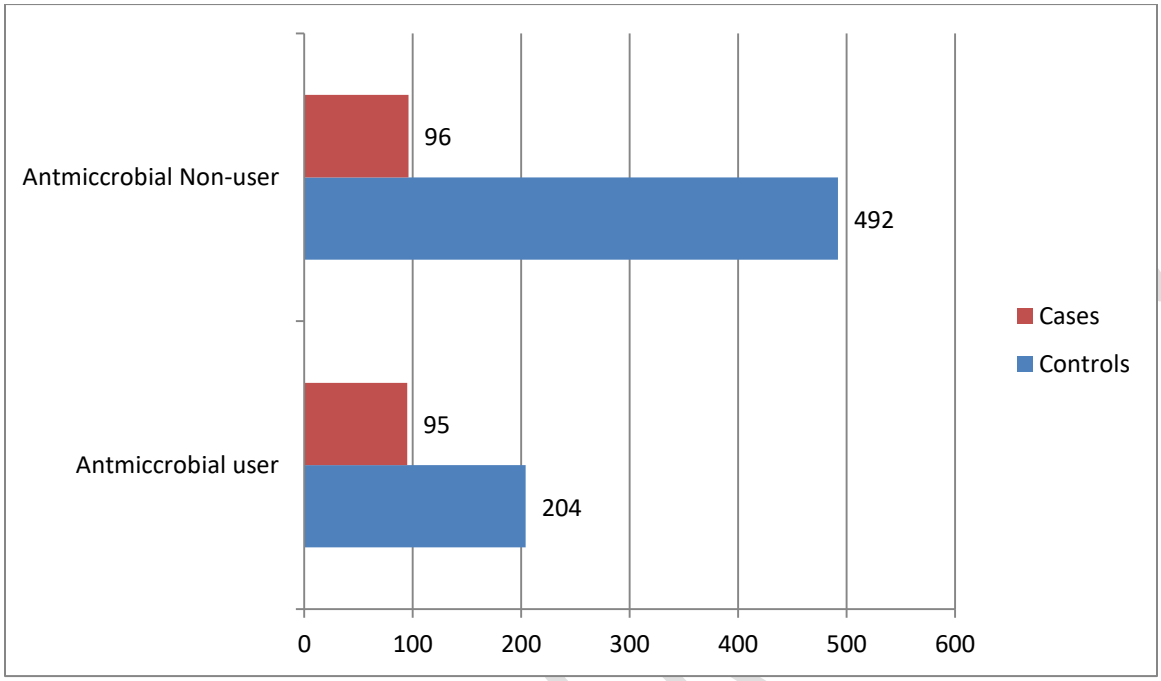

Fig:-1. Bar chart representation of antimicrobial users and non-users

Table-1: Comparison between cases and controls for antimicrobial usage

Study Subject	Antimicrobial User	Antimicrobial Non-User	Total	P-Value
Cases	95	96	191	0.0001
Controls	204	492	696	
Total	299	588	887	

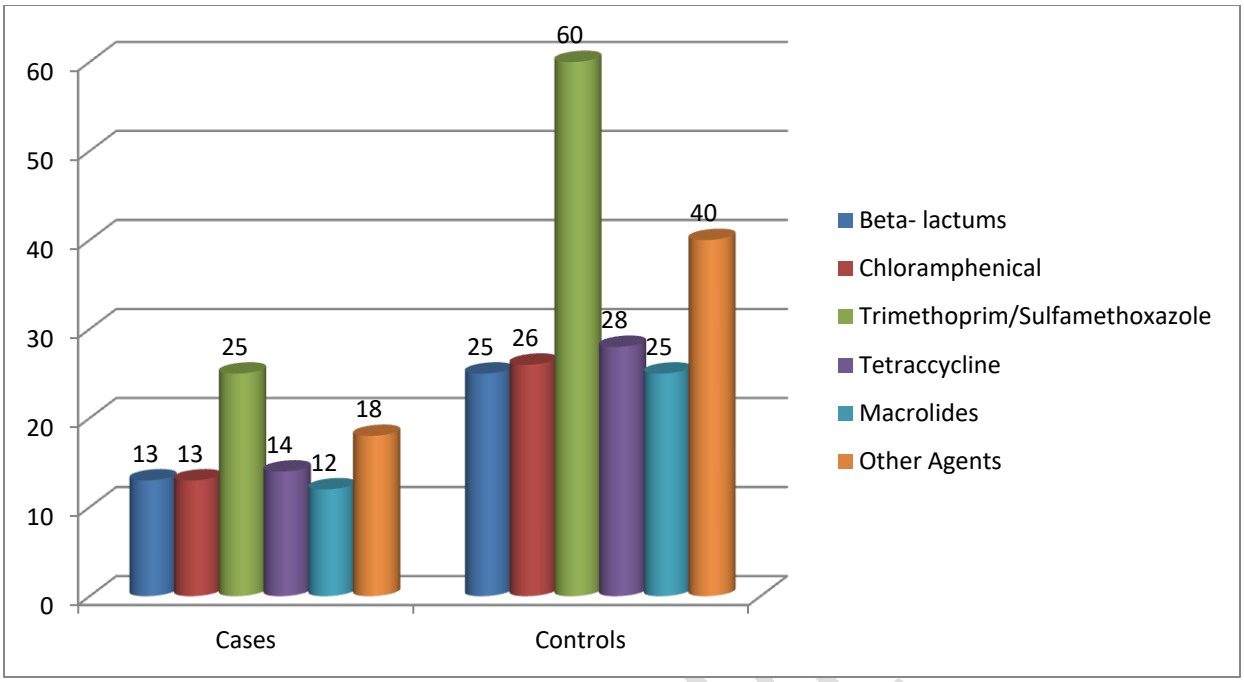

Fig:-2. Types of antimicrobial agents used by cases and controls

Table-2: Usage of various antibiotics among cases and controls

Antibiotics	Cases	Controls
Beta lactam Antibiotics	**13 (6.81%)**	**25 (3.59%)**
Chloramphenicol	**13(6.81%)**	**26(3.74%)**
Trimethoprim/Sulfamethoxazole	**25 (13.09%)**	**60 (8.62%)**
Tetracycline	**14 (7.31%)**	**28 (4.02%)**
Macrolides	**12 (6.28%)**	**25 (3.59%)**
Other agents	**18 (9.42%)**	**40 (5.75%)**

DISCUSSION:

Several studies illustrated a possible association between use of chloramphenicol and aplastic anemia[10]. In the current study we didn't found any link with the chloramphenicol, which may be associated with the limited (only tropical) use. We currently found significant

association between the antimicrobial agents use with aplastic anemia that was inconsistent to a study results from Thailand with no significant association [11]. There are studies that have individually tested many other drugs with positive association. The results data from Kaufman et al showed the associated risk for aplastic anemia with trimethoprim [12]. However in current research we didn't observe relationship of trimethoprim with illness. This may be due to difference in study setting, sample size and information bias. Aplastic anemia is a potential rare fatal side effect of tetracycline group of antibiotics reported in patients with preexisting renal dysfunctions due to marrow toxicity possibly. Aplastic anemia reported with other antimicrobial groups like sulfonamides was already globally accepted [13]. Although the need of antimicrobial therapy is the utmost solution for infections but what it can done for the miss use or over use prevention in the community is to promote the culture and sensitivity tradition in the healthcare system all around the provinces of the country. This study deserves further investigation to investigate its role of antibiotics with association of AA.

CONCLUSION:

Antimicrobials were found to be more frequently used by the aplastic anemia cases in comparison to controls proving it as a potential risk factor for the development of aplastic anemia.

RECOMMENDATIONS:

Use of appropriate antimicrobial agent for an appropriate duration is recommended along with its rationale use

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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