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Research Article

Antibiotic Resistance in Pediatric Pneumonia Patients: Assessing Prevalence and Prescribing Practices

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Corresponding author: Abstract: Antimicrobial resistance (AMR) has become a significant worldwide health issue, endangering public health through diminished opportunities for treatments, an increasing incidence of morbidity and mortality, and increasing healthcare costs. This study investigates the prevalence of antibiotic resistance, prescribing patterns and antibiotic responsiveness in pediatric pneumonia with an effort to highlight the urgent need to address this issue. This study assessed the antibiotic prescriptions, hospital longevity and treatment outcomes in 73 pneumonia patients. A total of 506 drugs were prescribed, with an average of 6.9 drugs per prescription, surpassing the recommended WHO standard of 1.6-1.8 drugs. Antibiotics accounted for 38.7% of the prescribed drugs (n=197). Injectable drugs, generic names, and drugs from the Essential Drug List (EDL) comprised 58.5%, 12.84%, and 95% of the prescriptions, respectively. The most common antibiotic combination was ampicillin-cloxacillin, prescribed to 33% of the patients, of which 84.5% of patients did not responded and switched to another drug combination. Ampicillin-cloxacillin-ceftazidime combination was prescribed to 14.6% of patients, however this combination received a non-response rate of 7.1%. Patients unresponsive to these regimens were switched to more efficacious antibiotics such as linezolid, vancomycin, amikacin, ceftriaxone, and cefotaxime. This study highlights the rapid emergence of antibiotic resistance in children with pneumonia, which is associated with their vulnerability to infections due to a compromised immune system. Empirical antibiotic therapy practices, which are frequently utilized in pediatric patients, have led to a rise in resistance to first-line antibiotics (amoxicillin-cloxacillin) used to treat pneumonia. In order to address this critical issue, collaborative efforts from healthcare professionals, policymakers, and the community will be required to raise awareness and promote appropriate antibiotic usage and combat the emergence of AMR in Pakistan.

Keywords: Antimicrobial resistance (AMR), Antibiotic responsiveness, Amoxicillin-cloxacillin, Pediatric pneumonia

1. INTRODUCTION

Pneumonia is a significant cause of mortality among children worldwide, with an estimated 120 million cases in children under the age of five each year, resulting in 1.3 million deaths [1]. It is characterized by lower respiratory tract infection accompanied by fever, respiratory symptoms, and evidence of lung involvement as observed through physical examination or chest radiography [2]. The term "walking pneumonia" is often applied to school-aged children and young people who have radiographic and clinical indications of pneumonia but have minor respiratory symptoms that do not impede with daily activities. *Mycoplasma pneumoniae* is commonly associated with walking pneumonia [3]. Community-acquired pneumonia

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(CAP) and is influenced by factors such as malnutrition, the use of charcoal for cooking, lack of exclusive breastfeeding in the first year of life, and overcrowding. Hospital-acquired pneumonia develops in children within 48 hours of hospital admission and tends to be more severe [4, 5].

On a global scale, pneumonia is one of the main reasons for death in children specifically under the age of five. In 2015, about 700,000 children under five years died from the pneumonia worldwide, with the highest incidence recorded in the African and South-East Asian regions [6]. The World Health Organization (WHO) estimates a clinical pneumonia incidence of 0.37 episodes per kid per year, with India accounting for 36% of the overall WHO South, East Asia regional burden [7]. In Pakistan the incidence is estimated to be 0.26 per child 2 year contributing to 28% of all childhood deaths [8]. Pneumonia risk factors include a lack of exclusive breastfeeding, low birth weight, undernutrition, indoor air pollution, crowded living environments, and a lack of measles vaccination [7]. According to a study conducted in Khyber Pakhtunkhwa, Pakistan, that focused on the prevalence of pneumonia, where 61.8% were children and 38.2% were babies. Male to female ratios were 31.4 and 68.6 percent, respectively. The percentage of economic loss among poor families was significant, at 60%, whereas it was 30% and 10% for middle and high economic status families, respectively. The percentages of rural and urban occurrences were around 51 and 49 percent, respectively [9].

Antibiotics have revolutionized medicine since Alexander Fleming's discovery of penicillin in the late 1920s, reducing pain and suffering, saving millions of lives each year, and even being used prophylactically to prevent infectious diseases. However, we are currently facing a situation where many medications are ineffective against even the less severe diseases [10]. The initial therapy for pneumonia should be effective against *Streptococcus pneumoniae* (the commonest cause of pneumonia) and *Streptococcus aureus*. High dose penicillin and ampicillin, amoxicillin-clavulanic acid, or a 2nd and 3rd generation cephalosporin (ceftriaxone and cefuroxime) are mostly used intravenously. However in areas where there is high prevalence of Methicillin resistance *S aureus*, it is advisable to add vancomycin along with first line agent [11]. The duration of intravenous antibiotic therapy is a topic of debate, but oral antibiotic therapy should be initiated as soon as possible [12].

The rising antimicrobial resistance (AMR) is considered one of the most threatening challenges to global public health, increasing morbidity, mortality, and costs, as well as limiting the choice of antimicrobials for potential treatment [13]. In response, global health organizations, including WHO, have introduced a Global Action Plan (GAP) in 2015 in response to complaints about AMR and its effects in 2016 assembly strengthening the GAP [14]. All nations supported GAP, including Pakistan, which is currently the sixth-most populated nation in the world and is projected to overtake fourth rank by 2050. AMR increases medical costs, prolong hospital stays, and elevates mortality. The world must quickly modify the way antibiotics are given and utilized [15]. Addressing AMR is crucial to prevent a post-antibiotic era marked by increased medical costs, prolonged hospital stays, and elevated mortality. Considering the growing threat of AMR in pediatric pneumonia, the current study aims to document the prescribing patterns of antibiotics and assess the prevalence of AMR and antibiotics resistance in pediatric pneumonia patients in a tertiary care hospital in Mardan, Khyber Pakhtunkhwa, Pakistan.

2. METHODOLOGY

2.1. Data Collection

The study included a total of 73 patients, and their case histories were collected with the official permission of the chief pharmacist and ward in-charge. The data collector received proper education and ethical guidance from the university prior to data collection. The data collection process was based on consent among physicians, nurses, and the patients themselves.

2.2. Study Setting and Design

This study was conducted as a retrospective study at a tertiary care teaching hospital in Mardan, Pakistan. The study specifically focused on the hospital's pediatric ward, which serves as a referral center for patients from different regions such as

Mardan, Dargai, Skhakot and Swabi.

2.3. Excluding and Including Criteria

Specific criteria were used to determine which patients were included or excluded from the study. Patients taking single medications, hospitalized for less than 1 day, had inadequate medical records, and were bedridden were excluded. However, the study also included patients who had already been discharged from the hospital and had complete medical records.

2.4. WHO Core Indicators

WHO has set the standard values for drugs per encounter which are known as core indicators. The core indicators dictate that how many drugs should be there in prescription, number of injectable, number of antibiotics, drugs from essential drug list and drugs prescribed by their generic name to ensure appropriate and rational use of medicines [16, 17]. WHO has also developed essential drug list to ensure the availability of drugs to all for safe and cost effective use [18]. Every WHO core indicator, including the total number of items per prescription, the proportion of drugs with generic names, the average number of antibiotics prescribed per prescription, the proportion of injectable prescribed per prescription, and the EDL of 2018, were carefully examined for each prescription. These measures were developed for any healthcare facility based on an analysis of clinical sessions with patients. A patient interaction is generally understood to be "the time spent interacting with the healthcare provider [19], and "Taking a patient's history, making a diagnosis, choosing between pharmaceutical and non-pharmacological therapy, and prescribing (and sometimes distributing) medication are all components of the ideal consultation, monitoring the patient, informing them about the treatment's side effects, and preventing future issues. Drug Regulatory of Pakistan (DRAP), a division of the Ministry of Health Services of Pakistan, has determined which drugs from the 2018 list of essential drugs are necessary [20].

2.5. Hospital Stay and Antibiotic Responsiveness

The study also considered the length of hospital stays and changes in antibiotic regimens among in-patients as indicators of antibiotic responsiveness. Hospital longevity and antibiotics switching indicates the declination of antibiotic responsiveness. So, along with CSTs, which is not mostly followed in pediatrics, especially in pneumonia infections, hospital longevity was followed for assessing antibiotics resistance. Switching-over from one class of antibiotics to another assist us in prevalence of AMR among pediatrics pneumonia. Date of admission, date of discharge, and antibiotic therapies schedule were regularly followed for antimicrobial therapy and associated resistance. CSTs report were not found throughout the study, as it is expensive process and take almost 48-72 hours Pneumonia in children is fatal, Prescribers can't wait for CST reports that's why empirical treatment was practiced.

2.6. Assessment of Antibiotic Resistance from Patient's Hospital Stay

Pneumonia hospitalized patients receive different types of antibiotics during their stay at the hospital [21]. After starting an antibiotic regimen, some patients indicate responsiveness to the antibiotics resulting in early discharge of patients from the hospital within 2-5 days [22]. However, some patients tend to show no responsiveness to that specific antibiotic regimen with results in antibiotic switching-over to another agents or class of antibiotics [23]. This switching-over increases the hospital stays and longevity of pneumonia patients [24]. This can be considered as an important factor for assessing the antibiotic resistance within pneumonia patients receiving therapy.

2.7. Data Analysis

Data analysis was performed using Microsoft Word while Graphpad prism (version 8.0.2) was used for tabulation and graphical presentation of the data. Pharma guide and pharmapedia were utilized as references for generic drug names.

3. RESULTS

3.1. Gender Wise Distribution of Patients

In this study, a total of n=73 prescriptions were collected and evaluated. The percentage of male

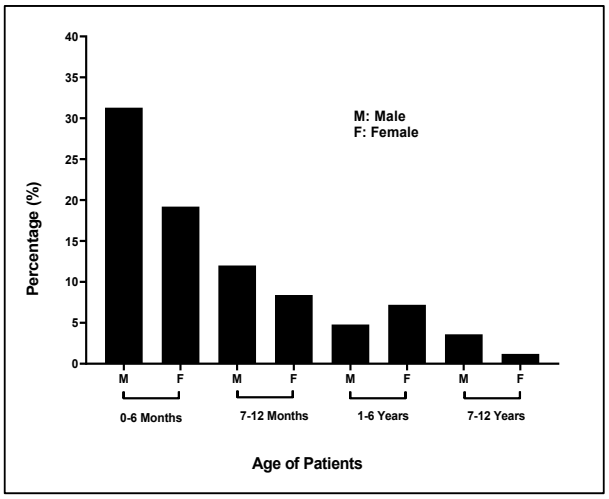

Figure 1. Gender and Age-wise distribution of patients.

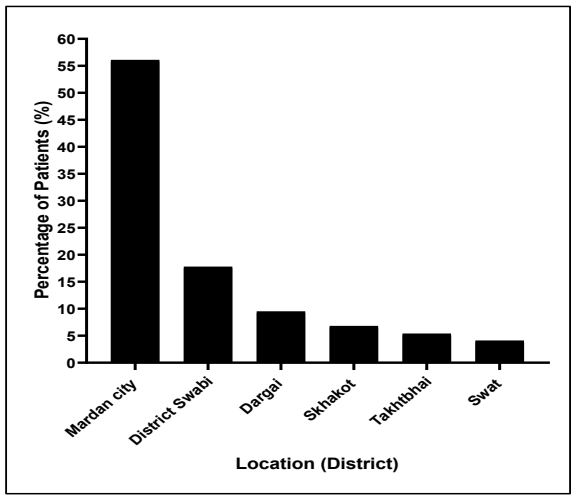

Figure 2. Geographical distribution of patients participated in the study.

patients was 58.9% (n=43) while the percentage of female patients was 41.1% (n=30).

3.2. Age Wise Distribution of Patients

Age-wise distribution showed 1 month and 12 years as minimum and maximum age of the admitted children's patients. The age groups were categorized in 04 groups that included 1-6 months (n=42, 57.5%), 7-12months (n=17, 23.2%,), 1-6 years (n=10, 13.7%) and 7-12years (n=4, 5.4%) years respectively. It shows that the prevalence of pneumonia is very common at age of 1 to 6 months as maximum n=42 patients among the 73 patients. The attack is less common at age 7 to 12 years as minimum n=4 patients reported among the total cases. Gender and aged based distribution of patients is shown in (Figure 1).

3.3. Geographical Distribution

The patients admitted belonged to six (06) different locations that included n=41 patients from Mardan city with a percentage of 56.1%, from district Swabi n=13 with a percentage of 17.8%, from Dargai n=7 with a percentage of 9.5%, from Skhakot n=5 with a percentage of 6.8%, from Takhtbhai n=4 with a percentage of 5.4%, the number of patients from Swat n=3 with a percentage of 4.1%, respectively (Figure 2).

3.4. WHO Core Indicators

In the current study, a total of n=73 prescriptions were evaluated, encompassing a total of n=506 drugs. The evaluation of drug prescribing practices was conducted using the WHO core indicators, as presented in (Table 1). The observed indicators were compared to the WHO proposed and standard core indicators to assess the appropriateness of prescribing practices.

3.5. Frequency and Percentage of the Prescri bed Antibiotics

In this study, a total of 197 antibiotics were prescribed with an average of 2.7 or 3 antibiotics per prescription. The most frequently prescribed antibiotics were ampicillin-cloxacillin, cefotaxime, ceftazidime, ceftriaxone, linezolid, vancomycin, amikacin, and clarithromycin as shown in (Figure 3). These antibiotics were commonly used in the treatment of pneumonia among the pediatric patients included in the study. The prescription patterns indicate the preferences of healthcare providers in selecting antibiotics for managing pneumonia cases in this particular setting. The most prescribed antibiotic ampicillin-cloxacillin accounted for n=65 (33%), cefotaxime n=46 (23.3%), linezolid n=32 (16.2%), vancomycin n=23(11.6%), ceftazidime n=17 (8.62%), ceftriaxone n=9 (4.45%), amikacin, meropenem and clarithromycin accounting for n=6 (3%) each having 1%, respectively.

3.6. Hospital Stay and Longevity

The average hospital stay of male and female patients was 3.79 and 3.2 days, respectively. Average hospital stay of male patients was found to be higher than the average hospital stays of female

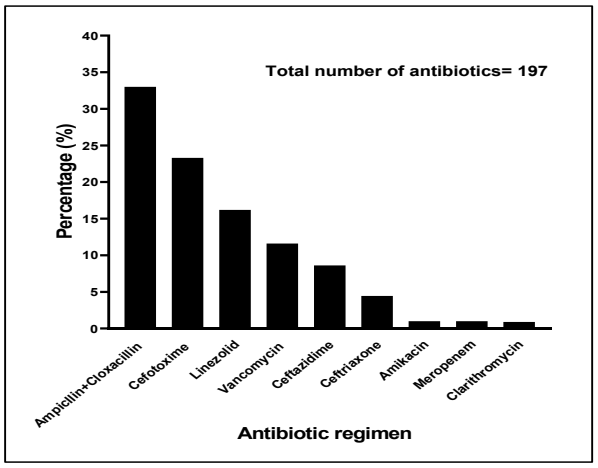

Figure 3. Percentage of the prescribed antibiotics.

patients (Figure 4).

3.7. Observed Antibiotics Resistance during the Study

In this study, the entire medical records of 73 patients were assessed to identify possible antibiotic resistance. The patients' antibiotic therapy was analyzed based on their hospital stay duration. Antibiotic sensitivity was thought to exist in patients who received their discharge quickly after the antibiotics regimen without switching-over to other class of antibiotics. Antibiotics switched-over is a sign of non-responsiveness and possibly prevalence of AMR.

A total of n=65 (79.2%) patients received the ampicillin-cloxacillin combination. However, out of 65 patients, n=55 (84.6%) of patients doesn't responded to ampicillin-cloxacillin combination and the antibiotic regimen was changed to linezolid, vancomycin, or 3rd generation cephalosporins including ceftazidime, ceftriaxone, and cefotaxime. Furthermore, some patients were found to have shown responsiveness to combination therapy having ampicillin-cloxacillin in combination with ceftazidime, ceftriaxone, and cefotaxime.

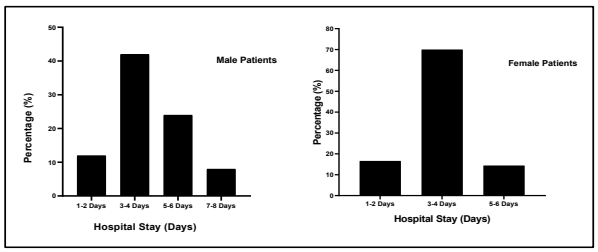

Figure 4. Hospital stay and longevity (Left: Male Patients, Right: Female Patients).

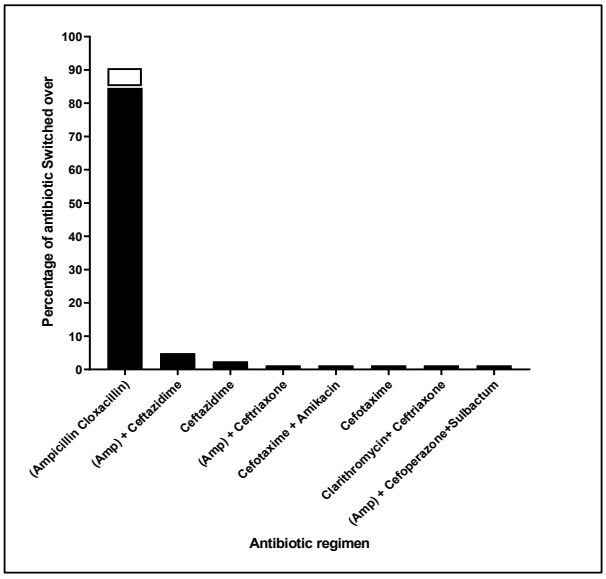

Figure 5. Antibiotic switching-over observed during the study.

Moreover, combination therapy resulted in patient discharge without further switching over. In conclusion, these results suggest that ampicillin-cloxacillin combination have lost its efficacy due to the onset of AMR strains in pediatric pneumonia patients. The antibiotic switching-over observed during the study is presented in (Figure 5). (Figure 6a and 6b) presents the overall consumption of antibiotics by individual patients.

4. DISCUSSION

The current research was carried out at Pediatric wards of a tertiary care hospital at District Mardan, Khyber Pakhtunkhwa, Pakistan. In this study, the percentage of male patients was 58.9% (n=43) while the percentage of female patients was 41.1% (n=30). Age-wise distribution showed 1 month and 12 years as minimum and maximum age of the admitted patients. The age groups were characterized into 04 groups that included infants age: 1-6 months (n=42, 57.5%), neonates age: 7-12months (n=17, 23.2%,), children age: 1-6 years (n=10, 13.7%) and grade-schooler kids: 7-12years of age (n=4, 5.4%) years respectively. The prevalence of pneumonia was found to be more common at age of 1 to 6 months as maximum n=42 patients among the 73 patients. The prevalence of pneumonia was found to be less common at the age of 7 to 12 years as minimum n=4 patients were reported among the total cases.

During evaluation prescription trends were

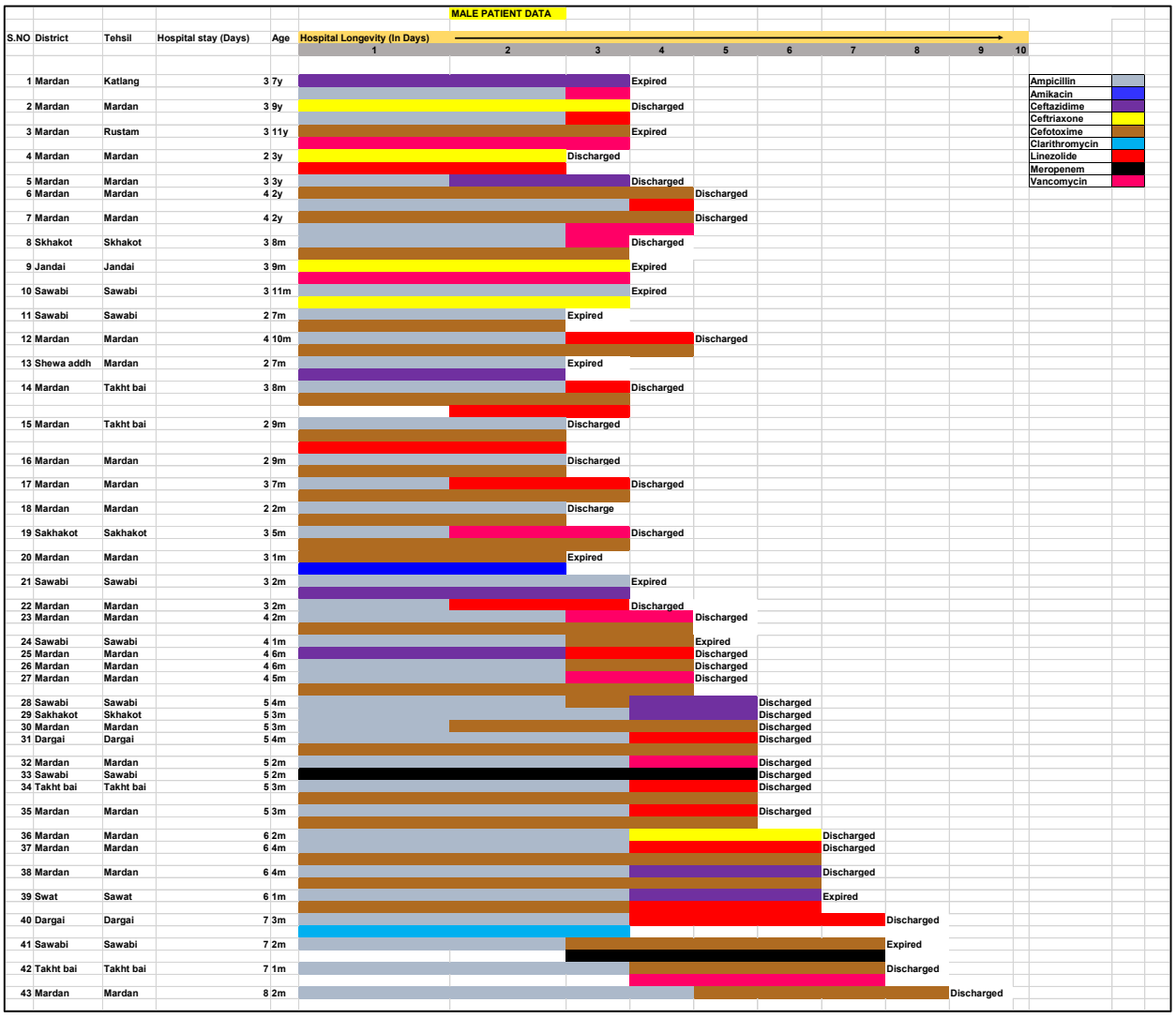

Figure 6a. Antibiotic consumption chart (Male Patients).
Note: The colored bar lines denote antibiotic regimen, while termination/change of colour denotes that antibiotic is switched-over to other antibiotic agent/class as a result of non-responsiveness as evident from patient condition during the study.

taken into consideration in a particular scenario and assessed multiple prescription drug-related factors. The average number of drugs prescribed per encounter was calculated as 6.9, which is higher than the value recommended by WHO (1.6-1.8). A similar nature study was conducted in 2 private and 2 government hospitals in Pakistan, the average number of drugs prescribed per encounter was 4.7 [25]. Comparing our findings with other studies conducted in Pakistan, another study carried out in Bahawalpur Pakistan, the average number of prescribed drugs per prescription was 3.4 [26]. In contrast to our findings, the average number of drugs prescribed per encounter was lower in Ethiopia where an average of 2.1 drugs were prescribed per encounter while in Nepal an average of 3.2 drugs were prescribed per encounter [27, 28].

The WHO (World Health Organization) has mentioned that the average number of drugs prescribed per encounter must be in the range of 1.6-1.8. Polypharmacy, defined regular use of at least 05 medications. During the study, we observed polypharmacy in the pediatric ward [29]. There are many reasons which causing polypharmacy including lack of proper medical knowledge, improper training, poor diagnosis, patient non-compliance, improper counselling and the shortage of therapeutically correct drugs. Polypharmacy leads to poor therapeutic response and many

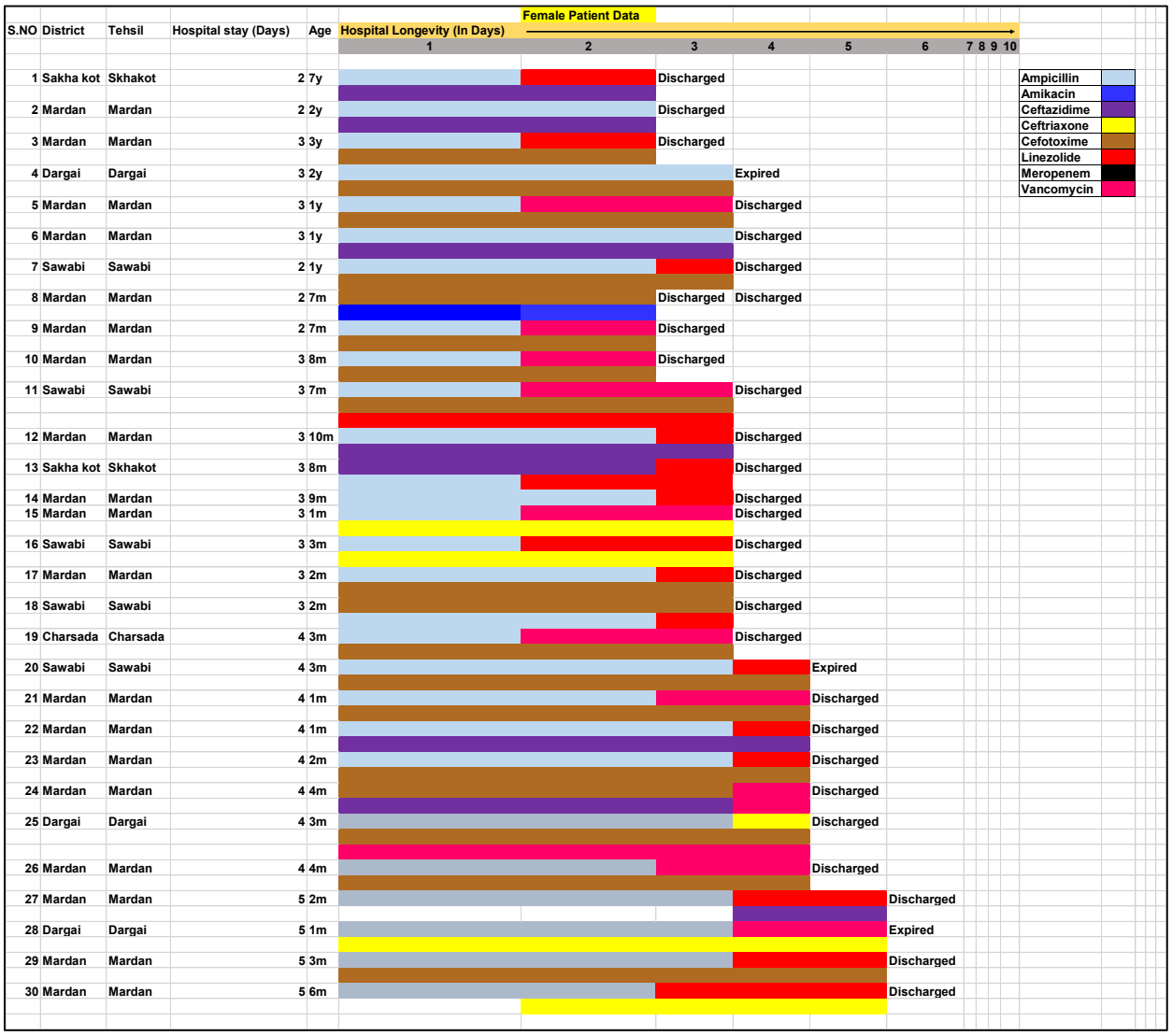

Figure 6b. Antibiotic consumption chart (Female Patients).
Note: The colored bar lines denote antibiotic regimen, while termination/change of colour denotes that antibiotic is switched-over to other antibiotic agent/class as a result of non-responsiveness as evident from patient condition during the study.

chances of drug-drug interactions [30]. According to WHO, 100% of drugs should be prescribed by generic names. In our study 12.84 % of drugs were prescribed by generic name. A study was conducted in Kenya, the prescription of drugs by generic name was 27.7% which very much high than our findings. Another study was conducted in the teaching hospitals of Punjab, 39.5% of drugs were prescribed by generic names [31, 32]. In contrast, a study conducted in Bangladesh reported that no drugs were prescribed using generic names [33].

Most pharmaceutical businesses in Pakistan employ sales personnel who pressure doctors to recommend their product in exchange for rewards, gifts, samples, and other inducements. Pharmaceutical representatives have a considerable impact on prescribing practices and are prejudiced in favor of name-brand drugs, which fosters an unfavorable perception of generic drugs. The benefit of prescribing medications by their generic names is that it is more affordable and patient access is made easier because they are not needed to search for a particular drug with a brand name [28]. According to WHO all drugs should be prescribed from EDL (Essential Drug List). Each country has developed its own NEDL (National Essential Drug List) based on the availability drugs and its cost understand the supervision on WHO. In our study total 506 drugs were prescribed in 82 prescriptions. 482 (95%)

drugs out of 506 were from EDL (essential drug list). Another study conducted in Tertiary care hospital Punjab, Pakistan the percentage of drugs prescribed from National Essential Drug List 2008 Pakistan was 70.37 %. In Nepal, 21.3% of the medications on the essential drug list were prescribed while in Ethiopia 83.0% of the drugs were prescribed from essential drug list [27, 28].

The lack of awareness about necessary medications or the pharmaceutical company's marketing of newer compounds might be the cause for not prescribing from the essential drug list. Prescriptions for pharmaceuticals from the essential drug list prevent adverse drug reactions and drug reactions, and they also increase the patient's financial and therapeutic benefit since essential medicines are safe, high-quality, and cost-effective [28]. The percentage of antibiotics prescribed in this study was 39.32%, which is significantly higher than the recommended value of 20-20.6% by the WHO. This high rate of antibiotic prescription raises concerns about antibiotic overuse and the associated risk of recurrent hospitalization. A study conducted in Tanzania reported that 51.9% of prescriptions included antibiotics, while in the Amhara regional state of Ethiopia, the percentage was even higher at 69.6% [34]. Due to the lack of culture and sensitivity tests (CSTs) in this study, clinicians had to treat patients on an empirical basis and give them broad-spectrum antibiotics, which ultimate results in antibiotic resistance.

The most frequently prescribed antibiotics were ampicillin-cloxacillin, cefotaxime, ceftazidime, ceftriaxone, linezolid, vancomycin, amikacin, and clarithromycin as shown in Figure 3. These antibiotics were commonly used in the treatment of pneumonia among the pediatric patients included in the study. The prescription patterns indicate the preferences of healthcare providers in selecting antibiotics for managing pneumonia cases in this particular setting. The most prescribed antibiotic ampicillin-cloxacillin accounted for n=65 (33%), cefotaxime n=46 (23.3%), linezolid n=32 (16.2%), vancomycin n=23(11.6%), ceftazidime n=17 (8.62%), ceftriaxone n=9 (4.45%), amikacin, meropenem and clarithromycin accounting for n=6 (3%) each having 1%, respectively. During this study, out of 65 patients, n=55 (84.6%) patients were found non-responsive to the first line of therapy ampicillin-cloxacillin combination for pneumonia, as a result the antibiotic regimen was switched-over to a more powerful antibiotic regimen such as linezolid, vancomycin or 3rd generation cephalosporins. In addition, resistance developed to the ampicillin-cloxacillin-ceftazidime combination administered to 14.6% of the patients, and 7.1% of the patients did not responded. Furthermore, some patients were found to have shown responsiveness to combination therapy having ampicillin-cloxacillin in combination with ceftazidime, ceftriaxone, and cefotaxime. Unsuitable antibiotic medication has been linked in the past to poor patient outcomes and a rise in AMR, according to research. According to Sano et al., improper early antibiotic therapy is substantially linked to emergence of AMR. Furthermore, when the detected bacteria are susceptible to narrow-spectrum antibiotics, usage of broad-spectrum antibiotics may increase mortality. Thus, it is critical to identify people at risk of AMR at the time of diagnosis [35]. A significant issue with hospital-acquired infections is biofilm-related multi-drug resistance, which raises patient morbidity and death rates as well as financial expenditures from high medical expenses and extended hospital stays [36].

Lastly, the current study highlights the urgent need for antibiotic stewardship programs in pediatric settings to ensure the rational use of antibiotics. In order to prevent the emergence of AMR, healthcare providers should receive education on the proper selection and administration of antibiotics. Furthermore, there is a strong need for policy making and implementation of guidelines regarding the empirical therapy in pediatric pneumonia which will reduce the onset of AMR. Additionally, there is a need for public education and proper surveillance to monitor the onset of resistant strains in the region and community.

As this study was confined to a single tertiary care hospital in District Mardan, Khyber Pakhtunkhwa, Pakistan, there remains a room for additional research studies on the mentioned topic to assess the prevalence of AMR in pediatric pneumonia patients on a national and global scale. Longitudinal studies are needed to evaluate the long-term impact of antibiotic therapy on pediatric patients with pneumonia, including the development of antibiotic resistance, recurrence of

infections, and clinical outcomes. Future research should explore non-antibiotic interventions, such as vaccination strategies, respiratory hygiene measures, and supportive therapies, to reduce the burden of pneumonia and minimize the reliance on antibiotics.

5. CONCLUSIONS

Antibiotics are slowly and gradually losing their efficiency due to their unintentional use in children for minor infections. During the current study, we came across a significant proportion of pediatric pneumonia drug-resistant cases. In particular, frequently prescribed therapy consisting of ampicillin-cloxacillin, 84.6% of patients doesn't responded to this combination while ampicillin-cloxacillin and cefotaxime (57.3% of cases) was unsuccessful in 26.82% of patients, necessitating the administration of different antibiotics. In addition, resistance developed to the ampicillin, cloxacillin, and ceftazidime combination administered to 14.6% of the patients, and 4.9% of the patients did not respond.

In conclusion, the current study showed an alarming increase in antibiotic resistance to the first line therapy (ampicillin-cloxacillin) in combination with 3rd generation Cephalosporins namely; cefotaxime and ceftazidime for pneumonia among children. Despite the fact that this study only focused on one hospital, it nonetheless highlights the urgent need for further investigation in order to completely comprehend the scope of this issue as well as develop effective AMR management strategies. In order to address this serious issue, collaborative efforts from healthcare professionals, policymakers, and the community will be required to raise awareness and promote appropriate antibiotic usage and combat the emergence of AMR.

6. ACKNOWLEDGEMENTS

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7. CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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