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Research Article

Prescribing Pattern of Ampicillin and Cloxacillin: Sensitivity and Responsiveness in Pneumonia

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Abstract: Antimicrobial resistance (AMR) is now a global pandemic and a future threat to the existence of many clinical antibiotics. The excessive overuse in fisheries, poultries, and dairy farms and its irrational prescribing practices are the key factors that lead us to AMR explosions. The current main research objective is to evaluate the empirical practices of ampicillin along with cloxacillin, which are one of the running antibiotics in clinical practices, in most of the tertiary care hospitals in Khyber Pakhtunkhwa, Pakistan. In this study, the prescribing attitude, sensitivity and responsiveness of these two combinatory antibiotics (ampicillin-cloxacillin) in pediatric/adult pneumonia patients were evaluated in one of the public sector tertiary care hospitals in Mardan. Retrospective data was collected from pediatric ward A and medical A ward (adult), among which a total of n= 90 patient's prescriptions were evaluated for prescribing practices, WHO core indicators, polypharmacy as well as responsiveness and sensitivity of ampicillin and cloxacillin from hospital longevity. The ampicillin responsiveness was sorted out among all those patients that stayed for a long time in the hospital, and during which the antibiotic therapies were switched from time to time. A total of n= 90 pneumonia patients (40 % & 60 % female) cases were evaluated for ampicillin/cloxacillin (combination) hospital stay longevity and responsiveness. 46 % of patients were under the age of 1–20 years, whereas 31 % were adults between the age of 61–80 years. WHO indicators revealed, that in the prescribed medications (n=918 drugs total, among n=90 patients) 22.33 % of antibiotics were prescribed, where 31.37 % consisted of injectables. Among the antibiotics classes, 17 % of pneumonia patients received penicillin, among which 26.25 % were ampicillin + cloxacillin in the prescribing practices. Ampicillin + cloxacillin responsiveness in pneumonia patients was recorded from the hospital stay and longevity (days) of the patients during their empirical therapy. 46.98 % of pneumonia patients recovered within three days, whereas 40.96 % of patients recovered within six days with ampicillin + cloxacillin (combination therapy). While 10.84 % were stabilized within nine days, though, some patients (1.20 %), recovered after 12 days with ampicillin/cloxacillin (combination therapy). Thus, it may be concluded from the current studies, that the decrease in responsiveness to ampicillin/cloxacillin (combination therapy) and the increase in the hospital longevity of patients, may be an indication of antimicrobial resistance (AMR) in pneumonia patients. Though the studies are limited to a very specific number of patients, as well as only to the hospital longevity (stay) parameters of the patients in a tertiary care hospital. These studies should be subjected further to more extensive vigilant research.

Keywords: Ampicillin, Cloxacillin, Antibiotic responsiveness , Antimicrobial resistance (AMR), Hospital longevity.

1. INTRODUCTION

Around the world, pneumonia is a major factor in both morbidity and death among children. Incidence of pneumonia in children under the age of five is thought to be 120 million per year worldwide, with 1.3 million cases ending in death. Pneumonia should be defined as an acute infection of lung parenchyma by one or more than one pathogens, excluding the well-defined state of bronchiolitis,

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which is almost caused by a viral agent [1]. Different types of pneumonia are bacterial pneumonia, viral pneumonia, and mycoplasma pneumonia. Viral pneumonia, which accounts for around one-third of all occurrences of pneumonia, is brought on by viruses like the flu, whereas bacterial pneumonia is brought on by bacteria. Atypical pneumonia, also known as mycoplasma pneumonia, is brought on by bacteria and affects people of all ages, mostly smokers, alcoholic individuals, asthmatics and people with weak immune systems are at higher risk to be affected by and diagnosed with pneumonia [2]. One million children kill under the age of 5 every year due to pneumonia and are responsible for 15 % of all pediatric fatalities, with 90 - 95 % of these deaths taking place in underdeveloped nations. Only 15 nations account for 2/3 of pneumonia episodes in children under the age of five mostly in the south- Asia and sub -Saharan African countries [3]. In Pakistan, mortality rate for meningitis and pneumonia range from 16 - 37 % and 10 - 30 %, respectively. Notably, the mortality rate among young infants is higher in underdeveloped nations (10 - 40 %) due to worse access to the health care system. Mortality rates were 3 % for children under the age of five, 14 % for people in the range of 5 to 65, and 24 % for adults over the age of 65 years [4, 5].

In preschool children with pneumonia, antimicrobial treatment is not typically advised (because of viral infections). Streptococcus pneumoniae is still the most usually implicated pathogen, amoxicillin or amoxicillin-clavulanate is the most recommended first-line antimicrobial treatment for community-acquired pneumonia (CAP) in children [6]. The ketolides, vancomycin, and the more recent anti-pneumococci fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin, trovafloxacin, and pefloxacin), as well as the newly available oxazolidinone linezolid, are all effective against drug resistance *Strepto coccus Pneumoniae* (DRSP) [7]. Since children are frequently the targets of infections with a variety of etiologies, ranging from the more common chest infections to the less common meningitis, they are thought to be the most frequent receivers of antibiotics than any other category of patient.

The discovery of antibiotics and the emergence of AMR goes side by side, since its discovery to date. AMR is a future pandemic and considers a global threat to the existence of many antibiotics [5]. Rising AMR is one of the greatest threats to global public health since it raises morbidity, mortality, and costs while reducing the selection of antimicrobials that may be used as possible treatments [8]. The proper administration of antibiotics in children is crucial because there are few antibiotic formulations acceptable for this demographic. In several countries, studies of antibiotic prescribing trends in primary care facilities for children have revealed improper antibiotic usage ranging from 19.6 - 79.8 %. Children, on the other hand, are special drug-using groups, as well as their organs and functions, are underdeveloped. They have a distinct digestive system, insufficient liver and renal metabolism, and insufficient blood-brain barrier function absorption of antibiotics. The distribution, metabolism, and excretion are all poorer than in adults. As a result, more emphasis should be placed on the antibiotics that are being used inappropriately in this group [9]. Resistance in bacteria developed, either through their drug-protein target modification, enzymes, or through genetic evolutions [10].

To preserve the efficacy of antimicrobials, the worldwide mostly implemented program and approaches comprised of public awareness campaigns and antimicrobial guidelines; though, further tactics and strategies concentrated on vaccination, and varying protocols around recommending and repayment [11, 12]. It includes rational antimicrobial usage, regulation of antibiotic over-the-counter access, improved hand hygiene, and improved infection prevention and control. The need is for a thorough knowledge of resistance mechanisms as well as innovation in novel medications and vaccines. To tackle antimicrobial resistance, a multidisciplinary, coordinated regulatory strategy is required [13]. Drug regulatory authority of Pakistan (DRAP) has also adopted various strategies and policies for the control of AMR various policies and strategies [14-17].

Reform is required to overcome policy implementation difficulties. Today, declining antibiotic efficiency poses a danger to human and animal health, and hence to global development. Deaths from drug-resistant illnesses are expected to

rise from 700,000 to 10 million per year, with costs estimated to reach $100 trillion by 2050 [18]. The Centers for Disease Control (CDC) in the United States declared in 2013 that the human race had entered the "post-antibiotic" age. Additionally, the rising prevalence of antimicrobial resistance traits in bacteria is an evolutionary reaction to the widespread use of antimicrobials [19]. The emergence of AMR in modern human civilization will increase the use of older, less efficient infection-control measures on an individual level. Such procedures, such as debridement, disinfection, amputation, and isolation, will result in a lengthier, more intrusive, and less effective treatment of infections [20].

The prescribing practices of antibiotics in our healthcare settings are mostly on empirical therapies (without culture sensitivity tests), which may be due to the either expensive or may be due to severity of diseases, for which the patient mostly needs urgent antimicrobial therapies. There is no proper method to identify or diagnose antibiotic sensitivity or responsiveness in healthcare settings. The only observations are from prescribing practices and attitude and the patient response to the respective antibiotics. In public sector hospitals, patients' antimicrobial therapies changed due to non-responsiveness to antibiotics, which seems to be AMR [17].

So the current study is also an approach to observe the clinical prescribing practices and attitude of one of the running antibiotics ampicillin and cloxacillin in public sector hospitals. Pediatric therapies start in most cases with these antibiotics and then changed due to non-responsiveness and sensitivities. This way, patient hospital stay (longevity) is prolonged, which may increase the hospital stay time, cost, and other associated consequences which may affect both patients and physicians.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

The current study of ampicillin and cloxacillin responsiveness in pediatric pneumonia was conducted in the paeds ward and medical A ward in a tertiary care public sector hospital of Mardan, KP, Pakistan. It is the 4th largest tertiary healthcare unit with 550 beds in Pakistan that has offering tertiary healthcare facilities to the local community and nearby cities, towns, and villages (Figure 1).

2.2 Data Collection

The two months' retrospective data were accessed from patient records (January-Feburaray, 2022). The patient's medical records, age, sex, dates

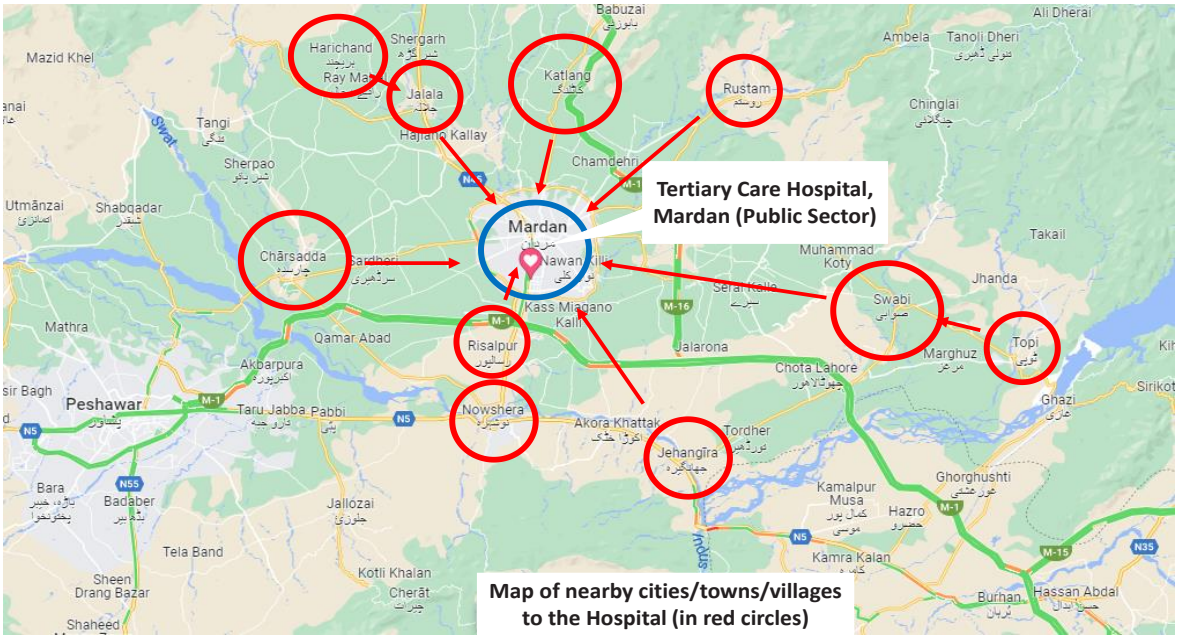

Fig. 1. Cities and districts within the vicinity of the tertiary care hospital, Mardan (copyright google map with modification)

of admission and discharge, medical history, presentation of signs and symptoms, and initial categorization of pneumonia during the hospital stay, treatment schedules, and hospital stay (longevity) were observed.

2.3 Inclusion/Exclusion criteria

All those patients (of all ages) who were diagnosed with pneumonia, and were under medication therapies, stayed for more than one day in the hospital ward, were included in the study. While patients who expired in the hospital or those with incomplete information were excluded from the studies.

2.4 Prescribing practices and WHO core indicators

Prescriptions are a legal document/consent between a physician and patients on medication management in a healthcare setting, on basis of which medications are administered by the pharmacist to the patients. In the current study, all prescription patterns in medical wards A and B in tertiary care hospitals, Mardan were evaluated for all those indicators that may assist in the rational use of medicines as well as the antibiotic prescribing attitude that comes under standard guideline procedures. Similarly, prescriptions writing was coordinated with the WHO core indicator utilized for each prescription, which includes the total number of items per prescription, drugs with generic names in percent, percent of prescriptions with antibiotics, injectable per encounters percentage of encounters, and EDL of 2020 was utilized. WHO baseline indicators standard guidelines for prescription writing were mentioned in Table 1, it should be noted, that WHO core indicators are recommended or proposed standard guidelines, they are not implemented by the drug regulatory authority of Pakistan (DRAP) or Pakistan medical and dental council (PMDC).

2.5 Hospital longevity and ampicillin/ cloxacillin responsiveness

Hospital stay and longevity of patients being affected by pneumonia were calculated from the date of admission and discharge of the patients. Where the ampicillin/cloxacillin responsiveness was observed from the antibiotic therapy from the patient history chart. During the medication schedules, antibiotics therapy was changed due to non-responsiveness and patient instability. As in the case of children, mostly empirical therapy was followed, no CSTs were conducted in most practices, as they need urgent treatment and CSTs took more than 72 hrs. Therefore, based on symptoms and lab findings, empirical therapy was started for proper treatment on physician directives.

2.6 Statistical analysis

Graphs were plotted and appropriate statistically significant differences were assessed by Student t-test and for multiple comparisons and co-relations using graph pad prism software 8.4.2 (679) version. The differences were significant statistically when * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$, **** $p < 0.0001$, where ns indicated non-significant.

Table 1. WHO core indicators standard values for prescribing practices/attitude.

WHO Core indicators	Standard values (recommended/proposed)
Total number of drugs per encounter	1.6-1.8 (~2)
Total number of Injectables (%)	13.4-24
Total number of Antibiotics (%)	20-26.8
Total number of drugs Prescribed on the generic name (%)	100
Total number of drugs from EDL (%)	100

3. RESULTS

3.1 Study area and locations

Mardan is one of the important and second largest cities of KP, while the 19th biggest city of Pakistan, which is located in the valley of Peshawar, has a population of 358, 604 inhabitants (2017 Census). Mardan is located at an altitude of 283 m and in the southwest of the district at 34°12′0 N 72°1′60 E. To the south, Risalpur, West Charsadda, Yar Hussain to the east, and Takhtbahi and many more districts in vicinities are shown in Figure 2. Where the tertiary care hospital is a 550-bed medical complex and teaching hospital that provides basic health to nearby cities, towns, and villages.

3.2 Patient demographics and locality

A total of n= 90, retrospective patient data were collected from both pediatric ward A and medical ward A (adults), within two months, Figure 2 and Figure 3 show gender-wise and age-wise information of all patient details collected respectively. The highest ratios of pneumonia were recorded among paeds (1-20 years) and adults (60-80 years).

3.3 Prescribing practices and WHO core indicators

Table 2 shows that the total number of drugs prescribed to the patients are n= 918 of which 370 (40.26 %) were prescribed to females and 548 (59.74 %) were prescribed to male patients. Figure 4 shows various dosage forms prescribed, among which injectables were prescribed in high percentages. Figure 5 shows the percentage of drugs per encounter (polypharmacy) in prescribing practices, whereas detail is given in Table 3.

3.4 Ampicillin/cloxacillin sensitivity and responsiveness in pneumonia patients

Table 4 shows the number of total drugs prescribed to pneumonia patients and their percentages, where Figure 6 shows, the number of patients and their hospital stay, while Figure 7 shows the hospital stay or longevity of patients using ampicillin/cloxacillin prescribing, its effects during the hospital stay and their responsiveness in pneumonia patients. Figure 8 shows the percentage of patients (longevity), who received ampicillin /cloxacillin therapy for pneumonia treatment during the hospital stay. It should be noted that a total of n=83 out of 90 pneumonia patients received ampicillin + cloxacillin therapy.

4. DISCUSSION

As per WHO core indicators findings, in this study, a total of n= 918 drugs were prescribed among all n=83 pneumonia patients, which makes an encounter of 10.21/ prescription, which is much higher than the recommended and proposed value of WHO core indicator (1.6–1.8). Though,

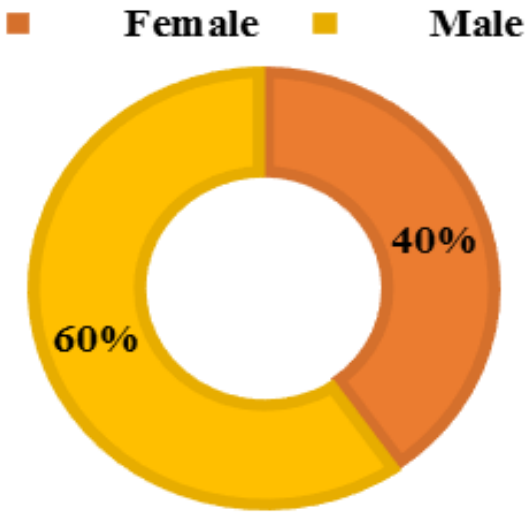

Fig. 2. Gender-wise pneumonia patient percentage collected

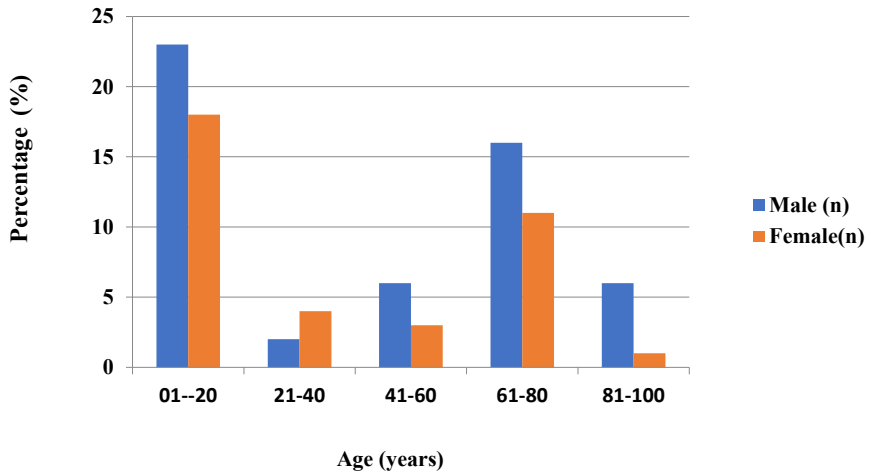

Fig. 3. Age wise distribution of patients in both pediatric and medical ward A.

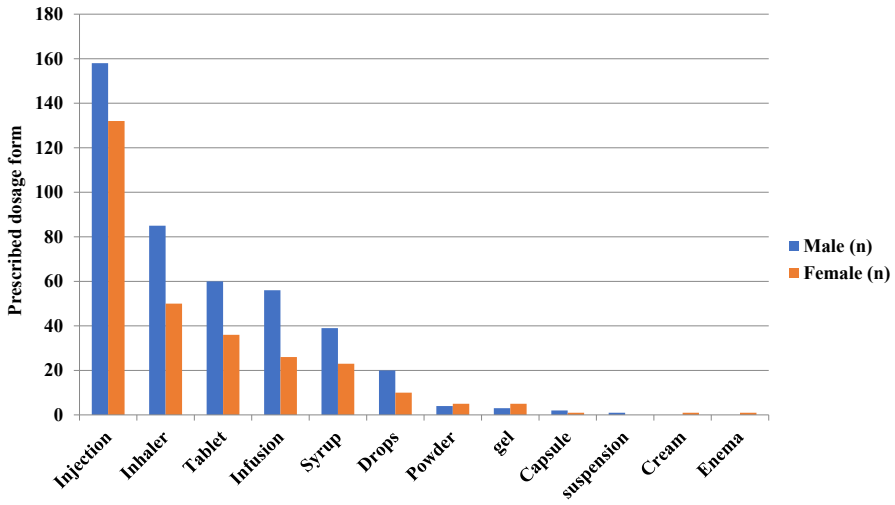

Fig. 4. Dosage form prescribed among the male and female pneumonia patients

Table 2. WHO Core indicator extracted from patient prescription in pediatric A and medical ward A (adults) of a public sector tertiary care hospital

WHO Core indicators			
WHO indicators	**Frequency (*n*)**	**Average number of drugs prescribed**	**Standard values recommended by WHO**
Total number of drugs per encounter	918	10.20	1.6-1.8 (~2)
Total number of Injectable (%)	288	31.37 %	13.4-24 %
Total number of Antibiotics (%)	205	22.33 %	20-26.8 %
Total number of drugs Prescribed on the generic name (%)	127	13.83 %	100 %
Total number of drugs from EDL (%)	898	97.82 %	100 %

*EDL: essential drug list

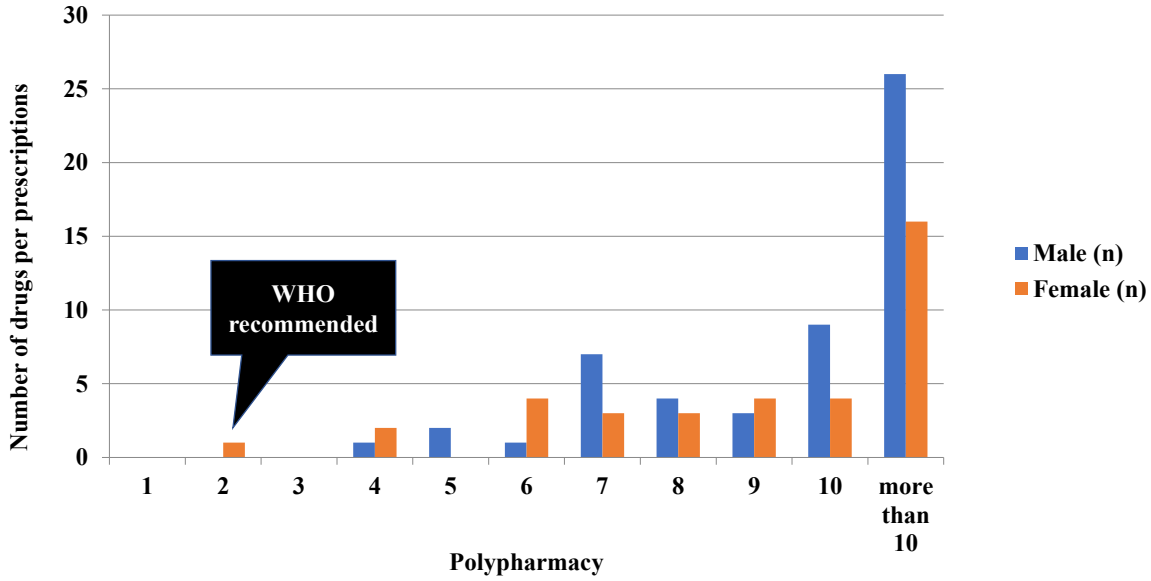

Fig. 5. Polypharmacy and number of drugs per prescription.

Table 3. Percentage of the class of antibiotics prescribed among pneumonia patients

Class of Drug	Male (n)	Female (n)	Total (*n*)	Percentage (%)
Other Antibiotics	42	33	75	36.58
Cephalosporin	44	31	75	36.58
Penicillin	**21**	**14**	**35**	**17.08**
Quinolones	8	4	12	5.86
Macrolide	4	2	6	2.92
Aminoglycoside	2	0	2	0.98
Total	121	84	205	100

Furosemide	8	0.87146
Zinc sulphate	13	1.416122
Miconazole	9	0.980392

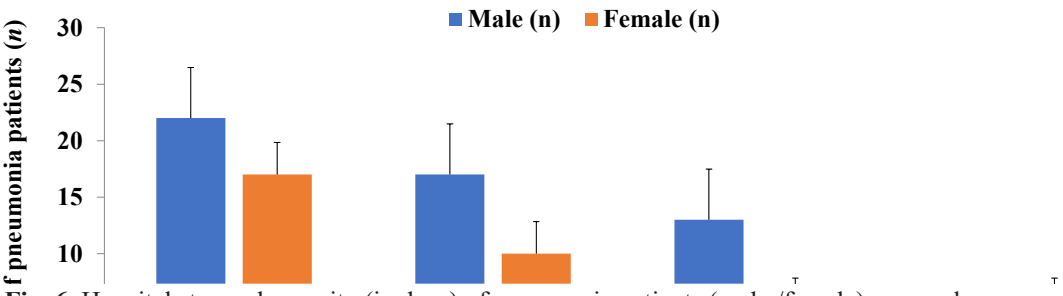

Fig. 6. Hospital stay or longevity (in days) of pneumonia patients (male /female), n=number

Table 4. Percentage of drugs prescribed to pneumonia patients

Prescribed medications	**Frequencies**	**Percentage**
Total number of Drugs prescribed in n=90 prescriptions	918	100%
Average no of Drugs/case	10.20	……
Ampicillin + Cloxacillin	**241**	26.25272
Paracetamol	148	16.122
Clarithromycin	40	4.357298
Cefotaxime	79	8.605664
Ceftriaxone	25	2.723312
Ceftazidime	22	2.396514
Cefoperazone +Sulbactam	26	2.832244
Ibuprofen	26	2.832244
Acefylline	15	1.633987
Amikacin	15	1.633987
Linezolid	57	6.20915
Dexamethasone	143	15.57734
Hydrocortisone	40	4.357298
Captopril	5	0.544662
Midazolam	6	0.653595
Furosemide	8	0.87146
Zinc sulphate	13	1.416122
Miconazole	9	0.980392

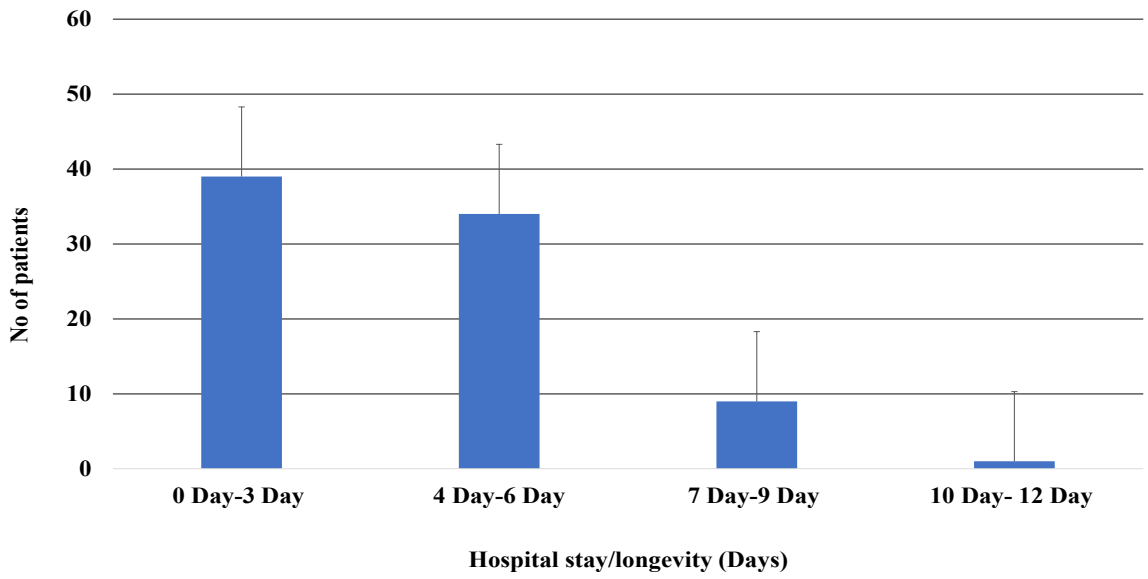

Fig. 7. Hospital longevity (days) among patient using ampicillin / cloxacillin and then therapy switched over to another antibiotic therapy.

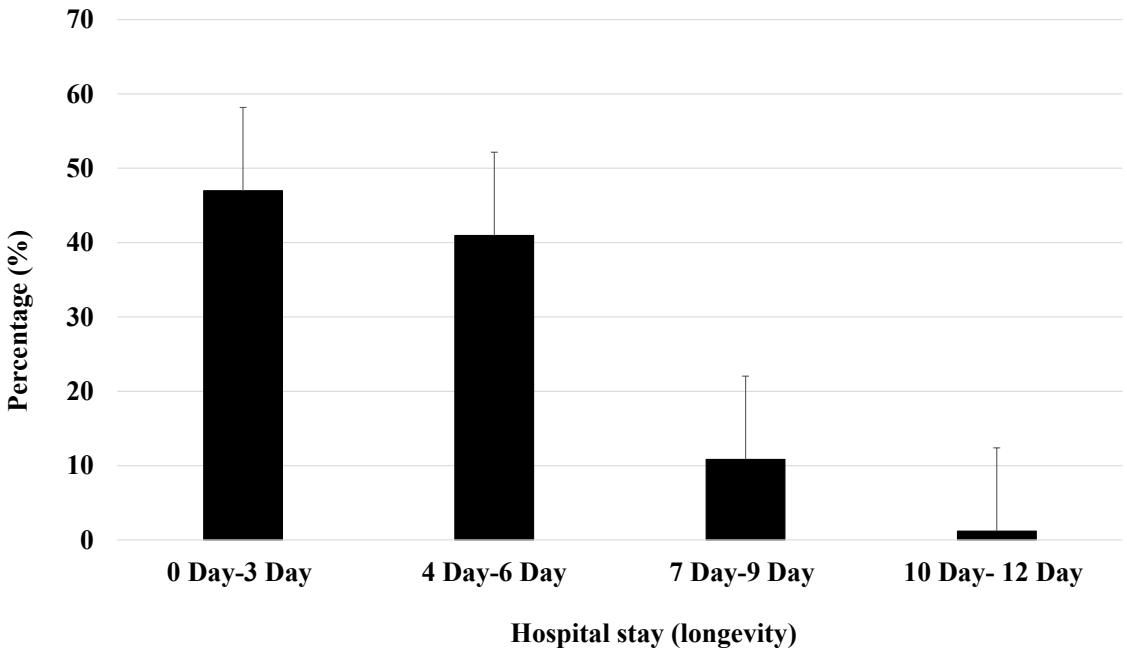

Fig. 8. Percentage of pneumonia patients receiving ampicillin /cloxacillin therapy and hospital stay (Note: *n*=83 pneumonia patients received ampicillin/ cloxacillin)

it's very common practice in Pakistan, where an average prescription may contain more than 5–7 drugs, which leads to polypharmacy or multidrug prescriptions. Polypharmacy may have serious consequences, such as enhancing the ADR, s drug interaction and decreasing the compliance rate in patients. Similarly, regarding the prescribing practices and attitude, the average no of antibiotics prescribed to the patients was 22.3 %, which is the same as that of WHO recommended value (20 - 26 %), and lower than 70 % in a study found in South West Ethiopia [24, 25].

According to WHO core indicators, antibiotics prescribing was 22.33 %, which is somewhat near the standard recommended guidelines (20 - 22.8 %). As, mostly, pneumonia patients are kept on injectable antibiotic therapies to achieve prompt therapeutic responses. Though higher injectables and antibiotic therapies are rational approaches, the main problem as to antimicrobial responsiveness and sensitivity, which may prolong our hospital stay [24, 26-29]. Here in our studies, regarding the antibiotics' responsiveness and hospital stay longevity, first evaluated the most highly prescribed antibiotics. In this regard, cephalosporins were prescribed to 36.58 % of pneumonia patients, whereas penicillin was prescribed to 17.08 %, which were mostly ampicillin and cloxacillin (combinations). Among the number of prescribed antibiotics, ampicillin/ cloxacillin (combinations) were highly prescribed (26.25 %) in pneumonia patients. Patients were initially kept on ampicillin/cloxacillin therapies and were mostly stabilized within three Days (n=39 patients), where n=34 patients recovered within six Days. While hospital stays responsiveness of patients n=9, longevity reached nine days while receiving ampicillin /cloxacillin therapy, whereas n=1 patients reached up to twelve days, while receiving the same therapy. So, patients receiving ampicillin /cloxacillin empirical therapies and associated hospital stay and longevity may be considered an indicator for AMR resistance, less responsiveness, and hospital longevity indicates weak responsiveness to the infections and may proceed for culture analysis. From the current findings, in pneumonia patients, it was observed 46.98 % of pneumonia patients (including both males and females), recovered within three days with empirical therapy of ampicillin /cloxacillin, while 40.96 % people show responsiveness within six days of their hospital stay, where 10.84 % patients, the hospital stay longevity increased up to nine days. Still, 1.2 % of the people's hospital stay increased up to 12 days. Further extensive studies should be carried out on its culture sensitivity tests

for sensitivity and responsiveness of ampicillin/ cloxacillin in both inpatients and outpatients.

5. CONCLUSION

From current findings, it can be concluded, that the responsiveness of ampicillin /cloxacillin combinations in reference to hospital stay and longevity is an alarming state in the existing therapy of pneumonia, especially in public sector hospitals in KP, Pakistan. Increasing hospital stay and longevity among patients may be an indication of less responsiveness and sensitivity, which may be due to AMR. Children and adults as well as both male and female genders are at equal risk of AMR, which needs further extensive research and proper evaluation for its control and prevalence. Secondly, hospital stay longevity also indicates the feeble and low responsiveness of antibiotics in hospital patients who are affected by bacterial infections. During their therapies, various antibiotics were changed, due to weak responsiveness to antibiotics. Therefore, keep in mind, all physicians and healthcare professionals should avoid empirical therapies, they should follow CSTs for sensitivity and resistance of most antibiotics and should also keep vigilant approaches for hospital stay and longevity, especially among pneumonia patients. The current, studies have limitations, as this was only confined to pneumonia, as well to a single public sector hospital, such studies should be extended to various bacterial infections as well to many more teaching hospitals and medical complexes in future endeavors.

6. ACKNOWLEDGEMENTS

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7. CONFLICT OF INTEREST

The authors declared no conflict of interest.

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