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ORIGINAL ARTICLE

Prevalence of Multi Drug Resistant Microbesisn Community Acquired Pneumonia Versus Hospital Acquired Pneumonia Among Pediatric Cardiac Patients

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ABSTRACT

Background: Pneumonia remains the leading infectious cause of death among children. Around 8,388 Egyptian children died every year due to pneumonia in the past 5 years. Pneumonia caused by multidrug-resistant organisms (MDROs) traditionally has been confined to the hospital setting, but the emergence of MDR bacteria that cause pneumonia in the community has created the need to identify risk factors for acquiring resistant pathogens by evaluating contacts of the patients with the healthcare environment

Methods: A cross-sectional study of 84 Egyptian cardiac paediatrics was designed, classified into two groups: Community Acquired Pneumonia (CAP) group: 73 cases and Hospital acquired pneumonia (HAP) group: 11 cases. Sputum samples were collected early in morning by sputum induction or cough swab technique, inoculated on blood agar, direct smear stained with Gram stain then incubated at 37 °C aerobically. The antimicrobial susceptibility was determined by the disk diffusion method

Results: Among CAP group, Klebsiella P. was the most common organism reported, it was isolated from 33 patients (45.2%) followed by Staph. Hominis 16.4%, then E. Coli 15%, then Pseudomonas 6.8%, then Acinetobacter and strept pneumonia 5.5%. Among HAP group, Klebsiella was also the most common organism accounting 42% of cases. It was mostly sensitive to Colistin and Amikacin. E. Coli was mostly sensitive to Amikacin, Tobramycin and Tigecycline. Pseudomonas was mostly sensitive to Colistin and aminoglycosides. Acinetobacter was mostly sensitive to Amikacin, Minocycline, Colistin. Strept. Pneumonia. was mostly sensitive to Vancomycin.

Conclusions: Resistance of pathogens to different antibiotics has increased with emergence of high percentage of MDROs. Amikacin, Colistin (not used in paediatrics), Tigecycline and Linezolid proved to be the most potent antibiotics against most of CAP and HAP, but restriction of their use is important to prevent emergence of resistant strains.

Keywords: Community acquired pneumonia; Hospital acquired pneumonia; ;Paediatric cardiac patients

INTRODUCTION

Pneumonia is a new lung infiltrates plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leucocytosis, and decline in oxygenation [1].

It is considered the leading infectious cause of death among paediatrics. Around 8,388 Egyptian children died every year due to pneumonia in the past five years. Mortality in childhood due to pneumonia is strongly linked to poverty-related factors such as under nutrition, lack of safe water and sanitation, indoor air pollution and inadequate access to health care [2].

Despite this, programs to fight childhood pneumonia remain critically underfunded. Estimates show that 1.3 million of childhood pneumonia deaths could be avoided if prevention and treatment efforts were implemented worldwide [3].

CAP is defined as an acute infection of the pulmonary parenchyma associated with an acute infiltrate on chest radiograph with two or

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Volume 28, Issue 3, May 2022, Page 479-488

more symptoms including fever (>38° C), rigors, sweats, new cough or change in colour of respiratory secretions, chest discomfort or dyspnoea [4].

Nosocomial pneumonia can include patients with HAP, Ventilator Acquired Pneumonia (VAP) and Health Care Associated Pneumonia (HCAP) [5].

HAP is pneumonia not incubated at the time of hospital admission and occurring 48 hours or more after admission [6].

VAP is pneumonia occurring >48 hours after endotracheal intubation [6].

HCAP includes any patient presenting with pneumonia with one of following features hospitalization for two or more days in an acute care facility within 90 days of infection, patients from a nursing home or long-term care facility, patient who attended a hospital or haemodialysis clinic and those who received intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection. These individuals were believed to be at an increased risk for infection with MDROs because of such contact [7].

The risk of infection with MDROs depends much more on specific risk factors of the given patient than on contact with various aspects of the healthcare system. Patients who had fulfilled the criteria for CAP shouldn`t be empirically treated with antibiotics to cover MDROs unless they have valid risk factors for acquiring MDROs [8].

AIM

Our study aimed at identifying the prevalence of MDROs in CAP versus HAP in paediatric cardiac patients.

METHODS

The present cross-sectional study was conducted at Paediatric Zagazig University Hospital; Faculty of Medicine, Egypt. A comprehensive sample formed of the all 84 cardiac patients admitted to Paediatric Zagazig University Hospital with CAP or developed HAP after 48 hours of hospitalization or after intubation during a period of six months from Jan to June, 2019, were included as cases and divided into two groups: CAP group: included 73 cases and HAP group: included 11 cases.

A written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Pneumonia was diagnosed by new onset of fever, cough, respiratory distress, leucocytosis, opacity in x-ray and positive sputum culture [1].

CAP was considered as acute infection of the pulmonary parenchyma associated with an acute infiltrate on chest radiograph with two or more symptoms including fever (>38° C), rigors, sweats, new cough or change in colour of respiratory secretions, chest discomfort or dyspnoea [4]. While HAP was pneumonia not incubated at the time of hospital admission and occurring 48 hours or more after admission [6].

Inclusion criteria: Patients admitted with CAP diagnosed 48 hours before hospitalization. Patients acquired pneumonia after 48 hours of hospitalization or after intubation.

Exclusion criteria: Patients with immunosuppressive therapy, patients with viral pneumonia, chronic lung disease, active neoplasms or active tuberculosis.

Intervention: All patients were subjected to history taking, including age, sex, residence, time of onset of complaint. Risk factors as hospitalization in previous 90 days, home infusion therapy in previous 30 days, chronic dialysis, previous intake of antibiotic (type of antibiotic and duration of intake).

Clinical examination to detect manifestations of pneumonia as fever, tachypnoea and respiratory distress. Auscultation of the chest to detect decreased breath sounds, bronchial breath sounds, crepitation and wheezing. Signs of complication as pneumothorax, pleural effusion, lung abscess and respiratory failure

Laboratory investigations include Sampling which was Blood sample for*:* Complete blood count (CBC) with differential, C-reactive protein **(**CRP).

Lower respiratory tract sample: (Sputum or endotracheal). Sputum samples were taken early in morning: Respiratory specimens were

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Volume 28, Issue 3, May 2022, Page 479-488

collected either by sputum induction or cough swab technique. Induced sputum samples were taken as previously described by [9]. Patients were pretreated with inhaled salbutamol delivered by a nebulizer device and then hypertonic saline 5.0% for 10 min. Sputum samples were then obtained by aspirating the nasopharynx through the nostrils with a disposable mucus extractor or by expectoration if the child was old enough to produce an adequate sputum sample. Cough swab was done by nebulization with normal saline first, and then, gag reflex was stimulated by irritation of uvula to initiate cough in the same time a sterile swab was put in front of the mouth droplets without touching the posterior pharynx [10].

All samples were transferred after collection to Medical Microbiology and Immunology Department of Zagazig University for further processing within one to two hours.

Microbiology work-up:

- Respiratory specimens were subjected to the following: 1. Inoculation on blood agar, heated blood agar, and MacConkey's agar media; 2. Direct smear staining with Gram stain for microscopic examination [10].
- All sputum cultures were screened for interpretability ;only those with >25 leukocytes and <10 epithelial cells/ low power field were selected. [10]
- Inoculated blood and MacConkey's agar plates were incubated at 37 °C aerobically while inoculated blood agar plates were incubated at CO2 10%. Isolates obtained from respiratory cultures were completely identified using standard techniques. [10]
- The antimicrobial susceptibility of those microbes was determined by the disk diffusion method [11].
- The following pathogens were considered MDROs on the basis of the knowledge available during the study period; extended spectrum β-lactamase-producing gram-negative Enterobacteriaceae, such as Klebsiella, E. coli, and Proteus spp.; Pseudomonas A. resistant to ceftazidime or carbapenems; other pan-resistant Enterobacteriaceae bacteria or those sensitive only to carbapenems; sulfonamide-resistant Stenotrophomonas spp.; Acinetobacter spp. resistant to ampicillin, ampicillin/sulbactam, or carbapenems; and vancomycin-resistant Enterococcus spp.
- Other pathogens were considered MDROs if they were found to be resistant to at least three of the following antibiotic classes: antipseudomonal cephalosporins/penicillin, macrolides, carbapenems, fluoroquinolones, and aminoglycosides [12].

4. Radiological investigations:

Chest x- rays and Echocardiography

Standard infection control measures in paediatric intensive care unit were ensured as Using a closed endotracheal tube suctioning system, changing close suctioning catheters only as needed, changing ventilator circuits only if damaged or soiled, change heat and moisture exchanger every 5-7 d and as clinically indicated, providing easy access to non-invasive ventilation equipment and institute protocols to promote use, using an early mobility protocol, performing hand hygiene, avoiding supine position or use of prophylactic systemic antimicrobials or nonessential tracheal suctioning and gastric over distention.

STATISTICAL ANALYSIS

Data were coded, entered and analysed using SPSS version 20 (SPSS Inc, USA). All numeric variables were expressed as mean standard deviation (SD). Tests of significance (Kruskal-Wallis, Wilcoxon's, Chi square, logistic regression analysis, and Spearman's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable. For all tests a probability (p) more than 0.05 was considered non-significant, less than 0.05 was considered significant and less than 0.001 was considered highly significant.

RESULTS

Eighty-four paediatric cardiac cases were included in our study, 73 cases of them were admitted with CAP and 11 cases developed HAP during their admition in the hospital. The demographic data and clinical presentation of all cases are summarised in table 1 and table 2 respectively. The

https://dx.doi.org/10.21608/zumj.2019.17780.1573
Volume 28, Issue 3, May 2022, Page 479-488

commonest CHD was combined VSD+PFO+PDA in 17/84 cases (20.2%) and pulmonary hypertension in 17/84cases (20.2%); ASD+VSD in 14/84 cases (16.6%) then cardiomyopathy in 9/84 cases (10.7%). Previous ventilation and hospitalization in previous 90 days increase the risk in HAP than CAP and it was statistically significant (P value <0.05). (figure 1). Concerning the previously taken antibiotics, there was a statistically significant difference between the both groups regarding previously taken Carbapenems, Vancomycin and BLBLIC, cephalosporins, Aminoglycosides, Macrolides and Piperacillin being higher in HAP than in CAP groups (P Value<0.05) (table 3). But regarding the MDROs, there was a statistically significant difference between CAP, HAP groups in E. coli and Staph. Hominis. (table 4). Bronchopneumonia was more common than lobar pneumonia in both groups and both of them were significantly higher in CAP than in HAP (P<0.05). There was a statistically significant difference between two groups regarding imaging data. (Increased bronchovascular marking and pleural effusion were significantly higher in HAP than CAP group while cardiomegaly was significantly higher in CAP than in HAP groups (table 5). The antibiotic activity against MDROs showed that the most sensitive antibiotic for Klebsiella p was Colistin sulphate in CAP group while in HAP group, there was Amikacin followed by Colistin but it was resistant to Cefepime (100%) in both CAP and HAP groups. E. coli was mostly sensitive to Amikacin, Tobramycin followed by Imipenem, Piperacillin in CAP group, while in HAP group it was sensitive to Tigecycline (100%). For Staph. Hominis we found that the most sensitive antibiotic in CAP group was Linezolid, Tetracycline (100%) followed by Moxifloxacin (90.9) but resistant to Erythromycin (83.4%) then Amikacin (76.7%) while in the single case of HAP group, it was sensitive to Tetracycline, Linezolid, Vancomycin, Cipro, Gentamycin and resistant to Ampicillin, Erythromycin. Concerning Pseudomonas A., the most sensitive antibiotic in CAP group was Colistin (80%) but resistant to Cefepime (80%) followed by Imipenem, Amikacin, Gentamicin, Piperacillin, Tobramycin, Ciprofloxacin (60%). Acinetobacter B. was mostly sensitive to Colistin and Amikacin (100%) and resistant to Piperacillin, Ciprofloxacin and Peflacin (100%) in CAP group but in HAP group, it was sensitive to Amikacin, Ampicillin Sulbactam and Cotrimoxazole, intermediately sensitive to Piperacillin but resistant to Imipenem, Ciprofloxacin and Gentamycin. Finally, for Streptococcus pneumonia the most sensitive antibiotic in CAP group was Vancomycin then Penicillin and Amikacin but resistant to Gentamycin and Cefepime (75%). There was a statistically significant difference regarding the fate of studied patients between CAP and HAP groups in favour of CAP group (figure 2).

Table (1): Demographic data of studied patients:

AGE(Mo.)	**CAP**		**HAP**		**T.test**	**P-value**
Mean +SD Range	20.95+ 7.9 (2-168)		22.68+7.6 3-144		-0.170	0.816
		CAP		HAP		P value
		N	%	N	%	X2
Sex	Female	24	32.9%	2	18.2%	0.490	0.272
	Male	49	67.1%	9	81.8%		
Residence	Urban	21	48.7%	4	36.4%	0.725	0.423

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Volume 28, Issue 3, May 2022, Page 479-488

AGE(Mo.)	CAP		HAP		T.test		P-value
	Rural	52	51.3%	7	63.6%		

Table (2): Comparison between CAP and HAP according to clinical presentation

	CAP		HAP		X2	P value
	N	%	N	%		
Fever	61	83.6%	11	100.0%	2.110	0.163
Cough	33	45.2%	5	45.5%	0.0023	0.618
Sputum production	33	45.2%	5	45.5%	0.0023	0.618
RD (grade)	46 19 5	65.7% 27.1% 7.1%	5 5 1	45.5% 45.5% 9.1	1.744	0.083
Wheezy chest	33	43.8	2	18.2	2.871	0.083
Toxemia	20	27.4%	11	100	21.641	0.01*
H. F	9	12.3%	9	81.2%	27.810	0.001*
Lymphadenopathy	0	0	1	9.1		
Chest pain	4	5.5%	5	45.5%	27.417	0.001*
CNS manifestations	5	6.8%	1	9.1%	31.361	0.581

Table (3): Comparison of the type of previous antibiotics intake between CAP and HAP

		CAP	HAP		
	N (73)	%	N (11)	%	P value
Cephalosporins	50	68.5%	11	100%	0.02*
Carbapenems	16	21.9%	5	45%	0.001 *
Vancomycin	7	9.6%	5	45%	0.002 *
BLBLIC	53	72.6%	11	100%	0.001*
Aminoglycosides	15	20.5%	3	27.3%	0.04*
Macrolide	8	10.9%	2	18.2%	0.03*
Piperacillin	3	4.1%	1	9.1%	0.01*

Table (4): Comparison of imaging data between CAP and HAP groups

	CAP N=73		HAP N=11		X2	P value
	N	%	N	%		
Broncho pneumonia	69	94.5%	9	81.8%	7.321	0.001*
Lobar Pneumonia	4	5.4%	2	18.2%		
Cardiomegaly	71	97.3%	9	81.8%	4.861	0.02*

https://dx.doi.org/10.21608/zumj.2019.17780.1573
Volume 28, Issue 3, May 2022, Page 479-488

	CAP N=73		HAP N=11		X2	P value
	N	%	N	%		
Increased Broncho vascular marking	1	1.4%	3	32.0%	6.093	0.02*
Pleural Effusion	1	1.4%	2	18.2%	7.425	0.03*
Pneumothorax	0	0%	1	9.1%		

*p<0.05 is statistically significant

Table (5): MDROs in CAP, HAP Groups

Organism	CAP(n=73)		HAP (n=11)			
	Number	%	Number	%	X2	P_value
Klebsiella Pneumonia	58	79.4	9	81.8	0.0176	0.674
E.Coli	31	42.4	1	9	27.01	0.001*
Staph. Hominis	29	39.7	1	9	25.02	0.001*
Pseudomonas aeruginosa	3	4.1	0	0		
Acinetobacter Baumannii	3	4.1	1	9	1.849	0.174
Streptococcus Pneumonia	5	6.8	0	0		

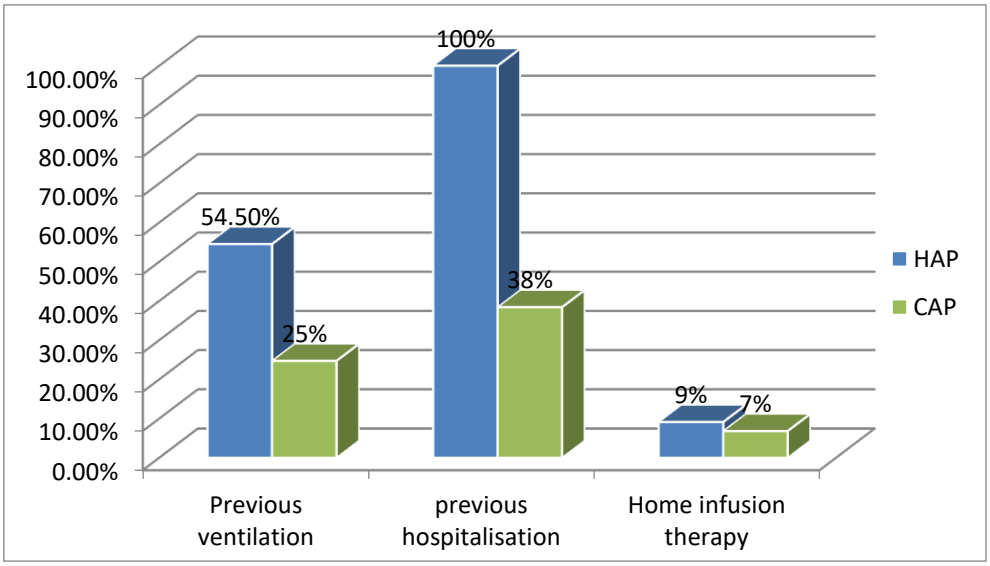

Figure 1: Comparison between HAP and CAP according to risk factor for pneumonia

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Volume 28, Issue 3, May 2022, Page 479-488

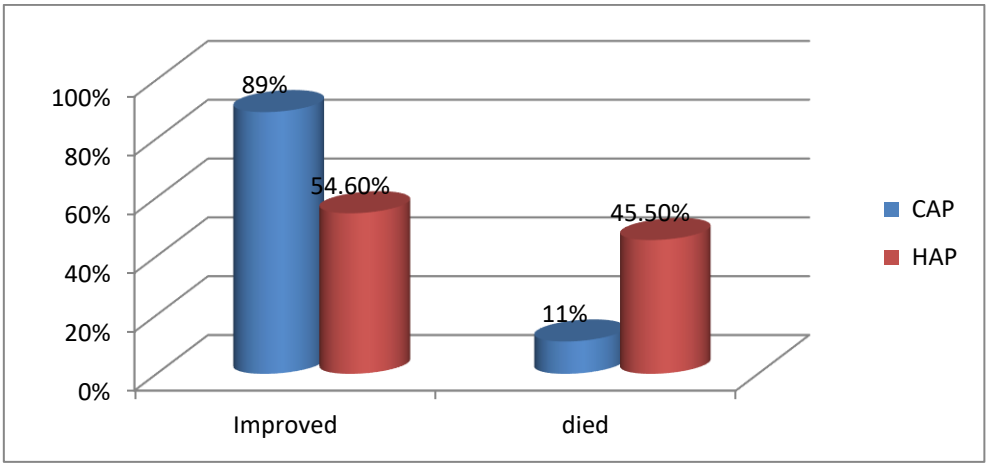

Fig (2): The fate of studied patients between HAP and CAP groups.

DISCUSSION

Over the last several decades, antibacterial drug use has become widespread with their misuse being an ever-increasing phenomenon. Consequently, antibacterial drugs have become less effective or even ineffective, resulting in a global health security emergency. The prevalence of MDROs varies widely among regions and countries. [13]

Concerning the demographic data mentioned in table (1), the higher incidence of males than females was supposed be due to the care of parents by male children and seeking medical advice for them more than female children especially in rural areas. In some of studies regarding the potential risk factors for development of CAP, the male sex was a risk factor for CAP or hospitalization for CAP [14].

The higher cases from rural areas than urban areas (table 1) may be due to the poor nutrition, bad hygiene, ignorance and low socio-economic level in general.

Congenital cardiac malformations (CCM) are the most frequent of all major birth defects. The incidence of CCM in the normal population is approximately 0.5–0.8% in live births [15].

Owayed et al., reported that children with CHD are at increased risk of recurrent chest infections because increased blood volume on the right side of the heart and increased pulmonary congestion [16].

Regarding the risk factors of pneumonia, the most common risk factor was previous intake of antibiotics. (BLBLIC) and 3rd generation cephalosporins were the most commonly used in both CAP and HAP groups which is explained by their easy use, availability in the pharmacy as their marketing is common in the public and most paediatricians prefer them as first line of treatment of pneumonia with low risk of development of complications, while in the HAP group, the 2nd most common used antibiotics were Carbapenems and vancomycin which is explained by limitation of their use to hospitals. Koh et al reported that patients with HAP were more likely to receive cloxacillin (P: 0.013), vancomycin (P: 0.025), carbapenems (P: 0.013) and Bactrim (P: 0.013) but patients with CAP were more likely to receive BLBLIC (P: 0.004) and macrolides (P: 0.012) [27].

Previous hospitalization increases the risk of development of nosocomial infection and bacterial resistance due to improper treatment of patients and mostly previous antibiotic intake. Our classification as a tertiary hospital increases the percentage of previous hospitalized patients. Previous hospitalization and antibiotic intake in the last 30days represent a risk factor of pneumonia [18]. Also, previous antibiotic use and nursing home were significant risk factors for developing MDR-HAP [19].

Among our studied patients; only 6 of them developed VAP and we fortunately encounter this low prevalence with appropriate implemented infection control measures . Maria et al., conducted a study to determine the

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Volume 28, Issue 3, May 2022, Page 479-488

prevalence, risk factors and outcomes associated with VAP in a European PICU and found (6.6%) of patients developed VAP [20].

Regarding clinical presentation, (table 2) there were significant difference between both groups regarding toxaemia, heart failure and chest pain being higher in HAP as mostly hospital acquired infection are usually caused by the most virulent organisms leading to more toxic manifestations.

Regarding the LAB data, Neutrophil count and CRP were significantly increased in HAP compared to CAP. The Mean+SD CRP in HAP group was 65+22.1 mg/L which was near to a study conducted in Zagazig university by Badr et al., who found the Mean+SD CRP in HAP 54.5+40.6 mg/L [21].

The radiological findings of our involved cases (table 4) came near to El Seify et al., who reported that, patchy consolidation was the predominant finding (81.1%), followed by lobar (15.6%) and interstitial (3.3%) patterns of consolidation [10].

We also found a significant cardiomegaly in CAP>HAP. Incident cardiac complications are common in patients with CAP and are related to increased short-term mortality. Nursing home residence, pre-existing cardiovascular disease, and pneumonia severity are associated with their occurrence [22].

Regarding sputum culture organisms in the current study, among the both CAP and HAP groups, Klebsiella P. was the most common organism (45% and 63%) in CAP and HAP groups respectively but Strept. pneumonia was the least common one (7% and 9%) in CAP and HAP respectively. Similarly, Wei et al., reported that Klebsiella P. has become the most common pathogenic bacterium accountable for nosocomial infections due to its high virulence factor and general occurrence of resistance to most antibiotics [23]. Also, Mansour et al., reported that the most frequent organisms were Klebsiella P. (40%), Acinetobacter B. (28%) but the least common isolates were streptococcus p. (8%) [24]. Also, in a study conducted by Tullu et al., the organisms commonly isolated were E. coli (34.4%), Klebsiella (30.2%), Pseudomonas (11.5%), and Acinetobacter (5.2%) [25]. These differences from our study are explained by the wide range of geographical endemic and clinical situations in which CAP and VAP develops also the exact prevalence of MDR organisms is variable between institutions and also within institutions [26].

The antibiotic activity against klebsiella P. showed that the most sensitive antibiotic was Colistin sulphate in CAP group while in HAP group, it was Amikacin followed by Colistin. But the use of polymyxins (colistin or polymyxin B) are not recommended according to the 2016 guidelines of the American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) [27]. Physicians hesitate to use colistin because of its increased risk of toxicity (mainly nephrotoxicity) and because of its restricted spectrum. Careful use of the antibiotic and avoidance of concomitant use of other nephrotoxic drugs will prevent undesirable effects on renal function, However Colistin application shows an upward tendency due to the emergence of MDR bacterial infections and VAP overseas [28].

The antibiotic activity against E. coli of the current study was near to Shah et al., who reported that E. coli highest sensitivity to Imipenem, moderate sensitivity to Tigecycline (70.83%), polymyxin B (68.75%), colistin (64.58%), Chloramphenicol and Amikacin (62.4%), Netilmicin (60.41%) [29].

The antibiotic activity against Staph Hominis of our study was similar to Priyamvada et al., who reported that their isolate was found to be sensitive to linezolid, gentamicin, clindamycin and vancomycin but resistant to erythromycin and trimethoprim/sulfamethoxazole, oxacillin [30].

Yayan et al., conducted a study to discuss antibiotic resistance of Pseudomonas A. in pneumonia at a single university hospital center in Germany over a 10-year period and showed no resistance to Colistin in either community-acquired or nosocomial-pneumonia; it was completely susceptible in both patient populations (100%). Also, it had a

high resistance to ciprofloxacin, levofloxacin, ceftazidime, piperacillin, imipenem, piperacillin and tazobactam, tobramycin, gentamicin, and meropenem [31]. These results are compatible with those of the current study as colistin was sensitive in 100% of cases.

The sensitivity of antibiotics against Acinetobacter B. of our study came near to a retrospective study on 60 strains of Acinetobacter B. by Huang et al., and showed that all MDR bacteria and reported that the lowest resistance rates of Acinetobacter B. were to Amikacin (68.3%), Imipenem (78.3%) and Tazobactam (78.3%) [28].

The fate of the our studied cases as mentioned in figure 2 comes in accordance with a study conducted at Ein Shams University by El Seify et al., who reported that in Egypt, it was estimated that 10% of children deaths below the age of 5 years is likely caused by pneumonia and other acute respiratory infections [10]. Also, Maartin et al., reported that the risk of death from VAP (between 0 and 70%) which has been primarily explained by differences in the patient population under study as well as by the absence of a reference standard diagnosis for VAP. [32]

CONCLUSIONS

Klebsiella P., Staph. Hominies and E. Coli were the most commonly isolated resistant strains from the clinical samples, followed by Pseudomonas A, Acinetobacter B. and Strept. Pneumonia.

Resistance of pathogens of lower respiratory tract infections to different antibiotics has increased with emergence of high percentage of multi-drug resistant strains.

Amikacin, Colistin (not used in paediatrics), Tigecycline and Linezolid proved to be the most potent antibiotics against most of CAP and HAP pneumonia, but restriction of their use is important to prevent emergence of resistant strains.

Cefepime, Penicillin, Ampicillin and erythromycin showed the highest resistance.

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