Pediatric Infectious Disease Society of the Philippines Journal
Vol 20 No 2 pp 16-25 July-December 2019
Dagani G, Yu D, Camomot S & Lopez EK. The Antibiogram of Isolated Pathogens from Tracheal Aspirate among Intubated Patients 2 Months – 5 Years Old with Very Severe Pneumonia Admitted in Pediatric Intensive Care Unit of a Tertiary Hospital in Cebu City from January 2013 to December 2016

ORIGINAL ARTICLE

THE ANTIBIOGRAM OF ISOLATED PATHOGENS FROM TRACHEAL ASPIRATE AMONG INTUBATED PATIENTS 2 MONTHS – 5 YEARS OLD WITH VERY SEVERE COMMUNITY-ACQUIRED PNEUMONIA ADMITTED IN PEDIATRIC INTENSIVE CARE UNIT OF A TERTIARY HOSPITAL IN CEBU CITY FROM 2013-2016

Glaiza S. Dagani, MD, DPPS*
Dahlia L. Yu, MD, FPPS, FPAPP*
Shanida L. Camomot, MD, FPPS, FPRA*
Elmer Kent A. Lopez, MD, FPPS, DPNSP, DPSN*

* Vicente Sotto Memorial Medical Center

Correspondence: Dr. Glaiza S. Dagani
Email: vsmmcpediatrics@gmail.com

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship

ABSTRACT

Objective: To determine the antibiogram of tracheal aspirate cultures (TACS) among intubated children aged 2 months to 5 years old with very severe community-acquired pneumonia (CAP).

Methodology: A retrospective chart review using total enumerative sampling.

Results: 66 out of the 343 patients had positive TACS. The top 5 most common isolates were *Klebsiella pneumoniae* (37.8%), *Pseudomonas aeruginosa* (25.7%), *Acinetobacter baumanii* (15.1%), *Enterobacter cloacae* (12.1%) and Methicillin Resistant Staphylococcus aureus (MRSA) (6%). The gram-negative isolates were highly sensitive to amikacin and carbapenems. Majority of these patients (92.42%) had history of Pentavalent immunization. Majority of patients who were TACS positive had history of antibiotic use prior to admission (92.42%), mostly second-generation cepahalosporin (cefuroxime, 32.42%). High rates of resistance to ampicillin and gentamicin were noted for patients with *Klebsiella pneumoniae* and *Enterobacter cloacae* isolates. Majority of patients with *Klebsiella pneumoniae, Acinetobacter baumanii* and MRSA expired.

Conclusion/Recommendation: Majority of those patients with positive isolates had MDR organisms thus for patients with very severe CAP who already received antibiotic as outpatient, broad spectrum antibiotics should be considered as empiric therapy and TACS be done on all patients with very severe CAP.

KEYWORDS: *Pneumonia very severe, Multi-drug resistant organisms, Tracheal aspirate culture*

INTRODUCTION

Pneumonia is the leading cause of death in children worldwide.[1] Each year > 2 million children younger than 5 years die of pneumonia, representing approximately 20% of all deaths in children within this age group.[2]

In the developed world, the annual incidence of pneumonia is approximately 3-4 cases per 100 children less than 5 years old.[2] In North America the annual incidence in children younger than 5 years of age is 34-40 cases per 1000. European figures taken from a study conducted in Finland are similar at 36/1000/year >5 years.[4]

According to World Health Organization (WHO), although pneumonia can often be treated and cured, most child deaths occur in the world's poorest regions with highest incidence in Sub-Saharan Africa and South Asia.

The Philippines is one of the 15 countries that together account for 75% of childhood pneumonia cases worldwide. In children age <5 years, pneumonia is the leading cause of mortality, with a mortality rate of 23.4 per 100,000 population recorded in 2009.[8]

Many pathogens are responsible for Community Acquired Pneumonia (CAP) in children, most prominently viruses and bacteria. Investigators have used a variety of laboratory tests to establish a microbial etiology of CAP having different sensitivity, specificity and positive and negative predictive values that are dependent on the prevalence of the pathogen at the time of testing. Tracheal aspirate for gram stain and culture are recommended as an additional diagnostic test for pediatric patients with severe or life-threatening CAP.[2]

Determining the antibiogram of tracheal aspirate cultures among intubated patients classified as having very severe pneumonia is important to improve the clinical management of cases and guiding therapeutic decisions.[6,7] This study is significant because it will provide information on the common organisms isolated and its sensitivity pattern to different antimicrobials. Likewise, this study determined resistance rates of isolated respiratory pathogens to the most widely used antimicrobials in this institution.

The goal of this study was to determine the frequency distribution and sensitivity pattern of isolated pathogens from tracheal aspirate cultures among intubated patients aged 2 months to 5 years old with very severe community-acquired pneumonia admitted in the Pediatric Intensive Care Unit (PICU) from January 2013- December 2016.

Specifically, to determine through Tracheal Aspiration Culture and Sensitivity (TACS) the top 5 most common pathogens and their antimicrobial sensitivity and to determine the clinical profile of these patients as to:

- history of Hemophilus influenzae b (Hib) vaccination (a component of Pentavalent vaccine)
- outcome
- history of antibiotic use prior to admission

METHODOLOGY

A. Study Design

This was a retrospective study wherein medical charts of all intubated patients aged 2 months–5 years with very severe CAP admitted in the Pediatric Intensive Care Unit (PICU) of a Tertiary Hospital in Cebu City from January 2013-December 2016 were reviewed.

B. Study Population/ Sampling Technique

Purposive sampling employing total enumerative was done on all intubated patients aged 2 months – 5 years of age with very severe pneumonia who fulfilled following criteria:

INCLUSION CRITERIA

- All intubated patients aged 2 months – 5 years old with very severe CAP as a primary diagnosis and admitted direct to PICU
- Patients who are admitted and intubated not more than 3 days after admission so as to rule out possibility of a hospital-acquired pneumonia

EXCLUSION CRITERIA

- All intubated patients aged 2 months – 5 years old wherein PCAP is not the primary reason for intubation
- Those with co-morbidities i.e. cardiac anomalies, neurologic abnormalities
- Intubated patients admitted at the wards

C. Study Setting

The study was conducted at a Tertiary Hospital in Cebu City where retrieval and review of charts were done at the Medical Records Section and Microbiology Laboratory Department.

Review of the PICU census and Medical Records showed that the total intubated children aged 2 months to 5 years due to very severe CAP during the study period was 341. Out of these 341 patients, 243 (71.26%) patients had TACS taken less than 72 hours after admission only 66 patients (19.35%) had positive TACS results and were enrolled in study.

E. Data Analysis

The top 5 most common pathogens and their antimicrobial sensitivity were expressed thru descriptive statistics using percentage.

F. Ethical Consideration

An approval was obtained from the Technical and Ethical Review Board. Anonymity and confidentiality were maintained throughout the study period through assignment of coded numbers. The data and information gathered were kept by the primary author in a password protected file where only the primary investigator can gain access to. This study was self-funded and there was no conflict of interest from this study.

RESULTS

The total intubated children aged 2 months to 5 years due to very severe CAP during the study period was 341. Out of these 341 patients, 243 (71.26%) patients had TACS taken less than 72 hours and 66 patients (19.35%) had positive TACS results (see table 1). The most common isolated bacterial pathogen was *Klebsiella pneumoniae* followed by *Pseudomonas aeruginosa.*

Table 1. Distribution of the Tracheal Aspirate Pathogens (n= 66)

Tracheal Aspirate Growth	Pathogen	No.	%
1	*Klebsiella pneumoniae*	25	37.8%
2	*Pseudomonas aeruginosa*	17	25.7%
3	*Acinetobacter baumanii*	10	15.1%
4	*Enterobacter cloacae*	8	12.1%
5	*Methicillin Resistant Staphylococcus aureus (MRSA)*	4	6%
6	*Acinetobacter lwoffi*	1	1.5%
7	*Haemophilus influenzae*	1	1.5%

Antimicrobial Pattern

Klebsiella pneumoniae isolates were highly resistant to cefuroxime, ampicillin and ceftriaxone. Sensitivity to carbapenems and 4th generation cephalosporin was high while sensitivity to aminoglycoside was variable. Figure 1.

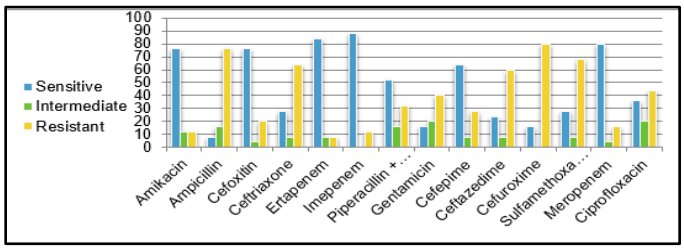

Figure 1. Percent Sensitivity and Resistance of *Klebsiella pneumoniae*

Pseudomonas aeruginosa were highly sensitive to ceftazidime at 94.1%, it also showed good sensitivity to piperacillin-tazobactam, 4th generation cephalosporin, ciprofloxacin, amikacin and carbapenems. Figure 2.

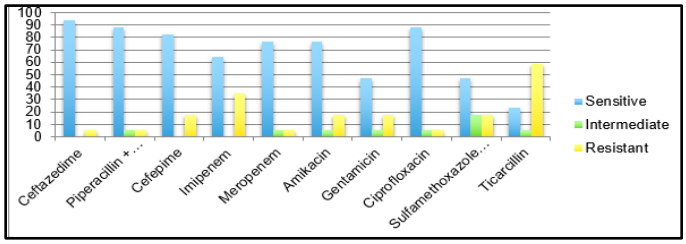

Figure 2. Percent Sensitivity and Resistance of *Pseudomonas aeruginosa*

Acinetobacter baumanii isolates were highly sensitive to amikacin and colistin. Other antimicrobials used for Acinetobacter such as carbapenems, cefepime, piperacillin-tazobactam had sensitivity rates ranging from 40-60%. This isolate showed high resistance rate to gentamicin, also an aminoglycoside. Figure 3.

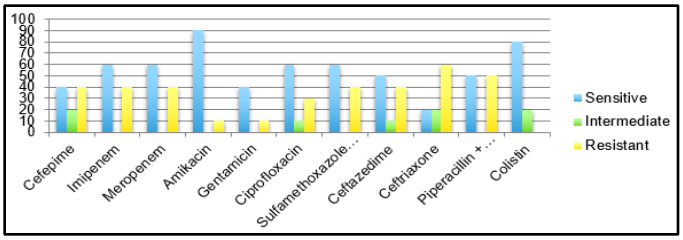

Figure 3. Percent Sensitivity and Resistance of *Acinetobacter baumanii*

Enterobacter cloacae were highly resistant to ampicillin, cefoxitin, cefuroxime and ceftriaxone. Carbapenems and aminoglycosides showed high coverage of this organism.

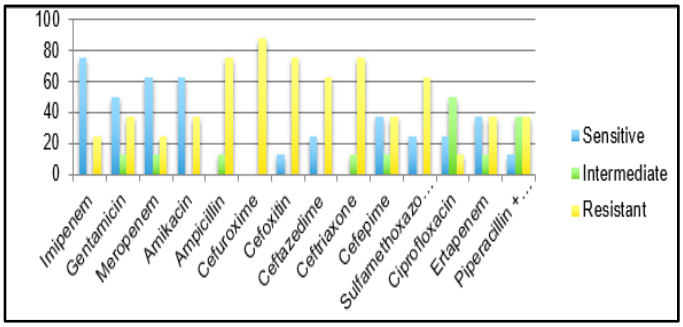

Figure 4. Percent Sensitivity and Resistance of *Enterobacter cloacae*

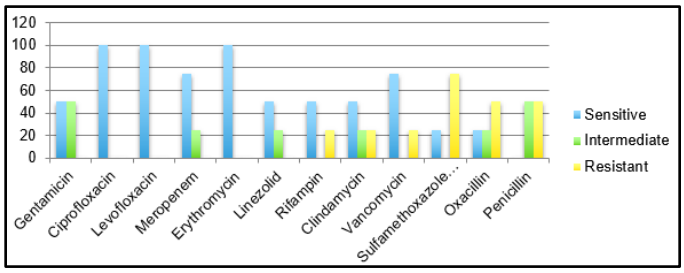

Figure 5. Percent Sensitivity and Resistance of MRSA

History of Immunization

Immunization is one of the factors that affect the etiology of a certain disease. Out of 66 patients with positive TACS, only 4 (6.06%) patients did not receive the Pentavalent vaccine as shown in figure 6. Of these 4 patients, 1 (6%) patient has positive TACS of *Haemophilus influenzae type b.*

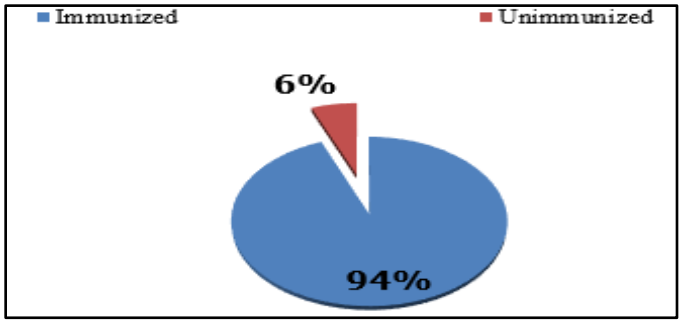

Figure 6. *Haemophilus influenzae b* (Hib) Immunization history of patients with positive TACS (n= 66)

Outcome

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death. As shown below, majority of patients with *Acinetobacter baumanii*, MRSA and *Klebsiella pneumoniae* died.

Table 2. Outcome of patients in relation to the isolated pathogens

Organism	Alive		Died	
	No.	%	No.	%
Acinetobacter baumanii (N= 10)	2	20%	8	80%
MRSA (N=4%)	1	25%	3	75%
Klebsiela pneumoniae (N= 25)	12	48%	13	52%
Pseudomonas aeruginosa (N=17)	9	53%	8	47%
Enterobacter cloacae (N = 8)	5	62%	3	38%

History of Antibiotic Use

Of the 66 patients with positive TACS, there were 61 (92.42%) patients who had previous history of antibiotic use prior to admission. Majority of the antibiotics given to the patients were cefuroxime, followed by amoxicillin and cefixime.

Table 3. History of Antibiotic used (n=61)

Name of antibiotics	Frequency
Cefuroxime	21 (34.42 %)
Amoxicillin	18 (29.50%)
Cefixime	7 (11.47%)
Clarithromycin	6 (9.83%)
Co amoxiclav	4 (6.55%)
Cefalexin	3 (4.91%)
Cefaclor	2 (3.27%)
TOTAL	61 (100%)

DISCUSSION

Acute respiratory infections namely pneumonia cause up to 5 million deaths annually among children less than 5 years old in developing nations. Of the estimated total of 12.9 million deaths globally in 1990 in children under 5 years of age, over 3.6 million were attributed to acute respiratory infections mostly due to pneumonia. This represents 28% of all deaths in young children and places pneumonia as the largest single cause of childhood mortality.[3] In the Philippines, more than 2 million children each year die due to pneumonia.[10] Pneumonia is defined by World Health Organization (WHO) as the presence of tachypnoea for which there is no apparent cause. Tachypnoea means respiratory rates above the following for age: at age 2-11 months, >50/min; age 1year–5 years >40/min; >5 years >20/min.[2,5] Severe pneumonia is defined as cough and tachypnoea plus one of the following:

chest indrawing, nasal flaring or grunting. Very severe pneumonia is defined as cough, tachypnoea plus one of the following: cyanosis, severe respiratory distress, inability to drink or vomiting everything, or lethargy/ unconsciousness/ convulsions. [2]

Etiologic agents of pneumonia vary depending on the age groups. Pneumonia can be due viruses, bacteria or fungi. Bacterial pathogens in newborns are Group B Streptococcus, *Escherichia coli, Klebsiella* species, and Enterobacteriaceae. For age 1-3 months, the most common pathogen is *Chlamydia trachomatis*. For preschool age, the following pathogens cause pneumonia: *Streptococcus pneumoniae, Haemophilus influenzae type b*, and *Staphylococcus aureus*. Less common pathogens for pre-schoolers are Group A Streptococcus, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.[1] The identification of the common pathogens causing severe morbidity and mortality as well as their sensitivity patterns is of utmost importance in order to guide the physicians on proper antibiotic use.

Community Acquired–Lower Respiratory Tract Infections (CA-LRTIs) are becoming difficult to manage. These difficulties are related to the greatly increased emergence of resistance to the most widely used antibiotics against some of the bacterial pathogens involved in the development of the disease.[18]

This study gathered 66 (19.35%) positive TACS samples among 243 (71.26%). In this study, the top 5 most common pathogens isolates were mostly gram-negative organisms like *Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Enterobacter cloacae* and with one gram-positive organism namely the Methicillin Resistant *Staphylococcus aureus*. These findings were similar to those reported in 2016 ARSP wherein it stated that the top 3 most common pathogens isolated in respiratory specimens were *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumanii.*[12] Similar pathogens were also reported in a study of Antibiotic Susceptibility Pattern in ICU at Philippine General Hospital, 2009 – 2013 and VSMMC Antimicrobial Susceptibility Pattern for both pediatric and adult patients, 2015.[24] These pathogens were also observed in mechanically ventilated children aged 0-59 months with Community Acquired Pneumonia admitted in PICU at Dhaka Hospital wherein forty-four of the 60 isolates were gram negative, in which 23% were *Klebsiella* species, 18% were *Escherichia coli*, 13 were *Acineto*bacter species and 4% were *Pseudomonas* species.[21] The pathogens isolated in this study are common hospital acquired pathogens and should rarely be found in these age groups. These results were not similar with various studies worldwide that showed *Streptococcus pneumoniae* to be the most common bacterial agent in children with pneumonia. Some possible explanation for this is that pneumococcal conjugate vaccine is part of the expanded program of immunization (EPI) vaccines being given in our local health center to this age group. Another is the widespread use of antibiotics that may have had an effect in the positivity of culture results especially for *Streptococcus pneumoniae* and lastly, it is important to note that majority of them didn't have any growth on TACS. Although included patients were those with tracheal aspirate done immediately after intubation, at most within 3 days and the duration time from admission was 72 hours, to exclude possibility of a hospital acquired infection or ventilator-associated pneumonia, most of the isolates were gram-negative organisms.

Antibiotic resistance is a worldwide problem, and unwise use of antibiotics has been recognized as a key contributor to the increasing rates of resistance. Antibiotic resistance refers specifically to the resistance to antibiotics that occurs in common bacteria that cause infections. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death.

A journal published on June 2003 in Malawi Medical Journal entitled Antibiotic Resistance Bacteria – An emerging Public Health Problem, stated the factors that favor the spread of antimicrobial resistance are as follows: general overuse of antibiotics, misuse of antibiotics by physician, misuse by unskilled practitioners and general public, poor quality antibiotics and increase in international travel[11]

In a study done in Dongguan, China from hospitalized children (0-5 years old) with Community Acquired Lower Respiratory Tract Infections (CA-LRTIs), the resistance rate of *Klebsiella pneumoniae* to ampicillin was 100% and co-trimoxazole at 75%.[18] Our results showed lower resistance level to ampicillin (76%), co- trimoxazole (68%) and gentamicin (40%). Cefuroxime showed the highest resistance rate at 80% in this study. This institution follows the WHO guidelines in treating pneumonia and the recommended treatment for pneumonia very severe according to WHO are ampicillin and gentamicin[14]. Based on the result of this study, there was a high resistance rate to ampicillin and gentamicin among the most commonly isolated pathogens in our institution. This result should be taken into account in updating the guideline on the treatment of very severe pneumonia in this institution. Although again it is important to note too that less than 20% of the patients had positive TACS isolate and majority didn't grow anything on TACS. Cefuroxime is one of the most widely prescribed antibiotics in the outpatient setting. This antimicrobial had high resistance rates to the commonly isolated pathogens. The threat of antimicrobial resistance is growing at an alarming rate and the situation is perhaps aggravated in developing countries due to gross abuse in the use of antimicrobials. It is well known that any use of antimicrobials however appropriate and justified, contributes to the development of resistance, but widespread unnecessary and excessive use makes the situation worse.[15] A study done by Cheol-In Kang et al, found that the recent use of cephalosporins appeared to be a risk factor for extended-spectrum cephalosporin (ESC) resistance in *K. pneumoniae* bacteremia.[17]

The emergence of carbapenem-resistant *Pseudomonas aeruginosa* has been an increasing problem in many parts of the world.[18] The use of prior antibiotic treatment was recognized as the only risk factor associated with CAP caused by multidrug resistant *P. aeruginosa*.[20] The resistance level of *P. aeruginosa* to imipenem is 35.2% but lower in meropenem (5.8%) in this study. Ceftazidime which has a good anti-Pseudomonal activity has a low resistance rate at 5.8% which was much lower compared to the result done in Dongguan, China wherein the resistance of *Pseudomonas aeruginosa* to ceftazidime was 13.61 and 30.99% in a separate study done in children 1-10 years old with lower respiratory tract infection in Nepal.[19]

Acinetobacter baumanii have become resistant to many classes of antibiotics.[10,16] In this study we noted that there was already an increasing rate of carbapenem resistance at forty percent and this reduces the existing therapeutic option. However, colistin as one of the choices in treating the Multidrug-resistant *Acinetobacter baumanii*, have the highest sensitivity rate of 90%. Although in this Institution, colistin is seldom used due to unavailability of this medication.

Community Acquired Lower Respiratory Tract Infections caused by *Enterobacter cloacae* has become a major worldwide problem. In a study done in patients under 5 years old with Community acquired Pneumonia admitted in Yulin Hospital, China, of the 759 samples tested, 177 strains were gram negative bacteria. The positive detection rate for *Enterobacter cloacae* was 8.45% and the isolates were completely resistant to amoxicillin and cefazolin at 100%, were resistant to ampicillin up to 96%, but had 100% sensitivity rate to levofloxacin. In our study, the highest resistance rate was to cefuroxime at 87.5% and ampicillin, ceftriaxone and

cefoxitin at 75%. This is alarming as these drugs are the first-line antibiotics we use for CAP. This resistance may be due to the production of constitutive AmpC B-lactamase enzyme by *E. cloacae* that exhibits a high frequency of enzymatic resistance to broad-spectrum cephalosporins.[22]

MRSA isolates were quite few but noteworthy is that out of the 4 patients with MRSA isolate, 3 of them expired and worrisome is the resistance rates noted to clindamycin and vancomycin, the drugs being given to MRSA.

While antibiotics are used for treatment, Immunization is the primary mode of prevention of infectious diseases. Prior immunization may reduce severity of disease, provide protection against shedding of pathogens and even raise the threshold load of pathogens required for infection.[15] In this study, out of 66 patients with positive TACS, only 4 (6.06%) patients did not receive the Pentavalent vaccine, wherein *Haemophilus influenzae type b* is included. Of these 4 patients, 1 patient has positive TACS to *Haemophilus influenzae type b*. Through this, we can appreciate the protective impact of immunizations received by the patients. Despite availability of vaccines, we still don't get 100% immunization rate in the intended population. [15]

Infection due to *Streptococcus pneumoniae* is a leading cause of morbidity and mortality in younger children, especially in developing countries. In this study, due to the limitation of a retrospective chart review the history of pneumococcal vaccination was not included as most of the charts didn't provide this information. It would have been an important finding if indeed we were not able to isolate any Streptococcus pneumoniae because of high immunization coverage for PCV.

Majority of patients with *Klebsiella pneumoniae, Acinetobacter baumanii* and MRSA expired with the following rate 52%, 80%, 75% respectively. The very high mortality rates is alarming considering that these patients come in with community-acquired pneumonia. *Acinetobacter baumanii* is recognized to be among the most difficult antimicrobial-resistant gram-negative bacilli to treat. This organism tends to occur in immunosuppressed patients and has the ability to survive under a wide range of environmental conditions and thus greatly limits the therapeutic options for patients who are infected with this organism.[10] A study done by Wah-Shing et al entitled Fulminant Community Acquired *Acinetobacter baumanii* Pneumonia as a Distinct Clinical Syndrome, the Community Acquired Pneumonia *A. baumanii* appears to be a unique clinical entity with a high incidence of bacteremia, ARDS, DIC and death when compared to Hospital Acquired Pneumonia *A. baumanii*.[16]

The results of this study highlight the varying levels of drug resistance amongst pathogens isolated in children with very severe pneumonia, and the need to control the increasing resistant strains before it reaches the alarming levels in this region. Of those with positive TACS and supposedly having CAP, the organisms isolated were more of the gram-negative organisms commonly seen in hospitalized patients. Rational antibiotic use in and out of the hospital cannot be overemphasized.

RECOMMENDATIONS

This study is limited by its retrospective and descriptive design. Thus, it is recommended that a prospective experimental study be conducted to collect a more robust data on various risk factors like previous antibiotic administration, immunosuppression, malnutrition, exposure to smoking etc that might affect the bacterial etiology of CAP and control for variables like receipt of vaccination.

For patients with very severe CAP who already received antibiotic as outpatient, the clinician should consider starting broader spectrum antibiotics and ensure that TACS be done as the possibility of having a MDR organism is there. The presence of an organism in gram staining, the result of which is obtained earlier than TACS can alert a physician to possibly start a broader spectrum

antibiotic since those with isolates mostly had MDR organisms. Prompt institution or shifting to an appropriate antibiotic is likewise recommended once results of TACS are available.

The researcher recommends strengthening the Antibiotic Stewardship in this institution if possible, to include the OPD in the hope of decreasing the incidence of multidrug resistant organisms.

The result of this study can be taken into consideration in the revision of the treatment protocols in very severe cases of pneumonia admitted in PICU of this hospital.

REFERENCES

1. Center for disease control and prevention. Pneumonia. [Online]. Available from: https://www.cdc.gov/pneumonia/index.html. [Accessed December 2017]
2. Bennett, et al, N.J. What is included in the PIDS and the IDSA guidelines for the management of community-acquired pneumonia (CAP) in infants and children older than 3 months?. [Online]. Available from:https://www.medscape.com/answers/967822-23630/what-is-included-in-the-pids-and-the-idsa-guidelines-for-the-management-of-community-acquired-pneumonia-cap-in-infants-and-children-older-than-3-months [Accessed January 2019]
3. Lakhanpaul, M, Atkinson, M, Stephenson, T. Community acquired pneumonia in children: a clinical update. BMJ Journal. 2004;89(2): 29-34
4 Harris, Michael & Clark, Julia & Coote, Nicky & Fletcher, Penny & Harnden, Anthony & McKean, Michael & Thomson, Anne. (2011). British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax. 66 Suppl 2. ii1-23. 10.1136/thoraxjnl-2011-200598.
5. Philippine Academy of Pediatric Pulmonologists, Inc. PAPP PERSPECTIVE 3rd PAPP Update [2016] in the Evaluation and Management of Pediatric Community-acquired Pneumonia 2016 PAPP Task Force on pCAP. (3rd ed.). Philippines: 2016.
6. Philippine Academy of Pediatric Pulmonologists, Inc. Update in the Evaluation and Management of Pediatric Community-acquired Pneumonia 2008 PAPP Task Force on pCAP. (1st ed.). Philippines: 2008.
7 World health organization. Focus on Pneumonia. [Online]. Available from: http://www.wpro.who.int/philippines/typhoon_haiyan/media/Pneumonia.pdf?ua%20=%201 [Accessed 30 November 2017]
8 Pneumonia: Tops Causes Of Death Among Pinoy Children Retrieved From: http://www.interaksyon.com/article/24063/pneumonia-tops-causes-of-death-among- pinoy-children [Accessed 24 September 2015]
9 Perez , F, Hujer, A.&.K, Decker, B, Rather, P, Bonomo, R. The Global Challenge of Multidrug Resistant (MDR) Acinetobacter baumannii. Antimicrobial agents and chemotherapy. 2007;51(10): 3471-3484
10 Komolafe OO. Antibiotic resistance in bacteria - an emerging public health problem. *Malawi Med J*. 2003 Jun;15(2):63-7. doi: 10.4314/mmj.v15i2.10780. PMID: 27528961; PMCID: PMC3345436.
11 Antimicrobial Resistance Surveillance Reference Laboratory. Antimicrobial Resistance Surveillance Program in Philippines. 2016 Data Summary Report.pp.2,22
12 Garcia, E, Makalinaw , S, Manipon, M.L.B. . Prevalence Of Healthcare-Associated Infections Among The Pediatric Patients Admitted At Philippine General Hospital From The Years 2011-2014. Pediatric Infectious Diseases Society of the Philippines Journal. 2015;16(1): 12-20.
13 World Health Organization. Hospital Care For Children. Guidelines for the Management of Common Childhood Illnesses, 2nd edition.p80-90
14 Ayukekbong, J, Ntemgwa, M, Atabe, A. The Threat of Antimicrobial Resistance in Developing Countries: Causes and Control Strategies. Antimicrobial Resistance Infection Control. 2017;6(47)
15 Leung, W.S, Chu, C.M, Tsang, K.Y, Lo, F.H.&.K.F, Ho, P.L. Fulminant Community-Acquired Acinetobacter baumannii Pneumonia as a Distinct Clinical Syndrome. Antimicrobial Resistance Infection Control. 2017;129(1): 2006
16 Kang CI, Kim SH, Bang JW, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. Community-acquired versus nosocomial Klebsiella pneumoniae bacteremia: clinical features, treatment outcomes, and clinical implication of antimicrobial resistance. *J Korean Med Sci*. 2006 Oct;21(5
17 He et al. Antimicrobial Resistance in Bacterial Pathogens among hospitalized Children with Community Acquired Lower respiratory Tract Infections in Dongguan, China (2011- 2016).BMC Infectious Diseases (2017)17:614

18 Salman Khan et.al., Bacteria Etiologic Agents causing Lower Respiratory Tract Infections and their Resistance Patterns. Iran Biomed J. 2015;19(4):240-246

19 Martin-loeches, C, Garcia-Vidal, C, San Jose, A, Torres, A. Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns. Int J Mol Sci. 2016;17(12)

20 Shahunja K.M. et al. Bacterial Isolates from Tracheal Aspirates and their Anti- Microbial Susceptibility in Mechanical –Ventilates Children with Pneumonia Admitted to an Urban Critical Care Ward. Bangladesh Crit Care J September 2014; 2 (2): 60-64

21 Davin-Regli A, Pagès JM. Enterobacter aerogenes and Enterobacter cloacae; versatile bacterial pathogens confronting antibiotic treatment. *Front Microbiol*. 2015 May 18;6:392. doi: 10.3389/fmicb.2015.00392. PMID: 26042091; PMCID: PMC4435039.

22 Mohammod JC, Tebruegge M, La Vincente S, Graham S, Duke T.Pneumonia in Severely Malnourished Children in Developing Countries – Mortality risk, Etiology and Validity of World Health Organization Clinical Signs: A Systematic Review. Tropical Medicine and International Health (2009) 14(10):1173-1189

23 Vicente Sotto Memorial Medical Center. Antimicrobial Susceptibility Pattern. VSMMC ICC; 2015