An observational study of antibiotic treatment in paediatric patients suffering from LRTI and Pneumonia in a tertiary care hospital

Subhradipta Bhattacharyya¹*, Manjushree Mohanty²

INTRODUCTION

Broad spectrum antimicrobials and improved supportive treatments are of immense importance in present healthcare system to cure devastating diseases like sepsis, meningitis or pneumonia in paediatric patients.¹

As resistance to commonly used and in general cheaper antibiotics has become more frequent, newer broad-spectrum antibiotics or combination therapy often are required. The expensive newer drugs have harmful effects on protective microflora and may even be too toxic or less effective.² Development of new antibacterial agents with activity against multi-drug resistant bacteria is therefore considered as a critical public health need.

One of the effective measures to circumvent growing resistance is to use the most appropriate narrower spectrum agent instead of broad-spectrum treatment when information on anti-microbial susceptibilities is available.

The antibiotic resistance profiles of MDR bacteria like GNB vary by species, geographic location, regional antimicrobial use, and hospital site (like, ICU Vs wards).³
Therefore extensive up to date data regarding antibiotic prescribing, sensitivity and resistance pattern are of utmost importance.

Keeping these things in mind, the present thesis work was started to evaluate patients suffering from pneumonia and LRTI admitted in Paediatric ward, NICU (Neonatal Intensive Care Unit) and PICU (Paediatric Intensive Care Unit).

Relatively fewer studies were conducted in Indian subcontinent in these fields of research till date. The present work was conducted to study antibiotic use and sensitivity-resistance pattern of infecting microbes.

METHODS

From September 2012 to February 2014 patients admitted in paediatric ward, PICU (Paediatric intensive care unit) and NICU (Neonatal intensive care unit) with provisional diagnosis of respiratory tract infection were evaluated.

The present study is a non-interventional, uncontrolled, open chart, pharmaco-epidemiological and pharmacovigilant study. It includes total 97 patients admitted in paediatric ward, NICU and PICU from September 2012 to February 2014.

The research protocol was approved by Institutional Ethical Committee, KIMS. Data were collected from case sheets of patients from the ward as well as Medical Record and Data section of the Indoor patients receiving antibiotics along with supportive medications with provisional or confirmed systemic infection of LRTI or pneumonia.

The primary efficacy parameters were respiratory rate, temperature, diastolic pressure, cough and rales, hypoxia and chest pain, SpO$_2$, FiO$_2$, sputum and consolidation. Secondary efficacy parameters like radiological assessment (CXR, USG chest, CT chest) or hematology (PBS or blood culture etc.) investigations.$^4$ Data were collected on each parameters at the beginning, mid of treatment and end of treatment to evaluate the improvement of the patients (like resolution of pneumonic consolidation in chest X-ray or normalisation of blood counts etc.).$^5$

Outdoor patients, patients with severe renal impairment or hepatic failure or patients who died were excluded from this study.

RESULTS

Patient demographic profile

The particulars of demographic profile of the admitted patients can be depicted in Table 1.

Table 1: Patient demographic profile.

| Total no of patients 97 with M:F ratio 4:1 |   |
|------------------------------------------|---|
| Male                                     | 78|
| Female                                   | 19|
| Mean age                                 | 6.2±4.8(sd) Days|
| Mean body wt.                            | 18.9±13.8 (sd) kg.|
| Mean days of hospitalization             | 8.95±4.8(sd) Days|

Among the 97 RTI cases 62 patients had pneumonia and LRTI in 35 patients.

The pneumonia patients can be classified into Moderate to Severe pneumonia (15.3%) Severe pneumonia (35.8%) and Very Severe pneumonia (12.5%).

50 patients out of 62 of pneumonia remained uncomplicated during the treatment and released after remission within short periods. 12 patients (12.4%) had complications of pneumonia, including parapneumonic effusions, necrotizing pneumonia and pneumothorax along with bacteremia or sepsis (Among them 4 patients had PTB), respiratory failure, septic shock, and multi-organ dysfunction.$^1$ (Figure 1) 3 patients received ionotropes with severe septic shock.

![Figure 1: Complications of pneumonia and LRTI.](image)

35 patients evaluated for LRTI, among them 5 patients were of very severe infection and received three antibiotics.

Pulmonary tuberculosis (4 patients), bronchial asthma, systemic infection like meningitis, AGE, UTI etc. were present in significant number of patients.

Therefore antibiotics were given intravenously at first according to severity (two antibiotic or three antibiotic combinations) and then switched to oral route when severity was decreased.

Antibiotics were prescribed in combination each and every time, all the patients received multiple antibiotics in combination, a single antibiotic was never found to be prescribed in this patients.$^6$

Drug combinations can be categorized as below mention:
Two β-lactam ± β-LI for moderate infection (Pneumonia/ LRTI):
Two different drugs (like amoxicillin with cefuroxime) were used in 6 (6.2%) patients of moderate pneumonia/LRTI.

Two drug combination for severe infection

Two drug combinations were used in severe infections. These are:

a) Extended spectrum cephalosporin+ aminoglycoside = 25.7%
b) Amino-penicillin+ aminoglycoside= 15.5%
c) Piperacillin + aminoglycoside= 15%
d) Macrolide + β-lactam= 11.4% (Figure 2).

Figure 2: Two drug combination for severe infection.

Three drug combination for very severe infection

Three different drug combinations were used in severe infections. These are:

a) Macrolide (azithromycin/ clarithromycin)+ cephalosporin+ aminoglycoside= 10 (10.1%) patients
b) Ceftriaxone± sul+ amikacin + anti-mrsa/ carbapenem= 5 (5.1%) patients
c) Amoxicillin+ aminoglycoside+ anti-mrsa/ carbapenem= 4 (4.1) patients
d) Piperacillin + aminoglycoside+ anti mrsa/ carbapenem = 3 (3.1) patients
e) β-lactam+ anti-mrsa+ metrogyl/ ofloxacin= 3 (3.1%) patients (Figure 3).

Figure 3: Three drug combination for very severe infection.

For very severe infection with/ without sepsis was treated with three or more than three drug combinations. These are:

- Ceftriaxone± sulbactam (59%) was most frequently used followed by Cefuroxime (13%), Cefoperazone± sulbactam (11%), and Cefixime (9.7%), Cefotaxime (3.3%), Cefadroxil (2.2%) and Cefotaxime (1.2%) (Figure 4).
- Ceftriaxone was used in a dose of 40-50 mg/kg I.V B.D for most of the patients though in a few patients of mild infection the drug was used in a dose of 20-25mg/kg B.D.
- Cefuroxime was used in a dose of 10-13 mg/kg BD in Tablet or Syrup form for severe pneumonia. In few cases lower doses 5 mg/kg BD in tablet form was used in RTI.
- Cefoperazone ± sulbactum was used in dose of 45 mg/kg BD I.V in most patients. Higher dose like 75 mg/kg BD I.V was used in a few patients.
- Cefixime was used in a dose of 2.5-5.5 mg/kg BD orally.
- Cefotaxime±Tazobactum was used in a dose of 33-50 mg/kg BD I.V.
- Cefadroxil was used in a dose of 50 mg/kg I.V BD.

International Journal of Basic & Clinical Pharmacology | February 2017 | Vol 6 | Issue 2 | Page 325
Percentage of Use

**Figure 4: % Use of different cephalosporins.**
- Aminoglycoside (28.8%) by i.v route was second most frequently used antibiotic. Aminoglycoside was used on average 7 days. The drug was given twice daily mostly, once daily in a few cases.
- Among the Aminoglycosides, Amikacin was used most of the time followed by Gentamicin and Netilmicin.
- Amikacin was used in a dose of 7-10 mg/kg I.V BD in most patients or 15 mg/kg I.V OD in few patients. For severe infections higher doses like 15-17 mg/kg I.V.BD was used.
- Gentamicin was used in the dose of 2-3 mg/kg I.V BD or 4 mg/kg I.V OD.
- Netilmicin was used in a dose of 2.5-5 mg/kg I.V BD/OD in most of the patients.

**Figure 5: % Use of different penicillins.**
- In 21% patients Penicillin+βLI were administered, firstly by i.v. route followed by oral route. In most cases penicillin was used in combination with Aminoglycosides.
- Amoxicillin+ clavulanic acid (use-9.6% and failure rate-7.1%) was used in dose of 35-50 mg/kg I.V BD. Lower doses like 15-20 mg/kg I.V BD was given in a few patients.
- Piperacillin+ tazobactum (use-7.5% and failure rate-14.8%) was second most frequently used antibiotic, was used in dose of 70-110 mg/kg IV TDS.
- Amoxicillin ± cloxacillin, Ampicillin ± cloxacillins were used each in 1.7% patients.
- Amoxicillin+ Cloxacillin was used in dose of 50-100 mg/kg I.V TDS. Ampicillin was used in dose of 30-35 mg/kg I.V QDS. Ampicillin + Cloxacillin was used in dose of 45 mg/kg I.V TDS (Figure 5).
- Macrolides were used in 8% of RTI patients. Azithromycin was used in 17 patients and Clarithromycin was used in 4 patients in oral route.
- Azithromycin was used orally in Tablet or Syrup form in a dose of 10-20 mg/kg OD.
- Clarithromycin was used also both in Tablet and Syrup form in a dose of 10 mg/kg BD.
- ANTI-MRSA agents like Linezolid was used in 10(10.3%) patients. For severe infections the dose was 10 mg/kg I.V TDS. The dose was 5 mg/kg BD in less severe infection.
- Meropenem was used in 3.1% patients in a dose of 25-50 mg/kg I.V BD/TDS.
- Fluoroquinolones was not used in considerable percentage of cases.

**Use of antifungal drugs:** Used in 1% patients.

**DISCUSSION**
- After evaluation of resistance-sensitivity of isolated bacteria from different samples high resistance was observed against Penicillin±βLI and Ceftriaxone±βLI (both gram +ve and -ve).
- InGram negative isolates significant sensitivity was observed to Meropenem (72%) and Aminoglycoside (65%). 100% sensitivity was observed to Vancomycin, Linezolid, Tigecycline and Quinpristin-dalfopristin in gram +ve isolates.
- This resistance-sensitivity pattern was reflected in mode of usage of the antibiotics. As an individual drug the Cephalosporins were stopped six times. Penicillin was changed in 7 patients. Aminoglycoside was changed five times whereas Piperacillin+tazobactam were stopped four times. Meropenem was stopped once.
- In few patients Piperacillin was replaced by Ceftriaxone.
- Two drug combinations have been used in severe infection. At first empirically two drug combination were started. Afterwards, according to c/s report in few cases or when adequate response was not seen, alteration in the regimen was done. Ceftriaxone±βLI/ Cefoperazone±βLI with Amikacin/Gentamicin have been used in most of the patients (25.7%). Piperacillin±βLI and Amoxi/ampicillin±βLI along with aminoglycoside have been used in 15% patinetns. The antimicrobial spectrum of cefotaxime and ceftriaxone with or without aminoglycosides is excellent for the treatment of community-acquired pneumonia, i.e., that caused by...
some pneumococci (achievable serum concentrations exceed MICs for many or most penicillin-resistant isolates), *H. influenzae*, or *S. aureus*, *Klebsiella* etc.  

- Piperacillin± tazobactum extends the spectrum of ampicillin to include most strains of *P. aeruginosa*, *Enterobacteriaceae*, many *Bacteroides* spp., and *E. faecalis*.

- The antimicrobial spectrum of aminoglycoside mostly against aerobic gram negative bacilli, limited activity against gram positive and inactive against anaerobic infections. In combination with a cell wall–active agent, such as a penicillin or vancomycin, an aminoglycoside produces a synergistic bactericidal effect in vitro against *enterococci*, *streptococci*, and *staphylococci*.  

- Therefore, on addition of Amikacin/Gentamicin with various β-lactum severe pneumonia/LRTI were effectively treated.

- Three drug combinations were used in very severe pneumonia. In most of these cases either Linezolid or Azithromycin were added to the two-drug regimen.

- Macrolide (azithromycin/ Clarithromycin) were used in combination with Cephalosporin+ Aminoglycoside in 10 patients of very severe pneumonia.

- Cephalosporin+ Aminoglycoside+ anti-MRSA/ carbapenem was used in 5 (5.1%) patients, Amoxicillin+ aminoglycoside+ anti-MRSA/ carbapenem was used in 4 cases and Piperacillin+ aminoglycoside+ anti MRSA/ carbapenem was used in 3 patients.

- Azithromycin/ Clarithromycin was used in combination with β-lactams from the beginning of treatment in few patients to cover atypical pathogens. In many patients Macrolides were added on the time of discharge from hospital for suspected residual pneumonitis.

- Anti-MRSA like Linezolid was used as second line drug added to previous regimen to control infection in six patients. Among them 3 patients were having ATT and developed septic shock with longer duration of hospitalization.

- It was used in IV route B.D in 6-7 patients at first and then in oral form when the patient was stabilized.

- In case of 2-3 patients were given linezolid empirically from the beginning who were suffering from very severe pneumonia along with other serious infection like meningitis and were in stage of septic shock at the time of admission.  

- Meropenem was used as second line drug in case of 3 (3.1%) patients to treat multi-drug resistant gram negative bacilli like *Pseudomonas, Klebsiella, Enterobacter* or *E. coli*. However, two of them were suspected to have PTB.  

- Meropenem and linezolid were both used in one patient.

- In order to evaluate the comparative efficacy between two combination of three drugs (β-Lactam+ BLI + Aminoglycoside + Macrolide or anti-MRSA) data of two groups of patients were compared. Mean duration of hospitalization (taken as efficacy parameter) of a group of patients (n=6) with very severe pneumonia having Linezolid/ Carbapenem along with β-Lactam+ BLI+ Aminoglycoside as empirical therapy with sterile B/S was found 10.6 days ± 2.73 (sd).

- Second group of patients (n=10) with very severe pneumonia having Macrolide along with β-Lactam+ BLI + Aminoglycoside as empirical therapy with sterile B/S was found to have mean duration of hospitalization 13.6 days± 4.24 (sd).

- It was found that after comparing between these two values of mean duration of hospitalization, addition of macrolides to β-Lactam+ BLI + Aminoglycoside has been emerged as equally efficacious as linezolid/ Carbapenem (p value >0.05, student's t-Test).

- Macrolides having wide gram negative/ gram positive/ atypicals coverage along with immuno modulation action responsible for their synergistic action in combination have strengthened the treatment.  

**CONCLUSION**

In the research work it was tried to depict the prescribing pattern of antimicrobials in a systematic way. In spite of high resistance observed among isolated bacteria, 3rd generation Cephalosporin with aminoglycoside were the mainstay of treatment. Linezolid/ Meropenem and Macrolides augmented the recovery when added to empirical therapy in patients of very severe infection with sepsis.

**Funding: No funding sources**

**Conflict of interest: None declared**

**Ethical approval: The study was approved by the Institutional Ethics Committee**

**REFERENCES**

1. Theodore C, Sandora J Thomas. Community acquired pneumonia. Nelson Textbook of Pediatrics. Vol.2, Part XVII-XXIII, 19th Edn; 2008.

2. Harrison; Principle of Internal Medicine. 18th Edition.

3. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clinical Infectious Diseases. 2011;53:25-76.

4. Shah SS, Dugan MH, Bell LM, et al. Blood cultures in the emergency department evaluation of childhood pneumonia. Pediatr Infect Dis J. 2011;30:475-79.
5. Virkki R, Juven T, Mertsola J, et al. Radiographic follow-up of pneumonia in children. Pediatr Pulmonol. 2005;40:7-223.
6. Combination antibiotic therapy for community-acquired pneumonia Jesus Caballero* and Jordi Rello Caballero and Rello Annals of Intensive Care. 2011;1:48. http://www.annalsofintensivecare.com/content/1/1/48
7. Goodman Gillman’s Manual of Pharmacology and Therapeutics; 12th edition. Chapter 44.
8. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J. 2009;33:153-9.
9. Rubinstein E, Kollef MH, Nathwani D. Pneumonia Caused by Methicillin-Resistant Staphylococcus aureus Clinical Infectious Diseases. 2008;46:S378-85.
10. Barton-Forbes M, Hawkes M, Moore D, et al. Guidelines for the prevention and management of community associated methicillin resistant Staphylococcus aureus (CA-MRSA): a perspective for Canadian health care practitioners. Can J Infect Dis Med Microbiol. 2006;17(C):1B-24B.
11. Sally A, Kate G. Clinical update on Linezolid in the treatment of gram positive infections. Infection and Drug Resistance. 2012;5:87-102
12. Tamma PD, Cosgrove SE, Maragakis LL. Combination Therapy for Treatment of Infections with Gram-Negative Bacteria Clinical Microbiology Reviews. 2012;25:3:450-70.
13. Goodman and Gilman’s the Pharmacological Basis of Therapeutics by Goodman, USA; 1985.

Cite this article as: Bhattacharyya S, Mohanty M. An observational study of antibiotic treatment in paediatric patients suffering from LRTI and Pneumonia in a tertiary care hospital. Int J Basic Clin Pharmacol 2017;6:323-8.