ISSN 2394–806X (Print), ISSN 2454-5139 (Electronic)
IJHRMLP, Vol: 04 No: 02 July, 2018
Printed in India

ORIGINAL PAPER

Adult community acquired pneumonia in a tertiary care teaching hospital of Assam: a hospital based study

Kalita Deepjyoti[1], Deka Sangeeta[2], Hazarika NK[3]

***Received** on May 31st, 2018; **editorial approval** on June 12, 2018*

ABSTRACT

Introduction: *Adult Community-acquired pneumonia(CAP) is a common problem-afflicting world over. Delay in isolation of pathogens, emergence of newer agent and rapidly evolving drug resistance globally are making the effective management of CAP, especially in developing countries, very challenging. Empirical therapy, based on knowledge of local pathogen profile and drug resistance pattern is the mainstay. This study was a preliminary work in local CAP subjects. Aim: To profile a pathogen list as well as to study the pattern of resistance in important pathogens.* ***Methods****:Semi quantitative culture method was employed on sputum sample followed by drug sensitivity testing based on disc diffusion technique. Biphasic PPLO media was employed with a view to isolate Mycoplasma pneumoniae as well. Epidemiological data were analysed in the backdrop of lab data generated.* ***Results****:Adult CAP was found to be more common in middle-aged to elderly male with Strpetococcus pneumoniae and Klebsiella pneumoniae being the major pathogens followed by other common. There were no Haemophilus influenzae isolate. Penicillin resistance in Pneumococci was high and drug resistance in other agents were found to be of moderate to high level.* ***Conclusion*** *:Drug resistance is a menace and it needs to be contained urgently. A larger study with more intensive experimental component is the need of the hour.*

Keywords: *CAP, Adult CAP, Drug resistance, DRSP, Respiratory pathogens, LRTI, Community-acquired LRTI, Mycoplasma culture*

INTRODUCTION

Despite considerable improvement and extensive use of variety of diagnostic tests, responsible pathogens remain uncertain in as many as 50% of Community-acquired pneumonia (CAP) cases.[1,2] Even in identifiable cases, few days are consumed before identification of agents from sputum or blood samples. Due to this uncertainty the antibiotic treatment for CAP empirically relies on epidemiological data on causative pathogens in a particular geographic area.[3] Also the relative frequency of aetiological agents varies among different geographical area.4 Thus it is crucial and necessary that large tertiary care centres determinethe peculiar microbial pattern prevalent in their own CAP patients.[4]

Common identifiable isolates of CAP can vary with factors like geographical locations, age of the patients, clinical profile of the patients, co-morbid conditions etc. Frequently isolated agents include Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Pseudomonas, Gram-negative-enteric bacilli (GNEB) like Klebsiella, E coli etc, atypical agents like Mycoplasma pneumoniae etc.[1]

Emergence of high rates of antimicrobial resistance has complicated the empiric management of CAP patients. Drug Resistance S. pneumoniae (DRSP) has been the focus of numerous recent studies, due to its high virulence and extraordinary rise in antibiotic resistance level in relatively short period.[1]

Some studies carried out in India indicate existence and increasing threat of drug resistant strains of pneumococci, especially in respiratory tract infections.[5,6] Unfortunately, to the best of our knowledge, so far there is no published study on CAP or CAP associated DRSP or other drug resistance

Address for correspondence:
[1]Associate Professor of Microbiology
AIIMS Rishikesh
Mobile: 7351962771
Email: deep.micro@aiimsrishikesh.edu.in
[2]Assistant Professor of Microbiology (Corresponding Author)
F. A. A. Medical College, Barpeta
Email: drsangeeta2009@gmail.com
Mobile: 9864606609
[3]Prof (Rtd) & Head, Microbiology, Gauhati Medical College

Cite this article as: *Kalita Deepjyoti, Deka Sangeeta, Hazarika NK. Adult community-acquired pneumonia in a tertiary care teaching hospital of Assam: a hospital based study. Int J Health Res Medico Leg Prae 2018 July;4(2):76-80. DOI 10.31741/ijhrmlp.v4.i2.2018.18*

from North Eastern part of India.

Objective

Identification of common agents of our CAP subjects and to study the pattern of drug resistant isolates.

METHODS

About 94 clinically and/or radiologically diagnosed (as per definition of ATS) subjects of CAP visiting Gauhati Medical College during October 2005 to September 2006 were included in this study.[1] Inclusion criteria were - age >15 years, New/progressive pulmonary infiltrate on a chest X-ray plus finding of at least one of the major criteria (cough/ sputum production/temperature > 37.8°C) or, at least 2 of the minor criteria (pleuritic chest pain/dyspnea/altered mental status/pulmonary consolidation/ WBC count of > 12,000 cells/ l).[3] Exclusion criteria were - previous hospitalization in last 3 weeks/An alternative diagnosis like pulmonary-emboli/ pulmonary-edema/malignancy etc. during follow-up,/ Tuberculosis/ lung cancer/ severe immunosuppression, HIV infection/solid-organ or BM transplantation, systemic corticosteroid treatment etc.[3]

Subjects were categorized into 3 categories - Mild (outdoor treated), Moderate (Indoor admitted) and Severe (ICU admitted).[1]

Sputum samples were collected as per standard guidelines, preferably before antibiotic administration.[7] Semiquantitative culture technique was adopted.[7] Suitability of Sputum samples (for culture) was checked as per Murray-Washington criteria defined elsewhere.[8] Selected samples were homogenized by use of dithiothreitol (Mucasol) and mechanical method (for Mycoplasma).[9]

Homogenized samples were subjected to culture by standard semi quantitative culture method.[7] 0.005 ml each of this (representing 0.000025 ml of original unhomogenized sputum sample) was inoculated into 4 different culture media {Blood agar, MacConkey agar, Chocolate agar and CVNG agar (Crystal violet, Nalidixic acid, gentamicin blood agar - selective for pneumococci)}. Blood agar and MacConkey agar plates were incubated aerobically at 37o C overnight while CVNG agar (with Optochin disc) and Chocolate agar were incubated with 5-10% CO2 under similar environment.[7,10] After incubation, presence of 25 or more colonies of the same agent (in any plate) implied presence of 106 or more of this agent per ml of original sputum, indirectly suggesting a pathogenic role. Any growth lesser than this was dis-regarded as commensal/contaminant.[7] For Mycoplasma, immediately after collection, sputum was homogenized with needle & syringe and about 0.1ml was inoculated into the biphasic media (with the help of a calibrated loop).[11] Two mycoplasma media were used i.e. Mycoplasma biphasic PPLO (pleuro-pneumonia like organism) media (PPLO agar & PPLO broth together) for primary isolation and Mycoplasma agar for identification of Mycoplasma pneumoniae.[11,12] Detection of mycoplasma growth was carried out by methods described elsewhere.[11,12] Help from local veterinary Institute was very forthcoming in this endeavour.

Identification and antibiotic susceptibility of the isolates were performed as per standard guidelines.[13,14]

RESULT

Table outlined below shows the general clinic-epidemiological features of 94 subjects included in the study.

Table 1.1 Age and sex distribution

Age group in years	Male	Female	Total	Percentage
20-29	8	3	11	11.70
30-39	13	5	18	19.15
40-49	20	7	27	28.72
50-59	14	5	19	20.21
60-69	10	2	12	12.77
70-79	5	2	7	7.46
Total: (%)	70(74.47)	24 (25.53)	94(100)	100

Table 1.2 Mean ages in different groups

Group	**Mean age in years**	**Standard deviation**
Male (n=70)	46.53	13.67
Female (n=24)	45.49	13.46
Outdoor patients (n=64)	44.03	13.49
Indoor patients (n=24)	52.08	12.42
ICU patients (n=6)	46.67	13.68
Over all (n=94)	46.23	13.55

Table 1.1 and Table 1.2 clearly shows Majority subjects belong to age group 40-60 years, mostly male and outdoor type, Mild CAP

Table 1.3 Clinical presentations

Clinical Findings	Number of subjects	Percentage
Cough	94	100%
Expectoration	89	94.68%
Fever (> 37.8°C)	81	86.17%
Chest pain	52	55.32%
Difficulty in respiration	24	25.53%
Alt. mental status	7	7.45%
Clinical consolidation	57	60.62%
Hemoptysis	4	4.26%

Table 1.4 Severity of illness

Age group in years	Mild CAP (Outdoor treated)	Moderate CAP (Indoor treated)	Severe CAP (ICU treated)	Total
20-29	9	1	1	11
30-39	16	2	0	18
40-49	18	7	2	27
50-59	11	6	2	19
60-69	6	5	1	12
70-79	4	3	0	7
Total	**64** (68.09%)	**24**(25.53%)	**6** (6.38%)	**94** (100%)

Table 1.3 and 1.4 shows that cough, fever and expectorations are the major clinical presentation. Mild CAP was more in young and severe in older subjects. (number was not sufficient for statistical evaluation)

Table 1.5 Culture result, growth pattern and isolates

Culture results & growth pattern	Samples: culture positive			Samples: culture negative:no (%)	Total
	Monomi-crobial: no (%)	Polymi-crobial: no (%)	Total (%)		
	53 (56.38)	2(2.13)	55(58.51)	39(41.49)	94(100)
Organism isolated	53 (92.98)	4 (7.02)	57 (100)		

Table 1.5 shows that 58.51% samples yielded significant growth with 53 samples mono-microbial, while 2 samples yielded double bacterial isolates. Total isolates recovered were 57 (53 & 4).

Table 1.6 Organisms isolated in culture positive samples

Organism isolated	Number of isolate from monomicrobial growth	Number of isolate from polymicrobial growth	Total	
			Number	Percentage
Streptococcus pneumoniae	24	0	24	42.1
Klebsiella pneumoniae	14	2	16	28.1
Staphylococcus aureus	4	2	6	10.5
Moraxella catarrhalis	5	0	5	8.77
Pseudomonas aeruginosa	3	0	3	5.26
β-hemolytic Streptococcus	1	0	1	1.75
Escherichia coli	1	0	1	1.75
Mycoplasma pneumoniae	1	0	1	1.75
Total	53	4	57	100

Table 1.6 depicts : *Streptococcus pneumoniae* to be the predominant isolate (42.1%), followed by *Klebsiella pneumoniae* (28.1%), *Staphylococcus aureus* (10.5%) and *Moraxella catarrhalis* (8.8%) . There were other isolates including 1 strain of *Mycoplasma pneumoniae* (after a very laborious culture procedure). Significantly, no *Haemophilus influenzae* isolate found.

Table 1.7 Isolation of pathogens in 3 different grades of illness severity

Organism / Severity	**S P (%)**	**Kleb (%)**	**S A (%)**	**M C (%)**	**P A (%)**	**β-HS (%)**	**EC (%)**	**MPn (%)**	**Total organism (%)**
Outdoor cases (mild CAP)	18 (51.4)	8 (22.9)	2 (5.7)	4 (11.4)	1 (2.9)	1 (2.9)	0	1 (2.9)	35 (100)
Indoor cases (moderate CAP)	4 (23.5)	7 (41.2)	4 (23.5)	1 (5.9)	0	0	1 (5.9)	0	17 (100)
ICU cases (Severe CAP)	2 (40)	1 (20)	0	0	2 (40)	0	0	0	5 (100)
Total	24 (42.1)	16 (28.1)	6 (10.5)	5 (8.77)	3 (5.26)	1 (1.75)	1 (1.75)	1 (1.75)	57 (100)

(Abbreviation used: SP=*S. pneumoniae*, Kleb=*K. pneumoniae*, SA=*S. aureus*, MC=*M.catarrhalis*, PA=*P.aeruginosa*, β-HS=β-hemolytic*streptococcus*, EC=*E.coli*, MPn=*Mycoplasma pneumoniae*)

Table 1.7 shows pneumococci to be predominant agent in outdoor setting (51.4%) followed by Klebsiella (22.9%) and Moraxella (11.4%). In Indoor Klebsiella was more common (41.2%) while in ICU Gram negative agents were more prevalent with Pneumococci

Table 1.8 Showing pathogen isolation with reference to comorbid illness/ risk factors

Organisms / Risk factors	*S P* (%, p value)	*Kleb* (%, p value)	*S A* (%, p value)	*M C* (%, p value)	*P A* (%, p value)	β-HS(%)	*EC* (%)	*MPn*(%)
Smoking	16 (43.2, 0.8679)	13 (35.1, 0.1145)	2 (5.4, 0.795)	2 (5.4, 0.2092)	1 (2.7, 0.4684)	1 (2.7)	1 (2.7)	1 (2.7)
Alcoholism	6 (33.3, 0.4040)	6 (33.3, 0.498)	2 (11.1, 0.6956)	0	1 (5.6, 0.9255)	1 (5.6)	1 (5.6)	1 (5.6)
Diabetes	0	5 (55.6, **0.0092**)	2 (22.2, 0.1666)	0	1 (11.1, 0.3424)	1 (11.1)	0	0
Old age	0	4 (80, **0.01**)	1 (20, 0.3478)	0	0	0	0	0
Chronic lung disease	2 (25, 0.2502)	2 (25, 0.7828)	0	3 (37.5, **0.0024**)	1 (12.5, 0.3424)	0	0	0
Previous hospitalization	14 (50, 0.2276)	7 (25, 0.6118)	2 (7.1, 0.1520)	3 (10.1, 0.6088)	2 (7.1, 0.5311)	0	0	0
Prior antibiotic exposure	19 (38.8, 0.2444)	16 (32.7, 0.499)	6 (12.20, 2842)	3 (6.1, 0.901)	3 (6.1, 0.4623)	1 (2)	1 (2)	0
Precedent viral fever	0	0	2 (100, **0.0001**)	0	0	0	0	0

Table 1.8 shows risk factors and co-morbidities associations with agents. Isolation of *Klebsiella pneumoniae* in diabetics and old age, *Moraxella catarrhalis* in chronic lung disease and *S aureus* in precedent viral disease only had statistically significant association.

Table 1.9 Antibiogram of Streptococcus pneumoniae

Streptococcus pneumonia			
Antibiotic	Sensitive (%)	Intermediate (%)	Resistant (%)
Oxacillin 1 µg	6 (25.0%)		18 (75.0%)
Chloramphenicol	14 (58.33%)	1 (4.17%)	9 (37.55%)
Tetracycline	5 (20.83%)	12 (50.0%)	7 (29.17%)
Erythromycin	15 (62.5%)	2 (8.33%	7 (29.17%)
Clindamycin	20 (83.33 %)	1 (4.17%)	3 (12.5%)
Linezolid	24 (100.0%)	0	0
Ciprofloxacin	8 (33.33%)	10 (41.67%)	6 (25.0%)
Gatifloxacin	15 (62.5%)	6 (25.0%)	3 (12.5%)
Levofloxacin	10 (41.67%)	10 (41.67%)	4 (16.67%)
Moxifloxacin	23 (95.83%)	1 (4.17%)	0
Ofloxacin	8 (33.33%)	7 (29.17%)	9 (37.5%)
Amoxyclav	13 (54.17%)	3 (12.5%)	8 (33.33%)
Co-trimoxazole	0	0	24 (100.0%)
Vancomycin	24 (100%)	0	0

Table 1.9 shows that all the 24 (100%) isolates of *Streptococcus pneumoniae* were sensitive to Linezolid and Vancomycin, followed by Moxifloxacin (95.84%), Clindamycin (83.33%) and Erythromycin (62.5%). Most importantly 75% isolates yielded Oxacillin (1mcg disc) resistance – indicating a probable PBP2a related resistance with epidemiological significance (needs confirmation by MIC and molecular testing).

Table 1.10 depicts β-lactam therapy in last 3 months was significantly associated with β-lactam resistant *Streptococcus pneumoniae* isolates.

Table 1.10 Risk factors for β-lactam resistant*S pneumoniae* causing CAP

Risk factors	β-lactam resistant*Streptococcus pneumoniae* (n=18)	Percentage	*p* value
β-lactam therapy in last 3 months	10	55.56	**0.0097**
Old age	4	22.22	0.2058
Alcoholism	4	22.22	0.7716
Multiple medical comorbidities	0	0	

DISCUSSION

CAP is easily one of the leading causes of disability and hospital attendance globally, especially in developing countries where health care system is not well equipped.[15] Pneumonia is increasingly recognized as a serious issue among older patients and those with comorbidity [1,2] Although not much new antibiotics are in pipeline to tackle this ailment, fast evolution of bacterial resistance here a reality staring at us now. Many respiratory pathogens have become resistant to widely used antimicrobials. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and a number of enteric Gram-negative bacteria are in forefront in this aspect.[1]

The subjects in this study were between 20 to 75 years with a highest prevalence in 40-49 year age group (28.72%). This observation was similar to study by Bansal *et al*. patient older than 40 years found to be more predisposed to development of CAP.[32] Cough, expectoration & fever were observed to be main features in this study. Bansal *et al.* observed cough in 97%, expectoration in 87%, while fever was present 90% cases.[15]

58.51% samples showed growth of isolates, which was similar to isolation rate of Sopena *et al.* at 58%.[16] Ozyilmaz*et al.* found similar rate at 59.4% of samples.[17] Ishida *et al.*in Japan were successful in isolating pathogen from 61% of CAP samples.[2] On the other hand Bansal*et al.* detected pathogen in 75% samples.[15]

The present study showed the dominance of *Streptococcus pneumoniae* (42.1%). Study by Bansal et al. (35.8%) Lim et al. (48.0%) and Jokinen et al. (41.0%) had similar rate while Peñafiel et al (10.5%), Ishida et al (23.0%) & Ruiz et al (29.0%) had lower rate.[2, 15, 18, 20, 21]

There was no *Haemophilus influenzae,* an important CAP agent worldwide, isolation in the present study,. Bansal et al and Almirall et al also did not find any *Haemophilus influenzae* in their subjects.[15,22] 75% of the pneumococci isolates were found to be resistant to β-lactam antibiotics. Song *et al.* found 52.4% pneumococcus with reduced susceptibly to penicillin.[23] Kanungo *et al.*found non-susceptibility at 11.6%.[5] Another study Kanungo et al found 7.3% of isolates to be intermediately resistant to penicillin.[6] Among many known factors of penicillin resistant Pneumococcus, only β-lactam therapy during last 3 months was found to be statistically significant (p value 0.0097). 62.5% of *Streptococcus pneumoniae* isolates were sensitive to Erythromycin. Amongst the fluoroquinolones, Moxifloxacin was sensitive in 95.83% of isolates while 41.67% isolates were sensitive to Levofloxacin.

Ciprofloxacin sensitivitiy was observed in 33.33% isolates. This resistance was high compared to other studies worldwide {e.g. Song et al. (11.8%)}.[23] Increasing and indiscriminate use of drugs like Ciprofloxacin could be an explanation of such high rate of resistance observed in this study.

CONCLUSION

The findings in this study revealed that *Streptococcus pneumoniae* and *Klebsiella pneumoniae* are the principal pathogen of CAP, especially the former in mild cases where hospitalization is not required, while the latter may be predominant in moderate to severe cases where patient needs hospitalization. An important aspect of this study finding is the absence of *Haemophilus influenzae*. Antibiotic susceptibility patterns of the isolates clearly suggest existence of drug resistant pathogen of CAP in our setup. The findings, of large proportion of β- antibiotic resistant *Streptococcus pneumoniae* as well as detection of resistance against other common use drugs is really alarming. A wider study with variety of samples and molecular methods may give a better picture of the situation.

Conflict of Interest: None.
Ethical clearance: Obtained.
Source of funding: Self funded.

Authors Contribution: All authors contributed equally.

REFERENCES

1. American Thoracic Society. Guidelines for the Management of Adults with Community-acquired Pneumonia Diagnosis, Assessment of Severity, Antimicrobial Therapy, and Prevention. Am J RespirCrit Care Med.2001 Jun;163(7):1730-54
2. Ishida T, Hashimoto T, Arita M, Ito I, Osawa M. Etiology of Community-acquired pneumonia in hospitalized patients: A 3 year prospective study in Japan. Chest. 1998 Dec;114(4):1588-93
3. Wattanathum A, Chaoprasong C, Nunthapisud P, Chantaratchada S, Limpairojn N, Jatakanon A et al. Community-Acquired Pneumonia in Southeast Asia:The Microbial Differences Between Ambulatory and Hospitalized Patients. Chest. 2003 May;123(5):1512-19
4. Shah P B, Giudice J C, Griseback Jr R, Morley T F, Vasoya A. The newer guideline for the management of Community-acquired pneumonia. J Am Osteopath Assoc.. 2004 Dec;104(12):521-526
5. Kanungo R, D'Lima D, Rajalakshmi B, Kumar A, Badrinath S. Emerging antibiotic resistant Pneumococci in invasive infections in south India. Indian J Pharmacol. 2002;34:38-43
6. Kanungo R, Rajalakshmi B. Serotype distribution & antimicrobial resistance in Streptococcus pneumoniae causing invasive & other infections in south India. Indian J Med Res. 2001 Oct;114:127-32
7.. Duguid J P, Collee J G, Fraser A G. Laboratory strategy in the diagnosis of infective syndromes. In: Collee J G, Duguid J P, Fraser A G, Marmion B P, editors. Mackie & McCartney Practical Medical Microbiology. 13th ed. Edinburgh: Churchill Livingstone; 1989: 600-649
8. Murray P R, Washington J A. Microscopic and bacteriologic analysis of sputum. Mayo Clin.Proc. 1975;50: 339-344
9. NHS Standards Unit, Evaluations and Standards Laboratory, Specialist and Reference Microbiology Division. Investigation of bronchoalveolar lavage, sputum and associated specimens, London: Department of Health; 2005 May 5
10. Nichols T, Freeman R. A new selective medium for Streptococcus pneumoniae. J ClinMicrobiol. 1980;33: 770-73
11. Smith T F. Isolation, Identification and Serology of Mycoplasma pneumoniae. In:Wahington II J A, editor. Laboratory procedure in Clinical Microbiology. 1st ed. Boston: Little, Brown and company; 1974. 205-214
12. Morton H E, Smith P F, Lieberman P R. Investigation of the cultivation of Pleuropneumonia-like organism from man. Am. J. Syph. Gon. V. D. 1951;35: 361-369
13. Clinical and Laboratory Standards Institute. Performance Standards for antimicrobial susceptibility testing. 21st Informational Supplement. M100-S21. Clinical and Laboratory Standards Institute, 2011. Villanova, Pa
14. Collee J G, Miles R S. Test for identification of bacteria. In: Collee J G, Duguid J P, Fraser A G, Marmion B P, editors. Mackie & McCartney Practical Medical Microbiology. 13th ed. Edinburgh: Churchill Livingstone; 1989: 141-160
15. Bansal S, Kashyp S, Pal L S, Goel A. Clinical and bacteriological profile of community acquired pneumonia in Shimla, Himachal Pradesh. Indian J Chest Dis Allied Sci. 2004;46: 17-22
16. Sopena N, Sabrià M, Pedro-Botet M L, Manterola J M, Matas L, Domínguez, J et al. Prospective Study of Community-Acquired Pneumonia of Bacterial Etiology in Adults. Eur J ClinMicrobiol Infect Dis. 1999 Dec;18(12):852-858
17. Ozyilmaz E, Akan O A, Gulhan M, Ahmed K, Nagatake T. Major Bacteria of Community-Acquired Respiratory Tract Infections in Turkey. Jpn J Infect Dis. 2005;58:50-52
18. Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Kleemola M, Koskela M et al. Microbial Etiology of Community-Acquired Pneumonia in the Adult Population of 4 Municipalities in Eastern Finland. Clin Infect Dis. 2001 Aprl15;32: 141-154
19. Lim D, Schlaeffer F, Boldur I, Lieberman D, Horowitz S, Friedman MG, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. Thorax. 1996; 51: 179-184
20. Lim W S, Macfarlane J T, Boswell T C J, Harrison T G, Rose D, Leinonen M et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax. 2001;56: 296–301
21. Peñafiela F S, O'Brien A, Gollerinoc A G, Gontupild G F, Fuenzalidaa A D. Community-Acquired Pneumonia Requiring Hospitalization in Immunocompetent Elderly Patients: Clinical Features, Prognostic Factors and Treatment. Arch Bronconeumol 2003;39(8): 333-40
22. Almirall J, BolõÂbar I, Vidal J, Sauca G, Coll P, Niklasson B et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. EurRespir J. 2000;15: 757-763
23. Song J, Jung S, Ko K S, Kim N Y, Son J S, Chang H, et al. High Prevalence of Antimicrobial Resistance among Clinical Streptococcus pneumoniae Isolates in Asia (an ANSORP Study). Antimicrob Agents Chemother. 2004 Jun;48(6): 2101-07