Comparison of the *in vitro* sensitivity of respiratory pathogens to roxithromycin, amoxicillin and amoxicillin + clavulanic acid

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Abstract

In India the information on trends of respiratory pathogens and their susceptibility to antibiotics used are lacking. Physicians resort to empiric therapy with antibiotics which has resulted in the emergence of antimicrobial resistance among the principal pathogens

This study was conducted to compare the resistance patterns among the common respiratory pathogens: S.pneumoniae, *S.aureus*, Klebsiella pneumoniae, Hemophilus influenzae, Moraxella catarrhalis to roxithromycin, amoxicillin and amoxicillin + clavulanic acid.

Materials and Methods: Samples of sputum were collected from 50 patients with pneumonia and bronchitis who were admitted to tertiary care hospital in a metro city in West India and from patients who presented with respiratory tract infections to the O.P.D.

The Kirby Bauer disc diffusion method was used to evaluate the susceptibility of the isolated pathogens to the antibiotics.

Results: Roxithromycin demonstrated a significantly higher sensitivity to isolated organisms compared to amoxicillin. Roxithromycin was found to be sensitive for isolates of Streptococcus pneumoniae, even when 3 samples were resistant to amoxicillin and 1 sample was resistant to amoxicillin + clavulanic acid.

Conclusion: Roxithromycin can be a good alternative option for the management of upper and lower respiratory tract infections in the community.

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Introduction

Lower respiratory tract infections have an incidence of about 20-30% in developing countries.[1] Upper respiratory infections involve the nasal passages, pharynx, tonsils and epiglottis.[2] Infections are usually limited to the upper respiratory tract and only 5% involve the lower respiratory tract.[2] Lower respiratory tract infections involve the bronchi and alveoli. Involvement of these results in bronchitis and pneumonia.[2]

In India, URTIs including nasopharyngitis, pharyngitis, tonsillitis and otitis media constitute 87.5% of the total episodes of respiratory infections and respiratory infections is one of the commonest condition with which patients present to public health care centres.[3]

The causative agents for LRTIs are not well recognized and documented. Most of the respiratory infections have a viral or atypical pathogenic aetiology with secondary superinfection with bacteria.[1]

In India the information on trends of respiratory pathogens and their susceptibility to antibiotics used, is lacking. There is a paucity of step wise guidelines for use of antimicrobials and antibiotic sensitivity testing.

Physicians resort to empiric therapy with antibiotics which has resulted in the emergence of antimicrobial resistance among the principal pathogens. Definitive bacteriological diagnosis and susceptibility testing is necessary for effective management.[4] Colonization and infection with antibiotic resistant bacteria will result in reduction of therapeutics options available, and in some cases make treatment virtually impossible.[4]

There is a need for timely diagnosis, uniform guidelines for empirical therapy and antibiotic susceptibility testing of pathogens to change antibiotics when necessary to prevent development and spread of resistant pathogens.[1] Prescription of antimicrobials for acute respiratory infections was found to be 69.4% on an average, and in some centres it was more than 80%.[5]

In a country wide survey, it was found that two thirds of all antimicrobials prescribed were penicillins and co-trimoxazole, and > 40 per cent of prescriptions from private sector were quinolones and cephalosporins.[5]

A study conducted in the capital region in India assessing use of antibiotics in acute respiratory tract infections showed that in private clinics, cephalosporins are the most commonly used agents (39%) and macrolides, least commonly used (15%), whereas at public facilities, macrolides are amongst the commonly used antibiotics (25%) second only to penicillins (31%). [6]

Cephalosporins, amoxicillin + clavulanic acid, and fluoroquinolones which are being increasingly used as first line treatment for RTIs.

Indiscriminate use of these agents is causing a rise in the resistance to these antibiotics amongst commonly encountered respiratory pathogens.

A study done in India on resistant patterns demonstrated MSSA (Methicillin sensitive staphylococcus aureus) to have resistance mainly to ampicillin/amoxicillin than to the fluoroquinolones with minimal resistance to other drugs such as macrolides, co-trimoxazole, clindamycin and doxycycline.[7] The most sensitive antibiotics for gram positive organisms were macrolides, clindamycin, gentamycin, nitrofurantoin, vancomycin.[7]

A study comparing macrolides and amino penicillins, in secondary use, demonstrated that only macrolides maintained comparable effectiveness rates after 20 years. (Table 1). This data lends credence to the corollary that macrolides are amongst the most effective antibiotic classes for both URTI and LRTI in initial and secondary antibiotic treatment when a further antibiotic course was prescribed.[8]

Woodhead et al. in a study found that in non-severe CAP oral β lactam antibiotics, macrolides, or fluoroquinolones are equally effective when judged by clinical cure and mortality.[9]

Oral cephalosporins have poor pharmacokinetics, so alternative drugs should be preferred as first line therapy.[10] To increase cure rates and reduce resistance to antibiotics that are reserved for use in severe infections, alternative antibiotics need to be used as a first line treatment in respiratory infections.

This study was conducted to compare the resis-

Table 1: Comparison of efficacy of macrolides in LRTI and URTI over two decades

	1991	2012
LRTI	80.7%	79.8%
Throat infections	85.1%	84.5%
Nasal infections	80.7%	82.3%
Unspecified URTI	83.5%	83.8%

tance patterns among the common respiratory pathogens to roxithromycin, amoxicillin and amoxicillin + clavulanic acid.

Materials and Methods

The study was conducted at a tertiary care hospital in a metro city in West India.

Samples of sputum were collected from 50 patients who were admitted in the hospital with pneumoniae and bronchitis and from patients who presented with respiratory tract infections to the O.P.D.

Samples where the isolated organisms were *Pseudomonas aeruginosa, Acinetobacter baumanii, Entero bacter spp* and *Proteus mirabilis* were excluded from the study.

The Kirby Bauer disc diffusion method was used to evaluate the susceptibility of the isolated pathogens to the antibiotics, roxithromycin and amoxicillin and amoxicillin + clavulanic acid.

The antibiotic susceptibility discs were obtained from Hi-Media, Mumbai (India). The results were interpreted as per the National Committee for Clinical Laboratory Standards (NCCLS). The criteria for susceptible, intermediate sensitive and resistant pathogens as defined by NCCLS were followed.

Test of proportions (Z test) was applied to see the significance of difference in the sensitivities of the organisms to the two antibiotics

Results

Roxithromycin demonstrated a significantly higher sensitivity to isolated organisms compared to amoxicillin (Table 2). However, there was no statistical difference between roxithromycin and amoxicillin + clavulanic acid. Roxithromycin was found to be sensitive for isolates of *Streptococcus pneumoniae*, even when 3 samples were resistant to amoxicillin and 1 sample was resistant to amoxicillin + clavulanic acid.

Out of the 7 samples of *staphylococcus aureus*, 2 samples were resistant to amoxicillin and 1 to amoxicillin + clavulanic acid, while roxithromycin was found to be sensitive in these samples. Roxithromycin was sensitive for all samples of *H. Influenzae* whereas 2 samples were resistant to amoxicillin. 1 sample of *Moraxella catarrhalis* which was resistant to both amoxicillin and amoxicillin + clavulanic acid was sensitive to roxithromycin.

Discussion

The study shows the current trends of susceptibility patterns in bacteria causing respiratory infections in India. There is a change in susceptibility pattern amongst the respiratory pathogens. Indiscriminate and empiric use of antibiotics such penicillins and cephalosporins at inappropriate dosages have resulted in resistance in the bacteria.

The results demonstrate that roxithromycin is an effective alternative to cephaloporins for respiratory tract infections. There is increasing B lactamase medi-

Table 2: Comparison of the *in vitro* activity of roxitromycin versus amoxcillin and roxithromycin and amox+clav. (Number of samples stated in *parenthesis*.)

	Roxithromycin	Amoxicillin	p value b/w roxithromycin & amoxicillin	Amox+clav	p value b/w roxithromycin & Amxo+clav
Streptococcus pneumoniae(12)	83.33%(10)	58.335(7)	0.178	75%(9)	0.615
Staphylococcus aureus(7)	85.71% (6)	57.14% (4)	0.237	71.43% (5)	0.515
Klebsiella pneumoniae (14)	64.29%(9)	28.57%(4)	0.058	78.57% (11)	0.403
Hemophilus influenzae(5)	100%(5)	60%(3)	0.114	100%(5)	No Difference
Moraxella catarrhalis(12)	100%(12)	83.33%(10)	0.140	91.67%(11)	0.307
% efficacy	84%	56%	0.002*	82%	0.999

ated resistance to amoxicillin in both Moraxella and H influenza and penicillin resistance in S pneumoniae.[12]

A collaborative study from eight Asian countries including India has revealed 35.1% resistance in *S. pneumoniae*.[11] A survey in Russia shows that the antibiotic resistance possessed by *S. pneumoniae* to aminopenicillins doubled from 2003-2012 (12.4% strains vs. 6.4% 3 years ago, $p<0.05$). The resistance to Cotrimoxazole and Ofloxacin was 27.9% and to macrolides it was 17.9%.[13]

Moraxella catarrhalis is now recognised as an important pathogen in respiratory infections including otitis media, sinusitis, acute bronchitis, and pneumonia and its rates of resistance to cefaclor, cefuroxime, tetracycline and cotrimoxazole areincreasing.[14] There is increasing B lactamase mediated resistance to amoxicillin in both *M.catarrhalis* and *H.influenzae* and penicillin resistance in *S pneumoniae*.[12]

Roxithromycin provides a good alternative option for respiratory tract infections in the community with a convenient dosing regimen.

Roxithromycin is acid stable macrolide with good absorption and tissue penetration and a long half-life. It has low propensity for drug interactions and is well tolerated without any adverse effects.[15,16]

Macrolide resistant bacterial strains have to be monitored, but to date they have not been of clinical importance.[17]

14-membered-ring macrolides like roxithromycin regulate the ability of leukocytes to produce proteases and reactive oxygen species, which induce tissue damage.[18]

It inhibits bleomycin-induced acute lung injury through its suppressive activity towards PMN recruitment.[19]

A study in Spain showed that Roxithromycin produced favourable clinical results in 92.5% of patients with CAP. The high clinical effectiveness makes it an eligible empirical option for therapy in patients of CAP who are candidates for ambulatory therapy.[21]

A study by Cooper *et al* 1994 showed roxithromycin was effective in 83% of cases of pneumonia due to H influenzae whereas comparator antibiotics such as amoxicillin/ clavulanic acid, cefaclor. doxycycline were effective in only 53% of cases ($p = 0.02$)[20]

A study in south India by Deepa Latha *et al* found Roxithromycin 300mg BD produce effective clinical response which was rated as excellent and well tolerated in treatment of chronic respiratory infections.[15]

Roxithromycin is found to be effective and safe in the therapy of ENT diseases exhibiting similar effects on the reduction of signs and symptoms as Amoxicillin + clavulanic acid but with better compliance because of once-a-day administration. An overall satisfactory clinical response was achieved by 82% of patients in the Roxithromycin group and 78% in the Amoxicillin clavulanic acid group.[22]

Roxithromycin is also effective and well-tolerated for the treatment of acute and recurrent sinusitis. Roxithromycin shows clinical, bacteriological and overall efficacy similar to that of amoxicillin clavulanic acid, but has better tolerability. A comparative study done by Chatzimanolis *et al* (1998) in patients with sinusitis showed that a clinical response was obtained in 93.1% patients receiving roxithromycin and 88.8% receiving amoxicillin clavulanic acid.[12]

The results of the current study are indicative of the efficacy of roxithromycin in respiratory tract infections in the real life setting in India. Roxithromycin can be an empiric drug for the management of upper and lower respiratory tract infections

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