Guiding Principles for the use of Fluroquinolones in Out-patient Community Settings of India: Panel Consensus

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Abstract

Introduction: Respiratory tract infections have been an important cause of morbidity and mortality worldwide that is looming large especially in context of antibiotic resistance that is confronted both by a pulmonologist as well as a general practitioner. A reflection to this trend has been the rising phenomenon of MICs as shown the respiratory pathogens towards conventional antibiotics including macrolides or β lactam/β lactamase inhibitor combinations. Respiratory fluoroquinolones offer broad yet potent cover of respiratory pathogens leading to their obvious choice for empirical therapy for clinical persisters or high risk cases with prior history of antibiotics not-withstanding the clinical concerns in tropical countries.

Aim: To further assess the clinical role of respiratory quinolones in outpatient settings of India especially in line with the known endemicity of chronic infections or tuberculosis.

Method: Cross-sectional, national survey questionnaire survey to explore the clinical perceptions, attitude and insights on the clinical use of respiratory fluoroquinolones was rolled out amongst pulmonologists and consultant physicians practicing respiratory medicine in India. Descriptive statistics was utilized to describe the numerical and categorical data.

Results: Nationwide representative sample of fourteen pulmonologists provided response and clinical insight on the current management strategies for community acquired pneumonia (CAP) with ‘respiratory’ fluoroquinolones. Each of the doctor in the panel agreed that the ideal antibiotic for the treatment in CAP or lower respiratory tract infection (LRTI) should be highly effective with lesser side effects and broader spectrum covering atypical bacteria. Doctors agreed that most the fixed dose combination (FDC) has gone into disrepute probably because of pharmacokinetic incompatibility that could have further fuelled the epidemic of antibiotic resistance. 9 (64%) doctors suggested that there is omnipresence if not overwhelming presence of patient poor response to beta-lactam or fluoroquinolones in clinical practice. It was agreed that fluoroquinolones would be the rightful choice for patients with prior history of antibiotic use with or without comorbidities. Amongst the newer fluoroquinolones available, Garenoxacin offers broad and potent action against resistant strains for CAP. Despite the overwhelming concern of tropical infection in Indian context, Garenoxacin could be considered for mono- or add-on therapy in moderate to severe yet stable cases of CAP. Short course therapy of 5 to 10 days should offer no complimentary masking of anti-mycobacterial activity since the relevant minimum inhibitory concentration (MIC₉₀) are high that are beyond the comprehension of suggested therapeutic dose of 400 mg tablets.

Conclusion: The growing incidence of Macrolide resistance suggests the clinical role of new generation fluoroquinolones including Garenoxacin as a clinically useful therapeutic strategy for moderate to severe CAP as monotherapy or in combination.

Introduction

Respiratory tract infections have been an important cause of morbidity and mortality worldwide that is looming large especially in context of antibiotic resistance. A reflection to this trend has been the rising phenomenon of MICs as shown by the respiratory pathogens towards conventional antibiotics including macrolides or β lactam/β lactamase inhibitor combinations. Again despite the availability of

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above agents, community acquired pneumonia (CAP) continues to remain as a leading cause of death.\(^1\) The mortality rate of the pneumonia patient in outpatient setting is low, in the range of 1-5%, but amongst patient who require admission to intensive care unit (ICU) it approaches 25%.\(^2\) Streptococcus pneumonia (S. pneumonia) is the common pathogen causing CAP and is associated with the greatest morbidity and mortality.\(^3\) Similarly, the high rates of macrolide-resistant M. pneumoniae reported in China (>90%) and Japan (87.1%) has limited the available therapeutic options while managing CAP empirically.\(^4\)

The successive generation of Quinolones introduced after 1962 have offered improved coverage of gram-positive and atypical pathogens. The fluoroquinolones for treatment of respiratory diseases, including gatifloxacin, moxifloxacin, and levofloxacin, have been the representative examples in this direction. The rate of fluoroquinolone-resistant pneumonia infection is < 3% in most countries.\(^5,6\) As a result, the fluoroquinolones for treatment of respiratory diseases have been recommended and are increasingly being used as preferred or alternative therapy for the treatment of CAP.\(^7\) Amongst the new generation fluoroquinolones, Moxifloxacin and Garenoxacin offer broad and potent coverage of gram +ve, gram –ve, atypical and anaerobic pathogens offering relevant therapeutic action in community acquired RTIs. Unlike other conventional fluoroquinolones, Garenoxacin shows negligible incidence of gastrointestinal, central nervous system and cardiovascular complications including QTc prolongation or Torsades pointes.\(^8,9\)

**Method**

A nationwide representative sample of fourteen pulmonologists provided responses to a standardized questionnaire with relevant insights and insights on the current management strategies of CAP with respiratory fluoroquinolones. The responses related to following items on the questionnaire, including:

a. Clinical challenges in the management in Community acquired pneumonia.

b. Likely risk factors or contributing mechanism for antibiotic resistances: FDC and rising resistance.

c. Feature of ideal Antibiotic in treating CAP.

d. Clinical perceptions on fluoroquinolones in RTI.

e. Role of respiratory fluoroquinolones in CAP.

**Results**

**What was the clinical challenges in the management in Community acquired pneumonia (CAP)?**

Panel Consensus: Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death. There exists a major controversy concerning the antimicrobial management of this infection.\(^10\) The mixed etiology and the changing susceptibility of pathogens causing CAP particularly with that of Streptococcus pneumoniae has created a circumstantial challenge to clinicians regarding appropriate therapeutic approaches in terms of optimal patient outcome.\(^11\) Normally empirical antimicrobial therapy is initiated before bacterial cause is determined which may continue due to lack of reliable microbiological data. An understanding of the possible pathogens and resistance patterns is helpful in guiding antibiotic choice. A detailed knowledge of the local susceptibility of the potential pathogens ensures an appropriate selection of the antimicrobial agent to be used. The panel agreed that managing CAP is a difficult task as doctor has to consider the severity of the disease, bacterial resistance to antibiotic and the cost of the therapy. The panel suggested that owing to the increased incidence of Streptococcus Pneumoniae resistance to macrolides, treating patients without laboratory finding is a big gamble towards developing antibiotic resistance.

**Which are the likely risk or contributing factors for mechanism for Antibiotic resistances?**

Panel Consensus: Of the respiratory pathogens, penicillin-resistant Streptococcus Pneumoniae (PRSP) has attracted the greatest interest. PRSP is a widespread problem, with rates of resistance ranging from 5% to 80% in various parts of the world.\(^12\) Panel discussed the probable mechanism for antibiotic resistance. The principal mechanism of penicillin resistance to beta-lactams in Streptococcus Pneumoniae is the production of altered penicillin-binding proteins (PBPs). Two main discussed mechanisms of macrolide resistance in Streptococcus Pneumoniae were ribosomal methylase, referred to as an MLSB-type resistance mechanism, and a macrolide efflux pump. The development of reduced susceptibility to fluoroquinolones in Streptococcus Pneumoniae due to presence of parC and gyrA mutations, especially in combination, was found to be a major contributing factor for high-level resistance. Efflux probably plays a lesser role in reduced susceptibility to some newer fluoroquinolones. Panel also discussed the risk factors for infection with PRSP strains include young age, day-care center attendance, prior administration of antimicrobial agents, and severe underlying diseases. As the use of nonpenicillin antimicrobials has increased, so has the development of resistance to these agents among Streptococcus Pneumoniae. Worldwide rate of macrolide resistance has risen dramatically in recent years. The prevalence of resistance is highly variable between countries, range
starting from 70%. Emergence of Streptococcus Pneumoniae with reduced susceptibility to quinolones has also been reported in England and US. However, the worldwide incidence of quinolone resistance is currently low (<1%). Panel discussed that due to irrational antibiotic use in recent years, stringent actions were taken to restrict FDC use that led to restricted resources available to doctors for treating CAP. Due to rising antibiotic resistance and limited resources of classical FDC, there was a major concern to select appropriate antibiotic without risking development of antibiotic resistance.

What would be an ideal feature of an Antibiotic in treating Community acquired pneumonia?

Panel Consensus: Panel debated a study conducted in India which showed 4% total resistance to penicillin and 10% intermediate resistance, suggesting the increase in emergence of resistance strains of S. pneumonia in India. Panel also discussed a three-year surveillance study for penicillin resistance from Vellore that revealed 4.6% of intermediate resistance to penicillin, whereas, a study conducted in north India reported 15.2% (26/170) intermediate resistance and 2.3% (4/170) penicillin resistance. The difference in the resistance pattern of S. pneumoniae as observed in South and North Indian studies has been explained by Lalitha et al. on the basis of the high genetic diversity that exists among strains isolated from different geographical areas within India making it difficult to choose appropriate antibiotic for the treatment of CAP and recent stringent action taken against fixed dose combination due to pharmacokinetic incompatibility that could have further fuelled the epidemic of antibiotic resistances making it more difficult for the doctors to treat CAP. Panel suggested that treating CAP would be a big challenge and they would look out for an ideal antibiotic which will be highly effective with lesser side effect with broader spectrum covering atypical bacteria without causing antibiotic resistance.

What is clinical perceptions on fluoroquinolones in RTI?

Panel Consensus: Panel suggested that there is a good pharmacological and clinical evidence to support the use of respiratory fluoroquinolones in CAP. Their favorable pharmacokinetic and pharmacodynamic profiles result in good penetration of respiratory tissues. The broad antibacterial activity of respiratory fluoroquinolones provides excellent coverage of the major CAP-causing pathogens, including penicillin- and macrolide-resistant S. pneumoniae. A meta-analysis of 23 clinical trials showed that pneumonia was cured or improved in significantly more patients treated with fluoroquinolones than those treated with macrolide or beta-lactam antibiotics. Fluoroquinolones were also more effective than macrolides with or without beta-lactams for patients with severe pneumonia, those who were hospitalized and those who required intravenous therapy.

Panel discussed that fluoroquinolones are generally recommended in different management guidelines for use in CAP, i.e., pneumonia in immunocompetent subjects arising outside of the hospital such as The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) consensus guidelines. The European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend that a fluoroquinolone is as effective as macrolide/beta-lactam combination particularly for patients with comorbid conditions or repeated infections in the last three months. Importantly, non-adherence to CAP treatment guidelines is a significant risk factor for treatment failure and mortality.

Is there a role of Respiratory fluoroquinolones in community acquired pneumonia?

Panel Consensus: Literature review suggests evolving documentation of antibiotic resistance amongst gm+ve pathogens exposed to fluoroquinolones. A prospective study of eleven Asian countries from 2000-01 cited Ciprofloxacin resistances in 6% of isolates; whereas fluoroquinolones resistances was highest in Hong Kong (11.8% to Ciprofloxacin and 8% to Levofloxacin) which concluded that there is resistance getting developed for Ciprofloxacin and Levofloxacin. Whereas in China 6.8% of 192 pneumococcal isolates were resistant to Levofloxacin and 4.2% were resistant to Moxifloxacin. Panel concluded that factors influencing fluoroquinolones are complex and frequency of resistance depends on the type of mutation and preferential binding site of the fluoroquinolones driving the transformation. Fluoroquinolones like Levofloxacin and Moxifloxacin preferentially bind with either topoisomerase IV or DNA gyrase respectively. Panel agreed that there is need of newer agents that would resist resistance development.

Despite the availability of fluoroquinolones i.e Levofloxacin and Moxifloxacin, their clinical use has been limited due to the considerations of tuberculosis in tropical countries including India. There is therefore a need of newer quinolones to be considered in the treatment of CAP. Panel suggested that Garenoxacin should be consider due to its unique structure compare to other fluoroquinolones and it should be called as des-fluoroquinolones. Panel agreed that Garenoxacin unique structure which offers an add-on advantage when compared with other fluoroquinolones such as lower MIC90 and higher AUC/MIC90 ratio governing higher potency and
killing power, lower susceptibility to efflux, and resistance mechanisms against prevailing respiratory Gram-positive/negative and atypical pathogens including Streptococcus pneumoniae. In a study conducted by Takagi H. et al. showed that Garenoxacin bacteriological eradication rates for S. pneumonia was effective for most of the resistant strains including quinolone resistant strain. Regarding the concern of Garenoxacin in mycobacterium tuberculosis about the in vitro susceptibility to mycobacterium tuberculosis being on the higher side and MIC 90 being 4 μg/ml along with lower sputum concentration as compared to plasma, the panel agreed that the lower penetration of Garenoxacin in sputum coupled with lower kill ratio or Cmax/MIC against mycobacterium tuberculosis would on the contrary, not mask the diagnosis or subjugude the therapeutic response by selection pressure for mutants. 

The panel concluded that the treatment of CAP is incomplete without des fluoroquinolone (Garenoxacin) as a monotherapy or as add on therapy. Garenoxacin can be given as an oral therapy in Mild to severe CAP. Garenoxacin can be used in OPD to hospital settings. It can be prescribed across age group (young adult to geriatric) with or without comorbidities. Garenoxacin therefore overcomes the limitations for classical or traditional FDC combination and can be suggested as a useful therapeutic strategy for moderate to severe CAP as monotherapy or in combination.

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