

that has been employed in the evaluation of antibiotics' ability to minimize or limit the development of resistant organisms. MPC has been defined as the MIC of the least susceptible single-step mutant. By definition, cell growth in the presence of antibiotic concentrations greater than MPC requires an organism to have developed two or more resistant causing spontaneous chromosomal point mutation.

Table 9 : Mutant prevention concentration (MPC).

Fluoroquinolone	Daily dose	Cmax	<i>Pseudomonas</i> MPC	<i>Streptococcus aeruginosa</i> MPC
Ciprofloxacin	500 bid	3	2	NR
	750 bid	3.6	2	NR
Levofloxacin	500 bid	5.7	8	8
Moxifloxacin	400 bid	4.5	NR	2
Gatifloxacin	400 bid	4.2	NR	4

A strategy for restricting the development of resistance is to find compounds that have narrow mutant selective windows (MPC/MIC=1) (Table 9).

Although the AUC/MIC and Cmax/MIC ratios are useful for predicting the potential for developing drug resistance, it is suggested that the AUC/MIC should exceed 100 for Gram-positive and gram-negative species to prevent selection of resistant strains. Alternatively, Zhao *et al.* have suggested that rate at which resistance develops to a fluoroquinolone is related to its MIC and MPC.¹³

Moxifloxacin exceeds the MPC for *S. pneumoniae* and ciprofloxacin exceeds the MPC for *P. aeruginosa* (both 2 µg/ml) by achieving a Cmax of 4.5 µg/ml and 3 µg/ml, respectively.

Evidence is emerging that suggests a link between appropriate fluoroquinolone use, development of resistance against the entire fluoroquinolone class and clinical failure. The major factors associated with increasing resistance to fluoroquinolone include:

- Under-dosing, i.e. use of a marginally potent agent whose-MIC is largely reached in the serum or infected tissue
- Overuse of agents known to encourage resistant mutants

- Inability to readily detect and respond to changes in antimicrobial susceptibility.

Ciprofloxacin, levofloxacin and gatifloxacin achieve a high concentration in urine, thus, they are appropriate choices for treating UTI in the community.

For infections in which *S. pneumoniae* is anticipated to be the most likely pathogen (CAP), moxifloxacin, which currently has the best anti-pneumococcal pharmacodynamic activity and the lowest MPC against this agent, would represent a prudent therapeutic choice.

Expecting a single fluoroquinolone to be suitable for all infections is unreasonable and excessive use of any single fluoroquinolone for all indications will lead to resistance that adversely affect the entire class.¹⁴

References

1. Zarenko GE, Yogi BH, Schaadt RD, *et al.* *In vitro* activities of U-100592 and U-100766, novel oxazolidinone antibacterial agent. *Antimicrob Agents Chemother* 1996;**40**:839–845.
2. Ford CW, *et al.* *In vivo* activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents, against experimental bacterial infections. *Antimicrob Agents Chemother* 1996;**40**:1508–13.
3. Zurenko GE, *et al.* Oxazolidinone: A new class of antibacterials. *Curr Opin in Pharmacol* 2001;**1**:470–76.
4. Diekema DJ, Jones RN. Oxazolidinone antibacterial. *Lancet* 2001; **358**:1975–82.
5. Kuter DJ, Tiltson GS. Hematologic effects of antimicrobials: focus on the oxazolidinone linezolid. *Pharmacotherapy* 2001;**21**:1010–13.
6. Tsiodras S, *et al.* Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* 2001;**358**:207–8.
7. Ackermann G, Rodloff AC. Drugs of the 21st century: Telithromycin (HMR 3647)–the first ketolide. *J Antimicrob Chemother* 2003;**51**: 497–511.
8. Okamoto H, *et al.* *In vivo* efficacy of telithromycin (HMR 3647) against *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Antimicrob Agents Chemother* 2001;**44**:3250–52.
9. Zhanel GG, *et al.* Review of macrolides and ketolides. *Drugs* 2001; **61**: 43–98.
10. Nilius AM, Ma Z. Ketolides: the future of the macrolides? *Curr Opin Pharmacol* 2002;**2**:1–8.
11. Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. *Emerg Infect Dis* 2003;**9**:1–5.
12. Lim S, Bast D, McGeer A, Azavedo JD, Low DE. Antimicrobial susceptibility breakpoints and first step mutations in *Streptococcus pneumoniae*: Redefining fluoroquinolone resistance. *Emerg Infect Dis* 2003;**9**:833–7.
13. Zhao X, Drlica K. Restricting the selection of antibiotic resistant mutants: A general strategy derived from fluoroquinolone studies. *Clin Infect Dis* 2001;**33**:S147–S156.
14. Fish DN, North DS. Gatifloxacin, an advanced 8-methoxy fluoroquinolone. *Pharmacotherapy* 2001;**21**:35–59.

Literature Review

Compiled by Dr. Pradeep Chatterjee

Antimicrobial treatment in Diabetic women with Asymptomatic Bacteriuria. Godfrey K, Harding MD, Nicoble MD *et al* (*N. Eng J. Med.* 2002;**347**:1576–83)

Asymptomatic bacteriuria is common among women with diabetes, and the treatment of such infections has been recommended to prevent complications related to symptomatic urinary tract infection. Thus the study in women (>16 years of age) with diabetes, bacteriuria (>10 colony-forming units of an organism per milliliter in cultures of two consecutive urine specimens) were enrolled with no urinary symptoms. 50 were randomly assigned to receive placebo and 55 to receive antimicrobial therapy. For the first six weeks which included the initial course of treatment, the study was placebo-controlled and double blind. Subsequently, the women were screened for bacteriuria every three months for up to three years, antimicrobial therapy was provided to women in the antimicrobial therapy group who had asymptomatic bacteriuria.

Four weeks after the end of the initial course of therapy 78% of placebo

recipients had bacteriuria, as compared with 20% of women who received antimicrobial agents ($p < 0.001$). During a mean follow up of 27 months, 20 of 50 women in the placebo group (40%) and 23 of 55 women in the antimicrobial therapy group (42%) had at least one episode of symptomatic urinary tract infection. The time to a first symptomatic episode was similar in the placebo group and the antimicrobial therapy group. $P = 0.67$ by the long rank test), as were the (ISD) rates of any symptomatic urinary tract infection (1.10 ± 0.17) and 0.93 ± 0.14 per 1000 days of follow up respectively; relative risk, 1.19; 95% confidence interval 0.28 to 1.81). Pyelonephritis (0.28 ± 0.08) and 0.13 ± 0.05 per 1000 days of follow up; relative risk, 1.93; 95% confidence interval 0.47 to 7.89). The women in the antimicrobial therapy group had almost five times as many days of antibiotic use for urinary tract infection as did the women in placebo group. (158.2 ± 1.7 vs $33.7 \pm 0.91/1000$ days of follow up).

Treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications. Diabetes itself should not be an indication for screening for or treatment of asymptomatic bacteriuria.

Conclusion

There have been tremendous advances in direct antigen detections and the sensitivity and specificity of assays detecting TORCH antibodies. It is the interpretation of the results in individual cases that need to be made carefully. The relatively poor degree of reliability can lead to unnecessary obstetric interventions or elective termination of pregnancy. Any positive pathogen-specific IgM in the maternal serum should be subjected to additional confirmatory testing in a reputed research laboratory before any intervention is carried out. No termination of pregnancy should be recommended only on the basis of a single antibody test. Antenatal diagnosis must be attempted by way of virus isolation or its antigen detection using molecular assays. Limitations of IgM serology by way of false-positive and negative results cannot be undermined; however, cord blood samples are preferred for IgM serology. At the same time, undue importance cannot be given to low-avidity IgG antibodies. Seroassays cannot be viewed in isolation, therefore, the results need to be correlated clinically to avoid their misinterpretation and minimize the anxiety of patients, especially if termination of pregnancy is being considered.

References

- Thokar MA, Malla N, Wattal C. Serological study of patients clinically suspected to have toxoplasmosis in Kashmir. *Indian J Med Res* 1988;**88**:29-34.
- Akoijam BS, Shashikant, Singh S, Kapoor SK. Seroprevalence of *Toxoplasma* infection among primigravida women attending antenatal clinic at a secondary level hospital in North India. *J Indian Med Assoc* 2002;**100**:591-2, 594-6, 602.
- Singh S, Nautiyal BL. Seroprevalence of toxoplasmosis in Kumaon region of India. *Indian J Med Res* 1991;**93**:247-9.
- Wilson M, McAuley JB. *Toxoplasma*. In Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover FC, Tenover FC (ed.) *Manual of clinical microbiology*. 7th ed. Washington, DC: ASM Press;1999:1874-82.
- Remington JS, McLeod R, Desmonts G. Toxoplasmosis. In: Remington JS, Klein JO (eds.) *Infectious diseases of the fetus and newborn infant*. 4th ed. Philadelphia: WB Saunders; 1995:140-267.
- Singh S. Mother to child transmission and diagnosis of *Toxoplasma gondii* infection during pregnancy. *Indian J Med Microbiol* 2003;**21**:69-76.
- Hohlfeld P, Daffos F, Costa JM, Thulliez P, Forestier F, Vidaud M. Prenatal diagnosis of congenital toxoplasmosis with polymerase chain reaction test on amniotic fluid. *N Engl J Med* 1994;**33**:695-99.
- Montoya JG, Remington JS. *Toxoplasma gondii*. In: Mandell GL, Bennett JE, Dolin R (eds) *Mandell's, Douglas and Bennett's principles and practice of infectious diseases*. 5th ed. Philadelphia: Churchill Livingstone; 2000: 2859-2885.
- Kaur R, Gupta N, Nair D, Kakkar M, Mathur MD. Screening for TORCH infections in pregnant women: A report from Delhi. *Southeast Asian J Trop Med Public Health* 1999;**30**:284-6.
- Singh S. Prevalence of TORCH infections in Indian pregnant women *Indian J Med Microbiol* 2002;**20**:57-58.
- Bodeus M, Feyder S, Goubau P. Avidity of IgG antibodies distinguishes primary from nonprimary cytomegalovirus infection in pregnant women. *Clin Diagn Virol* 1998;**9**:9-16.
- Lazzarotto T, Spezzacatena P, Pradelli P, Abate DA, Varani S, Landini MP. Avidity of immunoglobulin G directed against human cytomegalovirus during primary and secondary infections in immunocompetent and immunocompromised subjects. *Clin Diagn Lab Immunol* 1997;**4**:469-473.
- Lazzarotto T, Varani S, Guerra B, Nicolosi A, Lanari M, Landini MP. Prenatal indicators of congenital cytomegalovirus infection. *J Pediatr*. 2000;**137**:90-5.
- Wattal C, Joshi S, Gupta A, Sharma A, et al. The pp 67 mRNA assay in treatment and monitoring in cytomegalovirus disease in renal transplant patients in India. *Transpl Infect Dis* 2004;**6**:90-92.
- Shanmugam J, Raveendranath M, Nair VR. Seroprevalence of rubella and cytomegalovirus (CMV) infection in pregnant women from Kerala state. *J Indian Assoc Commun Dis*. 1982;**5**:58-63.
- Thomas HI, Morgan Capner P, Roberts A, Hesketh L. Persistent rubella specific IgM activity in the absence of recent primary rubella and rubella reinfection. *J Med Virol* 1992;**36**:188-92.
- Hedman K, Rousseau SA. Measurement of avidity of specific IgG for verification for recent primary rubella. *J Med Virol* 1989;**27**:288-92.
- Kingham GR. Debate: The argument for, 'Should all pregnant women be offered type specific serological screening for HSV infection?' [Comment] *Herpes* 2002;**9**:46-7.
- Arvin AM. Debate: The argument for, 'Should all pregnant women be offered type specific serological screening for HSV infection?' [comment] *Herpes* 2002;**9**:46-7.
- Rouse DJ, Stringer JS. An appraisal of screening for maternal type-specific herpes simplex virus antibodies to prevent neonatal herpes. *Am J Obstet Gynecol* 2000;**183**:400-6.
- Helfgott A. TORCH testing in HIV-infected women. *Clin Obstet Gynecol* 1999;**42**:149-62 174-5.

Literature Review

Compiled by Dr. DDS Kulpati

Inhibitory effect of Nicotine on Experimental Hypersensitivity Pneumonitis (HP) on Vivo and in Vitro. Blanchet, Mr, Assayag E1 and Cormier Y. *Am J Respir Crit Care Med* 2004;**169**:903-909.

The nicotine, which is a major component of cigarette smoke, has immunomodulatory and antifibrotic effects. In fact, it inhibits lymphocyte proliferation, interleukin (IL), IB, tumour necrosis factor (TNF) IL-6 and IL-12 production by macrophages and fibroblast proliferation. Interestingly certain inflammatory diseases, such as sarcoidosis and ulcerative colitis are less frequent in smokers than in non-smokers and cigarette smoking protects against radiation pneumonitis. When exposed to an environment that can cause hypersensitivity pneumonitis, smokers have lower level of specific antibodies to causative antigen. On the other hand when HP occurs in smokers, it promotes an insidious and more chronic form of the disease and worsens the clinical outcome.

In this study HP was induced mice that were treated with nicotine either intraperitoneally (IP) (0.5 to 2.0 mg/kg/day or intranasally (IN) (0.025 to 2.0 mg/kg/day) both IP & IN - treated animals had fever bronchoalveolar larvae total cells and lymphocytes and a decreased lung-tissue inflammation IFN - but not interleukin - 10-m RNA expression was reduced in lung tissue of 2.0 mg/kg. IN - treated animals. To test the effect of nicotine on alveolar macrophages, AMJ2-C11 cells were treated with nicotine and stimulated with LPS or saccharo-polyspora rectivirgula (SR) a causative agent of HP.

Nicotine reduced TNF release & TNF, interleukine-10, & IFN- γ mRNA expression after stimulation and decreased CD-80 expression by 55% in LPS stimulated cells and by 41% in SR-stimulated cells. It was concluded that

nicotine could be at least impart, responsible for the protection observed in smokers against HP. The inhibitory effect of nicotine on alveolar - macrophages could be one of the mechanisms involved.

The Bactericidal activity of Moxifloxacin in patients with pulmonary tuberculosis. Gosline, RED, Viso, LO, San N E et al. *Am J Respir Crit Care Med*. 2003;**16**:1342-40

Fluoroquinolones, which inhibit DNA-gyrase, are highly active against Mycobacterium tuberculosis, including strains resistant to first line drugs. The minimum inhibitory conc. of moxifloxacin, is four fold lower than that of levofloxacin. It has the greatest sterilizing activity. The combination of rifampin, pyrazinamide, and moxifloxacin had substantially greater sterilizing activity compared with the standard regimen.

In this study, patients in whom acid-fast bacilli smear-positive tuberculosis was newly diagnosed, were randomized to receive 400mg moxifloxacin, 300mg isoniazid, or 600mg rifampicin daily for 5 days. Bactericidal activity was estimated by the time taken to kill 50% of viable bacilli (Vt50) and the fall in sputum viable count during first 2 days designated as the early bactericidal activity (EBA). The mean Vt50 of moxifloxacin was 0.88 days (95% confidence interval) and the EBA was 53 (95% CI). For the isoniazid group the (Vt50) was 0.40 days (95% CL) and the mean EBA was .77. For rifampin, the mean Vt50 was .71 days (85cl) and the mean EBA was .28 (5%CI). Using EBA method isoniazid was significantly more effective than rifampin (p<0.01) but not moxifloxacin. Using Vt50 method isoniazid was more effective than both rifampin and moxifloxacin.

Moxifloxacin has an activity similar to rifampin in human subjects with pulmonary tuberculosis, suggesting that it should undergo further assessment as a part of a short course regimen for the treatment of drug resistant tuberculosis