J Formos Med Assoc 2010;109(9):624–631

Contents lists available at ScienceDirect

Journal of the Formosan Medical Association

Journal homepage: http://www.jfma-online.com

Review Article

Fluoroquinolone Prophylaxis Against Febrile Neutropenia in Areas With High Fluoroquinolone Resistance—An Asian Perspective

*Esther Shu-Ting Ng,[1] Yixin Liew,[2] Liang Piu Koh,[3] Li Yang Hsu[1]**

Febrile neutropenia remains a major cause of morbidity and mortality in patients receiving chemotherapy. Major prophylactic strategies include granulocyte colony-stimulating factor and antibiotics, the most widely used of which are fluoroquinolones. While fluoroquinolone prophylaxis has been shown to be effective in areas where fluoroquinolone resistance is low, this same efficacy has not been proven in areas where resistance is high, such as in Asia. Given the increase in antimicrobial resistance with the use of prophylaxis, the risks and benefits of this strategy need to be carefully considered. This review presents the evidence for and against fluoroquinolone prophylaxis in areas of high fluoroquinolone resistance.

Key Words: antimicrobial resistance, Asia, febrile neutropenia, fluoroquinolone, prophylaxis

Febrile neutropenia (FN) remains a major cause of morbidity and mortality in patients receiving chemotherapy. Given the risks and costs involved in the treatment of FN, prophylactic approaches directed against its development have gained popularity and traction at many oncology and hematology units worldwide. The two major prophylactic strategies currently employed are the use of granulocyte colony-stimulating factors (G-CSF) and the use of antibiotics.

The use of G-CSF as primary prophylaxis to reduce the risk of FN is well established. While it has little measurable impact on overall survival, it may reduce the risk of FN and early deaths, allowing for increased dose intensity of chemotherapy.[1–4] The role of antibiotic prophylaxis has been somewhat more controversial, particularly for patients at low risk of FN. In the past, various types of antibiotic prophylaxis against FN have been evaluated, including trimethoprim-sulfamethoxazole, fluoroquinolones and various antibiotic combinations (mainly fluoroquinolones in combination with Gram-positive agents such as rifampicin, vancomycin, amoxicillin or roxithromycin).[5,6] However, fluoroquinolones have rapidly emerged as the most commonly used prophylactic agents because of their broad antimicrobial spectrum, preservation of anaerobic gut flora (with the exception

Departments of [1]Medicine and [3]Hematology/Oncology, National University Health System, and [2]Department of Pharmacy, Singapore General Hospital, Singapore.

Received: December 1, 2009
Revised: May 24, 2010
Accepted: May 27, 2010

***Correspondence to:** Dr Li Yang Hsu, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, 119074 Singapore.
E-mail: liyang_hsu@yahoo.com

of moxifloxacin), good oral bioavailability and high therapeutic index.[7]

Benefits and Risks of Fluoroquinolone Prophylaxis

Two recent large randomized controlled trials demonstrated that fluoroquinolone prophylaxis resulted in a lower incidence of FN episodes post-chemotherapy in different patient populations.[8,9] Bucaneve et al showed that levofloxacin prophylaxis was effective in reducing FN incidence in hospitalized patients receiving chemotherapy for lymphoma, leukemia and solid tumors in an Italian center.[8] Findings from Cullen et al also corroborated this observation by demonstrating decreased febrile episodes and hospitalization in an UK sample of outpatients given chemotherapy for solid tumors or lymphomas.[9] Both studies failed to show any overall survival benefit for patients prescribed fluoroquinolones.

Meta-analyses, however, have tended to favor fluoroquinolone prophylaxis as a strategy to decrease overall mortality post-chemotherapy. Based on studies performed prior to 2003, Gafter-Gvili et al showed that for patients with acute leukemia who had undergone bone marrow transplantation, the relative risk (RR) of death with fluoroquinolone prophylaxis was 0.67 (95% confidence interval = 0.55–0.83) in comparison to the control group.[10] Among patients with solid tumors and lymphomas, fluoroquinolone prophylaxis had a significant impact on all-cause mortality during the first cycle of chemotherapy, with a RR of 0.48 (95% confidence interval = 0.26–0.88) compared with controls.[11] A later meta-analysis incorporating only randomized placebo-controlled trials showed a statistically non-significant, but consistent, trend towards decreased mortality when fluoroquinolone prophylaxis was employed (RR = 0.76; 95% confidence interval: 0.54–1.08; $p = 0.13$).[12]

However, the use of fluoroquinolone prophylaxis is not without risk. In neutropenic patients, prior fluoroquinolone usage is a strong risk factor for the development of fluoroquinolone-resistant *Escherichia coli* bacteremia,[13] which may be related to the selection of pre-existing resistant mutants of *E. coli* in the gastrointestinal tracts of these patients.[14] In addition, an increased rate of fluoroquinolone-resistant streptococcal bacteremia has been reported,[15,16] likely arising from a higher risk of oral colonization with fluoroquinolone-resistant viridans streptococci.[17]

Nonetheless, Kern et al argued that fluoroquinolone prophylaxis may still be beneficial despite increased resistance.[18] In a 6-month fluoroquinolone prophylaxis discontinuation intervention trial among acute leukemia patients, the investigators found that the Gram-negative bacteremia incidence rate increased to 20% from a low of 8% during the pre-intervention period. The resumption of fluoroquinolone prophylaxis thereafter decreased the incidence of Gram-negative bacteremia back to 9% while the proportion of fluoroquinolone resistance in *E. coli* bacteremia isolates again increased from 15% during the intervention period to more than 50% in the post-intervention period.[18] The authors believed that the relative proportion of resistance among *E. coli* did not correlate with, and was not a good indicator of, the protective efficacy of fluoroquinolone prophylaxis. As with other studies, however, no statistically significant impact on mortality was found with regards to the initial rise and subsequent decline of Gram-negative bacteremia rates.[18]

Geographic Fluoroquinolone Resistance is Higher in Asian Countries

Several surveillance studies in varied clinical settings suggest that fluoroquinolone resistance is widespread in most parts of Asia. In the 2004 Study for Monitoring Antimicrobial Resistance Trends, which included worldwide data on Gram-negative bacilli that caused intra-abdominal infections, the highest rate of fluoroquinolone resistance was found in the Asia-Pacific region.[19] In China, 53–57% of clinical strains of *E. coli* were resistant to ciprofloxacin.[20] In a Korean study on outpatient

urinary tract infections, ciprofloxacin resistance rates were 43.4% in *E. coli*, 43.9% in *Klebsiella pneumoniae* and 86.8% in *Pseudomonas aeruginosa*.[21] In Singapore, a hospital-based surveillance program showed that 34.4% and 42.5% of clinical *E. coli* and *K. pneumoniae* isolates, respectively, were resistant to ciprofloxacin.[22]

In comparison, the European Antimicrobial Resistance Surveillance System[23] reported that in 2007, only 19.7% and 19.0% of bloodstream *E. coli* and *K. pneumoniae* isolates in Europe were resistant to fluoroquinolones. In North America, the data have been variable but resistance rates are generally lower than those reported in Asia. As an example, Zhanel et al studied urinary tract pathogens among outpatients with urinary tract infection. Among all isolates, 9.7% were resistant to ciprofloxacin, whereas only 5.5% of *E. coli* isolates were resistant to ciprofloxacin.[24]

We conducted a PubMed search specific to adult patients with febrile neutropenia in Asia, using the following keywords in combination: "Asia", "Korea", "China", "quinolones", "fluoroquinolones", "ciprofloxacin", "levofloxacin", "antibiotics" and "febrile neutropenia". English language articles and foreign language articles with English translation were included in our review. Data on antimicrobial use and antimicrobial resistance were collected. The results of representative studies are shown in the Table.[25–33]

Unlike European and US reports, where the majority of bacteremias in patients with FN are due to Gram-positive bacteria,[34,35] the majority of Asian reports demonstrate overall predominance of Gram-negative bacilli, in particular Enterobacteriaceae.[25–33] The reason for this discrepancy is unclear, as it is likely that the use of central catheters, fluoroquinolone prophylaxis and aggressive chemotherapy with significant mucositis—touted as the reasons for the predominance of Gram-positive organisms in FN—are just as widespread in Asian centers as in Western centers.

Fluoroquinolone resistance was high among the Gram-negative bacteria cultured in the Asian studies, ranging up to 80% of all isolates. Chen et al reported 33% of *E. coli* isolates as resistant to fluoroquinolones, even though no fluoroquinolone prophylaxis was used.[28] With such high baseline rates of resistance, it is conceivable that fluoroquinolone prophylaxis would not only be ineffective in preventing FN in post-chemotherapy patients from Asian countries, but could further augment the resistance rates. The above observations imply a decreased applicability of findings from Western studies and meta-analyses, such as Kern et al,[18] to an Asian context, where the fluoroquinolone resistance rates are generally higher compared to European and US populations.

Current Recommendations on Fluoroquinolone Prophylaxis

In 2008, the US National Comprehensive Cancer Network published guidelines on the prevention and treatment of cancer-related infections. Prophylactic fluoroquinolones were recommended for high-risk and intermediate-risk groups, comprising patients receiving high-dose chemotherapy and those in whom the anticipated duration of neutropenia is longer than 7 days.[1] Cullen and Baijal further recommended that patients with solid malignancies undergoing standard outpatient cyclical chemotherapy should also receive fluoroquinolone prophylaxis especially in the first cycle, if grade 4 neutropenia is expected, i.e. regimens containing docetaxel, doxorubicin or vinorelbine.[36] However, concerns had previously been raised about whether the selection of fluoroquinolone-resistant flora during the first cycle of chemotherapy would increase the incidence of resistant Gram-negative organisms in subsequent courses.[37]

Efficacy and Impact of Fluoroquinolone Prophylaxis in Institutions With High Pre-existing Gram-negative Fluoroquinolone Resistance

A Mexican study on the use of ciprofloxacin among patients with acute leukemia found that bacteremia

Table. Fluoroquinolone resistance rates among Enterobacteriaceae isolated from patients with febrile neutropenia from Asian countries

Study (yr)	Location	Sample population	Bacterial isolates	Fluorouinolone resistance of bacterial isolates	Prevalence of antibiotic prophylaxis (%)	Reference
Baskaran et al (2007)	Malaysia	Leukemia, lymphoma, post-SCT	60.3% G– 30.7% G+	62.5% of *E. coli* and 18.2% of *Klebsiella spp.* were resistant to ciprofloxacin	11.2	25
Chayakulkeeree et al (2003)	Thailand	HM, solid tumors	88.6% G–	–	3.6	26
Gupta et al (2009)	India	AML	72.0% G– 40.0% G+	82.0% of G– were ESBL positive	–	27
Chen et al (2004)	Taiwan	HM	58.0% G– 32.0% G+	33.0% of *E. coli*, 13.0% of *K. pneumoniae* and 2.0% of *P. aeruginosa* were resistant to ciprofloxacin	0	28
Irfan et al (2008)	Pakistan	HM, solid tumors	42.0% G– 53.0% G+	55.0% of Enterobacteriaceae and 76.0% of *P. aeruginosa* were resistant to ciprofloxacin	–	29
Park et al (2009)	Korea	Leukemia, lymphoma, myelodysplastic syndrome, multiple xmyeloma, aplastic anemia	52.0% G– 30.2% G+	–	–	30
Lee et al (2002)	Korea	AML	14.6% G– 34.1% G+	5/5 (100%) of G– in the control group and 3/23 (13%) G– in the prophylaxis group were resistant to quinolones	Randomized study (prophylaxis group, $n=46$; control group, $n=49$)	31
Park et al (2006)	Korea	Hematopoietic SCT patients	51.0% G– 27.0% G+	76.6% of *E. coli* were resistant to quinolones	100	32
Khan et al (2004)	Pakistan	HM	47.0% G– 53.0% G+	62.0% of *E coli* and 31.0% of *Pseudomonas spp.* were resistant to fluoroquinolones	–	33

AML = Acute myeloid leukemia; HM = Hematological malignancies; SCT = stem cell transplantation; ESBL = extended spectrum beta-lactamase; G– = Gram-negative isolates; G+ = Gram-positive isolates.

was similar between the prophylaxis and control group.[38] In that population, the prevalence of ciprofloxacin resistance was relatively high; 24% of adults and 26% of children who visited the emergency room with no known exposure to fluoroquinolones in the preceding 3 months harbored ciprofloxacin-resistant *E. coli* in their feces. Gomez et al found that there was a trend towards a higher rate of Gram-positive bacteremia in the control group and a higher rate of Gram-negative bacteremia in the ciprofloxacin group. Resistance to fluoroquinolones was greater in *E. coli* blood isolates from patients in the ciprofloxacin group.[38]

The evidence thus far is mixed with regards to the question of whether fluoroquinolone prophylaxis is efficacious in preventing FN in patients who have documented infection or colonization with fluoroquinolone-resistant organisms.[18,37]

Patients who are colonized by fluoroquinolone-resistant bacteria are more likely to have previous exposure to antibiotics. These may also be patients with previous episodes of FN. As previous FN is an independent predictor for further FN,[39] high-risk patients might be deprived of effective prophylaxis if fluoroquinolones are withheld. After all, colonization with resistant Gram-negative bacteria might well be transitory. In a study conducted by Perea et al, 10 out of 21 patients were colonized by fluoroquinolone-resistant *E. coli* after 8 days of prophylaxis. There were no differences in infectious complications in patients colonized with resistant flora. After discontinuation of prophylaxis, only two out of the 10 patients remained colonized, hence previous documentation of colonization or infection with resistant flora does not reliably predict that fluoroquinolone prophylaxis would be ineffective.[37]

However, the use of fluoroquinolones has also been associated with the emergence of other antibiotic-resistant pathogens, including carbapenem-resistant organisms.[40,41] In patients at high risk of FN who are already colonized with fluoroquinolone-resistant organisms, the further use of fluoroquinolones may not prevent FN, but may instead lead to the development of carbapenem or other antibiotic resistance.

Role of Further Studies on Fluoroquinolone Prophylaxis in Regions With High Existing Fluoroquinolone Resistance

Are further studies regarding fluoroquinolone prophylaxis necessary? Kern et al documented the effectiveness of fluoroquinolone prophylaxis despite its effect on increasing resistance rates. However, this study used a German sample, where baseline resistance rates were low.[18] Another study (from a hospital in Barcelona) also showed that the discontinuation of norfloxacin prophylaxis led to a rapid increase in the rate of fluoroquinolone-susceptible enterobacterial infections; however, there was little impact on infectious morbidity.[42]

Studies in Asian populations with high population resistance rates are necessary as results may differ significantly from those described by Kern et al. Such studies would not be without risk. First, the discontinuation of prophylaxis in high-risk patients may result in an increase in FN episodes. Second, the discontinuation and reinitiation of antibiotics may add to resistance selection pressure.

Where baseline fluoroquinolone resistance is high and fluoroquinolone prophylaxis may be less effective, alternative strategies of prophylaxis should be considered.

Current guidelines recommend that patients whose risk of FN is 20% or greater should be given primary prophylactic G-CSF.[43] A large study has shown that the addition of G-CSF to prophylactic antibiotics led to a further decrease in the incidence of FN.[38] In this study, the antibiotic prophylaxis used was a combination of ciprofloxacin and roxithromycin.[38] In areas of high fluoroquinolone resistance, where fluoroquinolone prophylaxis may be less effective, we suggest lowering the threshold for G-CSF prophylaxis, especially in patients with documented previous infection or colonization with fluoroquinolone resistant organisms.

However, the use of G-CSF is not without potential risk in certain clinical situations. There is a small theoretical risk of stimulating underlying disease during allogeneic stem cell transplantation

of patients with monosomy 7 acute myeloid leukemia.[44] No conclusive benefit in terms of survival has been documented with regards to its use in leukemia or allogeneic stem cell transplantation.[44]

We need better models of neutropenia risk that incorporate both G-CSF and fluoroquinolone prophylaxis that take into account the population baseline resistance rates.

Conclusions

FN is a major cause of mortality and morbidity in cancer patients worldwide. Antibiotic prophylaxis, most commonly with fluoroquinolones, has been shown to be effective in preventing FN within areas with low prevalence of fluoroquinolone resistance, but this may not hold true in areas of high prevalence.

The prevalence of fluoroquinolone resistance is higher in Asia compared with the United States and Europe, and further studies are required to evaluate the efficacy of fluoroquinolone prophylaxis in Asia. This is due to the view that the use of prophylaxis has been proven to cause an increase in fluoroquinolone-resistant organisms. Better models of neutropenia risk are needed, which incorporate both G-CSF and antibiotic prophylaxis. These models should include individualized calculation of FN risk, so as to permit the identification of high-risk patients who may benefit from fluoroquinolone prophylaxis while minimizing antibiotic selection pressure from less discriminate prescription of these antibiotics.

Acknowledgments

We would like to thank Ms Siew Woon Lim for her assistance in collating data.

Dr Liang Pin Koh is currently the site principal investigator for a multicenter study funded by Pfizer Inc. Dr Li Yang Hsu has received honoraria from Pfizer Inc and Janssen-Cilag. He has also received research funding from Pfizer Inc, Janssen-Cilag, AstraZeneca, and Merck, Sharpe & Dohme. Dr Esther Shu-Ting Ng and Yixin Liew report no potential conflicts of interest.

References

1. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw* 2008;6:122–74.
2. Kuderer NM, Dale DC, Crawford J, et al. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol* 2007;25:3158–67.
3. Aapro MS, Cameron DA, Pettengell R, et al. European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42:2433–53.
4. Smith TH, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–205.
5. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol* 1998;3:1179–87.
6. Cruciani M, Malena M, Bosco O, et al. Reappraisal with meta-analysis of the addition of Gram-positive prophylaxis to fluoroquinolone in neutropenic patients. *J Clin Oncol* 2003;1521:4127–37.
7. Del Favero A, Menichetti F. The new fluorinated quinolones for antimicrobial prophylaxis in neutropenic cancer patients. *Eur J Cancer* 1993;29A(Suppl 1):S2–6.
8. Bucaneve G, Micozzi A, Menichetti F, et al for the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program: Levofloxacin to prevent bacterial infection in patients in cancer and neutropenia. *N Engl J Med* 2005;353:10977–87.
9. Cullen M, Steven N, Billingham L, et al for the Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy ± Antibiotic in a Number of Tumours (Significant) Trial Group: Antibacterial prophylaxis after chemotherapy for solid cell tumours and lymphomas. *N Engl J Med* 2005;353:988–98.
10. Gafter-Gvili A, Fraser A, Paul M, et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Int Med* 2005;142:979–95.
11. Leibovici L, Paul M, Cullen MH. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. *Cancer* 2006;107:1743–51.
12. Imran H, Tleyjeh IM, Arndt CA, et al. Fluoroquinolone prophylaxis in patients with neutropenia: a meta-analysis of

randomized placebo-controlled trials. *Eur J Clin Microbiol Infect Dis* 2008;27:53–63.
13. Carratalá J, Fernández-Sevilla A, Tubau F, et al. Emergence of quinolone-resistant Escherichia coli bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis* 1995;20:557–60.
14. Baum HV, Franz U, Geiss HK, et al. Prevalence of ciprofloxacin-resistant Escherichia coli in hematologic-oncologic patients. *Infection* 2000;28:278–81.
15. Bochud PY, Calandra T, Francioli P. Bacteremia due to viridans streptococci in neutropenic patients: a review. *Am J Med* 1994;97:256–64.
16. Oppenheim BA, Hartley JW, Lee W, et al. Outbreak of coagulase-negative staphylococcus highly resistant to ciprofloxacin in a leukemia unit. *Br Med J* 1989;299:294–7.
17. Prabhu RM, Piper KE, Litzow MR, et al. Emergence of fluoroquinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving fluoroquinolone antimicrobial prophylaxis. *Eur J Clin Microbiol Infect Dis* 2005;24:832–8.
18. Kern WV, Kern WV, Klose K, et al. Fluoroquinolone resistance of *Escherichia coli* at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. *Eur J Clin Microbiol Infect Dis* 2005;24:111–8.
19. Rossi F, Baquero F, Hsueh PR, et al. In vitro susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *J Antimicrob Chemother* 2006;58:205–10.
20. Wang M, Tran JH, Jacoby GA, et al. Plasmid-mediated quinolone resistance in clinical isolates of Escherichia coli from Shanghai, China. *Antimicrob Agents Chemother* 2003; 47:2242–8.
21. Ko YH, Oh JS, Cho DY, et al. Changes of causative organisms and antimicrobial sensitivity of urinary tract infection between 1979 and 2001. *Korean J Urol* 2003;44:342–50.
22. Hsu LY, Tan TY, Jureen R, et al. Antimicrobial drug resistance in Singapore hospitals. *Emerg Infect Dis* 2007;13:1944–7.
23. *European Antimicrobial Resistance Surveillance System (EARSS) Annual Report 2007.* Bilthoven, the Netherlands, October 2008. Available at: http://www.rivm.nl/earss/Images/EARSS%202007_FINAL_tcm61-55933.pdf [Date accessed: November 22, 2009]
24. Zhanel GG, Hisanaga TL, Laing NM, et al. NAUTICA Group: Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 2005;26:380–8.
25. Baskaran ND, Gan GG, Adeeba K, et al. Bacteremia in patients with febrile neutropenia after chemotherapy at a university medical center in Malaysia. *Int J Infect Dis* 2007;11:513–7.
26. Chayakulkeeree M, Thamlikitkul V. Risk index for predicting complications and prognosis in Thai patients with neutropenia and fever. *J Med Assoc Thai* 2003;86:212–23.
27. Chen CY, Tang JL, Hsueh PR, et al. Trends and antimicrobial resistance of pathogens causing bloodstream infections among febrile neutropenic adults with hematological malignancy. *J Formos Med Assoc* 2004;103:526–32.
28. Gupta A, Singh M, Singh H, et al. Infections in acute myeloid leukemia: an analysis of 382 febrile episodes. *Med Oncol* 2009;Oct 15. [Epub ahead of print]
29. Irfan S, Idrees F, Mehraj V, et al. Emergence of Carbapenem resistant Gram negative and vancomycin resistant Gram positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study. *BMC Infect Dis* 2008;8:80.
30. Park Y, Kim DS, Park SJ, et al. The suggestion of a risk stratification system for febrile neutropenia in patients with hematologic disease. *Leuk Res* 2009;34:294–300.
31. Lee DG, Choi SM, Choi JH, et al. Selective bowel decontamination for the prevention of infection in acute myelogenous leukemia: a prospective randomized trial. *Korean J Intern Med* 2002;17:38–44.
32. Park Sh, Choi SM, Lee DG. Current trends of infectious complications following hematopoietic stem cell transplantation in a single center. *J Korean Med Sci* 2006;21: 199–207.
33. Khan MA, Siddiqui BK, Shamim A, et al. Emerging bacterial resistance patterns in febrile neutropenic patients: experience at a tertiary care hospital in Pakistan. *J Pak Med Assoc* 2004;54:357–60.
34. Viscoli C. Infectious complications in neutropenic cancer patients. Available at: http://cme.medscape.com/viewarticle/468938 [Date accessed: November 10, 2009]
35. Feld R. Bloodstream infections in cancer patients with febrile neutropenia. *Int J Antimicrob Agents* 2008;32 Suppl 1: S30–3.
36. Cullen M, Baijal S. Prevention of febrile neutropenia: use of prophylactic antibiotics. *Br J Cancer* 2009;101 Suppl 1: S11–4.
37. Perea S, Hidalgo M, Arcediano A, et al. Incidence and clinical impact of fluoroquinolone-resistant Escherichia coli in the faecal flora of cancer patients treated with high dose chemotherapy and ciprofloxacin prophylaxis. *J Antimicrob Chemother* 1999;44:117–20.
38. Gomez L, Garau J, Estrada C, et al. Ciprofloxacin prophylaxis in patients with acute leukemia and granulocytopenia in an area with a high prevalence of ciprofloxacin-resistant Escherichia coli. *Cancer* 2003;97:419–24.
39. Timmer-Bonte JN, de Boo TM, Smit HJ, et al. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch randomized phase III study. *J Clin Oncol* 2005;23:7974–84.
40. Lautenbach E, Weiner MG, Nachamkin I, et al. Imipenem resistance among Pseudomonas aeruginosa isolates: risk factors for infection and impact of resistance on clinical

and economic outcomes. *Infect Control Hosp Epidemiol* 2006;27:893–900.

41. Tanimoto K, Tomita H, Fujimoto S, et al. Fluoroquinolone enhances the mutation frequency for meropenem-selected carbapenem resistance in Pseudomonas aeruginosa, but use of the high-potency drug doripenem inhibits mutant formation. *Antimicrob Agents Chemother* 2008;52: 3795–800.
42. Martino R, Subira M, Altés A, et al. Effect of discontinuing prophylaxis with norfloxacin in patients with hematologic malignancies and severe neutropenia. A matched case-control study of the effect on infectious morbidity. *Acta Haematol* 1998;99:206–11.
43. Kelly S, Wheatley D. Prevention of febrile neutropenia: use of granulocyte colony-stimulating factors. *Br J Cancer* 2009;101 Suppl 1:S6–10.
44. Battiwalla M, McCarthy PL. Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice. *Bone Marrow Transpl* 2009;43:351–6.