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Commentary

# Fluoroquinolone prophylaxis during neutropenia: what can we expect nowadays?

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Prophylaxis with fluoroquinolones (FQ) during prolonged neutropenia has been standard of care in many centres based on the results of meta-analyses and a large prospective study performed in Italy in patients with haematological malignancies. A meta-analysis from 2005, which included studies published between 1973 and 2005, found significantly lower rates of mortality, infections, and fever episodes in patients receiving FQ prophylaxis [1]. The randomized study by Bucaneve and colleagues reported significantly lower rates of fever episodes (65% vs. 85%) and bacteraemia (18% vs. 34%) in patients receiving prophylaxis with levofloxacin, with no significant impact on mortality (3% vs. 5%) [2]. An updated meta-analysis, which incorporated these data, confirmed the benefit of FQ on fever, bacteraemia, and mortality, with a number-needed-to-treat to prevent one death of 55 [3]. A meta-analysis limited only to stem cell transplant patients, mainly autologous (ASCT), who were not included in the Bucaneve trial, found lower rates of bacteraemia and febrile episodes but no impact on mortality [4].

However, a decade later, considering the threat of increasing antimicrobial resistance worldwide, the utility of FQ prophylaxis has been questioned for two main reasons. First, doubts about its efficacy were prompted by high rates of resistance to FQ, reported both in the community and in the hospital setting. Indeed, resistance to FQ in strains from invasive infections in 2016 reached over 40% for *E. coli* in Slovakia, Bulgaria, Italy, and Cyprus, and over 60% for *K. pneumonia* in Romania, Slovakia, Poland, and Greece [5]. As patients with haematological malignancies usually undergo repeated cycles of in-patient chemotherapy, they are likely to be colonized by FQ-resistant pathogens. Second, the risk of inducing or selecting multidrug-resistant (MDR) strains by prolonged and repeated exposure to FQ has been reported. Indeed, the possibility of FQ promoting infections caused by multidrug-resistant pathogens, such as those producing extended spectrum β-lactamase (ESBL), has been observed [6], particularly in settings with a high prevalence of resistant strains [7,8]. Indirect evidence concerning this issue came from a large recent study which included 65 SCT centres from 25 countries (Europe, Australia, Asia) reporting data on 655 episodes of Gram-negative bacteraemia [9]. This observational trial reported that 45% of ASCT centres provided FQ prophylaxis. The rates of resistance to β-lactams other than carbapenems and MDR were significantly higher in centres providing versus those not providing fluoroquinolone prophylaxis (respectively, 36% vs. 13%, p 0.002 and MDR 35% vs. 8%, p <0.001) [9].

In this issue of *Clinical Microbiology and Infection*, Yeshurun et al. [10] report findings of a single-centre retrospective study on the effect of ciprofloxacin prophylaxis discontinuation on infectious complications in patients with multiple myeloma and lymphoma undergoing ASCT. The authors compared febrile episodes, infectious complications (bacteraemia, pneumonia, and *Clostridium difficile* associated disease (CDAD)), and mortality in 177 patients transplanted between March 2007 and October 2012 who received prophylaxis with ciprofloxacin versus 179 patients transplanted between October 2012 and July 2016 who did not receive any antibiotic prophylaxis. During the second period, they observed higher rates of febrile neutropenia (83.1% vs. 90.4%, p 0.002), bacteraemia (4.5% vs. 15%, p <0.0001), and pneumonia (6.2% vs. 12.3%, p 0.04). The rate of CDAD did not change significantly (2.8% vs. 6.7%, p 0.08), and mortality was similar (2.3% vs. 1.1% p 0.4). The authors concluded that patients with multiple myeloma and lymphoma undergoing ASCT may benefit from antibacterial prophylaxis with ciprofloxacin.

Association between FQ prophylaxis and lower rate of bacteraemia in ASCT recipients, particularly with multiple myeloma, has

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been recently reported by other groups [11,12]. A recent literature review on FQ prophylaxis in haematology patients with neutropenia performed by the European Conference on Infections in Leukemia (ECIL) group [8], found that FQ might still prevent infectious episodes, particularly in settings of low prevalence of MDR strains, such as in the Yeshurun et al. cohort, in which no patient was colonized with any MDR strain [10]. Other recent studies with similar retrospective comparisons with historical cohorts evaluated the effect of discontinuing prophylaxis. While some, but not all, reported higher rates of bacteraemia with no prophylaxis, none of them, even one that included 1987 patients, found any difference in mortality [8].

The crucial issue is the clinical benefit of a reduction in fever and/or bacteraemia episodes, usually caused by susceptible strains, in times of the need of antibiotic stewardship due to a worldwide increase in MDR strains. Yeshurun et al. assumed that as bacteraemia was associated with higher mortality (8.6% vs. 0.8% at 30 days) and ciprofloxacin prophylaxis was associated with a lower rate of bacteraemia, the prophylaxis would result in lower mortality. However, the mortality in neutropenic patients with bacteraemia is influenced mostly by the time between the onset of infection and the administration of appropriate antibiotic therapy [13]. Bacteraemia episodes that can be prevented by ciprofloxacin are typically caused by susceptible bacteria, and as such, empirical therapy would be effective against them and they should not result in increased mortality. Bacteraemia-associated mortality is usually caused by MDR pathogens, which are unlikely to be prevented by FQ [12,14]. For example, in a recent multicentre study, 78% of carbapenem-resistant *Enterobacteriaceae* were resistant to FQ [9]. This study also noted that the negative impact on survival was mainly caused by infections caused by resistant Gram-negative pathogens, which are unlikely to be prevented by FQ prophylaxis. A recent observational study from Italy which included 1625 ASCT recipients, reported that infections caused by resistant pathogens were predominantly responsible for increased mortality [12]. The probability of survival at 4 months from transplant in 1479 patients who did not develop bacteraemia because of Gram-negative bacteria was 97.5%, compared with 98.4% in 63 patients with cephalosporin-susceptible *E. coli* infection (p 0.66), 93.1% in 29 patients with cephalosporin-non-susceptible but carbapenem-susceptible *E. coli* infection (p 0.13), but only 66.7% in six patients with carbapenem-resistant *K. pneumoniae* infections (p <0.0001) [12]. This might explain the lack of effect of FQ prophylaxis on mortality despite the presence of a reduced rate of infection, reported also in other recent studies [8].

Two recent guidelines invite the readers to interpret the data in the light of the lack of significant benefit on mortality, and despite a possible reduction in the rate of infection and fever episodes in some settings, they do not recommend FQ prophylaxis [15,16]. This cautious policy is in agreement with what we, on behalf of the ECIL group, have recently published [8].

In conclusion, it is unlikely that FQ prophylaxis would reduce mortality, because (1) infections by susceptible strains are easily treated with standard empirical therapy, and (2) mortality is mainly driven by infections caused by pathogens resistant to standard therapy employed in febrile neutropenia and to FQs. In the era of increasing antibiotic resistance, even in settings with low prevalence of MDR bacteria so far, routine use of FQ prophylaxis should be reconsidered. Further research should focus on rapid identification of infecting pathogens and their susceptibility profile to allow for early start of adequate treatment even in case of resistant bacteria.

## Transparency declaration

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## References

[1] Gafter-Gvili A, Fraser A, Paul M, van de Wetering M, Kremer L, Leibovici L. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 2005, CD004386.
[2] Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977–87.
[3] Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer 2006;107:1743–51.
[4] Kimura S, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al. Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of randomized controlled trials. J Infect 2014;69:13–25.
[5] Control ECfDPa. Antimicrobial resistance surveillance in Europe 2016. Annual report of the European antimicrobial resistance surveillance network (ears-net). Stockholm: ECDC; 2017.
[6] Mendelson G, Hait V, Ben-Israel J, Gronich D, Granot E, Raz R. Prevalence and risk factors of extended-spectrum beta-lactamase-producing escherichia coli and klebsiella pneumoniae in an israeli long-term care facility. Eur J Clin Microbiol Infect Dis 2005;24:17–22.
[7] Garnica M, Nouer SA, Pellegrino FL, Moreira BM, Maiolino A, Nucci M. Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance. BMC Infect Dis 2013;13:356.
[8] Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect 2018;76:20–37.
[9] Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the infectious diseases working party of the european bone marrow transplantation group. Clin Infect Dis 2017;65:1819–28.
[10] Yeshurun M, Vaxman I, Shargian L, Yahav D, Bishara J, Pasvolsky O, et al. Antibacterial prophylaxis with ciprofloxacin for patients with multiple myeloma and lymphoma undergoing autologous haematopoietic cell transplantation: a quasi-experimental single centre before-after study. Clin Microbiol Infect 2018;24:749–54.
[11] Satlin MJ, Vardhana S, Soave R, Shore TB, Mark TM, Jacobs SE, et al. Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transpl 2015;21:1808–14.
[12] Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. Clin Infect Dis 2017;65:1884–96.
[13] Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (esbl) production and fluoroquinolone resistance in bloodstream infections caused by escherichia coli in patients with hematological malignancies. J Infect 2009;58:299–307.
[14] Mikulska M, Raiola AM, Galaverna F, Balletto E, Borghesi ML, Varaldo R, et al. Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: impact of t cell-replete transplantation from a haploidentical donor. Biol Blood Marrow Transpl 2018;24:109–18.
[15] Slavin MA, Lingaratnam S, Mileshkin L, Booth DL, Cain MJ, Ritchie DS, et al. Use of antibacterial prophylaxis for patients with neutropenia. Australian consensus guidelines 2011 steering committee. Intern Med J 2011;41:102–9.
[16] Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropenia: ESMO clinical practice guidelines. Ann Oncol 2016;27:v111–8.