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Ciprofloxacin: One Drug – Numerous Collateral Damages

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Usage of antibiotic drugs results in the development of antibiotic resistant bacteria [1]. Methicillin resistant *Staphylococcus aureus* (MRSA), enterobacteria exhibiting broad spectrum beta-lactamase activity (ESBL), *Clostridium difficile*, and multi-drug resistant nonfermenters, e.g. *Pseudomonas aeruginosa*, have become matter of concern. Oddly, these bacteria started to spread worldwide within the same timeframe although antibiotics typically used to treat infections caused by these bacteria had been introduced decades before. This temporal coincidence raises the question for a common event resulting simultaneously in the raise of MRSA, ESBL, *C. difficile*, and other multi-drug resistant bacteria.

In my mind, the most probable event has been the market introduction of ciprofloxacin for treatment of bacterial infections. In the 1960s and 1970s first generation inhibitors of bacterial topoisomerase (gyrase) have been manufactured. In 1981 Ciprofloxacin has been developed and in 1987 the drug has been approved by the U.S. Food and Drug Administration (FDA). In 2003 ciprofloxacin patent expired resulting in generic production by umpteen companies and subsequently in a decay of cost. While in the 1990s and the early 2000s ciprofloxacin was predominately applied in hospitals collapse of price let to continuously increasing prescription rates in ambulatory settings [2]. Various studies have shown that increased usage of ciprofloxacin resulted in increased bacterial resistance to the antibiotic. Interestingly, in a region with high ciprofloxacin consumption quinolone consumption in the community had a higher impact on ciprofloxacin resistance of *E. coli* in a regional university hospital than did inpatient quinolone consumption, possibly due to a large reservoir of resistant bacteria in the community becoming detected in the hospital later on [3]. Taking this interaction into account increasing ciprofloxacin consumption in the community, as observed at least in Europe [4], will worsen resistance situation in hospitals despite of decreasing ciprofloxacin consumption by inpatients. Even more alarming, ciprofloxacin induces cross-resistance to other antibiotics as shown for amoxicillin and co-trimoxazole in *E. coli* [5,6] and imipenem and ceftazidim in *Pseudomonas aeruginosa* [7,8].

In gram-negative bacteria resistance to ciprofloxacin is commonly achieved either by mutations of *gyr*A gene or by carriage of *qnr* genes of which a variety has been discovered [9]. In enterobacteria prevalence of *qnr* genes was associated with prevalence of genes mediating ESBL resistance [10]. Moreover, use of ciprofloxacin has been identified as a risk factor of ESBL carriage [11] whereas reduction of ciprofloxacin consumption resulted in decreased incidence rates of ESBL [12]. These findings indicate that in gram-negative bacilli ciprofloxacin, besides inducing bacterial resistance to itself, mediates immeasurable resistances to not related classes of antibiotics.

In *S. aureus* ciprofloxacin applied in subinhibitory concentrations induced increased expression of fibronectin binding proteins [13] facilitating adhesion of the bacteria. In comparison to methicillin susceptible *S. aureus*, MRSA is more often resistant to ciprofloxacin. Consequently, ciprofloxacin induced upregulation of fibronectin binding proteins raises spread of MRSA rather than spread of methicillin susceptible *S. aureus*. Accordingly, use of ciprofloxacin has been identified as a risk factor for colonization by MRSA [14] while restricted use of fluoroquinolones decreased the burden of MRSA [8].

C. difficile infection (CDI) is most frequent infectious cause of antibiotic induced diarrhea and it is assumed that destruction of the microflora allows *C. difficile* to overgrow the bowel. In early studies performed in the 1980s, clinical isolates of *C. difficile* were somewhat susceptible to ciprofloxacin while nowadays most isolates are resistant [15,16]. In agreement to this finding, in recent studies association between the consumption of ciprofloxacin and CDI was stronger than that of other antibiotics and CDI [17]. Before millennium CDI was restricted to inpatients while at the moment also outpatients get affected [16]. Interestingly, ciprofloxacin consumption of outpatients was strongly associated to the number of in- and outpatients suffering from CDI [18]. Beside antibiotic resistance ciprofloxacin has been demonstrated to induce germination of *C. difficile* spores and to induce production of *C. difficile* toxins [19]. In contrast to other broad spectrum antibiotics (aminoglycosides, carbapenems, cephalosporins third generation) ciprofloxacin can be applied orally allowing the antibiotic to get in contact with *C. difficile* spores in the bowel and by this means to mediate germination and production of toxins.

Ciprofloxacin is not approved for antibiotic treatment of children. Children become rarely infected or colonized by MRSA, ESBL, *C. difficile* or other drug-resistant bacteria even when suffering from severe underlying disease, supporting the requirement of ciprofloxacin restriction also in adults.

In summary, application of ciprofloxacin is accompanied by a variety of collateral damages. These damages result from resistance situation of pathogen bacteria but also from the induction of (patho-) physiological processes. Since increased used of ciprofloxacin in ambulatory settings has negative implications to regional hospitals it is essential that hospital physicians and also practitioners reduce subscription rates of ciprofloxacin.

To reach this goal, you are invited to contribute to this discussion by submitting articles to the Journal of Bacteriology and Parasitology to convince decision makers of the necessity of rationale antibiotic use. At this, you will have the opportunity to learn about the exceptional tools of the OMICS group: digital books, audio listening, language translation, and social networking.

References

1. Praveenya P, Singh BK, Kumar SD, Kalyan P (2012) Antibiotic resistance creating new epoch. J Bacteriol Parasitol 3: 131.

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2. Jensen US, Muller A, Brandt CT, Frimodt-Møller N, Hammerum AM, et al. (2007) Effect of generics on price and consumption of ciprofloxacin in primary healthcare: the relationship to increasing resistance. J Antimicrob Chemother 65: 1286-1291.

3. Gallini A, Degris E, Desplas M, Bourrel R, Archambaud M, et al. (2010) Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. J Antimicrob Chemother 65: 2650-2657.

4. Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, et al. (2011) European Surveillance of Antimicrobial Consumption (ESAC): outpatient quinolone use in Europe (1997-2009). J Antimicrob Chemother 66: 47-56.

5. Borgmann S, Jakobiak T, Gruber H, Schröder H, Sagel U (2009) Ciprofloxacin treatment of urinary infections results in increased resistance of urinary *E. coli* to ciprofloxacin and co-trimoxazole. Pol J Microbiol 58: 371-373.

6. Kahlmeter G, Menday P (2003) Cross-resistance and associated resistance in 2478 *Escherichia coli* isolates from the Pan-European ECO.SENS Project surveying the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections. J Antimicrob Chemother 52: 128-131.

7. López-Dupla M, Martínez JA, Vidal F, Almela M, Soriano A, et al. (2009) Previous ciprofloxacin exposure is associated with resistance to beta-lactam antibiotics in subsequent *Pseudomonas aeruginosa* bacteremic isolates. Am J Infect Control 37: 753-758.

8. Thabet L, Memmi M, Turki A, Messadi AA (2010) The impact of fluoroquinolones use on antibiotic resistance in an intensive care burn department. Tunis Med 88: 696-699.

9. Jacoby G, Cattoir V, Hooper D, Martínez-Martínez L, Nordmann P, et al. (2008) qnr Gene nomenclature. Antimicrob Agents Chemother 52: 2297-2299.

10. Jeong HS, Bae IK, Shin JH, Jung HJ, Kim SH, et al. (2011) Prevalence of plasmid-mediated quinolone resistance and its association with extended-spectrum beta-lactamase and AmpC beta-lactamase in Enterobacteriaceae. Korean J Lab Med 31: 257-264.

11. Lonchel CM, Meex C, Gangoué-Piéboji J, Boreux R, Assoumou MC, et al. (2012) Proportion of extended-spectrum ß-lactamase-producing Enterobacteriaceae in community setting in Ngaoundere, Cameroon. BMC Infect Dis 12: 53.

12. Aldeyab MA, Harbarth S, Vernaz N, Kearney MP, Scott MG, et al. (2012) The impact of antibiotic use on the incidence and resistance pattern of ESBL-producing bacteria in primary and secondary healthcare settings. Br J Clin Pharmacol [Epub ahead of print].

13. Bisognano C, Vaudaux P, Rohner P, Lew DP, Hooper DC (2000) Induction of fibronectin-binding proteins and increased adhesion of quinolone-resistant *Staphylococcus aureus* by subinhibitory levels of ciprofloxacin. Antimicrob Agents Chemother 44: 1428-1437.

14. Melo EC, Fortaleza CM (2009) Case-case-control study of risk factors for nasopharyngeal colonization with methicillin-resistant *Staphylococcus aureus* in a medical-surgical intensive care unit. Braz J Infect Dis 13: 398-402.

15. Spigaglia P, Barbanti F, Mastrantonio P, Brazier JS, Barbut F, et al. (2008) Fluoroquinolone resistance in *Clostridium difficile* isolates from a prospective study of *C. difficile* infections in Europe. J Med Microbiol 57: 784-789.

16. Reil M, Hensgens MP, Kuijper EJ, Jakobiak T, Gruber H, et al. (2012) Seasonality of *Clostridium difficile* infections in Southern Germany. Epidemiol Infect 8: 1-7.

17. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, et al. (2005) A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 353: 2442-2449.

18. Borgmann S, Jakobiak T, Gruber H, Reil M, Schroder H, et al. (2010) Association of ciprofloxacin prescriptions to outpatients to *Clostridium difficile* infections. Euro Surveill 15: 19479.

19. Saxton K, Baines SD, Freeman J, O'Connor R, Wilcox MH (2009) Effects of exposure of *Clostridium difficile* PCR ribotypes 027 and 001 to fluoroquinolones in a human gut model. Antimicrob Agents Chemother 53: 412-420.