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Short Communication

Advantages and disadvantages of rifampicin use in orthopedic patients to avoid *Clostridium difficile* infections

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Clostridium difficile (new taxonomy *Clostridioides difficile* [1] is a gram-positive spore forming rod shaped bacterium being the main cause for nosocomial diarrhea. *C. difficile* infection (CDI) may include mild to severe symptoms up to fulminant colitis resulting in toxic megacolon, sepsis, multiorgan dysfunction, permanent impairment contributing to a high mortality rate. Antibiotics are thought to be the main driver for CDI, as *C. difficile* can strive when the gut microbiome is disrupted [2]. Classically the "4 C" antibiotics clindamycin, fluoroquinolones, cephalosporins and aminopenicillins with beta-lactamase inhibitors (e.g. amoxicillin/clavulanic acid) are associated with high risk of CDI development [3]. Antibiotics with a lower risk of CDI are tetracyclins (e.g. doxycycline) and tigecyclin as well as vancomycin and daptomycin [3] CDI is treated with metronidazole, vancomycin and fidaxomicin and resistance testing is usually not necessary [4] For epidemiological purposes isolates can be differentiated by their Ribotype (RT) [5]. In recent years virulent RTs such as RT027 showed global spreading [6] leading to a higher CDI incidence and more severe courses of disease.

Virulence factors of this pathogen are the toxins A (*tcdA*) and B (*tcdB*) [7]. Some isolates inhabit additionally the binary toxin which is encoded by *cdtA* and *cdtB* [7]. Binary toxin is found preferably in epidemic isolates associated with more severe infections [7]. One of these strains is RT027 which has showed global spreading in recent years [8]. An important factor for selection and spreading of virulent strains like RT027 is their resistance towards a variety of antibiotics, mainly macrolides and flourochinolones [9]. In orthopedic surgery often antibiotics are administrated over long periods due to complicated soft tissue or osteoarticular infections resulting in an increased risk for CDI. In recent years an increase in CDI incidence has been noted in orthopedic patients [10] with a CDI rate of 0.19% in one major study including more than 100.000 patients [11]. Especially in patients with non-elective procedures (e.g. following trauma) CDI incidence is much more prevalent [11,12].

Rifampicin is a drug frequently used in orthopedics. The mode of action is inhibition of bacterial RNA polymerases [13] while resistance might be triggered by mutations in the *rpoB* gene in *C. difficile* isolates [14]. One major field of use are infections with biofilm formations due to staphylococci [15].

In the past it has been proposed that rifampicin might hold a protective effect towards CDI development [14,16, 17]. This effect might be favored by the usually low resistance rate of *C. difficile* strains against rifampicin [18].On the other hand other data indicate that rifampicin might favor CDI [19], especially with *C. difficile* strains harboring rifampicin resistance. In German patients suffering from osteoarticular infections rifampicin resistant RT027 isolates seemed to be a major driving factor for CDI [20]. In this study application of antibiotic stewardship which resulted in a reduction of overall antimicrobial use was able to significantly lower the CDI incidence. Similarly, in Poland, another study concluded that in an epidemiological setting with a dominance of a rifampicin resistant *C. difficile* strain (RT046) patients on tuberculosis treatment with

rifampicin are at a higher risk do develop CDI [21].

Thus, rifampicin might work as a double-edged sword: In rifampicin sensitive RTs it might protect from CDI, however, it might select rifampicin resistant *C. difficile* strains, and these are often strains with a higher virulence such as RT001, RT017, RT027 and RT176 [18]. The main goal of preventing CDI is to reduce the antibiotic use in general with a switch to drugs associated with a low risk of inducing CDI (e.g. tetracyclins). As a consequence, rifampicin should be used restrictively in orthopedic surgery and other medical fields to avoid selection of emerging resistant *C. difficile* strains and CDI development. In case of an increased CDI rate on wards with a relevant rifampicin use, ribotyping and resistance testing might be an option to identify driving factors for CDI development and to optimize antibiotic treatment.

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