Editorial

Antimicrobial prophylaxis is critical for preventing surgical site infection

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Surgical antimicrobial prophylaxis reduces the risk of surgical site infection by around 50%. Guidelines recommend the type of antibiotic, the duration of treatment, the route of administration and the dosage (1,2). The choice of antibiotic should be based on the pathogens that are frequently associated with surgical site infection in a specific surgery. A single administration is the rule for the vast majority of procedures. The treatment should never exceed 48 hours. Except for specific procedures as prostate surgery (3), the favorite route of administration is intravenous. For cephalosporins, most guidelines recommend doubling the standard dose for obese patients even outside bariatric surgery (1,2,4).

The best timing for the surgical antimicrobial administration is based on a theoretical principle: the peak of antibiotic concentration at the surgical site should be reached at the time of incision. Thus, the timing depends on the pharmacokinetics of each antibiotic. Guidelines provide divergent duration comprised between 30 and 60 min before incision (1,2,4). The administration of vancomycin and fluoroquinolones should be starter within 120 minutes before surgical incision due to the prolonged infusion times required for these drugs (2). However, the relation between the timing of the surgical antimicrobial prophylaxis and the incidence of surgical site infection remains unclear.

In a randomized clinical trial, Weber *et al.* administered 1.5 g of cefuroxime early (30–75 min before scheduled incision) in the anesthesia room or late in the operating room (0–30 min before scheduled incision) to 5,580 patients who were followed for a 30-day duration (5). The antibiotic was given 42 min before incision in the early group and 16 min before incision in the late group. The rate of surgical site infection was 5.1%. It did not significantly differ in the early group and the late group. This finding was confirmed in each population: surgical division, wound class, immunosuppressive drugs, body mass index, diabetes and age.

Weber *et al.* should be congratulated for conducting such massive study (5). This randomized clinical trial is pragmatic, clear and well-conducted. An impressive number of patients were included. The result, which does not support the "*old theoretical model of pharmacokinetics*", is confirmed in each subgroup of patients, even those considered at high risk for surgical site infection. This study is a model for future studies: its pragmatic design makes it possible to clearly respond to a critical clinical question.

One of the limitations is probably the follow-up duration that was limited to 30 days, while surgical site infection in patients with prosthetic material should have been observed for 1 year. Can we really believe that this limitation would change the main finding? Another limitation is that surgical antimicrobial prophylaxis represents one step of a series of measures aiming at preventing surgical site infection. The WHO guidelines include 9 preoperative recommendations, 13 preoperative and/or intraoperative measures and 3 postoperative measures (2). Thus, one can suggest that it would be surprising that few minutes in the administration of antibiotic play a major role in terms of outcome. In the

present study, due to its design and the research constraints, the practices were probably optimal in the two groups. In addition, the definition and surveillance of surgical site infection are not as consensual as they can first appear (6,7). Finally, the authors tested the use of cefuroxime as surgical antimicrobial prophylaxis. We do not know if the result would have been similar with other antibiotics.

In a previous observational study, the same group of authors suggested that the infection risk enhanced when surgical antimicrobial prophylaxis was administrated in the last 30 minutes before incision compared with a 31–60 minutes interval (8). Another observational study concluded, at variance, that risk of surgical site infection was reduced when antimicrobial prophylaxis was infused in the last 30 minutes before incision (9). Using an unadjusted model, a large study including 32,459 patients found higher rates of surgical site infection for timing more than 60 min prior to incision. When the model was adjusted for patient, procedure, and antibiotic variables, no association was identified between antibiotic timing and surgical site infection (10). In conclusion, a large scale randomized clinical trial and a well-conducted observational study showed that timing, if the deviation remains reasonable, i.e., between 30 and 60 min, is not critical for the prevention of surgical site infection. However, once again, in those studies, no major deviation, as prolonged delay or administration after surgical incision, was reported.

Weber *et al.* concluded that "*even though the present study does not rule out a beneficial effect of early administration of surgical antimicrobial prophylaxis on the risk of surgical site infection, they do not support changing current recommendations to administer surgical antimicrobial prophylaxis during the 60 min before incision*" (5). We agree with this pragmatic conclusion. The study results do not allow deviating from current WHO guidelines, which suggested randomized controlled trials to clarify the optimal timing of surgical antimicrobial prophylaxis.

However, the research agenda around the prevention of surgical site infection still require future investigations. In intensive care unit, a continuous infusion of beta-lactams, after an initial bolus, is used to optimize the efficiency of antimicrobial treatments. The time above the minimal inhibitory concentration of the causative pathogen is a critical determinant for its clearance. A meta-analysis showed a positive effect on the outcome of patients (11). If this strategy was transferred to the operating room, at least for high-risk procedures, it would partly resolve the issue related to the timing of surgical antimicrobial prophylaxis administration. Elsewhere, the long-term ecological effect of the surgical antimicrobial prophylaxis was never clearly assessed, which is a major bias in the era of increasing antimicrobial resistances.

The study of Weber *et al.* raises two comments. The first comment is the relevance of control quality studies. The timing between surgical antimicrobial prophylaxis and incision has been used as surrogate for guidelines adherence (12,13). Depending on study, a timing different from either 30 or 60 min was considered as an optimal practice. In a Dutch survey, the timing of the first dose was not in compliance with guideline in 50% of cases (14), which can be penalizing in some circumstances. In addition, in routine practice, the timing between surgical antimicrobial prophylaxis and surgical incision appears difficult to control for all the operating room team. The present results raise questions about the interest of such quality criteria. This suggests that audit should preferentially focus on end-points that were confirmed in randomized clinical trials. The second comment is the value of randomized clinical trials. The theoretical translation of concept at the bedside did not often result in clinical success. Observational studies include inherent bias that make their findings uncertain. International, national, and institutional organizations should support the use of randomized clinical trials in an attempt to improve the practices.

In conclusion, Weber *et al.* show that the timing of surgical antimicrobial prophylaxis does not affect the incidence of surgical site infection, if its administration occurs in a reasonable range. One should keep in mind that surgical antimicrobial prophylaxis is a single element of a large bundle for the prevention of surgical site infection. This study also shows that randomized clinical trials remain mandatory in an attempt to confirm (or not) theoretical concepts.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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