Editorial

Is *Clostridium difficile* the new bugaboo after cardiac surgery?

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Clostridium difficile is a ubiquitous, anaerobic, spore-forming, Gram-positive bacterium.

The occurrence of Clostridium difficile infection (CDI) in healthy individuals is relatively uncommon due to the protective effect of the gut microbiota. The incidents and severity of CDI has risen significantly over the last decade (1), and it is now recognized as the main causative agent of healthcare-associated infectious diarrhea in hospitals worldwide, it compromises patient safety (2) and increases the length of hospital stay and costs (3-5).

The longer antibiotic duration, the multiple antibiotics (versus a single antibiotic) use, the diminished immune response due to age and/or medical comorbidities (6,7) and the use of proton pump inhibitors are identified as the main risk factors for CDI. Thus, it is easy to acknowledge that cardiac surgery deserves further investigation compared to other surgeries: patients undergoing cardiac interventions usually are older and have multiple comorbidities; cardiopulmonary bypass, hypothermia, length of surgery, and indwelling chest catheters after surgery could increase the risk for any kind of infection (antibiotic use) (5,8); furthermore, the recommend antibiotic prophylaxis after cardiac surgery is longer than noncardiac surgery (48 hours in contrast to the usual 24-hour in non-cardiac surgery) (9).

Nevertheless, the CDI on adult patients undergoing cardiac surgery are not well known and no literature data had been published before 2000 about that. Perhaps it wasn't an issue?

In the twenty-first century this condition is still increasing and in the last two decades more and more studies have focused on this problem. Previous retrospective studies reported the prevalence of CDI after cardiac surgery ranged between 0.21% and 0.79% (2,5,10,11).

In the current manuscript, Kirkwood *et al.* reported 50 (0.97%) CDI out of a total of 5,158 patients during a 65-day follow-up period. CDI is reported as the third more common infection after bloodstream and pneumonia and death in patients with CDI rose up to 10% (*vs.* 1.8% in patients without CDI). Another important evidence of this study is that nearly half of all CDIs (48%) occurred after index hospital discharge, and 25% of all CDIs occurred after day 30. CDI compromised discharge and caused readmission to the hospital in thirteen patients who contracted CDI during the follow up period. In this population CDI onset is frequently after two weeks after surgery.

As already found in others studies, Kirkwood and the coauthors as well found an association between CDI and other comorbidities, particularly with preoperative renal failure (P=0.0008) and postoperative acute hyperglycemia (P<0.001). The association between renal failure and CDI is supported and explained by some studies as related to the immune-suppressed state mediated by uremia and other factors (12); or due to the intestinal dysmotility frequently observed in patients with chronic kidney disease (13,14). We could suppose also that the variable antibiotic blood level due to compromised metabolism could increases the risk for CDI. As renal failure, hyperglycemia as well induces an impairment of host defenses and could favor other kind of infections. For this reason, a rigorous control of glycemia in the postoperative period is recommended by guidelines (15) to reduce surgical site infections.

The last but very important piece of evidence highlighted in this manuscript was that "only" 8.6% of patients (442/5,158) received antibiotic prophylaxis for over 48 h. The article confirmed that the long duration of antibiotic prophylaxis was associated with CDI (P<0.001) but unlike the literature data [in literature data clindamycin, fluoroquinolones, cephalosporins, aztreonam, and carbapenems carry a higher risk (16-18)], the authors didn't find an association between CDI and the type of antibiotic.

This article has two important limitations: firstly, it is a sub-study and used the old data [2010] from another study published on 2014 (19). Secondly, only 50 patients in this cohort contracted CDI, it is a small number to draw relevant conclusions.

However, this is still a good manuscript as it focuses on two huge issues: the impact of CDI after cardiac surgery and the debated antibiotic prophylaxis duration after cardiac surgery.

In the present article the Authors studied in deep this topic and emphasized the role of CDI as a serious infection after cardiac surgery, whose incidence is underestimated. Kirkwood and the coauthors confirmed that CDI worsened significantly the already long and difficult recovery from cardiac surgery, compromised the discharge and that it is often the cause of readmission to the hospital.

The article strengthens the risk for CDI caused by long antibiotic prophylaxis. In fact, a prolonged prophylaxis is a non-sense therapy and it delays the "early treatment" while significantly increasing drug resistance and major infections (19-22). However, an oft-overlooked risk of antibiotic use is the development of CDI, which is increasing in incidence and virulence in the cardiac surgery population.

Even if guidelines (9) are suggesting the antibiotic prophylaxis interruption within 48 hours, many physicians worldwide are not confident for that while the patients have indwelling catheters after major surgeries. Most of the discrepancies between guidelines and practice are to be attributed to the poor comprehension of the difference between "prophylaxis" and "early treatment".

The important dose of the antibiotic prophylaxis, the important dose is the preoperative one (to be given 30 minutes before surgery for cefazolin) and the second most important, but probably the most neglected one, is the one that has to be administered "if the duration of the procedure exceeds 2 half-lives of the antibiotic agent or when there is excessive intraoperative blood loss or haemodilution" (9). All other administrations of antibiotics are of limited importance and become detrimental if continued for more than 48 h.

Considering all of analyzed conditions above, CDI could become a common complication after cardiac surgery procedure. The goal of the clinical community should be to prevent CDI minimizing the new event, and to treat the clinical manifestations.

How?

As prevention against CD, also on the light of this manuscript, we should encourage the clinicians to thoroughly follow the guidelines for antibiotic prophylaxis.

Unfortunately, as standard therapies against *C. difficile*, metronidazole (for mild to moderate infections) and oral vancomycin or fidaxomicin (for severe infections and relapses) affect greatly the gut microbiota, which result in persistence of infection, relapses, and the administration of more antibiotics, which further depletes the commensal bacteria.

Currently new strategies are researched intensively and scientific research focus on the therapeutic gut microbiota restoration. These include also the gut microbiota manipulation and recently more and more studies identified fecal microbiota transplantation as the new frontier (23).

Hopefully that literature data will still update and that scientific research will find a better treatment options for CDI.

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Footnote

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

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