Clostridioides (Clostridium) difficile pacemaker infection

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Abstract

*Clostridioides difficile* is the leading cause of antibiotic-associated nosocomial diarrhoea, but extra-intestinal manifestations are rare. We describe the first documented case of bacteraemia, pacemaker pocket and lead infection with the toxigenic *C. difficile* ribotype 014 with a lack of abdominal symptoms. The patient underwent pacemaker extraction and treatment with intravenous and oral vancomycin. Genotyping and molecular subtyping revealed clonality between pacemaker and intestinal isolates. This case illustrates the risk of intravascular device infections due to *C. difficile*. Even asymptomatic *C. difficile* colonisation might pose as a risk factor for prosthetic material infection.
Visual abstract

*Clostridioides (Clostridium) difficile* pacemaker infection

C. difficile pacemaker-infection with device-associated endocarditis in patient with asymptomatic C. difficile colonization

Successful treatment with device removal and prolonged course of intravenous and oral vancomycin followed by tapering regimen and reimplantation

With rising numbers of implanted cardiac electronic devices and high incidence of C. difficile infections/colorectalizations clinical awareness and treatment recommendations for extraintestinal C. difficile infections are needed

Berkefeld et al. 2020
Clostridioides (Clostridium) difficile is an anaerobic, spore-forming Gram-positive bacterium causing nosocomial diarrhoea with high mortality and morbidity. Previous antibiotic treatment is the main risk factor for *C. difficile* infection (CDI) and the clinical appearance of CDI varies from asymptomatic carriers to severe pseudomembranous colitis and toxic megacolon. Approximately 11-27% of all CDI cases seem to be community acquired. Up to 30% of adult hospitalized patients and 0-15% of healthy adults are estimated to be asymptptomatically colonised. The major pathogenic factors expressed by *C. difficile* are enterotoxin A and cytotoxin B, but more virulent strains can express a third “binary toxin” encoded by *cdtAB*. Strains associated with outbreaks and severe infections are ribotypes 078 and 027. In Europe RT027, RT001, RT014, RT020 are dominating with regional differences. Extra-intestinal *C. difficile* manifestations are rare given the high incidence of intestinal CDI. The majority of extra-intestinal manifestations are either abdominopelvic infections, wound infections after antibiotic exposure or after gastrointestinal surgery. *C. difficile* bacteraemia is mainly polymicrobial and primarily seen in patients with abdominal pathologies. Mortality can be as high as 35%, however, patients usually have severe underlying medical conditions.

Infections of cardiovascular implantable electronic devices are increasing due to a rising number of implanted devices and more complex implantation procedures, with an incidence of 0.5%-3.4%. Bacterial colonization can occur during implantation or hematogenously and the most common pathogens are staphylococcal species followed by gram-negative pathogens, streptococci, enterococci and anaerobic species. Pocket infection with bacteremia and lead-associated endocarditis is associated with higher morbidity and mortality compared to pocket infection alone. The presence of ghosts after lead extraction is associated with infective endocarditis and leads to increased mortality. Standard treatment is complete device removal with antibiotic therapy and reimplantation at an alternate site after adequate antibiotic treatment.

Up to this date, no *C. difficile* pacemaker pocket and lead infection has been described. We present a case of *C. difficile* pacemaker pocket and lead infection with bacteraemia in a patient without gastrointestinal CDI symptoms. Written informed consent was obtained from the patient for publication.
Case report

A 75-year-old male was referred to our stroke unit from a secondary care hospital with acute ischemic stroke due to thrombotic occlusion of the M1 segment of the left A. cerebri media following coronary angiography and intervention for non-ST-elevation myocardial infarction. He was referred to our hospital with right-sided hemiplegia for successful mechanical thrombectomy. An aspiration pneumonia was treated empirically with piperacillin/tazobactam for a total of 7 days. Additionally, ECG revealed recurrent sinus bradycardia with intermittent ventricular escape rhythm and third-degree sinoatrial block. He underwent two-chamber pacemaker implantation (Medtronic Ensura®, Dublin, Ireland). According to national recommendations, Povidone-Iodine-solution was used for preoperative skin antisepsis (exposure time one minute). No specific antibiotic prophylaxis was used for the procedure as the patient was still under piperacillin/tazobactam at time of pacemaker implantation.

Post-implantation measurements and wound inspections were normal. The patient was discharged to a neurological rehabilitation facility four days after pacemaker implantation and a total of 16 days after initial admission.

He was readmitted after seven days with fever and a hyperthermic, reddened pacemaker incision site. Laboratory examination revealed leucocytosis and elevated C-reactive protein. Blood cultures were collected before empirical antibiotic therapy with ampicillin/sulbactam was initiated. With suspected pacemaker pocket infection, system extraction was performed. Intraprocedural inspection of the pacemaker pocket revealed no pus but an old hematoma. Swab samples of pacemaker and pocket, as well as the explanted leads were retained for microbiological diagnostic. The patient was transferred to our intensive care unit with persisting sinoatrial block for further monitoring and transoesophageal echocardiography (TEE). TEE revealed mobile vegetation from the right atrium to the superior vena cava (Figure 1) consistent with the presence of ghost indicating bacterial colonization of the intravascular segment of the lead with device-associated endocarditis.

Five sets of blood cultures (BACTEC™, Becton Dickinson, Franklin Lakes, USA) were positive on culture day two for C. difficile isolated on schaedler agar (Becton Dickinson, Franklin Lakes, USA). The pacemaker samples (swabs and lead culture) as well as pocket swab cultures were positive for C. difficile on culture day two. In order to detect an intestinal colonization with C. difficile a stool sample was obtained. Two toxigenic C. difficile strains and one non-toxigenic isolate were obtained.
from the stool cultures. All acquired isolates underwent antimicrobial testing and ribotyping. Minimum inhibitory concentration of the isolate from the pacemaker was 0.5 mg/L for vancomycin and 1 mg/L for metronidazole (Table 1). Genotyping detected the toxigenic ribotype RT014 (Clade 1, MLST sequence type 2) in the stool and pacemaker isolate. Clonality of the RT014 isolates was confirmed by whole genome sequencing (cgMLST)\textsuperscript{13}. Additionally, one RT020 (toxigenic) and one unclassified non-toxigenic isolate were detected in the stool sample, indicating mixed strain colonisation. Detailed medical history of the patient uncovered no signs of previous \textit{C. difficile} infection. The patient neither suffered from nor previously had contact with infectious diarrhoea and abdominal ultrasound revealed no pathologies. In our institution, prevalence of \textit{C. difficile} associated diarrhoea is low (0.29 CDI cases/100 patients were reported in 2019).

Antibiotic treatment was switched to intravenous vancomycin and oral metronidazole according to susceptibility testing and under continuous drug monitoring. Laboratory tests revealed normalization of leukocytes and C-reactive protein. On the third day of treatment, oral antibiotic therapy was switched from metronidazole to vancomycin due to increasing liver enzymes. Repeated blood cultures and stool samples under therapy remained negative.

The patient was transferred back to the rehabilitation facility on day 23 of antibiotic treatment. Intravenous vancomycin was continued for a total of 30 days. To decolonize the intestine as a possible reservoir for reinfection oral vancomycin was administered for a total of 42 days using a tapering regime\textsuperscript{14}. Seven days after discontinuation of oral vancomycin the patient was readmitted for pacemaker reimplantation. Prior to reimplantation TEE revealed complete elimination of vegetations (Figure 2). Repeated blood cultures and skin swabs of groin, axilla, rump and pacemaker pocket were negative for \textit{C. difficile}. Colonoscopy showed no signs of intestinal inflammation, but few non-inflamed sigmoid diverticula. However, toxigenic \textit{C. difficile} was again isolated from follow-up stool samples but genotyping revealed a different toxigenic RT005 indicating reinfection.

After three days of treatment with intravenous vancomycin, reimplantation of the pacemaker was performed on the contralateral side. The patient was released to a rehabilitation facility on day five with an oral vancomycin tapering regime for another 50 days. Upon scheduled follow-up visit 2 months after reimplantation, normal pacemaker function with no sign of infection was documented.
Discussion

To our best knowledge no case of *C. difficile* pacemaker pocket and lead infection has been described previously. In the literature, three cases of *C. difficile* infection of endovascular grafts \(^{15-17}\) and one case with infected epicardial patch could be identified \(^{18}\).

Two cases of *C. difficile* infection of endovascular aortic graft had preceding abdominal pathologies and underwent surgical treatment in addition to intravenous vancomycin and metronidazole \(^{15,16}\).

One case with mycotic aneurysm of an axillo-bifemoral bypass after pseudomembranous colitis was treated with surgical debridement and intravenous ampicillin/sulbactam and metronidazole \(^{17}\).

*C. difficile* infection of an epicardial patch occurred after transverse colectomy nine years post patch implantation and was treated with patch removal and intravenous vancomycin and metronidazole \(^{18}\).

Another case with mycotic abdominal aortic aneurysm caused by *C. difficile* is of special interest as the patient was an asymptomatic community-acquired carrier of *C. difficile* without any history of hospital admission three years prior to infection. He did however suffer from severe diverticulosis and haematogenous spread from the colonised gut was postulated as the most likely origin of infection \(^{19}\).

In all cases, the pathway of graft infection was most likely through bacteraemia, as all patients had gastrointestinal pathologies and preceding antibiotic therapies. In these cases, surgical removal and prolonged antibiotic treatment was successful.

In contrast, in our case no underlying gastrointestinal pathologies or diarrhoea were evident. One may speculate that even diverticulosis without active diverticulitis might pose as a translocation route leading to transient bacteraemia and prosthetic material infection especially as skin swabs remained negative. This finding is in contrast to other cases, where severe intestinal pathologies were present in extra-intestinal *C. difficile* manifestations \(^{7}\). Possible pathomechanisms for *C. difficile* bacteraemia are bacterial transfer in mucosal injury or bacterial translocation in disrupted mucosal barrier function \(^{8,20}\).

In our case, three *C. difficile* strains were detected in stool samples (two toxigenic, one non-toxigenic) but only the toxigenic RT014 strain was isolated from pacemaker probes and blood cultures. Clonality of the RT014 strain might suggest haematogenous translocation to the bloodstream from the
intestine. Coinfections by multiple different *C. difficile* ribotypes can occur but data is lacking on the question if toxigenic strains or some ribotypes translocate more easily \(^8,21\).

The asymptomatic *C. difficile* reinfection after initial eradication in our patient might indicate a higher susceptibility for *C. difficile* colonization but studies do not indicate a higher prevalence or reinfection risk of *C. difficile* when diverticulosis is present \(^22\). Notably, the majority of short-term *C. difficile* recurrences are rather relapses than reinfections \(^23,24\).

Infections of cardiac implantable electronic devices can occur hematogenously or more commonly due to contamination with skin flora at initial implantation \(^25\). This is particularly the case for early-onset-infections within six-months \(^26\). Hematogenous infection of cardiac implantable electronic devices usually presents late and without concomitant pocket infection. Seeding to an implanted device in patients with bacteraemia is primarily described in infections due to *Staphylococcus aureus* \(^25\) but rarely occurs with gram-negative pathogens \(^25,27\). Therefore, another explanation for the presented *C. difficile* pacemaker infection is surgical site infection due to skin colonization by *C. difficile*.

In patients with CDI, skin-colonisation of multiple body sites including chest, groin, forearms and hands has been shown \(^28\). Asymptomatic toxigenic *C. difficile* colonisation is found in 7-15% of healthy adults and up to 50% of residents of long-term care facilities \(^3\). Our patient might have contracted *C. difficile* during his first hospital admission or a community-acquired colonisation might have occurred. Asymptomatic *C. difficile* carriers show skin and environmental contamination \(^29\). Spores of asymptomatic carriers can easily be transmitted since skin and hand disinfectants do not inactivate spores. The presented patient had asymptomatic intestinal colonization. Skin contamination of multiple body sites could have occurred, resulting in a risk of periprocedural pacemaker-contamination. Swabs taken before reimplantation remained negative, nevertheless skin contamination preceding the initial implantation cannot be ruled out since no testing was initially performed.

For pacemaker implantations, infection prevention measures such as special procedure room, double gloving, annually hygiene inspections and glucoprotamin-based surface disinfection (Incidin® Plus 0.5%, exposure time 30 minutes) are in place at our institution. Povidone-Iodine solution (exposure time one minute) was used for preoperative skin antisepsis during all procedures, however this
preparation has no sporicidal efficacy in short term application.

At this point the route of infection in our patient remains unclear but contamination during the implantation procedure seems to be the more likely route of infection.

We present a highly unique case of pacemaker pocket infection, lead endocarditis and bacteraemia with \textit{C. difficile}. This is the first reported case of \textit{C. difficile} causing a cardiac device infection and unique since no acute gastrointestinal inflammatory pathologies nor diarrhoea were present. Given the high numbers of asymptomatic \textit{C. difficile} carriers and the growing use of cardiac implantable electronic devices it remains unclear why this problem has not become apparent before.

Up to this date \textit{C. difficile} bacteraemia was associated with underlying gastrointestinal pathologies, severe comorbidities or immunosuppression. In our patient neither was the case. Hence CDI would never have been suspected. With rising numbers of implanted cardiac electronic devices and the high incidence of \textit{C. difficile} infections and colonisations, bloodstream and device infections with \textit{C. difficile} might be a potentially growing issue. Recommendations for management of extra-intestinal \textit{C. difficile} infection risk and treatment are needed.
Abbreviations
CDI: C. difficile infection, TEE: transesophageal echocardiography.

Authors’ contributions
AB and KLL were the patient's internal medicine physicians and provided images. KR was the consulting microbiologist for the case. FKB and BCG at the national reference laboratory supported the microbiological analysis of the case. KR and AB wrote the manuscript, analyzed the case and did the review of the literature. DB, KLL, FKB, NW, AP and BCG reviewed and edited the manuscript.

Conflict of interest
The authors declare no conflict of interest.

Role of the funding source
Not applicable

Patient Consent Statement
Written informed consent was obtained from the patient for publication. Publication of the retrospectively obtained and anonymized data is conformable to article 27 of the “Bayerisches Krankenhausgesetzes”.

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**Figure Legend:**

**Figure 1:** Transesophageal echocardiography (TEE) results

1A: TEE revealing mobile vegetation from the right atrium to the superior vena cava

1B: Control TEE with elimination of endocarditis vegetation
Table 1: Results of antimicrobial susceptibility testing of the RT014 isolate from blood cultures (according to EUCAST version 9.0, 2019) for C. difficile

S: susceptible. *: no breakpoints for interpretation of results of susceptibility testing available

| Antimicrobial                     | Minimum inhibitory concentration (mg/L) | Interpretation |
|-----------------------------------|-----------------------------------------|----------------|
| Vancomycin                        | 0.38                                    | S              |
| Metronidazole                     | 0.75                                    | S              |
| Moxifloxacin                      | 3.0                                     | S              |
| Benzylpenicillin                  | 1.5                                     | *              |
| Ampicillin                        | 3.0                                     | *              |
| Ampicillin/sulbactam              | 3.0                                     | *              |
| Piperacillin/tazobactam           | 6.0                                     | *              |
| Cefuroxime                        | >256                                    | *              |
| Cefepime                          | >256                                    | *              |
| Cefotaxime                        | >32                                     | *              |
| Ceftriaxone                       | >32                                     | *              |
| Imipenem                          | 3.0                                     | *              |
| Meropenem                         | 2.0                                     | *              |
| Ertapenem                         | 2.0                                     | *              |
| Ciprofloxacin                     | 16.0                                    | *              |
| Levofloxacin                      | 8.0                                     | *              |
| Trimethoprim/sulfamethoxazole     | >32                                     | *              |
| Teicoplanin                       | 0.38                                    | *              |
| Clindamycin                       | 4.0                                     | *              |
| Rifampicin                        | 0.002                                   | *              |
| Clarithromycin                    | 2.0                                     | *              |
