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Case Report
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Can Treatment of COVID-19 Patients with Broad-Spectrum Antibiotics Unleash Multi-Drug Resistant Bacterial Pathogens?

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Abstract

Background: Broad-spectrum antibiotic therapy is part of the pharmacological treatment of COVID-19 patients. A potential side effect of antibiotic therapy is the loss of colonization resistance provided by a diverse and balanced gut-microbiota.

Case Report: A 74 year old female patient was admitted to hospital due to acute renal failure. During her stay in hospital she acquired a COVID-19 infection and was transferred to a dedicated COVID-19 clinic, where pharmaceutical therapy also comprised the administration of a broad-spectrum antibiotic (ceftriaxone). The patient suffered from diarrhea, with a negative first test for fecal *Clostridioides (C.) difficile* toxin. Retesting after four days confirmed a *C. Difficile* Infection (CDI) which was successfully treated with metronidazole and vancomycin. After the patient was COVID-19 symptom-free for three days she was discharged from hospital.

Thirty days after the discharge, the patient was re-admitted to hospital because of diarrhea and abdominal pain. Fecal *C. difficile* toxin was found again but this time vancomycin and metronidazole treatment failed. A stool sample was collected for culture of pathogenic bacteria, several of which (*Klebsiella pneumoniae* and *Enterococcus faecium*) were found. Despite intensive treatment, the patient's condition gradually deteriorated and she died on day 18 of her last hospital stay due to multi-organ failure resulting from infection with pathological bacteria.

Conclusion: Awareness of the risk of antibiotic therapy of COVID-19 patients triggering proliferation of antibiotic-resistant pathogenic bacteria with potentially fatal consequences has to be increased.

Keywords: Antibiotic therapy; *Clostridioides difficile*, COVID-19; *Enterococcus faecium*, Gut microbiome; *Klebsiella pneumoniae*; Multi-drug resistance

Introduction

Coronavirus Disease 2019 (COVID-19), a highly infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is currently overwhelming hospitals and Intensive Care Units (ICUs) around the world. Significant alterations in fecal microbiomes were found in COVID-19 patients, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensal, at time of admission to hospital and at all stages during hospitalization. Depleted symbionts and gut dysbiosis persisted even after clearance of SARS-CoV-2 (determined from throat swabs) and resolution of respiratory symptoms [1]. Early reports from Wuhan showed that 2% to 10% of patients with COVID-19 had Gastrointestinal (GI) symptoms, including diarrhea, but a recent meta-analysis reported that up to 20% had GI symptoms [2-5]. Studies have detected SARS-CoV-2 virus in anal swabs and stool samples in almost 50% of patients with COVID-19, suggesting that the digestive tract might be an extra-pulmonary site for virus replication and activity [6,7]. Moreover, fecal calprotectin was found to be elevated in patients with COVID-19, with diarrhea an indicator of inflammatory responses in the gut [8].

In addition to the potential direct effects of COVID-19 on the composition of the gut microbiota, broad-spectrum antibiotics administered to COVID-19 patients are also affecting the bacterial

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colonization of the gut. Most patients are not screened for being carriers of multi-drug resistant bacterial pathogens before an antibiotic therapy is initiated. Administration of broad-spectrum antibiotics can result in the loss of colonization resistance normally provided by the gut microbiota [9-11]. In patients who are (symptomatic or non-symptomatic) carriers of certain multi-drug resistant bacterial pathogens, e.g. *Clostridioides (C.) difficile*, *Klebsiella (K.) pneumoniae*, or *Enterococcus (E.) faecium*, this loss of colonization resistance can result in overgrowth of the gut by the respective bacterial pathogen, followed by disease manifestation. China's National Health Commission already recommended in early (and also in their latest) versions of their guidelines for diagnosis and treatment of COVID-19 patients, to avoid the unselective and inappropriate use of antibiotics, especially the usage of broad-spectrum antibiotics [12].

Case Presentation

A74 year old female patient was admitted to the District Hospital of Jarocin, Poland with severe epigastric pain, loss of appetite and body weight due to acute renal failure. A SARS-CoV-2 test (Panbio Antigen Test, Abbott Laboratories Poland Sp. Z o.o., Warsaw, Poland), performed as part of the admission diagnostics, was found to be negative. Routine laboratory tests performed at admission showed hemoglobin: 9.8 mg/dl, creatinine 27.06 mg/dl, hyperkalemia: 7.24 mmol/l. Abdominal ultrasound examination revealed liver not enlarged, homogeneous, with increased echogenicity; thin-walled gall bladder, with an echo of calculus; kidneys bilaterally with hydronephrosis and a narrowed parenchyma layer, visible echoes of deposits in the calyxes; with no other significant deviations. Chest X-rays showed pulmonary fields without focal changes and a normal heart.

The patient was treated with omeprazole 20 mg (b.i.d., p.o.), 500 ml 5% glucose plus insulin (Gensulin® R) 100 IU (b.i.d., i.v.), furosemide 2 amp. (b.i.d, i.v.), 500 ml 0.9% NaCl (b.i.d, i.v.), potassium 391 mg (b.i.d., p.o.). A noticeable normalization of laboratory parameters was observed. After 16 days of therapy, creatinine levels leveled at 4.23 mg/dl.

On day 16 of her hospital stay, a second SARS-CoV-2 test was performed and was found to be positive. The patient didn't report symptoms of respiratory tract infection, was respiratory efficient, had no fever and was in fairly good general condition. As per the standard process for all COVID-19 patients of the District Hospital in Jarocin, the patient was transferred to the Multispecialist City Hospital in Poznan, Poland, some 75 km away from Jarocin. At admission the patient suffered from diarrhea, which was considered to be related to the COVID-19 infection. The patient was treated with Clexane® (s.c) for thromboprophylaxis, empiric broad-spectrum antibiotic therapy with ceftriaxone 1 g (b.i.d., i.v.), and oxygen therapy to reach an O2 saturation ≥ 95%. On the third day of hospitalization two units of red cell concentrate were transfused to address the patient's anemia. Dexamethasone was not administered to the patient. The patient's hyperkalemia was treated by administration of Resonium A 30g (p.o.), glucose 10% plus insulin (i.v.) 500 ml, furosemide 20 mg (t.i.d., i.v.). Due to significant diuresis and the lowering of creatinine concentration, the intervention was abandoned in favor of forcing diuresis with furosemide only. As diarrhea persisted, administration of a multi-strain probiotic (Lakcid® forte, containing a total of 1 × 109 colony forming units as a mixture of the *Lacticaseibacillus (L.) rhamnosus* strains E/N (40%), Oxy (20%) and Pen (40%)) was initiated on day three of the antibiotic therapy. Administration of the probiotic was maintained until the patient was discharged from hospital. On day 4 of the antibiotic therapy, the patient was re-tested for the presence of fecal *C. difficile* toxin and this time the test was positive. Treatment of CDI was initiated with the administration of metronidazole 500 mg (t.i.d., p.o.) and after 3 days, due to lack of improvement, vancomycin 125 mg (q.i.d., p.o.) was added, followed by 13 days of treatment with vancomycin only. As the general condition of the patient had improved, and she had been isolated for 13 days and had been COVID-19 symptom-free for 3 days, she was released after 19 days in the Poznan hospital. In line with the recommendations of the Polish Ministry of Health, no final SARS-CoV-2 test was performed before the discharge from hospital.

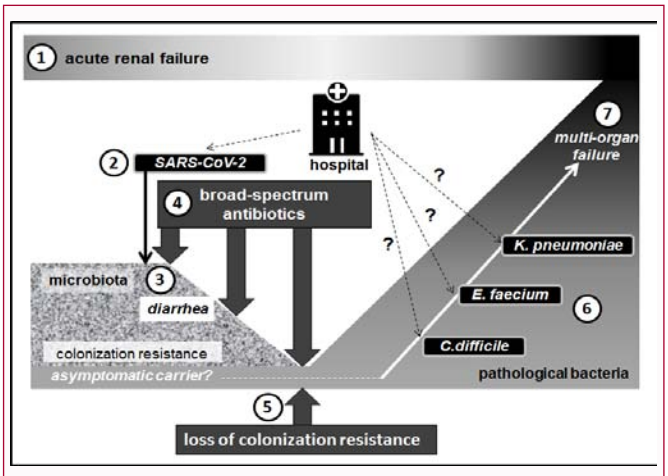

Figure 1: Chain of events: (1) Patient admitted to hospital because of acute renal failure, (2) acquisition of COVID-infection in the hospital, (3) manifestation of diarrhea, (4) treatment with broad-spectrum antibiotic, (5) loss of colonization resistance, (6) proliferation of multi-drug resistant pathological bacteria, (7) death of patient due to multi-organ failure.

After 30 days at home, the patient was re-admitted to the District Hospital in Jarocin due to diarrhea and abdominal pain. Presence of *C. difficile* toxin was confirmed in a stool sample and a new cycle of treatment with vancomycin 250 mg (q.i.d., p.o.) and metronidazole 500 mg (t.i.d., i.v.) was initiated. As several days of treatment showed no improvement of the patient's condition, a stool sample was collected for culture of pathological bacteria. Presence of Extended-Spectrum Beta-Lactamase (ESBL) producing *K. pneumoniae* and vancomycin-resistant *E. faecium* was confirmed in the sample, while *C. difficile* couldn't be cultivated from the sample. Despite intensive treatment of the patient, renal function deteriorated and symptoms of circulatory failure worsened. The patient died 18 days after her second admission to the District Hospital in Jarocin due to multi-organ failure resulting from infection with pathological bacteria.

Discussion

Administration of broad-spectrum antibiotics to COVID-19 patients is part of the established pharmacological treatment standard. All broad-spectrum antibiotic therapy carries the intrinsic risk of triggering the uncontrolled proliferation of multi-drug resistant bacterial pathogens in patients. The patient in this case report was not tested for the presence of multi-drug resistant bacterial pathogens before the antibiotic therapy was initiated, as this is not an established routine in the Polish (and most other) healthcare system(s). Therefore it is not known if the bacterial pathogens which finally killed the patient originated from the patient herself, being a carrier of these pathogens, or had been acquired during her hospital stay.

The likely reason for triggering the proliferation of pathogenic multi-drug resistant bacteria by broad-spectrum antibiotic therapy is the destruction of the protective gut-microbiota (colonization resistance) as shown in Figure 1 as point no. 5 in the graphical representation of the chain of events of this case report [9-11].

The majority of bacteria in the gut are susceptible to antibiotics. However, the gut microbiota may also comprise bacterial pathogens in low amounts (e.g. *C. difficile* strains [13], *K. pneumoniae* strains [14] and *E. faecium* [15]), which are resistant against a broad range of commonly used antibiotics. While the commensal bacteria of the gut normally keep proliferation of these pathogens at bay, treatment with broad-spectrum antibiotics can destroy this control function of the gut microbiota (loss of colonization resistance). Culturing pathogenic bacteria from a stool sample taken from the patient revealed the presence of ESBL *K. pneumoniae* and vancomycin-resistant *E. faecium*. Despite earlier findings of fecal *C. difficile* toxin, cultivation of *C. difficile* from the stool sample was not possible. The reasons for failing to cultivate *C. difficile* could be (i) that vancomycin treatment had already successfully eliminated the pathogen from the gut of the patient or (ii) that the sample taken contained an amount of vancomycin, which made in-vitro cultivation of the (vancomycin-sensitive) *C. difficile* impossible. The proliferation of pathogenic bacteria finally resulted in disease manifestation with fatal consequences for the patient. To strengthen the colonization resistance of the patient's gut microbiota a probiotic containing three different strains of *L. rhamnosus* had been administered. The potential of products containing probiotic microorganisms to support the colonization resistance of the gut has been discussed in-depth in a recent review [9]. Unfortunately, the administration of the probiotic had no long-lasting protective effect in the presented patient case. Potential reasons for this failure could be that the administration of the product had been initiated only 3 days after the initiation of the antibiotic therapy or that the administered product failed to inhibit the proliferation of the specific bacterial pathogens causing the patient's problems [16]. It is important to note that there is growing evidence that complex multi-strain synbiotics are more effective in inhibiting pathogenic bacteria than less complex probiotics [17].

Conclusion

The awareness of the risk associated with the empiric administration of broad-spectrum antibiotics to COVID-19 patients has to be increased, as in some patients this can result in fatal bacterial infections. The potential benefits of products containing probiotic microorganisms in these patients should be investigated in more detail in clinical studies.

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