**Clostridioides Difficile Infection in the Neurorehabilitation Setting: Importance of a Multidisciplinary Approach and Impact of the Faecal Microbiota Transplantation**

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**Abstract**

Clostridioides difficile infection (CDI) is considered to be one of the most frequent causes of bacterial infectious diarrhea in nosocomial settings. Both the prolonged hospitalization in bed-ridden conditions and the frequent administration of antibiotics therapy are usually encountered among the risk factors for CDI. Therefore, it is not surprising that CDI rates among rehabilitation hospitals are higher in neurologic facilities. In the neurorehabilitation setting, CDIs - especially if they present with refractory or recurrent aspects- may interrupt the normal course of rehabilitation, influencing, subsequently, the neurological outcomes.

CDI treatment depends on the severity of the disease and includes both conservative and surgical approaches, whereas these latter are reserved to severe-complicated CDI. Another emerging, highly effective therapeutic option is represented by the faecal microbiota transplantation (FMT), which consists in the transfer of screened healthy donor stool to a recipient’s gastrointestinal tract.

In this paper, we report two cases of refractory CDI, affecting patients in the neurorehabilitation pathway; both cases were resolved through FMT. If on the one hand our cases provide more evidence of FMT-efficacy in refractory CDIs, from the other they emphasize the need of a multidisciplinary approach to grant the best care to CDI patients.

**Introduction**

Clostridioides difficile infection (CDI) is one of the most common healthcare associated infections and a significant cause of morbidity and mortality among hospitalized patients. Clostridioides difficile (CD) are Gram-positive, spore-forming, anaerobic bacilli, which are widely distributed in the intestinal tract of humans and animals and in the environment. Transmission of these pathogens occurs by the fecal-oral route. The most important risk factors for CDI include female sex, old age, recent and prolonged hospitalization, bed-ridden conditions, recent antibiotics therapy, active proton pump inhibitors treatment, active cancer, hypoalbuminemia and leukocytosis [1]. CD produce two potent toxins: toxin A and toxin B. Toxin A is an enterotoxin with mild cytotoxic activity. It can cause initial damage to the intestinal villi, destroying the brush borders of the membrane. The resulting damage of the intestinal mucosa due to inflammation can lead to its erosion. From other side, toxin B is one of the most potent cytotoxins known, showing a cytotoxic effect 100 times more potent than toxin A. The related main effects include the loss of intracellular potassium and the inhibition of protein and nucleic acid synthesis [2].

The clinical presentation of CDI is blunt and ranges from asymptomatic carrier status, through various degrees of diarrhea, to the life-threatening and sometimes fatal colitis. The diagnosis of CD-induced diarrhea should be suspected in any patient who develops diarrhea within 2 months of antibiotic use or 72 hours of hospital admission. CDI diagnosis is based on the enzyme immunoassays (EIA) testing for the direct detection of CD toxins or toxin nucleic acid amplification-based assays, both in feces.

Several guidelines on the treatment of CDI have recently been updated. These guidelines identified three CDI severity-degrees: non severe, severe and severe-complicated (“fulminans”) CDI. Therefore, CDI treatment depends on the severity of the disease and embodies both conservative and surgical approaches [3].

The conservative strategy in the CDI management includes the administration of both antibiotics and the
monoclonal antibody bezlotoxumab (BZT). While vancomycin (VCM) is still proposed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines [4] for the first CDI episode, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines [5] suggest fidaxomicin (FDX) preferentially over VCM for initial CDI. This latter is related to the fact that FDX has been demonstrated to be superior in preventing CDI recurrence [3].

BZT is a monoclonal antibody against C. difficile toxin B and its efficacy in preventing recurrent CDI was confirmed in two randomized controlled trials [6]. The IDSA/SHEA guidelines suggest the administration of BZT (along with standard antibiotics) in case of primary and severe infection [5]. According to the ESCMID guidelines [4], BZT should be given in primary infection only if FDX is not available. Both guidelines agree with BZT use in all patients with recurrent CDIs.

A further and highly effective therapeutic option is the faecal microbiota transplantation (FMT), which consists in the transfer of screened healthy donor stool to a recipient’s gastrointestinal tract. Different routes of administration (nasogastric tube, enema, colonoscopy or capsules) are possible to perform the transfer. In the last 15 years multiple trials demonstrated that the transplantation of healthy donor feces is an effective therapeutic strategy for recurrent CDI [7]. FMT requires an accurate donor screening; in fact, the potential transmission of viruses and pathogenic bacteria remains possible. A documented transmission of Escherichia coli from donors to recipients has induced IDSA/SHEA to restrict FMT to third (or subsequent) CDI recurrence, while ESCMID and Australasian guidelines [8] suggest FMT for the second recurrence.

Finally, the surgical approach to CDI is represented in mostly cases by the execution of a total colectomy; this latter should be considered only in case of severe-complicated (refractory) CDI and reserved to the associated presence of toxic megacolon [3].

A study [9] demonstrated that the CDI rates among rehabilitation hospitals are higher in neurologic facilities. Another study [10] revealed that patients admitted to acute neurorehabilitation may have an elevated rate of intestinal colonization with CD without having clinical symptoms. In addition, the prevalence of CD as source of acute diarrhea in the rehabilitation setting is higher if compared with the prevalence of other micro-organisms, such Campylobacter, Salmonella, Shigella, Yersinia, and Giardia [11]. As suggested by Mardjan [9], rehabilitation facilities should need additional efforts to grant a higher standard in infection prevention and control. In particular, a multidisciplinary approach to the problem (also in this setting is absolutely essential to achieve the above-mentioned goals.

In this article, we present two cases of refractory CDI in neurorehabilitation setting; the peculiarity of these two cases consists in the fact that CDI interrupted the normal course of rehabilitation of our patients. A coordinated action between different professionals, operating in two separated hospitals - a neurological team and a gastroenterological one - was paramount in treating (and solving) CDI in both cases.

**Case Presentation**

**Case 1**

A polytraumatized 17-year-old man was brought to the emergency department (ED) following a road accident. On admission, the patient presented with a Glasgow Coma Scale (GCS): 7 (E1-V2-M4). In the emergency room, vital signs included temperature of 36.9 degrees Celsius, heart rate of 123 beats per minute, blood pressure of 150/90 mmHg. His past medical history was unremarkable. Because of the neurological status and respiratory distress, the patient underwent orotracheal intubation; after, he was moved to computed tomography (CT). Head CT showed in both hemispheres hemorrhagic lesions. A small mesencephalic lesion was also described. In addition, head bone CT demonstrated the presence of multiple fractures of the facial mass (mandible, maxilla, sphenoid sinus walls, major wings of the sphenoid, both orbits, right carotid canal). Thorax CT reported fractures from V to X right ribs.

An intracranial pressure sonde was placed and removed after 6 days because of persistent unremarkable pressure values. The patient was moved to the local intensive care unit (ICU); a percutaneous tracheostomy, as well as a percutaneous endoscopic gastrostomy (PEG) were carried out; a progressive weaning from mechanical ventilation was started. Four weeks later, he was moved to our neurorehabilitation department. On admission, the patient was still deeply sedated. After a progressive suspension of the sedation, it was possible to evaluate his neurological conditions. In particular, the patient presented an impaired consciousness, with activation of decortication patterns after nociceptive stimulation and inability to follow simple orders.

To quantify the cerebral, post-traumatic lesions load, we performed a Magnetic Resonance Imaging, which showed the presence of multiple hemosiderin deposits, compatible with diffuse axonal damage (Figure 1).
According to the general health and neurological state, the patient underwent multidisciplinary rehabilitation, which included daily sessions of physiotherapy, speech and language therapy and neuropsychological rehabilitation. Through these interventions, clinical and neurological conditions of our patient improved consistently. The patient experienced a good recovery from his consciousness disorder and started to follow simple orders. After an initial phase of relative flaccidity, generalized spasticity developed over few weeks. Because of emerging tonus abnormalities, a therapy with a muscle relaxant (baclofen) was started and administered via PEG. A daily dose of 30 mg (10 mg x 3) was initially given; anyway, this dose was progressively increased because of spasticity progression. To achieve the maximum therapeutic benefit, a daily dose of 75 mg of baclofen was ultimately administered. Since only a partial control of the spasticity was reached, we performed a lumbar punction to evaluate the patient’s response to intrathecal baclofen (ITB) therapy. As result of this procedure, the patient was classified as ITB responder, and he was scheduled for the ITB-pump placement.

Unfortunately, four days before the planned surgical procedure, the patient was found to have fever (38.2 degrees Celsius) and explosive diarrhea. Laboratory test showed a raised C reactive protein of 59 mg/dL, white cell count 12.1\times 10^3/\mu L and neutrophils 8.2\times 10^3/\mu L. A bacteremia could be excluded by several negative blood cultures. In the following days, also other cultures (urine- and bronchoscopic cultures) resulted negative. A performed chest x-ray was not indicative for an active infection. We started a symptomatic therapy (including paracetamol and re-hydratation) and fever resolved on its own (without administration of antibiotic therapy) within a couple of days. Almost all laboratory inflammatory biomarkers returned to baseline within few days. What still remained and became persistent was dysentery. In particular, the patient showed more than five bowel evacuations daily.

As multiple risk factors were present, the presence of a CDI was suspected, and promptly confirmed by toxin detection in stool sample. The patient was isolated, and all hygienic precautions were adopted. In the first instance, a VCM therapy (250 mg x 4 via PEG) was started. After the normal course of therapy (10 days), the feces consistency was almost, but not entirely, normal. We decided to extend the VCM cycle to 14 days; unfortunately, in the following days, the patient still presented with diarrhea. An infectious disease consultancy suggested an antibiotic switch-off, replacing VCM with FDX. As recommended, we administered FDX 200 mg every 12 hours via PEG. After 10 days (usual period of therapy), no evident changes in feces consistency were noted. Another antibiotic therapy with tigecycline (TGC), was administered, but also this attempt failed. A combination of FDX with BZT was furtherly attempted, without obtaining a clinical benefit.

During this long period (almost 6 weeks) of ineffectiveness of the antibiotic therapy, the patient could not profit from a “complete” rehabilitation.

Although if all the preventive measures to avoid dehydratation and weight loss were adopted, the patient has lost more than 4 kilograms in 6 weeks. From a pharmacologic point of view, some drugs (proton pump inhibitors) were interrupted and the therapy with baclofen was decreased in its dose. In fact, a decrement in the baclofen dose is commonly suggested during a CDI to avoid abnormalities in intestinal motility. As consequence of this latter, the spasticity led to formation of distal limbs deformities (Figure 2).
Spasticity is a condition in which there is an abnormal increase in muscle tone or stiffness of muscle, which might interfere with movement. The degree of spasticity varies from mild muscle stiffness to severe and uncontrollable muscle spasms. In our case, the spasticity progression - due to the baclofen-dose reduction - led to the development of muscle contractures and distal limbs deformities.

In addition, the "isolation status" of our patient did not allow him to profit from the robot assisted neurorehabilitation.

Since the neurorehabilitation process was blocked by the presence of CDI, we contacted the nearest FMT center. In Italy, FMT is (actually) performed only in some selected hospitals. In addition, it is not allowed in underage patients yet [12]. At this time-point, our patient has to wait almost two weeks to come of age. In agreement with parents and FMT center, we waited for this time and two weeks later we moved the patient to undergo to FMT. Instillation of feces from an healthy donor into right colon was performed during a colonoscopy.

To our great surprise, the patient showed no feces abnormalities in the following days. We repeated the direct detection of CD toxins in feces three times in following weeks, but both toxins were persistent absent. According to the clinical course and to the laboratory suggestions, the patient was considered recovered from CDI; 6 weeks later, an ITB-pump was placed. At the time of writing of the present article, the patient is still admitted in our rehabilitation department. In the last weeks, the patient has shown a slow, but progressive recovery of his neurological deficits. In particular, the spasticity is actually controlled through the ITB-therapy. A neuro-orthopedic approach to treat the distal limbs deformities has already been planned.

Case 2

A 64-year-old man was brought to the ED because of sudden appearance of unresponsiveness and respiratory distress. On admission, the patient was unconscious (GCS: 8). In the emergency room, vital signs included temperature of 37.2 degrees Celsius, heart rate of 112 beats per minute, blood pressure of 165/90 mmHg. His past medical history was significant for arterial hypertension and ischemic heart disease. After undergoing orotracheal intubation, the patient was moved to brain CT scan, which showed an ischemic stroke in the left middle cerebral artery (MCA) territory. Anglo-CT showed an occlusive disease in the M1 segment of the left MCA and in the left internal carotid due to presence of thrombus formations. The patient underwent subsequently to endovascular treatment with placement of two stents in the above-mentioned sites, after partial removal of thrombotic clots. Consequently, the patient was admitted in the ICU. Because of a progressive neurological worsening, which was associated to a CT-demonstrated, increased oedema in the ischemic territory, the patient underwent to left fronto-parieto-temporal decompressive craniotomy some hours later.

During following days, the clinical health and neurological conditions remained critical. A percutaneous tracheostomy, as well as a PEG were carried out; after three weeks, because of a new diagnosed anisocoria, a brain CT was repeated. This exam showed the haemorrhagic transformation of the ischemic stroke. After reaching a stable state, a progressive weaning from mechanical ventilation was started. Five weeks later, the patient was moved to our neurologic ICU (n-ICU). On admission, the patient presented awake, with right hemiplegia and global aphasia. We repeated a brain CT, which showed an organized hematoma in the context of the hemorrhagic transformation of the ischemic stroke (Figure 3).
FIGURE 3: Brain Computed Tomography (CT)

a, b: organized hematoma in the context of the hemorrhagic transformation of the ischemic stroke (orange arrowheads)

c: the lateral ventricle on the left side (yellow star) appears dilated in the context of a hydrocephalus ex vacuo due to the previous territorial stroke (red arrows)

d: a stent in the M1 segment of the left middle cerebral artery (blue arrowhead) was previously placed to treat and prevent the occlusive disease; in addition, the presence of a little amount of ventricular blood following the stroke’s hemorrhagic transformation can be demonstrated in the left lateral ventricle (green arrowhead)

e: in this section, the presence of a hydrocephalus ex vacuo involving the left ventricle (yellow arrowhead) appears evident. The right lateral ventricle (blue arrowhead) is not dilated. The described hydrocephalus is due to the previous territorial stroke (red arrows)

f: no subtentorial lesions were detected

The initial clinical course in our n-ICU has been characterized by the onset of multiple infections (involving the airways and urinary tract). Our patient was included in a multidisciplinary early-rehabilitation program, made up of daily sessions of conventional physiotherapy, speech and language therapy and neuropsychological rehabilitation. In addition, as soon as the resorption-process of the haemorrhagic transsormation was completed, we started to verticalize and mobilize the patient with the rehab-tilt table (Erigo®, Hocoma, Switzerland) daily. Through this rehabilitative strategy, the patient could improve his neurologic conditions. In particular, after four months from the acute event, the patient’s assessment was remarkable for a right hemiparesis (2/5 degree on the Medical Research Council Scale on both upper and lower limbs). At this time point of the clinical course, the strength improvement was not overall functional; however, considering the initial deficit (hemiplegia without rest-motor faculty) and the brain imaging (compatible with a territory infarct), the reached improvement was rather encouraging. From other side, no improvements in speech and language were noted. Supposing that the execution of the cranioplasty at this time-point could have showed a positive effect on the patient recovery, we performed a three-dimensional brain CT and we planned the neurosurgical head-bone reconstruction (Figure 4).
Unfortunately, the patient was found to have explosive diarrhea some days before the planned OP. In addition, the patient developed fever (38.0 degrees Celsius), which resolved with symptomatic therapy. Since a CD was confirmed by toxin detection in stool sample, we were forced to delay the planned neurosurgical treatment. An antibiotic treatment with VCM (250 mg every 6 hours) was initially started. In presence of persistent diarrhea, VCM was replaced by FDX (200 mg twice/die) after 5 days, according to infectious consultancy. Because of the persistence of high frequency of bowel movements, FDX (after 10 days, namely at the end of its cycle) was replaced with TGC. Since this latter attempt also failed, we decided to resort to FMT (according to gastroenterology consultancy) and the patient underwent to the same procedure of the previous case.

FMT was performed without complications and the patient was thereafter moved back to our neurorehabilitation department. Upon return to our clinic and during following weeks, the patient showed physiologic intestinal movements.

A direct detection of both toxins - done few weeks later - resulted negative; thus, the patient was finally transferred to the local neurosurgical department, where the planned cranioplasty operation could be finally performed.

Discussion
In this article, we reported two cases of refractory, non-severe CDIs. In both cases, no criteria for severe or severe-complicated CDI (white blood cell count of > 15,000 cells/mL or a rise in serum creatinine level > 50% above baseline or core body temperature > 38.5°C) were fulfilled. According to the guidelines, we initially administered a conventional antibiotic therapy. The main features of the most used antibiotics in case of CDI are reported in Table 1.

<table>
<thead>
<tr>
<th>Antibiotic name</th>
<th>Antibiotic Class</th>
<th>Metabolism</th>
<th>Therapy regimen</th>
<th>Indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCM</td>
<td></td>
<td>VCM is not metabolized in</td>
<td>Standard regimen: 125 mg PO 6 hourly for 10 days Tapered/pulsed regime: 125 mg four times daily</td>
<td>1. Initial, non-severe episode, as alternative to FDX -standard regimen (IDSA/SHEA and ESCMID) 2. First recurrence, non-severe episode: tapered and pulsed regimen OR standard regimen with adjunctive bezlotoxumab (IDSA/SHEA and ESCMID) 3. Severe episode: standard regimen with adjunctive bezlotoxumab</td>
<td>Common adverse drug reactions (≥1% of patients) associated with ___</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Class</td>
<td>Metabolism</td>
<td>Excretion</td>
<td>Dosage</td>
<td>Recurrence</td>
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<tr>
<td>Vancomycin (VCM)</td>
<td>Glycopeptide</td>
<td>excreted in the urine</td>
<td>urine</td>
<td>for 10–14 days, two times daily for 7 days, once daily for 7 days, and then every 2–3 days for 2–8 weeks</td>
<td>Higher dose regimen: 500 mg 6 hourly PO</td>
</tr>
<tr>
<td>Fidaxomicin (FDX)</td>
<td>Tiacumicin (new class of narrow spectrum macrocyclic antibiotic)</td>
<td>metabolized to its active metabolite via hydrolysis of the isobutyryl ester, which occurs primarily in the intestine and therefore does not depend on hepatic CYP450 enzymes.</td>
<td>PO every other day for 2–3 days</td>
<td>Higher dose regimen: 500 mg 6 hourly PO</td>
<td>if other risk factors for recurrence (such as age ≥65 years, immune-compromission) are present (IDSA/SHEA) 4. Severe-complicated ‘fulminant’ episode: higher dose regimen. In this case, if ileus is associated, an administration of VCM per rectum should be considered (IDSA/SHEA); ESCMID guidelines suggest VCM standard regimen and eventual adjunctive TGC</td>
</tr>
<tr>
<td>Metronidazole (MTD)</td>
<td>Nitroimidazol</td>
<td>metabolized in the liver and undergoes biotransformation through hydroxylation, oxidation of side chains, and glucuronidation. Both unaltered MTD and its metabolites are excreted primarily by the kidney, although biliary excretion does occur</td>
<td>PO 12 hourly for 10 days</td>
<td>Extended-pulsed regimen: 200 mg PO 12 hourly for 5 days followed by 200 mg PO every other day for 20 days</td>
<td>1. Initial episode, non-severe: standard regimen only if VCM and FDX are not available (IDSA/SHEA and ESCMID) 2. First recurrence, non-severe episode: standard regimen (IDSA/SHEA and ESCMID) or extended-pulsed regimen (IDSA/SHEA). 3. Severe episode: standard regimen (IDSA/SHEA and ESCMID) 4. Severe-complicated ‘fulminant’ episode: standard regimen (ESCMID)</td>
</tr>
<tr>
<td>Tigecycline (TGC)</td>
<td>Tetracycline</td>
<td>slightly eliminated via glucuronidation. TGC is mainly eliminated as unchanged drug and metabolites in the bile and feces (59%). Another 22% of the drug is excreted as unchanged drug in the urine.</td>
<td>PO 8 hourly for 10–14 days</td>
<td>Standard regimen: 100 mg for the first intravenous administration (antibiotic load), then 50 mg 12 hourly</td>
<td>Gastrointestinal symptoms are the most common reported side effect.</td>
</tr>
</tbody>
</table>

**TABLE 1: Main features of the most used antibiotics in case of Clostridioides difficile infection**

Abbreviations: VCM: vancomycin; FDX: fidaxomicin; MTD: metronidazole; TGC: tigecycline; IDSA/SHEA: Infectious Diseases Society of America / Society for Healthcare Epidemiology of America; ESCMID: European Society of Clinical Microbiology and Infectious Diseases.
Anyway, both cases were unresponsive to the first-line therapy (VCM and FDX), but even to subsequent lines of antibiotics therapy, showing refractory features.

With the term "refractory CDI" is meant a CDI which is unresponsive to treatments, leading to persistence of diarrhea (with positive CD toxins or with negative CD toxins but in the absence of other possible causes of diarrhea) [13]. For patients suffering from refractory, non-complicated CDI, ESCMID guidelines suggest reconsidering the diagnose, since VCM and FDX resistance is rare. In fact, an alternative diagnosis in combination with CD colonization may be consistent in a significant number of "supposed" refractory CDI patients. According to both guidelines, we excluded other common causes of persistent diarrhea; subsequently, we administered "second line" antibiotics (TGC), without obtaining significant effects. Finally, both cases were resolved by rescue FMT. In fact, after performing FMT, we noted the immediate diarrhea disappearance; furthermore, the direct detection of CD toxins in feces (8 weeks after FMT) was - in both cases - negative.

Both above mentioned guidelines suggest FMT preferentially in case of CDI recurrence or in case of severe CDI; on other hands, the Australasian guidelines [8] recommend FMT in case of medical therapy failure.

A peculiarity of the presented cases consists in the fact that our patients were included in the neurorehabilitation pathway. In this context, solving CDI through FMT made possible to overcome a dangerous impasse that was causing a harmful delay in the patient care pathway. The importance of an integrated, multidisciplinary approach in the management of CDI-patients in the neurorehabilitation setting should be underlined. In fact, the cooperation between different specialized professionals (neurorehabilitation specialists, specialists from other disciplines, such as gastroenterology, internal medicine, infectious diseases medicine, and nutrition service professionals) is absolutely needed in improving treatment efficiency and patient care. Only the integration of all these professionals is effective in granting an optimal treatment of this infection and of its consequences - especially in the neurorehabilitation-context.

A recent study [14] on a small number of chronic stroke patients who experienced CDI during the rehabilitation process demonstrated that these patients do not show statistically significant difference in rehabilitation outcomes when compared to control group. Even if these results may be consistent in the chronic rehabilitation-phase, future research should demonstrate if similar results could be extended to patients in the acute and sub-acute neurorehabilitation setting. Anyway, some considerations on this point may be taken into account. As presented in our cases, an effective neurorehabilitation may request the execution of different surgical interventions, and these treatments are (obviously) contraindicated in case of active CDI. In fact, some inpatients in the neurorehabilitation setting may benefit from a number of invasive procedures (i.e. cranioplasty, ITB-pump placement, diagnostic and therapeutic lumbar punctures, ventriculoperitoneal shunts placement etc.), especially in the acute and sub-acute phases. Even if there are no sufficient data on this topic in the literature, it is reasonable to suppose that a delay of invasive procedure due to the CDI presence may lead to worst neurorehabilitative outcomes.

In addition, the isolation of CDI patients is mandatory. As consequence, CDI patients in the neurorehabilitation setting are mostly treated by rehabilitative staff in their room and the entry to appropriate rehabilitation gyms is denied due to infectious risk. Moreover, the continue stimulation related to the surroundings and the interactions with other patients are limited. For the same reasons, the accessibility to the robot-assisted rehabilitation is restricted in case of active infection. Future research should also clarify the impact of these limitations on the neurorehabilitative outcome.

Conclusions

In conclusion, there is a paucity of literature about CD and neurorehabilitation; from a mere neurorehabilitative point of view, delayed treatments bring to poorer neurological outcomes. CDIs may cause a delay of important therapeutical interventions in the acute neurorehabilitation setting, therefore influencing the neurological outcome. In this context, FMT should be considered as an important resource, especially in case of medical failure. Even if FMT presents some complexities in immunosuppressed patients and requires an accurate donor screening, this procedure seems to be effective and well tolerated also in the acute phase of the neurorehabilitation pathway. Future studies should definitively clear the impact of CDI on outcomes during the acute phase of the neurorehabilitation; finally, the FMT feasibility in acute neurologic patients should be further pursued and investigated.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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