A Risk Assessment of *Clostridium Difficile* Infection after Antibiotherapy for Urinary Tract Infections in the Urology Department for Hospitalized Patients

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Antibiotherapy is the treatment of choice for the urinary tract infections in hospitalized urological patients. Antibiotic associated diarrhea (ADD) caused by the Clostridium difficile cytotoxin producer represents one of the most severe side effects of the antibiotic treatment. It is important to evaluate the risk factors for a hospitalized patient to develop a C. difficile healthcare associated infection during hospitalization in order to put in practice effective preventive measures. The aim of the study is to analyzed the risk factors associated with the demographic status: age, sex, and also risk factors related to healthcare conditions: use of antibiotics (number, type, duration of treatment), other significant medication taken prior to the onset of diarrhea (histamine-2-receptor antagonists and proton-pump inhibitors, comorbidities, possible contamination from other in-patients who developed ADD in the same period and data about in-hospital mortality.

Keywords: Clostridium difficile infections, antibiotherapy for UTI, antibiotic associated diarrhea

Urinary tract infections are among the most commonly diagnosed diseases in the Urology Department, because many of them are directly related to the urological diseases: urolithiasis, obstruction of the urinary tract, complications after urological surgery. All of the above mentioned urological diseases are treated with antibiotics. Since early 1900s, antibiotics have been used in infectious diseases, the most of them being used to treat infections in humans and animals.[1] Antibiotic associated diarrhea (AAD) is one of the most severe side effects of the antibiotic treatment. The etiology of AAD varies. According to the literature, 20% of all AAD and nearly all cases of pseudomembranous colitis (PMC), the most severe manifestation of AAD, are produced by the cytotoxin-producing Clostridium difficile (C. difficile) [2]. The interest in this pathogen is big because of its association with health care services impact on morbidity and mortality in the elderly [3]. Because the urological patients are, most of them, elderly people, and the urinary tract infections are treated with antibiotics, these patients are at risk to develop healthcare associated Clostridium difficile infection (HA CDI).

Clostridium difficile is a gram positive, strictly anaerobic, spore forming bacterium that is very difficult to cultivate. The identification of this pathogen in the patients stools is very difficult using classical microbiology testing, but in the last years another technique was developed, an immunoassay that easily identifies the C difficile toxins in feces. The test is available on the market at a reasonable price; so many hospitals began using the diagnosis of CDI. The magnitude of HA CDI in different patient populations is not well known, varying widely between hospitals and countries [4]. Most of the studies were made, over the years, in the USA and Western Europe.

Because our department Urology Department of Sibiu was confronted in the last years with a real increase in the number of cases with this pathology and because our Microbiology Laboratory was able to determine the C.difficile toxins A&B in our patients feces, we could perform a systematic diagnose of HA CDI in all the cases of UTI, treated with antibiotics. We set up urgent specific measures for the prevention and limitation of this disease among the urology hospitalized patients.

In the last years, the importance of evaluating risk factors associated to healthcare treatments has risen. Due to the numerous public debates about the hospital acquired infections it was observed that the patients concern of such a complication has grown significantly, when being admitted to a hospital, leading to an increased number of questions regarding the possibility of getting such an HAI (Healthcare Associated Infection) during hospitalization.

HA CDI is not only a difficult medical problem, but also rises an important economic problem, because the treatment of these patients increases the cost of hospitalization, increases the number of hospitalization days, and sometimes, because of the severity of the disease, despite all medical treatments, the patient dies, so the in-hospital mortality increases too. Being aware of this life threatening disease we made a study regarding the risk factors that predispose for HA CDI in order to give correct answers to our patients and to be able to take the best preventive effective measures during hospitalization.

Experimental part

The Academic Emergency Hospital Sibiu is a teaching hospital related to the University Lucian Blaga Sibiu. The department of Urology has 48 beds and offers all kind of surgical and medical treatments for its patients. Being an accredited hospital all the patients data are in the electronic system of the Hospital, ATLAS, for the last 5 years. For this study we reviewed all medical records between 1st of January 2015 to 1st January 2017 and we selected the patients with the diagnosis of UTI .We found 458 patients, confirmed with a positive uroculture. All the patients were treated with antibiotics during their hospitalization, according to the antibiogram. We then focused our research on those 59 patients who developed an AAD. We analyzed their stools in our Hospital Microbiology Laboratory with microbiological methods (classical coproculture for Salmonella spp, Shigella spp, Yersinia enterocolitica) and also with immunological methods, for the detection of C.

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difficile toxins A&B. We defined diarrhea as CDI when the patient has: 1- 6 watery stools during the previous 36 h, 3 unformed stools in 24 h periods over 2 days or 8 unformed stools during 48 h period, or 2- fever, abdominal pain and / or ileus, addition laboratory confirmation for stool sample positive for C difficile toxins A or B, or a positive tissue culture assay, or 3- diagnosis of pseudomembranous colitis on colonoscopy, or 4- histological or pathological diagnosis of CDI. The infection is considered to be HA CDI if the patient's symptoms occurred at least 72 h after hospital admission or if symptoms result in readmission of a patient who had been hospitalized within the 2 months before the symptoms onset date and who was not resident in a long term care facility or nursing home [5].

The immunological test used for the detection of C. difficile toxins A&B was an immunocromatographic test for the direct qualitative detection of C. difficile toxin A and /or B in human fecal specimens. This test has 86.3% Sensitivity (95% Ci=79-91.3% and 96.2 Specificity (95% Ci 94.5-97.5%). Positive predictive value 84.1% (95% Ci 77.4-89.4%). Negative predictive value 96.8% (95% Ci 95.2-98.0%), % correlation (94.4) (95% Ci 92.5-95.8%). (Ci = Confidence interval). We do not have the possibility of typing the C. difficile in our Laboratory and determine the strain type [6,7].

Reviewing the clinical chart information on our 43 patients with the confirmed diagnosis of HA CDI, we studied the following variables: demographic status: age, sex, and also risk factors (RFs) related to healthcare conditions: use of antibiotics (number, type, duration of treatment) , other significant medication taken prior to the onset of diarrhea (histamine-2-receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs), comorbidities, possible contamination from other inpatients who developed ADD in the same period and data about in-hospital mortality.

Results and discussions

We analyzed 458 cases, admitted in the Urology Department with the diagnose of UTI, confirmed with a positive uroculture. The UTI diagnose was associated to an obstructive nephropathy: urolithiasis 65%, neoplasia 32% and malformative 3 %. In these UTI cases we analyzed all the urocultures and we found that, according to our statistics, the etiologic agents of these infections were E. Coli (72%), Enterobacter (10%), Klebsiella spp. (8%), Pseudomonas aeruginosa (5%) and Proteus (5%). All the patients had an antibiotic treatment, according to the antibiogram.

From the 458 cases of UTI treated with antibiotics during their hospitalization, we found 57 patients of clinical diarrhea, defined as AAD. After the stools immunological testing for the identification of C. difficile toxins A&B we confirmed 43 patients with positive C. difficile toxins. These patients could be categorized as HA CDI.

We focused into the analysis of this 3rd category: patients with UTI, treated with antibiotics, who developed a diarrhea after the treatment, positive to the immunological testing for C. difficile toxins A&B. These patients were analyzed according to their age, sex and RFs associated to the healthcare treatment: types of antibiotics, treatment for the diarrhea, comorbidities.

The age distribution was as follows: 30-40 years -1 patient (2%), 40-50 years -7 patients (18%), 50-60 years - 9 patients (23%), 60-70 years - 14 patients (30%,) 70-80 years- 8 patients (17%), 80-85 years - 4 patients (10%). We found most of the patients with HA CDI were older than 60 years (60.4%).

We analyzed the sex distribution of these 43 patients and we found 28 males (65%) and 15 females (35%) with a ratio of 1.86 males/1 female.

We carrefully looked then to the antibiotics we used in those 43 cases. We used antibiotics of the following classes: fluoroquinolones in 19 cases, cefalosporines in 9 cases, aminoglicozides in 6 cases, carbapenem in 6 cases, ampicilines in 3 cases.

According to our hospital epidemiological rules, the patients with AAD were isoalted (remained in the same room during all hospitalization period and we did not bring any new patient into that room. We stoped the previous antibitoherapy and started the treatment for CDI for a period of 7-10 days. Between the 43 patients 40% received Vancomycin 4x250 mg/day; 25% of them Metronidazole 500 mg 2 x 2 tablets/day and 35% of them Metronidazole and Vancomycin.

The patients had important comorbidities: cardio vascular diseases, diabetes, genital malignancies treated with chemotherapy, digestive malignancies. No patients received antisecretory therapy , but most of them received the antibiotherapy associated with a proton pump inhibitor (PPI).

We also studied the possible contamination from other inpatients who developed AAD in the same period, but we found no correlation between the cases because the patients were in different rooms, and the staff who treated them took all the preventive necessary measures.

We studied also the in-hospital mortality for the 43 cases because 2 patients, aged 65 and 77 years, died due to the complications of acute diarrheal disease: pseudo-membranous colitis, ileus, septic shock, multiple organ deficiency, after 15, respectively 21 days of treatment. So, our in hospital mortality due to the HA CDI was (0.86%).

Recent data suggest that *C. difficile* has replaced Methicillin-Resistant *Staphylococcus aureus* (MRSA) and became the first common cause of Healthcare-Associated Infection [11, 13, 14, 20].

That is why we have to evaluate the risk to get a HA CDI for a patient admitted in the Urology Department, who received antibiotic treatment for his obstructive nephropathy complicated with UTI.

According to our results, the incidence rate (IR) for HA CDI in our Urology surgical department was 9.3%, 43 of 458 over the last 2 years. Looking into the literature we can see differences with other studies, made in surgical patients, where the figures are variable. Most studies have been conducted in the USA or Western European countries, where there are well-developed healthcare systems [8, 10, 12]. We have less data from Romania, a country in socio-economic transition, with a resource limited healthcare system. [10, 12].

An European, multicenter, prospective, biannual point-prevalence study of CDI in hospitalized patients with diarrhea (EUCLID) showed a mean IR of 7.0 of HA CDI (country range 0.7–28.7). [12].

The analyzed risk factors for developing a HA CDI were: gender, age, intake of antibiotics, treatment for the CDAD, comorbidities.

Concerning the gender of the patients, our results showed a male gender association with CDI, with 1.8 males/1 female. It is a big variability between the studies; in the USA population-based studies have reported an association between female gender and CDI, but in Portugal, the studies reported no association between gender and CDI. [13, 14, 16, 17].

The age can be a risk factor in our study, 60.4 % of the patients, being more then 60 years. Advance age is an

independent RF for CDI in many studies [5,9,10]. Another study, made in Romania in 2016, [18], found similar percentages: 58.8% patients older then 65 years bur a study, made in a Urology department in UK, found 82% of the patients more than 60 years [19].

Other studies concluded that the risk of developing AAD is not related to age per se, but rather to other host factors, age-related changes in physiology, including immune senescence and changes of the gut microbiome or medical interventions [20].

Antibiotic intake represents one of the most important risk factor, for HA CDI. Alteration of the normally protective indigenous colonic microbiota by antibiotics is the mechanism most commonly proposed to make the host susceptible to C. difficile infection [21, 22].

All our patients received at least one class of antibiotics, the most commonly used being quinolones. In the literature certain classes seem to cause higher risk for CDI [23]. The administration of quinolones emerged as the most important RF for CID in Quebec during an epidemic caused by a hipervirulent strain of C. difficile [24]. A recent study from England showed that restricting quinolones prescribing was associated with a decline in incidence of CDI [25].

Studies demonstrated that the use of specific antibiotics in hospitalized patients predisposes to infections with specific strains that are resistant to those antibiotics and thereby facilitates epidemic spread. A meta-analysis supported fluoroquinolone use as a risk factor for infection with PCR ribotype 027 [26], whereas Clindamycin use was a risk factor for non BI strains [24]. The conclusion of all these studies was that both BI and non BI cases received intensive and prolonged antibiotic exposure prior to CDI, but categorical exposure to specific antibiotics predicted infection with specific C difficile strains [27]. It is a possibility that the last years increase in the number of cases with CDI to be the spread in Eastern Europe, and also in Romania, of a specific strain that is more aggressive, but there are not molecular studies in Romania referring to the ribotype of the CDI. Last data from a European multicenter, prospective, biannual point-prevalence study of CDI showed that overall prevalence of ribotype 027 has risen more than three-fold (from 5 to 18%) and high endemicity of ribotype 027 has shifted from the UK and Ireland in 2008, to Germany and Eastern Europe in 2012–13. This could be an explanation for the increasing number of cases in our Department [25, 27, 28].

We also remarked that not all patients that received antibiotics and are exposed to C. difficile develop an AAD. Host factors also appear to play an important role in CDI development because some patients with both exposures do not become symptomatic [11, 28]. The studies shows that there is colonization also in healthy non hospitalized adults (rate <5%), but the colonization is high among hospitalized patients and especially nursing home residents (25 to 55%), without them having CDI symptoms. [30]. This is attributable to other variables involved in this disease: the immune system ability to produce an antitoxin A IgG antibody as a response to C difficile infection [29].

In our study the patients with HA CDI had a combination of antibiotics with PPI. It is demonstrated that the medication that suppress gastric is associated with the alteration of gastrointestinal flora and the increased susceptibility to gastrointestinal infections [32]. Mice model demonstrated that PPIs administration can increase the severity of CDI induced by an antibiotic cocktail [31].

The mortality rate in our study, as the primary cause of death mentioned in the clinical chart information, was low, 0.86% , comparing with other studies, (5.3% reported in Veterans Health Administration) [34], both cases being associated with ages over 65.

Important limitation of this study is that CDI testing was based on toxin A/B enzyme immunoassay (EIA) as the only diagnostic procedure in laboratory (no EIA detecting glutamate dehydrogenase, no nucleic acid amplification tests, and no isolation of *C. difficile* and detection of toxigenic isolates). This procedure has shown poor sensitivity of less than 50% in studies of Shin [33] and Swindells [34]. The meta-analysis of Crobach et al. showed that no single test can be used as a stand-alone test for diagnosing CDI, as a result of inadequate positive predictive values at low CDI prevalence [35, 36].

C. difficile toxins can degrade at room temperature, so the quality of CDI diagnostic also depends on transport time of the samples.

The strengths of our study include its setting in a teaching hospital, and its 2-year duration as well as a good sample size.

Conclusions

Antibiotic treatment does not induce diarrhea in all treated patients but HA CDI is a life threatening diagnose in hospitalized patients. We can take additional preventive measures for the patients considered at risk to develop a HA CDI during hospitalization if they are older then 60 years, males, have comorbidities, and take antisecretory medication associated with the antibiotherapy.

It is also very important to have an early diagnose of AAD etiology for precise and rapid medical and epidemiological measures. Because there is a link between the antibiotic class used for the treatment and the C.difficile strains involve in the etiology of the disease, there is a real need for the implementation of molecular diagnosis in the hospital laboratory for a quick, specific diagnosis and for a better surveillance of the disease in hospitalized patients.

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