SYSTEMATIC REVIEW

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Clostridium difficile – an emerging plague

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Abstract: Introduction: Clostridium difficile infection stands nowadays as one of the major emerging health problems still underestimated. Only in 2009 the European Society of Clinical Microbiology and Infection (ESCMID) was able to publish guidelines for this serious disease. Actually the guidelines were updated in 2013 so we can speak of a united action towards the resolution of this healthcare problem.
Methods: This is a review article aiming to shed light in various aspects of clostridium difficile infection as clinical presentation, symptoms and signs, therapeutic options and risk factors with a focus on urologic pathology.
Conclusions: This type of infection represents a challenge from many points of view like treatment, relapse approach, mortality, morbidity, germ' s adaptability to treatment and last but not the least the outbreak of different aggressive strains like B1,NAP1 or ribotype 027 toxinotype III.

Keywords: Clostridium difficile infection, treatment, diarrhea

INTRODUCTION

C difficile was first described in 1935 by Hall and O'Toole as a Gram positive anaerobic commensal rod[1]. It took 43 years to discover the C difficile toxin in patients with pseudomembranous colitis.

The classic strains release two toxins A and B both of them monoglycosyltransferases causing colonic tissue damage. The name Difficile was given because of the the difficulty they had culturing this anaerobic bacterium on conventional media.

The interesting part is that from a nosocomial infection nowadays it appears to have spread to communities and what is more problematic to antepartum period, pregnant women and children[2].

The problem with this pathogen was that it evolved. In the early 2000 there was an outbreak in North America and Europe with a new strain, the ribotype 027 strain which has evolved and adapted. Metronidazole resistance was higher; the strain had modified genetic structure permitting to produce much more toxins than the classic types and incorporated another binary toxin which role is still unknown[3,4]. First time discovered in 1980s it presented high resistance to fluoroquinolones.

METHODS

A comprehensive search using PubMed, Medline and Google Scholar without publication status or other restrictions was conducted.

Studies using comparaisons between different antibiotics, reviews of risk factors, case presentations and all sorts of guidelines were included. The main

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objective of this paper was to review the main features and also to raise awareness of this health problem.

RESULTS

Diagnosis

Diagnosis is based on: clinical presentation, diagnostic tests, imaging and miniinvasive surgery.

The classical clinical exam reveals usually diarrhea in a patient with current or recent antibiotic use, frequent loose or watery stools. Occult blood or mucus may appear but melena or hematochezia are rare. Sometimes patients can develop colonic ileus or toxic megacolon. Both of them are very serious and unfortunately because of the ileus there can be no diarrhea so there can be a fatal delay in diagnosis. In this case diffuse abdominal pain, fever, abdominal distension are precious clinical signs. Finally there are those patients with very serious signs like septic shock or multiple organ failure.

All diagnostic tests have their strengths and weaknesses, the most used are EIA (enzyme immunoassays) for toxins A and B and then we have PCR, tissue culture cytotoxicity and assays for clostridial glutamate dehydrogenase (as a first line test).

Imaging unfortunately it is not specific for this kind of disease; still an abdominal X-ray or a computed tomography is of great value when we have to differentiate for other cases of occlusion or ileus.

There is another way of diagnosing the infection; still it holds a higher degree of invasiveness with all the secondary aspects.

We are talking about colonoscopies which can biopsy the membranes and solve the diagnosis in an ironclad manner.

Risk factors

Antibiotics

Multiple studies, some of them multicentric focused on what classes of antibiotics are involved in this disease. Most of them imply clindamycin, fluoroquinolones, cephalosporines(generations II, III, IV but not first generation). Rarely are cited also carbapenems and trimethoprim/sulphonamides, also peniclins seem to be involved[5].

Proton pump inhibitors and H2 antagonists

Normally they should be in same group but this affiliation is a bit forced. Proton pomp inhibitors are one of the most used therapies worldwide instead of H2 antagonists. Also there are some studies that recommend the use of H2 antagonists instead of proton pump inhibitors. Their role as a risk factor or not is not so clear. Some of them say that more than 2 days of proton pump inhibitor greatly increases the risk to develop C Difficile infection[6,7].

There are studies that demonstrated that one of those two protective agents can be administred concurentially with C Difficile treatment may it be metronidazole / vancomycin / fidaxomicin[8]. There are also studies that could not find any connection between the infection and the use of PPI[9].

Age> 65 years

This is one of the risk factors almost universally recognized. Almost all organisms at this age present somehow reduced turn-over, their innate resources are more limited so the immune response in this case is not so good, and the antibodies production rate is not so high so the host has lesser chances to suppress the infection.

Underlying illness

It is pure logic to assume that a weakened body would be more presumptuous to an infection. There are studies that associate this factor to the development of severe C. Difficile infections. In fact most of the studies at least agree to two of these factors respectively age and underlying illness.

In this category we include also neoplasia, gastro-intestinal surgery, naso-gastric tubes and gastro-intestinal disorders.

Long term hospitalization

This is also true for nursing homes. Both types of facilities present a high risk of infection given the high concentration of resistant germs and the difficulty to identify and isolate the infected persons. C Difficile is a spore type germ so the isolation is a must for the infected, and in this dormant form it can stay alive for months, so it is easy to assume the worst has passed[10].

The European Society of Clinical Microbiology and Infectious Diseases established a biochemical set of risk factors to predict an increased risk of developing severe disease[11].

1. Marked leucocytosis (leucocyte count >15 9 109/L)

2. Decreased blood albumin (<30 g/L)

3. Rise in serum creatinine level (≥133 lM or ≥1.5 times the premorbid level)

Treatment

For decades the only recognized and valuable tools were metronidazole and vancomycin. Both of them still stand as valuable medication.

A new antibiotic appeared a few years ago the fidaxomicin. As a last resort the infectionists use last tier drugs like Tygecycline.

Until 2009 there were no regulations for the treatment of this infection so there were a lot of medication schemes, some of them more or less efficient.

Fortunately nowadays there are international guidelines for the treatment of this infection. Less used substances have been tried some of them using great promise (Teicoplanin, Nitazoxanide, Rifaximin).

Tygecycline is a new glycylcyline from the tetracycline drug class. It has been shown to have activity against a wide variety of bacteria, including the antimicrobial-resistant strains. As with all tetracycline drugs, it is not recommended for pregnant or nursing women. One of the most important aspect especially for the urologic patient is that renal function monitoring is not necessary.

There are studies which compare vancomycin with fidaxomicin. Cure status are similar, however, fidaxomicin is associated with significantly lower recurrence rates than vancomycin for patients infected with non-NAP1 strains of C. difficile. For patients with the NAP1 strain, recurrence rates did not differ by treatment.

Emerging therapies

Toxin-binding resins and polymers and probiotics are two of the novel therapies which have been used in the treatment of this infection.

Unfortunatelly the results are still inconclusive, they are included in guidelines but not as a stand alone treatment but more as a adjuvant therapy[12].

As for immunotherapy, human monoclonal antibodies have been used with success, the main shortcoming is that the studies included few patients and we can not generalise the results. Still they show promising results some of them being in phase III trial.

In one of those studies at about 4 weeks after the resolution of symptoms the diarrhea reappeared. The question asked was if it was a relapse or the lifetime of antibodies just ran out and the organism was left defenseless[13].

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In case of non-severe infection (no signs of severe colitis) in non-epidemic situations and with CDI infection clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 h, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. Metronidazole is recommended as oral antibiotic treatment of initial CDI in mild/moderate disease. There is insufficient evidence to support administration of probiotics, toxin-binding resins and polymers, or monoclonal antibodies.	Based on its pharmacokinetic properties vancomycin is considered superior to metronidazole in severe C. difficile disease.The use of high doses of vancomycin (500 mg orally four times daily) was included in the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America treatment guidelines for management of severe complicated CDI as defined by the treating physician. However, there is insufficient evidence to support the use of doses >125 mg four times daily in the absence of ileus. Fidaxomicin was not inferior to vancomycin for initial cure of CDI, but there are no data available on the efficacy of this drug in severe life-threatening disease.	Total abdominal colectomy should be performed to treat CDI in case of: _ Perforation of the colon _ Systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy; this includes the clinical diagnoses of toxic megacolon, acute abdomen and severe ileus. Colectomy should preferably be performed before colitis becomes very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mM). A future alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treatment (intracolonic antegrade vancomycin and intravenous metronidazole).

Treatment of the relapse

There is evidence that suggests that vancomycin and fidaxomicin can be equally used in case of relapse. What is to be observed is that metronidazole is considered as a second line for the treatment of relapse.

In case of a secondary relapse or multiple relapses the medication conduit remains basically the same with some alterations of the alternative therapies.

DISCUSSIONS

This type of infection is usually an underestimated one. From the surgeon's point of view it may mean less but in our case the urologist must be very careful when dealing with this type of disease.

Not only most of the patients are > 65 years old but we must not forget that urinary sepsis is one of the most insidious ones, usually presenting with few symptoms and signs.

Being unable to diagnose fast enough the Clostridium Difficile infection usually is fatal for an old already surgically manipulated patient with lots of co morbidities.

Another problem luckily rare is the time to operate a patient with toxic colon. It is difficult to differentiate between the underlying surgical problem of the patient (may it be kidney, urether, prostate or bladder) and the acute onset of a colonic disease.

More, in these cases we find an ileus that is masking the underlying diarheea, making the moment to intervene very hard to choose.

It is very important for the urologists to be aware of this type of disease, to be capable of dealing with it and most important to recognize it fast enough.

References:

1. Rui Li, Laichun Lu, Yu Lin, Mingxia Wang, Xin Liu - Efficacy and Safety of Metronidazole Monotherapy versus Vancomycin Monotherapy or Combination Therapy in Patients with Clostridium difficile Infection: A Systematic Review and Meta-Analysis - PLOS ONE | DOI:10.1371/ journal.pone. 0137252 October 7, 2015

2. J. Yoo, A.L. Lightner - Clostridium difficile Infections: What Every Clinician Should Know - The Permanente Journal/ Summer 2010/ Volume 14 No. 2

3. Anilrudh AV, Kathleen R, Shilpa MP, Susanna S, Houssein J, Sharon V, et al. Lack of association of outcomes with treatment duration and microbiologic susceptibility data in Clostridium difficile infections in a non-NAP1/BI/027 setting. Scand J Infect Dis. 2012; 44: 243–249. doi: 10.3109/00365548.2011. 631029 PMID: 2207714839.

4. L.D. Bobo, E.R. Dubberke, M. Kollef - Clostridium difficile in the ICU The Struggle Continues - CHEST / 140 / 6 / DECEMBER, 2011

5. C. Slimings, T.V. Riley - Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis - J Antimicrob Chemother doi:10.1093/jac/dkt477

6. J.F. Barletta, D.A. Sclar - Proton pump inhibitors increase the risk for hospital-acquired Clostridium difficile infection in critically ill patients - Critical Care (2014) 18:714 DOI 10.1186/s13054-014-0714-7

7. Leonard J, Marshall JK, Moayyedi P: Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol 2007, 102:2047–2056. quiz 2057.

8. K. Weiss, T. Louie, M.A. Miller, K. Mullane, D.W. Crook, S.L. Gorbach - Effects of proton pump inhibitors and histamine-2 receptor antagonists on response to fidaxomicin or vancomycin in patients with Clostridium difficile-associated diarrhea - BMJ Open Gastro 2015;2:e000028. doi:10.1136/bmjgast-2014-000028

9. D.E. Freedberg, H. Salmasian, C. Friedman, J.A. Abrams - Proton Pump Inhibitors and Risk for Recurrent Clostridium Difficile Infection Among Inpatients - Am J Gastroenterol. 2013 November; 108(11): 1794–1801. doi:10.1038/ ajg.2013.333.

10. S. B. Debast, M. P. Bauer, E. J. Kuijper - European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection Clinical Microbiology and Infection, Volume 20 Supplement 2, March 2014

11. S. Johnson, P.J. Maziade, L.V. McFarland, W. Trick, C. Donskey, B. Currie, D.E. Low, E.J.C. Goldstein - Is primary prevention of Clostridium difficile infection possible with specific probiotics? International Journal of Infectious Diseases 16 (2012) e786–e792

13. J Salcedo, S Keates, C Pothoulakis,M Warny, I Castagliuolo, J T LaMont, C P Kelly - Intravenous immunoglobulin therapy for severe Clostridium difficile colitis - Gut 1997; 41**:** 366–370