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Rassegna

Review

Infezione da *Clostridium difficile* nel paziente geriatrico

Clostridium difficile infection in the elderly

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INTRODUCTION

Clostridium difficile is a Gram-positive anaerobic spore-forming bacterium, known to be the causative agent of pseudomembranous colitis. With increasing life expectancy in Western countries, the geriatric patient is well recognized as a high risk host for *C. difficile* infection (CDI). Advanced age, age-related changes of the intestinal flora, immunosenescence, presence of comorbidities, frequent hospitalizations and high exposure to antibiotics are some of the risk factors for CDI in this patient population. Prompt recognition of the clinical picture with a rapid and accurate diagnosis are necessary to reduce complications and mortality in this group of patients.
This review provides an update on the currently available literature regarding the epidemiology and clinical management of *C. difficile* in the elderly.

MATERIALS AND METHODS

Using the PubMed database, we undertook a review of articles in the literature using the following keywords: *Clostridium difficile* (primary keyword), geriatric, elderly, older age, advanced age, nursing homes (secondary keywords). The search was performed using the following string: "(*Clostridium difficile*) AND (geriatric) OR elderly) OR older age) OR advanced age) OR nursing homes) OR long term care facilities".

RESULTS

The search yielded 1968 articles which have been published since the year 1978. Figure 1 highlights the exponential recent increase in the number of publications on this topic. Of note, the histogram shows that between 2006 and 2008, the number of published articles doubled. This suggests that over the past decade, the scientific community has increasingly directed its attention to the impact of CDI in the geriatric population. To refine the search, those articles with the secondary keywords present in the "title" were reviewed and in total, 100 articles spanning from the year 1981 to present, were included in our review.

EPIDEMIOLOGY

Elderly patients in hospital or long term care facilities are frequently affected by CDI and are more likely to suffer from complications secondary to this infection [1, 2]. As described more than 30 years ago, the majority of patients with symptoms compatible with CDI are aged 60 years or over and the more severe sequelae e.g. *C. difficile* colitis mainly affects individuals in this age group [3, 4]. Indeed, *C. difficile* is the most common infectious cause of acute diarrhea in nursing homes residents [5, 6].

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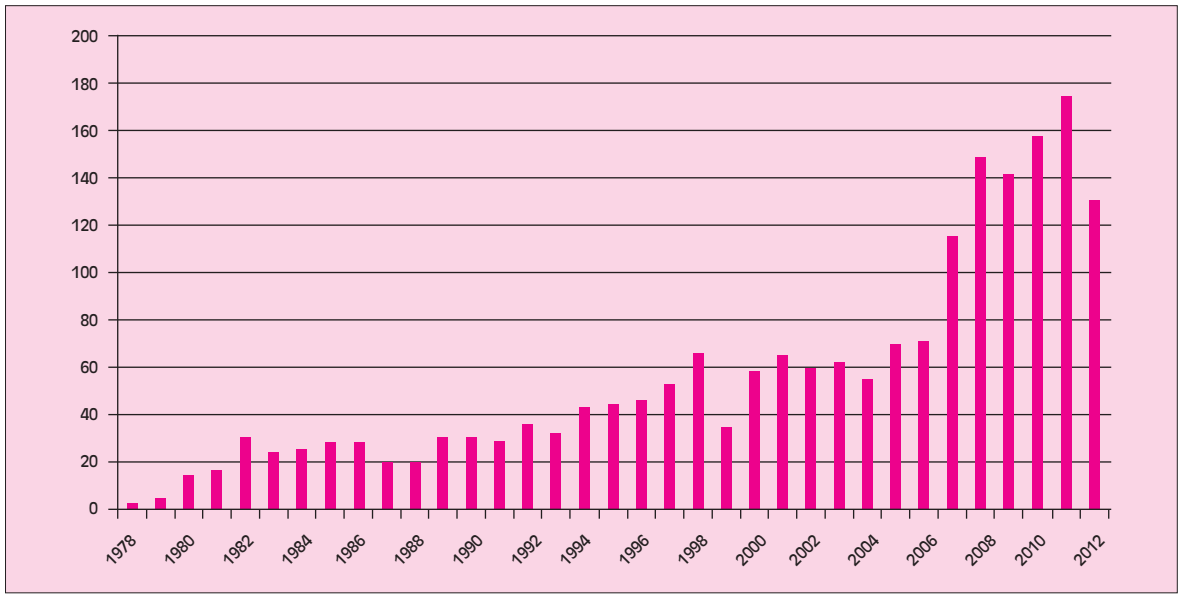

Figure 1 - Articles on *Clostridium difficile* in the elderly patient published per year.

In the last two decades, the incidence of, and mortality associated with, CDI has markedly increased, both in Europe and North America [1, 7, 8]. In particular, CDI cases have increased disproportionately in the age group >65 years compared to others, confirming the greater susceptibility of elderly patients [9]. In 2006, data from mandatory notifications in Ohio, USA, showed that more than half of health care associated CDI cases originated from in patients residing in long-term care facilities and/or nursing homes [10]. In 2008, 93% of deaths from *C. difficile* were in patients aged ≥65 years, and *C. difficile* was identified as the eighteenth most common cause of death within that age group [11].

In Italy, the literature mostly focused on the molecular characterization of *C. difficile* strains and published data on the epidemiology are lacking. Recently, we have described that between the years 2006 and 2011, the incidence of infection with *C. difficile* in 5 hospitals in Rome, has increased approximately 8-fold: from 0.3 to 2.3 cases per 10,000 patient-days (unpublished data).

Asymptomatic carriers of *C. difficile*, contribute significantly to the nosocomial spread of this bacteria. Approximately 3% of asymptomatic adults are colonized with *C. difficile* and this rises to 20-30% in hospitalized patients and up to 50% in patients resident in long-term care facilities [12].

The emergence of ribotype NAP1/027/BI *C. difficile* has significantly contributed to the observed increase in over the past twenty years [13]. Ribotype NAP1/027/BI is the so-called "hypervirulent strain" as it is associated with toxin hyperproduction and an associated increased mortality rate, especially among elderly patients [13]. A recent study conducted in a long-term care facility showed that 52% of patients were asymptomatic carriers of toxigenic strains of *C. difficile* and of these, more than one third were NAP1/027/BI [14].

PATHOGENESIS

C. difficile was first described in 1935 as part of the normal intestinal flora of infants [15]. Over forty years later, in 1978, it was demonstrated to be the causative agent of pseudomembranous colitis [16]. Infection is transmitted via the fecal-oral route: spores excreted in the faeces are ingested and on reaching the large bowel, they reactivate to a vegetative state capable of producing toxins and can cause clinically evident disease.

C. difficile exerts its pathogenic effect mainly through the production of two exotoxins, toxin A and B encoded by the genes tcdA and tcdB respectively, located in the pathogenicity locus of *C. difficile* [17]. Both are potent cytotoxins which, through the glycosylation of proteins Rho and Ras (important for maintaining the integrity of the cytoskeleton), cause the disintegration of the cytoskeleton and tight junctions of

enterocytes, thus leading to a secretory diarrhea [17]. A further toxin known as the binary toxin is a transferase that consists of two different proteins called cdtA and cdtB. The binary toxin has been associated with hypervirulent strains, although its role in the pathogenesis of the disease is not yet fully understood. Some studies suggest a role for binary toxin in increasing the adhesion of clostridia to the intestinal epithelial cells [18].

Asymptomatic carriers and the humoral response to C. difficile in the elderly

It has been shown that asymptomatic carriers of *C. difficile* have higher serum concentrations of antibodies against toxin A compared to symptomatic patients and that such carriers have a lower risk of developing clinically active disease [19-21]. Moreover, individuals with low levels of IgG directed against the toxin A are at an increased risk of developing active infection with *C. difficile* and are also at increased risk of recurrent disease [20, 22]. However, individuals with adequate levels of IgG tend to remain asymptomatic carriers and if they do develop clinical disease they often have a shorter duration of disease and a lower risk of relapse [23, 24]. In the elderly, immunosenescence may provide a partial explanation for the increased susceptibility to infection [25].

Risk factors

The two main risk factors for CDI are antibiotic exposure and older age but other factors should also be considered. The prevalence of spores of *C. difficile* in the environment is relatively higher in hospitals and long term care facilities, which is thought to be why the rate of asymptomatic colonization is significantly higher in hospitalized patients when compared to the general population [26]. Duration of stay in intensive care units, prolonged hospitalization and physical proximity to colonized/infected individuals are other important risk factors for acquisition of *C. difficile* [27, 28]. The acquisition of a toxigenic strain capable of causing clinical disease often occurs during or following antibiotic therapy, which alters the balance of intestinal flora. It would appear that the disease is not due to "reactivation" of previously colonizing strains, but rather to new acquisitions in a bowel with altered microbiata. Whilst colonized individuals may have an important role in the spread of the microorganism and therefore in ongoing transmission events, they rarely develop clinically evident disease. This observation may be attributable to a greater antibody response induced by the chronic carrier state [21, 29].

Clinical manifestations in the elderly

Clinical manifestations of CDI vary from mild diarrhea to life-threatening pseudomembranous colitis with toxic megacolon, however, the commonest clinical presentation is that of a patient with diarrhea and a history of antibiotic exposure. The antibiotics most frequently associated with the development of CDI are: clindamycin, cephalosporins and fluoroquinolones [30]. Stools are usually watery and malodourous, but macroscopic bloody stools are rare [31]. Patients can be febrile with cramping abdominal pain localized to the lower abdomen. In the presence of pseudomembranous colitis, symptoms are often more marked, with tenderness on palpation of the abdomen and/or signs of peritoneal irritation, such as the Blumberg sign. Notably, however, clinical disease can be present without a diarrhea illness and presence of constipation and abdominal pain as the main presenting features make the diagnosis more "difficile". Leukocytosis, increased creatinine, hypoalbuminemia, signs of a systemic inflammatory response, increased lactate and abdominal distension are associated with a more severe clinical picture [32].

There are no data to suggest that the clinical manifestations of *C. difficile* in the elderly are different from those in other patients. However the frequency of complications and mortality is higher in elderly patients and it is well documented that older age is associated with an increased risk of recurrent disease [33].

DIAGNOSIS

Laboratory

The most widely used diagnostic test for the diagnosis of CDI is the enzyme immunoassay (EIA) for toxin A or toxins A and B. The advantages of this diagnostic test include the ability to obtain a rapid result with high specificity, but this is offset by its lack of sensitivity and up to 40% of diagnoses can be missed [31, 34].

In recent years, an antigen test that detects the mitochondrial enzyme glutamate dehydrogenase (GDH) within *C. difficile* has been introduced. This test has a good sensitivity (96-100%) but is not able to distinguish between toxigenic and non-toxigenic strains; therefore it is used

predominantly as a screening test and has been incorporated as such in recently proposed diagnostic algorithms [35, 36].
The cell-culture cytotoxicity assay is considered the gold standard for the diagnosis of CDI [31, 37, 38]. This test involves inoculation of stool onto a medium of cell cultures with the demonstration of the characteristic cytopathic effect of *C. difficile* after 24-48 hours. A specific antitoxin is used to identify the characteristic cytopathic effect of *C. difficile* [38].
The culture of stool for toxigenic *C. difficile* strains remains the most sensitive test but requires selective media and is slow, usually taking up to 7 days. However, this is the only method that allows the isolation of the strain that can then be used for further studies within the scientific research community.
Most recently, molecular methods have been introduced (polymerase chain reaction, PCR) to identify toxigenic strains of *C. difficile* by amplification of gene sequences encoding for toxins. Despite a high sensitivity, this method detects presence of the gene only and cannot confirm or refute whether the toxin is being expressed and hence causing disease. Variations in the design of the PCR primers allows such methods to also identify with high specificity, the presence of specific strains of *C. difficile* e.g. certain PCR assays can identify the "hypervirulent" strain NAP1/027/BI by amplification of the deletion in the tcdC gene [39].

Imaging
A definitive diagnosis of CDI requires, in addition to symptoms, the identification of the toxin of *C. difficile* in a fecal sample and/or endoscopic evidence of pseudomembranous colitis [31]. Colonoscopy is the procedure of choice to detect pseudomembranous colitis, as up to one third of patients have only involvement of the proximal colon only, which would be missed by sigmoidoscopy [40, 41]. However, endoscopic evidence of pseudomembranous colitis is often not present, which makes colonoscopic investigation very specific but with low sensitivity (51%). Furthermore, in cases of fulminant colitis, colonoscopy has a risk of bowel perforation [42].
Computed tomography (CT) of the abdomen can be helpful in the diagnosis of pseudomembranous colitis or fulminant CDI. Particular features may include thickening of the colonic wall, the "sign of the accordion", the "sign of the double halo" (alternatively known as the "target" sing) and ascites, the latter being suggestive of hypoalbuminemia [42].
Plain abdominal radiographs are usually normal in patients with CDI, but they can provide useful information, for example, in cases of ileus or toxic megacolon [31].
It must be re-iterated that abdominal imaging can be useful in defining clinical cases or characterising subsequent complications but is not a tool of fundamental importance in the acute diagnostic setting. Pros and cons of main diagnostic tools for *Clostridium difficile* infection are summarized in Table 1.

Medical therapy
On suspicion of CDI, management should include the discontinuation of antibiotic therapy where possible or changing antibiotic therapy to a narrower spectrum agent. This approach alone is clinically effective for a small percentage of patients, without the need for further interventions. In the majority of patients however, pharmacological treatment is needed and the recommended antibiotics for the initial episode are metronidazole and oral vancomycin.
Metronidazole is inexpensive, with few side effects (if used for short periods) and therefore is used in mild-moderate disease in either oral or intravenous formulation. At a dosage of 500 mg 3 times a day orally for 10-14 days, metronidazole is first line for mild to moderate CDI (first and/or second episode) [37]. In cases of severe CDI, the use of metronidazole is not recommended due to the high rate of treatment failures reported [43].
Vancomycin, which has been shown to be more effective than metronidazole, is recommended in severe disease. It is administered orally since it does not reach appropriate concentrations in the lumen of the colon when administered intravenously. As it is not absorbed though the intestinal lumen, oral vancomycin reaches faecal concentrations far above the MIC of *C. difficile* [44]. Vancomycin is given orally at a dose of 125 mg 4 times per day for 10-14 days and is considered the drug of choice for an initial severe episode [37].
Fidaxomicin is a macrocyclic antibiotic which has been recently introduced into clinical practice in the United States and Europe for the treatment of CDI, at a dose of 200 mg twice daily orally. It has been shown to be non-inferior to oral vancomycin and superior in preventing relapses, probably due to a lower tendency to alter the flora of the colon [45].

Table 1 - Pros and cons of main diagnostic tools for Clostridium difficile infection.

Diagnostic test	*Pros*	*Cons*
Culture	High sensitivity Able to isolate the strain	Long time for results (>7 days) A second test is necessary to look for toxin production Labour intensive
Cell-culture cytotoxicity assay	Moderate/high sensitivity High specificity	48-72 h turn-around time Requires expert laboratory personnel Labour intensive
TcdA and/or TcdB detection (EIA)	High specificity Low cost Rapid and easy to perform	Low sensitivity
GDH detection (EIA)	High sensitivity Good as screening test	Cannot distinguish between toxigenic and non-toxigenic strains Cannot distinguish between active disease and colonisation
Nucleic acid amplification tests (PCR)	High sensitivitity and specificity Rapid Can identify NAP1/027/BI strains	High cost Requires expert laboratory personnel Sometimes "too sensitive"
Colonoscopy	Enables the diagnosis of pseudomembranous colitis if present Allows exclusion of concomitant disorders (i.e. IBD)	Low sensitivity Invasive test Risk of bowel perforation High cost
Imaging (CT, X-ray)	Non-invasive Allows recognition of possible complications of CDI	Indirect diagnostic tools Low sensitivity Low specificity

CDI: Clostridium difficile infection; EIA: enzyme immunoassay; GDH: glutamate dehydrogenase; CT: computed tomography, IBD: inflammatory bowel disease; PCR: polymerase chain reaction; TcdA: toxin A; TcdB: toxin B.

In a recent study, nitazoxanide (a drug often used for intestinal parasites) was compared to oral vancomycin in a randomized controlled trial. Nitazoxanide was at least as effective as oral vancomycin for the treatment of CDI, but the small number of patients enrolled in this study (23 received vancomycin and 18 received nitazoxanide) precludes definitive conclusions about its effectiveness [46].

Teicoplanin, tigecycline, bacitracin, fusidic acid and rifampicin have all been used for infections caused by *C. difficile* both *in vivo* and *in vitro* but with discordant results [47-49].

Finally in patients with CDI it is important (especially in the elderly) to avoid the use of anti-peristaltic agents such as loperamide, as they increase the risk of toxic megacolon [50, 51]. Probiotics, although much studied and widely used in clinical practice, are not recommended by current guidelines since their effectiveness is yet to be proven [37].

Recurrent/refractory disease

The recommendations provided by international guidelines for the treatment of relapsing CDI are not currently supported by good quality evidence [37]. Relapses usually occur approximately 1-2 weeks after discontinuation of treatment with metronidazole or oral vancomycin but are known to occur at an interval of up to 12 weeks after cessation of *C. difficile* treatment [52]. Patients who have a single recurrence of CDI have a high risk (up to 40%) of further relapses, whilst patients who go on to have two or more recurrences have a relapse risk that exceeds 60% [53].

Although vancomycin is a highly effective drug for CDI, a recurrence rate of around 25% has recently been reported [54]. It is hypothesized that because vancomycin is only active against the vegetative but not spore-forming elements of *C. difficile*, this may explain the significant proportion of patients who relapse after discontinuation of the drug i.e. the remaining spores undergo germination.

The management of the first recurrence is the same as that of the first episode of CDI. The management of patients with multiple recurrences is difficult and less clear. One approach that has proved effective is to administer a prolonged course of vancomycin with a tapering dose (e.g. a gradually decreased frequency of administration over 1-6 weeks) or in a "pulsed" regimen (e.g. vancomycin is given on alternate days initially, then every 3 days and so on) [55]. Prolonged use of metronidazole is not recommended because of the potential side effects such as peripheral neuropathy. In patients with CDI refractory to standard doses of metronidazole and/or vancomycin, vancomycin can be given at higher doses (2 g per day) which has been effective in some cases [56].

Rifaximin is a non-absorbable antibiotic, commonly used for traveler's diarrhea and for the prevention of portosystemic encephalopathy in patients with liver cirrhosis. It belongs to the class of rifamycins and has been used to prevent recurrence of CDI after a treatment course of vancomycin in patients with multiple recurrences [57-59]. A single center study reported that 79% of rifaximin treated (following vancomycin treatment) patients had no relapse at follow-up (4-26 months) [58, 59]. In another recent study, 64% of patients who did not respond to metronidazole as initial therapy i.e. stools remained positive for toxins A and B after oral metronidazole 500 mg three times daily for 5 days, were treated with rifaximin for 14 days. Follow up stool samples at the end of treatment and 56 days later were investigated for the presence of *C. difficile* using toxin gene PRC. All were negative at both time points although the study enrolled only a small number of patients [60]. Larger studies are needed to confirm these findings and provide reassurance that the potential development of resistance of the pathogen to this agent is deemed to be low as this would constitute an important limitation to its use.

Nitazoxanide has demonstrated efficacy *in vitro* against *C. difficile*. It has been tested *in vivo* on 35 patients who did not respond to treatment with metronidazole and showed an initial cure rate of 54% [61]. Its effectiveness, however, should be confirmed in the course of further clinical trials.

Since relapsing CDI has been associated with low serum levels of immunoglobulins directed against toxin A, intravenous immunoglobulin has been used as a potential therapy [62, 63]. While the effectiveness of immunoglobulins remains controversial, monoclonal antibodies directed against toxins A and B have been shown to be protective against further relapses when compared to placebo, leaving the door open for future research [64].

An increasingly studied alternative or additional approach is represented by fecal bacteriotherapy, which consists of the introduction of fecal material from healthy donors into the digestive tract of patients with CDI. The stool may be introduced by esophagogastroduodenoscopy, colonoscopy or enema. Whilst ongoing investigation and guidelines for incorporating this into routine clinical practice are needed, fecal bacteriotherapy is very promising, with success rates greater than 90% in patients with recurrent infections [65].

Surgical treatment

In patients with fulminant infection, early surgery is important. A retrospective study of 165 cases of complicated/fulminant colitis caused by *C. difficile* in patients requiring ICU admission, showed a benefit of surgery compared to medical therapy, especially in patients with serum lactate ≥5 mmol/L and/or leukocytosis ≥50 x 10^9/L [66]. A recent study has shown that the prolonging medical therapy for longer than 6 days in patients with severe unresponsive infection, was associated with increased mortality [67]. The treatment of choice in patients with CDI requiring surgery is the subtotal colectomy with ileostomy formation [67].

Infection control

Due to their intrinsic resistance, spores of *C. difficile* can easily spread in the nosocomial environment. Hand sanitizers containing alcohol are inactive against spores of *C. difficile* and standard hygiene measures including hand washing with soap and water as well as the use of personal protective equipment such as gloves and apron are essential before and after contact with patients with suspected or confirmed CDI [37, 68]. The use of antiseptic ch-

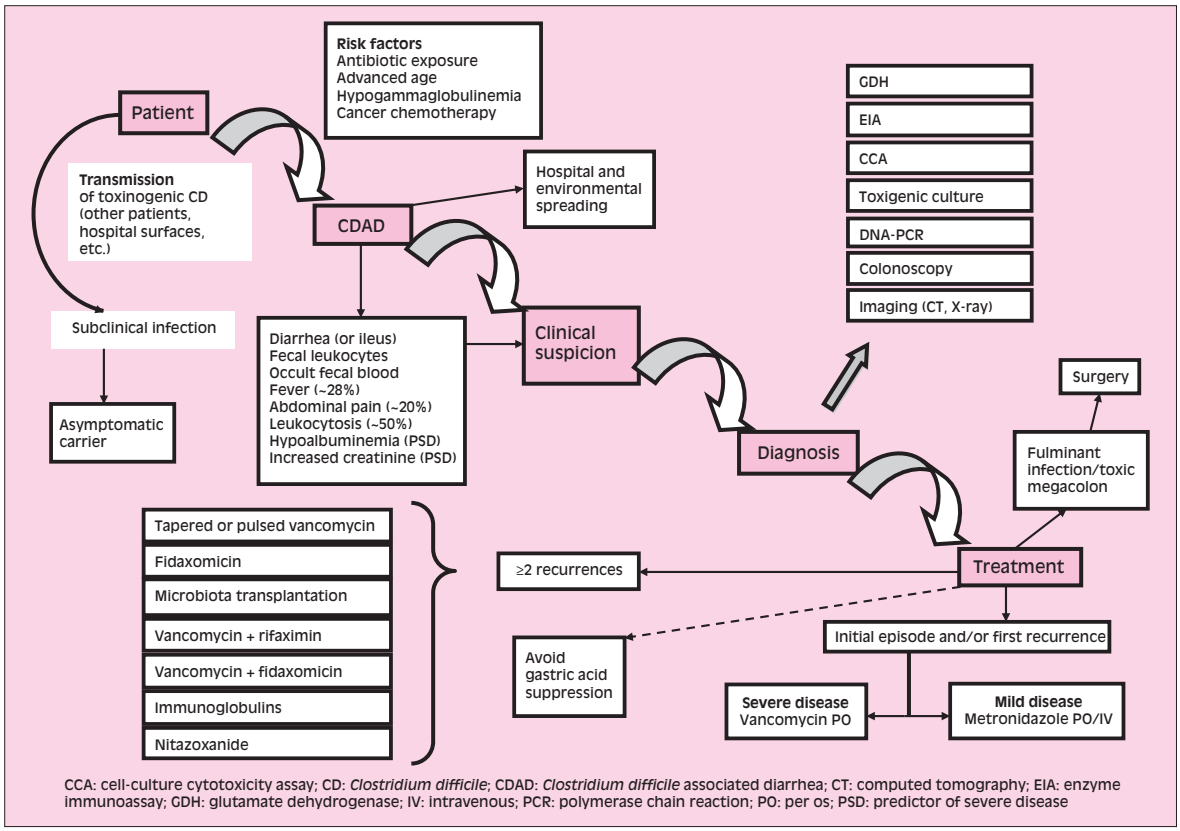

Figure 2 - Clostridium difficile facts.

lorhexidine handwash is a viable alternative to soap. Where possible, all patients with suspected CDI should be placed in isolation in a single room until 2 days after the last episode of diarrhea or at least until the stool becomes formed [68]. Chlorine-based disinfectant is the optimal of choice for the environmental decontamination of surfaces contaminated with *C. difficile* [37, 68]. Decontamination is also important for shared hospital equipment such as thermometers, sphygmomanometers and toilets. A multi-disciplinary approach involving house-keeping staff, infection control nurses, microbiology and infectious disease physicians in addition to the attending physician is key to ensuring compliance with good infection control practices [69]. A summary of *C. difficile* facts is shown in Figure 2.

CONCLUSIONS

The geriatric population is vulnerable to CDI due to the physiological and immunological changes that occur with age. High exposure to antibiotic therapy and the increased propensity to be admitted to health and social care institutions are known to contribute to the high incidence of disease in this group of patients. As discussed in this review, difficulties in the diagnosis and treatment of CDI however remain similar irrespective of patient age. Perhaps most pertinent to this group is the increased risk that the elderly patients have for progressing to a complicated disease course. If fulminant disease develops, an aggressive surgical approach will not always be possible due to the presence of co-morbidities and weakened physiological reserve. With that in mind, optimal treatment strategies need further investigation. Finally, prevention will continue to prevail over cure and prudent antibiotic prescribing, effective environmental cleaning and minimizing duration of hospital admissions remain essential.

Keywords: *Clostridium difficile*, elderly, epidemiology, treatment

SUMMARY

The incidence of *C. difficile* infections (CDI) in the elderly continues to rise and infection is associated with increased morbidity and mortality when compared to those affected in younger age-groups. Immunosenescence may be a contributory factor yet the exact immune responses that may protect against CDI are incompletely understood. Increased exposure to antibiotics, frequent and/or prolonged hospital admissions and residing in long-term care facilities provide multiple opportunities for host and pathogen to coincide. This review explores the epidemiology, diagnostic parameters and management of the spectrum of disease in the geriatric population. Deaths attributed to CDI are most common in the elderly population and are a major contributor to gastroenteritis-associated mortality in many countries. The elderly represent an "at-risk" population from this pathogen and efforts must be directed to preventing infection and optimising treatment in this group.

RIASSUNTO

L'incidenza dell'infezione da C. difficile *nel paziente geriatrico è in progressivo aumento e contribuisce alle maggiori mortalità e morbosità nella popolazione anziana rispetto alla più giovane. L'immunosenescenza sembra rivestire un ruolo importante come fattore predisponente sebbene i meccanismi immunologici alla base dell'infezione da* C. difficile *non siano ancora del tutto chiari.*

L'elevata esposizione agli antibiotici, così come ricoveri ospedalieri frequenti e/o prolungati e l'ospedalizzazione in reparti di lungodegenza rappresentano il substrato per l'infezione da C. difficile *nel paziente anziano. La nostra revisione della letteratura analizza l'epidemiologia, la diagnostica e la gestione di questa infezione in ambito geriatrico. I decessi attribuibili all'infezione da* C. difficile *sono più frequenti negli anziani e rappresentano un'importante causa di mortalità associata alle gastroenteriti in molti paesi. I pazienti anziani fanno parte di una popolazione a rischio per l'infezione da* C. difficile *per cui è fortemente auspicabile il miglioramento delle misure di prevenzione e l'ottimizzazione della gestione terapeutica.*

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