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Medico-legal implications of medical treatments and infection preventions' missteps resulting in Clostridium difficile Infection

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Abstract: *Introduction.* Clostridium difficile infection (CDI) was previously considered a nosocomial infection associated with antibiotic exposure, but now is more present in the communities and is obviously associated with acid-suppressive therapies. CDIs are common both in hospitalized and ambulatory patients, in nursing homes residents, being initiated by antibiotics and acid-suppressive therapies.

Material and methods. A retrospective chart review of medical records for all inpatients of Arad Clinical County Hospital aged over 18 years, positive for C. difficile toxin, from January 2016 through June 2018, (30 months) was performed, to determine risks factors involved in CDIs cases with exitus, starting from the hypothesis that death rates for CDIs patients are higher in those with Proton Pump Inhibitors (PPIs) and antibiotic associations regimens prior to disease onset.

Results. There were 221 CDIs cases registered in this period. Death rate was 17,19%. Death Odds Ratio was extremely high for those with CDIs complications (40,75), for residents of nursing homes (5,615), for those who had had previous hospital contacts (3,165) and for those with PPIs regimens. Death Relative Risks was double for the elderly compared to adults (2,177), and for hospital contacts patients *versus* others (2,301); PPIs raised this risk to 1,869 and being nursing homes residents to 3,8642. Nososcomials cases reached 57,46%; possible iatrogenic causes were found in 23,98% of cases.

Conclusions. When a patient has host-related risk factors for CDI, clinical and iatrogenic procedures can add crucial elements for the development of a Clostridium difficile infection.

Key Words: CDI, nosocomiality, Odds ratio.

INTRODUCTION

Clostridium difficile, a species of Gram-positive bacteria of the genus Clostridium, identified in 1935, has become a leading cause of hospital-acquired infections [1], which are increasing in severity and morbidity within the last decade. Infection with a toxigenic strain of *C. difficile* can be clinically significant by its signs and symptoms, varying from diarrhoea and cramping to pseudomembranous colitis and even death in severe disease. Although most cases of CDI are health care-related, one-third of CDI cases occurs in the community, unrelated to antibiotic use or prior health care exposure [2]. Also, only one-third of cases were genetically related to each other, suggesting an alternative source of *C. difficile* exposure. The central point of CDI pathogenesis

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is disruption of the microbiota, by losing its colonization resistance[3].

C. difficile, a member of the normal gut microflora, is suppressed by the more dominant anaerobes and so the rate of its colonization in human gut is different in age groups, being highest in early infancy and decreasing with age [4]. As an ecological community of microorganisms, microbiota colonize [5], humans in a non-harmful coexistence and microorganisms presence is essential for their host homeostasis; microbiota can provide functions the host alone cannot supply, such as the breakdown of essential nutrients, drug metabolism, immune development, and pathogen resistance [6]. These associations play a critical role in conservation of mucosal immune function, epithelial barrier integrity, motility, and nutrient absorption; a healthy gut flora is largely responsible for overall health of the host [7]. It is estimated that almost 90% of newborns are *C. difficile* carriers without suffering from infection [8]. *C. difficile* does not cause any disease when it is present in small numbers. Every dysbiosis may result in unlimited expansion of *C. difficile* in the microbiota, leading to damage of the gut mucosa. Antibiotics reduce colonization resistance against pathogens, including *C. difficile*. The mechanisms responsible for this are still unknown.

The healthcare associated infections surveillance has been regulated by European legislation in EC Recommendation no. 2009 / C151 / 01, Decision no. 2119/98 / EC, and by Law 46/2006 on Patient Safety and Ord.MS no. 1101/2016 in Romania.

Iatrogenic risk factors for CDI are [9]: use of antibiotics (broad and specific), of proton pump inhibitors, of histamine 2 receptor antagonists, of anti–ulcer medications (not specific), non–steroidal anti–inflammatory drug, of aspirin, corticosteroids.

Host–related risk factors: age: ≥65 years, chronic kidney disease, diabetes mellitus, lymphoma or leukaemia, solid cancer or malignancy, severity of co–morbidity, inflammatory bowel disease, congestive heart disease, chronic obstructive pulmonary disease, peptic ulcer, diverticular disease, gastroesophageal reflux disease, low mean concentration of 25 hydroxyvitamin D, female sex, previous diagnosis of CDI, additional points Charlson index.

Clinical interventions or characteristics at risk for CDIs are: duration of hospitalization, nasogastric tube feeding, stay in intensive treatment unit, on–surgical gastrointestinal procedure, vomiting, previous gastrointestinal hospitalization and procedure, history of surgery, leucocytes >20 cells/hpf, high faecal interleukin–8, low day–3 IgM anti–toxin A, serum albumin <2.5g/dL, hyponatremia, lymphopenia, colonization with vancomycin–resistant enterococci.

Many pharmacoepidemiologic cohort studies [10] show that acid-suppressive therapy elevates the risk of CDIs at the patient level, with or without an association between antibiotics, particularly the use of cephalosporins or fluoroquinolones [11].

Aim

To determine risks factors involved in CDIs cases with exitus.

Hypothesis

Death rates for CDIs patients are higher in those with PPIs and antibiotic associations regimens prior to disease onset.

Material and methods

A retrospective chart review of medical records for all inpatients >18 years of age who had had a positive fecal result for *C. difficile* toxin, by *C. difficile*- GDH and toxin A/B EIA, from January 2016 through June 2018, (30 months) was performed. CDIs hospital reports were analysed for ID cases, age, gender, anamnestic informations such as previous antibiotics and PPIs regimens and/or hospital exposure, comorbidities and disease evolution. We collected a number of antimicrobial drug classes used 2 months before hospitalization, use of immunomodulating drugs, chemotherapy for malignancies, and proton pump inhibitors.

Cases incidence was calculated according to National Statistic Institute [12] data; Life Expectancy was esthablished after World Population Review[10].

In the first stage were explored all cases in relation to age groups. After that, univariate analyses were used to identify significant differences in variables for patients with possible nosocomial or iatrogenic disorders which might have caused the disease. Chi-square testing was used to compare intergroup variation between nonparametric variables. Then a logistic regression model was designed to evaluate independent associations between death and antimicrobial or PPIs drug use, demographics, and significant clinical variables identified from univariate analyses (prior nursing home or acute-care hospitalizations, immuno compromisation). Odds ratios (OR) and 95% confidence intervals were calculated for each variable in the regression models. Statistics were performed with IBM SPSS Statistics 20, MedCalc and Epi Info 7. Cases were classified after age in adults (18–64 years), and elderly (≥65 years) and for incidence patients were classified in 19 age categories by five-year age groups.

RESULTS

There were 221 CDIs cases registered between january 2016-july 2018 (30 months) in Arad Clinical County Hospital.

The trimestrial CDIs cases distribution between January 2016-June 2018 (Fig. 1), shows an ascending trendline.

Table 1. Patients characteristics, Odds Ratios, Relative Risks for Mortality and CDIs Causes

Characteristics	**percent**	**adults**	**elderly**	**2016**	**2017**	**2018**
Recovered	82,8	82	101	62	66	56
Deceased	17,2	9	29	9	13	15
Total	100	91	130	71	79	71
Death rate	17,19	8,89%	22,30%	12,67%	16,45%	21,12%
Medical department	84,16	79	107	13	13	9
Surgical department	15,84	12	23	58	66	62
F	52,50	42	74	43	41	32
M	47,50	49	56	28	38	39
Previous 3rd generation cephalosporins regimens	39,81	41	47	37	15	36
Previous quinolones regimens	27,14	27	33	19	11	30
Previous AB associations	32,12	36	35	25	16	30
Previous PPIs regimens	28,95	26	38	8	12	44
Previous hospital contacts	47,51	38	67	38	22	45
CDIs symptoms at admission	30,76	29	39	14	30	24
CDI incidence to 1000	**adults**	**elderly**	**M adults**	**F adults**	**M elderly**	**F elderly**
Total = 0,543	0,275	1,714	0,297	0,253	1,839	1,630
Death Odds Ratio	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**
Host-related risk factors	1,987	0,750	7,023	1	0,008	7,296
Previous hospital contacts	1,152	0,394	8,546	1	0,003	3,165
PPIs	0,851	0,381	4,982	1	0,026	2,342
CDI complications	3,707	0,675	30,134	1	0,000	40,75
Nursing home residents	1,725	0,378	20,885	1	0,000	5,615
Sum of risk factors	2,656	0,443	36,010	1	0,000	14,243
Death RR (Relative Risk)			**95% CI**		**Significance level**	
Death RR elderly versus adults		2,177	1,0797 to 4,3926		P = 0,0297	
Death RR PPIs regimens versus no PPIs		1,869	1,0446 to 3,3443		P = 0,0351	
Death RR hospital contacts versus no contacts		2,301	1,2189 to 4,3461		P = 0,0102	
Death RR nursing homes residents versus others		3,8642	2,1853 to 6,8331		P < 0,0001	
Percent CDIs Causes/year			**2016**	**2017**	**2018**	**total**
unknown			1,809	3,619	2,262	7,692
community			1,809	8,144	0,904	10,859
nosocomial			19,004	16,289	22,171	57,466
possible iatrogenic			9,502	7,692	6,787	23,981

Legend: B=the set of coefficients estimated for the model; SE=standard error of the mean; Wald= Wald's statistic for testing significance od parameter estimates; df= the degrees of freedom used to obtain the significance level; Sig.=the level of statistical significance indicated fot the Score test for the coefficient; Exp(B)= the value by which the odds of the event changewhen the independent variable increases by one unit. If the value is greater than 1the odds are increased.

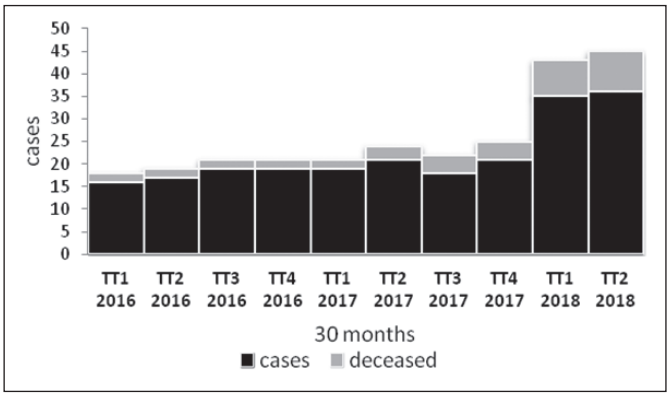

Figure 1. The trimestrial CDIs cases distribution January 2016-June 2018.

Patients characteristics (Table 1), were: 41,17% adults (n= 91), which is surprinsing because CDIs is normally found in more than 70% in elderly (≥65 years); gender ratios, where females are fourth times more affected than men in literature, is also different, being just 1,1:1 with F=116 and M =105.

Death rate was 17,19%, 8,89% for adults (n=9), 22,30% for elderly (n=29), with minimum 12,67% (n=9) in 2016 and maximum 21,12% (n=15) in the first six months of 2018.

Patients were diagnosed mainly in medical departments (84,16%, n=186) with 15,84%, (n=35) treated in surgical ones.

With previous third generation cephalosporins regimens were 39,81%, with previous quinolones regimens were 27,14%, with antibiotics associations regimens were 32,12%.

Acid-suppressive therapies with PPIs were used in 28,95%.

Previous hospital contacts were found in 47,51% and 30,76% of the patients presented CDI symptoms before hospital admissions.

CDI incidence to 1000 was 0,543, with maximum in elderly male, (1,839), three times more than mean value.

Death OR was extremely high for patients who developed CDIs complication (40,75), for those with sum of risk factors (14,243), with host-related risks (7,296), for residents of nursing homes (5,615), for those who had

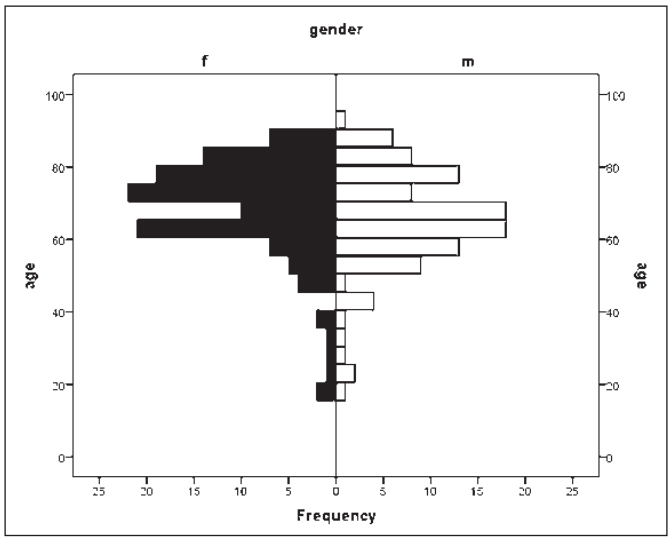

Figure 2. Population Pyramid for CDIs cases.

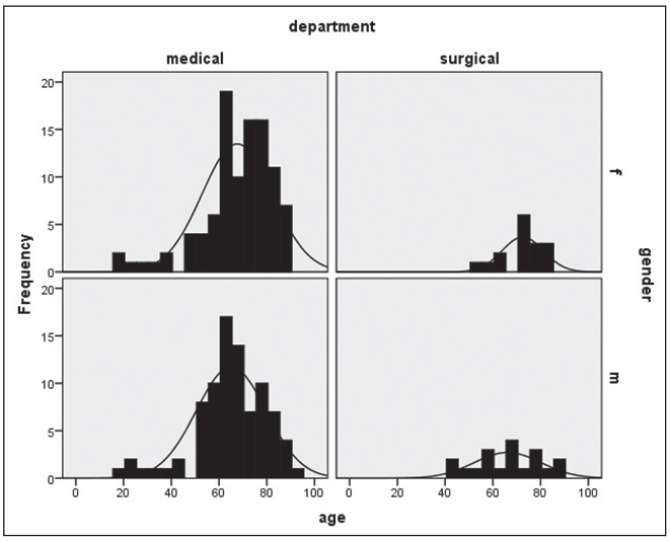

Figure 3. Age and gender histograms on hospital departments.

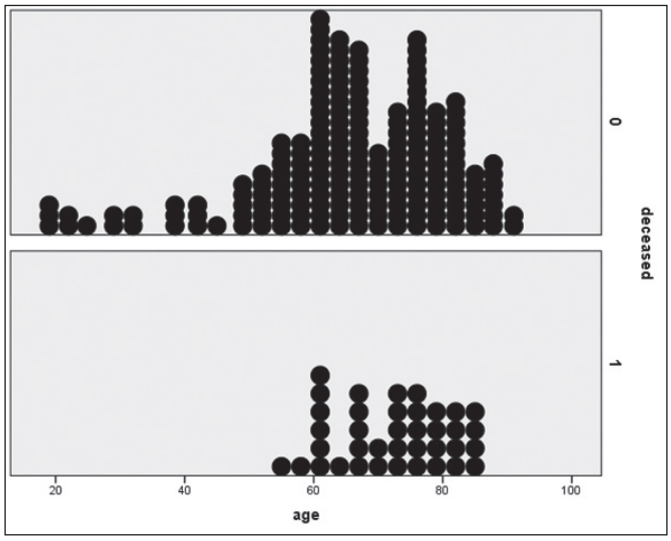

Figure 4. Age for favourable and fatal evolution of CDIs.

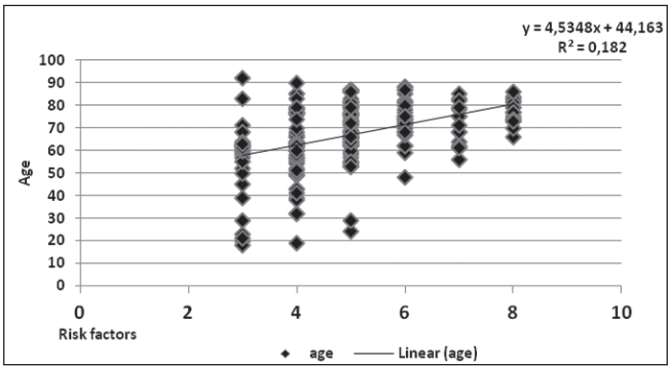

Figure 5. Relationship between age and risk factors.

had previous hospital contacts (3,165) and for those with PPIs regimens prior to CDI symptomatology (2,342).

Death Relative Risks was double for elderly compared to adults (2,177), and for hospital contacts patients versus others(2,301); PPIs raised this risk to 1,869 and being nursing homes residents to 3,8642.

Nososcomials cases reached 57,466%; possible iatrogenic causes were found in 23,981% of cases.

Unknown and community sources represented 7,692% and 10,859% respectively (Table 1).

CDIs age category incidence rate (IR) in 1000 population is the lowest IR 0,055 in 19-25 age category and highest IR 2,485 in over 85 years.

The greatest CDI incidence was in men over 85 years old, IR 3,789.

Population Pyramid for CDIs cases is "constrictive" type, narrowed at the bottom, almost gender-equilibrated (Fig. 2).

Patients' mean age was 66,8371, with median 68 and mode 62, Standard deviation (SD) 14,36918, minimum 18 and maximum 92, P =0,0001. Cross tabulation for adult (n=91) and elderly (n=130) categories is significant, P = 0,0260.

The mean age for females was 68,26724, median 72 and mode 64, SD 14,18104, min 18, max 90.

The mean age for males was 65,25714, median 66 and mode 68, SD 14,47746, min.19 and max. 92.

CDIs cases were treated in both medical and surgical departments of the hospital; histograms for age, sex and hospital department in Figure 3.

The mean age for CDIs cases with favourable evolution was 65,65, SD 15,065.

There were 38 deaths representing 17,19%, aged minimum 56-maximum 86 (Fig. 4).

The mean age for deceased cases was 72,55263, median 74 and mode 62, SD 8,413944, without gender difference.

An important item is the moment for death related to CDI: 34 cases were fatal within 30 days of onset, meaning 89,47%, mean age being 72,24 with SD 8,352, P=0,017.

Single regression analyses show the relationships between age and the risk factors sum (Fig. 5).

Years of potential life lost (YPLL) or potential years of life lost (PYLL), an estimate of the average years a person would have lived if he or she had not died were calculated at 176 years, taking into account a Life

Expectancy of 78 years for women and 71 years for men, according to life tables [13].

Analysing risks factors for mortality in CDI results shows that PPIs elevated this risk to 2,342, P=0,003, compared to cases of mortality without previous PPIs regimens. PPIs were more effective than H2RA in preventing gastrointestinal (GI) bleeding, while others reported no significant difference between PPIs and H2 Receptor Antagonist (H2RAs) [14]. PPIs could promote CDI by raising pH, thereby preventing gastric contents from killing ingested *C. difficile*. However, *C. difficile* exists primarily in the acid-resistant spore form in the environment [15], so it is plausible that *C. difficile* spores could germinate in the gastric contents of PPI-treated patients. PPI use is certainly associated with an increased risk for development of CDI and with higher mortality OR.

There is a significant correlation between CDI deaths and previous PPIs regimens (P=0,018), between PPIs and CDIs complication (P=0,009), penicillines (P=0,000) and immunodepression (P=0,018) (Table 2).

Age is correlated with hospital contacts (P=0,033), and deaths (P=0,007).

Once a CDI complication appears, mortality OR reaches 40,75 (P=0,000) (Table 1).

There is a significant correlation between CDI deaths and CDI complications (P=0,000) (Table 2).

Previous hospitalisation also raised mortality OR to 3,16 (P=0,003).

There is a significant correlation between previous hospitalisation and antibiotics regimens (P=0,034) (Table 1).

Risk factors correlations (Table 2), are positive for: age and previous hospital contacts; relapse and previous rifamycine and carbapenems regimens; CDIs complications and previous hospital contact, PPIs, penicillines and quinolones regimens; quinolones and PPIs; hospital contacts and antibiotic association, penicillines, quinolones, immunodepression, third generation cephalosorins and PPIs; rifamycine and immunomodulators etc.

Mortality is also correlated with CDIs complications, PPIs regimens, hospital contacts and age. CDIs are clearly correlated with previous antibiotics regimens in asociation such as quinolones, penicillines, rifamicyns and third generation of cephalosporins.

A positive correlation of quinolones and PPIs exists.

Table 2. CDIs Risk factors and their positive correlations

Item1	Item2	Pearson r	Sig. (2-tailed)	Item1	Item2	Pearson r	Sig. (2-tailed)
Previous AB regimens	Quinolones	0,27	0,000	Nursing homes	Death under 30 days	0,316	0,000
	Penicillines	0,194	0,004		CDIcomplications	0,161	0,017
	Rifamicyns	0,141	0,036		PPIs	0,231	0,001
	AB associations	0,361	0,000		Death	0,328	0,000
CDIs complications	Ceph3	0,416	0,000	Rifamicyns	Immunomodulators	0,689	0,001
	Previous hospital contact	0,18	0,007	Death	CDIs complications	0,522	0,000
	Penicillines	0,151	0,024		Age	0,182	0,007
	Quinolones	0,159	0,018		Previous hospital contact	0,191	0,004
	PPIs	0,175	0,009		PPIs	0,159	0,018
Quinolones	Death under 30 days	0,423	0,000	AB associations	Death under 30 days	0,936	0,000
	PPIs	0,152	0,024		Penicillines	0,244	0,000
	Previous AB regimens	0,209	0,002		Rifamicyns	0,263	0,000
	AB associations	0,16	0,017		Quinolones	0,358	0,000
Previous hospital contact	Penicillines	0,151	0,024		Ceph2	0,272	0,000
	Quinolones	0,144	0,033		Immunodepression	0,213	0,001
	Ceph3	0,189	0,005		PPIs	0,18	0,007
	PPIs	0,172	0,011	Penicillines	Quinolones	0,372	0,000
	Immuno depression	0,195	0,004		PPIs	0,237	0,000
Immuno depression	Ceph3	0,143	0,034		Ceph2	0,183	0,006
Cytostatics	Penicillines	0,138	0,04	Age	Previous hospital contact	0,144	0,033
	Immuno depression	0,265	0,000	Relapse	Rifamicyns	0,133	0,048
Ceph3	AB associations	0,272	0,000		Carbapenems	0,27	0,000

Legend. AB = antibiotics; PPI = Protons Pumps Inhibitor; Ceph2 = second generation cephalosporins; Ceph3 = third generation cephalosporins.
Interpretation Pearson correlation coefficient, r: 0=no linear relationship; +0.30 a weak positive linear relationship; +0.50, a moderate positive relationship; +0.70, a strong positive linear relationship; Exactly +1, a perfect positive linear relationship.

CDIs complications appeared mainly in those with previous hospital contacts, penicillines, quinolones, PPIs and mortality was under 30 days from the first symptoms.

Most previous hospital contacts cases were treated with PPIs, antibiotics associations of penicillins, quinolones and third generation of cephalosporins and were cases with immunodepression. A part of them were under cytostatic treatment.

Those who received carbapenems and rifamycins were more likely to relapse.

Patients institutionalised in nursing homes were the first to develop CDIs complications, were given PPIs and fatality evolution appeared in the first 30 days after symptoms.

In general CDIs elderly patients had had a history with previous hospital contacts (Table 2).

In Table 1 are illustrated OR for CDIs with exitus, which are elevated for patients who had had previous hospital contacts to OR= 3,165, who received PPIs regimens to OR= 2,342 and are extremely high when CDIs complications are present, OR=40,75.

Fatality was higher for elderly compared to adult, RR=2,177, and for nursing homes residents compared to others, RR=3,8642.

Medical records show that most of CDIs were nosocomials (57,466%); previous antibiotic regimens and acid-suppressive therapy, as possible iatrogenic causes represent 23,981% of all cases; with infectious contacts in community were 10,859% and with unknown sources for CDI were 7,692% of them.

DISCUSSIONS

This study shows a specific profile of CDI in the last 30 months in Arad County: the CDIs' incidence is the same as other studies suggested, but a marked increase in incidence and severity is registered in the last six months, being double compared to the previous 12 months; there is almost no difference between patients' gender; mortality rate is comparable to those reported in other studies; risks factors are more likely to be host-related, nosocomial and iatrogenic, community sources for *Clostridium difficile* being sporadic; even so, CDIs can also emerge in the communities, populations previously considered low risk being now no longer protected from it; adults are also frequently the victims of these infections along with the elderly; deaths rates were double for those who had had previous PPIs regimens; and death relative risk was three times more elevated for nursing homes residents versus others.

Connecting with the last consideration, this will be a future demanding problem because nursing homes are relatively new in Romania, Romanian culture previously being more focused on nursing the elderly members in their families, a tendency which has changed rapidly in the last 10 years.

CONCLUSIONS

When a patient has host-related risk factors for CDI, clinical and iatrogenic procedures can add crucial elements for the development of a *Clostridium difficile* infection.

Once a CDI's complication occurs, death odds ratio triples.

Risks factors should be known by now because *Clostridium difficile* was first identified in 1978 as the predominate bacterial cause of antibiotic-associated diarrhoea and pseudomembranous colitis (PMC) [16].

All patients taking antibiotics might be considered at risk and all of them require early recognition and aggressive medical intervention.

For controlling this ascending trendline, drastic measures are required including education, infection control measures, contact precautions and patient isolation, rigorous cleaning and disinfection protocols, and mainly antibiotic restrictions.

All hospitals should reduce iatrogenic or clinical procedures which increase the risk for CDIs, but also general practitioners and physicians from the ambulatory network should be cautious in administering antibiotics and PPIs as methods of preventing and controlling these infections.

And last but not least, nursing homes should limit all risks to their patients, because they are the most vulnerable to this infection.

This study strongly supports the use of antibiotic stewardship, the right policies and procedures, appropriate training, and adherence to best practices as measures of preventing CDIs .

Conflict of interest. This article is the authors' original work, has not been published previously, and is not under consideration for publication elsewhere. There are no financial or personal interests or beliefs that could affect our objectivity.

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