



Factors associated with severe *Clostridium difficile* infection according to 4 different severity definitions

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Transparency declaration

- Sanofi Pasteur
- Bio Mérieux

Background

- Incidence and Severity of CDI appear to be increasing
- Emergence of **virulent strains** (027, 078,...)
- Increased infection in “**low-risk**” populations

Severe CDI

- Definitions (surveillance, clinically..)
- Most frequent associated factors: age, leukocytosis and creatinine
- Study population
- Mainly retrospective
- Confounding factors

Death

Study	Definition of severe CDI	Identified associated factors
<i>Andrews et al. Can J Gastroenterol 2003</i>	Hospitalization (> 14 d), colectomy, ICU admission, death	Age (> 70 years), co-morbidities, relapse
<i>Boone et al. Eur J Clin Microbiol Infect Dis 2013</i>	WBC (>15,000/mL), >10 stools/d, abdominal radiological signs, co-morbidities, ≥65 years	Elevated lactoferrin and WBC, hypoalbuminemia
<i>Gujja et al. Aliment Pharmacol Ther 2009</i>	Colectomy, death	WBC (>30,000/mL), creatinine (>1.5 baseline)
<i>Hardt et al. World J Gastroenterol 2008</i>	Profuse diarrhea, shock the day of diagnosis	Charlson score, CRP
<i>Henrich et al. Emerg Infect Dis 2009</i>	Death within 30 days, admission in ICU, colectomy, intestinal perforation	Age (>70 years), ileus, colorectal inflammation, WBC (>20,000/mL), albumin (<2.5 g/dL), creatinine (>2 mg/dL)
<i>Lungulescu et al. JHI 2011</i>	Related death during hospital stay, admission in ICU, colectomy, LOS (>10 d)	Cancer, albumin (<3 mg/dL), WBC (>20,000/mL), creatinine (>1,5 baseline)
<i>Morrison et al. CID 2011</i>	Megacolon, surgery, ICU admission, death	Antiacids, admission in ICU, age (>80 y), corticosteroids
<i>Rao et al. CID 2015</i>	Within 30 days: admission to ICU, surgery (colectomy), death	Age, female gender, metastatic cancer, concurrent ATB, PPI, ribotype 027
<i>Shivashankar et al. Clin Gastroenterol Hepatol 2013</i>	Colectomy, admission in ICU, death within 30 days	Age, PPI, narcotics, WBC (>15 ,000/mL), creatinine (>1.5 baseline)
<i>Valiquette et al. CID 2009</i>	Megacolon, perforation, colectomy, shock, death within 30 days	Pleural effusion, immunosuppression, thickening of colon, WBC (>30,000/mL), albumin (<20 g/L)
<i>Wenish et al. Eur J Clin Microbiol Infect Dis 2012</i>	Surgery, admission in ICU, death within 30 days	Severe diarrhea, chronic pulmonary disease, chronic renal failure, diabetes

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Wenish et al. Eur J Clin Microbiol Infect Dis 2012	Surgery, admission in ICU, death within 30 days	Severe diarrhea, chronic pulmonary disease, chronic renal failure, diabetes

Objective

Identification of factors associated with severe CDI according to four definitions

Def 1 SHEA/IDSA guidelines, 2010

Def 2 ESCMID guidelines, 2014 (except age)

Def 3 Complicated CDI at the end of diarrhea

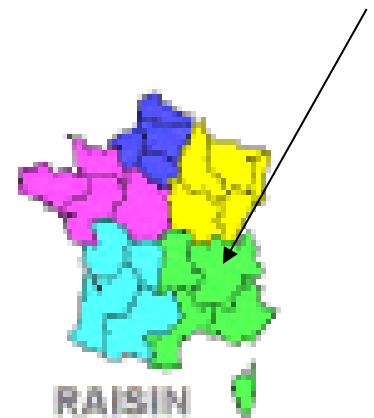
PMC, megacolon, colectomy, intestinal perforation, septic shock requiring ICU admission, or death

Def 4 Clinically severe

WBC $\geq 15,000/\text{mL}$, serum creatinine level $>50\%$ above the baseline, PMC, megacolon, intestinal perforation, septic shock requiring ICU admission

Study: location and design

- Edouard Herriot hospital, Lyon: Large University hospital, 860 beds, ~83,000 admissions/year
- Prospective cohort study (since Feb 2011)
- **Inclusion criteria**
 - ≥ 18 years
 - Hospitalized patient (≥ 48 h)
 - Confirmed CDI
 - Informed consent by the patient
- **Data collection**
 - Standardized questionnaire
 - Hospital laboratory database
 - Patient medical report
 - Referent clinician



Definitions

Case of CDI

Patient with a positive toxins result and/or with a positive toxigenic culture result or PCR

Origin

- HA-CDI: \geq 48h after admission, or within 4 weeks of discharge from a healthcare facility
- CA-CDI: within 48h of admission and over 12 weeks following discharge from a healthcare facility (*Cohen et al. ICHE 2010*)

Results (1)

- **Feb 2011- Feb 2014:** 233 patients with CDI
- **Median of age:** 66.6 years (IQR: 52.7-79.8)
- **Gender:** male (58.4%) and female (41.6%)
- **Past medical history:** 91%
 - Cancer: 29.6
 - CV: 55.4%
 - DM: 25.3%
 - GI: 18.5%
 - Malnutrition: 45.1%
 - Neurological: 21.5%
 - Pulmonary: 23.6
 - Renal: 31.8%

Results (2)

■ Exposure to factors associated with CDI

- ATB: 72.5% (mostly C3G, FQ, Tazocillin, Metronidazole, Vancomycin)
- Hospitalization: 39.1%
- Immunosuppressors: 39.1%
- PPI: 67.4%

■ Symptoms (other than diarrhea)

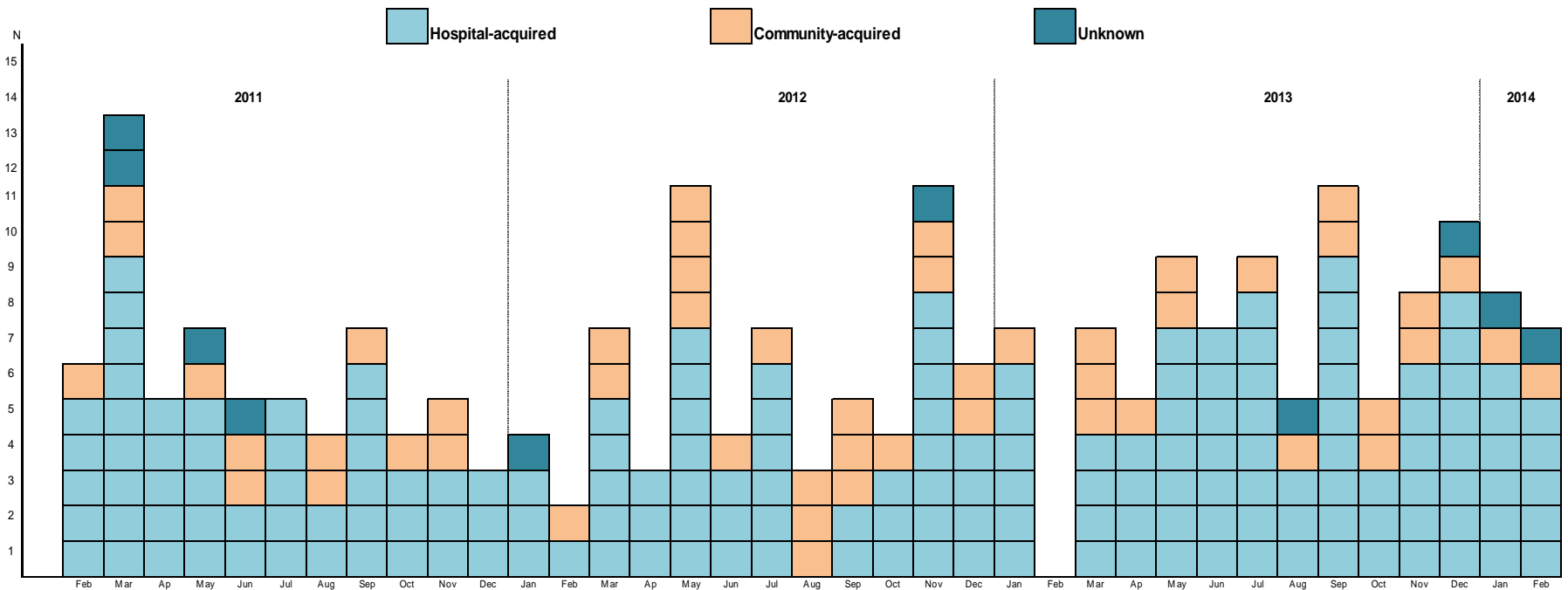
Fever $>38^{\circ}\text{C}$: 33%; abdominal pain: 33.9%; and dehydration 12.4%

■ Biological data

- Albumin (g/L): 26 (21-31)
- Creatinine ($\mu\text{mol/L}$): 87 (58.8-178)
- CRP (mg/L): 72.3 (25.8-133)
- Neutrophils ($\times 10^9/\text{L}$): 7.3 (4.6-11.1)
- WBC ($\times 10^9/\text{L}$): 10.1 (6.7-14.9)

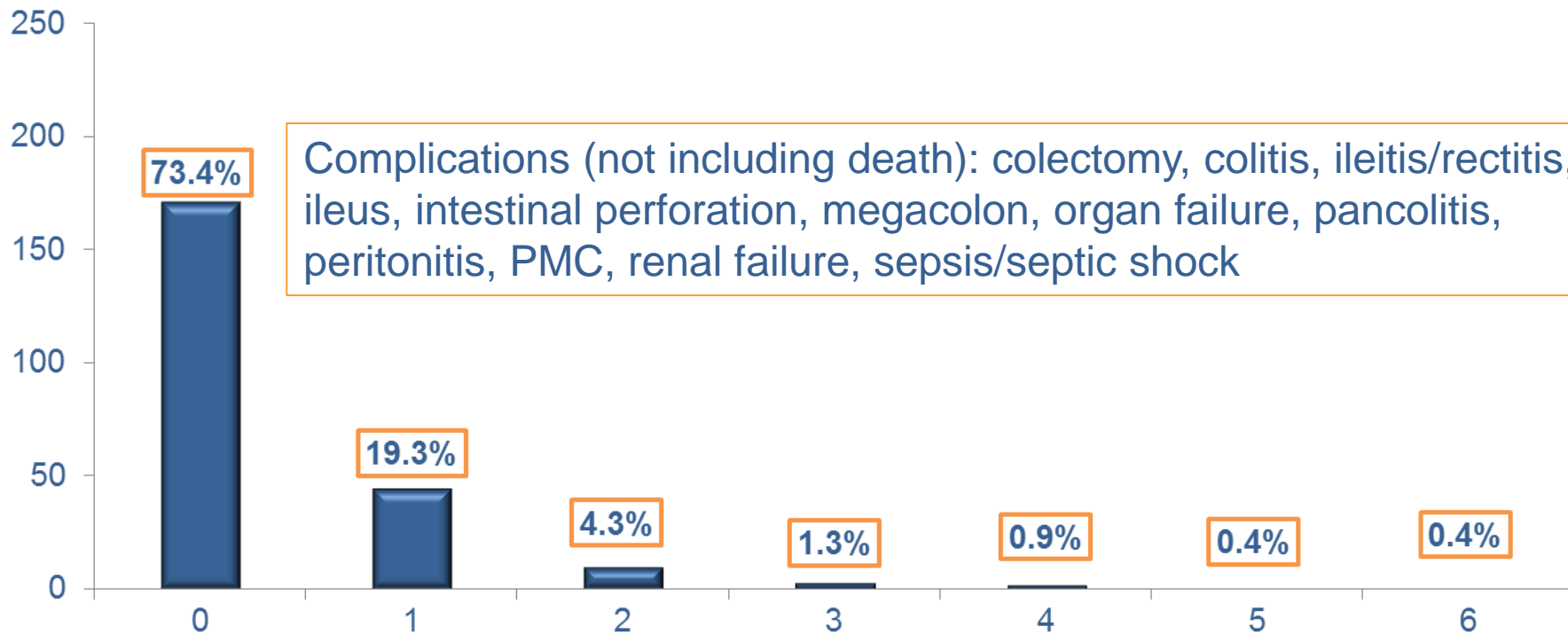
Results (3)

- **Health care associated:** 175 (75.1%)
- **Community-acquired:** 48 (20.6%)
- **Unknown origin:** 10 (4.3%)



Results (4)

Number of complications



Complications (not including death): colectomy, colitis, ileitis/rectitis, ileus, intestinal perforation, megacolon, organ failure, pancolitis, peritonitis, PMC, renal failure, sepsis/septic shock

	At day 30, N (%)	At day 60, N (%)
Death	25 (10.7)	36 (15.9) ¹
Readmission for diarrhea	15 (6.4)	19 (8.4)
Relapse not diagnosed	15 (6.4)	4 (1.8)
Relapse diagnosed at GHEH	8 (3.4)	2 (0.9)

Death: 15.9% (15 deaths related to CDI, 40.5%)
Relapses: 9% at D30 & 4% at D60

¹ Cumulative rate at day 60

Results (5)

Def 1: SHEA/IDSA guidelines 2010

At least one of the following criteria:

- Leukocytosis with WBC \geq 15,000 cells/mL
- Serum creatinine level \geq 1.5 times the premorbid level
- Complicated: hypotension or shock, ileus, megacolon

N=106 (45.5%)

➤ Univariate analysis

➤ Variables with P value \leq 0.35 included in the multivariate analysis

Results (6)

	OR (95%CI)	P
Age ≥ 68 years	1.87 (1.10-3.16)	0.02
Gender (male)	1.34 (0.79-2.27)	0.27
Exposure to factors associated with CDI		
In the last 60 days		
ATB (any)	1.31 (0.73-2.35)	0.36
Aminoglycosides	1.14 (0.54-2.44)	0.73
Amoxicillin or ticarcillin with clavulanic acid	0.65 (0.34-1.23)	0.18
C3G	1.39 (0.82-2.37)	0.22
Carbapenems	1.47 (0.63-3.44)	0.37
Clindamycin	0.90 (0.17-4.09)	0.89
FQ	1.25 (0.72-2.18)	0.43
Macrolides	0.79 (0.27-2.29)	0.66
Metronidazole	0.80 (0.40-1.62)	0.54
Penicillins	1.06 (0.49-2.28)	0.89
Tazocillin	1.97 (1.01-3.83)	0.047
Vancomycin	1.61 (0.79-3.30)	0.19
In the last 30 days		
Antivirals	1.33 (0.62-2.83)	0.46
Immunosuppressors	1.30 (0.77-2.20)	0.33
Recent hospitalization	1.38 (0.82-2.32)	0.23
GI surgery	0.89 (0.40-1.97)	0.77
Nasogastric tube	0.60 (0.32-1.13)	0.11
Current use since at least 30 days		
PPI	1.05 (0.60-1.81)	0.87
H2 blockers	0.89 (0.30-2.66)	0.84

Results (7)

	OR (95%CI)	P
In the last 3 days		
Anti-peristaltic	0.75 (0.28-2.0)	0.56
Colic preparation	0.79 (0.27-2.29)	0.66
Laxatives	0.98 (0.56-1.71)	0.93
Opioids	0.77 (0.46-1.30)	0.32
Past medical history at inclusion		
Any disease	1.61 (0.62-4.20)	0.33
Cancer	0.90 (0.51-1.58)	0.71
Cardio-vascular	2.34 (1.37-3.90)	0.002
Diabetes Mellitus	1.76 (0.97-3.19)	0.06
Gastro-intestinal	0.63 (0.32-1.24)	0.18
Hepatic	1.24 (0.63-2.46)	0.53
Malnutrition	1.13 (0.67-1.90)	0.64
Neurological	1.14 (0.61-2.13)	0.69
Previous CDI	1.59 (0.57-4.43)	0.37
Peripheral vascular	1.41 (0.70-2.83)	0.34
Pulmonary	1.53 (0.84-2.80)	0.17
Renal	6.53 (2.49-12.23)	<10 ⁻³
Systemic	1.80 (0.62-5.25)	0.28

Results (8)

	OR (95%CI)	P
Symptoms & biological data the day of diagnosis		
Abdominal pain	0.80 (0.46-1.38)	0.41
Dehydration	1.33 (0.61-2.90)	0.47
Delay onset of symptoms and test	0.91 (0.97-1.03)	0.91
Duration of diarrhea	1.0 (0.98-1.02)	0.88
Fever (> 38.5°C)	1.26 (0.73-2.18)	0.41
Vomiting	0.95 (0.43-2.14)	0.91
Albumin (< 30g/L)	2.33 (1.22-4.47)	0.01
CRP (>5 mg/L)	1.07 (0.32-3.62)	0.92
LDH (> 245 IU/L)	1.63 (0.81-3.26)	0.17
Neutrophils (x10 ⁹ /L)		
1,8-7,5	Ref.	
<1,8	1.97 (0.46-8.38)	0.36
>7,5	2.93 (1.65-5.22)	<10 ⁻³

Results (9)

	aOR (95%CI)	P
Age \geq68 years	3.11 (1.21-7.98)	0.02
Gender (male)	2.99 (1.20-7.45)	0.02
Amoxicillin or ticarcillin with clavulanic acid in the last 60 days	0.17 (0.05-0.61)	0.007
Renal disease	3.60 (1.44-8.98)	0.006
Albumin (<30g/L)	3.06 (1.16-8.02)	0.02

Model adjusted on the level of LDH

Results (10)

Def 2: ESCMID guidelines 2014

At least one of the following criteria:

- fever (38.5° C)
- septic shock, peritonitis, ileus, megacolon
- leukocyte count > 15,000 cells/mL
- serum creatinine (>50% above the baseline)
- elevated serum lactate
- PMC (endoscopy)
- ICU admission
- colectomy
- death

N=138 (59.2%)

➤ Univariate analysis

➤ Variables with P value ≤ 0.35 included in the multivariate analysis

Results (11)

	OR (95%CI)	P
Age ≥ 68 years	1.32 (0.78-2.23)	0.30
Gender (male)	1.11 (0.66-1.89)	0.70
Exposure to factors associated with CDI		
C3G	1.39 (0.80-2.39)	0.24
Carbapenems	2.23 (0.85-5.83)	0.10
Tazocillin	2.09 (1.01-4.30)	0.046
Antivirals	3.28 (1.29-8.35)	0.01
Immunosuppressors	1.86 (1.07-3.22)	0.03
Past medical history at inclusion		
Any disease	2.35 (0.91-5.99)	0.07
Cardio-vascular	1.92 (1.13-3.26)	0.02
Diabetes mellitus	1.48 (0.80-2.74)	0.22
Pulmonary	1.63 (0.86-3.07)	0.13
Renal	9.68 (4.36-21.50)	<10 ⁻³
Systemic	2.71 (0.74-9.92)	0.13
Symptoms & biological data the day of diagnosis		
Dehydration	1.62 (0.70-3.73)	0.26
Delay onset of symptoms and test	0.98 (0.95-1.01)	0.21
Duration of diarrhea	0.99 (0.97-1.01)	0.26
Albumin (< 30g/L)	1.99 (1.04-3.80)	0.04
Neutrophils (x10⁹/L) (ref: 1,8-7,5)		
<1,8	1.81 (0.41-7.99)	0.43
>7,5	2.61 (1.46-4.67)	0.001

Results (12)

	aOR (95%CI)	P
Antivirals in the last 30 days	3.39 (1.12-10.22)	0.03
Tazocillin in the last 60 days	2.21 (0.95-5.12)	0.06
Neutrophils (x10 ⁹ /L)		
1,8-7,5	Ref.	
<1,8	0.94 (0.17-5.24)	0.95
>7,5	3.80 (1.92-7.52)	<10 ⁻³
Renal disease	9.94 (4.21-23.47)	<10 ⁻³

Results (13)

Def 3: complicated CDI

At least one of the following criteria:

- PMC
- Megacolon
- Intestinal perforation
- Septic shock requiring ICU admission
- Related death

N=27 (11.6%)

- Univariate analysis
- Variables with P value ≤ 0.35 included in the multivariate analysis

Results (14)

	OR (95%CI)	P
Age ≥ 68 years	1.46 (0.65-3.27)	0.36
Gender (male)	0.74 (0.33-1.66)	0.47
Exposure to factors associated with CDI		
In the last 60 days		
C3G	1.88 (0.84-4.21)	0.13
Penicillins	0.24 (0.03-1.80)	0.16
In the last 30 days		
Antivirals	0.23 (0.03-1.73)	0.15
Immunosuppressors	1.52 (0.68-3.41)	0.31
Past medical history at inclusion		
Cardio-vascular	2.03 (0.85-4.85)	0.11
Diabetes mellitus	1.56 (0.66-3.69)	0.31
Neurological	1.65 (0.67-4.02)	0.28
Renal	2.26 (1.01-5.09)	0.049
Symptoms & biological data the day of diagnosis		
Abdominal pain	2.34 (1.04-5.25)	0.04
Dehydration	2.27 (0.83-6.21)	0.11
Albumin (< 30g/L)	11.64 (1.53-88.88)	0.018
Creatinine (> 133 µmol/L)	2.68 (1.19-6.06)	0.02
Neutrophils (x10⁹/L)		
1,8-7,5	Ref.	
<1,8	2.19 (0.23-7.63)	0.50
>7,5	2.85 (1.07-7.63)	0.04
WBC > 10x10 ⁹ /L	2.60 (1.09-6.20)	0.03

Results (15)

	aOR (95%CI)	P
Abdominal pain	4.17 (1.55-11.27)	0.005
Albumin (<30 g/L)	9.39 (1.19-74.28)	0.03
WBC > 10,000 /mL	3.07 (1.02-9.23)	0.046

Model adjusted on the level of creatinine

Results (16)

Definition 4: Clinically severe CDI

At least one of the following criteria:

- PMC
- WBC $\geq 15,000/\text{mL}$,
- Serum creatinine level $>50\%$ the baseline
- Megacolon
- Intestinal perforation
- Septic shock requiring ICU admission

N=113 (48.5%)

➤ Univariate analysis

➤ Variables with P value ≤ 0.35 were included in the multivariate analysis

Results (17)

	OR (95%CI)	P
Age ≥ 68 years	1.96 (1.16-3.30)	0.01
Gender (male)	1.16 (0.69-1.95)	0.59
Exposure to factors associated with CDI		
In the last 60 days		
ATB (any)	1.30 (0.73-2.32)	0.37
Amoxicillin or ticarcillin with clavulanic acid	0.69 (0.37-1.28)	0.24
C3G	1.32 (0.78-2.25)	0.30
Carbapenems	1.56 (0.66-3.66)	0.31
Metronidazole	0.70 (0.35-1.40)	0.31
Tazocillin	1.90 (0.97-3.72)	0.06
Vancomycin	1.60 (0.78-3.29)	0.20
In the last 30 days		
Immunosuppressors	1.42 (0.84-2.41)	0.19
Recent hospitalization	1.37 (0.82-2.31)	0.23
Nasogastric tube	0.69 (0.37-1.29)	0.25
Past medical history at inclusion		
Cardio-vascular	2.02 (1.19-3.41)	0.009
Diabetes mellitus	1.64 (0.90-2.97)	0.11
Gastro-intestinal	0.69 (0.35-1.33)	0.27
Pulmonary	1.44 (0.79-2.63)	0.24
Renal	6.62 (3.48-12.58)	<10 ⁻³
Systemic	2.17 (0.72-6.57)	0.17

Results (18)

	OR (95%CI)	P
Symptoms & biological data the day of diagnosis		
Abdominal pain	0.90 (0.53-1.56)	0.72
Dehydration	1.59 (0.72-3.06)	0.25
Duration of diarrhea	1.00 (0.98-1.02)	0.76
Fever (>38°C)	1.23 (0.71-2.12)	0.46
Vomiting	0.83 (0.37-1.86)	0.65
Albumin (< 30g/L)	2.55 (1.34-4.89)	0.005
CRP (>5 mg/L)	1.21 (0.36-4.11)	0.76
LDH (> 248 IU/L)	1.73 (0.86-3.45)	0.12
Neutrophils (x10 ⁹ /L)		
1,8-7,5	Ref.	
<1,8	3 (0.68-13.31)	0.15
>7,5	3.03 (1.07-5.39)	<10 ⁻³

Results (19)

	aOR (95%CI)	P
Age \geq 68 years	2.56 (1.01-6.46)	0.047
Renal disease	4.09 (1.48-11.31)	0.007
Albumin (<30 g/L)	3.14 (1.16-8.52)	0.024
Neutrophils ($\times 10^9/L$)		
1,8-7,5	Ref.	
<1,8	4.85 (0.86-27.43)	0.07
>7,5	3.05 (1.16-8.02)	0.024

Model adjusted on the level of LDH

Discussion and conclusion

	Def1	Def2	Def3	Def4
Severe cases	106 (45.5%)	138 (59.2%)	27 (11.6%)	113 (48.5%)

Factors associated with severe CDI

Age ≥ 68 years	3.11 (1.21-7.98)			2.56 (1.01-6.46)
Gender (male)	2.99 (1.20-7.45)			
Abdominal pain			4.17 (1.55-11.27)	
Amoxiclav (last 60 days)	0.17 (0.05-0.61)			
Tazocillin (last 60 days)		2.21 (0.95-5.12)		
Antivirals (last 30 days)		3.39 (1.12-10.22)		
Albumin ($<30\text{g/L}$)	3.06 (1.16-8.02)		9.39 (1.19-74.28)	3.14 (1.16-8.52)
Neutrophils ($> 7,5 \times 10^9/\text{L}$)		3.80 (1.92-7.52)		3.05 (1.16-8.02)
WBC $> 10,000 /\text{mL}$			3.07 (1.02-9.23)	
Renal disease	3.60 (1.44-8.98)	9.94 (4.21-23.47)		4.09 (1.48-11.31)

Discussion and conclusion

- Which definitions for severe cases?
- Time to collect biological data, symptoms..?
- Chronic renal failure
- Ribotypes uncertain association
- Early identification of patients at risk is crucial
- Large, multi-center study is needed

Acknowledgments

Co-authors

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Patients