

**Table S4- Characteristics of included studies addressing risk factors for multiple outcomes**

Study Year of diagnosis* Country	Main outcome(s) definition	Design Follow- up (days)	Diagnostic test	Population	Comparison group	Quality variables	Mean/ median age $\pm$ SD Dispersion	N	% Rec <sup>‡</sup> (n)	% Com <sup>†</sup> (n)	% Death (n)	Method	Nv	EPV
Bauer 2011[46] 2008 34 European countries	<b>Recurrence Complication:</b> ICU admission or colectomy, or death	PC 90	Toxin A and B EIA, direct CTA, PCR	Out and inpatients with CDI	Non-recurrent and cured patients	SI, PE, AB, IS	71 <sup>¥</sup> IQR=56-81	509	18 (86)	7.4 (34)	22 (101)	2-levels MLR	13 <sup>‡</sup> /15 <sup>†</sup>	6.6 <sup>‡</sup> / 2.9 <sup>†</sup>
Cadena 2010 [54] 2003-2005 USA	<b>Recurrence:</b> recurrent symptoms of CDI after completion of therapy and initial complete resolution; <b>90-day death</b>	RC >90	Toxin A and B EIA	Inpatients in veterans' health care system	Non-recurrent CDI	SI, PE, IS, RS, AB, AU	All ages	129	29 (38)	-	29 (38)	MLR	3	12.7
Cloud 2009 [43] 2004-2006 USA	<b>Severe CDI:</b> death or CDI as contributor, ICU admission or with CDI as contributing factor, toxic megacolon or colectomy; <b>60-day inhospital death</b> <b>Treatment failure:</b> change from MTZ to or addition of vancomycin	PC 60	Toxin A EIA	Inpatients with CDI	Cured patients Survivors	SI, AB, AU	67.3 <sup>§</sup>	272	-	22.1 (60) 21 (53) <sup>£</sup>	4 (11)	MLR	5	12
Cober 2009 [51] 2006 USA	<b>90-day death</b> <b>Treatment failure:</b> lack of improvement after 5 days or change in treatment regimen	RC	Toxin A or B EIA	80 and older inpatients	Survivors	RS, AB, AU	84 $\pm$ 4.1 <sup>§</sup> 80-94	70	17 (12)	25.7 (18) <sup>£</sup>	17.1 (12)	MLR	9	1.3
de Isusi 2003 [102] 1999-2001 Spain	<b>Failure or recurrence:</b> absence of clinical resolution or reappearance of clinical symptoms $\geq$ 7 days; <b>Death:</b> Inhospital all- cause	RC	Toxin A EIA	Inpatients CDI	Cured patients Survivors	SI, PE, IS, RS, AB, AU	71.7 <sup>§</sup> 20-99	113	18 (20)	20.7 (23) <sup>£</sup>	30.1 (34) 19.5 (22) CDI related	MLR	7	2.6

Khanna 2012 [52] 1991- 2005 USA	<b>Recurrence:</b> CDI within 8 weeks after symptom resolution; <b>Severe-complicated:</b> hypotension, sepsis, ileus, toxic megacolon, perforation, need for ICU admission, surgery or 30-day death; <b>Treatment failure:</b> persistent symptoms leading to change initial treatment within 14 days due to nonresponse or intolerable adverse effects	RC	Direct CTA	All cases of CDI	None	SI, PE, AB, AU	67.6 <sup>¥</sup> 10d- 102yrs	385	30.1 (116)	7 (27)/ 20.2 (75) <sup>£</sup>	-	MLR	5	23.2 <sup>‡</sup> / 5.4 <sup>†</sup>
Kim 2013[91] 2005- 2010 South Korea	<b>Response failure to treatment:</b> no improvement in diarrhoea by day 10 <b>All cause 30-day mortality</b>	RC 30	Toxin A EIA (2005- 2008); Toxin A and B EIA (2008-2010)	Patients with CDI	Response/ survivors	AB	64.4 <sup>§</sup> ±14.1	536	-	4.9 <sup>£</sup> (26)	9 (48)	MLR	4 <sup>£</sup> /6	6.5 <sup>£</sup> /8
Jung 2010 [103] 1998-2008 South Korea	<b>Recurrence:</b> reappearance of symptoms or positive toxin assay within 90 days of treatment response <b>Treatment failure:</b> persistence or incomplete resolution of symptoms, or positive toxin assay, >10 days of treatment	RC	Toxin A EIA	Adult inpatients	Non-recurrent and cured patients	IS, AB, AU	62.5±13.8 <sup>§</sup> 23-88	117	11 (13.4)	12.6 (14) <sup>£</sup>	-	MLR	3 <sup>£</sup>	4.3
Morrison 2011 [58] 2004-2008 USA	<b>Complications:</b> CDI-associated mortality, surgery and toxic megacolon	RC	NS toxin assay	Active-duty military, spouses, children and retirees	NR	IS, RS, AB, AU	53 <sup>¥</sup> 1-99	485	-	9.7 (47)	4.7 (23)	MLR	4 <sup>†</sup> /2	11.7 <sup>†</sup> / 11.5
Pepin 2006 [26] 1991-2005 Canada	<b>Recurrence</b> <b>Complications during 1<sup>st</sup> recurrence :</b> toxic megacolon, perforation, colectomy, shock requiring vasopressors or 30-day all-cause death	RC 60	Direct CTA	Patients who experienced at least 1 recurrence	Patients without a 2 <sup>nd</sup> recurrence	SI, IS, AB	All ages	463	63.6 (98)	11 (51)	9.3 (43)	Cox hazards model	3 <sup>‡</sup> /6 <sup>†</sup>	32.7 <sup>‡</sup> / 8.5 <sup>†</sup>

Søes 2012 [49] 2006- 2007 Denmark	<b>Clinical severity score (≥1.5 pts):</b> level of diarrhoea, systemic symptoms, result of sigmoidoscopy <b>Mortality:</b> 30- day	PC 30	PCR on positive culture	Inpatients positive for <i>C. difficile</i> stool culture	None	SI, IS, RS, AB	69 <sup>¥</sup>	82	-	47.6 (39)	11 (9)	MLR/ Cox hazards model	6	6.5/ 1.5
Solomon 2013 [93] 2008- 2009 Ireland	<b>All-cause 30-day mortality</b> <b>Mortality directly attributable to CDI</b> <b>Recurrence</b> 60 days after resolution of primary diarrhoeal episode	PC	Toxin A and B EIA	Consecutive CDI cases	Survivors	None	74.5 <sup>§</sup> 35-97	86	18.6 (16)	-	16.3 (14)	MLR	5	2.8
Wilson 2010 [104] 2007-2008 UK	<b>Mortality:</b> 30-day all-cause and CDI-related <b>Early treatment failure:</b> change of 1 <sup>st</sup> choice, dose, or route of administration	PC 30	Toxin A and B EIA	New CDI cases	Survivors B1/027, DH/106 and other strains	SI, IS	NR	128	19.6 (22)	50 (57) <sup>£</sup>	35.9 (46) overall 17.2 (22) CDI related**	MLR	6	3.7**

Nv= number of variables in the final model. EPV= events per variable. MLR=multivariate logistic regression. NR= not reported.

\*Year of diagnosis= year(s) of cases diagnosis.

‡ Rate or % of recurrence. † Rate or % of complicated CDI. £ Treatment failure. \*\* Death in treated patients.

§ Mean age. ¥ Median age.

Design: RC= retrospective cohort; PC=prospective cohort; RCC=retrospective case-control; PCC=prospective case-control.

Diagnostic test: NS= Not specified, EIA= Enzyme immunoassay, CTA= cytotoxin assay, PCR= Polymerase chain reaction.

Quality variables: SI= site of acquisition of the infection (nosocomial vs. community-acquired), PE= previous episode(s) of CDI, IS= immunosuppression, RS= recent surgeries and procedures, AB= recent antibiotherapy, AU= use of anti-ulcer medication.