



Does This Patient Have *C. difficile* Infection? A Systematic Review and Meta-Analysis



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Background

- Clinical features of *C. difficile* encompass a variable spectrum of disease
- Early and accurate diagnosis is essential for improving patient care
- Thoughtful clinical evaluation is important for testing and treatment decisions

Question

What is the diagnostic utility of clinical features associated with *C. difficile*?

Methods

- Systematic review** of studies that reported *C. difficile* features with a reference standard
- Databases:** MEDLINE, EMBASE, CINAHL, Cochrane from earliest date to Sept. 2021
- Outcomes:** Sensitivity, Specificity, Positive likelihood ratio (LR), Negative likelihood ratio (LR)
- Analysis:** Bivariate random-effects (for 4 or more studies), univariate random-effects (for 3 or more studies), range (for 2 studies) and point estimate (for 1 study)
- Excluded:** small studies ($n \leq 20$), recurrent *C. difficile*, case reports, selected patient groups

Feature

- History
- Exam
- Labs
- Imaging
- Antibiotics
- Risk Factors

Reference Standard

to diagnose *C. difficile*
(stool NAAT, enzyme immunoassays, cell cytotoxicity assay, toxigenic culture)

Comparison

of patients with and without *C. difficile*

Results

15,427 Studies on *C. difficile* → 4,196 Duplicates removed
 ↓
 11,231 Studies screened → 10,891 Studies irrelevant (titles and abstracts)
 ↓
 340 Full-text studies → 294 Studies excluded assessed for eligibility
 ↓
43 Studies Included, 67 Clinical Features Assessed

Clinical Examination

Finding	Total patients (patients with <i>C. difficile</i>)	Sensitivity	Specificity	Positive LR	Negative LR
Diarrhea	17213 (1937)	0.61 (0.27-0.88)	0.51 (0.29-0.74)	1.23 (0.90-1.48)	0.73 (0.38-1.05)
Watery diarrhea	1783 (378)	0.73 (0.60-0.83)	0.42 (0.33-0.51)	1.25 (0.95-1.64)	0.66 (0.39-1.09)
Bloody diarrhea	3277 (701)	0.09 (0.05-0.16)	0.92 (0.89-0.95)	1.20 (0.84-1.64)	0.98 (0.94-1.01)
Mucus in stool	1310 (274)	0.23-0.66	0.46 to 0.75	0.19-0.48	0.49-0.88
Abdominal pain	10978 (2454)	0.33 (0.19-0.50)	0.65 (0.50-0.77)	0.93 (0.69-1.20)	1.04 (0.90-1.19)
Abdominal distention	544 (285)	0.10 (0.04-0.22)	0.94 (0.90-0.96)	1.71 (0.68-4.34)	0.95 (0.86-1.04)
Ileus	464 (169)	0.10 (0.06-0.16)	0.93 (0.90-0.96)	1.51 (0.78-2.92)	0.95 (0.88-1.03)
Nausea or vomiting	1802 (255)	0.20 (0.04-0.51)	0.80 (0.45-0.97)	1.06 (0.66-1.72)	1.01 (0.89-1.12)
Fever	20151 (2443)	0.26 (0.15-0.39)	0.80 (0.68-0.88)	1.29 (1.02-1.60)	0.93 (0.85-0.99)
Hypotension (SBP ≤ 90)	74 (50)	0.34 (0.21-0.47)	0.79 (0.63-0.95)	1.63 (0.76-2.50)	0.83 (0.55-1.12)

Radiographic Findings

Finding	Total patients (patients with <i>C. difficile</i>)	Sensitivity	Specificity	Positive LR	Negative LR
Colon wall ≥ 4mm	283 (149)	0.80 (0.67-0.90)	0.78 (0.71-0.85)	3.80 (2.74-5.30)	0.26 (0.12-0.56)
Colon wall nodularity	110 (54)	0.19 (0.08-0.29)	0.99 (0.97-1.02)	20.93 (18.11-23.74)	0.82 (0.69-0.95)
Colon dilation	35 (28)	0.07 (0.00-0.17)	0.93 (0.75-1.11)	1.07 (0.00-4.06)	0.99 (0.78-1.21)
Accordion sign	110 (54)	0.04 (0.00-0.09)	0.99 (0.97-1.02)	4.19 (1.11-7.26)	0.97 (0.91-1.03)
Pericolonic stranding	110 (54)	0.57 (0.44-0.71)	0.95 (0.89-1.01)	10.72 (9.59-11.84)	0.45 (0.13-0.77)
Ascites	283 (149)	0.32 (0.18-0.49)	0.88 (0.81-0.93)	2.91 (1.76-4.80)	0.75 (0.60-0.93)
Internal ring present	137 (68)	0.24 (0.14-0.34)	0.99 (0.97-1.01)	34.15 (31.35-36.94)	0.77 (0.63-0.90)
External ring present	137 (68)	0.15 (0.06-0.23)	0.99 (0.97-1.01)	21.34 (18.52-24.16)	0.86 (0.75-0.96)
Large bowel content diminution	137 (68)	0.16 (0.08-0.25)	0.99 (0.96-1.01)	11.67 (9.64-13.68)	0.85 (0.74-0.96)
Toxic megacolon	348 (98)	0.01 (0.00-0.02)	1.00 (0.99-1.00)	2.54 (0.00-6.46)	1.00 (0.98-1.01)

Laboratory Findings

Finding	Total patients (patients with <i>C. difficile</i>)	Sensitivity	Specificity	Positive LR	Negative LR
Leukocytes in stool	867 (111)	0.36 (0.19-0.57)	0.93 (0.91-0.94)	5.31 (3.29-8.56)	0.68 (0.45-1.03)
Leukocytosis	14731 (1748)	0.44 (0.34-0.55)	0.71 (0.66-0.75)	1.50 (1.24-1.75)	0.79 (0.67-0.91)
Low albumin	1305 (248)	0.42 (0.31-0.54)	0.60 (0.54-0.82)	1.43 (1.06-1.97)	0.83 (0.73-0.95)
Elevated creatinine	1457 (238)	0.18 (0.06-0.38)	0.87 (0.67-0.97)	1.54 (0.94-2.49)	0.94 (0.85-1.02)

Antibiotic Exposure (Selected results)

Finding	Total patients (patients with <i>C. difficile</i>)	Sensitivity	Specificity	Positive LR	Negative LR
Antibiotics in past 3 months	66647 (3369)	0.75 (0.64-0.84)	0.41 (0.27-0.55)	1.27 (1.10-1.52)	0.62 (0.48-0.78)
Penicillin	4117 (1211)	0.37 (0.27-0.48)	0.65 (0.54-0.75)	1.09 (0.90-1.31)	0.96 (0.86-1.06)
Cephalosporin	4835 (1318)	0.50 (0.31-0.68)	0.65 (0.46-0.81)	1.46 (1.18-1.87)	0.77 (0.64-0.88)
Aminoglycoside	3072 (876)	0.11 (0.05-0.19)	0.89 (0.81-0.95)	1.02 (0.71-1.42)	1.00 (0.96-1.05)
Fluoroquinolone	4710 (1269)	0.24 (0.17-0.33)	0.80 (0.74-0.85)	1.22 (0.99-1.48)	0.95 (0.88-1.00)
Macrolide	1498 (501)	0.06 (0.03-0.09)	0.94 (0.89-0.97)	0.98 (0.56-1.60)	1.00 (0.97-1.04)
Tetracycline	1437 (202)	0.06 (0.03-0.10)	0.96 (0.93-0.97)	1.39 (0.63-2.67)	0.99 (0.94-1.02)
Vancomycin	2737 (738)	0.19 (0.09-0.33)	0.84 (0.72-0.93)	1.25 (0.86-1.78)	0.96 (0.87-1.03)
Carbapenem	3306 (979)	0.22 (0.13-0.35)	0.84 (0.75-0.91)	1.43 (1.19-1.71)	0.92 (0.86-0.97)
Metronidazole	2816 (655)	0.15 (0.09-0.23)	0.89 (0.85-0.92)	1.27 (0.92-1.67)	0.96 (0.90-1.01)
Clindamycin	2376 (793)	0.12 (0.07-0.18)	0.92 (0.86-0.95)	1.44 (1.05-1.93)	0.96 (0.93-1.00)
TMP-SMX	1205 (403)	0.09 (0.05-0.14)	0.94 (0.88-0.98)	1.62 (0.82-2.90)	0.97 (0.93-1.02)

Patient Risk Factors (Selected results)

Finding	Total patients (patients with <i>C. difficile</i>)	Sensitivity	Specificity	Positive LR	Negative LR
Proton pump inhibitor use	49668 (2007)	0.64 (0.53-0.73)	0.49 (0.35-0.63)	1.26 (1.08-1.51)	0.75 (0.63-0.88)
Age 65 or higher	44398 (739)	0.38 (0.22-0.56)	0.67 (0.48-0.82)	1.15 (0.88-1.50)	0.94 (0.80-1.08)
Chronic kidney disease	1117165 (11272)	0.17 (0.14-0.22)	0.92 (0.86-0.96)	2.39 (1.49-3.71)	0.90 (0.87-0.92)
Heart failure	1115558 (10871)	0.16 (0.06-0.32)	0.94 (0.86-0.98)	3.01 (2.26-3.80)	0.89 (0.79-0.95)
Malignancy	1078693 (11499)	0.16 (0.12-0.22)	0.88 (0.82-0.93)	1.46 (1.20-1.77)	0.95 (0.93-0.96)
HIV	1075997 (10727)	0.03 (0.02-0.05)	0.98 (0.96-0.99)	1.60 (1.05-2.36)	0.99 (0.98-1.00)

Conclusions

- Bedside clinical examination alone is insufficient for diagnosis of *C. difficile*
- Microbiologic testing still needed to confirm diagnosis in all suspected cases