Cas cliniques interactifs
Pr F. Caron

Journée des référents en antibiothérapie

Cette femme de 67 ans aux antécédents de BPCO post-tabagique avec exacerbation fréquente et de reflux gastro-oesophagien indiquant des inhibiteurs de la pompe à protons au long cours consulte pour une diarrhée abondante survenue à J5 d'un traitement de cefpodoxime pour nouvelle exacerbation bronchique.

Malgré l'arrêt de tout antibiotique depuis 4 jours la symptomatologie persiste.

Une recherche de *Clostridium difficile* toxinogène a été réalisée, s'avérant positive.

Vous vous interrogez sur la meilleure stratégie thérapeutique.

Q

Pour guider votre choix vous vous penchez sur les recommandations disponibles.

A quand remonte le dernier référentiel thérapeutique français relatif aux ICD ?

1. 52 avant JC
2. 2006
3. 2014
4. 2016
5. 2018

Pour guider votre choix vous vous penchez sur les recommandations disponibles.

A quand remonte le dernier référentiel thérapeutique français relatif aux ICD ?

1. 52 avant JC

✓2

2. 2006

3. 2014

4. 2016

5. 2018

RAISIN
Réseau d'alerte d'investigation et de surveillance des infections nosocomiales

2006

InVS
INSTITUT DE VEILLE SANITAIRE

Conduite à tenir :

diagnostic,

investigation, surveillance,

et principes de prévention

et de maîtrise des

infections à *Clostridium difficile*.

- 42 pages

- Une demie page consacrée à la thérapeutique :

  - « Le retrait de l'ATB suffit à la guérison en 2-3 jours dans 25 % des cas »

  - « En cas d'échec de ce retrait ou de poursuite indispensable de l'ATB ou de forme sévère :
    - métronidazole 1 g/j *PO* 10 j
    - ou vancomycine 0,5-2 g/j *PO* 10 j »

ORIGINAL ARTICLE 10.1111/1469-0691.12418

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Clin Microbiol Infect 2014;20 (suppl 2):1-26

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Edward Hines Jr Veterans Administration Hospital, Hines, and [3]Loyola University Medical Center, Maywood, Illinois; [4]St Luke's Hospital, Duluth, Minnesota; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]Children's Hospital of Philadelphia, Pennsylvania; [7]Washington University School of Medicine, St Louis, Missouri; [8]University of Houston College of Pharmacy, Texas; [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [10]McGill University Health Centre, McGill University, Montréal, Québec, Canada; [11]Boston Children's Hospital, Massachusetts; and [12]Leeds Teaching Hospitals NHS Trust, United Kingdom

Clin Infect Dis 2018;66:e1-48

Pro-européens ?

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Pro-américains ?

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Clin Infect Dis 2018;66:e1-48

Q

Quel traitement vous apparaît ici indiqué en 1ère intention ?

1. Métronidazole PO
2. Vancomycine PO
3. Fidaxomycine PO

Q

Quel traitement vous apparaît ici indiqué en 1ère intention ?

1. Métronidazole PO

2. Vancomycine PO

3. Fidaxomycine PO

Quel traitement vous apparaît ici indiqué en 1ère intention ?

ESCMID 2014 :

1. Métronidazole PO
2. Vancomycine PO
3. Fidaxomycine PO

Quel traitement vous apparaît ici indiqué en 1ère intention ?

IDSA 2017 :

1. métronidazole PO

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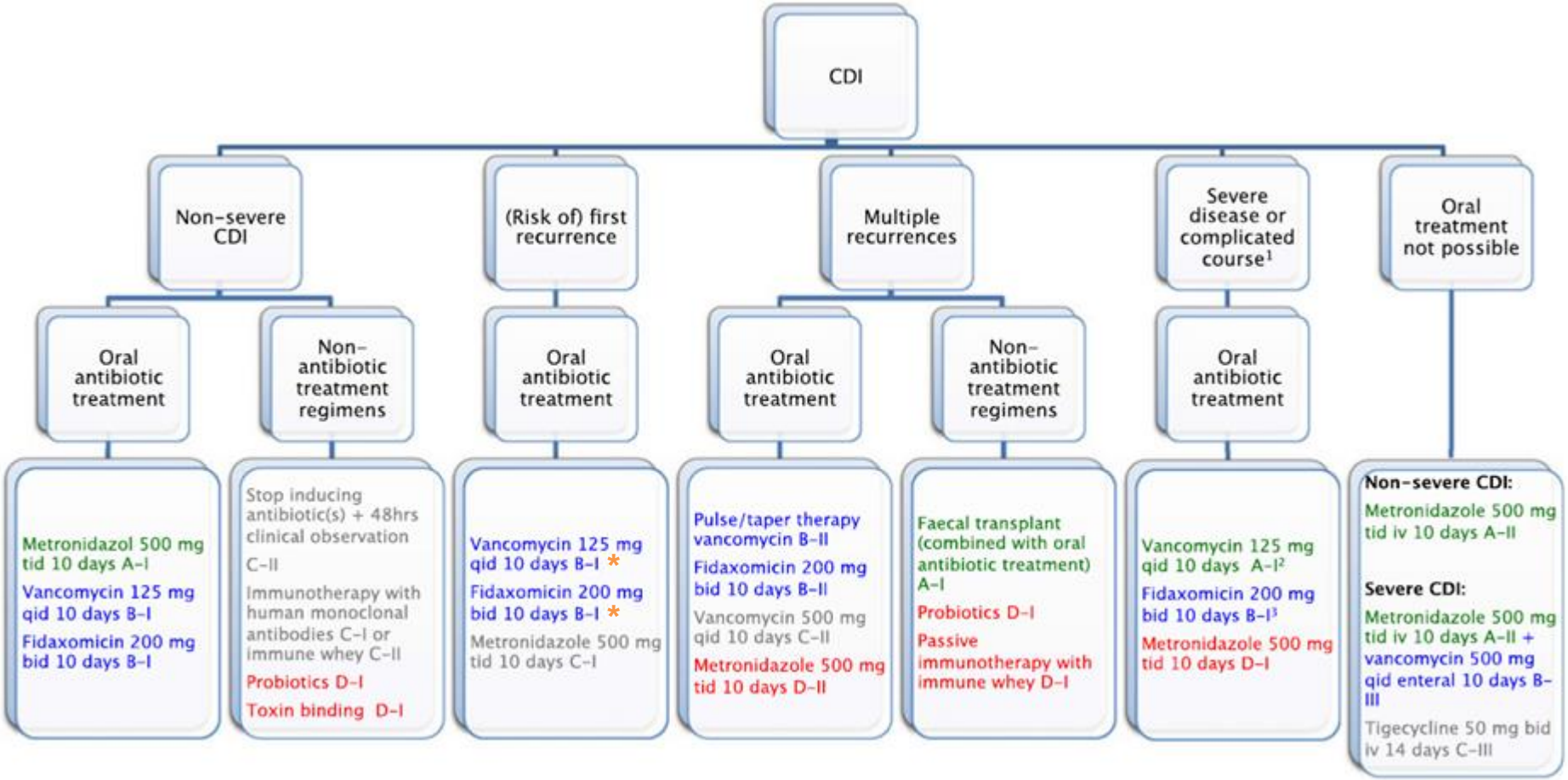
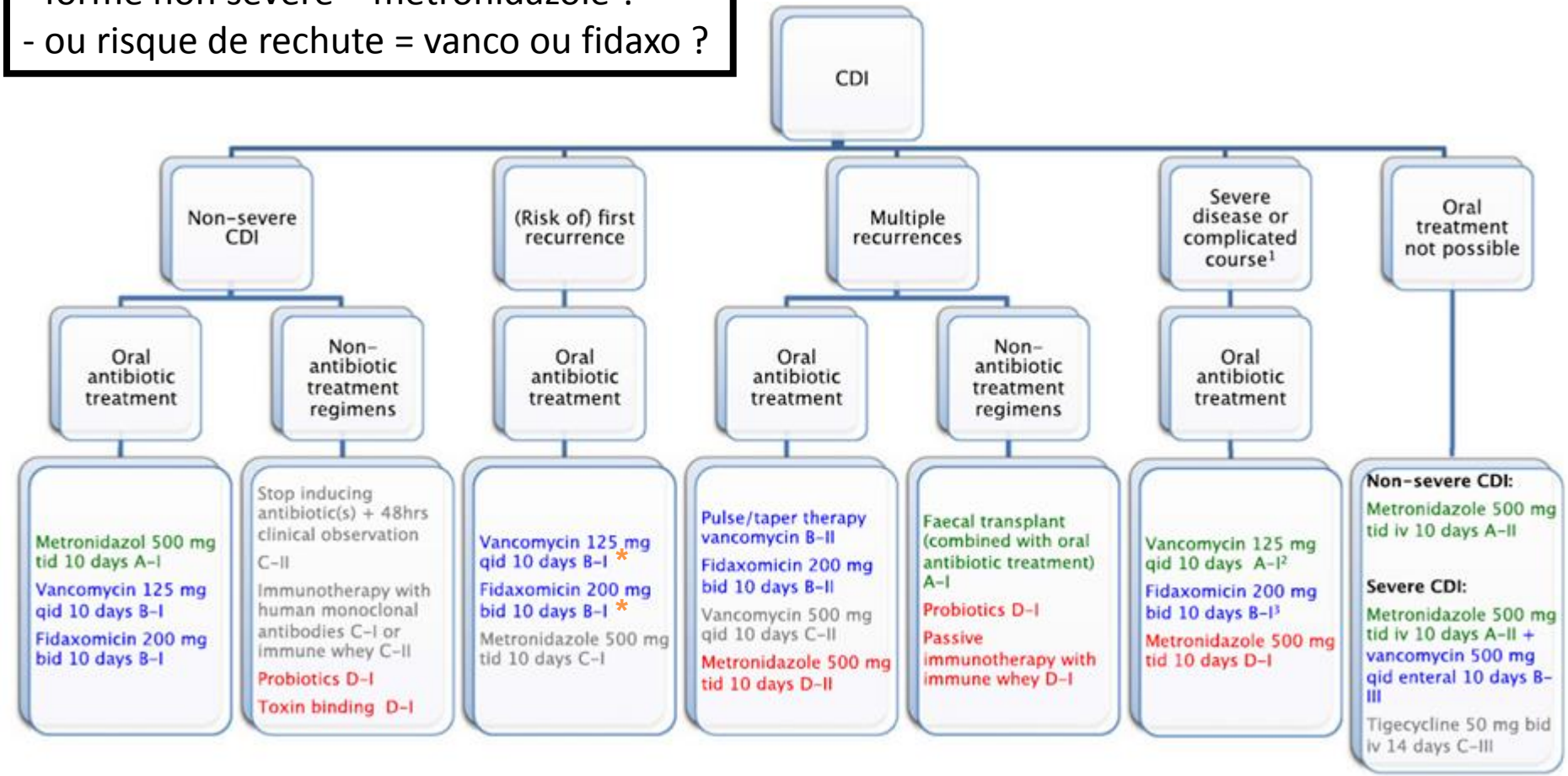
European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

2014



*** ordre alphabétique dans le texte pour B-I : fidaxo, vanco**

Dans le cas présent :
- forme non sévère = métronidazole ?
- ou risque de rechute = vanco ou fidaxo ?



*** ordre alphabétique dans le texte pour B-I : fidaxo, vanco**

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

2014

- Cinq facteurs de rechutes retenus, dont deux très fréquents : âge > 65 ans & IPP

- Porte ouverte à la prévention large des rechutes « [Risk of] first recurrence »

TABLE 6. Prognostic markers that can be used to determine (increased risk of) recurrent *Clostridium difficile* infection (CDI)

Characteristics	SoR[a]	QoE	Ref (s) not exhaustive	Comment(s)
Age (>65 years)	A	IIrh	[42,43,46,67]	Meta-analysis: [43]. Systematic review: [46]. Prospective validation study of risk factor: [42].
Continued use of (non-CDI) antibiotics after diagnosis of CDI and/or after CDI treatment	A	IIrh	[42,43]	Meta-analysis: [43]. Prospective validation study of risk factor: [42].
Comorbidity (severe underlying disease) and/or renal failure	A	IIh	[42,45,68]	Prospective validation study of risk factor: comorbidity conditions rated by Horns' index (scoring system for underlying disease severity) [42].
A history of previous CDI (more than one recurrence)	A	IIt	[26,40,69–71]	Data from randomized controlled trials: [26,70]. Meta-analysis of pivotal randomized controlled trials [40].
Concomitant use of antacid medications (proton pump inhibitors)	B	IIrh	[43,72]	Meta-analysis on recurrent CDI: [43]. Meta-analysis on CDI: [72].
Initial disease severity	B	IIth	[42,67]	Prospective validation study of risk factor [42]. Long-term population based cohort study [67].

[a]SoR: degree of recommendation to use a (clinical) characteristic as a prognostic marker.

Clin Microbiol Infect 2014;20 (suppl 2):1-26

Traitement des ICD en 2018 : oubliez le métronidazole !

- Cochrane revue 2017
- IDSA guideline 2017

Cochrane Database Syst Rev. 2017 Mar 3;3:CD004610. doi: 10.1002/14651858.CD004610.pub5.

Cochrane Library

Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults.

Nelson RL[1], Suda KJ[2], Evans CT[3].

AUTHORS' CONCLUSIONS:

- *« No firm conclusions can be drawn regarding the efficacy of antibiotic treatment in severe CDI as most studies excluded patients with severe disease. »*
- *« The lack of any « no treatment » control studies does not allow for any conclusions regarding the need for antibiotic treatment in patients with mild CDI beyond withdrawal of the initiating antibiotic. »*
- ***« Nonetheless, moderate quality evidence suggests that vancomycin is superior to metronidazole… »***

IDSA 2017 : « Summary of the evidence »

- **métronidazole** : depuis 2000, plusieurs essais contrôlés en défaveur *versus* vanco, même dans des formes non sévères

  → métronidazole à réserver aux formes non sévères, en cas de CI ou d'indisponibilité des autres thérapeutiques

- **10 jours** : la durée de la plupart des essais une résolution des symptômes le plus souvent acquise avant ce terme

  → 10 jours en général, jusqu'à 14 si non résolution à J10

- **critères de sévérité** : variables dans la littérature

  → restriction à 2 critères disponibles dès l'entrée, mais restant à conforter en prospectif : GB > 15 G/L et créatininémie > 132 µmol/L

- **fidaxomicine** : rappel factuel des deux essais et du bénéfice en prévention des rechutes

  → « *la fidaxo devrait être considérée avec la vanco comme médicament de choix pour un premier épisode* »

Le métronidazole étant désormais non recommandé, quel est votre choix ?

1. vancomycine (« préparation maison »)

2. fidaxomicine (DIFICLIR®)

Le métronidazole étant désormais non recommandé, quel est votre choix ?

1. vancomycine (« préparation maison »)

2. fidaxomicine (DIFICLIR®)

ICD : vanco *versus* fidaxomicine

vanco	fidaxo
	spectre ultra-étroit
efficacité idem (> 95 %) tolérance idem (excellente)	
pression ERG potentielle	
	moindre risque de rechute (15 % *vs* 25 % - NEJM 2011)
préparation « magistrale »	
≈ 50 € la cure	≈ 1500 € la cure

Infect Dis Ther (2016) 5:207–230
DOI 10.1007/s40121-016-0122-1

REVIEW

A Comparison of Current Guidelines of Five International Societies on *Clostridium difficile* Infection Management

Csaba Fehér · Josep Mensa

IDSA/SHEA	2010	USA	infectiologues/hygiénistes
ACG	2013	USA	gastroentérologues
ESCMID	2014	Europe	infectiologues/microbiologistes
WSES	2015	Monde	chirurgiens (d'urgence)
ASID	2016	Australasie	infectiologues

Table 2 Recommendations on pharmacological treatment of CDI according to five current international guidelines

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28]	WSES 2015 [29]	ASID 2016 [31]
First episode					
Mild-moderate	Metronidazole 500 mg/8 h p.o. 10–14 days (A-I)	Metronidazole 500 mg/8 h p.o. 10 days (strong/moderate) Vancomycin 125 mg/6 h p.o. 10 days in case of no response after 5–7 days of metronidazole therapy (strong/moderate), metronidazole intolerance/allergy, or pregnant/breastfeeding women (strong/high) Add vancomycin 500 mg (in 100–500 mL of normal saline)/6 h via enemas if oral antibiotics cannot reach a segment of the colon (conditional/low)	Metronidazole 500 mg/8 h p.o. 10 days (A-I) Vancomycin 125 mg/6 h p.o. 10 days (B-I) (preferred over metronidazole if risk of recurrence) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) (preferred over metronidazole if risk of recurrence) Metronidazole 500 mg/8 h i.v. 10 days if intolerance of oral treatment (A-II) Stop systemic antibiotics + 48 h clinical observation (C-II) Immunotherapy with human monoclonal antibodies (C-I) or immune whey (C-II)	Metronidazole 500 mg/8 h p.o. 10 days (1-A) Vancomycin 125 mg/6 h p.o. 10 days in case of no response to metronidazole (1-A) Fidaxomicin 200 mg/12 h p.o. 10 days in case of high risk of recurrence (1-A)	Metronidazole 400 mg/8 h p.o. 10 days Vancomycin 125 mg/6 h p.o. 10 days in case of refractory CDI

Fidaxo

Table 2 continued

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28]	WSES 2015 [29]	ASID 2016 [31]
Severe	Vancomycin 125 mg/6 h p.o. 10–14 days (B-I)	Vancomycin 125 mg/6 h p.o. 10 days (conditional/moderate) Add vancomycin 500 mg (in 100–500 mL of normal saline)/6 h via enemas if oral antibiotics cannot reach a segment of the colon (conditional/low)	Vancomycin 125 mg/6 h p.o. 10 days (A-I) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) Metronidazole 500 mg/8 h i.v. 10 days (A-II) + vancomycin 500 mg (en 100 mL normal saline)/6 h via enemas or via NGT 10 days if oral treatment not possible (B-III) Tigecycline 50 mg/12 h i.v. 14 days if oral treatment not possible (C-III) DO NOT use metronidazole in monotherapy (D-I)	Vancomycin 125 mg/6 h p.o. 10 days (1-A) Vancomycin 500 mg/6 h via enemas + metronidazole 500 mg/8 h i.v. when oral antibiotics cannot reach the colon (1-B) or in case of fulminant colitis (1-C)	Vancomycin 125 mg/6 h p.o. 10 days (first-line therapy) Metronidazole 500 mg/8 h i.v. + vancomycin 125 mg/6 h via NGT ± vancomycin 500 mg (in 100 mL normal saline)/6–8 h via enemas in refractory CDI or when unable to tolerate oral therapy (second-line therapy) Intestinal microbiota transplantation after 3–5 days of vancomycin or fidaxomicin treatment (third line therapy) Fidaxomicin 200 mg/12 h p.o. 10 days (third-line therapy) Tigecycline 50 mg/12 h i.v. 14 days if oral therapy not possible (third line therapy)
Severe complicated	Vancomycin 500 mg/6 h p.o. or via NGT + Metronidazole 500 mg/8 h i.v. Consider adding Vancomycin 500 mg (in 100 mL normal saline)/6 h via enemas if ileus is present (C-III)	Vancomycin 125 mg/6 h p.o. + metronidazole 500 mg/8 h i.v. (strong/low) Vancomycin 500 mg/6 h v.o. + 500 mg (in 500 mL of normal saline) via enemas + metronidazole 500 mg/8 h i.v. if ileus or significant abdominal distension is present (strong/low)			
First recurrence	Same treatment as for initial episode (A-II) stratified according to disease severity (C-III)	Same treatment as for initial episode, according to disease severity	Vancomycin 125 mg/6 h p.o. 10 days (B-I) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) Metronidazole 500 mg/8 h p.o. 10 days (C-I)	Same treatment as for initial episode according to disease severity (1-B) Fidaxomicin 200 mg/12 h p.o. 10 days (1-B)	Vancomycin 125 mg/6 h p.o. 10 days

Fidaxo

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

IDSA 2017

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

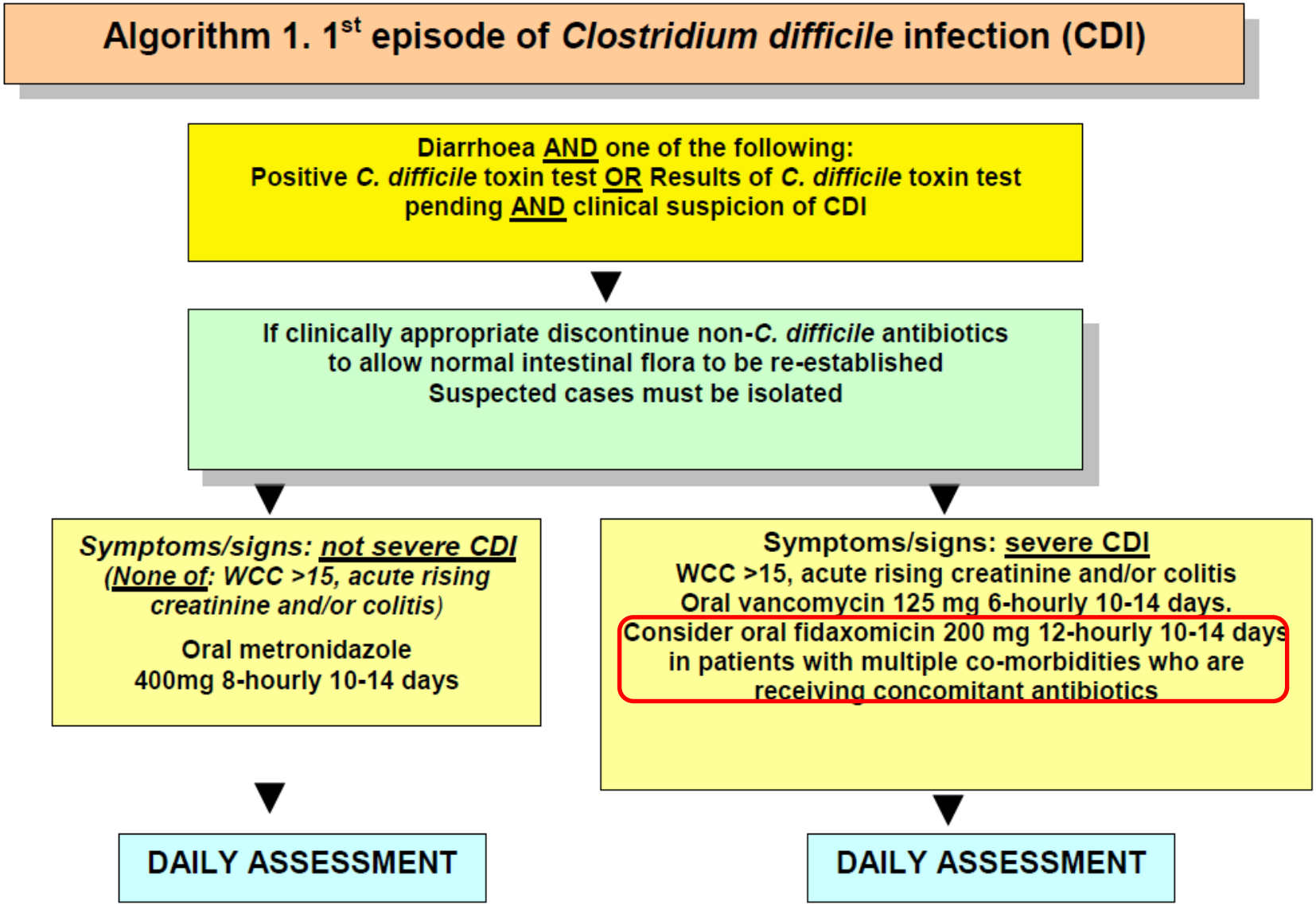
[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

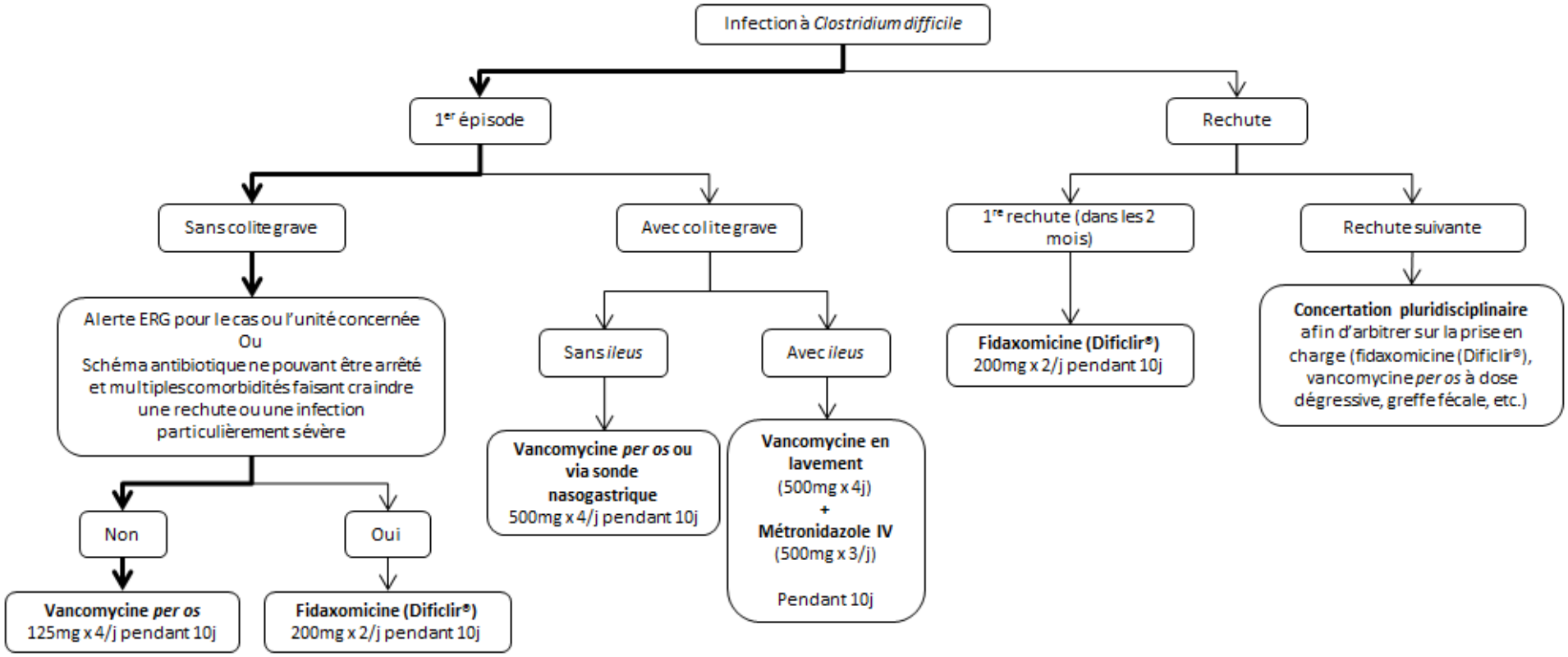
[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

UK 2013

4. Treatment algorithms



ICD : stratégie 2018 au CHU de Rouen



ICD : ne pas oublier la prévention !

« Les ATB critiques, encore moins !!! »

ICD : ne pas oublier la prévention !

LES ANTIBIOTIQUES
C'EST PAS AUTOMATIQUE
l'Assurance Maladie

« Les ATB critiques, encore moins !!! »

- L'ICD est la seule exception aux SHA
- Je vous passe un savon si vous ne vous en souvenez pas