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Complications infectieuses digestives liées aux traitements immunomodulateurs

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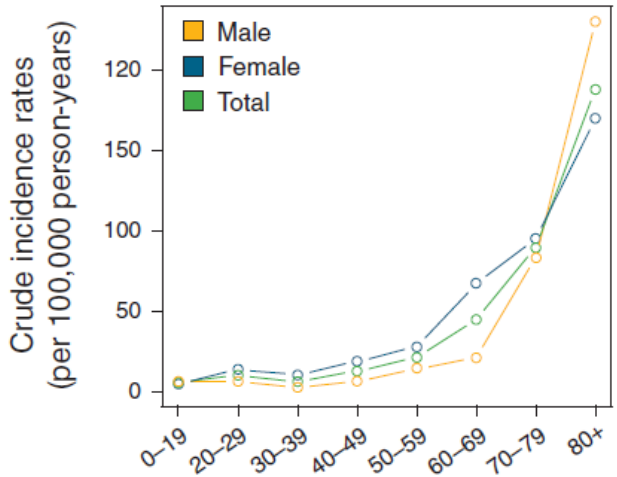
Complications infectieuses digestives liées aux traitements immunomodulateurs

- Est-ce que c’est fréquent ?
- Est-ce que c’est grave ?
- Faut-il arrêter les immunomodulateurs ?
- Faut-il traiter différemment ?

Complications infectieuses digestives liées aux traitements immunomodulateurs

- Est-ce que c'est fréquent ?
  - *On ne sait pas…….*
- Est-ce que c'est grave ?
  - *On ne sait pas…….*
- Faut-il arrêter les immunomodulateurs ?
  - *On ne sait pas…….*
- Faut-il traiter différemment ?
  - *On ne sait pas…….*

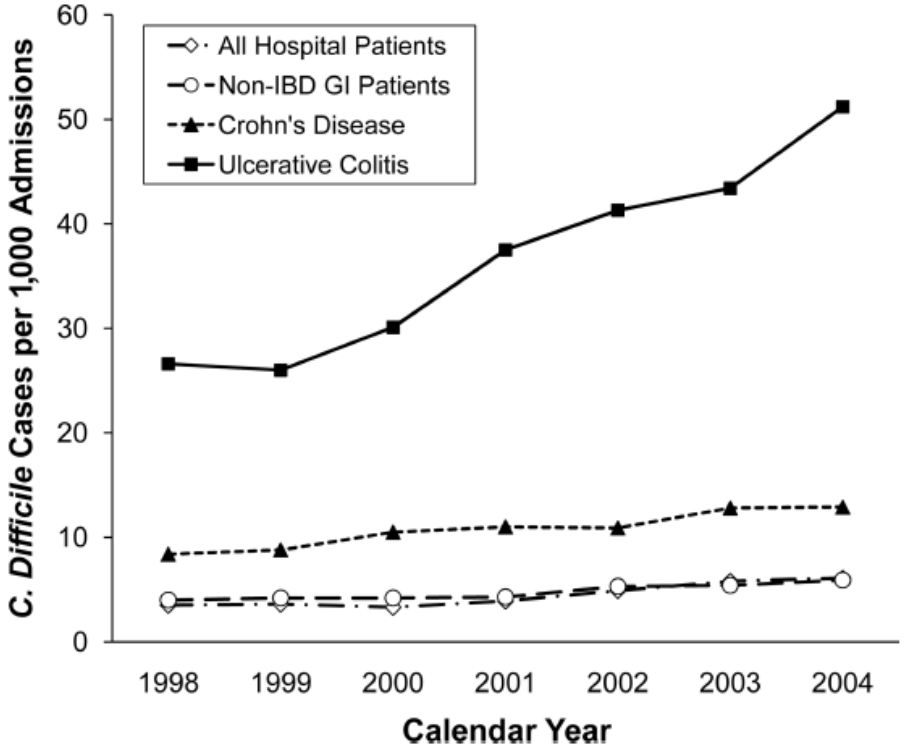
Clostridium difficile et immunomodulateurs



- Incidence colites à CD = 25,2/100 000 patients-années
- Favorisées par les immunomodulateurs

Kanna S, Am J Gastroenterol 2012
Dallal RM, Ann Surg 2002

Augmentation de fréquence des infections à CD au cours des MICI



- OR 2,1 (CI 3-3,4) MC
- OR 4 (CI 2,4-6,6) RCH

Nguyen et al., Am J Gastroenterol 2008;103:1443-50
Nationwide (US) Inpatient Sample

Immunomodulateurs: Facteur de risque de *Clostridium difficile* ?

Characteristics of patients with or without *Clostridium difficile* infection (univariate analysis).

	Clostridium difficile infection (n = 34)	No *Clostridium difficile* infection (n = 449)	p
Age (years)			
Median (range)	33 (22–46)	32 (25–44)	0.85
Gender, n (%)			
Male	17 (50)	246(55.1)	0.58
Body mass index, n (%)			
<18.5	11(32.3)	103 (23)	0.04
18.5–25	14(41.2)	275(61.6)	
>25	8(23.5)	57(12.7)	
Charlson index			
Median (range)	3 (2–5)	2 (1–3)	0.85
Inflammatory bowel disease type, n (%)			
Crohn's disease	20(58.8)	258(57.8)	0.85
Ulcerative colitis	14(41.2)	191(42.2)	
Colonic involvement, n (%)	27(79.4)	337(75.5)	0.58
Duration of disease			
Median (range)	4 (2–6)	6 (2–13)	0.26
Smoking, n (%)	11(32.3)	144(32.2)	0.97
History of *Clostridium difficile* infection, n (%)	2(5.8)	16(3.5)	0.37
Maintenance therapy			
Corticosteroids[a]	8	103	0.93
Immunomodulators[b]	8	121	
Anti-TNF	9	108	
Total (%)	25(73.5)	332(73.9)	
Antibiotics, n (%)	12(35.3)	110(24.5)	0.16
Proton pump inhibitors, n (%)	3(8.8)	51(11.3)	0.64
Nonsteroidal anti-inflammatory drugs, n (%)	4(11.7)	15(3.3)	0.01
White blood cell count			
Median (range)	9900 (7200–12,320)	8235 (6088–11,315)	0.0037

p is significant if <0.05.

[a] >20 milligrams prednisolone equivalent.

[b] In the two months prior to the admission, immunomodulators include azathioprine, methotrexate and purinethol.

Regnault et al., DLD 2015

Corticoïdes: Le facteur de risque de *Clostridium difficile*

Table 2. Rates and rate ratios of serious infection outcomes for any use of the study drugs (Model 1)

Endpoints and drug exposures	Patient years	Events	Event rate per 1000	95% CI‡	Unadjusted rate ratio	95% CI	Adjusted rate ratio§	95% CI
Bacteriaemia:								
Immunosuppressive drug* use†	3973.4	15	3.78	2.11, 6.22	Reference	-	Reference	-
Infliximab use†	678.1	5	7.37	2.39, 17.2	1.95	0.71, 5.37	1.41	0.47, 4.24
Corticosteroid use†	4077.3	17	4.17	2.42, 6.68	1.11	0.55, 2.21	1.12	0.52, 2.41
Serious bacterial infection:								
Immunosuppressive drug* use†	3963.8	27	6.81	4.49, 9.91	Reference	-	Reference	-
Infliximab use†	677.8	6	8.85	3.25, 19.3	1.30	0.54, 3.15	1.08	0.42, 2.74
Corticosteroid use†	4065.8	32	7.87	5.38, 11.1	1.16	0.69, 1.93	1.08	0.62, 1.87
Clostridium difficile infection:								
Immunosuppressive drug* use†	3971.9	14	3.52	1.93, 5.91	Reference	-	Reference	-
Infliximab use†	682.1	0	0	0, 5.41	-	-	-	-
Corticosteroid use†	4063.4	57	14.03	10.6, 18.2	3.98	2.22, 7.14	3.38	1.88, 6.10

* Immunosuppressant drugs incl. MTX = Azathioprine, mercaptopurine, methotrexate.
† With or without ongoing use of other immunomodulating drugs at initiation of the study drug.
‡ 95% confidence interval.
§ Adjusted for all covariates listed in Table 1 plus 2nd degree polynomials for comorbidity index, number of visits, number of medications (generic entities).

Schneeweiis, Aliment Pharmacol 2009

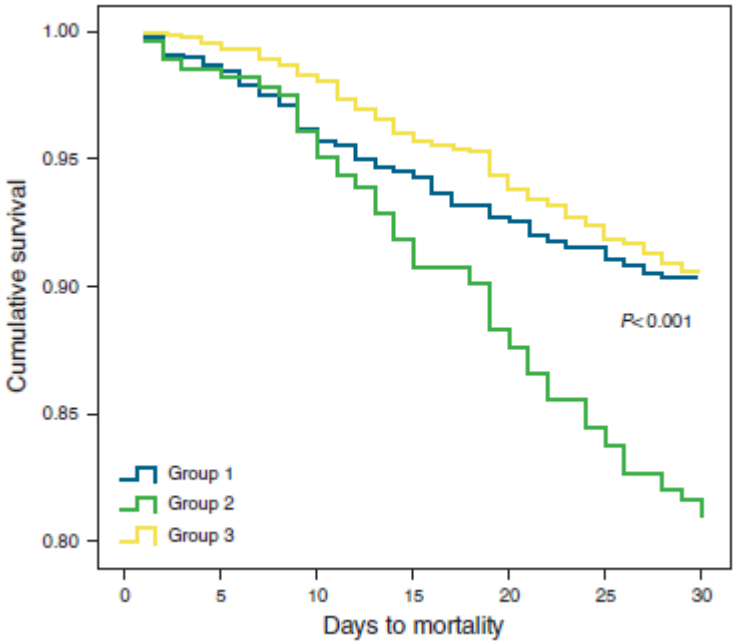
Glucocorticoids Are Associated With Increased Risk of Short-Term Mortality in Hospitalized Patients With *Clostridium difficile*-Associated Disease

Rohit Das, MD[1], Paul Feuerstadt, MD[1] and Lawrence J. Brandt, MD, MACG[1]

Am J Gastroenterol 2010; 105:2040–2049;

Table 2. Indications for glucocorticoid use in Groups 2 and 3

	Group 2	Group 3	*P* value
Indication for glucocorticoid use (%)			
Respiratory	42.5	42.6	0.97
Rheumatologic	15.1	15.5	0.87
Chemotherapy	10.9	3.0	<0.001
Endocrine	9.8	6.4	0.05
Neurologic	6.0	2.9	0.02
Hematologic	3.9	2.1	0.10
Immunosuppression following transplant	3.9	12.9	<0.001
Gastrointestinal (IBD)	2.8	6.0	0.03
Other	1.9	6.4	0.01
Renal	1.8	1.0	0.31
Dermatologic	1.4	1.1	0.70



Colites à CD: Diagnostic

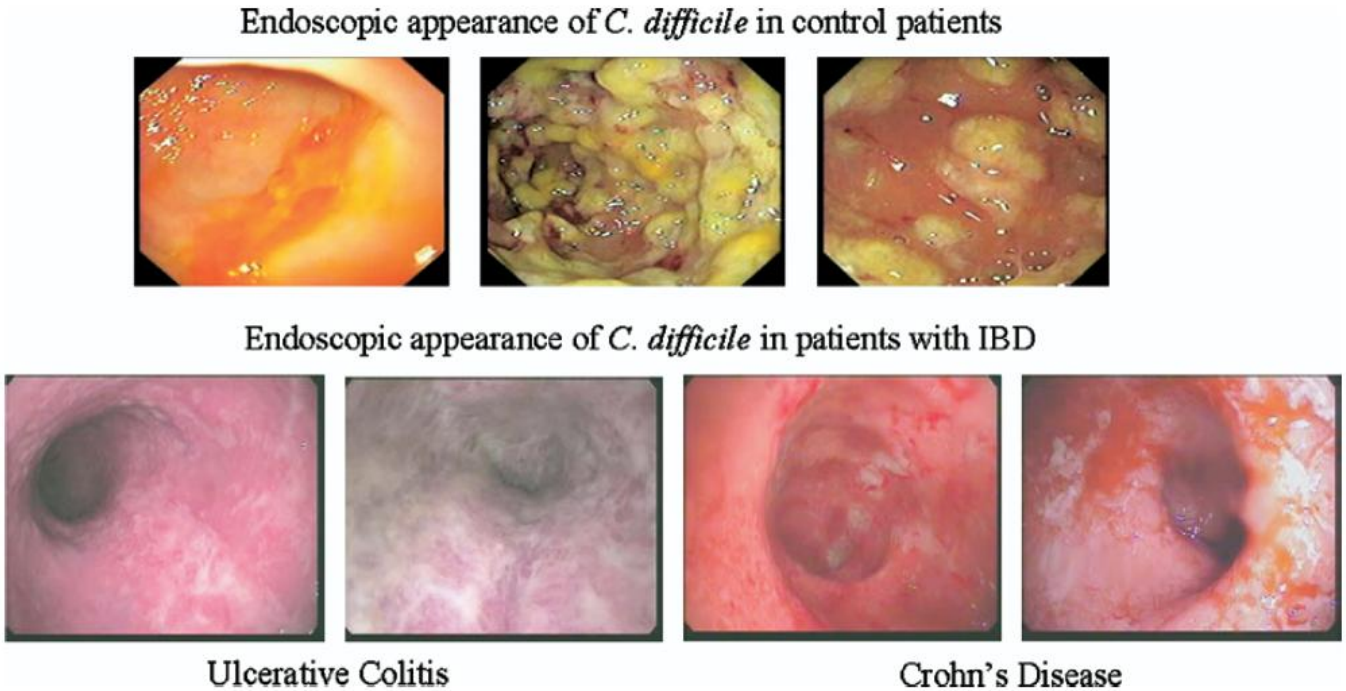
- Ce qui devrait être le standard :
  - Détection rapide DES toxines (A et B)
    - méthode immuno-enzymatique, ELISA, (PCR),
    - Se et Sp actuelles ~ 80-90%

  ET
  - Culture

- La cytotoxicité de la toxine B reste la méthode de référence mais n'est guère plus utilisée (longue, coûteuse)

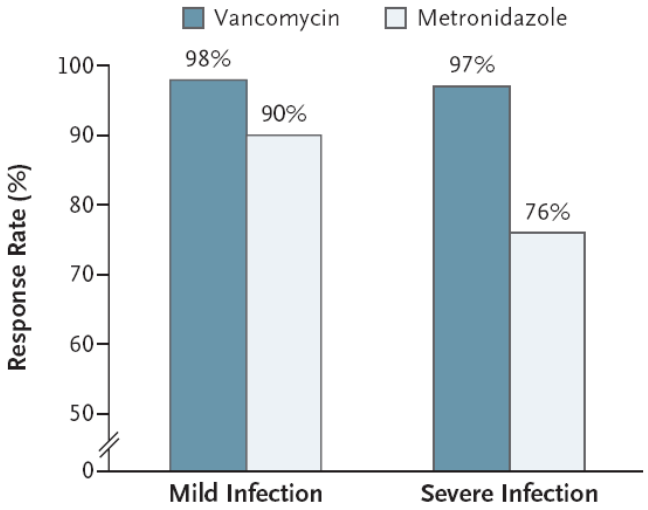
- Introduction récente d'un test antigénique rapide « stop »
  - **Glutamate déshydrogénase (agglutination latex ou test immuno-enzymatique)**
  - **Valeur Prédictive Négative proche de 100%**

Les pseudomembranes (endoscopique et histologiques) sont absentes ou rares



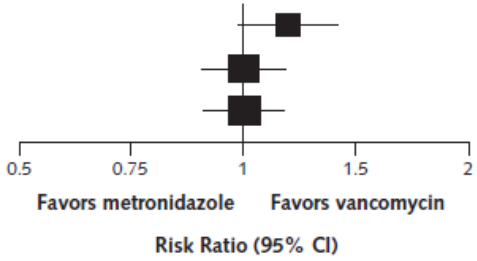
[1] *Issa M et al. Clin Gastroenterol Hepatol 2007;5:345-51*
[2] *Ben-Horin S et al. Aliment Pharmacol Ther 2009;7:981-7*

Traitement médical des infections à *Clostridium difficile*



Clin Infect Dis 2007;45:302

Study, Year (Reference)	Clinically Cured, *n/N*	
	Vancomycin	Metronidazole
Zar et al, 2007 (3)	69/82	66/90
Wenisch et al, 1996 (6)	29/31	29/31
Teasley et al, 1983 (7)	51/56	39/43



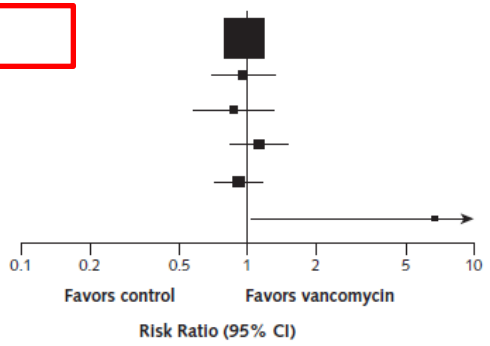
Ann Inter Med 2011

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

Study, Year (Reference)	Control Comparator	Clinically Cured, *n/N*	
		Vancomycin	Control
Louie et al, 2011 (26)	Fidaxomicin	265/313	253/289
Musher et al, 2009 (17)	Nitazoxanide	20/27	17/22
Dudley et al, 1986 (15)	Bacitracin	15/23	12/16
Young et al, 1985 (4)	Bacitracin	18/21	16/21
Fekety et al, 1989 (13)	Low-dose vancomycin	22/28	24/28
Keighley et al, 1978 (11)	Placebo	9/12	1/9



Ann Inter Med 2011

Pas de données dans les MICI (critère d'exclusion…)

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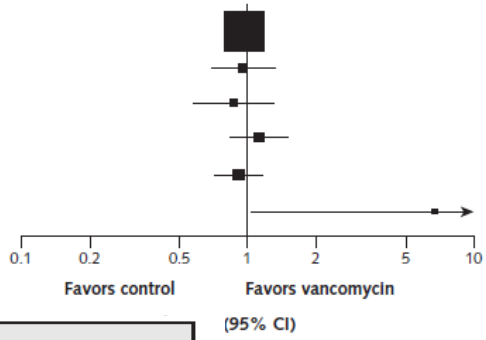


Ann Inter Med 2011

ECCO Statement OI 7K

Metronidazole and oral vancomycin are equally effective in treating mild to moderate CDAD [EL1]. It remains to be established if this applies to patients with inflammatory bowel disease. Other antibiotics should be stopped if possible. For severe CDAD, vancomycin has been shown to be superior in patients without inflammatory bowel disease [EL1] and is therefore preferable. In CDAD, use of immunomodulators should be guided by careful risk benefit evaluation and clinical judgement [EL4]

Rahier JF, JCC 2014

Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

The American Journal of GASTROENTEROLOGY

Colleen R. Kelly, MD, FACG[1], Chioma Ihunnah, MD, MPH[1], Monika Fischer, MD, MSCR[2], Alexander Khoruts, MD[3], Christina Surawicz, MD, MACG[4], Anita Afzali, MD, MPH[4], Olga Aroniadis, MD[5], Amy Barto, MD[6], Thomas Borody, MD, PhD, FACG[7], Andrea Giovanelli, BS[8], Shelley Gordon, MD, PhD[9], Michael Gluck, MD[10], Elizabeth L. Hohmann, MD[11], Dina Kao, MD[12], John Y. Kao, MD[13], Daniel P. McQuillen, MD[6], Mark Mellow, MD, FACG[14], Kevin M. Rank, MD[3], Krishna Rao, MD[13], Arnab Ray, MD[15], Margot A. Schwartz, MD, MPH[10], Namita Singh, MD[16], Neil Stollman, MD, FACG[8], David L. Suskind, MD[16], Stephen M. Vindigni, MD, MPH[4], Ilan Youngster, MD[11] and Lawrence Brandt, MD, MACG[5]

Table 1a. Study patient demographics and pre-FMT data

Total number of study patients	**80**
Adults	75 (94%)
Women	38 (48%)
Men	42 (52%)
Mean adult age (years)	53 (range 20–88)
Mean pediatric age (years)	10.9 (range 6.5–16)
Mean follow-up (months)	11 (range 3–46)
CDI Classification before FMT	
Recurrent	44 (55%)
Refractory	9 (11%)
Severe/complicated	1 (1%)
Overlap (severe/complicated and recurrent or refractory)	26 (33%)
Reason for immunocompromise	
Immunosuppressive agents for IBD	36
Solid organ transplant recipients	19
HIV/AIDS	3
Cancer and treatment with antineoplastic agents	7
Other chronic medical conditions[a]	15

Table 1b. Immunosuppressant agents used concurrently or within 3 months of FMT, indication, and number of patients exposed

Agent	Indication(s)	Number of patients exposed
Tumor necrosis factor-alpha inhibitors[a]	IBD	16
Alpha-4 integrin inhibitor	IBD	2
Steroids	SOT, COPD, IBD, RA, adrenal insufficiency	30
Antimetabolites[b]	IBD, RA, SOT	19
Calcineurin inhibitors[c]	SOT	18
Other anti-rejection agents[d]	SOT	7
Antineoplastic agents[e]	Cancer	8
Other immunomodulary agents[f]	RA, Sjogren's	3

Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

The American Journal of GASTROENTEROLOGY

Efficacy. Resolution of CDI occurred in 62 (78%) patients after a single FMT. Twelve patients who either had recurrence or did not respond after one FMT underwent repeat FMT, of whom eight were cured. Thus, *overall cure* (defined as resolution of CDI after one or more FMTs) within a minimum of 12 weeks was observed in 70 (89%) patients. In the subset of patients with IBD, resolution of CDI occurred in 31 patients (86%) after a single FMT, with an overall cure in 34 (94%).

Table 2. Adverse events

Adverse event	Number of patients sustaining this AE	Reason for Immuno-compromise	Day post-FMT event occurred
Deaths[a]			
Pneumonia	1	SOT	13
Aspiration	1	SOT and esopha-geal cancer	1
Hospitalizations[a]			
Fever, diarrhea, encephalopathy and pancytopenia	1	Cirrhosis and non-Hodgkin's lymphoma	4
Abdominal pain post FMT colonoscopy	1	SOT	0
IBD flare: Crohn's (2), UC (1)	3	IBD	<84
Cerebrovascular ac-cident; nausea and vomiting	1	ESRD and panhy-popituitarism	21
Colectomy	1	IBD	<28
Fall and sustained hip fracture	1	End-stage COPD	84
Influenza B and diarrhea (non-CDI)	1	SOT	3
Catheter infection	1	Cancer	14
Other adverse events			
Self-limited diarrheal illness	3	ESRD; Sjogren's; SOT	≤84
Fever	1	SOT	1
Bloating and abdominal discomfort immediately post FMT	3	HIV; ESRD; IBD	1–2
Hip pain	1	IBD	≤84
Crohn's flare	1	IBD	≤84
Pertussis	1	IBD	≤30
Nausea	1	IBD	30
Minor mucosal tear during colonoscopy used to administer FMT	1	SOT	0

Cytomégalovirus

- Infection chronique latente à CMV
  - 40 à 80 % des adultes
  - Réactivation favorisée par l'immunosuppression
  - Tropisme du CMV pour les tissus malades (cancer, inflammation)

Rowshani et al., Transplantation 2005

- Facteurs médicamenteux influençant la réactivation CMV:
  - Corticoïdes dans la RCH
    - 9,7% vs 50% dans la RCH sévère avant et après corticoïdes IV (1)
    - Augmentation de la protéine virale du CMV sous hydrocortisone (2)
  - Cyclosporine:
    - 75% des patients développent une infection à CMV sous CyA (3)

Les anti-TNF n'augmentent pas le risque de réactivation du CMV

	Sous Anti-TNF	Pas d'anti-TNF	Total
CMV+	12	14	26
CMV-	33	23	56
Total	45	37	82

26,7% sous anti-TNF versus 37,8% sans anti-TNF
Test Khi2 : NS

5 : 10-250 copies/mg de tissu
7 : >250 copies/mg de tissu
Médiane : 381 copies/mg
(extrêmes : 10 – 3 840)

3 : 10-250 copies/mg de tissu
11 : >250 copies/mg de tissu
Médiane : 8680 copies/mg
(extrêmes 10 – 696 000)

P = 0,06

Pillet S, Inflamm Bowel Dis. 2015 Jul

La présence de CMV dans les tissus n'est pas associée à l'échec d'optimisation des anti-TNF

	Echec	Succès	Total
CMV+	6	6	12
CMV-	20	13	33
Total	26	19	45

23,1% en échec versus 32% succès anti-TNF
Test Khi2 : NS

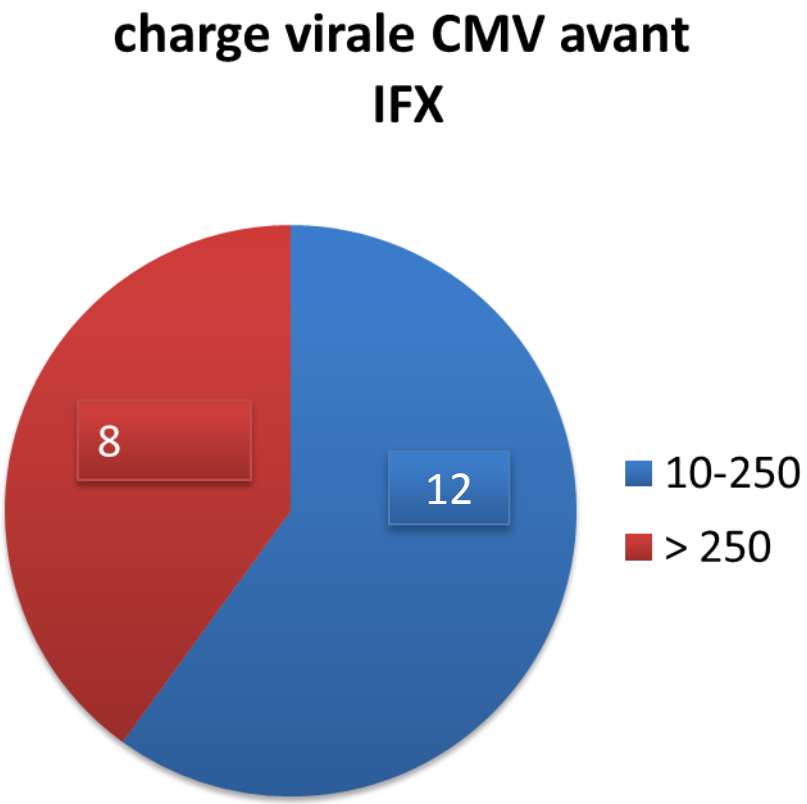
2 : 10-250 copies/mg de tissu
4 : >250 copies/mg de tissu
Médiane : 1365 copies/mg
(extrêmes : 22 - 3840)

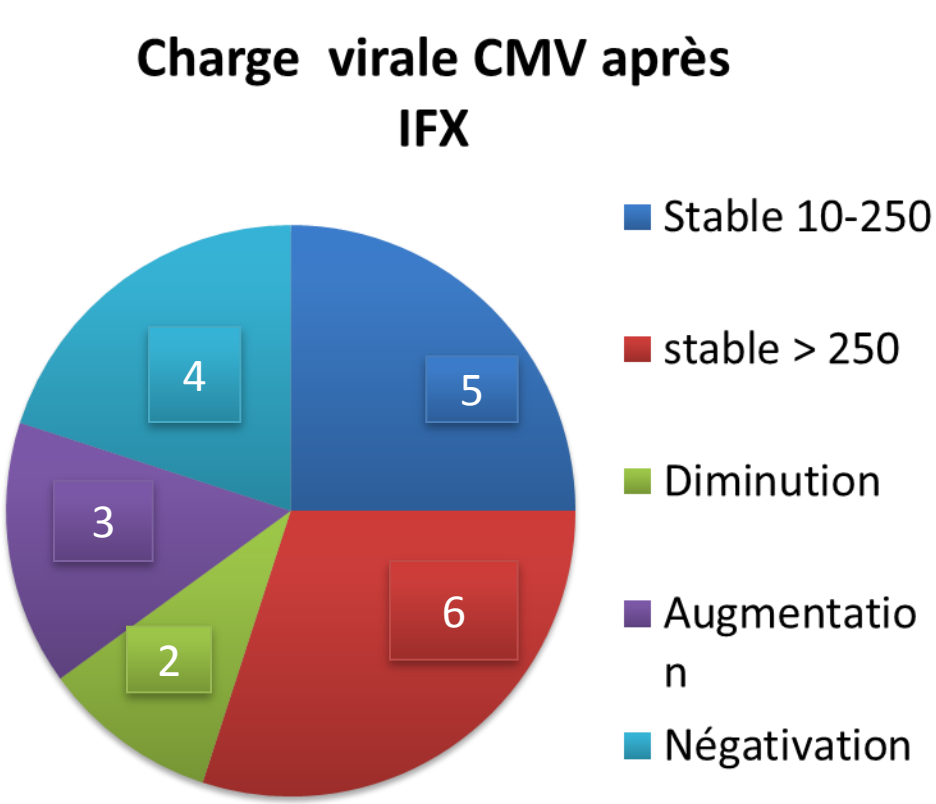
3 : 10-250 copies/mg de tissu
3 : >250 copies/mg de tissu
Médiane : 220 copies/mg
(extrêmes : 10 - 616)

P = 0,128

Pillet S, Inflamm Bowel Dis. 2015 Jul

Evolution de la charge virale CMV par PCR tissu sous anti TNF





Pas de différence en fonction de la dose d'IFX

- **Présence de CMV tissu colique par PCR temps réel**
  - **Est comparable avec ou sans anti TNF**
  - **Charge virale plus élevée sans anti TNF**
  - **N'est pas associée à une échec dans l'optimisation thérapeutique à l'IFX**

- **Pas de modification de la charge virale par PCR sous IFX**
  - **Simple ou double dose**

Pillet S, Inflamm Bowel Dis. 2015 Jul

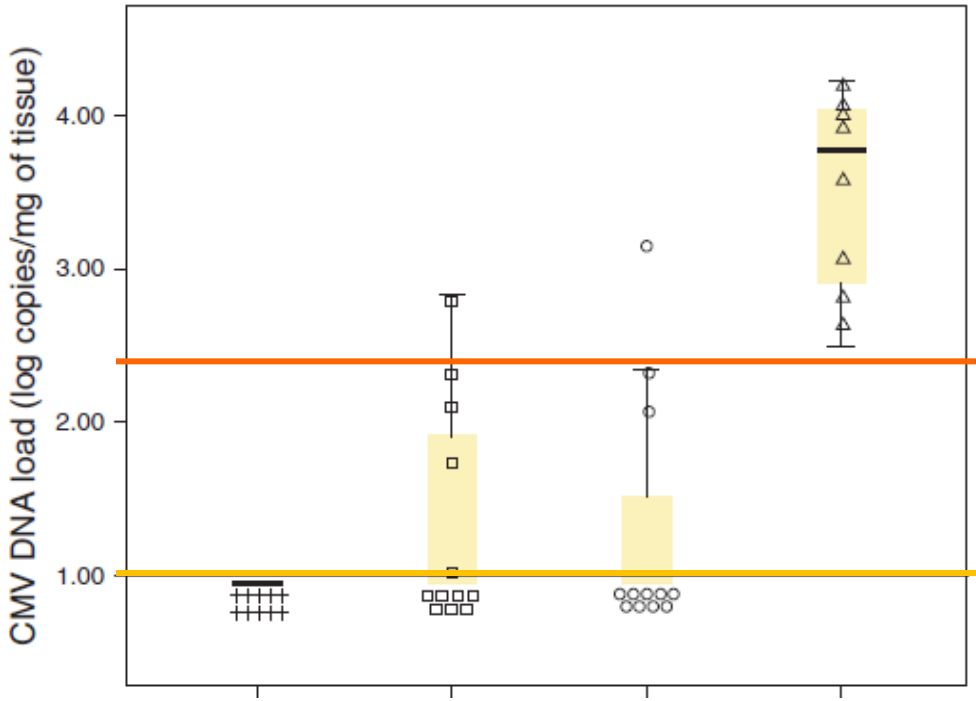
CMV et Immunosupression: l'expérience des MICI

- Diagnostic
  - D'une infection systémique active : charge virale par PCR (copies ADN)
  - De la présence de CMV dans l'intestin malade
    - Inclusions en HE ± immunohistochimie
    - PRC *in situ,* hybridation *in situ*

- Les infections significatives à CMV sont celles avec une charge virale tissulaire élevée et des inclusions dans les tissus malades (H&E et/ou IHC)

Rahier JFF, JCC 2014

La charge virale CMV est prédictive de la réponse aux immunomodulateurs



Corticoïdes	S	**R**	**R**	**R**
2ème ligne (anti-TNF ou cyclosporine)	S	**R**	**R**	**R**
3ème ligne (cyclosporine ou anti-TNF)		S	**R**	

Roblin X, AMJ 2014

Corticorésistance si CMV>10 copies/mg de tissu inflammatoire

Résistance à 3 lignes d'immunosuppresseurs si CMV>250 copies/mg de tissu inflammatoire

CMV et MICI : en pratique

• Determiner la charge virale (systémique et tissulaire) CMV pour les poussées sévères de MICI (en particulier colites aiguës graves de MICI)

- A l'admission
- A chaque changement de ligne thérapeutique
- **A chaque ré-aggravation inexpliquée au sein d'une ligne donnée, toutes choses égales par ailleurs**

• En cas de charge tissulaire élevée

- Ganciclovir IV puis oral
- Au moins jusqu'à ce que la charge virale devienne faible ou indétectable

Rahier JFF, JCC 2014

CMV et MICI

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Cytomegalovirus Is Frequently Reactivated and Disappears Without Antiviral Agents in Ulcerative Colitis Patients

Katsuyoshi Matsuoka, M.D., Ph.D.,[1] Yasushi Iwao, M.D., Ph.D.,[2] Takeshi Mori, M.D., Ph.D.,[3] Atsushi Sakuraba, M.D.,[1] Tomoharu Yajima, M.D., Ph.D.,[1] Tadakazu Hisamatsu, M.D., Ph.D.,[1] Susumu Okamoto, M.D., Ph.D.,[1] Yuichi Morohoshi, M.D.,[1] Motoko Izumiya, M.D.,[1] Hitoshi Ichikawa, M.D.,[1] Toshiro Sato, M.D., Ph.D.,[1] Nagamu Inoue, M.D., Ph.D.,[2] Haruhiko Ogata, M.D., Ph.D.,[1] and Toshifumi Hibi, M.D., Ph.D.[1]
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CLINICAL REVIEW

Cytomegalovirus in Inflammatory Bowel Disease: Pathogen or Innocent Bystander?

Garrett Lawlor, MD and Alan C. Moss, MD†*

(Inflamm Bowel Dis 2010;16:1620–1627)

	CMV + (n = 26)	CMV − (n = 26)	P
Sex (%): M/F	14 (54%)/12 (46%)	14 (54%)/12 (46%)	1
Age (years ± s.d.)	36.8 ± 12.3	38.6 ± 12.1	0.53
Duration of disease (years ± s.d.)	4.2 ± 5.1	7.6 ± 7.9	0.08
Ongoing immunosuppressants on induction			
Steroids (%)	15 (60%)	14 (56%)	1
Steroid dosage	30 ± 28	30 ± 32	0.85
Time on steroids (d)	32 ± 56	10 ± 17	0.22
Azathioprine (%)	10 (40%)	2 (8%)	0.02
Methotrexate (%)	1 (4%)	1 (4%)	1
Ciclosporin (%)	2 (8%)	0	0.49
Anti-TNFα (%)	5 (20%)	1 (4%)	0.19
Lichtiger index ± s.d.	9.5 ± 4.2	10.4 ± 3.2	0.61
Lichtiger ≥10 (%)	16 (61.5%)	17 (65.4%)	0.77
Endoscopic Mayo index	2.3 ± 0.7	2.1 ± 0.9	0.56

CMV, cytomegalovirus; PCR, polymerase chain reaction; M, male; F, female.

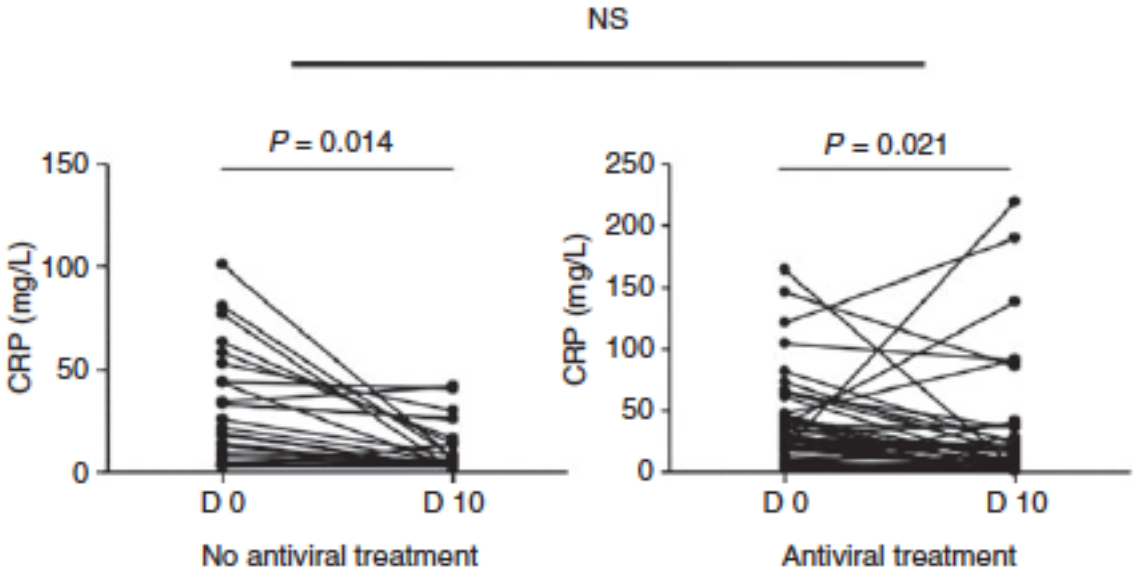
Categorical variables reported as absolute values and %. Continuous variables reported as mean ± standard derivation.

Delvincourt S et al, Amilent Pharmacol Ther 2014

	CMV + (n = 26)	CMV − (n = 26)	P
Sex (%): M/F	14 (54%)/12 (46%)	14 (54%)/12 (46%)	1
Age (years ± s.d.)	36.8 ± 12.3	38.6 ± 12.1	0.53
Duration of disease (years ± s.d.)	4.2 ± 5.1	7.6 ± 7.9	0.08
Ongoing immunosuppressants on induction			
Steroids (%)	15 (60%)	14 (56%)	1
Steroid dosage	30 ± 28	30 ± 32	0.85
Time on steroids (d)	32 ± 56	10 ± 17	0.22
Azathioprine (%)	10 (40%)	2 (8%)	0.02
Methotrexate (%)	1 (4%)	1 (4%)	1
Ciclosporin (%)	2 (8%)	0	0.49
Anti-TNFα (%)	5 (20%)	1 (4%)	0.19
Lichtiger index ± s.d.	9.5 ± 4.2	10.4 ± 3.2	0.61
Lichtiger ≥10 (%)	16 (61.5%)		
Endoscopic Mayo index	2.3 ± 0.7		

CMV, cytomegalovirus; PCR, polymerase chain reacti

Categorical variables reported as absolute values and as mean ± standard derivation.



Delvincourt S et al, Amilent Pharmacol Ther 2014

Complications infectieuses digestives liées aux traitements immunomodulateurs

- Est-ce que c'est fréquent ?
  - *OUI, CD et CMV*
- Est-ce que c'est grave ?
  - *Oui pour CD, CMV?*
- Faut-il arrêter les immunomodulateurs ?
  - *Dans les formes sévères*
- Faut-il traiter différemment ?
  - *Dans les formes sévères ou CV CMV élevée*