ECIL 2024

Clostridioides difficile infection in haematology patients

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10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

CONFERENCE
From September 19th to 21st, 2024

Mercure Sophia Antipolis
Nice, France

Clostridioides difficile

- An anaerobic gram-positive, spore-forming bacillus, with **non-toxigenic and toxigenic strains**
- *C. difficile* may either colonize the GI tract or cause *C. difficile* infection (CDI)
- Colonization
  - Rare in healthy adults (2-3%) , but much more frequent (up to 25%) in **hospitalized** patients, particularly **HCT recipients** (up to 39% a US study) (1,2);
  - Very frequent in **infants below the age** of 2 (testing is usually not recommended); and in HM HM/HCT children (30%) (3,4), with up to 70% acquiring transient or permanent colonisation during admission (5)

1) Sandlund J, Davies K, Wilcox MH. Ultrasensitive Clostridioides difficile Toxin Testing for Higher Diagnostic Accuracy. J Clin Microbiol. 2020 May 26;58(6):e01913-19. doi: 10.1128/JCM.01913-19; 2) Kinnebrew et al. PlosONE 2014; 3) Dominguez et al. 2014; 4) Al-Rahawi 2019, 5) Yang et al. 2024; 6) Warny M et al. Lancet. 2005 Sep 24-30;366(9491):1079-84. doi: 10.1016/S0140-6736(05)67420-X

Clostridioides difficile

- CDI is a toxin-mediated disease, and two exotoxins - the enterotoxin toxin A (TcdA) and the cytotoxin toxin B (TcdB) - cause diarrhoea and inflammation by cytopathic and cytotoxic effects
- CDI results in a disease with variable spectrum of severity: from mild diarrhoea to severe pseudomembranous colitis, ileus or toxic megacolon (with **acute neutrophil-predominant inflammatory response responsible for pseudomembrane formation**)
- Hypervirulent strains (NAP1/O27 and 078) producing binary toxin have been reported to cause outbreaks of severe colitis (6).
- Microbiota disruption is the major predisposing factor and is also thought to be responsible for high recurrence rate (up to 40%)

1) Sandlund J, Davies K, Wilcox MH. Ultrasensitive Clostridioides difficile Toxin Testing for Higher Diagnostic Accuracy. J Clin Microbiol. 2020 May 26;58(6):e01913-19. doi: 10.1128/JCM.01913-19; 2) Kinnebrew et al. PlosONE 2014; 3) Dominguez et al. 2014; 4) Al-Rahawi 2019, 5) Yang et al. 2024; 6) Warny M et al. Lancet. 2005 Sep 24-30;366(9491):1079-84. doi: 10.1016/S0140-6736(05)67420-X; Kamboj BBMT 2014

Diagnosis of CDI is not perfect

Undertreatment

- CDI can cause a severe, frequently recurrent, disease
- Current assays for direct toxin detection have **high rate of false negative results** (low sensitivity, toxin lability) – **sensitivity 42.6%-57.6%; 57% in the immunocompromised**
- More sensitive assays required
- Significant number of patients with NAAT+EIA- can have severe CDI and treatment of patients with NAAT+/toxin- result was associated with lower mortality

Overtreatment

- Risk of overdiagnosis of CDI when **NAAT** toxin detection assays are used **in the absence of true diarrhoea (e.g. laxative use, single episodes of unformed stools)** or in populations with a **high rate of diarrhoea due to other, frequently non-infectious, causes** and high rate of **colonisation** – both conditions particularly frequent in HM/HCT population
  - ➢ diagnostic and therapeutic stewardship interventions successfully implemented in HCT setting

Alonso CID 2022; Ford 2020; Ford et al. Transpl Cell Ther 2023; Pergam 2024; NixTransplant Cell Ther. 2021; Prosty CID 2024

Materials and methods

- **Literature review**
  - Epidemiology and outcome in HM (considering the diagnostic methods used, use of antimicrobial prophylaxis, treatment, etc.) **since 2010** (meta-analyses for previous periods, if available, to be mentioned)
  - Epidemiology and outcome in cellular therapy settings (considering the diagnostic methods used, use of antimicrobial prophylaxis, GI GvHD risk, etc.) since 2010 (meta-analyses for previous periods, if available, to be mentioned)
  - RCT on treatment and prevention in the general population and HM/HCT
  - Observational studies in HM/HCT or any other immunocompromised
  - Infection control - review of existing guidelines in the general population
- **Evaluations of particularities of CDI in HM/HCT**
  - In diagnosis – applicability of definitions, impact of defining CDI based on diagnostic methods use
  - In evaluation: definitions for severe and complicated CDI
  - In treatment: additional objectives of successful treatment in HM/HCT
    - Impact on GvHD
    - Treatment in case of prolonged / repeated antibiotic therapies
  - In prevention
  - In children
- **Survey** on the current practices and impact of *C. difficile* in hematology sent to current and past ECIL participants

ECIL-10:Definitions for adults and children

Clinical picture compatibile with CDI	Presence of diarrhea (≥ 3 unformed stools/24 hours), in the absence of the use of laxatives In patients with pre-existing diarrhoea – significant worsening of diarrhoea (particularly if with additional negative impact on daily activities) OR Ileus or megacolon Additional signs and symptoms suggestive of severe CDI: pseudomembranes, colonic thickening in the absence of other causes of colitis Exclusion of other potential causes should be pursuit following local protocols
Colonisation	Absence of symptoms/signs but laboratory detection of toxigenic *C. difficile*
Clinical response (final evaluation 48 h after end of treatment)	Resolution of symptoms OR Sustained improvement (<3 unformed stools/day) for at least 48 hours during therapy OR Significant reduction in unformed stools/day in case of pre-existing diarrhea OR Attainment of bowel movements of Bristol Stool Form Scale types 1–4

ECIL-10: Definitions for adults and children

Recurrence	Clinical • New onset of symptoms (as per initial episode) after clinical response • Following completion of therapy With laboratory confirmation • Positive laboratory test as per initial episode Timeframe: In the literature multiple time frames have been utilised, either with diagnosis of CDI or end of treatment as starting point. For CDI treatment trials: 30 days or 8 weeks from the end of treatment For clinical studies/practice: 12 weeks from diagnosis of CDI

ECIL-10

Recomendations on diagnosis of CDI

	Grading
Test for CDI only in case of compatible signs and symptoms	A II u
Screening for asymptomatic colonization is not recommended	D II u
For stool testing use diagnostic algorithms that include both toxin detection (more specific) and more sensitive tests for detection of toxigenic CD (NAAT or GDH+ plus NAAT if toxin negative), in accordance with ESCMID recommendations Rectal swabs can be tested with NAAT in case of ileus	A II t u
In case of partial or absent clinical response to CDI treatment, additional testing for other pathogens should be performed and non-infectious causes of diarrhea should be considered	A II t
No repeated testing is necessary in case of a negative result obtained during the previous 7 days of the same diarrhea episode	B II t
Testing for proof of cure is not recommended	D II t

ECIL-10
C. difficile: Diagnosis in HM/HCT children

- Testing for *C. difficile* should be performed in immunocompromised children aged 2 or older who are symptomatic and fulfill the criteria for diarrhea
- In the population aged <2 years, high rate of colonization should be taken into account, and testing only in case of high clinical suspicion is recommended
- Algorithm for testing in children remains the same as per adult recommendation
- Laboratory diagnostics for CDI should be combined with diagnostics for other gastrointestinal pathogens relevant in the immunocompromised pediatric host
- Clinical correlation should guide the interpretation of laboratory results and the decision to treat

Definitions of CDI, based on diagnostic probability

For clinical studies and not individual treatment decisions

Level of certainty	Clinical	Laboratory	Other causes of diarrhea
Proven	Presence of diarrhea (≥ 3 episodes of unformed stools /24 hours) or ileus/megacolon	Direct detection of toxin of *C. difficile*	Non-infectious causes considered to be unlikely on clinical assessment * No other infectious causes Formal microbiological exclusion of co-infections is recommended for clinical trials
	Histopathological confirmation of pseudomembranes	Detection of toxigenic *C. difficile*	
Probable	Presence of diarrhea (≥ 3 unformed stools/24 hours) or ileus/megacolon	Direct detection of toxin of *C. difficile*	Other non-infectious or infectious causes possible
		Detection of toxigenic *C. difficile*	No other non-infectious and other infectious causes
Possible	Presence of diarrhea (≥ 3 unformed stools/24 hours) or ileus/megacolon	Detection of toxigenic *C. difficile*	Other non-infectious or infectious causes possible

*Consideration of non-infectious causes: GvHD, mucositis, chemotherapy

Defining severe CDI in HM/HSCT

- Various scores of severity exist in the general population
- Classical signs of severity are not validated in alloHCT and HM patients:
  - Leucocyte count can be highly variable due to underlying disease and HM treatment, including aplasia and not interpretable for severity assessment
  - Clinical signs and symptoms
    - can be less evident due to neutropenia - probable role of immunosuppression on the low rate of inflammation-mediated complications
    - but also have other causes frequent in this setting (chemotherapy)
  - In observational studies, low rate of classic severity markers:
    - leukocytosis, hypoalbuminemia, acute renal failure and complications*:* surgery/colectomy, ileus, hypotension, septic shock, perforation

Abdominal pain, requiring pain medications, could be often present in severe CDI, but it is not specific enough to be considered a severity criterion “per se”

AIM: early identification of patients at higher risk of complications, rCDI and death to provide appropriate management

1. Scappaticci JAC 2017, 2. Robin MMI 2017, 3. Jain BBMT 2016, 4. Piekarska BMT 2022, 5. Lavallée Transpl Inf Dis 2017, 6. Wang Infect Contr Hosp Epidemiol 2013, 7. Toon Support Care Cancer 2014, 8. Yoon Supp Care 2014, 9. Dubberke Transpl Inf Dis 2018, 10. Dubberke Transpl Dir 2017, 11. Alonso CID 2012, 12 Bruminhent BBMT 2014, 13 Kinnebrew PlosOne 2014, 14 Kamboj BBMT 2014, 15 Bouza J Crit Care 2015, 16 Luo Front Cell Inf Microbiol 2022, 17 Blumberg TID 2021, 18 Scardina Pharmacotherapy 2017, 19 Akahoshi Clin Transpl 2016, 20 Lavallée IRD 2016

Severity of CDI in allogeneic HCT and HM patients

- Hematological malignancy should NOT be considered as a severity criterion (Bloomfiels J Hosp Inf Dis 2012) or a risk factor of complicated CDI (Chakra CID 2015)
- Neutropenia should NOT be considered automatically as a criterion for severity since most of cases suspected to be colonization occur during neutropenia (Ford 2020, 2023, Pergam 2024)
- Only one study reported specific severity criteria for allogeneic HCT patients which had an impact on mortality (Dubberke Inf Control Hosp Epidemiol 2007)
  - Definition of severity of CDI:
    - Mild CDI: grade 1 diarrhea (≤500 mL) and/or colitis.
    - Moderate CDI: grade 2 diarrhea (501 to 1000 mL) and/or colitis.
    - Severe CDI: grade 3 or higher diarrhea (≥1001 mL) and/or colitis
  - Median survival time after CDI: 266 days (mild or moderate CDI) and 55 days (severe CDI) p=0,003

→**Clinical criteria, especially diarrhea volume, are more appropriate to define severity in HCT patients**

An overlap between severe CDI and GI GVHD, that both had diarrhea volume as severity grading, could occur in clinical practice, but this does not change the management of both diseases

ECIL definition for severe or complicated CDI

Severe CDI : ≥1 of the following criteria	Severe-complicated CDI: ≥1 of the following criteria
Diarrhea >1000 mL or ≥6 stools /24h*	Hypotension or septic shock
Rise in creatinine >50% baseline**	ICU admission for CDI
Leukocyte count > 15 G/L***	Including **fulminant** CDI: ileus, megacolon, performation, abdominal surgery for CDI
Colitis including distension of large intestine, pericolonic fat stranding, colonic wall thickening, pneumatosis intestinalis	
Pseudomembranous colitis	

*Not applicable if pre-existing diarrhea; **Without another cause of renal failure; ***Except in cases leucocyte count is not interpretable (neutropenia, ongoing or recent chemotherapy, GVHD, recent cellular therapy, hyperleukocytosis for other reason…);

Ideal definition for severe CDI in pediatric cancer/HCT patients does not exist
For severe-complicated, the same criteria as for adults apply

Final slide set
Post meeting

Treatment of CDI

TREATMENT (1) Primary episode, non-severe and severe

Intervention	Grading	Comment
Discontinue unnecessary antibiotics	**Good clinical practice**	
Fidaxomicin 200mg BD	**A II t u r**	Fidaxomicin and vancomycin were associated with similar rates of cure at the end of treatment Fidaxomicin was associated with lower rate of recurrence and less impact on microbiome and VRE selection Thus, fidaxomicin should be preferred in patients at high risk of rCDI or microbiota disruption-related complications, e.g. severe CDI, concomitant antibiotic treatment, allo-HCT
Vancomycin 125mg QID, oral solution or tablets	**A II t u r**	
Metronidazole monotherapy, IV or oral	**D II t**	Not recommended as first line due to lower rates of cure at end of treatment and higher rates of recurrence
If no oral intake, NGT administration of first line agents, with or without IV metronidazole	**B II t**	
Consider adding bezlotoxumab* in patients with the highest risk for rCDI	**B II t**	Evidence of benefit mainly if CDI therapy with vancomycin or metronidazole *Expected to be shortly out of commercial production
<u>Duration</u>		
Standard duration of treatment with fidaxomicin or vancomycin is recommended - 10 days	**A II t**	
Extended pulse dosing of fidaxomicin	**B II t**	Utilize the same total number of tablets over 25 days vs 10 days to reduce the rate of recurrence (200 mg BID for 5 days, then 200 mg QOD), particularly useful e.g. in patients on concomitant antibiotics

ECIL Pediatric Recommendations for Antimicrobial Agents and Interventions

Considerations for recommendations on antimicrobial agents and interventions in children:

- **Efficacy in phase II and III trials in adults, corresponding to adult ECIL recommendation *(since underlying conditions are similar)***
- **Availability / assessment of pediatric data**
  - quality PK data
  - safety data
  - supportive efficacy data
- **regulatory approval also being considered and incorporated (Y/N)**

European Medicines Agency. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99). http://www.tga.gov.au/docs/pdf/euguide/ich/271199en.pdf; 2001. Accessed April 22, 2019
Groll et al. Lancet Oncol. 2021

ECIL-10

C. difficile: Treatment in Children with cancer or HCT

- All agents approved in adults are also approved in children
- All agents (metronidazole, vancomycin, fidaxomicin) are approved for first-line; bezlotoxumab in children ≥ 1 year ‘at high risk for recurrence’.
- FMT not routinely recommended

  ➢ Taken together, there is no rationale for different recommendations for pediatric patients relative to adults

- Metronidazole iv monotherapy might be reasonable for non-severe CDI in selected patients in case of inability of oral intake and no NGT in place, taking into account its lower efficacy compared to oral fidaxomicin or vancomycin

TREATMENT (2)
Severe complicated/fulminant CDI

Intervention	Grading	Comment
Vancomycin, oral or via gastroenteric administration plus either -metronidazole IV 500mg TID or -tigecycline IV standard dose	A II t A II u C II t r	Most observational data with metronidazole plus vancomycin Limited published data on tigecycline, mainly in-vitro, observational studies used in complicated infection, mainly in combination
In case of ileus/megacolon Add endorectal vancomycin 500mg every 6 hours	A II t	
Multidisciplinary consultation with a surgeon, also to consider eventual loop ileostomy (LI) aimed to avoid colectomy, and an ID specialist	B II t r	Mortality similar to colectomy, but colon preservation with LI, no specific data in immunocompromised (steroid use reported in 20% of one large study)

PREVENTION OF RECURRENCE
Current strategies

- Risk factors for rCDI:
  - severe CDI,
  - concomitant antibiotics during CDI episode or follow-up [post-hoc analysis of two RCTs in general population],
  - toxin-positive cases (vs NAAT-positive)
- **Therapeutic strategies** aimed at reducing the risk of recurrence
  - Use of treatment regimen for primary episode associated with lower recurrence rates
  - Extending and tapering of the primary treatment regimen
    - Tapering of vancomycin after standard therapy course (taper usually over 4 weeks)
    - Pulsed dosing of treatment with fidaxomicin
  - Prolonging the treatment duration (e.g. in the setting of concomitant antibiotics or neutropenia, frequent in HCT studies)
  - Adjunctive therapies during or after treatment
    - Bezlotoxumab
    - FMT or live microbiota products
- **Secondary prophylaxis** during at risk period

TREATMENT (3)
Recurrent CDI episode (second or greater)

Intervention	Grading	Comment
Fidaxomicin 200 mg BID	A II t	Particularly if not used during the previous episode(s) Standard 10 days course or the extended pulse dosing can be used
Vancomycin 125 mg QID standard duration, then taper-and-pulse regimen over 4 weeks	A II t r	Taper and pulse regimen: 125 mg TID for 1 week, then 125 mg BID for 1 week, then 125 mg OD for 1 week, then 125 mg QOD for 1 week No data on treatment of r-CDI in HM/HCT
Vancomycin standard regimen	B II t	
Metronidazole monotherapy IV or oral	D II t	
Add bezlotoxumab*	A II t	Evidence of benefit in addition to standard of care antibiotics, mainly if CDI therapy with vancomycin or metronidazole *Expected to be shortly out of commercial production

TREATMENT (4)
Recurrent CDI episode (second or greater)
In case of concomitant antibiotic therapy which cannot be discontinued during treatment of the CDI episode

Intervention	Grading	Comment
If fidaxomicin is used, prefer extended pulse dosing	B II t	
If vancomycin is used, in selected patients at high-risk of r-CDI, instead of prolonging full-dose therapy regimen, use alternative strategies, as taper-and-pulse regimen or low-dose maintenance therapy (125 mg BID)	B II t u	Indirect evidence suggest that continuation of CDI treatment until completion of concurrent antibiotics could be associated with lower rates of recurrence

Secondary prophylaxis - antibiotics

Summary

- 9 retrospective cohort studies used vancomycin PO (variable doses/frequency, mostly 125 mg 1-2/day), 2 in HCT recipients: 4 (1 in HCT recipients) with reduced CDI incidence in prophylaxis vs controls. Data with large variability, benefit consistent in 4 well-executed studies

- 3 additional (2 prospective randomized and 1 retrospective) studies assessed : rifaximin (2) and fidaxomicin (1): trend for CDI incidence reduction in prophylaxis vs controls (no hematology patients included in any of those)

RECOMMENDATIONS	Grading
Routine secondary CDI prophylaxis is not recommended in hematology patients	D II
In select patients at high risk for r-CDI, such as prior severe CDI and concomitant treatment with broad spectrum antibiotics during follow-up or previous r-CDI, secondary prophylaxis with PO vancomycin 125 mg BID could be considered until discontinuation of antibiotic treatment	C II u

FMT

- No RCTs or comparative observational study (FMT vs placebo or SOC) in immunocompromised patients
- Some of the published studies and trials included immunocompromised patients, but unable to obtain separate outcomes data for the immunocompromised subgroups

FMT in patients with CDI, data in HM/HCT	
Reviewed studies (full text analyzed)	58
Patients with hematologic malignancy	69
Neutropenic patients	9

EBMT survey on FMT
Use of FMT was considered safe in allo-HCT patients with recurrent CDI by 106/137 responders (77.4%);
Its use was declared by only 36 (38.3%) adult and 4 (13.3%) paediatric centres

Gastroenterology 2024;166:409–434

Bone Marrow Transplantation (2023) 58:1419–1421

Final slide set
Post meeting

ECIL-10 Recommendations on FMT and LBP

- **FMT is effective and safe in moderately immunocompromised adults** with recurrent *C. difficile* infection
- The potential role of the new live biotherapeutic products (LBP) in hematological population needs to be determined (excluded from RCT, including those of products commercially available in the US)
- Efficacy of FMT/LBP might be compromised in case of concomitant antibiotic treatment
- For FMT, repeated administration might be required
- FMT has been used in HCT for treatment or prevention of GVHD in > 100 patients, with reports of severe BSIs

RECOMMENDATIONS	**Grading**
There are no data to routinely recommend FMT in hematological patients for the treatment of rCDI	
FMT can be considered for multiple recurrent CDI in non profoundly neutropenic patients following multidisciplinary consult with FMT specialists	**B II t**
More data are required in profoundly neutropenic patients, patients with GvHD or with fulminant CDI	

Primary prophylaxis - 1

Summary

- 4 studies (3 cohort and 1 prospective randomized) used vancomycin PO (125 mg 1-2/day), 1 including allogeneic HCT recipients with reduced incidence of CDI in prophylaxis vs controls
- 3 prospective RCTs assessed metronidazole, ribaxamase, and fidaxomicin (only latter in HCT recipients): potential benefit in prophylaxis vs controls
- 5 Phase 2 or 3 RCTs on vaccines were performed in healthy adults

RECOMMENDATIONS	**Grading**
Routine primary CDI prophylaxis is not recommended in hematology patients	D II
In very select high-risk settings, e.g. such as centers with high prevalence during an outbreak, primary prophylactic interventions with fidaxomicin 200 mg or vancomycin 125mg QD or BID could be effective, combined with strict infection control measures. Fidaxomycin could be preferred due to its minor impact on microbiota compared to vancomycin.	C II u
Probiotics should not be used as primary prophylaxis For safety reasons during neutropenia, and due to the lack of demonstrated benefit in non-neutropenic/general population	D II t
There is not enough evidence to recommend vaccination for primary CDI prophylaxis	

C. difficile: Infection control
ECIL-10 Good practice statements

- Ensure the implementation of general prerequisites for management of patients with CDI
  - Working infection control team
    - Infection surveillance
    - Implementation of measures
    - Education
  - Working antimicrobial stewardship team
  - Sufficient number of patient rooms for contact isolation
- Apply general infection control practices in patients with CDI (contact precautions, appropriate cleaning)

Follow international ESCMID, IDSA/SHEHA, ISID guidelines * and national jurisdictional infection control policies

Tschudin-Sutter et al. Clin Microbiol 2018; McDonald et al. Clin Infect Dis 2018; Doll et al. Int J Infect Dis 2021