Antimicrobial and Diagnostic stewardship nell'immunodepresso

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DISCLOSURES

Lecture or board meeting or grants to my institution from

- Allovir
- bioMerieux
- Gilead
- Janssen
- Moderna
- Mundipharma
- Pfizer

None related to this presentation

Antimicrobial and diagnostic stewardship in immunocompromised patients

Bacterial infections

1. Early diagnosis (also of the absence of bacterial infection)
2. Active treatment since the onset of infection
    1. local epidemiology
    2. individual risk factors (colonization, previous infection)
3. Discontinuation of unnecessary, particular combination, therapy
4. Monitoring of CDI
5. Correct management of CDI
6. Antibiotic prophylaxis only in the highest risk patients (> 14 days of chemotherapy-induced neutropenia), mainly in low resistance setting or absence of colonization with FQ-R bacteria
7. Adequate (?) length of treatment

Studies evaluating long vs short course therapy
Few data in immunocompromised, not neutropenic

Author, Year	Clinical syndrome and population	Comparison arms	Included immunocompromised patients?
Chastre et al, 2003 [1]	VAP	8 vs 15 days	Excluded
Capellier et al, 2012 [2]	VAP	8 vs 15 days	Excluded
Montravers et al, 2018 [3]	IAI with source control among ICU patients	8 vs 15 days	Did not report whether immunocompromised patients were included
Von Dach et al, 2020 [4]	Uncomplicated GNB	7 vs 14 days vs CRP-guided	Did not report whether immunocompromised patients were included
Hepburn et al, 2004 [5]	Uncomplicated cellulitis	5 vs 10 days	Did not report whether immunocompromised patients were included
Yahav et al, 2019 [6]	Uncomplicated GNB	7 vs 14 days	Yes; see text
Molina et al, 2022 [7]	Enterobacterales BSI	7 vs 14 days	Yes; outcomes not reported specifically in this subset
Sawyer et al, 2015 [8]	IAI with source control	4 days vs clinically guided cessation[a]	Yes; outcomes not reported specifically in this subset
Cranendonk et al, 2020 [9]	Severe cellulitis	6 vs 12 days	Yes; outcomes not reported specifically in this subset
Singh et al, 2000 [10]	Pulmonary infiltrates among ICU patients	3 days[b] vs clinician discretion	Yes; outcomes not reported specifically in this subset
Talan et al, 2000 [11]	Uncomplicated pyelonephritis in women	7 days of ciprofloxacin vs 14 days of TMP/SMX	Excluded
Dinh et al, 2017 [12]	Uncomplicated pyelonephritis in women	5 vs 10 days	Excluded
Peterson et al, 2008 [13]	Complicated UTI and pyelonephritis	5 days of levofloxacin vs 10 days of ciprofloxacin	Did not report whether immunocompromised patients were included
Sandberg et al, 2012 [14]	Pyelonephritis in women	7 vs 14 days	Did not report whether immunocompromised patients were included

VAP, Ventilator associated pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; GNB, Gram negative bacteremia; BSI, bloodstream infection; UTI, urinary tract infection

[a]Clinically guided cessation: antibiotics given until 2 days after resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy

[b]In the interventional group, antibiotics were stopped among patients with clinical pulmonary infection score (CPIS) ≤6 at day 3

Antimicrobial stewardship in haematology Plan for success

1. Analyze the **epidemiology of different infections** in your center
2. If feasible, also clinical presentation patters: clinical signs and symptoms might be very limited in immunocompromised
3. Analyze the **availability of diagnostic methods, implement/modify diagnostic protocols if necessary**
4. Analyze the **prescription patterns** in your center

Febrile neutropenia – protocol for HSCT unit

- Protocols for management since 2009
- 2009
  - 25 yo female undergoing second HCT for AML
  - Previous BSI and colonisation with CR *K. pneumoniae*
  - chart annotation for neutropenia: in case of fever during neutropenia, start colistin 9.000.000 IU > 4.500.000 BID + amikacin 20mg/kg daily

Changes since 2009:

vanco > dapto;

hypotension mer + amika, even without vanco/dapto

Tampone vaginale: *K. pneumoniae*			Emocolture: *K. pneumoniae*	
Amikacina	>64	R	>64	R
Ciprofloxacina	>4	R	>4	R
Amox/clav	>32	R	>32	R
Tobramicina	>16	R	>16	R
Aztreonam	>64	R	>64	R
Cefotaxime	>64	R	>64	R
Ceftazidime	>64	R	>64	R
Gentamicina	4	S	>16	R
Imipenem	>16	R	>16	R
Meropenem	>16	R	>16	R
Piperacillina	>128	R	>128	R
Pip/taz	>128	R	>128	R
Colistina	<0.5	S	>16	R

Individualisation of approach to empirical antibiotic treatment during febrile neutropenia

Strategy	Escalation	De-escalation
Definition	Empirical treatment active against susceptible Enterobacteriaceae and *P. aeruginosa*	Starting upfront an empirical coverage of **MDR** bacteria, particularly Gram-, which is later **(72-96h) reduced (= de-escalated)** if a MDR pathogen is **NOT** isolated • Susceptible strain isolated • No microbiological results
Who?	All patients without risk factors for MDR (G-) infection	Patients at risk for infections due to **resistant bacteria (colonisation, previous infection, local epidemiology) or** presenting in **severe clinical conditions**
Antibiotics usually used	• Anti-pseudomonal cephalosporin (cefepime, ceftazidime) • Piperacillin/tazobactam	• Carbapenem • **Combinations**, e.g. with aminoglicosides or colistin • New BL/BLI
Main advantages	Less selection of resistant strains (carbapenem sparing) Less toxicity	Appropriate therapy for MDR before culture results are available > **hopefully lower mortality**
Main limitations	In case of infection due to a resistant Gram-, prognosis is significantly worsened	**Overuse of broad-spectrum antibiotics/combinations > high antibiotic pressure, particularly in case of failure to de-escalate**

ECIL: Averbuch D. et al. Haematologica 2014

Febrile neutropenia – protocol for HSCT unit

1st line

Piperacillin/tazobactam (4.5g LD then 18g/die); add:

- daptomycin 10-12 mg/kg/day if CVC or skin infection, positive blood culture for Gram+ cocci or vancomycin (1g loading dose followed by 2g/24 hours) in case of suspected pneumonia; both to be suspended **after 72 hours** in the absence of evidence of resistant Gram-positive infections

Individualize the empirical therapy scheme in patients with colonization or previous infection with MDR pathogens, according to the antibiogram

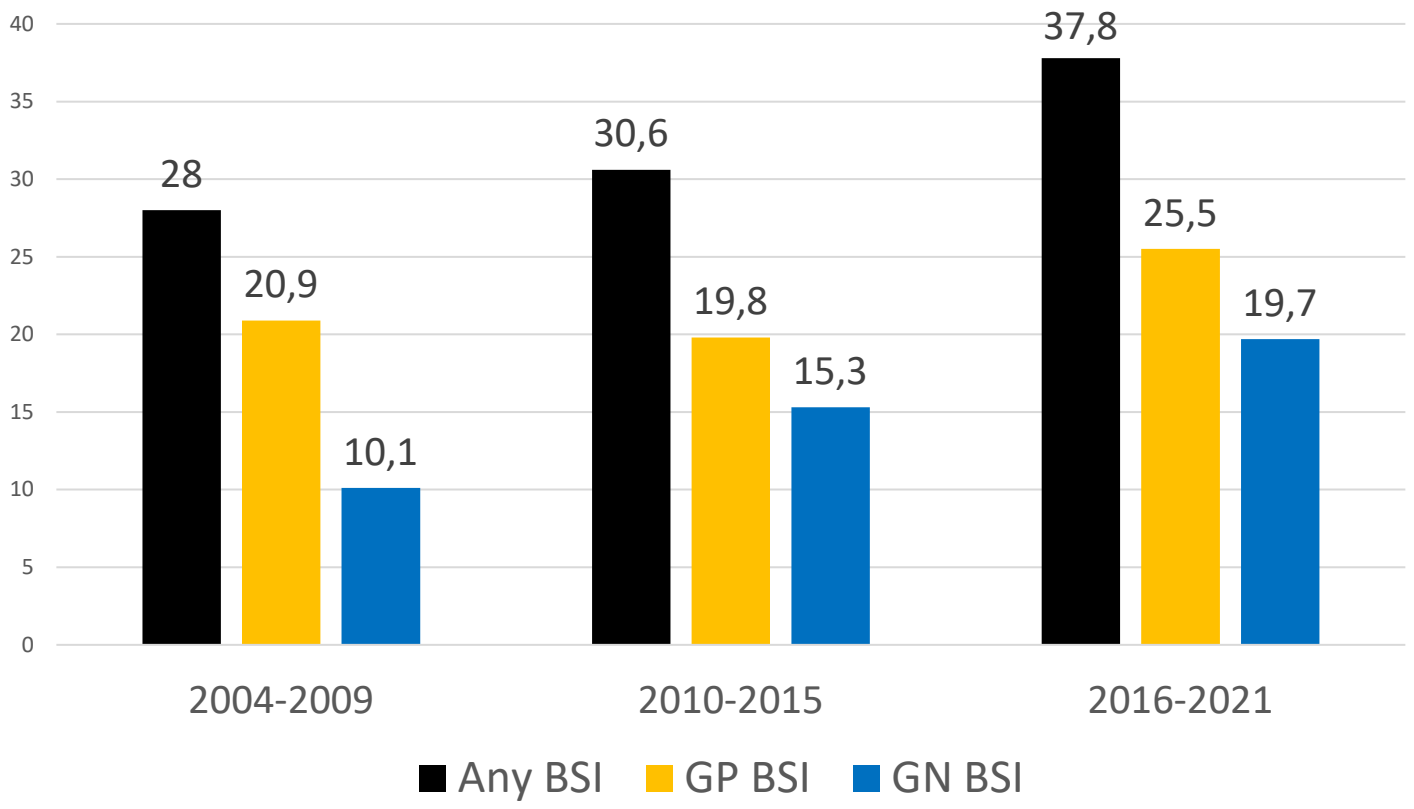
- Duration: to be suspended after 72-96h if patient is afebrile for at least 24h and no microbiologically or clinically documented infection

2nd line

Severe clinical presentation, e.g. hemodynamic instability, presence of an important infectious focus such as pneumonia, ileotyphlitis, important comorbidities, etc.

- Meropenem (1g q8h over 4 hours)
- Amikacin 15-20mg/kg/day, to be suspended in case of absence of MDR pathogens, if IRA, perform blood levels before subsequent doses
- Daptomycin 10-12mg/kg/day, to be suspended after 72 hours in the absence of evidence of resistant Gram-positive infection or signs/symptoms of an infectious focus, replace with vancomycin in case of suspected pneumonia
- **Individualize the empirical therapy scheme in patients with MDR colonization or previous infection**
- **Modify the therapy (de-escalate) based on the susceptibility and clinical response to reduce the duration of antibiotic**

Audit and feedback
Pre-engraftment BSI in 1364 recipients of 1st allo-HCT in years 2004-2021

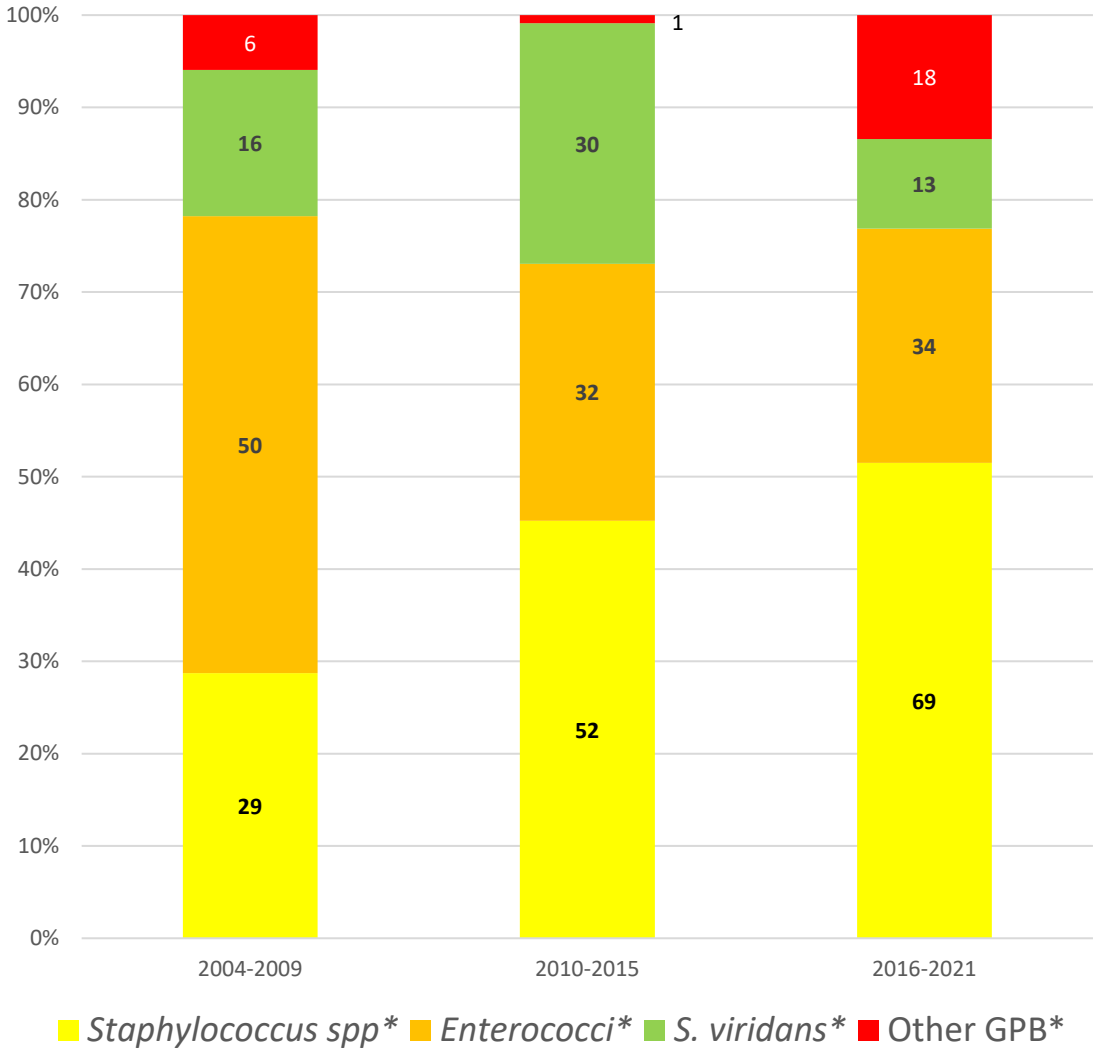


Median time to 1° BSI: +8 (-7;+28)

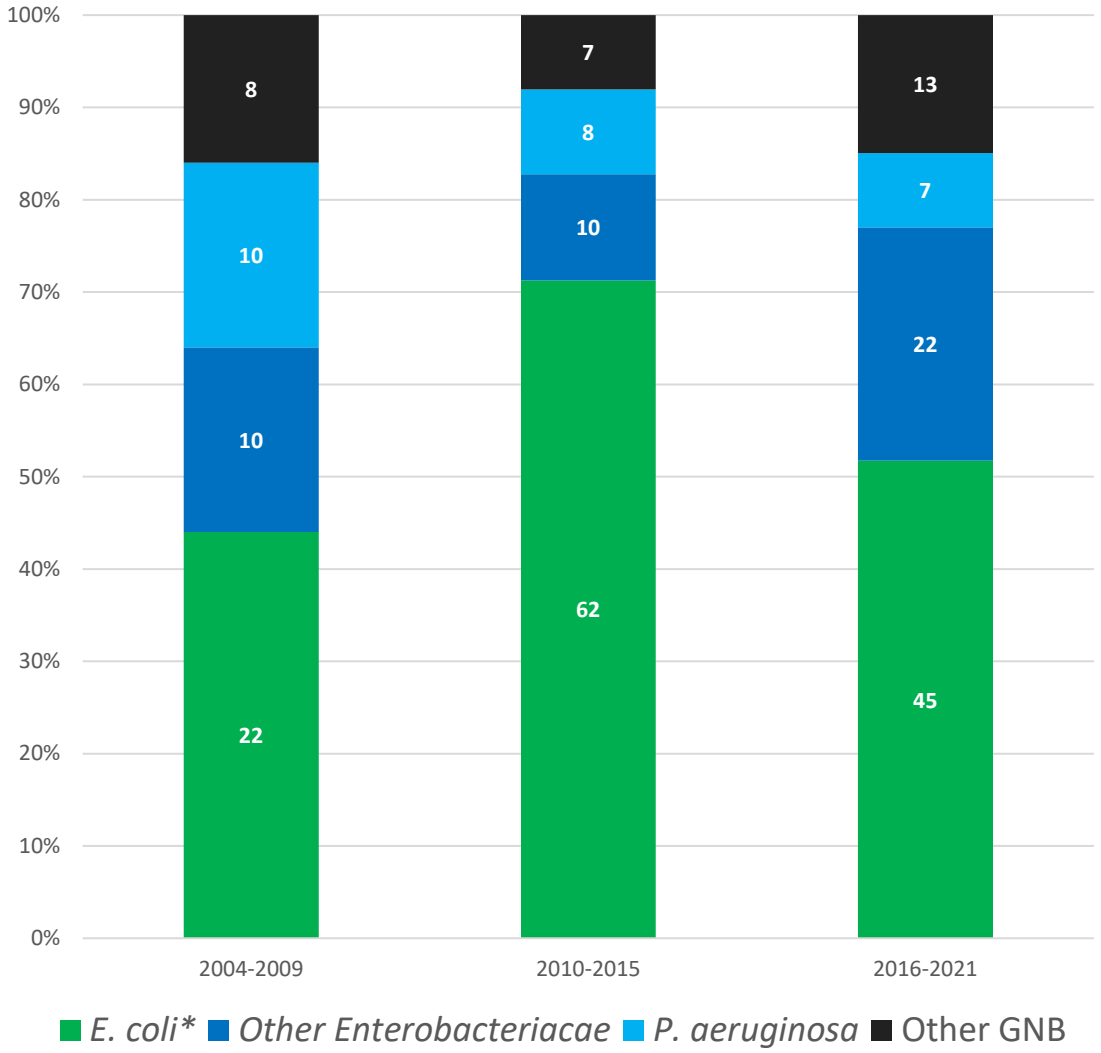
Median time to the first fever, day +1

Rate of patients who have developed any BSI, at least one BSI caused by gram-positive (GP) or gram-negative (GN) bacteria during the three periods of time. GP BSI remained stable over the years (p = 0.112) while the rate of any BSI and GN BSI increased significantly (p = 0.008 and p = 0.001).

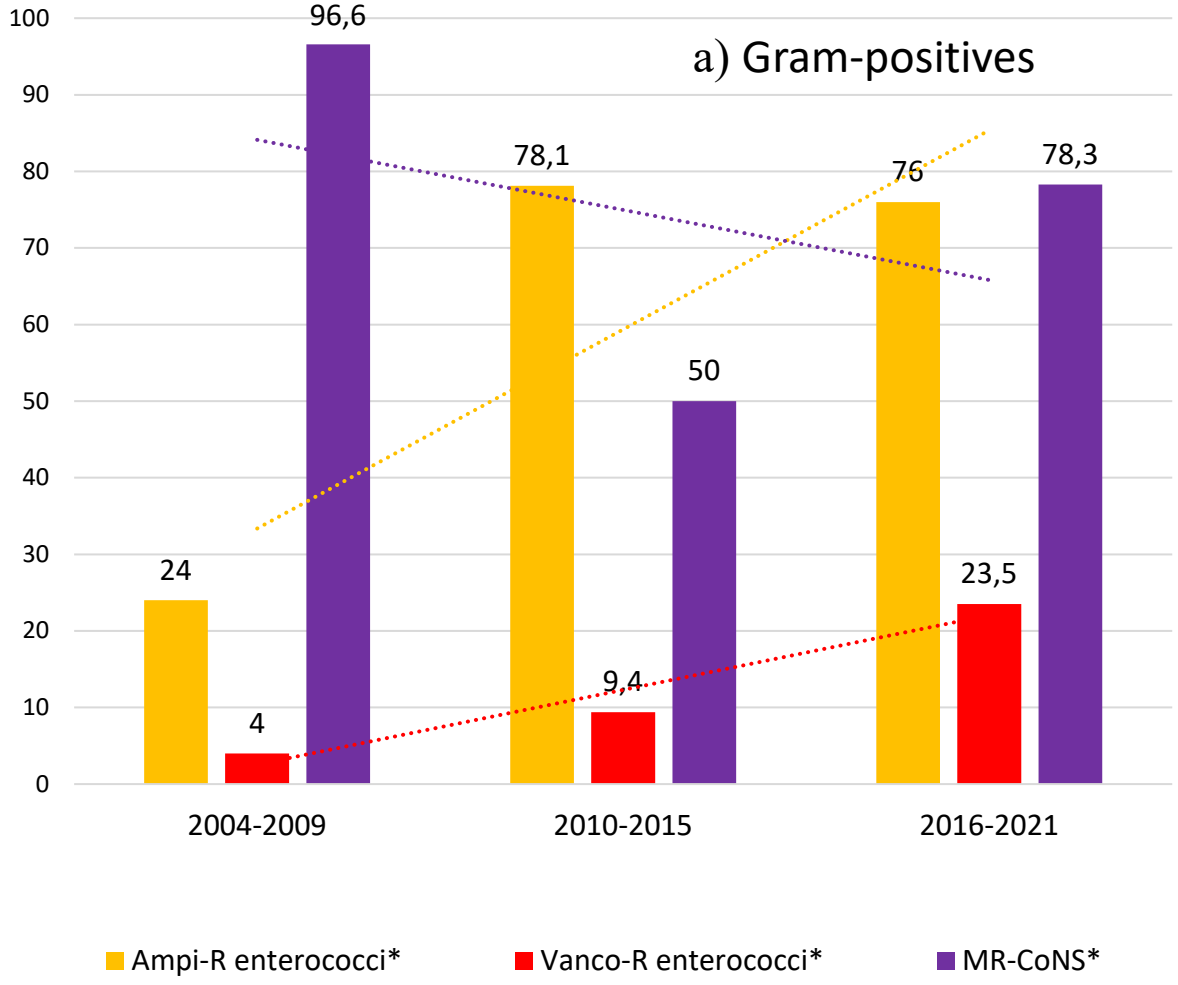
a) Gram positives

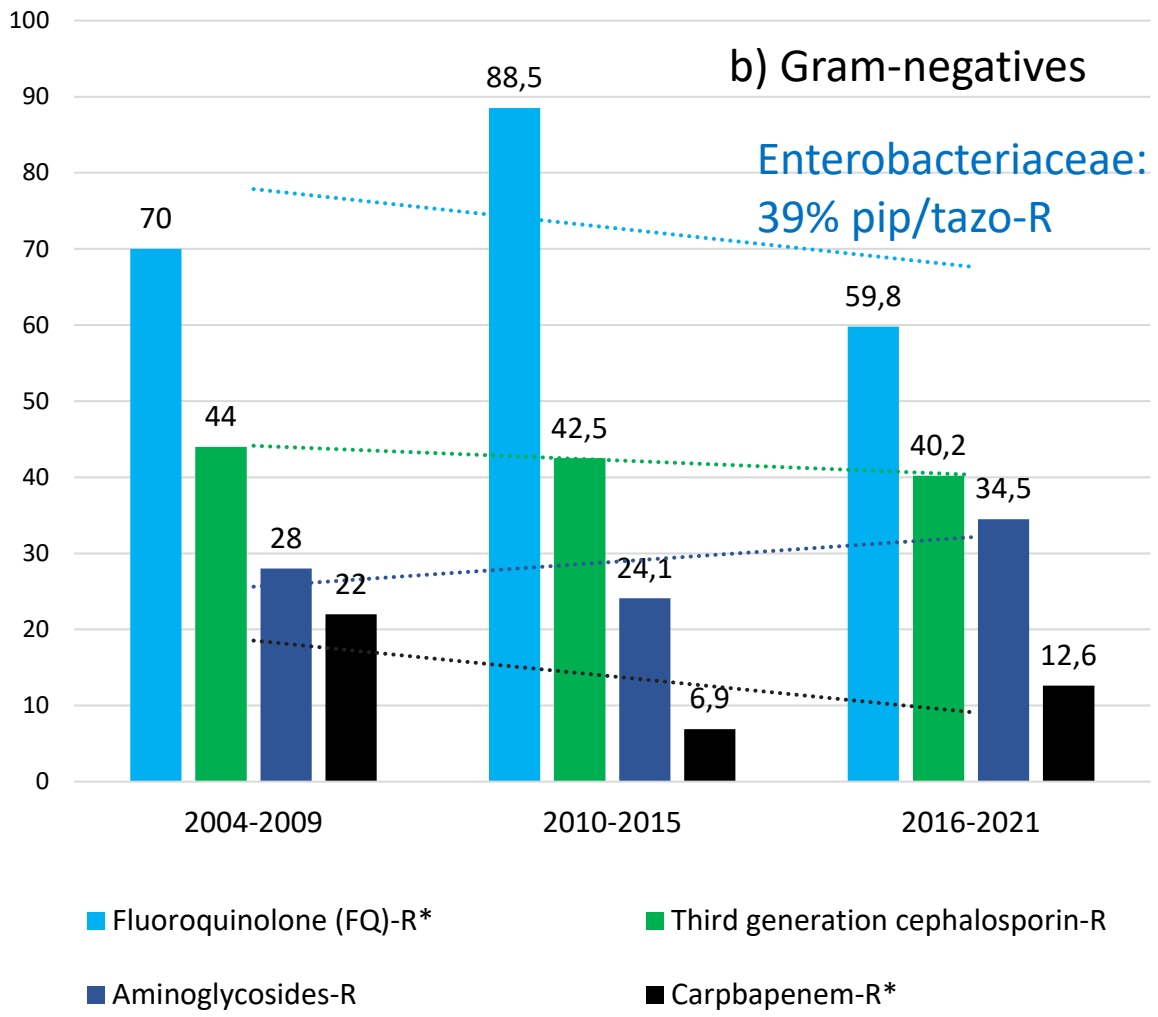


b) Gram negatives



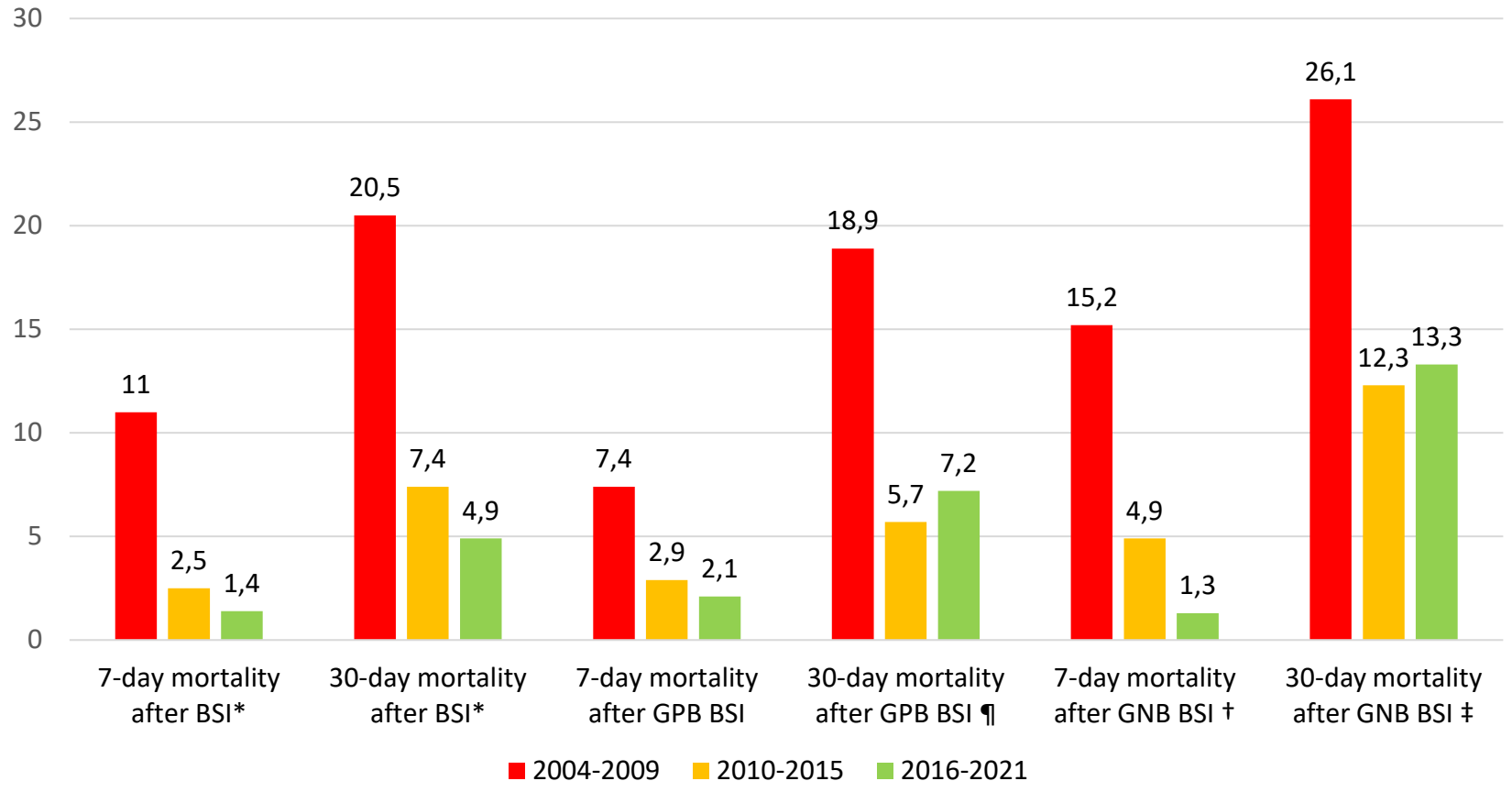
Rates of resistance during 3 study periods





2a - rates of resistance to oxacillin, ampicillin, vancomycin among GPB in three periods, with respective lines for trends. Resistance to oxacillin among staphylococci decreased along the study periods (p = 0.001). Both ampicillin and vancomycin-resistance among enterococci increased during the three periods (p = 0.001 and p = 0.051, respectively); 2b - rates of resistance to fluoroquinolones (FQ), 3rd generation cephalosporins (3CG), aminoglycosides (AG) and carbapenems among gram-negative isolates in three periods, with respective lines for trends. FQ resistance and carbapenem resistance decreased during the three study periods (p = 0.001 and p = 0.036 respectively), 3CG resistance and AG resistance remained stable (p = 0.903 and p = 0.318 respectively); *Changes which are statistically significant are marker with an asterisk.

Overall mortality 7- and 30-days after the first BSI, after the first gram-positive (GP) BSI and after the first gram-negative (GN) BSI divided into 3 periods



*p < 0.001; ¶ p = 0.004; † p = 0.006; ‡ p = 0.049

Rapid molecular diagnostics

BSI

- 13 samples for FilmArray in 7 patients
  - 5 *P. aeruginosa*, no enzymes present, MDR in 2
  - 2 for yeasts, not present in the panel > *Saprochetae clavata* > L-AmB
  - 2 *S. maltophilia* (1 patient)
  - 2 *K. pneumoniae* (1 patient), no enzymes (MIC meropenem 2)
  - 2 Gram positives

Respiratory samples

- 14 samples
  - Mainly viruses
  - Missed *A. flavus*
  - P. aeruginosa with VIM, not confirmed in culture

CDI in HSCT

Both an object and an outcome of antimicrobial stewardship

CDI in HSCT

- elevated risk of CDI compared with other hospitalized populations
  - Prolonged hospital admission
  - Exposure to antibiotics
  - Microbiota damage
- Considered in most guidelines as high risk patients > fidaxomicin treatment

- High rate of diarrhoea, also due to non-infectious causes
- Severity scores poorly aplicable
- Rates of CDI up to 48%
- CDI colonisation
  - Up to 12% of HSCT recipients on admission
  - a significant risk factor for CDI

Meta-analysis of 43 studies in HCT

TABLE 2 | Summary estimates.

CDI	Studies (Articles)	N	Combined Effect (95% CI)	τ^2	Bias	$\chi 2$	p-value
All studies	44 (43)	15,911	13.2% (11.6%–15.0%)	0.0054	1.654		
Age						0.256	0.613
Ped	6	1,095	14.8% (10.8%–19.2%)	0.0037	4.536		
Adult	31	10,515	13.7% (11.5%–16.1%)	0.0076	1.919		
Graft type						70.990	0.000
Autologous	17	3,840	9.2% (7.5%–11.2%)	0.0026	1.168		
Allogeneic	34 (33)	10,685	15.3% (13.2%–17.5%)	0.0061	1.806		
Population						30.709	0.000
≥200 patients	28	14,100	12.3% (10.5%–14.2%)	0.0049	1.546		
<200 patients	16	1,811	15.8% (12.5%–19.4%)	0.0064	-2.203		
Geographical region							
North America	32 (31)	12,371	14.1% (12.1%–16.4%)	0.0063	2.352		Ref
Europe	6	2,298	10.7% (7.6%–14.3%)	0.0034	0.762	11.966	0.001
Asia	4	553	11.6% (8.6%–14.8)	0.0005	0.762	1.436	0.231
Study design						50.827	0.000
Prospective	13	3,873	16.5% (11.9%–21.7%)	0.0125	1.806		
Retrospective	31	12,038	12.0% (10.6%–13.5%)	0.0029	1.335		
Duration of follow-up							
Early term	3	1,314	10.5% (7.9%–13.4%)	0.0010	2.876	6.002	0.014
Middle term	16	6,135	12.7% (10.5%–15.2%)	0.0039	1.409		Ref
Long term	11	4,786	16.5% (12.0%–21.5%)	0.0116	5.737	24.227	0.000
Detection method							
EIA	9	3,010	11.5% (9.9%–13.1%)	0.0005	0.713	5.449	0.020
EIA+PCR/CC	10	3,078	14.4% (11.2%–18.0%)	0.0044	1.984		Ref
PCR	10	2,517	17.7% (13.4%–22.4%)	0.0074	2.146	14.991	0.000
Detection years						15.531	0.000
Before 2010s	7	3,120	10.1% (8.7%–11.7%)	0.0004	1.393		
After 2010s	21	14,100	12.3% (10.5%–14.2%)	0.0049	0.952		

CDI, Clostridium difficile infection; Ped, pediatric; EIA, enzyme immunoassay; PCR, polymerase chain reaction; CC, culture cytotoxin assay; Ref, reference.

Luo et al. Front Cell Infect Microb 2022

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DOI: 10.1111/tid.13279

ORIGINAL ARTICLE

WILEY

Are *Clostridioides difficile* infections being overdiagnosed in hematopoietic stem cell transplant recipients?

Clyde D. Ford[1] | Bert K. Lopansri[2,3] | Jana Coombs[2] | Brandon J. Webb[2,4] | Julie Asch[1] | Daanish Hoda[1]

- Both diarrhea due to other causes and gastrointestinal colonization with toxigenic *Clostridioides difficile* are common in HSCT
- Possibility of false-positive diagnoses of *C difficile* infections
- **Methods:** We estimated the probability of a patient being colonized by toxigenic *C difficile* by testing non-diarrheal surveillance stools from 223 HSCT recipients and the probability that a specimen submitted for *C difficile* testing was not CDI by determining the number of clinical tests that returned negative from this cohort.
- The number of expected false-positive CDI was estimated using these probabilities and compared with observed clinical test results.

TABLE 2 Results of *C difficile* testing on stools submitted for VRE surveillance screening and calculation of expected positive tests and comparison with observed positive tests

	Total	Allos	Autos	*P*=
Surveillance Testing Data				
Number of patients	223	122	101	
Total Hospital Days without CDI[a] (THD)	5732	2283	3040	
Number of surveillance stools tested	648	323	325	
Number of GDH-positive stools	73(11%)	26 (8%)	47 (14%)	.01
Positive for toxin	16(2%)	6 (2%)	10 (3%)	
Toxin negative/PCR positive	25(4%)	9 (3%)	16 (5%)	
PCR positive and/or toxin positive	41(6%)	15 (5%)	26 (8%)	
Toxin and PCR negative	32(5%)	11 (3%)	21 (6%)	

Colonised with a toxigenic strain: 6%

Ford et al. TID 2019

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- The expected false-positive and the observed numbers of positive clinical results were similar.
- The 20 patients diagnosed with CDI were also similar to 142 patients with diarrhea and *C difficile*-negative stools

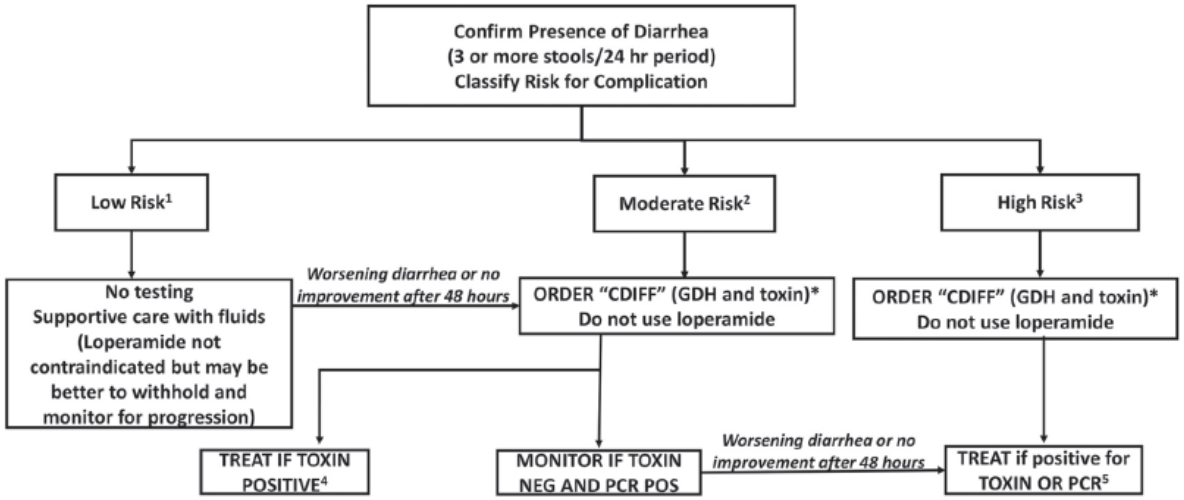
- **Conclusions**
- Although several assumptions could impact the accuracy of our false positive CDI estimates, it appears that many HSCT recipients diagnosed with CDI may actually represent colonized status and an alternative cause of diarrhea.
- Diagnostic stewardship, including limiting CDI diagnoses to patients with positive toxin and restricting stool submissions to patients with more severe symptoms, may decrease the number of false-positive diagnoses.

TABLE 3 Comparison of patients with CDI and those with a negative *C difficile* stool test

	CDI	No CDI	*P*=
Number of Patients	20	142	
Age,yr	65 (24-67)[a]	59 (21-75)[a]	.48
Gender female	11 (55%)	68 (48%)	.64
Allo-HSCT	11 (55%)	58 (41%)	.24
Day stool submitted	8.5 (3-20)	10 (3-24)	.045
Number of stools on day of testing	5 (1-10)	5 (1-16)	.87
Fever	7 (35%)	63 (44%)	.48
Abdominal Pain	7 (35%)	49 (34%)	1.0
Length of Stay,d	24.5 (15-62) [a]	22 (14-79) [a]	.51

[a]Median(range).

Beneficial or leading to underdiagnosis or delayed diagnosis of true cases?



*Order toxin genes PCR if toxin negative

1. Low-Risk: 3-4 stools per 24 hours and no/minimal impact on ADLs
2. Moderate Risk:
   a. 5-6 stools per 24 hours and/or minor modifications in ADLs needed
   b. AlloHSCT with suspected GI GvHD
3. High Risk:
   a. >6 stools/24 hour period, or
   b. Severe impact on ADLs from diarrheal illness, or
   c. Diarrhea with fever, abdominal pain, tenderness or distension, hematochezia, acute kidney injury, e/o sepsis with concerns for C. difficile as a cause of illness
4. Moderate Risk:
   - Treat only if Toxin is positive (vancomycin 125 mg po qid)
   - Monitor if PCR positive only and treat with clinical progression or lack of improvement in 48 hours
5. Severe Risk
   - Non-fulminant – Vancomycin 125 mg po qid
   - Fulminant (ileus, severe colitis, megacolon)
     - Vancomycin 500 mg po qid
     - Metronidazole 500 mg iv q8 hours

Figure 2. CDI diagnosis algorithm.

All samples sent for C. difficile testing during 757 consecutive admissions for HSCT or post-HSCT between October 2016 and September 2021

- Subjective diarrhea severity (mild, moderate, or severe) was as defined in the American College of Gastroenterology clinical practice guidelines 2016

ADLs, activities of daily living

Results

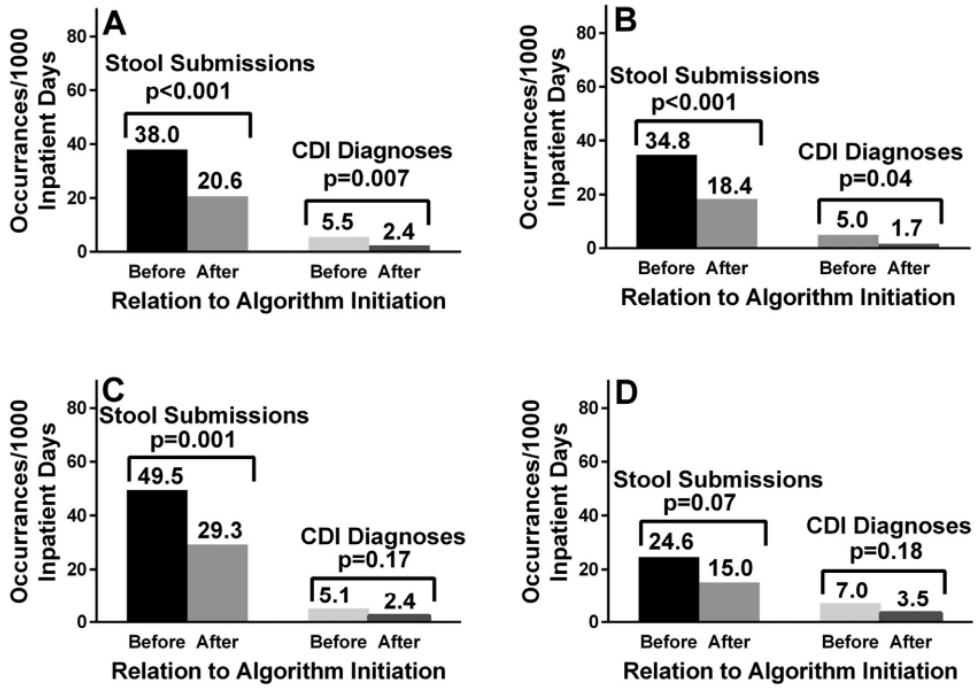


Figure 3. Rates of stool sample submissions and CDI diagnoses before (dark bars) and after (light bars) algorithm initiation for all admissions (A), first allogeneic HSCT admissions (B), first autologous HSCT admissions (C), and all HSCT readmissions (D).

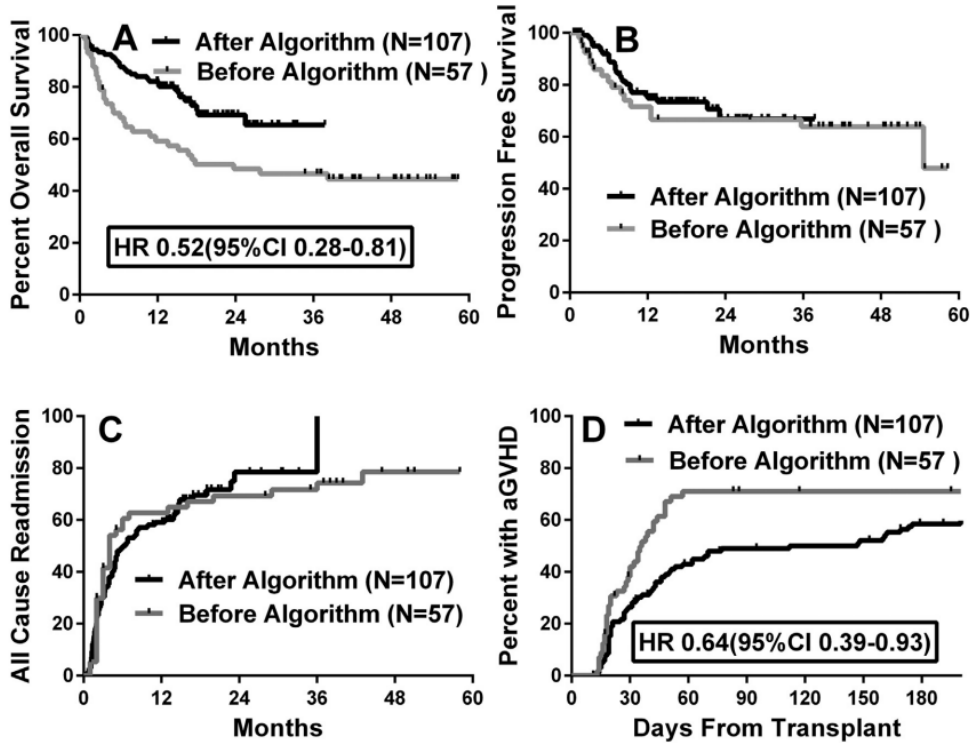


Figure 4. First allogeneic HSCT outcomes before (light curve) and after (dark curve) algorithm initiation: (A) overall survival; (B) progression-free survival; (C) readmission; (D) incidence of acute GVHD.

Ford et al. TCT 2023

Req. date : 04/06/2024 17:32 - Coll. date : 05/06/2024 10:51 - Rif.: 4069828412 - Doc: MEDICO SCONOSCIUTO (0) - Loc: EMAT.TRAP.STAM,DEG. PAD6 P1 (H27D2)

[redacted]

Clinical notes :

Parassi.Feci 1		In corso
Toss.Clostridium Dif		Presenza di C.difficile produttore di tossina
Adenovirus feci		Negativo
Rotavirus feci		Negativo
Norovirus feci		Dubbio

Il referto originale in formato elettronico e digitalmente firmato è stampabile mediante icona PDF

Clinical notes :

Pann.Mol.Gastro		
Batteri		
Campylobacter		Non rilevato
Clostridioides diffi		Non rilevato
Plesiomonas shigello		Non rilevato
Salmonella		Non rilevato
Vibrio		Non rilevato
Vibrio cholerae		Non rilevato
Yersinia enterocolit		Non rilevato
E.Col Ent. Shigella		
E. coli enteroaggreg		Non rilevato
E. coli enteropatoge		Non rilevato
E. coli enterotossig		Non rilevato
E. coli produttore d		Non rilevato
E.coli O157		Non applicabile
Shigella/E.coli ent		Non rilevato
Parassiti		
Cryptosporidium		Non rilevato
Cyclospora cayetanen		Non rilevato
Entamoeba histolytic		Non rilevato
Giardia lamblia		Non rilevato
Virus		
Adenovirus F 40/41		Non rilevato
Astrovirus		Non rilevato
Norovirus GI/GII		Non rilevato
Rotavirus A		Non rilevato
Sapovirus		Non rilevato
Nome infettivologo		Dr.ssa Mikulska

Molecular panels
False (?) negatives and co-infections

Table 1. Proportion of Patients With Positive Result From Central Laboratory ELISA for *Clostridioides (Clostridium) difficile* Toxin A/B in Stool, by Study Visit (mFAS)

Visit		EPFX (N = 177)	Vancomycin (N = 179)	Total (N = 356)
Screening	n	165	164	329
	Positive, n (%)	116 (70.3)	114 (69.5)	230 (69.9)
	Negative, n (%)	49 (29.7)	50 (30.5)	99 (30.1)

BioFire FilmArray analysis in the EXTEND trial of 327 patients with locally documented presence of toxin

- Sensitivity BioFire FilmArray for toxin-positive CDI:
  - 287/327 (87.8%) among all samples from screening
  - 225/230 (97.8%) among samples that tested positive for *C difficile* by ELISA in the central lab

- Rate of co-detection of other pathogens in the general population
  - 105 pathogens in 327 samples; only CDI in 70% of samples (230/327)
    - mainly different *E.coli* strains (EAEC, EPEC, ETEC): 61 (58%)
    - *Campylobacter*, n=19 (18%)
    - Virus, n=11
- Reported rate of co-infections with norovirus: 40/236, 17%, (Stokely Clin Epidem 2016)

EXTEND trial, Wilcox et al. OFID 2019

Protocollo diagnostico DIARREA: scelta degli esami da effettuare sulla base della presentazione clinica

Current

- Ricerca della tossina di *Clostridium difficile*
- Antigene Rotavirus, Norovirus, Adenovirus
- CMV DNA
- Ricerca Campylobacter
- Coprocoltura
- Antigene *Cryptosporidium, Entamoeba* e *Giardia*
- Es parassitologico
- In casi selezionati ricerca molecolare con FilmArray (su indicazione infettivologica)

New

3 scariche diarroiche/24h (o ileo paralitico)

1° step - Ricerca della tossina di *Clostridium difficile*

2° step

- Non ricoverato in reparto (ambulatorio, DH):
  - Ricerca Ag Campylobacter
  - Coprocoltura
  - Antigene Rotavirus, Norovirus, Adenovirus ?
    - Solo se persistente
  - Adenovirus-DNA and CMV-DNA solo se clinicamente indicato (colite, riattivazioni di CMV o ADV)
  - Risultati negativi, ma persiste diarrea: FilmArray
- Se ricoverato da > 14 gg
  - Adenovirus-DNA and CMV-DNA solo se clinicamente indicato (colite, riattivazioni di CMV o ADV)
  - Risultati negativi, ma persiste diarrea: FilmArray

Antimicrobial stewardship in haematology

Conclusions

1. Analyze the **epidemiology of different infections** in your center
2. If feasible, also clinical presentation patters: clinical signs and symptoms might be very limited in immunocompromised
3. Analyze the **availability of diagnostic methods, implement/modify diagnostic protocols if necessary**
4. Analyze the **prescription patterns** in your center
5. Involve **dedicated hematologists**
6. Provide **written (therapeutic and diagnostic) protocols known and shared by all the staff**
7. **Support autonomous decision making and provide support when required**
8. Provide a regular feedback on stewardship and most challenging cases


Thank you for your attention
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