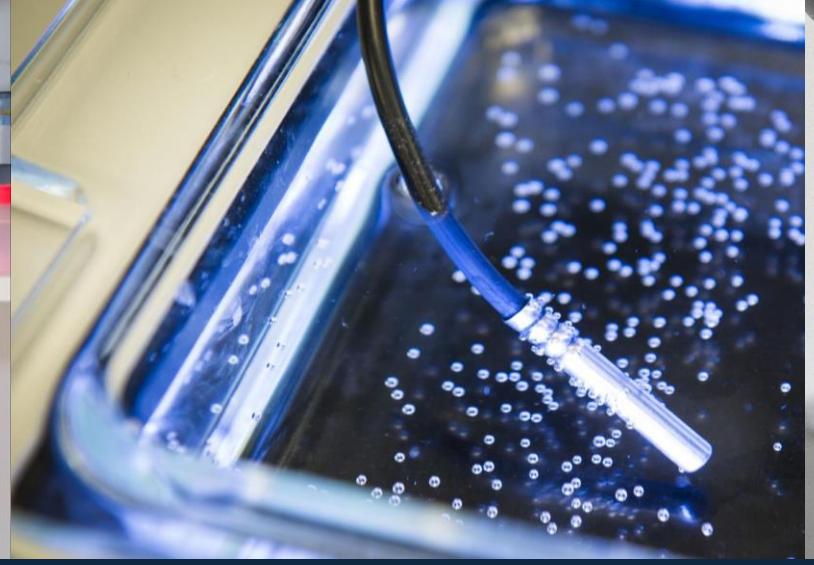
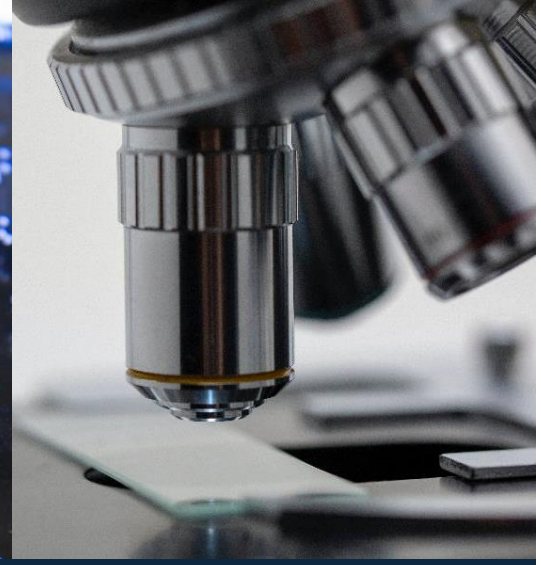




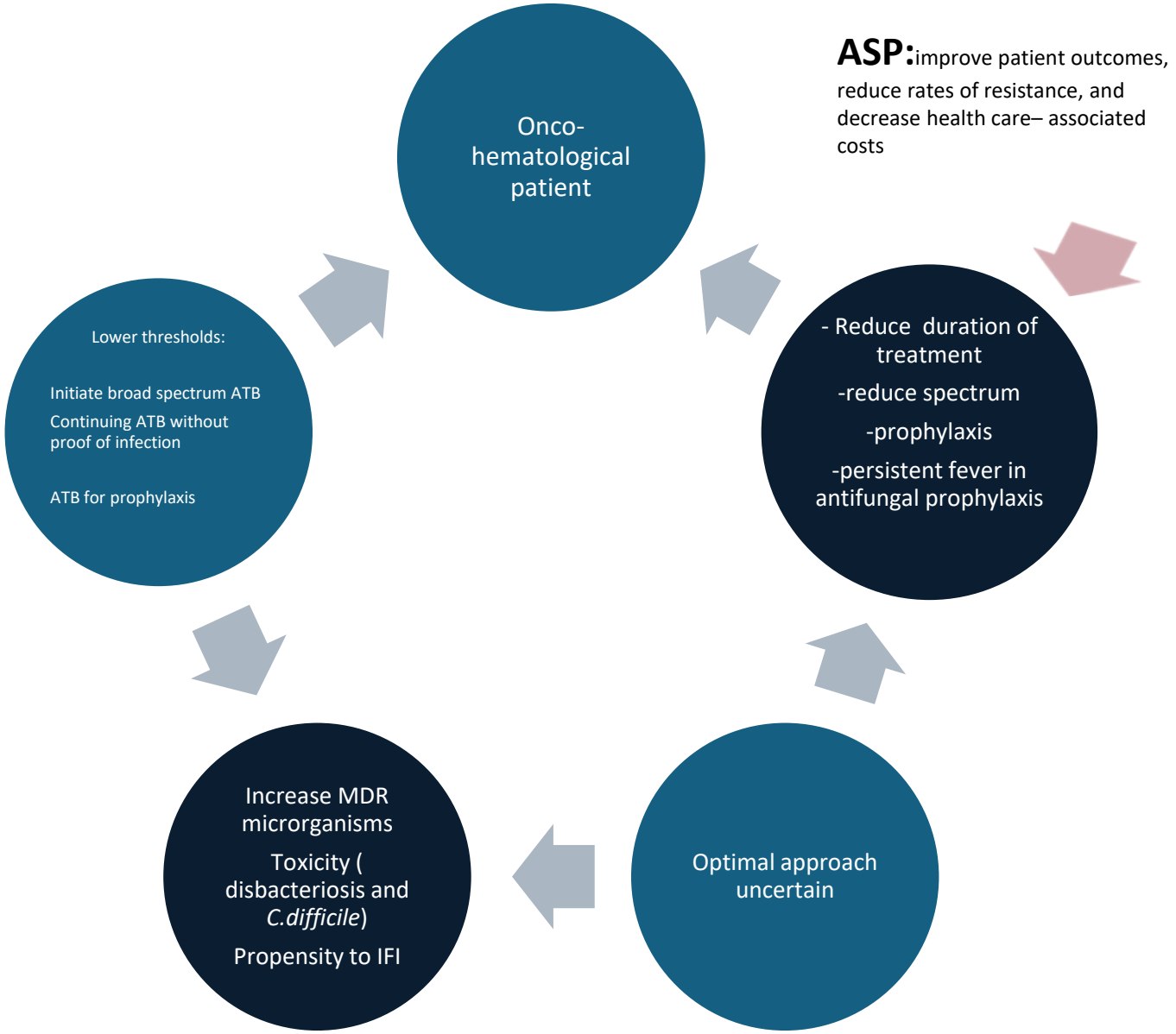
PROA EN ONCOHEMATOLOGIA
Jornada PROA hospitalaria Catalunya

Isabel Ruiz Camps

VHIO VALL D'HEBRON Institute of Oncology

Conflicto de Intereses

- Honoraria: Gilead, MSD, Pfizer, Janssen, BMS, Roche, GSK
- Advisory board: Gilead, Pfizer
- Consultancy: Gilead, Pfizer
- Shareholder: no disclousures



ASP: improve patient outcomes, reduce rates of resistance, and decrease health care– associated costs

Abbo LM. Infect dis Clin N Am 2014; 28: 263-79./ Aitken SL. JNCCN 2019; 17(7): 772-4/Pillinger KE. Annals of Pharmacotherapy 2020; 54(6):594-610/Barlam, T.FClin. Infect. Dis. 2016, 62, e51–e77.

Puntos a tratar

- Profilaxis antibacteriana
- Neutropenia febril:
  - Tratamiento empírico
  - Escalada/desescalada
  - Stop tratamiento
- Antifúngicos
  - Profilaxis
  - Tratamiento

Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

Summary *Objectives:* Fluoroquinolone (FQ) prophylaxis was recommended in 2005 by European Conference on Infections in Leukemia (ECIL) for patients with prolonged neutropenia. In consideration of a worldwide increase in antibiotic resistance, the issue of FQ prophylaxis during neutropenia was re-evaluated.
Methods: Literature review of randomised controlled trials (RCT) and observational studies published in years 2006–2014 was performed. Their results were analysed in meta-analysis. Meta-regression model was applied to evaluate whether the rates of FQ resistance in community and hospital settings influenced the efficacy of FQ prophylaxis. The impact of FQ prophylaxis on colonisation and infection with resistant bacteria was reviewed.
Results: Two RCTs and 12 observational studies were identified. FQ prophylaxis did not have effect on mortality (pooled OR 1.01, 95%CI 0.73–1.41), but was associated with lower rate of bloodstream infections (BSI) (pooled OR 0.57, 95%CI 0.43–0.74) and episodes of fever during neutropenia (pooled OR 0.32, 95%CI 0.20–0.50). No effect of the background rate of FQ resistance on the efficacy of FQ prophylaxis was observed. In few studies, FQ prophylaxis resulted in an increased colonisation or infection with FQ- or multi-drug resistant strains.
Conclusions: The possible benefits of FQ prophylaxis on BSI rate, but not on overall mortality, should be weighed against its impact in terms of toxicity and changes in local ecology in single centres.

Malgorzata Mikulska Journal of Infection (2018) **76**, 20–37

Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial

- prospective, multicentre, double-blind, placebo-controlled randomised trial in patients with newly diagnosed myeloma in 93 UK hospitals
- randomly (1:1) to levofloxacin (500 mg) or placebo **for 12 weeks**, within 14 days of starting active treatment.
- 977 patients included to receive **levofloxacin prophylaxis (489 patients)** or placebo (488 patients). Median follow-up was 12 months
- **95 (19%) first febrile episodes or deaths** occurred in 489 patients in the levofloxacin group versus **134 (27%)** in 488 patients in the placebo group (hazard ratio 0·66, 95% CI 0·51–0·86; p=0·0018.
- the benefit of levofloxacin was **greatest in older and less fit patients**.

Lancet Oncol. 2019; 20(12): 1760–1772.

Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial

- continuing infection risk beyond 12 weeks raises the question of whether the absence of survival benefit at 12 months might be due to early stopping of the intervention—12 months of prophylaxis might be beneficial.
- **Recommendation of levofloxacin prophylaxis should be considered** in the context of the incidence of local levofloxacin resistance in other countries. In the UK in 2017, the prevalence of *Escherichia coli* **resistance to fluoroquinolones was reported to be 17.5%,** HUVH 35%
- less than 1% risk of tendonitis with no or mild sequelae after stopping levofloxacin

	Levofloxacin group			Placebo group		
	C difficile	ESBL	MRSA	*C difficile*	ESBL	MRSA
Present at baseline (785 stool, 928 nasal samples)	1	19	5	5	37	9
Week 4 (706 stool, 805 nasal samples)	4	8	0	3	11	4
Week 8 (662 stool, 759 nasal samples)	0	5	1	2	7	1
Week 12 (634 stool, 719 nasal samples)	3	3	1	2	7	2
Week 16 (593 stool, 650 nasal samples)	4	9	2	1	5	0
Total new acquisitions (2595 stool, 2933 nasal samples)	11	25	4	8	30	7

ESBL=extended-spectrum β-lactamase. MRSA=methicillin-resistant *Staphylococcus aureus*.

***Table 4*: Acquisition of carriage of *Clostridium difficile*, ESBL, and MRSA organisms**

Lancet Oncol. 2019; 20(12): 1760–1772.

Interventions to reduce infections in patients with hematological malignancies: a systematic review and meta-analysis

Study or subgroup	Prophylactic antibiotics Events	Total	Standard care Events	Total	Weight	Risk ratio IV, random, 95% CI	Year
Oken 1996	5	28	12	26	3.2%	0.39 [0.16, 0.95]	1996
Vesole 2012	30	138	14	63	7.7%	0.98 [0.56, 1.71]	2012
Gregersen 2018	16	27	18	31	11.9%	1.02 [0.66, 1.57]	2018
Drayson 2019	190	489	221	488	45.1%	0.86 [0.74, 0.99]	2019
Puig 2021	78	143	76	143	32.1%	1.03 [0.83, 1.27]	2021
Total (95% CI)		**825**		**751**	**100.0%**	**0.91 [0.78, 1.08]**	
Total events	319		341				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.64$, df = 4 (P = 0.23); $I^2 = 29\%$
Test for overall effect: Z = 1.08 (P = 0.28)

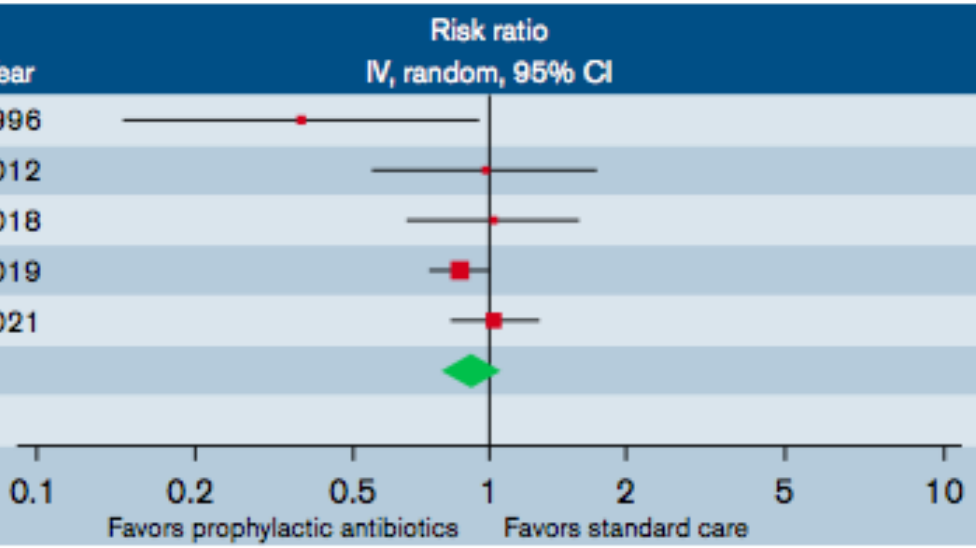


Figure 4. Prophylactic antibiotics vs standard care. Outcome: patients with ≥1 CDI.

Profilaxis antibacteriana NO ha demostrado beneficio

Chai K. Blood Adv. 2022

Contexto neutropenia febril

- Elevada morbi-mortalidad
- Alto riesgo: LMA; LLA; ALOTPH, TASPE
- Tratamiento empírico adecuado y precoz es indispensable
- Conocer nuestra propia epidemiología
- Recomendaciones ECIL-4: parar si FUO estable, apirexia 48h independientemente cifra neutrófilos (no colitis y mucositis severa)

Risk factors

Resistances

- **Previous exposure to broad-spectrum antibiotics** (cephalosporins, carbapenems, fluoroquinolones)
- **Baseline caracteristics:** Serious illness, end-stage disease, sepsis, pneumonia, immunosupression, >70 years, Charlson index >3, SOT, neutropenia…)
- **Epidemiological background**: Prolonged hospital stay and/or repeated hospitalizations, ICU stay, local epidemiology or outbreak, travel from high endemic area (Central western Asia), nosocomial infection
- **Prior colonization:** gut ESBL, CRE or endotracheal Pseudomonas
- **Indwelling devices:** Urinary catheters, gastrostomy or jejunostomy, nasogastric tube, CVC, mechanical ventilation, hemodialysis

Mortality

- **Inappropiate initial ATB therapy**
- **Time to adequate ATB therapy >48h** (OR: 2.36; 95% CI, 0.62-8.93; p=0.008)[2]
- **BSI with MDR organism** (OR: 3.6; 95% CI, 1.40-9.32; p=0.008)[3]
- Other factors:
  - ICU admission
  - Solid Tumor
  - GVHD
  - Increased severity of illness (Charlson comorbidity index, SOFA,...)

1.- Hussein K et al. Infect. Control Hosp Epidemiol 2009; 30: 666-671/ 2.- Hussein K. J Hosp Infect 2013; 83: 307-313/ 3.- Baker TM: Leukemia &Lymphoma 2016; 57 (10): 2245-2258/ 4.- Satlin MJ. Clin Infect Dis 2014; 58: 1274-83/ 5.- Dumford DM. Infect Clin N Am 2016; 30: 465-489/7.- Gudiol C. JAC 2011; 66:657-63 / 8.- Baker TM: Leukemia &Lymphoma 2016; 57 (10): 2245-2258/ 9.- Basetti M. Expert Rev Anti-Infect Ther 2016 (accepted 21/10)

1.- Baker TM: Leukemia &Lymphoma 2016; 57 (10): 2245-2258 /2.- Gudiol C. JAC 2011; 66:657-63 /3.- Macesic N. Traspl Infect Dis 2014; 16:887-96 /4.- Dumford DM. Infect Clin N Am 2016; 30: 465-489/ 5.-Moreno A. Am J Transplant 2007; 7: 2579-86 /6.- Lupei MI Surg Infect 2010; 11:33-9 /7.- Kitazono H. Clin transplant 2015; 29:227-32.

Escalation/De-escalation Strategies

Escalation approach

1. Uncomplicated clinical presentation
2. absence of risk factors for resistant bacteria infection
3. in centers having a low prevalence of resistant microorganisms

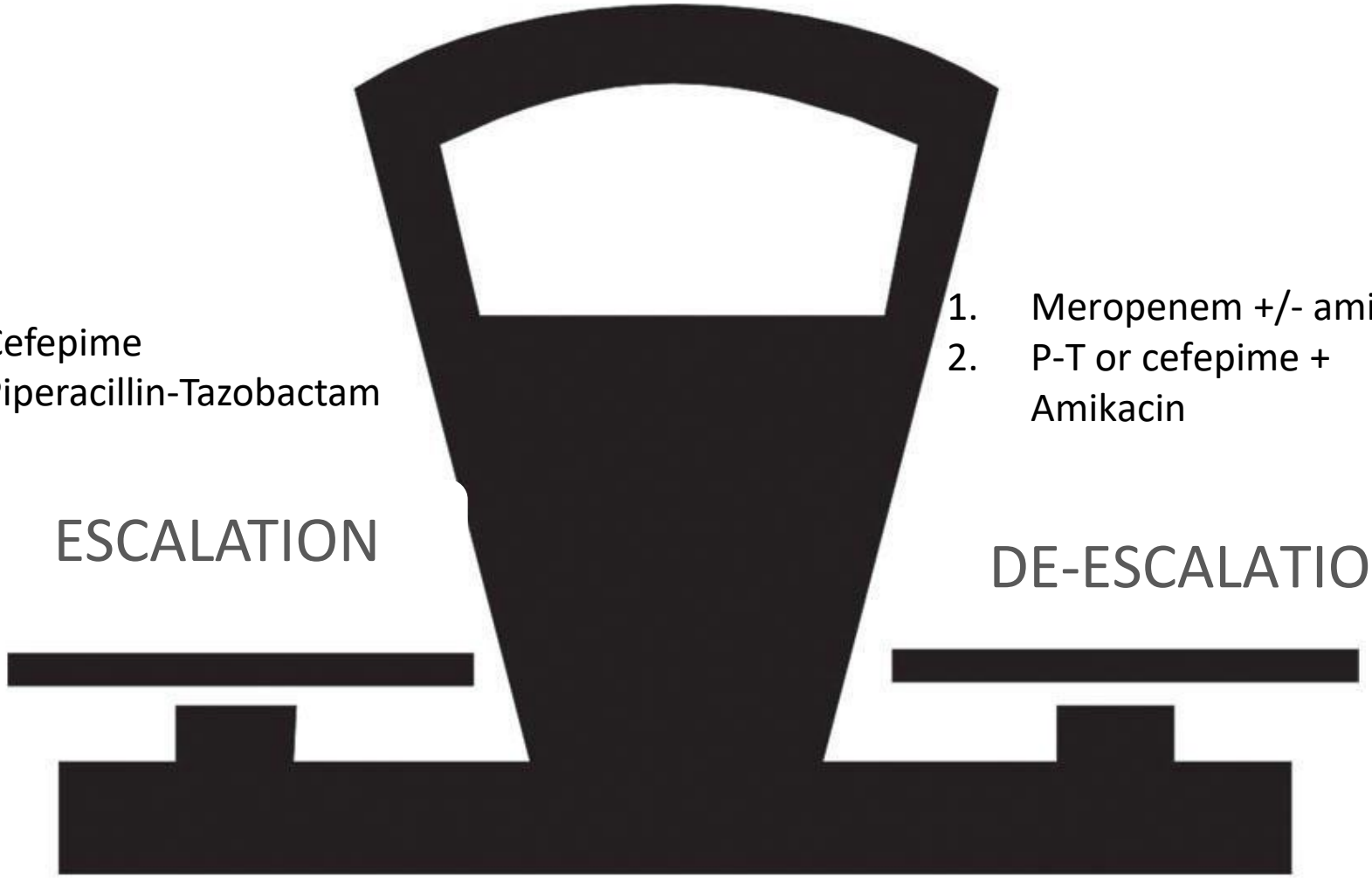
De-escalation approach

1. in complicate clinical presentations
2. when there are risk factors for infection by resistant bacteria
3. in those centers with a high prevalence of resistant microorganisms.

1.- Averbuch D. Hematologica 2013; 98:1826-35 / 2.- Virizuela JA. Clin Transl Oncol. 2016;18(6):557-70./ 3.- Gudiol C. Expert Rev Anti Infect Ther 2014; 12 (8): 1003-1016

Empirical treatment in FN

1. Cefepime
2. Piperacillin-Tazobactam



1. Meropenem +/- amika
2. P-T or cefepime + Amikacin

Adaptada de Dra. Gudiol

Averbuch D. Haematologica 2013

Stopping antibiotic therapy after 72 h in patients with febrile neutropenia following intensive chemotherapy for AML/MDS (safe study): A retrospective comparative cohort study

270 p

305 p

Table 2.
(Upper) number of patients experiencing bacteremia and types of bacteremia found in their blood cultures. (below) number of patients with candidemia. When more than 1 microorganism was detected in the same patients in one or more blood culture (e.g. gram-positive -and negative bacteria), both were documented. However, when different bacteria were classified in the same category, they were only counted once for that category (e.g. staphylococcus epidermidis and hominis). CNS = coagulase-negative staphyloccus.

	EMC (n = 99)	UZL (n = 73)	p-value
Gram-positive	97 (98%)	67 (91·8%)	0·338
Staphylococcus	80 (80·8%)	47 (64·4%)	0·139
CNS	77 (77·8%)	46 (63%)	0·238
S. Aureus	3 (3%)	1 (1·4%)	1·000
Streptococcus	11 (11·1%)	5 (6·8%)	1·000
Enterococcus	13 (13·1%)	21 (28·8%)	0·109
Other gram-positives	9 (9·1%)	6 (8·2%)	1·000
Gram-negative	10 (10·1%)	11 (15·1%)	1·000
Candidemia	9 (3%) of all patients	1 (0·4%) of all patients	0·181

	EMC (N=305)	UZL (N=270)
EBAT duration (<30d)	9 days	19 days
Serious medical complications	36/12.5%	24/8.9%
30d ICU admission	28/9.2%	19/7%
30d OM	8.5%	4.4%

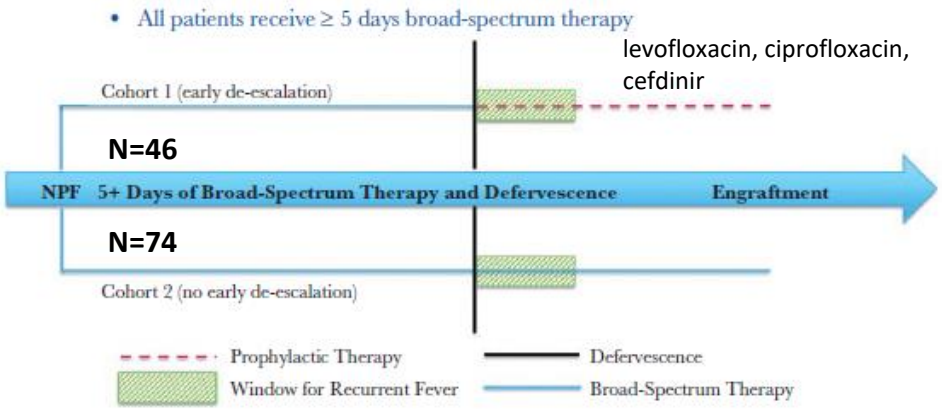
EBAT: Empirical broad- spectrum antibiòtic therapy/ OM: overall mortality

Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer

- We included RCTs that compared a **SAT course** (discontinuation regardless of the neutrophil count) to a **LAT** (until neutropenia resolution in FN).
- Primary outcome was 30-day or end of follow-up all-cause mortality.
- 8 RCTs comprising **662 FN episodes** (adults and children). All studies included people with FUO and excluded microbiological documented infections.
- **NO significant difference between SAT arm and LAT arm for all-cause mortality** (RR 1.38, 95%CI 0.73 to 2.62; RD0.02, 95%CI -0.02 to 0.05)
- Number of fever days was significantly lower for people in the SAT (mean difference -0.64, 95% CI -0.96 to -0.32; I^2 = 30%).
- In all studies, **total antibiotic days were fewer in the intervention arm by 3 vs 7**
- **No significant differences in the rates of clinical failure** (RR 1.23, 95% CI 0.85 to 1.77; very low-certainty evidence).
- No significant difference in the incidence of bacteraemia occurring after randomization (RR 1.56, 95% CI 0.91 to 2.66; very low-certainty evidence), while the incidence of any documented infections was significantly higher in the short-antibiotic therapy arm (RR 1.67, 95% CI 1.08 to 2.57).
- **No significant difference in the incidence of IFI** (RR 0.86, 95% CI 0.32 to 2.31) and development of **antibiotic resistance** (RR 1.49, 95% CI 0.62 to 3.61).

Stern A. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD012184.

Early Antimicrobial De-escalation and Stewardship in Adult Hematopoietic Stem Cell Transplantation Recipients: Retrospective Review



Variable	Cohort 1 (Early De-escalation) (n = 46)	Cohort 2 (No Early De-escalation) (n = 74)	*P* Value
Hospitalization course			
Recurrent fever within 72-hour time frame, n (%)[d]	7 (15)	14 (19)	.026
Length of stay, d[b]	20 (15–35)	20 (14–49)	.668
Among survivors[e]	20 (15–35)	20 (14–34)	.949
ICU admission, n (%)	0 (0)	2 (3)	.523
Clostridium difficile–associated infections, n (%)[f]	2 (4)	1 (1)	.558
Mortality, n (%)	0 (0)	3 (4)	.285

De-escalating after at least 5 days of broad-spectrum therapy and defervescence did **not appear to affect the rate of recurrent fever**. This allowed for significant reductions in gram-positive broad-spectrum antimicrobial utilization, with trends toward lower use of broad-spectrum gram-negative agents and associated costs and no difference in clinical outcomes compared with those continuing such therapy until neutrophil engraftment.

Snyder et al. Open Forum Infectious Diseases 2017

Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	..	..
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	−2·4 (−4·6 to −0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (−1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	..	..
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	−3·8 (−6·1 to −1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (−1·1 to 2·8)	0·38
Modified per-protocol population				
Number of patients (%)	36 (46%)	30 (38%)	..	..
Efficacy variable				
EAT-free days	17·5 (6·4)	11·3 (7·0)	−6·4 (−9·7 to −3·0)	0·0003
Safety variables				
Crude mortality	0 (0)	0 (0)	NA	1·00
Days of fever	4·9 (5·4)	5·4 (6·3)	0·5 (−2·4 to 3·4)	0·72

Data are n (%) or mean (SD), unless otherwise stated. EAT=empirical antimicrobial therapy. NA=not applicable.

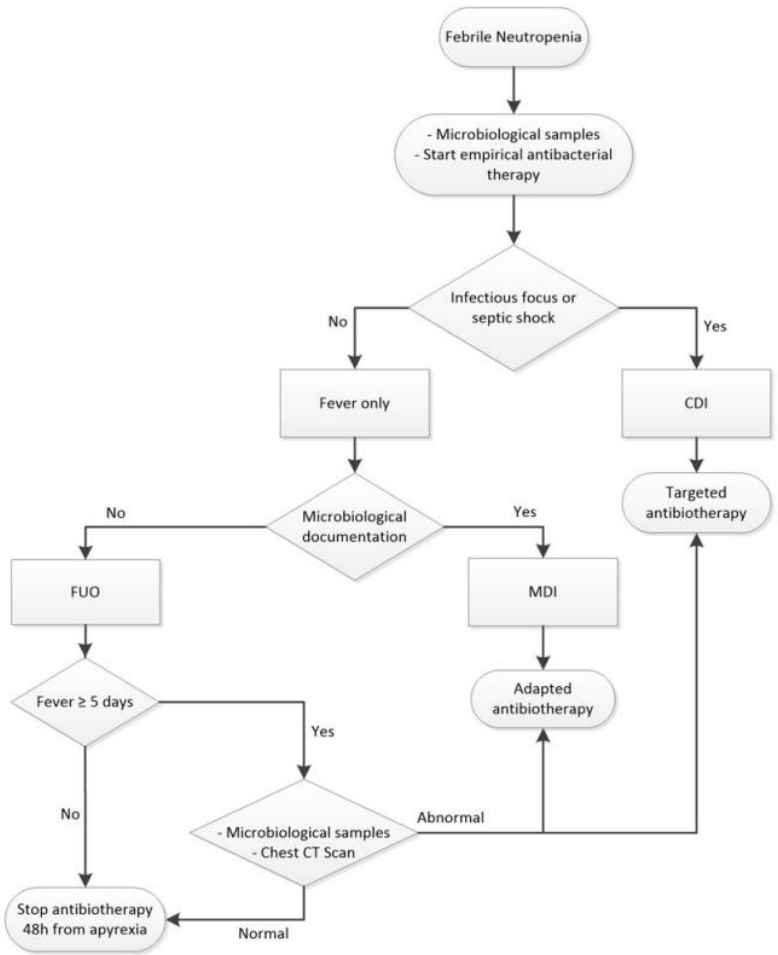
Table 3: Efficacy and safety endpoints

EAT was withdrawn after 72 h or more of apyrexia plus clinical recovery; for the control group, treatment was withdrawn when ANC ≥0·5 × 10^9 cells per L

In high-risk patients with haematological malignancies and febrile neutropenia, EAT can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. This clinical approach reduces unnecessary exposure to antimicrobials and it is safe.

Aguilar-Guisado. Lancet Haematol 2017; 4: e573–583

Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study

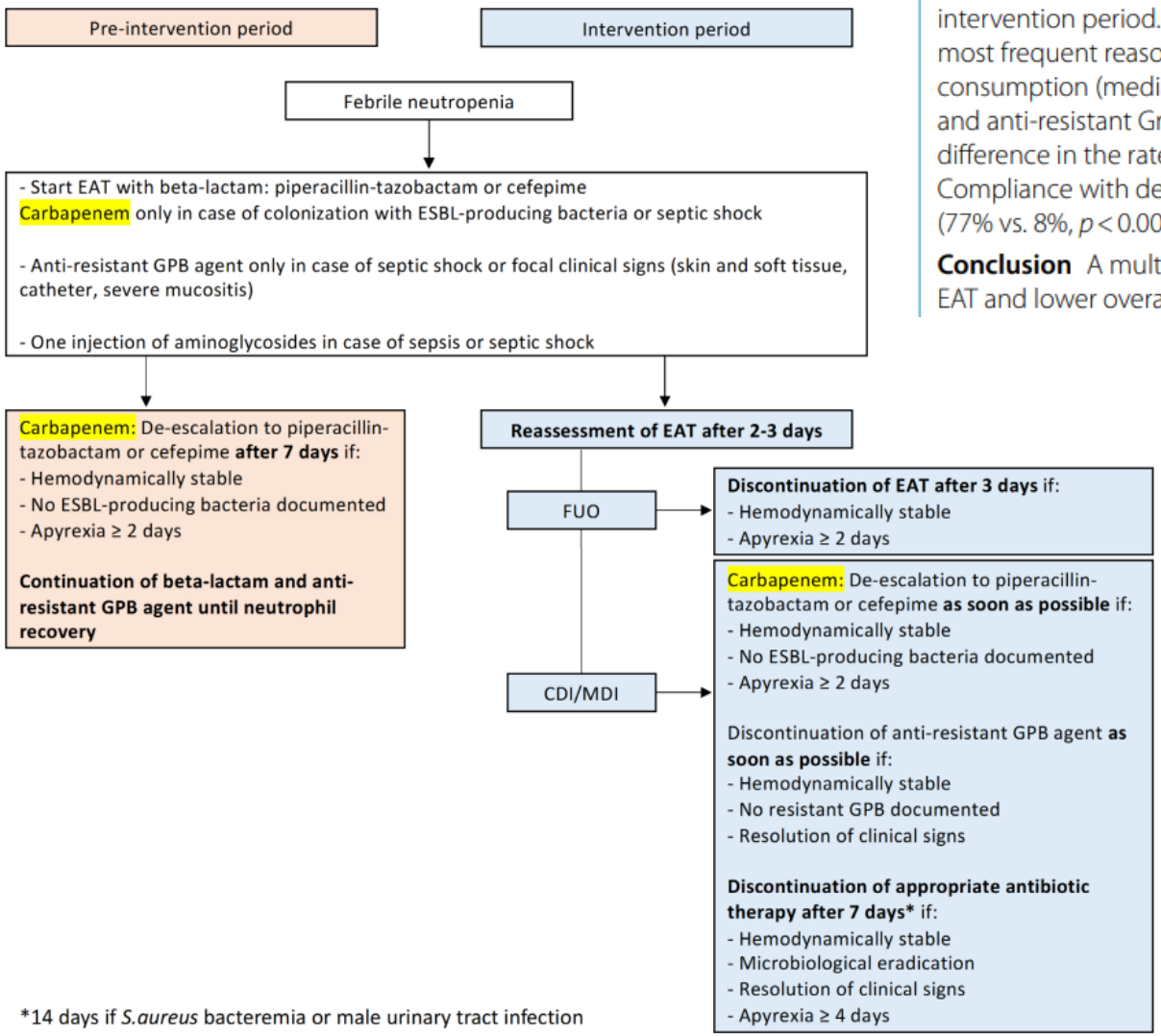


- 238 cases of FN in 123 patients were included
- First phase: EAT in FUO was stopped after 48 h of apyrexia (ECIL guidelines) (n=45). Second phase: no later than day 5, regardless of body temperature or leukocyte count (n=37).
- Violation of protocol occurred in 17/82 episodes of FUO without any major impact on statistical results.

	Number of FUO episodes with an event (%)		Event free survival (median in days)	
	1st phase of the study (n=45 FUO)	2nd phase of the study (n=37 FUO)	1st phase of the study	2nd phase of the study
Primary endpoint	10 (22.2%)	12 (32.4%)	1.5	2
In-hospital mortality	1 (2.2%)	2 (5.4%)	20	28
Intensive care admission	1 (2.2%)	5 (13.5%)	9	10
Relapse of fever ≤48 hours after antbiotics discontinuation	9 (20%)	8 (21.6%)	1	1.5

Lenaïg Le Clech[a,b]
INFECTIOUS DISEASES, 2018; VOL. 0, NO. 0, 1–11

Efficacy of an antimicrobial stewardship intervention for early adaptation of antibiotic therapy in high-risk neutropenic patients



*14 days if *S.aureus* bacteremia or male urinary tract infection

Results A total of 113 admissions were included: 56 during the pre-intervention period and 57 during the intervention period. Induction chemotherapy and conditioning for allogeneic stem cell transplantation were the most frequent reasons for admission. In the intervention period, there was a significant decrease in overall antibiotic consumption (median DOT 20 vs. 28 days, $p=0.006$), carbapenem consumption (median DOT 5.5 vs. 9 days, $p=0.017$) and anti-resistant Gram-positive agents consumption (median DOT 8 vs. 11.5 days, $p=0.017$). We found no statistical difference in the rates of intensive care unit admission (9% in each period) and 30-day mortality (5% vs. 0%, $p=0.243$). Compliance with de-escalation and discontinuation strategies was significantly higher in the intervention period (77% vs. 8%, $p<0.001$).

Conclusion A multifaceted AMS intervention led to high compliance with early de-escalation and discontinuation of EAT and lower overall antibiotic consumption, without negatively affecting clinical outcomes.

Durand *et al. Antimicrobial Resistance & Infection Control* (2024) 13:5
https://doi.org/10.1186/s13756-023-01354-5

Early Antibiotic Deescalation and Discontinuation in Patients with Febrile Neutropenia after Cellular Therapy: A Single-Center Prospective Unblinded Randomized Trial

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[3] *Sackler Faculty Of Medicine, Tel Aviv University, Tel Aviv, Israel*

- **Unblinded, single center, randomized clinical trial** (2020-2021)
- **Allogenic SCT, Autologous SCT or CAR-T cell therapy recipients.**
    - **Intervention Group**: **Empirical antibiotic treatment STOP at 48-72h if no infectious event and sustained clinical stability**, regardless of neutrophil count or fever.
    - **Control Group**: antibiotic treatment untill neutrophil recovery.

- **Primary Endpoint**: number of antibiotic-free days and antibiotic-free neutropenia days.
- **Secondary safety endpoint:** combination of continuation of clinical improvement on day 5 after initiation of antibiotic treatment; no recurrence of bacteremia, fever, or clinical signs of infection on day 5; and no need for additional therapy on day 4 to 5 after starting treatment.

Ram R. Transplantation and Cellular Therapy. 2023

Results Early STOP Clinical Trial

Vall d'Hebron Hospital

Table 1
Patient Characteristics

Characteristic	ITT			Per Protocol		
	Standard Duration Arm (N = 51)	EDD Arm (N = 59)	*P*	Standard Duration Arm (N = 41)	EDD Arm (N = 50)	*P*
Age, yr, mean ± SD)	60.6 (8.3)	61.2 (12.5)	.79	60.3 (8.2)	60.7 (12.9)	.85
Male sex, n (%)	26 (51)	38 (64)	.18	21 (51)	31 (62)	.4
Primary diagnosis, n (%)			.33			.13
Acute leukemia/MDS	9 (18)	14 (23)		4 (10)	13 (25)	
Lymphoma	17 (33)	27 (46)		16 (39)	21 (41)	
Multiple myeloma	24 (47)	18 (31)		20 (49)	17 (34)	
Other	1 (2)	0 (0)		1 (2)	0 (0)	
Reason for admission, n (%)			.93			.54
Allogeneic HCT	13 (25)	17 (29)		8 (20)	15 (30)	
Autologous HCT	26 (51)	30 (51)		22 (53)	24 (48)	
CAR-T therapy, n (%)		12 (20)		11 (27)	11 (22)	
HCT-CI, mean ± SD*		2 (2)	.78	2.2 (1.9)	2.1 (2.1)	.97
Karnofsky Performance Status, mean ± SD		80 ± 10	.28	80 ± 10	80 ± 10	.32
Neutropenia < 500/μL, d, median (IQR)	7 (6-11)	7 (6-10)	.31	7 (6-10)	7 (6-10)	.55
Neutropenia <100/μL, d, median (IQR)	6 (5-7)	6 (4-8)	.42	6 (5-7)	6 (4-7)	.71
Fluoroquinolone prophylaxis, n (%)	20 (39)	28 (47)	.55	17 (41)	24 (48)	.59

* Assessed only in patients who underwent HCT.

Ram R. Transplantation and Cellular Therapy. 2023

Results Early STOP Clinical Trial

Vall d'Hebron Hospital

- **14 patients (15.3%) had a clinical documented infection.**
  - Six (6.5%) central venous catheter exit site or tunnel infection, 5 (5.4%) opacities on chest imaging consistent with inflammatory infiltrates, 2 (2.1%) dental infection, and 1 (1.0%) had enterocolitis.

- **18 patients had a microbiological documented infection (19.7%), all of which were bloodstream infections**

Table 2
Antibiotic-Free Neutropenia Days and Fraction in the Study Cohort

Treatment	Antibiotic-Free Days			Antibiotic-Free Fraction		
	Standard Duration Arm	EDD Arm	*P*	Standard Duration Arm	EDD Arm	*P*
ITT cohort						
Total	4 (1-6)	6 (4-8)	.0017	.51 (.17-.86)	.8 (.62-.86)	.016
Allogeneic HCT	6.5 (2.75-8)	12 (4-16)	.053	.55 (.48-1)	.75 (.57-.88)	.60
Autologous HCT	5 (2-6)	5 (4-6)	.062	.73 (.33-.83)	.8 (.66-.85)	.15
CAR-T	1 (0-2.25)	5.5 (1.5-7.25)	.092	.088 (0-.32)	.75 (.47-.84)	.049
Per-protocol cohort						
Total	3 (1-6)	6 (4-8)	.00088	.42 (.12-.72)	.75 (.61-.83)	.000083
Allogeneic HCT	7 (6.5-8)	13 (6-17)	.11	.5 (.40-.51)	.75 (.57-.86)	.0046
Autologous HCT	4 (1.25-5)	5 (4-6)	.079	.59 (.19-.81)	.66 (.62-.83)	.077
CAR-T	1 (0-2)	7 (2-7.5)	.014	.066 (0-.28)	.7 (.45-.82)	.025

Secondary safety endpoint:

- Twenty patients (18%) experienced treatment failure.
- The treatment success rate was similar for patients in the standard duration arm and those in the EDD arm (84.7% and 78%, respectively; p =.45).

Ram R. Transplantation and Cellular Therapy. 2023

¿Qué ayudará a parar el tratamiento precozmente?

- Biomarcadores pronósticos: ¿procalcitonina?
- Técnicas rápidas de diagnóstico microbiológico
- Perder el miedo médico

Antifungal stewardship
Why?

- **IFI** have **increased** in frequency over the last 2 decades :
  - More patients at risk (immunosuppressors, surgery, age)
- **Antifungal resistances** as emerging problem (*Candida* and *Aspergillus*)
  - Resistances to azols and echinocandins
  - Ambiental exposures (TR34/L98H)
- **Adverse events:** Potential for toxicity with prolonged use with of these drugs,
- **High cost**
- **Need for expertise** to guide clinicians in prescribing

Muñoz P. JAC 2016; 71 (suppl.2):ii5-ii12/ Hamdy RF. Virulence 2017; 8(6): 658-672/ Abbo LM. Infect dis Clin N Am 2014; 28: 263-79./Aitken SL. Journal of the National Comprehensive Cancer Network 2019; 17(7): 772-775

Antifungal stewardship
How?

- **Improving diagnosis**
- **Antifungal treatment:**
  - Targeted therapy instead of empirical
  - spectrum of activity, pharmaco- kinetic and pharmacodynamic (PK-PD) properties, interactions, TDM,
  - duration, route of administration, de-escalation,
- **Prophylaxis**
  - Based on risk factors
- **Stop therapy if no infection**

Muñoz P. JAC 2016; 71 (suppl.2):ii5-ii12/ Hamdy RF. Virulence 2017; 8(6): 658-672/ Abbo LM. Infect dis Clin N Am 2014; 28: 263-79./ Aitken SL. Journal of the National Comprehensive Cancer Network 2019; 17(7): 772-775

Antifungal stewardship considerations for adults and pediatrics

Table 3. Suggestions for process and outcome metrics for antifungal stewardship.

Process metrics	Examples of metric
Antifungal drug consumption	Days of therapy per 1000 patient-days OR Defined daily doses per 1000 patient-days
Compliance with institutional guidelines	
• Choice of drug	Proportion of patients treated with drug of choice for indication
• Dose	Proportion of patients prescribed appropriate dosing for indication
• Therapeutic drug monitoring	Proportion of patients on azole for whom serum level was checked appropriately from time of initiation
• De-escalation	Proportion of patients with fluconazole-sensitive *Candida* for whom therapy was switched from echinocandin (or other broad-spectrum agent) to fluconazole
• Intravenous-to-oral conversion	Proportion of patients taking an azole who were switched from intravenous to oral formulation
• Use of diagnostic tests	Proportion of high-risk patients in compliance with institutional recommendations for monitoring serum galactomannan
• Source control	Proportion of patients with candidemia with catheter removal
Outcome metrics	Examples of metric
Preventive strategies in high-risk patients	Episodes of invasive fungal infection in target groups
Treatment of invasive fungal infection	Proportion of patients with clinical cure Proportion of patients with candidemia with recurrent infection
Resistance	Proportion of *Candida* isolates caused by fluconazole-resistant strains
Cost	Total cost of prescriptions per year, stratified by antifungal drug

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Table 1. Score for evaluating appropriateness of antifungal (AF) therapy.

Feature	Question	Answer	Points
Indication	Did the patient need an antifungal?	Yes	2
		No	0
Selection	Did the antifungal cover the suspected fungi and was it the first option recommended by the guidelines?	It covered the suspected fungi and was the first option	2
		It covered the suspected fungi but was the alternative option	1
		It did not cover the suspected fungi	0
Dosage [1]	Was the dosage correct according to the body weight, hepatic and renal function, and potential interactions with other drugs?	Yes	1
		No	0
Microbiological adjustment	Was the antifungal adjusted after microbiological results (identification of microorganism, antifungal susceptibility tests, and indirect tests) became available?	Yes	2
		No	0
Administration route	Was the intravenous route switched to the oral route when possible?	Yes	1
		No	0
Duration	Was the duration of therapy correct according to the guidelines? [2]	Yes	2
		No	0
Total score (From 0 to 10)			

[1] Both low and high doses were considered incorrect. Adjustment for renal and hepatic failure and drug-to-drug interactions were also addressed. At the time of the study, monitoring of serum voriconazole and posaconazole was not available. [2] Durations that were too short and too long were considered incorrect.

<10 considered inappropriate

Adequate duration of therapy in severe fungal infections

Matteo Bassetti[a,b], *Daniele R. Giacobbe*[a], *Marco Berruti*[a], *Filippo Del Puente*[a], *and Antonio Vena*[a]

KEY POINTS

- Current data suggest there is no additional benefit at a certain point after initiation of antifungal treatment in patients with IFD.
- Prolonged antifungal exposure can be associated with an increased risk of toxicity, development of antifungal resistance and unnecessary healthcare costs.
- New stratified approaches integrating clinical judgment, biomarkers and microbiological eradication, should be considered as an alternative to the current 'one-size-fits-all' duration.
- Until such strategies will be identified, the optimal duration of antifungal therapy should be defined according to the host characteristics, the pathogen, initial antifungal therapy and the promptness of source control.

Recent findings

Plenty of published data available suggest that there is no additional clinical benefit at a certain point after initiation of antifungal treatment in patients with confirmed IFD. Moreover, the prolonged antifungal exposure can be associated with an increased risk of side effects and toxicity as well as striking risk for developing antifungal resistance or rising unnecessary healthcare costs. Recent data suggest that, in the presence of an adequate initial antifungal therapy and adequate source control of the infection, new stratified approaches integrating clinical judgment, biomarkers and microbiological eradication, should be considered as an alternative to the 'one-size-fits-all' treatment duration currently used worldwide.

Summary

The optimal duration of antifungal therapy is still an unresolved issue that depends by many key elements including the host; the pathogen and its microbiological eradication, the adequateness of initial antifungal therapy and the promptness of source control of the infection. In general, many patients with invasive candidiasis can be treated with a 2 weeks course of antifungal therapy. Longer antifungal course (6 weeks or more) is generally required for patients with invasive aspergilosis.

Curr Opin Crit Care 2020, 26:466–472

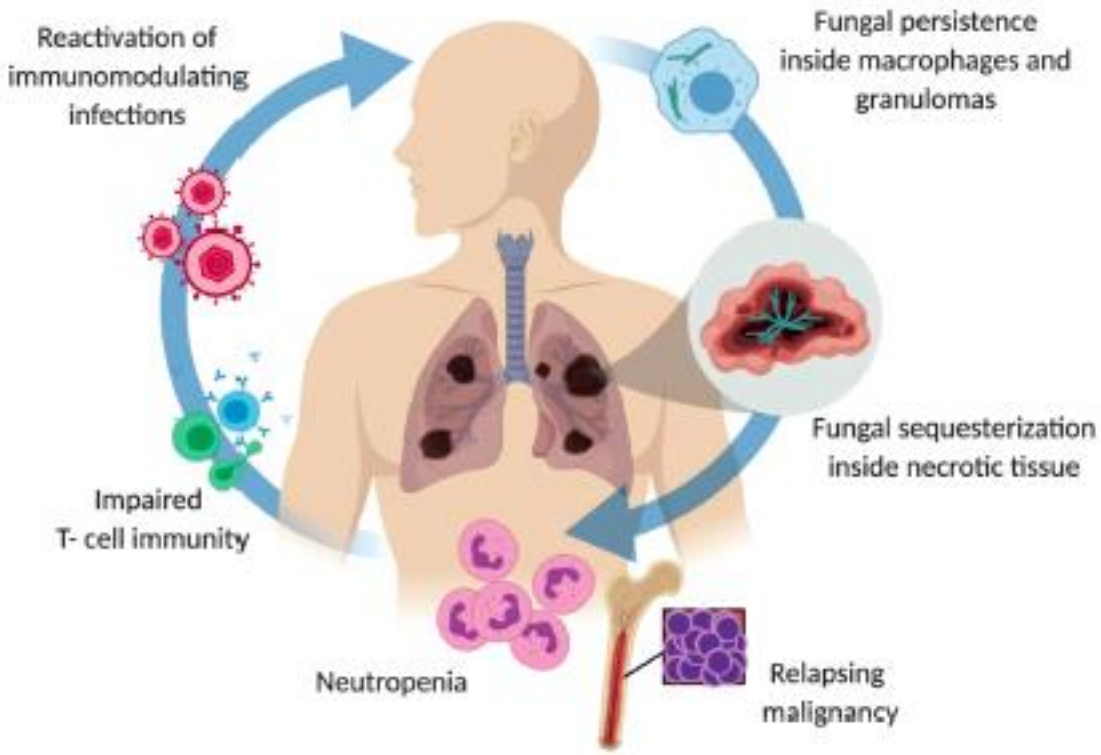


Figure 1. Pathophysiology of relapsing or persistent invasive mold disease.

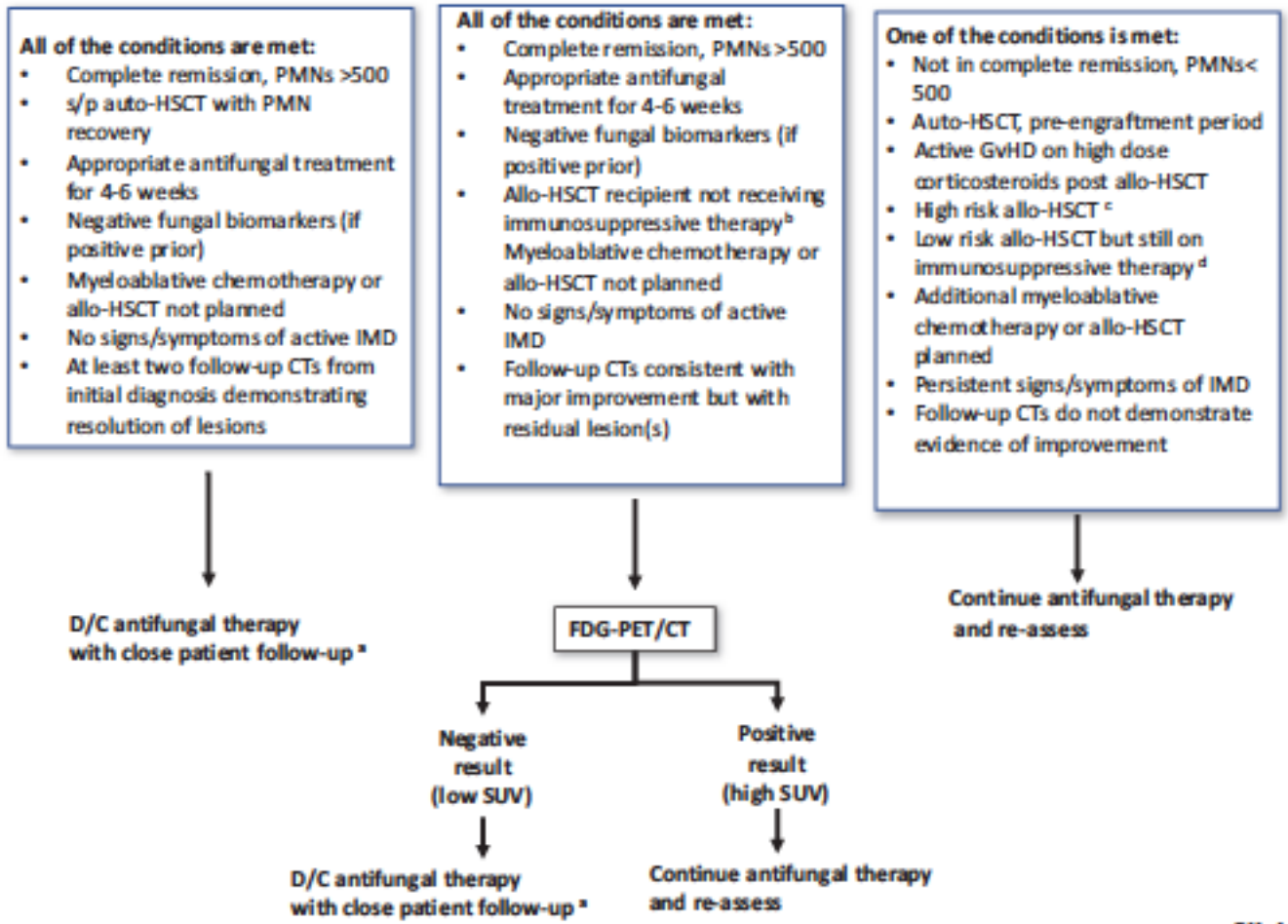
Table 1. Factors Influencing the Duration of Antifungals in Invasive Mold Disease in Patients With Hematologic Cancer

Risk Factor	Type of Factor
Underlying disease and treatment-related factors	Cytopenia (granulocytopenia, lymphocytopenia, monocytopenia)
	Relapsed or refractory leukemia
	HSCT and GvHD
	High-risk allogeneic HSCT
	Matched unrelated donor
	Cord stem cell
	T-cell depleted
	Haploidentical
	Mismatched
	CLL as the indication for HSCT
	Acute leukemia not in CR
	Small-molecule kinase inhibitors targeting immune-signaling pathways (eg, ibrutinib)
Type of mold infection	*Aspergillus*
	Mucorales
	Other molds
Extent of lung infection	Bilateral versus unilateral disease
	Number of lung lesions
	Type of lesion, especially cavitary masses
Presence of residual sequestra of infected lung tissue	
Coinfections	CMV
	Pseudomonas
Comorbidities	Poorly controlled diabetes mellitus, malnutrition, iron overload

Abbreviations: CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CR, complete remission; GvHD, graft versus host disease; HSCT, hematopoietic stem cell transplant

How Long Do We Need to Treat an Invasive Mold Disease in Hematology Patients? Factors Influencing Duration of Therapy and Future Questions

Ana Fernández-Cruz,[1] Russell E. Lewis,[2] and Dimitrios P. Kontoyiannis[3]



Profilaxis individualizada
Cambiar posología de algunas profilaxis
Nuevos fármacos

IFI risk stratification of haematological malignancies

High risk	Intermediate risk	Low risk
AML undergoing Induction CHT with any of the following Risk Factors: Neutropenia at baseline, low CR probability (Adverse K, secondary AML), age >65 yrs., significant pulmonary disfunction, high e-TRM score.	AML not meeting criteria for High or Low Risk groups.	AML <45 yrs.; Undergoing first remission-induction or consolidation CHT and without ANY Risk Factors for IFI
AML with Prior IA		APL treated with ATRA/ATO
AML undergoing salvage regimens for Relapsed/Refractory disease.		
Allogeneic Stem Cell transplantation (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previous IFI)	Allogeneic Stem Cell transplantation (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)	
MDS/AML receiving azacitidine as salvage therapy after intensive regimens	MDS with IPSS >1.5 treated with azacitidine 75 mg/m(2) for 7 days MDS during the first 2–3 cycles of AZA/Decitabine	
Acute lymphoblastic leukemia: elderly patients (≥55 y); intensive pediatric regimens (induction);HD dexametazone; previously treated (relapsed/refractory)	Acute Lymphoblastic Leukemia: Adults (30–54 y); Standard induction chemotherapy; Intensive consolidation treatment; TKI + reduced cht (Ph + ALL) Autologous Stem Cell Transplantation: Previous IFI; >3 lines of therapy (disease burden); Prolonged neutropenia (ANC <500/mm3 for more than 14 days); corticosteroid therapy; Colonization by *Candida* spp.; Previous Fludarabine treatment	Acute Lymphoblastic Leukemia: Younger adults (30 y); Maintainance treatment (complete remission); TKI + steroids (Ph + ALL) MPN (Chronic Myeloid Leukemia, Essential Thrombocitemia, Idiopathic Thrombocytosis, Policytemia Vera)
	CLL treated with multiple lines of CTX Multiple myeloma in 3 or more lines or during ASCT DLBCL relapsed/refractory HD if treated with "escalating BEACOPP"	Low or high grade NHL, CLL, MM, HD treated with conventional frontline chemotherapy

ANC, absolute neutrophil count; ALL, acute lymphocytic leukaemia: AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; ASCT, Autologous stem cell transplant; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; AZA, azacitidine; BEACOPP, bleomycin etoposide doxorubicin cyclophosphamide vincristine procarbazine prednisolone; CHT, chemotherapy; CLL, chronic lymphocytic leukaemia; CR, complete remission; CTX, chemotherapy treatment; DLBCL, diffuse large B-cell lymphoma; IFI, invasive fungal infection; HD, Hodgkin's disease; HM, haematological malignancies; IA, invasive aspergillosis; IPSS, International Prognostic Scoring System ; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; MM, multiple myeloma;
NHL, non-Hodgkin's lymphoma; Ph, Philadelphia chromosome; TKI, Tyrosine kinase inhibitors ; TRM, treatment-related mortality; y or yr, year

Pagano L, *et al. Blood Rev*. 2017;31(2):17–29.

Profilaxis???

- **Ibrutinib**
  - No primera línea
  - Si cortis asociados
  - Primeros meses?
  - En EICR
- **Venetoclax**
  - En LMA
  - Asociada a AZA
- **Ruxolitinib**
  - En EICR crónica
- **CAR-T**
  - > 3L,
  - neutropenia prolongada o IFI previa
  - uso cortis y/o tocilizumab
- **Check-point inhibitors** + cortis o IS por efecto inmunomediado
- **Enf hematológica + gripe grave** mala evolución

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium

Melissa D. Johnson,[1,a] Russell E. Lewis,[2,a] Elizabeth S. Dodds Ashley,[1,a] Luis Ostrosky-Zeichner,[3] Theoklis Zaoutis,[4] George R. Thompson III,[5] David R. Andes,[6] Thomas J. Walsh,[7] Peter G. Pappas,[8] Oliver A. Cornely,[9,10,11,12] John R. Perfect,[1] and Dimitrios P. Kontoyiannis[13]; for the Mycoses Study Group Education and Research Consortium

Table 4. Essential, Achievable, and Aspirational Antifungal Stewardship Activities

Stewardship Activity Level	Description
Essential	Development of institutional treatment pathways or bundles for antifungal prophylaxis and empiric therapy
	Development of targeted education programs for appropriate diagnosis and treatment
	Antifungal prescription review for drug–drug interactions
	Handshake rounds or postprescription review and feedback
	Intravenous to oral transition program
	Local surveillance and reporting of IFD to prescribers
Achievable	Rapid non-culture-based diagnostic tests for *Candida* and *Aspergillus* spp communicated to AFS team/clinicians
	Provide timely antifungal susceptibility testing results provided and communicated in a timely manner to AFS team/clinicians
	Specific comments to guide therapy and antifungal dosing recommendations are provided on microbiology reports
	Cumulative antifungal susceptibility reports reported to prescribers
	Timely TDM reported to AFS team and clinicians
	Review of autopsy reports and patient outcomes systematically to assess for undiagnosed IFDs and/or underutilization of antifungal agents
Aspirational	Participate in regional or national surveillance systems
	Individualized patient risk assessment (eg, institutional risk model, genetic risk factor screening)
	Optimize use of point-of-care microbiological tests, when available
	Utilize personalized TDM-dose adaptation (such as Bayesian methods) for antifungal therapy
	Incorporate advanced radiologic approaches for invasive aspergillosis (CT pulmonary angiography, FDG PET/CT)

Table adapted and modified from Morency-Potvin et al [152].

Abbreviations: AFS, antifungal stewardship; CT, computed tomography; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; IFD, invasive fungal disease; TDM, therapeutic drug monitoring.

Trabajando juntos los programas PROA son posibles en pacientes oncohematológicos .....

Long-Term Impact of an Educational Antimicrobial Stewardship Program on Management of Patients with Hematological Diseases

- **Antimicrobials showed a sustained reduction with a relative effect of - 62.3%** (95% CI -84.5 to -40.1) 9 years after the inception of the ASP, being especially relevant for:
  - antifungals (relative effect -80.4%, -90.9 to -69.9),
  - quinolones (relative effect -85.0%, -102.0 to -68.1)
  - carbapenems (relative effect -68.8%, -126.0 to -10.6).

- **Incidence density of MDR BSI remained low and stable** (mean 1.10 vs. 0.82 episodes per 1000 occupied bed days for the pre-intervention and the ASP period, respectively.)

- **Early and late mortality of MDR BSI presented a steady trend** (quarterly **percentage of change** -0.7%, 95% CI -1.7 to 0.3 and -0.6%, 95% CI -1.5 to 0.3, respectively).

- Volume and complexity of healthcare activity increased over the years.

- **The ASP effectively achieved long-term reductions in antimicrobial consumption and improvements in the prescription profile, without increasing the mortality of MDR BSI.**

Ana Belen Guisado-Gil. Antibiotics 2021 (10): 136

Mensajes

- Los programas PROA son necesarios y posibles en los pacientes oncohematológicos.
- La implementación del PROA en oncohematologia no incrementa la mortalidad ni la morbilidad de los pacientes.
- La multidisciplinaridad en el PROA es necesaria.