

Less Is More. Or Is It? Early vs Late Antibiotic De-Escalation in Febrile Neutropenia

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TOPA
Tennessee Oncology Pharmacists Association

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Disclosures

- Drs. Holman and Marjoncu have no relevant financial relationships with ineligible companies to disclose

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Objectives

- Review current guideline recommendations for the management of antibiotics in patients with febrile neutropenia (FN)
- Summarize recent literature describing de-escalation strategies for antibiotics in patients with FN
- Apply evidence-based recommendations to patient cases

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What is Febrile Neutropenia (FN)?

Neutropenia

- ANC ≤500 cells/mcL
- ANC ≤1000 cells/mcL and a predicted decline to ≤500 within the next 48 hr
- Severe: ANC ≤100 cells/mcL
- Prolonged: neutropenic for ≥7 days

Fever

- Single oral temperature ≥38.3°C (101°F)
- Temperature ≥38°C (100.4°F) orally sustained over 1 hr

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Risk Factors for FN

Chemotherapy regimen	Age	Advanced disease
History of prior FN	No antibiotic prophylaxis	No GCSF
Poor performance status	Cardiovascular disease	

Kalitsky J, et al. Ann Oncol. 2016; 27 (5):111-118.

GCSF = granulocyte colony-stimulating factor

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FN in Hematologic Malignancies

Longer durations of neutropenia

- Lead to weeks of broad-spectrum antibiotics

Mortality

- Up to 10% in autologous HSCT
- Highly variable in allogeneic HSCT
- 80% graft failure
- 20-26% in the first 2 months in AML

HSCT = hematopoietic stem cell transplant.

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Prognosis

Febrile Neutropenia Mortality

# Major Comorbidities	No Documented Infection (%)	Documented Infection (%)
0	1.2	4.9
1	6.7	14.7
2	12.9	28.9
3	23.8	47.4
>4	38.3	57.4

Kuderer NM, et al. Cancer. 2006; 106(10):2258-66.

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Prognosis

Febrile Neutropenia Mortality by Cancer

Cancer Type	N	% Mortality
Breast (N=3077)	3077	3.6
Colorectal (N=957)	957	8.8
Lymphoma (N=8871)	8871	8.9
Lung (N=3339)	3339	13.4
Leukemia (N=8703)	8703	14.3
Solid Tumors (N=22142)	22142	8.1

Kuderer NM, et al. Cancer. 2006; 106(10):2258-66.

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Prophylaxis – GIMEMA

Inclusion Criteria:

- ≥18 years
- Solid tumor or heme malignancy
- At risk ANC <1000

Exclusion Criteria:

- Undergoing alloHCT
- Treated with antimicrobial therapy previous 5 days
- Fever of infectious origin or documented infection at time of enrollment

1st endpoint:

- Fever requiring EAT

2nd endpoint:

- Type and number of microbiologically documented infections
- Mortality

AE = adverse event
EAT = Empirical antibacterial therapy

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Prophylaxis - GIMEMA

Baseline Demographics	Levofloxacin (N=339)	Placebo (N=336)
Age, mean (range)	47 (18-75)	49 (18-75)
Malignancy, n (%)		
Acute leukemia	164 (48)	163 (49)
Lymphoma and Hodgkin's disease	112 (33)	100 (30)
Solid Tumor	24 (7)	22 (6)
Other heme malignancies	39 (12)	51 (15)
autoHCT, mean (range)	170 (50)	158 (47)
Duration of neutropenia, mean (range)	15 (3-54)	14 (2-67)

P values not reported

Bucaneve G, et al. NEJM. 2005; 353:977-987.

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Prophylaxis – GIMEMA

Primary Outcome, n (%)	Levofloxacin (N=339)	Placebo (N=336)	RR Absolute Difference (95% CI)	P value
Fever requiring EAT	221 (65)	290 (86)	0.76 -0.20 (-0.26 to -0.14)	0.001

Bucaneve G, et al. NEJM. 2005; 353:977-987.

RR = relative risk

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Prophylaxis – GIMEMA

Secondary Outcome, n (%)	Levofloxacin (N=339)	Placebo (N=336)	Absolute Difference (95% CI)	P value
Microbiologically documented infection	74 (22)	131 (39)	-0.17 (-0.24 to -0.10)	<0.05
Gram-positive infections	42 (12)	61 (18)	-0.06 (-0.11 to -0.03)	NS
Gram-negative infections	21 (6)	47 (14)	-0.08 (-0.12 to -0.03)	NS
Bacteremia	62 (18)	115 (34)	-0.16 (-0.22 to -0.09)	NS
Gram-positive infections	37 (11)	54 (16)	-0.05 (-0.10 to 0.00)	NS
Gram-negative infections	15 (4)	38 (11)	-0.07 (-0.10 to -0.02)	<0.05
Mortality	10 (3)	18 (5)	-0.02 (-0.05 to 0.005)	0.15

Bucaneve G, et al. NEJM. 2005; 353:977-987

NS = Not significant

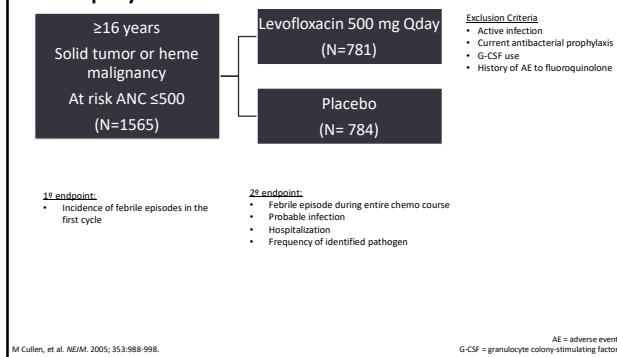
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Prophylaxis – GIMEMA

- Prophylactic levofloxacin significantly decreased the number of febrile episodes requiring empiric antibiotics
- Fewer numbers of gram-negative infections
- Studied patients at high risk for febrile neutropenia

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Prophylaxis – SIGNIFICANT



M Cullen, et al. NEJM. 2005; 353:988-998.

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Prophylaxis – SIGNIFICANT

Baseline Demographics	Levofloxacin (N=781)	Placebo (N=784)
Age, median (IQR)	55 (42-63)	55 (43-65)
Malignancy, n (%)		
Breast cancer	275 (35)	279 (36)
Testicular cancer	114 (15)	111 (14)
Small-cell lung cancer	79 (10)	72 (9)
Non-Hodgkin's lymphoma	24 (3)	25 (3)
Hodgkin's disease		
Other	179 (23)	187 (24)
Adjuvant chemotherapy, n (%)	354 (45)	335 (43)
Previous myelosuppressive chemotherapy, n (%)	73 (9)	88 (11)
Previous radiotherapy given, n (%)	33 (4)	40 (5)

P values not reported

IQR = interquartile range

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Prophylaxis – SIGNIFICANT

Primary Outcome, n (%)	Levofloxacin (N=781)	Placebo (N=784)	RR (95% CI)	P value
Febrile episode cycle 1	27 (4)	62 (8)	0.44 (0.28-0.68)	<0.001

Secondary Outcome, n (%)	Levofloxacin (N=781)	Placebo (N=784)	RR (95% CI)	P value
Probable infection	267 (34)	325 (42)	0.72 (0.57-0.90)	0.005
Febrile episode any cycle	84 (11)	119 (15)	0.71 (0.55-0.92)	0.01
Hospitalization	52 (7)	81 (10)	0.64 (0.46-0.90)	0.01
Bacteria identified	16 (5)	59 (13)	NR	NR

M Cullen, et al. NEJM. 2005; 353:988-998.

NR = Not reported

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Prophylaxis – SIGNIFICANT

- Levofloxacin given for 7 days during period of severe neutropenia reduced incidence of fever, infection, and hospitalization
- The bacterial organism was isolated less frequently with levofloxacin use
- Routine prophylaxis can increase antibiotic resistance

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Prophylaxis

GCSF

- High risk (>20%)
- Intermediate risk (10-20%)

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Multinational Association of Supportive Care in Cancer (MASCC)

Risk-Index Score/Model	
Characteristic	Weight
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No COPD	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age <60 years	2

Freireich AG, et al. CID. 2011; 52:e56-93.
Zimmer AJ, et al. JCO. 2019; 37(9):1103-1110.
NCCN Prevention and Treatment of Cancer-Related Infections. V3.2022

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Multinational Association of Supportive Care in Cancer (MASCC)

Low Risk: ≥ 21

- Outpatient
- Oral antibiotics
- Short duration severe neutropenia
- Adequate hepatic/renal function

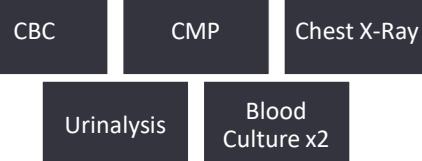
High Risk: < 21

- Inpatient
- IV antibiotics
- Anticipated prolonged and severe neutropenia
- Significant comorbidities or clinical instability
- Grade 3-4 mucositis

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Initial Workup



Site specific diagnostic tests

- Diarrhea: *Clostridioides difficile* assay, enteric pathogen screen
- Skin: aspirate/biopsy/PCR of lesions or drainage
- Lung: respiratory viral panel

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Infectious Findings

- Clinically documented infections rare (20-30%)
 - Bacteremia occurs in 10-25%
- Mortality close to 40%
 - Higher if GNR bacteremia

Freireich AG, et al. CID. 2011; 52:e56-93.
Wisplinghoff H, et al. CID. 2003; 36(9):1103-1110.

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Common Pathogens

Gram positive	Gram negative
<i>Coagulase negative staphylococci</i>	<i>Escherichia coli</i>
<i>Staphylococcus aureus</i>	<i>Klebsiella spp.</i>
<i>Enterococcus spp.</i>	<i>Enterobacter spp.</i>
<i>Viridans group streptococci</i>	<i>Pseudomonas aeruginosa</i>
<i>Streptococcus pneumoniae</i>	<i>Citrobacter spp.</i>
<i>Streptococcus pyogenes</i>	<i>Acinetobacter spp.</i>
	<i>Stenotrophomonas maltophilia</i>

Freireich AG, et al. CID. 2011; 52:e56-93.

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Low-Risk Treatment

Oral antibiotic therapy

Ciprofloxacin + amoxicillin/clavulanate	Ciprofloxacin + clindamycin if penicillin allergic	Levofloxacin	Moxifloxacin
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Not recommended if previous FQ prophylaxis

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High-Risk Treatment

Anti-pseudomonal β-lactam monotherapy

- Cefepime, ceftazidime, piperacillin/tazobactam, meropenem, imipenem-cilastatin

Vancomycin or additional gram-positive cocci coverage

- Not part of standard initial regimen
- Use if clinically indicated

Additional antimicrobials

- Suspected/proven antimicrobial resistance

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Inpatient Burden of FN

- ~75% of deaths occur in inpatients with hematologic malignancies; 66.7% >65 years old
- Death associated with longer length of stay (12.9 vs 4.3 days)
- Hospitalizations that resulted in death had 4x cost as those who did not die (\$230,601 vs \$53,963)

Makhani SS, et al. Blood. 2022; 140(Supplement 1):5154-5155.

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BR is a 48 year old AA male who was recently diagnosed with AML. He presents with a fever (39 C), ANC 0, BP 125/83, chest X-Ray is clear and there is no obvious source of infection, blood cx are pending. What is an appropriate empiric antibiotic regimen?

Piperacillin-tazobactam 2.25 g IV Q6H + vancomycin 15 mg/kg IV Q12H 0%

Doxycycline 100 mg PO Q12H 0%

Cefepime 2g IV Q8H 0%

Ciprofloxacin 750 mg Q12H + amoxicillin/clavulanate 875 mg Q12H 0%

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Case

CH is a 68 yo WM admitted for alloHCT. He has been receiving levofloxacin 500 mg Qday, flucloxacile 400 mg Qday, and acyclovir 400 mg QID as prophylactic. On Day +5 his ANC is 0 and he becomes febrile to 39 C. He is started on cefepime 2g Q8H. On Day +6 he has been afebrile for 72 hr, vital signs stable, ANC 0, and no source of infection has been identified. What do you recommend to the attending regarding his antimicrobials?

Continuing cefepime until ANC ≥500 for 2 days 0%

Treating for a total duration of 14 days 0%

De-escalating cefepime back to prophylactic levofloxacin until ANC ≥500 for 2 days 0%

Stopping antibiotics entirely and monitoring for recurrent fever 0%

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HOW LONG

≥18 years
Heme malignancy including alloHCT
ANC ≤500 for ≥7 days
Fever (N=157)

Experimental group (N=78)
EAT stopped after ≥72 hr afebrile AND clinical recovery

Control Group (N= 79)
EAT stopped when ANC ≥500

Exclusion Criteria

- Microbiologically documented infections
- Fever for non-infectious etiologies
- Antibiotic use before the fever began

1st endpoint:

- Number of EAT-free days

2nd endpoint:

- All-cause mortality
- Total number of days of fever

alloHCT = allogeneic hematopoietic cell transplant
EAT = empirical antimicrobial therapy

Aguilar-Guisado M, et al. Lancet Haematol. 2017; 4:e573-583.

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HOW LONG

Baseline Demographics	Experimental (N=78)	Control (N=79)
Age, median (IQR)	52 (42-61)	54 (39-63)
Malignancy, n (%)		
Acute leukemia	40 (51)	31 (39)
Lymphoma	23 (29)	29 (37)
MM	7 (9)	14 (18)
Other	8 (10)	5 (6)
Treatments, n (%)		
Chemotherapy or IST	39 (50)	31 (39)
autoHCT	29 (37)	43 (54)
alloHCT	9 (12)	5 (6)
G-CSF treatment, n (%)	29 (37)	29 (37)
Days of neutropenia before fever onset, median (IQR)	2.5 (1-7)	2 (1-4)

P values not reported

IST = immunosuppressive therapy
IQR = interquartile range
MM = multiple myeloma
G-CSF = granulocyte-colony stimulating factor

Agular-Guisado M, et al. *Lancet Haematol.* 2017; 4:e573-583.

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HOW LONG

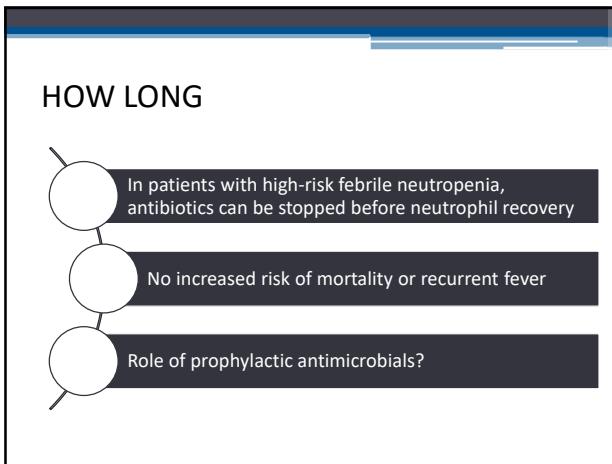
Outcome	Experimental group (N=78)	Control Group (N=79)	P value
EAT-free days*, mean ± SD	16.1 ± 6.3	13.6 ± 7.2	0.026
Mortality, n (%)	1 (1)	3 (4)	0.62
Days of fever, mean ± SD	5.7 ± 5	6.3 ± 5.9	0.53

*Primary outcome

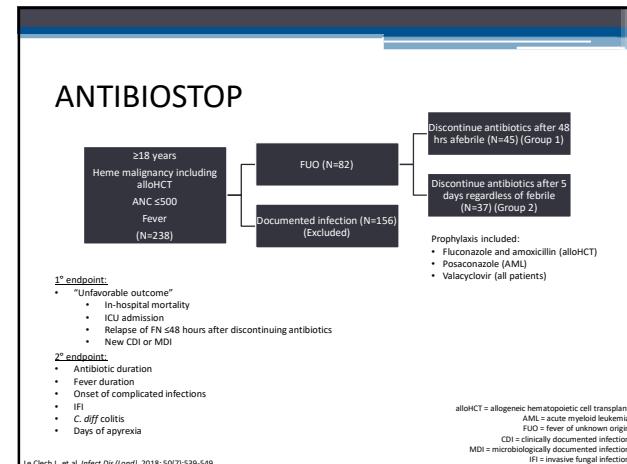
Agular-Guisado M, et al. *Lancet Haematol.* 2017; 4:e573-583.

SD = standard deviation

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ANTIBIOSTOP

Baseline Demographics	Group 1 (N=45)	Group 2 (N=37)	P-value
Age, mean ± SD	49.6 ± 16.2	54.3 ± 12.8	0.14
Malignancy, n (%)			
AML	26 (58)	25 (68)	
ALL	6 (13)	0	
MM	4 (9)	6 (16)	0.09
DLBCL	3 (6)	4 (11)	
Other	6 (13)	2 (5)	
Chemotherapy, n (%)			
Induction	16 (36)	10 (27)	0.03
Consolidation	4 (9)	7 (19)	0.18
Salvage	3 (7)	7 (19)	0.09
alloHCT	14 (31)	3 (8)	0.01
autoHCT	7 (15)	10 (27)	0.2
Other	1 (2)	0	0.36

SD = standard deviation
AML = acute lymphoblastic leukemia
MM = multiple myeloma
DLBCL = diffuse large B-cell lymphoma

Le Clech L, et al. *Infect Dis (Lond).* 2018; 50(7):539-549.

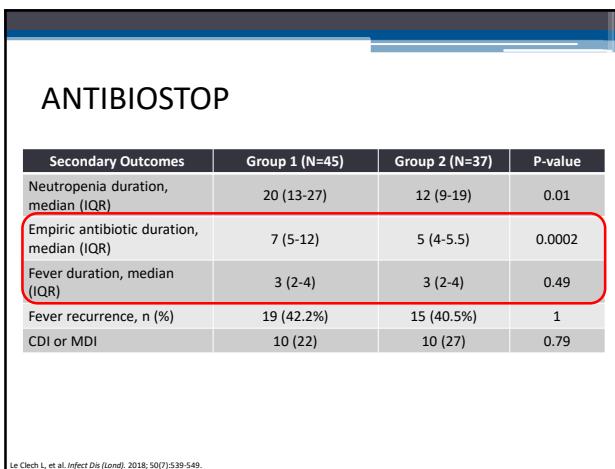
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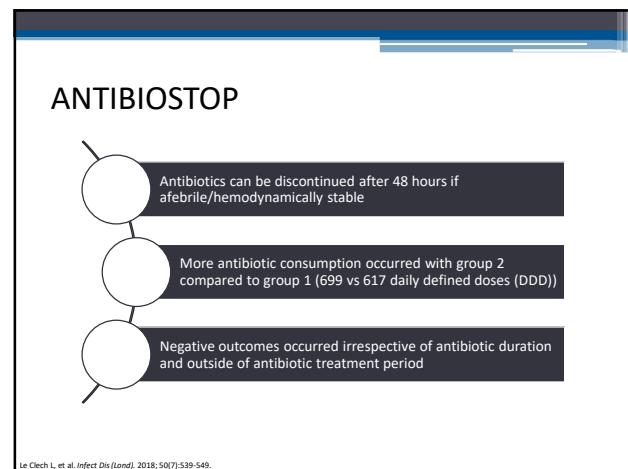
Primary Outcome, n (%)	Group 1 (N=45)	Group 2 (N=37)	HR (95% CI)	P-value
"Unfavorable Outcome"	10 (22)	12 (32)	0.49 (0.19 – 1.23)	0.11
In-hospital Mortality	1 (2)	2 (5)	0.7 (0.04 – 11.7)	0.8
ICU Admission	1 (2)	5 (14)	0.38 (0.03 – 4.34)	0.48
Fever relapse ≤48 hours after antibiotic discontinuation	9 (20)	8 (22)	0.92 (0.35 – 2.4)	0.82

Le Clech L, et al. *Infect Dis (Lond).* 2018; 50(7):539-549.

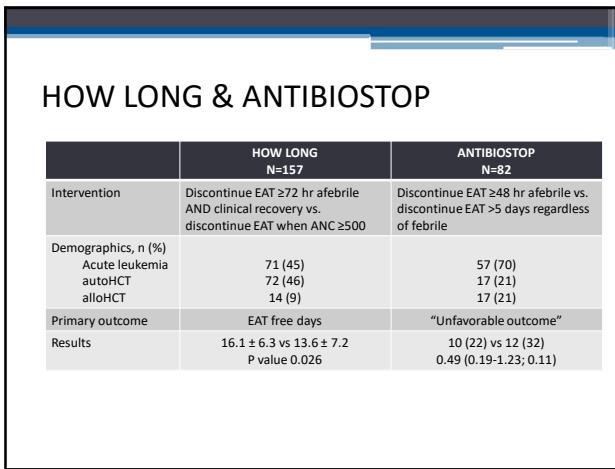
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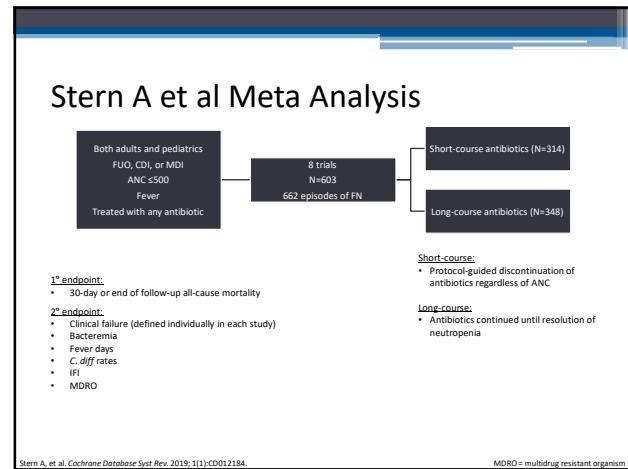
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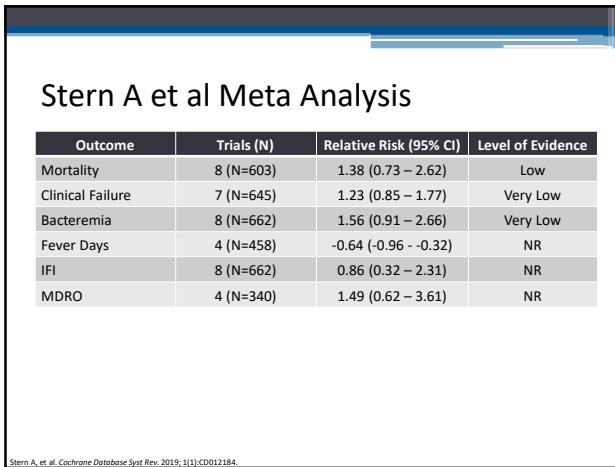
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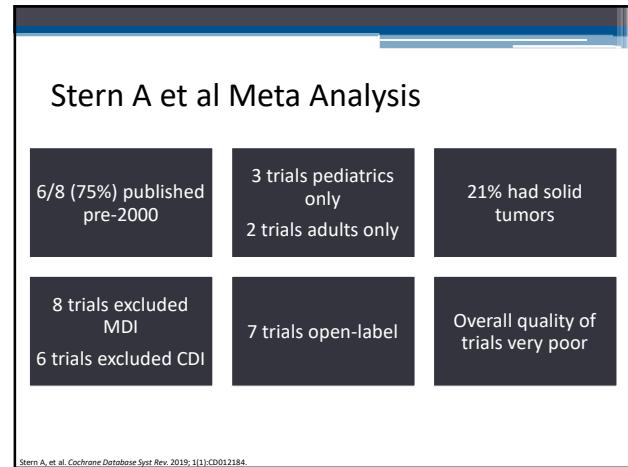
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Author's Conclusion

"We could make no strong conclusions on the safety of antibiotic discontinuation before neutropenia resolution among people with cancer and febrile neutropenia"

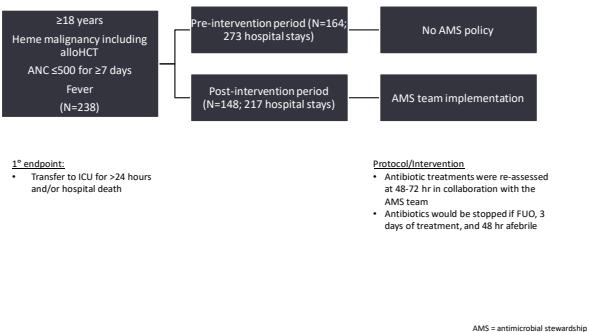
Stern A, et al. Cochrane Database Syst Rev. 2019; 1(1):CD012184.

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Can antibiotics be stopped if neutropenic in the absence of fever recurrence?

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Stewardship in High-Risk Patients



Contejean A, et al. Antimicrob Resist Infect Control. 2022; 11(1):52.

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Stewardship in High-Risk Patients

Baseline Demographics	Pre-Intervention (N=164; 273 hospitalizations)	Post-Intervention (N=148; 217 hospitalizations)	P-value
Age, median (years)	60.4	65.2	0.049
Male, n (%)	86 (52.4)	83 (56.1)	0.6
Malignancy, n (%)			
MM	37 (22.6)	45 (30.4)	0.44
AML	31 (18.9)	32 (21.6)	
Aggressive lymphoma	28 (17.1)	26 (17.6)	
Cause of hospitalization, n (%)			
Induction chemotherapy	57 (20.9)	38 (17.5)	0.28
Consolidation chemotherapy	32 (11.7)	27 (12.4)	
AutoHCT	51 (18.7)	48 (22.1)	
Stays with febrile episode, n (%)	118 (43.2)	116 (53.5)	0.031

Contejean A, et al. Antimicrob Resist Infect Control. 2022; 11(1):52.

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Stewardship in High-Risk Patients

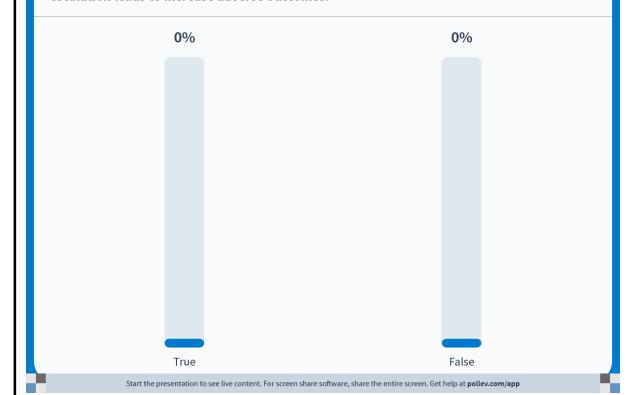
Outcomes	Pre-Intervention (N=164; 273 hospitalizations)	Post-Intervention (N=148; 217 hospitalizations)	P-value
ICU transfer or death	49 (17.9)	18 (8.3)	0.002
ICU transfer	42 (15.4)	10 (4.6)	0.00022
Length of stay, median (days)	9	13	0.061
ESBL infection, n (%)	9 (3.3)	2 (0.9)	0.12
MRP, n (%)	4/5 (80)	2/8 (25)	0.1
Antibiotic Use Δ			
Aminoglycosides	-49%	0.64	
Glycopeptides	-42%	0.34	
Carbapenems	-85%	0.03	
	-72%	0.04	

Contejean A, et al. Antimicrob Resist Infect Control. 2022; 11(1):52.

MRP = meropenem-resistant *Pseudomonas* spp.

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Emerging literature on de-escalating antibiotics before count recovery showed early de-escalation leads to increase adverse outcomes.

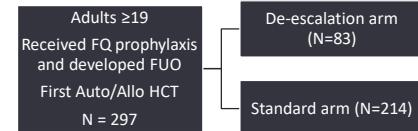


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Is returning to prophylaxis beneficial?

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Rearigh et al. – Returning to FQ

1st endpoint:

- Days of BSA within 30 days of FN

2nd endpoint:

- 30-day mortality
- Re-hospitalization
- Clinical decompensation needing ICU transfer or pressor support
- New infections
- LOS from FN

De-escalation:

- Antibiotics de-escalated to FQ
- No documented infection
- Hemodynamically stable
- Afebrile x48 hours

Standard:

- Antibiotics continued until resolution of neutropenia

BSA = broad-spectrum antibiotics
LOS = length of stay

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Rearigh et al. – Returning to FQ

Baseline Demographics	De-Escalation (N=83)	Standard (N=214)	P-value
Age, median (years)	53.7	56.8	0.01
Male, n (%)	59 (71)	130 (61)	0.11
HCT, n (%)			
Auto	47 (57)	183 (86)	
Allo	36 (43)	31 (14)	<0.001
Matched alloHCT, n (%)	31 (86%)	31 (100%)	0.06
Malignancy, n (%)			
AML	13 (16)	11 (5)	0.01
ALL	9 (11)	3 (1)	<0.001
MM	8 (10)	80 (38)	<0.001
Neutropenia duration, median (day)	9.1	8	<0.001
Fever duration, median (day)	2.7	3.5	<0.001

Rearigh L, et al. Ann Hematol. 2020; 99(8): 1917-1924.

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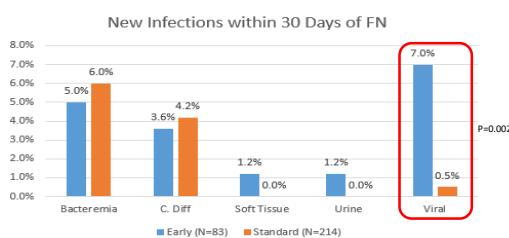
Rearigh et al. – Returning to FQ

Outcomes	De-Escalation (N=83)	Standard (N=214)	P-value
BSA duration, median (days)	3.86	4.62	0.03
30-day mortality	0	1 (0.4)	1
Re-hospitalization	6 (7.2)	23 (10.7)	0.51
Decompensation, n (%)			
ICU transfer	0	3 (1.4)	0.56
Vasopressor use	0	2 (0.9)	1
Fever recurrence, n (%)	15 (18)	18 (8)	0.02
New infection	11 (13.2)	18 (8.4)	0.27
LOS, median (days)	6.96	6.4	0.048

Rearigh L, et al. Ann Hematol. 2020; 99(8): 1917-1924.

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Rearigh et al. – Returning to FQ



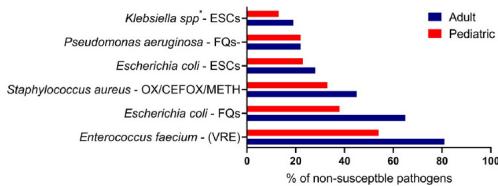
Rearigh L, et al. Ann Hematol. 2020; 99(8): 1917-1924.

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Are there any negative effects to prolonged antibiotics?

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Risk of Resistance



Nanayakkara AK, et al. CA Cancer J Clin. 2021; 71(6):488-504.

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Risk of Resistance

Caro et al.	FQ prophylaxis in area with high FQ resistance did not increase antimicrobial resistance
Gudiol et al.	Increased MDR GNR in patients who had prior antibiotics as well as prior inappropriate antibiotics for an initial infection
Maakaron et al.	FQ prophylaxis reduces bacteremia rates in autoHCT but increases resistant organisms, particularly in MM compared to lymphoma ($p=0.01$)
Mikulska et al.	Meta analysis: FQ prophylaxis did not impact OS (OR 1.01; 0.73-1.41). No increased risk in FQ-resistant infections, but increased risk of colonization
Zhang et al.	In low-risk FN patients, an increased risk of FQ-resistant isolates are seen (37%)

Caro J, et al. Clin Lymphoma Myeloma Leuk. 2022; 22(12):903-911.
 Gudiol C, et al. J Antimicrob Chemother. 2011; 66(3):657-673.
 Maakaron JE, et al. Biol Blood Marrow Transplant. 2020; 26(8):e198-e201.
 Mikulska M, et al. J Infect. 2018; 76(1):20-37.
 Zhang S, et al. BMC Cancer. 2015; 15:42.

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Secondary Infections

Schalk et al.	In AML patients, increased risk of <i>C diff</i> . with increased antibiotics (2 vs 1) , use of ceftazidime , longer antibiotic duration (mean 7 vs 4 days), and extended duration of neutropenia
Dingle et al.	Restricting FQ decreases incidence of <i>C diff</i> .

Schalk E, et al. Ann Hematol. 2010; 89(1):8-14.
 Dingle KE, et al. Lancet Infect Dis. 2017; 17(4):411-421.

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Ethics

Inclusion (N=7)

- Neutropenic AML patients
- BSA >7 days
- Afebrile ≥5 days (fever of unknown origin)
- Clinically stable

Intervention

- All antibiotics discontinued
- Temperature monitored every 3 hours
- Antibiotics reintroduced for fever

Micol JB, et al. Clin Microbiol Infect. 2014; 20(7):O453-5.

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Ethics

3/7 patients had rapid (<3 days) recurrent fever

2/3 had documented bacteremia; one transferred to ICU for septic shock

Micol JB, et al. Clin Microbiol Infect. 2014; 20(7):O453-5.

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Summary

No clear guideline directed consensus on duration of empiric antibiotics

Emerging literature indicates early de-escalation of antibiotics before ANC >500 did not lead to adverse outcomes

Risk of resistance with antibiotics cannot be ruled out

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Case

CH is a 68 yo WM admitted for alloHCT. He has been receiving levofloxacin 500 mg Qday, fluconazole 400 mg Qday, and acyclovir 400 mg BID as prophylaxis. On Day +5 his ANC is 0 and he is febrile. His WBC is 2.5. He has been on cefepime 2g Q8hr. On Day +9 he has been afebrile for 72 hr, vital signs stable, ANC 0, and no source of infection has been identified. What do you recommend to the attending regarding his antimicrobials?

Continuing cefepime until ANC \geq 500 for 2 days 0%

Treating for a total duration of 14 days 0%

De-escalating cefepime back to prophylactic levofloxacin until ANC \geq 500 for 2 days 0%

Stopping antibiotics entirely and monitoring for recurrent fever 0%

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Future Questions

- Which strategy is better – early de-escalation to prophylaxis or discontinuing antibiotics entirely
- Which patients are ideal candidates for early de-escalation
- Will implementing early de-escalation policies help curb rising bacterial resistance rates

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After listening to this lecture, my opinion on early vs late antibiotic de-escalation has changed

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Less Is More. Or Is It? Early vs Late Antibiotic De-Escalation in Febrile Neutropenia

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