Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Antimicrobial Stewardship Opportunity: Discontinuing Antibiotics in Febrile Neutropenia

Fever (single temp ≥ 101°F or ≥ 100.4°F sustained over a 1 hour period) is common during neutropenia (absolute neutrophil count (ANC) < 500 cells/mm^3). Empiric broad spectrum antibiotics are recommended, but blood cultures are often negative and a source of infection is never found. In patients who have defervesced, Infectious Diseases Society of America (IDSA) guidelines recommend to continue empiric antibiotics until ANC is > 500 cells/mm^3 and rising.[1] To reduce the risk for drug toxicity, *C. difficile* infection, and the emergence of drug resistant bacteria, can antibiotics be stopped sooner in neutropenic patients who have defervesced?

Why was continuing antibiotics until neutrophil recovery recommended by the IDSA?

The 2010 IDSA guidelines base their recommendation on expert opinion and note that "years of experience have proven this approach to be safe and effective."[1]

What do other guidelines recommend?

The 2011 4th European Conference on Infections in Leukemia (ECIL-4) guideline recommends that antibiotics can be stopped after 72 hours in patients who have been hemodynamically stable and afebrile for at least 48 hours, **irrespective of the neutrophil count or expected duration of neutropenia**. Patients should be monitored inpatient for at least another 24 -48 hours. If fever recurs, clinical evaluation, blood cultures, and restarting antibiotics is indicated. The ECIL-4 guideline bases this recommendation on evidence from small numbers of pediatric patients from randomized controlled trials and observational studies in adults and pediatrics.[2]

Is new, stronger evidence available?

Yes. The 2017 HOW LONG study randomized febrile neutropenia patients without an initial explanation for fever to either discontinue empiric antibiotics after 72 hours of clinical stability and no fever, irrespective of neutrophil count (experimental group) or continue antibiotics until clinical stability, no fever, and ANC > 500 cells/mm^3 (control group). Patients were followed for 28 days after start of empiric antibiotics. Outcomes of interest in summarized in the table below.[3]

	Experimental Group, n=78	Control Group, n=79	p value
Antibiotic free days, mean (SD)	16.1 (6.3)	13.6 (7.2)	0.026
Crude mortality, n (%)	1 (1.3%)	3 (3.8%)	0.62
Days of fever, mean (SD)	5.7 (5)	6.3 (5.9)	0.53
Recurrent fever*, n (%)	11 (14%)	14 (18%)	0.54
All bacterial infections*, n (%)	14 (39%)	16 (46%)	-
All fungal infections*, n (%)	8 (22%)	13 (37%)	-
All serious adverse events*, n (%)	11 (14%)	27 (34%)	-

***during 28 day follow-up period**

Antibiotic use was less in the experimental group, while mortality and days of fever were similar between groups. Recurrent fever and secondary bacterial and fungal infections were **NOT** more common in the experimental group, despite less antibiotic exposure. More serious adverse events occurred in the control group.

Key Takeaway: Febrile neutropenic patients can be safely monitored off antibiotics after ≥ 72 hours of no fever and clinical stability, irrespective of neutrophil count.

References:

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2. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia [published correction appears in Haematologica. 2014 Feb;99(2):400]. *Haematologica*. 2013;98(12):1826-1835. doi:10.3324/haematol.2013.091025
3. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol*. 2017;4(12):e573-e583. doi:10.1016/S2352-3026(17)30211-9

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