Safety and Efficacy of Antibiotic De-escalation and Discontinuation in High-Risk Hematological Patients With Febrile Neutropenia: A Single-Center Experience

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Background. There is currently no consensus on optimal duration of antibiotic treatment in febrile neutropenia. We report on the clinical impact of implementation of antibiotic de-escalation and discontinuation strategies based on the Fourth European Conference on Infections in Leukaemia (ECIL-4) recommendations in high-risk hematological patients.

Methods. We studied 446 admissions after introduction of an ECIL-4–based protocol (hereafter "ECIL-4 group") in comparison to a historic cohort of 512 admissions. Primary clinical endpoints were the incidence of infectious complications including septic shock, infection-related intensive care unit (ICU) admission, and overall mortality. Secondary endpoints included the incidence of recurrent fever, bacteremia, and antibiotic consumption.

Results. Bacteremia occurred more frequently in the ECIL-4 group (46.9% [209/446] vs 30.5% [156/512]; $P < .001$), without an associated increase in septic shock (4.7% [21/446] vs 4.5% [23/512]; $P = .878$) or infection-related ICU admission (4.9% [22/446] vs 4.1% [21/512]; $P = .424$). Overall mortality was significantly lower in the ECIL-4 group (0.7% [3/446] vs 2.7% [14/512]; $P = .016$), resulting mainly from a decrease in infection-related mortality (0.4% [2/446] vs 1.8% [9/512]; $P = .058$). Antibiotic consumption was significantly reduced by a median of 2 days on antibiotic therapy (12 vs 14; $P = .001$) and 7 daily antibiotic doses (17 vs 24; $P < .001$) per admission period.

Conclusions. Our results support implementation of ECIL-4 recommendations to be both safe and effective based on real-world data in a large high-risk patient population. We found no increase in infectious complications and total antibiotic exposure was significantly reduced.

Keywords. antibiotic discontinuation; antimicrobial stewardship; febrile neutropenia.

Treatment of hematological malignancies with intensive chemotherapy is associated with an exceedingly high incidence of febrile neutropenia, reported at 80%–95% [1, 2]. Prompt initiation of empiric broad-spectrum antimicrobial therapy (EAT) has played a pivotal role in decreasing infection-related morbidity and mortality [3–5]. However, uncertainty remains around the timing of antibiotic de-escalation and/or discontinuation, especially in neutropenic patients without documented infection. In contrast to the Infectious Diseases Society of America (IDSA) and the European Society for Medical Oncology (ESMO), which recommend continuation of EAT until neutrophil recovery, guidelines of the Fourth European Conference on Infections in Leukaemia (ECIL-4) propose earlier discontinuation under specific conditions [6–8].

The feasibility and safety of more restrictive use of EAT has been reported in several recent publications. These include retrospective studies either comparing early vs late discontinuation [9–11] or using a before-after design to assess the effects of implementation of de-escalation/discontinuation strategies [12–14]. Prospective observational data were reported by Slobbe et al [15] with a single-arm study describing early discontinuation of EAT in 177 episodes of unexplained fever, and by Le Clech et al [16] comparing 2 different discontinuation strategies with a sequential design in 82 episodes of fever of unknown origin (FUO). The abovementioned studies used different de-escalation/discontinuation strategies and variable outcome measures, including recurrent fever, all-cause mortality, and number of antibiotic treatment days. Aguilar-Guisado et al reported the results of a randomized controlled trial in 157 episodes of febrile neutropenia without etiological diagnosis, which demonstrated that discontinuation of EAT after 72 hours of apyrexia and clinical recovery is safe and able to reduce unnecessary exposure to antimicrobials [17].

Despite the increasing amount of data confirming its safety, discontinuation of EAT in persistently neutropenic patients remains an issue of debate and has not been widely adopted in clinical practice across Europe [18–20]. Concerns remain that stopping EAT during neutropenia may increase the risk for recurrent infection and subsequent need for reescalation of antimicrobials [21]. Uncertainty around extrapolation of published results to a specific local distribution of pathogens and antimicrobial susceptibilities adds to this innate fear of early antibiotic de-escalation/discontinuation. Furthermore, antimicrobial practices are strongly affected by historical antibiotic prescription habits and experience in infection management. However, taking measures to limit antibiotic exposure is clinically relevant and timely, as prolonged use of broad-spectrum antibiotics has been associated with development of multidrug-resistant (MDR) bacteria, *Clostridioides difficile*, and fungal infections [22]. Rising rates of antimicrobial resistance have been observed in hematology patients and hematopoietic stem cell transplant recipients [23, 24].

In our center, standard operating procedures (SOPs) for treatment of febrile neutropenia were adapted in accordance with ECIL-4 recommendations as of February 2017. With this article we report on the safety and efficacy of these policy changes aimed at reducing antimicrobial consumption in a large population of high-risk [6] hematological patients.

METHODS

Study Design

We performed an interventional study without concurrent controls to analyze the clinical impact of implementation of ECIL-4 recommendations at the Antwerp University Hospital hematology ward. Our primary objective was to evaluate the safety of these policy changes, represented by the incidence of infectious complications including septic shock, infection-related intensive care unit (ICU) admission, and mortality. Secondary endpoints included the incidence of recurrent fever and bacteremia, compliance with SOPs, and changes in antibiotic consumption. As we studied a general policy change in line with published guidelines, approval of the hospital ethical committee was not required.

Intervention

Historically, initial EAT for febrile neutropenia consisted of meropenem and amikacin combination therapy. In absence of MDR strains, amikacin was discontinued after 5 days. A glycopeptide (usually vancomycin) was added empirically when fever persisted after 48–72 hours. This EAT was generally continued until neutrophil recovery irrespective of the etiology of the fever episode. This policy was based on IDSA/ESMO guidelines, previous experience, and local microbial profile.

Revision of SOP included creation of flowcharts (Supplementary Materials 1) on de-escalation/discontinuation of antibiotics, approved by the medical staff after collegial discussion. Implementation was achieved through an informative physician training session and initiated from February 2017 onward. In comparison to historic standard of care, main changes included:

- Increasing number of blood cultures drawn: In case of fever (≥38°C), blood cultures were obtained during the first 3 temperature spikes from each lumen (vs only 1 lumen) of the central line as well as peripherally.
- De-escalating combination therapy with amikacin to meropenem monotherapy after 3 instead of 5 days in absence of MDR strains.
- Adding a glycopeptide only in case of hemodynamic instability, ≥2 positive blood cultures for gram-positive bacteria, or clinical suspicion of catheter-related or skin/soft tissue infection.
- Introducing a clinical algorithm for antibiotic de-escalation/discontinuation in line with ECIL-4 recommendations [8] (Supplementary Materials 1): Without documented infection, EAT was discontinued after 72 hours or more in stable patients who had been afebrile for at least 48 hours, irrespective of neutrophil count or expected duration of neutropenia. In documented infections, targeted antibiotics were continued for at least 7 days until the infection was microbiologically eradicated, all clinical signs of infection were resolved, and fever had subsided for at least 4 days.

Infection Prevention and Control

All patients were admitted to single rooms equipped with high-efficiency particulate air filtration. Infection prophylaxis—consisting of fluconazole 200 mg and acyclovir 800 mg once daily—was initiated on the first day of chemotherapy. Fluoroquinolone prophylaxis was not provided according to local policy [25].

Data Collection

All patients admitted for induction/consolidation chemotherapy or hematopoietic stem cell transplantation (HSCT) resulting in a prolonged neutropenic episode from November 2011 through January 2017 (control group) and February 2017 through January 2021 (ECIL-4 group) were included. Their charts were evaluated for occurrence of febrile neutropenia, bacteremia, severe sepsis, septic shock, and ICU admission. Febrile neutropenia was defined as axillary temperature ≥38.0°C on 2 or more occasions in a 12-hour period or ≥38.3°C on a single occasion while experiencing neutropenia (absolute neutrophil count <500 cells/μL). Fever recurrence was defined as relapse of fever in patients who had been afebrile for 48 hours. Febrile episodes were classified into 3 categories based on clinical and microbiological findings: microbiologically

documented infection (MDI, ie, proven microbial pathogen), clinically documented infection (CDI, ie, diagnosed site of infection without proven microbiologic pathogenesis), and FUO [26]. Initial diagnostic workup consisted of a thorough physical examination, blood/urine cultures, and chest radiography. Additional investigations were performed according to clinical presentation. When fever persisted for >4 days, reassessment included thoracoabdominal computed tomographic scan and bronchoscopy with bronchoalveolar lavage in case of suspicious imaging.

Severe sepsis and septic shock were defined in accordance with the Surviving Sepsis Campaign [27]. Infection-related and overall mortality were recorded per studied admission period. Compliance with SOPs on treatment of febrile neutropenia was registered. As a measure of antibiotic consumption, the overall number of days on antibiotic therapy was recorded. To account for the use of combination therapy, total antibiotic exposure was calculated by adding the number of daily doses of every antibiotic administered. Data from blood cultures and surveillance stool cultures (performed twice weekly in both groups) were reviewed, including their resistance pattern.

Statistical Analysis

All data were analyzed using a statistical software package (SPSS, Inc, Chicago, Illinois). Comparison of the distribution of categorical covariates between groups was performed using the Pearson χ^2 test with significance levels at .05. For continuous variables, which were not normally distributed, comparisons were done by the Mann-Whitney U test.

RESULTS

During the 9-year study period, 958 consecutive admissions in 596 patients were included: 512 before (control group) vs 446 after (ECIL-4 group) introduction of SOPs according to ECIL-4 recommendations. Admission characteristics are shown in Table 1. Median age was 59 years (range, 16–84 years) with similar distribution between groups. The ECIL-4 group included a larger proportion of female patients (44.2% vs 35.7%; $P = .005$). Acute myeloid leukemia (45.9% [440/958]) was the most common underlying hematological disease, followed by multiple myeloma (18.6% [178/958]), non-Hodgkin lymphoma (9.6% [92/958]), myelodysplastic syndrome (8.5% [81/958]), and acute lymphoblastic leukemia (7.6% [73/958]). Intensive chemotherapy (induction/consolidation) was the most frequent reason for admission (43.9% [421/958]), whereas autologous HSCT was performed in 28.9% (277/958) and allogeneic HSCT in 27.1% (260/958) of admissions. This distribution did not change significantly over time. Median duration of hospitalization and profound neutropenia was 27 days and 15 days,

Table 1. Admission Characteristics

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	P Value
Age, y, median (range)	58 (16–84)	59 (17–81)	
Sex, male/female	329/183	249/197	.005
Hematologic disease			
Acute myeloid leukemia	223 (43.5)	217 (48.7)	
Multiple myeloma	96 (18.7)	82 (18.4)	
Non-Hodgkin lymphoma	51 (10.0)	41 (9.2)	
Myelodysplastic syndrome	50 (9.8)	31 (6.9)	
Acute lymphoblastic leukemia	42 (8.2)	31 (6.9)	
Other (Hodgkin, PMF, CMML, CML, SAA)	50 (9.8)	44 (9.9)	
Treatment			
Chemotherapy	232 (45.3)	189 (42.4)	
Acute myeloid leukemia	167/232 (72.0)	152/189 (80.4)	
Acute lymphoblastic leukemia	28/232 (12.1)	18/189 (9.5)	
Myelodysplastic syndrome	28/232 (12.1)	10/189 (5.3)	
Autologous transplant	143 (27.9)	134 (30.0)	
Multiple myeloma	85/143 (59.4)	79/134 (59.0)	
Non-Hodgkin lymphoma	43/143 (30.1)	40/134 (29.9)	
Hodgkin lymphoma	15/143 (10.5)	9/134 (6.7)	
Allogeneic transplant	137 (26.8)	123 (27.6)	
Acute myeloid leukemia	56/137 (40.9)	64/123 (52.0)	
Myelodysplastic syndrome	22/137 (16.1)	21/123 (17.1)	
Acute lymphoblastic leukemia	14/137 (10.2)	13/123 (10.6)	
Duration of hospitalization, d, median (range)	27 (10–101)	27 (12–79)	
Duration of profound neutropenia, d, median (range)	15 (2–78)	15 (3–45)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; ECIL-4, Fourth European Conference on Infections in Leukaemia; PMF, primary myelofibrosis; SAA, severe aplastic anemia.

respectively. A total of 15 637 neutropenic patient-days were evaluated.

Impact on Clinical Outcome

Impacts on clinical outcome are shown in Tables 2 and 3. Febrile neutropenia occurred more frequently in the ECIL-4 group (91.0% [406/446] vs 86.1% [441/512]; $P = .020$), with a higher number of fever episodes per admission. Of the 1367 recorded fever episodes, 419 (30.6%) were classified as MDI, 329 (24.1%) as CDI, and 619 (45.3%) as FUO. In the ECIL-4 group, more MDIs were diagnosed (35.3% [245/695] vs 25.9% [174/672]; $P < .001$), mainly due to an increase in gram-negative bacteremia. This resulted in a lower proportion of FUO (41.6% [289/695] vs 49.1% [330/672]; $P < .001$). Despite more frequent bacteremia in the ECIL-4 group, there was no increase in severe sepsis (7.6% [51/672] vs 7.3% [51/695]; $P = .860$), septic shock (3.7% [25/672] vs 3.0% [21/695]; $P = .474$), or infection-related ICU admission (3.1% [21/672] vs 3.3% [23/695]; $P = .847$).

In the ECIL-4 group, 3 patients died: 2 from an infectious cause (*Enterococcus faecium* sepsis complicated by ileal perforation, *Clostridium perfringens* sepsis) and 1 from multiorgan failure due to treatment toxicity. In the control group, 14 patients died: 9 from an infectious cause (3 pulmonary infections complicated by respiratory insufficiency and septic shock, 2 infectious colitis complicated by septic shock, 1 vancomycin-resistant *E faecium* sepsis, 1 *Escherichia coli* sepsis, 1 invasive pulmonary aspergillosis, 1 *Scedosporium* sepsis), 3 from relapsed refractory disease, and 2 from cardiogenic shock related to treatment toxicity.

Antibiotic Discontinuation

When applicable, the flowchart was implemented correctly in 91.8% of MDI, 94.5% of CDI, and 82.7% of FUO (Table 3). EAT was discontinued more frequently prior to neutrophil recovery in the ECIL-4 group (41.6% [289/695] vs 13.5% [91/672]; $P < .001$). Incidence of fever relapse was 53.2% (202/380) in case of antibiotic discontinuation vs 32.4% (320/987) while still on antibiotic therapy prior to neutrophil recovery. This was similar between groups. Overall, fever recurrence was more common in the ECIL-4 group (41.6% [289/695] vs 34.7% [233/672]; $P = .009$), resulting from more frequent antibiotic discontinuation. In the ECIL-4 group, the cause of fever relapse was a different MDI in 43.8% (67/153), a different CDI in 17.6% (27/153), the same MDI or CDI each in 3.9% (6/153) of cases, and FUO in 30.7% (47/153).

Antibiotic Consumption

Antibiotic therapy is shown in Tables 3 and 4. The total amount of days on antibiotic therapy per admission was significantly lower in the ECIL-4 group with a median of 12 vs 14 days ($P = .001$), whereas median duration of hospitalization remained unchanged. The number of antibiotic days saved was similar for different etiologies of fever. Total antibiotic exposure was more extensively reduced with a median of 24 daily doses per admission in the ECIL-4 group vs 17 in the control group ($P < .001$). Meropenem and amikacin were used in 90.0% (862/958) and 87.5% (839/958) of admissions, respectively. In the ECIL-4 group, the duration of therapy was significantly shorter with a median of 10 (range, 1–46) days vs 12 (range, 1–53) days for meropenem ($P = .002$) and 4 (range, 0–20) days vs 5 (range, 1–23) days for amikacin ($P < .001$). Amoxicillin-clavulanic acid (9.4% vs 5.5%; $P = .019$), temocillin (8.5% vs 1.4%; $P < .001$), and flucloxacillin (3.1% vs 1.2%; $P = .034$) were used more frequently in the ECIL-4 group. Use of vancomycin (38.8% vs 55.1%; $P < .001$) and teicoplanin (2.2% vs 16.0%; $P < .001$) declined significantly in the ECIL-4 group. Treatment with vancomycin was continued for a shorter period with a median of 8 (range, 1–35) days vs 10 (range, 1–38) days

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Table 2. Clinical Impact (Admission Periods)

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	P Value
Febrile neutropenia	441 (86.1)	406 (91.0)	.020
No. of fever episodes, median (range)	1 (0–4)	1 (0–4)	<.001
0	71 (13.9)	40 (9.0)	
1	250 (48.8)	193 (43.3)	
2	156 (30.5)	145 (32.5)	
3	31 (6.1)	60 (13.5)	
4	4 (0.8)	8 (1.8)	
Bacteremia	156 (30.5)	209 (46.9)	<.001
Severe sepsis	51 (10.0)	48 (10.8)	
Septic shock	23 (4.5)	21 (4.7)	
Infection-related ICU admission	21 (4.1)	22 (4.9)	
Mortality during hospitalization			
Overall mortality	14 (2.7)	3 (0.7)	.016
Infection-related mortality	9 (1.8)	2 (0.4)	.058

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECIL-4, Fourth European Conference on Infections in Leukaemia; ICU, intensive care unit.

Table 3. Clinical Impact (Fever Episodes)

Characteristic	Control Group (n = 672)	ECIL-4 Group (n = 695)	P Value
Type of fever			
Microbiologically documented infection	174 (25.9)	245 (35.3)	<.001
Bacteremia gram-negative	78/174 (44.8)	135/245 (55.1)	.038
Bacteremia gram-positive	59/174 (33.9)	75/245 (30.6)	
Bacteremia coagulase-negative staphylococci	14/174 (8.0)	24/245 (9.8)	
Fungal sepsis	9/174 (5.2)	1/245 (0.4)	.002
Pneumonia	6/174 (3.4)	8/245 (3.3)	
Proven invasive pulmonary aspergillosis	1/174 (0.1)	1/245 (0.1)	
Urinary tract infection	6/174 (3.4)	2/245 (0.8)	
Clinically documented infection	168 (25.0)	161 (23.2)	
Pneumonia	104/168 (61.9)	88/161 (54.7)	
Possible invasive pulmonary aspergillosis	24/168 (14.3)	21/161 (13.0)	
Probable invasive pulmonary aspergillosis	25/168 (14.9)	20/161 (12.4)	
(Entero)colitis	26/168 (15.5)	36/161 (22.4)	
Skin/soft tissue infection	18/168 (10.7)	7/161 (4.3)	
Oral cavity/dental abscess	6/168 (3.6)	10/161 (6.2)	
Sinusitis	6/168 (3.6)	3/161 (1.9)	
Fever of unknown origin	330 (49.1)	289 (41.6)	.005
Time to defervescence, d, median (range)	2 (1–23)	2 (1–20)	.001
Severe sepsis	51 (7.6)	51 (7.3)	
Septic shock	25 (3.7)	21 (3.0)	
Infection-related ICU admission	21 (3.1)	23 (3.3)	
Compliance with stewardship SOP flowchart (when applicable)			
Microbiologically documented infection	…	179/195 (91.8)	
Clinically documented infection	…	120/127 (94.5)	
Fever of unknown origin	…	215/260 (82.7)	
Antibiotic discontinuation prior to neutrophil recovery	91 (13.5)	289 (41.6)	<.001
Microbiologically documented infection	14/174 (18.9)	75/245 (30.6)	
Duration of antibiotic therapy, d, median (range)	9.5 (5–14)	7 (5–21)	
Antibiotic days saved, d, median (range)	1 (0–8)	4 (0–22)	
Clinically documented infection	15/168 (8.9)	54/161 (33.5)	
Duration of antibiotic therapy, d, median (range)	10 (6–17)	8 (4–15)	
Antibiotic days saved, d, median (range)	4 (3–7)	3.5 (1–10)	
Fever of unknown origin	62/330 (18.8)	160/289 (55.4)	
Duration of antibiotic therapy, d, median (range)	9 (3–17)	5 (0–19)	
Antibiotic days saved, d, median (range)	3 (0–12)	5 (0–19)	
Recurrent fever			
Overall	233/672 (34.7)	289/695 (41.6)	.009
After discontinuation prior to neutrophil recovery	49/91 (53.8)	153/289 (52.9)	
While still on antibiotics prior to neutrophil recovery	184/589 (31.7)	136/406 (33.5)	
Cause of recurrent fever after discontinuation			
Microbiologically documented infection—same as before	1/49 (2.0)	6/153 (3.9)	
Microbiologically documented infection—different	20/49 (40.8)	67/153 (43.8)	
Clinically documented infection—same as before	2/49 (4.1)	6/153 (3.9)	
Clinically documented infection—different	11/49 (22.4)	27/153 (17.6)	
Fever of unknown origin	15/49 (30.6)	47/153 (30.7)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECIL-4, Fourth European Conference on Infections in Leukaemia; ICU, intensive care unit; SOP, standard operating procedure.

(P = .011). Glycopeptide association was performed in line with recommendations in 45.5% (143/314) of cases in the control group vs 82.5% (146/177) in the ECIL-4 group (P < .001). The primary rationale was persisting fever in the control group (43.0% [135/314] vs 7.9% [14/177]; P < .001) and ≥2 positive blood cultures for gram-positive bacteria in the ECIL-4 group (61.6% [109/177] vs 28.3% [89/314]; P < .001).

Microbiological Impact

Microbiological impact is shown in Table 5. Of 382 bacteremia episodes, 211 (55.2%) were caused by gram-negative vs 171 (44.8%) by gram-positive bacteria. The majority of gram-negative bacteremia was caused by *E coli* (118/211 [55.9%]), followed by *Klebsiella* species (35/211 [16.6%]) and *Pseudomonas aeruginosa* (19/211 [9.0%]). Of the 211 isolated gram-negatives,

Table 4. Antibiotic Consumption

Characteristic	Control Group (n = 512)	ECIL-4 Group (n = 446)	P Value
Days of antibiotic therapy, median (range)	14 (0–69)	12 (0–60)	.001
Total antibiotic exposure, median (range of daily doses)	24 (0–129)	17 (0–82)	<.001
Amikacin			
Used (yes/no)	444 (86.7)	395 (88.6)	
Duration of treatment, d, median (range)	5 (1–23)	4 (1–20)	<.001
Meropenem			
Used (yes/no)	455 (88.9)	407 (91.3)	
Duration of treatment, d, median (range)	12 (1–53)	10 (1–46)	.002
Piperacillin-tazobactam			
Used (yes/no)	9 (1.8)	12 (2.7)	
Duration of treatment, d, median (range)	6 (2–10)	3.5 (3–18)	
Cefipime			
Used (yes/no)	57 (11.1)	9 (2.0)	<.001
Duration of treatment, d, median (range)	7 (1–25)	10 (4–19)	
Aztreonam			
Used (yes/no)	23 (4.5)	16 (3.6)	
Duration of treatment, d, median (range)	7 (2–31)	8.5 (1–38)	
Temocillin			
Used (yes/no)	7 (1.4)	38 (8.5)	<.001
Duration of treatment, d, median (range)	5 (1–8)	4 (1–7)	
Vancomycin			
Used (yes/no)	282 (55.1)	173 (38.8)	<.001
Duration of treatment, d, median (range)	10 (1–38)	8 (1–35)	.011
Teicoplanin			
Used (yes/no)	82 (16.0)	10 (2.2)	<.001
Duration of treatment, d, median (range)	9 (1–32)	12.5 (2–26)	
Amoxicillin-clavulanic acid			
Used (yes/no)	28 (5.5)	42 (9.4)	.019
Duration of treatment, d, median (range)	6 (1–20)	3 (1–16)	.004
Flucloxacillin			
Used (yes/no)	6 (1.2)	14 (3.1)	.034
Duration of treatment, d, median (range)	5 (2–8)	4 (1–12)	
Total glycopeptide			
Used (yes/no)	314 (61.3)	177 (39.7)	<.001
Compliance with start rules	143/314 (45.5)	146/177 (82.5)	<.001
Rationale for association of glycopeptide			
Prophylaxis	10/314 (3.2)	0/177 (0.0)	
Persisting fever	135/314 (43.0)	14/177 (7.9)	<.001
Rising inflammatory parameters	9/314 (2.9)	3/177 (1.7)	
MDI ≥2 sets gram positive	89/314 (28.3)	109/177 (61.6)	<.001
MDI 1 set pathogenic gram positive	10/314 (3.2)	10/177 (5.6)	
MDI 1 set contaminant gram positive	17/314 (5.4)	14/177 (7.9)	
MDI pneumonia	2/314 (0.6)	2/177 (1.1)	
CDI central line	7/314 (2.2)	4/177 (2.3)	
CDI skin/soft tissue/oral cavity/dental	27/314 (8.6)	14/177 (7.9)	
Septic shock	8/314 (2.5)	7/177 (4.0)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CDI, clinically documented infection; ECIL-4, Fourth European Conference on Infections in Leukaemia; MDI, microbiologically documented infection.

20 (9.5%) were fluoroquinolone resistant and 9 (4.3%) MDR. The most frequently occurring cause of gram-positive bacteremia was *Streptococcus viridans* (54/171 [31.6%]), followed by coagulase-negative staphylococci (47/171 [27.5%]; methicillin-resistant 32/47 [68.0%]), *E faecium* (29/171 [17.0%]; vancomycin-resistant 1/29 [3.4%]), and *Staphylococcus aureus* (21/171 [12.3%]; methicillin-resistant 2/21 [9.5%]). There were

no significant differences between groups in the distribution of isolated bacteria or resistance patterns.

Surveillance stool cultures confirmed colonization with carbapenemase-producing Enterobacteriaceae in 0.5% (5/958) and vancomycin-resistant enterococci (VRE) in 1.8% (17/958). The latter were more significantly present in the control group (16/512 vs 1/446; *P* < .001). *Clostridioides difficile* was

Table 5. Microbiological Impact

Type of Culture	Control Group (n = 149)	ECIL-4 Group (n = 233)	P Value
Blood cultures			
Gram-positive	73/149 (49.0)	98/233 (42.1)	.184
Streptococcus viridans	26/73 (35.6)	28/98 (28.6)	
CoNS	20/73 (27.4)	27/98 (27.6)	
Enterococcus faecium	10/73 (13.7)	19/98 (19.4)	
Staphylococcus aureus	7/73 (9.6)	14/98 (14.3)	
Other gram-positive	10/73 (13.7)	10/98 (10.2)	
Quinolone resistant	12/73 (16.4)	29/98 (29.6)	
MRSA	1/7 (14.3)	1/14 (7.1)	
Methicillin-resistant CoNS	11/20 (55.0)	21/27 (77.8)	.098
Vancomycin-resistant enterococci	1/10 (10.0)	0/19 (0.0)	
Gram-negative	76/149 (51.0)	135/233 (57.9)	.184
Escherichia coli	47/76 (61.8)	71/135 (52.6)	
Klebsiella species	7/76 (9.2)	28/135 (20.7)	
Pseudomonas species	7/76 (9.2)	12/135 (8.9)	
Other gram-negative	15/76 (19.7)	24/135 (17.8)	
Multidrug susceptible	51/76 (67.1)	93/135 (68.9)	
Quinolone resistant	9/76 (11.8)	11/135 (8.1)	
Multidrug resistant	5/76 (6.6)	4/135 (3.0)	
Stool cultures	Control group (n = 512)	ECIL-4 group (n = 446)	
CPE	1 (0.2)	4 (0.9)	
Vancomycin-resistant enterococci	16 (3.1)	1 (0.2)	<.001
Clostridioides	15 (2.9)	12 (2.7)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CoNS, coagulase-negative staphylococci; CPE, carbapenemase-producing Enterobacteriaceae; ECIL-4, Fourth European Conference on Infections in Leukaemia; MRSA, methicillin-resistant *Staphylococcus aureus*.

diagnosed in 2.8% (27/958) and equally distributed between groups.

DISCUSSION

The need for implementation of antimicrobial stewardship interventions in hematological patients is emphasized by an increasing prevalence of multidrug resistance among gram-negative pathogens, with prior antibiotic exposure as primary independent risk factor [24, 28]. Additionally, extended use of broad-spectrum antibiotics for prophylaxis or empirical treatment of febrile neutropenia predisposes patients to *C difficile* and invasive fungal infections [29–31].

We report on the safety and efficacy of implementing ECIL-4 recommendations for treatment of febrile neutropenia in high-risk hematological patients, including antibiotic discontinuation prior to neutrophil recovery. It is important to note that fluoroquinolone prophylaxis is not routinely used based on previous experience [25]. The proposed policy changes were well accepted, mirrored by high compliance rates (>80%) with predefined flowcharts. Noncompliance occurred more frequently in the on-call setting and when patients were believed not to be in good enough clinical condition to support fever relapse.

Implementation of the recommendations was accompanied by a shift of fever episodes from FUO (49.1% to 41.6%) to MDI (25.9% to 35.3%). This may be explained by the increased number of blood cultures drawn in the ECIL-4 group (ie, 34% increase in mean number of blood cultures per month), resulting in a higher diagnostic yield as we noted regularly that only 1 of several blood culture sets came back positive. This created the opportunity to de-escalate more frequently to targeted and smaller-spectrum antibiotics, reflected by increased prescription of amoxicillin-clavulanic acid, temocillin, and flucloxacillin. The higher incidence of bacteremia in the ECIL-4 group was not associated with an increase in infectious complications, such as severe sepsis, septic shock, or infection-related ICU admission. This confirms safety of implementation of ECIL-4 recommendations in our patient population, corroborating reports by other authors using a variety of early antibiotic discontinuation strategies [9, 11, 13–16]. In contrast to previous studies, we found a decrease in overall mortality, in large part resulting from a reduction in fatal respiratory and fungal infections. Patient characteristics did not differ between groups, but influence of other possible confounders—such as functional status of the patient or remission status of the underlying disease—cannot be excluded.

In contrast with earlier studies, we did find an increase in fever relapse resulting from antibiotic discontinuation prior to neutrophil recovery [9–12, 16, 17]. The reported rate of

recurrent fever varies between 14% and 40%. We observed fever relapse in 53.2% of cases after discontinuation vs 32.4% while still on antibiotic therapy. This may be related to the fact that fluoroquinolone prophylaxis is not routinely used at our center. In the ECIL-4 group, antibiotic treatment was reinitiated in 52.9% of cases and new fever episodes were most commonly (92.2%) related to a different underlying cause. It is not surprising that antibiotic discontinuation during profound neutropenia is frequently followed by subsequent new fever episodes. However, this did not lead to any infection-related deaths as all patients responded well to reinitiation of the same first-line antibiotic regimen.

Implementation of ECIL-4 recommendations reduced the number of days on antibiotic therapy by a median of 2 days relative to a 27-day median duration of hospitalization, in line with previously published studies [9–11, 14, 17]. To account for the effect of combination therapy, we calculated total antibiotic exposure, which was more extensively reduced by a median of 7 daily doses. It is important to underline the possible benefit of this reduction in antibiotic pressure, as unnecessarily prolonged antimicrobial therapy may lead to difficult-to-treat breakthrough infections [24, 28]. We did not find a significant impact on resistance patterns of cultured microorganisms. However, baseline resistance rates were low to begin with. Surveillance stool cultures showed a higher incidence of VRE due to an outbreak in the control group, which led to weekly screening thereafter.

The strengths of our study lie in the large population size and the use of standardized objective criteria for antibiotic discontinuation according to ECIL-4 recommendations. The most important limitation is the pre–post interventional design without concurrent controls. Comparison with a historical cohort during a longer time frame may cause bias through adapted treatment strategies and supportive care. However, no changes were made to our standard diagnostic workup and no new antibiotics/antifungals were introduced into our daily practice throughout the past decade. Our low baseline resistance rates may also limit extrapolation of results to other centers as local distribution of pathogens and antimicrobial susceptibilities should always be considered when making decisions regarding antibiotic treatment.

CONCLUSIONS

Antibiotic stewardship recommendations put forward in the ECIL-4 guidelines are not widely implemented in clinical practice throughout Europe because of concern for recurrent infection and subsequent need for reescalation of antibiotic treatment. Our study results support implementation of ECIL-4 recommendations to be both safe and effective based on real-world data in a large patient population. There was no increase in infectious complications, and total antibiotic exposure was reduced by a median of 7 daily antibiotic doses.

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