Clinical Infectious Diseases

MAJOR ARTICLE

Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group

Diana Averbuch,[1] Gloria Tridello,[2] Jennifer Hoek,[3] Malgorzata Mikulska,[4] Hamdi Akan,[5] Lucrecia Yañez San Segundo,[6] Thomas Pabst,[7] Tülay Özçelik,[8] Galina Klyasova,[9] Irene Donnini,[10] Depei Wu,[11] Zafer Gülbas,[12] Tsila Zuckerman,[13] Aida Botelho de Sousa,[14] Yves Beguin,[15] Aliénor Xhaard,[16] Emmanuel Bachy,[17] Per Ljungman,[18] Rafael de la Camara,[19] Jelena Rascon,[20] Isabel Ruiz Camps,[21] Antonin Vitek,[22] Francesca Patriarca,[23] Laura Cudillo,[24] Radovan Vrhovac,[25] Peter J. Shaw,[26] Tom Wolfs,[27] Tracey O'Brien,[28] Batia Avni,[1] Gerda Silling,[29] Firas Al Sabty,[30] Stelios Graphakos,[31] Marja Sankelo,[32] Henrik Sengeloev,[33] Srinivas Pillai,[34] Susanne Matthes,[35] Frederiki Melanthiou,[36] Simona Iacobelli,[24] Jan Styczynski,[37] Dan Engelhard,[1,a] and Simone Cesaro[2,a]

[1]Hadassah University Hospital, Jerusalem, Israel; [2]Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; [3]European Bone Marrow Transplantation Data Office, Leiden, The Netherlands; [4]Ospedale San Martino, Genova, Italy; [5]Faculty of Medicine, Ankara University, Turkey; [6]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [7]University Hospital, Bern, Switzerland; [8]Florence Nightingale Sisli Hospital, Istanbul, Turkey; [9]National Research Center for Hematology, Moscow, Russia; [10]Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; [11]First Affiliated Hospital of Soochow University, Suzhou Jiangsu, China; [12]Anadolu Medical Center Hospital, Kocaeli, Turkey; [13]Rambam Medical Center, Haifa, Israel; [14]Hospital dos Capuchos, Lisbon, Portugal; [15]University of Liege, Belgium; [16]Hospital St Louis, Paris, France; [17]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, France; [18]Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden; [19]Hospital de la Princesa, Madrid, Spain; [20]University Hospital Santariskiu Klinikos, Vilnius, Lithuania; [21]Hospital Vall d'Hebron, Barcelona, Spain; [22]Institute of Hematology and Blood Transfusion, Prague, Czech Republic; [23]Azienda Ospedaliero Universitaria, Udine, Italy; [24]Tor Vergata University, Rome, Italy; [25]University Hospital Center Rebro, Zagreb, Croatia; [26]The Children's Hospital at Westmead, Sydney, Australia; [27]University Hospital for Children, Utrecht, The Netherlands; [28]Sydney Children's Hospital, Randwick, Australia; [29]University of Münster, Germany; [30]University Hospital, Bratislava, Slovakia; [31]St Sophia Children's Hospital, Athens, Greece; [32]Tampere University Hospital, Finland; [33]Rigshospitalet, Copenhagen, Denmark; [34]University Hospital of North Staffordshire, Stoke, United Kingdom; [35]St Anna Kinderspital, Vienna, Austria; [36]Nicosia General Hospital, Nicosia Strovolos, Cyprus; and [37]Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland

Background. This intercontinental study aimed to study gram-negative rod (GNR) resistance in hematopoietic stem cell transplantation (HSCT).

Methods. GNR bacteremias occurring during 6 months post-HSCT (February 2014–May 2015) were prospectively collected, and analyzed for rates and risk factors for resistance to fluoroquinolones, noncarbapenem anti-*Pseudomonas* β-lactams (noncarbapenems), carbapenems, and multidrug resistance.

Results. Sixty-five HSCT centers from 25 countries in Europe, Australia, and Asia reported data on 655 GNR episodes and 704 pathogens in 591 patients (Enterobacteriaceae, 73%; nonfermentative rods, 24%; and 3% others). Half of GNRs were fluoroquinolone and noncarbapenem resistant; 18.5% carbapenem resistant; 35.2% multidrug resistant. The total resistance rates were higher in allogeneic HSCT (allo-HSCT) vs autologous HSCT (auto-HSCT) patients ($P < .001$) but similar in community-acquired infections. Noncarbapenem resistance and multidrug resistance were higher in auto-HSCT patients in centers providing vs not providing fluoroquinolone prophylaxis ($P < .01$). Resistance rates were higher in southeast vs northwest Europe and similar in children and adults, excluding higher fluoroquinolone- and β-lactam/β-lactamase inhibitor resistance rates in allo-HSCT adults. Non-*Klebsiella* Enterobacteriaceae were rarely carbapenem resistant. Multivariable analysis revealed resistance risk factors in allo-HSCT patients: fluoroquinolone resistance: adult, prolonged neutropenia, breakthrough on fluoroquinolones; noncarbapenem resistance: hospital-acquired infection, breakthrough on noncarbapenems or other antibiotics (excluding fluoroquinolones, noncarbapenems, carbapenems), donor type; carbapenem resistance: breakthrough on carbapenem, longer hospitalization, intensive care unit, previous other antibiotic therapy; multidrug resistance: longer hospitalization, breakthrough on β-lactam/β-lactamase inhibitors, and carbapenems. Inappropriate empiric therapy and mortality were significantly more common in infections caused by resistant bacteria.

Conclusions. Our data question the recommendation for fluoroquinolone prophylaxis and call for reassessment of local empiric antibiotic protocols. Knowledge of pathogen-specific resistance enables early appropriate empiric therapy. Monitoring of resistance is crucial.

Clinical Trials Registration. NCT02257931

Keywords. antimicrobial resistance; gram-negative rods; hematopoietic stem cell transplantation; bacteremia.

Received 17 May 2017; editorial decision 7 July 2017; accepted 24 July 2017; published online July 26, 2017.

Presented in part: 42nd Annual European Bone Marrow Transplantation conference, Valencia, Spain, 2016.

[a]D. E. and S. C. contributed equally to this work.

Correspondence: Diana Averbuch, Pediatric Infectious Diseases, Hadassah-Hebrew University Medical Center, Jerusalem, Israel (dina8282@walla.co.il).

Clinical Infectious Diseases® 2017;65(11):1819–28

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cix646

Hematopoietic stem cell transplantation (HSCT) is increasingly used to cure a wide range of malignant and nonmalignant disorders [1]. Growing antimicrobial resistance, especially among gram-negative rods (GNRs), negatively affects prognosis and can influence eligibility for HSCT [2]. Treatment options remain limited [3], although the proportion of GNRs among infectious etiologies is rising [4–6] and resistant GNR infections are

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

associated with delay in giving appropriate therapy, increased mortality, and high risk of infection recurrence [7–9]. Several studies, mainly limited to single centers or countries, describe rates and risk factors for specific resistant pathogens, such as extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae or multidrug-resistant (MDR) bacteria in patients with cancer and HSCT recipients [10–13]. The majority, however, were performed in countries with high resistance rates in both the hospitalized and general populations [12–14]. The risk of infection is influenced by local factors, among them prevalence of resistance, prophylactic practices, empiric treatment, and antimicrobial stewardship. Only a handful of studies focus on children and autologous HSCT (auto-HSCT) patients [12, 15, 16]. This study aimed to describe resistance rates and risk factors in GNR bacteremia in HSCT patients, based on large intercontinental data.

METHODS

Study Design and Data Collection

This was a noninterventional prospective study. All patients in whom allogeneic HSCT (allo-HSCT) or auto-HSCT was performed during February 2014–May 2015 in the participating centers were included. Data on GNR bacteremia episodes that occurred from the initiation of the conditioning regimen until 6 months after the HSCT were reported, including pathogen and its antimicrobial susceptibility, presence of risk factors, and mortality. This study was performed in accordance with the appropriate regulations in the participating countries including approval by the ethical committees as required, and registered at ClinicalTrials.gov (NCT02257931).

The primary endpoint was to determine the proportion of GNRs resistant to (1) one of noncarbapenem anti-*Pseudomonas* β-lactams (noncarbapenems), including ceftazidime or cefepime or β-lactam/β-lactamase inhibitors (βL/βLIs); (2) carbapenems (one of meropenem/imipenem/doripenem); (3) one of fluoroquinolones; (4) MDR pathogens.

The secondary endpoints were to determine (1) proportion of GNRs resistant to other antibiotics; and (2) risk factors for resistant GNRs, as defined in the primary endpoints.

Microbiological Workup

Guidelines used to determine isolates' susceptibility were by the European Committee for Antimicrobial Susceptibility Testing in 41 (64.1%) laboratories, the Clinical and Laboratory Standards Institute in 19 (29.7%) laboratories, and others in 4 (6.2%) laboratories. Resistance to antibiotics was studied by in vitro sensitivity tests in the local laboratories using disk diffusion in 46 of 64 (71.9%) and/or minimum inhibitory concentration determination in 60 of 64 (93.8%) centers. Pathogens with intermediate susceptibility to antibiotics were considered resistant.

Definitions

An MDR GNR was defined as bacteria resistant to ≥1 agent in ≥3 of the following categories: (1) broad-spectrum cephalosporins (ceftazidime or cefepime); (2) anti-*Pseudomonas* βL/βLIs; (3) carbapenems; (4) aminoglycosides; (5) fluoroquinolones. All *Stenotrophomonas maltophilia* strains were considered MDR. Extensively drug-resistant (XDR) bacteria defined if checked for susceptibility to all relevant antimicrobials and found nonsusceptible to ≥1 agent in all but ≤2 categories [17]. Infections occurring >48 hours since the hospitalization were considered hospital acquired.

Neutropenia was defined as an absolute neutrophil count <500 cells/μL.

Breakthrough bacteremia was defined as bacteremia developing during antibiotic treatment (including fluoroquinolone prophylaxis) provided for ≥48 hours before obtaining the blood culture.

Geographic regions [4] included Northwest (Austria, Belgium, Denmark, Finland, France, Germany, Netherlands, Sweden, Switzerland, United Kingdom); Southeast (Croatia, Cyprus, Czech Republic, Greece, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovakia, Spain, Turkey); other countries (Australia, China).

Statistical Analysis

The main characteristics of patients were reported by descriptive statistics on the total of the available information.

The incidence of resistance was computed as a percentage, the denominator being the number of GNR pathogens and the numerator being the number of pathogens classified as "resistant." Early mortality was computed as a percentage of death occurred within 7 days after bacteremia on the episodes with a follow-up available at the same time.

The relationship between resistance and the following risk factors was investigated:

- Background: sex, age at HSCT, underlying disease, myeloablative conditioning, fluoroquinolone prophylaxis.
- At the time of bacteremia: time since HSCT, duration of neutropenia, neutrophil recovery, duration of hospitalization, hospital-acquired infection, breakthrough bacteremia, graft-vs-host disease (GVHD), acute GVHD grade II–IV, veno-occlusive disease.
- Before bacteremia, within 1 month: urinary catheter, ≥2 weeks of steroids, and/or other immunosuppressive treatment; within 3 months: any hospitalization, hospitalization in the intensive care unit (ICU), any bacteremia, previous antibiotic therapy, and number of antibiotic classes.

Differences between groups were tested using linear or logistic regression models, using the generalized estimating equation method to take into account the dependence of observations

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

nested by patient and center [18]. The same models were used to study all relationships between resistance and characteristics or prognostic factors. Variables showing significance from the univariate model entered a multivariable model. The results obtained from these analyses are considered as exploratory and hypothesis-generating.

A *P* value <.05 was considered statistically significant. All *P* values are 2 sided. All the analyses were performed using the statistical software SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patients and Episodes

Sixty-five HSCT centers from 25 countries reported data on 655 GNR episodes in 591 patients (1.1 episodes [range, 1–4] per patient) (Supplementary Table 1). Characteristics of the background patients and episodes are presented in Tables 1 and 2. Median time to develop GNR bacteremia was 8 (range, –15 to 183) days after HSCT. Fluoroquinolone prophylaxis was provided in 34 of 45 (75.6%) allo-HSCT and 22 of 49 (44.9%) auto-HSCT adult centers, and in 6 of 24 (25.0%) allo-HSCT and 2 of 23 (8.7%) auto-HSCT pediatric centers.

Microbiological Results

Seven hundred four GNRs included Enterobacteriaceae (514 [73%]), nonfermentative rods (167 [24%]), and others (23 [3%]) (Figure 1). Five hundred forty-six (83.4%) episodes were monomicrobial and 109 (16.6%) polymicrobial, including GNRs only (47 [7.2%]) or together with other pathogens (62 [9.5%]).

Resistance Rates

Half of GNRs were resistant to fluoroquinolones and to noncarbapenems, 18.5% were carbapenem resistant, and 35.2% were MDR (Table 3). One of 73 (1.4%) *Pseudomonas aeruginosa* and 4 of 14 (28.6%) *Acinetobacter* species were XDR. Resistance rates to other antibiotics are presented in Table 3.

There was no strong correlation between the rates of GNR bacteremia and resistance to noncarbapenems and carbapenems per country; and no correlation between fluoroquinolone resistance and bacteremia rate per center (Supplementary Figure 1*A*–*C*).

Resistance Rates According to Pathogens

Fluoroquinolone resistance was significantly more frequent among Enterobacteriaceae (57.2% vs 30.7%; $P < .0001$); carbapenem resistance (50.9% vs 8.4%; $P < .0001$), and multidrug resistance (46.6% vs 31.9%; $P = .001$) in nonfermentative rods (Table 4).

Six of 31 (19%) *S. maltophilia* isolates were resistant to trimethoprim-sulfamethoxazole.

One-third of noncarbapenem-resistant, and half of MDR pathogens, were carbapenem resistant (Supplementary Table 2). Six of 33 (18.2%) carbapenem-resistant *P. aeruginosa* isolates were susceptible to both cephalosporins and βL/βLIs (Supplementary Table 3); 1 of 29 (3.5%) was colistin resistant.

Among carbapenem-resistant Enterobacteriaceae, 15 of 41 (36.6%) were resistant to amikacin, 16 of 41 (39.0%) to gentamicin, 4 of 41 (9.8%) to both aminoglycosides; 32 of 40 (78%) to fluoroquinolones, 5 of 17 (29.4%) to tigecycline, and 6 of 33 (18.2%) to colistin.

Resistance Rate According to Hematopoietic Stem Cell Transplantation Type

The resistance rates to fluoroquinolones (55.6% vs 41.4%), noncarbapenems (59.2% vs 36.0%), carbapenems (23.7%

Table 1. Patient Characteristics (N = 591)

Characteristic	No. (%)
Age, y, median (range)	50.9 (0.3–72.9)
Children (<18 y)	79 (13.4)
Male sex	357 (60.4)
Underlying disease	
Acute leukemia	212 (35.9)
Lymphoma	148 (25.0)
Plasma cell disorders	109 (18.4)
Myelodysplastic/myeloproliferative syndromes	54 (9.1)
Chronic leukemia	8 (1.4)
Solid tumor	12 (2.0)
Nonmalignant disease	48 (8.1)
Time since diagnosis of the underlying disease until HSCT, mo, median (range)	10.4 (1.0–256.2)
Allogeneic HSCT	360 (60.9)
Donor (allogeneic HSCT)	
Unrelated	175 (48.9)
Matched related	114 (31.8)
Mismatched related	69 (19.3)
Stem cell source	
Peripheral blood	451 (76.4)
Bone marrow	101 (17.1)
Both bone marrow and peripheral blood	10 (1.7)
Umbilical cord blood	28 (4.7)
Conditioning (allogeneic HSCT)	
Myeloablative	241 (68.1)
Nonmyeloablative	113 (31.9)
Karnofsky score, median (range)	90 (0–100)
Disease status after HSCT	
Continued complete remission	317 (75.1)
Never in complete remission	79 (18.7)
Partial remission/stable disease	26 (6.2)
Graft-vs-host disease prophylaxis before bacteremia (allogeneic HSCT)	
Total provided	339
Cyclosporine/tacrolimus alone	51 (15.0)
Cyclosporine/tacrolimus + methotrexate	136 (40.1)
Cyclosporine/tacrolimus + MMF or prednisone	117 (34.5)
Other	35 (10.3)
Graft manipulation ex vivo (including T-cell depletion)	31 (6.2)

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

Abbreviations: HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil.

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

Table 2. Episode Characteristics

Characteristic	Transplant Type		Total (N = 655)	*P* Value
	Allogeneic (n = 414)	Autologous (n = 241)		
Neutropenia at the time of episode <500 cells/μL	296 (71.5)	199 (82.9)	495 (75.7)	.005
Neutropenia at the time of episode <100 cells/μL	259 (73.4)	175 (77.8)	434 (75.1)	.4
Duration of neutropenia <500 cells/μL, d, median (range)	7 (1–246)	2.5 (1–124)	5 (1–246)	<.0001
Duration of neutropenia <500 cells/μL <7 d, median (range)	153 (37.0)	189 (78.8)	342 (52.3)	<.0001
Duration of neutropenia <100 cells/μL, d, median (range)	5 (1–80)	2 (1–28)	3 (1–80)	<.0001
Duration of neutropenia <100 cells/μL <7 d	176 (49.9)	171 (76.0)	347 (60.0)	<.0001
Absolute neutrophil count recovered before bacteremia	147 (39.9)	24 (10.8)	171 (28.9)	<.0001
Previous hospitalization	255 (64.6)	121 (50.4)	376 (59.2)	.001
Number of hospitalization days during 3 mo preceding bacteremia, median (range)	38 (1–186)	15 (1–94)	30 (1–186)	<.0001
Duration of current hospitalization before episode, d, median (range)	17 (0–266)	11 (0–87)	14 (0–266)	<.0001
Hospital-acquired bacteremia	355 (86.8)	215 (90.7)	570 (88.2)	.08
Previous ICU hospitalization	28 (6.9)	4 (1.7)	32 (4.9)	.01
Bacteremia developed during hospitalization in the ICU	17 (4.2)	0 (0.0)	17 (2.6)	…
Breakthrough bacteremia	303 (73.4)	98 (40.7)	401 (61.3)	<.0001
Cephalosporins[a]	30 (7.3)	8 (3.3)	38 (5.8)	.04
Anti-*Pseudomonas* βL/βLIs	65 (15.7)	16 (6.6)	81 (12.4)	.001
Carbapenems[b]	54 (13.1)	7 (2.9)	61 (9.3)	<.0001
Any β-lactam[c]	159 (38.5)	36 (14.9)	195 (29.8)	<.0001
Fluoroquinolones	118 (28.6)	50 (20.7)	168 (25.7)	.03
Aminoglycosides	22 (5.3)	5 (2.1)	27 (4.1)	.04
Others[d]	79 (19.1)	13 (5.4)	92 (14.1)	<.0001
Previous antibiotic therapy	309 (77.3)	104 (44.4)	413 (65.1)	<.0001
Cephalosporins[a]	46 (11.5)	8 (3.4)	54 (8.5)	.001
Anti-*Pseudomonas* βL/βLIs	88 (22.0)	17 (7.3)	105 (16.6)	<.0001
Carbapenems[b]	86 (21.5)	10 (4.3)	96 (15.1)	<.0001
Any β-lactam[c]	198 (49.5)	42 (17.9)	240 (37.9)	<.0001
Fluoroquinolones	121 (30.3)	45 (19.2)	166 (26.2)	.003
Aminoglycosides	30 (7.5)	5 (2.1)	35 (5.5)	.007
Others[d]	101 (25.3)	12 (5.1)	113 (17.8)	<.0001
No. of antibiotic classes of previous antibiotic therapy[e]				
1 antibiotic class	86 (21.4)	36 (15.3)	122 (19.2)	<.0001
2 classes	73 (18.2)	24 (10.2)	97 (15.2)	
≥3 antibiotic categories	131 (32.6)	18 (7.7)	149 (23.4)	
GVHD at the time of bacteremia (% of all allo-HSCT)	71 (17.3)			…
Acute GVHD at the time of bacteremia (% of all allo-HSCT)	62 (15.1)			…
Grade II–IV of acute GVHD before bacteremia (% of all allo-HSCT)	12 (4.5)			…
Chronic GVHD (% of all allo-HSCT)	9 (2)			…
Veno-occlusive disease at the time of bacteremia	12 (2.9)	3 (1.3)	15 (2.3)	.2
Urinary catheter	38 (9.5)	7 (2.9)	45 (7.0)	.007
Previous bacteremia	127 (30.7)	24 (9.9)	151 (23.1)	<.0001
Recent immunosuppression	335 (81.1)	57 (23.8)	392 (60.1)	<.0001
Recent steroid treatment	142 (34.5)	53 (22.3)	195 (30.0)	.008
Time since HSCT, d, median (range)	11 (–15 to 183)	7 (–8 to 177)	8 (–15 to 183)	<.0001
Central line infection	138 (38.4)	73 (32.3)	211 (36.1)	.1

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

Abbreviations: allo, allogeneic; auto, autologous; βL/βLI, β-lactam/β-lactamase inhibitor; GVHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

[a]Cephalosporins: ceftazidime, cefepime, ceftriaxone, cefotaxime, cefuroxime, cefazolin.

[b]Carbapenems: meropenem, imipenem, ertapenem, doripenem.

[c]Any β-lactam: either cephalosporin, anti-*Pseudomonas* βL/βLI, carbapenem, or any other β-lactam antibiotic.

[d]Others: any antibiotics, excluding any β-lactam, fluoroquinolones, aminoglycosides, and prophylactic use of trimethoprim-sulfamethoxazole or dapsone.

[e]Previous antibiotic exposure to the following antibiotic classes was reported: (a) any cephalosporins; (b) anti-*Pseudomonas* βL/βLIs; (c) carbapenems (meropenem, imipenem, ertapenem, doripenem); (d) fluoroquinolones (either treatment and prophylaxis); (e) aminoglycosides; (f) macrolides; (g) anti–gram-positives (glycopeptides, linezolid, daptomycin); (h) antianaerobes (metronidazole, clindamycin); (i) colistin; (j) tigecycline; (k) aztreonam; (l) other antibiotics.

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

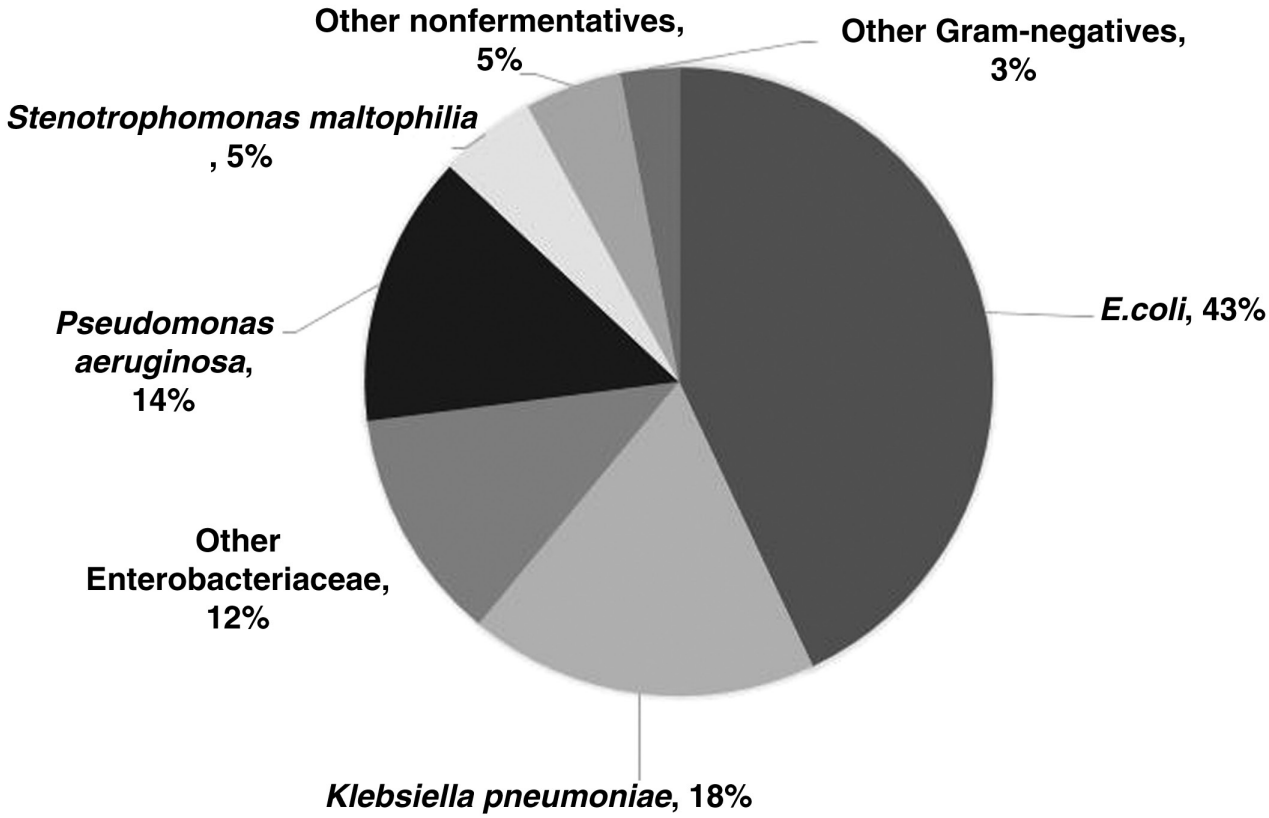

Figure 1. Distribution of gram-negative pathogens. Other Enterobacteriaceae include *Enterobacter* spp (n = 41), *Klebsiella* spp (n = 24), *Citrobacter* spp (n = 12), *Serratia* spp (n = 6), *Proteus* spp (n = 3), *Raoultella* spp (n = 1). Other nonfermentative rods include *Acinetobacter* spp (n = 17), 1 each of *Sphingomonas paucimobilis, Shewanella putrefaciens, Sphingobacterium multivorum, Comamonas testosterone, Ochrobactrum* spp, *Ralstonia pickettii, Paracoccus yeei, Achromobacter xylosoxidans*. Other gram-negative rods include *Capnocytophaga* spp (n = 8), *Moraxella* spp (n = 4), *Aeromonas* spp (n = 3), *Campylobacter* spp (n = 2), *Rhizobium radiobacter* (n = 2), and 1 each of *Salmonella enteritidis, Haemophilus influenzae, Burkholderia cepacia, Elizabethkingia meningoseptica.*

vs 8.9%), and multidrug resistance (43.7% vs 20.2%) were higher in GNRs isolated in allo-HSCT vs auto-HSCT recipients ($P < .001$ for all) (Table 3). Among community-acquired infections, there were no significant differences in fluoroquinolone resistance (38.8% vs 63.2%), noncarbapenem resistance (42.0% vs 42.1%), carbapenem resistance (15.1% vs 18.2%), and multidrug resistance (28.3% vs 19%) between allo-HSCT and auto-HSCT patients (Supplementary Tables 4 and 5).

Resistance Rate in Children Versus Adults

Similar resistance rates were observed in children and adults. Only the resistance rate to fluoroquinolones and βL/βLIs was significantly higher in adults compared with children following allo-HSCT ($P < .0001$ and $P = .048$, respectively) (Table 3); the difference was significant in southeast countries only.

Geographical Distribution of Resistance Rates

There was a wide distribution in the resistance rates between countries (Supplementary Table 6). Resistance rates were more frequent in the southeast vs northwest European region: for noncarbapenems (266/481 [55.3%] vs 32/116 [27.6%], $P < .0001$); fluoroquinolones (270/496 [54.4%] vs 44/121 [36.4%]; $P = .002$); carbapenems (109/526 [20.7%] vs 6/123 [4.9%]; $P < .0001$); and multidrug resistance (201/514 [39.1%] vs 16/118 [13.6%]; $P < .0001$).

Risk Factors for Resistance

Univariate analysis of risk factors for resistant GNRs in allo-HSCT and auto-HSCT recipients is presented in Supplementary Tables 4 and 5. Multivariable analysis was possible in allo-HSCT patients only (Table 5), as rate of resistance was low in auto-HSCT patients.

To study the association between fluoroquinolone prophylaxis and resistance, we compared resistance rates in GNRs cultured during the period when prophylaxis is provided (in neutropenic patients without empiric or targeted antibiotics therapy), in centers that do and do not provide prophylaxis.

The rate of fluoroquinolone-resistant GNRs was higher in centers providing prophylaxis (79% vs 50%, $P = .001$ in allo-HSCT; 74% vs 25%, $P < .001$ in auto-HSCT). The rate of noncarbapenem-resistant (36% vs 13%; $P = .002$) and MDR (35%

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

Table 3. Antibiotic Resistance Rates in Gram-Negative Rods: Total, According to Transplant Type, and in Children Versus Adults

	Resistance to						
	Total Isolates	GNRs in Allo-HSCT	GNRs in Auto-HSCT	GNRs in Allo-HSCT Adults	GNRs in Allo-HSCT Children	GNRs in Auto-HSCT Adults	GNRs in Auto-HSCT Children
Primary endpoints							
Fluoroquinolone	325/645 (50.4)	227/408 (55.6)*	98/237 (41.4)*	205/326 (62.9)**	22/82 (26.8)**	95/228 (41.7)	3/9 (33.3)
Noncarbapenem β-lactam	322/632 (50.9)	241/407 (59.2)*	81/225 (36.0)*	199/322 (61.8)	42/85 (49.4)	78/214 (36.4)	3/11 (27.3)
Carbapenem	127/688 (18.5)	105/443 (23.7)*	22/245 (8.9)*	80/349 (22.9)	25/94 (26.6)	20/234 (8.6)	2/11 (18.2)
Multidrug resistant	236/671 (35.2)	187/428 (43.7)*	49/243 (20.2)*	149/334 (44.6)	38/94 (40.4)	46/231 (19.9)	3/12 (25.0)
Secondary endpoints							
Anti-*Pseudomonas* cephalosporin	255/656 (38.9)	199/416 (47.8)	56/240 (23.3)	160/332 (48.2)	39/84 (46.4)	55/229 (24.0)	1/11 (9.1)
Anti-*Pseudomonas* βL/βLI	230/627 (36.7)	177/399 (44.4)	53/228 (23.2)	146/310 (47.1)***	31/89 (34.8)***	51/217 (23.5)	2/11 (18.2)
Aminoglycoside	216/662 (32.6)	162/422 (38.4)	54/240 (22.5)	135/335 (40.3)	27/87 (31.0)	51/228 (22.4)	3/12 (25.0)
Colistin	22/358 (6.1)	18/250 (7.2)	4/108 (3.7)	12/205 (5.9)	6/45 (13.3)	4/102 (3.9)	0/6 (0.0)
Tigecycline	15/182 (8.2)	12/124 (9.7)	3/58 (5.2)	10/109 (9.2)	2/15 (13.3)	3/58 (5.2)	Not checked

Data are presented as no./No. (%). The following differences were significant: the resistance rates to fluoroquinolones, noncarbapenems, carbapenems, and multidrug resistance were significantly higher in GNRs isolated in allogeneic HSCT vs autologous HSCT recipients (*$P < .001$ for all). The rate of resistance to fluoroquinolones and anti-*Pseudomonas* βL/βLIs was significantly higher in adults vs children following allogeneic HSCT (**$P < .0001$ and ***$P = .048$, respectively).

Abbreviations: allo, allogeneic; auto, autologous; βL/βLI, β-lactam/β-lactamase inhibitor; GNR, gram-negative rod; HSCT, hematopoietic stem cell transplantation.

vs 8%; $P < .001$) bacteria was higher in auto-HSCT patients in centers providing prophylaxis (Supplementary Table 7).

Outcome

The 7-day mortality was 38 of 589 (6.5%). The mortality according to resistance pattern was 9% vs 2% ($P = .002$) in episodes caused by noncarbapenem resistant vs sensitive GNRs; 18% vs 4% ($P < .001$) in those carbapenem resistant vs sensitive; and 11% vs 4% ($P = .002$) in MDR vs non-MDR. Inappropriate empiric therapy was provided for 124 of 586 (21.2%) GNRs; being 101 of 270 (37.4%) for noncarbapenem resistant vs 12 of 274 (4.4%) noncarbapenem susceptible bacteria; 62 of 97 (63.9%) for carbapenem resistant vs 61 of 481 (12.7%) carbapenem susceptible; and 91 of 197 (46.2%) for MDR vs 30 of 368 (8.1%) non-MDR GNRs ($P < .001$ for all).

DISCUSSION

In this study, we demonstrate antimicrobial susceptibility patterns among GNRs causing bacteremia in HSCT patients, and geographical distribution of resistance in 25 countries from Europe, Asia, and Australia. We compare allo- and auto-HSCT recipients, and children and adults; and analyze risk factors for antibiotic resistance.

The emerging resistance challenges antibacterial prophylaxis policy and complicates empiric and targeted treatment choices. Benefit of fluoroquinolone prophylaxis was demonstrated in a country with a baseline resistance of approximately 20%

Table 4. Resistance Rates According to Pathogens

	Resistance to						
Pathogens	Fluoro-quinolones	Noncarbapenem β-Lactams	Carbapenem	Multidrug Resistant	Aminoglycoside	Colistin	Tigecycline
Escherichia coli	185/283 (65.4)	140/281 (49.8)	7/301 (2.3)	81/290 (27.9)	96/298 (32.2)	0/144	2/105 (1.9)
Klebsiella pneumoniae	71/111 (63.9)	79/118 (66.9)	31/124 (25.0)	63/121 (52.1)	53/124 (42.7)	5/77 (6.5)	6/37 (16.2)
Enterobacter spp	8/39 (20.5)	19/39 (48.7)	3/41 (7.3)	9/39 (23.1)	8/41 (19.5)	0/15	1/12 (8.3)
Other Enterobacteriaceae	7/41 (17.1)	9/43 (20.9)	2/45 (4.4)	5/44 (11.4)	8/45 (17.8)	9/28 (32.1)	1/14 (7.1)
Total Enterobacteriaceae	271/474 (57.2)[a]	247/481 (51.4)	43/511 (8.4)[a]	158/494 (31.9)[b]	165/508 (32.5)	14/264 (5.3)	10/168 (6.0)
Pseudomonas aeruginosa	29/96 (30.2)	33/92 (35.9)	36/95 (37.9)	28/96 (29.2)	26/97 (26.8)	1/66 (1.5)	Not checked
Acinetobacter baumannii	7/10 (70.0)	8/10 (80.0)	7/11 (63.6)	7/11 (63.6)	5/11 (45.5)	1/9 (11.1)	2/3 (66.6)
Stenotrophomonas maltophilia	6/22 (27.3)	14/16 (87.5)	34/34 (100)	34/34 (100)	9/9 (100)	3/10 (30.0)	0/6
Other nonfermentative rods	4/22 (18.2)	13/20 (65.0)	5/21 (23.8)	7/22 (31.8)	5/23 (21.7)	0/1	2/2 (100)
Total nonfermentative rods	46/150 (30.7)[a]	68/138 (49.3)	82/161 (50.9)[a]	76/163 (46.6)[b]	45/140 (32.1)	5/86 (5.8)	4/11 (36.4)

Data are presented as no./No. (%).

[a]Significant differences between Enterobacteriaceae and nonfermentative rods ($P < .0001$).

[b]Significant differences between Enterobacteriaceae and nonfermentative rods ($P = .001$).

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

Table 5. Multivariate Analysis of Risk Factors for Resistance in Gram-Negative Rods in Allogeneic Transplant Patients

	Fluoroquinolone-Resistant GNRs		Noncarbapenem β-Lactam-Resistant GNRs		Carbapenem-Resistant GNRs		Multidrug-Resistant GNRs	
Risk Factor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Duration of neutropenia (≥7 d)	1.79 (1.10–2.91)	.02		NS		NS		NS
Breakthrough bacteremia on fluoroquinolones	7.26 (3.84–13.72)	<.0001		NS		NS		NS
Age (adults)	3.87 (2.07–7.25)	<.0001		NS		NS		NS
Hospital-acquired infection		NS	2.09 (1.08–4.03)	.029		NS		NS
Breakthrough bacteremia on βL/βLI		NS	2.45 (1.14–5.23)	.02		NS	2.30 (1.20–4.41)	.013
Breakthrough bacteremia on cephalosporins		NS	6.36 (1.68–24.07)	.01		NS		NS
Previous antibiotic therapy with other antibiotics[a]		NS	2.59 (1.30–5.15)	.007	2.07 (1.15–3.73)	.016		NS
Longer duration of current hospitalization before episode		NS		NS	1.01 (1.00–1.02)	.041	1.01 (1.00–1.03)	.032
Current bacteremia developed during hospitalization in the ICU		NS		NS	3.92 (1.18–3.03)	.026		NS
Breakthrough bacteremia on carbapenems		NS		NS	9.08 (4.57–18.02)	<.0001	3.49 (1.96–6.21)	<.0001
Matched related vs matched unrelated donor		NS	1.82 (1.05–3.14)	.01		NS		NS
Mismatched vs matched unrelated donor			2.29 (1.21–4.35)					

Abbreviation: βL/βLI, anti-*Pseudomonas* β-lactam β-lactamase inhibitor; CI, confidence interval; GNR, gram-negative rod; ICU, intensive care unit; NS, not significant; OR, odds ratio.

[a]Other antibiotics: any antibiotic therapy excluding β-lactams, fluoroquinolones, aminoglycosides.

in GNRs from the community and medical departments [19, 20]. In our study, 39% of GNRs causing community-acquired infections in allo-HSCT and 63% in auto-HSCT were fluoroquinolone resistant (Supplementary Tables 4 and 5). High rates of fluoroquinolone resistance may be the price to pay for lower rates of bacteremia in centers providing prophylaxis. We could not, however, demonstrate correlation between the rates of bacteremia and fluoroquinolone resistance (Supplementary Figure 1*A*). Doubts regarding the benefits of fluoroquinolone prophylaxis are accompanied by concern about increased rates of resistance to other antibiotics following exposure to fluoroquinolones. No association between fluoroquinolone prophylaxis and the increase in MDR bacteria was shown in the meta-analysis of studies published up to 2005 [21]. Later published studies, however, correlated exposure to fluoroquinolones with increase in infections resulting from fluoroquinolone-resistant, ESBL-producing, carbapenem-resistant, and MDR pathogens [14, 22, 23]. In our study, in auto-HSCT patients, treatment in centers providing fluoroquinolone prophylaxis, breakthrough on fluoroquinolones, and previous exposure to fluoroquinolones (Supplementary Tables 5 and 7) were associated with resistance to noncarbapenems and MDR. The risk could, however, be influenced by other factors, as outpatient vs inpatient transplantation setting, which were not reported in our study. The benefits and potential risks of fluoroquinolone prophylaxis must be carefully assessed, especially in centers with high fluoroquinolone resistance rates among GNRs [24].

Empiric treatment with noncarbapenem β-lactams, or even carbapenems [25], can be inappropriate in centers with high resistance rates to these antibiotics and lead to increased mortality [2, 13]. In our study, approximately 40% of community-acquired infections were resistant to noncarbapenems and 15%–18% to carbapenems (Supplementary Tables 4 and 5), probably due to acquisition of resistant bacteria during previous hospitalizations. This can lead to inappropriate empiric therapy. Carbapenem treatment increases the chance of providing appropriate empiric therapy, especially in southeast European countries. In centers with low rate of noncarbapenem resistance at the onset of febrile neutropenia, noncarbapenems, however, can still be a good option. Universal recommendations for empiric therapy are tricky because of significant geographical variations. Practical decisions on empiric therapy must be based on continuously updated data concerning local resistance patterns and bacteremia rates [26]. We are thus unable to recommend the specific resistance rate threshold that indicates change in the empiric therapy protocol as our study was not designed to answer this question. While the proportion of resistant bacteria was high in some centers, its impact on patient outcome can be low if GNR bacteremia is rare (Supplementary Figures 1*B* and 1*C*).

Resistance to multiple antibiotics complicates the targeted therapy choice. Susceptibility to tigecycline, polymyxins, fosfomycin, and aminoglycosides must be promptly reported in the centers with carbapenem-resistant infections, as some

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

bacteria were resistant to these last-resort antibiotics in our and other studies [8, 27]. Eighteen percent of carbapenem-resistant *P. aeruginosa* was susceptible to both cephalosporins and βL/βLIs in our study and, in contrast to carbapenem-resistant Enterobacteriaceae, can be treated with these agents, especially administered as high-dose prolonged infusion [28].

Knowledge of pathogen-specific resistance patterns can help direct appropriate empiric therapy following rapid bacterial identification by matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF), prior to susceptibility results. Carbapenem monotherapy should be appropriate on identification of non–*Klebsiella pneumoniae* Enterobacteriaceae, which are usually carbapenem susceptible. A carbapenem/colistin with or without aminoglycoside combination should, however, be considered for *K. pneumoniae* or *Acinetobacter* pending susceptibility results, as a significant proportion of them are carbapenem resistant. Streamlining of antibiotic therapy, of course, should be performed when susceptibilities are available.

Data on resistance rates in post-HSCT children are scarce [12, 16, 29]. Surprisingly, resistance rates were mostly similar in children and in adults in our study. This differs from the lower resistance rates in children vs adults reported in a literature review of studies published until 2011 [4]. Resistance rates in a retrospective multicenter US study (2004–2014) in pediatric allo-HSCT recipients [16] are also lower than in our study. Our data may indicate the trend toward increasing resistance in children, which emphasizes the importance of monitoring and prevention in this population. Fluoroquinolone prophylaxis is rarely provided in children, which may explain lower rates of fluoroquinolone resistance.

Information about resistance rates and risk factors in auto-HSCT patients is limited and mainly concerns fluoroquinolones [15, 30], as bacteremia is relatively less frequent in auto-HSCT patients [31]. Certain factors predisposing to resistant infections—such as breakthrough bacteremia and prolonged neutropenia—are less frequent in auto-HSCT vs allo-HSCT patients (Table 2). Although total resistance rates were higher in allo-HSCT patients, resistance rates in community-acquired infections were similar. These data reinforce the importance of monitoring antibiotic susceptibilities in auto-HSCT patients.

Several studies reported risk factors for cephalosporin-resistant, ESBL-producing or MDR bacteria in cancer and HSCT patients [10, 12, 13, 16, 22, 29, 32]. Only a handful describe risk factors for carbapenem-resistant infections in populations involving but not limited to transplant patients, mainly for *K. pneumoniae*. Distinct from other studies, we found that breakthrough on noncarbapenems does not predispose to carbapenem resistance in allo-HSCT patients [8, 14]. Noncarbapenem β-lactams and carbapenems are both recommended for empiric treatment in febrile neutropenic patients [25], half of whom have neither microbiological nor clinical infection. Limitation of carbapenem treatment, de-escalation to a narrower-spectrum regimen following culture results, and shortening treatment duration, as recommended by European Conference on Infections in Leukaemia guidelines, will slow development of carbapenem resistance without increasing mortality [26, 33].

Geographical differences in resistance rates are striking. In certain countries, we found higher resistance rates than those previously reported in the literature. In France, for example, 34.4% of GNRs were noncarbapenem resistant, compared with 4% third-generation cephalosporin resistance among Enterobacteriaceae cultured in hematological malignancies and post-HSCT patients during 2003–2010, which may be explained by increased resistance rates over time [5]. Information about resistance rates in each country may, of course, be skewed by local epidemiology of the participating centers, and not reflective of the situation countrywide. While carbapenem-resistant GNRs were not reported at all in some countries, approximately 40% of GNRs were carbapenem resistant in Russia and the Czech Republic, countries for which existing resistance data are very limited. GNR resistance rates to carbapenems in other studies, including HSCT patients, varied from 0% in Sweden [34] to 4.7%–5.8% in the United States [8, 35] to 20.9%, and even 75.9% among *K. pneumoniae*, in Italy [7, 11, 14, 27]. Overall, we found significantly higher resistance rates in southeast as compared with northwest Europe. This correlates with lower rates of antimicrobial resistance among the general population [36], which is probably explained by lower consumption of systemic antibacterials in the community, as well as in veterinary medicine, in northwest Europe [37, 38].

The multidrug resistance rate (~30%) among Enterobacteriaceae and *P. aeruginosa* in our study was within that reported in cancer and HSCT patients [11–13, 35]. The rate of cotrimoxazole resistance among *S. maltophilia*, the drug of choice for this MDR pathogen, was higher in our study (19%) compared to 4%–10% in other studies [5, 29]. Susceptibility of *Acinetobacter* species in cancer and transplant patients has been infrequently studied [5, 29, 39]; XDR *Acinetobacter* infections were not previously reported. In our study, a third of *Acinetobacter* species were XDR.

We demonstrated higher mortality rates in infections caused by resistant bacteria, similar to other studies [8, 12]. Analysis of mortality risk factors is beyond the scope of this manuscript.

Our study has limitations. GNR resistance rates and patterns in our study are influenced by the epidemiology of countries with more participating centers. Antimicrobial susceptibility data were incomplete for some GNRs. Resistance rates to certain agents, such as tigecycline, could be overestimated, as susceptibility was likely checked in bacteria resistant to other treatment options, or reflecting local epidemiology. We could, however, demonstrate resistance rates to salvage treatments among their main targets, harder-to-treat pathogens. We did not assess important risk factors for resistance: history of recent residency in another country (information unavailable) and

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

prior colonization with resistant GNRs (not all participating centers performed colonization screening).

The study has important strengths. It is the first intercontinental prospective study focusing on antimicrobial resistance of GNRs specifically in HSCT patients, including countries underrepresented in the literature (eg, Russia, Switzerland), and countries with lower resistance rates, which makes our data more applicable to large-scale HSCT centers. The large sample size enables unique resistance analysis in 2 important subgroups—that is, auto-HSCT patients and children, about whom data in the literature are very scarce. It also allows comparison of data between auto- and allo-HSCT patients and between children and adults. Contrary to many studies, we analyze risk factors for different resistance patterns and pathogens, rather than focusing on specific bacteria or mechanisms.

In conclusion, the problem of antibiotic resistance is worrying in all HSCT patients, including subgroups of children and auto-HSCT recipients. It is associated with inappropriate empiric therapy and increased mortality. Benefits of fluoroquinolone prophylaxis and the approach to empiric therapy should be reassessed and grounded in continuous monitoring of the local bacteremia rates and susceptibility data of infecting pathogens. Knowledge of pathogen-specific resistances enables early appropriate empiric therapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. This is a multicenter study. We are deeply indebted to the members of the Infectious Diseases Working Party of the European Bone Marrow Transplantation group for fruitful discussions and to all collaborators: Czech Republic: Alexandra Jungova, Petra Keslova, Milan Navratil; France: Aziza Abaza Nedhif; Emmanuelle Nicolas; Germany: Arnold Ganser; Greece: Anastasia Pouli; Israel: Elizabeth Neparstek; Italy: Claudio Annaloro, Elisabetta Calore, Katia Codeluppi, Edoardo Lanino, Francesco Lanza, Katia Perruccio, Roberto Raimondi, Ivana Sartor, Cristina Tecchio, Michele Vespignani; Netherlands: Michel Schaap; Poland: Jolanta Gozdzik, Anna Waszczuk; Portugal: Antonio Campos; Russia: Valentina Pirumova; Spain: Montserrat Batlle, José López, Rodrigo Martino, Rafael Rojas; Turkey: Alphan Kupesiz, Gülsan Sucak; United Kingdom: Rachel Hall.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant **2017**; 52:811–7.
2. Girmenia C, Viscoli C, Piciocchi A, et al. Management of carbapenem resistant *Klebsiella pneumoniae* infections in stem cell transplant recipients: an Italian multidisciplinary consensus statement. Haematologica **2015**; 100:e373–6.
3. Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica **2013**; 98:1836–47.
4. Mikulska M, Viscoli C, Orasch C, et al; Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. J Infect **2014**; 68:321–31.
5. Bousquet A, Malfuson JV, Sanmartin N, et al. An 8-year survey of strains identified in blood cultures in a clinical haematology unit. Clin Microbiol Infect **2014**; 20:O7–12.
6. Weisser M, Theilacker C, Sutter ST, et al. Secular trends of bloodstream infections during neutropenia in 15,181 haematopoietic stem cell transplants: 13-year results from a European multicentre surveillance study (ONKO-KISS). Clin Microbiol Infect **2017**. doi:10.1016/j.cmi.2017.03.020.
7. Girmenia C, Rossolini GM, Piciocchi A, et al; Gruppo Italiano Trapianto Midollo Osseo (GITMO); Gruppo Italiano Trapianto Midollo Osseo GITMO. Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant **2015**; 50:282–8.
8. Satlin MJ, Cohen N, Ma KC, et al. Bacteremia due to carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic malignancies. J Infect **2016**; 73:336–45.
9. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant **2009**; 15:47–53.
10. Vehreschild MJ, Hamprecht A, Peterson L, et al. A multicentre cohort study on colonization and infection with ESBL-producing Enterobacteriaceae in high-risk patients with haematological malignancies. J Antimicrob Chemother **2014**; 69:3387–92.
11. Trecarichi EM, Pagano L, Candoni A, et al; HeMABIS Registry—SEIFEM Group, Italy. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. Clin Microbiol Infect **2015**; 21:337–43.
12. Caselli D, Cesaro S, Ziino O, et al; Infection Study Group of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). Multidrug resistant *Pseudomonas aeruginosa* infection in children undergoing chemotherapy and hematopoietic stem cell transplantation. Haematologica **2010**; 95:1612–5.
13. Gudiol C, Tubau F, Calatayud L, et al. Bacteraemia due to multidrug-resistant gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother **2011**; 66:657–63.
14. Trecarichi EM, Pagano L, Martino B, et al; Haematologic Malignancies Associated Bloodstream Infections Surveillance (HEMABIS) registry—Sorveglianza Epidemiologica Infezioni Funginein Emopatie Maligne(SEIFEM) group, Italy. Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey. Am J Hematol **2016**; 91:1076–81.
15. Wang CH, Chang FY, Chao TY, et al. Characteristics comparisons of bacteremia in allogeneic and autologous hematopoietic stem cell-transplant recipients with levofloxacin prophylaxis and influence on resistant bacteria emergence. J Microbiol Immunol Infect **2016**. doi:10.1016/j.jmii.2016.02.003.
16. Satwani P, Freedman JL, Chaudhury S, et al. A multicenter study of bacterial blood stream infections in pediatric allogeneic hematopoietic cell transplantation recipients: the role of acute gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant **2017**; 23:642–7.
17. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18:268–81.
18. Lipsitz SR, Fitzmaurice GM, Orav EJ, Laird NM. Performance of generalized estimating equations in practical situations. Biometrics **1994**; 50:270–8.
19. Bucaneve G, Micozzi A, Menichetti F, et al; Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med **2005**; 353:977–87.
20. Leibovici L, Paul M, Cullen M, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer **2006**; 107:1743–51.
21. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrob Chemother **2007**; 59:5–22.
22. Liss BJ, Vehreschild JJ, Cornely OA, et al. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. Infection **2012**; 40:613–9.
23. Liu CY, Lai YC, Huang LJ, et al. Impact of bloodstream infections on outcome and the influence of prophylactic oral antibiotic regimens in allogeneic hematopoietic SCT recipients. Bone Marrow Transplant **2011**; 46:1231–9.
24. Kim JH, Goulston C, Zangari M, Tricot G, Boyer MW, Hanson KE. Impact of a change in antibacterial prophylaxis on bacteremia and hospitalization rates following outpatient autologous peripheral blood stem cell transplantation for multiple myeloma. Transpl Infect Dis **2014**; 16:421–9.

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017

25. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2011**; 52:e56–93.
26. 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. Haematologica **2013**; 98:1826–35.
27. Pagano L, Caira M, Trecarichi EM, et al. Carbapenemase-producing *Klebsiella pneumoniae* and hematologic malignancies. Emerg Infect Dis **2014**; 20:1235–6.
28. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis **2013**; 56:272–82.
29. Averbuch D, Avaky C, Harit M, et al. Non-fermentative gram-negative rods bacteremia in children with cancer: a 14-year single-center experience. Infection **2017**; 45:327–34.
30. Satlin MJ, Vardhana S, Soave R, et al. Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2015**; 21:1808–14.
31. Bock AM, Cao Q, Ferrieri P, Young JA, Weisdorf DJ. Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. Biol Blood Marrow Transplant **2013**; 19:102–8.
32. Patriarca F, Cigana C, Massimo D, et al. Risk factors and outcomes of infections by multidrug-resistant gram-negative bacteria in patients undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2017**; 23:333–9.
33. Mokart D, Slehofer G, Lambert J, et al. De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. Intensive Care Med **2014**; 40:41–9.
34. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. Transpl Infect Dis **2014**; 16:106–14.
35. See I, Freifeld AG, Magill SS. Causative organisms and associated antimicrobial resistance in healthcare-associated, central line-associated bloodstream infections from oncology settings, 2009–2012. Clin Infect Dis **2016**; 62:1203–9.
36. European Centre for Disease Prevention and Control. Summary of the latest data on antibiotic resistance in the European Union. Available at: http://ecdc.europa.eu/en/eaad/Documents/antibiotics-EARS-Net-summary-2016.pdf. Accessed 7 April 2017.
37. European Centre for Disease Prevention and Control. Geographical distribution of antimicrobial consumption. Available at: http://ecdc.europa.eu/en/health-topics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/esac-net-database/Pages/geo-distribution-consumption.aspx. Accessed 7 April 2017.
38. European Medicines Agency. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf. Accessed 7 April 2017.
39. Kim SB, Min YH, Cheong JW, et al. Incidence and risk factors for carbapenem- and multidrug-resistant *Acinetobacter baumannii* bacteremia in hematopoietic stem cell transplantation recipients. Scand J Infect Dis **2014**; 46:81–8.

Downloaded from https://academic.oup.com/cid/article-abstract/65/11/1819/4036247
by Central Lib Agricultural Science user
on 16 November 2017