Clinical Infectious Diseases

MAJOR ARTICLE

Colonization With Levofloxacin-resistant Extended-spectrum β-Lactamase-producing Enterobacteriaceae and Risk of Bacteremia in Hematopoietic Stem Cell Transplant Recipients

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Veronika Bättig

Hintergrund

- Wahl der empirischen Antibiotika-Therapie bei Fieber in Neutropenie entscheidend, MDR-Erreger zunehmend
- ECIL-4 Guidelines: Eskalation- vs. De-Eskalation-Strategie

Table 3. ECIL-4 recommendation for initial empirical treatment in high-risk patients (anticipated to have neutropenia for more than 7 days), by indication and escalation or de-escalation approach.

	Escalation approach	De-escalation approach
Indication B-II for all		
	1) Uncomplicated presentation;	1) Complicated presentations;
	2) No known colonization with resistant bacteria;	2) Known colonization with resistant bacteria;
	3) No previous infection with resistant bacteria;	3) Previous infection with resistant bacteria;
	4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia;	4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy		
	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) AI	1) Carbapenem monotherapy BII[g]
	2) Piperacillin-tazobactam AI	2) Combination of anti-pseudomonal β–lactam + aminoglycoside or quinolone[g] (with carbapenem as the β–lactam in seriously ill patients) BIII
	3) Other possible options include[†]:	3) Colistin + β–lactam ± rifampicin BIII[¶]
	- Ticarcillin-clavulanate[g]	4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII
	- Cefoperazone-sulbactam[g]	
	- Piperacillin + gentamicin[‡]	

Averbuch et al., Haematologica. 2013 Dec;98(12):1826-35

Pseudomonas-Screening?

Is admission screening for *Pseudomonas aeruginosa* useful in haematologic patients? A prospective study with 1310 patients

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- Pseudomonas-Screening von 1310 Patienten bei Eintritt auf die Isolierstation: 108 (8.2%) positiv, 9 (0.7%) Entwicklung BSI mit *P.aeruginosa*
- Positive predictive value 8.6%, negative predictive value 99.5%

« Routine screening for *P.aeruginosa* at admission **did not sufficiently predict subsequent bloodstream infections caused by *P.aeruginosa*.**»

Clin Microbiol Infect. 2015 Jun;21(6):572

Studien-Hypothese: gezielter Carbapenem-Einsatz bei Fieber in Neutropenie

- ESBL-Kolonisation als Risikofaktor für die Entwicklung einer ESBL-Bakteriämie in Neutropenie

- Frühzeitige Identifikation von Risikopatienten mittels rektalem ESBL-Screening

Methodik

- Prospektive observationelle Studie
- Single center (New York City, 862 Betten)
- April 2014 – September 2016

- Einschluss/Setting:
  - Patienten >18jährig, Eintritt zur autologen oder allogenen HSCT
  - Transplantationseinheit mit Einzelzimmer
  - Levofloxacin-Prophylaxe ab d-1
  - Wöchentliches Screening auf Ceftriaxon-res. Enterobacteriaceae/ESBL
  - Bei Fieber: Abnahme von BK und Beginn mit Anti-Pseudomonas-Betalactam

Datenerfassung

- Demographie, zugrundeliegende Erkrankung und Transplantation
- Vorgängige Antibiotika-Therapie, Kolonisationen/Infektionen mit MDR-Erregern
- **Febrile Episoden und Bakteriämien (ESBL?)**
- **Screening auf Ceftriaxon-res. Enterobacteriacae mittels Rektalabstrich bei Eintritt, danach wöchentlich bis Entlassung**
  - Ceftriaxon-resistente Enterobacteriacea? (chromogene Agar Platten)
  - Subkulturen und Resistenzprüfung
  - CRO-R-E Isolate: weitere phänotypische und molekulare ESBL-Abklärung

Auswertungen/Statistik

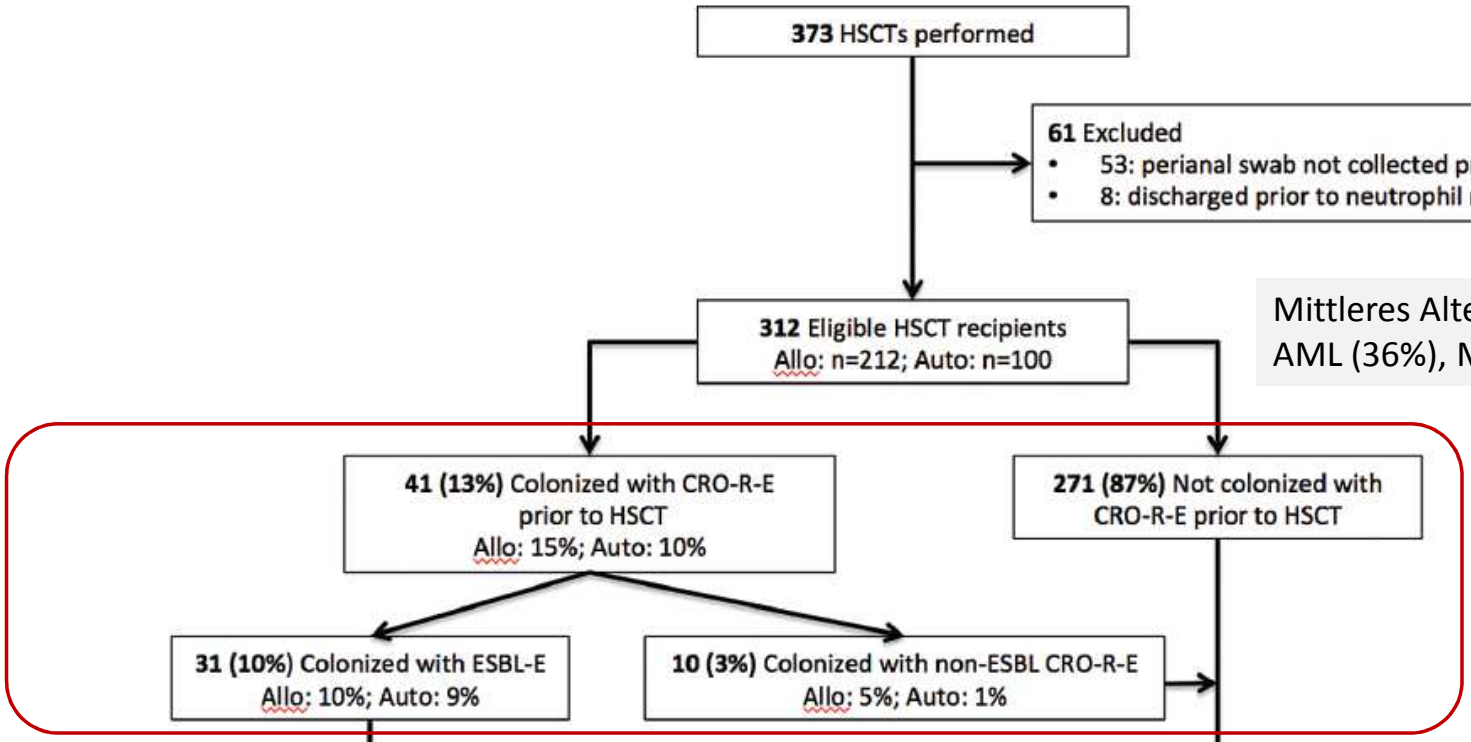
- Anzahl Patienten mit CRO-R-E und ESBL-E Kolonisation bei Eintritt
  - Risikofaktoren (Fisher exact, chi-square bzw. Wilcoxon rank-sum)

- **Kum. Inzidenz von ESBL-Bakteriämien bei vorgängiger Kolonisation im Vergleich zu Patienten mit negativem Screening**
  - Initiale empirische Therapie
  - outcome

- **Falls CRO-R-E Rektalabstrich und Bakteriämie: identischer Stamm?**
  - Multilocus sequence typing (MLST) und Pulse-field gel electrophoresis (PFGE)

- Neue ESBL-Kolonisation während der Hospitalisation, Risiko

Resultate ESBL Kolonisation bei Eintritt



Mittleres Alter 58 Jahre
AML (36%), MM (19%), Hodgkin Lymphom (19%)

28 *E.coli*, 4 K*lebsiella pneumoniae*
91% CTX-M, 9 % SHV-Betalaktamasen
zus. Betalaktamasen in 50%
75% Levofloxacin-resistent

Resistenzen

Antimicrobial Agent	ESBL-E %Susceptible (n = 32)	Non-ESBL CRO-R-E[a] %Susceptible (n = 10)
Amikacin	97%	80%
Ampicillin	0%	0%
Ampicillin-sulbactam	25%	0%
Amoxicillin-clavulanate	44%	10%
Aztreonam	25%	10%
Cefepime	9%	60%
Ceftazidime	13%	10%
Ceftolozane-tazobactam	88%	70%
Ceftazidime-avibactam	100%	100%
Ciprofloxacin	25%	70%
Ertapenem	94%	40%
Imipenem	97%	70%
Gentamicin	59%	90%
Levofloxacin	25%	70%
Meropenem	97%	70%
Piperacillin-tazobactam	84%	40%
Tigecycline	100%	100%
TMP-SMX	16%	40%
Tobramycin	47%	60%

Abbreviations: CRO-R-E, ceftriaxone-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; ESBL-E, ESBL-producing Enterobacteriaceae; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]This group includes AmpC- and carbapenemase-producing Enterobacteriaceae.

Risikofaktoren ESBL-Kolonisation

Patient Characteristic	Colonized With ESBLE[a] (n = 31)	Colonized With Non-ESBL CRO-R-E (n = 10)	Not Colonized With CRO-R-E (n = 271)	*P* Value[b]
Demographics				
Age, years	59 (43–65)	50 (42–63)	58 (48–65)	0.76
Female gender	12 (39)	5 (50)	123 (45)	0.48
Ethnicity/Race				
Hispanic, White	6 (19)	1 (10)	26 (10)	0.12
Hispanic, Black	0	0	2 (1)	1.00
Non-Hispanic				
White	15 (48)	6 (60)	174 (64)	0.085
Black	3 (10)	1 (10)	31 (11)	1.00
Asian	2 (6)	2 (20)	22 (8)	1.00
Middle Eastern	5 (16)	0	16 (6)	**0.051**
Residence outside of the United States	3 (10)	0	9 (3)	0.11
Underlying malignancy				
AML	7 (23)	5 (50)	101 (37)	0.11
ALL	4 (13)	0	16 (6)	0.14
CML	1 (3)	0	6 (2)	0.72
CLL	0	0	2 (1)	1.00
Non-Hodgkin's lymphoma	4 (13)	3 (30)	52 (19)	0.39
Hodgkin's lymphoma	2 (6)	0	12 (4)	0.64
Multiple myeloma	7 (23)	1 (10)	51 (19)	0.62
MDS or MPD	6 (19)	0	18 (7)	**0.025**
Others	0	1 (10)	13 (5)	0.38
ASBMT RFI risk classification				
Low risk	13 (42)	4 (40)	103 (38)	0.67
Intermediate risk	6 (19)	3 (30)	52 (19)	0.98
High risk	10 (32)	2 (20)	107 (39)	0.43
N/A	2 (7)	1 (10)	9 (3)	0.38
Prior transplant	3 (10)	0	19 (7)	0.59
Type of transplant				
Allogeneic	22 (71)	9 (90)	181 (67)	0.88
Autologous	9 (29)	1 (10)	90 (33)	
Conditioning regimen				
Fludarabine-melphalan	16 (52)	8 (80)	145 (54)	0.84
BEAM[c]	5 (16)	1 (10)	48 (18)	0.83
Melphalan	7 (23)	0	38 (14)	0.19
Bendamustine-melphalan	0	0	9 (3)	0.61
Other	3 (10)	1 (10)	31 (11)	1.00
Adjunctive conditioning therapies				
Use of rituximab	3 (10)	1 (10)	29 (11)	1.00
Use of total body irradiation	9 (29)	1 (10)	55 (20)	0.26
Anti-T cell therapies for GVHD prophylaxis				
Anti-thymocyte globulin	7 (23)	4 (40)	71 (26)	0.66
Alemtuzumab	12 (38)	5 (50)	104 (38)	0.97
Hospitalization within previous 90 days	18 (58)	5 (50)	153 (56)	0.86
Antibacterials within previous 90 days				
Beta-lactams	14 (45)	4 (40)	113 (42)	0.71
Fluoroquinolones	5 (16)	1 (10)	58 (21)	0.49
Vancomycin	4 (13)	3 (30)	66 (24)	0.15
History of MDR bacteria colonization or infection[d]				
CRO-R-E	2 (6)	0	6 (2)	0.18
VRE	0	2 (20)	29 (10)	0.09
Clostridium difficile	5 (16)	1 (10)	28 (10)	0.35
Duration of neutropenia, days	10 (8–15)	7 (6–10)	10 (8–14)	0.60

ESBL-Bakteriämie

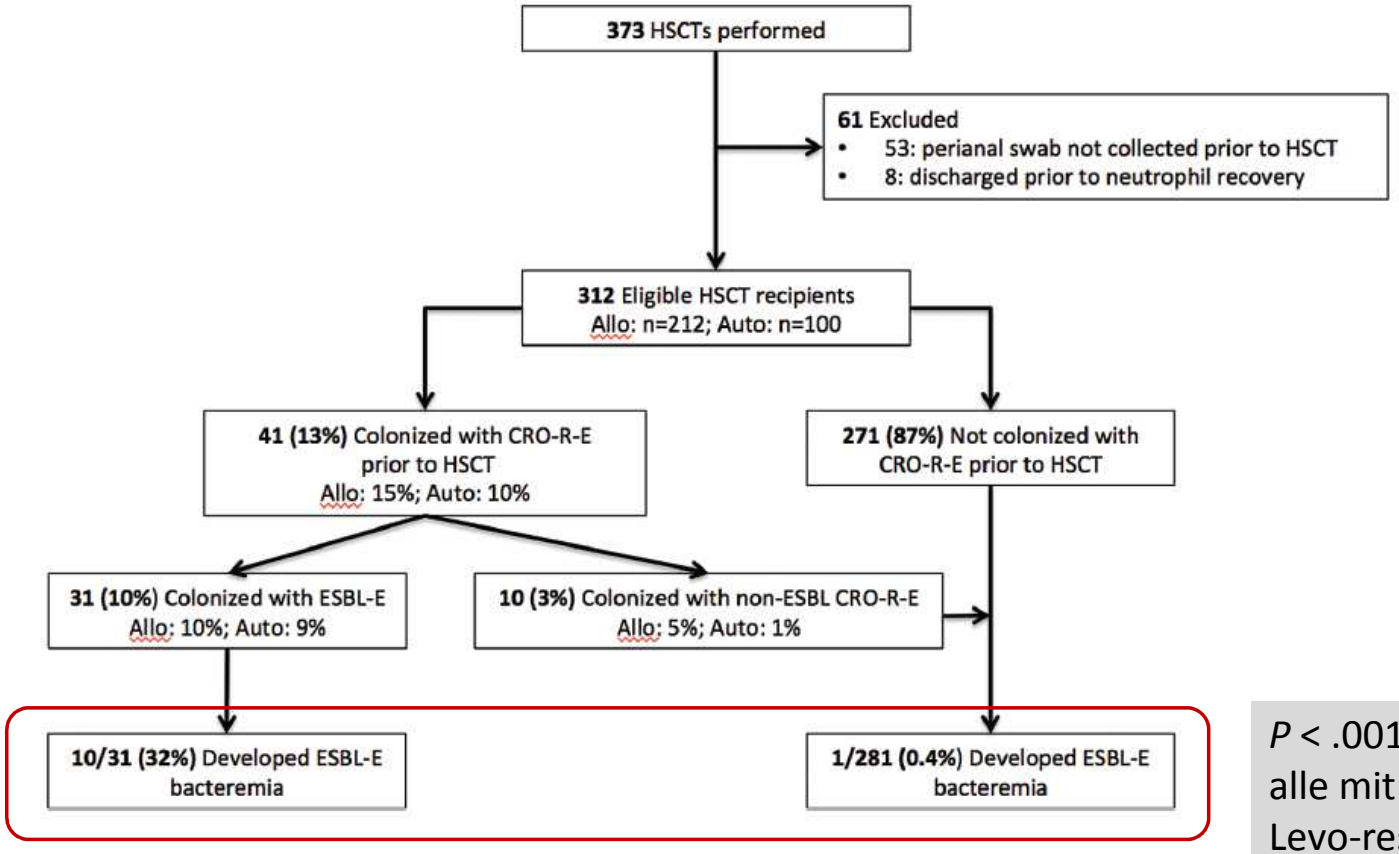


Figure 1. Flow diagram of patients included in the study and their risk of ESBL-E bacteremia, stratified by colonization status. Abbreviations: CRO-R-E, ceftriaxone-resistant Enterobacteriaceae; ESBL-E, extended-spectrum β-lactamase-producing Enterobacteriaceae; HSCT, hematopoietic stem cell transplantation.

$P < .001$
alle mit Levo-resistentem ESBL-Keim, CTX-M
Levo-resistente Subgruppe: 10/24 = 42%

Kolonisierender identisch mit invasivem ESBL-E: Resistenzprüfung, MLST und PFGE

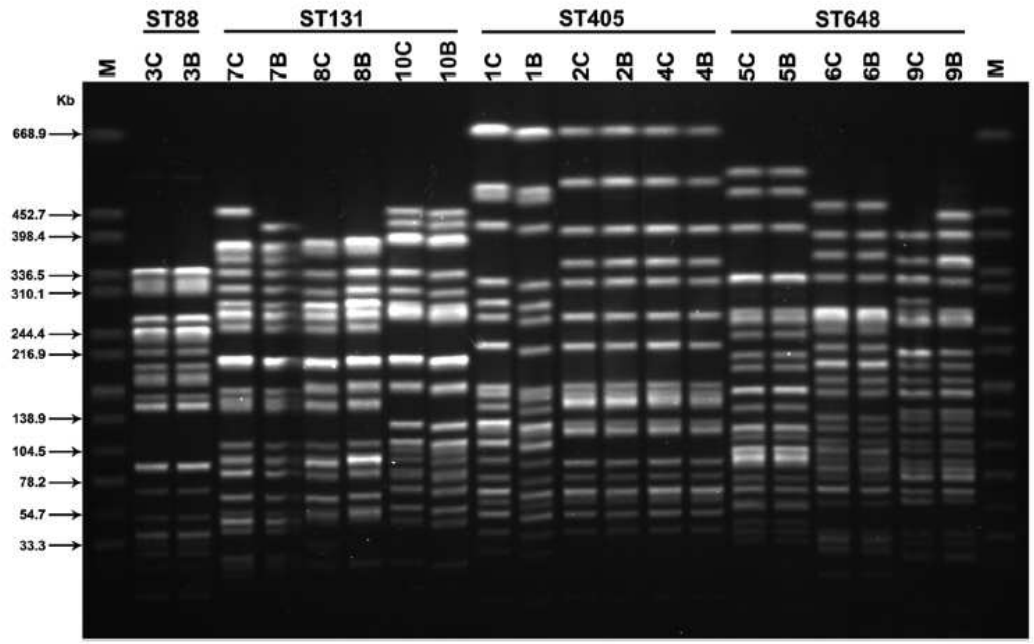


Figure 2. Pulsed-field gel electrophoresis profiles of XbaI digested DNA of paired colonizing and bloodstream ESBL-producing Enterobacteriaceae, stratified by multilocus sequence type (ST). Each number refers to a unique patient, C refers to their colonizing strain, and B refers to their bloodstream strain. Strains from patients 1, 2, 4, 5, and 10 harbored $bla_{CTX\text{-}M\text{-}15}$; 3, 6, and 9 harbored $bla_{CTX\text{-}M\text{-}14}$; and 7 and 8 harbored $bla_{CTX\text{-}M\text{-}27}$. Strains from patients 3, 5, 6, and 9 co-harbored $bla_{TEM\text{-}1}$. Lane M: DNA size maker *Salmonella enterica subsp. enterica serovar Braenderup* (ATCC BA-664).

Febrile Episoden:
Vergleich ESBL vs. non-ESBL Kolonisation

	Colonized With ESBL-E (n = 31)	Not Colonized With ESBL-E (n = 281)	*P* Value
FN	22 (71%)	150 (53%)	.062
Initial Gram-negative empirical therapy for FN			
Piperacillin-tazobactam	6/22 (27%)	111/150 (74%)	**<.001**
Meropenem	14/22 (64%)	35/150 (23%)	**<.001**
Other	2/22 (9%)	4/150 (3%)	.16
Etiology of FN[a]			
Bloodstream infection	12/22 (55%)	42/150 (28%)	**.012**
Gram-positive bacteremia	0	26 (17%)	**.034**
Viridans group streptococci[b]	0	15 (10%)	.12
Vancomycin-resistant *Enterococcus faecium*	0	5 (3%)	1.00
Coagulase-negative staphylococci[c]	0	3 (2%)	1.00
Other[d]	0	3 (2%)	1.00
Gram-negative bacteremia	12 (55%)	13 (9%)	**<.001**
Escherichia coli	11 (50%)	11 (7%)	**<.001**
Ceftriaxone-resistant	9 (41%)[e]	1 (1%)	**<.001**
Ceftriaxone-susceptible	2 (9%)	9 (6%)	.64
Klebsiella pneumoniae	1 (5%)	1 (1%)	1.00
Fusobacterium nucleatum	0	1 (1%)	1.00
Polymicrobial	0	2 (1%)	1.00
Candidemia	0	1 (1%)	1.00

ESBL-Kolonisierte:

- Häufiger Carbapeneme
- Häufiger Bakteriämien
- Nur gramnegative Erreger
- Auch Bakteriämien mit nicht-kolonisierendem Stamm
- Keinen Unterschied hinsichtlich Mortalität und GvHD-Entwicklung

ESBL-Akquisition während Hospitalisation:

- 8/248 = 3.2%
- 7/8 Levo-resistent

Konklusion und Implikationen

- ESBL-Kolonisation = erhöhtes Risiko eine ESBL-E-Bakteriämie in Neutropenie zu entwickeln (32% vs. 0.4% bei Nicht-Kolonisierten)
- Invasiver Erreger identisch mit dem kolonisierenden
- Alle Bakteriämien mit Levo-resistentem ESBL-E
  - Hypothese: Levofloxacin-Prophylaxe führt zur Selektion mit folgender Translokation im Rahmen der Mukositis

- Carbapeneme als first line Therapie bei neutropenem Fieber und bekannter ESBL-Kolonisation
- Keine Chinolon-Prophylaxe
- Screening sinnvoll

Diskussion

- Single center Studie
- Relativ hohe Rate an Bakteriämien
- Chinolon-Prophylaxe
- Keine outcome-Daten

- In unserer Klinik bereits etablierte (Weissbuch, Kapitel «Fieber in Neutropenie»)