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CLINICAL AND EPIDEMIOLOGICAL STUDY

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

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Abstract
Background In patients with haematological or oncological malignancies, we aimed to assess the rate of intestinal colonisation and blood stream infections (BSI) with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) and vancomycin-resistant enterococci (VRE), mortality and risk factors associated with ESBLE/VRE BSI, as well as the impact of faecal screening for ESBLE and VRE in combination with adapted empiric treatment of febrile neutropenia.
Methods Within 72 h of admission to our department, an ESBLE and VRE screening stool sample was collected. In the case of neutropenic fever, blood cultures were drawn. Data of all admitted patients were prospectively documented. Explorative forward-stepwise logistic regression analyses were used to identify risk factors for progression from intestinal colonisation to BSI.
Results During the study period, 1,805 stool samples were obtained from 513 patients during 1,012 inpatient stays, and 2,766 blood cultures were obtained from 578 patients during 1,091 inpatient stays. Ninety (17.5 %) of these patients were colonised with ESBLE and 51 (9.9 %) with VRE. Proportions of 40 % (36/90) of ESBLE and 61 % (31/51) of VRE colonisations were healthcare-associated. Six of 90 (6.6 %) ESBLE-colonised patients and 1/51 (2 %) VRE-colonised patients developed BSI with the respective organism. None of these patients died after receiving early appropriate empiric antibiotics based on colonisation status. Colonisation with ESBLE or VRE was associated with increased risk ratios (RR) towards developing ESBLE BSI [RR 4.5, 95 % confidence interval (CI): 2.89–7.04] and VRE BSI (RR 10.2, 95 % CI: 7.87–13.32), respectively. Acute myelogenous leukaemia and prior treatment with platinum analogues or quinolones were identified as independent risk factors for ESBLE BSI in colonised patients.
Conclusions Intestinal ESBLE/VRE colonisation predicts BSI. Faecal screening in haematology/oncology patients in combination with directed empiric treatment may reduce ESBLE BSI-related mortality.

Keywords Extended-spectrum beta-lactamase · *Enterobacteriaceae* · Vancomycin-resistant enterococci · Febrile neutropenia · Bacteraemia · Blood cultures · Intestinal colonisation

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Introduction

Bacterial blood stream infections (BSI) remain the leading cause of mortality in neutropenic patients under treatment for

haematological and oncological malignancies [1, 2]. The timely initiation of adequate empiric antibiotic treatment is of crucial importance in the management of these infections. With rising incidence rates of multidrug-resistant bacteria, particularly extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) and vancomycin-resistant enterococci (VRE), choosing an adequate empiric antibiotic can be challenging [3, 4]. A delay in the initiation of adequate treatment might have a negative impact on patient outcome. On the other hand, the use of antibiotic agents with activity against ESBLE and VRE should remain restricted to specific indications, to prevent further spread of high-level resistance. Penetration of the mucosal barrier by gut-colonising bacteria is a frequent cause of BSI during neutropenia [5–7]. Therefore, intestinal colonisation status with ESBLE and VRE prior to an episode of febrile neutropenia may help to guide empiric antibiotic treatment.

To further assess this hypothesis in patients with haematological or oncological malignancies, the following aspects were studied at a German tertiary care centre: (1) the rate of intestinal colonisation and BSI with ESBLE/VRE and the associated mortality, (2) risk factors for developing BSI after intestinal colonisation, (3) the impact of faecal screening for ESBLE and VRE in combination with adapted empiric treatment on patient outcome.

Materials and methods

Setting

On 1st September 2008, a new standard of care was introduced at the general wards of the 1st Department of Internal Medicine (Haematology and Oncology) of the University Hospital Cologne (Fig. 1). Within 72 h of admission, a stool sample was collected from all patients with an expected duration of hospitalisation of >72 h to test for ESBLE and VRE colonisation of the gut. In case of neutropenic fever or suspicion of a BSI for other reasons, two blood culture sets were drawn.

All stool and blood specimens were processed at the Institute for Medical Microbiology, Immunology and Hygiene (IMMIH) of the University Hospital Cologne according to the "Microbiology Procedures Quality Standards (MiQ)" issued by the German Society for Hygiene and Microbiology (DGHM) [8]. The chromogenic culture media chromID^{TM} ESBL and chromID^{TM} VRE (both by bioMérieux Deutschland GmbH, Nürtingen, Germany) were used in addition to non-selective, non-chromogenic media to enhance the detection of the respective bacteria in stool samples. Species identification and susceptibility testing including confirmatory tests for ESBLE identification was performed using Vitek2 (bioMérieux) according to Clinical

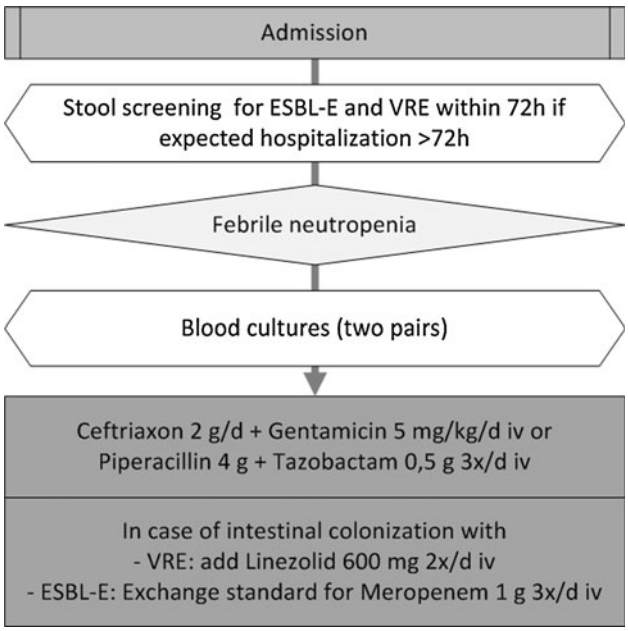

Fig. 1 Standard of care. *VRE* vancomycin-resistant enterococci, *ESBLE* extended-spectrum beta-lactamase-producing *Enterobacteriaceae*

Laboratory and Standards Institute (CLSI) standards [9]. Susceptibilities were confirmed with gradient diffusion (E-test) or the double-disk diffusion test, where appropriate.

After blood cultures had been obtained, empiric antibiotic treatment was initiated immediately. In patients without prior documentation of ESBLE or VRE colonisation, ceftriaxone 2 g per day i.v. plus gentamicin 5 mg/kg per day i.v. or piperacillin 4 g plus tazobactam 0.5 g three times daily i.v. were used as the empiric treatment. In patients known to be colonised with ESBLE, meropenem 1 g three times daily i.v. was used as the first empiric treatment. In patients colonised with VRE, linezolid 600 mg twice daily i.v. was added to the above-mentioned treatment regimen.

During the study period, all patients found to be colonised with VRE or ESBLE were treated in single rooms under contact isolation.

Study design

The present study was designed as a prospective observational study assessing the period from 1st September 2008 to 22nd June 2009. All hospitalisations during the study period were documented using the Cologne Cohort of Neutropenic Patients (CoCoNut) database, a documentation platform based on Microsoft SQL Server 2005 and Microsoft Access 2003 (both by Microsoft Corporation, Redmond, WA, USA), developed in cooperation with System AG für IT-Lösungen, Lohmar, Germany [10]. Data extracted from patient files included the variables age, gender, underlying malignancy, number of prior

hospitalisations, chemotherapy, stem cell transplantation, neutropenia, antibiotic therapy, immunosuppressive therapy, antacids, central venous catheter, parenteral nutrition, diarrhoea and body mass index (BMI).

Faecal screening for ESBLE and VRE was only conducted on the general wards (see "Setting"). Patients admitted directly to the department's intensive care unit (ICU) did not undergo screening, but were also included into the database to allow for the identification of all patients at risk of ESBLE and VRE BSI.

Definitions

Colonisation was defined as the detection of VRE or ESBLE in at least one stool sample and BSI as the growth of ESBLE or VRE from at least one blood culture. A patient was considered to be colonised until the documentation of three consecutive negative stool cultures. If consecutive stool samples from the same patient revealed a switch from a non-carrier to a carrier status, the patient was considered to have acquired healthcare-associated colonisation. If a patient presented with a positive stool sample within 72 h of his or her first admission, colonisation was considered to be community-acquired.

Empiric therapy was defined as the administration of antibiotics in response to a suspected infection without prior identification of the causative pathogen. Targeted treatment was defined as the administration of antibiotics with documented in vitro activity against the blood stream isolate.

Adequate therapy of ESBLE and VRE BSI was defined as the use of one drug with proven in vitro activity, such as carbapenems, tigecycline or colistin against ESBLE and linezolid, daptomycin or tigecycline against VRE.

Mortality associated with ESBLE and VRE BSI was defined as death within 14 days of a respective positive blood culture.

Statistical analysis

Frequencies of ESBLE and VRE colonisation and BSI in screened and unscreened patients were calculated. Colonised, uncolonised and unscreened patients who developed an ESBLE or VRE BSI were compared with respect to adequacy of treatment and 14-day survival rates.

All occurrences of ESBLE and VRE BSI among colonised patients were analysed using separate explorative forward-stepwise logistic regression analyses including the above-mentioned variables.

Ethical considerations

All investigators were directly involved in patient care at the 1st Department of Internal Medicine of the University Hospital Cologne. No interventions were performed as part of this epidemiological cohort study. Data collection and storage were performed on-site by site personnel using current techniques of privacy assurance. In this scenario, neither approval by an Ethics Committee nor patient consent is required by German law.

Results

During the study period, 1,805 stool samples were obtained from 513 patients during 1,012 inpatient stays, and 2,766 blood cultures were obtained from 578 patients during 1,091 inpatient stays. Of the patients receiving stool screening, 46 % had their first hospitalisation at our institution during the study period. Of the 513 patients with stool screening, 90 (17.5 %) were found to be colonised with ESBLE and 51 (9.9 %) with VRE, respectively. The demographic characteristics of the colonised patients are shown in Table 1. During the same time period, 427 patients were admitted without undergoing screening either due to a short duration of stay, admittance to a ward not participating in the screening, e.g. the ICU, or due to non-compliance of the staff with the standard of care.

Overall, ESBLE colonisations were healthcare-associated in 40 % (36/90), while 17 % (15/90) represented

Table 1 Demography of VRE- and ESBLE-colonised patients

Variable	ESBLE ($n = 90$)	VRE ($n = 51$)
Gender, *n* (%)		
Male	57 (63.3)	30 (58.8)
Female	33 (36.6)	21 (41.1)
Underlying disease, *n* (%)		
AML/MDS	19 (21)	18 (35.2)
ALL	13 (14)	6 (11.7)
NHL	14 (15)	10 (19.6)
CLL	7 (7.7)	4 (7.8)
Hodgkin's lymphoma	11 (12)	5 (9.8)
MM	5 (5.5)	3 (5.8)
Solid tumour	9 (10)	2 (3.9)
Other[a,b]	12 (13)	3 (5.8)
Age (years)		
Median (min–max)	52 (18–81)	58 (19–78)

VRE vancomycin-resistant enterococci, *ESBLE* extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, *AML* acute myelogenous leukaemia, *MDS* myelodysplastic syndrome, *ALL* acute lymphoblastic leukaemia, *NHL* non-Hodgkin lymphoma, *CLL* chronic lymphoblastic leukaemia, *MM* multiple myeloma

[a] ESBLE others: cystic fibrosis ($n = 3$), HIV ($n = 3$), malaria tropica, myeloproliferative syndrome, aplastic anaemia, idiopathic thrombocytopaenia, pancreatitis, liver cirrhosis (all $n = 1$)

[b] VRE others: myeloproliferative syndrome ($n = 1$)

community-acquired colonisations. In patients with no prior admissions at our institution, the rates of healthcare-associated and community-acquired ESBLE colonisation were 40 % (25/52) and 34 % (18/52), respectively. The remaining patients (43 %; 39/90) had been screened after the first 72 h of hospitalisation or had been previously hospitalised at our department before initiation of the study. Therefore, these patients were not evaluable with respect to their mode of ESBLE acquisition. Of the colonised patients, 64.4 % (51/90) were subsequently re-screened, and 25 (49 %) of them had three consecutive negative stool samples and were, thus, considered to be no longer colonised with ESBLE.

VRE colonisations were healthcare-associated in 61 % (31/51), while 18 % (9/51) represented community-acquired colonisations. In patients with no prior admissions at our institution, the rates of healthcare-associated and community-acquired VRE colonisation were 54 % (14/26) and 19 % (5/26), respectively. In 11/51 patients (21 %), the mode of VRE acquisition was not evaluable. Of the colonised patients, 68.6 % (35/51) were subsequently re-screened and 14 (56 %) of them were no longer colonised with VRE.

A total of 7/513 patients (1.4 %) were colonised with both VRE and ESBLE at the same time.

Overall, 2,079 blood cultures were obtained from 352/513 (69 %) patients who had received stool screening. From 20 % of these cultures ($n = 422$), at least one pathogen could be isolated. Isolate distribution was documented as follows: coagulase-negative staphylococci ($n = 227$), Gram-negative rods ($n = 106$), *Enterococcus* spp. ($n = 41$), *Streptococcus* spp. ($n = 33$), methicillin-sensitive *Staphylococcus aureus* ($n = 8$), methicillin-resistant *Staphylococcus aureus* ($n = 4$) and other miscellaneous species ($n = 10$).

In 6/90 (6.6 %) patients colonised with ESBLE, BSI with ESBLE was diagnosed. During the same period, only two (0.5 %) of the 423 patients with negative stool screening and two (0.5 %) of the 427 patients without screening developed ESBLE BSI. For both patients contracting ESBLE BSI after negative stool screening, there was an interval of more than 4 weeks since their last stool sample; an undetected healthcare-associated colonisation may, therefore, have occurred in the meantime. The risk ratio for colonised patients to develop BSI by ESBLE was 4.5 (95 % confidence interval [CI]: 2.89–7.04).

Two patients died within 14 days of ESBLE BSI from septic shock—both had not been screened. In addition to ESBLE, one of them also presented with several blood cultures positive for methicillin-resistant *Staphylococcus aureus* (MRSA). The time from acquisition of the first positive blood culture to death was 4 and 7 days, respectively.

Concerning VRE, BSI was found in 1/51 (2 %) patients colonised with VRE, none of 462 patients with negative stool screening and two (0.5 %) of 427 patients without screening. Colonised patients had a risk ratio of 10.2 (95 % CI: 7.87–13.32) to develop VRE BSI. Prior colonisation status, treatment and 14-day mortality of the corresponding patients are shown in Table 2.

Table 3 depicts the results of an explorative forward-stepwise logistic regression analysis for the identification of independent risk factors for progression from intestinal ESBLE colonisation to BSI. The following variables were identified: acute myelogenous leukaemia or myelodysplastic syndrome as the underlying haematological malignancy, administration of platinum analogues and administration of quinolones. Concerning risk factors for progression from VRE colonisation to BSI, a logistic regression analysis was not carried out as planned, because the low number of VRE BSI ($n = 3$) did not permit a meaningful statistical analysis.

Discussion

Our study demonstrates considerable colonisation rates of haematological/oncological patients with ESBLE and VRE, most of which have to be considered healthcare-associated.

Colonisation was demonstrated to be a significant predictor of later BSI with pathogens, which are commonly not accounted for by empiric antibiotic treatment

Table 2 Screening status, treatment and mortality of patients with VRE or ESBLE BSI

	VRE		ESBLE		
	Colonised ($n = 1/51$)	Not screened ($n = 2/427$)	Colonised ($n = 6/90$)	Not colonised ($n = 2/423$)	Not screened ($n = 2/427$)
Treatment					
Adequate empiric	1	0	4	0	0
Adequate targeted	0	2	2	1[a]	1
Inadequate	0	0	0	1[a]	1
14-day mortality	0	0	0	0	2

VRE vancomycin-resistant enterococci, *ESBLE* extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, *BSI* blood stream infections

[a] Last screening performed >4 weeks before positive blood culture

Table 3 Risk factors for ESBLE BSI among ESBLE-colonised patients

Dependent variable: ESBLE BSI		
Univariate		Multivariate (only remaining variables)
Variable	*p*-value	Odds ratio
Gender	0.45	
Age	0.90	
Duration of hospitalisation	0.55	
No. of prior hospitalisations	0.60	
Neutropenia	0.77	
Immunosuppressive drugs	0.71	
Central venous catheter	0.13	
Antacids	0.53	
Dialysis	0.56	
Parenteral nutrition	0.83	
Diarrhoea	0.10	
Allogeneic SCT	0.36	
Autologous SCT	0.61	
Radiation	0.31	
ALL	0.25	
AML/MDS	0.12	20.33
NHL	0.23	
Any chemotherapy	0.59	
Anthracyclines	0.50	
Methotrexate	0.39	
Mitoxantrone	0.61	
Nitrogen mustard alkylating agents	0.12	
Platinum analogues	0.01	46.53
Purine anti-metabolites	0.18	
Pyrimidine anti-metabolites	0.28	
Topoisomerase inhibitors (anti-neoplastic)	0.98	
Aminoglycosides	0.98	
Carbapenems	0.82	
Cephalosporins	0.92	
Penicillins	0.07	
Quinolones	0.24	11.16

ESBLE extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, *BSI* blood stream infections, *SCT* stem cell transplantation, *ALL* acute lymphoblastic leukaemia, *AML* acute myelogenous leukaemia, *MDS* myelodysplastic syndrome, *NHL* non-Hodgkin lymphoma

strategies. In patients identified as ESBLE/VRE carriers by stool screening, adapted empiric treatment with appropriate antibiotics ensured a good prognosis of BSI.

Concerning ESBLE colonisation, prior screening studies conducted in patients with haematological malignancies and in mixed patient populations reported colonisation rates between 3 and 29 % [11–13]. Considering recently published data identifying certain agricultural products as a reservoir for ESBLE, it appears necessary to take the role of food-associated colonisation into account [14]. However, cancer patients at our department receive instructions on food processing—particularly the thermal inactivation of pathogens—and hygienic precautions in between chemotherapy cycles. Such measures have been shown to inactivate bacterial food contaminants [15, 16]. Therefore, this route of ESBLE acquisition might be of minor importance in the examined patient population.

Rates of ESBLE BSI in colonised patients vary substantially as well. In the above populations, rates of 2–9 % were observed, while a rate of 6.6 % was documented in the present study [11, 13]. None of the comparator studies was, however, conducted in Germany, but in Spain, Israel and the USA.

Based on these data, the threat of ESBLE—in particular to immunocompromised patients—should not be underestimated. While all six patients receiving empiric treatment for ESBLE based on a prior positive screening result survived their ESBLE BSI, two of four patients receiving ESBLE active treatment only after pathogen identification from a blood culture died of severe sepsis. Overall, this yields an 80 % survival rate. A previous study on ESBLE BSI in a mixed patient population reported a survival rate of only 39 % in unscreened patients. Furthermore, it was shown that delays in the initiation of appropriate antibiotic therapy were associated with death [17]. We hypothesise that screening for ESBLE colonisation may have reduced the time to adequate treatment initiation and, thus, improved survival rates. However, fatal outcome in two patients with ESBLE BSI could also be attributed to other factors (e.g. disease severity), since these patients were treated in the ICU.

Concerning VRE colonisation, data from an observational study performed at our haematology–oncology department and the nephrology department between 1997 and 1998 was available, demonstrating an increase in the colonisation rate from 3.5 % [18] to 10 % in our current observation. However, the rate was still lower than the rates in most previous studies among patients with haematological malignancies, reporting rates between 5 and 88 % [19–23]. Again, none of these studies was conducted in adult German patients, so regional epidemiology is the probable driver of the observed differences.

In line with our findings, VRE BSI rates between 0 and 34 % have been reported from VRE-colonised patients [19–22, 24–26]. However, only one of our patients developed VRE BSI after a positive VRE screening result had been obtained. Therefore, our results on this aspect do not allow for conclusions on the clinical use of VRE screening and adapted empiric therapy.

None of the three patients who developed VRE BSI died from the infection or another cause within 14 days of

the diagnosis. These findings are in line with prior studies, where mortality rates of 0–8 % had been observed [19–28]. Given the low rate of VRE BSI in VRE-colonised patients and since all of our patients with VRE BSI survived, even though two of them obtained only targeted and not empiric treatment, the value of screening for intestinal VRE colonisation in a low-incidence setting may be questioned.

A major limitation of our study was that bacterial isolates were compared on the basis of biochemical identification and susceptibility testing. Molecular characterisation at the subspecies level, e.g. by pulsed-field gel electrophoresis (PFGE), might have provided more reliable information on the transition of bacteria from gut to blood. To overcome this limitation and to further assess the risk factors for progression from ESBLE colonisation to ESBLE BSI identified in our exploratory regression analysis, a multicentre study is warranted.

In conclusion, ESBLE and VRE gut colonisation are predictors of later BSI by bacteria expressing the same resistance mechanisms. Early empiric treatment based on colonisation status may have prevented lethal outcomes. This approach may be less effective for VRE-colonised patients, given the low incidence and favourable outcomes of VRE BSI.

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