Different screening frequency of carbapenem-resistant Enterobacteriaceae in patients undergoing hematopoietic stem cell transplantation: which one is better?

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Abstract

Background

Consensus has been reached that carbapenem-resistant *Enterobacteriaceae* (CRE) screening in immunosuppressed individuals can reduce the incidence of severe CRE infection. However, there is no standard for effective screening and relevant studies has been fewer reported, especially for hematopoietic stem cell transplantation (HSCT) population.

Methods

We retrospectively studied the clinical data of 395 consecutive HSCT patients admitted in our center from September 2017 to April 2019 during two periods, single screening and continuous screening. During period 1 (September 2017 to June 2018), 200 patients received single stool CRE screening within one week before transplantation. During period 2 (July 2018 to April 2019), we implemented continuous weekly stool CRE screening after admission. For patients colonized with CRE, target management were received:(1) contact precaution;(2) preemptive CRE-targeted treatment if necessary.

Results

During period 1 , three patients with CRE colonization were detected (1.5%). The BSI percent of CRE was 2.0% (4 patients) and related 30-day mortality was 50.0% (2 out of 4 patients). During period 2, twenty-one patients with CRE colonization were detected and the detection rate was significantly higher than that in period 1(P<0.001). The CRE BSIs rate decreased to 0.5% (1/195) and there was no CRE-related mortality.

Conclusion

The increase of screening frequency contributed to the detection of patients with CRE colonization. Targeted management for these colonized patients may contribute to reduce the incidence and related mortality of CRE bloodstream infection, therefore improving the prognosis of HSCT patients.

Introduction

With the extensive use of carbapenems, a global dissemination of carbapenem-resistant Enterobacteriaceae (CRE) has been reported over the recent decades.[1] A recent national multicenter study from 25 provinces in China reported that the rate of carbapenem resistance in Escherichia coli (E.coli)and Klebsiella pneumoniae (K. pneumoniae)was up to 0.6–3.6% and 1.2–18.9%, with 1.8% and 12.3% in Zhejiang province, which increased year by year.[2] Long-term hospitalization, frequent use of broad-spectrum antibiotics, high-dose chemotherapy, neutropenia, compromised immunity, and gastrointestinal mucosal destruction are risk factors favoring CRE colonization and bloodstream infections (BSIs) in patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT). [3–8] The overall incidence of BSIs caused by CRE in HSCT recipients is about 1.8-2%.Due to lack of effective antibiotic treatment, the death rate for CRE BSIs after HSCT is high (51%-65%).[3, 6, 9, 10] More studies begin to emphasize the importance of preemptive intervention in prevention and treatment of CRE BSIs.

Gut colonization by CRE is an independent risk factor for CRE infection. [7, 8, 11, 12] An Italian multicenter study showed that in patients underwent autologous and allogeneic HSCT, CRE colonization rates were between 1% and 2.4%. Of these patients with CRE colonization, 25.8% and 39.2% subsequently developed CRE BSIs, which was significantly more frequent than hospitalized patients in general (16.5%).[6] Early identification of CRE colonization made it easier to adopt early strategies to control CRE dissemination.[13] Many guidelines and studies also recommend HSCT patients as target population for CRE screening and stool was considered as the preferred sample for screening because of the better patient compliance and fewer side effects.[5, 14–19] However, for HSCT centers where CRE are endemic nosocomial pathogens, the effect of weekly active screening on morbidity and mortality of CRE BSIs has been fewer reported.

In our center, the first patient with CRE BSI was identified in May 2016, and the incidence and related mortality of CRE BSIs between May 2016 and August 2017 was retrospectively analyzed to be 1.9% and 66.7%. Given the high CRE-related mortality, we initiated active screening from September 2017 in an attempt to identify CRE-colonized patients and to reduce the risk of CRE infection. We compared the frequency of CRE screening and assessed outcomes in HSCT patients.

Patients And Methods

Patients and Study design

This was a retrospective observational study of 395 consecutive patients who underwent HSCT in our center from September 2017 to April 2019. From September 2017 to June 2018 (period 1), we implemented single CRE rectal screening within one week before transplantation. From July 2018 to April 2019 (period 2), to improve the detection rate, the screening frequency was modified to weekly screening until discharge. CRE screening would be repeated in patients who had symptoms of fever or underwent gut complications such as abdominal pain, diarrhea and perianal inflammation. Data retrospectively collected from two groups were compared. The CRE gut detection rate, BSI rate and attributed mortality were also evaluated. Informed consent for HSCT, collection of stool swabs, data analysis, and publication was obtained from patients. The study protocol complied with the Declaration of Helsinki.

Surveillance

Stool was the surveillance material in our center. Specimens were collected in an aseptic manner and immediately transported to the microbiology laboratory. The technician inoculated the samples in Columbia blood agar for microbial identification and antibiotic susceptibility testing were performed. CRE was

defined as any isolated Enterobacteriaceae resistant to meropenem (disc diffusion diameter ≤ 19 mm) or Ertapenem (MIC ≥ 2ug/ml) or Imipenem (MIC ≥ 4ug/ml).[20] Patients who had a positive stool swab for CRE during the screening period were defined as colonized, while patients continuously detected negative for CRE during the whole screening period were defined as noncolonized.[21]

Target Management of CRE colonization

For patients colonized with CRE, contact precaution were conducted: a single room, hanging sign, hand hygiene performed before and after entering the room, use of disposable gloves and gowns and strengthened environmental cleaning and disinfection. Patients who were colonized with CRE but had no fever also received contact precaution but were not treated with prophylactic antibiotics.

A single oral temperature of ≧ 38.3° C or a persistent oral temperature > 38.0° C sustained over 1 hour was defined as fever and an absolute neutrophil count (ANC) below 0.5×10^9/L was defined as neutropenia in this study.[22] CRE BSI was diagnosed with the collection of blood culture that yielded the CRE strain. When the colonized patient appeared febrile episodes, treatment should be considered according to the patient's condition, neutropenic severity, infection clinical symptoms and laboratory examination. At least two consecutive blood cultures were sent before starting of antibiotics for patients developing clinical symptoms. Preemptive CRE-targeted treatment with tigecycline was performed under all the following conditions: (i) CRE colonization identified at the onset of fever; (ii) neutropenic fever persistent over 12 hours or fever with obvious symptoms of intestinal infection, such as abdominal pain, diarrhea, and perianal pain; (iii) C-reactive protein (CRP) was 5 times higher than normal with or without a significant increase in procalcitonin(PCT). Polymyxin were added if there were signs of progression of sepsis or if there was a lack of response for tigecycline treatment within 48 hours.[18, 23]

Statistical analysis

Data analyses were performed with SPSS (version 20.0 SPSS Inc., IBM Co., Chicago, IL, USA). Continuous variables were evaluated using the Kruskal-Wallis test; categorical variables were evaluated with Fisher's exact test or Pearson chi square test. All tests and P-values were two-sided and a P-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 395 patients undergoing HSCT were summarized from September 2017 to April 2019. 221 (55.9%) were male and 174 (44.1%) were female, with a median age of 36 years (range, 9–67). Table 1 shows the demographic and clinical characteristics of the patients. There were no significant differences among the two groups on age, sex, underlying disease and type of HSCT.

Table 1
Baseline demographic and clinical characteristics of the study population

Variable	Single screening group(N = 200)	Continuous screening group(N = 195)	P Value
Age, median (range)	35.7(9–64)	37.2(12–67)	0.319
Sex, N (%) Male Female	115(57.5) 85(42.5)	106(54.4) 89(45.6)	0.530
Underlying disease, N (%) AML ALL MDS NHL/HL MM others	78(39.0) 62(31.0) 18(9.0) 21(10.5) 12(6.0) 9(4.5)	66(33.8) 66(33.8) 9(4.6) 20(10.3) 20(10.3) 14(7.2)	0.208
Type of HSCT, N (%) Allogeneic MUD Haplo Sib Autologous	13(6.5) 127(63.5) 37(18.5) 23(11.5)	14(7.2) 117(60.0) 34(17.4) 30(15.4)	0.697

Abbreviations: AML = Acute myeloid leukemia; ALL = Acute lymphatic leukemia; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; MM = multiple myeloma; MUD = matched-unrelated donor allogeneic HSCT; Haplo = HLA-Haploidentical allogeneic HSCT; Sib = HLA-sibling allogeneic HSCT.

CRE incidence and clinical outcomes

During period 1, 3 patients (3/200, 1.5%) were identified as colonized with CRE in the gut: one of whom died of septic shock, and the other two survived. Four patients who were screened negative for CRE colonization before HSCT later developed CRE BSIs (4/200, 2%) during the HSCT period. 2 (50%) out of the 4 patients died, with one patient died of CRE-related septic shock and the other of CRE BSI-induced thrombotic microangiopathy. During period 2, 21 (10.8%) out of 195 patients were identified to be colonized with CRE, which a significantly higher percentage than that identified by single screening ($p < 0.001$). Among these patients, the median times of screening performed in patients was 6 (ranged from 4 to 15 times): only 4 (19.0%) patients were identified

positive for CRE at the first screening, 5 (23.8%) at the second screening, and the remaining 12 (57.1%) at the third or more screening. One of these colonized patients with neutropenia subsequently developed CRE BSI (1/21, 4.8%) but survived (Table 2).

Table 2
Implementation Rate and Results of CRE Screening

	Without screening (N = 311)	Single screening (period 1, n = 200)	Continuous screening (period2, n = 195)
Patients diagnosed as CRE colonization,N (%)	/	3(1.5%)	21(10.8%)
CRE BSIs,N(%) patients with CRE colonization patients without CRE colonization	6 (1.9%) 0 6	4(2.0%) 4 0	1(0.5%) 0 1
Mortality in patients with CRE BSI, N (%)	4 (66.7%)	2(50.0%)	0

Targeted management

24 patients (3 detected during period 1 and 21 detected during period 2) were identified to be colonized with CRE in the gut and the clinical manifestations are summarized in Table 3. Among the 3 patients who received single screening, 2 patients were detected positive for CRE before transplantation and developed fever at day + 7 and day + 5 after screening, respectively. They received tigecycline-based treatment and the body temperatures were controlled within 72 hours. The other patient (patient 1) was detected negative for the CRE screening before HSCT. However, due to symptoms of persistent neutropenic fever, abdominal pain, diarrhea and significantly increased CRP (over 100 mg/L) after HSCT, stool swab of this patient was sent for another CRE screening, which indicated positive CRE colonization 3 days after fever initiation. She was then treated with tigecycline but finally died of septic shock.

Table 3
Clinical manifestations of the 24 patients colonized with CRE

Pt	Age /Sex	Disease/ HSCT	CRE Isolate	Which times screening turned positive	Febrile episodes in carriers	Time from colonization to fever (day)	Time from fever to the use of tigecycline (hour)	ANC at fever (× 10^9/L)	Symptoms at fever	CRP (mg/L) /PCT (ug/L)	30 days status
Single screening											
1*	36/F	ALL/Haplo	E.coli	/	Yes	-3	> 72	0	Abdominal pain, diarrhoea	216.8/1.0	Dead
2	56/F	MM/Auto	E. coli	1	Yes	7	< 24	0	Chills, tremble	95.1/4.1	Alive
3	32/m	ALL/MUD	K.pneumoniae	1	Yes	5	< 24	0	No	48.9/normal	Alive
Continuous screening											
4	36/M	AML/Haplo	K.pneumoniae	5	No	/	/	/	/	/	Alive
5	15/M	AML/Haplo	E. coli	2	Yes	9	< 24	0	Chills, tremble	73.0/normal	Alive
6	27/M	ALL/Haplo	E. coli	3	Yes	8	< 24	0	No	52.2/normal	Alive
7	48/M	AML/Haplo	E.coli	2	Yes	4	< 24	0	Perianal inflammation	112.3/ normal	Alive
8	45/M	AML/Haplo	K.pneumoniae	4	No	/	/	/	/	/	Alive
9	40/M	AL/Haplo	K.pneumoniae	1	No	/	/	/	/	/	Alive
10	38/M	T-LBL/Haplo	E. coli	3	Yes	11	< 24	0.5	No	43.2/normal	Alive
11	16/F	ALL/Haplo	E. coli	1	Yes	17	< 24	0	No	54.2/normal	Alive
12	18/M	ALL/MUD	E.coli	2	Yes	9	< 24	0	Chills, tremble	64.5/normal	Alive
13	25/M	ALL/Haplo	E.coli	2	Yes	8	< 24	0	No	61.2/normal	Alive
14	34/F	AML/Haplo	K.pneumoniae	3	No	/	/	/	/	/	Alive
15	44/M	MM/Auto	E.coli	4	No	/	/	/	/	/	Alive
16	50/M	AML/Sib	K.pneumoniae	1	Yes	15	< 24	0	sore throat	70.4/normal	Alive
17	18/M	ALL/Haplo	K.pneumoniae	5	No	/	/	/	/	/	Alive
18	51/M	ALL/Haplo	E.coli	5	No	/	/	/	/	/	Alive
19	22/M	ALL/Haplo	K.pneumoniae	4	No	/	/	/	/	/	Alive
20	22/F	AML/Haplo	K.pneumoniae	3	Yes	1	> 48	0	Chills, tremble	65.2/0.6	Alive
21	26/M	ALL/MUD	K.pneumoniae	1	Yes	13	< 24	0	No	73.4/normal	Alive
22	27/M	ALL/Haplo	K.pneumoniae	6	No	/	/	/	/	/	Alive
23	21/M	AML/Haplo	K.pneumoniae	2	Yes	12	< 24	0	Perianal inflammation	307/ normal	Alive
24	62/M	AML/Haplo	K.pneumoniae	6	Yes	2	< 24	0	No	141.7/normal	Alive

Abbreviations: AML = Acute myeloid leukemia; ALL = Acute lymphatic leukemia; AL = Acute leukemia; Auto = Autologous HSCT; CRP = C-reactive protein (normal value: 0–8 mg/L)E.coli = Escherichia coli; Haplo = HLA-Haploidentical allogeneic HSCT; K.pneumoniae = Klebsiella pneumoniae; MM = multiple myeloma; MUD = matched-unrelated donor allogeneic HSCT; PCT = Procalcitonin (normal value:<0.5ug/L); Sib = HLA-sibling allogeneic HSCT; T-LBL = T-lymphoblastic lymphoma.

*The patient 1: single screening was negative for the patient, but subsequent screening indicated positive three days after the onset of fever and the patient died of septic shock.

1.Four patients (2,12,20,23) were combined with polymyxin because of persistent fever after 48 hours of tigecycline treatment, one of them (patient 20) developed CRE BSIs later.

During period 2, febrile episodes didn't occur after positive screening in 9 patients and antibiotics were not used. For the other 12 colonized patients, they developed neutropenic fever and the median time from colonization identification to fever was 9 days (1–17 days).They received treatment with tigecycline

considering the emergence of the neutropenic fever, accompanied clinical signs of infection and significantly increased inflammatory biomarkers: the body temperatures of 9 patients were controlled within 72 hours. Three patients (patient 12,20,23) continued to suffer high fever (over 38.5 ℃) 48 hours after tigecycline treatment, and were additionally treated with polymyxin. One of them (patient 20) developed CRE BSIs three days after fever, and we had to stop polymyxin due to abnormal renal function, and used ceftadime-avibatin instead. The body temperatures of 3 patients turned normal after the implantation of targeted treatment. Finally, 21 colonized patients were discharged successfully after hematopoietic reconstruction.

Microbiological data

CRE strains were isolated in 11 patients in blood cultures including strains detected in the unscreened phase and 24 patients in stool swabs during the screening period (the first positive result was documented for samples from the same position), consisting of 22 K.pneumoniae and 13 E.coli. K.pneumoniae was predominant, accounting for 81.8% for the CRE BSIs (9/11) and 54.2% (13/24) for the CRE colonization. One patient with CRE colonization subsequently developed CRE BSIs and the resistance to antibiotics were exactly consistent between blood culture and stool sample. The resistance rates to antibiotics of the 35 CRE isolates are shown in Table 4. Among three carbapenems (Meropenem, Imipenem and Ertapenem), there was a slight difference in the antibiotic resistance rate of the two strains, which cannot be ruled out for technical reasons. The resistance rate of tigecycline and amikacin were 0% and 28.6%, respectively.

Table 4
The Resistance of CRE to antibiotics in transplant patients (%)

Antibiotics	CRE resistance rate in stool samples			CRE resistance rate in blood cultures		
	Total(24)	K.pneumoniae (13,54.2%)	E.coli(11,45.8%)	Total(11)	k.pneumoniae(9,81.8%)	E.coli(2,18.2%)
Ceftazidime	100%	100%	100%	100%	100%	100%
Ceftriaxone	100%	100%	100%	100%	100%	100%
Cefepime	100%	100%	100%	100%	100%	100%
Piperacillin/tazobactam	100%	100%	100%	100%	100%	100%
Fluoroquinolones	95.8%	100%	90.9%	100%	100%	100%
Gentamicin	82.6%	84.6%	80.0%	63.6%	66.7%	50.0%
Amikacin	16.7%	23.1%	9.1%	54.5%	66.7%	0
Aztreonam	79.2%	92.3%	63.6%	100%	100%	100%
Meropenem	100%	100%	100%	83.3%	100%	50.0%
Imipenem	91.6%	92.3%	90.9%	100%	100%	100%
Ertapenem	100%	100%	100%	100%	100%	100%
Tigecycline	0	0	0	0	0	0
SMZ co	91.7%	84.6%	100%	81.8%	77.8%	100%
Nitrofurantin	/	/	NR	77.8%	100%	0
Tobramycin	/	/	NR	77.8%	85.7%	50.0%
Abbreviations: E.coli = Escherichia coli; K.pneumoniae = Klebsiella pneumoniae; SMZ co = Compound Sulfamethoxazole.						

Discussion

CRE BSIs have become a major challenge and are always associated with crude mortality rates. In China, the overall annual CRE incidence was about 4 per 10,000 discharges, with the highest in partial region (0.15%), which was highly endemic in China and caused severe disease burden.[24]

Active surveillance for CRE colonization, as part of a multifactorial intervention, is an effective strategy to decrease rates of nosocomial CRE infection and related mortality.[25–27] CRE screening with stool is considered as an effective method for surveillance of CRE colonization.

Before the implementation of active screening, the incidence and attributable mortality of CRE BSI at our center was higher (1.9% and 66.7%) and similar to the previous studies. Thus, active surveillance was added to control CRE infection. During period 1, only 1.5% patients were identified positive for CRE, and the 4 patients who developed CRE BSIs were negative at single screening. The incidence and mortality of CRE-BSIs were 2% and 50%. These results suggested that single screening alone could not effectively detect patients with CRE colonization. Considering the poor efficiency, we started continuous screening during period 2 and significant difference was observed with respect to CRE detection rate between patients and patients (10.8% vs 1.5%, $P < 0.001$). Additionally, it's worth noting that of the patients who were positive in continuous screening, only 4 were positive at the first screening, and 80.9% (17 out of 21colonized patients) got positive results for CRE at the second or more screening, which again demonstrated the deficiencies of single screening. Meanwhile, due to the increased positive rate of continuous screening and the preemptive treatments used in these patients with infectious symptoms, the morbidity and mortality of CRE-BSIs were obvious reduced (only 0.5% and 0), for which the difference didn't statistically significance probably owing to the

small sample size. Forcina et al also demonstrated that after the introduction of regular surveillance, the cumulative incidence of CRE BSI and septic shocks at 1 year after HSCT was significantly reduced.[4] The CRE infection-mortality rate dropped from 62.5–16.6%. These results strongly support the role of continuous screening in prevention and control of CRE BSI.

Consistent with published data, the resistance rate of tigecycline and amikacin in our study were low of 0 and 28.6%, respectively; and therefore tigecycline was used as the first-line antibiotic for CRE infection in our study.[2, 28, 29] Clinical signs of infection are usually attenuated or absent in neutropenic patients and fever is often the only symptom of a serious potential infection. The purpose of screening itself is to effectively manage CRE colonizers who are at high risk to develop BSIs through contact precaution and preemptive CRE-targeted treatment, and therefore reduce spread of CRE and improve outcomes in infected patients. Early targeted antibiotic therapy is considered vital to cover possible infections in febrile neutropenic patients with CRE colonization even if blood cultures remain negative. [22, 30–33] In our study, we gave preemptive treatment with tigecycline (within 24 hours) to patients with CRE colonization combined with neutropenic fever/clinical signs of infection/significant elevation of inflammatory markers and they achieved rapid temperature control. However, two patients with neutropenic fever received tigecycline later than 48 hours and 72 hours respectively. The first patient subsequently developed CRE BSIs but survived due to timely combination with polymyxin (changed to ceftadime-avibatin because of nephrotoxicity later). The second patient received tigecycline 72 hours since the single screening was negative and died of septic shock. These results also highlighted that for patients with CRE colonization, prompt and active CRE -targeted treatment in the case of febrile neutropenia accompanied with clinical signs of infection could contribute to improvement of prognosis.[4, 34] For patients found to be colonized with CRE, but not accompanied with fever, contact precaution were also necessary and the administration of antibiotics should be cautious and avoid abuse. In our study, patients colonized with CRE, in the absence of febrile episodes were only isolated and observed, and tigecycline was not used. The prognosis of them were good. These results also indicate that gut CRE colonization alone was not the indication for further antibiotic treatment.

There are several limitations in this study. Firstly, this was a single-center, retrospective observational study in a particular geographical area. Secondly, the resistance mechanism was not examined. Finally, the cohort of patients with CRE colonization or BSIs was small. A multi-center, large continuous screening study is being performed by our center to furtherly demonstrate the optimal surveillance methods for CRE colonization in HSCT patients.

Conclusion

In summary, for patients undergoing HSCT, regular continuous screening for CRE colonization is necessary to assist in early detection and management of CRE carriers including contact precaution and prompt implementation of CRE-targeted preemptive treatment to improve outcomes in patients after HSCT CRE BSIs. Regular continuous gut screening is recommended as a feasible and reliable measure for HSCT patients at high risk of infection.

Abbreviations

CRE: Carbapenem-resistant *Enterobacteriaceae*

HSCT: Hematopoietic stem cell transplantation

E.coli: *Escherichia coli*

K. pneumoniae: *Klebsiella pneumoniae*

BSI: bloodstream infection

CRP: C-reactive protein

PCT: procalcitonin

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JMS and HH designed the study. QY and HCC collected the data. YL, YMZ, YSS, XYL, JY, YT, GQW were participants in the workshop and the round-table and either gave presentations, moderated the workshop. TTY and XPL analyzed the data and wrote the first draft of the manuscript, which was significantly edited by JMS. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Neither medical nor ethical approval was required to conduct the surveillance since it was part of the local hospital policy, patients provided oral informed consent and all data were processed anonymously. The, non-invasive, rectal swabs were collected as part of the local hospital policy which is considered routine care. The weekly performed surveys for the presence of Carbapenem-resistant Enterobacteriaceae are part of the infection control policy in our hospital. This includes contact tracing, active search in patients with risk factors and routinely check-ups like the yearly prevalence survey. Swabs were not specifically collected for the purposes of this publication.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflict of interest.

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