EJMO

DOI: 10.14744/ejmo.2024.79645
EJMO 2024;8(1):15–23

Systematic Review

Escherichia Coli Bloodstream Infections and Associated Antibiotic Resistance Pattern in Hematological Malignancy Populations, A Global Systematic Review

Mina Jafarabadi,[1] Azad Khaledi[2]

[1]Vali-E-Asr Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran

Abstract

Objectives: Among Gram-negative bacteria, *Escherichia coli* (*E.coli*) has a major role in BSI in hematological malignancies recipients. So, this study aimed to survey *Escherichia coli* bloodstream infections (BSI) and associated antibiotic resistance pattern in hematological malignancy populations via a global systematic review.

Methods: Articles were searched by different databases such as Scopus, PubMed, and Web of Science (ISI) to search studies that reported *E. coli* bloodstream infections and associated antibiotic resistance patterns in hematological malignancies populations by two researchers independently. Then, the articles were selected based on the inclusion and exclusion criteria, and finally, using scientific methods, the quality assessment of the studies was done, and finally, the data was analyzed by comprehensive meta-analysis (CMA) software.

Results: Lastly, 36 studies were included in the current systematic review. Median age of patients was between 1-75 years. Most of the patients who underwent HSCT were men. The prevalence of bacterial BSI in various studies varied between 8.8- 51.2%. The prevalence of *E.coli* was between 9-54%. *E.coli* MDR isolates were reported between 0-25 percent. Also, the prevalence of *ESBL E.coli* strains in BSI of HSCT recipients was between 13-80%. The BSI related death by *E.coli* was varied between 6-27%.

The highest antibiotic resistance was reported to ciprofloxacin, cefepime, Third- and Fourth-generation cephalosporins, and amikacin with prevalence of 100%, while the lowest antibiotic resistance was reported against Tigecycline with a prevalence of 0-8%.

Conclusion: Our review showed the high prevalence of *E.coli*, particularly MDR/ESBL strains, and antibiotic resistance, consequently BSI-related mortality in HSCT recipients. Therefore, more serious infection control measures/regular continuous screening should be taken in the wards/centers where these patients who underwent HSCT to prevent the spread of such isolates, and also, empirical therapy with effective antibiotics such as tigacycline and imipenem should be done immediately.

Keywords: *Escherichia coli*, Bloodstream Infections, Antibiotic Resistance, Hematological Malignancy

Cite This Article: *Jafarabadi M, Khaledi A. Escherichia Coli Bloodstream Infections and Associated Antibiotic Resistance Pattern in Hematological Malignancy Populations, A Global Systematic Review. EJMO 2024;8(1):15–23.*

Considering the importance of blood malignancies (HM), the most important treatments include hematopoietic stem cell transplantation (HSCT), chemotherapy, and radiotherapy.[1] Among complications and dilemmas following chemotherapy and harsh treatment regimens, we can mention damage to the mucous membrane, neutropenia, depressed immunity, and so on, which ultimately all contribute to the development of bloodstream infections (BSI).[2, 3] However, despite the recent advances in the treatment of HM, especially in stem cell transplantation, still BSI is a major concern.[4].

Address for correspondence: Azad Khaledi, MD. Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran
Phone: +98 912 7804713 **E-mail:** azadkh99@gmail.com

Submitted Date: December 23, 2023 **Revision Date:** February 08, 2024 **Accepted Date:** February 18, 2024 **Available Online Date:** March 06, 2024

Depending on the available studies and documentation, blood infection affects between 20 and 60% of patients in the pre-and post-transplant phase, and the death rate is reported to be more than 6%.[5, 6] Bloodstream infection (BSI) caused by bacteria is the main cause of death, as it accounts for half of nosocomial infections.[7] Bloodstream infection is responsible for patients' longer hospital stays, imposing more costs on the patient and healthcare systems, and subsequently disrupting people's quality of life.[8] Some studies have considered BSI as one of the independent predictors of mortality after HSCT.[9]

The prevalence of multidrug-resistant (MDR) strains is increasing today and has become a major concern, as this is especially prominent in patients undergoing HSCT who are treated with broad-spectrum antibiotics and antibiotic prophylaxis, and it seriously affects the patient's survival.[10]

Both groups of Gram-positive and negative bacteria as well as fungi have been identified as contributory agents in BSI, where some studies have reported Gram-positive as the predominant agents, while others have reported Gram-negatives.[11, 12] Among Gram-negative bacteria, *Escherichia coli* (*E.coli*) has a major role in BSI due to the presence of MDR and Extended-spectrum β-lactamase (*ESBL*) strains.[13]

Assessing the prevalence of common pathogens causing BSI and their antibiotic resistance patterns in stem cell transplant patients can be a guide in the course of prevention, control and clinical treatment of BSI.[14] Therefore, considering that there is no comprehensive study related to *E. coli*, antibiotic resistance pattern, and its mortality rate in patients undergoing HSCT, we decided to do this globally.

Methods

Search Strategy

From January 2000 to the end of 2023, according to PRISM guidelines, various databases such as Scopus, Medline, and Web of Science, as well as the Cochrane Library, were searched for the prevalence of *Escherichia coli* bloodstream infections and associated antibiotic resistance pattern in hematological malignancies populations.

Two researchers independently searched the databases with keywords such as; *Escherichia coli*, Bloodstream infection, Antibiotic resistance, and put the found studies into a database and compared them. If two people disagreed about a study, they would try to conclude the discussion and exchange opinions, and if this did not happen, they would get help from the third author.

Inclusion and Exclusion Criteria

In this review, the studies that reported the prevalence and antibiotic resistance in the blood infection of stem cell transplant recipients were included. Systematic reviews, meta-analyses, narrative reviews, seminars, mornings, meetings and letters to editor, editorials, and abstracts were also not enrolled.

Quality Assessment

As presented in Supplementary 1, Critical Appraisal Skills Programme (CASP) checklist (www.casp-uk.net) was used to assess the quality of the studies.[15]

Data Extraction

Data such as first author, study type, Location, Year of Study, Publication (year), Patients, BSI, allo/auto HSCT, Median age, Sex (male/female), All bacteria, GNB, GPB, *E.coli*, *E.coli* MDR, *E. coli ESBL*, Total BSI, poly-microbial BSI, BSI by *E.coli*, BSI-related death, BSI related death by *E.coli*, and antibiotic resistance pattern were extracted by two authors independently and entered into the extraction form.

Results

Screening and Selection of Studies

Figure 1 contains PRISMA flow diagram that shows the correct selection of articles included in this review based on PRISMA protocols. Searching in different databases led to the identification of 2017 studies, of which 765 were excluded from the review due to various reasons before screening. In the next step, the screening

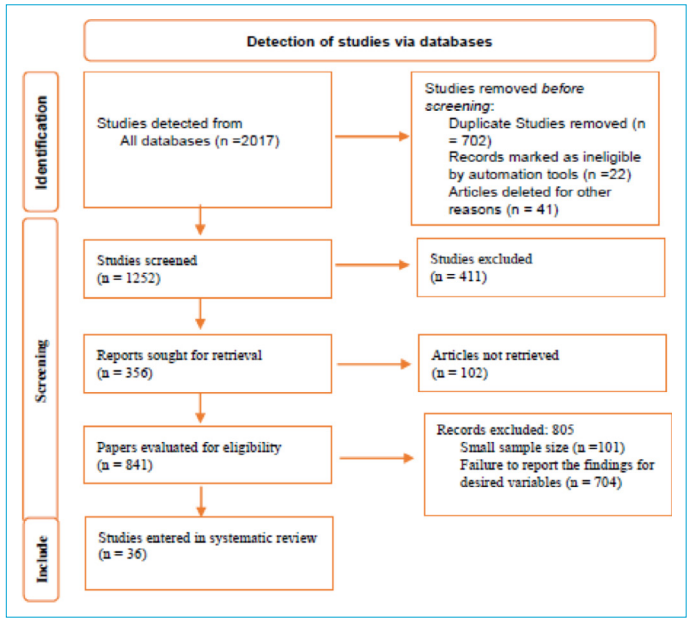

Figure 1. PRISMA flow diagram for studies selection.

process was carried out for 1252 articles, of which 411 were removed. Among 356 were evaluated studies, 102 were excluded. Next, 841 Papers were evaluated for eligibility, of these 805 were excluded due to some reasons. Lastly, 36 Studies were included in the current systematic review.

Features of Studies

The location of 36 studies included in this review was as follows: Brazil (n=1), China (n=3), Lebanon (n=2), Bulgaria (n=1), Belarus (n=1), Australia (n=1), Turkey (n=2), Italy (n=4), USA (n=4), Egypt (n=1), South Korea(n=3), Spain (n=3), Japan (n=2), Pakistan (n=1), Denmark (n=1), Thailand (n=1), Swiss (n=1), Colombia(n=1), Germany(n=1), and multi countries (n=2). Both allo/auto-transplantation were performed for patients. Study type enrolled in this review was as follows: Retrospective (24), cohort (4), Retrospective cohort (5), prospective longitudinal observational-cohort (1), and prospective observational (1). Median age of patients was between 1-75 years. Most of the patients who underwent HSCT were men (Table 1).

Prevalence of Bacterial Bloodstream Infection (BSI)

Prevalence of bacterial BSI in various studies varied as some studies reported a high prevalence and some others reported a low BSI rate. This rate varied between 8.8-51.2% (Table 1).

Prevalence of Gram Negative/Positive Microorganisms in BSI

The prevalence of Gram negatives varied between 17.16-88%, while this rate among Gram positive bacteria was between 7-83% (Table 2).

Prevalence of *E.coli*, *E.coli* MDR, and *ESBL E.coli* strains in BSI of HSCT Recipients

Prevalence of *E.coli* was between 9-54%. *E.coli* MDR isolates were reported between 0-25 percent. Also, the prevalence of *ESBL E.coli* strains in BSI of HSCT recipients was between 13-80% (Table 2).

Prevalence of Polymicrobial BSI, BSI-Related Death and BSI Related Death by *E.coli*

Prevalence of Polymicrobial BSI varied between 7-41% in different studies. Total BSI-related deaths in various studies were reported between 3-59%. BSI related death by *E.coli* was varied between 6-27% (Table 2).

Antibiotic Resistance Pattern in *E.coli* Isolated from BSI

The highest antibiotic resistance was reported to ciprofloxacin, cefepime, Third- and fourth-generation cephalosporins, and amikacin with the prevalence of 100%, while the lowest antibiotic resistance was reported against Tigecycline with the prevalence of 0-8%. Resistance rate against carbapenems in some studies was reported at 0% but others reported it at about 80% (Table 3).

Discussion

In this present review, the prevalence rate of BSI in HSCT recipients varied between 8.8- 51.2%, which is in agreement with other studies reported the same.[16, 17] Mortality due to BSI is generally higher in high risk patients compared to uncontrolled patients undergoing HSCT, due to reasons such as exposure to more antibiotics and consequently the emergence of resistant strains, prolonged chemotherapy, and subsequently more severe immunosuppression, the presence of serious infections pre-transplantation, and prolonged neutropenia pre-transplantation.[13, 18]

The prevalence of Gram negative bacteria varied between 17.16-88%, while this rate among Gram positive bacteria was between 7-83%, this showed no significant difference between the prevalence of Gram-positive (GP) and, Gram-negative (GN) bacteria in BSI. Among GNB, Enterobacteriaceae predominate, particularly *E. coli* occur at a frequency of 6-54%.[19-21] This wide variation depends on the geographical difference of the place where the studies were conducted because these reports were from different countries.[16] *E.coli* MDR isolates were reported between 0-25 percent. Also, the prevalence of *ESBL E.coli* strains in BSI of HSCT recipients was between 13-80%. BSI resulting from MDR strains is of main concern owing to limits in antimicrobial choice, ineffective treatment, and subsequently, persistence and development of infections.[22] The interesting thing is that in various European studies that have been included in this review, despite the high level of hygiene and infection control measures, the prevalence of *ESBL E.coli* strains was high, which indicates the circulation of these strains among medical/health centers in European countries.[14, 23] Bloodstream infection (BSI) with such *ESBL* strains causes the spread of drug resistance and subsequently the high BSI-related death in patients who undergo HSCT.[14, 23]

The highest antibiotic resistance was reported to ciprofloxacin, cefepime, third- and Fourth-generation cephalosporins, and amikacin with prevalence of 100%, while the lowest antibiotic resistance was reported against Tigecycline with the prevalence of 0-8%. Resistance rate against

Table1. Characteristics of studies included in the present systematic review

First author	Study	Location	Year of Study	Publication (year)	Patients (n)	BSI	Hematopoietic Stem Cell Transplantation		Median Age, Years	Sex, n/%	
							Allo n/%	Auto n/%		Female	Male
A.M. Ferreira	Retrospective	Brazil	2014 - 2015	2018	232	62/232 (26.7)	60 (26&)	172 (74)	49	93 (40)	139 (60)
Qiang Zeng	Retrospective	China	2013 -2019	2022	741	65/741 (8.8)	52/65	12/65	38 (14-58)	31 (47.7%)	34 (52.3%)
Rima Moghnieh	Retrospective	Lebanon	2005 - 2015	2018	190	24/190 (12.6)	-	-	46.70±14.95	9 (37.5)	15 (62.5)
Denis Niyazi	Retrospective	Bulgaria	2019 – 2021	2023	75	6/35 (17.1)	-	-	-	-	-
Igor Stoma	prospective observational	Belarus	2013 - 2015	2016	360	135/360 (27.5)	51/135 (37.8)	84/135 (62.2)	44 (32–53)	-	64 (47.4)
L.Wang	Retrospective	China	2008 - 2014	2015	273	85/273 (31.1)	63 (74.1)	22 (25.9)	31 (15-60)	39 (46)	46 (54)
N. Macesic	Retrospective	Australia	2001 - 2010	2014	508	380/586 (51.2)	244 (46)	281 (53)	50 (17-71)	194 (40)	314 (60)
M.Yemişen	Retrospective	Turkey	2000 - 2011	2016	312	142/312 (45.5)	194 (62)	186	39 (12-73)	137 (44)	175 (56)
Malgorzata Mikulska	Cohort	Italy	2010 - 2016	2018	553	64/213 (30)	553	-	48 (31-57)	232 (42)	321 (58)
M. Mikulska	Retrospective	Italy	2004-2008	2011	382	149/382 (39)	-	382	41 (16–65)	54/149 (36)	95/149 (64)
M. Weisser	Prospective-Cohort	Germany, Switzerland, Austria	2002 - 2014	2017	19 472	2388 (15.8)	8644 (56.9)	6537 (43.1)	55 (44-63)	5977 (39.4)	9204 (60.6)
Hadir El-Mahallawy	retrospective	Egypt	2009	2014	50	39/90 (43)			3 - 62 (29±15)	22 (44)	28 (56)
Allison M. Bock	cohort	USA	2005- 2010	2013	834	349/834 (42)	555/834	279/834	48 (18-74)	153/349 (44)	196/349 (56)
Junshik Hong	retrospective cohort	Korea	2002 - 2012	2013	134	36/134 (26.9)	59/134	75/134	45 (18-68)	57/134()	77/134 (57.5)
Prakash Satwani	retrospective cohort	USA	2004 - 2014	2017	395	395	-	-	9.4±7	143/395 (36)	252/395 (64)
Sara Haddad	retrospective	Lebanon	2007 - 2017	2021	165	226	22 (13.3)	40 (24.2)	46.65±17.21	62 (37.6)	103 (62.4)
Pedro Puerta-Alcalde	Retrospective	Spain	2008 - 2017	2021	293	402	503	510	-	-	-
Sho Ogura	Retrospective	Japan		2020	410	169/410 (41.22)	410	-	55 (20–75)	73	96
Pedro Puerta-Alcalde	Retrospective	Spain	1993–2017	2021	1164	1164	834/1164 (71.6)	340/1164 (29.2)	44 (32–54)	477 (41)	687 (59)
N. Ali	Retrospective	Pakistan	2004 - 2012	2014	108	22	108	-	18±12.6	32	76
Elio Castagnola	Retrospective	Multi-country	2015 - 2017	2021	1031	1291	83.1%		3–13	275	756 (58.6)
Weijie Cao	Retrospective	China	2013 - 2017	2021	397	52/397 (13.1)	397	-	21 (1–62)	155/397	242/397
Michele Malagola	Retrospective	Italy	2010 - 2015	2017	162	80/162 (49)	162	-	48 (17-68)	59 (36)	103 (64)
Gjærde	Prospective- cohort.	Denmark	2008 - 2014	2017	460	114/460 (24.7)	460	-	49.9 (38.6-65.3)	177/460 (38.5)	283/460 (61.5)
Jae-Cheol Kwon	Retrospective	South Korea	2009 - 2010	2013	159	159/851 (18.7)	-	-	44.6 (13.5)	382/851 (44.9)	469 /851 (55.1)
Davide Mattei	Retrospective	Italy	2010 - 2019	2022	111	149			0.3-18 (8.5)	46/111 (41.44)	65/111 (58.56)
Hyeah Choi	Retrospective	South Korea	2020	2022	334	380	66 (17.4)	23 (6.0)	53 (18 – 78)	196/380 (51.6)	184/380 (48.4)
Esma Eryilmaz-Eren	Retrospective	Turkey	2015 - 2019	2022	553	68/553 (12.3)	223/553 (40.3)	330/553 (59.7)	48.4 (17 - 82)	211/553 (38.2)	342/553 (61.8)

Table1. Cont.

First author	Study	Location	Year of Study	Publication (year)	Patients (n)	BSI	Hematopoietic Stem Cell Transplantation		Median Age, Years	Sex, n/%	
							Allo n/%	Auto n/%		Female	Male
Andrea J. Zimmer	Cross- sectional observational	USA	2016 - 2019	2022	343	-	46/343 (13)	65/343 (19)	57 (20–89)	145/343 (42)	198/343 (58)
José Luis Piñana	Cohort	Spain	1998 - 2003	2014	720	145/720 (20.1)	-	-	50 (18-74)	342 (48)	378 (52)
Worawut (55.3) Choeyprasert	Retrospective	Thailand	2002 - 2014	2017	215	33/215 (15.34)	-	25/215 (11.6)	0.1-21.6 (8.32)	96/215 (44.7)	119/215
Maja Weisser	prospective longitudinal observational- Cohort	Swiss	2009 - 2018	2022	1364	451/1364 (33)	1688	-	53 (42 - 61)	-	-
Shinsuke Takagi	cohort	Japan	2003 -2014	2021	782	333/782 (42.6)	782		54 (17 - 82)	299/782 (38.2)	483/782 (61.8)
Michael J. Satlin	Retrospective	USA	2007 - 2011	2014	-	306	238	287	56 (45 - 63)		
Paola Perez	Retrospective cohort	Colombia	2012 - 2017	2019	111	46/111 (41.4)			9.75 (2.7 - 14.8)	23/46 (50)	23/46 (50)
Sebastian Scheich	Retrospective	Germany	2012 - 2015	2017	184	20/184 (10.9)			55 (19 - 75)	77/184 (41.8)	107/184 (58.2)

Mortality related to bacterial BSI was defined as death within seven days of diagnosis with no other ascertainable cause. Allison M. Bock: 66/349 (19) auto graft with BSI.

carbapenems in some studies reported low (0%), but others reported about 80%. The resistance rate against piperacillin/tazobactam was reported between 0-83 percent.[24, 25] The great prevalence of *ESBL*-producing *E. coli* in our review sheds light on the need to do empirical therapy with carbapenems,[26] or tigecycline[10, 14] rather than cefepime or piperacillin/tazobactam, as recommended in the protocols. Notably, researchers showed that combination therapy with antibacterial agents such as cyclin and polymyxin can decrease the mortality rate.[14, 27]

Total BSI-related death in various studies reported between 3-59%, also, BSI-related death by *E.coli* varied between 6-27%. The high prevalence of *E. coli* as well as the death rate of 6-27% indicated the high quota of this microorganism among the bacteria causing BSI in patients who underwent HSCT. Based on the opinion of some studies, inadequate empirical antibacterial therapy is related to augmented mortality. This discrepancy recommends that we should focus on the prevention and treatment guidelines of BSI in HSCT recipients and the formulation of treatment and prevention strategies should be based on the distribution pattern of pathogens and antibiotic resistance in order to reduce drug resistance and lead to survival of more patients with BSI who have undergone HSCT.[14, 28, 29]

Most studies included in the present review presented a high resistance against ciprofloxacine (resistance rate 80 100%),[14, 24, 25] except a study conducted by M.Yemişen and et.al that reported 30%.[19] Also, Weijie Cao et al showed antibiotic resistance of about 55% against Levofloxacin.[14] This high level of resistance against fluoroquinolones suggests that the prophylaxis of fluoroquinolones in people with febrile neutropenia should be reconsidered because their widespread use has led to high-level resistance.[30, 31] Similar to these reports, a cohort study conducted in Lebanon believes that prophylaxis prevents bacteremia for 7 days and more than this time leads to disruption of the ecological niches of normal intestinal flora and the emergence of fluoroquinolone-resistant strains.[25]

In general, despite more care and drug prophylaxis, BSI in HSCT recipients is still a major problem and gram negative microorganisms such as *E.coli* have a great role. Our review showed the high prevalence of *E.coli*, particularly MDR and *ESBL* strains and antibiotic resistance, and consequently BSI-related mortality in HSCT recipients. Therefore, more serious infection control measures/regular continuous screening should be taken in the wards/centers where these patients who underwent HSCT to prevent the spread of such isolates, and also, empirical therapy with effective antibiotics such as tigacycline and imipenem should be done immediately.

Table 2. Characteristics of studies included in the present systematic review

First author	Location	All bacteria (n)	GNB n/%	GPB n/%	*E.coli* n/%	*E.coli* MDR, n/%	*E. coli* ESBL	Total BSI, n (%)	Poly-microbial BSI, n/%	BSI by *E.coli*, n/%	BSI-related death, n/%	BSI related death by *E.coli*, n/%
A.M. Ferreira	Brazil	67	37 (52.2)	30 (44.78)	8/67(11.9)	0		62	5	8/67(11.9)	13 (21)	-
Qiang Zeng	China	61	47/61(77)	14/61(23)	25/61(41)	0		65/741(8.8)	8/61(13.1)	4/25()	27/57(47.4)	-
Moghniyee	Lebanon	-	19/24(79.2)	8/24(33.33)	7/24(29.1)	0		24/190(12.6)	0	7/24	3 (12.5)	
Denis Niyazi	Bulgaria	6	-	-	3/6(50)	-		6	-	3/6		
Igor Stoma	Belarus	135	88/135(65.2)	47/135(34.8)	25/135(18.5)	-		135/360(37.5)	-	25/135(18.5)	N(31.1)	
L.Wang	China	105	50 (58.8)	22 (25.9)	36/105(34.3)	9/36 (25)		85/273(31.1)	12(14.1)	36/85	11/85(12.94)	3/11(27.3)
N. Macesic	Australia	380	137/380(36)	225/380(64)	43/380(11)	-		380/586(51.2)	-	43/380(11)	25/212(12)	2/27 (7)
M.Yemişen	Turkey	186	74/186 (39.8)	112/186 (60.2)	13/186(7)	3/13(23)	3/13(23)	142/312 (45.5)	14	13/142()	40/142 (28.1)	-
Malgorzata Mikulska	Italy	213	91/213 (43)	116/213 (54)	66/213 (31)	-	24/66(36)	64/213(30)	8/166 (4%)	66/213 (31)	9/178(5)	3/50(6)
M. Mikulska	Italy	149	49/149 (32.9)	80/149 (53.7)	25/149(16.8)			149/382(39)	15/149 (10.1)	25/149(16.8)	40/149 (26.8)	10/149(6.7)
M. Weisser	Germany, Switzerland, Austria	2296	767 (32.1)	1529 (63.9)	476/2296(20.7)	-	-	2388	-	476/2388(19.9)	477 (3.1)	-
Hadir El-Mahallawy	Egypt	39	26/50(52)	13/50(26)	-			39/90(43)		1/39(2.5)		
Allison M. Bock	USA	834	88%	7%	18			349/834 (42)	8%	18(	9/80(11)	-
Junshik Hong	Korea	44	29/44(66)	15/44(34)	8			36/134		8/44	4/36	
Prakash Satwani	USA	848	352/848(41.5)	496/848(58.5)	50/848(5.9)			395		50/848(5.9)	21.6%	-
Sara Haddad	Lebanon		147/226 (65.0)	75/226 (33.2)	103/226 (45.6)		82/103(80)	226		103/226 (45.6)	37/226(16.4)	
Pedro Puerta-Alcalde	Spain	397	169/397 (42)	228/397 (56.7)	54/397 (13.4)		17/54 (31.5)	402	33/402 (8.2)	54/397(13.4)	77/293 (19.2)	
Sho Ogura	Japan	169	29/169 (17.16)	140/169(82.84)	21/169		10/21(47.61)	169/410(41.22)	26/169	21/169(12.4)	12/169(7)	-
Pedro Puerta-Alcalde	Spain		438/1164 (37.6)	719/1164 (61.8)	140/1164 (12)		21/140 (15)	1164	126/1164 (10.8)	140/1164 (12)	148/1164 (12.7)	
N. Ali	Pakistan	25	17/25(68)	8/25(32)	10/25(41)	-	-	22/108		10/25(41)	10/108(9.2)	8/108(7.4)
Elio Castagnola	Multi-country	1289	831/1289 (64.4)	458/1289 (35.53)	-		20.5%	1291	81/1210 (6.3)	264/1289(20.5)	67/1291(5.2)	
Weijie Cao	China	53	43/53(81.1)	10/53	15/53(28.3)	-	7/15 (46.7)	52/397(13.1)		15/52(28.8)	33/52(36.5)	
Michele Malagola	Italy	119	42/119(35)	77/119(65)	24/119(20.1)		18/24(76)	80/162(49)		24/80(30)	47/80(59)	8/80(10)
Gjærde	Denmark	153	38/153 (24.8)	115/153 (75.2)	7/153(7.8)			114/460(24.7)	16/114(14)	7/147(4.8)		
Jae-Cheol Kwon	South Korea	241	119/241(49.37)	122/241(50.63)	72/241(29.87)		23/72(32)	159/851(18.7)	20/220(9.1)	72/220(32.7)	29/222 (13.1)	
Davide Mattei	Italy	-	59/149(39.6)	77/149(60.4)	30/149(20.1)				12/154(7.8)	30/149(20.1)	6/154(3.8)	

Table 2. Characteristics of studies included in the present systematic review

First author	Location	All bacteria (n)	GNB n/%	GPB n/%	*E.coli* n/%	*E.coli* MDR, n/%	*E. coli* ESBL	Total BSI, n (%)	Poly-microbial BSI, n/%	BSI by *E.coli*, n/%	BSI-related death, n/%	BSI related death by *E.coli*, n/%
Hyeah Choi	South Korea	438	242/438(55.2)	196/438(44.8)	107/43824.4		40/107(37.4)	380	53/380 (13.9)	107/380(28.1)	-	-
Esma Eryilmaz-Eren	Turkey	73	57/73 (80.2)	16/73(19.8)	39/73 (53.4)	-	-	68/553 (12.3)	-	39/68(57.3)	-	-
Andrea J. Zimmer	USA	389	183/389 (47)	189/389 (49)	86/389 (22)			343	41/343(12)	86/343(25)	33/343(9.6)	
José Luis Piñana	Spain	-	62/145(43)	94/145(65)	30/145(20.7)	-	-	145/720(20.1))	11/145(8)	30/145(20.7)	13/145(9)	-
Worawut Choeyprasert	Thailand	39	18/39(46.1)	12/39(30.8)	9/39 (23.1)		2/9(18)	33/215 (15.34)	4/39(10.25)	9/33(27.3)	2/33(6)	
Maja Weisser	Swiss	781	270/781 218 (34.6)	454/781 (58.1)	142/781 (18.2)	-	-	451/1364 (33)	199/781 (25.5)	142/451(31.4)	263/451 (58.3)	-
Shinsuke Takagi	Japan	380	100/380(26.3)	280/380(73.7)	30/380(7.9)		13/30(43.3)	333/782(42.6)	44/333 (13.2)	30/333(9)	143/333(43.1)	
Michael J. Satlin	USA	343	155/343(45)	188/343(55)	39/343(11.4)	-	-	306	-	39/306(12.7)	(16)	-
Paola Perez	Colombia	62	37/62(59.7)	25/62(40.3)	6/62(9.7)	-	-	-	46/11(41.4)	6/46(13)	14/46(30.4)	
Sebastian Scheich	Germany	-	-	3/20(15)	-			20/184(10.9)		3/20(15)	n=12/20 60)	

M. Weisser: Allo-HSCT patients had a higher BSI incidence than auto-HSCT patients (1471/8644 (17.1%) and 917/6537 (14.0%), respectively; relative risk (RR) 1.2, 95% confidence interval (CI) 1.1e1.3).

Table 3. Antibiotic resistance pattern of E.coli in studies included in the present systematic review

First author	Total *E.coli*	Antibiotics n/%																				
		CIP	TZP	FEP	Aminoglycosides, n/%	Colistin, n/%	Third- and Fourth-Generation Cephalosporins	Semisynthetic Penicillins/ Lactamase Inhibitors	Carbapenems	Fluoroquinolones	AM/SM	Amikacin	SXT	Tigecycline	Cefazolin	Cefotetan	CZ	CRO	IMP	Amikacin	Gentamicin	Levofloxacin
A.M. Ferreira	8	8/8	0	5	0	0	-	-	-	-												
Davide Mattei	30	-	-	-	8/30 (26.7)	-	9/30 (30)	6/30 (20.7)	0	16/30 (53.3)												
Michele Malagola	24								0	22 (92)												
Rima Moghnieh	6	6/6 (100)	5/6 (83.3)	6/6 (100)			6/6 (100)		5/6 (83.3)			6/6 (100)	4/6 (66.7)									
Qiang Zeng	25								4/25(16)					2/25(8)								
L.Wang	36								27/36(75)													
Weijie Cao	15	12/15 (80)	5/15 (33.33)	7/15 (46.7)									13/15 (86.7)	0	14/15 (93.3)	5/15 (33.33)	8/15 (87.1)	12/15 (80)	1/15 (6.7)	2/15 (13.3)	10/15 (66.7)	11/15 (6.7)
M.Yemişen		4/13 (30.8)	3/13 (23)	2/13 (15.4)													3/13 (23)	3/13 (23)	-	5/13 (38.5)		

AK: Amikacin; CIP: ciprofloxacin; CAZ: ceftazidime; CTX/CRO: cefotaxime/ceftriaxone; TZP: piperacillin/tazobactam; FEP: cefepime; ESBL: extended-spectrum beta-lactamase; IPM/MEM: imipenem/ meropenem; MDR: multidrug-resistant; XDR: extensively drug resistant; PDR: pandrug resistant, ampicillin-sulbactam/AM/SM, SXT: sulfamethoxazole/trimethoprim.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.J.; Design – M.J.; Supervision – A.K.; Materials – A.K.; Data collection – A.K.; Analysis – A.K.; Literature search – M.J.; Writing – M.J.; Critical review – A.K.

References

1. Chen S, Lin K, Li Q, Luo X, Xiao M, Chen M, et al. A practical update on the epidemiology and risk factors for the emergence and mortality of bloodstream infections from real-world data of 3014 hematological malignancy patients receiving chemotherapy. J Cancer 2021;12:5494.
2. Marín M, Gudiol C, Ardanuy C, Garcia-Vidal C, Jimenez L, Domingo-Domenech E, et al. Factors influencing mortality in neutropenic patients with haematologic malignancies or solid tumours with bloodstream infection. Clin Microbiol Infect 2015;21:583–90.
3. Yan CH, Wang Y, Mo XD, Sun YQ, Wang FR, Fu HX, et al. Incidence, risk factors, microbiology and outcomes of pre-engraftment bloodstream infection after haploidentical hematopoietic stem cell transplantation and comparison with HLA-identical sibling transplantation. Clin Infect Dis 2018;67(suppl 2):S162–73.
4. Xu L, Chen H, Chen J, Han M, Huang H, Lai Y, et al. The consensus on indications, conditioning regimen, and donor selection of allogeneic hematopoietic cell transplantation for hematological diseases in China - recommendations from the Chinese Society of Hematology. J Hematol Oncol 2018;11:1–17.
5. Sava M, Bättig V, Gerull S, Passweg JR, Khanna N, Garzoni C, et al. Bloodstream infections in allogeneic haematopoietic cell recipients from the Swiss Transplant Cohort Study: Trends of causative pathogens and resistance rates. Bone Marrow Transplant 2023;58:115–8.
6. Mattei D, Baretta V, Mazzariol A, Maccacaro L, Balter R, Zaccaron A, et al. Characteristics and outcomes of bloodstream infections in a tertiary-care pediatric hematology–oncology unit: A 10-year study. J Clin Med 2022;11:880.
7. Delebarre M, Tiphaine A, Martinot A, Dubos F. Risk-stratification management of febrile neutropenia in pediatric hematology-oncology patients: Results of a French nationwide survey. Pediatr Blood Cancer 2016;63:2167–72.
8. Felix A, Leblanc T, Petit A, Nelkem B, Bertrand Y, Gandemer V, et al. Acute myeloid leukemia with central nervous system involvement in children: Experience from the French protocol analysis ELAM02. J Pediatr Hematol Oncol 2018;40:43–7.
9. Hafez HA, Yousif D, Abbassi M, Elborai Y, Elhaddad A. Prophylactic levofloxacin in pediatric neutropenic patients during autologous hematopoietic stem cell transplantation. Clin Transplant 2015;29:1112–8.
10. Zeng Q, Xiang B, Liu Z. Profile and antibiotic pattern of bloodstream infections of patients receiving hematopoietic stem cell transplants in Southwest China. Infect Drug Resist 2022;15:2045–54.
11. Gudiol C, Bodro M, Simonetti A, Tubau F, González-Barca E, Cisnal M, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. Clin Microbiol Infect 2013;19:474–9.
12. Ruhnke M, Arnold R, Gastmeier P. Infection control issues in patients with haematological malignancies in the era of multidrug-resistant bacteria. Lancet Oncol 2014;15:e606–19.
13. Wang L, Wang Y, Fan X, Tang W, Hu J. Prevalence of resistant gram-negative bacilli in bloodstream infection in febrile neutropenia patients undergoing hematopoietic stem cell transplantation: A single center retrospective cohort study. Med 2015;94(45):e1931.
14. Cao W, Guan L, Li X, Zhang R, Li L, Zhang S, et al. Clinical analysis of bloodstream infections during agranulocytosis after allogeneic hematopoietic stem cell transplantation. Infect Drug Resist 2021;14:185–92.
15. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag 2014;3:123.
16. Misch EA, Andes DR. Bacterial infections in the stem cell transplant recipient and hematologic malignancy patient. Infect Dis Clin 2019;33:399–445.
17. Balletto E, Mikulska M. Bacterial infections in hematopoietic stem cell transplant recipients. Mediterr J Hematol Infect Dis 2015;7:e2015045.
18. Mikulska M, Del Bono V, Bruzzi P, Raiola A, Gualandi F, Van Lint M, et al. Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients. Infection 2012;40:271–8.
19. Yemişen M, Balkan İİ, Salihoğlu A, Eşkazan AE, Mete B, Ar MC, et al. The changing epidemiology of bloodstream infections and resistance in hematopoietic stem cell transplantation recipients. Turk J Hematol 2016;33:216.
20. Satwani P, Freedman JL, Chaudhury S, Jin Z, Levinson A, Foca MD, et al. A multicenter study of bacterial bloodstream 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.
21. Eryilmaz-Eren E, Izci F, Ture Z, Sagiroglu P, Kaynar L, Ulu-Kilic A. Bacteremia in hematopoietic stem cell recipients receiving fluoroquinolone prophylaxis: Incidence, resistance, and risk factors. Infect Chemother 2022;54:446.
22. Poutsiaka D, Price L, Ucuzian A, Chan G, Miller K, Snydman D. Bloodstream infection after hematopoietic stem cell transplantation is associated with increased mortality. Bone Marrow Transplant 2007;40:63–70.
23. Mikulska M, Raiola AM, Galaverna F, Balletto E, Borghesi ML, Varaldo R, et al. Pre-engraftment bloodstream infections af-

ter allogeneic hematopoietic cell transplantation: Impact of T cell-replete transplantation from a haploidentical donor. Biol Blood Marrow Transplant 2018;24:109–18.
24. Ferreira A, Moreira F, Guimaraes T, Spadão F, Ramos J, Batista M, et al. Epidemiology, risk factors and outcomes of multidrug-resistant bloodstream infections in haematopoietic stem cell transplant recipients: Importance of previous gut colonization. J Hosp Infect 2018;100:83–91.
25. Moghnieh R, Abdallah D, Awad L, Jisr T, Mugharbil A, Youssef A, et al. Bacteraemia post-autologous haematopoietic stem cell transplantation in the absence of antibacterial prophylaxis: A decade's experience from Lebanon. Infection 2018;46:823–35.
26. Haddad S, Jabbour JF, Hindy JR, Makki M, Sabbagh A, Nayfeh M, et al. Bacterial bloodstream infections and patterns of resistance in patients with haematological malignancies at a tertiary centre in Lebanon over 10 years. J Glob Antimicrob Resist 2021;27:228–35.
27. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase - producing K. pneumoniae: Importance of combination therapy. Clin Infect Dis 2012;55:943–50.
28. Stoma I, Karpov I, Milanovich N, Uss A, Iskrov I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. Blood Res 2016;51:102.
29. Stoma I, Littmann ER, Peled JU, Giralt S, van den Brink MR, Pamer EG, et al. Compositional flux within the intestinal microbiota and risk for bloodstream infection with gram-negative bacteria. Clin Infect Dis 2021;73:e4627–35.
30. Alexander S, Fisher BT, Gaur AH, Dvorak CC, Luna DV, Dang H, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: A randomized clinical trial. JAMA 2018;320:995–1004.
31. Widjajanto PH, Sumadiono S, Cloos J, Purwanto I, Sutaryo S, Veerman AJ. Randomized double-blind trial of ciprofloxacin prophylaxis during induction treatment in childhood acute lymphoblastic leukemia in the WK-ALL protocol in Indonesia. J Blood Med 2013;4:1–9.