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Clinical and microbiological analysis of risk factors for breakthrough bloodstream infection during Tigecycline Therapy

Sol Jin[1], So Yun Lim[2], Yun Woo Lee[2], Heungsup Sung[3], Mi-Na Kim[3], Seongman Bae[2], Jiwon Jung[2], Min Jae Kim[2], Sung-Han Kim[2], Sang-Oh Lee[2], Sang-Ho Choi[2], Yang Soo Kim[2], Eun Hee Song[4,5]✉ & Yong Pil Chong[2,5]✉

Background Tigecycline is widely used to treat a variety of bacterial infections despite concerns regarding increased mortality in severe infections. Previous case reports have documented breakthrough bloodstream infections (BSI) during tigecycline therapy. This study aimed to investigate the incidence of, and risk factors for, breakthrough BSI during tigecycline monotherapy.
Methods A retrospective matched case–control study was conducted in a 2700-bed tertiary referral center, involving patients who received tigecycline monotherapy. Patients with breakthrough BSI (1:1) were matched with controls without breakthrough BSI based on age, sex, and date of tigecycline therapy.
Results Of 4505 patients treated with tigecycline, 115 (2.6%, 95% confidence interval 2.1 to 3.1%) developed breakthrough BSI. The most frequently identified pathogen in breakthrough BSI was *Klebsiella pneumoniae* (22.8%), followed by *Candida* species (17.1%), *Pseudomonas aeruginosa* (16.3%), and *Acinetobacter baumannii* (14.6%). Of the *K. pneumoniae* and *A. baumannii* isolates for which tigecycline susceptibility results were available, 50% and 23%, respectively, were tigecycline-resistant (MIC > 2 mg/L). Intraabdominal (33.9%), catheter-related (30.4%), and hepatobiliary (19.1%) infections were the main sources of breakthrough BSI. In multivariable analysis, independent risk factors for breakthrough BSI during tigecycline therapy were liver cirrhosis (adjusted odds ratio [aOR], 3.09), indwelling catheter (aOR, 3.42), previous *Candida* colonization (aOR, 14.95), and previous multi-drug resistant bacteria colonization (aOR, 10.30).
Conclusion In cases where there is a high suspicion of breakthrough BSI during tigecycline therapy, meticulous management and prudent selection of empirical antibiotics are crucial due to the diverse range of causative microorganisms involved.

Keywords Tigecycline, Breakthrough bacteremia, Risk factors, Breakthrough infection

Tigecycline is the first glycylcycline antibiotic, with broad-spectrum activity against most gram-positive and gram-negative bacteria, including pathogens causing nosocomial infections such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and extended-spectrum β-lactamase producing bacteria[1]. It is a semisynthetic derivative of minocycline with a modified chemical structure that allows it to avoid the two major types of tetracycline resistance: efflux pumps and ribosomal protection[2]. This property contributes to its broad in vitro activity against multidrug-resistant (MDR) bacteria[3]. Originally, tigecycline was approved for complicated skin and soft tissue infection, complicated intraabdominal infection, and community-acquired pneumonia. Although it is considered bacteriostatic, tigecycline is often used to treat MDR bacterial infections

[1]Department of Infectious Diseases, Kosin University Gospel Hospital, Busan, Republic of Korea. [2]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. [3]Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. [4]Departments of Internal Medicine, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Gangwon-Do, Republic of Korea. [5]Eun Hee Song and Yong Pil Chong have contributed equally to this work. ✉email: songeh@gnah.co.kr; drchong@amc.seoul.kr

in countries like South Korea, where newer treatment options such as ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are not yet available.

Breakthrough bloodstream infections (BSIs) are continuous or new-onset BSIs that occur after at least 48 h of appropriate antibiotic treatment[4–7]. Inadequate control of the infection source and use of unsuitable antibiotics due to either antimicrobial resistance of microorganisms or suboptimal concentrations of active drugs in the affected organ may account for breakthrough BSI. In two recent studies on breakthrough BSIs, cases of persistent bacteremia that continued despite appropriate antibiotic therapy for the initial bacteremia were excluded, with the focus placed on superinfection[7,8].

Tigecycline is a mainly bacteriostatic antibiotic; it achieves poor serum concentrations due to a high volume of distribution[9]. For this reason, there have been concerns that its use in severe infections such as BSI and endocarditis may lead to a poorer prognosis. In addition, there have been case reports of breakthrough BSI during tigecycline therapy despite efficacy in abdominal and soft tissue infections and community-acquired pneumonia[10,11]. Since data on breakthrough BSI during tigecycline therapy are limited, we aimed to investigate the incidence and risk factors associated with the development of breakthrough BSI during tigecycline monotherapy. We focused on new-onset BSI that developed during tigecycline therapy for prior infection, aiming to guide empirical treatment when a patient becomes septic during tigecycline therapy.

Materials and methods

Study population and design

This matched case–control study was performed at the Asan Medical Center, a 2700-bed tertiary referral center in Seoul, Republic of Korea. Patients over 18 years old who received tigecycline between March 1, 2009 and July 31, 2021 were retrospectively identified. Case patients were individuals who developed breakthrough BSI after at least 48 h of tigecycline monotherapy. Breakthrough BSI was defined as new-onset BSI that arose during appropriate empirical or definitive tigecycline therapy that had been administered for more than 48 h[7,8,12]. When a BSI, which prompted the initiation of tigecycline therapy, persisted despite treatment, it was not classified as a breakthrough BSI. The control group was patients who received tigecycline monotherapy for at least 48 h and had no breakthrough BSI. The controls were matched 1:1 with case patients based on age, sex, and date of tigecycline therapy (within 3 months). In our hospital, tigecycline was administered with a loading dose of 100 mg, followed by a maintenance dose of 50 mg every 12 h. For patients with liver dysfunction, the maintenance dose was reduced by half based on the attending physician's decision.

Data collection and definition

Medical records of the case and control patients were reviewed. Demographic characteristics, underlying diseases, sites of infection, antibiogram results, duration of hospital stay before tigecycline therapy, presence of indwelling catheter, microbiological data, and clinical outcomes were reviewed. The onset of BSI was defined as the day the first positive blood culture was drawn. The severity of underlying illness was based on the McCabe and Jackson classification[13]. The Charlson comorbidity index was used to evaluate comorbid conditions[14], and the severity of illness at the time of BSI was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score[15]. Sites of infection causing breakthrough BSI were defined according to the Centers for Disease Control and Prevention criteria[16]. MDR pathogens were defined as: vancomycin-resistant *Enterococcus* species, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa,* and carbapenem-resistant Enterobacterales. Treatment outcome of BSI was evaluated based on all-cause mortality. This information was entered into an electronic case report form, and all information was processed anonymously.

Microbiological data

Species identification and antimicrobial susceptibilities were determined using a Vitek (bioMérieux, France) or Microscan (Beckman Coulter, CA, USA), in accordance with the standard criteria of the Clinical and Laboratory Standards Institute (CLSI). Gram-negative bacterial isolates with tigecycline MIC ≤ 2 mg/L were considered susceptible to tigecycline.

Statistical analysis

Categorical variables were compared using the chi-square or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. To identify risk factors for breakthrough BSI during tigecycline therapy, all significant variables in the univariate analysis were included in a multiple logistic regression model. The final model was constructed using the backward stepwise selection procedure. All tests of significance were 2-tailed and a *P* value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed with SPSS for Windows, version 21 (SPSS Inc, Chicago, Illinois).

Ethical approval

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2022–0100). The requirement for obtaining informed consent from the patients was waived by the IRB of Asan Medical Center. To protect personal privacy, identifying information in the electronic database was encrypted. All methods were performed in accordance with the relevant guidelines and regulations and followed the principles stipulated in the Declaration of Helsinki.

Results

Microorganisms causing breakthrough BSI

During the study period, a total of 4,505 patients were treated with tigecycline, and 144 had breakthrough BSI. Of these 144 patients, 29 whose blood cultures were considered to be contaminated were excluded from the analysis, and a total of 115 patients with breakthrough BSI (2.6%, 95% confidence interval [CI], 2.1 to 3.1%) were included (Fig. 1). The contaminated blood cultures were caused by coagulase-negative staphylococci and *Micrococcus* species[17].

The causative pathogens of the breakthrough BSI are shown in Fig. 2. There were five cases of polymicrobial breakthrough BSI, resulting in a total of 123 breakthrough BSI isolates. *Klebsiella pneumoniae* (28/123, 22.8%) was the most common pathogen, followed by *Candida* species (21/123, 17.1%), *P. aeruginosa* (20/123, 16.3%), and *A. baumannii* (18/123, 14.6%). Gram-negative non-fermentative bacilli were isolated in 37.4% of the patients, Enterobacterales in 34.8%, and gram-positive cocci such as staphylococci and enterococci in 11.3%. Most *A. baumannii* isolates (94.4%) were resistant to meropenem, and about one-third of the *K. pneumoniae* and *P. aeruginosa* isolates were resistant to meropenem. Among isolates in which tigecycline susceptibility test was performed, half of *K. pneumoniae* isolates (8/16) were resistant to tigecycline (MIC > 2 mg/L), and 23.0% of the *A. baumannii* isolates (3/13) were resistant to tigecycline (Table 1).

Clinical characteristics and outcomes of patients with breakthrough BSI

The clinical features and outcomes of breakthrough BSI are shown in Table 2. The most common site of infection considered to be the cause of the breakthrough BSI was intraabdominal infection (33.9%), followed by catheter-related infection (30.4%) and hepatobiliary infection (19.1%). The median duration of tigecycline therapy before breakthrough BSI was 8 days. After the onset of BSI, 72 patients (62.6%) received intensive care unit (ICU) care, and the in-hospital crude mortality rate was 42.7%.

Risk factors for the development of breakthrough BSI during tigecycline therapy

The baseline and clinical characteristics of patients with breakthrough BSI and controls are shown in Table 3. There were no significant differences between the two groups in age, gender, prior antibiotic use, hospital stay before tigecycline therapy, and type of infection. However, the cases were more likely to have liver cirrhosis ($P < 0.001$), solid organ transplantation ($P = 0.013$), and indwelling catheters such as central venous catheters (CVC) and percutaneous drainage catheters ($P = 0.012$). The Charlson comorbidity index was also higher in the cases ($P = 0.027$), and previous colonization with *Candida* ($P < 0.001$) or MDR bacteria ($P < 0.001$) was also associated with breakthrough BSI. Regarding the severity of infection leading to tigecycline therapy, patients with breakthrough BSI had higher APACHE II score than controls ($P < 0.001$).

Significant univariate variables were included in a logistic regression model to identify independent risk factors for breakthrough BSI (Table 4). Because ICU care was highly correlated with APACH II score, we retained only APCHE II score in the model. In multivariable analysis, liver cirrhosis (adjusted odds ratio [aOR], 3.09; 95% CI, 1.13 to 8.46), indwelling catheter (aOR, 3.42; 95% CI, 1.38 to 8.48), previous *Candida* colonization (aOR, 14.95; 95% CI, 3.58 to 62.49), and previous MDR bacteria colonization (aOR, 10.30; 95% CI, 5.20 to 20.43) were independently associated with breakthrough BSI during tigecycline therapy.

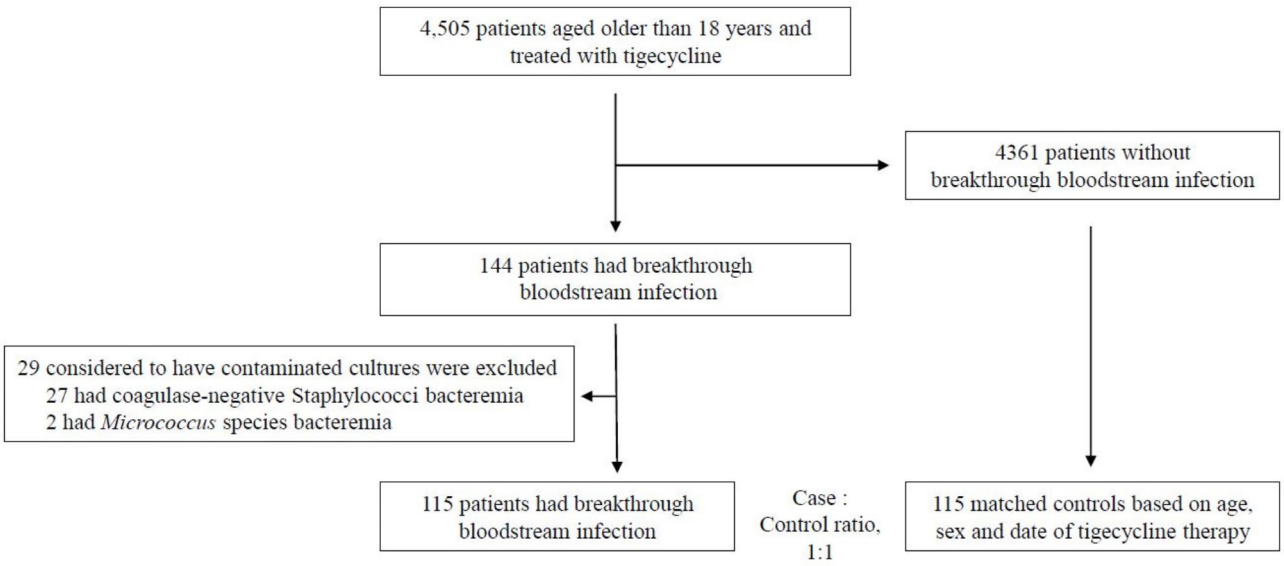

Fig. 1. Flow diagram of the study.

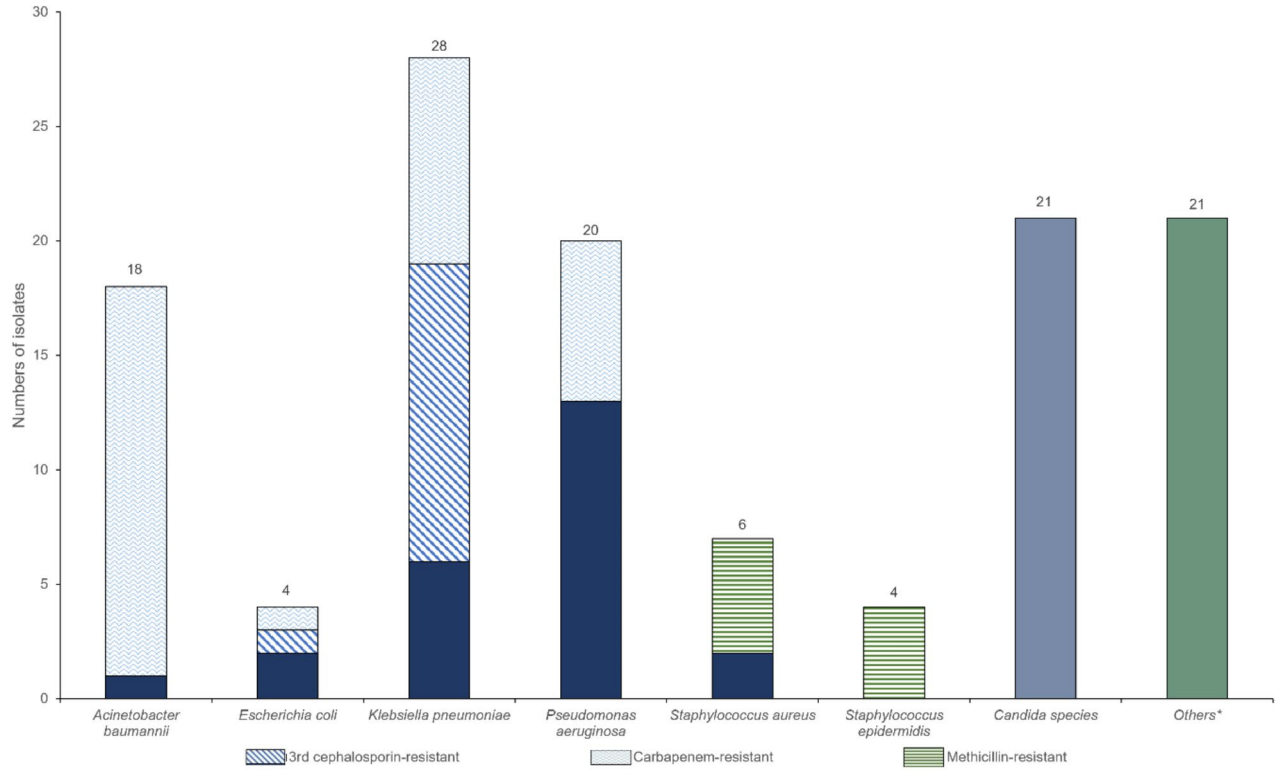

Fig. 2. Distribution of causative pathogens in 115 patients with breakthrough bloodstream infection during tigecycline therapy. This figure includes polymicrobial bloodstream infections in which each microorganism was counted. *Others include *Bacteroides fragilis* (2 cases), *Enterococcus faecium* (2), *Klebsiella oxytoca* (2), *Stenotrophomonas maltophilia* (2), *Serratia marcescens* (2), *Actinomyces species* (1), *Alcaligenes faecalis* (1), *Burkholderia cepacian* (1), *Chryseobacterium indologenes* (1), *Citrobacter amalonaticus* (1), *Enterobacter aerogenes* (1), *Enterobacter asburiae* (1), *Enterococcus faecalis* (1), *Klebsiella aerogenes* (1), *Moraxella osloensis* (1) *and Morganella morganii* (1).

Discussion

We have investigated the incidence, causative microorganisms, and risk factors associated with breakthrough BSI during tigecycline therapy. The overall incidence of breakthrough BSI was 2.6% (95% CI, 2.1 to 3.1%), and the main causes of breakthrough BSI were intraabdominal infection and catheter-related infection. Major microorganisms were Enterobacterales, gram-negative non-fermentative bacilli such as *A. baumannii* and *P. aeruginosa*, and *Candida* species. Risk factors for the development of breakthrough BSI included liver cirrhosis, presence of indwelling catheter such as CVC and percutaneous drainage catheter, and previous colonization with *Candida* or MDR bacteria.

The main causes for which tigecycline therapy was initiated were intraabdominal, hepatobiliary, and respiratory infections, whereas the main causative foci of breakthrough BSI were intraabdominal, catheter-related, and hepatobiliary infection. In intraabdominal and hepatobiliary infections, it appears that complications such as anastomotic leak and biliary obstruction may arise during tigecycline therapy, potentially leading to breakthrough BSI due to inadequate source control. Furthermore, catheter-related infection, the second main cause of breakthrough BSI, is thought to be related to a suboptimal serum concentration of tigecycline. Indwelling catheter was an independent predictor of breakthrough BSI in our patients with tigecycline therapy. In previous studies of breakthrough BSI during various antibiotics therapy, the presence of indwelling catheter was identified as an independent risk factor for breakthrough BSI[18,19]. Infections that led to tigecycline therapy did not include catheter-related infection. However, when breakthrough BSI occurred, catheter-related infection was the infection source in 30.4% of cases. It is well known that maintaining a peak serum concentration of tigecycline above 2 mg/L is difficult[9,20], so tigecycline is not an ideal agent for treating BSI or other endovascular infections. Thus, it is possible that many catheter-related breakthrough BSIs in our study occurred because of low serum concentration of tigecycline.

Another major cause of breakthrough BSI can be resistance or reduced susceptibility to tigecycline. The microorganism most frequently involved in our breakthrough BSIs was *K. pneumoniae*; 32.1% of the *K. pneumoniae* isolates were carbapenem-resistant, and 50% were tigecycline-resistant (MIC > 2 mg/L). *A. baumannii* and *P. aeruginosa* were also major pathogens in our breakthrough BSIs. In a previous report, breakthrough BSIs were caused by intrinsically tigecycline-resistant microorganisms (*P. aeruginosa*) or microorganisms with reduced susceptibility to tigecycline[21].

Pathogen and antibiotic	No. of susceptible isolates /total no. of isolates (%)
Klebsiella pneumoniae (n = 28)	
Amikacin	20/28 (71.4)
Aztreonam	7/20 (35)
Cefepime	5/28 (17.9)
Cefotaxime	5/28 (17.9)
Ciprofloxacin	6/28 (21.4)
Meropenem	19/28 (67.9)
Piperacillin/tazobactam	15/28 (53.6)
Tetracycline	1/28 (3.6)
Tigecycline	8/16 (50)
Pseudomonas aeruginosa (n = 20)	
Amikacin	18/20 (90)
Cefepime	14/20 (70)
Ceftazidime	15/20 (75)
Ciprofloxacin	14/20 (70)
Meropenem	13/20 (65)
Piperacillin/tazobactam	14/20 (70)
Acinetobacter baumannii (n = 18)	
Amikacin	3/18 (16.7)
Cefepime	2/18 (11.1)
Ceftazidime	1/18 (5.6)
Levofloxacin	1/18 (5.6)
Meropenem	1/18 (5.6)
Piperacillin/tazobactam	1/7 (14.3)
Tetracycline	0/10 (0)
Tigecycline	10/13 (76.9)
Candida species (n = 21)	
Amphotericin B	21/21 (100)
Fluconazole	15/21 (71.4)
Voriconazole	20/21 (95.2)

Table 1. Antimicrobial susceptibility of causative microorganisms of breakthrough bloodstream infection. Data are presented as number of cases (with corresponding percentage).

Liver cirrhosis was also identified as a risk factor for breakthrough BSI. Tigecycline is metabolized primarily by liver glucuronidation, and significant hepatic dysfunction and hepatic failure have been reported in some patients[22]. For this reason, dose reduction and close monitoring are recommended for patients whose liver function has deteriorated to Child–Pugh C[23]. In clinical practice, tigecycline dose is often reduced in patients with only mild liver function. Hence, it is plausible that the serum level of tigecycline may have been low in patients with liver cirrhosis due to inadequate dosage, potentially leading to breakthrough BSI.

Candida species were also identified as major microorganisms causing breakthrough BSI during tigecycline therapy. Risk factors for developing *Candida* infection included *Candida* colonization, severity of illness, use of CVC, and exposure to broad-spectrum antibiotics[24]. The high incidence of *Candida* breakthrough BSI is most likely caused by an increase in selection pressure for *Candida* because tigecycline is active against both gram-positive and gram-negative bacteria[1,23]. In addition, 88.9% of the patients who developed candidemia had CVCs, and 55.6% were in an ICU at the start of tigecycline therapy. We found that previous colonization with *Candida* or MDR bacteria was an independent risk factor for breakthrough BSI. Of the breakthrough BSI patients with MDR gram-negative bacilli (GNB), 76.5% had previous MDR GNB colonization; of those with *Candida* breakthrough BSI, 27.8% had previous *Candida* colonization. Indwelling catheter, compromised liver function, and high Charlson comorbidity score may contribute to the development of breakthrough BSI in these patients.

The present study has several limitations. First, it was a retrospective observational study conducted in a single tertiary center, so the potential effect of unmeasured variables and residual confounding cannot be excluded. A larger prospective study involving multiple centers is needed to validate the results. Second, since our hospital's antimicrobial susceptibility panel does not include tigecycline, we were only able to assess susceptibility to tigecycline in a limited number of breakthrough BSI isolates. Therefore, a correlation between tigecycline resistance and breakthrough BSI could not be definitively established. Third, high-dose tigecycline (200 mg as a single dose, followed by 100 mg every 12 h) is recommended in severe infections or MDR bacterial infections to address the low serum concentration of tigecycline associated with conventional dose[25–27]. If high-dose tigecycline had been routinely used in our patients, the rate and causes of breakthrough BSI might have

Variable	No (%) of patients
Source of breakthrough BSI	
Intraabdominal infection	39 (33.9)
Hepatobiliary infection	22 (19.1)
Catheter-related infection	35 (30.4)
Primary BSI	7 (6.1)
Skin and soft tissue infection	6 (5.2)
Respiratory tract infection	3 (2.6)
Urinary tract infection	3 (2.6)
Length of tigecycline therapy before BSI (day), median (IQR)	8.0 (4–13.5)
Pitt bacteremia score, median (IQR)	2 (1–5)
Sepsis grade	
Without SIRS	5 (4.3)
Sepsis	37 (32.2)
Severe sepsis	42 (36.5)
Septic shock	31 (27.0)
ICU care after BSI	72 (62.6)
Outcome	
7-day mortality	9 (7.8)
30-day mortality	25 (21.7)
In-hospital mortality	49 (42.6)
Time to death (day), median (IQR)	33 (14–89.5)

Table 2. Clinical features and outcomes of patients with breakthrough bloodstream infection (BSI) during tigecycline therapy. Data are presented as numbers of patients (with the corresponding percentages shown in parentheses) unless otherwise specified. IQR, interquartile range; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit.

differed. These limitations highlight the need for further research to enhance our understanding of breakthrough BSI during tigecycline therapy and its implications for patient management and treatment outcomes.

In conclusion, this study found an incidence of approximately 2.6% of breakthrough BSI during tigecycline therapy. Patients with liver cirrhosis, indwelling catheter, previous *Candida* colonization, and previous MDR bacterial colonization were found to be at increased risk. In addition, breakthrough BSI involves a diverse spectrum of causative microorganisms such as *Candida*, carbapenem-resistant gram-negative bacilli, and methicillin-resistant staphylococci. Consequently, when breakthrough BSI is suspected in patients receiving tigecycline, switching to a single antibiotic for empirical treatment is not feasible. These findings emphasize the need for careful management and appropriate empirical antibiotic therapy when breakthrough BSI is suspected in patients receiving tigecycline. Further research is warranted to develop optimal strategies for the prevention and management of breakthrough BSI during tigecycline therapy.

Characteristic	No. (%) with characteristic		*P* value
	With Breakthrough BSI (n = 115)	Without breakthrough BSI (n = 115)	
Age (year), median (IQR)	69 (58–79)	70 (60–79)	0.96
Male	74 (64.3)	74 (64.3)	> 0.99
ICU care at the start of tigecycline therapy	49 (42.6)	24 (20.9)	0.001
Hospital stay before tigecycline therapy (day), median (IQR)	29 (15–65)	30 (16–50.5)	0.38
Comorbidity[1]			
Solid cancer	58 (50.4)	56 (48.7)	0.90
Diabetes mellitus	29 (25.2)	38 (33)	0.25
Liver cirrhosis	29 (25.2)	8 (7.0)	< 0.001
Solid organ transplantation	23 (20.0)	9 (7.8)	0.013
Chronic renal failure	24 (20.9)	14 (12.2)	0.11
Hemodialysis dependence	12 (10.4)	11 (9.6)	> 0.99
Heart failure	15 (13.0)	13 (11.3)	0.84
Hematologic malignancy	3 (2.6)	2 (1.7)	> 0.99
Chronic lung disease	2 (1.7)	2 (1.7)	> 0.99
Charlson comorbidity index	3 (2–5)	2 (1–5)	0.027
Previous antibiotic therapy			
Carbapenem	54 (47.0)	43 (37.4)	0.18
Piperacillin-tazobactam	10 (8.7)	15 (13)	0.40
3rd cephalosporin	7 (6.1)	16 (16.9)	0.08
Indwelling catheter[2]	104 (90.4)	89 (77.4.)	0.012
Previous colonization			
Candida species	19 (16.5)	3 (2.6)	0.001
Multidrug-resistant pathogen[3]	76 (66.1)	19 (16.5)	0.001
Type of infection[4]			
Intraabdominal infection	62 (53.9)	59 (51.3)	0.79
Hepatobiliary infection	22 (19.1)	17 (14.8)	0.48
Respiratory tract infection	21 (18.3)	20 (17.4)	> 0.99
Skin and soft tissue infection	9 (7.8)	16 (13.9)	0.20
Urinary tract infection	1 (0.9)	3 (2.6)	0.61
APACHE II score[5], median (IQR)	17.0 (13.0–23.0)	13 (9.0–18.0)	< 0.001
60-day mortality after tigecycline initiation	36 (31.3)	25 (21.7)	0.135
In-hospital mortality	49 (42.6)	22 (19.1)	< 0.001

Table 3. Clinical characteristics of patients with and without breakthrough bloodstream infection (BSI). Data are presented as numbers of patients (with the corresponding percentages shown in parentheses) unless otherwise specified. IQR, Interquartile range; APACHE II, Acute physiologic assessment and chronic health evaluation II. [1,5]Comorbidity and APACHE II score at the start of tigecycline therapy. [2]Indwelling catheter includes central venous catheter and percutaneous drainage catheter. [3]Multidrug-resistant isolate was defined as vancomycin-resistant *Enterococcus*, carbapenem-resistant Enterobacterales, carbapenem-resistant *P. aeruginosa*, or carbapenem-resistant *A. baumannii*. [4]Cause of infection that led to initiation of tigecycline.

Variable	Univariate analysis		Multivariable analysis[1]	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Liver cirrhosis	4.51 (1.96–10.37)	< 0.001	3.09 (1.13–8.46)	0.028
Solid organ transplantation	2.94 (1.30–6.68)	0.01		
Charlson comorbidity score	1.13 (1.01–1.27)	0.043		
Indwelling catheter[2]	2.76 (1.29–5.90)	0.009	3.42 (1.38–8.48)	0.008
Previous *Candida* colonization	7.39 (2.12–25.73)	0.002	14.95 (3.58–62.49)	< 0.001
Previous multidrug-resistant pathogen colonization[3]	9.85 (5.27–18.40)	< 0.001	10.30 (5.20–20.43)	< 0.001
APACHE II score	1.08 (1.04–1.12)	< 0.001		

Table 4. Risk factors associated with development of breakthrough BSI during tigecycline therapy. [1]The model fitted the data well in terms of discrimination (C-statistic, 0.84) and calibration (Homer-Lemeshow goodness of fit statistic, 1.46; $P = 0.69$). [2]Indwelling catheter includes central venous catheter and percutaneous drainage. [3]Multidrug-resistant isolate was defined as vancomycin-resistant *Enterococcus*, carbapenem-resistant Enterobacterales, carbapenem-resistant *P. aeruginosa*, or carbapenem-resistant *A. baumannii*.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author contributions
Study conceptation and design : EH song, YP Chong; Data collection and analysis : S Jin, SY Lim, YW Lee; Manuscript writing : S Jin, EH song, YP Chong; Manuscript editing : H Sung, MN Kim, S Bae, J Jung, MJ Kim, SH Kim, SH Choi, SO Lee, YS Kim, EH song, YP Chong. All authors meet the ICMJE authorship criteria.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to E.H.S. or Y.P.C.