# Isolation, Identification, and Profile of Antibiotic Resistance of Bacteria in Patients with Cancer

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## Abstract

**Background:** Blood stream infection is one of the main causes of morbidity and mortality in patients with cancer. The purpose of this study was to evaluate the prevalence of aerobic and anaerobic-bacteremia in hospital inpatients with cancer and to determine the antibiotic resistance profile in isolated organisms in Kerman, southeast Iran.

**Methods:** Total of 240 blood cultures from 136 patients were examined. The blood cultures performed in BACTEC media and were assessed for four weeks in aerobic and anaerobic conditions. Identification of isolates and antibiotic susceptibility test were performed by standard methods.

**Results:** 24.6% of blood cultures were positive. The prevalence of polymicrobial bacteremia was 12%. Forty-three out of 65 isolated bacteria (66%) were gram positive and others (34%) were gram negative. Coagulase negative *Staphylococci* (21.5%), *Propionibacterium spp* (15.4%), *Diphtheroid spp* (12.3%), and *Escherichia coli* (12.2%) were the dominant isolated bacteria. All *Staphylococci* were methicillin resistant. The only isolated *Pseudomonas putida* and 37% of isolated *Escherichia coli* were multi-drug resistant. A number of *Streptococci*, *Klebsiella,* and *Alcaligenes spp* were also resistant in part to the antibiotics.

**Conclusion:** Patients with cancer may be readily infected by many opportunistic pathogens including multi-drug resistant strains.
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**Keywords** ● Cancer ● bacteremia ● antibiotic resistance

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## Introduction

Blood stream infection is one of the main causes of morbidity and mortality in patients who receive cancer treatment.[1,2] Most of infections in such patients are related to the neutropenia, aplastic anemia, tissue necrosis, and hypogammaglobulinemia.[2] Normal microflora and semi-pathogen organisms can play a significant role in such acute medical conditions.[3-5] It was found that 15-25% of bacteremia in cancer patients is polymicrobial. The polymicrobial infections are associated with higher mortality, sometimes more than 50%.[2] Literature review indicates that the risk of anaerobic blood stream infection in malignancy is high.[6-8]

Fever is the principle and sometimes the only manifestation

the of bacteremia.[9,10] However, fever can also be present in patients receiving chemotherapy and biologic therapy as part of flu-like syndrome.[11] Thus it is important that physicians and patients' family be aware of usual course of fever during chemotherapy.[2] Early diagnosis and prompt treatment of bacteremia can reduce mortality in cancer patients who receive chemotherapy.[12,13]

Many blood cultures in Iran are performed in non-selective culture media with simple formula. However a range of bacteria can cause systemic infections in cancer patients. Among them, more fastidious organisms, including anaerobic bacteria, require a variety of specialized growth factors that are not available in commonly used culture media. We do not know if simple blood culture media give the same results of more specific media to establish bacteremia in patients with cancer. In order to determine the prevalence of bacteremia in cancer patients who receive chemotherapy, blood cultures of symptomatic patients were performed in more specific media.

## Materials and Methods

One hundred and thirty six patients with cancer (60 children and 76 adults) who were receiving chemotherapy were included in the present study. They were admitted with suspected bacteremia in the oncology wards of Bahonar and Afzalipour Hospitals in Kerman, southeast Iran.

Demographic data and clinical characteristics of the patients were collected in a questionnaire. The questionnaire was designed for the specific needs.[13] According to the patients' clinical status, the number of blood samples and the time of sample collection were determined by the physicians.

The blood cultures were performed in BACTEC blood culture media (BD, BACTEC-USA). The pediatric type, Ped/plus medium was used for children under 3 years and anaerobe/F medium (for aerobic and anaerobic organisms) was used for other patients. The quality of the culture media were evaluated by

cultivation of strictly aerobic and anaerobic reference strains including *Pseudomonas aeruginosa* (ATCC:27853), *Fusobacterium nucleatum* (ATCC:25576), and *Porphyromonas gingivalis* (ATCC:33277). BACTEC media contain resin particles that adsorb and inactivate most antibiotics.[14]

In order to reduce the potential microflora contamination, careful skin antisepsis preparation was performed by ethanol 70% and commercial iodophor solution.[13,14] The ratio of blood to culture media volume was 1:5 to 1:10.[13] The blind subculture was done in ≤24, ≤48, and ≤72 hours after sample collection. It was repeated at the end of the 1st to 4th week. The bottles were evaluated visually for any changes in the appearance including hemolysis, turbidity, and gas bubbles formation.[13-15] The subcultures were performed on the sheep blood and Chocolate agars (Highmedia, India) in anaerobic jar, using Gas pack (Aerotec A, Merk, Germany) and Candle jar. The plates were incubated for 48-72 hours in 35-37°C.[13-15] For rapid and presumptive diagnosis, two smears were prepared from blood cultures and inspected concurrently.

Species-level identification of isolates was performed by using conventional diagnostic methods such as gram stain, catalase, coagulase, oxidase, optochin, bacitracin, and CAMP test for gram positive isolates, and catalase, oxidase and biochemical tests for gram negatives.[13,14,16-22]

Antibiotic susceptibility tests were performed by disk diffusion (Kirby-Bauer method).[13,14] Depending on the aerobic or anaerobic nature of isolated bacteria, the antibiotic sensitivity test was performed in a particular condition.[13,14]

Most of the data in this study are shown as frequencies. The *t* test was used for the group statistics of dependent and independent samples.

## Results

Demographic and clinical data of the study popu-

| **Table 1:** Baseline demographic and clinical characteristics of the study population (No:136) | | |
|---|---|---|
| **Variable** | | **No (%)** |
| Age groups (year) | 1-14 | 60 (44) |
| | 15-87 | 76 (56) |
| Malignancies | Leukemia | 86 (63) |
| | Others | 50 (37) |
| Fever* | Yes | 106 (78) |
| | No | 30 (22) |
| With antibiotics treatment* | Yes | 64 (47) |
| | No | 72 (53) |

*At the time of sample collection

lation are shown in table 1. The mean age of the patients was 47 years for adults and 6.5 years for children. Of 136 patients, 63% suffered from different types of leukemia and the remaining (37%) had other various forms of malignancies.

Fifty nine (24.6%) of the 240 blood cultures were positive. The prevalence of polymicrobial (more than one species) bacteremia was 12%. In 10 (17%) of the positive results, more than one blood sample were taken. Among patients with positive results, about 10% had no fever and 33% were receiving antibiotic at the time of sample collection. *E. coli*, *Pseudomonas putida*, *Propionibacterium*, and *Klebsiella spp* were isolated from the patients receiving antibiotic. Forty three (66%) of 65 isolated bacteria were G$^+$ and the remaining (34%) were G$^-$. The genus and species of isolated organisms are shown in table 2. The coagulase negative *Staphylococci* (21.5%), *Propionibacterium spp* (15.4%), *Diphtheroid spp* (12.3%), and *E. coli* (12.2 %) were prevalent bacteria in the present study. In patients with polymicrobial bacteremia, the coagulase negative *Staphylococci* were the dominant organism.

Based on the sensitivity tests, all of the isolated *Staphylococci* were methicillin resistant. The resistance rate among coagulase positive *Staphylococci* to penicillin + oxacillin was 100%. It was 67% for ampicillin (table 3). All three *Strepcoccus agalactiae* (group B) were semi sensitive to ampicillin. Resistance to penicillin, azithromycin, and cefazolin were also found among isolated *Streptococci*.

For gram negative bacteria, 37% of *E. coli*, 33% of *Klebsiella* spp and the only isolated *Pseudomonas putida,* were multidrug resistant (table 3).

## Discussion

According to the global reports, the prevalence of bacteremia in patients with cancer is 5.7-44%.[23,24] In the present study, 59 (24.6%) of 240 blood cultures were positive, which were similar to the studies of Husseinpoor, Jenson, El-Mahallawy and their colleagues.[25-27] Obtaining multiple blood samples will increase the accuracy of blood culture.[28,29]

In our study 70.5% of positive results were associated to the multiple samples.

Fever is the main clinical sign of bacteremia.[23] However five (10%) patients with positive blood culture had no fever at the time of sample collection. Seven samples (12.3%) with positive results were from patients with polymicrobial bacteremia. Of them, four (57%) had been caused by two types of gram positive bacteria. In a comparable study, more cases of polymicrobial bacteremia were caused by a combination of G$^+$ and G$^-$ bacteria.[27]

Thirty three percent of patients with positive results had history of antibiotic treatment. BACTEC media contain neutralizing resin particles that can effectively adsorb and inactivate antibiotics in the blood samples.[14] In 54 cases, two different types of culture media -ordinary culture medium and BACTEC- were compared. The ordinary type did not support bacterial growth in the 13% of the culture-positive specimens.

In our study, a significant heterogeneity was detected within the isolated organisms. The dominant group was gram-positive bacteria (66% versus 34%; table 2). Before 1986, the G$^-$ bacteria were responsible for most cases of bacteremia.[2,24,30] Routine use of intravenous

| Table 2: Isolated organisms | |
|---|---|
| **Gram Positive** | **No (%)** |
| Coagulase$^+$ *Staphylococci* | 4 (6.15) |
| Coagulase$^-$ *Staphylococci* | 14 (21.5) |
| *Streptococcus agalactiae* | 3 (4.6) |
| *Streptococcus viridans* | 2 (3 ) |
| *Bacillus cereus* | 2 (3) |
| *Propionibacterium spp* | 10 (15.4) |
| *Diphteroid spp* | 8 (12.3) |
| Total | 43 (66) |
| **Gram Negative** | |
| *E. coli* | 7 (10.7) |
| *E .coli* (inactive) | 1 (1.5) |
| *Salmonella typhi* | 2 (3) |
| *Serratia spp* | 3 (4.6) |
| *Alcaligenes feacalis* | 3 (4.6) |
| *Klebsiella* spp | 5 (7.7) |
| *Pseudomonas putida* | 1 (1.5) |
| Total | 22 (34) |

**Table 3:** Antibiotic sensitivity profile of organisms causing bacteremia in patients with cancer

Sensitivity rate No (%)

| Organisms | Pen (10 µg) | Oxa (1 µg) | Van (30 µg) | Amp (10 µg) | Cip (5 µg) | Imi (10 µg) | Mero (10 µg) | Cefa (30 µg) | Cefe (30 µg) | Azit (15 µg) | Clin (2 µg) | Ami (30 µg) | Ceft (30 µg) | Cefo (30 µg) | Gen (10 µg) | Chlo (30 µg) | Doxy (30 µg) | SXT* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coagulase⁺ Staphylococci | R | R | 4 (100) | 2 (50) | 4 (100) | 4 (100) | 4 (100) | ND | 4 (100) | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Coagulase⁻ Staphylococci | 2 (14) | R | 14 (100) | 4 (29) | 14 (100) | 14 (100) | 14 (100) | ND | 14 (100) | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Streptococcus group B | 2 (67)MS | ND | 3 (100) | R | ND | ND | ND | 1 (33.3) | ND | 1 (33.3) | ND | ND | ND | ND | 3 (100) | ND | ND | ND |
| S. Viridans | 1 (100) MS | ND | 1 (100) | R | ND | ND | ND | 1 (100) | ND | 1 (100) | ND | ND | ND | ND | 1 (100) | ND | ND | ND |
| S. Non A Non B | 1 (100) MS | ND | 1 (100) | R | ND | ND | ND | 1 (100) | ND | R | ND | ND | ND | ND | 1 (100) | ND | ND | ND |
| B. cereus | ND | ND | 2 (100) | ND | 2 (100) | ND | ND | ND | ND | ND | 2 (100) | ND | ND | ND | 2 (100) | ND | ND | ND |
| Propionibacterium | 10 (100) | ND | 10 (100) | ND | ND | ND | 10 (100) | ND | 10 (100) | 10 (100) | 10 (100) | ND | ND | ND | ND | ND | ND | ND |
| Diphtheroid | 8 (100) | ND | 8 (100) | ND | ND | ND | 8 (100) | ND | ND | 8 (100) | ND | ND | ND | ND | ND | ND | ND | ND |
| E. coli | ND | ND | ND | ND | 3 (37) | 3 (37) | ND | 1 (12) | 6 (75) | ND | ND | 6 (75) | 3 (37) | ND | 3 (37) | ND | ND | ND |
| Salmonella | ND | ND | ND | 2 (100) MS | 2 (100) | ND | ND | ND | ND | ND | ND | ND | 2 (100) | ND | 2 (100) | 2 (100) | ND | 2 (100) |
| Klebsiella | ND | ND | ND | ND | 4 (100) | 3 (75) | 3 (75) | ND | 4 (100) | ND | ND | 2 (50) | 1 (25) | 4 (100) | 2 (50) | ND | ND | ND |
| Serratia | ND | ND | ND | ND | 3 (100) | 1 (33) | ND | ND | 3 (100) | ND | ND | 1 (33) | 1 (33) MS | ND | 1 (33) | ND | ND | 1 (33) |
| Alcaligenes | ND | ND | ND | ND | 3 (100) | 2 (67) | 3 (100) | R | 3 (100) | ND | ND | ND | ND | 2 (67) | R | ND | ND | ND |
| Pseudomonas | ND | ND | ND | R | 1 (100) | R | 1 (100) | R | ND | ND | ND | ND | R | R | 1 (100) | R | 1 (100) | R |

Pen; penicillin, Oxa; oxacillin, Van; vancomycin, Amp; ampicillin, Cip; ciprofloxacin, Imi; imipenem, Mero; meropenem, Cefa; cefazolin, Cefe; cefepime, Azit; azithromycin, Clin; clindamycin, Gen; gentamicin, SXT; Cotrimoxazole (*Trimethoprim 1.25 µg + Sulfamethoxazole 23.75 µg), Ceft; ceftriaxone, Ami; amikacin, Cefo; cefotaxime, Chlo; chloramphenicol, Doxy; doxycycline. R; resistance, ND; not determined, MS; moderate sensitive.

catheter in neutropenic cancer patients on one hand and the increased use of prophylactic treatment with quinolones on the other hand, have amplified the prevalence of $G^+$ bacteremia in such patients.[2,24,26,31] However, some studies showed different results.[12,30] Among aerobic and anaerobic isolates, the coagulase negative *Staphylococci* (21.5%) and *Propionibacterium spp* (15.4%) were the most prevalent bacteria. Although *antiseptic preparation* of skin was performed by standard method,[13,32] the contamination of some blood samples with skin microflora should be considered. We did not find any association between the isolation of normal flora from blood cultures and the type of cancer in the patients.

Compared with some other studies,[5,24,29] the prevalence of coagulase positive *Staphylococci* bacteremia was not significant but *Streptococcus agalactiae* (group B) was isolated in three patients that was more than the expected rate.[33] The prevalence of *S. viridans* bacteremia in neutropenic patients is increasing.[31] This bacterium was isolated from two patients. Among opportunistic pathogens, the *Bacillus cereus* and *Diphtheroid spp* were isolated from two and eight patients, respectively. This finding is consistent with the results of El-

Mahallawy and co-workers.[27] Because of the frequent injection via venous access devices, patients with cancer are more susceptible to blood infection with specific opportunistic pathogens.[34] Prompt diagnosis and treatment of bacteremia could save their lives.

The bacterium *E. coli* (including one strain of inactive *E. coli*) was the most prevalent $G^-$ isolated bacteria. This finding was similar to the results of Cherif (Sweden), Kim (Korea), and Elting (USA).[12] *Pseudomonas putida* was isolated from one patient and *Alcaligenes faecalis* was isolated from three patients. These two bacteria have been isolated infrequently from cancer patients.[12,35,36] *Salmonella typhi* was isolated from two pediatric patients. This finding was similar to the results of Ali El-Din and colleagues.[37]

No anaerobic $G^-$ bacteria were isolated from the 240 blood cultures. 63% of patients were diagnosed as having hematological malignancies. Anaerobic bacteremia is most prevalent in patients with gastrointestinal malignancies.[32] No fungemia was found in the present study. This could be the result of anti-fungal prophylaxis in neutropenic patients, with or without fungal lesions, which is a routine practice in cancer wards.[38] The prevalence of

beta-lactam antibiotic resistance in coagulase positive (and coagulase negative) *Staphylococci* was similar to a Korean study but was different from two other studies reported from USA and Sweden.[24,29,30]

The isolated group B *Streptococci* were semi-sensitive to penicillin, ampicillin, and azithromycin. For *Streptococci*, decreased sensitivity to β-lactam antibiotics has been reported rarely.[39,40] Consistent with other studies,[24,29,30] no case of resistance to vancomycin and broad-spectrum antibiotics (imipenem, meropenem) was detected in G$^+$ isolates. However, Part of isolated *E. coli*, *Klebsiella*, and the only isolated *Pseudomonas putida* were multidrug resistant. The initial empirical treatment *of* bacteremia in febrile granulocytopenic patients are ceftriaxone or ceftriaxone/ceftazidime + vancomycin.[26,31] During the present study, we found that some of our patients did not respond to the empirical treatment. They recovered and improved within few days of cause-specific treatments that were based on microbiology test results.

## Conclusion

Patients with cancer, who are treated in ill-equipped hospitals, are easily infected by many opportunistic pathogens including multidrug resistant strains. For saving their lives, blood culture and the cause-specific treatment of bacteremia are mandatory.

## Acknowledgment

**Conflict of Interest:** None declared

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