

Original Article

Bacteremia due to *Stenotrophomonas Maltophilia* in Patients with Hematological Malignancies

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ABSTRACT

Background: The incidence of *Stenotrophomonas maltophilia* infections in immunocompromised cancer patients has increased recently. Treatment of these infections is usually difficult because drug resistance of *S. maltophilia* renders therapeutic options limited.

Materials and Methods: A retrospective study of *S. maltophilia* bacteremia was carried out at the Riyadh Armed Forces Hospital between January 1993 and December 2002. The records of patients confirmed to have *S. maltophilia* bacteremia were reviewed.

Results: Seventeen episodes of bacteremia caused by *S. maltophilia* were identified. The main risk factors were: underlying hematological malignancy, administration of

immunosuppressive therapy and broad spectrum antibiotics particularly carbapenems, having indwelling intravascular catheters and prolonged hospitalization. Antimicrobial susceptibility testing showed cotrimoxazole to be the most active agent, followed by ceftazidime, colistin and piperacillin/tazobactam. Eight episodes of bacteremia were successfully treated.

Conclusions: *Stenotrophomonas maltophilia* is a significant cause of morbidity and mortality in immunocompromised hosts especially those with underlying hematological malignancies receiving broad spectrum antibiotics. Early administration of appropriate antibiotics is vital to overcome these life threatening infections.

KEYWORDS: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), intensive care unit (ICU), non-Hodgkin's lymphoma (NHL), *S.maltophilia* (*Stenotrophomonas maltophilia*)

INTRODUCTION

Stenotrophomonas maltophilia (previously called *Pseudomonas maltophilia* and *Xanthomonas maltophilia*) was first described by Hugh and Ryschenkow in the year 1961^[1,2]. It is a non-fermentative gram negative bacillus which is widespread in the environment^[2-4]. It is an important nosocomial pathogen in immunocompromised patients^[1,3,5]. Incidence of infection is increasing in debilitated individuals due to the advances in medical therapeutics including the aggressive treatment of malignancy and the increased utilization of broad spectrum antibiotics^[1-11].

Bacteremia is a common manifestation of infection with this organism although the organism can be isolated from clinical specimens in the absence of infection^[1,2,4,9-12]. Treatment of *S. maltophilia* infections is difficult as isolates are frequently resistant to most of the β -lactams and aminoglycosides^[1,2,4-8].

In the light of reports of increasing frequency of infection with *S. maltophilia* worldwide, a retrospective

study of bacteremia due to *S. maltophilia* at our institution was undertaken.

MATERIALS AND METHODS

The Riyadh Armed Forces Hospital is a tertiary care centre comprising 1200 beds with specialty services including intensive care and solid organ and bone marrow transplantation. Cases of *S. maltophilia* were identified through review of the clinical microbiology reports and the medical records of these patients over a ten-year period (January 1993 to December 2002).

Definitions

Bacteremic episode: positive blood cultures for *S. maltophilia* in one or more culture bottles. Multiple isolates belonging to the same patient were considered to be the same bacteremic episode if they occurred within a 10 day period. Each blood culture was evaluated to determine whether the isolate represented a clinically significant bacteremia or a contaminant. This decision was based on

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Table 1: Details of patients in the study

Patient number	Sex	Age (Years)	Primary diagnosis	Number of courses of chemotherapy given	Number of positive blood culture sets	Primary site of infection	Length of stay in hospital (days)
1	M	13	ALL	1	9	Central line	28
2	M	30	NHL	10	1	Lungs	23
3	M	20	NHL	5	13	Lungs	31
4	M	30	AML	5	4	Lungs	180
5	M	25	ALL	1	2	Unknown	22
6	M	26	AML	3	5	Pharynx	46
7	M	22	ALL	4	2	Unknown	36
8	M	25	AML	1	12	Skin (EG)	14
9	M	33	AML	1	4	Unknown	30
10	M	30	AML	2	5	Lungs	20
11	M	16	ALL	1	2	Central line	14
12	F	30	ALL	1	7	Unknown	29
13	F	72	AML	0	3	Central line	10
14	F	62	ALL	1	11	Abdomen	29
15	F	42	AML	4	3	Unknown	48
16	F	39	AML	1	4	Pharynx	31
17	F	34	ALL	1	11	Central line	47

ALL: acute lymphoblastic leukemia, EG: ecthyma gangrenosum, AML: acute myeloid leukemia, M: male, NHL: non - Hodgkin's lymphoma, F: female

several factors including: clinical manifestations of the systemic infection, sampling procedures (direct or catheter-sampled specimen), number of positive blood culture bottles in each episode and the culture results from other body sites.

Nosocomial bacteremia: bacteremia occurring at 48 hours or more, after admission.

Prolonged hospitalization: hospital stays for two or more weeks prior to bacteremia

Primary site or focus of infection: was considered to be the portal of entry, if the organism was isolated from that site prior to the day on which blood cultures became positive for the first time.

Immunosuppressive therapy: included steroid therapy, cytotoxic chemotherapy or radiotherapy given within one month prior to the episode of bacteremia.

Prior antibiotic therapy: administration of antibiotics (intravenous route usually) within four weeks prior to the onset of bacteremia.

Appropriate antibiotic therapy: use of IV antibiotic(s) to which the organism was susceptible within 72 hours of blood culture collection.

Polymicrobial bacteremia: more than one clinically significant organism isolated from a single blood culture or from separate blood cultures within ten days.

Outcome: death within two weeks of bacteremic episode or survival beyond two weeks.

Microbiological analysis and antibiotic susceptibility testing: isolates from positive blood cultures were identified by Gram stain and subculture on blood, chocolate and MacConkey agars. Formal identification was done by using the Analytic Profile Index (API 20NE) system, Biomerieux, France. Sensitivities of

the isolates were determined for nine antibiotics using disc diffusion method according to National Committee for Clinical Laboratory Standards (NCCLS) criteria. Sulphamethoxazole-trimethoprim were routinely tested as one agent (cotrimoxazole). For patients with multiple positive blood cultures, the sensitivity results from the first isolates were used in the analysis of data.

RESULTS

Seventeen episodes of *S. maltophilia* bacteremia were encountered in 17 patients over a ten year period. All their records were retrieved for analysis. All the positive blood cultures represented true infection based on clinical and laboratory findings. Very few cases were reported between the years 1992 and 1994. An increase in the number of cases was noted in the year 1995 and then a large peak (six cases) was reached in the year 1996. Thereafter, the number of cases declined to one to two cases per year till a smaller peak (three cases) was seen in the year 2002. Details of the patients studied are shown in Table 1.

Of the 17 patients, 11 were male and six were female. The mean age of patients was 32.4 years (range: 13-72 years). The main risk factors were: underlying hematological malignancy, presence of neutropenia, other coexisting infections and central venous catheters; administration of cytotoxic chemotherapy, steroids and broad spectrum antibiotics including carbapenems; admission to ICU and artificial ventilation; prolonged duration of hospitalization and travel to hospital by air. The details are shown in Tables 2 and 3.

Table 2: Risk factors for infection with *S. maltophilia*

Risk Factor	Number	Percentage
Hematological malignancy	17	100
Cytotoxic chemotherapy	16	94.1
Steroid therapy	10	58.8
Radiotherapy	2	11.8
Bone marrow transplant	3	17.6
Neutropenia	17	100
Presence of central venous catheter	17	100
Treatment with broad spectrum antibiotics	17	100
Prior treatment with carbapenems	15	88.2
Polymicrobial	16	94.1
Monomicrobial	1	5.9
Admission to ICU/artificial ventilation	11	64.7
Travel to hospital by air	8	47

Out of the 17 patients studied, 15 (88.2%) had acute leukemia and two (11.8%) had lymphoma. All patients were neutropenic at the time of bacteremia. Sixteen episodes were polymicrobial and only one episode was monomicrobial. The coexisting infections were predominantly bacterial (16 patients, 88.2%) although candida and cytomegalovirus infections were present in a substantial proportion of patients (35.3% and 17.65% respectively). Indwelling intravascular catheters were present in all 17 patients. Cytotoxic chemotherapy was administered to 16 patients (94.1%) and only one patient did not receive chemotherapy because of her old age and the presence of other medical illnesses. Ten patients (58.8%) received steroid therapy during the last month prior to the bacteremic episode (as part of acute lymphoblastic leukemia protocols in seven patients, as part of lymphoma treatment in two patients and as graft versus host disease treatment in one patient). Only two patients (11.8%) received radiotherapy prior to the bacteremic episode. All patients were on broad spectrum antibiotics at the time of *S. maltophilia* bacteremia. Eleven patients (64.7%) were admitted to the general ICU and they received artificial ventilation during the bacteremic episodes.

The mean duration of ventilation was 8.4 days per patient ventilated. Eleven episodes of bacteremia (64.7%) were complicated by septic shock and nine of these patients died within two weeks of the bacteremic episode. It was noted that eight patients (47%) traveled to hospital by air prior to the bacteremic event.

The mean duration of stay in hospital prior to bacteremia was 37.5 days. All the bacteremic episodes were nosocomial. The primary sites of infection were: lungs (four cases), central venous catheters (four cases) and upper respiratory tract (two cases). However, the portal of entry was not identified in five cases (primary bacteremia).

Table 3: Characteristics of infections with *S. maltophilia* in this study

Feature	Number	Percentage
Number of patients ventilated	11	64.7
Septic shock	11	64.7
Other coexisting Infections :	16	94.1
Bacterial	6	35.3
Cytomegalovirus	3	17.6
Candida	6	35.3
Pneumocystis carinii	1	5.9
Relapses of primary disease	12	70.6
Before infection episode	6	35.3
After infection episode	6	35.3
Surgical Procedures (required) :	9	52.9
During septic episode	2	11.8
Before septic episode	6	35.3
After septic episode	1	5.9
Appropriate antibiotic treatment :		
Not Given	7	41.2
Given :	10	58.8
1 antibiotic	4	23.5
2 antibiotics	6	35.3
Outcome of treatment of episode :		
Successful	8	47.1
Unsuccessful	9	52.9

The sources of the positive blood cultures were central lines in nine patients (53%) and both central lines and peripheral veins in eight patients (47%). Organisms were never grown from peripheral venous cultures alone. The number of positive blood culture sets ranged between one and 13 sets per episode and the mean was 5.7 positive blood culture set per bacteremic episode .

All the isolates were found to be sensitive to cotrimoxazole and all of them were resistant to carbapenems. Approximately 82% of the isolates were sensitive to ceftazidime and 70% were sensitive to colistin. Sensitivity to other antibiotics was as follows: 53% to piperacillin/tazobactam, 35% to ciprofloxacin and approximately 23.5% to aminoglycosides (Fig. 1).

All the 17 episodes of bacteremia were treated with IV antibiotics. Appropriate antibiotic therapy was administered to 10 patients: four patients received one antibiotic to which organism was susceptible and six patients were given two antibiotics to which the organism was sensitive. All four patients who had catheter related sepsis were successfully treated by removal of infected catheters and administration of appropriate antibiotic therapy, while all the four patients who had pneumonia died, even though appropriate antibiotic therapy had been given to one of them .

Follow up of patients who survived the bacteremic episode revealed interesting data: five patients who had successful treatment for their bacteremic episodes died in the following two years from conditions including relapse of

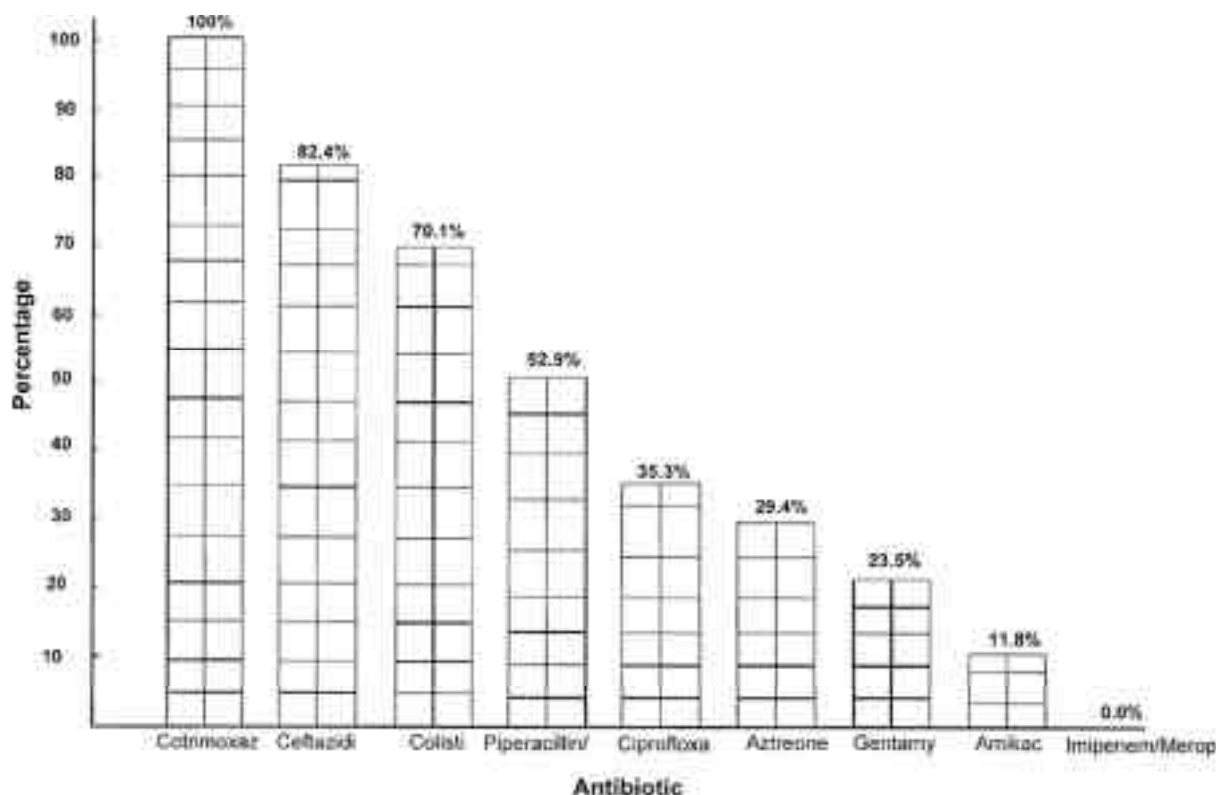


Fig. 1: Shows antibiotic sensitivity for *S. Maltophilia*

leukemia and presence of other bacterial or fungal infections. A relationship was observed between the episodes of *S. maltophilia* bacteremia and relapse of the malignant hematological disorders. Six patients (35.3%) suffered relapses of their malignant hematological disorders within the last two months prior to the bacteremic episode. Out of the eight patients who survived the bacteremic episode, six patients (35.3%) had relapses of their hematological malignancy within the next two years. Also another relationship was noted between surgical procedures and the episodes of *S. maltophilia* bacteremia: nine of the patients studied (52.9%) required surgical interventions, six of them (35.3%) needed surgery prior to bacteremic episode, two patients (11.8%) required surgical intervention during the bacteremic episode and only one patient (5.9%) had surgery after treatment of the septic episode .

DISCUSSION

S. maltophilia is a free living, motile, oxidase negative, glucose non-fermenting and strictly aerobic Gram-negative bacillus^[2,4,6]. It is widespread in environment and has been isolated from water, soil, sewage, fish, raw milk and feces of humans and rabbits^[2,4,6]. The organism can cause colonization and contamination of various items of hospital equipment and even hands of hospital staff^[1,2,5]. It

causes a wide variety of infections particularly in debilitated hosts^[1-8,10]. The vast majority of infections are nosocomial^[11-3,7-10,13]. The following risk factors predispose to infection with *S. maltophilia*: underlying disease especially hematological and non-hematological malignancy, immunosuppressive therapy including corticosteroids and cytotoxic chemotherapy, prolonged neutropenia and bone marrow aplasia, admission to intensive care units and artificial ventilation, the use of broad spectrum antibiotics particularly carbapenems and air travel^[11-12,13-24]. In our study, all episodes of infection with *S. maltophilia* were nosocomial. The main predisposing factors for infection were: hematological malignancy (mostly acute leukemia), presence of neutropenia, central venous catheters and other infections especially bacterial infections, administration of immunosuppressive therapy, broad spectrum antibiotics including carbapenems, ICU admission, mechanical ventilation and recent travel by air. It was observed that 35.3% of patients had surgical intervention and an equivalent proportion had relapse of their malignant hematological disorders before the development of the bacteremic episode of *S. maltophilia*. These previously undescribed observations can be explained as follows: both, surgical procedures and relapse of hematological malignancy are associated with prolonged hospitalization and further reduction of immunity;

thus development of more serious infections and drug resistance are the likely consequences.

Clinical manifestations of infections with *S. maltophilia* depend on the sites involved and they include primary bacteremia, endocarditis, meningitis, pneumonia and upper respiratory tract infections, primary and metastatic cellulitis, keratitis and conjunctivitis, wound infections, gut and urinary tract infections^[1-6,9,11,13-19,22,25]. High mortality rates are encountered in immunocompromised hosts, ICU residents and patients having lung involvement or bacteremia in addition to patients exposed to carbapenems^[2,4,5,10,12-14,26]. In our group of patients, the primary sites of infection were as follows: central venous catheter related sepsis (four episodes: 23.5%), pneumonia (four episodes: 23.5%), pharyngitis (two episodes: 11.8%), skin (one episode: 5.9%) and abdominal sepsis (one episode: 5.9%). The primary focus of infection was unknown in five episodes (29.4%). Two of the patients with lung involvement had pleural effusions. The patient with skin involvement developed ecthyma gangrenosum which unfortunately progressed into necrotizing cellulitis. The ultimate outcome of the bacteremic episode depends to a large extent on the primary site of infection. As demonstrated in other studies. All four patients with catheter related sepsis survived after removal of the infected catheters and giving the appropriate antibiotics, while all patients with lung involvement died. On the other hand, giving appropriate antibiotic alone might not save a patient, if his or her condition is far advanced. For example: two of our patients with bacteremia died despite receiving two antibiotics to which the organism was susceptible (cotrimoxazole and piperacillin / tazobactam). One of these patients had severe pneumonia and the other one had complicated ecthyma gangrenosum.

Most studies indicate that the organism is usually resistant to carbapenems, aminoglycosides, quinolones, aztreonam and most of the cephalosporins and antipseudomonal penicillins^[1-7,13-17,26,27]. It has been found to be susceptible to: trimethoprim sulphamethoxazole, ticarcillin - clavulanate, salbactam-cefoperazone, minocycline, doxycycline, chloramphenicol, moxalactam, lactamoxef and cerumonam^[1-6,8,10,13-15,18,19,22-25,27,30]. Successful management of infections depends upon: administration of antibiotics to which the organism is sensitive, removal of infected catheter or foreign material, recovery of bone marrow function and taking enough preventive and isolation measures^[1,3,4,6,7,10,22,27]. In our study, *S. maltophilia* was found to be susceptible to: cotrimoxazole, which is regarded as the agent of choice for treatment of *S. maltophilia* infections. Also in full agreement with other studies, the lowest sensitivity rates were encountered with carbapenems

and aminoglycosides. In contrast with other studies, the organism showed more than 50% sensitivity rates to: ceftazidime, colistin and piperacillin/tazobactam. However, the rate of sensitivity to ciprofloxacin was unexpectedly low (35.3%) and therefore its use as empirical therapy should be considered with care. Treatment with imipenem or meropenem has been found to increase the incidence of infection with *S. maltophilia* considerably, sometimes upto 10 to 15 fold^[5,9,12,15]. Fifteen of our patients (88.2%) were receiving imipenem or meropenem at the time of *S. maltophilia* bacteremia or within two weeks before the onset of sepsis.

CONCLUSION

Stenotrophomonas maltophilia is an important nosocomial pathogen. It causes significant morbidity and mortality in immunocompromised individuals. Patients with acute leukemia having chemotherapy-induced neutropenia, indwelling intravascular catheters and those receiving broad spectrum antibiotics are particularly affected. Successful management depends upon: having high index of suspicion, removal of infected intravascular catheters and early administration of appropriate antibiotics, preferably in combinations, including cotrimoxazole and one of the following: ceftazidime, colistin or piperacillin / tazobactam.

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REFERENCES

1. Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev 1998; 11:57-80.
2. Victor MA, Arpi M, Bruun B, Jonsson V, Hansen MM. *Xanthomonas maltophilia* bacteremia in immunocompromised hematological patients. Scan J Infect Dis 1994; 26:163-170.
3. Friedman ND, Korman TM, Fairley CK, Franklin JC, Spelman DW. Bacteremia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. J Infect 2002; 45:47-53.
4. Wagener Muder RR, Harris AP, Muller S, Edmond M, Chow JW, Papadakis K, MW, Bodey GP, Steckelberg JM. Bacteremia due to *Stenotrophomonas (Xanthomonas) maltophilia*: A prospective multicenter study of 91 episodes. Clin Infect Dis 1996; 22:508-512.
5. Spencer RC. The emergence of epidemic, multiple - antibiotic - resistant *Stenotrophomonas (Xanthomonas) maltophilia* and *Burkholderia (Pseudomonas) cepacia*. J Hosp Infect 1995; 30:453-464.

6. Sefcick A, Tait RC, Wood B. *Stenotrophomonas maltophilia*: an increasing problem in patients with acute leukemia. *Leuk Lymphoma* 1999; 35:207-211.
7. Marshall WF, Keating MR, Anhalt JP, Steckelberg JM. *Xanthomonas maltophilia*: an emerging nosocomial pathogen. *Mayo Clin Proc* 1989; 64:1097-1104.
8. Penzak SR, Abate BJ. *Stenotrophomonas (Xanthomonas) maltophilia*: a multidrug resistant nosocomial pathogen. *Pharmacotherapy* 1997; 17:293-301.
9. Krcmery V, Pichna P, Oravcova E, Lacka J, KuKuchova K, Studena M, Gransova S, Stopkova K, Krupova I. *Stenotrophomonas maltophilia* bacteremia in cancer patients, report of 31 cases. *J Hosp Infect* 1996; 34:75-77.
10. Jang TN, Wang FD, Wang LS, Liu CY, Liu IM. *Xanthomonas maltophilia* bacteremia: an analysis of 32 cases. *J Formosan Med Assoc* 1992; 91:1170-1176.
11. Khardori N, Elting L, Wong E, Schable B, Bodey GP. Nosocomial infections due to *Xanthomonas maltophilia (Pseudomonas maltophilia)* in patients with cancer. *Rev Infect Dis* 1990; 12:997-1003.
12. Elting LS, Khardori N, Bodey GP, Fainstein V. Nosocomial infection caused by *Xanthomonas maltophilia*: a case - control study of predisposing factors. *Infect Control Hosp Epidemiol* 1990; 11:134-138.
13. Maningo E, Watanakunakorn C. *Xanthomonas maltophilia* and *Pseudomonas cepacia* in lower respiratory tracts of patients in critical care units. *J Infect* 1995; 31:89-92.
14. Fujita J, Yamadori I, Xu G, Hojo S, Negayama K, Miyawaki H, Yamaji Y, Takahara J. Clinical features of *Stenotrophomonas maltophilia* pneumonia in immunocompromised patients. *Respir Med* 1996; 90:35-38.
15. Sanyal SC, Mokaddas EM. The increase in carbapenem use and emergence of *Stenotrophomonas maltophilia* as an important nosocomial pathogen. *J chemotherapy* 1999; 11:28-23.
16. Arp M, Victor MA, Moller JK, Jonsson V, Hansen MM, Peterslund NA, Bruun B. Changing etiology of bacteremia in patients with hematological malignancies in Denmark. *Scand J Infect Dis* 1994; 26:157-162.
17. Moser C, Jonsson V, Thomsen K, Albrechtsen J, Hansen MM. Subcutaneous lesions and bacteremia due to *Stenotrophomonas maltophilia* in three leukaemic patients with neutropenia. *British J Dermatol* 1997; 136:949-952.
18. Gopalakrishnan R, Hawley HB, Czachor JS, Market RJ, Bernstein JM. *Stenotrophomonas maltophilia* infection and colonization in the intensive care units of two community hospitals. *J Crit Care* 1999; 28:134-141.
19. Papadakis KA, Vartivarian SE, Vassilaki ME, Anaissie EJ. *Stenotrophomonas maltophilia* meningitis: report of two cases and review of the literature. *J Neurosurg* 1997; 87:106-108.
20. Elsner HA, Duhrsen U, Hollwitz B, Kaulfers PM, Hossfeld DK. Fatal pulmonary haemorrhage in patients with acute leukemia and fulminant pneumonia caused by *Stenotrophomonas maltophilia*. *Ann Haematol* 1997; 74:155-161.
21. Kato N, Marioka T. Purpura fulminans secondary to *Xanthomonas maltophilia* sepsis in an adult with aplastic anaemia. *J Dermatol* 1991; 18:225-229.
22. Vartivarian SE, Papadakis KA, Palacios JA, Manning JT, Anaissie EJ. Mucocutaneous and soft tissue infections caused by *Xanthomonas maltophilia*: a new spectrum. *Arch Intern Med* 1994; 121:969-973.
23. Van Couwenberghe CJ, Farver TB, Cohen SH. Risk factors associated with isolation of *Stenotrophomonas (Xanthomonas) maltophilia* in clinical specimens. *Infect Control Hosp Epidemiol* 1997; 18:316-321.
24. Winston DJ, Ho WG, Bruckner DA, Champlin RE. Beta-lactam antibiotic therapy in febrile granulocytopenic patients. A randomized trial comparing cefoperazone plus piperacillin, ceftazidime plus piperacillin and imipenem alone. *Ann Intern Med* 1991; 115:849-859.
25. Gutierrez Rodero F, Del mar Masia M, Cortes J, Ortiz de la Tabla V, Mainar V, Vilar A. Endocarditis caused by *Stenotrophomonas maltophilia*: case report and review. *Clin Infect Dis* 1996; 23:1261-1265.
26. Aoun M, Van der Auwera P, Devleeshouwer C, Daneau D, Seraj N, Meunier F, Gerain J. Bacteremia caused by *non-aeruginosa Pseudomonas* species in a cancer centre. *J Hosp Infect* 1992; 22:307-316.
27. Vartivarian S, Anaissie E, Bodey G, Sprigg H, Rolston K. A changing pattern of susceptibility of *Xanthomonas maltophilia* to antimicrobial agents: implications for therapy. *Antimicrob Agents Chemother* 1994; 38:624-627.
28. Sanders CC, Sanders WE. Beta-lactam resistance in gram-negative bacteria: global trends and clinical impact. *Clin Infect Dis* 1992; 15:824-839.
29. King A, Boothman C, Philips I. Comparative in vitro activity of meropenem on clinical isolates from the United Kingdom. *J Antimicrob Chemother* 1989; 24:31-45.
30. Garcia - Rodriguez JA, Garcia Sanchez JE, Garcia Garcia MI, Garcia Sanchez M, Munoz Bellido JL. Antibiotic susceptibility profile of *Xanthomonas maltophilia*. In vitro activity of beta-lactam/ beta - lactamase inhibitor combination. *Diagn Microbiol Infect Dis* 1991; 14:239-243.