Causative Pathogens of Fever in Neutropenic Patients at King Chulalongkorn Memorial Hospital

Pitiya Roongpoovapatr MD*,
Chusana Suankratay MD, PhD*

** Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: *Infections cause substantial morbidity and morbidity in neutropenic patients. In King Chulalongkorn Memorial Hospital, Gram-negative bacteria remained the most common causative pathogen of febrile neutropenia in all three studies conducted before 2002. However, Gram-positive bacteria have become more commonly isolated etiologic pathogens, and the incidence of fungal infection has been increasing since 2005.*

Objective: *Determine the infectious etiology of fever in neutropenic patients at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Material and Method: *A retrospective chart review of all medical records of febrile neutropenic patients hospitalized at Department of Medicine between January 1 and December 31, 2006 in accompanying with microbiologic, radiologic, and serologic results was analyzed.*

Results: *There were 125 patients (61 males and 64 females) and 172 episodes of febrile neutropenia with a mean age of 46.5+18.5 years (range: 15-81 years). The three most common primary diseases associated with neutropenia were acute myeloid leukemia, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia (36.6%, 33.1%, and 10.5%). Infections could be documented microbiologically and clinically in 84 episodes (48.8%), and primary bacteremia or fungemia was the most common cause of infection (40.5%). Gram-negative bacteria were the most frequently isolated pathogens (63.9%), followed by Gram-positive bacteria (29.9%) and fungi (6.2%). Escherichia coli (46.8%) and coagulase-negative Staphylococcus (27.6%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively. Among 53 episodes (30.8%) of bloodstream infections, Gram-negative bacteria were the most commonly isolated pathogens (38 episodes, 71.7%), followed by Gram-positive bacteria (19 episodes, 35.8%) and Candida tropicalis (1 episode, 1.9%). Surprisingly, invasive mold infections were noted in eight episodes (5, 1, and 2 episodes of proven, probable, and possible infections, respectively). The overall mortality was 19.2%.*

Conclusions: *Although Gram-negative bacteria are the most common etiology of fever in neutropenic patients, the occurrence of infections caused by coagulase-negative Staphylococcus and molds has been increasing in comparison with the observations from previous studies in King Chulalongkorn Memorial Hospital. To authors knowledge, the present study is the first in Thailand to determine the occurrence of invasive fungal infections using the standard criteria recommended by EORTC/MSG.*

Keywords*: Aspergillosis, Bacterial infections and mycoses, Fever, Gram-negative bacteria, Gram-positive bacteria, Mucormycosis, Neutropenia*

J Med Assoc Thai 2010; 93 (7): 776-83
Full text. e-Journal: *http://www.mat.or.th/journal*

Infections cause substantial morbidity and morbidity in neutropenic patients[1-7]. In King Chulalongkorn Memorial Hospital (KCMH), Gram-negative bacteria remained the most common causative pathogen of febrile neutropenia in all four studies conducted before 2002[8-11]. A previous study conducted in 5 universities in Thailand including KCMH revealed Gram-negative bacteria were the most frequently isolated pathogens (90.9%) in patients with febrile neutropenia[8]. Another study at KCMH between 1994 and 1995 also showed Gram-negative bacteria were the most common causative pathogens of febrile neutropenia (71.8%), followed by Gram-positive bacteria (22.5%) and fungi (1.9%)[9]. Another study in pediatric patients with febrile neutropenia in KCMH showed Gram-negative bacteria were still the most

Correspondence to: Suankratay C, Division of Infectious Diseases, Department of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand. Phone: 0-2256-4578, Fax: 0-2256-4578. E-mail: chusana.s@chula.ac.th

commonly isolated pathogens (71%), followed by Gram-positive bacteria (19%) and *Candida* (10%)[10]. A recent study in KCMH between 2001 and 2002 in adult patients with non-hematologic malignancy also showed Gram-negative bacteremia were the most common causative pathogens of fever in neutropenia (78.1%), followed by Gram-positive bacteremia (21.9%)[11]. In addition, Gram-negative bacteria were the most frequently isolated pathogens of febrile neutropenia in other hospitals in Thailand[12-14]. In contrast to the observations from some institutes in the United States and Europe, Gram-positive bacteria have become more frequently isolated among patients with febrile neutropenia, whereas the occurrence of infections caused by Gram-negative bacteria has been decreasing since 2000[5,7,15-21]. In KCMH, the authors observed that Gram-positive bacteria and fungi have become more commonly isolated as etiologic pathogens of fever in patients with neutropenia since 2005[22]. In addition, there has been no study in Thailand to determine the occurrence of invasive fungal infections in febrile neutropenia using the standard criteria recently recommended by European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and infectious Diseases Mycoses Study Group (EORTC/MSG)[23]. The present study was thus aimed to determine the infectious etiology of fever, both bacterial and fungal infections, in patients with neutropenia at KCMH in 2006.

Material and Method

The medical records of all patients who were diagnosed febrile neutropenia and hospitalized at Department of Medicine of KCMH, Bangkok, Thailand from January 1 to December 31, 2006 were retrospectively reviewed. Patients were included in the study if they had fever of $\geq$ 38.0 degree C for 1 hour or $\geq$ 38.3 degree C once, in association with an absolute neutrophil count of less than 500 celss/mL or < 1,000 cells/mL with a predicted decrease to < 500 cells/mL[16]. The institutional review board approved the protocol.

A diagnosis of invasive fungal infection was classified as a proven, probable and possible infection according to the revised definitions of invasive fungal disease from the EORTC/MSG[23].

Statistical analysis

The statistical analyses were performed using the SPSS software version 13.0. The continuous and categorical variables were compared using the independent sample t-test and Chi-square or Fisher's exact test, respectively.

Results

Demography

One hundred twenty five patients (64 males and 61 females) with 172 episodes of febrile neutropenia were hospitalized at KCMH during the study period. The mean age was 46.5 $\pm$ 18.5 years (range: 15-81 years).

The primary diseases associated with neutropenia included hematologic malignancies (88.9%), solid tumors (10.5%) and propylthiouracil-induced agranulocytosis (0.6%) (Table 1). The three most common primary diseases were acute myeloid leukemia (36.6%), non-Hodgkin's lymphoma (33.1%), and acute lymphoblastic leukemia (10.5%).

Clinical manifestations and microbiology

Community- and hospital-onset febrile neutropenia were noted in 65 (37.8%) and 107 (62.2%) episodes, respectively. Infections could be documented microbiologically and clinically in 84 episodes (48.8%) and primary bacteremia or fungemia was the most common cause of infection (34 episodes, 40.5%). The most common site of infection was the urinary tract (23 episodes, 27.4%), followed by the respiratory tract (17 episodes, 20.2%) with pneumonia (13 episodes, 15.5%) and sinusitis (4 episodes, 4.8%), the central venous catheter-related bloodstream (8 episodes, 9.5%), and the skin and soft-tissue (5 episodes, 6%) (Table 2). Gram-negative bacteria were the most frequently isolated pathogens (63.9%), followed by Gram-positive bacteria (29.9%) and fungi (6.2%). *Escherichia coli* (46.8%) and coagulase-negative *Staphylococcus* (27.6%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively (Table 3).

Among eight episodes (9 isolates of bacteria) of catheter-related bloodstream infection, there were coagulase-negative *Staphylococcus* (3 episodes), methicillin-*resistant Staphylococcus aureus* (MRSA) plus *Klebsiella pneumoniae* (1 episode), *K. pneumoniae* (1 episode), *Enterococcus faecalis* (1 episode), *Acinetobacter lwoffii* (1 episode) and *Pseudomonas aeruginosa* (1 episode).

Blood cultures were positive in 53 episodes (30.8%) and Gram-negative bacteria were the most commonly isolated pathogens (38 episodes, 65.5%), followed by Gram-positive bacteria (19 episodes, 32.7%) (both Gram-negative and Gram-positive bacteria were isolated from 5 of 53 episodes) and *Candida*

Table 1. Primary diseases leading to neutropenia and related mortality

Primary disease	Number of episode (%)	Mortality (%)
Hematologic malignancies	153 (88.9)	28 (18.3)
Acute myeloid leukemia	63 (36.6)	5 (7.9)
Non-Hodgkin's lymphoma	57 (33.1)	11 (19.3)
Acute lymphoblastic leukemia	18 (10.5)	5 (27.8)
Multiple myeloma	7 (4.1)	4 (57.1)
Chronic myeloid leukemia	4 (2.3)	1 (25)
Hodgkin's lymphoma	2 (1.2)	1 (50)
Myelodysplastic syndrome	2 (1.2)	1 (50)
Solid tumor	18 (10.5)	5 (27.7)
Breast cancer	10 (5.8)	3 (30)
Lung cancer	2 (1.2)	0 (0)
Ovarian cancer	2 (1.2)	2 (100)
Nasopharyngeal cancer	1 (0.6)	0 (0)
Rhabdomyosarcoma	1 (0.6)	0 (0)
Liposarcoma	1 (0.6)	0 (0)
Primitive neuroectodermal tumor	1 (0.6)	0 (0)
Agranulocytosis	1 (0.6)	0 (0)
Total	172 (100)	33 (19.2)

Table 2. Microbiologically documented sites of infections*

Sites	Number
Blood	53
Urine	23
Sputum	7
Sinus	4
Stool	3
Total	90

* 125 patients with172 episodes of febrile neutropenia had 84 episodes and 90 sites of microbiologically documented infection

tropicalis (1 episode, 1.8%). *E. coli* (47.4%) and coagulase-negative *Staphylococcus* (42.1%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively.

Urine cultures were performed in 158 episodes and grew organisms in 23 specimens (14.6%). *E. coli* was the most commonly isolated pathogen (9 episodes, 39%), followed by *Enterococcus* spp. (4 episodes, 17.4%), *Acinetobacter baumannii* (2 episodes, 8.7%), *K. pneumoniae* (2 episodes, 8.7%), *Pseudomonas* spp. (2 episodes, 8.7%), *Proteus mirabilis* (1 episode, 4.3%), *A. lwoffi* (1 episode, 4.3%), *S. aureus* (1 episode, 4.3%), *Streptococcus agalactiae* (1 episode, 4.3%) and *Corynebacterium* spp. (1 episode, 4.3%) (Tables 2, 3).

Of eight episodes of pneumonia, there were seven and one episodes of bacterial and fungal pneumonia, respectively. Of clinically documented pneumonia, the sputum culture grew organism in seven specimens. Of these seven microbiologically documented bacterial pneumonia, there were two, two, two, and one isolates of *S. aureus*, *E. coli*, *A. baumannii* and *P. aeruginosa*. The fungal pneumonia was a *Aspergillus fumigatus* isolated from the pleural fluid and subcutaneous nodule (Tables 2, 3).

Invasive mold infections were noted in eight episodes. There were five episodes of proven infection, one episode of probable infection and two episodes of possible infection. All patients had an associated hematologic malignancy. Of five proven infections, there were three, one, and one isolates of hyaline filamentous molds, *Aspergillus* spp. and *Mucor* spp., respectively. Invasive sinusitis and pneumonia were noted in four patients each (Tables 3, 4). One patient with invasive pulmonary aspergillosis had pleural effusion and metastatic subcutaneous nodule. All except one patient survived with the treatment of amphotericin B and remission of underlying hematologic malignancy.

The overall mortality rate was 19.2% (33 episodes) with the rates of 18.3% and 27.7% in patients

Table 3. Causative pathogens and sites of infection

Pathogens	Primary bacteremia/ fungemia[1]	CRBSI[2]	UTI[3]	Respiratory tract infection	
				Pneumonia	Sinusitis
Gram-negative bacteria	26	4	17	5	-
Escherichia coli	13	-	9	2	-
Klebsiella pneumoniae	6	2	2	-	-
Pseudomonas aeruginosa	2	1	2	1	-
Aeromonas sobria	3	-	-	-	-
Acinetobacter baumannii	-	-	2	2	-
Acinetobacter lwoffii	-	1	1	-	-
Enterobacter aerogenes	1	-	-	-	-
Proteus mirabilis	-	-	1	-	-
Citrobacter freundii	1	-	-	-	-
Gram-positive bacteria	11	5	8	2	-
Coagulase-negative *Staphylococcus*	3	3	-	-	-
Staphylococcus aureus	-	1	2	2	-
Bacillus spp.	2	-	-	-	-
Corynebacterium spp.	2	-	1	-	-
Enterococcus spp.	1	1	4	-	-
Streptococcus bovis	1	-	-	-	-
Group G *Streptococcus*	1	-	-	-	-
Streptococcus mitis	1	-	-	-	-
Streptococcus agalactiae	-	-	1	-	-
Fungus	1	-	-	1	4
Candida tropicalis	1	-	-	-	-
Aspergillus spp.	-	-	-	1	-
Mucor spp.	-	-	-	-	1
Filamentous mold	-	-	-	-	3
Total	39	9	25	8	4

[1] Of 34 specimens, 5 specimens had 2 organisms
[2] Of 8 specimens, 1 specimens had 2 organisms
[3] Of 23 specimens, 3 specimens had 2 organisms, 1 specimen had 3 organisms
CRBSI = catheter-related bloodstream infection; UTI = urinary tract infection

with hematologic malignancy and solid tumor, respectively (Table 1).

Discussion

Febrile neutropenia commonly occurs in patients with hematologic malignancy receiving chemotherapeutic agents. In KCMH, the three most common primary diseases associated with febrile neutropenia were acute myeloid leukemia, non-Hodgkin lymphoma, and acute lymphoblastic leukemia.

Infection is still the most common cause of fever in febrile neutropenic patients especially after receiving chemotherapy[1,2]. In most studies, infections have been documented in the range from 30% to 50%[1-6]. In the present study, infections could be documented microbiologically and clinically in approximately half of our patients. Primary bacteremia or fungemia was the most common cause of infection (40.5%), followed by urinary tract infection (27.4%), respiratory tract infection (20.2%), catheter-related bloodstream infection (9.5%) and skin and soft-tissue infection (6%). This observation was different from previous studies conducted in adult patients with febrile neutropenia in our institute[9,11]. A study conducted between 1994 and 1995 showed that pneumonia was the most common cause of infection (23.5%), followed by primary bacteremia or fungemia (17.6%) and urinary tract infection (13.7%)[9]. Another study conducted between 2001 and 2002 in febrile neutropenic patients with non-hematologic malignancy

Table 4. Demography, clinical manifestations, mycology, and treatment outcome in patients with invasive mold infection

Sex, ages (years)	Primary disease	Prophylaxis antifungal	Site of infection	Serum galactomannan	Species	Diagnosis	Outcome
M, 20	AML	No	Sinusitis	0.805	Hyaline mold	Proven	Survived
F, 32	AML	No	Sinusitis	2.80	Hyaline mold	Proven	Survived
M, 25	NHL	No	Pleural fluid, skin	1.00	*Aspergillus fumigatus*	Proven	Survived
F, 35	AML	No	Sinusitis	ND	Hyaline mold	Proven	Survived
M, 21	ALL	Fluconazole	Sinusitis	ND	*Mucor* spp.	Proven	Died
F, 35	AML	No	Lung	2.87	NA	Probable	Survived
F, 16	AML	No	Lung	ND	NA	Possible	Survived
F, 28	AML	No*	Lung	0.85	NA	Possible	Survived

* The patient had received empirical amphotericin B deoxycholate treatment for 18 days, 3 months prior to admission
M = male; F = female; AML = acute myeloid leukemia; NHL = non-Hodgkin's lymphoma; ALL = acute lymphoblastic leukemia; ND = not done; NA = not applicable

also revealed that the lower respiratory tract was the most common site of infection (12.2%), followed by the skin and soft-tissue (10.6%) and the urinary tract (8.9%)[11]. In other studies both in the United States and Europe, pneumonia in the febrile neutropenic patients is relatively low in the range of 0.5-10%[24,25]. The difference in KCMH may be due to the higher number of patients with hematologic malignancy, with the central venous catheter and receiving aggressive chemotherapy, as well as the recent utilization of automated blood culture system, which increased the recovery rate of bloodstream pathogens.

In the present study, Gram-negative bacteria were the most frequently isolated pathogens (63.9%), followed by Gram-positive bacteria (29.9%) and fungi (6.2%). *E. coli* (46.8%) and coagulase-negative *Staphylococcus* (27.6%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively. A study conducted in KCMH between 1994 and 1995 showed that Gram-negative bacteria, Gram-positive bacteria and fungi were isolated in 71.8%, 22.5% and 1.9% of patients, respectively[8]. *E. coli* (23.9%) and *S. aureus* (16.9%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively. A study at Phramongkutklao Hospital conducted between 1999 and 2001 revealed that Gram-negative bacteria were the most commonly isolated pathogens (73%)[13]. At Srinagarind Hospital, the occurrence of Gram-negative bacterial infections was 78% in febrile neutropenic patients hospitalized between 1994 and 1995[12]. A study in pediatric patients at Chiang Mai Hospital from 2002 to 2004 showed that Gram-negative bacteremia were the most commonly isolated pathogens (82.5%), followed by Gram-positive bacteria (17.5%)[14]. Another study at Khon Kaen Hospital during 2003 and 2004, Gram-negative bacteria, Gram-positive bacteria and fungi were isolated in 61.3%, 35.5% and 3.2% of patients, respectively[26]. In conclusion, the common etiologic pathogens in febrile neutropenic patients in Thailand are still Gram-negative bacteria. In the United States and Europe, the spectrum of etiologic pathogens responsible for fever in neutropenic patients varies from hospital to hospital, and has changed during the last three decades[5,7,15-21]. Gram-positive bacteria have become more frequently isolated among patients with febrile neutropenia, accounting for 50-60% in some institutes. The increase may be partly due to the aggressive chemotherapy regimens, the frequent use of central venous catheter, and the increased use of prophylactic antibacterials including fluoroquinolones. All of these strategies have been increasing utilized in KCMH during the past decade as well. However, several recent reports revealed that Gram-negative bacteria especially multidrug-resistant strains have been increasing in frequency again in some institutes[7,18-21].

In the present study, the occurrence of invasive mold infections was higher than those observations from previous studies in KCMH and in Thailand[8-14]. The increasing frequency of invasive mold infections may be partly due to the increased use of more sensitive diagnostic tests including imaging (computed tomogram and magnetic resonance imaging), serologic test (serum galactomannan) and bronchoscopy with cytological or pathological

examination, the higher number of patients with stem cell transplantation, the aggressive use of chemotherapy regimens resulting in more prolonged duration of neutropenia and severe mucositis, and the increased use of prophylactic antibacterials.

In the present study, the mortality rate was approximately 19%, in consistent with those of previous studies in KCMH[8-11] and other hospitals in Thailand[12-14], even though the occurrence of bacterial infections caused by multidrug- and pandrug-resistant strains as well as invasive mold infections has been increasing.

In conclusion, although Gram-negative bacteria are still the most common etiology of fever in neutropenic patients, the occurrence of infections caused by coagulase-negative *Staphylococcus* and molds has been increasing in comparison with the observations from previous studies in our institute. To authors knowledge, the present study is the first in Thailand to determine the occurrence of invasive fungal infections using the standard criteria recommended by EORTC/MSG.

Potential Conflicts of Interest

All authors have no conflicts of interest.

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จุลชีพที่เป็นสาเหตุของไข้ในผู้ป่วยเม็ดเลือดขาวต่ำในโรงพยาบาลจุฬาลงกรณ์

ปิติญา รุ่งภูวภัทร, ชุษณา สวนกระต่าย

***บทนำ**: การติดเชื้อก่อให้เกิดอัตราป่วยและอัตราตายที่สำคัญในผู้ป่วยเม็ดเลือดขาวต่ำ ในโรงพยาบาลจุฬาลงกรณ์ พบแบคทีเรียแกรมลบยังเป็นสาเหตุที่พบบ่อยที่สุดในภาวะไข้และเม็ดเลือดขาวต่ำจากการศึกษาที่รวบรวมก่อนปี พ.ศ. 2545 อย่างไรก็ตามแบคทีเรียแกรมบวกเริ่มมีรายงานการพบเพิ่มขึ้น และอุบัติการณ์ของการติดเชื้อราก็เพิ่มขึ้นตั้งแต่ปี พ.ศ. 2548*

***วัตถุประสงค์**: การศึกษาครั้งนี้มีวัตถุประสงค์ในการประเมินจุลชีพ ที่เป็นสาเหตุของไข้ในผู้ป่วยเม็ดเลือดขาวต่ำในโรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร ประเทศไทย*

***วัสดุและวิธีการ**: รวบรวมเวชระเบียนผู้ป่วยที่มีไข้และเม็ดเลือดขาวต่ำทั้งหมดที่รับไว้ในโรงพยาบาล ที่ภาควิชาอายุรศาสตร์ ตั้งแต่ 1 มกราคม ถึง 31 ธันวาคม พ.ศ. 2549 โดยศึกษาแบบย้อนหลัง เก็บรวบรวมข้อมูลทางจุลชีววิทยา รังสีวิทยา และน้ำเหลืองวิทยาร่วมด้วย และนำมาวิเคราะห์*

***ผลการศึกษา**: มีผู้ป่วย 125 ราย (ผู้ป่วยชาย 61 ราย ผู้ป่วยหญิง 64 ราย) ซึ่งมี ไข้และเม็ดเลือดขาวต่ำ 172 ครั้ง โดยมีอายุเฉลี่ยเท่ากับ 46.5 $\pm$ 18.5 ปี (พิสัย 15-81 ปี) โรคปฐมภูมิที่พบบ่อยที่สุด 3 โรคที่เกี่ยวข้องกับภาวะเม็ดเลือดขาวต่ำ ได้แก่ มะเร็งเม็ดเลือดขาวชนิด acute myeloid มะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's และมะเร็งเม็ดเลือดขาวชนิด acute lymphoblastic (ร้อยละ 36.6 ร้อยละ 33.1 และร้อยละ 10.5) การติดเชื้อที่ถูกวินิจฉัยทางจุลชีววิทยาและคลินิกพบ 84 ครั้ง (ร้อยละ 40.5) แบคทีเรียแกรมลบเป็นเชื้อที่เป็นสาเหตุบ่อยที่สุด (ร้อยละ 63.9) และตามมาด้วยแบคทีเรียแกรมบวก (ร้อยละ 29.9) และเชื้อรา (ร้อยละ 6.2) Escherichia coli (ร้อยละ 46.8) และ coagulase-negative Staphylococcus (ร้อยละ 27.6) เป็นสาเหตุที่พบบ่อยที่สุดในแบคทีเรียแกรมลบ และแกรมบวกตามลำดับ การติดเชื้อในกระแสเลือด 53 ครั้ง (ร้อยละ 30.8) พบเกิดจากแบคทีเรียแกรมลบบ่อยที่สุด (38 ครั้ง ร้อยละ 71.7) ตามมาด้วยแบคทีเรียแกรมบวก (19 ครั้ง ร้อยละ 35.8) และ Candida tropicalis (1 ครั้ง ร้อยละ 1.9) เป็นที่น่าสนใจการติดเชื้อราแบบลุกลามมีจำนวน 8 ครั้ง (5, 1 และ 2 ครั้ง สำหรับการติดเชื้อแบบพิสูจน์ได้ น่าจะเป็น และมีโอกาสตามลำดับ) อัตราตายทั้งหมดเท่ากับร้อยละ 19.2*

***สรุป**: ถึงแม้แบคทีเรียแกรมลบยังคงเป็นสาเหตุที่พบบ่อยที่สุดของไข้ในผู้ป่วยเม็ดเลือดขาวต่ำ แต่อุบัติการณ์ของการติดเชื้อที่เกิดจาก coagulase-negative Staphylococcus และเชื้อรา มีอัตราเพิ่มสูงขึ้นโดยเทียบกับการศึกษาในอดีตจากความรู้ทั้งหมดในสถาบันของผู้นิพนธ์ การศึกษาครั้งนี้ถือเป็นการศึกษาแรกของประเทศไทยที่จะประเมินอุบัติการณ์ของการติดเชื้อราแบบลุกลาม โดยใช้เกณฑ์ที่มาตรฐานที่แนะนำโดย European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group*