Original
ISSN 2521-8492

Overview on common fungal infections, recovered in Baghdad teaching hospitals in five years

Wifaq M.Ali Al-Wattar*

Unit of Clinical and Communicable Diseases, College of medicine, University of Baghdad, Baghdad, Iraq.
*Correspondence to: Wifaq M.Ali Al-Wattar (E-mail: wifaq.m.alwattar@comed.uobaghdad.edu.iq)
(Submitted: 21 December 2019 – Revised version received: 04 February 2020 – Accepted: 27 February 2020 – Published online: 26 June 2020)

Abstract

Objective To evaluate the burden of invasive fungal infections, recovered in a group of patients who were non-responsive to antibiotic therapy and have been referred from some Iraqi hospitals in 5 years interval in a clinical and microbiological scope.

Methods Samples were collected during from May 25, 2012 to November 5, 2017 which enrolled 1444 Iraqi adult patients who were referred by hematology-oncology unit, medical wards, bone marrow transplant unit, and respiratory care unit with some other cases received from other hospitals in the capital Baghdad.

Samples from any infected sites were sent to the central medical mycology lab to identify the causative fungi using wet mount, direct examination, culture and sensitivity tests, biochemical, and some serological examinations as galactomannan testing for invasive aspergillosis and PCR test to detect some pathological properties of a group of Aspergillus species.

Results Although 387 (26.6%) samples revealed no fungal isolates most of them were of blood culture. The commonest fungus noticed in all samples was *Cryptococcus neoformans* in the first place **646 samples** (38.63%), the next was *Candida albicans* and non-albicans in **594 samples** (35.52%). *Aspergillus* species in **252 samples** (15.07%), *Penicillium* **27 samples** (1.61%), *Gieotrichum* candidum**15 samples** (0.89), *Zygomycetes* and *Rhizopus* 20 (1.18%), *Trichosporon* and *Rhodotorula glutinis* yeasts **14** (0.83%), *Sporothrixes schenkii* **5** (0.29%), **2** (0.11%) cases of systemic mycosis, 1 *Histoplasma capsulatum*, and the other is *Coccidiomycosis immitus*. *Blastomycetes dermatitidis* was seen in **5 samples** (0.29%), those cases with a history of travel outside Iraq like India, USA, and Lebanon. Some other samples showed a higher bacterial infection, cocci and bacilli mostly of resistant strains causing persistent fever despite of good antibiotic cover.

Conclusions The incidence of fungal infection is greatly increased in Iraq in relation to global and local risk factors with tendency for multiple fungal isolates in one patient representing a major health problem in a wide variety of disease conditions ranging from hematology oncology to uncontrolled diabetic cases with high case of fatality among hematological malignancies with neutropenia.

Keywords Invasive fungal infection, Baghdad teaching hospital, Acute myeloid leukemia.

Introduction

Invasive fungal infections (IFIs) represent a major problem in patients with hematologic malignancies solid tumors, hematopoietic stem cell transplant (HSCT) and kidney recipients. Intensive chemotherapeutic regimens and new antineoplastic drugs have resulted in an increased IFI with a higher morbidity and mortality.[1]

The patients with solid tumors were at higher risk of invasive candidiasis than hemtogenic tumor.[2]

The common risk factors for invasive candidiasis were the candidal colonization of the GIT as a result of multiple antibiotics use, loss of its mucosal barrier, IV nutrition, surgery, radiation therapy, and/or chemotherapy and systemic immunosuppressive status resulting from the latter two treatment.[3]

Blood culture is the current gold-standard for diagnosis of candidemia, although it is slow and needs for antifungal drugs sensitivity. Other tests like API20 are accurate, and others based on non-culture-based methods, such as mannan antigen and antimannan antibodies, may be useful for diagnosing invasive candidiasis.[4] Neutropenia represent a heterogeneous population with varying rates of infection-related morbidity and mortality. Invasive candidias is seen more frequently during neutropenia[5] in addition to that, those patients were more susceptible to invasive moldy infections like Aspergillosis.[6]

Patients and methods

1440 Iraqi patients aged 18–63 years were enrolled in this descriptive cross-sectional study who attended wards of the hematology oncology unit at Baghdad Teaching Hospital and the bone marrow transplant unit, with neutropenic fever. Some other patients were from other hospitals and respiratory outpatient units between May 2012 and November2017 from both sexes.

Clinical evaluation of patient

Patients were evaluated, thorough history and examination. A set of investigations (like complete blood count, full chemistry and radiological evaluations) were done for each patient. Finally their blood, sputum, BAL and different swab. Inclusion criteria for hematology oncology patients was absolute neutrophil count < 0.5 x 10^9/L plus either:

1. Body temperature of 38.8 C for a single episode or
2. Body temperature of >38.0 twice over 1 hr achieving definitions of neutropenic fever.
3. Symptoms and signs of new, resistant or progressive respiratory tract infection, e.g. pleuritic pain, pleural rub.
4. Periorbital swelling.
5. Maxillary swelling and tenderness.
6. Papular or nodular skin lesions
7. Antibiotic resistant fever without localizing sign extended beyond 5 days.
8. Patients with unresolved chest, throat, and ear infections.

We did exclude other causes of fever such as blood and blood product transfusion, drug fever. Medical information: case diagnosis and duration of disease, type of chemotherapy received, steroid usage, history of chronic disease like diabetes mellitus were included for each patient.

Specimen to be tested for fungal infection were: sputum, blood, swab from suspected infected site, BAL, CSF, plural fluid, biopsies kept in normal saline and urine.

Microbiological tests

a. Direct microscopical examination with culture and sensitivity for fungal and concomitant bacterial infections.
b. Blood culture for fungi.

Initially, direct microscopical examination done for each sample as wet mounts and stained cotton blue, Gram stain to take a general impression about the causative pathogens, capsule stain (India ink) and Giemsa stain for detection of *Pneumocystis jiroveci*. Sputum was immediately cultured on Sabouraud dextrose agar (SAB), BHI, blood and MaConkey agar media, labeled with same code number of that sputum, incubated for 14 days under 35–37°C for yeasts, and 18–20°C for molds, in humid environment to be examined every day. Also on examination it showed hyphae from positive cultures resulting from normally sterile and clinically or radiologically abnormal sites consistent with infection, with exclusion of urine and mucus membrane swabs exception of serious UTI and mouth ulcers. Identification of fungal genus and species was done by biochemical testing and API 20 for yeasts afterwards the antifungal sensitivity testing was done using dick supplied by **Oxoid** labs for Amphotracine B 20 µ, Fluconazole 20 µ, Econazole 20 µ, Itraconazole 20 µ, Miconazole 20 µ, all measured in micrograms the zone of inhibition was considered as detectable when it measures 5mm and more.

Microbiological results for all patients were provided by specialists in medical microbiology and in culture positive aspergillosis cases, galactomannan antigens testing by ELISA for conformation and some virulence factors were tested by PCR as well.

Results

The age range for all 1444 patients in this study was 18–63 years. Mean age was 32.51±15.89 years, age groups were as follows: 28.9% patients were in the 18–20 year groups, 40% patients in the 21–40 years, 31.1% patients in the 41–63 years. Of the 1000 patients referred from hematology oncology department, 57.8% were females and 42.2% were males, 60% patients were from Baghdad (p value < 0.00001), 29% patients were from south of Iraq, and 11% patients were from northwest of Iraq.

In hematology patients, 40% of them had acute myeloid leukemia, 17.8% with lymphoblastic leukemia, 17.8% with relapsed Hodgkin lymphoma also, and 15.6% patients had relapsed non-Hodgkin lymphoma, while only 4.4% patients had multiple myeloma, and another 4.4% patients had CLL as shown in Table 2.

Out of 1444 fungal samples, 383 (26.52%) showed no evidence of fungal or bacterial growth, 571 showed combined bacterial growth, 228 cases showed combined fungal growth in the same sample.

In all blood culture samples, no Aspergillus growth was isolated. Regarding the common yeasts and molds recovered in all samples, the commonest were *Cryptococcus neoforman* 646(38.63%), *Candida albicans* and *Saccharomycetes* 594 (35.52%), *Aspergilus* 252 (15.07%), *Gieotrichum candidum* 15(0.89), *Rhizopus* 8 (0.47%), *Zygomycetes* 12 (0.71%),

Table 1. **Social – demographic characteristics.**

Factor	Frequency
< 20years	28.9%
21 – 40 years	40%
> 40 years	31.1%
Mean ± SD	32.51 ± 15.89
Gender	
Male	42.2%
Female	57.8%
Residence of patients	
Baghdad	60%
South of Iraq	29%
Northwest of Iraq	11%

Table 2. **Types of hematological malignancies.**

Type of blood disease		Frequency
Acute Myeliod Leukemia	**AML**	40
Hodgkin Lymphoma	**HL**	17.8
Acute Lymphoblastic Leukemia	**ALL**	17.8
Non Hodgkin Lymphoma	**NHL**	15.6
Multiple Myeloma	**MM**	4.4
Chronic myeloid leukemia	**CML**	4.4

Trichosporon and *Rhodetella* spp yeasts14 (0.83%), *Spothrixes schenkii* 5 (0.29%), *Penicillium* spp. 27 (1.61%), 2 cases of dimorphic mycosis like *Histoplasma capsulatum, Coccidiomycosis immitus* (0.11%) and 5 cases (0.29%) of *Blastomycetes dermatitidis* with a history of travel outside Iraq.

The most common Aspergillus species were *fumigatus, flavus, niger,* and *terrus*. Subsequently, some other species of higher bacteria were isolated. 13 (0.77%) *Nocardia asteriodis* recovered in sputum samples cultured on blood agar media cultured aerobically.

Bacterial infections were also diagnosed in 571 samples, *Entrobactraceae* family was the commonest as the Gram negative bacilli as was noticed in 327 samples (57.26%) as *Klebsiella pneumonia, E. coli, Acenitobacter bomanii, Pseudomonas aeruginosa and Proteus mirabilis* subsequently.

Other samples showed Gram positive cocci infections in 244 samples (42.73%) as *Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus viridans*, and *Staphylococcus tropicalis*.

We sometimes recovered two species in sputum samples rather than a single one in a specimen. Among hematological neoplasm patients, 41% of them had IFIs with AML at *p* value <0.022 (statistically significant when compared to other malignancies).

Fungal pneumonia was the commonest mode of presentation among those patients at 62.9% in (*p* value <0.255). The association between the duration and the severity of neutropenia with fungal infections showed no statistically significant

Table 3. **Distribution of fungal and bacterial isolates in all 1444 samples during five years interval at the medical city mycology lab.**

Year	Total Sample	No growth	Bacterial growth		Candida spp.	Cryptococcus spp.	Aspergillus spp.	Penicillium App.	Rhzopus spp.	Trichosporone spp.	Zygomycetes spp.	Sporotrichosis	Geotrichum spp	Systemic mycosis	PCJ	Nocardia Spp.	Blastomycosis
			G-ve	G+ve													
2012	64	5	-	-	35	10	22	-	4	-	-	1	1	-	-	-	-
2013	186	34	-	-	132	119	48	8		-	9	-	6	1	-	-	-
2014	227	40	-	-	82	120	30	10		3	3	4	5		3	-	1
2015	287	48	56	45	76	118	54	2		-	-	-	2	2	8	8	3
2016	391	104	141	121	163	166	52	2		3	-	-	-		30	2	-
2017	289	152	130	78	106	113	46	5	4	8	-	-	1		38	3	1
Total	**1444**	**383**	**327**	**244**	**594**	**646**	**252**	**27**	**8**	**14**	**12**	**5**	**15**	**2**	**79**	**13**	**5**
Percentage	**100%**	**26.52%**	**57.26%**	**42.73%**	**35.52**	**38.63**	**15.07**	**1.61**	**0.47**	**0.83**	**0.71**	**0.29**	**0.89**	**0.11**	**4.72**	**0.77**	**0.29**

difference when compared to non-neutropenic cases at (p value< 0.585), and there was no statistical significant difference between old fungal infection and new invasive fungal disease.

Among 1000 hematological neoplasm cases suspected to have IFIs, 41% were AML cases with p value less 0.022 (statistically significant when compared to other malignancies). 29%patients had ALL, 23.8% patients had lymphoma and only 5.8% were CLL.

Fungal pneumonia was the commonest mode of presentation among the infected patients accounted for 62.9% patients of cases (p value <0.23). Association between the duration and the severity of neutropenia with fungal infections was statistically non-significant at (p value< 0.6) and there was no statistical significant difference between medical history of old fungal infection and new invasive fungal disease.

Invasive candidiasis had affected patients with AML ALL lymphoma (HL, NHL), while myeloma and CLL patients escape the documented infection with invasive *Cryptococcosis* was isolated from cases of AML, ALL, and CLL, while invasive Aspergillosis had been found among 23.5% patients with AML, 11.7% patients with ALL, while the other malignancy showed 5.8% patients had HL, NHL except two cases MM and CLL patients which showed no documented infection.

A small group of leukemic patients were tested for the relation of neutropenia and ANC with fungal infection as (33.3%) infected patients suffered from profound neutropenia ANC <200 in comparison to 51% non-documented infected patients, while only 4.4% infected patients had severe neutropenia with ANC <500 in comparison to 11.1% non-documented infected patients, neither the duration (p value< 0.255) nor the depth or severity of neutropenia (p value <0.585) had statistically significant effect between infected and non-documented infected patients as shown in Table 4.

More than 80% of cases with culture positive aspergillosis showed raising titter of anti-Galactomannan antibodies in their serum, as it was standardize to 0.5 and 1 for the BAL samples, it was tested twice weekly for the culture proved cases of aspergillosis.

Discussion

Infections are a major cause of morbidity and mortality in hematological disorders, chemotherapy, and immunosuppressive drugs-induced neutropenia. A good progress has been made in the diagnostic procedures for IFIs.[7] Recently, many studies have been conducted to study the risk factors and the prognosis for IFI, but only a few attempts have been done to assess the real incidence of these infections in Iraqi patients with hematologic malignancies and autoimmune diseases.[8]

The present study was designed to establish and to evaluated the load of serious IFI referred to medical mycology lab unit.

Data on transplanted patients were enrolled in this study as well as treated early diagnosed hematologic malignancies.[9]

It is not easy to judge the pathogenic role of fungal isolates from the respiratory tract, i.e., infections, colonization, or contamination. However, pulmonary fungal infection has been evaluated since diagnosis was confirmed by serum level of certain antigens like anti-Galactomannan antigens seen elevated over normal values.[10]

Although the real incidence of the fungal infections had increased, its actual frequency is often under-evaluated because of the difficulty in diagnosis but the invasive procedures, e.g. histological samples, broncoalveolar lavage, and biopsies to be cultured is often in association with cytopenia or critical condition of those patients.[11]

64.4% of all samples were proven or probable fungal infections in this study when clinical and CT scan results meet the laboratory results after the exclusion of negative blood, sputum culture samples and pure bacterial infections, while it is much lower in incidence reaching to 1.6% in some studies like Mitsutoshi et al[12] other found much higher rate reaching up to 40%.[13,14]

In autopsy obtained from patients with hematological malignancies, the incidences of 13%–21% was reported.[15,16] Others described a higher rate from up to 60% of patients with pulmonary lesions respond to antifungal drugs, whereas only about 30% respond to antibiotic therapy alone.[17]

The incidence of IFI in our hospital was still higher than the wide range in reported numbers (5%–24%).[18]

Such higher figures may be due to impaired hospital infection control and poor prophylactic antifungal agent usage among studied patients in addition to hospital hygiene, including cleaning and hand washing policies and isolation policies. Another factor is the hospital environment which varies widely from one to another.

The incidence of invasive aspergillosis tends to vary greatly between institutions. In part, this relates to patient, differences in chemotherapy regimens, or other supportive measures. However, one critical factor influencing the infection rate is the level of spore counts that has been detected in hematological units with ongoing adjacent building work or defective air filtration, and these have been associated with an increase in the rate of infection. As in candidiasis, prolonged neutropenia, low level of functioning lymphocytes are a major host factors for this infection.[19]

There were significant differences in the distribution of fungal infection in blood and sputum sample in which the majority of blood samples revealed yeasts and Gram negative bacilli and in sputum samples, the predominant yeast was cryptococcus neoformans. This could be linked to the large number of pigeons available in the gardens surrounding the hospital as well as to the presence of eucalyptus trees all around the area, as their leaves represent a good reservoir for the yeast to grow and survive,[20] *Candida albicans*, *Aspergillus fumigatus* and *flavus* accounted. This result was in agreement with Rawa et al[21] and Soukeina G et al.[22]

Table 4. **Relation of fungal infections with neutropenia.**

Duration of neutropenia	No.	%	No.	%	P value
	Positive		Negative		
1 – 7 days	1	2.2	6	13.3.	
8 – 14 days	13	28.9	20	44.4	0.255
> 14 days	3	6.7	2	4.4	
Neutrophil count					
<200	15	33.3	23	51.1	0.585
<500	2	4.4	5	11.1	

Kami et al[23] stated that blood cultures remain negative in over 90% of the patients even in disseminated invasive mycosis, which is totally agreed with our results from blood cultures. On the other hand, the isolation of Aspergillus spp. (particularly *Aspergillus fumigatus* or *Aspergillus flavus* and *niger*) from sputum of a high-risk patient, on even a single occasion, is often indicative of infection and should never be dismissed.[24]

Our data showed that molds (aspergillosis and zycomycetes) were responsible for IFI in 20% of patients, which is higher to what had been reported by Denning (12–16%)[18] and others[25–27] which is probably explained by lacking of high-efficiency air filters with or without laminar air flow ventilation, and positive pressure in the patient's room, in addition to other neutropenic room precautions.[28]

On the other hand, several studies have evaluated the incidence of candidemia, particularly in critical care settings. Conversely, there are far fewer reports on the frequency of candidemia among patients with hematologic malignancies.[28,30]

In our study the yeast had accounted for 17% from all neutropenic patients and 35.5% of all patients with IFI, candidemia were confirmed in 8.8% cases. Our results differ from the results of Jutta et al,[31] who reported that in 1.6% of cases, and our data even higher to other records by Mor et al.[32]

The high and striking yields of yeast infections in our study are probably due to defective response to antifungal agent prophylaxis like fluconazole which is reflected by increase infection chance.

Among hematological malignant patients, the present study showed AML is at highest risk of developing an IFI (41%). Probably because the duration of neutropenia in AML patients during intensive induction and consolidation chemotherapy is markedly longer than in any other treatment protocol for malignancies.[33,23]

Brakhage et al.[34] found in his study that in hematological malignancies, the most common manifestation of IFI is fungal pneumonia, often caused by molds (Aspergillus species) which is closed to our work, in which fungal pneumonia accounted for 52% of all presentations.

Lastly although *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus fumigatus* are the most common causes of IFIs,[35] Cryptococcosis had been described in our analysis much higher to the results of Pappas et al in which he underestimates the rate of cryptococcosis infection to less than 1%.[35,36] Still no single case of Fusarium spp. was seen in Iraqi patients involved in our study but still the use of antifungal prophylaxis and hospital environment play a role in such picture but the pan drug resistance of cryptococcus yeasts to all tasted antifungal therapy was an alarming sign to dangerous strains of yeasts responsible for high morbidity and mortality in immunocompromized cases unlike those yeasts recovered from skin and burn in immunocompetant patients who showed some sensitivity to antifungals.[37]

Conclusion

The present findings indicate that *Cryptococcus*, *Candida* and *Aspergillus* spp. are the most commonly isolated fungal organisms from patients with hematological malignancy suffering from IFIs and all isolated cryptococcal yeasts isolated in all samples was resistant to amphotracin, fluconazole, itraconazole, econazole, and miconazole drugs. The IFIs among hematological malignancies carried a high mortality rate.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee and all patients provided informed written informed consent prior to entering the study by referring to the lab.

Funding Acknowledgment

This research received no specific grant from public, commercial or not_for _profit sectors.

Conflict of interest

The authors that he has no conflict of interest.

References

1. Wingard JR. New approaches to invasive fungal infections in acute leukemia and hematopoietic stem cell transplant patients. Best Pract Res Clin Haematol. 2007;20:99-107.
2. Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol. 2005;43:1829-1835.
3. Bow EJ, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. Clin Infect Dis. 1995;21:361-369.
4. Mikulska M, Calandra T, Sanguinetti M, et al. Third European Conference on Infections in Leukemia Group. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. Crit Care 2010;14:R222.
5. Thursky K, Byrnes G, Grigg A, Szer J, Slavin M. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. Bone Marrow Transplant. 2004;34:115-121.
6. Muhlemann K, Wenger C, Zenhausern R, Tauber MG. Risk factors for invasive aspergillosis in neutropenic patients with hematologic malignancies. Leukemia. 2005;19:545-550.
7. Kobayashi R, Kaneda M, Sato T, Suzuki D, Ichikawa M, Ariga T. Evaluation of risk factors for invasive fungal infection after allogeneic stem cell transplantation in pediatric patients. J Pediatr Hematol Oncol. 2007;29:786-791.
8. Pagano L, Girmenia C, Mele L, Ricci P, Tosti ME, Nosari A, et al. Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA Infection Program. GIMEMA Infection Program; Gruppo Italiano Malattie Ematologiche dell'Adulto. Haematologica 2001;86:862-70.
9. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34:909-17.
10. Chen KY, Ko SC, Hsueh PR, et al. Pulmonary fungal infections. Emphasic on microbiology spectra, patient outcome, and prognosis factors. Chest. 2001;120:177-184.
11. Hsiao H.H., Tsai H.J., Liu Y.C., Tseng Y.T., Lu P.L., Yang W.C., Liu T.C., Lin S.F. Invasive fungal infections in patients with acute leukemia. Kaohsuing J Med Sci 2006;22:217–222.
12. Mitsutoshi Kurosawa, Masakatsu Yonezumi, Satoshi Hashino et al. Epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol 2012;96:748-757.
13. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34:909–17.

14. Cuenca-Estrella M, Bernal-Martinez L, Buitrago MJ, et al. Update on the epidemiology and diagnosis of invasive fungal infection. Int J Antimicrob Agents. 2008;32(Suppl 2):S143–7.
15. Mühlemann K, Wenger C, Zenhäusern R, et al. Risk factors for invasive aspergillosis in neutropenic patients with hematologic malignancies. Leukemia. 2005;19:545–50.
16. Donhuijsen K, Petersen P, Schmid KW. Trend reversal in the frequency of mycoses in hematological neoplasias. Dtsch Ärztebl Int. 2008;105:501–6.
17. Maschmeyer G, Link H, Hiddemann W, et al. Pulmonary infiltrations in febrile patients with neutropenia: risk factors and outcome under empirical antimicrobial therapy in a randomized multicenter study. Cancer. 1994;73:2296–304.
18. Seyyed A.A, Sanas H, Mahshid L. The study on rate of morbidity of fungal infection exiting in educational hospitals Iran. Comp Clin Pathol. 2018:1-6..
19. Wiley JM, Smith N, Leventhal BG, Graham ML, Strauss LC, Hurwitz CA et al. Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. J Clin Oncol.1990;8:280–6.
20. Schmertmann LJ, Irinli L, et al. The mycobiome of Australian tree hollows in relation to the *Cryptococcus gattii* and *C. neoformans* species complexes. Ecol. Evol. 2019;9:9684-9700.
21. Rwaa MA, Alwattar, WM, Jawad AM. Detection of galactomannan antigen in the serum of Iraqi patients with invasive aspergillosis. J Facult Med. 2016;2:370–6.
22. Soukeina G, Fatma S, Wadiaa B, et al. Characteristics of invasive aspergillosis in neutropenic haematology patients (Sousse, Tunisia). Mycopathologia 2014;177:281-289.
23. Kami M, Murashige N, Fujihara T, Sakagami N, Tanaka Y. The mechanism for low yield of blood culture in invasive aspergillosis; the clinical importance of antigen detection tests revisited. Bone Marrow Transplant 2005;36:85-86.
24. Treger TR, Visscher DW, Bartlett MS, Smith, JW. Diagnosis of pulmonary infection caused by Aspergillus: usefulness of respiratory cultures. J Infect Dis. 1985;152:572–6.
25. Muhlemann K, Wenger C, Zenhausern R, Tauber MG. Risk factors for invasive aspergillosis in neutropenic patients with hematologic malignancies. Leukemia 2005;19:545-50.
26. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive Aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant. 2002;29:15-19.
27. Ninin E, Milpied N, Moreau P, et al. Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. Clin Infect Dis. 2001;33:41-47.
28. Anaissie E, Stratton SL, Dignani MC, Lee CK, Mahfouz TH, Rex JH, et al. Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized Aspergillus species and other opportunistic molds. Clin Infect Dis 2002;35:86-8.
29. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36:1103-10.
30. Annissis EJ. Opportunistic mycosis in the immunocompromized host: experience at a cancer center and review clin.infect. Dis.1992;14(suppl):S43-S53.
31. Jutta Auberger, Cornelia Lass-Flörl, Hanno Ulmer, et al. Significant alterations in the epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol. 2008;88:508-515.
32. Mor M, Gilad G, Kornreich L, et al. Invasive fungal infections in pediatric oncology. Pediatr Blood Cancer 2011;56:1092-7.
33. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006 Aug;91(8):1068-75.
34. Brakhage AA. Systemic fungal infections caused by Aspergillus species: epidemiology, infection process and virulence determinants. Curr Drug Targets. 2005;6:875–86.
35. Pfaller MA, Diekema DJ. Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus.* J Clin Microbiol. 2004;42:4419-4431.
36. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network. Clin Infect Dis. 2010;50(8):1101.
37. Jassem IK, AL-Wattar WM, Karhoot JM. 2015. Mycological study of wound infections among Iraqi patients in Baghdad city. IMJ. 2014;60(1):80-84.