Original article:

Point prevalence study for antifungal usage in intensive care units of a tertiary care hospital-A pilot study

Dr.Rup Jyoti Chandak,Dr,Bibhabati Mishra,Dr,Poonam Sood Loomba,Dr.Abha Sharma, Dr.Ashish Bajaj Dr.Archana Thakur

Institute Of Post Graduate Medical Education &Research,JL.N marg,New Delhi-110002
Corresponding author :Dr.Bibhabati Mishra

Abstract:

Background: Empirical use of antifungal in critical care patients is increasing rampantly in critical care settings which is detrimental in terms of drug toxicity,resistance and cost to the patient. The present study was conducted with the aim of knowing the prevalence of use of antifungal therapy in ICUs of a tertiary care hospital ,correlations and risk factors relating to antifungal use.

Methods: A cross-sectional prospective study was conducted in a tertiary care hospital. A proforma based three point prevalence surveys was conducted for the use of antifungal therapy in three months in eight different intensive care units.Risk ratio for developing invasive fungal infections and p value was calculated for patients on antifungal therapy and those not on antifungal therapy was calculated using SPSS version 12.

Results: A total of 213 patients were covered in three point prevalence surveys, out of which 74(34.74%) had underlying risk factors and 7(3.28%) were on antifungal. The most common risk factor was major abdominal surgery (37.31%) while relative risk for developing fungal infections in patients without antifungal therapy was highest in patients with Diabetes Mellitus(14.667).Empirical therapy was most commonly practiced (42.85%) while fluconazole was the most common antifungal prescribed(57.14%).Omitting of loading dose and insufficient maintenance dose were the most common type of prescription error.

Conclusion: A high rate of inappropriate antifungal use was found which needs to be addressed timely.

Key-words: antifungal, critical,echinocandins,empirical,inappropiate, prescription

Introduction:

Invasive fungal infection has been involved in increasing mortality over the past decade, especially in immunocompromised patients.A number of guidelines have been formulated on empirical treatment with antifungal agents and surveillance for *Candida* species which is done either through culture or diagnostic biomarkers.[1]Empirical use of antifungal in high-risk Intensive Care Unit (ICU) patients with signs of sepsis, in the absence of microbiological evidence of infection has become a common practice.[2] Emergence of infections due to rare and atypical organisms has also contributed to more intense use of antifungal drugs.[3]

There is a scarcity of benchmarking surveillance data on antifungal consumption which are essential for developing policies and program and for evaluating their effectiveness in preventing and efficiently controlling public health problems.[4] This pilot study was conducted with the aim of knowing the prevalence of use of antifungal therapy in Intensive Care Unit (ICUs) of a tertiary care hospital ,correlations and risk factors relating to antifungal use

Materials and Methods:

Setting: A 700 bedded tertiary care centre.

Study design & Data collection:

A cross-sectional prospective study using a point prevalence survey (PPS) for the use of antifungal therapy was

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conducted in eight intensive care units.Point prevalence surveys for the use of antifungal in ICU were undertaken thrice in three months duration from June to August 2017.All inpatients in the various ICUs present on the day of survey were included in the study as per the inclusion criteria. Informed Consent was taken from all the patients included specifying the confidentiality of the patient.

Ethical clearance was waivered off by the ethical committee of the institute.

Inclusion criteria:

1) Duration of admission must be more than 24 hours at the time of surveillance.

Exclusion criteria:

1) Duration of admission less than 24 hours at the time of surveillance.

A Performa based point prevalence for antifungal use in various ICUs of this hospital was conducted on a given day of a month. An in-house proforma was prepared taking into consideration Infectious Disease Society Of America (IDSA) guidelines.[5]

Definitions:

The following definitions were used in the study[6]:**Prophylactic therapy:** Treatment is given to patients in whom there is no clinical evidence of fungal infection, although they are at risk of developing it, before any signs, symptoms or microbiological results appear.

Empirical therapy is defined as the use of treatment in patients with clinical features consistent with a fungal aetiology or, alternatively, the initiation of treatment to patients without such features but in the setting of a very probable fungal infection, but without proven microbiological confirmation.

Presumptive therapy is defined as initiation of treatment in response to a probable fungal infection, without microbiological confirmation (as in the case of the empirical treatment), but supported by the identification of one or more biological markers of infection risk.

The appropriateness of the therapy in terms of risk factors,indication,choice of antifungal drug ,dosage were considered as per IDSA guidelines 2017.[5]Duration of treatment could not be assessed as the patient were not followed up.*Candida* score was calculated for the patients receiving antifungal therapy by the author at the time of study, Risk ratio(RR) for developing invasive fungal infections in patients having any risk factors was calculated and P value was calculated for patients on antifungal therapy and those not on antifungal therapy using SPSS version 12.

Results:

Surveillance for antifungal use in hospitals have been studies by different workers, however by different methods,[3,4,7,8,9] the results of which can be together applied to understand the brighter and the darker side of antifungal use in ICUs .Use of Antifungal therapy in intensive care settings has been debated and been studied worldwide.[10-15] .As a matter of fact, results and interpretations vary in different studies due to difference in ICU settings with different sets of risk factors.

In the present study, the author tried to highlight the antifungal practices followed in the different ICUs of the hospital by conducting three point prevalence carried on by the same observer.

Table 1: Bed strength and patients in various ICUs

ICU	Bed strength	Number of patients covered
Gastroenterology & Gastro-surgery	19	50
Neurology	16	45
Neurosurgery	22	47
General	9	14
Cardio-thoracic surgery	26	57
Total	92	213

Table 2: Demographic and clinical details of the patients

Characteristic	Figure
Male: Female	2.45(152:62)
Median length of stay	6(1-587)
Age(median)	0.33 -87 years(43.83 years)
Patients having risk factors for invasive fungal infection	67(31.45%)
Patients on emperical antifungal therapy	3(42.85%)
Patients on prophylactic antifungal therapy	2(28.58%)
Patients on therapeutic antifungal therapy	2(28.58%)
Age(average) of patients on antifungal therapy	53.85
Most common antifungal prescribed	Fluconazole (57.14%)

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Table 3: Risk factors for patients with and without antifungal therapy.

Risk factors	Patients on antifungal		Patients without antifungal		Total	R.R*	95% CI[#]	P value
	Fungal culture positive	Fungal culture negative	Fungal culture positive	Fungal culture negative				
Major abdominal surgery	0	0	0	25	25	10.33	0.8434 to 126 .6107	0.067
Diabetes	1	1	1	20	23	14.667	1.8408 to 116 .8591	0.0112
TPN**	0	0	0	2	2	3	0.1222 to 73. 6467	0.0511
Steroid therapy	0	0	0	5	5	7	0.2548 to 192 .2727	0.2496
TB	0	0	1	5	6	2.333	0.2076 to 26. 2266	0.4925
Sepsis/septi c shock	2	0	0	3	5	6.667	0.4749 to 93. 5861	0.1593
malignancy	0	0	0	1	1	2	0.0902 to 44. 3530	0.6611
Total					67			

[#]Confidence Interval, **Total Parenteral Nutrition, *Risk Ratio.

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Table 4:Results of fungal culture

Sample	Risk factor	Fungus isolated	Repeated isolation	Antifungal given before culture	Changed as per culture report
Blood	sepsis	*Candida albicans*	no	yes	no
Blood and urine	septic shock	*Candida albicans*	no	yes	no
Urine	TB,steroid	NAC**	no	no	no
Urine	none	NAC	no		
Urine	DM**	NA	Twice	no	yes
Urine	none	NAC	no		
Urine	none	NAC	Twice	no	yes
Urine	diabetes	NAC	no		
Pus	diabetes	NAC	no		

DM:Daibetes Mellitus,NAC**:Nonalbicans *Candida*

Table 5:Clinical details of patients on antifungal

Antifungal (route & dose)	**ICU**	**Indication**	**Risk factor**	**Indication correct /dose correct**	**Fungal culture report**	**Changed as per culture report**	**C.S**
Caspofungin(i.v 70mg ,loading dose 50 mg daily once daily)	Gastroenterology	Empirical	Diabetic	yes/yes	negative	-	0
Amphoterecin(i.v 200mg twice daily)	Gastrosurgery	Empirical	Sepsis	yes/no	blood-NAC*** spp.	No	2
caspofungin (i.v 50mg once daily)	Gastroenterology	Empirical	Sepsis	Yes/no	blood & urine-*C.albicans*	Yes,switched over to oral fluconazole	2+2=4
Fluconazole(oral 200 mg daily in divided dose)	CTVS**	Prophylactic	None	No/no	Negative	-	0
Fluconazole(oral150 mg twice daily)	CTVS	Prophylactic	None	No/no	Negative	-	0
Fluconazole(oral 200 mg in divided dose)	Neurology	Therapeutic	Diabetic	-	Urine-NAC spp.		0
Fluconazole (oral 200 mg in divided dose)	Neurosurgery	Therapeutic	Diabetic	-	Urine-NAC spp.	AS per culture report	0

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Demographic & Clinical characteristics:

The total number of ICUs included in this study were 8 and 213 patients were included during 3 point prevalence study conducted monthly**.(Table 1)**

Majority of the patients were male and median age of patients was 43.83 years.7 out of 213 patients were found to be on antifungal therapy(3.28%),with median age of 53.85**.(Table 2)**

Risk factors

Table 3 shows the risk factors for invasive fungal infection in patients with and without antifungal therapy. The most common risk factor present in this study was major abdominal surgery [25/67(37.31%)] followed by Diabetes mellitus(DM) [23/67(34.32%). Relative risk for developing fungal infections in patients without antifungal therapy was highest in patients with DM(14.667),followed by major abdominal surgery(10.33).P value was significant only for DM. Similar results was found in another study where DM was found to be significantly associated with early invasive fungal disease.[16] While in another study prior surgery was reported as the highest associated risk factor followed by acute renal failure and TPN[17].Another study showed TPN use, sepsis, surgical patients, mechanical ventilation and an indwelling urinary catheter as independent risk factors.[18]

Candida Score(C.S) is an useful tool as to determine the benefit of antifungal therapy in patient as it has a good negative predictive value to determine the likelihood of colonization and presence in surveillance cultures. *Candida* score has a 81% sensitivity and 74% specificity for invasive *Candida* infection in non-neutropenic patients. [6]. *Candida* score proved to be a useful tool in this study also.It was observed that amongst patients with associated risk factors and were administered antifungal therapy, fungal culture was positive in only those with a higher *Candida* score.Thus, unnecessary administration of antifungal therapy could have been prevented in two patients, if *Candida* score had been bedside applied before initiation of therapy.

Fungal culture versus risk factor:

Table 4 shows the details of the patients in whom clinical sample was sent for fungal culture.The most common type of sample sent for culture was urine[7/9(77.77%)]The most common risk factor for suspected fungal infection was DM(33.33%) followed by sepsis (22.22%).Majority of the species isolated were non-speciated and grouped as Non-albicans *Candida*(NAC) [7/9(77.77%)].However,*Candida albicans* was the species isolated from blood in both the cases for septicemia or septic shock.Predominance of NAC(77.77)% in this study revealed an important fact that inadvertent use of antifungals leads to proliferation of drug resistant NAC.Taking into consideration fungal growth positivity in patients with underlying risk factor,culture positivity rate was highest for DM.[3/9(33.33%)]. Of this 66.66%,that is two patients had urinary tract infection,while 33.33%(1 patient) had fungal wound infection. Yang S.P, et al in his study showed urinary tract infection (54.8%) followed by blood stream infection (30.6%) to be the commonest type of fungal infections in criticallly ill patient.[18]

Choice of antifungal and dosage appropriateness

In this study, the most common choice of antifungal was fluconazole[4/7 (57.14%)]. The main reasons for incorrect use of fluconazole included the lack of loading dose(all four patients) and insufficient maintenance dosages in one patient [150 milligram(mg) twice daily]. High rate of incorrect fluconazole prescription has also been reported earlier too [7,8,19]Empiric use of fluconazole in intensive-care units is widely practiced despite not being clearly proven to improve outcome compared with placebo.It should be reserved only for patients with a high risk of developing fungal infections or in units with high incidence of Candidemia.[7] An inappropriate prescription has been seen to dramatically affect patient

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outcome[10,19]

Caspofungin [2/7(28.57%)] was the second most commonly used agent in this study. Caspofungin dosage incorrectness was seen in one patient where the loading dose was omitted.

Third antifungal prescribed in this study was Amphoterecin B in one patient its use could not be justified as it was incorrectly administered empirically in absence of any evidence of intolerance, limited availability, or resistance to other antifungal agents. Dosage given of Amphoterecin B however was correct.

Overall,Echinocandins was the most common choice for empirical therapy while fluconazole was chosen for culture directed therapy in this study.Results were similar in another study.[10] Such interpretations reflect the concept of selecting a broad coverage for azole-non-susceptible species and also for rapid reduction of fungal load .Selection of fluconazole based on antifungal susceptibility patterns was considered as an easy and comfortable choice for the physicians.

No Difference in choice of route of administration could be elicited in this study as the distribution of both the route was 50 % each.

Prophylactic thearapy.

In this study,2 out of 7(28.57%) patients were receiving prophylactic antifungal therapy. Both of these patients belonged to Cardiothoracovascularsurgery(CTVS) ICU.As per IDSA guidelines,prophylactic therapy was not indicated and *Candida* score and microbiological culture also showed that both these patients did not require any antifungal treatment.Fluconazole was the choice of drug in both the cases . Unnecessary prescription of antifungal therapy may actually lead to increase in invasive fungal infections by fluconazole resistant bugs like *C.krusei* and *C.glabrata*. In many hospitals fluconazole prophylaxis has been shown to decrease the cases of *Candida*emia but actually increased the *C. glabrata* isolation rate .It also promotes the development of resistance in *Candida* species that are usually considered to be fluconazole susceptible(*C. albicans*).[7]

Empirical therapy

Empirical antifungal therapy was administered in 3 out of seven(42.85%) patients in this study. ,(66.67%) i.e.,2 out of these 3 were from gastroenterology ICU and one (33.33%) from gastrosurgeryICU**.** Patients undergoing gastrological procedure or gastrosurgery are at especially high risk for IC. Empirical antifungal therapy with regard to the type of ICU was found to be appropriate as abdominal surgery is a well identified predisposing factor for invasive candidial infection as it leads to gross contamination of intra-abdominal space,especially in emergency surgeries. The benefit of starting early empiric antifungal treatment in these patients will probably outweigh any potential risks of experiencing drug-related adverse effects.[6,10]

As per IDSA guidelines[5] ,indication was considered to be correct as all three had underlying risk factors and were febrile with sterile bacterial culture.*Candida* score was also high as well as fungal culture was positive for 2 out of 3 patients.If *Candida* score had been utilized at bedside as a tool for assessing requirement of empirical therapy,one patient could have been saved from inadvertent treatment.However,follow-up of the patients could have demonstrated the actual benefit or no benefit of such therapy as these patient had independent risk factors.Choice of drug for empirical therapy was considered correct in 2 out of 3 patients considering sepsis/shock as the indication ,as echinocandin is indicated in suspected fungal blood stream infection in the face of rising trend of fluconazole resistance [5]However ,dose & duration of treatment was incorrect .Compliance with guidelines to change of treatment as per microbiological culture report was seen in only one of the patients. Patients with inappropriate empirical antifungal therapy for Candidaemia (therapy initiation delayed by 24 hour inadequate dosage) has been known to present a higher death rate.[20] contrastingly adequate dose has been shown to be independently associated with a reduced risk of death[21].

Therapeutic therapy

The third group of patients receiving antifungal therapy were those receiving therapeutically after confirmation by microbiological report [2 out of 7(28.57%)]. One patient was from neurology ICU and the other was from neurosurgery ICU and both were diabetic with NAC isolated in urine.There was satisfactory compliance with the choice of drug and dose administered.

Results in this study showed an interesting trend of trend or practice of clinicians in antifungal prescriptions with regard to a particular speciality ICU.Empirical therapy preferred in gastroenterology and gastrosugery branches,prophylactic therapy commonly practiced by cardiothoracic speciality,while neurologist and neurosurgeons preferred to play safely by opting only antifungal therapy in culture confirmed cases with other underlying conditions. *Candida* score was also high in patients from gastrology speciality. However,Statistical analysis could not be done because of smaller sample size. Katze de,et al found a more intense antifungal use in the hematology-oncology services and intensive care areas than in general internal medicine.[3] Another study reported a predominant parenteral route of administration as compared to oral preference in medical wards.[7]

It is crucial to understand that every critical care setting with patients having varied levels of immune-suppression has its own trend of fungal infection with unique drug susceptibility pattern. If the rate of invasive fungal infections is high enough prophylaxis is outweighed against drug resistance and toxicity in terms of patient benefit, otherwise, it is not warranted because of selection of resistant isolates, drug reactions, and cost.[22]

Combination therapy.

All the patients were on multiple antibiotic combination simultaneously.The most common combination was fluroquinolone(levofloxacin or ofloxacin) with metrogyl(42.85%), followed by fluroquinolone with carbapenem(meropenem or imepenem)(28.57%),colistin with meropenem(14.28%) and vancomycin and meropenem(14.28%).

The practice of prescribing multiple or mixed therapy should be considered with cautions as to avoid drug interactions as well as drug toxicity.Some authors have studied drug interactions and contraindications for multiple therapy in appropriateness of antifungal therapy.[19

Limitations of the study

There were several limitations to this study.Firstly,the number of patients with antifungal therapy was small.It was a cross-sectional study,so patients could not be followed –up for

Appropriateness of duration of treatment.Outcome of the patients with risk factors could not be compared in those on antifungal and those not on antifungal therapy. Appropriateness for combination of antibiotics or antacids with antifungal was not assessed.

Conclusion:

This study is a small effort to understand the antifungal prescription patterns prevalent in various ICU of tertiary care hospital. In three-month point prevalence surveillance, seven patients were on antifungal therapy.DM and Abdominal surgery showed the highest risk of invasive fungal infection in the absence of antifungal therapy The most common therapy was empirical ,while the most common choice of antifungal was fluconazole.A poor awareness amongst the clinicians could be sensed as high rate of non-compliance with standard guidelines was elicited.Use of bedside guiding tools like *Candida* score was lacking.

Confounded by a small population size, however, this study torched upon the immense need to rethink about the actual implications of inadvertent antifungal use in regards to patient's underlying clinical conditions,drug toxicity and risk associated .A collaborative effort is required to scale down the decisions for empirical and prophylactic therapy.

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