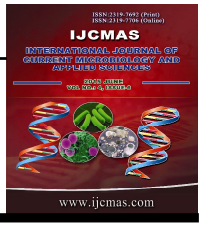
Int.J.Curr.Microbiol.App.Sci (2015) 4(6): 423-435

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 4 Number 6 (2015) pp. 423-435**
http://www.ijcmas.com



Original Research Article

Nosocomial respiratory tract infection in patients with liver cirrhosis

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Keywords

Noscomial infection; Respiratory tract infections; Cirrhosis

A B S T R A C T

The noscomial respiratory tract infection creates a serious health problem in hospitals all over the world. It is the second most common noscomial infection and the most common cause of death among nosocomial infections. This study was carried out to determine the incidence of nosocomial respiratory tract infection in cirrhotic patients. In an analytical cross-sectional study, 366 cirrhotic patients were studied from Tropical Medicine and Gastroenterology Department, Assiut University Hospital. For all participants, the following was conducted: clinical evaluation, abdominal US examination, and laboratory investigations including complete blood picture, renal function tests, liver function tests, plain chest x-ray, sputum or throat swab culture and antibiotic sensitivity testing. The frequency of nosocomial respiratory tract infection in cirrhotic patients was 10.9%. The most significant risk factor was artificial respiration (OR=9.81). Gram negative bacilli (38.5%) were the first cause followed by Gram positive cocci (35.5%) then fungi (26.0%). The mortality rate was 15%. The incidence of noscomial respiratory tract infection in cirrhotic patients was not low. Artificial respiration was the most significant risk factor. All types of noscomially important bacteria were present in patients' isolates especially *Staphylococci* and *E. coli*. The mortality rate in those patients reached 15%.

Introduction

A noscomial infection (NI), also known as a hospital-acquired infection (HAI), is an infection that became clinically evident after 48 hours of hospitalization and do not originate from patient's original admitting diagnosis (Nguyen, 2004). These infections cause significant morbidity and mortality and have a considerable impact on healthcare costs (Tandon and Garcia-Tsao, 2008).

Among all types of NIs, the noscomial respiratory tract infections create a serious health problem in hospitals all over the world (Sŭljagić *et al.*, 2005). In addition, patients admitted to intensive care units (ICUs) carry an even higher risk of noscomial respiratory tract infections than those admitted to other types of units (Navasa *et al.*, 1999).

About 15%–35% of cirrhotic patients admitted to hospital develop noscomial bacterial infection, which is higher than the infection rate **(**5%–7%) in the general hospital patient setting (Sŭljagić *et al.,* 2005). The percentage increases up to 45% of those with GI hemorrhage (Navasa *et al.*, 1999, Fernandez *et al.,* 2002) .

Cirrhotic patients are frequently subjected to several invasive diagnostic and therapeutic procedures such as intravenous or urethral catheters; endoscopic sclerotherapy for bleeding varices, or the placement of transjugular intrahepatic portosystemic shunts (TIPS) that may alter the natural defense barriers and therefore increase the risk of infections with an increased incidence of bacteremia (Borzio et al., 2001). Cirrhotic patients are susceptible to infections due to abnormal immune response and bacterial translocation which enables alteration of local immunity and bacterial growth (Tikhomirov, 1987; Vilstrup, 2003). The phagocytosis process is deeply altered in patients with liver cirrhosis due to rearrangement of antigens, affecting cellular and humoral Immune response (Talwani, 2011, Kalaitzakis *et al.,* 2006).

Once infection develops, renal failure, shock, and encephalopathy may follow, which adversely affect survival. In fact, the in hospital mortality of cirrhotic patients with infection is approximately 15% more than that of patients without infection. More importantly infection is directly responsible for 30–50% of deaths in cirrhosis (Christou *et al.,* 2007) .

Hospital-acquired pneumonia (HAP) or noscomial pneumonia is the second most common noscomial infection (after urinary tract infections) and accounts for 15–20% of the total. It is the most common cause of death among nosocomial infections and is the primary cause of death in intensive care units (Gheorghe *et al.,* 2005, Navasa and Rodés, 2004).

Among the factors contributing to contracting HAP are mechanical ventilation (ventilator-associated pneumonia), old age, decreased filtration of inspired air, intrinsic respiratory, neurologic, or other disease states that result in respiratory tract obstruction, trauma, (abdominal) surgery, medications, diminished lung volumes, or decreased clearance of secretions may diminish the defenses of the lung. Also, poor hand-washing and inadequate disinfection of respiratory devices cause cross-infection and are important factors (Goez *et al.,* 1994; Caruntu and Benea, 2006). Cirrhotic patients with hydrothorax can develop spontaneous bacterial empyema, which is thought to have the same pathogenesis as SBP, since their isolated bacteria are the same (Gheorghe *et al.,* 2005).

The causative organisms of nosocomial infections are Gram positive cocci (60%) and Gram negative bacilli (30–35%), due to previous antibiotic exposure. With E. coli being the commonest in community, the next most frequently isolated bacteria are *Staphylococcus aureus, Enterococcus faecalis* and *Streptococcus pneumoniae* (Runyon *et al.,* 1994). Fungal infections (Candida species) are responsible for up to 15% of severe sepsis in patients with cirrhosis (Garcia-Tsao and Wiest, 2004).

Early and appropriate initiation of antibiotics correlates with higher survival rate. A retrospective study by Kumar *et al.* suggested that each hour of delay decreased survival by 7.6% (Garcia-Tsao and Wiest, 2004). Choosing adequate empiric antimicrobial treatment will therefore improve the prognosis of patients (Runyon *et al.,* 1994). Microbiological samples should be taken as early as possible when infection is suspected, before starting

empiric antibiotic therapy and empiric anti-microbial therapy will need to be adapted to local epidemiology, prevalence of antibiotic resistance and results of bacterial cultures (Ghassemi and Garcia-Tsao, 2007).

Our aim in this study was determination of the incidence of nosocomial respiratory tract infection in cirrhotic patients, identification of the most common pathogens responsible for nosocomial respiratory tract infection and identification of the pattern of antibiotic resistance among isolates to detect the proper needed antibiotic for treatment of this infection.

Patients and methods

In an analytical cross-sectional study, all cirrhotic patients admitted to Tropical Medicine and Gastroenterology department, Assiut University Hospital, from February 2013 to January 2014 were included in the study.

Patients with apparent clinical manifestations of any respiratory tract infection at time of admission or within three days of admission were not included.

All included patients were subjected to: complete history taking, thorough physical examination, complete blood picture, renal function tests, liver function tests, plain chest x-ray and abdominal ultrasonographic examination to determine if there is chest infection at time of admission. Patients were classified according to Child-Pugh classification (Christensen, 2004).

Follow up of the patients after 3 days of admission were done to identify any clinical manifestations of respiratory tract infection.
The diagnosis of respiratory tract infection was made by: clinical symptoms and signs [cough, expectoration, pulmonary sounds, fever], positive radiologic signs (patchy alveolar opacities), and/or positive bacteriologic examination [sputum or throat swab].

Samples were collected under complete aseptic conditions (sputum and throat swabs) from the infected sites for culture, antibiotic sensitivity testing and biochemical reactions. All samples were collected by the Infection Control nurses and were subjected to both bacterial and fungal cultures at the Infection Control laboratory of Assiut University Hospital

Bacteria were identified by the following methods:

All specimens were cultured on blood agar and incubated at 37 °C for 24hs, suspected colonies were identified with Gram's stain.

MacConkey agar is a selective and differential media used for the isolation of Gram-negative enteric bacteria particularly members of the family enterobacteriaceae and the genus pseudomonas. Gram-negative bacteria growing on the media are differentiated by their ability to ferment the sugar lactose .

EMB agar, a differential microbiological medium, which slightly inhibits the growth of Gram-positive bacteria and provides a color indicator distinguishing between organisms that ferment lactose (e.g., *E. coli*) and those that do not (e.g. *Salmonella*, *Shigella*).

TSI Agar is used for the determination of carbohydrate fermentation and hydrogen sulfide production in the identification of gram-negative bacilli.

The urease test identifies those organisms that are capable of hydrolyzing urea to produce ammonia and carbon dioxide.

Single separate lactose fermenter colonies on MacConkey agar were cultured on urease agar, and slopes were incubated at 35-37°C for 24–48hs.

Fungi were identified by the following methods:

All collected specimens were cultured on Sabouraud's Dextrose agar supplemented with chloramphenicol, Germ tube test, Dalmau plate culture, Culture on casein agar and Sugar assimilation test.

Genotypic identification of Candida isolates:

PCR amplification of *Candida* rDNA with universal fungal primers.

Ethical considerations

Before enrollment in, all participants signed a consent certificate. Before signing, they were able to discuss in details the certificate subjects and study aim.

Participants were clearly informed that refusing to participate will not affect having full benefit of available medical service and treatment. Data were collected by personal interview with participants taking in consideration data confidentiality **.**

Statistic analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS- version 17). All data was expressed as mean ± SD or frequencies. For statistical evaluation, Student T test was used. Significance was accepted at p value <0.05.

Results and Discussion

This study included 366 cirrhotic patients admitted to Tropical Medicine and Gastroenterology department, Assiut University Hospital during the period of one year (from February 2013 to January 2014).

Results revealed that the frequency of nosocomial respiratory tract infection in cirrhotic patients was 10.9%. This is shown in table 1. The mean age of patients was 55.37 ± 9.20 years and the percentage of infection was higher in old age and male patients than other groups but the difference was not statistically significant (p-value > 0.05) (Table 2).

As shown in table 3, analysis of the risk factors of noscomial respiratory tract infection revealed that the most significant risk factor was artificial respiration (OR=9.81), followed by anemia (OR=2.97) and Ryle intubation(OR=2.81). Regarding Child-Pugh classification, the infection was higher in Child grade C than grade B and A (52.5% versus 42.5% and 5% respectively) but the difference was not statistically significant (p-value > 0.05).

Results of culture of throat swabs and sputum samples revealed that 75% of patients were infected by multiple microorganisms which were statistically significant (p-value < 0.05) as shown in table 4.

According to culture results of throat swab and sputum samples, Gram negative bacilli were the first cause followed by Gram positive cocci then fungi but the difference was not statistically significant (p-value > 0.05) as shown in table 5.

Regarding bacterial causes, *Staphylococci* were found to be the commonest (39.5%) gram positive cocci and *E. coli* were found to be the commonest (21.2%) Gram negative bacilli (Figure 1).

In our study, we observed that there was difference in the frequency of

microorganisms between department wards and ICU. The most common microorganism in the department wards was *Candida* (32.7%), on the other hand the most common microorganism in ICU were *Staphylococci*(61.8%)as shown in table 6.

Table 7 showed results of sensitivity of numerous gram negative bacilli to multiple groups of antibiotics. The most sensitive antibiotics were imipeneme (87.8%), meropeneme (82.4%) and gatifloxacin (58.3%).

Table 8 determined sensitivity of Gram positive cocci. The most sensitive antibiotics were levofloxacin (100%), ceftriaxone (57.1%), cefazoline (55.6%) and ciprofloxacin (52.3%).

In table 9, we determined the most sensitive and most resistant antibiotic for each organism and this revealed that levofloxacin was the most sensitive antibiotic for *Staphylococci*, the most sensitive antibiotic for *E. coli* was lomefloxacin, and the most resistant antibiotic for all these bacteria was ampicillin.

Our results revealed that fungal causes were considered important causes. *Candida albicans* was the most common cause (60%), followed by *Candida tropicalis* (16%), *Candida glabrata* (12%), *Candida krusei* (8%) and *Candida parapsilosis* (4%). This is shown in figure 2.

Antifungal susceptibilities of isolates revealed that the most sensitive antifungals were nystatin (71.4%) and fluconazole (60%) but the most resistant antifungals were itraconazole (87.9%), as shown in table 10.

Culture and sensitivity revealed that *Candida albicans* was most sensitive to nystatin but most resistant to itraconazole. On the other hand, fluconazole was the most sensitive antifungal to *Candida tropicalis* and the most resistant one was ketoconazole . These results are shown in table 11.

Table 12 revealed that *Staphylococci* were considered the most resistant gram positive cocci to prophylactic antibiotics used. *Enterococci* appeared resistant only to cefotaxime. Klebsiella was the most resistant gram negative bacilli to prophylactic antibiotics. Other gram negative bacilli like *E. coli* and pseudomonas were also resistant to these prophylactic antibiotics. *Candida albicans* appeared in all isolates of patients given prophylactic antibiotics as shown in table 13. The mortality rate in cirrhotic patients exposed to noscomial respiratory tract infection was 15% (Table 14).

In Our study we observed that the incidence of noscomial respiratory tract infection in cirrhotic patients was 10.9%. The incidence of nosocomial respiratory tract infection in cirrhotic patients as mentioned by Fernandez *et al.* (2002) was 15%–35% but in the general population was 5%–7%.

Our study revealed that the mean age of patients exposed to noscomial respiratory tract infection was 55.37 ± 9.20 years. This agreed with Tandon and Garcia-Tsao (2008) who said that nosocomial pneumonia is more common in old age.

The frequency of noscomial respiratory tract infection was proportionally related to Child classification as we observed that there was increase in the frequency of infection in Child C than both B and A. This agreed with Fernandez *et al.* (2002) who said that bacterial infections are commoner in patients with cirrhosis than in the general population, and those with decompensated cirrhosis are more susceptible to infection than those with compensated liver cirrhosis.

Table.1 Frequency of nosocomial respiratory tract infection in cirrhotic patients in department wards and intensive care unit (ICU)

	Number of admission	Number of infection	Percentage (%)	P-value
Total	366	40	10.9%	
ICU	112	7	6.3%	0.057
Department wards	254	33	13.0%	

Table.2 Personal characteristics of cirrhotic patients with nosocomial respiratory tract infections

Personal characteristics	Number of patients with infection (n= 40).	Number of patients without infection (n=326)	Percentage (%)	P-value
Age:				
< 60 years	25	218	62.5%	0.527
≥ 60 years	15	108	37.5%	
Mean ± SD	55.37 ± 9.20			
Sex:				
Male	28	207	70%	0.492
Female	12	119	30%	

Table.3 Risk factors for nosocomial respiratory tract infection in cirrhotic patients

Risk factors	Infection (n= 40)		No infection (n= 326)		OR	P-value
	Number Of Infection	Percentage (%)	Number	Percentage (%)		
Artificial Respiration	3	7.5%	0	0%	9.81	0.000*
Anemia	38	95%	282	86.5%	2.97	0.126
Ryle	2	5%	6	1.8%	2.81	0.473
Intravenous cannula	35	87.5%	249	76.4%	2.17	0.111
Obesity	13	32.5%	74	22.7%	1.64	0.169
Malnutrition	26	65%	186	57.1%	1.40	0.337
Diabetes mellitus	13	32.5%	85	26.1%	1.37	0.386
Hypertension	2	5.0%	17	5.2%	0.96	0.954
Child-Pugh classification						
A	2	5.0	7	2.1	2.40	0.576
B	17	42.5	142	43.6	0.96	0.899
C	21	52.5	159	48.8	1.16	0.656

*: statistically significant
OR: odds ratio

Table.4 Number of microorganisms isolated in patients with nosocomial respiratory tract infections

	Number of patients (n= 40)	Percentage (%)	P-value
Patients with single microorganism	10	25%	0.000*
Patients with multiple microorganisms	30	75%	

*: statistically significant

Table.5 Percentage of different isolates in nosocomial respiratory tract infections

Type of organism	Number of isolates (n= 96)	Percentage (%)	P-value
Gram negative bacilli	37	38.5%	0.067
Gram positive cocci	34	35.5%	
Fungi	25	26.0%	

Table.6 Frequency of different isolates in nosocomial respiratory tract infections in department wards versus intensive care unit (ICU)

Organism	Department	N (n=60)	%	ICU	N (n=36)	%
Gram positive cocci						
	Staphylococci	8	13.3%	*Staphylococci*	20	56%
	Enterococci	6	10%	*Enterococci*	0	0%
Gram negative Bacilli						
	E. coli	10	16.7%	*E. coli*	5	13.9%
	Klebsiella	9	15%	*Klebsiella*	3	8.3%
	Pseudomonas	5	8.3%	*Pseudomonas*	2	5.6%
	Acinetobacter	2	3.3%	*Acinetobacter*	0	0%
	Proteus	1	1.7%	*Proteus*	0	0%
Fungi						
	Candida	19	31.7%	*Candida*	6	16.7%

N=number of isolates.

Table.7 Antibiotic susceptibilities of Gram negative bacilli isolated in nosocomial respiratory tract infection in cirrhotic patients

Antibiotic	Percentage Of Sensitivity	Percentage Of Resistance
Imipenem	87.5%	12.5%
Meropenem	82.4%	17.6%
Gatifloxacin	58.3%	41.7%
Lomefloxacin	48.8%	51.2%
Levofloxacin	48.3%	51.7%
Trimethoprim sulphamethoxazole	41.55	58.5%
Ciprofloxacin	40.9%	59.1%
Ceftriaxone	40.6%	59.4%
Norfloxacin	36.1%	63.9%
Cefipime	33.3%	66.7%
Piperacillin	25.8%	74.2%
Cefoperazone	25.0%	75%
Amoxicillinclavulanic acid	22.9%	77.1%
Cefaclor	14.3%	85.7%
Carbenicillin	13.3%	86.7%
Cefazolin	11.8%	88.2%
Ampicillin	8.8%	91.2%

Table.8 Antibiotic susceptibility of Gram positive cocci isolated in noscomial respiratory tract infections in cirrhotic patients

Antibiotic	Percentage Of Sensitivity	Percentage Of Resistance
Levofloxacin	100%	0%
Ceftriaxone	57.1%	42.9%
Cefazolin	55.6%	44.4%
Ciprofloxacin	52.9%	47.1%
Gatifloxacin	50%	50%
Amoxicillinclavulinic acid	40.6%	59.4
Lomefloxacin	37.9%	62.1%
Trimethoprim sulpha	37.9%	62.1%
Carbenicillin	33.3%	66.7%
Ampicillin	32.1%	67.9%
Benzyl penicillin	22.7%	77.3%
Norfloxacin	20.7%	79.3%
Cloxacillin	7.7%	92.3%
Cefipime	0%	100%

Table.9 Antibiotic susceptibility of the most common bacteria causing nosocomial respiratory tract infection

Pathogen	The most common sensitive antibiotics.	N (n=66)	%	The most common resistant antibiotics.	N (n=59)	%
Staphylococci	Levofloxacin	8	12.1%	Ampicillin	10	17%
E.coli	Lomefloxacin	8	12.1%	Ampicillin	9	15.3%
Klebsiella	Imipeneme	5	7.6%	Ampicillin	10	17%
Enterococci	Amoxycillinclavulinic acid	3	4.5%	Ampicillin	2	3.4%

*N=number of bacterial isolates.

Table.10 Antifungal susceptibilities of fungi isolated in noscomial respiratory tract infections in cirrhotic patients

Antifungal	Percentage Of Sensitivity	Percentage Of Resistance
Nystatin	71.4%	28.6%
Fluconazole 10	60%	40%
Fluconazole 25	47.1%	52.9%
Clotrimazole	33.3%	66.7%
Ketoconazole	31.0%	69.0%
Voriconazole	25.0%	75.0%
Itraconazole	12.1%	87.9%

Table.11 Antifungal sensitivity against most common fungi causing noscomial respiratory tract infection

Fungi	The most common sensitive antifungal.	Number Of fungal isolates (n=25)	Percentage (%)	The most common resistant antifungal	Number Of fungal isolates (n=25)	Percentage (%)
Candida albicns	Nystatin	3	12%	Itraconazole.	9	36%
Camdida tropicalis	Fluconazole	2	8%	Ketoconazole	1	4%
Candida glabrata	Nystatin	1	4%	Ketoconazole	3	12%
Candida krusei	Ketoconazole	1	4%	Itraconazole	2	8%
Candida parapsilosis	Fluconazole	1	4%	Itraconazole	1	4%

Table.12 Common bacteria isolated in nosocomial respiratory tract infections in relation to prophylactic antibiotics used in cirrhotic patients

Antibiotic Used	Gram positive cocci	Total number of Gram positive cocci (n=34)	Percentage (%)	Gram negative bacilli	Total number Of Gram negative bacilli (n=37)	Percentage (%)
Cefotaxime	*Staphylococci* *Enterococci*	5 2	14.7% 5.9%	*E. coli* *Klebsiella* *Pseudomonas*	3 4 1	8.1% 10.8% 2.7%
Amoycillinclavulinic acid	*Staphylococci*	2	5.9%	*Klebsiella* *Pseudomonas*	2 1	5.4% 2.7%
Ampicillin sulbactam	*Staphylococci*	1	3%	*Klebsiella*	1	2.7%
Ciprofloxacin	*Staphylococci*	1	3%	*E. coli*	1	2.7%
Cefipime	*Staphylococci*	1	3%	*Klebsiella*	1	2.7%

Table.13 Common fungi isolated in nosocomial respiratory tract infections in relation to prophylactic antibiotics used in cirrhotic patients

Antibiotic used	Fungi	Total number of fungal isolates (n=26)	Percentage (%)
Cefotaxime	*Candida*	7	27%
Amoycillinclavulinic acid	*Candida*	4	15.4%
Ampicillin sulbactam	*Candida*	1	3.9%
Cefipime	*Candida*	1	3.9%

Table.14 Prognosis of exposure to noscomial respiratory tract infections in cirrhotic patients

Prognosis	Number of patients (n=40)	Percentage %
Improvement	26	65%
Complications	8	20%
Death	6	15%

Figure.1 Percentage of different types of bacteria causing nosocomial respiratory tract infections in cirrhotic patients

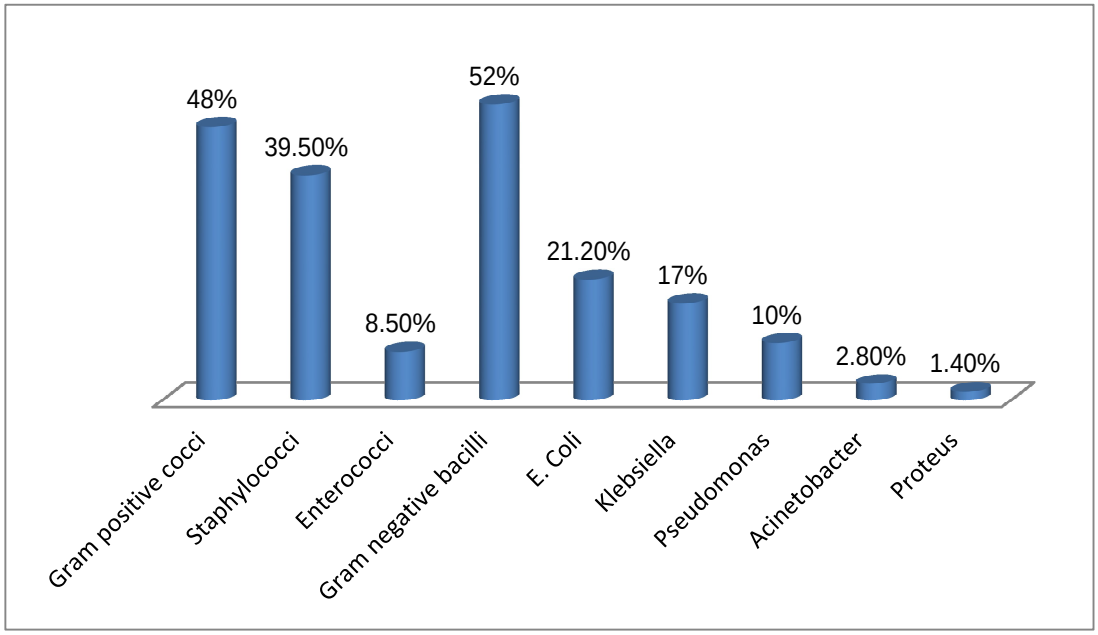
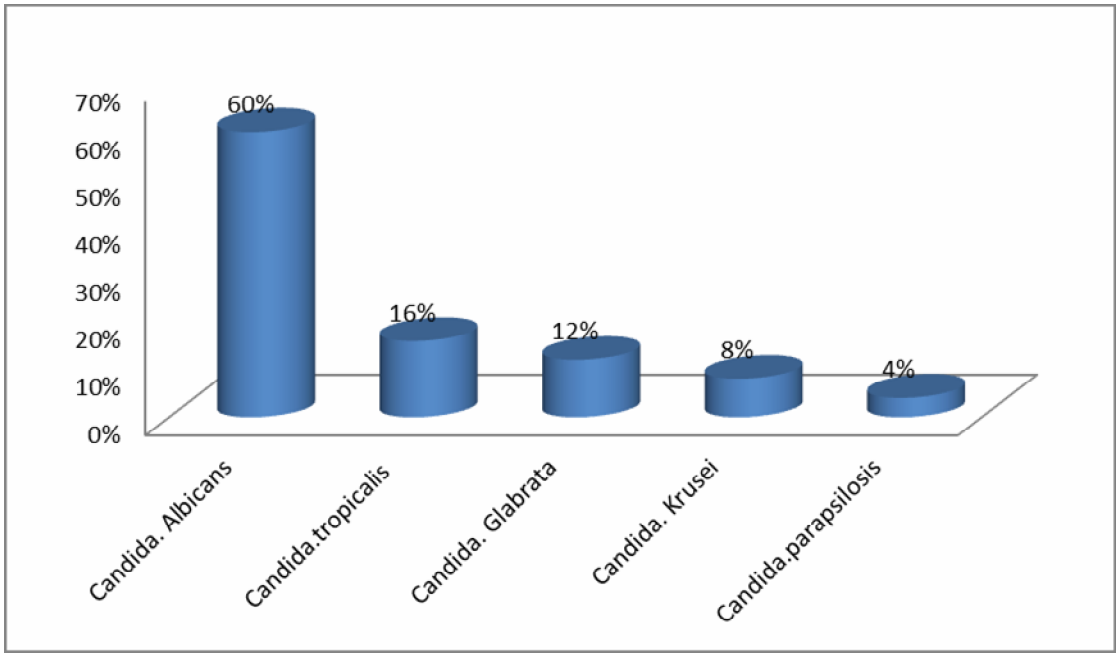


Figure.2 Percentage of different fungi isolated in nosocomial respiratory tract infections in cirrhotic patients



Analysis of risk factors affecting nosocomial respiratory tract infection in cirrhotic patients revealed that the most important risk factor was artificial respiration. This agreed with Tandon and Garcia-Tsao (2008) who mentioned that mechanical ventilation is one of the most important risk factors of nosocomial pneumonia.

From our study, we observed that bacterial causes of noscomial respiratory tract infection were 74%. Navasa *et al.* (1999) mentioned that the incidence of noscomial bacterial infection in cirrhotic patients during hospital stay was 30-60%.

In our study cultures Gram negative bacilli were more prevalent (38.5%) than Gram positive cocci (35.5%). Muder (1998) also observed that the percentage of Gram negative bacteria was more than the percentage of Gram positive bacteria as a cause of pneumonia in cirrhotic patients.

We observed that the most important Gram positive bacteria were *Staphylococci* and the most important Gram negative bacteria were *E. coli* and *Klebsiella*. Brito and Niederman (2009) discovered that the commonest causative organisms in noscomial pneumonia are *S. pneumonia*, *S. aureus* and *E. coli*.

Our results of culture and sensitivity revealed that methicillin resistant Staph aureus (MRSA) was considered one of the important causes of resistant bacteria present in isolates of patients. Muder (1998) said that it is well known that nursing home residents have high rates of colonization with MRSA.

Culture and sensitivity of Gram negative bacteria revealed that these bacteria were sensitive to numerous antibiotics as imipenem, meropenem and gatifloxacin. Also they were resistant to multiple antibiotics as penicillins, cephalosporins, levofloxacin, norfloxacin and ciprofloxacin. This agreed with Brito and Niederman (2009).

In case of Gram positive bacteria, these bacteria (*Staphylococci* and *Enterococci*) were sensitive to levofloxacin by 100%. Also these bacteria were sensitive to other antibiotics as ceftriaxone and cefazoline. They were highly resistant to Amoxycillin-clavulinic acid, lomefloxacin, ampicillin, carbenicillin and trimethoprim-sulphamethoxazole. This resistance of Gram positive bacteria was mentioned by Brito and Niederman (2009) who said that *Staphylococci* were one of the most resistant Gram positive bacteria.

Our study revealed that fungal causes were considered important causes of nosocomial respiratory tract infection. *Candida albicans* was the most common cause (60%), followed by *Candida tropicalis* (16%), and *Candida glabrata* (12%).

Antifungal susceptibilities of isolates revealed that the most sensitive antifungals were nystatin (71.4%) and fluconazole (60%) but the most resistant antifungals were itraconazole (87.9%). This agreed with results of a study done by Talwani et al (2011).

The mortality rate in cirrhotic patients exposed to nosocomial respiratory tract infection in our study was 15%. Fernandez et al (2002) said that the in hospital mortality of cirrhotic patients with infection was approximately 15%.

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