Central Venous Catheter-Related Infections in the Intensive Care Units in Egypt

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Abstract: Central venous catheter-related blood stream infection (CRBSI) is associated with high rates of morbidity and mortality in critically ill patients. This study was conducted to determine the incidence of central venous catheter-related infections (CRIs) according to different access sites, isolation, identification and determination of the predominant microorganisms involved and to determine the risk factors for infection by statistical analysis of the results to contribute the elaboration of actions to prevent and control blood stream infections and mortality among those patients. A total of 160 adult patients with indwelling central venous catheters hospitalized at intensive care units (ICUs) were enrolled in this study. A total of 640 clinical samples were collected from the patients; 4 different samples collected from each patient: 320 blood samples; 160 (pre-catheterized) and the other 160 (post-catheterization), 160 catheter tips and 160 swabs. The clinical samples were cultured on ordinary media for isolation and identification of the isolated microorganisms. Antibiotic sensitivity was determined by disk diffusion method according to National Committee of Clinical Laboratory Standard 2007 (NCCLS). Microscan automated system was also used for both identification and antimicrobial sensitivity testing. Statistical analysis used SPSS-10 version statistical software. One hundred forty two out of 160 patients (88.75%) suffered from CRIs. Catheter related infections were categorized according to CDC guidelines into Catheter-Related Blood Stream Infection (CR-BSI), Clinical Blood Stream Infection (C-BSI), Bloodstream Infection (BSI), Catheter bacteremia (CB) and Exit Site Infection (ESI), their rates were 23.2%, 8.5%, 47.9%, 2.8 % and 0.7% respectively and 16.9% were mixed infections. Semiquantitative culture was used for CRIs diagnosis. The total number of pathogens was 293 microorganisms were isolated from 261 positive cultures. Out of them 139 (47.4%) were Gram positive bacteria, 136 (46.4%) were Gram negative bacteria and 18 (6.1%) were Fungi. High frequency of microorganisms were isolated from post catheterization blood specimens (80.63%) followed by catheter tip samples (44.3%), swabs (29.4%) and the pre-catheterization blood specimens showed the lowest frequency of isolated microorganisms (6.88%).The isolated microorganisms identified by conventional and semiquantitative methods were belonging to 17 different species. The main etiological Gram positive bacteria was Coagulase negative *Staphylococci* (CoNS) representing (30.8%) and the main etiological Gram negative bacteria was *Klebsiella pneumonia* representing (10.6%). Pathogens isolated from CR-BSI were 42 isolates belonging to 13 different species; the most prevalent isolate was CoNS representing (42.9%). Pathogens isolated from C-BSI were 12 isolates belonging to 6 different species, the most prevalent isolate was *S. aureus* representing (41.7%) while 83 pathogens were isolated from BSI and they were belonging to 14 different species, the most prevalent isolates were CoNS representing (38.6%). *Pseudomonas aeruginosa* was the microorganism isolated from the single ESI detected in the study. The isolated pathogens from CRIs showed a wide range of antibiotic resistance. The emergence of multi-resistant pathogens in ICUs was highly detected in the present study. The most Gram positive and Gram negative bacteria causing CRIs were sensitive to imipenem and vancomycin. Proper insertion and care of catheters are essential to avoid infection. Education and training of health professionals on the practice of dealing with the CVC is an important tool in preventing and reducing CRIs.

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Introduction

A central venous line is a catheter which is placed directly via one of the large veins of the body (jugular, subclavian or femoral) and whose tip lies in one of the central veins (superior vena cava or inferior vena cava). Central venous catheters (CVCs) are commonly used in critically ill patients for the measurement of central venous pressure, the administration of fluids, toxic drugs, blood products and /or parenteral nutrition, in patients who have limited peripheral access, for short-term haemodialysis and insertion of a transvenous pacing electrode ***(Lorente et al., 2005).*** Central venous catheterization may cause different complications,

including infection, hemorrhage and thrombosis. Interest in catheter-related infection lies in the mortality and the costs it represents ***(Lorente et al., 2005).***

It is estimated that about 50% of all patients admitted to hospitals will receive intravenous therapy, creating a large population at risk for local and systemic blood stream infections**.** Mortality is difficult to be calculated directly, but has been estimated to range from 12 to 25% ***(Knight et al., 2008).***

Infective complications can occur in several ways, including contamination of the CVC by skin flora at the point of insertion, skin bacteria migration down the tunnel tract, bacteria transfer during manipulation and seeding from another site of infection.

Catheter related infections (CRIs) were found to be associated with several risk factors, including patient related risk factors such as age, gender, clinical status and catheter related risk factors such as the vascular access location, dwelling time, catheter type and number of lumens. In addition to the inserted solution type and the experience of the professional who performs the procedure. These factors constitute important strategic points for actions to prevent these infections ***(Mesiano and Hamann, 2007).***

Diagnosis of catheter related blood stream infection (CRBSI) is best achieved by quantitative or semi-quantitative culture of the catheter, or by paired quantitative blood cultures or paired qualitative blood cultures from a peripheral vein and from the catheter, with continuously monitoring of the differential time to positivity ***(Pittiruti et al., 2009).***

The aim of the study was to analyze the incidence of CRIs according to different access sites. In addition, the study aimed for isolation and identification of the microbial isolates, with determination of the predominant microorganisms involved and their antimicrobial sensitivity testing. Finally, determination of the risk factors for infection by statistical analysis of the results to contribute the elaboration of actions to prevent and control blood stream infections and mortality among those patients.

Material and methods

Patients & Clinical samples

A total of 160 adult patients, 86 males (53.75%) and 74 females (46.25%) with mean age of 53.3 ± 19.6 years old hospitalized at ICUs of five hospitals: Al Salam International Hospital, Sayed Galal University Hospital, El Hussein University Hospital, Al Zahraa University Hospital and Al Bank Al Ahly Hospital were included in the study.

A total of 640 clinical samples, 4 different samples collected from each patient: 320 blood samples; 160 blood samples collected before the catheter insertion (pre-catheterization) and the other 160 blood samples after the catheter removal (post-catheterization), 160 catheter tips and 160 swabs. The clinical samples were cultured on ordinary media for isolation and identification of the microorganisms. Antibiotic sensitivity was determined by disk diffusion method according to National Committee of Clinical Laboratory Standard ***(NCCLS, 2007)***. Microscan automated system (WalkAway 96) was used for both identification of some isolates and antimicrobial sensitivity testing.

Catheters

The catheters used were not antimicrobial-coated, but were radio-opaque polyurethane catheters (Arrow, Reading, PA, USA) 20 cm. The catheters were inserted by physicians with complete sterile-barrier precautions. The catheters were percutaneously inserted using the Seldinger technique and were fixed to the skin with 2-0 silk suture. The decision to remove the catheter was made by the patient's physician. Catheters were removed when they were no longer needed, if a systemic or local complication occurred or his/her death and removed by an ICU nurse using a sterile technique.

Questionnaire

The following data were collected: name, age, sex, clinical case, presence of cancer, presence of diabetes, body temperature, anti-microbial agents used, solutions used in the catheter, catheter dwelling time, number of catheter lumens and the insertion site.

Media and reagents

Different media were used for microbial isolation and identification such as Oxoid Signal Blood culture system (OXOID®, Hamsphire, England), Nutrient agar (Lab M, United Kingdom), blood agar, chocolate agar and Sabouraud agar. The isolates were preserved in skimmed milk and antimicrobial sensitivity test was done on Muller Hinton agar (Bacto, France) using 12 different antimicrobial agents ***(NCCLS, 2007)***.

Microscan automated system

A MicroScan WalkAway 96 instrument (Dade, Inc., MicroScan Inc.) with the Rapid Negative ID3 panel was used. The Rapid Negative ID3 panel is designed for the identification to species level of rapidly growing aerobic and facultatively anaerobic non-glucose-fermenting and non-Enterobacteriaceae glucose-fermenting Gram-negative bacilli. The software version was 22.28 ***(Winstanley and Courvalin, 2011)***.

Methods

1. Clinical sample collection

Blood cultures: Two blood culture bottles (2 sets) were used where 20 ml of blood was withdrawn from the puncture site (10 ml for each bottle). The 2 blood culture bottles were taken before catheterization labeled "pre" and the other 2 bottles were taken after catheterization labeled "post".

Tips: After catheter removal under sterile conditions, all catheter tips were collected and cut a 5 cm from the distal segment with sterile scissors and transported to the laboratory in tubes containing 10 ml of phosphate-buffered saline (PBS) and 0.1% Tween 80 to be cultured by a "Semi-quantitative roll-plate" method.

Swabs: Swabs were taken immediately after catheter removal, they were taken from the insertion site and 20 cm around it in circular motion by a sterile clean swab and labeled "swab". The swab tubes filled with a nutrient broth until transferred to the laboratory to be cultured at the same day.

2. Bacteriological cultivation and isolation

Blood cultures: The 4 bottles were placed immediately in an incubator at 37ºc up to 7 days. They were watched daily for signs of growth, including cloudiness or a color change in the broth, gas bubbles, or clumps of bacteria. If any sign from above observed in the 2 bottles, sub-culturing were performed as the following: By a syringe, we drew blood from each bottle into a sterile clean swab and then direct plating of the swab by streaking technique onto blood agar plate to support growth of bacteria either Gram positive or Gram negative, chocolate agar plate to support growth of fastidious bacteria and Sabouraud agar plate to support growth of fungi ***(Bridson, 1998)***.

Tips: The tip was cultured by "Semiquantitative roll-plate catheter culture" technique as mentioned by ***Maki et al. (1977*)**. The catheter-tip segment is transferred to the surface of a blood agar, chocolate agar, Sabouraud agar plate for semi-quantitative culturing. While downward pressure is exerted with a flamed forceps, the catheter tip was rolled back and forth across the surface at least 4 times. At the end of incubation period, all colony types appearing on the plates are enumerated and the criteria for positivity ≥ 15 CFU.

Swabs: 0.1 ml of the fluid of the swabs was inoculated onto blood agar, chocolate agar and Sabouraud agar plates**.**

3. Determination of antibiotic sensitivity by disk diffusion method

Antibiotic sensitivity of the isolates was determined using the Kirby-Bauer disk-diffusion breakpoint assay on Mueller-Hinton agar using Oxoid disks as recommended by the Clinical and Laboratory Standards Institute guidelines ***(NCCLS, 2007)***.

4. Automated identification (walkAway microscan)

A total of 25 isolates of Gram-negative bacilli from recently sub-cultured colonies. The collection included both oxidase-negative and oxidase- positive strains. The strains were cultured onto sheep blood agar before being transferred onto MacConkey's agar and incubated at 37ºc for 24 hrs. Rapid Negative ID3 panels were removed from the refrigerator and allowed to warm to room temperature before being inoculated according to the manufacturer's directions and loaded into the MicroScan Walk/Away 96 instrument. WalkAway panel processing functions were controlled and monitored via the LabPro computing system (not included - available from manufacturer). The bar code printer produces bar code labels to be affixed to panels during panel setup. The WalkAway instrument reads each bar code and stores the panel identification information with the panel. With the optional Report Printer LabPro provides several reports based on panel results. Results are reported in the next day, when resistance has developed and can be properly expressed.

5. Criteria used for diagnosis

The criteria recommended by the CDC guidelines **(*O'Grady et al., 2002*)** were used for the diagnosis: Catheters with negative results of microorganism cultures were considered sterile.

Bloodstream Infection (BSI): was defined as isolation of microorganism from peripheral venous blood in a patient with systemic inflammatory response while other infection sources were excluded.

Clinical Blood Stream Infection (C-BSI): was diagnosed when the patient presented at least one of the signs or symptoms without another identified cause: fever (temperature 38º C), pain, erythema or heat of the involved vascular site and >15 Colony Forming Units (CFU) isolated from the tip of the intravascular catheter, and blood culture with a negative result or not accomplished.

Catheter-Related Blood Stream Infection (CR-BSI): was diagnosed as isolation of the same microorganism from a semi-quantitative culture of a catheter tip and a peripheral blood culture with systemic inflammatory response syndrome (such as fever, pain, erythema or heat of the involved vascular site) after exclusion of other infection sources.

Exit Site Infection (local): purulent discharge at the exit site or/tenderness, erythema with induration of

>2 centimeters (cm) around the exit site, with a positive culture of serous discharge. This is confirmed by a swab of the catheter exit site.

Central Venous Catheter Tip Colonization (TC) : an intermediate value of greater than 15 colony-forming units (CFU) on roll plate culture represents a positive colonization obtained from skin swabs, intraluminal brushings and/or catheter tips.

6. Statistical analysis

Categorical data were summarized as percentages. Comparisons among different groups of patients were performed by Graphpad Instat by one way analysis of variance (ANOVA), one or two tail *P* value and student t- test. *P*-values<0.05 were considered significant.

Results:

This study was carried out on 160 patients hospitalized in five hospitals, 86 out of them were males (53.75%) and 74 were females (46.25%). Among them 14.4% were 20-39 years old, 29.4% were 40-59 years old and 56.2% were ≥60 years old with mean age 53.3±19.6 years old. In the present study, a total of 640 clinical samples were microbiologically studied, 40.3% were positive culture and 59.7% were negative.

High frequency of microorganisms were isolated from post catheterization blood specimens (80.63%) followed by catheter tip samples (44.3%), swabs (29.4%) and the pre-catheterization blood specimens showed the lowest frequency of isolated microorganisms (6.88%).

In the present study, a total number of 293 microorganisms were isolated from 261 positive cultures. Out of them 139 (47.4%) were Gram positive bacteria, 136 (46.4%) were Gram negative bacteria and 18 (6.1%) were fungi. The distribution of these pathogens among different clinical samples was shown in figure (1).

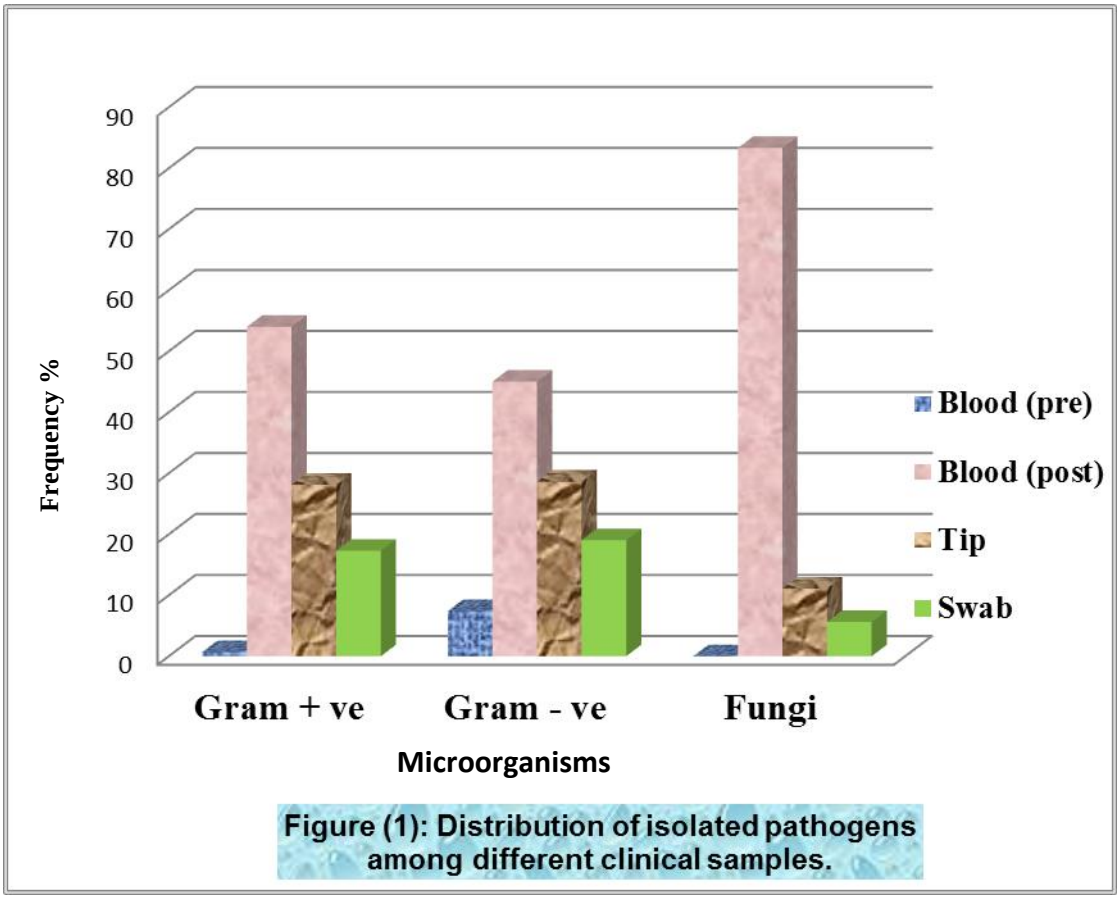

Figure (1): Distribution of isolated pathogens among different clinical samples.

Belonging to 17 different species the most prevalent one was coagulase negative *Staphylococcus* (CoNS) (30.7%) followed by *S. aureus* (12.61%) and the least common one was *Yersinia pseudotuberculosis* (0.34%). The most prevalent Gram negative bacteria isolated was identified as *Klebsiella pneumonia* (10.6%). In the present study, eleven isolates recovered from pre-catheterization blood sample, they were *Kluyvera cryocrescens* (45.45%), *Klebsiella pneumonia* (27.27%), *E. coli*

(18.18%) and *S. aureus* (9.09%) suggesting they might have been contaminants. Only one isolate of *Yersinia pseudotuberculosis* isolated from swab of a patient suffering from Izumi- fever which was confused with CRI. On the other hand, CoNS was the main pathogen isolated from post-catheterization blood cultures, catheter tips and swabs (35.1%, 27.5%, and 29.4% respectively) as in table (1).

The prevalence of CRIs in the current study was 142 out of 160 catheterized patients (88.75%). Catheter related infections were categorized according to CDC guidelines into five different types of infections: CR-BSI, C-BSI, BSI, CB and ESI. The most prevalent infection type were BSI (49%) followed by CR-BSI (27%), C-BSI (21.25%), CB (2.5%) and ESI (0.6%). Their frequency rates among the studied catheterized patients were 23.2%, 8.5%, 47.9%, 2.8% and 0.7% respectively and 16.9% were mixed infections as shown in table (2).

A total of 42 microorganisms isolated from the catheter tips and peripheral blood culture specimens of CR-BS infected patients where 25 (59.5%) Gram +ve while 16 (38.1%) of them were Gram – ve and only one isolate (2.4%) was fungus. A total of 12 microorganisms isolated from the tip samples of C-BS infected patients where 9 (75.0%) of isolated microorganisms were Gram + ve while 2 (16.7%) of them were Gram –ve and only one isolate (8.3%) was Fungus. A total of 83 microorganisms isolated from the peripheral blood culture specimens of BS infected patients where 42 (50.6%) of isolated microorganisms were Gram +ve, 31 (37.35%) were Gram –ve and 10 (12.05%) were Fungi. The isolated microorganisms from CB were 4 isolates belonging to 2 different species which were CoNS (50%) and *Serratia marcescenes* (50%).

Table (1): Distribution of pathogens isolated from the four different clinical samples.

M.O.	No.	%	Pre	%	Post	%	Tips	%	Swabs	%
CoNS	90	30.7	-	-	53	(35.10)	22	(27.50)	15	(29.40)
S. aureus	37	12.61	1	(9.09)	15	(9.90)	13	(16.25)	8	(15.70)
Klebseilla pneumonia	31	10.6	3	(27.27)	10	(6.60)	8	(10.00)	10	(19.60)
E. coli	22	7.5	2	(18.18)	9	(6.00)	6	(7.50)	5	(9.80%)
Serratia marcescenes	20	6.8	-	-	15	(9.90)	3	(3.75)	3	(5.90%)
Candida spp.	18	6.1	-	-	15	(9.90)	2	(2.50)	1	(2.00)
Stenotophomonas maltophilia	13	4.45	-	-	7	(4.60)	3	(3.75)	3	(5.90)
Acinetobacter lwoffii	12	4.1	-	-	-	-	10	(12.50)	1	(2.00)
Enterococci spp.	12	4.1	-	-	7	(4.60)	4	(5.00)	1	(2.00)
Kluyvera cryocrescens	11	3.77	5	(45.45)	3	(2.00)	2	(2.50)	1	(2.00)
Enterobacter cloacae	10	3.4	-	-	6	(4.00)	3	(3.75)	1	(2.00)
Alcaligenes spp.	4	1.37	-	-	2	(1.30)	1	(1.25)	1	(2.00)
Cedecea spp.	4	1.37	-	-	2	(1.30)	2	(2.50)	-	-
Pseudomonas fluorescens	3	1.0	-	-	3	(2.00)	-	-	-	-
Pseudomonas aeruginosa	3	1.0	-	-	2	(1.30)	1	(1.25)	-	-
Chryseobacterium memingosepticum	2	0.68	-	-	2	(1.30)	-	-	-	-
Yersinia pseudotuberculosis	1	0.34	-	-	-	-	-	-	1	(2.00)
Total	**293**	**100**	**11**	**100**	**151**	**100**	**80**	**100**	**51**	**100**
±S.E	**±5.188**		**±0.8539**		**±3.319**		**±1.577**		**±1.238**	
±S.D.	**±21.391**		**±1.708**		**±12.853**		**±5.902**		**±4.462**	
***P* value**	**0.0043***		**0.0486****		**0.0089***		**0.0031***		**0.0081***	

* Considered very significant, ** Considered significant

Pre= pre catheterization blood samples, Post= post catheterization blood samples, Tips= catheter tips

Table (2): Frequency of different catheter related infections among patients.

Type of infection	No. of infected patients	%
CR-BSI	33	**23.2**
C-BSI	12	**8.5**
BSI	68	**47.9**
CB	4	**2.8**
ESI	1	**0.7**
Mixed infections	24	**16.9**
Total	**142**	**100**
±S.E	**±10.148**	**-**
±S.D.	**±24.857**	**-**

P value was 0.0670, considered not quite significant. CR-BSI= catheter-related blood stream infection, C-BSI= clinical blood stream infection, BSI= blood stream infection, CB= catheter bacteremia, ESI= exit site infection

The major mixed infections detected in this study were C-BSI and BSI (66.7%) as shown in figure (2).

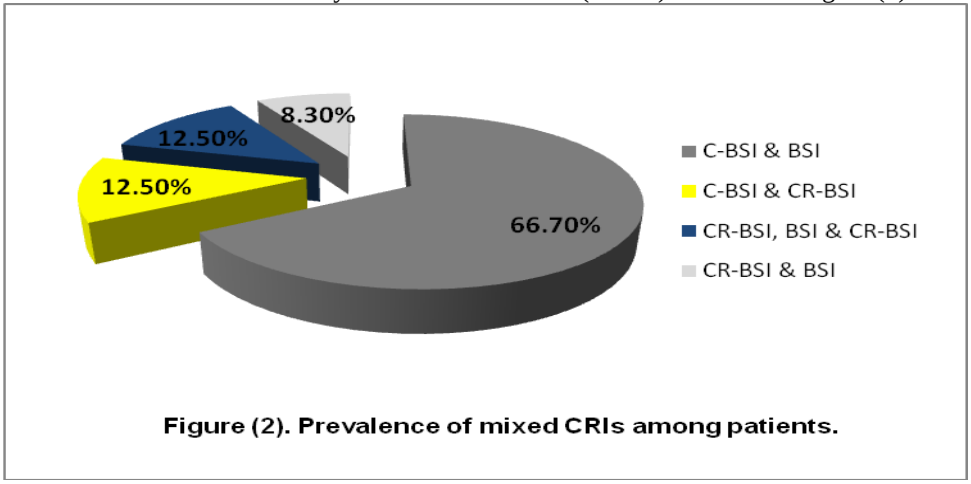

Figure (2). Prevalence of mixed CRIs among patients.

CR-BSI= catheter-related blood stream infection, C-BSI= clinical blood stream infection, BSI= blood stream infection

Fever associated with all types of CVC infections where all infected patients were feverish. Erythema and inflammation associated with some types of infections. Purulent associated with CR-BS, C-BS and C-BS plus BS infections as the following percentages 45.5%, 100% and 18.7% respectively as shown in table (3).

Only one catheterized patient diagnosed as ES infected where no bacteria or fungi isolated from her samples but she suffered from local catheter related symptoms as erythema, tenderness, induration and exudates over the skin within 2 cm around the insertion site.

Table (3): Signs and symptoms associated with different CRIs.

Sign/ Symptom	CR-BSI (n= 33)	C-BSI (n=12)	BSI (n=68)	C-BSI & BSI (n=16)	CR-BSI & BSI (n=2)	C-BS & CR-BSI (n=3)	C-BSI & CR-BSI & BSI (n=3)
Fever	33 (100%)	12 (100%)	68 (100%)	16 (100%)	2 (100%)	3 (100%)	3 (100%)
Erythema	24 (72.7%)	7 (58.3%)	0	8 (50%)	2 (100%)	3 (100%)	3 (100%)
Inflammation	20 (60.6%)	2 (16.7%)	43 (63.2%)	0	1 (50%)	2 (66.7%)	3 (100%)
Purulent	15 (45.5%)	12 (100%)	0	3 (18.7%)	0	0	0
±S.E.	±3.808	±2.394	±16.815	±3.497	±0.4787	±0.7071	±0.75
±S.D.	±7.616	±4.787	±33.629	±6.994	±0.9574	±1.414	±1.5

The *P* value was 0.0500, considered significant.

CR-BSI= catheter-related blood stream infection, C-BSI= clinical blood stream infection, BSI= blood stream infection

Risk factors associated with CVC infections were divided into two categories, patient related risk factors and catheter related risk factors. Table (4) shows the analysis of both related risk factors associated with different CRIs.

Among CoNS isolated in the present study, resistance was high to cefotaxime, erythromycin, oxacillin and penicillin G (100%), imipenem (98.9%) and cefepime (90%), while it showed high sensitivity to vancomycin (84.4%) and rifampin (72.2%). On the other hand, *S. aureus* was highly resistant to chloramphenicol, erythromycin, and penicillin G (100%), cefotaxime (89.5%), imipenem (89.2%), ciprofloxacin (86.5%) and oxacillin (83.8%) while it was highly sensitive to vancomycin (81%). In the present study *Klebsiella pneumonia* isolates were highly resistant to erythromycin (96.8%), chloramphenicol (90.3%) and cefotaxime (74.2%), while it showed highly sensitivity to imipenem (93.5%). The isolated *E.coli* was highly resistant to erythromycin (100%), chloramphenicol (95.5%), while it showed high sensitivity to imipenem (90.9%), meanwhile *Pseudomonas* spp. were highly resistant to chloramphenicol (100%) and erythromycin (96.8%) followed by cefepime, cefotaxime, co-trimoxazole & rifampin (66.7%) while it was sensitive to amikacin and imipenem (66.7%). The isolated *Enterobacter cloacae* showed high resistant to erythromycin (100%) and chloramphenicol (90%), while it showed high susceptibility to vancomycin (80%). *Stenotrophomonas maltophilia* was highly resistant to chloramphenicol, erythromycin & imipenem (100%) while it showed high susceptibility to co-trimoxazole (84.6%) and vancomycin (83.3%). *Acinetobacter lwoffii* isolates showed high resistance to erythromycin & chloramphenicol (100%) and cefotaxime (73.3%), while it showed susceptibility to vancomycin (83.3%) and ciprofloxacin (58.3%). *Serratia marcescenes* was highly resistant to erythromycin (100%), while it showed high susceptibility to ciprofloxacin (100%) and cefotaxime (85%). The isolated *Kluyvera cryocrescens* showed high susceptibility to chloramphenicol & vancomycin (100%), amikacin & cefotaxime (90.1%) and cefepime & co-trimoxazole (72.7%).

Table (4): Analysis of both patient and catheter related risk factors associated with different CRIs.

CRI Type / Risk Factor	CR-BSI (n=33)	C-BSI (n=12)	BSI (n=68)	CB (n=4)	Mixed Infections		
					C-BSI &BSI (n=16)	C-BSI & CR-BSI (n=3)	C-BSI & CR-BSI &BSI (n=3)
Patient related risk factors							
Age = 40-59	-	-	-	-	-	2(66.7%)	2(66.7%)
Age ≥ 60	27(81.8%)	11(91.7%)	40(58.8%)	4(100%)	6(37.5%)	-	-
Male	19(57.6%)	7(58.3%)	35(58.3%)	-	12(75%)	3(100%)	3(100%)
Neurological disease	19(57.6%)	-	22(32.4%)	-	8(50%)	-	-
Heart disorder	-	-	-	-	-	2(66.7%)	-
Trauma	-	5(41.7%)	-	2 (50%)	-	-	-
Cancer	18(54.5%)	2(16.7%)	-	-	-	-	2(66.7%)
Diabetes	33(100%)	3(25%)	-	-	-	-	2(66.7%)
Catheter related risk factors							
Insertion site							
Femoral	13(39.4%)	5(41.6%)	-	-	-	-	2(66.7%)
Internal Jugular	-	-	35(51.5%)	3(75%)	-	-	-
Sub-clavian	-	-	-	-	16(100%)	3(100%)	-
Catheter dwelling time							
≤ 7 (Mean=8.3)	-	-	-	-	14(87.5%)	2(66.7%)	
8 – 14	21(63.6%)	9(75%)	48(70.5%)	4(100%)	-	-	2(66.7%)
No. of catheter lumens							
Single	-	-	44(64.7%)	-	15(93.75%)	-	-
Double	29(87.9%)	11(91.7%)	-	-	-	-	-
Triple	-	-	-	-	-	2(66.7%)	2(66.7%)
TPN/ LCS*	31(93.9%)	10(83.3%)	9(13.2%)	-	-	-	-
Use of antimicrobials	33(100%)	12(100%)	68(100%)	4(100%)	16(100%)	3(100%)	3(100%)

***TPN/ LCS: Total parenteral nutrition/ Lipid containing solution

CR-BSI= catheter-related blood stream infection, C-BSI= clinical blood stream infection,
BSI= blood stream infection, CB= catheter bacteremia

All *Alcaligenes* spp. were susceptible to amikacin, co-trimoxazole, imipenem and rifampicin. All *Cedecea* spp. were susceptibile to amikacin, cefepime, cefotaxime, ciprofloxacin and co-trimoxazole. All *Chryseobacterium memingosepticum* were susceptible to amikacin, cefotaxime, ciprofloxacin, co-trimoxazole, imipenem, rifampicin and vancomycin. *Yersinia pseudotuberculosis* isolate was susceptible to amikacin, cefotaxime, ciprofloxacin, co-trimoxazole, imipenem, rifampicin and vancomycin.

Discussion

Catheter-related bloodstream infections (CR-BSIs) is a recognized complication associated with central venous access devices and an important cause of hospital-acquired infection associated with morbidity, mortality and cost. CR-BSIs also have important adverse consequences for both patient and institution ***(Scales, 2011)***. In the present study, the semiquantitative technique was used in diagnosis of CRIs due to its advantages which are rapid, efficient and its result must be part of a set of factors that can indicate diagnosis and a specific treatment ***(Marconi et al., 2008).*** However, it requires careful interpretation. In the current study, the isolates of all species obtained from both catheter tips and from blood each had the same profile of antibiotic sensitivity, so it is regarded as CR-BSI as reported by ***Stratton (1998)*** who stated that the isolated microorganism must be of the same genus and species, and have the same antibiotic sensitivity test profile and the indicator for the risk of bacteraemia was the presence of ≥15 colonies/plate according to the criterion stated by ***Maki et al. (1977)*** and ***Bouza et al. (2004).*** In the present study, a total of 640 clinical isolates from 160 catheterized patients were recovered during the period from 2007 to 2009; samples were obtained from five hospitals which were Al Salam, Sayed Galal, Al Husin, Al Zahraa and Al Bank Al Ahly Hospitals in Cairo, Egypt.

The rate of CRIs was recorded as (88.75%) which was more than that reported in many studies **(*Maki et al., 1991; Lorente et al., 2005*).** This may be attributed to that most developing countries do not have laws mandating health care–associated infection control programs, and hospital accreditation is not required. Hand hygiene also greatly varies in most centers.

Catheter related infections were categorized in the present study according to CDC guidelines ***(O'Grady et al., 2002)*** into CR-BSI, C-BSI, BSI, CB and ESI. In the present study, the rates of BSI and CR-BSI detected were high representing 47.9% and 23.2% respectively. Although BSI and CR-BSI were reported to range between 1-13% in many studies **(*Lorente et al., 2005; Mesiano and Hamann, 2007; Salomao et al., 2008; Porto et al., 2010*), Fathy *et al.* (2010)** found higher rate of CR-BSI (47.8%) than our results in the present study. The rate of C-BSI detected in the present study was slightly higher (8.5%) than those reported by ***Chen et al. (2006)*** **and** ***Mesiano and Hamann (2007)*** which were 5% and 4.9% respectively.

The reason of high rates of infections in the present study may be due to insertion of catheters in an emergency situations, this can lead to the breaking of aseptic techniques besides the risk of traumatic vessel injuries. It has been significantly associated with higher risk of CRIs. Because of this, catheters placed under emergency situations were replaced as soon as possible. On the other hand, the rate of CB detected in the present study was 2.8% which was lower than that showed by ***Chen et al. (2006)*** which was 8.5%. Meanwhile, only one patient (0.7%) categorized to have ESI. This rate is compatible with other different studies reported by ***Chen et al. (2006)*** and ***Hobbs and Taylor (2006)*** which was 0.7% and 0.5% respectively.

The microbiological diagnosis of CRIs is very important, once the therapy can be targeted according to the isolated agent and its spectrum of resistance ***(Porto et al., 2010)***. In the current work, it was noticed that there was no significant difference between Gram positive and Gram negative predominance in CRIs (47.4% and 46.4% respectively), in CR-BSI predominance (59.5% and 38.1% respectively), and in BSI predominance which was 50.6% and 37.3% respectively. On the other hand, it was noticed that there was a significant difference between Gram positive and Gram negative in C-BSI predominance (66.7% and 16.6% respectively). These results were in consistence with ***Gupta et al. (2011)*** who reported that Gram positive bacteria represented 47.6% and Gram negative bacteria represented 45.8% respectively in CRIs.

Catheter related infections are often difficult to be treated because they are caused by organisms often resistant to antimicrobial agents that embed themselves in a biofilm layer on the catheter surface and attached to thrombin sheath on the surfaces of intravascular devices ***(Raad and Hanna, 2002)***. Our study revealed that *S. aureus* was resistant to Chloramphenicol, Erythromycin, and Penicillin G (100%), Cefotaxime (89.5%), Imipenem (89.2%), Ciprofloxacin (86.5%), Oxacillin (83.8%), Cefepime (78.4%), Amikacin (59.5%), Co-trimoxazole (56.8%), Rifampin (46%) and Vancomycin (19%). These results were in consistent with ***Storti et al. (2006)*** who found that *S. aureus* was highly resistant to different antimicrobials including Gentamycin, Chloramphenicol, Ciprofloxacin, Co-trimoxazole,

Erythromycin, Oxacillin and Penicillin G (100%) and showed the same resistance to Rifampin (48.7%) but they did not report any Vancomycin resistance.

Among CoNS isolated in the present study, resistance was also high to Cefotaxime, Erythromycin, Oxacillin and Penicillin G (100%), Imipenem (98.9%), Cefepime (90%), Co-trimoxazole (76.7%), Ciprofloxacin (53.3%), Amikacin (52.2%), Chloramphenicol (49%), while it showed high sensitivity to Vancomycin (84.4%) and Rifampin (72.2%). These results were in line with ***Gupta et al. (2011)*** who reported that CoNS was resistant to Amikacin, Cefotaxime, Cipofloxacin and Erythromycin (100%). ***Sadoyma and Gontijo (2000)*** attributed the growing frequency of Oxacillin-resistant CoNS and *S. aureus* infections among CRI agents to that CoNS usually adhere to the surface of the CVC polymer to form slime/glycocalyx after catheter insertion into the vascular system and that *S. aureus* produce protein adhesions on the bacterial cell wall, involving fibrinogenic receptors and fibronectine in the biofilm of the CVC tip.

Concerning Enterobacteriaceae β-lactamase production is the most common mechanism of resistance. Extended-spectrum beta-lactamase (ESBL) produced by Enterobacteriaceae have variable resistance to cephalosporins, penicillins, β-lactamase inhibitors, and monobactams. ESBLs are plasmid-encoded and associated with a great ability to spread between bacteria ***(Giske et al., 2008).*** The present study showed that *Klebsiella pneumonia* isolates were resistant to Erythromycin (96.8%), Chloramphenicol (90.3%), Cefotaxime (74.2%), Rifampin (71%), Co-trimoxazole (67.7%) and Cefepime (61.3%) while it showed sensitivity to Imipenem (93.5%), Vancomycin (74.2%), Amikacin (64.5%) and Ciprofloxacin (58%). These findings were in consistent with ***Sallam et al. (2005), Storti et al. (2006)*** and ***Rosenthal et al. (2010)*** who detected the same frequencies of resistance and susceptibility of *Klebsiella pneumonia*. Regarding *E.coli* isolated in our study, it was highly resistant to Erythromycin (100%), Chloramphenicol (95.5%), Co-trimoxazole (81.4%), Rifampin (72.7%), Cefepime and Cefotaxime (68.2%), Ciprofloxacin (54.5%) while showed sensitivity to Imipenem (90.9%), Amikacin (77.4%) and Vancomycin (77.3%). These results were in consistent with ***Sallam et al. (2005), Salomao et al. (2008)*** and ***Rosenthal et al. (2010).*** The emergence of *E.coli* resistance to quinolones and extended-spectrum cephalosporins remains a considerable challenge, since these agents are often used as first-line therapy. Unfortunately, the plasmids carrying these ESBL genes often carry resistance determinants targeting fluoroquinolones as well ***(Peleg and Hooper, 2010).***

Enterobacter cloacae isolated in this study showed high resistant to Erythromycin (100%), Chloramphenicol (90%), Co-trimoxazole (80%), Cefepime and Cefotaxime (70%), Amikacin and Rifampin (60%) while it showed susceptibility to Vancomycin (80%) and Ciprofloxacin & Imipenem (60%). These results were in consistent with ***Fathy et al. (2010)*** and ***Rosenthal et al. (2010). Jacoby (2009)*** explained the resistance of *Enterobacter* spp. by presence of AmpC enzymes which are inducible and can be expressed at high levels by mutation. Over expression of these genes confer resistance to broad-spectrum cephalosporins including cefotaxime, ceftazidime, and ceftriaxone. The previous study also reported that transmissible plasmids have acquired genes for AmpC enzymes. Resistance due to plasmid-mediated AmpC enzymes is less common than ESBL production in most parts of the world but may be both harder to detect and broader in spectrum. In the present study, *Serratia marcescenes* was resistant to Erythromycin (100%), Amikacin (55%), Imipenem (40%) while it showed high susceptibility to Ciprofloxacin (100%), Cefotaxime (85%), Cefepime and Chloramphenicol (80%) and Co-trimoxazole (70%). These results were in consistent with ***Sethuraman et al. (2011)*** who reported that largest number of *Serratia marcescenes* was resistant to Amikacin. The phenomenon of resistance to aminoglycoside antibiotics (gentamicin, tobromycin and amikacin) occurred in early 1980s.

Regarding *Acinetobacter lwoffii* isolated in the present study, it showed high resistance to Erythromycin and Chloramphenicol (100%), Cefotaxime (73.3%), Cefepime, Penicillin G (66.7%) and Rifampin (66.7%), Co-trimoxazole & Oxacillin (58.3%) and Amikacin (50%) while it showed susceptibility to Vancomycin (83.3%), Ciprofloxacin (58.3%) and Imipenem (50%). These results were in line with ***Constantiniu et al. (2004)*** who found that *Acinetobacter* spp. were 79.2 % resistant to Cefepime, 75% to Cefotaxime, Amikacin and 41.6% to Co-trimoxazole. Most of the strains were sensitive to Ciprofloxacin and Imipenem. ***Bayuga et al. (2002)*** reported 45% multi-resistant *Acinetobacter* spp. and ***Joshi et al. (2003)*** showed that 75% of the isolates were multidrug resistant and more than 70% were lactamases-producers.

Our results found that *Pseudomonas* spp. were highly resistant to Chloramphenicol (100%) and Erythromycin (96.8%) followed by Cefepime, Cefotaxime, Co-trimoxazole and Rifampin (66.7%) and Ciprofloxacin (50%) while it was sensitive to Amikacin and Imipenem (66.7%). This result is in consistent with ***Storti et al. (2006)*** who reported that all *Ps. aeruginosa* strains cultured from blood were susceptible to Imipenem where Ceftazidime did not

have any activity against *Ps. aeruginosa*. Also ***Sader et al. (2001)*** noted that Carbapenem (imipenem) is the third most active compound against *Pseudomonas* spp. (predicted by meropenem and piperacillin/ tazobactam) and they observed that *Ps. aeruginosa* isolated from ICU had a tendency to express higher resistance rates. ***Engel (2009)*** suggested that *Pseudomonas* spp. have intrinsic antibiotic resistance and have also acquired other mechanisms of resistance, including β-lactamases, carbapenemases, and multidrug efflux pumps. The high resistance of *Pseudomonas* spp. causing CRIs was attributed to formation of a biofilm layer on catheter tips ***(Frasca et al., 2010).***

Regarding *Stenotrophomonas maltophilia,* many specific risk factors are related to infection with it including an extended stay in a critical care unit and prolonged exposure to broad-spectrum antibiotics **(*Engel, 2009*)**. In the current study, *S. maltophilia* was highly resistant to Chloramphenicol, Erythromycin & Imipenem (100%), Amikacin (77%) and Cefotaxime & Ciprofloxacin (69.2%), while it showed susceptibility to Co-trimoxazole (84.6%), Vancomycin (83.3%), Rifampin (77%) and Cefepime (53.8%). These findings were consistent with ***Gautam et al. (2009)*** who found that *S. maltophilia* was resistant to Imipenem (72.22%) while it was sensitive to Cefepime (81.1%) and Co-trimoxazole (81.25%). ***Engel (2009)*** recorded that *S. maltophilia* has a high-level intrinsic resistance to many antibiotics, including β-lactams, quinolones, aminoglycosides and tetracycline, as well as to some disinfectants and silver used to line catheters.

Catheter related infections were found to be associated with several risk factors, including patient related risk factors such as age, gender, clinical status, cancer and diabetes. Also, catheter related risk factors such as insertion site, dwelling time, number of catheter lumens and use of TPN/LCS and antimicrobials.

Regarding patient underlying condition in the present study, it was found that neurological disease and trauma were risk factors associated with CRIs. It was found that 57.6% of patients with CR-BSI and 32.4% of BSI were suffering from neurological disease. Even though, neurological disease was statistically non significant risk factor for CR-BSI but statistically very significant risk factor for BSI. It was found that trauma was statistically significant risk factor for C-BSI in the present study (41.7%). Also, 50% of CB infected patients have trauma but statistically it was not quite significant risk factor for CB. This result is in agreement with those reported by ***Lorente et al. (2005)***. In the present study, there was significant increase in CR-BSI, BSI and CB among cancer patients. This finding was in consistent with ***Mollee et al. (2011)*** who reported that cancer was a significant risk factors associated with CR-BSI, BSI and CB. Concerning diabetes, CR-BSIs were greatly higher among diabetic patients (82.5%) than non diabetic patients (8.3%). Oppositely, C-BSI rate was the same in diabetic and non diabetic patients (7.5%). These results were in consistence with those reported by ***Mollee et al. (2011)***. Although patients aged ≥ 60 years old were the main age group develops CRIs in the present study (49.6%, 53.4%, 54.3% and 55.1% of CR-BSI, C-BSI, BSI and CB respectively), there was no statistically significant relation between CRIs and age group. This result was found to be more or less in consistent with ***Lorente et al. (2005), Chen et al. (2006)*** and ***Porto et al. (2010)***. ***Jean et al. (2002)*** and ***Gupta et al. (2011)*** found that age group is a non significant parameter in developing CRIs. Our results showed that there was a slight increase in CRIs among males than females where 57.6%, 58.3% and 58.8% of CR-BSI, C-BSI and BSI were males. Statistically gender was not significant risk factor in the present study. These results were in partial agreement with ***Holton et al. (2006)*** who found that 52.9% of patients infected with CRIs were males.

The present study revealed that the femoral site of insertion was a significant risk factor for CR-BSI and C-BSI. However, there was no significant increase in BSI or CB among different insertion sites. This was in agreement with ***Merrer et al. (2001)*** **and** ***Lorente et al. (2005)***. Femoral vein access shows a higher incidence of CR-BSI than the other sites, probably because of the higher density of local skin flora in the groin area **(*Lorente et al., 2005*)**.The higher incidence of CR-BSI with jugular access compared to subclavian access is probably due to three factors favoring skin colonization; the proximity of the insertion site to the mouth and the oropharyngeal secretion, the higher density of local skin flora due to the higher local skin temperature and the difficulties in maintaining occlusive dressings ***(Lorente et al., 2005)***. Regarding the catheter dwelling time, there was a statistically significant increase in CB, CR-BSI but no significant increase in C-BSI among patients catheterized for 8-14 days (100%, 63.6% and 75% respectively). ***Chen et al. (2006)*** suggested that catheterization for more than seven days was a risk factor for CR-BSI. Although there was no statistical increase in CRIs in the present study related to the number of catheter lumens, the rates of CR-BSI and C-BSI were greatly higher in double lumen catheters (87.9% and 91.7% respectively). On the other hand, the rate of BSI was higher in single lumen catheters (64.7%). This result was in agreement with ***Mesiano and Hamann (2007)*** who reported higher usage and consequently, higher

incidence of CRIs in patients with double lumen catheters. In the present study, total parenteral nutrition/ lipid containing solution (TPN/LCS) was a significant risk factor for CR-BSI and C-BSI (93.9% and 83.3%). On the other hand, there was no statistical increase in BSI and CB with TPN/LCS. These results were in accordance with ***Chen et al. (2006)*** and ***Porto et al. (2010)*** who reported that the parenteral nutrition was a significant risk factor linked mainly to the bacteremia caused by Gram-negative bacilli. Our results showed that CRIs were found to be associated with prior antibiotic therapy. This result is in consistent with ***Chen et al. (2006)*** who found that 87% of patients with CRIs had prior antibiotic therapy. Regarding the CRIs sign and symptoms, fever is the most predominant sign associated with CRIs. This result was in consistence with ***Gupta et al. (2011).*** In this study, only one catheterized patient diagnosed as ESI where *Pseudomonas aeruginosa* isolated from her swab and she suffered from local catheter related symptoms as erythema, tenderness, indurations and exudates over the skin within 2 cm around the insertion site. The result of the present study was in agreement with ***Chen et al. (2006)*** and ***Hobbs and Taylor (2006).***

Education and training of health professionals on the practice of dealing with the central venous catheter is an important tool in preventing and reducing infections related to central venous catheter. Catheters placed under emergency situations, during which optimal aseptic conditions cannot always be fully respected, have been significantly associated with higher risk of CRI, besides the risk of traumatic vessel injuries. Because of this, catheters placed under these situations were replaced as soon as possible. However, with respect to the frequency of central catheter replacement, no advantage has been observed in terms of infection reduction ***(Lorente et al., 2005***; ***Mesiano and Hamann, 2007).***

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