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Full Length Research Paper

Risk factors for drug resistant bacterial infections: Hospital based study

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The aim of this study is to assess the possible risk factors of patients from whom were isolated microorganisms which were resistant to broad spectrum antibiotics so as to shed light on the measures that should be taken in hospitals and community. These patients were those admitted to Çan secondary care hospital between January, 2009 and November, 2010. The strains isolated from them were evaluated and compared with respect to extended spectrum beta lactamases (ESBL)-producing gram negative bacteria, MRSA and *Enterococcus* spp. A total of 289 patients and their 338 isolated strains were included in the study. The patients with 72 ESBL- producing gram negative bacteria were compared with the patients with 224 non-ESBL-producing gram negative bacteria, and five patients with MRSA were compared with 19 patients with MSSA. The patients treated with vancomycin which is sensitive 18 *Enterococcus* spp. strains were evaluated descriptively. Hospitalization in the previous three months, underlying conditions, and usage of quinolones were found to be significant risk factors for infections with ESBL-producing organisms. Urinary system disorders or malformations, chronic renal failure and hospitalization in the previous three months were found to be risk factors for MRSA infection. It is most likely that hospitalization and underlying conditions contribute to the spread and increase of antimicrobial resistance rates at community and hospitals.

Key words: Drug resistance, antimicrobial, risk factor, community-acquired infections, extended spectrum beta lactamases (ESBL), methicillin-resistance for *S.aureus* (MRSA).

INTRODUCTİON

Antimicrobial resistance has been on a steady increase worldwide. It was considered as a hospital challenge at first, but many reports and articles have now revealed that it has already invaded the farms, long-term care facilities and communities. Clonal spreading of the bacteria, replicons and transposons are the important steps for development of resistance. Even though antimicrobial resistance occurs by chance, its rate could be neglected as compared to rates related with resistance mechanisms as mentioned earlier. Antimicrobial use increase resistance rates at hospitals and communities thus, leading to selection of resistant bacteria in the flora. Resistant microorganisms related infections prompt the use of broad spectrum antibiotics and caused the vicious circle between antimicrobial resistance and antimicrobial use (Seppala et al., 1995; Anderson, 2003; Chiew et al., 1998). Many strategies and measures have been presented to reduce the rates of resistant bacteria such as automatic stop orders for use of antibiotics, required pharmacy or infectious disease consultations for prescription of certain antibiotics, surveillance of pathogen-specific resistance rates, and the development of local antimicrobial control policies and guidelines. This problem also contributes to increase health care expenditure (Boyce, 2001; Shlaes et al., 1997; Critchley et al., 2004; Zoutman et al., 2005; Hoban et al., 2011). The aim of this study is to assess the possible risk factors of the patients whose isolated microorganisms were resistant to broad spectrum antibiotics associated with extended spectrum beta lactamases (ESBL's) and methicillin-resistance for *S.aureus* (MRSA) to shed on light on the measures that

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should be taken in the hospitals and community.

MATERIALS AND METHODS

Study location and patient population

This study was conducted in Çan public hospital (ÇPH), a secondary care hospital with 120 beds without intensive care unit. From January, 2009 to November, 2010; the patients who yielded microorganisms with relevant symptoms, fever, increased C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and had been treated by physicians as being inpatient or outpatient in that hospital, were eligible for inclusion.

Study design and data collection

Using a retrospective case control study design, the patients with bacterial infections were identified by the presence of a sample that cultivated either Gram-negative or Gram positive bacteria. Patient-specific baseline characteristics including age, gender, history of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), chronic liver disease (CLD), underlying conditions and end-stage renal disease requiring dialysis and process of care variables were collected from the automated hospital medical record, microbiology database, and pharmacy database of ÇPH. Data collection was uniform regardless of the initial location of their hospitalization for all patients. Electronic medical records of the inpatients and outpatients which were available for all patients in the automated medical database of ÇPH were reviewed to determine prior antibiotic exposure. And also the patients were called to complete their missing data about their antibiotic use, underlying conditions, *etc.* and to receive their signed consent forms. Patients, who could not be inquired, and had incomplete data and had not signed the consent form, were excluded from this study. Consent form was signed by parents whose children were included to the study.

Blood samples drawn from vein or catheter were inoculated into Bact Alert 3D bottles (bioMérieux Diagnostics, France) and also other samples including urine, sputum, wound, conjunctive, abscess, blood and catheter were inoculated onto 5% sheep-blood agar (Salubris Inc., Istanbul, Turkey), or chocolate agar (Salubris Inc., Istanbul, Turkey) and MacConkey agar (Salubris Inc., Istanbul, Turkey). Identification, antimicrobial susceptibility and presence of ESBLs were examined by Sensititre system (Trek Diagnostic Systems, Cleveland, OH, USA). The isolated strains, which were defined as asymptomatic bacteriuria or colonisation or contamination by physicians or microbiologists, were excluded from study. Isolated microorganisms did not incubated during hospitalisation. Nosocomial infection rates of the hospital were officially reported as ‘’zero’’ to National Nosocomial Infection Surveillance Control Center of Turkey in 2009 and 2010 according to Centers for Disease Control (CDC) surveillance definition criteria for health care–associated and specific types of infections of the acute care settings. Microorganisms which were acquired during health care of an outpatient, were evaluated with the others due to the fact that they could not be discriminated exactly.

Definitions

All definitions were selected before initiation of the study. Patients were classified as yielding ESBLs producing Gram negative bacteria, non-ESBL producing bacteria, and Gram positive bacteria divided into methicillin resistance and methicillin sensitive for *S. aureus* and *Enterococcus* spp. strains. Antimicrobial exposure was defined as taking at least one daily dose of those antibiotics including ceftriaxone, cefixim, amoxycillin-clavulanate, quinolones (ciprofloxacin, levofloxacin, moxifloxacin), cefuroxim and amoxycillin within the preceding 90 days. Hospitalization in the previous three months was inquired with underlying conditions and comorbid diseases. Resistance to third generation cephalosporins of any isolated Gram negative bacteria strain was defined as resistance to one of those antibiotics including cefepime, cefotaxime, ceftriaxone, cefixime.

The patients infected with ESBL-producing Gram negative bacteria were compared with the patients with non-ESBL-producing Gram negative bacteria and the patients infected with MRSA were compared with the patients with the patients infected with methicillin sensitive *S.aureus* (MSSA) for antimicrobial usage in the previous three months, underlying conditions, and hospitalisationin the previous three months . Due to the fact that vancomycin resistant *Enterococcus* spp.(VRE) was not isolated, isolated vancomycin sensitive *Enterococcus spp.* strains were evaluated to to reveal the situation of Enterococcal infections in the community.

Statistical analysis

Statistical analysis was conducted using SPSS, 13.0 (Chicago, IL, USA). Continuous variables were compared by the two-sample *t*-test and dichotomous variables were compared by Pearson χ^2. Received antimicrobial therapy was grouped into antimicrobials to assure adequate cell counts. Logistic regression analysis was conducted to obtain unadjusted odds ratios and revealed as (Odd ratio; 95% Confidence interval; p value). To determine the risk factors including exposure to antimicrobial agents at last three months, co-morbidity, and hospitalisation in the patients with Gram negative ESBL-producing bacteria and the patients with MRSA were conducted using a logistic regression model, likelihood ratio test. Risk factors that reached statistical significance ($P < 0.05$) using a forward selection process remained in the model. Pearson correlation test was used to test correlation different quantitative variables. *P* value was always set at 0.05. Patients who were infected with Gram negative ESBL-producing bacteria were compared with patients who were infected with Gram negative non-ESBL-producing bacteria. And also patients who were infected with methicillin resistant *S. aureus* (MRSA) were compared with patients who were infected with methicillin sensitive *S. aureus* (MSSA). Resistance to at least one of 3rd generation cephalosporins was evaluated for only Gram negative microorganisms.

RESULTS

A total of 289 patients who met the criteria were included in the study with their 338 strains. The 63 (25%) patients infected with 72 ESBL- producing gram negative bacteria were compared with the patients infected with 224 (76%) non-ESBL-producing gram negative bacteria (Table 1), and also five (20%) patients infected with MRSA were compared with 19 (80%) patients infected with MSSAin this study (Table 2). Vancomycin sensitive 18 *Enterococcus* spp. strains that contain 15 (84%) *E. faecalis* strains from 12 (80%) patients and three (16%) *E. faecium* from three (20%) patients were evaluated descriptively (Table 3). Age distributions and female/male proportions of both ESBL (+) and ESBL (-) groups were similar (p: 0.228; p: 0.756, respectively). ESBL producing microorganisms were more isolated from patients who were older than 65 year age (p: 0.001) and younger than first age (p: 0.006), and also from blood (p: 0.007) and

Table 1. Characteristics and risk factors of patients that had infections with Gram negative bacteria.

Variable	ESBL (+) gram negative strains	ESBL (-) gram negative strain	p
	n (%)	n (%)	
Patıents	63 (25)	184 (75)	
Female/Male	36 (57)/27 (43)	101 (54)/83 (46)	0.756
Age (year)			
Median	1	1	
Range	0-78	0-77	
Mean	22.96±31.66	14.36±23.11	0.228
0-1 age	16 (22)	86 (38)	0.006
1-5 age	17 (23)	31 (13)	0.102
5-15	11 (16)	24 (10)	0.411
15-65	14 (19)	31 (13)	0.386
> 65	15 (20)	12 (5)	0.001
Underlyıng condıtıons			
Urinary system malformations or disorders	9 (14)	35 (19)	0.396
Chronic obstructive lung disease	6 (9)	14 (7)	0.636
Diabetes mellitus	12 (19)	1 (0.5)	0.0001
Chronic renal failure	8 (12)	1 (0.5)	0.0001
Central venous dialysis catheter	6 (9)	1 (0.5)	0.001
Urinary catheter	13 (20)	5 (2)	0.0001
Surgical procedure	7 (11)	11 (6)	0.127
Antıbıotıc usage			
Cefixim	45 (71)	123 (66)	0.363
Ceftriaxon	33 (51)	78 (42)	0.144
Amoxycillin-clavulanate	46 (73)	129 (70)	0.221
Amoxycillin	41 (65)	127 (69)	0.077
Cefuroxim	15 (23)	40 (22)	0.710
Quinolones	12 (19)	11 (6)	0.004
Hospitalisation	44 (70)	68 (37)	0.018
Samples	72 (24)	224 (76)	
Urine	51 (70)	189 (85)	0.91
Sputum	6 (8)	7 (3)	0.09
Blood	5 (6)	1 (0.4)	0.007
Wound	4 (5)	5 (2)	0.132
Catheter	12 (16)	1 (0.4)	0.0001
Abscess	1 (1)	21 (9)	0.03
Mıcroorganısms	72 (24)	224 (76)	
E.coli	11 (15)	122 (54)	0.0001
K.pneumoniae	13 (18)	29 (12)	0.238
Enterobacter cloacea	14 (19)	17 (7)	0.004
Enterobacter sakazakii	9 (12)	1 (0.4)	0.0001
Pseudomonas aeruginosa	1 (1)	9 (4)	0.157
Enterobacter aerogenes	4 (5)	2 (0.8)	0.02
Citrobacter freundii	10 (13)	7 (3)	0.405
Morganella morganii	3 (4)	3 (1)	0.157
Providencia stuartii	1 (1)	3 (1)	1
Acinetobacter baumannii	4 (5)	1 (0.4)	0.02
Enterobacter gergoviae	1 (1)	6 (2)	0.414

Table 1. Contd.

Klebsiella oxytoca	1 (1)	24 (10)	0.001
Resistance to at least one of 3rd generation cephalosporins	19 (26)	15 (6)	0.001

catheter (p: 0.0001) samples. ESBL production rates were higher in *Enterobacter cloacea* (p: 0.004), *Enterobacter sakazakii* (p: 0.0001), *Acinetobacter baumannii* (p: 0.02), and *Enterobacter aerogenes* (p: 0.02) strains as compared to other Gram negative bacteria, significantly (Table 1). Urinary catheter (OR = 9.3; 95% CI 3.16 to 27.35; p: 0.0001), central venous dialysis catheter (CVDC, OR= 19.26; 95% CI 2.27 to 163.36; p: 0.001), chronic renal failure (CRF, OR = 26.02; 95% CI 3.25 to 217.49; p = 0.0001), diabetes mellitus (DM, OR = 43; 95% CI 5.46 to 339.01; p = 0.0001) were found significant risk factors as underlying conditions in ESBL (+) group (Table 1). The rates of surgical procedure, COPD, and urinary system malformations or disorders were similar in both groups (p > 0.05). Hospitalisation in the previous three months (OR = 2.6; 95% CI 1.16 to 6; p = 0.018), underlying conditions (OR = 2.1, 95%; CI 1.12 to 7.3; p = 0.024) and usage of quinolones (OR = 3.7; 95% CI 1.54 to 8.88; p = 0.004) were found to be significant independent risk factors for infection associated with ESBL-producing organisms. In ESBL (+) group, 12 patients yielded 24 strains related with recurrent infections and six of them had DM, CFR and CVDC and also six of them had COPD. In ESBL (-) group, 27 patients yielded 54 strains regarding with recurrent infections and six of them had urinary system abnormality. There was a significant relation between recurrent infection related with ESBL-producing organisms and underlying conditions (OR = 0.22, 95% CI 0.75 to 0.662; p = 0.004). Presence of ESBL production was correlated with antimicrobial resitance to those antibiotics including aminoglycosides (amikacin, tobramycin, gentamicin), quinolones (ciprofloxacin, ofloxacin, norfloxacin, levofloxacin), amoxycillin-clavulanate, ampicillin-sulbactam, third generation cephalosporins (cefepime, cefotaxime, ceftriaxone, cefixime), second generation cephalosporins (cefoxitin, cefuroxime), piperacillin, trimethoprim-sulfamethoxazole (p < 0.05; Pearson correlation r = 0.78) excluding piperacillin-tazobactam (TZP, p > 0.05). There was no relationship between resistance to one of third generation cephalosporins and antibiotic use that contains third generation cephalosporins, quinolones, amoxycillin-clavulanate, cefuroxim and amoxycillin in the previous three months, but there was a relation between hospitalisation in the previous three months and usage of those antibiotics (OR = 2.4; 95% CI 0.9 to 6.3; p = 0.04). Male/female proportion and age distribution were similar in both MRSA and MSSA groups (p: 0.611). All MRSA strains were isolated from patients who were between 15 to 65 years old (Table 2). Urinary system disorders or malformations (OR = 12.75; 95% CI 1.26 to 128.77; p: 0.042), chronic renal failure (OR = 12.75; 95% CI 1.26 to 128.77; p: 0.042) and hospitalization (OR = 21.33; 95% CI 1.72 to 263.67; p = 0.014) in the previous three months were found as risk factors for MRSA infection. In Gram positive group, 3 patients yielded 6 strains including four *E. faecalis* from urine samples (Table 3). Most of *E. faecalis* strains were isolated from patients who were between 0 to 5 years old. Urinary system disorders or malformations were the most significant risk factor for *E. faecalis.* All *E. faecium* and most of *E. faecalis* strains were isolated from urine samples (Table 3). All *Enterococcus* spp. strains were susceptible to vancomycin.

DISCUSSION

Our findings reveal that ESBL-producing Gram negative bacteria related infections are more likely to be observed in patients with risk factors including those that are older than 65 years of age and younger than one year of age, possessing underlying conditions such as urinary catheter, CVDC, DM, CRF, history of recurrent infections, hospitalization in the preceeding three months and quinolone use in the preceeding three months. Antibiotic should be chosen, taking into consideration this situation in the infected patients with one or more risk factors. Antibiotic should be revised in case of infection with *E.* cloacea, *Enterobacter sakazakii*, *A. baumannii*, and *E. aerogenes* species that are more likey to produce ESBLs. Those ages are vulnerable to infections especially Gram negative bacteria infections due to immaturity of organ and systems in in the newborn and infants, for example immunity, and also impaired immunity with underlying conditions such as DM, COPD, congestive heart failure, etc in older ages. Even though, broad spectrum antibiotics use, prolonged hospitalization, invasive procedures, parenteral nutrition, comorbidities, inappropriate surgical procedures, decubitus wounds, hospital flora and fecal carriage were described to predispose to infection with ESBL-producing Gram negative bacteria at hospital, it was seen that those bacteria may be isolated from outpatients with risk factors as presented previously (Schwaber et al., 2004; Colodner et al., 2004). Urinary catheter is an important problem especially in long-term catheterized patients due to colonisation and also becoming a niche for selection of bacteria producing biofilms (Hoban et al., 2011). Patients

Table 2. Characteristics and risk factors of patients that had infections with MRSA and MSSA.

Variable	MRSA (n:5)	MSSA (n:19)	p
	n (%)	n (%)	
Patients	5 (20)	16 (80)	
Female/Male	3 (60)/2 (40)	6 (37)/10 (63)	0.611
Age (year)			
Median	22	24	
Range	18-42	0-66	
Mean	29.4±9.6	21.73±20.91	0.445
0-1 age	-	3 (18)	
1-5 age	-	2 (12)	
5-15	-	3 (18)	
15-65	5 (100)	7 (43)	0.046
> 65	-	1 (6)	
Underlying conditions			
Urinary system disorders or malformations	3 (60)	2 (12)	0.034
Chronic obstructive lung disease	2 (40)	3 (18)	0.27
Diabetes mellitus	2 (40)	5 (31)	0.608
Chronic renal failure	3 (60)	2 (12)	0.034
Central venous dialysis cathater	1 (20)	1 (6)	0.564
Antıbiotic usage			
Cefixim	-		
Ceftriaxon	2 (40)	3 (18)	0.257
Amoxycillin-clavulanate	4 (80)	12 (75)	0.637
Amoxycillin	-	3 (18)	
Cefuroxim	-	3 (18)	
Quinolones	5 (100)	14 (87)	0.513
Hospitalization	4 (80)	3 (18)	0.021
Samples	5 (100)	19 (100)	
Urine	2 (40)	2 (10)	0.102
Sputum	-	1 (5)	
Blood	1 (20)	2 (10)	0.564
Wound	1 (20)	5 (26)	0.655
Conjunctiva	-	5 (26)	
Cathater	-	1 (5)	
Abscess	1 (20)	3 (15)	0.325

with DM frequently encounter with redundant antibiotic use in relation to asymptomatic bacteriuria and increased colonisation due to impairment of immunity and local defense system (Daoud et al., 2009). CRF and CVDC predispose to catheter infections related with ESBL producing bacteria as in our study and also with MRSA and non-fermentative Gram negative bacteria causing to impairment of immunity and mucosa and local defense systems, colonisation and biofilm production of bacteria (Kato et al., 2008). Hospitalized patients encounter with higher antimicrobial pressure that increases the selection for resistant strains and the transmission of resistance mechanisms (Moodley et al., 2009; Souza et al., 1999; Yagci et al., 2009) . Subsequent to colonization, patients become harbour for resistant bacteria in the community after discharge. Immunity is a main impaired system due to risk factors as mentioned earlier. The immune response pressurizes the mutant selection window (MSW), contribute to alleviate the negative effects of non-compliance, and influences the optimum dosing strategy. If antibiotic drug concentrations in the blood can be sustained at relatively high levels, the synergistic effect

Table 3. Characteristics and risk factors of patients that had infections with *E. faecalis and E. faecium.*

Variable	*E. faecalis*(n:15)	*E. faecium* (n:3)
	n (%)	n (%)
Patıents	12 (80)	3 (20)
Female/Male	7 (58)/5 (42)	1(33)/2 (66)
Age (year)		
Median	2	31
Range	0-67	0-43
Mean	40.12±26.18	32.09±4.16
0-1 age	6 (40)	1 (33)
1-5 age	5 (33)	-
5-15	1 (6)	-
15-65	2 (13)	2 (66)
> 65	1 (6)	-
Underlyıng condıtıons		
Urinary system disorders or malformations	6 (50)	2 (66)
Chronic obstructive lung disease	3 (25)	1 (33)
Diabetes mellitus	4 (33)	-
Chronic renal failure	2 (16)	1 (33)
Central venous dialysis cathater	1 (8)	-
Antıbıotıc usage		
Cefixim	2 (16)	1 (33)
Ceftriaxon	7 (58)	2 (66)
Amoxycillin-clavulanate	12 (100)	2 (66)
Amoxycillin	3 (25)	-
Cefuroxim	5 (41)	-
Quinolones	10 (83)	2 (66)
Hospitalization	3 (25)	2 (66)
Samples	15 (100)	3 (100)
Urine	9 (60)	3 (100)
Sputum	3 (20)	-
Blood	-	-
Wound	1 (6)	-
Conjunctiva	-	-
Cathater	-	-
Abscess	2 (13)	-

between immune response and antibiotic in reducing resistance emergence is best for immune response matters that are independent of the dynamics of the bacteria widely (Handel et al., 2008).

Quinolones, which are frequently prescribed for treatment of outpatients' infections such as urinary system infections, exacerbations of COPD, pneumonia, etc due to their broad spectrum, should not be frequently used in treatment of patients with risk factors. Since they contribute to the selection of Gram positive and Gram negative resistant bacteria that can evolve by rapid dissemination of novel resistance genes under selective pressure of antibiotic use. Oral quinolones and amoxycillin-clavulanate are frequently misused antibiotics with by physicians (Hawkey and Jones, 2009). TZP was found significantly sensitive to antibiotic and uncorrelated with ESBL producing bacteria related infections although other beta lactam-beta lactam inhibitor combinations were resistant for ESBL positive strains in our study. It seems that piperacillin-tazobactam could be opted for preventing the development of infection with ESBL-producing organisms. However, piperacillin-tazo-bactam

was the most commonly administered antibiotic; the clinical cure rate was described as only 55% in the study of Burgess et al. (2003).MRSA causes to nosocomial infections and also community acquired infections that is prominent in the United States in patients that have risk factors such as DM, immunsuppression, use of quinolones, elderly, young children, as well as urinary system malformations and disorders, hospitalisation and chronic renal failure that were found as risk factors in our study (Tacconelli et al., 2008). Although use of both quinolones and amoxycillin-clavulanate was not found a risk factor for MRSA and MSSA infections, their use rates were very high with least 80% in our study. *E.faecalis* was more isolated from patients that were between the ages of 0 and 5 years. *Enterococcus* spp. strains were isolated from patients with urinary system malformations or disorders and higher antibiotic use rates. Co-morbid conditions predispose to enterococcal infections and also development of resistance to antimicrobials that should in kept mind in choice of antibiotic.

Consequently, it is more likely that hospitalisation and co-morbidity contributes to spreading and increasing antimicrobial resistance at community and hospitals Immunity and infection control program at health care settings are basic factors against development of resistant microorganisms related infections.

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