International Journal of Current Research and Review
DOI: http://dx.doi.org/10.31782/IJCRR.2019.11182

Research Article

IJCRR
Section: Healthcare
Sci. Journal Impact Factor: 5.385 (2017)
ICV: 71.54 (2015)

Cephalosporins and Metronidazole as Risk Factors for ESBL-Producing Organisms

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ABSTRACT

Prevalence of Extended-spectrum β-lactamase (ESBL)-producing organisms is increasing in healthcare associated (HCA) institutions and community. We conducted a matched case-double control study to assess the risk factors for acquisition of these multi-drug resistant organisms (MDRO), in a cardiac center in Brazil. We studied two hundred and thirty-eight patients (58 cases). Two groups of comparison were included: control Group 1 (N=120), with patients without infection; and control Group 2 (N=70), with patients with infection by non-ESBL producers *Klebsiella* spp., *E. coli* or *Proteus mirabilis*. On multivariate analysis, risk factors for hospital acquisition of ESBL-producing organisms were as follows: previous use of second-generation cephalosporins (OR 5.73; 95% CI 1.30-25.31), fourth-generation cephalosporins (OR 3.62; 95% CI 1.24-10.53) and metronidazole (OR 11.68; 95% CI 1.20-114.00). Previous identification of MDRO (OR 8.98, 95% CI 1.61-50.18), number of days on antibiotic use (OR 1.12; 95% 1.04-1.20) was also independently associated with ESBL-producing organisms. Interestingly, the presence of other MDRO in ward (OR 0.30; 95% CI 0.13-0.71) was associated as a protector factor for ESBL identification. When there was a low consumption of third-generation cephalosporins and quinolones, the second- and fourth-generation cephalosporins and metronidazole were, associated with ESBL-producing bacteria. In addition, adherence to isolation precautions and infection control recommendations can help to prevent ESBL-resistance dissemination.

Key Words: ESBL, Multidrug resistance, Enterobactereaceae, Infection control

INTRODUCTION

Extended-spectrum β-lactamase (ESBL)-producing organisms pose a great challenge to epidemiologists, infection control practitioners and physicians[1,2]. The dissemination of these broad spectrum resistant bacteria is difficult to control and the therapeutic options for severe infections are limited[1,3,4]

The emergence of ESBL-producers bacteria is increasing in both hospitals and community[5]. This resistant mechanism is most found in *Klebsiella pneumoniae* in hospital and *Escherichia coli* in community as well[5,6].

There are several reasons for the increasing prevalence of these organisms in hospitals[4,7], such as, the selective pressure of antimicrobials overuse, the use of invasive devices, cross-transmission between patients, hospital cross-infection, and the increase in prevalence of community origin[6,8,9,10].

Infection by these organisms is associated with higher mortality rates[11,12]. Carbapenems use is associated with lower mortality in patients with serious infections[8,13]. Although other agents may be used in non-severe infected patients, this use must be viewed with caution[14,15,16,17]

We conduct a case control-study in a cardiac center in Brazil to identify risk factors for ESBL-producing organisms identification.

METHODS

A matched case-double control study was conducted at Instituto de Cardiologia, a 250-bed hospital for cardiology patients in southern Brazil. Instituto de Cardiologia attends adult and pediatric, surgical and clinical cardiology patients. In addition, the hospital has a cardiac transplant service, and three intensive care units (ICUs), which account for 16% of institution's beds.

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ISSN: 2231-2196 (Print) **ISSN:** 0975-5241 (Online)
Received: 25.07.2019 **Revised:** 20.08.2019 **Accepted:** 13.09.2019

Adult (age ≥ 18 years) inpatients were selected from the entire hospital irrespective of unit. Case patients were those with identification of ESBL-producing bacteria at any site, after 48 hours of admission. For this analysis, we included two control groups: Group 1 was composed of patients from hospital units but not with ESBL-producing organisms; and patients with non ESBL-producing composed Group 2 *Klebsiella* spp., *Escherichia coli*, or *Proteus mirabilis*. Controls were matched in terms of age (± 3 years), date of sample identification (± 3 days), gender, and hospital ward.

From January 2008 to December 2009 all ESBL-producing organisms were included (patient cases). Controls were selected in a rate 1:2 (Group 1): 1 (Group 2).

All samples were processed at the microbiology laboratory at Instituto de Cardiologia. Detection of ESBL-producing bacteria was made according to the National Committee for Clinical Laboratory and Standards guidelines[18]. The susceptibility to antibiotics used agar disc diffusion method tested. For detection ESBL-producing strains, Double-disc synergy test was used. Bacteria considered as multidrug resistant organism (MDRO) were as follows: methicillin resistant *Staphylococcus aureus* (MRSA), ESBL-producing *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, carbapenems resistant *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, vancomycin resistant enterococci (VRE).

We reviewed data from patients' medical charts. Antibiotic use was measured for 24 months of study period, for the entire hospital. Data from prescribed drugs, such as, carbapenems, fluoroquinolones, cephalosporin's, piperacillin/tazobactam, vancomycin, ampicillin+sulbactam and oxacillin, metronidazole, clindamycin, sulfametoxazole+trimetoprrim were reviewed. Patient comorbidities, invasive devices use and surgical procedures, ICU admission, previous MDRO identification in the previous 90 days, previous hospital stay during the last year, and other than ESBL-producing MDRO identified in patient ward were also reviewed.

Previous antibiotic use was at least 48h of inpatient use in the current admission. Time-at-risk is defined as the duration of time between admission and the detection of the antibiotic-resistant organism on culture for cases; as the number of days between admission and detection of the susceptible organism on culture, for non-resistant enterobactereacea infected controls; and the time between admission and discharge for non-infected control patients. Antibiotic consumption counted a number of defined daily doses (DDD), expressed as DDD per 100 patient-days. Central venous catheter (CVC), urinary catheterization, and mechanical ventilation were considered as invasive devices.

A descriptive analysis of the variables collected from each patient was performed. The chi-squared test or Fisher's exact test were used for univariate analysis of selected categorical variables. All odds ratios on univariate analysis were controlled for time at risk exposure. Associations were considered statistically significant when *P* value was ≤.05. Multivariate analysis, along with 95% confidence intervals (CI) and Odds ratios were calculated using the Logistic regression model. We divided the analysis in three models. The first model included the risk factors other than specific antimicrobials that were statistically significant on univariate analysis; the second model included the antimicrobials with statistical significance on univariate analysis and days on antimicrobial use. The final model included the variables that were statistically significant in the first two models. All analysis was corrected for time at risk. All collected data was stored in Excel® 2000 version and analyzed using SPSS® 18.0 program.

The research and ethics committee of Fundação Universitária de Cardiologia (Brasil) approved the study and waived the need for informed consent because of the nature of the study.

RESULTS

Patient characteristics are shown in Table 1. Through the study period, we included fifty-eight case patients. Most of them infected with *Klebsiella* spp. (65.5%; N=38). The rest of patients were infected with *Proteus* spp. (25.9%; N=15) and *E. coli* (8.6%; N=5). Control Group 2, were composed by 70 patients with identification of non ESBL-producing *Klebsiella* spp. (85.7%; N=60), *Proteus* spp. (10.0%; N=7), and *E. coli* (4.3%; N=3). One hundred and twenty patients were included in control Group 1.

Most patients were at general ward (55.2%; N=137); 26.6% (N=66) at post-surgical ward; 15.7% (N=39) at ICU; and 2.4% (N=6) were at emergency department. From case patients, most specimens were from urinary tract (39.6%; N=23), respiratory tract (32.8%; N=19), and surgical wound (12.1%; N=7). From control group 2 sites of specimen identification were as follows: respiratory tract (45.7%; N=32), urine (31.4%; N=22), blood culture (10.0%; N=7), and surgical wound (7.1%; N=5).

From January 2008 to December 2009 the mean consumption of antibiotics (in DDD/100 patient-days) were as follows: fourth-generation cephalosporins (5.9), third-generation cephalosporins (0.3), second-generation cephalosporins (2.0), first-generation cephalosporins (4.1), oxacillin (5.7), ampicillin+sulbactam (4.4), piperacillin+tazobactam (2.2), quinolones (2.1), vancomycin (1.4), and carbapenems (0.8).

Table 2 shows the multivariate analysis of statistically significant variables on univariate model, for both control groups.

Antimicrobials, associated with ESBL-producing organism, on univariate analysis of control Group 1, controlled for time

at risk, were: piperacillin+tazobactam (OR 3.14, IC 95% 1.33-7.39; P<0.01), first-generation cephalosporins (OR 0.35, IC 95%, 0.16-0.73; P<0.01), second-generation cephalosporins (OR 4.99, IC 95% 1.44-17.27; P=0.01), fourth-generation cephalosporins (OR 3.71, IC 95%, 1.65-8.33; P<0.01), metronidazole (OR 11.14, IC 95%, 1.24-100.39; P=0.03). From the analysis of control group 2: second-generation of cephalosporins (OR 3.97, IC 95%, 1.00-15.46; P=0.05), and fourth-generation cephalosporins (OR 3.06; IC 95%, 1.24-7.55; P=0.01). Multivariate analysis of specific antimicrobial use is shown in Table 3.

The table 4 illustrates the final multivariate model, where specific antimicrobial drugs, with statistical significance on previous multivariate model and length of antimicrobial use are tested with significant statistical variables related to patient severity, previous presence of MDRO, or MDRO in patient ward.

DISCUSSION

To answer the question "What are the risk factors for acquiring ESBL-producers pathogen among hospitalized patients?" Our study concluded that the second-generation cephalosporins, metronidazole, days on antibiotic use and previous MDRO other than ESBL were independently associated with ESBL-producer. For the question "What are the risk factors for developing ESBL-producers pathogen among patients with non-ESBL *Klebsiella* spp. *E. coli*, and *Proteus* spp.?" The answer was the second- and fourth generation cephalosporins, previous identification of a MDRO other than ESBL, and, interestingly, the presence of other MDRO in ward were associated with protection form ESBL-producers identification.

In our setting where there is a high consumption of cephalosporins, especially fourth-generation cephalosporins, but a low consumption of third-generation cephalosporin and quinolones, use of second- and fourth-generation cephalosporins were associated with ESBL production. Besides the use of piperacillin+tazobactam was not associated with ESBL production. The hospital antimicrobial stewardship program (ASP) recommends the use of fourth- and second- instead of the third-generation cephalosporins and quinolones, because the associated risk of resistance linked to these drugs[19,20]. Besides the use of penicilins and piperacillin+tazobactam are stimulated, the carbapenems are the drugs reserved for infection by ESBL-producers[21,22].

A variety of antimicrobial classes and antimicrobial drugs have been associated with ESBL-production in bacteria[23,24]. Cephalosporins, especially third-generation cephalosporins, fourth-generation cephalosporins, the quinolones, piperacillin+tazobactam, vancomycin, penicilins and beta-lactamase-inhibitors penicilins, and gentamicin all have been linked to ESBL-producing bugs[25]. Although a few studies have assessed important methodological principles like those that control group selection derived from appropriate sampling of the base population, time at risk and comorbid illnesses for studies on ESBL resistance.

Behar et al, evaluated risk factors for ESBL resistance in *Klebsiella pneumoniae* in four different groups of comparisons, with two types of controls: non-resistant *Klebsiella pneumoniae* and patients without infection derived from the same source of cases[26]. They found the cephalosporins use as a consistent risk factor. Besides, time at risk and CVC use were also identified as risk factors.

Furthermore, Odds ratios were slightly higher considering antimicrobial use in the comparison between case and control Group 2, as stated by others. Furthermore, the cephalosporins as risk factors confirms the risk associated with ESBL-producers, however, our study confirms that second- and fourth-generation cephalosporins can also be related to ESBL-resistance in a setting of low use of other cephalosporins. In addition, this is the first study to link metronidazole use to ESBL-producers. Interestingly, this association was only seen in control group 1. We speculate that this might be related to the suppression of intestinal anaerobic flora and the rise of resistant enterobactereacea. The use of other antimicrobial with activity against anaerobes like meropenem, ampicillin+sulbactam, and piperacillin+tazobactam were not related to resistance probably because enterobactereacea suppression flora too[20].

A few institutions implemented the use of piperacillin+tazobactam intended to reduce ESBL-producers. Other independently factors associated with ESBL were: previous MDRO isolation and days on antibiotic use. Interestingly, the presence of any MDRO in case patient ward was a protector factor for identification of ESBL-resistance, a group from Baltimore suggests that patient-to-patient transmission is not an important cause of the acquisition of ESBL-producing[27]. Although, we have not studied the association between adherence to contact precautions and resistance, we suppose that with the identification of a MDRO other than ESBL-producers in the ward, the implementation of contact precautions protected other patients from ESBL-producing bacteria. In our hospital, most general wards were composed of three to five patients dividing the same room.

Control-group selection in antimicrobial resistant studies is of great importance[26]. As recommended, we choose to include controls selected from the same unit of cases patients that were in hospital in a period near to the case patient resistant bacteria identification. Besides, using two control groups we try to control for the selection bias that arises when only antimicrobial-susceptible organisms are used as control patients[28]. Although we could not include in the final analysis a severity score for our patients, the inclusion of comorbities

that were statistically related to the outcome on univariate analysis and the adjustments for time-at-risk on multivariate analysis could reduce bias to this confounding. Patients admitted for longer periods are more likely to receive a greater number of antibiotics[20]. In addition, time-at-risk correlates with illness severity.

CONCLUSION

Our study has some limitations: our patients are from a specific cardiac center, which caused difficult generalization of results. We could not study the mechanisms of resistance in our patients. Our patients' selection was based on clinical specimens collected as decision from the attending physician. We did not systematically collected surveillance samples, this way we could not ascertain about previous colonization.

In order to review our antimicrobial policy we aim to investigate which specific antimicrobial or other risk factor was associated with ESBL-producing bacteria. Although cefepime and cefuroxime have been used for preserving third-generation cephalosporins, they were also associated with ESBL-resistance[29]. The implementation of contact precautions and a strict adherence to this measure contributes to the control of resistance in our setting[30].

ACKNOWLEDGEMENTS

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

FUNDING

This study was conducted without financial support, study resources came from the authors.

CONFLICT OF INTERESt

The authors declare that they have no competing interests.

REFERENCES

1. Hyle EPEA. Risk Factors for Increasing Multidrug Resistance among Extended-Spectrum b-Lactamase–Producing Escherichia coli and Klebsiella Species. Clinical Infectious Diseases 2005;40:1317–24.
2. Ben-Ami REA. Influx of Extended-Spectrum B-Lactamase–Producing Enterobacteriaceae into the Hospital. Clinical Infectious Diseases 2006;42:925–34.
3. Serefhanoglu K, Turan H, Timurkaynak FE, Arslan H. Bloodstream infections caused by ESBL-producing E. coli and K. pneumoniae: risk factors for multidrug-resistance. Braz J Infect Dis 2009;13(6):403-7. ISSN 1678-4391.
4. Bradford, PA. Extended-Spectrum -Lactamases in the 21st Century: Characterization, Epidemiology, and Detection of This Important Resistance Threat. Clinical Microbiology Reviews 2001;14(4):933-951.
5. Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Ruíz M, Peña C, et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. Clin Infect Dis 2010;50(1):40-8. ISSN 1537-6591.
6. Rodríguez-Baño J. Epidemiology and Clinical Features of Infections Caused by Extended-Spectrum Beta-Lactamase-Producing Escherichia coli in Non hospitalized Patients. Journal Of Clinical Microbiology 2004;42(3):1089–1094.
7. Fernández A, Pereira MJ, Suárez JM, Poza M, Treviño M, Villalón P, et al. Emergence in Spain of a Multidrug-Resistant Enterobacter cloacae. J Clin Microbiol 2011;49(3):822-828.
8. Graffunder EMEA. Risk factors associated with extended spectrum B-lactamase-producing organisms at a tertiary care hospital. Journal of Antimicrobial Chemotherapy 2005;56:139–145.
9. Giamarellou, H. Multidrug resistance in Gram-negative bacteria that produce extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect Jul 2005;11 Suppl 4:1-16. ISSN 1198-743X.
10. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker MB, Lautenbach E. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing enterobacteriaceae: variability by site of infection. Arch Intern Med Jun 2005;165(12):1375-80. ISSN 0003-9926.
11. Alanis A. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res Nov-Dec 2005;36(6):697-705. ISSN 0188-4409.
12. Paterson DL, Bonomo RA. Extended-Spectrum -Lactamases: a Clinical Update. Clinical Microbiology Reviews 2005;18(4):657-686.
13. Shaikh NK, Mundhada SG, Lalngaihzuali R, Ingole KV. Comparison of different phenotypic methods for the detection of Extended Spectrum ß- lactamase (ESBL) in bacterial isolates from Tertiary Care Centre. Int J Cur Res Rev Jun 2016;8(1):10-14.
14. Quirante OF, Cerrato SG, Pardos SL. Risk factors for bloodstream infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae. Braz J Infect Dis 2011;15(4):370-376.
15. Marchaim D, Gottesman T, Schwartz O, Korem M, Maor Y, Rahav G, et al. National multi-center study of predictors and outcomes of bacteremia upon hospital admission caused by enterobacteriaceae producing extended-spectrum {beta}-lactamases. Antimicrob Agents Chemother Dec 2010;54(12):5099-5104.
16. Dropa M, Balsalobre LC, Lincopan N, Mamizuka EM, Murakami T, Cassettari V, et al. Extended-spectrum beta-lactamases among Enterobacteriaceae isolated in a public hospital in Brazil. Rev Inst Med Trop Sao Paulo Aug 2009;51(4):203-209.
17. Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing E. coli compared to non-ESBL producing E. coli. J Infect Sep 2007;55(3):254-9.
18. CLSI, C. A. L. S. I.-. Performance standards for antimicrobial susceptibility testing: Seventeenth Informational Supplement. M100 2007.
19. Van Der Starre WEEA. Risk factors for fluoroquinolone-resistant Escherichia coli in adults with community-onset febrile urinary tract infection. J Antimicrob Chemother 2011;66:650–656.
20. Falagas M, Karageorgopoulos D. Extended-spectrum beta-lactamase-producing organisms. J Hosp Infect Dec 2009;73(4):345-54.

21. Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. Int J Med Microbiol Aug 2010;300(6):371-9.
22. Falagas ME, Rafailidis PI, Kofteridis D, Virtzili S, Chelvatzoglou FC, Papaiannou V, et al. Risk factors of carbapenem-resistant Klebsiella pneumoniae infections: a matched case control study. J Antimicrob Chemother Nov 2007;60(5):1124-30.
23. Lee CH, Su LH,Tanq YF, Liu JW. Treatment of ESBL-producing Klebsiella pneumoniae bacteraemia with carbapenems or flomoxef: a retrospective study and laboratory analysis of the isolates. J Antimicrob Chemother 2006 Nov;58(5):1074-7. ISSN 0305-7453.
24. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal Colonization With Extended-spectrum Beta-lactamase-Producing Enterobacteriaceae and Risk Factors Among Healthy Individuals: A Systematic Review and Metaanalysis. Clin Infect Dis 2016 Aug;63(3):310-8. Epub 2016 May 3.
25. Vergidis P, Falagas M. New antibiotic agents for bloodstream infections. Int J Antimicrob Agents Nov 2008;32 Suppl 1:60-5. ISSN 0924-8579.
26. Tumbarello MEA. Bloodstream infections caused by extended-spectrum-beta-lactamase producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. Antimicrob Agents Chemother 2006;50:498-504.
27. Behar PR, Teixeira PJ, Fachel JM, Kalil AC. The effect of control group selection in the analysis of risk factors for extended spectrum beta-lactamase-producing Klebsiella pneumoniae infections. A prospective controlled study. J Hosp Infect 2008 Feb;68(2):123-9. ISSN 0195-6701.
28. Harris AD, Kotetishvili M, Shurland S, Johnson JA, Morris JG, Nemoy LL, Johnson JK. How important is patient-to-patient transmission in extended-spectrum beta-lactamase Escherichia coli acquisition. Am J Infect Control 2007 Mar;35(2):97-101. ISSN 0196-6553.
29. Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Cisneros JM, Peña C, et al. Risk factors and prognosis of nosocomial bloodstream infections caused by extended-spectrum-beta-lactamase-producing Escherichia coli. J Clin Microbiol 2010 May;48(5):1726-31. ISSN 1098-660X.
30. Wener KM, Schechner V, Gold HS, Wright SB, Carmeli Y. Treatment with fluoroquinolones or with beta-lactam-beta-lactamase inhibitor combinations is a risk factor for isolation of extended-spectrum-beta-lactamase-producing Klebsiella species in hospitalized patients. Antimicrob Agents Chemother 2010 May;54(5):2010-6. ISSN 1098-6596.
31. Siegel JD et al. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007.

Table 1: Patient characteristics. Univariate analysis of risk factors for ESBL-producing organisms in patients at Instituto de Cardiologia de Porto Alegre, 2008-2009.

	Case patients	Control Group 1			Control Group 2		
	N=58	N=120	OR[1] (95% CI)	*P*	N=70	OR[1] (95% CI)	*P*
Mean age (SD)	68.4 (16.8)	69.1 (13.2)	0.99 (0.97-1.02)	0.79	68.8 (15.1)	1.0 (0.97-1.02	0.88
Male sex	36 (62.1)	73 (60.8)	0.89 (0.46-1.73)	0.73	45 (64.3)	0.99 (0.47-2.07)	0.97
Diabetes	13 (22.4)	25 (20.8)	1.08 (0.50-2.35)	0.84	23 (32.9)	0.59 (0.26-1.32)	0.20
Hypertension	29 (50.0)	63 (52.5)	0.86 (0.45-1.63)	0.64	46 (65.7)	0.50 (0.24-1.04)	0.06
Myocardial infarction	0 (0.0)	23 (19.2)	-	0.99	10 (14.3)	-	0.99
CHD	28 (48.3)	55 (45.8)	1.25 (0.65-2.40)	0.49	28 (40.0)	1.52 (0.74-3.12)	0.25
Stroke	12 (20.7)	6 (5.0)	4.37 (1.51-12.64)	<0.01	8 (11.4)	1.94 (0.72-5.20)	0.19
Dyslipidemia	3 (5.2)	24 (20.0)	0.20 (0.06-0.73)	0.01	6 (8.6)	0.64 (0.15-2.70)	0.54
ICU stay	22 (37.9)	31 (25.8)	1.41 (0.69-2.85)	0.34	19 (27.1)	1.41 (0.65-3.06)	0.37
Surgery	35 (60.3)	63 (52.9)	1.14 (0.59-2.22)	0.69	38 (54.3)	1.14 (0.55-2.35)	0.73
Invasive devices	44 (75.9)	68 (57.1)	1.83 (0.87-3.86)	0.11	43 (61.4)	1.54 (0.67-3.54)	0.31
Previous hospital stay	24 (41.4)	36 (30.3)	1.81 (0.92-3.56)	0.08	23 (32.9)	1.77 (0.83-3.78)	0.14
Previous antibiotic use	38 (65.5)	29 (24.2)	5.22 (2.50-10.92)	<0.01	32 (45.7)	1.83 (0.84-43.97)	0.13
Mean (SD) of Days on antibiotic	10.31 (10.63)	3.03 (5.40)	1.16 (1.08-1.24)	<0.01	5.55 (7.37)	1.05 (1.00-1,11)	0.04
Previous MDRO	13 (22.4)	2 (1.7)	12.97 (2.73-61.67)	<0.01	3 (4.3)	5.22 (1.36-20.04)	0.02
MDRO in ward	18 (31.0)	16 (13.3)	2.44 (1.11-5.40)	0.03	37 (52.9)	0.33 (0.15-0.71)	<0.01
Mean (SD) time-at-risk in days	22.90 (23.06)	15.17 (10.41)	1.03 (1.01-1.05)	<0.01	15.49 (15.49)	1.02 (1.00-1.04)	0.04

Note. Data are no. (%), unless otherwise indicated. OR, odds ratio; SD, standard deviation; CI, confidence interval; CHD, congestive heart disease; ICU, intensive care unit; MDRO, multidrug resistant organism.1Odds ratio controlled for time at risk.

Table 2: Multivariate analysis of risk factors related to ESBL-producing organism, controlled for time at risk.

	Control Group 1			Control Group 2		
	OR	95% CI	P	OR	95% CI	P
Stroke	3.85	1.17-12.65	0.03	-	-	-
Dyslipidemia	0.26	0.06-1.16	0.08	-	-	-
Previous antibiotic use	1.26	0.41-3.88	0.68	-	-	-
Days on antibiotic	1.12	1.02-1.22	0.01	1.05	1.00-1.10	0.06
Previous MDRO	8.63	1.67-45.59	0.01	4.58	1.12-18.75	0.03
MDRO in ward	2.28	0.92-1.01	0.08	0.35	0.16-0.78	0.01
Time-at-risk in days	0.98	0.95-1.01	0.23	1.01	0.98-1.03	0.52

Note. OR, odds ratio; CI, confidence interval; MDRO, multidrug resistant organism.

Table 3: Multivariate analysis of antimicrobials related to ESBL-producing organism, controlled for time at risk.

	Control Group 1			Control Group 2		
	OR	95% CI	P	OR	95% CI	P
1rst gen. cephalosporins	0.44	0.19-1.04	0.06	-	-	-
2nd gen. cephalosporins	4.85	1.20-19.57	0.03	4.61	1.14-18.66	0.03
4th gen. cephalosporins	2.68	1.05-6.85	0.04	3.02	1.16-7.84	0.02
Piperacillin+tazobactam	0.98	0.32-2.97	0.97	-	-	-
Metronidazol	12.01	1.27-113.30	0.03	-	-	-
Days on antibiotic	1.13	1.04-1.22	<0.01	1.04	0.99-1.09	0.11

Note. OR, odds ratio; CI, confidence interval; MDRO, multidrug resistant organism

Table 4: Multivariate model of variables associated with resistance on the two first analysis.

	Group 1 Controls			Group 2 Controls		
	OR	IC 95%	P	OR	IC 95%	P
Stroke	3.32	0.97-11.30	0.05	-	-	-
2nd gen. cephalosporins	5.11	1.28-20.47	0.02	5.73	1.30-25.31	0.02
4th gen. cephalosporins	2.20	0.81-5.95	0.12	3.62	1.24-10.53	0.02
Metronidazol	11.68	1.20-114.00	0.03	-	-	-
Days on antibiotic	1.12	1.04-1.20	<0.01	1.04	0.99-1.09	0.14
Previous MDRO	8.98	1.61-50.18	0.01	4.48	1.03-19.45	0.04
MDRO in ward	-	-	-	0.30	0.13-0.71	<0.01
Time-at-risk in days	0.97	0.93-1.00	0.07	0.99	0.97-1.02	0.92

Note. OR, odds ratio; CI, confidence interval; MDRO, multidrug resistant organism.