Differences in Microbiological Profile between Community-Acquired, Healthcare-Associated and Hospital-Acquired Infections

Diferenças no Perfil Microbiológico entre as Infecções da Comunidade, Associadas a Cuidados de Saúde e Nosocomiais

Teresa CARDOSO[1], Orquídea RIBEIRO[2], Irene ARAGÃO[1], Altamiro COSTA-PEREIRA[2], António SARMENTO[3]
Acta Med Port 2013 Jul-Aug;26(4):377-384

ABSTRACT

Introduction: Microbiological profiles were analysed and compared for intra-abdominal, urinary, respiratory and bloodstream infections according to place of acquisition: community-acquired, with a separate analysis of healthcare-associated, and hospital-acquired.
Material and Methods: Prospective cohort study performed at a university tertiary care hospital over 1 year. Inclusion criteria were meeting the Centers for Disease Control definition of intra-abdominal, urinary, respiratory and bloodstream infections.
Results: A total of 1035 patients were included in the study. More than 25% of intra-abdominal infections were polymicrobial; multi-drug resistant gram-negatives were 38% in community-acquired, 50% in healthcare-associated and 57% in hospital-acquired. *E. coli* was the most prevalent among urinary infections: 69% in community-acquired, 56% in healthcare-associated and 26% in hospital-acquired; ESBL producers' pathogens were 10% in healthcare-associated and 3% in community-acquired and hospital-acquired. In respiratory infections *Streptococcus pneumoniae* was the most prevalent in community-acquired (54%) and MRSA in healthcare-associated (24%) and hospital-acquired (24%). A significant association was found between MRSA respiratory infection and hospitalization in the previous year (adjusted OR = 6.3), previous instrumentation (adjusted OR = 4.3) and previous antibiotic therapy (adjusted OR = 5.7); no cases were documented among patients without risk factors. Hospital mortality rate was 10% in community-acquired, 14% in healthcare-associated and 19% in hospital-acquired infection.
Discussion and Conclusion: This study shows that healthcare-associated has a different microbiologic profile than those from community or hospital acquired for the four main focus of infection. Knowledge of this fact is important because the existing guidelines for community-acquired are not entirely applicable for this group of patients.

Keywords: Anti-Bacterial Agents; Community-Acquired Infections; Cross Infection; Delivery of Health Care; Respiratory Tract Infections; Urinary Tract Infections; Catheter-Related Infections; Blood-Borne Pathogens.

RESUMO

Introdução: Analisamos e comparamos os perfis microbiológicos, das infecções intra-abdominais, urinárias, respiratórias e bacteriemias, conforme o local de aquisição: da comunidade, com separação das infecções associadas a cuidados de saúde, ou nosocomiais.
Material e Métodos: Coorte prospectiva, desenvolvida num hospital universitário ao longo de um ano. Critério de inclusão: cumprir a definição de infecção intra-abdominal, urinária, respiratória ou bacteriemia do *Centers for Disease Control*.
Resultados: Foram incluídos 1035 doentes. Nas infecções intra-abdominais mais de 25% eram polimicrobianas; a percentagem de gram-negativos multi-resistentes foi 38% na comunidade, 50% nas associadas a cuidados de saúde e 57% nas nosocomiais. A *E. coli* foi o agente mais frequente nas infecções urinárias: 69% na comunidade, 56% nas associadas a cuidados de saúde e 26% nas nosocomiais; a produção de ESBL foi 10% nas associadas a cuidados de saúde e 3% na comunidade e nosocomiais. Nas infecções respiratórias o *Streptococcus pneumonia* foi o agente mais frequente na comunidade (54%) e o MRSA o mais frequente nas associadas a cuidados de saúde (24%) e nosocomiais (24%). Foi encontrada uma associação significativa entre a infecção por MRSA e a hospitalização no último ano (OR ajustado = 6,3), instrumentação prévia (OR ajustado = 4,3) e antibioterapia prévia (OR = 5,7); não se documentaram casos em doentes sem estes factores de risco. A mortalidade hospitalar foi 10% na infecção da comunidade, 14% nas associadas a cuidados de saúde e 19% na nosocomial.
Discussão e Conclusão: Este estudo demonstra que as infecções associadas a cuidados de saúde apresentam perfis microbiológicos diferentes das da comunidade e nosocomiais para cada foco de infecção. Este conhecimento é importante porque as recomendações existentes para as infecções da comunidade não se aplicam a este grupo de doentes.

Palavras-chave: Infecções Comunitárias Adquiridas; Infecção Hospitalar; Prestação de Cuidados de Saúde; Infecções Respiratórias; Infecções Urinárias; Infecções Relacionadas a Cateter.

INTRODUCTION

Over the last decade the massive increase in outpatient clinical care has led to a new context for the emergence of HCAI. This is a new name for the new group of infections from patients in the community that have a history of exposure to the healthcare system and that do not fit the nosocomial infection criteria.[1]

In 2002, Deborah Friedman[1] proposed a new classification for community-acquired bloodstream infections (CAI - BSI) in patients with recent hospital admission or exposure to significant medical care - healthcare-associated bloodstream infections (HCAI - BSI) - after a cohort study of 504 patients with BSI where she noticed significant differences

1. Unidade de Cuidados Intensivos Polivalente. Hospital de Santo António. Centro Hospitalar do Porto. Universidade do Porto. Porto. Portugal.
2. Departamento de Ciências da Informação e da Decisão em Saúde. Centro de Investigação em Tecnologias e Sistemas de Informação em Saúde. Faculdade de Medicina da Universidade do Porto. Porto. Portugal.
3. Departamento de Doenças Infecciosas. Hospital de São João. Universidade do Porto. Porto. Portugal.
Recebido: 11 de Março de 2013 - Aceite: 12 de Julho de 2013

in the microbiological profiles of HCAI, CAI and hospital-acquired bloodstream infections (HAI - BSI).

This new concept of HCAI is spreading throughout the scientific world and evidence has emerged suggesting that this might represent a new group of infections with microbiological and outcome characteristics that are different from CAI and HAI.[2-5]

The studies performed previously have focused primarily on single focus of infection: pneumonia,[3,4,6] BSI[2,5,7] or urinary (UTI).[8] To the best of our knowledge, no study has been published concerning intra-abdominal infections (IAI), although these are among the three most common infections that result in hospitalization.[9]

The objective of this study is to analyse differences in the microbiological profiles and outcomes of the major focus of infection that drive patients into hospital care: IAI, UTI, respiratory and BSI - HCAI, CAI and HAI. Additionally independent risk factors for respiratory infection by MRSA will be described.

MATERIAL AND METHODS

Study design and patient population

This prospective cohort study included all consecutive adult patients admitted to the intensive care unit (ICU), medical, surgical, nephrology and haematology wards of a 600-bed university, tertiary care hospital from 1st June 2008 until 31st May 2009.

The inclusion criterion was diagnosis of the infection according to the Centers for Disease Control (CDC) criteria,[10] in an adult patient (age ≥ 18 years) admitted onto one of the previously mentioned wards. Infections were classified as CAI, HCAI or HAI, according to the place of acquisition. Only the first episode of infection in the current hospital admission was characterized for each patient.

The primary outcome was detailed microbiological characterization of the microbiological profile of IAI, UTI, respiratory infections and BSI, according to the place of acquisition, including analysis of the prevalence of multi-drug resistant (MDR) pathogens. Secondary outcomes are differences in hospital length of stay (LOS) and mortality for different focus of infection according to the place of acquisition of infection.

This study was approved by the Institutional Review Board of Hospital de Santo António, Oporto Hospital Centre, Portugal, and informed consent was waived due to the observational nature of the study.

Definitions

CAI was defined as an infection detected within 48 hours of hospital admission in patients who did not fit the criteria for a HCAI.

HAI was defined as a localized or systemic condition that resulted from an adverse reaction to the presence of an infectious agent(s) or its toxin(s), and that occurred 48 hours or more after hospital admission and was not incubating at the time of admission.[11] Infections in patients recently discharged from the hospital within the previous 2-week period were also included in this group.

HCAI was defined using the same criteria that Deborah Friedman used for HCAI - BSI.[1] The infection must have been present at the time of hospital admission or within 48 hours of admission in patients that fulfilled any of the following criteria:

- Received intravenous therapy at home, wound care or specialized nursing care through a healthcare agency, family or friends; or, self-administered intravenous medical therapy in the 30 day period before the onset of the infection. Patients whose only home therapy was oxygen use were excluded.
- Attended a hospital or haemodialysis clinic, or received intravenous chemotherapy in the previous 30 days.
- Were hospitalized in an acute care hospital for 2 or more days in the previous 90 days.
- Resided in a nursing home or long-term care facility.

The CDC definitions were used to define infections at different anatomic sites.[10] BSI were classified as primary or secondary. Primary BSI were defined according to the National Nosocomial Infection Surveillance System,[12] and include intravascular device-associated infections. A secondary BSI was defined as the presence of an organism isolated from a blood culture that was related to an infection at another site.[10]

MDR organisms were those resistant to one or more classes of antimicrobial agents that are recommended as first line therapy.[13] Enteric gram-negative rods were considered MDR if they were resistant to amoxicillin-clavulanate, piperacillin-tazobactam, carbapenems, aztreonam, fluoroquinolones, 3rd generation cephalosporins, aminoglycosides or trimethoprim-sulfamethoxazole. *Acinectobacter* spp and *Pseudomonas* spp were considered MDR if they were resistant to piperacillin-tazobactam, imipenem/meropenem, aztreonam, ciprofloxacin, cefepime, ceftazidime, aminoglycosides or colistin. The presence of ESBL production among *E. coli* and *Klebsiella* spp strains was screened by the automatic analyzer Vitek2 (BioMérieux). It was always confirmed by a disk diffusion test that detects synergism between the cephalosporins/monobactam and clavulanate. If the interpretation of the results was doubtful we also performed Etest®: the combination strains of cefotaxime and cefotaxime/clavulanate and ceftazidime and ceftazidime/clavulanate allows the detection of ESBL whenever the ratio antibiotic/antibiotic + inhibitor is equal or above 8.

The comorbidities of patients in the study included immunosuppression (administration of chemotherapy in the 12 months prior to hospital admission, either radiation therapy or administration of 0.2 mg/kg/day prednisolone for at least 3 months prior to hospital admission, administration of 1mg/kg/day of prednisolone for 1 week in the 3 months prior to hospital admission or infection with human immunodeficiency virus), chronic liver disease,[14] chronic heart failure,[14] chronic respiratory disease,[14] chronic renal failure (defined as the need for chronic renal support or a history of chronic renal insufficiency with a serum creatinine level over 2 mg/dl), haematological disease,[15] cancer,[15] diabetes mellitus re-

quiring insulin therapy or oral hypoglycaemic agents before the infection and/or atherosclerosis (defined as a previous history of a transient ischemic attack, stroke, angina, myocardial infarction or peripheral arterial disease).

General medical condition was assessed by the Karnofsky index.[16] A score of lower than 70 implies that the patient is unable to perform normal activities or do active work.

Sepsis and sepsis-related conditions were diagnosed according to the criteria proposed by the ACCP/SCCM.[17] For the first day of antibiotic therapy, the acute physiological score, SAPS II,[15] and the acute organ dysfunction score, SOFA,[18] were recorded.

The initial empirical antibiotic treatment was considered 'adequate' if the antibiotic prescribed within the first 24 hours matched in vitro susceptibility of a pathogen deemed to be the likely cause of infection and when the dosage and route of administration were appropriate for current medical status (focus and severity of infection); only patients with positive microbiology were considered in this analysis.

Statistical analysis

Data were described with medians and inter-quartile ranges. Comparisons were performed using Pearson χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney-U-test for continuous variables.

Independent risk factors associated with infection by MRSA were assessed in respiratory infections, through a logistic regression model, with gender, age, Karnovsky index < 70, severity of infection, SAPS II, total SOFA score, hospitalization in the previous year, previous instrumentation, previous antibiotic therapy, atherosclerosis, diabetes, cancer, haematologic disease, chronic respiratory disease, chronic heart failure, chronic renal failure, chronic hepatic disease and imunossupression as independent variables. Factors found to be significant at the $p < 0.05$ level in the univariate analysis or that were considered clinical important were included in the initial model, and forward stepwise variable elimination was then performed to develop the final model. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Statistical significance was defined as $p < 0.05$. Data were analyzed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period a total of 3733 patients were admitted into the wards and assessed: 1035 (28%) met the inclusion criteria of having infection according to the CDC definitions of infection. Of all patients, 48% (n = 493) were diagnosed with CAI, 22% (n = 225) with HCAI and 30% (n = 317) with HAI.

Among the patients with HCAI: 6 (3%) received intravenous therapy, wound care or specialized nursing care at home, 95 (42%) attended a hospital or a haemodialysis clinic or received intravenous chemotherapy in the previous 30 days, 98 (44%) were admitted to an acute care hospital for 2 or more days in the previous 90 days and 42 (19%) resided in a long-term care facility or in a nursing home; 16 (7%) had more than one.

Table 1 – Patient characteristics, according to place of acquisition of infection

Patients' characteristics	TOTAL (n = 1035)	CAI (n = 493)	HCAI (n = 225)	HAI (n = 317)	HCAI vs. CAI *p value*	HCAI vs. HAI *p value*
Male sex, n (%)	506 (49)	236 (48)	108 (48)	162 (51)	0.974*	0.476*
Age, median (IQR)	68 (52-81)	67 (49-81)	74 (56-83)	67 (53-80)	0.009†	0.004†
SAPSII, median (IQR)	29 (22-34)	28 (20-34)	30 (24-35)	28 (22-34)	0.039†	0.119†
Total SOFA score	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	0.561†	0.678†
Severity of infection, n (%)					0.117*	0.243*
Infection	281 (27)	126 (26)	69 (31)	86 (27)		
Sepsis	364 (35)	178 (36)	73 (32)	113 (36)		
Severe sepsis	296 (29)	139 (28)	70 (31)	87 (27)		
Septic shock	94 (9)	50 (10)	13 (6)	31 (10)		
Previous comorbidities, n (%)	671 (65)	270 (55)	190 (84)	211 (67)	< 0.001*	< 0.001*
Chronic hepatic disease, n (%)	22 (2)	11 (2)	7 (3)	4 (1)	0.454‡	0.214‡
Chronic renal disease, n (%)	149 (14)	31 (6)	63 (28)	55 (17)	< 0.001*	0.003*
Chronic heart failure, n (%)	74 (7)	25 (5)	21 (9)	28 (9)	0.031*	0.841*
Chronic respiratory disease, n (%)	66 (6)	34 (7)	18 (8)	14 (4)	0.597*	0.081*
Hematologic disease, n (%)	60 (6)	9 (2)	26 (12)	25 (8)	< 0.001*	0.149*
Cancer, n (%)	45 (4)	10 (2)	16 (7)	19 (6)	0.001*	0.602*
Diabetes, n (%)	204 (20)	91 (19)	53 (24)	60 (19)	0.114*	0.191*
Atherosclerotic disease, n (%)	242 (23)	101 (21)	67 (30)	74 (23)	0.006*	0.093*
Immunosuppression, n (%)	198 (19)	66 (13)	71 (32)	84 (27)	< 0.001*	0.019*
Karvosky index < 70, (%)	319 (31)	115 (23)	112 (50)	106 (33)	< 0.001*	< 0.001*
Previous antibiotic therapy, n(%)	367 (36)	51 (10)	86 (38)	230 (73)	< 0.001*	< 0.001*

CAI – community-acquired infection, HCAI – healthcare-associated infection, HAI – hospital acquired infection, IQR – Inter-quartile range.

* Pearson Qui-square Test; † Independent samples median test; ‡ Fisher exact test.

Table 2 – Distribution of focus of infection, according to place of acquisition of infection

Focus of infection	TOTAL (n = 1035) n (%)	CAI (n = 493) n (%)	HCAI (n = 225) n (%)	HAI (n = 317) n (%)	HCAI vs. CAI *p value*	HCAI vs. HAI *p value*
Respiratory	419 (40)	244 (50)	70 (31)	105 (33)	< 0.001*	0.622*
Urinary	344 (33)	140 (28)	102 (45)	102 (32)	< 0.001*	0.002*
Intra-abdominal	213 (21)	104 (21)	31 (14)	78 (25)	0.020*	0.002*
Primary bloodstream infection	57 (6)	4 (1)	21 (9)	32 (10)	< 0.001†	0.719†
Other	2 (0)	1 (0)	1 (1)	0 (0)	< 0.001†	1.000†
Microbiological confirmation	703 (68)	274 (56)	165 (73)	264 (83)	< 0.001*	0.005*

CAI – community-acquired infection, HCAI – healthcare-associated infection, HAI – hospital acquired infection.

*Pearson Qui-square Test; † Fisher exact test.

Table 3 – Microbiological profiles of monomicrobial infections, according to place of acquisition of infection.

Positive microbiology	TOTAL (n = 703) n (%)	CAI (n = 274) n (%)	HCAI (n = 165) n (%)	HAI (n = 264) n (%)	HCAI vs CAI *p value*	HCAI vs HAI *p value*
Type of microorganism					0.975†	0.849†
Gram negative	384 (55)	163 (60)	90 (55)	131 (50)		
Gram positive	204 (29)	83 (30)	47 (28)	74 (28)		
Fungi	15 (2)	5 (2)	3 (2)	7 (3)		
Polymicrobial	100 (14)	23 (8)	25 (15)	52 (20)		
Pathogen					< 0.001†	< 0.001†
E. coli	197 (32)	96 (39)	59 (42)	42 (20)		
S. pneumoniae	65 (11)	58 (23)	6 (4)	1 (1)		
Pseudomonas aeruginosa	43 (7)	6 (2)	5 (4)	32 (15)		
MRSA	39 (6)	2 (1)	8 (6)	29 (13)		
MSSA	39 (6)	7 (3)	18 (13)	14 (6)		
Klebsiella pneumoniae	36 (6)	11 (4)	10 (7)	15 (7)		
Proteus mirabilis	22 (3)	9 (4)	4 (3)	9 (4)		
Haemophilus influenzae	18 (3)	16 (7)	1 (1)	1 (1)		
Enterococcus faecalis	16 (2)	6 (2)	2 (1)	8 (4)		
Enterobacter cloacae	13 (2)	3 (1)	1 (1)	9 (4)		
Acinectobacter baumannii	13 (2)	1 (0)	2 (1)	10 (5)		
Enterococcus faecium	13 (2)	0 (0)	4 (3)	9 (4)		
Others	89 (15)	36 (15)	20 (14)	33 (16)		
TOTAL monomicrobial	**603 (100)**	**251 (100)**	**140 (100)**	**212 (100)**		
MDR	324 (54%)	80 (32%)	87 (62%)	157 (74%)	< 0.001*	0.019*
ESBL	21 (3%)	4 (2%)	11 (8%)	6 (3%)	0.005†	0.023*

CAI – community-acquired infection, HCAI – healthcare-associated infection, HAI – hospital acquired infection, MRSA – Methicillin resistant *Staphylococcus aureus*, MSSA – Methicillin sensitive *Staphylococcus aureus*. ESBL - Extended-spectrum beta-lactamases producer. MDR – Multi-drug resistant

*Pearson Qui-square Test, † Fisher exact test.

Patients with HCAI were older (74 years) than patients with CAI (67 years, $p = 0.009$) or HAI (67 years, $p = 0.004$), had higher prevalence of previous comorbidities (84% *vs* 55% *vs* 67%, $p < 0.001$), namely chronic renal disease (28% *vs* 6% *vs* 17%, $p < 0.005$), immunossupression (32% *vs* 13% *vs* 27%, $p < 0.005$) and more frequently needed help in daily activities (measured by a Karnofsky index of less than 70) (20% *vs* 23% *vs* 33%, $p < 0.05$) (Table 1).

In HCAI the main focus of infection was urinary (45%); in CAI, respiratory (50%) and in HAI, intra-abdominal and respiratory (25% and 21% respectively). Overall microbiology documentation of infection was 68%: 56% in CAI, 73% in HCAI and 83% in HAI, ($p < 0.05$) (Table 2).

No significant differences were found between the 3 groups (CAI, HCAI or HAI) regarding type of microorganism, namely gram-negatives, gram positives or fungi (table 3), but there was an increase in polymicrobial infection from CAI (8%), to HCAI (15%) and HAI (20%), as well as of MDR organisms: 32%, 62% and 74% ($p < 0.05$). The prevalence of ESBL producer micro-organisms was significantly higher in HCAI (8%), when compared with the other two groups (2% in CAI, 3% in HAI, $p < 0.005$).

The overall microbiological profile considering the 12 most frequent microorganisms according to place of acquisition of infection was also significantly different with: *E. coli* (39%), *Streptococcus pneumoniae* (23%) and *Haemo-*

Table 4 – Comparison of the microbiological profiles, according to place of acquisition and focus of infection.

CAI (*n* = 251) n (%)	HCAI (*n* = 140) n (%)	HAI (*n* = 212) n (%)	HCAI vs. CAI *p* value	HCAI vs. HAI *p* value
Intra-abdominal infection, 124 patients with microbiologic documentation				
45 (100)	**23 (100)**	**56 (100)**		
E. coli, 15 (33)	*E. coli*, 4 (17)	*E. coli*, 10 (18)	0.015†	0.008†
Salmonella, 3 (7)	MSSA, 3 (13)	*Clostridium difficile*, 5 (9)		
Klebsiella pneumoniae, 2 (4)	*Bacillus cereus*, 2 (9)	*Candida albicans*, 4 (7)		
		MRSA, 4 (7)		
Others, 11 (25)	Others, 8 (35)	Others, 10 (18)		
Polymicrobial, 14 (31)	Polymicrobial, 6 (26)	Polymicrobial, 23 (41)	0.418*	0.280*
MDR, gram negative, 9 (38)	MDR, gram negative,3 (50)	MDR, gram negative, 8 (57)	0.660†	1.000†
ESBL producers, 1 (2)	ESBL producers, 1 (4)	ESBL producers, 2 (4)	1.000†	1.000†
Urinary infection, 306 patients with microbiologic documentation				
117 (100)	**92 (100)**	**97 (100)**		
E. coli, 81 (69)	*E. coli*, 51 (56)	*E. coli*, 25 (26)	< 0.115†	< 0.001†
Proteus mirabilis, 9 (8)	*Klebsiella pneum.*, 8 (9)	*Pseudomonas aeruginosa*,12 (12)		
Enterococcus faecalis, 6 (5)	*Proteus mirabilis* , 4 (4)	*Enterococcus faecalis*, 8 (8)		
Others, 16 (14)	Others, 14 (15)	Others, 31 (32)		
Polymicrobial, 5 (4)	Polymicrobial, 15 (16)	Polymicrobial, 21 (22)	0.002*	0.270*
MDR, gram negative, 49 (47)	MDR, gram negative,49 (70)	MDR, gram negative, 43 (69)	0.003*	1.000*
ESBL producers, 3 (3)	ESBL producers, 9 (10)	ESBL producers, 3 (3)	0.032†	0.134†
Respiratory infection, 215 patients with microbiologic documentation				
107 (100)	**29 (100)**	**79 (100)**		
S. pneumoniae, 58 (54)	MRSA, 7 (24)	MRSA, 19 (24)	< 0.001†	0.042†
Haemophilus influenza, 14 (13)	*S. pneumoniae*, 5 (17)	*Pseudomonas aeruginosa*, 14 (18)		
MSSA, 5 (5)	*Pseudomona aeruginosa*, 4 (14)	MSSA, 8 (10)		
		Acinectobacter baumannii, 8 (10)		
Others, 26 (24)	Others, 9 (31)	Others, 24 (30)		
Polymicrobial, 4 (4)	Polymicrobial, 4 (14)	Polymicrobial, 6 (8)	0.077†	1.000†
MDR, 11 (10)	MDR,12 (41)	MDR, 45 (57)	0.001*	0.453*
Bloodstream infections (primary and secondary), 153 patients with microbiologic documentation				
57 (100)	**50 (100)**	**46 (100)**		
E. coli, 22 (39)	*E. coli*, 16 (32)	MRSA, 8 (17)	< 0.001†	0.001†
S. pneumoniae, 17 (30)	MSSA, 13 (26)	*E. coli*, 4 (9)		
		Enterococcus faecium, 4 (9)		
		MSSA, 4 (9)		
		Pseudomonas aeruginosa, 4 (9)		
		Staphylococcus epidermidis, 4 (9)		
Others, 18 (31)	Others, 19 (38)	Others, 14 (30)		
Polymicrobial, 0 (0)	Polymicrobial, 2 (4)	Polymicrobial, 4 (9)		0.422†
MDR, 17 (30)	MDR, 24 (50)	MDR, 36 (86)	0.073*	0.341*

CAI – community-acquired infection, HCAI – healthcare-associated infection, HAI – hospital acquired infection, MRSA – Methicillin resistant *Staphylococcus aureus*, MSSA – Methicillin sensitive *Staphylococcus aureus*, MDR – multidrug resistant microorganism.

*Chi-square test; †Fisher exact test.

philus influenza (7%) as the most frequent among CAI; *E. coli* (42%), MSSA (13%) and *Klesiella pneumoniae* (7%) in HCAI and E. *coli* (20%), *Pseudomonas aeruginosa* (15%) and MRSA (13%) in HAI (Table 3).

In patients with CAI, HCAI or HAI - IAI, the most prevalent pathogen was *E. coli*, followed by *Salmonella* in CAI, MSSA in HCAI and *Clostridium difficile* in HAI. There was a high prevalence (> 25%) of polymicrobial infections independently of the place of acquisition of infection (Table 4).

Of the 31 patients with IAI (14% of all HCAI): 23 (74%) had microbiological confirmation, being 17 (74%) monomicrobial and off those 6 (35%) were caused by gram-negative *bacilli*. Among the gram-negative *bacilli* the resistance rates were 33% to ciprofloxacin, 33% to amoxicillin-clavulanate, 17% to gentamicin and 17% to 3rd generation cephalosporins. No resistance to piperacillin-tazobactam, trimethroprim-sulfamethoxazole, amikacin or carbapenem was observed. In patients with UTI the most prevalent pathogen was also *E. coli*, followed by *Proteus mirabilis* in CAI, *Klebsiella pneumoniae* in HCAI and *Pseudomonas aeruginosa* in HAI. There was an increasing prevalence of polymicrobial infections from CAI (4%), to HCAI (16%, p = 0.002) and HAI (22%, p = 0.270). The proportion of MDR-gram-negatives was also higher in HCAI (70%) and HAI (69%, p = 1.000) than in CAI (47%, p = 0.003). In HCAI there was a higher prevalence of ESBL producers (10%) than in CAI (3%,

Table 5 – Hospital length of stay and crude hospital mortality rate, according to focus of infection and place of acquisition.

Intra-abdominal infections	Total	CAI	HCAI	HAI	HCAI vs. CAI *p value*	HCAI vs. HAI *p value*
Inadequate antibiotic therapy, n (%)	24 (19)	6 (13)	3 (13)	15 (27)	1.000†	0.245†
Hospital LOS (days), median (IQR)	14 (7-25)	8 (5-20)	13 (8-24)	22 (13-33)	0.022‡	0.154‡
Hospital mortality, n (%)	29 (14)	9 (9)	3 (10)	17 (22)	1.000†	0.177†
Urinary infections						
Inadequate antibiotic therapy, n (%)	69 (23)	25 (21)	26 (28)	18 (19)	0.249*	0.115*
Hospital LOS (days), median (IQR)	11 (7-17)	9 (6-13)	9 (6-13)	19 (11-37)	0.923‡	< 0.001‡
Hospital mortality, n (%)	35 (10)	14 (10)	12 (12)	9 (9)	0.662*	0.489*
Respiratory infections						
Inadequate antibiotic therapy, n (%)	44 (21)	5 (5)	15 (52)	24 (30)	< 0.001*	0.041*
Hospital LOS (days), median (IQR)	11 (8-22)	10 (8-18)	10 (7-13)	21 (24-39)	0.054‡	< 0.001‡
Hospital mortality, n (%)	63 (15)	22 (9)	14 (20)	27 (26)	0.011*	0.382*
Bloodstream infections						
Inadequate antibiotic therapy, n (%)	26 (17)	6 (11)	7 (14)	13 (28)	0.583*	0.086*
Hospital LOS (days), median (IQR)	15 (9-28)	12 (8-23)	10 (8-16)	30 (22-48)	0.229‡	< 0.001‡
Hospital mortality, n (%)	25 (16)	9 (16)	5 (10)	11 (24)	0.395*	0.068*
All patients included in the study						
Inadequate antibiotic therapy, n (%)	148 (21)	37 (14)	45 (27)	66 (25)	< 0.001*	0.601*
Hospital LOS (days), median (IQR)	11 (7-22)	10 (7-17)	10 (7-14)	23 (12-39)	0.876‡	< 0.001‡
Hospital mortality, n (%)	138(13)	47 (10)	32 (14)	59 (19)	0.063*	0.173*

LOS – length of stay, IQR – inter-quartile range, *chi-square test, † Fisher exact test, ‡Mann-Whitney-U-Test.

p = 0.032) or HAI (3%, *p* = 0.134) (Table 4).

There were 102 patients with UTI (45% of all HCAI); off those 92 (90%) had microbiological confirmation being 77 (84%) monomicrobial. In monomicrobial HCAI - UTI, 70 (91%) were caused by gram-negative bacilli. Among the group of gram-negative bacilli, resistance rates were: 50% to trimethroprim-sulfamethoxazole, 49% to ciprofloxacin, 24% to amoxicillin-clavulanate, 13% to gentamicin, 3% to 3rd generation cephalosporins, 1% to piperacillin-tazobactam and 1% to carbapenem. No resistance to amikacin was observed.

In patients with respiratory infection the most prevalent pathogens were *Streptococcus pneumoniae* and *Haemophilus influenza* in CAI and MRSA and *Pseudomonas aeruginosa* in HCAI and HAI. Patients with HCAI had a higher rate of polymicrobial infections (14%) than those with CAI (4%) or HAI (8%) (Table 4).

A significant association of MRSA respiratory infection (*n* = 26) and hospitalization in the previous year [adjusted OR = 6.3; 95% CI (2.3 - 17.0)], previous instrumentation [adjusted OR = 4.3; 95% CI (1.5 - 12.8)] and previous antibiotic therapy [adjusted OR = 5.7; 95% CI (1.7 - 18.8)] was found. No cases of MRSA respiratory infection were documented in patients without those risk factors.

In patients with BSI the most prevalent pathogens were *E. coli* and *Streptococcus pneumoniae* in CAI, *E. coli* and MSSA in HCAI and MRSA, *E. coli*, *Enterococcus faecium*, MSSA, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* in HAI. There was an increasing prevalence of polymicrobial infection from 0% in CAI, to 4% in HCAI and 9% in HAI (Table 4).

There were 21 (9%) primary HCAI - BSI, all monomicrobial, with MSSA accounting for 62%, *Enterococcus faecium* for 10% and *Citrobacter freundii* for another 10% of all cases. Gram-negative bacilli were present in 4 patients (19%). MRSA was the responsible pathogen in only 1 case. No fungal or polymicrobial infections were found among this group.

Out of the CAI, only 4 patients had primary BSI. All infections were monomicrobial with different pathogens.

In HAI there were 32 episodes (10%) of primary BSI. MRSA was the predominant agent (19%), followed by *Pseudomonas aeruginosa* (12%), MSSA (12%) and *Staphylococcus epidermidis* (12%). Polymicrobial infections were present in 2 patients (6%), and fungal infection in 1 patient. Patients with HCAI respiratory infection had an increased rate of inadequate antibiotic therapy (52%) by comparison with CAI (5%) and HAI (30%); they also had a significantly higher mortality rate (20%) than those with CAI (9%, *p* = 0.011) (Table 5).

No significant differences in crude hospital mortality were observed in the remaining focus of infection (Table 5). Hospital LOS was higher in HAI when compared to CAI or HCAI (Table 5).

DISCUSSION

This study confirms that healthcare-associated infections have distinct microbiological profiles when compared

with CAI and HAI, considering the overall microbiological profiles and the rates of resistance.

Previous studies have been restricted to respiratory, urinary and BSI.[2-8,19] Our study broadens the clinical application of the new classification of HCAI to include intra-abdominal infections. The need for studies in this area is clearly stated in the 2007 HCAI summit[20] where experts declare that 'no studies specifically related to healthcare-associated infections were identified' and that 'future studies will need to be conduct to examine whether healthcare-associated IAI should be delineated as a separate category of IAI before specific recommendations can be made'. They are fundamental for understanding the microbiological profile involved in each focus of infection, according to place of acquisition, in order to develop up-to-date recommendations for adequate initial empirical antibiotic treatment, a well-known prognostic factor.[3,21]

In IAI - HCAI, polymicrobial infections played an important role as well as MDR gram-negatives. The IDSA guidelines for diagnosis and management of complicated intra-abdominal infection[22] recommend an antipseudomonal cephalosporin, carbapenem or β-lactam/β-lactamase inhibitor plus metronidazol, for IAI - HCAI. Based in our results these recommendations would be appropriate for our group of patients.

In UTI- HCAI, we found a high rate of MDR gram-negative bacilli (70%). The HCAI Summit Critical Appraisal[20] suggested that serious HCAI due to suspected gram-negative bacteria, independently of the site of infection, should be treated empirically with dual coverage that includes aminoglycosides. That broad approach may not be needed in our group of patients with UTI and IAI, due to the lower rate of resistance to piperacillin-tazobactam observed. The rate of ESBL producers is still low (10%), this not justifying empirical coverage among our patients.

Our data on respiratory infections provides further evidence for the application of ATS and IDSA recommendations,[20,23] with empirical coverage of *Pseudomonas aeruginosa*. However regarding MRSA coverage, although it was the second more prevalent pathogen in HCAI and HAI respiratory infections, it was found only in patients with identified risk factors: previous instrumentation, hospital admissions in the previous year or previous antibiotic therapy. No MRSA respiratory infections were diagnosed in patients without any of those risk factors. So empirical coverage of MRSA is only justified in patients with HCAI and previous risk factors for infection by this pathogen.

Regarding BSI clinicians must considerer whether the likely bacteremia reflects a primary process or results secondarily from an infection elsewhere. This distinction is not always made in epidemiological studies.[1,2,24,25] but it is fundamental for initial antibiotic treatment planning.

We selected the definition of HCAI that is most frequently found in the literature.[1,5,6] This allowed us to compare our results to those of other studies, but this concept is clearly an evolving topic.

The prospective design of this study, with consensual definitions in the protocol, the inclusion of different wards of the hospital including intensive care and of the four major focus of infection with a thorough comparison of those with HCAI with those with CAI and HAI, allowed a more clear microbiology characterization.

This study had a thorough data collection made by a single trained doctor allowing full completion of all protocols with no missing data per item, along with a complete follow up of all patients until hospital discharge, minimizing any information bias.

Despite being a single-centre study, the microbiological profile we describe for respiratory HCAI is very similar to the one described in the USA.[3,19] The microbiological profile found in BSI was similar to the descriptions in Canadian,[5] Spanish[7] and USA[2] studies suggesting that our results might be generalized for other settings.

CONCLUSIONS

Our results confirm that HCAI have a unique microbiological profile and higher rates of resistance, when compared with CAI and HAI, for the four main focus of infection. Failure to recognize this may lead to adverse outcomes as a result of an increased risk of treatment failure.

Physicians need to be aware of this new classification of infections for patients from the community that have previous exposure to the healthcare system for which the existing guidelines may not apply.

Further research involving a large number of patients from different institutions and geographic areas is warranted to confirm our findings and evaluate the need to develop specific guidelines for this new group of patients.

ACKNOWLEDGEMENTS

We are indebted to Luís Filipe Azevedo for the critical reading of this manuscript.

CONFLICT OF INTERESTS

None stated.

FUNDING SOURCES

Teresa Cardoso received a Scholarship for Academic Research included in Phd Thesis granted by Departamento de Formação, Ensino e Investigação do Centro Hospitalar do Porto. Funding by Associação de Apoio à Unidade de Cuidados Intensivos Polivalente, Hospital de Santo António, Porto, Portugal (ASSUCIP).

REFERENCES

1. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137:791-7.
2. Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large US database. Crit Care Med. 2006;34:2588-95.
3. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epi-

demiology and outcomes of health-care-associated penumonia, results from a large US database of culture-positive pneumonia. Chest. 2005;128:3854-62.
4. Park HK, Song JU, Um SW, Koh WJ, Suh GY, Chung MP, et al. Clinical characteristics of health care-associated pneumonia in a Korean teaching hospital. Respir Med. 2010;1-7.
5. Lenz R, Leal JR, Church DL, Gregson DB, Ross T, Laupland KB. The distinct category of healthcare associated bloodstream infections. BMC Infect Dis. 2012;12:85.
6. Catarralà J, Mykietiuk A, Fernández-Sabé N, Suárez C, Dorca J, Verdaguer R, et al. Health care-associated pneumonia requiring hospital admission. Arch Intern Med. 2007;167:1393-99.
7. Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infection in adults: importance of healthcare-associated infections. J Infect. 2007;56:27-34.
8. Aguilar-Duran S, Horcajada JP, Sorli L, Montero M, Salvado M, Grau S, et al. Community-onset healthcare-related urinary tract infections: comparison with community and hospital-acquired urinary tract infections. J Infect. 2012;64:478-83.
9. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
10. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. Am J Infect Control. 1988;16:128-40.
11. Pop-Vicas AE, D'Agata EMC. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin Infect Dis. 2005;40:1792-8.
12. Horan TC, Emori TG. Definitions of key terms used in NNIS System. Am J Infect Control. 1997;25:112-6.
13. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Organisms In Healthcare Settings, 2006. Atlanta: Centers for Disease Control and Prevention; 2006.
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818-29.
15. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:2957-63.
16. Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod, editor. Evaluation of Chemotherapeutic Agents. Columbia: University Press; 1949.
17. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644-55.
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707-10.
19. Micek ST, Kollef KE, Reichley RM, Roubinian N, Kollef MH. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. Antimicrob Agents Chemother. 2007;51:3568-73.
20. Kollef MH, Napolitano LM, Solomkin JS, Wunderink RG, Bae IG, Fowler VG, et al. Health care-associated infection (HAI): a critical appraisal of the emerging threat - proceedings of the HAI Summit. Clin Infect Dis. 2008;47:S55-99.
21. Fraser A, Paul M, Almanasreh N, Tacconelli E, Frank U, Cauda R, et al. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. Am J Med. 2006;119:970-6.
22. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133-64.
23. Documents, A.T.S. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388-416.
24. Siegman-Igra Y, Orni-Wasserlauf R, Noy A, Schwartz D, Giladi M. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis. 2002;34:1431-9.
25. Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E et al. Bloodstream infection in adults: importance of healthcare-associated infections. J Infect. 2007;56:27-34.