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FROM AROUND THE GLOBE

Surveillance of multi-drug resistant pathogens in two Romanian university hospitals

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Abstract

Health care associated infections (HCAIs) and bacterial multi-drug resistance (MDR) involve high costs and are difficult to manage in medical systems with limited resources. This study, part of the PNCDII 42121/2008 national research project, proposed the investigation of multidrug-resistant bacteria prevalence, concurrent with costs evaluation in two intensive care units (ICUs) from Timisoara university hospitals: Emergency Clinical County Hospital (ECCH) and Institute of Cardiovascular Diseases (ICD). During January-October 2010, we performed a surveillance focused on the following major exponents: meticillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL) producing enterobacteria and carbapenem-resistant non-fermentative Gram negative bacilli, with duplicates and colonisation germs exclusion. Selected germs identification and phenotyping were performed with the help of automatic VITEK 2 compact system, using VITEK 2 GP/GN identification cards and AST cards for antimicrobial sensitivity tests. We also performed Hodge tests for ESBL producing carbapenem resistant enterobacteria. At ECCH we isolated 534 bacterial strains, with a 35.44% prevalence for MRSA, 37.32% ESBL enterobacteria and 43.94% carbapenem-resistant non-fermenters. From 73 strains isolated from ICD, the MRSA prevalence was 8.00%, 23.33% ESBL enterobacteria and 11.11% carbapenem-resistant non-fermentatives. The average number of antimicrobial treatment days/ MDR infectious episode was 9.11 days in ECCH and 29.57days in ICD, with an average hospitalisation cost of

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€3,657.35 per patient in ECCH and €3,780.87 per patient in ICD. As a conclusion, the study established high prevalence rates of Gram negative bacteria, especially of carbapenem-resistant non-fermenters and evaluated the burden produced by infections with MDR bacteria on our sanitary system.

Key words
Drug resistance, multiple, bacterial; Cross infection+epidemiology+prevention and control; Cost and cost analysis; Romania

Introduction

The purpose of our study was the investigation of multidrug-resistant (MDR) bacterial prevalence, concurrent with costs evaluation in two intensive care units (ICUs) from Timisoara university hospitals: Emergency Clinical County Hospital (ECCH) and Institute of Cardiovascular Diseases (ICD). This study is part of the PNCDII 42121/2008 Romanian national research project.

Background

Health care associated infections (HCAIs) and bacterial MDR involve high costs and are difficult to manage in medical systems with limited resources. World Health Organisation (WHO) considers that the emergence of MDR pathogens represents an alarming phenomenon for the modern medicine, leading to the increased treatment failure and increasing treatment costs, often beyond what can be afforded by patients in developing countries. The development of MDR has been accelerated by a growing connectivity of regions and populations and by the speed and volume of air travel, the way in which food is produced and environment is managed.[1]

According with The European Centre for Diseases Prevention and Control (ECDC), antimicrobial resistance (AMR) is still a growing European and global health problem.[2] In Europe it is estimated that 4,544,100 episodes of HCAI occur every year, with more than 37,000 deaths each year and 16 million extra days of hospital stay. Approximately half of the deaths attributable to HCAI, being due to the 7 most common MDR bacteria, in the 4 main types of HCAI: blood stream infections (BSI), pneumonia, surgical site infections (SSI) and urinary tract infections (UTI). The annual economic impact is approximately 7 billion Euro (direct costs only).[3,4]

According to the European Antimicrobial Resistance Surveillance System Network (EARS-Net), Improving Patient Safety in Europe (IPSE) and ECDC data, Romania, together with other south-eastern European countries, is confronting one of the highest prevalence of MDR pathogens.[5-9]

That's why, the role of the microbiology laboratories in the surveillance of HCAIs and AMR is increasing. Their periodic reports should be able to demonstrate trends of specific pathogens, being very useful in the management of preventive measures.[10]

The aim of surveillance is to reduce the incidence of HCAIs. Surveillance programmes should contribute to the quantification of multidrug-resistance risk, outbreaks detection and prioritization of the infection prevention and control (IPC) activities. The establishment of increasing prevalence of MDR hospital or community acquired strains, description of the main geographical differences of the circulating phenotypes are other tasks of these programmes. Surveillance also intervenes in the IPC policies and MDR guidelines elaboration process at hospital/regional/national level and educational campaigns for patients or medical staff.[11]

Patients admitted to intensive care units (ICUs) are at an especially high risk of acquiring HCAI, because of many intrinsic and extrinsic risk factors: their clinical condition/severity of illness or impaired immunity, mechanical ventilation/central line catheterisation and the frequency of antimicrobial agents used. HCAI BSI and pneumonia increase mortality and pneumonia increase the length of stay in ICUs. In Europe, 3.0% of patients staying more than 2 days in ICUs acquire BSI, and 6.2% acquire pneumonia. These patients are especially at high risk.[12]

Methods

During January-October 2010, we performed a prospective surveillance study of bacterial resistance, in two ICU departments from Timisoara university hospitals: Emergency Clinical County Hospital (ECCH) and Institute of Cardiovascular Diseases (ICD). Our study was focused on the following major exponents: meticillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL) producing enterobacteria and carbapenem-resistant non-fermenters, with duplicates and colonisation germs exclusion. Our primary outcome was prevalence determination for these strains, and as secondary outcome, estimation of the financial impact for MDR pathogens in the studied departments.

TECCH is the most representative tertiary health care unit from the western part of Romania, with more than 1000 beds. It has one 28-bed principal ICU department with mixed pathology (medical and surgical) and an annual rolling of 56.28 hospitalized patients per bed in 2009, and 50 patients/bed in 2010.

Regarding ICD, this is the only cardiovascular surgery tertiary health care unit, from the western part of Romania, with 200 beds. The ICU surgical department has 15-bed and an annual rolling of 58.86 patients/bed in 2010.

Both, TECCH's and ICD's laboratories transferred all the MDR strains (collected from bronchial aspirates, blood samples, urines, surgical wound secretions, etc.) for confirmation, to the University Microbiology Department's Laboratory. These microorganisms have been re-identified and phenotyped using the BioMerieux® VITEK 2 automated microbiology system, with VITEK 2 GP/GN identification cards and AST cards for antimicrobial sensitivity tests (EUCAST standards).

Regarding our inclusion criteria, only the first strain of *S. aureus*, Enterobacteriaceae family, *P. aeruginosa* and *A. baumannii*, with clinical relevance and a specific sensitivity pattern, isolated from one patient, was included in the study. The patients with clinical symptomatology for a HCAI, hospitalized at least 48 hours before in ICU, have been introduced consecutively in the study, independent of their gender or age. We excluded the following groups of patients: those with community acquired infections, infections started before ICU hospitalization (in other departments), fungal infections, or bacterial infections other than mentioned strains.

Quality control strains used in the testing were: *E. coli* ATCC 3521, for the ESBL producing strains, *E. coli* ATCC 25922 for sensitive strains, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 43300 for MRSA strains and *S. aureus* ATCC 29213 for sensitive strains. The production of ESBLs was detected using the double disc diffusion method. We also performed Hodge tests, in the case of suspicion of carbapenemase producing strains of Enterobacteriaceae.

Our institutional review board approved the protocol and granted a waiver of informed consent. The TECCH and ICD-ICU specialists created a database that calculated the total cost afforded by the Romanian medical system for supporting the antimicrobial treatment for infections produced by MDR bacteria in their departments in 2010.

Results

From 1102 monitored patients in TECCH-ICU, we collected 699 biological samples, with 534 isolated strains. Regarding ICD-ICU, from 817 monitored patients, only 161 had clinical symptomatology for HCAI and therefore collecting specimens and 73 strains have been isolated from them. From these 607 bacterial non-repetitive strains, the majority, 503 were Gram negative bacilli (GNB) (enterobacteria and non-fermenters) and 104 were Gram positive bacteria (GPB) (*S. aureus* strains) (Table I).

The most frequently collected samples were: bronchial aspirates, blood samples, urines and surgical wound secretions. Distribution of the main resistance phenotypes in these samples is represented in Figure 1. We noticed the highest prevalence of MDR pathogens at the level of ECCH-ICU. From the total number of 534 isolated bacterial strains, the highest prevalence was noticed in the case of GNB. The ESBL producing *K. pneumoniae* showed a percentage of 56.86%, followed by carbapenem-resistant *A. baumannii* with 56.06%, than ESBL producing *K. oxytoca* (37.5%), carbapenem-resistant *P. aeruginosa* (*35.16%),* ESBL producing *E. coli* and other enterobacteria. We also noticed 35.44% prevalence for MRSA (Table I).

Table I. Prevalence of MDR pathogens in ECCH and ICD - ICUs

Species	Total number of strains		Species prevalence		Number of strains from the main phenotypes*		The main phenotypes prevalence*	
	ECCH	ICD	ECCH	ICD	ECCH	ICD	ECCH	ICD
S. aureus	79	25	14.79%	34.25%	28	2	35.44%	8.00%
E. coli	47	12	8.80%	16.43%	14	2	29.78%	16.66%
Klebsiella pneumoniae	51	2	9.55%	2.74%	29	1	56.86%	50.00%
Klebsiella oxytoca	8	0	1.49%	0	3	0	37.5%	0
Pseudomonas aeruginosa	91	7	17.04%	9.58%	32	1	35.16%	14.28%
Acinetobacter baumannii	66	1	12.35%	1.36%	37	0	56.06%	0
Other enterobacteria	111	16	20.78%	21.91%	35	4	31.53%	25.00%
Other bacteria	81	10	15.16%	13.69%	0	0	0	0
Total	**534**	**73**	**100%**	**100%**	**178**	**10**	**33.33%**	**13.69%**

Legend: * MRSA for *S. aureus*; ESBL for Enterobacteriaceae; carbapenem-R for non-fermenters

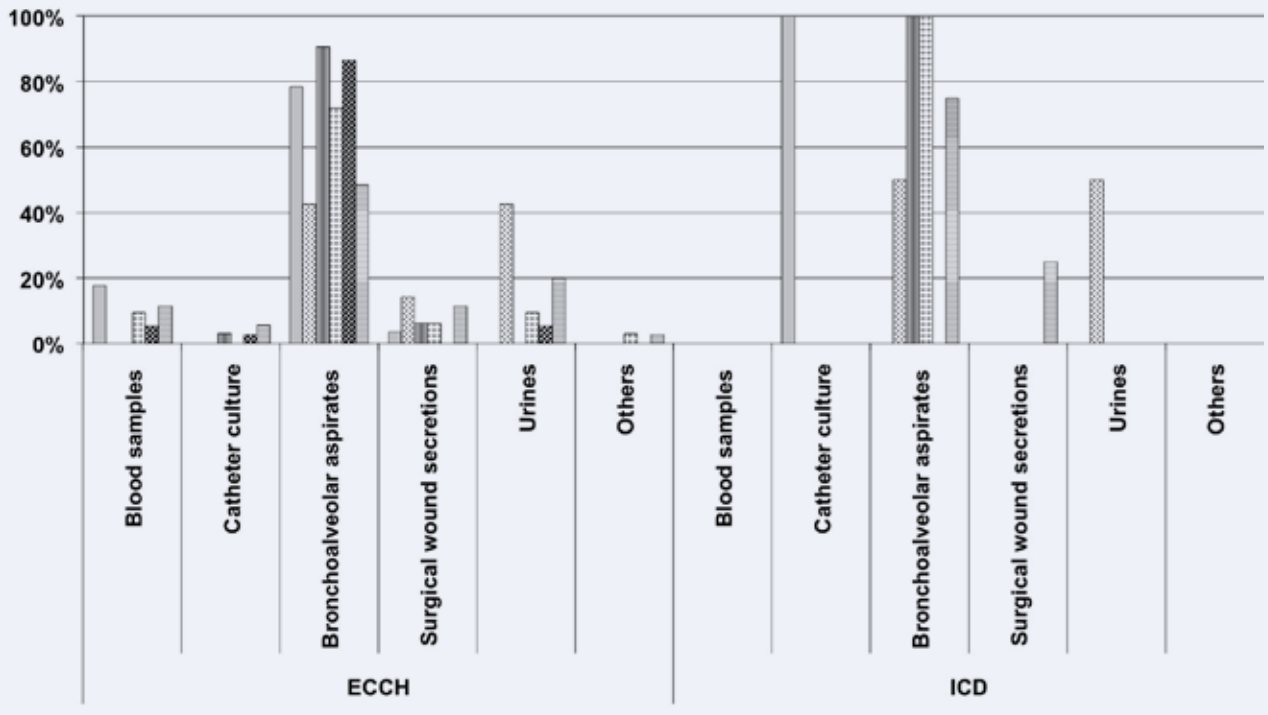

Figure 1. Distribution of the most important MDR pathogens in collected biological samples

Regarding ICD-ICU, a lower prevalence of MDR pathogens was noticed here, with aproximatively the same distribution. The ESBL producing *K. pneumoniae* was on the first place, with 50.00%, followed by *E. coli* and other enterobacteria. The prevalence of carbapenem-resistant *P. aeruginosa* was 14.28% and MRSA showed 8.00% (Table I). All our Hodge test results were negative. Therefore, no carbapenemase-producing Enterobacteriaceae were noticed.

The average number of antimicrobial treatment days/ MDR infectious episode, was higher in the case of ICD-ICU, with 29.57 days versus 9.11 days for ECCH-ICU. The average hospitalisation cost was similar in both studied ICUs: with €3,657.35/patient in ECCH and €3,780.87/patient in ICD (Table II). The maximum identified cost was in ECCH, with €4,121 administered for 29 days of antimicrobial treatment of a HCAI pneumopathy, with associated MDR germs (*P. aeruginosa, E. coli, S. aureus*).

Discussions

Our study established high prevalence rates especially in the case of GNB. Higher values were reported in ECCH-ICU than in ICD – ICU, because of the bigger capacity, mixed pathology and non-clean surgical procedures performed in the case of these patients (general surgery, orthopaedics, urology, etc). The highest cumulative percentage was noticed here in the case of carbapenem-resistant non-fermenters, which amounted to 43.94%, followed by 37.32% ESBL producing enterobacteria and 35.44% MRSA.

We noticed an increasing prevalence of resistance when comparing 2010 data to that collected from the same hospital and department (ECCH-ICU) in 2005. This trend was seen in the majority of the studied organisms. From 15.00% to 56.06% for carbapenem-resistant *A. baumannii* strains, from 10.00% to 35.16% for carbapenem-resistant *P. aeruginosa* strains and from 23.91% to 29.78% in the case of ESBL producing *E. coli* strains. The only ESBL *K. pneumoniae* decreased from 63.00% to 56.86%.[8] When comparing the same 2005 ECCH-ICU prevalence rates with those from other thirty-four ICUs participating in the Improving Patient Safety in Europe (IPSE) surveillance study, we noticed high rates of resistance for us and for other Eastern and South-Eastern European countries, for the same MDR pathogens.[8]

In the case of the second studied hospital, because of the smaller capacity of the ICD-ICU and the clean cardiovascular surgical procedures performed on these patients, the prevalence rates were smaller than in the case of ECCH-ICU. We noticed 23.33% ESBL producing enterobacteria, followed by 11.11% carbapenem-resistant non-fermenters and 8.00% MRSA. However, these resistance rates are still high comparing with other studies.[8,12,13]

Another comparison should be made with results obtained from another Romanian national project (MAR-T) conducted during 2008-2010 and coordinated by Matei Bals University Hospital. The percentage of ESBL producing Enterobacteriaceae was higher in ECCH than the MAR-T study (29.78% and 56.86% respectively for *E. coli* and *Klebsiella pneumoniae* in our study vs. 11.1% and 39.2% in MAR-T study). Contrariwise, in the case of non-fermenters, a higher prevalence of carbapenem-resistance was noted in MAR-T project than in our project (50.00% meropenem-resistant *P. aeruginosa* and 72.6% meropenem-resistant *A. baumannii* vs. 35.16 % and 56.06 % in the current study).[14]

Actually, other published literature also indicate that the prevalence of MDR pathogens, especially of GNB, is escalating in Europe.[15,16,17] Because of the diversity of the resistance rates at the national levels, reliable information about the local distribution of the pathogens and their resistance rates are needed. According to data from Tigecycline Evaluation and Surveillance Trial (T.E.S.T), the prevalence of ESBL producers doubled in Europe amongst *E. coli* strains in the last 2 years, whilst in the case of *K. pneumoniae* over the last 4 years.[17] This trend was observed in our study as well.[8] According to T.E.S.T., the rates of ESBL producing strains, both for *E. coli* and *K. pneumoniae* were three to five times higher for East European countries, e.g. Hungary, Romania and the Slovak Republic, compared with those in the Western Europe. Greece is recognised as the European country with the highest antimicrobial resistance in *K. pneumoniae*.[17]

In 2009, ECDC data also highlighted multi-drug resistance, which is often observed in GNB, further increases the threat posed by antibiotic resistance, since it limits the number of options for treating infections. A few countries have reported a high proportion

Table II. Total costs for infections produced by MDR pathogens in ECCH and ICD ICU-s

	ECCH	ICD
Average number of antimicrobial treatment days/MDR infectious episode	9.11days	29.57days
Average hospitalisation cost	3,657.35 €/patient	3,780.87 €/patient

of resistance to carbapenems in the case of *K. pneumoniae*. According to ECDC data, *E. coli* showed a Europe-wide increase in resistance to all antibiotic classes under surveillance, except carbapenems.[16] The same increasing in resistance was noticed in the case of our *E. coli* strains. Fortunately, in our study, no carbapenemase-producing Enterobacteriaceae were noticed.

Regarding MRSA prevalence, this was also higher in ECCH-ICU (35.44%) than in ICD–ICU (8.00%), but fortunately a decreasing trend was noticed when comparing with 2005 ECCH data (50.00% MRSA prevalence).[8] According to the literature, MRSA remains one of the principal MDR pathogen causing complicated HCAI: SSIs, BSIs or ventilator-associated pneumonia (VAP).[15,17,18] It is estimated to cause 44% of all HCAIs in Europe every year, with 5,400 attributable extra death and over a million extra days of hospitalization with worse prognosis.[19]

A comparison of MRSA prevention and control recommendations, as stated in national/regional guidelines of 13 European countries was performed based on a structured questionnaire filled by representatives of professional societies or institutions. The survey indicates that the practices of isolating MRSA positive patients in single room, perform MRSA screening based on risk categories in hospitals and nursing homes, and decolonisation of MRSA carriers may well be the most successful, and are commended as best practices.[20]

MDR bacteria do not respect borders and physicians, laboratories should be aware of the risk posed by transfer of patients from hospitals in other countries.[21] In this context, rapid and effective international communication is important to prevent the further spread of emerging MDR microorganisms. Also, prudent use of antibiotics, compliance with hand hygiene and other infection control measures are essential to reduce selection and spread of MDR microorganisms.[12, 22]

Regarding costs, these are particularly high for treating patients with MDR-HCAI, especially in ICUs. Although the total number of ICU beds totals only 5% to 10% of the total hospital beds, these consume more than 30% of the hospital budget and 8% of the healthcare system budget.[23] However, the global burden of AMR remains unknown and data are limited in many countries, in particular in developing, low and middle-income countries.

We estimated the high financial burden afforded by the Romanian medical system for supporting the antimicrobial treatment for infections produced by MDR bacteria in both the TECCH and ICD-ICUs in 2010 was more than €3,000. The average number of antimicrobial treatment days/MDR infectious episode, was higher in the case of ICD-ICU, with almost 30 days, because of the high complexity of the cardiovascular pathology.

Based on the BSI and HCAI identified in 2003 and 2007 respectively, the Belgian Institute for Public Health estimated that the most expensive are lower respiratory tract infections (LRIs) costing 100 million Euro and BSIs costing 80 million Euro. The average excess in hospital stay (average days/case) was 10.2 for BSIs and 11.4 for LRIs, and the cost mean/case was €7,140 and €7,980 for BSI and LRIs respectively. Per total, the excess cost was 17.3 million Euro for BSIs and 48.8 Million Euro for LRIs. It is clear that from a hospital's perspective, resources will be saved by preventing infections. [24]

The limitations of our study were that we couldn't totally exclude the "denominator effect", although people involved in collecting data have been instructed to include in the study all the patients from which we collected only sensitive strains. Also, we cannot generalize our results, because only two hospitals with their ICU departments were evaluated, although they are the biggest ICUs departments in the western part of the country, and patients are cumulating many intrinsic and extrinsic risk factors, being the perfect candidates for acquiring HCAI. They were also two different types of ICUs (clean cardiovascular surgery/general surgery). This difference was reflected in different resistance rates.

As a conclusion, in Romania and other developing countries, better costs and mortality rate surveillance, as a consequence of AMR, is needed in the future, with a differential approach, from the hospital, patient and health care assurance system point of view. We also need more government initiatives (like mandatory reporting of all BSI, and deaths due to MRSA). Prevention and control of AMR can be achieved by a more prudent use of the existing antimicrobial agents, development of novel antimicrobial agents active on resistant bacteria, with the need to ascertain the perceived gap between infections due to resistant bacteria. Also, more competent infection control teams and identifying strategies (bundles) for reducing risk factors for HCAIs with MDR are needed, especially in developing countries.

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