

MULTIDRUG-RESISTANT PATHOGENS IN A ROMANIAN INTENSIVE CARE UNIT – TRENDS AND AFFORDABLE COSTS

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Abstract

The emergence of multidrug-resistant (MDR) pathogens is a major challenge in terms of treatment failure and increased costs, especially for intensive care unit (ICU) patients. The objective of our study was to assess the incidence of MDR and extensive drug resistant (XDR) strains isolated in a Romanian intensive care unit and to estimate the costs for antibacterial medication during hospitalization. A prospective surveillance was conducted between January-October 2010 and January-October 2012. From the 1,534 collected samples, there were isolated 1,001 bacterial non-repetitive, clinically relevant strains from *S. aureus*, *P. aeruginosa*, *A. baumannii* species and *Enterobacteriaceae* family. Identification and sensitivity tests were performed using the BioMerieux® VITEK 2 Compact automated microbiology system. Of the detected bacterial strains, 783 were Gram-negative (GNB) and 218 were Gram-positive bacteria (GPB). Eighty-eight patients (7.39% of the ICU patients) were infected with MDR strains, totalizing 784 treatment days for infectious episodes. The average number of antimicrobial treatment days/MDR-strains episodes was 9.11 days, with an average medication cost of 3,744 € per patient and an average antibiotic therapy cost of 577.4 € per patient.

Rezumat

Emergența patogenilor multirezistenți (MDR) reprezintă o provocare majoră datorită eșecurilor terapeutice și costurilor mari pe care le antrenează, în special pentru pacienții internați în secții de terapie intensivă (ATI). Am efectuat acest studiu în scopul evaluării tulpinilor microbiene MDR și cu rezistență extinsă (XDR) și a estimării costurilor pentru medicația antibacteriană aferentă perioadei de spitalizare într-o secție de terapie intensivă din România. Studiul prospectiv de supraveghere s-a realizat în perioada ianuarie - octombrie 2010 și ianuarie - octombrie 2012. Din 1534 probe recoltate, am izolat 1001 tulpini bacteriene non-repetitive cu relevanță clinică, din speciile *S. aureus*, *P. aeruginosa*, *A. baumannii* și din familia *Enterobacteriaceae*. Identificarea și testarea sensibilității la chimioterapice antiinfecțioase au fost efectuate cu ajutorul sistemului automat VITEK 2 Compact (BioMerieux®). Din tulpinile izolate, 783 bacterii au fost Gram negative și 218 bacterii Gram pozitive. Optzeci și opt de pacienți (7,39% din pacienții internați în secția de ATI) au fost infectați cu tulpini MDR, totalizând 784 zile de tratament pentru episoadele infecțioase. Numărul mediu al zilelor de tratament cu antimicrobiene/tulpina MDR a fost de 9,11 zile, cu o medie a costurilor pentru medicație de 3744 € per pacient și o medie a costurilor cu antibioterapie de 577,4 € per pacient.

Keywords: multi-drug resistance (MDR), extensive drug resistance (XDR), gram positive, gram negative, antibiotics, costs

Introduction

The emergence of multidrug-resistant (MDR) pathogens represents an alarming phenomenon for modern medicine, leading to increased treatment failure and increased treatment costs, often beyond what patients in developing countries can afford [1].

The European Centre for Disease Prevention and Control (ECDC) data reveal 4,544,100 episodes of

healthcare-associated infections (HCAI) with more than 37,000 attributable deaths each year and 16 million extra days of hospital stay in Europe.

Approximately 50% of the deaths are attributable to four main types of HCAI: blood stream infections (BSI), pneumonia, surgical site infections (SSI), and urinary tract infections (UTI). The annual economic impact of HCAs is approximately 7 billion € (direct costs only) [2, 12].

Patients admitted to intensive care units (ICUs) have an especially high risk of acquiring HCAs, and many of these are caused by antimicrobial-resistant (AMR) pathogens.

According to the European Antimicrobial Resistance Surveillance Network (EARS-Net), Improving Patient Safety in Europe (IPSE), and ECDC data, Romania, together with other South-Eastern European countries, is confronted with one of the highest prevalence rates of MDR pathogens [3-5, 8].

Unfortunately, Europe is facing not only MDR microorganisms (resistant to more than three classes of antimicrobial agents) but also extensively drug-resistant (XDR) and even pandrug-resistant (PDR) microorganisms [10 - 12, 15].

Materials and Methods

We assessed the resistance patterns of the main bacterial species isolated during January - October 2010 and January - October 2012, in Timisoara Emergency Clinical County Hospital (TECCH), the most-representative tertiary healthcare unit in the Western part of Romania, with more than 1,000 beds. It has one 28-bed main ICU department with mixed pathology (medical and surgical) and an annual occupancy of 56.28 inpatients/bed in 2010 and 50 inpatients/bed in 2012, respectively.

The TECCH's laboratory selected MDR strains isolated in samples collected from 2,404 adult patients. We excluded patients under 18 years of age, those with community-acquired infections, those with infections prior to ICU hospitalization (infection contracted in other hospitals/departments), and patients with infections caused only by other microorganisms (bacterial or fungal) than *S. aureus*, *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii*.

Identification and phenotyping were performed with the BioMerieux® VITEK 2 Compact automated microbiology system, with VITEK 2 GP/GN identification cards and AST cards for antimicrobial sensitivity tests (CLSI standards). Quality control strains were used. Only the first clinically relevant strains isolated from each patient were included, regardless of the patient's gender or age.

The production of extended spectrum β -lactamases producers (ESBLs) was detected using the VITEK ESBL test (AST-GN27 cards), which included cefotaxime, ceftazidime, and cefepime with and without clavulanic acid. The Hodge test was performed in four imipenem-resistant isolates, where carbapenemase-producing *Enterobacteriaceae* (CPE) strains were suspected. According to the new ECDC standardized terminology, MDR was defined as

resistance to at least one agent in three or more antimicrobial categories, while XDR was defined as bacterial isolates that remained susceptible to only one or two categories [11].

Statistical analysis

For statistical analysis, we used the EPI-INFO, version 6.04. Numerical data distribution was tested for normality with the Kolmogorov-Smirnov test. Numeric variables were compared with the t test for independent samples. Categorical variables were compared by contingency tables, using the chi-squared test. All tests were two-sided and $p \leq 0.05$ was considered statistically significant.

Our study was approved by the Ethical Committee for Research Activity of the VBUMPT (No. 10/22.10.2008 and the participants signed the informed consent.

In 2010, the TECCH-ICU specialists also created a database and calculated the total cost of medication as well as the total cost of antibiotic therapy used to treat MDR episodes.

Results and Discussion

During the studied period, we collected 1,534 samples from 2,404 adult patients hospitalized in TECCH-ICU, from whom we isolated 1,001 bacterial non-repetitive strains with clinical relevance. Of these, 783 were Gram-negative (GNB) and 218 were Gram-positive bacteria (GPB).

K. pneumoniae and *A. baumannii* were predominantly isolated in bronchial aspirates, *E. coli* and *A. baumannii* in urine samples, SSIs were most frequently infected with *E. coli*, *K. pneumoniae* and *P. aeruginosa* strains, whereas *P. aeruginosa* and *A. baumannii* were most frequently identified in blood cultures.

A significant increase in the incidence of other enterobacteria (e.g. *Proteus* spp., *Providencia stuartii*, *Morganella morganii*, *Serratia* spp., *Enterobacter* spp.) and *P. aeruginosa* strains was noticed in 2012 as compared to 2010 (Table I).

No significant variations were reported for the most-important resistance phenotypes: methicillin-resistant *S. aureus* (MRSA), ESBL-producing *Enterobacteriaceae*, and carbapenem-resistant non-fermenters, except for the decrease of other ESBL producing *Enterobacteriaceae* in 2012.

In 2012 we noticed a significant increase of aminoglycoside ($p = 0.019$) and quinolone resistance ($p = 0.007$) in *S. aureus* strains, quinolone resistance in *P. aeruginosa* strains ($p = 0.019$), and third-generation cephalosporin resistance ($p = 0.014$) in *A. baumannii* strains as compared to results recorded in 2010 (Table II).

Table I

Evolution of the incidence for the studied strains

Species	Total number of strains		Species incidence		p	Number of strains from the main phenotypes*		The main phenotypes incidence		p
	2010	2012	2010	2012		2010	2012	2010	2012	
<i>S. aureus</i>	139	79	25.36%	17.44%	0.002	61	28	43.88%	35.44%	0.222
<i>E. coli</i>	66	47	12.04%	10.37%	0.406	21	14	31.81%	29.78%	0.817
<i>Klebsiella pneumoniae</i>	137	51	25.00%	11.26%	< 0.001	78	29	56.93%	56.86%	0.992
<i>Klebsiella oxytoca</i>	7	8	1.27%	1.77%	0.526	3	3	42.85%	37.50%	1.000
<i>Pseudomonas aeruginosa</i>	51	91	9.30%	20.09%	< 0.001	22	32	43.13%	35.16%	0.347
<i>Acinetobacter baumannii</i>	75	66	13.68%	14.57%	0.689	44	37	58.66%	56.06%	0.754
Other <i>Enterobacteriaceae</i>	73	111	13.32%	24.50%	0.001	35	35	47.94%	31.53%	0.024
Total	548	453	100%	100%	/	264	178	48.17%	39.29%	0.004

* MRSA for *S. aureus*; ESBL for *Enterobacteriaceae*; carbapenem-R for non-fermenters**Table II**

Antimicrobial resistance for the studied strains

Species	Aminopenicillines N (%)		Third generation cephalosporins N (%)		Carbapenems N (%)		Aminoglycosides Amikacin/Gentamicin N (%)		Quinolones N (%)	
	2010	2012	2010	2012	2010	2012	2010	2012	2010	2012
<i>E. coli</i>	66 (100)	47 (100)	21 (31.81)	14 (29.78)	/	/	15/55 (22.72/83.33)	15/41 (31.91/87.23)	58 (87.87)	44 (93.61)
<i>Klebsiella pneumoniae</i>	NA	NA	78 (56.93)	29 (56.86)	3 (2.18)	1 (1.96)	55/115 (40.14/83.94)	22/48 (43.14/94.11)	127 (92.7)	50 (98.03)
<i>Pseudomonas aeruginosa</i>	NA	NA	22 (43.13)	38 (41.75)	22 (43.13)	32 (35.16)	7/29 (13.72/56.86)	23/59 (25.27/64.83)	29 (56.86)	69 (75.82)
<i>Acinetobacter baumannii</i>	NA	NA	68 (90.66)	66 (100)	44 (58.66)	37 (56.06)	30/70 (40/93.33)	28/66 (42.42/100)	74 (98.66)	66 (100)
<i>S. aureus</i>	139 (100)	79 (100)	61 (43.88)	28 (35.44)	61 (43.88)	28 (35.44)	96 (69.06)	66 (83.54)	93 (66.9)	66 (83.54)

All Hodge test results were negative. Therefore, no Carbapenemase-Producing *Enterobacteriaceae* (CPE) were seen.

We noticed statistically significant increases in the incidence of MDR strains, especially in the case of

K. pneumoniae and *P. aeruginosa* strains. On the contrary, the only significant variation for XDR strains was represented by the decrease in the incidence of *K. pneumoniae* (Table III).

Table III

The incidence of MDR and XDR strains for the period studied

Species	Number of MDR strains		MDR incidence		p	Number of XDR strains		XDR incidence		p
	2010	2012	2010	2012		2010	2012	2010	2012	
<i>S. aureus</i>	93	52	66.90%	65.82%	0.870	30	14	21.58%	17.72%	0.494
<i>E. coli</i>	55	44	83.33%	93.61%	0.101	15	15	22.72%	31.91%	0.275
<i>Klebsiella pneumoniae</i>	115	50	83.94%	98.03%	0.008	55	12	40.14%	23.53%	0.034
<i>Klebsiella oxytoca</i>	3	3	42.85%	37.50%	1.00	3	3	42.85%	37.50%	1.00
<i>Pseudomonas aeruginosa</i>	29	69	56.86%	75.82%	0.019	7	22	13.72%	24.17%	0.138
<i>Acinetobacter baumannii</i>	74	66	98.66%	100%	1.00	30	28	40.00%	42.42%	0.770
Other <i>Enterobacteriaceae</i>	52	73	71.23%	65.76%	0.437	10	14	13.69%	12.61%	0.830
Total	421	357	76.82%	78.80%	0.453	150	108	27.37%	23.84%	0.203

In 2010, 88 patients representing 7.39% of the ICU patients were infected with MDR strains, totalizing 784 treatment days for infectious episodes, or 23.25% of the total number of hospitalization days in the ICU.

The total costs of antibiotic treatment for the MDR strains in 2010 were 52,271 €, representing 15.86% of the total medication costs (329,547 €). The total cost of the medication included the costs of

empirical/targeted antibiotic therapy, symptomatic medication - analgesics, sedatives, vasopressors, inotropes, insulin, drug infusion fluids and total parenteral nutrition.

The average number of antimicrobial treatment days/MDR-strains episodes for the studied ICU was 9.11 days [IC: 8.26 - 9.97], with an average medication cost of 3,744 € per patient and an average antibiotic therapy cost of 577.4 € per patient.

According to the ECDC 2009 and 2012 reports, AMR remains a serious threat to patient safety and public health in Europe, mostly because of the increasing percentages of MDR-GNB (with combined resistance to aminopenicillins, fluoroquinolones, third-generation cephalosporins and aminoglycosides) and increasing trends of CPE in European healthcare settings [3, 5].

The increasing number of reports for XDR-GNB is particularly alarming, especially because no alternative therapeutic options has been developed. The antibiotics that usually remain active against XDR isolates are colistin and tigecycline, yet resistance to this last line of defence drugs is being increasingly reported [6, 14, 15].

The significant increases in the incidence of *K. pneumoniae* and *P. aeruginosa* MDR strains aligned in our study with ECDC antimicrobial resistance reports [3, 5].

The same increase in resistance was noticed in the case of our *E. coli* strains when comparing 2012 data to data collected from the same hospital and department in 2005. The increasing trend of resistance was seen in the majority of the studied germs [7].

Regarding costs, these are particularly high for treating patients with MDR-HCAIs, especially in ICUs. Although the total number of ICU beds is only 5% to 10% of the total number of hospital beds, these require more than 30% of the hospital budget and 8% of the healthcare system budget [13].

Based on BSIs and nosocomial infections, the Belgian Institute for Public Health estimated that lower respiratory tract infections (LRIs) are the most expensive as compared to BSIs (100 million € versus 80 million € costs). The average excess in-hospital stay (average days/case) was 10.2 for BSIs and 11.4 for LRIs. The average cost /case was 7,140 € for BSIs and 7,980 € for LRIs, respectively [17]. It is clear that from a hospital's perspective, resources will be saved by preventing infections.

Antimicrobial stewardship, compliance with hand hygiene, contact precautions, active screening cultures, environmental cleaning, decolonization, education, and the existence of national guidelines are also essential for reducing the selection and spread of MDR microorganisms [9, 11, 15, 16].

Regarding limitations of our study, we cannot generalise our results, because only one hospital with one ICU department was evaluated, although

it is the biggest ICU department in the western part of the country, and patients are cumulating many intrinsic and extrinsic risk factors, being the perfect candidates for acquiring HCAI (health care associated infections). Also, we cannot totally exclude the "denominator effect" although those involved in data collection were instructed to include in the study all the strains of the target species, regardless of their sensitivity or resistance to antimicrobial agents.

Conclusions

Comparing the antimicrobial resistance results in 2012 with those recorded in 2010, we noticed an increasing percent of MDR *K. pneumoniae* and *P. aeruginosa* strains, but a decreasing trend for XDR *K. pneumoniae*. No significant variations for MRSA, ESBL producing *E. coli* and *Klebsiella* spp., or for carbapenem-resistant *Acinetobacter baumannii* were observed.

The total costs of antibiotic treatment for the MDR strains in 2010 were 52,271 €, representing 15.86% of the total medication costs in the TECCH-ICU.

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