

Emergence of extensive drug-resistant (XDR) *Acinetobacter baumannii* in the Clinical Center University of Sarajevo, Bosnia and Herzegovina

Amela Dedeić-Ljubović¹, Đana Granov¹, Mirsada Hukić^{2,3}

¹Department of Clinical Microbiology, Clinical Centre University of Sarajevo, ²Department of Medical Science, Academy of Sciences and Arts of Bosnia and Herzegovina, ³International Burch University; Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim Recently increased attention and interest for *Acinetobacter baumannii* are the result of the occurrence of multidrug resistant (MDR), extensive drug resistant (XDR) and pandrug resistant (PDR) isolates around the world. The aim of this study was to examine the resistance of *A. baumannii* isolates to antimicrobials in Clinical Centre University of Sarajevo, Bosnia and Herzegovina.

Methods Two hundred and fifty-seven *A. baumannii* isolates were collected between July 2011 and June 2012 in different wards and from different clinical samples. Multidrug resistant, XDR and PDR were defined according to international expert proposal for interim standard definitions for acquired resistance.

Results A total of 257 *A. baumannii* isolates showed eleven different patterns of resistance, of which ten patterns corresponded to MDR and one corresponded to XDR (sensitive only to colistin). Multidrug resistant and XDR strains were the most common at Intensive Care Units and surgical departments. The largest numbers of isolates were found in wound swabs, blood and bronchial aspirate.

Conclusion This is the first report of XDR *A. baumannii* in the 2000-bed Clinical Centre University of Sarajevo, Bosnia-Herzegovina. Although XDR strains have been detected, the resistance to colistin has not. The elevated prevalence of these strains indicates that local antibiotic prescription policies should be revised and infection prevention and control should be improved.

Key words: antimicrobials, nosocomial infections, intensive care unit

Corresponding author:

Amela Dedeić-Ljubović
Department of Clinical Microbiology,
Clinical Centre University of Sarajevo
71 000 Sarajevo, Bolnička 25,
Bosnia and Herzegovina
Phone: +387 63 51 25 60;
Fax: +387 33 29 85 25;
E-mail: amela.ljubovic@hotmail.com

Original submission:

23 February 2015;

Revised submission:

21 April 2015;

Accepted:

27 April 2015.

INTRODUCTION

Acinetobacter baumannii is a nonfermentative, gram-negative, nonmotile, oxidase-negative bacillus, whose natural reservoir still remains to be determined (1). Its ability to survive in a hospital milieu and its ability to persist for extended periods of time on surfaces makes it a frequent cause for healthcare-associated infections that include pneumonia, bacteremia, meningitis, urinary tract infection, wound infection and it has led to multiple outbreaks (2).

Acinetobacter spp. can develop antibiotic resistance extremely rapidly what is in contrast to other clinical bacteria, which require greater time to acquire resistance, usually in response to therapeutic strategies (3). The emergence of antimicrobial-resistant *Acinetobacter* species is due both to the selective pressure exerted by the use of broad-spectrum antimicrobials and transmission of strains among patients, although the relative contributions of these mechanisms are not yet known (3). Antimicrobial resistance greatly limits the therapeutic options for patients who are infected with this organism, especially if isolates are resistant to the carbapenem class of antimicrobial agents (3).

Definitions of multidrug-resistant *Acinetobacter* species vary and different terms like multidrug resistant (MDR), extensive drug resistant (XDR), and pandrug resistant (PDR) have been used to describe the extent of antimicrobial resistance among *Acinetobacter* spp. (4). A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in all bacteria often responsible for healthcare-associated infections and prone to multidrug resistance (4). In the current review MDR *Acinetobacter* spp. is defined as the isolate resistant to at least one agent in three or more antimicrobial categories, XDR *Acinetobacter* spp. as an isolate that is resistant to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories), and PDR *Acinetobacter* spp. as the XDR *Acinetobacter* spp. that is resistant to all agents in all antimicrobial categories (4).

To date, there has been no record about extensive drug resistance (XDR) *Acinetobacter baumannii* isolates in Bosnia and Herzegovina. Given the scarcity of data the aim of the present study was to examine the occurrence of resistant isolates of *A. baumannii* in the Clinical Centre University of Sarajevo.

MATERIALS AND METHODS

In this retrospective study which was conducted in Clinical Centre University of Sarajevo resistance to antimicrobials was observed in 257 *Acinetobacter baumannii* isolates in the period from July 2011 to June 2012. Isolates were detected from different clinical samples including urine, wound swab, blood, bronchial aspirate and other samples which were collected from patients admitted to various hospital wards.

Identification of *A. baumannii* isolates was done on the basis of morphological, cultural and biochemical characteristics (5). In addition, automated VITEK 2 Compact system (bioMérieux, Marcy l'Étoile, France) was used to help with the confirmation of the *A. baumannii* and for antimicrobial susceptibility testing. Antimicrobial resistance profile was determined by disk-diffusion method for: amoxicillin/clavulanic acid, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, amikacin, gentamicin, tobramycin, imipenem, meropenem, ciprofloxacin, trimethoprim-sulphamethoxazole, colistin, minocycline. *P.aeruginosa* ATCC 27853 was used as quality control strain. Results were interpreted according to EUCAST breakpoints (5).

Multidrug resistant, XDR and PDR were defined according to international expert proposal for interim standard definitions for acquired resistance (4).

RESULTS

The survey contained 257 primo isolates of *A. baumannii* isolated from different samples and clinical departments in Clinical Centre University of Sarajevo from July 2011 to June 2012.

Results of testing for antimicrobial resistance showed the presence of eleven (I-XI) different patterns of resistance (Table 1). The pattern VII belonged to XDR.

Resistotype III (sensitive to colistin, tobramycin and minocycline) was the most frequent, 84 (33%)

Table 1. Different patterns of resistance of *A. baumannii* isolates

Pattern of resistance	Antimicrobial agent*															MDR/XDR
	AN	GA	MEM	IM	FEP	CAZ	PIP	AMC	COL	TOB	TS	CIP	CRO	MYN		
I	R	S	R	R	R	R	R	R	S	R	R	R	R	S	MDR	
II	R	R	S	S	R	R	R	R	S	S	R	R	R	S	MDR	
III	R	R	R	R	R	R	R	R	S	S	R	R	R	S	MDR	
IV	R	S	R	R	R	R	R	R	S	R	R	R	R	S	MDR	
V	R	S	R	R	R	R	R	R	S	S	R	R	R	S	MDR	
VI	S	R	R	R	R	R	R	R	S	S	R	R	R	S	MDR	
VII	R	R	R	R	R	R	R	R	S	R	R	R	R	R	XDR	
VIII	S	S	R	R	R	R	R	R	S	S	R	R	R	S	MDR	
IX	S	S	S	S	R	R	R	R	S	R	R	R	R	S	MDR	
X	R	R	R	R	R	R	R	R	S	S	R	R	R	S	MDR	
XI	S	R	R	R	R	R	R	R	S	R	R	R	R	S	MDR	

R, resistant; S, sensitive; *AN, amikacin; GA, gentamycin MEM, meropenem; IM, imipenem; FEP, cefepime CAZ, ceftazidime; PIP, piperacillin+tazobactam; AMC, amoxicillin+clavulanate; COL, colistin; TOB, tobramycin; TS, trimethoprim- sulfamethoxazole; CIP, ciprofloksacin; CRO, ceftriakson; MYN, minocycline

strains, followed by the resistotype I (sensitive to colistin, gentamycin and minocycline), 59 (23%), resistotype VII (sensitive only to colistin), 37 (14.4%) and resistotype V (sensitive to colistin, gentamycin, tobramycin and minocycline), 21.8 (8.5%) isolates. From the total number of isolates of *A. baumannii*, 220 (85.6%) were MDR strains, while 37 (14.4%) were XDR strains (Figure 1).

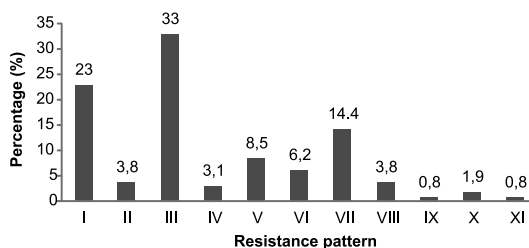


Figure 1. Prevalence of different resistance patterns of 257 *A. baumannii* isolates

The examination of time of the occurrence of XDR isolates showed that first strains were recorded in July 2011 (six isolates). The highest number of isolates were recorded in March 2012 (nine isolates). Multidrug resistant strains were isolated in the largest number in September 2011, May and April 2012, with 25 and 29 isolates, respectively (Figure 2).

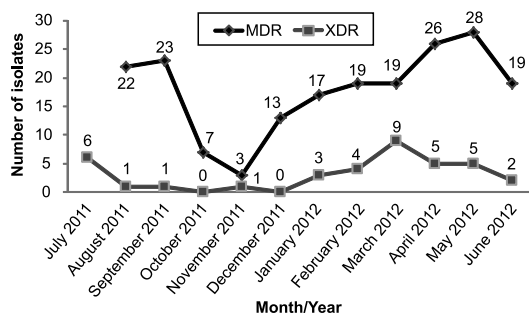


Figure 2. Distribution 257 *A. baumannii* isolates in the period 2011-2012

Multidrug resistant strains were most commonly obtained from Anesthesiology and Reanimation Unit, 39 (18.3%), Intensive Internal Therapy Unit, 33 (15.5%), and from Neurosurgery Intensive Care Unit (ICU), 22 (10.3%), while XDR strains were most commonly obtained from Plastic Surgery Unit, nine (24.3%), following with Anesthesiology and Reanimation Unit and Intensive Internal Therapy Unit, seven (18.9%) strains in each (Figure 3).

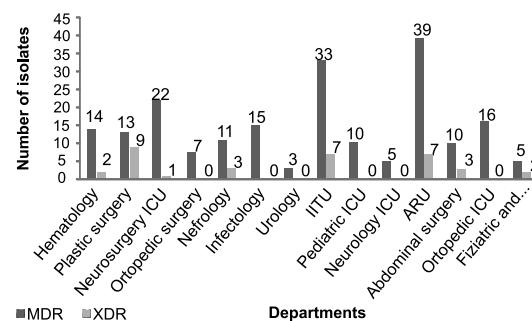


Figure 3. Multidrug resistant (MDR) and extensive drug resistant (XDR) *Acinetobacter baumannii* according to hospital departments

ICU, Intensive Care Unit; IITU, Intensive internal Therapy Unit; ARU, Anesthesiology and Reanimation Unit

Analysis of isolates distribution according to the samples showed that the largest number of isolates were from wound swabs, 81 (31.5%), blood 48 (18.6%), and bronchial aspirate, 39 (15.1%) (Figure 4).



Figure 4. Multidrug resistant (MDR) and extensive drug resistant (XDR) *A. baumannii* according to the samples origin
CVC, central venous catheter

Monitoring of total resistance of isolates showed that there was no resistance to colistin, while resistance to minocycline was 14.4%. Resistance to aminoglycosides varied among isolates, toamikacin was the highest (87.9%), while the lowest was tobramycin (45.2%). Resistance to other antimicrobials was higher than 90% (Figure 5).

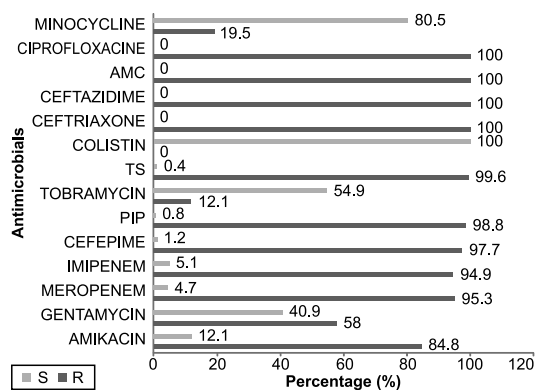


Figure 5. Overall resistance of *A. baumannii* to antimicrobials PIP, piperacillin + tazobactam; AMC, amoxicillin + clavulanate; TS, trimethoprim-sulfamethoxazole; S, Sensitive; R, Resistant

DISCUSSION

A. baumannii once considered opportunistic species and insignificant clinical pathogen today is one of the most important Gram-negative bacteria (6). It is responsible for various serious nosocomial infections particularly in intensive care units (7). *A. baumannii* can complicate the primary disease in severely ill patients and to increase the cost of the treatment (7). Studies has shown that the costs of treating patients infected with *A. baumannii* increased by an average of \$ 60,916, and the hospital stay is longer by 13 days compared to patients who are not infected with this agent (7).

Beside the ability of expressing resistance to many antibiotics, MDR, XDR and PDR strains have the ability for long-lasting survival in the inanimate surfaces, as well as the tendency for epidemic spread (8).

Results of this study have shown 11 different resistance patterns among 257 *A. baumannii* isolates; 85.6% isolates had 10 MDR patterns and 14.4% of isolates had one XDR pattern (sensitive only to colistin). Resistotypes III (sensitive only to colistin, tobramycin and minocycline) was the most frequent (33%). First XDR strains were recorded in July 2011 (6 isolates). In March 2012 9 isolates were recorded. In September 2011, May and April 2012 increased

number of MDR strains were recorded with 25 and 29 of isolates, respectively.

Multi-drug resistant and extensive resistant isolates of *A. baumannii* are increasingly reported all over the world, with the incidence range from 75% (Spain) (9), up to 100% (Italy, Greece, Turkey, Bulgaria) (10-12). In the neighboring countries there was also a high percentage of multi-drug resistant isolates of *A. baumannii* and it ranges from 96.1% in Serbia to 100% in Croatia (13). Similar data were observed in distant parts of the world (USA, Taiwan, Iran, Jordan, China) where multidrug resistance in this microorganism ranged 65-100% (14-18).

Study of Kuo et al. (19) showed that the prevalence of XDR *A. baumannii* increased significantly from 1.3% in 2002 to 41.0% in 2010. Tertiary Hospital in Central Part of Iran, also recorded elevated prevalence of XDR strains over a six-month period (20).

A. baumannii isolates are common among patients in intensive care units and various surgical departments, primarily at the department for burns treatment. Incidence in the intensive care units ranges from 22% in Tunisia, 47-49% in China and Spain to 58.8% in Turkey, while in the departments of surgery from 30% to 62% (9, 21-23). Our data showed that *A. baumannii* isolates were commonly isolated among patients at the Anesthesiology and Reanimation Unit, Neurosurgery ICU, Intensive Internal Therapy Unit and Plastic Surgery Unit. It could be because patients in these sections were all in critical condition, they had extended hospitalization, lower immune defense, suffering from severe underlying diseases or frequent invasive procedures like tracheotomy. Risk factors for colonization or infection with multidrug-resistant *Acinetobacter* species include prolonged length of hospital stay, hospital size (over 500 beds), exposure to ICU, receipt of mechanical ventilation, colonization pressure, exposure to antimicrobial agents, recent surgery, invasive procedures, and underlying severity of illness (24-26).

Wilkes et al. reported a recent outbreak of multi-drug-resistant *Acinetobacter* infection, caused by environmental contamination (curtains, laryngoscope blades, patient lifting equipment, door handles, mops, and keyboards) (27). Medical equipment has been implicated, emphasizing the need for special attention to disinfection of shared items and extra

caution with respiratory care and wound care procedures. One or more epidemic *Acinetobacter* clones often coexist with endemic strains making it difficult to detect and control transmission (3).

In the present study, nearly 32% of *A. baumannii* recovered from clinical specimens were from wounds, blood, bronchial aspirate, and urine.

A. baumannii causes a wide range of nosocomial infections. The most common infections are pneumonia in patients on artificial ventilation, bacteremia, urinary tract infections, wound infections, and less frequently meningitis. Very often these infections are associated with a high mortality rate (28).

A. baumannii bacteremia caused a significant problem in hospitals worldwide. They are usually the result of pneumonia or catheter use and it is the most common cause of mortality in intensive care units (14). Studies from various parts of the world show different frequency of *A. baumannii* bacteremia. High prevalence of 92.5% is found in Korea (29). Slightly lower, but still high percentage of the *A. baumannii* bacteremia is found in studies from Brazil (78%) and Iran (60.5%) (30,14), while the incidence was significantly lower in China, Iran, Turkey and England and ranged from 15% to 52% (18,28,31,32).

In our study over the period 2011-2012 the isolates of *A. baumannii* exhibited high rate of resistance to all antibiotics tested. Resistance to carbapenems, cephalosporins (third and fourth generation), as well as to piperacillin-tazobactam, quinolones, and cotrimoxazole was over 95%. Among aminoglycosides resistance was lowest on tobramycin (below 50%). There was no resistance to colistin.

The results of monitoring hospital infections caused by *A. baumannii* show that in recent years there has been a significant increase in its resistance to the most commonly used group of antibiotics (33). Except still good sensitivity to colistin *A. baumannii* is in high percentage (over 80%) resistant to cephalosporins (ceftazidime and cefepime), and the combination of piperacillin/tazobactam (34-36). The frequency of resistance to ciprofloxacin ranges from 85%, and even up to 100% (34-36). Among aminoglycosides data are different (34-36). The incidence of isolates resistant to gentamicin and amikacin ranges from 80-90%, while for tobramycin is below 75% (34-36). The percentage of carbapenem resistant varies from one country to another and ranges from 45% to over 90% (34-36).

Development of multiresistance is contributed by previous usage of carbapenems, cephalosporins III generation, as well as fluoroquinolones and aminoglycosides (33). Certainly the most important is its ability to acquire resistance genes. Isolates of *A. baumannii* usually contain a set of genes encoding resistance to different groups of antibiotics at the same time (14).

Of all multidrug resistant organisms (MDROs), carbapenemase-producing *Acinetobacter* spp. require special attention; this organism can be resistant to all currently available antimicrobial agents or remain susceptible only to older, potentially more toxic agents such as the polymyxins, leaving limited and suboptimal options for treatment (37).

The problem of increasing resistance of *A. baumannii* is even more threatening when considering the very limited number of new antimicrobial agents that are in development (38,39).

Management of *Acinetobacter* spp. infections is a great challenge for physicians and clinical microbiologists (40). Often colistin or tigecycline are the only available treatments for *A. baumannii* infections (41). Unfortunately, resistance to colistin has recently emerged in Europe. The European arm of the SENTRY surveillance program identified 2.7% of polymyxin B-resistant *A. baumannii* isolates collected during 2001 – 2004 (41). In a recent surveillance study from Greece, among 100 *A. baumannii* strains derived from ICU patients, 3% were colistin resistant, whereas the minimum inhibitory concentration (MIC) levels of tigecycline ranged between 0.12- 4 µg/mL (42). A surveillance study performed in 34 centers across UK, during 2000, reported a 2% resistance rate to colistin among 443 *A. baumannii* tested, while tigecycline MICs ranged from < 0.032-16 µg/mL (43). These data suggest that an antibiotic therapy should always be guided by *in vitro* susceptibility profile of the organism.

The selective pressure caused by indiscriminate usage of broad-spectrum antibiotics in empirical therapy of hospital infections and environmental contamination is the main reason for such increased number of colonization and infection due to this highly resistant pathogen (20).

In conclusion, *A. baumannii* are rapidly spreading with emergence of extended resistance to even newer antimicrobials. In this study we confirmed emergence of XDR *A. baumannii* strains in the most compromised patients in the ICUs, where all

patients are in critical conditions, mostly intubated with long stay in hospital. Although we detected XDR strains, resistance to colistin was not detected. Carbapenem resistance was high, while somewhat lower resistance to aminoglycosides was recorded. The elevated prevalence of these strains indicates that local antibiotic prescription policies should be revised and infection control should be improved.

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FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

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Pojava ekstremno rezistentnih (XDR) sojeva *Acinetobacter baumannii* u Kliničkom centru Univerziteta u Sarajevu (Bosna i Hercegovina)

Amela Dedeić-Ljubović¹, Đana Granov¹, Mirsada Hukić^{2,3}

¹Klinički centar Univerziteta u Sarajevu, ²Odjel za medicinske nauke, Akademija nauka i umjetnosti Bosne i Hercegovine, ³Internacionalni Burch univerzitet; Sarajevo, Bosna i Hercegovina

SAŽETAK

Cilj Nedavno povećana pažnja i interesovanje za *Acinetobacter baumannii* rezultat je pojave multipli otpornih (MDR), ekstremno otpornih (XDR) i potpuno otpornih (PDR) sojeva širom svijeta. Cilj ovog istraživanja bio je ispitati otpornost *A. baumannii* izolata na antimikrobna sredstva u Kliničkom centru Univerziteta u Sarajevu (Bosna i Hercegovina).

Metode Dvije stotine i pedeset sedam izolata *A. baumannii* prikupljeno je u periodu od jula 2011. do juna 2012. godine na različitim odjelima i iz različitih kliničkih uzoraka. Multipli otporni (MDR), XDR i PDR definirani su u skladu s prijedlogom međunarodnih stručnjaka za donošenje privremene standardne definicije stečene rezistencije.

Rezultati Kod 257 izolata *A. baumannii* otkriveno je jedanaest različitih tipova otpornosti od kojih deset odgovara MDR, a jedan XDR sojevima (osjetljiv samo na kolistin). Multipli otporni i XDR sojevi najčešće su izolirani u jedinicama intenzivne njege i hirurgskim odjelima. Najveći broj izolata izolirano je iz brisa rane, krvi i aspirata bronha.

Zaključak Ovom studijom su dokazani prvi izolati ekstremno otpornih sojeva (XDR) *A. baumannii* u Kliničkom centru Univerziteta u Sarajevu (Bosna i Hercegovina) koji raspolaže s 2.000 bolesničkih kreveta. Iako su dokazani XDR sojevi, otpornost na kolistin nije otkrivena. Povišena prevalenca ovih sojeva pokazuje da se lokalna antibiotska politika treba revidirati, a kontrola i prevencija infekcija unaprijediti.

Ključne riječi: antimikrobna sredstva, bolničke infekcije, jedinice intenzivne njege
