Ann Ig 2021 Aug-Sept; 33(5): 401-409. doi: 10.7416/ai.2020.2395. Epub ahead of print 2020 Dec 4.

Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii* in Italy

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Key words: Acinetobacter baumannii, genotyping, carbapenem resistance genes, molecular epidemiology, Italy

Parole chiave: Acinetobacter baumannii, genotizzazione, geni di resistenza ai carbapenemi, epidemiologia molecolare, Italia

Abstract

Background. *Carbapenem-resistant (CR) Acinetobacter baumannii has been increasingly recognized as a major cause of health care-associated infections in critically ill patients and hospital outbreaks.*

Methods. *A narrative review of literature was conducted, searching PubMed database for articles on CR Acinetobacter spp. isolates from Italy published between January 2010 and December 2019.*

Results. *CR A. baumannii isolates assigned to international clonal lineage II (ICL II) and to ST78 clonal lineages were responsible for several epidemics in Italian hospitals during 2002-2018. Molecular analysis of carbapenem resistance showed the presence of OXA-58 CHDL in A. baumannii isolates assigned to ICL II and ST78 clonal lineage, which was replaced by OXA-23 CHDL in A. baumannii isolates assigned to ICL II since 2007 in several hospitals. CR A. baumannii was mainly responsible for respiratory tract infections and at a lesser extent for sepsis in intensive care unit patients.*

Conclusions. *Our data reinforces the need to monitor the molecular epidemiology of CR A. baumannii and its associated antimicrobial resistance genes at national level.*

Introduction

Acinetobacter spp. are glucose non-fermentative Gram-negative coccobacilli, which have emerged since 1970s as a major cause of health care-associated infections in critically ill patients and hospital outbreaks (1-3). *A. baumannii*, *A. nosocomialis*, *A. pittii*, *A. seifertii*, and *A. dijkshoorniae/lactucae*, five of the most clinically relevant species, are genetically and phenotypically similar to the environmental species *A. calcoaceticus* and are therefore grouped into a species complex called the *A. calcoaceticus- A. baumannii* (Acb) complex (3, 4). Because of this, identification of *Acinetobacter* isolates to the species level needs to be confirmed by a molecular method, such as MALDI-TOF mass spectrometry (4) or a genotypic method among those validated for *Acinetobacter* spp. (1, 5, 6). The species that is most frequently recognized as a pathogen is *A. baumannii* (3, 6), which is responsible for hospital-acquired and ventilator-associated pneumonia, bacteremia, urinary tract infection and wound infection, especially in intensive care unit patients (3). Italian Nosocomial Infections Surveillance in Intensive Care Units (ICUs) network (SPIN-UTI) showed that *A. baumannii* was the most

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

frequently reported microorganism (16.9%) as cause of health care-associated infections in Italian ICUs during 2010-2011 (7). Also, *A. baumannii* was responsible for 15% of sepsis in Italian ICUs from 2008 to 2017 (8). Resistance rates of CR *A. baumannii* in Italian ICUs raised from 78.4% during 2006-2007 to 97.9% during 2012-2013 (9). Incidence density of CR *A. baumannii* in Italian ICUs increased from 1.1 per 1,000 patient-days during 2006-2007 to 3.0 during 2012-2013 surveillance period although not significantly (9). Large outbreaks of *A. baumannii* have been described worldwide, which have been sustained by the spread of distinct clonal lineages among bacterial population (1, 6). Molecular epidemiological investigations have shown the occurrence of three lineages, which are distributed worldwide and defined as International Clones (IC) I to III, and of additional epidemic clonal lineages, which are isolated at national and international level (1, 6, 10).

Resistance to disinfection, desiccation and oxidative stress, biofilm formation on abiotic surfaces might contribute to survival of *A. baumannii* in contaminated hospital environment (3, 11). Antibiotic resistance is the other important determinant in clinical outcomes of *Acinetobacter baumannii* infections and spread in the hospital setting (1, 2). *A. baumannii* isolates can be classified as multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) if they are resistant to three or more, all but one or two, and all classes of potentially effective antimicrobial agents, respectively (12). The occurrence of an XDR phenotype and a carbapenem-resistant (CR) phenotype among MDR and particularly XDR isolates is very common for *A. baumannii* (1, 2). Therefore, CR *A. baumannii*, irrespective of its MDR or XDR susceptibility, is included in the global priority list of antibiotic resistant bacteria as a "critical" pathogen by the World Health Organization (13).

The aim of the current review is to analyze: i) the molecular epidemiology of CR *A. baumannii* in Italy during the last 16 years, ii) the carbapenemases responsible for acquisition of carbapenem resistance, iii) risk factors for acquisition of CR *A. baumannii* in Italian hospitals.

Methods

A narrative review of literature was conducted, searching PubMed database for articles on CR *Acinetobacter* spp. isolates from Italy published between January 2010 and December 2019. We selected studies, which reported the following information: study period, city/hospitals, ward, identification of *Acinetobacter* isolates at species level confirmed by MALDI-TOF mass spectrometry (4) or a genotypic method (1, 5, 6), antimicrobial susceptibility profiles and identification of carbapenemase and/or mechanisms of carbapenem resistance of *Acinetobacter* spp. isolates (1, 2), genotyping of *Acinetobacter* isolates and assignment to clonal lineages (1, 6). The total number of CR *A. baumannii* isolates included in each study was considered, even if it corresponded to multiple isolates for single patient. Because two MLST schemes, the Oxford Scheme and the Pasteur scheme, are available for *Acinetobacter*, and the Oxford MLST scheme suffers from several technical problems and duplication at the *gdhB* locus (6), we selected studies, which used the Pasteur MLST scheme or both the Pasteur and the Oxford MSLT schemes for genotyping of *Acinetobacter* spp. isolates. Eighteen articles met our inclusion criteria and were appropriate for in-depth assessment of molecular epidemiology of CR *A. baumannii* in Italy and molecular analysis of carbapenem resistance in *A. baumannii* (Table 1 and Figure 1). Of the 18 selected article, 5 studies reported the clinical features associated with CR *A.*

baumanniii isolates and were considered to analyze risk factors for CR *A. baumannii* acquisition. Sixteen additional articles on CR *A. baumannii* published during 2010-2019 were included in the study.

Results

Molecular epidemiology of carbapenem resistant A. baumannii in Italy during 2002-2018

The epidemiological and genotypic features of CR *A. baumannii* isolates described in the eighteen selected studies are included in Table 1. The studies were different respect to time of occurrence and geographical location, reporting data from 2002 to 2018 and from 22 Italian cities. All 18 studies took place in inpatient hospital setting, particularly in intensive care units, medical or surgical wards, or transplantation units. All studies reported the isolation of CR *A. baumannii*, while the isolation of non-*baumannii Acinetobacter* species unlike other countries (4, 6) were not described in Italy during 2002-2018.

The majority of studies were case series studies on CR *A. baumannii* isolates from Italian ICUs (14- 21) or outbreak investigations describing *A. baumannii* epidemics in different hospital (22-27). Four articles described multicenter studies, which involved a representative group of Italian hospitals in different cities (28-30) or in Roman urban area (31).

The first epidemic of CR *A. baumannii* in Italy occurred during 2002 in ICU of Federico II University Hospital of Naples (28), then other epidemics were increasingly described in ICUs and other wards of other hospitals in Naples and in other Italian cities (22-28). Moreover, the isolation of CR *A. baumannii* during 2002-2018 study period was reported in several Italian hospitals (Table 1 and Figure 1).

Genotyping analysis of CR *A. baumannii* isolates showed cross-transmission and intra-hospital (15- 17, 20, 22-28) or inter-hospital spread (14, 22, 28-31) of genotypic distinct clones. Moreover, genotyping of CR. *A. baumannii* isolates from Italian hospitals using Pasteur MLST scheme assigned 82% of isolates to ICL II, 15% to ST78, 2% to ICL I, and few others to ST31, ST25 and ST577 clonal lineages (Table 1 and Figure 1). In particular, CR *A. baumannii* assigned to ICL II and to ST78 were isolated in 21 and 4 Italian cities, respectively (Table 1 and Figure 1). This is in accordance with previous data, showing the worldwide occurrence of *A. baumannii* international clone II in the hospital settings (1, 6, 10) and the national spread of ST78 epidemic clonal lineage, which was isolated into different hospitals of one single city (22) and then in several Italian hospitals (30). The elevated biofilm growth and resistance to desiccation shown by *A. baumannii* isolates belonging to ICL2 and emerging genotype ST78, which may sustain their survival in the contaminated hospital environment (3, 11), could contribute to the high prevalence of *A. baumannii* isolates assigned to ICL II and ST78 clonal lineages in Italian hospitals.

Molecular analysis of carpabenem resistance in A. baumannii in Italy during 2002-2018

The acquisition of carbapenem-hydrolyzing class D β-lactamases (CHDLs) is the most frequently reported mechanism responsible for resistance to carbapenems in *A. baumannii* (1, 2). CHDLs major gene clusters identified in *A. baumannii* include the $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-24/40-like}}$, $bla_{\text{OXA-58-like}}$ and $bla_{\text{OXA-143}}$ genes. CHDLs genes are located into transposons and/or plasmids, which are acquired by bacteria through horizontal gene transfer (2, 10). The chromosomal $bla_{\text{OXA-51-like}}$ gene, a class D β-lactamases intrinsic to *A. baumannii*, may confer carbapenem resistance when flanked by IS elements and over expressed (2).

Table 1 - Epidemiological and genotypic features of CR *Acinetobacter baumannii* in Italy 2002-2017

Year	Hospital/City	ward	Isolates	Genotype		CHDL	Reference
				ST	Clonal lineage		
2002	F-Na	ICU	43	ST2	ICL II	OXA-58	28
2003-2004	M- Na	ICU	44	ST2	ICL II	OXA-58	
2009	M- Na	ICU	3	ST25	ST25	OXA-72	
2006	M- Na	ICUs	12	ST2	ICL II	OXA-58	22
2006-2007	M-Na	ICUs	62	ST78	ST78	OXA-58	
2007	CT-Na	ICU	4	ST78	ST78	OXA-58	
2004-2005	Multiple Hospitals/ cities	ICUs MU, SU, TU	110	ST2	ICL II	OXA-58	29
			4	ST1	ICL I	OXA-58	
			6	ST20	ICL I	OXA-58+OXA-23	
2008-2009	Multiple Hospitals cities		27	ST2	ICL II	OXA-58	29
			27	ST2	ICL II	OXA-23	
			12	ST2	ICL II	OXA-58 + OXA-23	
			2	ST1	ICL I	OXA-58	
			3	ST1	ICL I	OXA-58+OXA-23	
			11	ST78	ST78	OXA-58	
2005-2008	Roman urban area	ICU	15	ST2	ICL II	OXA-58	31
2007-2008			13	ST2	ICL II	OXA-23	31
2007	Multiple Hospitals/cities		44	ST78	ST78	OXA-58	30
			31	ST2	ICL II	OXA-58	
2009-2013	SS-Aq	ICU, MU, SU	114	ST2	ICL II	OXA-23	15
2010	M-NA	ICU	4	ST78	ST78	OXA-58	18
2010-2011	CB-Pa	ICU	49	ST2	ICL II	OXA-23	16
			2	ST2	ST2	OXA-58	
2010-2011	F-Na	NICU	22	ST2	ICL II	OXA-23	23
2010-2011	C-Ct, OVE-Ct	ICUs	26	ST2	ICL II	OXA-82	14
2011	OR-Ts	ICUs	49	ST2	ICL II	OXA-23	26
2012	UO-Ss	ICU	10	ST31	ST31	OXA-23	24
2012	UO-Ss	ICU	16	ST2	ICL II	OXA-23	25
2013	C-Ct	ICU	52	ST2	ICL II	OXA-23	17
2014-2015	C-Ct	ICU	12	ST2	ICL II	OXA-23	19
2015-2017	SC-Bs	ICUs	9	ST2	ICL II	OXA-23	20
			1	ST195	ICL II		
			1	ST632	ICL II		
			3	ST19	ICL I		
			1	ST577	ST577		
2016-2017	S-Rm	ICU	7	ST2	ICL2	OXA-23	27
2018	C-Ct	ICUs	4	ST2	ICL II	OXA-23	21

F-Na, Federico II Hospital-Napoli; M-Na, Monaldi Hospital-Napoli; CT-Na, Cotugno Hospital-Napoli; SS-Aq, San Salvatore Hospital-L'Aquila; CB-Pa, Civico e Benfratelli Hospital-Palermo; C-Ct, Cannizzaro Hospital-Catania; OVE-Ct, Ospedale Vittorio Emanuele-Catania; OR-Ts, Ospedali Riuniti-Trieste; UO-Ss, University Hospital-Sassari; Spedali Civili Hospital-Bergamo; S-Rm, Spallanzani Hospital-Roma; CHDL, class D carbapenem-hydrolysing oxacillinase; ST, sequence type according to Pasteur's MLST scheme; ICL, international clonal lineage; ICU, intensive care unit; NICU, neonatal intensive care unit; MU, medical unit; SU, surgical unit; TU, transplantation unit.

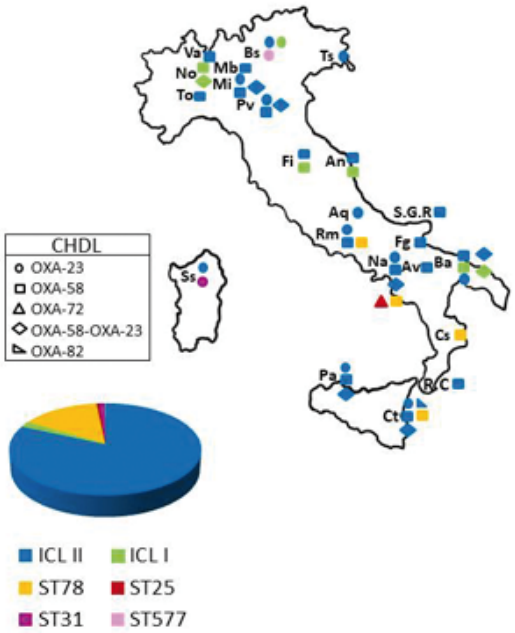

Figure 1 - Geographical distribution of carbapenem-resistant *A. baumanii* in Italy during 2002-2018. Coloured pie charts indicate the prevalence of *A. baumanii* isolates assigned to different STs and ICL. Coloured symbols on Italy's picture indicate the prevalence of *A. baumanii* isolates assigned to different CHDL. Abbreviations: CHDL, class D carbapenem-hydrolysing oxacillinase; ST, sequence type; ICL, international clonal lineage; An, Ancona; Aq, Aquila; Av, Avellino; Ba, Bari; Bs, Brescia, Ct, Catania; Cs, Cosenza; Fg, Foggia; Fi, Firenze; Mb, Monza; Mi, Milano; Na, Napoli; No, Novara; Pa, Palermo; Pv, Pavia; R.C, Reggio Calabria; Rm, Roma; S.G.R, San Giovanni Rotondo; Ss, Sassari; To, Torino; Ts, Trieste; Va, Varese.

Accordingly, all CR *A. baumannii* isolates in Italy during 2002-2017 carried a CHDL gene (Table 1 and Figure 1). In details, OXA-58 carbapenemase was identified in CR *A. baumannii* isolates assigned to ICL II (28, 29, 31) and ST78 clonal lineage (18, 22, 28, 30). The $bla_{\text{OXA-58}}$ genes of CR *A. baumannii* isolates were flanked by Insertion Sequence (IS) elements, which regulated their expression, and were located into plasmids (22, 31-33). Because similar plasmids carrying $bla_{\text{OXA-58}}$ gene were found in *A. baumannii* isolates assigned to ICL II and ST78 clonal lineage (22, 32, 33), it was hypothesized that those plasmids were transferred among genotypic distinct *A. baumannii* isolates (22). The $bla_{\text{OXA-72}}$ gene encoding OXA-72 carbapenemase, which is a single-locus variant of OXA-24/40 CHDL, was found in plasmids in CR *A. baumannii* isolates assigned to ST25 epidemic clonal lineage (28, 33).

The $bla_{\text{OXA-23}}$ gene became more prevalent than $bla_{\text{OXA-58}}$ gene among epidemic ICL-II strains in Italian Hospitals from Roman Urban area during 2007-2008 (31) and from multiple cities from 2008 to 2018 (15- 17, 19- 21, 23- 27, 29). The presence of both $bla_{\text{OXA-58}}$ and $bla_{\text{OXA-23}}$ was found in CR *A. baumannii* isolates assigned to ICL I (29). The bla_{OXA23} gene was either plasmid or chromosomal located (31) within Tn2006-like transposon structures (21, 23, 26, 31) or Tn2008-like transposon structures (19, 20), which may have been responsible for the acquisition of CHDL $bla_{\text{OXA-23}}$ gene (10). The presence of the $bla_{\text{OXA-82}}$ class D beta-lactamase genes flanked by *ISAba1* sequences was the mechanism identified as responsible for carbapenem resistance in *A. baumannii* isolates from two ICUs in Catania, which were assigned to ICL II (14).

Similarly to data reported by other countries (2, 34), the occurrence of colistin resistance was observed among CR *A. baumanni*i isolates from Italian hospitals (14, 18, 21). The spread of CR and colistin-resistant *A. baumannii* isolates assigned to ICL II was reported in two NICUs of two hospitals in Catania (14). Moreover, CR and colistin-resistant sporadic *A. baumannii* isolates assigned to ST78 or ICL II clonal lineages were identified in ICUs from Monaldi hospital in Naples (18) and from hospital in Catania (21). Interestingly, CR and colistin-resistant *A. baumannii* isolates were selected following colistin-therapy (14, 18) and were replaced by colistin susceptible

isolate belonging to similar PFGE type and identical ST78 clonal lineage once colistin-therapy was interrupted (18).

Risk factors for carbapenem-resistant A. baumannii acquisition in Italy during 2002-2018.

The epidemiological and clinical features associated with CR *A. baumannii* isolation in Italy during the study period were analyzed in three case series studies (14, 16, 20), one case report study (18) and one case-control study (23).

A case series of 36 patients in a general ICU in Palermo showed that the respiratory tract was the most common site of infection, 26 out of 36 cases (72%) having lower respiratory tract infection or pneumoniae (16). A high infection related mortality rate was observed (18 out of 35 patients, 51.4%). Nineteen patients tested positive for other multidrug resistant organisms in addition to CR *A. baumannii*. CR *A. baumannii* isolates were all assigned to ST2 and ICL II and carried OXA-23 carbapenemase (16). Another case series study included 15 patients from ICUs of Spedali Civili, Brescia (20). Fourteen patients were classified as infected, 13 having respiratory tract infection and one sepsis, 1 patient as carrier. The majority (11 out of 15) of CR *A. baumannii* isolates were assigned to ICL II, 3 to ICL I, one to ST577 (20). The third case series study on 16 patients having CR and colistin-resistant *A. baumannii* identified 7 clinical infection/colonization episodes, 3 colonizations, 3 clinical infections (two bloodstream infection and one pneumonia), and 3 carriage-only status (14). All CR *A. baumannii* isolates were assigned to ST2 and ICL II. Antimicrobial therapy with meropenem and/or colistin was administered to nine of the patients before isolation of the CR *A. baumannii* (14). The case report study showed the emergence of colistin resistance after prolonged colistin administration in a patient with CR *A. baumannii* (18). The patient had CR *A. baumannii* isolates on bronchial aspirate and KPC-producing *K. pneumoniae* from blood, lung, and urine cultures and was treated with colistin and tigecycline for 45 days. Following the appearance of colistin resistance, colistin was withdrawn. Ten days later, other CR *A. baumannii* strains were isolated from bronchial aspirates, showing susceptibility against colistin. Colistin-susceptible and colistin-resistant strains isolated from the same patients showed identical ST78 genotype but 1 to 3 bands difference at PFGE profile (18). Data suggested that colistin resistant strain originated from colistin susceptible strain during colistin therapy by at least 1 genetic mutation and that reversion to colistin susceptibility occurred by another mutation a colistin susceptible isolate, which outcompeted resistant isolates upon colistin withdrawal (18). Overall, the three case series studies showed that the majority of infections caused by CR *A. baumannii* were respiratory tract infections and at a lesser extent sepsis occurring in ICU patients. In agreement with this, surveillance data on hospital-acquired infections in Italian ICU showed that *A. baumannii* was responsible for 22% of pneumonia, 12.5 % of central venous catheter-related infections, 12.5% of urinary tract infections, 11.1% of bloodstream infections in Italian ICUs during 2010-2011 (7) and that *A. baumannii*, *Klebsiella pneumoniae* (15% each) and *Pseudomonas aeruginosa* (13.1%) were the most frequent isolated microorganisms responsible for sepsis in Italian ICUs from 2008 to 2017 (8).

Risk factors for CR *A. baumannii* acquisition and or colonization/infection of neonates during an outbreak in neonatal intensive care unit (NICU) of Federico II University Hospital in Naples were analyzed in a case-control study (23). The outbreak occurred because the index case neonate was born by caesarean section to a mother who was admitted to the adult ICU

of the hospital where CR *A. baumannii* was endemic and included 22 neonates, six of whom developed 5 ventilator associated pneumonia and one urinary tract infection (23). CR *A. baumannii* isolates responsible for outbreaks in the NICU were all assigned to ST2 and ICL II and expressed OXA-23 carbapanemase. Length of NICU stay and low gestational age were identified as risk factors for XDR *A. baumannii* acquisition at univariate analysis. Length of exposure to central venous catheter and to assisted ventilation were risk factors of XDR *A. baumannii* acquisition at multivariate analysis (23). Similarly, low birth-weight, the use of assisted ventilation and vascular devices were identified as risk factors for MDR *A. baumannii* acquisition in neonates in the NICU worldwide (35).

Conclusions

CR *A. baumannii* was responsible for several epidemics in Italian ICUs during 2002-2018. Genotypic analysis showed intra-hospital and inter-hospital spread of CR *A. baumannii* isolates assigned to ICL II at national level and to ST78 clonal lineages in 4 different cities (15-17, 19, 20, 22-31). Molecular analysis of carbapenem resistance showed the presence of OXA-58 CHDL in *A. baumannii* isolates assigned to ICL II and ST78 clonal lineage (22, 28-31), which was replaced by OXA-23 CHDL in *A. baumannii* isolates assigned to ICL II since 2007 in several cities and predominated in the last years (15-17, 19, 20, 23-27). The occurrence of colistin resistance was observed in CR *A. baumannii* isolates assigned to ICL II and ST78 clonal lineage following colistin therapy (14, 18). CR *A. baumannii* was mainly responsible for respiratory tract infections and at a lesser extent for sepsis (14, 16, 18, 20, 23). This reinforces the need to monitor the molecular epidemiology of *A. baumannii* and its associated antimicrobial resistances. A network of regional reference laboratories should be established for the surveillance of CR *A. baumannii* and risk factors for their acquisition in single hospitals.

Acknowledgements

Work performed in the authors' laboratory was supported in part by grant from the Italian Ministry of Education, University and Research (MIUR): PRIN2017 (Grant 2017SFBFER to RZ).

Riassunto

Epidemiologia molecolare di Acinetobacter baumannii resistente ai carbapenemi in Italia

Introduzione. *Acinetobacter baumannii* resistente ai carbapenemi è sempre più frequentemente riconosciuto come una delle principali cause di infezioni associate all'assistenza sanitaria nei pazienti critici e di epidemie ospedaliere.

Metodi. È stata condotta una revisione narrativa della letteratura, ricercando nel database PubMed articoli su *Acinetobacter* spp. resistenti ai carbapenemi isolati in Italia pubblicati tra gennaio 2010 e dicembre 2019.

Risultati. Gli isolati di *Acinetobacter baumannii* resistente ai carbapenemi assegnati al clone internazionale II (ICL II) e al genotipo epidemico ST78 sono stati responsabili di diverse epidemie negli ospedali italiani nel periodo 2002-2018. L'analisi molecolare della resistenza ai carbapenemi ha mostrato la presenza di OXA-58 CHDL in isolati di *A. baumanni*i assegnati ai complessi clonali ICL II e ST78, che è stata sostituita da CHDL OXA-23 in isolati di *A. baumannii* assegnati al clone internazionale ICL II dal 2007 in diversi ospedali. *A. baumannii* resistente ai carbapenemi è stato principalmente responsabile di infezioni del tratto respiratorio e, in misura minore, di sepsi in pazienti in terapia intensiva.

Conclusioni. I nostri dati rafforzano la necessità di sorvegliare l'epidemiologia molecolare di *A. baumannii* resistente ai carbapenemi e dei suoi geni di resistenza a livello nazionale.

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