POLISH ARCHIVES OF
Internal Medicine
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Article type: Original article

Received: January 4, 2024.

Revision accepted: April 18, 2024.

Published online: April 23, 2024.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.16734

Molecular epidemiology and clinical significance of carbapenemase genes among carbapenem-resistant *Acinetobacter baumannii* isolates in southern Poland

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What's new?

The diversity of genes encoding carbapenemases in carbapenem-resistant *Acinetobacter baumannii* (CRAB) varies not only globally but also regionally. These mechanisms of resistance are encountered frequently in southern Poland, but formal assessments of CRAB β-lactamases are lacking. Such knowledge has important implications for patient outcomes since knowing the most prevalent CRAB resistance mechanisms in a region can guide initial therapy to ensure patients are started on optimal treatment as quickly as possible. The CRAB isolates in this study produced carbapenemases that are not identified on commercial rapid screening tests, so their use in identifying CRAB for prevention and control is limited. Therefore, the use of such screening methods, specifically for carbapenem-producing organisms, can be misleading for clinical practitioners and may lead to suboptimal empiric therapy choices.

Abstract

Introduction: The complex interplay between Acinetobacter spp., patients, and the environment has made it increasingly difficult to optimally treat patients infected with Acinetobacter spp., mainly due to rising antimicrobial resistance and challenges with surveillance.

Objectives: This study evaluated carbapenem-resistance Acinetobacter baumannii (CRAB) isolates to determine their resistance profiles and the presence of specific β-lactamase enzymes to inform the use of CRAB surveillance upon hospital admission and regional empiric antibiotic therapies.

Patients and methods: The study was conducted at 4 hospitals in southern Poland between June 2022 and December 2022. Only healthcare-associated infections caused by Acinetobacter baumannii were considered. 82 CRAB isolates were included in the analysis.

Species identification was performed by MALDI TOF, antimicrobial susceptibility was determined phenotypically, and PCR methods were performed to identify resistance genes.

Results: Depending on the hospital, the ICU incidence of CRAB infections was from 428.6 to 759.5 per 10,000 admissions and from 0.3 to 21.0 per 10,000 admissions in non-ICUs. CRAB antibiotic susceptibility was highest with cefiderocol (100%), colistin (96%), tigecycline (77%), gentamicin (51%) and ampicillin / sulbactam (36%). The most prevalent blaOXA genes were blaOXA-66-1 (95%) and blaOXA-40 (71%) and additionally, the extended-spectrum β-lactamase gene blaTEM-1 (41%).

Conclusion: An unexpectedly high incidence of CRAB infections occurred in Polish hospitals. There is a need for effective CRAB prevention and control that includes effective hospital screening, national surveillance, and improved treatment options.

Key words

Acinetobacter baumannii, antimicrobial resistance, oxacillinases, Poland

Introduction

Acinetobacter spp. are nonfermenting Gram-negative opportunistic pathogens that can colonize the skin, respiratory system, and gastrointestinal tract. They are responsible for many healthcare-associated infections, including ventilator-associated pneumonia (VAP) and bloodstream infections (BSI), especially in patients hospitalized in intensive care units (ICUs) [1]. An ability to evade the host immune system significantly complicates efforts to manage and treat these infections [2]. Consistently since 2017, carbapenem-resistant *Acinetobacter baumannii* (CRAB) remains a critical priority pathogen and urgent threat to the public by the World Health Organization (WHO) and the United States (US) Centers for Disease Control and Prevention (CDC) [3,4].

Importantly, the epidemiology of *Acinetobacter* spp. can vary greatly by region. In the European Union (EU)/European Economic Area (EEA), approximately 1/3 of all *Acinetobacter* spp. isolates between 2017−2021 were carbapenem resistant [5]. After the peak of the COVID-19 pandemic in 2021, there was more than double the number of reported *Acinetobacter* spp. cases resistant to carbapenems, fluoroquinolones and aminoglycosides when compared to the 2018−2019 average. The greatest increases in *Acinetobacter* spp. antimicrobial resistant (AMR) cases were reported by countries that already had high AMR prevalence, such as Poland [5].

In the US, incidence of CRAB has decreased from 3.3 per 10 000 hospitalizations in 2012 to 2.47 per 10 000 in 2017 [4]. The decrease is generally attributed to improved infection control and antibiotic stewardship practices that have become requirements for hospital accreditation in the US [6]. There is concern this progress has been hampered by the COVID-19 pandemic which led to increased antibiotic use and breakdown of infection control practices leading to reports of CRAB outbreaks [7]. The global impact of CRAB is in part due to the ability of its resistance genes to spread via mobile genetic elements, as well as widespread antibiotic use [2]. This has a negative impact on patient outcomes as the mortality rate of *A. baumannii* infections ranges from 45 to 70%. One of its main predictors is carbapenem resistance [1] and carbapenems are frequently an empiric treatment choice for infections in areas such as Poland where the prevalence of extensively drug resistant (XDR) organisms was 22.6% in the ICU and 14.8% in non-ICUs [8], leading to delays in optimal antibiotic coverage for CRAB infections. This is further emphasized by CRAB being the 5th leading cause of death from resistant organisms worldwide [9].

In terms of resistance, *A. baumannii* employs a variety of mechanisms to reduce the effectiveness of antibiotic therapy. They include the use of efflux pumps, changes to antibiotic active sites, reduction of cell membrane permeability, and – probably the most common – the

use of enzymes to inactive antibiotics, in particular β-lactamases [10]. *A. baumannii* has two intrinsic types of β-lactamases: AmpC-type cephalosporinases (no effect on extended-spectrum cephalosporin efficacy) and oxacillinases, mainly represented by the OXA-51-like variants [11,12] and belong to the OXA*Ab* enzyme group, including OXA-66 [13]. In addition to the intrinsic β-lactamases, other β-lactamases have also been identified in *A. baumannii* as a source of resistance to carbapenems, including OXA-23, OXA-40, OXA-48, and OXA-58 [14]. Mechanisms of resistance related to carbapenemase production fall into 3 groups: Ambler Class A (plasmid-mediated KPC and chromosomal IMI, SME, GES and NMC-A), Ambler Class B (metallo-β-lactamases whose genes are located on integrons and plasmids (NDM, IMP, VIM, GIM, SPM, and SIM)) and Ambler Class D (plasmid-mediated oxacillinases, e.g., OXA-48, OXA-23) [15]. Resistance gene prevalence is geographically specific which results in difficulty generalizing local studies to other regions and highlights the importance of local and regional studies to guide locally relevant optimal treatment approaches.

Treatment of CRAB is difficult both from a diagnostic and antibiotic standpoint. Rapid diagnostics (e.g., based on nucleic acid amplification tests) to confirm infections with CRAB are often lacking in areas with high CRAB prevalence which may result in delay of appropriate antibiotics and negatively affect patient outcomes [16]. Most infections from CRAB are pneumonia [17] and there are specific pharmacokinetic/pharmacodynamic properties of antibiotics used against CRAB that result in difficulty achieving appropriate drug levels in lung tissues [18,19]. In addition, MIC breakpoints for antibiotics against CRAB differ by organization [20,21] (the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations apply in Poland) or do not exist, posing challenges for antibiotic choice and dosing. In other infections, especially those involving medical devices

like endotracheal tubes or tracheostomies, CRAB's ability to form biofilms can prevent antibiotics from penetrating and reaching the organism [22,23].

In this study, we evaluated the resistance profiles of CRAB in 4 hospitals in southern Poland to characterize the prevalence of various CRAB β-lactamases and to inform regional empiric therapies for these difficult-to-treat infections in southern Poland. We also comment on the utility of commercial rapid tests in CRAB surveillance upon hospital admission. The resistance genes identified by these tests are not commonly found in CRAB. Consequently, there is a potential risk of missing CRAB infections or colonization when these tests are utilized.

Patients and methods

This laboratory-based study was carried out at the University Hospital in Kraków, St. Luke's Provincial Hospital in Tarnów, the Provincial Hospital No. 5 in Sosnowiec and the District Hospital in Bochnia.

Ethical approval was waived by the Bioethics Committee of Jagiellonian University (approval no 118.6120.42.2023 from 15.06.2023) in view of the retrospective nature of the study, all procedures being performed as part of routine care, and the analysis did not include any identifying participant data. All data analyzed during this study were anonymized prior to analysis. As a result, no statements of consent were required from participants.

The samples were collected between 06.2022–12.2022. The total number of admissions was 70 859. During the study, the multiplex polymerase chain reaction (PCR) (GeneXpert System, Cepheid, USA) was used for screening of carbapenemase genes (types: bla_{VIM}, bla_{NDM}, bla_{IMP}, bla_{KPC}, $bla_{\text{OXA-48}}$) for confirmed presence of carbapenemase-producing Enterobacterales (CPE) isolates at admission to the hospital in cases of suspected CPE colonization (e.g., antibiotic therapy, previous hospitalization, stay in the long-term-care

facilities). A bacterial healthcare-associated infection (HAI) of adult patients was defined as a symptomatic infection diagnosed (or recognized) >48h since hospital admission. HAI cases were analyzed retrospectively using definitions from the Healthcare-Associated Infections Surveillance Network [24], which included bloodstream infections (BSI), pneumonia (PNA), and urinary tract infections (UTI). As recommended by the European Centre for Disease Prevention and Control, bacterial diagnostic testing and its interpretation were performed according to the specimen type.

Some of the specimens were analyzed quantitatively; these included urine and positive quantitative cultures from minimally or possibly contaminated lower respiratory tract (LRT) specimens. Interpretation of quantitative results in mono- and polymicrobial cultures depended on the relative quantity of each microorganism. For a urine culture to be positive, the sample was required to have no more than 2 organism species and $\geq 10^5$ colony forming units (CFU) per mL. For a LRT culture to be positive, a broncho-alveolar lavage (BAL) was required to have $\geq 10^4$ CFU/mL or ≥5% of BAL-obtained cells needed to contain intracellular bacteria on direct microscopic exam; specimens from the LRT using a protected brush (PB Wimberley) required $\geq 10^3$ CFU/mL; distal protected aspirate (DPA) needed $\geq 10^3$ CFU/mL; and endotracheal aspirate needed $\geq 10^6$ CFU/mL [24].

Microbiologic samples were obtained from the sites of infection. Only laboratory confirmed *A. baumannii*-HAI cases based on culture growth qualified for the analysis; only the first isolate from each HAI case was analyzed. During the study period, 120 *A. baumannii*-HAI cases were identified as a specific infectious syndrome (pneumonia is an example of one of the syndromes) from a particular organism. One hundred seven of the 120 (89.2%) isolates were identified as carbapenem-resistant (CRAB), and 82 CRAB isolates were analyzed (25 isolates were lost to follow up for reasons independent from authors).

Isolated organisms were identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF, Bruker, USA or VITEK MS, bioMérieux, France). Antibiotic susceptibilities were performed by the hospital diagnostic laboratories using the automatic VITEK 2 method (bioMérieux, France), Phoenix M50 system (Becton Dickinson and Company, Sparks, MD, USA), disc diffusion (OXOID, UK), MIC Test Strips (LIOFILCHEM, Italy) or broth microdilution in the case of colistin (MIC STRIPPED PLATES COL, Diagnostics, Slovakia), according to the EUCAST guidelines [20].

The GeneMATRIX Bacterial & Yeast Genomic DNA Purification Kit (EURx, Gdansk, Poland) was used to extract genomic DNA from CRAB isolates following the manufacturer's protocol. The concentration and purity of the isolated DNA was assessed using a Nano Drop Lite spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). DNA extracted from pure cultures was stored at -20°C for further study.

Carbapenemase genes were identified using multiplex PCR (*bla*$_{\text{VIM}}$, *bla*$_{\text{OXA-48}}$, *bla*$_{\text{OXA-23}}$, *bla*$_{\text{KPC}}$, *bla*$_{\text{NDM}}$, *bla*$_{\text{OXA-40}}$, *bla*$_{\text{OXA-58}}$, *bla*$_{\text{IMP}}$, *bla*$_{\text{GIM}}$, *bla*$_{\text{GES}}$, *bla*$_{\text{OXA-51}}$, *bla*$_{\text{IMI}}$, *bla*$_{\text{VIM}}$) [25] and real time PCR (*bla*$_{\text{OXA-66}}$ and *bla*$_{\text{TEM}}$) [26]. PCR amplification was performed using the Color OptiTaq PCR Master Mix (EURx Ltd., Gdańsk, Poland) in a final volume of 25 μL and a final primer concentration of 0.1 μL for each primer. Bacterial DNA functioned as the template. For the multiplex PCR, PCR was conducted with an initial denaturation step of 3 min at 94°C, followed by 30 cycles of 30s at 94°C, 15s at 58 °C, and 1 min at 72°C for amplification. A final extension step of 5 min at 72°C was performed. PCR products were analyzed via gel electrophoresis. For the real time PCR, cycling was carried out at 50°C for 2 minutes and then 95°C for 2 minutes, followed by 40 cycles of 95°C for 15 seconds, 55°C for 15 seconds, and 72°C for 1 minute (primer data are described in Supplementary material, *Table S1*).

In the statistical analysis, relative and absolute frequencies were used for nominal variables (described as n (%)) and mean values with standard deviation for quantitative variables. For data with a non-normal distribution, the median with interquartile range (IQR) was used. For independent samples with nominal variables, the Chi2 test was used. The Yates correction was used for 2x2 tables of nominal variables (when expected values were <5) and the Fisher's exact test was used for 2x(n) tables (when expected values were below 5 and there was a small overall sample size (N <40)). For continuous data with a normal distribution, the Student's t-test was used. For continuous variables without a normal distribution and independent samples, the U-Mann Whitney's test was used.

The analysis was carried out in the International Business Machines Corporation Statistical Package for the Social Sciences, version 29 (IBM Corporation, Armonk, New York, United States). In all analyses, the significance level was $\alpha = 0.05$.

Results

In total, 82 CRAB isolates were analyzed from the cases of *A. baumannii* infection. The median age of patients was 65 (median ICU age: 65; median non-ICU age: 68) (Table 1). Sources of infection included lower respiratory tract (n = 38), bloodstream (n = 23), urinary tract (n = 13), and others (n = 8, included 6 wounds and 2 cerebrospinal fluid sources). Fifty-two CRAB isolates were collected from ICU patients and the most common CRAB sources in the ICU were lower respiratory tract infections (n = 28; 54%) and bloodstream infections (n = 14; 27%). In the non-ICU settings, 30 CRAB isolates were collected and the most common CRAB sources were also lower respiratory tract infections (n = 10, 33%) and bloodstream infections (n = 9, 30%).

Depending on the hospital, the incidence rate of CRAB infections was from 428.6 to 759.5 per 10 000 admissions in ICUs and from 0.3 to 21.0 per 10 000 admissions in non-ICUs. The

proportion of CRAB isolates (in all *A. baumannii*) ranged from 81.8% to 100% in the ICUs and 75.7% to 100% in the non-ICUs (Table 1).

The most prevalent bla_{OXA} genes were $bla_{\text{OXA-66-1}}$ (95%), $bla_{\text{OXA-40}}$ (71%), $bla_{\text{OXA-23}}$ (24%) and $bla_{\text{OXA-51}}$ (12%). bla_{NDM} genes were detected in 2 (2%) isolates, and $bla_{\text{TEM-1}}$ genes were detected in 41% of isolates. No $bla_{\text{OXA-48}}$, $bla_{\text{OXA-58}}$, bla_{VIM}, bla_{KPC}, bla_{IMI}, bla_{GES}, bla_{GIM}, or bla_{IMP} genes were detected (Table 2). $bla_{\text{OXA-23}}$ was found significantly more in males (32.2%) than females (4.3%, $P = 0.019$).

Only 4 isolates had a single gene coding for carbapenemases while the others had multiple β-lactamase genes. 43 isolates had 2 genes, 29 – 3 and 5 – 4. Frequency of detected gene patterns is shown in Table 3 (additional data are described in Supplementary material, *Table S2*).

CRAB antibiotic susceptibility was highest with cefiderocol (100%), colistin (96%), tigecycline (77%), gentamicin (51%) and ampicillin / sulbactam (36%). Less than 4% susceptibility was found to ciprofloxacin, levofloxacin, meropenem, imipenem, trimethoprim / sulfamethoxazole, piperacillin / tazobactam, piperacillin and imipenem / relebactam (Table 4) (additional data are described in Supplementary material, *Table S3*). Statistical analysis did not reveal significant differences between the source of infection (blood, urine, or lower respiratory tract) and the susceptibility of CRAB to individual antibiotics.

Discussion

The observed prevalence and incidence of CRAB in the studied hospitals significantly exceeded expected values. In addition, CRAB resistance was high against most antibiotics and the antibiotics with better susceptibility profiles are generally associated with toxicities (e.g., colistin). This highlights the urgency in prevention of CRAB infection, including preventing the spread of CRAB and the need for new treatments against CRAB infections.

Most *A. baumannii* harbored multiple carbapenemase genes highlighting its ability to use many resistance mechanisms. The most common combination was $bla_{\text{OXA-66-1}}$ with $bla_{\text{OXA-40}}$. $bla_{\text{OXA-66-1}}$ (part of the $bla_{\text{OXA-51-like}}$ genes) is intrinsic to *A. baumannii* [12]. At appropriate levels of expression, it has been associated with high levels of imipenem resistance in *A. baumannii* [27] but there is evidence that the degree of carbapenem resistance can be reliant on expression of other genes and resistance mechanisms within the organism [28]. In our sample of carbapenem resistant organisms, $bla_{\text{OXA-66-1}}$ was found with another β-lactamase in all but 4 organisms, indicating possible reliance on other enzymes for carbapenem resistance. $bla_{\text{OXA-40}}$ gene prevalence has previously been described in southern Poland from 2005–2010 where 51 out of 104 (49%) isolates harbored this gene [29] and its enzyme is capable of hydrolyzing carbapenems as well as other β-lactams [28]. Our sample consisted of 59% $bla_{\text{OXA-40}}$ genes, thus showing approximately a 10-percentage point increase in its prevalence. This is a worrying phenomenon that indicates the prevalence of $bla_{\text{OXA-40}}$ in Poland is approximately 3-fold higher than in the rest of Europe [30]. Almost half of studied isolates, 41%, possessed bla_{TEM} genes. TEMs typically confer resistance to penicillins and early cephalosporins but have expanded their activity to include resistance against second-, third- and fourth generation cephalosporins, monobactams and β-lactamase inhibitors [31]. TEMs are found at high frequencies in hospitals and clinics around the world [32] and often co-occur with other chromosomal (AmpC) or plasmid-mediated (SHV, OXA, CTX-M) β-lactamases [33]. The 24% $bla_{\text{OXA-23}}$ prevalence in our sample is 3-fold lower than in Europe where $bla_{\text{OXA-23}}$ were identified in 74.5% of analyzed *A. baumannii* isolates [30]. Of note, commercially available rapid diagnostic tests only cover 5 enzymes (or their genes) (VIM, NDM, IMP, KPC and OXA-48). Unfortunately, these genes/enzymes are not the major driver of resistance in *A. baumannii* (as noted in our study and the above cited studies), complicating efforts to detect resistance in *A. baumannii*.

A. baumannii is inherently difficult to treat due to a variety of resistance mechanisms. In CRAB, resistance to carbapenems is often associated with resistance to other categories of antibiotics, such as fluoroquinolones [34]. Thus, a goal of this study was to provide clinicians insight on empiric antibiotic regimens in Poland. There is no clear answer which antibiotic or which combination of antibiotics is a superior choice in CRAB infections. Yet even with this uncertainty, both the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) guidelines are mostly consistent in their CRAB treatment recommendations; they recommend use of combination therapy when treating CRAB infections [35,36]. This increases the likelihood that one of the agents has activity against the CRAB given the lack of efficacious single antibiotic regimens. Many CRAB infections occur in the ICU where severely ill patients are at high risk for these infections and increased antibiotic use predisposes patients to infection with resistant organisms [37]. The ICU setting often involves advanced life support interventions such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO), further complicating antibiotic treatment and dosing considerations due to diffusion, convection and ultrafiltration mechanisms which alter antimicrobial concentrations in tissues [38].

IDSA guidance recommends the use of a sulbactam backbone in most treatment regimens [35] regardless of the susceptibility profile of ampicillin / sulbactam [39]. Our CRAB isolates were only 36% susceptible to ampicillin / sulbactam so in accordance with IDSA guidance, most isolates would need to be treated with high dose ampicillin / sulbactam (9g of the sulbactam component) over an extended infusion due to ampicillin / sulbactam resistance [35].

ESCMID, contrary to IDSA, recommends ampicillin / sulbactam only when susceptibility is confirmed. Polymyxin (colistin) or high dose tigecycline, if susceptible in

vitro, can be used when resistance to ampicillin / sulbactam occurs [36]. Our sample had relatively high susceptibilities with these antibiotics (colistin 96% and tigecycline 77%). Unfortunately, issues arise with their use. Colistin has toxicities that include kidney injury, poor lung penetration [16,40] and the most recent Clinical and Laboratory Standards Institute (CLSI) update on its colistin breakpoints does not include a susceptible interpretation [21], though one in EUCAST exists [20]. The use of tigecycline against CRAB infections needs to be considered in the context of limited clinical data (ESCMID suggests usage in complicated intraabdominal infections and in skin and soft tissue infections [36]). Cefiderocol is an option against CRAB, especially for pneumonia [41], and has been suggested in combination with a sulbactam backbone [16]. Our isolates are uniformly susceptible to cefiderocol but there have been issues with laboratory techniques and obtaining accurate cefiderocol MICs [42]. Studies have not found an association with *bla*$_{\text{OXA}}$ genes and cefiderocol resistance [43] which is reflected in the 100% sensitivity of our isolates to cefiderocol. Fluoroquinolones are not recommended by IDSA and would not be useful given our low susceptibility results [35]. ESCMID does not refer to fluoroquinolones in CRAB treatment [36]. Thus, the combination antibiotic regimen of choice depends on multiple factors that include the site of infection, pharmacokinetic/pharmacodynamic considerations, and the organism's susceptibility profile. Shields et al., for example, recommends ampicillin / sulbactam with tigecycline or cefiderocol for pneumonia and ampicillin / sulbactam with polymyxin B or cefiderocol for bloodstream infections [16].

The use of meropenem in combination with other antibiotics has fallen out of favor. There were two clinical trials comparing colistin versus colistin plus meropenem [44,45] and they showed no difference between the colistin arm versus the combination meropenem plus colistin therapy in patients with CRAB. This suggests the use of meropenem did not add to the efficacy of colistin even when dosed appropriately and over an extended infusion. Thus,

the IDSA guidelines do not recommend the use of carbapenems in CRAB infections [35]. ESCMID allows high-dose extended-infusion carbapenem use when the MIC is ≤8μg/L but as part of combination therapy. It is worth noting that this is a good practice statement and expert opinion [36].

New treatments against CRAB are thus urgently needed. One of the most recent agents is sulbactam / durlobactam. It, in combination with imipenem / cilastatin, was studied in a clinical noninferiority trial [46] that showed favorable mortality outcomes compared to colistin in combination with imipenem / cilastatin. The active component in sulbactam / durlobactam is sulbactam; durlobactam was designed to inactivate OXA carbapenemases which allows the sulbactam to reach its target. Sulbactam / durlobactam was recently approved by the US Food and Drug Administration against *A. baumannii* pneumonia but further data are needed to determine whether it should be used as monotherapy or in combination with other active antibiotics [47]. Due to its novelty, we were not able to include sulbactam / durlobactam in our study and it has not yet been approved for clinical use in Europe. The CDC indicates that another β-lactam/β-lactam inhibitor, meropenem/vaborbactam, can be important in resistant Gram-negative infections but specifically in infections caused by CPE that produce KPC and OXA-48–like enzymes, not in CRAB infections [48].

Given the difficulty in treating CRAB infections, prevention is a key component in their surveillance. Screening for CRAB can decrease prevalence of CRAB infections in the ICU by reducing transmission between patients when early isolation is implemented [49]. It is important to consider which body site to utilize for CRAB screening since sites differ in their sensitivity [50]. Screenings utilizing skin swabs have the highest sensitivity (92% sensitivity from skin alone and 99% sensitivity from combination of buccal mucosal and skin samples). Other sites can result in high false-negative results (e.g., 50% sensitivity in detecting CRAB

colonization from the rectal site) [50]. The prevalence of CRAB colonization in our hospitals is unknown since screening is not routinely performed.

Carbapenem resistance markers found on routine early detection tests are common in Enterobacterales but not in *A. baumannii*, limiting these methods' use in detecting CRAB. These early detection tests include phenotype-based methods detecting the activity of selected carbapenemase enzymes (e.g., rapid colorimetric methods), immunochromatographic tests and molecular methods (mainly based on the polymerase chain reaction). The main limitation preventing their use is the small number of detected carbapenemases (only KPC, NDM, OXA-48, IMP, VIM, or the genes coding them). All of them are characteristic for the Enterobacterales order [51]; almost none of them occurred in the *A. baumannii* isolates we tested. Only 5% (4 of 82) of the tested isolates had at least one gene encoding these carbapenemases. Other tests, detecting OXA-23, OXA-40 and OXA-58 dedicated to *A. baumannii*, can be used for screening, but this still does not fully solve the surveillance problem of CRAB. Hence, infection control and prevention of carbapenemase-producing microorganisms, including CRAB infections is limited to non-specific methods, such as hand hygiene.

Limitations Poland does not have an effective national system of surveillance for AMR [52], limiting the comparability of the current data to the rest of the country and limiting the ability to properly assess temporal trends. Such systems are crucial to understand the epidemiology of CRAB and to evaluate the effect of interventions to slow its spread. Our samples were from four different hospitals of various acuity but geographically in a similar area, limiting the generalizability of this study to other parts of Poland. These limitations provide opportunities for further research into the epidemiology of CRAB in Poland and support the need for a national plan to better understand and curb antimicrobial resistance.

Conclusions CRAB is an urgent public health threat. It is widespread throughout the world and is a major pathogen in Polish hospitals. Understanding its epidemiology, resistance mechanisms, and antibiotic susceptibility is crucial to implement focused infection control and antibiotic stewardship techniques and to help inform empiric and directed antibiotic treatments. This study provides up-to-date data on CRAB epidemiology in southern Poland and interprets international treatment guidance into the context of these regional results. It indicates that southern Poland's CRAB prevalence is higher compared to the rest of Europe and is likely rising. This is concerning since the antibiotic susceptibility profiles demonstrated in this study are highly resistant to most used antibiotics, regardless of infection syndrome, leaving patients with less effective and more toxic options. The genes involved in CRAB resistance are also not detected by routine surveillance tests, further complicating surveillance efforts. Thus, our study highlights the need for effective AMR prevention initiatives, better diagnostic surveillance tests, and improved treatment options against this difficult-to-treat pathogen.

Supplementary material Supplementary material is available at www.mp.pl/paim.

Article information

Acknowledgments We would like to thank the staff of the participating units for their help and interest in the study.

Funding This publication was supported by the National Centre for Research and Development through the initiative "Support for specialist hospitals in fighting the spread of SARS-CoV-2 infection and in treating COVID-19" (contract number: SZPITALE-JEDNOIMIENNE/18/2020) and by a grant from the Jagiellonian University Medical College (N41/DBS/001019). This study was carried out as part of our routine work.

Contribution statement PS, DAH, AK, EJM, JWM conceived the concept of the study. PS, DAH, AK, AP, JWM contributed to the design of the research. PS, AK, AP, EJM, ARG, WŚ-K, IP, ZG, KG, MG were involved in data collection and analyzed the data. PS & DAH are considered equally as first authors. JWM supervised the entire project and coordinated its financing. All authors edited and approved the final version of the manuscript.

Conflict of interest None declared.

Informed consent statement Not applicable. All data entered the electronic database and analyzed in this study had been anonymized.

Data availability statement The datasets analyzed during the current study are available from Jadwiga Wójkowska-Mach (e-mail: jadwiga.wojkowska-mach@uj.edu.pl) upon reasonable request.

How to cite Serwacki PA, Hareza DA, Kujawska A, et al. Molecular epidemiology and clinical significance of carbapenemase genes among carbapenem-resistant Acinetobacter baumannii isolates in southern Poland. Pol Arch Intern Med. 2024; XX: 16734. doi:10.20452/pamw.16734

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Table 1 Patient demographics and epidemiology of Acinetobacter baumannii hospital-acquired infections in southern Poland from 06.2022–12.2022

Demographics	**ICU (n = 52)**	**non-ICU (n = 30)**	***P*-value**
Age [year] Me (Q1; Q3)	65 (63; 73)	68 (52; 80)	0.44
Sex [n] (%)			
Male	42 (80.8)	17 (56.7)	0.04
Female	10 (19.2)	13 (43.3)	
Admissions, [n] (%)			
Tarnów	199 (21.4)	14,114 (20.1)	<0.001
Sosnowiec	210 (22.6)	13,323 (19.1)	
Kraków	441 (47.5)	31,398 (44.9)	
Bochnia	79 (8.5)	11,095 (15.9)	
Non-CRAB infections [n] (%)			
Tarnów	1 (25.0)	0 (0.0)	0.15
Sosnowiec	2 (50.0)	9 (100.0)	
Kraków	0 (0.0)	0 (0.0)	
Bochnia	1 (25.0)	0 (0.0)	

CRAB infections[a] [n] (%)			
Tarnów	12 (21.4)	20 (39.2)	<0.001
Sosnowiec	9 (16.1)	28 (54.9)	
Kraków	29 (51.8)	1 (2.0)	
Bochnia	6 (10.7)	2 (4.0)	
Prevalence of CRAB [%]			
Tarnów	92.3	100.0	0.73
Sosnowiec	81.8	75.7	
Kraków	100.0	100.0	
Bochnia	85.7	100.0	
Incidence rate of CRAB infections [10,000 admissions]			
Tarnów	603.0	14.2	<0.001
Sosnowiec	428.6	21.0	
Kraków	657.6	0.3	
Bochnia	759.5	1.8	
[a]CRAB infections by hospital type are out of the 107 isolates identified as CRAB Abbreviations: CRAB, carbapenem-resistant *Acinetobacter baumannii*; ICU, intensive care unit; Me, Median; Q1, first quartile; Q3, third quartile			

Table 2 β-lactamase gene prevalence in 82 carbapenem-resistant *Acinetobacter baumannii* isolates from 4 hospitals in southern Poland from 06.2022–12.2022

Gene[a]	**Ward**		***P* value**
	ICU n = 52 n (%)	Non-ICU n = 30 n (%)	

bla$_{\text{OXA-23}}$	15 (28.8)	5 (16.7)	0.33
bla$_{\text{OXA-40}}$	33 (63.5)	25 (83.3)	0.10
bla$_{\text{OXA-51}}$	10 (19.2)	0	0.03
bla$_{\text{OXA-66-1}}$	52 (100)	26 (86.7)	0.03
bla$_{\text{NDM}}$	2 (3.8)	0	0.73
bla$_{\text{TEM}}$	17 (32.7)	17 (56.7)	0.06

a There were no carbapenem-resistant *Acinetobacter baumannii* isolates with *bla*$_{\text{OXA-48}}$, *bla*$_{\text{OXA-58}}$, *bla*$_{\text{GES}}$, *bla*$_{\text{GIM}}$, *bla*$_{\text{IMI}}$, *bla*$_{\text{IMP}}$, *bla*$_{\text{KPC,}}$ and *bla*$_{\text{VIM}}$ genes

Abbreviations: ICU, intensive care unit

Table 3 Prevalence of detected gene patterns in 82 carbapenemase-producing Acinetobacter baumannii isolates from healthcare-associated infections at 4 hospitals in southern Poland from 06.2022–12.2022

Gene Pattern	**Number of strains**	**%**
bla$_{\text{OXA-40}}$; *bla*$_{\text{OXA-66-1}}$	27	32.9%
bla$_{\text{OXA-40}}$; *bla*$_{\text{OXA-66-1}}$; *bla*$_{\text{TEM}}$	22	26.8%
bla$_{\text{OXA-23}}$; *bla*$_{\text{OXA-66-1}}$	8	9.8%
bla$_{\text{OXA-23}}$; *bla*$_{\text{TEM}}$	4	4.9%
bla$_{\text{OXA-66-1}}$	4	4.9%
bla$_{\text{OXA-40}}$; *bla*$_{\text{OXA-66-1}}$; *bla*$_{\text{OXA-51}}$	2	2.4%
bla$_{\text{OXA-40}}$; *bla*$_{\text{OXA-23}}$; *bla*$_{\text{OXA-66-1}}$	2	2.4%
bla$_{\text{OXA-23}}$; *bla*$_{\text{OXA-66-1}}$; *bla*$_{\text{OXA-51}}$	2	2.4%
bla$_{\text{OXA-40}}$; *bla*$_{\text{OXA-66-1}}$; *bla*$_{\text{OXA-51}}$; *bla*$_{\text{TEM}}$	2	2.4%
bla$_{\text{OXA-66-1}}$; *bla*$_{\text{TEM}}$	2	2.4%

bla$_{OXA-40}$; *bla*$_{OXA-23}$; *bla*$_{OXA-66-1}$; *bla*$_{TEM}$	2	2.4%
bla$_{OXA-40}$; *bla*$_{OXA-23}$; *bla*$_{OXA-66-1}$; *bla*$_{OXA-51}$	1	1.2%
bla$_{OXA-23}$; *bla*$_{OXA-66-1}$; *bla*$_{OXA-51}$; *bla*$_{NDM}$; *bla*$_{TEM}$	1	1.2%
bla$_{OXA-66-1}$; *bla*$_{OXA-51}$	1	1.2%
bla$_{OXA-66-1}$; *bla*$_{OXA-51}$; *bla*$_{TEM}$	1	1.2%
bla$_{OXA-66-1}$; *bla*$_{NDM}$	1	1.2%

Table 4 Antibacterial susceptibilities[a] of 82 carbapenemase-producing Acinetobacter baumannii isolates from healthcare-associated infections at 4 hospitals in southern Poland from 06.2022–12.2022 by infectious syndrome

Antibiotics	**Susceptibility (%)**			
	Total (n = 82)[b]	**Respiratory (n = 38)**	**Bloodstream (n = 23)**	**Urine (n = 13)**
β-lactam antibiotics, penicillins				
Ampicillin-sulbactam	52.4	52.6	65.2	30.8
Piperacillin	0.0	0.0	0.0	0.0
Piperacillin-tazobactam	0.0	0.0	0.0	0.0
Carbapenems				
Imipenem	1.2	0.0	0.0	0.0
Imipenem-relebactam	0.0	0.0	0.0	0.0
Meropenem	2.4	0.0	4.3	0.0
Aminoglycosides				
Amikacin	24.4	26.3	21.7	23.1
Gentamicin	51.2	60.5	39.1	38.5

Tobramycin	19.5	23.7	13.0	15.4
Fluoroquinolones				
Ciprofloxacin	4.9	5.3	0.0	7.7
Levofloxacin	3.7	2.6	4.3	7.7
Other antibiotics				
Cefiderocol	100.0	100.0	100.0	100.0
Colistin	96.3	97.4	91.3	100.0
Minocycline	39.0	47.4	30.4	30.8
Tigecycline	76.8	78.9	73.9	69.2
Trimethoprim-sulfamethoxazole	2.4	2.6	4.3	0.0

a Antibiotic susceptibility results were interpreted using the European Committee on Antimicrobial Susceptibility Testing guidelines

b Includes 8 other sources

Short title: Carbapenem resistance genes in *Acinetobacter baumannii* in Poland