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Clinical Analysis of Acinetobacter Species Infections in Children and Adolescents Treated for Cancer or Undergoing Hematopoietic Cell Transplantation – a Multicenter Nationwide Study

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Clinical Analysis of Acinetobacter Species Infections in Children and Adolescents Treated for Cancer or Undergoing Hematopoietic Cell Transplantation—A Multicenter Nationwide Study

Ewelina Truszkowska [1,*], Krzysztof Czyżewski [2], Katarzyna Derwich [1], Kamila Jaremek [2], Oliwia Grochowska [2], Patrycja Zalas-Więcek [3], Katarzyna Pawińska-Wąsikowska [4], Wojciech Czogała [4], Szymon Skoczeń [4], Walentyna Balwierz [4], Małgorzata Salamonowicz-Bodzioch [5], Krzysztof Kałwak [5], Aleksandra Królak [6], Tomasz Ociepa [6], Tomasz Urasiński [6], Filip Pierlejewski [7], Małgorzata Nowak [7], Maciej Zdunek [7], Wojciech Młynarski [7], Olga Gryniewicz-Kwiatkowska [8], Magdalena Łukszo [8], Bożenna Dembowska-Bagińska [8], Anna Szmydki-Baran [9], Łukasz Hutnik [9], Aleksandra Minkowska [9], Katarzyna Pikora [9], Paweł Łaguna [9], Marcin Płonowski [10], Maryna Krawczuk-Rybak [10], Tomasz Brzeski [11], Katarzyna Mycko [11], Wanda Badowska [11], Weronika Stolpa [12], Karolina Baranowska [12], Agnieszka Mizia-Malarz [12], Ewa Bień [13], Ninela Irga-Jaworska [13], Renata Tomaszewska [14], Agnieszka Książek [14], Tomasz Szczepański [14], Wioletta Bal [15], Radosław Chaber [15], Agnieszka Urbanek-Dądela [16], Grażyna Karolczyk [16], Sonia Pająk [17], Stefania Krawczyk [17], Katarzyna Machnik [17], Jan Styczyński [2] and Olga Zając-Spychała [1]

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Abstract: Background: *Acinetobacter*, significantly *A.baumannii*, are becoming a great threat to hospitalized patients due to increasing antibiotic resistance. The aim of this study was to describe the epidemiology, clinical characteristic, antimicrobial susceptibility pattern and outcome of *Acinetobacter* infections in pediatric cancer patients and HSCT recipients in Poland. **Methods**: a total of 125 episodes of *Acinetobacter* species infections were reported in patients <18 years treated in Polish pediatric hematology and oncology centers over a period from 2012 to 2023. Infections were subdivided into oncohematological diseases (OHD) group (n=106; 84,8%) and hematopoietic stem cell transplant (HSCT) group (n=19; 15,2%). **Results**: *A.baumannii* is the most common *Acinetobacter* species in all groups. The most common diagnoses of infected patients in OHD group were: ALL (n=32; 30.2%) and AML (n=13; 12.3%). The most common underlying disease that was indication for HSCT among infected patients were hemophagocytic lymphohistiocytosis (n=3; 15.8%) and neuroblastoma (n=3; 15.8%). In OHD group, deaths did not correlate with the type of antibiotic, with an exception for gentamicin, which correlates with higher mortality. In HSCT group, deaths did not correlate with the type of antibiotic, except for levofloxacin that was correlated with higher mortality rate. Mortality was significantly higher in the HSCT group compared to the OHD group. **Conclusions**: *Acinetobacter* infections are a great danger to immunocompromised patients. More research is needed in order to prevent and treat antibiotic resistant bacteria.

Keywords: acinetobacter; pediatric oncology; antibiotic resistance

1. Introduction

Acinetobacter genus comprises a large group of glucose non-fermentative, catalase positive, oxidase negative, aerobic Gram-negative coccobacilli. *A. baumannii* is the most common among them [1], leading to ventilator-associated pneumonia, bacteriemia related to the presence of central venous catheter, urinary tract infections in patients with urinary catheters or percutaneous nephrostomy tubes, wound infections as well as meningitis [2]. It is a nosocomial pathogen, which occurs mainly in Intensive Care Units (ICUs) [1] patients. *A. baumannii* develops resistance to numerous antibiotics, including carbapenems, becoming one of the greatest epidemiological threats worldwide. Taking this into account, World Health Organization (WHO) declared *A. baumannii* the one of the ESKAPE pathogens. The acronym comprising the scientific names of six highly virulent and antibiotic resistant bacterial pathogens including *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species [1]. *A. baumannii* exhibits an intrinsic resistance to several antibiotics, including aminopenicillins, trimethoprim, ertapenem, tetracycline, aztreonam [3], and fosfomycin [4]. There are various mechanisms of *A. baumannii* antibiotic resistance. For instance, the production of specific AmpC beta lactamase, called ADC (Acinetobacter-derived cephalosporinase) and ESBL (extended spectrum beta-lactamase) makes the bacteria resistant to all cephalosporins, including those from the third and fourth generation [5]. When resistance to carbapenems is concerned, it is possible due to the production of OXA group carbapenemases (class D carbapenemases) [6] and decrease in the membrane permeability. *A. baumannii* produces also aminoglycoside-modifying enzymes leading to aminoglycoside resistance. Removal by efflux pumps is another major mechanism of antibiotic resistance [7]. Another species of *Acinetobacter* spp., so called non-baumannii species, becoming clinically significant as well, most notably *A. pittii* and *A. nosocomialis* [8]. However, literature concerning their clinical and microbiological characteristic, especially antibiotic, is limited.

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The aim of this multicenter nationwide study was to describe the epidemiology, clinical characteristic, antimicrobial susceptibility pattern and outcome of *Acinetobacter* infections in pediatric cancer patients and HSCT recipients in Polish pediatric hematology and oncology (PHO) centers and pediatric HSCT centers, over a period of 12 years (2012-2023).

2. Materials and Methods

Design of the study. The retrospective study was performed. Given the nature of the study the requirement for obtaining informed consent from each patient was waived. The medical records of the patients were reported by each Polish pediatric oncology center and transplant center and the data were analyzed centrally.

Patients. Over a period from 2012 to 2023 a total of 125 episodes of Acinetobacter species infections were reported in children and adolescents <18 years treated in Polish pediatric hematology and oncology centers who were enrolled into the retrospective, multicenter nationwide study. Infections were subdivided into oncohematological diseases (OHD) group (n=106; 84,8%) and hematopoietic stem cell transplant (HSCT) group (n=19; 15,2%). The characteristics of analyzed group of patients is given in Table 1 and Table 2.

Table 1. Baseline characteristics of oncohematological diseases (OHD) and hematopoietic stem cell transplant (HSCT) group.

Characteristics	Total	OHD group	HSCT group
Number of patients	125	106	19
Sex			
Female	49	40	9
Male	76	66	10
Median age at diagnosis	5,98	5,62	1,69
Deaths			
In general	15	10	5
Treatment-related complications	4	1	3
Disease progression	7	6	1
Infection	3	2	1 (*A. baumannii* sepsis)
Unknown causes	1	1	0
Median of days from infection dg to death	86	109	72

Table 2. Characteristics of underlying disease in oncohematological diseases (OHD) and hematopoietic stem cell transplantation (HSCT) group.

Diagnosis	Number of patients (OHD group; n=106)	Diagnosis	Number of patients (HSCT group; n=19)
Hematological malignancies		Hematological malignancies	
acute leukemias	35	acute leukemias	3
lymphomas	5	lymphomas	2
other	7	Solid tumors	
Solid tumors		neuroblastoma	3
central nervous system tumors		Bone marrow failures	
bone tumors	8	severe aplastic anemia	2

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soft tissue sarcoma	8	other	3
neuroblastoma	6	Primary immunodeficiencies	
hepatoblastoma	4	congenital neutropenia	1
nephroblastoma	3	chronic granulomatous disease	1
germ cell tumor	2	other	3
other	6	Metabolic diseases	
		Niemann Pick disease	1

All patients were treated according to currently used chemotherapy regimens and all transplantations were performed according to institutional procedures and treatment protocols. For all patients uniform, standard anti-microbial prophylaxis was applied, including trimethoprim/sulfamethoxazole three times weekly against *Pneumocystis jiroveci* and non-pharmacological prophylaxis; i.e. hand hygiene before contact with the patient and use of maximal sterile barrier precautions with central line placement. In all transplanted patients, routine antibacterial prophylaxis with penicillin, cephalosporins, or ciprofloxacin was administered during the neutropenic phase and immunosuppressive therapy.

Statistical analysis. Statistical analysis was performed using the PQStat Software (2024). PQStat v.1.8.6.122. Poznan, Poland. The normality of the distribution of the continuous variables was checked by the Shapiro-Wilk test. Descriptive statistics were presented as percentages for categorical variables, as mean (standard deviation [SD]) for normally distributed continuous variables, or as median (interquartile range [IQR]) for non-normally distributed continuous. The prevalence of variables was assessed by the χ2test or the χ2 test with Yates correction as appropriate. A p-value <0.05 was considered significant. Differences between the two groups were determined using the Mann-Whitney test.

3. Results

3.1. Demographics and Incidence

During the study period, within analyzed oncohematological diseases (OHD) subgroup (without HSCT), a total of 106 *Acinetobacter* infections occurred in 41 girls, 65 boys with median age of 5,62 years (range: 2,42-13,57 years). The most common diagnoses of infected patients were: ALL (n=32; 30.2%), AML (n=13; 12.3%), CNS tumors (n=8; 7.5%).

During the study period, within analyzed HSCT subgroup a total of 19 *Acinetobacter* spp. infections occurred in 9 girls and 10 boys with median age of 1,69 years (range: 0,84-9,52). The most common underlying disease that was indication for HSCT among infected patients were hemophagocytic lymphohistiocytosis (n=3; 15.8%) and neuroblastoma (n=3; 15.8%).

3.2. Clinical and Microbiological Characteristics

106 episodes of *Acinetobacter* infections among OHD patients, we identified the most commonly blood stream infections (BSI; n=69; 65.1%), soft tissue infections (STI; n=6; 5.7%), respiratory tract infections (RTI; n=5; 4.7%) and urinary tract infections (UTI; n=4; 3.8%). The most common identified species were *A. baumannii* (n=54; 51%), *A. lwoffii* (n=18; 17.0%) and *A. ursingii* (n=9; 8.5%). *A. junii* was identified (n=7; 6.6%), *A. pitii* (n=6; 5.7%).

Within 19 episodes of *Acinetobacter* infections among HSCT recipients we identified the most often BSI (n=13; 68.4%) and central venous catheter infections (n=3; 15.8%). The most common identified species were *A. baumannii* (n=13; 68.4%) and *A. lwoffii* (n=2; 10.5%), followed by *A. johnsonii* n(=1; 5.3%), *A. lactucae* (n=1; 5.3%) and *A. dijkshoorniae* (n=1; 5.3%).

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Microbiological and clinical characteristics of *Acinetobacter* infections in both groups are given in Table 3.

Table 3. Microbiological and clinical characteristics of *Acinetobacter* infections in oncohematological diseases (OHD) and hematopoietic stem cell transplantation (HSCT) group.

	OHD group (n=106)	HSCT group (n=19)
Site of infection		
bloodstream	73	16
soft tissues	10	0
gastrointestinal tract	9	1
respiratory tract	8	1
urinary tract	4	0
other	2	1
Species		
A. baumanii	54	13
A. lwofii	18	2
A. ursingi	9	0
A. junii	7	1
A. pitii	6	0
A. jejuni	1	0
A. parvus	1	0
A. schindleri	1	0
A. johnsonii	1	1
A. haemolyticus	1	0
A. dijkshoorniae	0	1
A. lactucae	0	1
Acinetobacter not specified	7	0

There was no significant correlation between age at the infectious episode and transplant status or between blood culture results and transplant status. Additionally, age did not correlate with blood culture positivity.

Antimicrobial susceptibility and resistance. In the OHD group *A. baumannii* strains were the most often susceptible to amikacin (n=20; 37.0%), further susceptibility included gentamicin (n=17; 31.5%), imipenem (n=17; 31.5%), meropenem (n=15; 27.8%) and trimethoprim/sulfamethoxazole (n=14; 25.9%); *A. lwoffii* strains were susceptible to meropenem (n=11; 61.1%), amikacin (n=11; 61.1%), imipenem (n=8; 44.4%), gentamicin (n=7; 38.9%), trimethoprim/sullfamethoxasole (n=5; 27.8%); *A .junii* strains were susceptible to meropenem (n=4; 57.1%), amikacin (n=4; 57.1%), ciprofloxacin (n=3; 42.9%), ceftazidime (n=3; 42.9%); *A. ursingii* strains were susceptible to meropenem (n=5; 55.6%), imipenem (n=4; 44.4%), trimethoprim/sulfamethoxazole (n=3; 33.3%), ciprofloxacin (n=3; 33.3%) and amikacin (n=3; 33.3%); while *A. pittii* strains were susceptible to imipenem (n=3; 50.0%), meropenem (n=3; 50.0%), amikacin (n=3; 50.0%) and trimethoprim/sulfamethoxazole (n=3; 50.0%). *A. baumannii* strains were the most often resistant to ciprofloxacin (n=11; 20.4%), followed by trimethoprim/sulfamethoxazole (n=8; 14.8%), amikacin (n=7; 13.0%) and piperacillin/tazobactam (n=7; 13.0%). Only three strains (n=3; 5.6%) were multidrug resistant (MDR).

In the HSCT cohort the identified *A. baumannii* strains were the most often multi susceptible (n=5; 38.5%), amikacin (n=3; 23.1%) and colistin (n=3; 23.1%); *A. johnsonii* strain was susceptible to trimethoprim/sulfamethoxazole (n=1; 7.7%); *A. dijkshoorniae* was susceptible to amikacin (n=1; 7.7%), levofloxacin (n=1; 7.7%), tobramycin (n=1; 7.7%), trimethoprim/sulfamethoxazole (n=1; 7.7%). The identified *A. lwoffii* and *A. lactucae* strains were multisensitive (n=2 and n=1, respectively). *A. baumannii* strains were the most often resistant to carbapenems (n=3; 23.1%). One strain (n=1; 7.7%) was MDR. *A. johnsonii* strain was resistant to carbapenems (n=1; 7.7%), aminoglycosides (n=1; 7.7%);

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specifically tobramycin (n=1; 7.7%); while *A. dijkshoorniae* was resistant to imipenem (n=1; 7.7%) and meropenem (n=1; 7.7%).

Antibiotic therapy applied. In OHD patients, one antibiotic was used in 16 (29.6%) cases of *A. baumannii* infections. Combined treatment with two antibiotics was administered in 15 (27.8%) episodes, three in 12 (22.2%), four in 3 (5.6%), and five in 2 (3.7%) episodes. Meropenem and amikacin were the most commonly used in *Acinetobacter* infections. For *A. baumannii* meropenem (n=18; 33.3%), amikacin (n=14; 25.9%) and piperacillin/tazobactam (n=8; 14.8%) were applied. For A. lwoffii strains, meropenem (n=8; 44.4) and amikacin (n=7; 38.9%). *Acinetobacter*, species unidentified: meropenem (n=3; 50.0%), cefepim (n=2; 33.3%). For *A. ursingii*, amikacin (n=6; 66.7%) and meropenem (n=4; 44.4%) were used, while for all episodes of *A. pittii* amikacin (n=4, for two cases, the treatment is unknown) was applied.

Among the HSCT recipients group, one antibiotic was used in 2 (15.4 %) cases of *A. baumannii* infections. Combined treatment with two antibiotics was administered in 5 (38.5 %) episodes, three in 3 (23.1%), and five in 1 (7.7%) infectious episode. Amikacin (n=6; 46.2%), meropenem (n=5; 38.5%), colistin (n=4; 30.8%), and teicoplanin (n=3; 23.1%) were the most commonly used for *A. baumannii* infections. For *A. lwoffii* infections meropenem (n=2; 100%), cefepime (n=1; 50.0%) and colistin (n=1; 50,0%) were administered; for *A. johnsonii* meropenem (n=1); for *A. lactucae* piperacillin/tazobactam (n=1) or meropenem (n=1); while for *A. dijkshoorniae* infection amikacin (n=1).

Treatment outcomes. In OHD patients, 10 deaths were reported; no deaths were attributed to *Acinetobacter* spp. infection. Cancer progression was the leading cause of death (n=6; 60.0%), followed by infections (n=2; 20.0%), treatment-related complications (n=1; 10.0%) and unknown cause (n=1;10.0%). In OHD group, deaths did not correlate with the type of antibiotic, with an exception for gentamicin, which correlates with higher mortality (p=0.021).

In HSCT patients, 5 deaths were reported; one death was attributed to *A. baumannii* infection. Transplant-related complications were the leading cause of death (n=3; 60.0%), including veno-occlusive disease (VOD, n=2; 40.0%) and Epstein-Barr virus-associated post-transplant lymphoproliferative disorder (EBV-PTLD, n=1; 20.0%), followed by cancer progression (n=1; 20.0%). In the transplant group, mortality did not correlate with gender and age. Also, it did not correlate with the strain type. Death rate did not correlate with the type of antibiotic, except for levofloxacin that was correlated with higher mortality rate. Mortality was significantly higher in the HSCT group compared to the OHD group.

4. Discussion

A. baumanii being the most common *Acinetobacter* species belongs to the ESKAPE group due to its rising antibiotic resistance, high prevalence, and mortality. It poses a major threat to public health, causing outbreaks in hospital departments. *Acinetobacter* spp. infections became an issue for pediatric cancer patients as well, who are particularly at risk due to severe immunosuppression caused by cancer itself or treatment and lengthy stays at the hospital.

Egyptian studies by Al- Hassan et al. [9] and Jalal et al. [10] investigated MDR *A. baumannii* strains from pediatric cancer patients using genetic sequencing. Al- Hassan et al. [9] show a concerning variety of blaOXA-51-like genes and acquired class-D carbapenemases (OXA-23, OXA-40, and OXA-58), contributing to carbapenem resistance. Whole genome sequencing of 31 MDR *A. baumannii* isolates by Jalal et al. [10] revealed plasmid lineages, a diverse pool of genes responsible for a range of resistance mechanisms, including beta-lactamases, efflux pumps, and insertion sequences ISAba1 and ISAba125 l enhancing beta-lactamase expression. New mutations in outer membrane proteins implicated resistance to colistin as well.

Costa et al. [11] focus on Gram-negative bacteria (GNB) infections among patients from pediatric oncology intensive care units of tertiary oncology public hospitals in Brazil. Almost 50% of infectious episodes were MDR GNB, and *A. baumannii* was the most common pathogen identified. Also, *A. baumanii* was the second most often determined species among the non-MDR GNB group. Contrary to our study, bacteria were most frequently isolated from the tracheal aspirate, followed by blood

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culture in the case of the MDR GNB group and urine culture for non-MDR GNB group. This difference can be explained by the increased use of procedures such as mechanical ventilation in the ICU. The most common diseases among both MDR GNB and non-MDR GNB group were central nervous system tumors and neuroblastoma, while in our study, ALL was the most often, followed by AML and CNS tumors. Interestingly, only one patient from the Brazilian study undergone HSCT. Significantly, Brazilian research shows the importance of proper antibiotic therapy since patients with an MDR GNB infection more frequently received inadequate initial empirical antibiotic therapy than those in the non-MDR GNB group, and the time to initiate adequate antibiotic therapy was longer for the MDR GNB group than for the non MDR GNB group. 30-day mortality was 25.5% for MDR GNB group while for non-MDR GNB 16.7%, however it was not statistically significant.

When pediatric studies are concerned, infections caused by *Acinetobacter* spp., especially MDR strains, play a key role as well. Shi et al. [12] investigated MDR *A. baumannii* infections in pediatric ICU. Similarly to Costa et al. [11] the majority of isolates were from lower respiratory tract. In fact, ventilator-associated pneumonia was the most common complication. *A. baumannii* related mortality rate was 16.7% while the most often were bloodstream infections and meningitis. Interestingly, these patients tend to have a lower NK cell activity, higher CD4+ T cell ratio and a higher serum level of interlukin-8. High serum level of creatinine and blood urea nitrogen /albumin level ratio were associated with high risk of mortality in MDR *A. baumannii* infected patients. After further research they may serve as potential biochemical markers. When resistance is concerned, drug resistance rates for β-lactams exceeded 75%.

Another study by Zhu et al. [13] focuses on MDR *A. baumannii* mainly ICU pediatric patients, emphasizing extremely high antibiotic resistance of specimens. Isolates had 100% resistance rate to imipenem, extended-spectrum cephalosporins ex. ceftazidime, ceftriaxone and cefepime, piperacillin/tazobactam, and more than 90% resistance rates to gentamicin, amikacin, tobramycin and ciprofloxacin. However, most of them were susceptible to levofloxacin, minocycline and tigecycline. The blaVIM, blaOXA-23 and blaOXA-51 genes were present in nearly all isolates, proving that beta-lactamases and OXA-carbapenem enzymes are among the most common resistance mechanisms for *A. baumannii*. Luckily, in our cohort the MDR strains ratio was much lower than given in the literature and, thus, infection-related mortality was also low.

In a study by Tripathi et al. [14] which analyzed children with cancer, similar to our cohort, leukemia was the most common diagnosis, followed by CNS tumors and bone sarcomas. However, when patients with Gram-negative infection are concerned, 70% had leukemia or lymphoma. *Acinetobacter* spp. was fourth, the most often identified pathogen. Mortality rate was 18%. Low neutrophil count and resistance to first-line antibiotics or antibiotic combinations were significantly associated with mortality. Susceptiblity to a combination of meropenem with amikacin was significantly associated. Interestingly, in our OHD group gentamicin usage correlated with higher mortality rate. In another study by Talukdar et al. [15], *A. baumannii* was also the most often identified pathogen; specifically if patients with febrile neutropenia were analyzed.

5. Conclusions

Increasing antibiotic resistance is one of the most important factors inhibiting further progress and improvement of survival in pediatric oncology. We describe the incidence, clinical, and microbiological characteristics and treatment of *Acinetobacter* infections in OHD patients and HSCT recipients in Poland over the past 12 years. The *Acinetobacter* spp. group causes severe infections, with BSI being the most common. Our study adds to the growing literature concerning emerging threats to public health, which *Acinetobacter* spp. has become.

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Abbreviations

The following abbreviations are used in this manuscript:
HSCT hematopoietic stem cell transplant
OHD oncohematological diseases
ICU intensive care unit
WHO world health organization
ADC Acinetobacter-derived cephalosporinase
ESBL extended spectrum beta-lactamase
ALL acute lymphoblastic leukemia
AML acute myeloid leukemia
CNS central nervous system
PHO pediatric hematology and oncology
SD standard deviation
IQR interquartile range
BSI blood stream infections
RTI respiratory tract infections
STI soft tissue infections
UTI urinary tract infections
MDR multi drug resistant
VOD veno-occlusive disease
EBV-PTLD Epstein-Barr virus-associated post-transplant lymphoproliferative disorder
GNB Gram-negative bacteria

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