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Multidrug resistant-bacterial infections in children with malignancy and undergoing hematopoietic stem cell transplantation

Zakażenia bakteriami wielolekoopornymi u dzieci z chorobami nowotworowymi i poddawanych przeszczepieniu komórek krwiotwórczych

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Słowa kluczowe

bakterie wielolekooporne, choroby nowotworowe, onkohematologia, przeszczepianie komórek krwiotwórczych, dzieci

Summary

Introduction. Bacterial infections are a well-known cause of morbidity and mortality in patients with malignancy or undergoing hematopoietic stem cell transplantion.

Aim. Analysis of incidence of multidrug resistant bacteria in children with malignant diseases undergoing chemo- and/or radiotherapy (CHT/RTX) in oncohematology department and hematopoietic stem cell transplantation (HSCT) in transplant unit over a period of 24 months in single pediatric center.

Material and methods. All consecutive patients with newly diagnosed malignant diseases in 2012-2013 (total 113 patients), and all consecutive patients undergoing hematopoietic stem cell transplantation in this period (total 61 patients). Multidrug resistant (MDR) bacterial strain were diagnosed according to EUCAST criteria.

Results. During analyzed 24 months, the incidence of patients with at least one bacterial microbiologically determined infection (MDI) reached 33.6% among children undergoing chemo- and/or radiotherapy, and 26.2% among children undergoing hematopoietic stem cell transplantation. Bacterial infections occurred significantly earlier in HSCT patients. More than half (9/16, i.e. 56%) of HSCT patients with bacterial MDI, had first infection before the day of HSCT, what suggests colonization with MDR bacteria during previous therapy. Among Gram-negative rods, the incidence of MDR bacteria was 56.1%, including 52.2% in patients undergoing chemo- and/or radiotherapy and 64.5% in transplant patients.

Conclusions. Presented results and data from literature suggest that the incidence of multidrug resistant bacterial strains among patients undergoing chemo-, radiotherapy or hematopoietic stem cell transplantation is increasing. This type of analysis, when repeated systematically may serve for designing and modification of antibacterial therapy in pediatric oncohematology and transplant centers with respect to prophylaxis, empirical and targeted therapy.

Streszczenie

Wstęp. Zakażenia bakteryjne są częstą przyczyną śmiertelności u pacjentów z chorobami nowotworowymi lub poddawanych przeszczepieniu komórek krwiotwórczych.

Cel pracy. Ocena występowania zakażeń bakteriami wielolekoopornymi u pacjentów z chorobami nowotworowymi poddawanych chemio- i/lub radioterapii (CHT/RTX) w oddziale hematologii i onkologii oraz poddawanych przeszczepieniu komórek krwiotwórczych w oddziale transplantacji szpiku kostnego (ang. *hematopoietic stem cell transplantation* – HSCT) w okresie kolejnych 24 miesięcy w pojedynczym ośrodku pediatrycznym.

Materiał i metody. Analizie poddano wszystkich pacjentów z nowym rozpoznaniem choroby nowotworowej (n = 113) oraz wszystkich pacjentów poddanych HSCT (n = 61) w latach 2012-2013. Szczep bakteryjny był klasyfikowany jako oporny, jeśli wykazywał oporność według kryteriów EUCAST.

Wyniki. W okresie analizowanych 24 miesięcy odsetek pacjentów, u których rozpoznano co najmniej jedno bakteryjne udokumentowane zakażenie (MDI), wyniósł 33,6% wśród poddawanych chemio- i/lub radioterapii oraz 26,2% wśród pacjentów poddawanych

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przeszczepieniu komórek krwiotwórczych. Zakażenia bakteryjne występowały znamiennie wcześniej u pacjentów HSCT. Ponad połowa (9/16, tj. 56%) pacjentów HSCT, u których doszło do zakażenia bakteryjnego, miała rozpoznane zakażenie jeszcze przed dniem przeszczepienia, co sugeruje, że pacjenci ci byli już skolonizowani podczas wcześniejszej terapii. Wśród bakterii Gram-ujemnych, odsetek bakterii wielolekoopornych wyniósł 56,1%, w tym 52,2% u pacjentów poddawanych chemio- i/lub radioterapii oraz 64,5% u pacjentów przeszczepowych.

Wnioski. Dane własne i literaturowe wskazują, że u pacjentów poddawanych chemio-, radioterapii i przeszczepieniu komórek krwiotwórczych zwiększa się odsetek bakterii wielolekoopornych. Tego typu analiza, zwłaszcza powtarzana w określonych odstępach czasu, może służyć do planowania i modyfikacji leczenia przeciwbakteryjnego w oddziałach onkohematologicznych i przeszczepowych, w odniesieniu do profilaktyki, leczenia empirycznego i leczenia celowanego.

INTRODUCTION

Despite significant advances in antimicrobial therapies and infection strategies, the appearance of antibiotic resistance represents an emergency situation, especially in immunocompromised hosts. Specifically, infections due to multidrug resistant (multidrug resistance – MDR), gram-negative pathogens are responsible for high mortality rates (tab. 1) (1).

Table 1. Mechanisms of resistance of Gram-negative bacteria.

Mechanism of bacterial resistance	Spectrum of resistance
ESBL (Extended-Spectrum Beta-Lactamases) – Bacteria producing extended-spectrum beta-lactamases	Penicillins, cephalosporins, monobactams
AmpC (AmpC β-lactamases) – Bacteria producing chromosomal cephalosporinase AmpC type	All beta-lactam antibiotics, except carbapenems and IV generation cephalosporins
KPC (Klebsiella pneumoniae carbapenemase) – *Enterobacteriaceae* producing carbapenemase KPC type	Penicillins, cephalosporins, monobactams, standard-dose carbapenems
NDM (New Delhi metallo-β-lactamase) – Bacteria producing metalo-beta-lactamases	Penicillins, cephalosporins, monobactams, carbapenems

Infections with multidrug resistant bacteria constitute a serious life threat for patients with neutropenia or immunosuppression. An increase in the number of infections with Gram-positive and negative bacteria with MDR phenotype is being observed over recent years. In clinical practice, when severe bacterial infection with resistant pathogen is suspected in patient with immunosuppression, immediate risk factor analysis and a de-escalation therapy with initial use of wide-spectrum antimicrobials followed by a re-assessment after 72 hours of treatment, after pathogen identification, is necessary (1-4).

Although new compounds are available for severe methicillin-resistant staphylococcal infections, there is a paucity of novel classes of antimicrobials to target resistant gram-negatives (1). A continuous careful assessment of the clinical conditions and underlying comorbidities, antibiotic stewardship along with knowledge about the previous history of colonization or infections due to multidrug-resistant bacteria, represent key points in approaching the patient with neutropenia or immunosuppression with signs of infection (2-4).

AIM

The objective of the study was the analysis of the incidence of infections with multidrug resistant bacteria in children undergoing chemo-/radiotherapy (CHT/RTX) in hemato-oncology department or undergoing hematopoietic stem cell transplantation (HSCT) in transplant unit over a period of 24 months in a single pediatric center.

MATERIAL AND METHODS

All consecutive patients aged < 18 years with newly diagnosed malignant diseases between 1.01.2012-31.12.2013 (total 113 patients), and all consecutive patients undergoing hematopoietic stem cell transplantation in this period (total 61 patients), diagnosed and treated in Department of Pediatric Hematology and Oncology in Bydgoszcz, were included into the study. Patients undergoing HSCT were included into standard anti-infectious prophylactic procedures (5).

Multidrug resistant bacteria

Multidrug resistant (MDR) bacterial strain were diagnosed according to EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing) (6-8). Infections with multidrug resistant bacteria listed in Law Gazette (Dziennik Ustaw; Dz. U. z 2011 nr 294 poz. 1741; Supplement 1) as “alert pathogens”, were the subject of the analysis. List of bacteria include 9 groups of pathogens (positions 1-8 and 17) (tab. 2).

Statistical analysis

Frequencies of infections were compared with chi-square test. Incidence and cumulative incidence of infections were determined by Kaplan-Meier method and compared with log-rank test. Risk of infection was determined in Cox model.

RESULTS

Patients undergoing chemo- and/or radiotherapy

Among 113 patients undergoing chemo-/radiotherapy, microbiologically documented infections (MDI) with bacteria etiology were diagnosed in 38 (33.6%) patients. Total number of diagnosed bacterial infections

Table 2. List of alert pathogens.

No	Alert pathogen
	Staphylococcus aureus resistant to methicillin (MRSA) or glycopeptides (VISA or VRSA) or oxazolidinones
2	*Enterococcus* spp. resistant to glycopeptides (VRE) or oxazolidinones
3	*Enterobacteriaceae* spp. bacteria producing extended spectrum of beta-lactamases (e.g. ESBL, AMPC, KPC) or resistant to carbapenems or two other groups of antibiotics or polymyxins
4	*Pseudomonas aeruginosa* strains resistant to carbapenems or two other groups of antibiotics or polymyxins
5	non-fermenting strains *Acinetobacter* spp. resistant to carbapenems or two other groups of antibiotics or polymyxins
6	pathogenic strains of anaerobic bacteria *Clostridium difficile* and their toxins A or B
7	anaerobic bacteria *Clostridium perfringens*
8	*Streptococcus pneumoniae* resistant to cephalosporines III generation or penicillin
9	fungi *Candida* resistant to fluconazole or other azoles or candines
10	fungi *Aspergillus*
11	rotavirus
12	norovirus
13	respiratory syncytial virus (RSV)
14	hepatitis B virus (HBV)
15	hepatitis C virus (HCV)
16	human immunodeficiency virus (HIV)
17	pathogens isolated from blood or cerebro-spinal fluid, causing generalized or invasive infection

was 81, including 7 patients with colonization. Cumulative incidence of bacterial infection among all 113 patients was 0.34 ± 0.04 (fig. 1A). In 20/38 patients subsequent bacterial infections were observed, including simultaneous infections with 3 pathogens in 2 patients and with 2 pathogens in 11 patients.

With respect to primary neoplastic diagnosis, the highest number of infections occurred in patients with: acute lymphoblastic leukemia (27 infections/24 patients), acute myeloblastic leukemia (8/6), bone tumors (13/8), central nervous system tumors (18/27), neuroblastoma (7/4), lymphomas (2/20) and soft tissue sarcomas (3/7).

Patients undergoing hematopoietic stem cell transplantation

Among 61 patients undergoing hematopoietic stem cell transplantation (HSCT) microbiologically documented infections (MDI) with bacteria etiology were diagnosed in 16 (26.2%) patients.

Total number of diagnosed bacterial infections was 36, including 5 patients with colonization. Cumulative incidence of bacterial infection among all 61 HSCT patients was 0.26 ± 0.06 (fig. 1A). In 7/16 patients subsequent bacterial infections were observed; in 2 cases, infections occurred 4-5 times (both reinfections and suprainfections).

Out of 16 HSCT patients with bacterial infections, in 9 (56%) of them, the first infection was found before HSCT, between days "-9" and "-4", while in 2 patients within initial 30 days after HSCT, and in 5 patients afterwards.

With respect to primary diagnosis, the highest number of infections occurred in patients with: acute lymphoblastic leukemia (5 infections/14 patients), acute myeloblastic leukemia (13/13), Ewing's sarcoma (3/3), bone marrow failure (4/7), neuroblastoma (4/9), lymphomas (4/8) and primary immunodeficiences (3/2).

With respect to the type of HSCT, the highest number of infections was found among patients receiving transplant from: matched unrelated donor (MUD, 19 infections/27 patients), mismatched unrelated donor (MMUD, 2/3), matched sibling donor (MSD, 5/9) or autologous transplantation (10/21).

There was no significant difference in comparison of cumulative incidence of bacterial infections in CHT/RTX and HSCT settings (0.34 vs 0.26, p = ns), however bacterial infections occurred in significantly earlier period in HSCT patients (p = 0.005) (fig. 1B). More than half (9/16, i.e. 56%) of HSCT patients with bacterial MDI, had first infection before the day of HSCT, what suggests colonization with MDR bacteria during previous therapy.

MDR bacteria

A total number of 98 Gram-negative bacterial strains were identified, including 55 (56.1%) with MDR phenotype: 33 (33.6%) ESBL, 15 (15.3%) AmpC and 7 (7.1%)

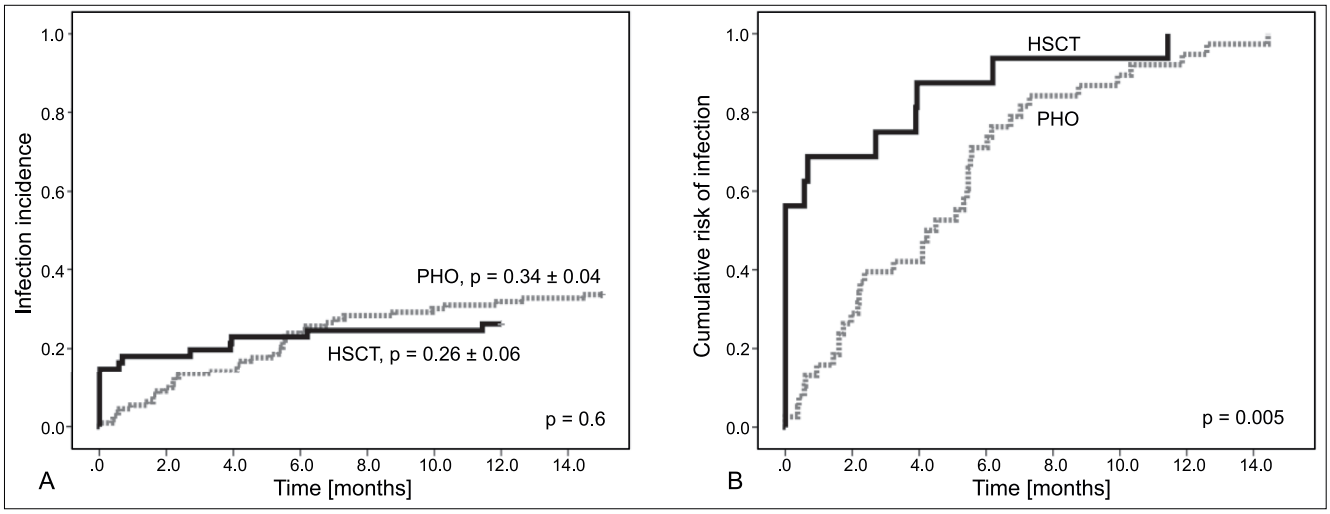

Fig. 1. Cumulative incidence of bacterial infections: (A) among all patients, (B) exclusively among patients with infections.

ESBL+AmpC (tab. 3). The frequency of Gram-negative MDR bacterial rods among HSCT patients showed a trend to be higher than among CHT/RTX patients (20/31 vs 35/67, i.e. 64.5 vs 52.2%, p = ns) (fig. 2). Among 19 Gram-positive strains, only 1 showed MDR phenotype (MRSA).

Table 3. Identification of bacteria.

Patients undergoing chemo- and/or radiotherapy	Patients undergoing hematopoietic stem cell transplantation
Infections (n = 74)	**Infections (n = 31)**
Gram-negative	**Gram-negative**
Pseudomonas aeruginosa (12)	*Pseudomonas aeruginosa* (6)
Stenotrophomonas maltophilia	*Escherichia coli* ESBL (6)
Escherichia coli ESBL (9)	*Escherichia coli* (3)
Escherichia coli (9)	*Klebsiella pneumoniae* ESBL (4)
Klebsiella pneumoniae ESBL (2)	*Klebsiella pneumoniae*
Klebsiella pneumoniae AmpC	*Klebsiella oxytoca* AmpC
Klebsiella pneumoniae	*Klebsiella oxytoca*
Klebsiella oxytoca ESBL	*Enterobacter cloacae* AmpC
Klebsiella oxytoca (2)	*Enterobacter absurdiae* AmpC
Klebsiella spp. ESBL	*Citrobacter freundi* AmpC ESBL
Enterobacter cloacae ESBL AmpC (4)	*Morganella morgani* AmpC
Enterobacter cloacae AmpC (4)	**Gram-positive**
Enterobacter cloacae (2)	*Staphylococcus aureus*
Citrobacter freundi AmpC ESBL	*Staphylococcus haemolyticus*
Citrobacter freundi ESBL	*Staphylococcus epidermidis*
Citrobacter freundi AmpC	*Enerococcus faecium* (2)
Serratia fonticola AmpC	
Morganella morgani AmpC (3)	
Acinetobacter baumani (2)	
Proteus mirabilis	
Pantoea spp.	
Gram-positive	
Staphylococcus aureus (4)	
Staphylococcus capitis	
Streptococcus mitis (3)	
Streptococcus oralis (2)	
Enterococcus faecium (2)	
Corynebacterium striatum	
Colonizations (n = 7)	**Colonizations (n = 5)**
Gram-negative	**Gram-negative**
Klebsiella pneumoniae ESBL (2)	*Klebsiella pneumoniae* ESBL (2)
Eschericha coli ESBL (2)	*Enterobacter cloacae* ESBL AmpC
Enterobacter faecium ESBL	*Citrobacter* spp. ESBL
Enterobacter cloacae AmpC	*Escherichia coli* ESBL
Gram-positive	
Staphylococcus aureus MRSA	

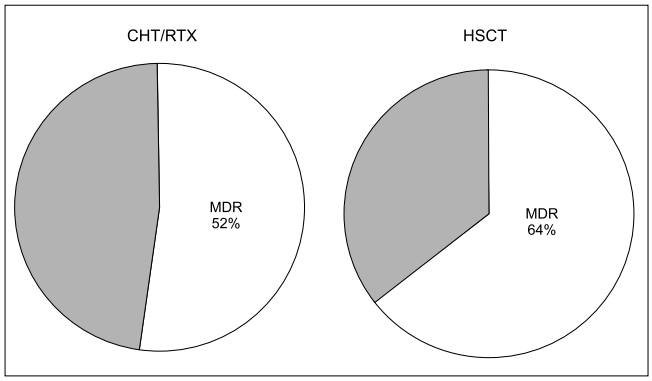

Fig. 2. Incidence of MDR bacteria among CHT/RTX and HSCT patients.

DISCUSSION

During analyzed period of 24 months, the rate of patients with at least one episode of microbiologically documented infections with bacteria etiology was 33.6% among children undergoing chemo- and/or radiotherapy, and 26.2% among children undergoing hematopoietic stem cell transplantation. These results match those obtained in studies performed by other centers (9-11), however the incidence of MDR bacteria seems to be very high. Among Gram-negative strains, the incidence of MDR bacteria was 56.1%, including 52.2% in patients undergoing chemo- and/or radiotherapy and 64.5% in transplant patients.

Mikulska et al. have shown documented bacterial blood-stream infections in 34% HSCT patients, and the incidence of 35% MDR bacteria among Gram-negative strains (11). Gil et al. have shown documented bacterial infections in 38.9% high-risk patients after auto-HSCT (9). In Italian centers, the rate of MDR phenotype among *Pseudomonas aeruginosa* strains in children undergoing CHT or HSCT was 31.4% (10). In some centers the incidence of MDR strains of *Pseudomonas aeruginosa* reached up to 71% (3).

Bacterial infections create a continuous problem in patients hemato-oncological and HSCT settings, in spite of improvement of environmental conditions, prophylaxis and basic and supportive therapy. Presented results and data from literature suggest that the incidence of multidrug resistant bacterial strains among patients undergoing chemo-, radiotherapy or hematopoietic stem cell transplantation is increasing. Unfortunately, although new compounds are available for severe methicillin-resistant staphylococcal infections, there is a paucity of novel classes of antimicrobials to target resistant Gram-negatives (1).

This type of analysis, when repeated systematically may serve for designing and modification of antibacterial therapy in pediatric hemato-oncology and transplant centers with respect to prophylaxis, empirical and targeted therapy.

CONCLUSIONS

The incidence of bacterial infections reached 33.6% among children undergoing chemo- and/or radiotherapy, and 26.2% among children undergoing hematopoietic stem cell transplantation.

Among Gram-negative rods, the incidence of MDR bacteria was 56.1%, including 52.2% in patients undergoing chemo- and/or radiotherapy and 64.5% in transplant patients.

Presented results and data from literature suggest that the incidence of multidrug resistant bacterial strains among patients undergoing chemo-, radiotherapy or hematopoietic stem cell transplantation is increasing.

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