Acta Haematologica Polonica 2023
Number 4, Volume 54, pages 260–262
DOI: 10.5603/AHP.a2023.0044
ISSN 0001–5814
e-ISSN 2300–7117

VIA MEDICA

Sepsis caused by multidrug-resistant bacteria: *Pseudomonas aeruginosa*, as a complication of B-cell acute lymphoblastic leukemia treatment

Natalia Zaj[1], Katarzyna Karska[2], Paulina Miciuda[1], Marika Jerzak[1], Monika Lejman[3], Joanna Zawitkowska[4*]

[1]Student Scientific Society of Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland

[2]Department of Pediatric Hematology, Oncology and Transplantology, University Children's Hospital, Lublin, Poland

[3]Independent Laboratory of Genetic Diagnostics, Medical University of Lublin, Lublin, Poland

[4]Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland

Recent years have seen huge progress in pediatric leukemia treatment [1]. Yet despite treatment progress, treatment-related toxicity is still common [2]. Infections are the predominant reason for treatment-related mortality in children with acute lymphoblastic leukemia (ALL). About 4% of pediatric patients die from infections [3]. Sepsis is the main cause of patient death related to infections, and is defined as serious organ dysfunction caused by inappropriate response to an infectious agent [4]. Gram-negative bacteria are the most common cause of sepsis, followed by gram-positive bacteria, fungi and viruses [5]. Primary triggers among bacteria are *Klebsiella pneumoniae*, followed by *Escherichia coli* and *Pseudomonas aeruginosa*. Sepsis caused by *Pseudomonas aeruginosa* has been limited to only a few case reports in pediatric patients [6].

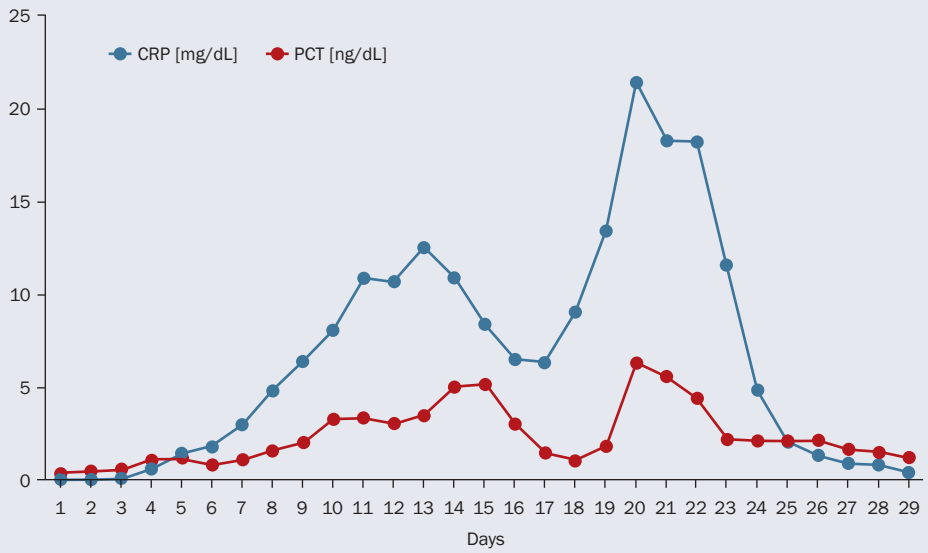
We present the case of an 8-year-old boy diagnosed with precursor B-cell acute lymphoblastic leukemia (BCP-ALL). In 2021, he was admitted to hospital with the following symptoms: entire body petechiae, enlarged peripheral lymph nodes, hepatosplenomegaly, and leukocytosis. Chemotherapy was started but was interrupted on day 22 due to severe treatment-related toxicity. Numerous complications, including acute pancreatitis, kidney failure, polyneuropathy, bowel obstruction and fungal infection of the lungs were reported during the induction phase of leukemia treatment. The patient was receiving sulfamethoxazole–trimethoprim prophylaxis against *Pneumocystis jiroveci*, caspofungin for fungal lungs' infection, and meropenem. On the 36th day from the beginning of chemotherapy, the child developed the first symptoms of infection, which started with a fever. Moreover, he had a prolonged neutropenia episode. Laboratory examinations showed the gradual growth of inflammatory parameters: C-reactive protein and procalcitonin (Figure 1A). A first blood culture was performed, and *Pseudomonas aeruginosa* were detected. Therapy was modified by increasing the doses of meropenem from 20 mg/kg to 40 mg/kg (3-hour infusion), three times per day. Metronidazol was added as a preventative measure due to the bowel obstruction. However, the boy's condition started deteriorating. He developed necrosis of the right conch and anal ulceration, and presented consciousness disorders. Magnetic resonance imaging showed enlarged ventricles and cerebral sulci deepening. Further tests showed osmotic demyelination syndrome of the pons. The antibiogram was extended due to the lack of treatment effects. A swab was taken from the central venous catheter to detect the suspected source of infection. Subsequent blood cultures revealed that the bacteria were multi-drug resistant. Antibiotic therapy had to be constantly modified according to the current bacteria's sensitivity (Figure 1B, C). Additionally, the central venous catheter was removed. The patient required parenteral nutrition. Granulocyte colony-stimulating factor (G-CSF), immunoglobulin substitution, and clotting factor supplementation were administered.

The patient's condition, laboratory tests and complete blood count began to improve, and current treatment was

*Address for correspondence: Joanna Zawitkowska, Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Gębali 6, 20–093 Lublin, Poland, e-mail: jzawitkowska1971@gmail.com

Received: 15.03.2023 Accepted: 17.05.2023 Early publication date: 06.08.2023

A



B

Antibiotic	5 day		13 day		21 day	
	MIC	Interpret.	MIC	Interpret.	MIC	Interpret.
Piperacillin/tazobactam	16	I	>64	R	>64	R
Ceftazidime	2	I	16	R	>32	R
Cefepime	8	I	>16	R	16	R
Imipenem	2	I	>8	R	>8	R
Meropenem	4	I	>8	R	>8	R
Amikacin	≤2	S	>32	R	32	R
Gentamicin	≤1	S	≤1	S	8	R
Tobramycin	≤1	S	4	R	4	R
Colistin	1	S	1	S	1	S
Ciprofloxacin	–	–	0.5	I	>2	R
Levofloxacin	–	–	–	–	>4	R
Ceftazidime/avibactam	–	–	–	–	16	R

C

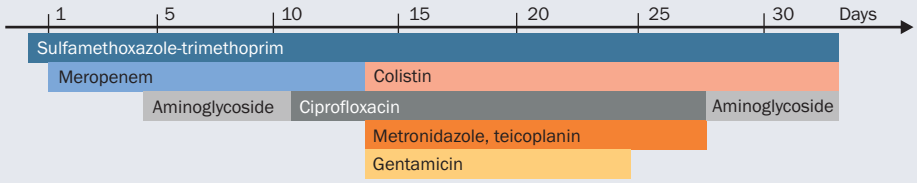


Figure 1A. Changes of inflammatory markers during sepsis from first day of sepsis to negative blood culture result; C-reactive protein (CRP); procalcitonin (PCT); **B.** Results of antibiograms on particular dates; **C.** Antibiotic therapy during sepsis from first day of sepsis; MIC — minimum inhibitory concentration; interpret. — interpretation; I — intermediate; R — resistant; S — susceptible

continued. Blood culture was negative 29 days after the first sepsis symptoms.

Chemotherapy toxicity impacted the decision not to resume the treatment protocol, but instead to replace it with two cycles of blinatumomab immunotherapy. Then an allogeneic hematopoietic stem cell transplantation (HSCT) was performed. Currently, the boy is in remission and under the control of the hemato-oncology center.

We here describe the medical history of a pediatric patient who developed sepsis during the induction phase of ALL treatment. Eradication of infection was obtained by the properly selected antibiotics in accordance with antibiograms, removal of the central venous catheter, and G-CSF infusions.

Repeated interruptions in chemotherapy can result in worse leukemia treatment outcomes [7]. Patients in the induction phase are at the highest risk of contracting infections. This is due to intensive chemotherapy and high-dose steroids which cause immunosuppression. In addition, frequent hospitalizations and numerous invasive procedures contribute to the occurrence of infections, for instance, in patients undergoing central catheter insertion, the use of which is an important factor contributing to nosocomial infections [8].

In a retrospective study, Inaba et al. conducted a trial on 409 patients with ALL between 2000 and 2010. Of the 409 children, four died due to infection. The authors showed that the longest neutropenia episodes were observed during induction therapy. Through induction, this was strongly related to white race, being a low-risk patient, age at diagnosis (1–9.9 years), and B-lineage immunophenotype [8].

In septic patients, empirical antibiotic administration is selected according to local epidemiology patterns. The therapy is started with broad-spectrum antibiotics followed by de-escalation when culture results are available [9]. It is important to detect the patient's current infection at an early stage and to use effective antibiotic treatment to limit the number of chemotherapy interruptions.

In this patient's case, sepsis and multi-organ complications forced the standard chemotherapy to be abandoned. A new therapeutic approach, intended for treatment-resistant or high-risk groups of patients, proved to be the treatment of choice for this patient.

Authors' contributions

JZ, KK — conceptualization. NZ, MJ — methodology. PM, MJ, NZ — writing, original draft preparation. JZ, KK — review and editing. All authors have read and agreed to published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Łęcka M, Czyżewski K, Dębski R, et al. Impact of ferritin serum concentration on survival in children with acute leukemia: a long-term follow-up. Acta Haematol Pol. 2021; 52(1): 54–60, doi: 10.5603/ahp.2021.0008.
2. Schilstra CE, McCleary K, Fardell JE, et al. Prospective longitudinal evaluation of treatment-related toxicity and health-related quality of life during the first year of treatment for pediatric acute lymphoblastic leukemia. BMC Cancer. 2022; 22(1): 985, doi: 10.1186/s12885-022-10072-x, indexed in Pubmed: 36109702.
3. Wolf J, Tang Li, Flynn PM, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. Clin Infect Dis. 2017; 65(11): 1790–1798, doi: 10.1093/cid/cix644, indexed in Pubmed: 29020310.
4. Shankar-Hari M, Phillips GS, Levy ML, et al. Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 775–787, doi: 10.1001/jama.2016.0289, indexed in Pubmed: 26903336.
5. Niederman MS, Baron RM, Bouadma L, et al. Initial antimicrobial management of sepsis. Crit Care. 2021; 25(1): 307, doi: 10.1186/s13054-021-03736-w, indexed in Pubmed: 34446092.
6. Kim HS, Park BoK, Kim SK, et al. Clinical characteristics and outcomes of Pseudomonas aeruginosa bacteremia in febrile neutropenic children and adolescents with the impact of antibiotic resistance: a retrospective study. BMC Infect Dis. 2017; 17(1): 500, doi: 10.1186/s12879-017-2597-0, indexed in Pubmed: 28716109.
7. Puła A, Zdunek M, Michalczyk K, et al. Chemotherapy delays in children with acute lymphoblastic leukemia might influence the outcome of treatment. Acta Haematol Pol. 2022; 53(2): 141–148, doi: 10.5603/ahp.a2022.0007.
8. Inaba H, Pei D, Wolf J, et al. Infection-related complications during treatment for childhood acute lymphoblastic leukemia. Ann Oncol. 2017; 28(2): 386–392, doi: 10.1093/annonc/mdw557, indexed in Pubmed: 28426102.
9. Kleinhendler E, Cohen MJ, Moses AE, et al. Empiric antibiotic protocols for cancer patients with neutropenia: a single-center study of treatment efficacy and mortality in patients with bacteremia. Int J Antimicrob Agents. 2018; 51(1): 71–76, doi: 10.1016/j.ijantimicag.2017.06.016, indexed in Pubmed: 28705670.