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CASE REPORT

Pediatric Acute Myeloid Leukemia: Unraveling Complexities in Intensive Chemotherapy and the Emergence of Superbugs – A Case Study

Sandip Patil, Xinye Li, Huirong Mai, Ying Wang, Xue Tang, Sixi Liu, Feiqiu Wen

Department of Haematology and Oncology, Shenzhen Children's Hospital, Shenzhen, Guangdong Province, People's Republic of China

Correspondence: Sixi Liu; Feiqiu Wen, Email tigar467@126.com; fwen62@163.com

Background: This case report underscores the intricate challenges in managing paediatric patients with acute myeloid leukaemia (AML) undergoing intensive chemotherapy, particularly when complicated by the emergence of multidrug-resistant pathogens such as Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA).

Case Presentation: An 11-year-old male with AML presented with skin purpura and persistent cough. Clinical and laboratory assessments revealed a high-risk AML profile with genetic mutations, leading to the initiation of intensive chemotherapy per the C-HUANA-AML-2015 protocol. Despite successful disease remission after initial chemotherapy courses, the patient experienced unexpected complications. Notably, septic shock, bone marrow failure, and the emergence of CRPA were encountered during the clinical course. Septic shock occurred following Course B3 chemotherapy, marked by a fever unresponsive to initial antibiotic therapy. Despite negative blood cultures, meropenem and vancomycin were initiated, successfully normalizing temperature. Subsequent challenges included persistent bone marrow suppression, perianal dermatitis, and the identification of CRPA in stool cultures, leading to altered antibiotic therapy guided by minimum inhibitory concentration (MIC) considerations. Whole-genome sequencing (WGS) of the CRPA strain revealed a highly virulent clone (ST-970) with numerous resistance and virulence genes.

Conclusion: This case report offers new insights into the complexities of pediatric AML management, with a focus on the emergence of CRPA. The discovery of a high-risk CRPA clone with detailed genomic data underscores the growing challenge of antimicrobial resistance in pediatric oncology. The persistent presence of CRPA and ongoing bone marrow failure highlight the difficulties in managing these complications. This case calls for a reassessment of treatment strategies and encourages further research to improve outcomes in pediatric AML, emphasizing the need for a multidisciplinary approach to address infectious complications and antimicrobial resistance.

Keywords: acute myeloid leukaemia, carbapenem-resistant *Pseudomonas aeruginosa*, paediatric oncology, antimicrobial resistance, superbugs

Introduction

Acute myeloid leukaemia poses a significant global challenge, particularly in the concern of paediatric oncology.[1] Managing this condition requires a delicate equilibrium between achieving disease remission and mitigating the risk of opportunistic infections during intensive chemotherapy.[2] The complexity is heightened by the rise of multidrug-resistant pathogens, such as Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA), commonly referred to as superbugs.[3] These pathogens introduce additional layers of difficulty in AML treatment, necessitating innovative strategies to address these evolving challenges in pediatric patients. AML is a life-threatening malignancy, characterized by the uncontrolled proliferation of abnormal myeloid progenitor cells in the bone marrow, and predominantly affects children.[4] Intensive chemotherapy has emerged as a pivotal component of AML treatment, leading to improved remission rates.[5] But its success is frequently accompanied by severe complications, notably infections. This issue is further exacerbated by the increasing prevalence of antibiotic-resistant pathogens, especially in pediatric oncology.[6] The

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several studies underscores the increasing prevalence of multidrug-resistant organisms in paediatric oncology, necessitating a nuanced understanding of their impact on treatment outcomes.[7] CRPA, a common nosocomial pathogen, poses a particular threat to immunocompromised pediatric patients undergoing chemotherapy, as it exhibits resistance to many conventional antibiotics.[4] Despite this issue, there is a notable scarcity of comprehensive case reports exploring the intricate interplay between AML, intensive chemotherapy, and the emergence of CRPA.[8] This case report seeks to expand current knowledge by examining the clinical course of an AML patient who initially achieved disease remission but subsequently faced septic shock, bone marrow failure, and the emergence of CRPA. The challenges encountered in managing this case highlight the shifting landscape of infectious complications in pediatric oncology, prompting a reevaluation of current treatment strategies. By incorporating Whole-Genome Sequencing (WGS) data, this report also aims to shed light on the resistance mechanisms and virulence factors of the CRPA strain, contributing to a broader understanding of antimicrobial resistance in pediatric oncology and guiding future therapeutic approaches.

Case Presentation

An 11-year-old male was admitted to Shenzhen Children's Hospital on May 29, 2023, presenting with skin purpura persisting for over a month and a persistent cough of two weeks duration. A comprehensive examination revealed alarming haematological findings, including a white blood cell count of 84.72 *10^9/L, haemoglobin of 102g/L, and a platelet count of 47 *10^9/L. Morphological analysis of bone marrow cells demonstrated 82.6% abnormal myeloid progenitor cells, prompting further investigation. Immunological analysis confirmed acute myeloid leukaemia (AML), with chromosomal karyotype 46, XY, and RNA sequencing revealing CEBPA gene double mutations, FLT3-TKD mutations, and GATA2 mutations, thereby confirming the diagnosis of AML. Following the conclusive diagnosis, the patient underwent peripherally inserted central catheter (PICC) placement on May 31, 2023, initiating chemotherapy on June 3, 2023, following the C-HUANA-AML-2015 protocol Course-B1. The chemotherapy regimen included Cytarabine at 100 mg/m² intravenously (IV) every 12 hours for 7 days, Daunorubicin at 60 mg/m² IV on days 1, 2, and 3, and Etoposide at 100 mg/m² IV daily for 5 days. Remarkably, successful disease remission marked the patient within the low-risk leukaemia group. However, the clinical course subsequently unfolded with unforeseen challenges and complications, leading to a complex narrative. This study was conducted according to the guidelines of the Declaration of Helsinki. The Institutional Ethics Committee of Shenzhen Children's Hospital granted ethical approval for the publication of the case details.

Clinical Course

Course B2 Chemotherapy (July 9, 2023): Administered without significant complications, reflecting initial treatment success. Post-chemotherapy assessments revealed no detectable tumor cells in the bone marrow, with minimal residual disease (MRD) <0.01%. The CEBPA gene, FLT3-TKD, and GATA2 mutations turned negative, indicating complete remission (CR). The patient was classified as low-risk leukaemia, and during Course 1 and Course 2, no serious complications were observed.

Bone Marrow Recovery (August 15, 2023): Course B3 chemotherapy was initiated, accompanied by an abrupt fever onset on the night of August 16, 2023, initially treated with cefoperazone sodium-sulbactam sodium (CSSS). The patient's clinical trajectory was meticulously monitored, recording body temperature, WBCs, neutrophils, platelets, and CRP from August 15, 2023, to Dec 9, 2023 (Figure 1).

Septic Shock (August 17, 2023): Despite negative blood cultures, complications intensified, necessitating intensified treatment with meropenem and vancomycin, successfully normalizing temperature. Chemotherapy resumed on August 19, 2023, with a return to CSSS for antibiotic therapy (Figure 1). Additionally, PCT, LAC, IL-2, −4, −6, TNF-a, and IFN-r were analyzed, revealing values within normal limits (Table S1).

Bone Marrow Failure (From August 20, 2023): Compounded by chemotherapy-induced myelosuppression and perianal dermatitis, linezolid was added on August 28, 2023. Subsequent blood tests indicated a significant increase in TNF-a (264.04 units), although no fever or diarrhoea was observed. CT chest was normal, and CT paranasal sinuses reported a small amount of paranasal sinusitis.

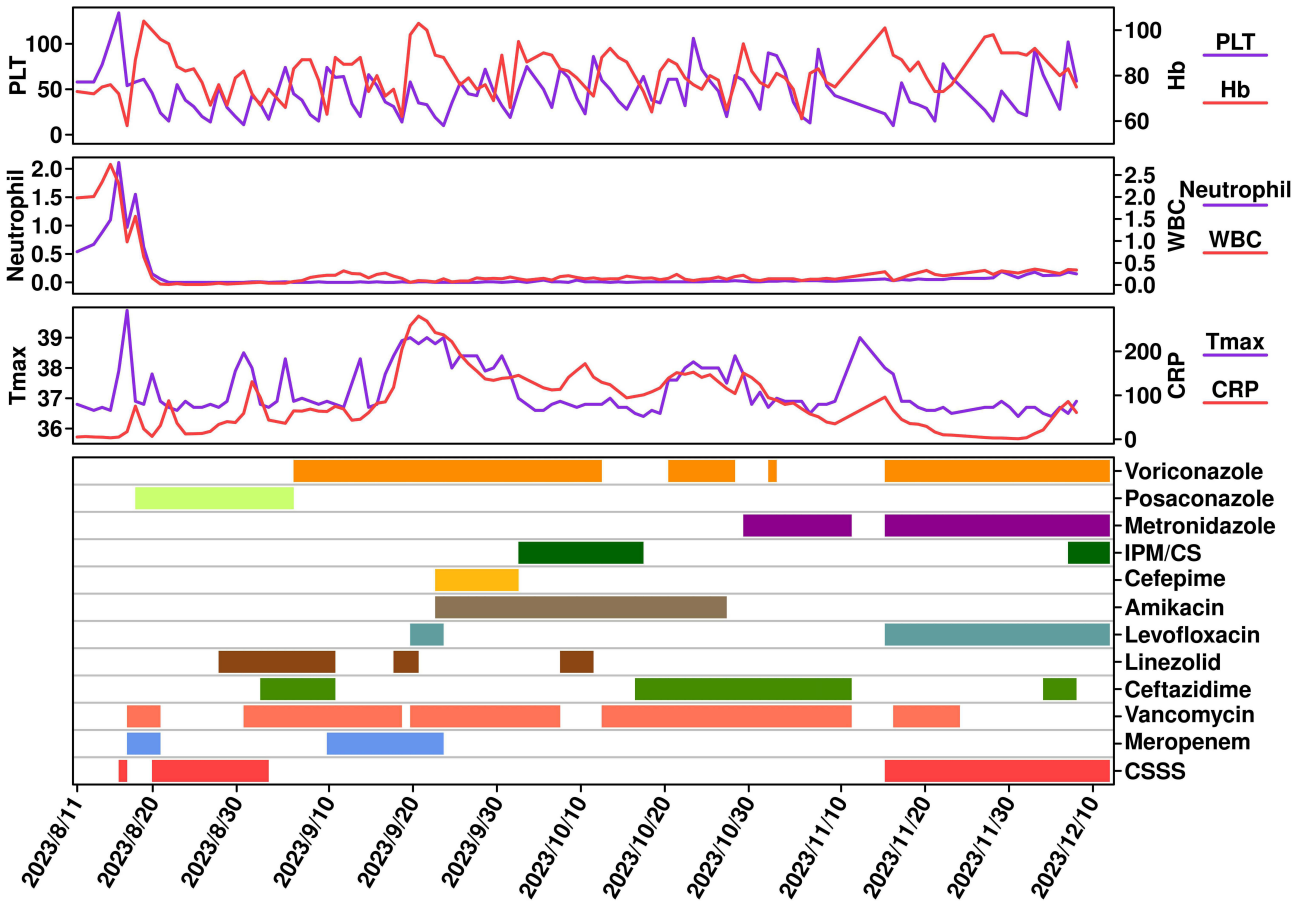

Figure 1 Case History Representation of *Pseudomonas aeruginosa* Infection in 11-Year-Old Children suffering from leukaemia.

Recurrent Fevers (August 30, 2023): Stool cultures on September 6, 2023, isolated *Enterococcus faecium* and *Pseudomonas aeruginosa*. Importantly, cultures tested negative for carbapenemase-producing or vancomycin-resistant organisms.

High Fever (September 19, 2023): Peaking at 39°C. Subsequent cultures and peripheral blood metagenomic next-generation sequencing (mNGS) identified carbapenem-resistant Pseudomonas aeruginosa (CRPA) in multiple samples, including peripheral blood, PICC catheter blood, and faecal cultures. PICC line removal ensued.

Altered Antibiotic Therapy (September 19, 2023): Adjusted based on the minimum inhibitory concentration (MIC) (Table S2), incorporating amikacin, vancomycin, cefepime, and voriconazole. The antibiotic regimen timeline for the patient, as detailed in Table S3, began on August 11, 2023, with the administration of Compound sulfamethoxazole to prevent Pneumocystis jirovecii infection. From August 16 to 22, the patient was treated with CSSS (1.5g Q8h) and later increased to 3g Q8h. On August 17, the regimen was augmented with Meropenem (0.8g Q8h) and Vancomycin (0.42g Q8h) due to septic shock. Posaconazole was added from August 18 and continued intermittently until September 2. During September, the regimen evolved to include Vancomycin (0.4g Q6h), Ceftazidime (2g Q12h), and Linezolid (po), with Voriconazole (300mg Q12h) introduced from September 6. From September 30 to October 8, treatment included Vancomycin (0.34g Q6h), Ceftazidime (1.7g Q12h), and Amikacin (0.6g Qd). IPM/CS (0.5g Q6h) was added from October 2 and continued intermittently. Voriconazole dosage varied between 260mg and 300mg Q12h. Upon re-admission on November 16, the patient was treated with CSSS (2.64g Q8h) and Vancomycin (0.35g Q6h), while continuing oral antibiotics including Compound sulfamethoxazole, Voriconazole, Metronidazole, and Levofloxacin. The regimen was modified with Contezolid upon discharge on November 25. In December, after re-admission, the patient was treated for H3N2 flu with Oseltamivir and received Ceftazidime (1.65g to 1.7g Q8h) along with IPM/CS (0.5g Q6h). The detailed timeline of antibiotic administration is summarized in Table S3.

Whole-Genome Sequencing (WGS) of CRPA: The case report integrates WGS insights, elucidating the genomic landscape and potential resistance determinants of the identified CRPA strain. The isolated clone matches with NC002516.2 superbugs, and the WGS data was submitted to NCBI assigned number AYEEP000000000. Our clones belong to ST-970, a highly virulent clone globally and reported in China, harbouring 59 different resistance genes including colistin resistance *mcr-1* co-existence with $bla_{\text{CTX-M-15, KPC-2, NDM-1, SHV, TEM}}$ and >200 virulence genes (Figure 2). Further studies are required to understand bone marrow failure linked to superbug infection.

Persistent Bone Marrow Suppression (As of October 31, 2023): Indicated by a low reticulocyte count, bone marrow smears showing reduced proliferation, and biopsies revealing only 15% hematopoietic tissue, suggestive of secondary bone marrow failure. Additional infection was observed by CT chest, and CT abdomen showed splenomegaly. Pathological findings of the oral mucosa indicated granulation tissue. Viral PCR testing for Epstein-Barr virus, Cytomegalovirus, BK Virus, John Cunningham Virus, Herpes simplex Virus-2, and Hepatitis B Virus showed negative results.

Ongoing Challenges (As of December 9, 2023): The patient continues to experience intermittent fever and persistent detection of CRPA in stool cultures, emphasizing the unresolved nature of bone marrow failure. Bone marrow failure in children remains challenging to define, potentially arising from chemotherapy or a combination of chemotherapy and infection. A bone marrow biopsy on December 1, 2023, indicated hematopoietic tissue at 5% −10%, lower than before, prompting consideration for hematopoietic stem cell transplantation as the next step.

Discussion and Conclusion

This case report provides a unique lens into the intricate challenges encountered in managing paediatric AML, shedding light on the unforeseen complications that can arise during intensive chemotherapy. The emergence of superbugs adds a layer of complexity, highlighting the urgent need for comprehensive understanding and strategic approaches in paediatric oncology.[9] Existing literature underscores the success achieved in AML treatment, marked by initial disease remission and the attainment of complete remission (CR) following intensive chemotherapy courses.[10] However, our prior research underscores the growing prevalence of multidrug-resistant pathogens, such as superbugs, presenting significant concerns for individuals with compromised immune systems.[11] The present case aligns with these broader observations, illustrating the unpredictable trajectory that may unfold even in the context of initial treatment success. The patient's clinical course, marked by successful remission after Course B2 chemotherapy, took an unexpected turn with the onset of septic shock following Course B3. Despite negative blood cultures, the intensity of complications necessitated intensified antibiotic therapy, indicative of the challenges in managing infectious complications in AML patients. The subsequent bone marrow failure, compounded by perianal dermatitis and the identification of superbug, unveils the intricate interplay between intensive chemotherapy and superbug infections. Notably, the case emphasizes the need for vigilance in monitoring both clinical and laboratory parameters to promptly identify and address complications that may arise during the course of treatment. The identification of a highly virulent superbug clone (ST-970) with extensive genomic data adds a significant dimension to the existing literature on antimicrobial resistance in paediatric oncology. The hypervirulent *Pseudomonas aeruginosa* ST970, implicated in both healthcare-associated infections (HAIs) and community-acquired infections (CAIs), possesses heightened capabilities for causing both acute and chronic infections. This strain demands immediate attention from public health systems, especially concerning immunocompromised patients.[12] The case underscores the importance of incorporating Whole-Genome Sequencing (WGS) insights to elucidate the genomic landscape and potential resistance determinants of superbugs, contributing valuable data for future therapeutic strategies. The persistent detection of superbug in stool cultures and the ongoing bone marrow failure emphasize the challenges in defining and addressing complications in paediatric AML. The relevance of this case extends beyond the individual patient, urging a reevaluation of treatment strategies and a multidisciplinary approach to enhance patient care. This case report not only contributes a detailed account of the clinical journey of a paediatric AML patient but also provides insights into the evolving challenges posed by superbug infections. The relevance of this case to the existing literature lies in its potential to inform and guide future research and clinical endeavours, fostering a deeper understanding of complications and antimicrobial resistance in paediatric oncology. This knowledge is crucial for optimizing treatment outcomes and advancing the field towards tailored and effective therapeutic approaches.

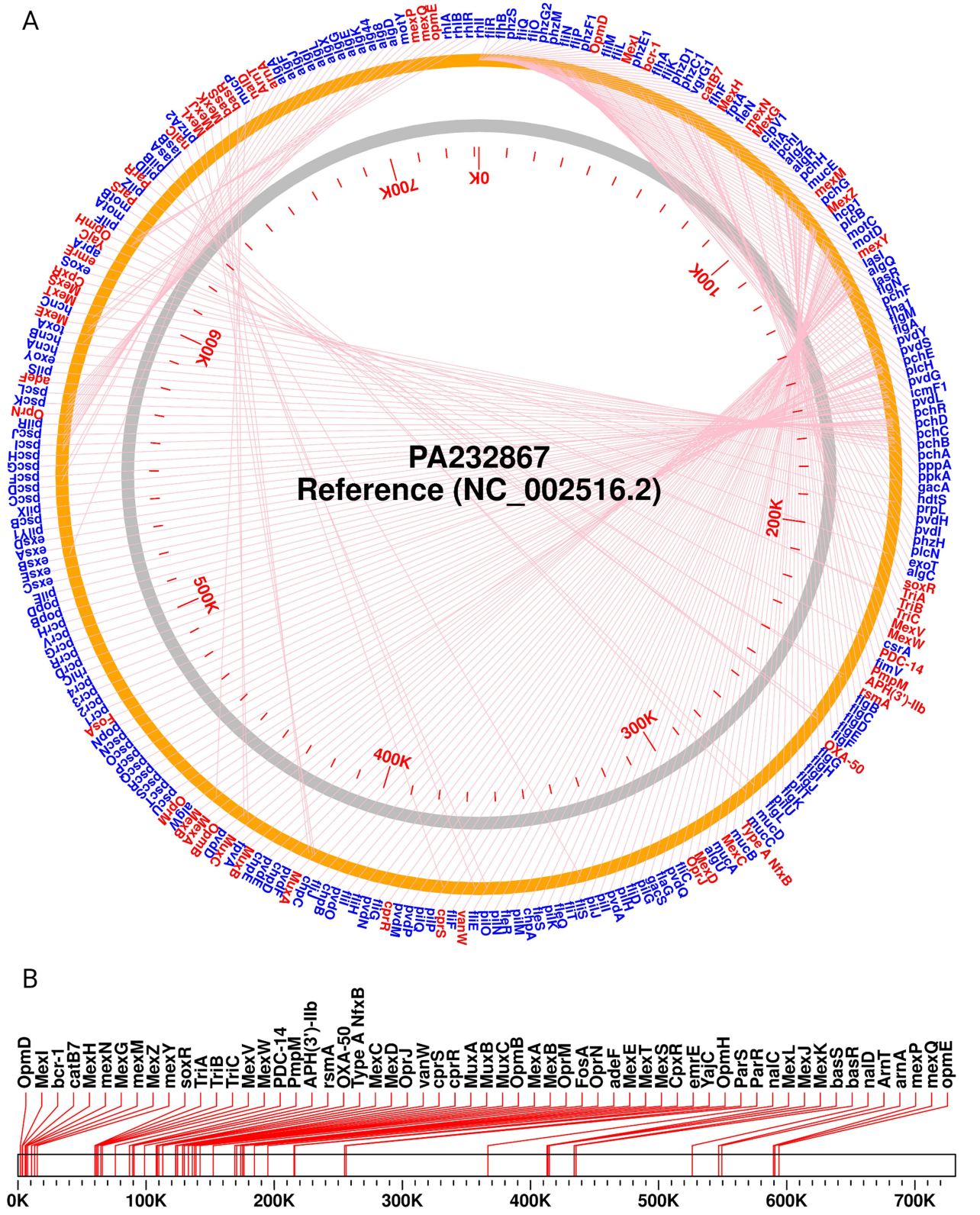

Figure 2 Genomic Landscape of *Pseudomonas aeruginosa* Recovered from 11-Year-Old Children suffering from leukaemia. (**A**) Circular mapping of genomic DNA marked with resistance determinant and virulence. (**B**) linear map of DNA organized selected genes.

Notes: Blue Icons (V): Indicate the presence of virulence genes within the genome, Red Icons (DR): Denote the locations of drug resistance genes within the *Pseudomonas aeruginosa* genome.

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Data Sharing Statement

The original data in this study are available upon reasonable request from the corresponding author Feiqiu Wen (fwen62@163.com).

Ethics Approval

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Shenzhen Children's Hospital Institutional Ethics Committee, reference number: 2018 (013) dated 2018/09/03, which complies with international ethical standards.

Consent to Participate

The guardians have provided "written informed" consent for publication of the case details.

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Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Tseng S, Lee ME, Lin PC. A review of childhood acute myeloid leukemia: diagnosis and novel treatment. *Pharmaceuticals*. 2023;16(11):1614. doi:10.3390/ph16111614
2. Carlesse F, de SAVL. Infections in children and adolescents with acute leukemia. *EJC Paediatric Oncol*. 2024;3. doi:10.1016/j.ejcped.2024.100142
3. Patil S, Chen X, Dong S, et al. Resistance genomics and molecular epidemiology of high-risk clones of ESBL-producing Pseudomonas aeruginosa in young children. *Front Cell Infect Microbiol*. 2023;13:1168096. doi:10.3389/fcimb.2023.1168096
4. Xing T, Lyu ZS, Duan CW, et al. Dysfunctional bone marrow endothelial progenitor cells are involved in patients with myelodysplastic syndromes. *J Transl Med*. 2022;20(1):144. doi:10.1186/s12967-022-03354-2
5. van Dijk AD, de Bont ESJM, Kornblau SM. Targeted therapy in acute myeloid leukemia: current status and new insights from a proteomic perspective. *Expert Rev Proteomics*. 2020;17(1):1–10. doi:10.1080/14789450.2020.1717951
6. Papan C, Reifenrath K, Last K, et al. Antimicrobial use in pediatric oncology and hematology in Germany and Austria, 2020/2021: a cross-sectional, multi-center point-prevalence study with a multi-step qualitative adjudication process. *Lancet Reg Health – Europe*. 2023:28. doi:10.1016/j.lanepe.2023.100599.
7. Battashi AA, Harrassi BA, Maskari NA, Hashami HA, Awaidy SA. Alarming antibiotic resistance in pediatric oncology patients: a three-year prospective cohort study from Oman. *IDR*. 2022;15:3939–3947. doi:10.2147/IDR.S369909
8. Vázquez-López R, Rivero Rojas O, Ibarra Moreno A, et al. Antibiotic-resistant septicemia in pediatric oncology patients associated with post-therapeutic neutropenic fever. *Antibiotics*. 2019;8(3):106. doi:10.3390/antibiotics8030106
9. Baral B, Mozafari MR. Strategic moves of "superbugs" against available chemical scaffolds: signaling, regulation, and challenges. *ACS Pharmacol Transl Sci*. 2020;3(3):373–400. doi:10.1021/acsptsci.0c00005
10. Eckardt JN, Röllig C, Metzeler K, et al. Prediction of complete remission and survival in acute myeloid leukemia using supervised machine learning. *Haematologica*. 2023;108(3):690–704. doi:10.3324/haematol.2021.280027
11. Chen H, Mai H, Lopes B, Wen F, Patil S. Novel Pseudomonas aeruginosa strains co-harbouring bla NDM-1 metallo β-lactamase and mcr-1 isolated from immunocompromised paediatric patients. *Infect Drug Resist*. 2022;15:2929–2936. doi:10.2147/IDR.S368566
12. Song Y, Mu Y, Wong NK, et al. Emergence of hypervirulent *Pseudomonas aeruginosa* pathotypically armed with co-expressed T3SS effectors ExoS and ExoU. *hLife*. 2023;1(1):44–56. doi:10.1016/j.hlife.2023.02.001