Received: 7 January 2024 | Accepted: 22 February 2024

DOI: 10.1111/bjh.19382

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

SHORT REPORT

Paediatrics

Pneumocystis jirovecii pneumonia in paediatric acute lymphoblastic leukaemia: A report from the multi-international clinical trial AIEOP-BFM ALL 2009

Anke Barnbrock[1] | **Anja Möricke**[2] | **Draga Barbaric**[3] | **Neil Jones**[4] | **Christa Koenig**[5] | **Reinhard Moser**[6] | **Marius Rohde**[7] | **Christina Salvador**[8] | **Julia Alten**[2] | **Sarah Elitzur**[9] | **Andreas H. Groll**[10] | **Thomas Lehrnbecher**[1]

[1]Department of Pediatrics, Division of Hematology, Oncology and Hemostaseology, Goethe University Frankfurt, Frankfurt/Main, Germany

[2]Department of Pediatrics, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

[3]Sydney Children's Hospital, Randwick, New South Wales, Australia

[4]Department of Pediatrics and Adolescent Medicine University Clinics Salzburg Salzburg Austria, Salzburg, Austria

[5]Pediatric Hematology/Oncology, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[6]Abteilung für Kinder- und Jugendheilkunde, Landeskrankenhaus Hochsteiermark Standort Leoben, Leoben, Austria

[7]Department of Pediatric Oncology and Hematology, University Hospital Giessen and Marburg, Giessen, Germany

[8]Department für Kinder- und Jugendheilkunde, Medizinische Universität Innsbruck, Innsbruck, Austria

[9]Pediatric Hematology-Oncology, Schneider Children's Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[10]Infectious Disease Research Program, Department of Pediatric Hematology/Oncology and Center for Bone Marrow Transplantation, University Children's Hospital Münster, Münster, Germany

Correspondence
Thomas Lehrnbecher, Department of Pediatrics, Division of Hematology, Oncology and Hemostaseology, Goethe University Frankfurt, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany.
Email: thomas_lehrnbecher@yahoo.com

Summary

Pneumocystis jirovecii can cause life-threatening pneumonia (PjP), and patients with haematological malignancies are at high risk of this infection. Prophylactic measures have significantly decreased morbidity and mortality, but there is a paucity of contemporary data on the incidence and clinical course of PjP in well-defined and homogenous patient populations, such as children suffering from acute lymphoblastic leukaemia (ALL). In the multi-international trial AIEOP-BFM ALL2009, PjP was diagnosed in six children (incidence 1/1000) and was associated with insufficient prophylaxis in five of them. Although none of the patients died of PjP, the long-term impact of the infection is unclear.

KEYWORDS

acute lymphoblastic leukaemia, child, *Pneumocystis jirovecii*, prophylaxis, therapy

INTRODUCTION

Pneumocystis jirovecii can cause life-threatening pneumonia (PjP) and patients with haematological malignancies, or undergoing haematopoietic cell transplantation, are at an especially high risk of this infectious complication.[1–3] Prophylactic measures such as the intermittent administration of trimethoprim/sulfamethoxazole (TMP/SMX) have significantly decreased morbidity and mortality due to this infection.[4] There is, however, a paucity of

Andreas H. Groll and Thomas Lehrnbecher jointly supervised this work.

contemporary data on the incidence and clinical course of PjP in well-defined and homogenous patient populations, such as in children suffering from acute lymphoblastic leukaemia (ALL). Here we provide a detailed analysis on PCP diagnosed in children with ALL who were enrolled and treated in the multi-international trial AIEOP-BFM ALL 2009.

PATIENTS AND METHODS

Details of the study population, anti-neoplastic treatment modalities and data collection have already been reported.[5] Briefly, a total of 6136 children diagnosed with ALL and enrolled as study patients in the international, multicentre and prospectively randomized Phase III clinical trial AIEOP-BFM ALL2009 (EudraCT 2007-004270-43) were included in the analysis. The study was performed in seven countries (Germany, Austria, Switzerland, Italy, Israel, the Czech Republic and Australia) between 1 June 2010 and 28 February 2017. The study was approved by the appropriate national and local review boards and was conducted in accordance with the Declaration of Helsinki and national laws. Informed consent was obtained from the parents or guardians of each patient included in the study, as required by ethical standards and national guidelines.

Invasive fungal disease, including PjP, was considered a serious adverse event (SAE) of special interest, and data were prospectively captured and reported by the participating institution. Reporting of SAEs was mandatory. PjP was categorized as proven or probable according to recently published and updated definitions of *Pneumocystis jirovecii* disease in individuals without human immunodeficiency virus infection[6] and severity according to a grading system reported in the European Conference on Infections in Leukaemia (ECIL) guidelines.[7]

RESULTS

Out of 6136 children and adolescents enrolled in the clinical trial, six patients [two females, four males, median age (range) 10.7 years (1.1–16.4)] were diagnosed with PjP (Table 1 and Figure 1). Five patients had precursor B-ALL, and one T-ALL. PjP prophylaxis was prescribed in all except one patient and consisted of TMP/SMX. In patient #6, TMP/SMX prophylaxis was switched to pentamidine prior to infection due to hepatopathy. In one patient (#2), oral TMP/SMX was delayed as he had difficulties tolerating oral medication, and the intake of prednisone was prioritized at that time. Insufficient compliance with TMP/SMX prophylaxis was documented in four patients (#1, #3, #4 and #5). PjP infection occurred at an early phase of treatment in one patient (patient #2, second phase of induction therapy) and in one patient (#6) during re-intensification, whereas it was diagnosed in four children during, or soon after, maintenance therapy (Table 1 and Figure 1).

At the onset of PjP infection, all patients had lymphocyte counts <1000/μL [median (range) 370/μL (220–600)]. In two patients, PjP infection was confirmed by microscopic detection, and in four patients, a 'probable' PjP was diagnosed by molecular detection.[6]

The clinical course was severe in all patients, with four being admitted to the ICU and three of them requiring mechanical ventilation. Primary treatment consisted of TMP/SMX, and adjunctive corticosteroids were given to five patients. Of note, anti-leukaemic chemotherapy was interrupted in all patients who were on anti-neoplastic treatment at the time of infection [median time (range): 22 days (15–20)]. PjP ultimately resolved in all patients, and all were alive 1 year after infection (Table 1 and Figure 1).

DISCUSSION

In the 1970s, it became clear that children with cancer, in particular those treated for haematological malignancies, have a high risk of PjP, and at that time, PjP was the most common cause of death in patients with leukaemia in remission.[1,2] The fact that T-cell deficiency and T-cell-specific therapy are the most important risk factors for PjP may explain the observation that the majority of infections occurred in patients during maintenance therapy.[8] This phase of therapy is characterized by long-lasting T lymphopenia, whereas T-cell recovery is relatively rapid after short courses of intensive cytotoxic therapy, particularly in younger patients.[9,10] Subsequently, it could be demonstrated that intermittent chemoprophylaxis with TMP/SMX significantly reduced the risk of PjP[4] and current guidelines recommend prophylaxis with TMP/SMX in children with haematological malignancies either once (recommendation grade BII) or twice to three times a week (AI).[11] Pentamidine aerosols and atovaquone are recommended as second-line prophylaxis in the paediatric setting (BII).[11] It is, however, important to note that second-line PjP prophylaxis has been reported to have a lower efficacy than TMP/SMX,[12,13] and therefore, PjP in patient #6 may be attributed to the switch to pentamidine. With these prophylactic regimens, PjP has become a rare infectious complication in children with cancer, and most infections occur in patients who do not receive, or fail to comply with, the prescribed prophylaxis, which is corroborated by our observation.[14]

Importantly, most analyses on PjP in the setting of paediatric cancer patients have major limitations as they are based on case series from surveys, which may be affected by reporting bias, or on heterogeneous patient populations, which do not allow for a solid conclusion on its actual epidemiology.[15] We believe our contemporary, prospective data of a large randomized multi-international trial on paediatric ALL is unique in that it demonstrates an incidence rate of 1/1000 of

TABLE 1 Clinical details of children developing PjP during treatment according to AIEOP-BFM ALL 2009.

Patient No.	1	2	3	4	5	6
Patients´ characteristics and PCP prophylaxis						
Age (years)/gender	13.4/f	16.4/m	3.6/m	1.1/m	14.7/m	8.3/f
Immunopheno-type/risk group	PB/MR	T/non-HR	PB/MR	PB/MR	PB/HR	PB/MR
PCP prophylaxis prescribed	TMP/SMX 3/15 mg/kg 3 consecutive days/ week	No PCP prophylaxis due to incompliance to all oral medication	TMP/SMX 4/20 mg/kg 3 days/week	TMP/SMX 5/25 mg/kg 3 consecutive days/week	TMP/SMX 5/25 mg/kg 3 days/week	TMP/SMX 5/25 mg/kg 3 days/ week until 6 months prior to infection, then pentamidine 300 mg 1x/month due to hepatopathy
Issues with prophypaxis	Incompliant	n.a.	Incompliant	Incompliant	Incompliant	None
Details of disease						
Therapy phase of infection	1 week after end of maintenance therapy	Protocol IB	Maintenance therapy	1 week after end of maintenance therapy	Interim Maintenance	Protocol IIB
Clinical symptoms	Fever, cough, dyspnoea, oxygen saturation decreased	Fever, tachycardia, cough, rigours, oxygen saturation decreased	Fever, cough, tachypnoea and dyspnoea, oxygen saturation decreased	Fever, tachypnoea, oxygen saturation decreased	Fever, headache, cough, rhinitis, reduced appetite	Reduced general condition, fever, dyspnoea, oxygen saturation decreased, abdominal pain
Neutrophil/lymphocyte count at diagnosis of PjP (per µL)	4280/220	2500/500	2500/300	400/300	1130/440	440/600
Imaging studies of the lung	Bilateral opacities and interstitial infiltrates	Pulmonary opacities with peribronchovascular distribution	Bilateral alveolar infiltrates	Round-glass opacity, left lung and upper right lung	Diffuse alveolar infiltrates	Bilateral interstitial infiltrates, hilar lymphadenopathy, discrete pleural effusion
Diagnostics for PjP	Positive PCR in BAL	Positive PCR in BAL	Positive immunofluore-scence in BAL	Positive PCR in sputum	Positive PCR in BAL	Positive microscopy in BAL
Coinfection	No	Probable pulmonary aspergillosis; Influenza A	No	No	No	No
Extra-pulmonary manifestations	No	No	No	No	No	No
Interruption of chemotherapy (time period)	No (infection after end of all chemotherapy)	Yes—1 month	Yes—23 days	No (infection after end of all chemotherapy)	Yes—3 weeks	Yes—15 days
Therapy and outcome						
Therapy of PjP	19/95 mg/kg TMP/SMX for 14 days and 4 mg/ kg pentamidine for 7 days	20/100 mg/kg TMP/SMX for 16 days	16/80 mg/kgTMP/SMX for 22 days	20/100 mg/kg TMP/SMX for 9 days	20/100 mg/kg TMP/ SMX for 4 days	20/100 mg/kg TMP/SMX iv for 8 days; then primaquin p.o. 1 × 30 mg/day for 13 days (liver enzymes elevated) + clindamycin 4 × 450 mg
Additional steroids	Yes	Yes	Yes	No	Yes	Yes
ICU admission/mechanical ventilation	12 days ICU/7 days mechanical ventilation	5 days ICU/2 days mechanical ventilation	11 days ICU/6 days mechanical ventilation	3 days/no	No/no	No/no
Outcome of infection	Resolved	Resolved	Resolved	Resolved	Resolved	Resolved
Alive after 1 y/5 y	Yes/no (relapse)	Yes/yes	Yes/yes	Yes/yes	Yes/yes	Yes/yes

Abbreviations: BAL, bronchoalveolar lavage; f, female; HR, high risk; ICU, intensive care unit; m, male; MR, intermediate risk; n.a., not applicable; PB, precursor B-ALL; PCR, polymerase chain reaction; PjP, *Pneumocystis jirovecii* pneumonia; SMX, sulfamethoxazole; TMP, trimethoprim.

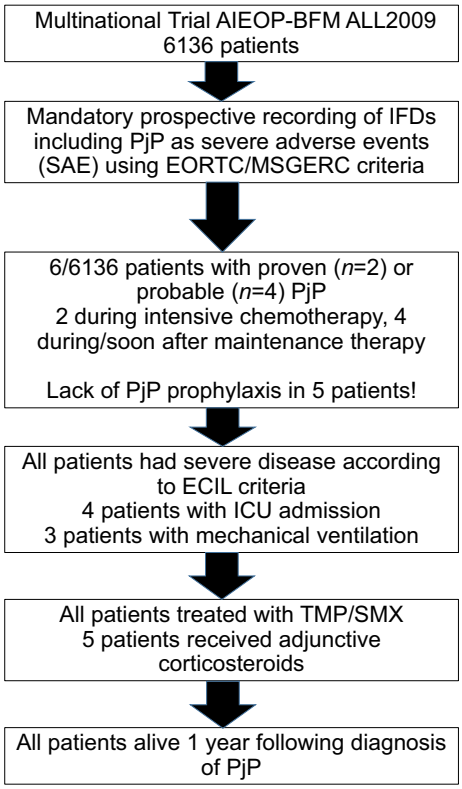

FIGURE 1 Summary of patients, treatment, course of disease and outcome. ICU, intensive care unit; IFD, invasive fungal disease; PjP, *Pneumocystis jirovecii* pneumonia; SMX, sulfamethoxazole; TMP, trimethoprim.

PCP in children and adolescents with ALL, whereas in other reports a reliable denominator is missing.[15]

Consistent with historical data, the clinical course of the infection was severe in all six patients, with four being admitted to ICU and three of them requiring mechanical ventilation.[16] One patient had a coinfection with *Aspergillus fumigatus* and influenza A, which has been reported to be not uncommon in cancer patients with PjP.[7] Atypical pulmonary presentations or extra-pulmonary manifestations, as occasionally observed in patients with advanced HIV infections, were not observed.[17] All patients received the recommended first-line therapy, and all but one received adjunctive therapeutic corticosteroids. The effect of corticosteroids, however, is not clear, as a significant proportion of cancer patients with PjP had been treated with corticosteroids prior to PjP infection, as was the case in two of the six patients in the present analysis.[7,8]

Whereas historical analyses reported a high mortality from PjP in cancer patients,[18] all our patients survived the infection. However, survivors of PjP may have a risk of chronic lung injury,[19] and the initiation of a specific follow-up should be discussed on a case-to-case basis. In addition, chemotherapy was interrupted in all patients who were on anti-neoplastic treatment at the time of infection, but it is unclear whether this treatment delay has an impact on overall outcome, as it was speculated in the overall analysis of invasive fungal disease in our cohort of patients.[5]

We recognize that our analysis also has limitations. For example, although prophylaxis is recommended by international guidelines,[11] we have no data on the actual prescription of and compliance with PjP prophylaxis in the different institutions. Nevertheless, our study in children with ALL treated according to AIEOP-BFM ALL 2009 demonstrates that PjP occurs with an incidence of 1/1000 in this patient population, and is mainly associated with insufficient prophylaxis. Although survival of the infection is excellent, the long-term impact is unclear.

AUTHOR CONTRIBUTIONS

A.B, A.M., S.E., A.H.G. and T.L. designed the study and analysed the data. D.B., N.J., C.K., R.M., M.R. and C.S. collected the data. A.B., A.H.G. and T.L. wrote the first draft of the manuscript. All authors critically read and discussed the draft, and approved the final manuscript.

FUNDING INFORMATION

This work did not receive funding.

CONFLICT OF INTEREST STATEMENT

AM has served as consultant to Protherics Medicines Development, Clinigen and JazzPharma. AHG has received grants from Gilead, Merck, Sharp & Dohme and Pfizer and has served as consultant to Amplyx, Astellas, Basilea, F2G, Gilead. Merck, Sharp & Dohme, Pfizer, Scynexis and Mundipharma. T.L. has received a grant from Gilead Sciences, has served as consultant to Gilead Sciences, Merck/MSD, Pfizer, Astellas, AstraZeneca, EUSA Pharma and Roche and has served at the speaker's bureau of Gilead Sciences, Merck/MSD, Astellas, Pfizer, GSK and EUSA Pharma. None of the other authors has to declare a conflict of interest regarding this work.

DATA AVAILABILITY STATEMENT

All data and material related to this study are available from the authors on request.

ETHICS STATEMENT

The study was approved by the appropriate national and local review boards and was conducted in accordance with the Declaration of Helsinki and national laws.

PATIENT CONSENT STATEMENT

Informed consent was obtained from the parents or guardians of each patient included in the study, as required by ethical standards and national guidelines.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

Clinical trial AIEOP-BFM ALL2009 (EudraCT 2007-004270-43).

ORCID

Thomas Lehrnbecher https://orcid.org/0000-0002-6022-3439

REFERENCES

1. Hughes WT, Price RA, Kim HK, Coburn TP, Grigsby D, Feldman S. *Pneumocystis carinii* pneumonitis in children with malignancies. J Pediatr. 1973;82:404–15.
2. Simone JV, Holland E, Johnson W. Fatalities during remission of childhood leukemia. Blood. 1972;39:759–70.
3. Robin C, Cordonnier C, Tridello G, Knelange N, Xhaard A, Chantepie S, et al. *Pneumocystis* pneumonia after allogeneic hematopoietic cell transplantation: a case-control study on epidemiology and risk factors on behalf of the infectious diseases working party of the European Society for blood and marrow transplantation. Transplant Cell Ther. 2024;30:235.e1–235.e10.
4. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for *Pneumocystis carinii* pneumonitis. N Engl J Med. 1987;316:1627–32.
5. Lehrnbecher T, Groll AH, Cesaro S, Alten J, Attarbaschi A, Barbaric D, et al. Invasive fungal diseases impact on outcome of childhood ALL—an analysis of the international trial AIEOP-BFM ALL 2009. Leukemia. 2023;37:72–8.
6. Lagrou K, Chen S, Masur H, Viscoli C, Decker CF, Pagano L, et al. *Pneumocystis jirovecii* disease: basis for the revised EORTC/MSGERC invasive fungal disease definitions in individuals without human immunodeficiency virus. Clin Infect Dis. 2021;72:S114–S120.
7. Maschmeyer G, Helweg-Larsen J, Pagano L, Robin C, Cordonnier C, Schellongowski P, et al. ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients. J Antimicrob Chemother. 2016;71:2405–13.
8. Cross SJ, Wolf J, Patel PA. Prevention, diagnosis and management of *Pneumocystis jirovecii* infection in children with cancer or receiving hematopoietic cell therapy. Pediatr Infect Dis J. 2023;42:e479–e482.
9. Lehrnbecher T, Foster C, Vazquez N, Mackall CL, Chanock SJ. Therapy-induced alterations in host defense in children receiving chemotherapy. J Pediatr Hematol Oncol. 1997;19:399–417.
10. El-Chennawi FA, Al-Tonbary YA, Mossad YM, Ahmed MA. Immune reconstitution during maintenance therapy in children with acute lymphoblastic leukemia, relation to co-existing infection. Hematology. 2008;13:203–9.
11. Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, et al. ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71:2397–404.
12. Geerlinks AV, Campigotto A, Science M, Gupta S. Impact of prophylaxis choice on risk of *Pneumocystis* pneumonia in children with cancer: a case-control study. Eur J Cancer. 2020;140:71–5.
13. Prasad P, Nania JJ, Shankar SM. Pneumocystis pneumonia in children receiving chemotherapy. Pediatr Blood Cancer. 2008;50:896–8.
14. Cordonnier C, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, et al. *Pneumocystis jirovecii* pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71:2379–85.
15. Proudfoot RH, Phillips B. UK paediatric oncology *Pneumocystis jirovecii* pneumonia surveillance study. Arch Dis Child. 2021;106:994–8.
16. Pagano L, Fianchi L, Mele L, Girmenia C, Offidani M, Ricci P, et al. *Pneumocystis carinii* pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. Br J Haematol. 2002;117:379–86.
17. Groll AH, Keul HG, Brodt R, Schneider M. AIDS-associated atypical *Pneumocystis carinii* pneumonia revisited. Clin Infect Dis. 1998;26:1005–6.
18. Thomas CF Jr, Limper AH. *Pneumocystis* pneumonia. N Engl J Med. 2004;350:2487–98.
19. Morris AM, Huang L, Bacchetti P, Turner J, Hopewell PC, Wallace JM, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The pulmonary complications of HIV infection study group. Am J Respir Crit Care Med. 2000;162:612–6.

How to cite this article: Barnbrock A, Möricke A, Barbaric D, Jones N, Koenig C, Moser R, et al. *Pneumocystis jirovecii* pneumonia in paediatric acute lymphoblastic leukaemia: A report from the multi-international clinical trial AIEOP-BFM ALL 2009. Br J Haematol. 2024;00:1–5. https://doi.org/10.1111/bjh.19382