UK paediatric oncology *Pneumocystis jirovecii* pneumonia surveillance study

Rebecca Hilary Proudfoot, Bob Phillips

**ABSTRACT**

**Background** *Pneumocystis jirovecii* pneumonia (PJP) is a serious infective complication of immunosuppressive therapy. There are insufficient data concerning the incidence or mortality rate in children undergoing treatment for malignancies and how these may be influenced by prophylaxis.

**Objective** Prospective collection of clinical information for all suspected and proven cases of PJP in children with cancer in the UK and Ireland.

**Design** A surveillance survey was undertaken using a key contact at each paediatric oncology Principle Treatment Centre (PTC).

**Main outcome measures** To describe the mortality, outcomes and use of prophylaxis in this at-risk group.

**Results** The study confirms that PJP is rare, with only 32 cases detected in the UK over a 2-year period reported from all 20 PTCs. No deaths were directly attributed to PJP, in contrast to previously reported high mortality rates. Breakthrough infection may occur despite prescription of ostensibly adequate prophylaxis with co-trimoxazole; 11 such cases were identified. Six infections occurred in patients for whom prophylaxis was not thought to be indicated. Two infections occurred in patients for whom prophylaxis was specifically omitted due to concerns about potential bone marrow suppression or delayed engraftment.

**Conclusion** PJP in children treated for malignant disease is rare. Breakthrough infection despite prophylaxis with co-trimoxazole may represent pathogen resistance or non-compliance. Further consideration of the use of PJP prophylaxis during acute myeloid leukaemia and non-Hodgkin’s lymphoma treatment is warranted, alongside appraisal of the clinical implications of the possible marrow suppressive effects of co-trimoxazole and its interactions with methotrexate.

**What this study adds?**

- No deaths were directly attributed to PJP, in contrast to previously reported high mortality rates of 20%–40%.
- Breakthrough infection despite prophylaxis with co-trimoxazole is more common compared with previously published data.
- Further consideration of prophylaxis use during acute myeloid leukaemia and non-Hodgkin’s lymphoma treatment is warranted.

**What is already known on this topic?**

- *Pneumocystis jirovecii* pneumonia (PJP) is a rare but serious complication of immunosuppressive therapy.
- Prophylaxis with co-trimoxazole 2 days per week is safe, effective and inexpensive.
- All children with malignancies undergoing immunosuppressive therapy should be offered prophylaxis unless there are clear contraindications.

**BACKGROUND**

*Pneumocystis jirovecii* is an opportunistic parasite that causes pneumonia (PJP) in severely immunocompromised hosts. The incidence of PJP among HIV-negative patients is increasing, perhaps due to more intense and diverse immunosuppressive therapies for malignancy, bone marrow and solid organ transplant and rheumatological disease. Even with prompt treatment, PJP has historically resulted in high mortality rates of 20%–40%. There are insufficient data concerning the incidence or mortality in children treated for malignancies and how these may be influenced by the use of prophylaxis.

After dissemination of a recently designed UK guideline for the prophylaxis of PJP in children with solid malignancies, a survey of compliance and analysis of PJP cases was undertaken.

**METHODS**

This was a national surveillance study of suspected or proven PJP over a 2-year period, January 2018–January 2020 in Children’s Cancer and Leukaemia Group (CCLG) networked UK paediatric oncology Principle Treatment Centres (PTCs). Every quarter, centres reported any suspected or proven cases of PJP in the past 3 months with anonymised clinical details (online supplemental appendix 1).

Age and treatment centre were used as identifiers for each case. As PJP is a rare condition this was considered sufficient to identify potential duplicates. All cases of PJP would be expected to come to the attention of the child’s PTC, even if that child presented with symptoms to their local hospital as these children’s care is highly centralised.

Data were collected regarding the diagnosis of PJP, the underlying malignancy diagnosis and comorbidities, the stage in anticancer therapy, the total white cell and lymphocyte count at time of presentation with PJP, along with the specific use of prophylaxis in the month prior to PJP and the clinical outcome.

Proven PJP was defined on the basis of positive respiratory samples, in a clinically relevant setting.
Suspected PJP was a clinical diagnosis, on the basis of imaging and response to therapy.

RESULTS
All 20 UK PTCs undertook the surveillance. Thirty-two cases (13 suspected, 19 proven) in 31 patients were identified over the 2-year period. One patient with acute lymphocytic leukemia (ALL) had a second suspected PJP infection following a microbiologically confirmed infection 6 months previously.

One case was diagnosed on positive immunofluorescence (IF) on samples obtained by bronchoalveolar lavage (BAL). The remaining 18 proven cases were diagnosed by polymerase chain reaction (PCR) on samples from BAL, blood, sputum and/or nasopharyngeal aspirate. Fourteen of the proven cases underwent BAL with positive results (12 PCR positive, 1 IF positive and one IF and PCR positive). No information was recorded regarding suspected cases who underwent BAL with negative microbiology for PJP. The median age was 9 years 4 months (range 18 months to 18 years).

Of the 20 PTCs, 4 did not report any cases of suspected or proven PJP over the 2-year period but the remainder reported between 1 and 4 cases each. The spread of suspected versus proven cases at the different PTCs was fairly even (see figure 1), suggesting no regional over-reporting or heightened awareness.

Table 1 shows the 32 cases by underlying diagnosis, the most common of which were haematological malignancies (26/31).

There were 7 suspected and 8 proven cases of PJP in 14 patients with ALL (1 patient had a proven infection, followed by a suspected infection 6 months later). Of these, 11 cases occurred during maintenance therapy or immediately after the end of treatment, 1 presented at diagnosis and later transpired to have an underlying immunodeficiency, 1 at presentation with a second relapse and 2 in the post stem cell transplant (SCT) phase.

Thirteen of the infections in children with ALL occurred during periods where prophylaxis had been prescribed. Four of these episodes were considered by their clinical team to be consequent to possible or definite non-compliance with prophylaxis. Five cases were apparent prophylaxis failures on oral co-trimoxazole, two on oral dapsone, one on intravenous pentamidine and one on nebulised pentamidine. Doses of oral co-trimoxazole were all as per the United Kingdom Acute Lymphoblastic Leukaemia (UKALL) 2011 trial protocol, given on 2 days per week.

There were seven cases of PJP associated with AML (five proven, two suspected). Three were not prescribed any prophylaxis as it was not thought to be indicated. One patient was receiving intravenous pentamidine and the remaining three co-trimoxazole. Only one patient was thought to be non-compliant with oral prophylaxis.

There were three proven and one suspected case of PJP in children with NHL (all mature B cell NHL treated on French-American-British-Lymphoma Malins B protocols). Only one had been prescribed prophylaxis (co-trimoxazole) as it was felt to be contraindicated with the frequent use of high-dose (HD) intravenous methotrexate.

The final six cases were in four patients with neuroblastoma, and two in patients with sarcomas. The neuroblastoma patients were treated on the European high-risk neuroblastoma study or CCLG high-risk guidelines. Three had received an autologous SCT and one had just completed induction therapy. Only one patient was not prescribed any prophylaxis post-SCT because of the theoretical delay to count recovery. The last two patients had relapsed rhabdomyosarcoma and Ewing’s sarcoma with suspected and proven PJP, respectively. The former was prescribed co-trimoxazole but thought not to be taking it, and the latter had not been receiving any PJP prophylaxis due to concerns about bone marrow suppression.

At presentation with PJP, the mean white cell count and lymphocyte count was $4.15 \times 10^3/L$ (range 0–14.8) and $0.44 \times 10^3/L$ (range 0–1.6), respectively for 29 cases (one case had no blood test results available and a further two cases were excluded from analysis as their cell counts may have been unreliable at presentation/relapse with leukaemia).

Most patients (64.5%, 20 out of 31) had no comorbidities other than their underlying malignancy. Only three patients had a comorbidity that was identified prior to the diagnosis of their malignancy: obesity, trisomy 21 and premature birth (28 weeks) with a history of chronic lung disease. None had a known immunodeficiency prior to their diagnosis of cancer but one patient was subsequently found to have mannose binding lectin deficiency.

Gut graft-versus-host disease (GVHD) has been reported to possibly interfere with oral absorption and efficacy of co-trimoxazole, but the only patient reported as having gut GVHD was prescribed intravenous pentamidine.

Twenty-seven patients (84%) made a full recovery, of whom 11 (34% of total) required paediatric intensive care admission. There were three deaths but none of these was thought to be directly attributable to PJP.

DISCUSSION
PJP remains a rare complication of treatment for malignancy in paediatric patients. Only 32 cases were identified in all of the UK PTCs over a 2-year period. It is unlikely that any child treated for PJP with an underlying malignancy was omitted from the study due to the centralisation of UK children’s cancer services.
It is remarkably challenging to get good denominator data, but we have attempted to provide an estimate by extrapolating from recent projections of the number of children with cancer treated with systemic anticancer therapy each week UK-wide: there are approximately 1700 children undergoing chemotherapy each week in the UK, and a similar number may be assumed to receive such treatment each year. We identified 16 cases of PJP per year, giving an estimated incidence rate of 9.4 per 1000 children treated. This is likely to be an overestimate of the true incidence as it is extrapolated from Public Health England data for children aged under 16 years and we included in our study any young person treated by paediatric oncologists, even if they were 16 years or older. This may be compared with historical data from the pre-prophylaxis era of 40.8 per 1000 children treated in one US institution over 9 years.  

The number of apparent co-trimoxazole prophylaxis failures was surprising (11 patients), although only prescription, not compliance could be ascertained. Early studies of co-trimoxazole prophylaxis used daily dosing regimens and reported only one case of treatment failure. However, these early studies generally had small numbers of children (80–229). The single case of prophylaxis failure was in a child with ALL included in a prospective open study of all confirmed cases of PJP in 3314 children treated in one US children’s cancer institution over 3 years. It is difficult to directly compare the present data with historical studies as the total number of children given prophylaxis over the time period of surveillance is not known. Furthermore, these older studies may be underpowered to detect rare events, such as prophylaxis failure, or over time it is possible that pathogen resistance is emerging.

The optimal dosing schedule for prophylaxis with co-trimoxazole remains to be defined. Subsequent to the first randomised controlled trial of daily co-trimoxazole prophylaxis in children with ALL, studies demonstrated that co-trimoxazole given on 3 days per week is equally effective. More recently, other groups have confirmed the use of cotrimoxazole twice, or even once weekly, has comparable efficacy. A single case study of once-weekly prophylaxis failure in a child undergoing allogeneic SCT was reported last year and was postulated to be due to poor absorption of co-trimoxazole given gastrointestinal (GI) GVHD. GI GVHD was not reported in any of the prophylaxis failures in the present study.

Only five patients were prescribed alternative prophylaxis to co-trimoxazole in the form of dapsone or pentamidine. These are considered less efficacious than co-trimoxazole, but were prescribed due to concerns about bone marrow suppression and delayed engraftment.

Six patients with PJP (five proven, one suspected) were not given prophylaxis as it was either not thought to be indicated or was actively contraindicated by either local guidance or trial protocol (three AML and three NHL). A further two patients (one suspected infection with neuroblastoma and one proven infection with relapsed Ewing’s sarcoma) were not given any form of prophylaxis due to concerns about potential delay in count recovery post-SCT and bone marrow suppression, respectively.

In our previously published PJP prophylaxis guideline, we recommended against interrupting prophylaxis with co-trimoxazole for patients receiving autologous SCT unless there is a delay in engraftment (weak recommendation, very low quality evidence). Three studies of low or very low quality considered the frequency of neutropenia in children taking co-trimoxazole prophylaxis. Reported rates of presumed co-trimoxazole induced neutropenia were only 0.5%–2%. There exist no studies of the effect of co-trimoxazole prophylaxis on time to neutrophil recovery in children undergoing SCT. However, a retrospective case-control study of 17 adult patients showed no difference in time to engraftment following SCT if prophylaxis with co-trimoxazole was interrupted versus given continuously. The benefit of prophylaxis needs therefore to be balanced against a lack of evidence that co-trimoxazole delays engraftment.

Some centres omit co-trimoxazole in patients receiving HD methotrexate as the former is thought to delay the excetration of the latter. At the time of writing our guideline, studies on the effect of concurrent co-trimoxazole on methotrexate administration were of moderate or low quality and gave conflicting results. Given the toxicity of delayed methotrexate excetration and the challenges of treating raised methotrexate levels, the guideline development group and peer review agreed that co-trimoxazole should be withheld in patients receiving HD methotrexate. Subsequently, a good quality prospective study of methotrexate clearance and toxicity in children with ALL given HD methotrexate and thrice weekly co-trimoxazole has been published. The maximum dose of methotrexate was the same as in the UKALL 2011 trial (5 g/m² over 24 hours) but the dose of co-trimoxazole was greater (75 mg/m² per dose of trimethoprim component 12 hourly on 3 days per week, opposed to 60 mg/m² 12 hourly given in the UK on 2 days per week). No evidence was found of an interaction between methotrexate and prophylactic co-trimoxazole. In the UK where lower doses of co-trimoxazole are prescribed, it can therefore be assumed safe to continue prophylaxis in those patients receiving HD methotrexate at doses of 5 g/m² or less. Subsequently, the Cancer Research UK Clinical Trials Unit amended the UKALL 2011 trial protocol in May 2018 to recommend that patients should continue co-trimoxazole throughout protocol M and MA.

Of the three patients with NHL who did not receive any prophylaxis, two were on protocols that included methotrexate at doses >5 g/m² (8–16 g/m²). If methotrexate doses are >5 g/m², it is still prudent to withhold co-trimoxazole, but an alternative prophylaxis agent could be considered.

Children with leukaemia have historically been recognised to be high risk for PJP. An analysis of all children with PJP at a US children’s oncology centre between 1962 and 1971 (pre-prophylaxis) reported incidence rates of PJP in 7.7% (41 of 532 children) of patients with ALL and 3.5% (4 out of 113) of patients with AML and monomyelocytic leukaemia. Underestimation is probable as diagnosis was established by identification of organisms in material obtained from percutaneous transthoracic needle aspiration of the lung or autopsy. Bronchoscopy with BAL and molecular diagnosis is the current gold standard for diagnosis and is more sensitive. There is a lack of data, subsequent to this publication, on risk for children with AML. The 2016 European Conference of Infections in Leukaemia (ECIL) guidelines for PJP prophylaxis do not recommend routine prophylaxis for children with AML. The MyeChild protocol, in agreement with the ECIL guidelines, only recommends PJP prophylaxis for those patients receiving fludarabine. In our study, three patients with AML who had not received fludarabine had shown PJP and had not been given any prophylaxis. Lymphocyte counts alone are considered a poor indication of PJP risk in children treated for malignancies. However, we identified only two patients at PJP diagnosis with a lymphocyte count below the lower limit of normal (1.5 x 10⁹/L) (see figure 2). As data were not collected on patients without PJP, a direct assessment of attributable risk cannot be made, but the finding remains supportive of lymphopenia being a risk factor.

There were no deaths directly attributable to PJP in this surveillance study, in contrast to high published mortality rates

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of 20%–40% in patients without HIV. These data are not contemporary and are largely drawn from adult populations. Paediatric studies are historical: the 1973 analysis found a mortality rate of 32% in 41 children with malignancies and PJP treated with intravenous pentamidine. A 1975 study of children with ALL found a mortality rate of 21% for those treated with intravenous pentamidine and 11% for those treated with co-trimoxazole. All the patients in the present study received the current standard treatment: HD intravenous co-trimoxazole. Pentamidine is less effective as a treatment and other aspects of supportive care have improved in recent years. Due to more sensitive diagnostic methods and improved awareness of PJP risk, diagnosis is probably made more promptly than in the past. Early treatment may contribute to the improved survival in our cohort. Half of the patients in our series made a full recovery without intensive care support.

CONCLUSION
PJP in children treated for malignant disease is rare, with only 32 suspected or confirmed cases detected in the UK over a 2-year period. There were no deaths directly attributable to PJP, in contrast to previously published high mortality rates. Breakthrough infection despite prescribed prophylaxis with co-trimoxazole may represent pathogen resistance or non-compliance with prophylactic therapy. Six infections occurred in patients for whom prophylaxis was not thought to be indicated and in a further two patients for whom no prophylaxis was prescribed due to concerns about toxicity. Further consideration of the use of PJP prophylaxis during AML and NHL treatment is warranted, alongside appraisal of the clinical implications of the possible narrow suppressive effects of co-trimoxazole and its interactions with methotrexate.

Twitter Bob Phillips @dbobphilips

PJP Surveillance Group Carla Kierulf, Aberdeen; Carole Cairns, Belfast; Beryl Rodrigues, Birmingham; Gitanya Naidoo, Bristol; Michael Gattens, Cambridge; Madeleine Adams, Cardiff; Cormac Owens, Dublin; Emma Johnson, Edinburgh; Jairam Sastry & Diana McIntosh, Glasgow; Danny Cheng, GOSH, London; Charlotte Leger, UCLH, London; Simon Bomken, Newcastle; Sophie Wilne, Nottingham & Leicester; Amrana Qureshi, Oxford; James Hayden, Liverpool; Anthony Penn, Manchester; Rubina Malik, Royal Marsden, Surrey; Dan Yeomanson, Sheffield; Jessica Bate, Southampton.

Contributors Both authors conceived the idea for the study. RHP wrote the proposal, approved by BP, for the Children’s Cancer and Leukaemia Group and helped establish key contacts in each PTC. RHP and BP both worked on the proforma for data collection. RHP collected and analysed all the data.

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ORCID iDs
Rebecca Hilary Proudfoot http://orcid.org/0000-0001-8770-2969
Bob Phillips http://orcid.org/0000-0002-4938-9673

Figure 2 Lymphocyte counts at presentation.
Original research

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Hypertrichosis is hair growth abnormal for age, sex or race or for a particular body part. It must be distinguished from hirsutism, which is male pattern hair growth in a female or child. Hypertrichosis is classified based on age of onset (congenital vs acquired), distribution (localised vs generalised) and type of hair (vellus vs terminal).

A growth-restricted female infant required a high glucose delivery rate of 14 mg/kg/min to maintain normoglycaemia. Hyperinsulinaemia was confirmed on day 6 and diazoxide was commenced as the first-line pharmacological agent for hyperinsulinism. Excessive facial hair was noted at 6 weeks post discharge (figure 1). Diazoxide was slowly weaned off and hirsutism resolved by 6 months of age (figure 2).

Besides diazoxide, several drugs for example, phenytoin, acetazolamide, minoxidil, streptomycin, ciclosporin and syndromes such as Cornelia de Lange and Rubinstein-Taybi are known to cause generalised hypertrichosis. It is postulated that diazoxide results in hypertrichosis secondary to action on potassium-gated channels in the skin. This side effect is related to the dose and duration of treatment and discontinuation results in resolution within 6 months.

Hypertrichosis can cause significant emotional distress for the patient and their family. It is important to explain this reversible side effect to parents prior to initiating treatment with diazoxide.