

**Guidelines for the prophylaxis of *Pneumocystis Jirovecii* Pneumonia (PJP)**

**in Children with Solid Tumours**

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Table of Contents

1. Executive summary 4

2. Introduction and background 6

Table 1: PJP attack rates in solid tumours 8

Current practice in UK CCLG centres 10

*Table 2: Summary of current practice in UK CCLG centres* (27) 10

3. Scope 11

4. Methods (see appendix C) 12

5. recommendatons 13

Identifying who is at risk 13

Corticosteroids 13

Temozolamide (TMZ) 14

Radiotherapy (RT) 14

Rituximab 14

Underlying lung pathology 14

Previous PJP infection 15

Comparison of Alternative PJP Prophylaxis Regimes 16

6. Other Considerations 18

G6PD deficiency 18

Potential for the development of resistant isolates 18

7. Research Recommendations 20

8. Glossary 21

9. Acknowledgements 22

10. Appendices 22

Appendix A: Drug doses, adverse effects & costs 23

Appendix B – Guideline Development Group 24

Disclosure of potential conflicts of interest: 24

Appendix C – Methods 25

How this Guideline was Developed: 25

Developing the Clinical Questions and Outcomes 25

Developing Recommendations and Stakeholder Review 25

Updating the Guideline 25

Funding 26

Summary of Review Questions and Outcomes 27

Searching for Evidence 32

Search strategy: 32

Appendix D: Structured clinical questions and answers identified in literature review 34

1. Background risk of PJP (*Pneumocystis jirovecii* Pneumonia) 34

PJP attack rates in paediatric solid tumours 34

Prevalence studies of PJP 34

2. Effectiveness of PJP prophylaxis 38

Studies on PJP prophylaxis efficacy 38

Studies of different co-trimoxazole regimens 42

3. Benefit v risk of PJP prophylaxis 45

Studies of alternatives to co-trimoxazole 46

4. Use of lymphocyte/CD4 counts as a marker of risk 47

5. Corticosteroids and brain tumours 47

7. Rituximab and other immunomodulating agents 48

8. Underlying lung pathology 49

9. Previous PJP 50

10. Myelosuppression with co-trimoxazole 50

11. Methotrexate (mtx) 51

12. Potential for development of resistant isolates 52

13. G6PD deficiency 52

Appendix E: Grading the Quality of Evidence 53

Appendix F: GRADE profiles for outcomes identified from the literature review: 56

Appendix G: Consensus Survey & Results 74

11. References 77

# Executive summary

|  |  |
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| **Recommendation** | **Strength of Recommendation[[1]](#footnote-1)** |
| 1. We suggest PJP prophylaxis is offered to all children with solid tumours undergoing treatment that is likely to render them lymphopaenic unless there are clear contraindications. | Consensus |
| 2. First line prophylaxis should be with co-trimoxazole | Strong recommendation, Moderate quality evidence |
| 3. Co-trimoxazole prophylaxis should be given twice weekly in dosage according to surface area (see [appendix A](#_Appendix_A:_)). | Strong recommendation,  Low quality evidence |
| 4. For patients intolerant of co-trimoxazole the choice of alternative prophylaxis is controversial. This decision should be made according to patient and physician preference and experience.  The risk/benefit of any prophylaxis at all should be re-evaluated on an individual basis as alternative drugs are all associated with poorer efficacy and increased toxicity and expense. | Weak recommendation,  Very low quality evidence |
| The following children should not receive PJP prophylaxis with co-trimoxazole: | |
| 5. Children undergoing treatment with high dose methotrexate | Weak recommendation,  Very low quality evidence |
| 6. Confirmed allergy to co-trimoxazole | Strong recommendation,  Very low quality evidence |
| For children undergoing autologous stem cell transplant: | |
| 7. Unless specifically mandated by a trial protocol, do not interrupt prophylaxis with co-trimoxazole unless there is a delay in engraftment | Weak recommendation,  Very low quality evidence |
| 8. If prophylaxis with co-trimoxazole is interrupted recommence once neutrophil count is >1 x109/litre | Consensus |
| 9. The duration of prophylaxis is uncertain – a pragmatic choice is to continue until 6 months after stem cell transplant, as long as the lymphocyte count has returned to normal. | Weak recommendation,  Very low quality evidence |
| 10. Children who are immunocompromised due to treatment for a solid malignancy should receive prophylaxis against PJP from the start of treatment. | Weak recommendation,  Low quality evidence |
| 11. The Duration of prophylaxis is uncertain  A pragmatic choice is to continue until 3 months after the end of treatment (or 6 months following stem cell transplant), as long as the lymphocyte count has returned to normal. | Weak recommendation,  Very low quality evidence |

# 2. Introduction and background

*Pneumocystis jirovecii*, previously known as *Pneumocystis carinii*[[2]](#footnote-2), is an opportunistic parasite that causes pneumonia (PJP) in immunocompromised hosts. *P. jirovecii* was originally thought to be a protozoan but more recent molecular studies have revealed greater homology to fungi (1). Most immunocompetent children acquire asymptomatic infection with *P. jirovecii* by the age of 4 years (2,3), whilst symptomatic disease occurs almost exclusively in severely immunocompromised hosts.

Pneumocystis has been recognized as a cause of pneumonia since the 1940s when epidemics of ‘plasma cell pneumonia’ were diagnosed in malnourished and premature infants in care homes in Eastern Europe (4). In the 1960s, as immunosuppressive therapy for malignancy became more widespread, the incidence of PJP increased. In the 1980s PJP was the first opportunistic infection associated with the newly recognised Acquired Immunodeficiency Syndrome (AIDS)(5,6). Even with prompt antimicrobial treatment, PJP has a high mortality rate (7) but prophylaxis with co-trimoxazole is safe, effective and inexpensive (8).

With the implementation of antiretroviral therapy and PJP prophylaxis the incidence of PJP associated with the Human Immunodeficiency virus (HIV) has sharply declined (9), whereas that associated with treatment for malignancy in non-HIV infected hosts has increased (10,11).

Before the routine use of prophylaxis, Hughes et al estimated a PJP infection rate in children with acute lymphoblastic leukaemia (ALL) as 22-43%, depending on the stage of the disease, and 25% in children treated for rhabdomyosarcoma (RMS)[[3]](#footnote-3) (12,13). Successful PJP chemoprophylaxis with daily co-trimoxazole was demonstrated in a randomised placebo-controlled trial (RCT) in children undergoing treatment for these 2 diseases (12). The incidence of PJP over a 2-year period in the placebo group was 21%, whereas there were no cases of PJP in the daily co-trimoxazole group. Later Hughes at al demonstrated that co-trimoxazole given on 3 days per week was equally effective (8) and more recently other groups have confirmed the use of cotrimoxazole for 2 days (14,15), or even just one day per week (16) has similar efficacy.

The use of cotrimoxazole for PJP prophylaxis is well established for children receiving treatment for ALL and bone marrow transplantation. (17,18) However evidence – based recommendations for children treated for solid malignancies are less certain. A 2007 Cochrane review found only 11 RCTs addressed PJP prophylaxis in non-HIV immunocompromised hosts. Of which, just 5 included children, all of whom were undergoing treatment for acute leukaemia. (19) The review concluded that co-trimoxazole prophylaxis should be considered when the risk of PJP exceeds the rate of severe adverse events associated with the drug. A severe adverse event was defined as a complication requiring discontinuation of co-trimoxazole and included leukopaenia, thrombocytopaenia and severe dermatological reactions. An adverse event rate of 3.1% in adults was described in the 11 RCTs, but no significant adverse events were identified in children receiving cotrimoxazole. Subsequent reviews and guidelines on the topic quote this ~3% risk of PJP as a threshold for advocating prophylaxis (17,20) but it cannot logically be applied to children if the adverse event rate is lower. Furthermore all the studies in the Cochrane review administered co-trimoxazole either daily or three times per week. The quoted toxicities may be lower with the equally efficacious twice-weekly regimen. (14)

One might conclude from the 2007 Cochrane review that all immunosuppressed children should be offered prophylaxis as the benefit exceeds the risk. However there are theoretical concerns regarding the development of antimicrobial resistance, hypersensitivity reactions and potential bone marrow suppression (see discussion below).

Currently little is known regarding the background PJP risk for children undergoing treatment for solid malignancies. Historical data (summarised in [table 1](#_Table_1:_PJP)) is sparse and variable and cannot account for new more intensive chemotherapy regimens that may include immunomodulating agents. New therapies and increasing survival may explain the rising incidence of PJP in the non-HIV population (10) and highlight the need to re-evaluate who is offered prophylaxis.

## Table 1: PJP attack rates in solid tumours

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Diagnosis** | **Population** | **Infection rate** | | **Reference** | **Diagnostic technique** |
| **%** | No. proven PJP/  no. cases at risk |
| Neuroblastoma\* | <19y | 0.05% | 3/58 | Perera el al, 1970 (21) | Morphological evidence by pulmonary aspirate or necropsy or both |
| Children & young people  ≤19 years | 3.8% | 3/78 | Hughes et al 1973(22) | CXR appearance and organism detected in lung aspirate |
| Hodgkin’s lymphoma | 1.3% | 1/77 |
| ‘Reticulum Cell Sarcoma’ =  Non-Hodgkin’s Lymphoma | 4% | 1/26 |
| Rhabdomyosarcoma | 25% | No figures given, origin of statistic not clear\*\* | Hughes et al 1975 & 1977 (12,13) | CXR appearance and organism detected in lung aspirate |
| <18 years | 3% | 5/159 | Wilber et al 1980 (23) | ‘Histologically confirmed’ |
| Ewing’s sarcoma | 0.9% | 1/114 |
| Neuroblastoma\* | 1.8% | 4/219 |
| Wilm’s | 0.4% | 1/261 |
| ‘lymphomas’ | 4.8% | 9/189 |
| Hodgkin’s lymphoma | 0.4% | 2/470 |
| 1-16 years | 26% | 7/27 | Cyklis & Zielinska 1983(24) | Some cases: clinical + radiological + cysts in laryngeal swabs  Some cases cysts in laryngeal swabs and *no clinical symptoms* |
| <19 years | 2% | 1/48 | Perra et al 1970 (21) | Morphological evidence by pulmonary aspirate or necropsy or both |
| Primary or metastatic brain neoplasm | 3 months – 80 years (median age 43 years) | 1.3% | 8/595 | Septkowitz et al 1992(25) | Morphological evidence in a respiratory specimen |
| ≥20 years | 1.7% | 10/587 | Henson et al 1991(26) | Morphological evidence in a respiratory specimen |

\*stage of disease not specified

\*\*In 1977 Hughes et al (12) write that they previously identified an attack rate of 25% in RMS patients treated with cyclophosphamide, adriamycin, dactinomycin and vincristine. They do not give any further details and reference their own previous paper where no mention of RMS is given (13). Consequently this figure should be interpreted with caution.

## Current practice in UK CCLG centres

Only 6 of the 20 UK CCLG centres currently have local guidelines for PJP prophylaxis. In most units prophylaxis tends to be given at the discretion of individual consultants and varying doses are used from daily to two or three times per week (27).

## *Table 2: Summary of current practice in UK CCLG centres* (27)

|  |  |
| --- | --- |
| **Number of Responses** | 20 (100%) |
| **Number of centres with a PJP guideline** | 6 (30%) |
| **Number of centres using co-trimoxazole dosing regimes other than twice weekly based on surface area** | 4 (20%) |

# 3. Scope

|  |  |
| --- | --- |
| Purpose: | Guidelines on the indications and methods for prophylaxis against *Pneumocystis Jirovecii* Pneumonia (PJP) in Paediatric Oncology Patients. |
| Target population: | Children ≤19 years of age undergoing treatment for solid malignancies. |
| Exclusion criteria: | Adults undergoing treatment for solid malignancies.  Children ≤19 years who are immunocompromised for reasons other than treatment for a solid malignancy. |
| Healthcare Setting: | Tertiary paediatric oncology units and 'shared care' centres in District General Hospitals. |
| Types of interventions: | Antibiotic prophylaxis with co-trimoxazole and alternatives, including atovaquone, pentamidine and dapsone. |
| Key Stakeholders: | Children's Cancer and Leukaemia Group (CCLG)  UK CCLG treatment centres  Paediatric oncology patients |
| Existing documents: | None |

# 4. Methods (see [appendix C](#_Appendix_C_–))

This guideline was developed in accordance with the methods outlined in the CCLG guideline development standard operating procedure, version 5. See [appendix C](#_Appendix_C_–_1) for details.

# 5. recommendatons

1. **We suggest PJP prophylaxis is offered to all children with solid tumours undergoing treatment that is likely to render them lymphopaenic unless there are clear contraindications**

*(Consensus recommendation).*

## Identifying who is at risk

Identifying which children are specifically at risk of PJP infection is difficult. In adults and older children with HIV the risk of PJP inversely correlates with the CD4+ T lymphocyte count and HIV positive patients are offered prophylaxis at CD4 counts persistently below 200 cells/μl (28). There is no clear equivalent biological marker to guide practice in HIV negative patients. Although some authors have suggested using CD4 counts or total lymphocyte counts for this purpose (29,30), lowering of these indices is not consistently associated with PJP infection in immunocompromised patients without HIV (30–32). Furthermore most of these studies have excluded paediatric patients and lack sufficient statistical power. The lymphocyte count is unlikely to be a reliable predictor of risk in immunocompromised HIV negative infants and young children because, unlike older children and adults, HIV positive infants can develop PJP at CD4 counts well in excess of 200 cells/μl (33).

Nine studies (12,13,21–26) (see [Table 1](#_Table_1:_PJP_1)) identified PJP infection in 0.05 to 26% of children undergoing treatment for a solid malignancy. Studies varied in the definition of infection and not all children were symptomatic. Some cases were identified at post mortem and it is not clear whether PJP was the underlying cause of death. Nonetheless these studies do confirm that children undergoing treatment for solid tumours are at risk of PJP infection and therefore the guideline development group (GDG) felt that it is appropriate to offer these children PJP prophylaxis.

### Corticosteroids

Corticosteroids were identified as a risk factor in 4 studies (25,26,32,34) of low or very low quality. There are no prospective trials.

In a review of 264 case reports of PJP in non-HIV adults at a tertiary centre in the USA, corticosteroids were implicated in 90% (34). The report concluded that patients receiving corticosteroids for primary or metastatic brain neoplasm are particularly at risk for PJP and should receive PJP prophylaxis (type unspecified). A retrospective analysis of 116 adults without HIV at the Mayo Medical Centre revealed corticosteroid use in the preceding month in 90.5% of cases of PJP infection (35). The median daily dose was 30mg of prednisolone equivalent and the median duration, 12 weeks prior to the development of infection. However significant numbers of patients were diagnosed with PJP at lower steroid doses given over shorter periods. More recently Worth et al (36) analysed 14 cases of PJP in adults receiving corticosteroids for malignancy and concluded that prophylaxis should be given if ≥20mg prednisolone equivalent for longer than one month is anticipated. National Comprehensive Cancer Network (NCCN) guidelines give the same recommendation (18) and recently published guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Oncology refer to ‘long –term steroids’ without specifying a dose or duration (17). Another retrospective case review of PJP cases with primary brain tumours at a tertiary centre in New York excluded those under 20 years old as children were routinely given co-trimoxazole as prophylaxis with ‘prolonged’ steroid treatment (26).

### Temozolamide (TMZ)

The literature review did not identify any studies specifically addressing the risk of PJP infection in children taking temozolamide (TMZ) to treat brain tumours. There are numerous case reports linking the use of TMZ with PJP infection, especially with concomitant steroid use (37–40) and TMZ is known to cause profound, long-lasting lymphopaenia with selective CD4 cell depletion (38,39,41). This recommendation was peer reviewed due to lack of identified evidence and peer review supported prophylaxis.

### Radiotherapy (RT)

Radiotherapy in combination with corticosteroids and / or chemotherapy can cause profound lymphopaenia (42)[[4]](#footnote-4). There are no identified studies of the risk of PJP infection in children receiving radiotherapy in combination with steroids and/or chemotherapy. Peer review and the GDG supported prophylaxis on the basis that lymphopaenia is an identified risk factor for PJP infection.

### Rituximab

No relevant studies were identified looking at the risk of PJP in children receiving rituximab in combination with other cancer treatments (chemotherapy, radiotherapy, corticosteroids). There are case reports of PJP infection in children receiving rituximab (43–47) and in paediatric oncology rituximab is usually administered in combination with chemotherapy to treat children with malignancies at high risk of treatment failure or relapsed disease. These children are therefore likely to be immunocompromised. The GDG and peer review supported PJP prophylaxis in children treated with rituximab in combination with corticosteroids, conventional chemotherapy and/or radiotherapy.

### Underlying lung pathology

One low quality study (10) of national PJP infections found that 17.5% patients had pre-existing lung disease including tuberculosis, chronic obstructive airway disease, cystic fibrosis, bronchiectasis, asthma or interstitial lung disease. Most of these patients were adults therefore the data may not be applicable to the paediatric population. Nonetheless the GDG felt that that children with pre-existing lung disease receiving chemotherapy should be given PJP prophylaxis.

### Previous PJP infection

No studies were identified looking at PJP prophylaxis in children previously treated for PJP infection whilst being treated for a solid malignancy. However previous infection will identify a high-risk group of immunocompromised patients. Peer review and the GDG supported PJP prophylaxis for children who had a previous PJP infection.

1. **First line prophylaxis should be with co-trimoxazole (trimethoprim and sulfamethoxazole)**

*(Strong Recommendation, moderate quality evidence)*

Three studies, including one high quality systematic review (19) and two low quality cohort studies (23,48) demonstrated that co-trimoxazole is highly effective prophylaxis against PJP in immunocompromised children. The systematic review reported a 91% reduction in the occurrence of PJP and a number needed to treat of 15 to prevent one case of PJP (95% confidence interval 13-20). The rate of PJP infection in the control group was 7.5% in patients of all ages with haematological malignancies and/or following bone marrow or solid organ transplantation.

1. **Co-trimoxazole prophylaxis should be given twice weekly in dosage according to surface area (see** [**appendix A**](#_Appendix_A:_)**).**

***(****Strong recommendation, low quality evidence)*

Four studies (8,14–16) of high, low or very low quality showed that twice weekly (on consecutive or non-consecutive days), three times weekly or daily co-trimoxazole are all prevent PJP infection in children receiving chemotherapy. As all regimes are effective the GDG recommends that used in the [UKALL 2011](http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=11319) trial (twice daily on 2 consecutive days, see [appendix A](#_Appendix_A:__2)) as this regime is well tolerated and found to be highly effective in a cohort of children who historically had a PJP infection rate of 22-43% (13,49).

**4. For patients intolerant of co-trimoxazole the choice of alternative prophylaxis is controversial. This decision should be made according to patient and physician preference and experience.**

**The risk/benefit of any prophylaxis at all should be re-evaluated on an individual basis as alternative drugs are all associated with poorer efficacy and increased toxicity and expense.**

*(Weak recommendation, very low quality evidence)*

Four low or very low quality studies (50–53) demonstrate that pentamidine is effective prophylaxis against PJP although probably not as effective as co-trimoxazole. The efficacy of intravenous pentamidine is likely to be inferior to co-trimoxazole as an observational study in paediatric HIV patients had a breakthrough PJP infection rate of 6.6% (2 out of 30 patients) (54) , although there was no comparison group. Nonetheless this is concerning as breakthrough infections on co-trimoxazole are often due to non-compliance, whereas this is not an issue with intravenous pentamidine. From the available data in paediatric oncology patients nebulised and intravenous pentamidine are likely to be equally efficacious but the administration of nebulised medications to very young children is challenging.

One low quality study (55) compared co-trimoxazole, dapsone, pentamidine and atovaquone. Co-trimoxazole was most effective (PJP rate 0.004*/* person-year) when compared with dapsone (0.03 /person-year) and intravenous pentamidine (0.04 /person-year).

One moderate quality study (56) in paediatric patients treated for haematological malignancies and aplastic anaemia showed that the risk of symptomatic methaemaglobinaemia was higher with dapsone (19.8%) than the risk of PJP infection. This risk might be lower with reduction in dose frequency but the study did not address this. However none of the patients suffered a ‘major’ complication (i.e. intensive care admission or death) and methaemaglobinaemia resolved on discontinuation of dapsone.

One low quality study (57) showed that atovaquone was well tolerated in adults undergoing stem cell transplants but there was a high incidence of adverse reactions to co-trimoxazole. However the rates of adverse reactions to co-trimoxazole have consistently be reported as higher in adults than children (19). There was early discontinuation of this study so comparative efficacy could not be estimated.

### Comparison of Alternative PJP Prophylaxis Regimes

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Issue** | **Co-trimoxazole** | **Dapsone** | **Nebulised Pentamidine** | **Intravenous Pentamidine** | **Atovaquone** |
| Efficacy | High | Moderate | Moderate | Moderate | Moderate |
| Toxicity | Low | Moderate | High | High | Moderate |
| Cost | Low | Moderate | High | High | Very High |
| Risk of extrapulmonary pneumocystosis | No | No | Yes | No | No |

### 

See [Appendix A](#_Appendix_A:__3) for drug doses, adverse effects, costs and further details.

**The following children should not receive PJP prophylaxis with co-trimoxazole:**

**5. Children undergoing treatment with high dose methotrexate**

*(Weak recommendation, very low quality evidence)*

**6. Confirmed allergy to co-trimoxazole**

*(Strong recommendation, very low quality evidence)*

Two studies of moderate or low quality (58,59) looked at the effect of concurrent co-trimoxazole on methotrexate administration. These gave conflicting results. One study did not demonstrate an association between co-trimoxazole and raised methotrexate levels however the patients received intermediate dose methotrexate (0.9-3.7 g/m2). The second study showed concurrent co-trimoxazole administration resulted in a 66% increase in exposure to free methotrexate but did not assess consequent toxicity or myelosuppression. Current practice is to omit co-trimoxazole in patients receiving high dose methotrexate and, given the toxicity of delayed methotrexate excretion and challenges of treating raised methotrexate levels, the GDG and peer review felt co-trimoxazole should be withheld in patients receiving high dose methotrexate.

**In children undergoing autologous stem cell transplant:**

**7. Unless specifically mandated by a trial protocol, do not interrupt prophylaxis with co-trimoxazole unless there is a delay in engraftment**

*(Weak recommendation, very low quality evidence)*

**8. If prophylaxis with co-trimoxazole is interrupted recommence once neutrophil count is >1 x109/litre**

*(Consensus)*

**9. The duration of prophylaxis is uncertain– a pragmatic choice is to continue until 6 months after stem cell transplant, as long as the lymphocyte count has returned to normal.**

*(Weak recommendation, very low quality evidence)*

Three studies of low or very low quality (14,15,23) considered the frequency of neutropaenia in children taking co-trimoxazole prophylaxis. They reported rates of presumed co-trimoxazole induced neutropaenia of only 0.5% to 2%. There are no studies of the effect of co-trimoxazole prophylaxis on time to neutrophil recovery in children undergoing autologous stem cell transplant. 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 (60).

The above recommendations are pragmatic as peer review reached no clear consensus.

**10. Children who are immunocompromised due to treatment for a solid malignancy should receive prophylaxis against PJP from the start of treatment.**

*(Weak recommendation, low quality evidence)*

**11. The duration of prophylaxis is uncertain**

**A pragmatic choice is to continue until 3 months after the end of treatment, as long as the lymphocyte count has returned to normal, or 6 months after SCT.**

*(Weak recommendation, very low quality evidence)*

There are no studies looking at the duration of PJP prophylaxis however studies of prophylaxis efficacy observed that PJP infections occurred in children with ALL who had stopped prophylaxis during maintenance treatment (23,53). The GDG therefore recommended that prophylaxis should continue until lymphocyte recovery and advised a longer duration of prophylaxis in children post stem cell transplant as they experience a greater degree of immunosuppression.

# 6. Other Considerations

## G6PD deficiency

In individuals with Glucose-6-phosphate Dehydrogenase (G6PD) deficiency haemolysis may be triggered by oxidant drugs, which include primaquine and dapsone. Dapsone should not be given unless G6PD deficiency is excluded, especially in susceptible ethnic groups. Haemolysis can also occur with sulphamethoxazole when given at the higher intravenous doses required for treatment of PJP. Prophylactic doses of sulphamethoxazole in co-trimoxazole are not usually problematic.

## Potential for the development of resistant isolates

Trimethoprim and sulfamethoxazole inhibit 2 different enzymes involved in the bacterial synthesis of folic acid and have been shown to act synergistically in vitro (61). They were originally combined in the hope that, by acting on the same bacterial pathway, development of resistance to either component alone would be prevented. However, following widespread use in the 1970s for the treatment of urinary, respiratory and gastro-intestinal infections, widespread resistance has emerged and co-trimoxazole can no longer be recommended as empirical or first line therapy for such common indications (61,62). The use of co-trimoxazole as PJP prophylaxis has also been temporally associated with an increase in resistant strains of *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) in HIV patients (63). An RCT in renal transplant patients comparing daily co-trimoxazole versus placebo for prevention of urinary tract infections and bloodstream infections showed significantly reduced infection rates in the treatment group, but when infection did occur the isolate was more likely to show co-trimoxazole resistance (62% versus 18% for prophylaxis versus placebo, p<0.001)(64).

There is concern that the use of co-trimoxazole as prophylaxis may promote the emergence of resistant *P. jirovecii* strains. Mutations resulting in amino acid substitutions in the enzymes targeted by co-trimoxazole have been implicated in failure of prophylaxis and treatment of PJP (65,66). Thus far such treatment failures are rare but more widespread use of prophylaxis may accelerate the emergence of resistant strains.

# 7. Research Recommendations

The evidence appraisal undertaken during the development of this guideline has identified areas where further information / research is required. The GDG has identified the following research questions:

1. What is the true frequency of PJP infection in children undergoing autologous stem cell rescue and during treatment for solid tumours?
2. What is the optimal second line agent in those who cannot tolerate co-trimoxazole?
3. Does co-trimoxazole prophylaxis against PJP significantly delay time to engraftment in children undergoing autologous stem cell transplant and does it increase the neutropaenic window during the standard treatment of solid tumours?
4. For how long following treatment do patients remain at risk of PJP? I.e. How long should prophylaxis continue at the end of treatment?
5. What is the effect of concomitant co-trimoxazole administration on methotrexate levels and rates of methotrexate excretion in patients receiving high dose methotrexate? Whilst it is not advised that patients receive co-trimoxazole with high dose methotrexate there may be patients that have inadvertently received both drugs and they might provide anecdotal evidence of the effect of co-trimoxazole on the excretion rates and subsequent toxicity of high dose methotrexate.

# 8. Glossary

|  |  |
| --- | --- |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALCL | Anaplastic Large Cell Lymphoma |
| ALL | Acute Lymphoblastic Leukaemia |
| AML | Acute Myelocytic Leukaemia |
| AP | Aerosolized pentamidine |
| BMT | Bone marrow transplant |
| BNF | British National Formulary |
| CCLG | Children’s Cancer and Leukaemia Group |
| CF | Cystic fibrosis |
| COPD | Chronic obstructive pulmonary disease |
| G6PD | Glucose-6-Phosphate Dehydrogenase |
| GDG | Guideline Development Group |
| GI | Gastrointestinal |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluations |
| HD/ HL | Hodgkin’s disease/lymphoma |
| HGG | High Grade Glioma |
| HIV | Human Immunodeficiency Virus |
| HPA | Health Protection Agency |
| HSCT | Haematopoeitic stem cell transplant |
| LCH | Langerhans cell histiocytosis |
| MAT | Myeloablative therapy |
| MTX | Methotrexate |
| NBL | Neuroblastoma |
| NR-STS | Non-rhabdomyosarcoma soft tissue sarcoma |
| PCP | *Pneumocystis carinii* Pneumonia |
| PJP | *Pneumocystis jirovecii* Pneumonia |
| RCT | Randomised Controlled Trial |
| RMS | Rhabdomyosarcoma |
| RT | Radiotherapy |
| SCR | Stem cell rescue |
| SCT | Stem cell transplant |
| TB | Tuberculosis |
| WBC | White blood cell count |

# 9. Acknowledgements

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# 10. Appendices

## Appendix A: Drug doses, adverse effects & costs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Dose Calculation** | | **Route** | **Frequency** | **Adverse Effects** | **Cost for 40Kg child per week** (67) |
| **Surface area** | **Dose** |
| Co-trimoxazole | <0.5m2 | 24mg/kg | oral | Twice Daily on 2 consecutive days per week | Fever, rash, transaminase elevation  GI intolerance, cholestatic hepatitis, renal failure and hyperkalaemia, pruritus, photosensitivity, Stevens-Johnson syndrome, potential bone marrow suppression | Tablets  £0.45 |
| 0.5-0.75m2 | 240mg |
| 0.76-1m2 | 360mg | Suspension  £0.88 |
| >1m2 | 480mg |
| Pentamidine | Age 5-18y | 300mg | nebulised | Once every 4 weeks | Cough, wheezing, extrapulmonary pneumocystosis, nephrotoxicity (25–50%), hypoglycaemia and hyperglycaemia, GI intolerance, hypotension, bone marrow suppression, electrolyte abnormalities  Teratogenic – risk to staff | £7.94\* |
| All ages | 4mg/kg  max 300mg(50) | Intravenous | Once every 4 weeks | Risk of cardiac arrest if given as rapid infusion (<60 minutes)  Allergy: hives, tachypnoea, subjective shortness of breath and hypoxaemia (incidence 8.5%) | £4.24\*\* |
| Dapsone | Age 1 month- 18y | 2mg/kg  max 100mg | oral | Once daily | Fever, rash, GI upset, methemoglobinemia (almost 20%), hemolytic anaemia (check for G6PD deficiency) | £14.90\*\*\* |
| Atovaquone | No recommended dose in BNF  30mg/kg once daily (max 1500mg/day) used in a study from USA  30mg/kg daily recommended in UKALL2011 trial protocol | | oral | Once daily | GI intolerance due to diarrhoea, rash and headache found in trials for the treatment of PJP  No treatment-limiting complications occurred in the 16 patients randomised to receive atovaquone as prophylaxis post SCT in a RCT in adults | £120.52 |

\*Does not include cost of nebulisation \*\*If 300mg vials cannot be split and used for another patient, the cost would be £7.94/week. Does not include cost of delivering IV infusion \*\*\*This is the cost for 100mg/day as the tablets come in only 50 and 100mg strengths

## Appendix B – Guideline Development Group

**Guideline Development Group Members**

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### Disclosure of potential conflicts of interest:

None

## Appendix C – Methods

### How this Guideline was Developed:

This guideline was developed in accordance with the methods outlined in the CCLG guideline development standard operating procedure, version 5 which has been developed according to Institute of Medicine guidelines.

### Developing the Clinical Questions and Outcomes

The guideline objectives were broken down into several clinical questions structured in the PICO format (patient and problem, intervention, comparison, outcomes).

See <http://www.usc.edu/hsc/ebnet/ebframe/PICO.htm>.

The clinical questions were then circulated around the Guideline Development Group (GDG) for approval before using as a basis for a systematic search of the published literature.

Due to a paucity of relevant studies the initial literature search was expanded to include adult data. In total 163 references were found. After discarding review articles, case reports, letters and irrelevant studies 34 titles were analysed (24 retrospective studies/reviews, 5 prospective surveys, 1 systematic review/meta-analysis (haematology patients only), 2 non-blinded RCTs (1 haematology patients only), 1 double blinded RCT (haematology and RMS patients only) and 1 unstructured prospective trial).

### Developing Recommendations and Stakeholder Review

Recommendations were drawn from the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical evidence was of poor quality or absent, the GDG drafted recommendations based on their expert opinion. Recommendations based on expert opinion alone were peer reviewed by the CCLG members using a formal consensus process (Delphi process) alongside a link to the full draft guideline. See [Appendix G](#_Appendix_G:_Consensus). The considerations for making consensus-based recommendations include the balance between potential harms and benefits, economic or cost implications compared to the benefits, current practices and patient preferences.

### Updating the Guideline

A formal review by the CCLG will be undertaken in 3 years’ time to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

### Funding

Provided by the CCLG.

### Summary of Review Questions and Outcomes

|  |  |  |
| --- | --- | --- |
| **Topic** | **Structured Clinical Question** | **Outcomes** |
| 1. **Background risk of PJP** | **Patients:** Children up to 19 years of age with solid malignancies  **Intervention:** undergoing chemotherapy +/- radiotherapy  **Outcome**: what is the risk of PJP?  **Control:** compared to the normal population | * Prevalence of PJP infection in children undergoing treatment for solid tumours |
| 1. **Effectiveness of PJP prophylaxis** | **Patients:** Children up to 19 years of age with solid malignancies undergoing chemotherapy +/- radiotherapy  **Intervention:** Does PJP prophylaxis with   1. co-trimoxazole 2. pentamidine 3. atovaquone or 4. dapsone   **Outcome**: prevent PJP  **Control:** compared with no prophylaxis. | * PJP infection in children receiving co-trimoxazole prophylaxis undergoing treatment for solid tumours * Effectiveness of pentamidine in preventing PJP infection in children * Effectiveness of atovaquone in preventing PJP in paediatric patients |
| **Patients:** Children up to 19 years' of age with solid malignancies undergoing chemotherapy +/- radiotherapy  **Intervention:** Does PJP prophylaxis with twice weekly co-trimoxazole  **Outcome**: prevent PJP  **Control:** compared with daily or thrice weekly co-trimoxazole | * Incidence of PJP infection in children undergoing treatment for solid tumours receiving co-trimoxazole 3 days per week v 2 days per week v one day per week |
| 1. **Benefit v risk of PJP prophylaxis** | **Patients:** In children up to 19 years of age with solid malignancies undergoing chemotherapy+/- radiotherapy with a low risk of PJP  **Intervention:** Does PJP prophylaxis with   1. co-trimoxazole 2. aerosolized pentamidine 3. atovaquone or 4. dapsone   **Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)  **Control:** compared with no prophylaxis. | * Comparison of effectiveness of co-trimoxazole, dapsone, pentamidine and atovoquone in preventing PJP in paediatric patients undergoing treatment for solid tumours * side effects of dapsone (risk versus benefit) in the prevention of PJP in paediatric patients undergoing treatment for solid tumours * Atovaquone versus co-trimoxazole for the prevention of PJP in paediatric patients undergoing treatment for solid tumours |
| 1. **Use of lymphocyte/CD4 counts as a marker of risk** | **Patients:** In children up to 19 years of age with solid malignancies undergoing chemotherapy+/- radiotherapy  **Intervention:** can lymphocyte and/or CD4 counts  **Outcome**: predict risk of PJP? | * Use of CD4 or lymphocyte counts to predict risk of PJP in paediatric patients undergoing treatment for solid tumours |
| 1. **Corticosteroids and brain tumours** | **Patients:** In children up to 19 years of age with brain tumours undergoing treatment with corticosteroids  **Intervention:** Does PJP prophylaxis  **Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)  **Control:** compared with no prophylaxis | * Risk/benefit of PJP prophylaxis in children with brain tumours undergoing treatment with corticosteroids |
| 1. **Temozolomide** | **Patients:** In children up to 19 years of age with solid malignancies undergoing treatment with temozolomide  **Intervention:** does PJP prophylaxis  **Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)  **Control:** compared with no prophylaxis. | * Risk/benefit of PJP prophylaxis in children being treated with temozolomide |
| 1. **Rituximab and other immunomodulating agents** | **Patients:** In children up to 19 years of age solid malignancies undergoing treatment with immunomodulating agents  **Intervention:** Does PJP prophylaxis  **Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)  **Control:** compared with no prophylaxis. | * Risk/benefit of PJP prophylaxis in children undergoing treatment with rituximab and other immunomodulating agents |
| 1. **Underlying lung pathology** | **Patients:** In children up to 19 years of age with solid malignancies and underlying chronic lung disease  **Intervention:** Undergoing chemotherapy +/- radiotherapy  **Outcome**: What is the risk of PJP?  **Control:** compared to children up to 19 years of age with solid malignancies but healthy lungs | * Does underlying lung pathology increase the risk of PJP in paediatric patients undergoing treatment for solid tumours? |
| 1. **Previous PJP** | **Patients:** In children up to 19 years of age with solid malignancies who have had previous PJP infection  **Intervention:** undergoing chemotherapy +/- radiotherapy  **Outcome**: What is the risk of PJP?  **Control:** compared to children up to 19 years of age with solid malignancies who have had not had previous PJP infection | * Does previous PJP increase the risk of repeat infection? |
| 1. **Myelosuppression with co-trimoxazole** | **Patients:** In children up to 19 years of age with malignancies undergoing chemotherapy +/- radiotherapy  **Intervention:** Does PJP prophylaxis with co-trimoxazole  **Outcome**: cause clinically significant myelosuppression  **Control:** compared with no prophylaxis. | * Myelosuppression with co-trimoxazole |
| **Patients:** In children up to 19 years of age with malignancies undergoing chemotherapy +/- radiotherapy  **Intervention:** Does PJP prophylaxis with twice weekly co-trimoxazole  **Outcome**: cause clinically significant myelosuppression  **Control:** compared with thrice weekly or daily co-trimoxazole |
| 1. **Methotrexate** | **Patients:** In children up to 19 years of age with malignancies undergoing treatment with methotrexate  **Intervention:** Does PJP prophylaxis with co-trimoxazole  **Outcome**: cause clinically significant increased rates of methotrexate toxicity  **Control:** compared with no prophylaxis. | * Increased methotrexate toxicity with co-trimoxazole |
| 1. **Potential for development of resistant isolates** | **Patients:** In children up to 19 years of age with malignancies  **Intervention:** Does PJP prophylaxis with co-trimoxazole  **Outcome**: cause an increase in resistant strains of PJP  **Control:** compared with no prophylaxis. | * Emergence of PJP infections resistant to co-trimoxazole |
| 1. **G6PD deficiency** | **Patients:** In children up to 19 years of age with malignancies and G6PD deficiency  **Intervention:** Does PJP prophylaxis with co-trimoxazole  **Outcome**: cause haemolysis  **Control:** compared with no prophylaxis. | * Haemolysis with co-trimoxazole |

### Searching for Evidence

An information specialist (see acknowledgements) undertook the evidence search. Medline, Embase, Cochrane Library, TRIP & NHS Evidence were searched, no date limits were applied, language was limited to English, French, Spanish. Literature reviews, letters and editorials and unpublished studies were excluded. Some potentially relevant adult studies were included after repeating the literature search to encompass all ages due to a paucity of paediatric data.

The search terms were generated from the structured clinical questions and are shown below.

Note: *Pneumocystis* species demonstrate a high degree of host species specificity. Those infecting humans have been named *P. jirovecii*, whilst *P. carinii* refers to those infecting rats. Previously *P. carinii* was thought to infect humans and therefore to ensure identification of all relevant evidence both *P. jirovecii* and *P. carinii* were included as search terms.

### Search strategy:

1. (infant? or infancy or baby or babies or child\* or schoolchild\* or boy? or girl? or p?ediatric? or teenage\* or adolescen\* or youth? or juvenile?).mp.

2. Langerhans cell histiocytosis/

3. neuroblastoma/

4. exp glioma/

5. retinoblastoma/

6. nephroblastoma/

7. exp sarcoma/

8. Hodgkin disease/

9. exp brain tumor/ or exp central nervous system tumor/

10. bone cancer/

11. solid tumor/

12. (langerhans adj3 histiocytosis).ti,ab.

13. (glioma\* or neuroblastoma\* or retinoblastoma\* or nephroblastoma\* or wilm\* tumo?r? or medulloblastoma\*).ti,ab.

14. (rhabdomyosarcoma\* or osteosarcoma\* or sarcoma\*).ti,ab.

15. (hodgkin\* adj3 (lymphoma\* or disease)).ti,ab.

16. ((brain or cerebral or cerebrovascular or cvs or central nervous system or cns) adj3 (tumo?r? or cancer? or neoplas? or malignan\*)).ti,ab.

17. (bone adj3 (tumo?r? or cancer? or neoplas? or malignan\*)).ti,ab.

18. (solid adj3 (tumo?r? or cancer? or neoplas? or malignan\*)).ti,ab.

19. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. 1 and 19

21. ((infant? or infancy or baby or babies or child\* or schoolchild\* or boy? or girl? or p?ediatric? or teenage\* or adolescen\* or youth? or juvenile?) adj5 (tumo?r? or cancer? or neoplas? or malignan\*)).ti,ab.

22. ((infant? or infancy or baby or babies or child\* or schoolchild\* or boy? or girl? or p?ediatric? or teenage\* or adolescen\* or youth? or juvenile?) and (tumo?r? or cancer? or neoplas? or malignan\*)).ti.

23. childhood cancer/

24. 20 or 21 or 22 or 23

25. pneumocystis/ or Pneumocystis pneumonia/ or pneumocystis carinii/ or pneumocystis jiroveci/

26. (pneumocystis adj3 (carinii or jiroveci)).ti,ab.

27. (p carinii or p jiroveci).ti,ab.

28. (pneumocystis adj5 pneumonia\*).ti,ab.

29. pneumocystis.ti.

30. 25 or 26 or 27 or 28 or 29

31. 24 and 30

32. prophylaxis/ or prevention/ or infection prevention/

33. (prophyla\* or prevent\*).ti,ab.

34. 32 or 33

35. 31 and 34

36. Pneumocystis pneumonia/pc [Prevention]

37. 24 and 36

38. 35 or 37

39. 31 not 38

Evidence analysis

The lead author:

* Identified potentially relevant studies from the search results by reviewing titles, abstracts and full papers
* Critically appraised relevant studies
* Extracted key outcomes into evidence tables

## Appendix D: Structured clinical questions and answers identified in literature review

### Background risk of PJP (*Pneumocystis jirovecii* Pneumonia)

**Patients:** Children up to 19 years of age with solid malignancies

**Intervention:** undergoing chemotherapy +/- radiotherapy

**Outcome**: what is the risk of PJP?

**Control:** compared to the normal population

#### PJP attack rates in paediatric solid tumours

See [Table 1](#_Table_1:_PJP_2)

#### Prevalence studies of PJP

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Paper** | **Design** | **Study population** | **Results** | **Summary** |
| (68)  Brown et al 2013 | Single institution retrospective review | Patients who underwent autologous SCR for malignant brain tumours at a Children’s Hospital between 1988-2010.  Only those without prior irradiation who were free of disease at 1 year without additional chemotherapy were evaluated. N=43, age range 0.8-19.8y | 14 episodes of bacteraemia  No fungal or pneumocystis infections  All patients were given PJP prophylaxis but duration and drug regimens varied. These included co-trimoxazole, dapsone, atavoquone or pentamidine (iv or aerosolized) and was started after day +42.  Median length of post-transplantation PJP prophylaxis was 7.7 months (0.8-11.9 months; n=38) with 8 patients still on prophylaxis at the end of follow up at 1y. | All patients received PJP prophylaxis but the duration and drug regimen varied. No details regarding drug doses and frequency given.  There were no cases of PJP but the numbers in the study are too small and the prophylaxis regimes too varied to determine either the background risk of PJP or the efficacy of prophylaxis. |
| (24)  Cyklis & Zielinkska 1983 | Observational study | Children aged 1-16y treated at Krakow haematology hospital Jan 1974- December 1980 | 7 out of 27 children (26%) with NHL were diagnosed with PCP. Results are combined with those of children with acute leukaemia, where 28 cases were diagnosed by clinical and radiological features plus cysts found in laryngeal swabs. However 8 cases of PCP were diagnosed by cysts in laryngeal swabs only and *no clinical symptoms*. | Unknown number of cases within the NHL group with PCP diagnosed by throat swab only, and no clinical symptoms. This implies carriage and not disease therefore the study is unreliable and cannot be used to determine a PCP rate for NHL patients. |
| (26)  Henson et al 1991 | Retrospective review | All histologically documented episodes of PJP in adult patients ≥ 20y with primary brain tumours treated at Memorial Sloan-Kettering Cancer Centre 1981-1989 | PJP was histologically documented 11 times in 10 patients. During same period approx. 587 adults were seen at the centre for a brain tumour.  At least 1.7% (10/587) developed PJP.  40% mortality  All the patients with PJP were receiving dexamethasone with a median duration of 2.75 months (5-9.5 months) at the onset of infection.  At the time of diagnosis the daily dose ranged from 2-60mg | PJP attack rates in adults with brain tumours are approximately 1.7%. All cases of PJP received corticosteroid treatment.  All paediatric patients excluded from the study because they were routinely treated with prophylactic co-trimoxazole during the study period. |
| (22)  Hughes et al 1973 | Retrospective review | 51 cases PJP in children with malignancies, out of total 1251 children with malignancies who were admitted and treated at St Jude Children’s Research Hospital 1962-1971.  Age of patients with PJP 4 months-19y, with median 6.2y. | Malignancies in children with PJP included HD, NBL, reticulum cell sarcoma and Letterer-Siwe disease (LCH) (51 cases out of a total of 872 children with these diseases).  PJP in 6.5% (45/684) of children with leukaemia, 1.3% (1/77) with HD, 3.8% (3/78) with NBL, 4% (1/26) with reticulum cell sarcoma and 14% (1/7) with Letterer-Siwe disease  Diagnosis by identification of organisms in material removed by percutaneous transthoracic needle aspiration from infected lung.  41 patients were treated with pentamidine and 28 recovered (68%) | Retrospective review in one institution of prevalence rates of PJP in paediatric oncology patients pre-prophylaxis.  Rates for solid tumours are summarized in table 1 above but the numbers are small. |
| (13)  Hughes et al 1975 | Surveillance study of effects of intensity of chemotherapyon incidence of PJP | Children with ALL randomized in a prospective study to receive gradations of chemotherapy agents, January 1972 – September 1974.  All received treatment with prednisolone, vincristine and asparaginase and cranial irradiation plus intrathecal methotrexate. Following cranial irradiation the patients were randomized to receive 1 of 4 maintenance therapies for 2-3y | PJP occurred in 29 (16%) of 180 patients.  The 4 drug maintenance regimen was associated with an incidence of PJP 4.5 times that of the one drug regimen (methotrexate only). Incidences of PJP in the 2 and 3 drug regimens were not significantly different form the one drug regimen.  The difference between the 3 and 4 drug regimen was the addition of cytarabine.  However some patients with more extensive malignancy did not receive cytarabine, but mediastinal irradiation in addition to maintenance with 3 chemotherapy agents. This group had the highest incidence of PJP. | Generally more intensive chemotherapy regimens are associated with higher risk of PJP.  This study only included children with ALL and all were treated with cranial irradiation and protocols that vary from those used today. |
| (12)  Hughes et al 1977 | Randomized double blind placebo controlled over 2y | 160 patients, 80 in each group.  9 months-24y  Patients selected as high risk for PJP (>15% attack rate) according to previous observational study.  136 ALL  17 with RMS  7 ‘other’.  Daily co-trimoxazole v placebo | PJP developed in 17 (21%) of patients in placebo group and none of the patients in the treatment group.  Diagnosis was by identification of organisms in fluid obtained by needle aspiration of the lung or at autopsy.  P<0.01  No difference in adverse events between 2 groups | Rate of PJP in placebo group was 21% (17 out of 80 patients, 70 of whom had ALL, 7 RMS and 3 ‘other’ malignancies). The underlying diagnoses of the patients who contracted PJP are not described. |
| (21)  Perera et al 1970 | Retrospective review of hospital-associated outbreak of PJP | Children <19y with malignancies at St. Jude’s Research Hospital, March 1968-August 1969 | 19 cases of PJP: 14 antemortem, 5 discovered postmortem.  14 had ALL, 2 NBL, 2 lymphosarcoma, 1 stage IV HD.  All had been receiving cytotoxics +/- steroids  Aged 19 months – 10y, mean 5.5y  In addition 301 consecutive postmortem specimens of lung tissue obtained since 1962 were stained for *P. jirovecci* organisms and a further 39 cases were identified in children with cancer, none of whom had clinically diagnosed PJP pre-death.  Overall ‘attack rate’ PJP in children with malignant disease pre-prophylaxis 2.3% | Clinical PJP was frequently associated with the more intensive chemotherapeutic protocols. Most of the cases of PJP occurred after these intensive protocols were introduced in 1968.  No pattern of person-to–person spread was elucidated.  PJP attack rates for solid tumours are given in [table 1](#_Table_1:_PJP_3)   * Combined figures for clinically diagnosed and cases only discovered at autopsy * All were histologically confirmed   Significance of cases discovered at autopsy only is not clear. |
| (69)  Peters & Prakash 1987 | Retrospective review | All microbiologically confirmed cases of PJP seen at the Mayo Clinic and affiliated hospitals 1976-1983.  N=53  Average age 49y (9 months- 78y)  Only 4 children <15y | All patients had underlying disease associated with defective immunity or were receiving treatment with corticosteroids or cytotoxic drugs.  Largest group haematological malignancies  Included patients with HIV and auto-immune conditions.  12 patients (22.6%) received corticosteroids alone  diagnoses for the 4 children not given | No specific data on incidence rates or risks of PJP for children.  No information on whether prophylaxis was used. |
| (70)  Sedaghatian & Singer 1972 | Retrospective review of autopsies | 267 children with cancer who were autopsied in Texas Children’s Hospital 1954-1969.  195 leukaemias, 25 lymphomas, 29 NBL, 8 Wilm’s, 5 HD, 5 other malignant tumours. | 15 (5.6%) cases had PJP:  9 (4.6%) with leukaemia, 4 lymphoma (16%), 1 Wilms (12.5%), 1 HD (20%). Aged 3.5-14y, nine were ≤ 8y  In 12 patients the infection was extensive but in the other 3 there were only a few isolated organisms without an associated inflammatory response.  None of the patients were treated for PJP because the respiratory illness was not recognized clinically or was obscured by other prominent symtpoms.  All the patients were treated with steroids and cytotoxic agents. The leukaemic patients were all in relapse at the time of death. Four patients with solid tumours also received irradiation and all had disseminated tumour at autopsy. | Prevalance rates of PJP at autopsy given for children treated for cancer pre-prophylaxis (1954-1969).  None were diagnosed with PJP pre-death and it is not clear from the data whether the patients died of PJP or of their primary malignant disease. |
| (25)  Sepkowitz 1992 | 12 y retrospective review | 140 patients without HIV, constituting 142 cases with morphologically proved PJP  1978-1989  median age 43y (3 months – 80y)  23 patients ≤ 18y | Lymphoma 27%  Leukaemia 18%  Solid tumour 31%  BMT 18%  25 cases (18%) diagnosed at autopsy  Corticosteroid use in 87%  Only 1 patient was receiving ‘adequate’ PJP prophylaxis at the time PJP was diagnosed (BMT recipient)  Increase in PJP in solid tumours over the study period. Increase occurred specifically among patients with primary or metastatic brain neoplasm (including breast and lung primary only) with an attack rate of 1.3% during 1988 and 1989. | PJP attack rate of 1.3% in patients with primary or metastatic brain neoplasms not on prophylaxis.  Almost all of these patients were adults (exact numbers not given). |

### 2. Effectiveness of PJP prophylaxis

**Patients:** Children up to 19 years of age with solid malignancies undergoing chemotherapy +/- radiotherapy

**Intervention:** does PJP prophylaxis with

1. co-trimoxazole
2. aerosolized pentamidine
3. atovaquone or
4. dapsone

**Outcome**: prevent PJP

**Control:** compared with no prophylaxis.

#### Studies on PJP prophylaxis efficacy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Paper** | **Design** | **Study population** | | **Results** | | **Summary** |
| **Co-**  **trimoxazole** | (12)  Hughes et al 1977 | Randomized double blind placebo controlled over 2y | 160 patients, 80 in each group.  9 months-24y  Patients selected as high risk for PJP (>15% attack rate) according to previous observational study.  136 ALL  17 with RMS  7 ‘other’.  Daily co-trimoxazole v placebo | | PJP developed in 17 (21%) of patients in placebo group and none of the patients in the treatment group.  Diagnosis was by identification of organisms in fluid obtained by needle aspiration of the lung or at autopsy.  P<0.01  No difference in adverse events between 2 groups | | Daily co-trimoxazole is highly effective in preventing PJP in patients <25y with ALL.  The numbers of patients included in this study with other diagnoses are too small. |
| (23)  Wilber et al 1980 | Prospective open study with unstructured delivery system.  Adverse events related to prophylaxis collected from medical records retrospectively | 786 patients deemed by attending oncologist to be at sufficient risk for PJP over a 3 y period. Risk assessment based on age of patient, intensity of therapy and annual PJP attack rates by category of malignancy in the same institution over the period 1970-1975. Rate for leukaemia given as 6.6%, data for other tumours presented in table 1 above.  618 of 786 (79%) patients in the trial had acute leukaemia, other tumour types as per table 1.  Data on confirmed cases of PJP collected for all patients treated at the institution over the study period (n=3314).  Daily dosing used.  Upper age limit not specified but all data was on patients treated in a children’s hospital. | | 9 cases of PJP during the study period. 8 patients were in remission and on maintenance therapy and had stopped taking prophylaxis (6 ALL and 1 NHL). Only 1 case of PJP whilst on prophylaxis in a patient with ALL.  No cases in patients excluded from defined population at risk.  43 (5.4%) with presumed adverse reactions. 24 mild skin rashes but relationship to co-trimoxazole unclear as rash resolved in all but 3 cases with no recurrence when drug reinstituted.  2 cases of erythema multiforme  1 fatal case of Stevens Johnson’s syndrome  2 cases of vomiting  14 of neutropaenia/anaemia  including 1 case of PJP in patient whose prophylaxis was stopped due to neutropaenia | | Unstructured delivery of co-trimoxazole prophylaxis is feasible.  Evidence of efficacy provided by continuing decline year by year of PJP rate at the same institution (1977, 1978, 1979: 0.3%, 0.45%, 0.08% of population deemed to be at risk) and comparison with historical attack rates (6.6% for leukaemia plus data in table 1).  Generally well tolerated  Supports argument for continuation of prophylaxis throughout the duration of anticancer chemotherapy (most of the PJP cases had discontinued prophylaxis in the maintenance phase of leukaemia therapy).  Limitations:  Most of the patients in this study had ALL  Data on adverse events collected retrospectively and in some cases by local physicians (not at primary treatment centre). |
| (19)  Green et al 2007 | Cochrane review – meta-analysis of RCTs or quasi-RCTs | 1155 non-HIV immunocompromised patients (520 children)  All the children had acute leukaemia | | Compared to no treatment or treatment with fluoroquinolones there was a 91% reduction in occurrence of PJP, RR 0.09, 8 trials, 821 patients  Occurrence of leukopaenia, neutropaenia and their duration were not reported consistently.  No significant adverse events seen comparing co-trimoxazole versus no treatment/placebo (4 trials, 470 patients)  No severe adverse events recorded in paediatric patients  No differences between once daily versus thrice weekly prophylaxis (2 trials, 207 patients)  NNT to prevent one episode of PJP = 15 | | Co-trimoxazole is effective in reducing PJP in paediatric patients with ALL.  No difference in daily versus 3 days/week treatment. Trials with 2 days/week not included.  No data on paediatric or adult patients with solid malignancies. |
| (71)  Harris et al 1980 | Prospective observational study.  Not randomized. | All children with a diagnosis of cancer included in study 1977-79. Only those who received chemotherapy or extensive radiation therapy were considered to be at high risk and received prophylaxis. ALL patients received prophylaxis with daily co-trimoxazole from day 28 for a minimum of one year. All other oncology patients started prophylaxis at the start of therapy and were continued for a period of 6 months after all cancer therapy had been stopped.  Prophylaxis received by 229 patients  Solid tumours = 110  ALL = 101  Acute non-lymphocytic leukaemia (ANLL) = 18  Solid tumours considered very  low risk = 19, not given prophylaxis  High risk patients inadventently not given prophylaxis = 10 | | No cases of PJP among 229 who received daily prophylaxis with co-trimoxazole or among the 19 low-risk patients not given prophylaxis.  Compared with previous attack rate of 15 +/- 7% in the same institution over the previous few years among patients with leukaemia.  5 cases PJP in the 10 high risk patients who failed to receive prophylaxis (3 with ALL, 1 with ALL, 1 with LCH)  Incidence of rash associated with co-trimoxazole = 3.5%  One case of Stevens-Johnson syndrome, which resolved.  3 cases of suspected nausea and vomiting associated with prophylaxis (1.5%). None experienced GI discomfort when rechallenged with co-trimoxazole at a later date.  Neutropaenia well documented to be associated with co-trimoxazole in 5 patients (4.8%) | | Daily prophylaxis is highly effective in preventing PJP in children with leukaemia and is generally well tolerated.  This study provides little insight into the risk/benefit for children with solid tumours. |
|  | (8)  Hughes et al 1987 | See details under [q 2b below](#_Studies_of_different) | | | | | |
| **Pentamidine** | (53)  Orgel & Rushing 2014 | Retrospective cohort study of patients who received either  intravenous or aerosolized pentamidine (IVP v AP) for over 2 consecutive months | 0.5-21y  50% ALL  27% brain tumours  ~5% others  n=312 | No clear difference in efficacy between IVP and AP.  Only 3 cases of proven breakthrough infection, all in ALL patients on maintenance.  Not statistically significant (nos too small)  Adverse reactions AP =0.7%, IVP 8.5% | | IVP is a well-tolerated and effective alternative to AP in children unable to tolerate co-trimoxazole or aerosolized pentamidine.  This paper does not specifically answer question 2.  No cases of proven PJP in solid tumour patients. 2 ‘possible’ cases, 1 in neuroblastoma patient on palliative care and the other on treatment for high grade glioma. Both were diagnosed on clinical context and radiographic findings. No broncheoalveolar lavage was performed. No control group. | |
| (72)  DeMasi et al 2012 | Retrospective review of medical records of children who underwent HSCT during a 5.5y period who received iv pentamidine as first line PJP prophylaxis initiated at admission | 167 transplants in 137 paediatric HSCT recipients  113 (68%) autologous stem cells received  32 (19%) neuroblastoma  24 (14%) other solid tumours  Others were haematological malignancies, immunologic disorders and bone marrow failure syndromes. | No cases of PJP.  10 (7%) mild side effects (nausea/vomiting)  2 (2%) anaphylaxis and hypotension, 1 required transfer to intensive care. | | IV pentamidine is safe and probably effective for prevention of PJP in paediatric HSCT patients.  Potential advantage over co-trimoxazole as the latter drug may cause neutropaenia, although this is not a comparative or prospective study.  Numbers are too small, especially for solid tumour patients, to determine efficacy. | |
| (51)  Kim et al 2008 | Retrospective chart review of patients who received iv pentamidine as 2nd line prophylaxis over 5y period | 232 paediatric oncology patients who received at least 1 dose iv pentamidine  50% leukaemia  brain tumours 11%  sarcomas 10%  lymphomas 6%  other solid tumours 10% | 3 cases PJP (confirmed on BAL specimens)  breakthrough rate 1.3%  no significant toxicities related to iv pentamidine identified  2 of proven cases were <2y. One had undergone 2nd unrelated BMT for recurrence of leukaemia and the other autologous BMT for stage 4 neuroblastoma. | | Use of iv pentamidine results in breakthrough rate of 1.3%.  No comparison group, not prospective. | |
| **Aerosolized pentamidine**  **(AP)** | (52)  Mustafa et al 1994 | Observational study | 60 children aged 3-19y prescribed AP for allergy/ intolerance/ myelosuppression or non-compliance with co-trimoxazole. 1989-1993  46 ALL  5 AML  2 NHL  7 solid tumours (osteosarcoma, Ewing’s & undifferentiated sarcoma) | No cases of PJP  Transient cough in 15% patients  10% developed one or more episodes of bronchospasm, necessitating bronchodilator therapy  5% discontinued AP because of toxicity (2 patients with bronchospasm and one with nausea, vomiting and cough) | | Study suggests AP is effective and safe for PJP prophylaxis in children ≥ 3y  Assumptions made about incidence of PJP in solid tumours, citing a mean attack rate without of prophylaxis of 6% referencing .  Numbers of children with solid malignancies in this study too small to show efficacy of AP for PJP prophylaxis  Adverse events to AP, although frequent, are usually mild and seldom necessitate discontinuation. | |
| **Co-trimoxazole dapsone, pentamidine & atovaquone** | (55)  Prasad et al 2008 | Retrospective review of children undergoing chemotherapy and receiving PJP prophylaxis | 223 children up to 18y  HL 17 (7.6%)  NHL 25 (11.2%)  Other solid tumours 11 (4.9%)  143 given co-trimoxazole  36 dapsone, 21 inhaled pentamidine, 12 iv pentamidine, 5 oral atovoquone, 6 no prophylaxis | 4 patients with confirmed PJP (demonstration of organisms on BAL specimen)  2 died  2 were on ALL maintenance, 1 RMS treated with steroids for radiation pneumonitis, 1 AML consolidation.  Only one was taking co-trimoxazole. The other 3 were changed to alternative prophylaxis due to myelosuppresion (2) and hypersensitivity -  2 out of 12 patients on iv pentamidine developed PJP  only 1 out of 143 on co-trimoxazole and 1 out of 36 on dapsone | | Iv pentamidine 4 weekly may be inferior to other forms of PJP prophylaxis.  Results not statistically significant between dapsone and pentamidine. | |
| **atovaquone** | (73)  Madden et al 2007 | Retrospective analysis | 86 children treated for ALL or AML during 10y period who were intolerant of co-trimoxazole and received daily atovaquone | No cases of PJP | | Suggests atovaquone is effective as PJP prophylaxis.  Limited by retrospective non-comparative design  No info about side effects | |
| **dapsone** | No relevant studies | | | | | | |

b)

**Patients:** Children up to 19 years of age with solid malignancies undergoing chemotherapy +/- radiotherapy

**Intervention:** does PJP prophylaxis with twice weekly co-trimoxazole

**Outcome**: prevent PJP

**Control:** compared with daily or thrice weekly co-trimoxazole

#### Studies of different co-trimoxazole regimens

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Regime** | **Paper** | **Design** | **Study population** | **Results** | **Summary** |
| **3 d/week v daily** | (8)  Hughes et al 1987 | Prospective RCT. Not blinded (daily v 3/week allocated on basis of even v odd dates of birth)  Patients with known allergy to sulfonamides were untreated controls | 167 patients with ALL enrolled consecutively in Total Therapy Study XI at St. Jude Children’s Research Hospital (ages not specified). | Only 1 case of PJP (in the only patient who did not receive prophylaxis due previous history of allergy). | Previous RCT by the same group in similar patient cohort showed PJP incidence of 21% in placebo group, versus none in treatment group. This study suggests that prophylaxis 3 d/week is equally as effective as daily prophylaxis as there were no cases of PJP in this treatment arm.  This paper does not address the situation for children with solid malignancies. |
| **3 d/week v 2 d/week v 1 d/week** | (16)  Caselli et al 2014 | Prospective survey | Children (ages not specified) requiring chemotherapy for which PJP prophylaxis was considered indicated according to local policy (not specified)  1093 solid tumours  1371 leukaemia/lymphoma  2 primary immunodeficiencies.  20 centres in Italy participated. Each used varying co-trimoxazole regimens from 1 to 3 days per week. | 2 cases (0.08%) of proven PJP during 2 year study period.  One non-compliant with prophylaxis, the other discontinued due to side effects and was not given an alternative.  Both were on 2 d/week regimen. | Single day course of co-trimoxazole may be sufficient to prevent PCP in children with cancer undergoing intensive chemotherapy regimens.  Study probably underpowered to detect an increase in PJP in the group receiving prophylaxis on only 1 day/week (n= 689, of whom 250 were solid tumours) |
| **2 non-consecutive days per week** | (15)  Ohata et al 2009 | Retrospective analysis | 181 children who received PJP prophylaxis during chemotherapy or HSCT during 5y period:  147 received co-trimoxazole on 2 non-consecutive days/week  34 received either iv or inhaled pentamidine  included:  48 brain tumours  11 lymphomas  43 other solid tumours  plus patients with leukaemia, myelodysplasia, histiocytosis, immunodeficiency and metablic disease. | No cases of PJP  Only 1 patient discontinued co-trimoxazole due to myelosuppression | Co-trimoxazole on 2 non-consecutive days per week is probably as effective as more frequent dosing schedules and is likely to be associated with less side effects.  This is not a comparative/controlled or prospective trial and the numbers are small. |
| **2 consecutive days per week** | (14)  Lindemulder & Albano 2007 | Retrospective review | All paediatric patients with leukaemia & lymphoma diagnosed over a 9y period, n=529  Of these 482 took co-trimoxazole 2 d/week (345 leukaemia  137 lymphoma) and the rest took an alternative drug or alternative co-trimoxazole regimen  238 patients with ALL/ lymphoblastic lymphoma on 2 d/week co-trimoxazole during maintenance therapy were compared with 13 on alternative medications for incidence of neutropaenia | No cases PJP in compliant patients  2 proven cases during study period, both had stopped taking prophylaxis  Patients on co-trimoxazole experienced neutropaenia on 4.11% of maintenance days versus 2.17% on alternative drugs (p<0.001), but the proportion of patients with 0 neutropaenic days was not significantly different between the 2 groups. *The statistical analysis here is difficult to comprehend.* | 2 consecutive days/week trimethoprim is an effective regime in paediatric patients with leukaemia and lymphoma.  Not prospective or comparative but large number of patients studied over long period of time.  No difference in neutropaenia during maintenance therapy between those treated with co-trimoxazole and an alternative (pentamidine or dapsone) but the number of patients treated with an alternative was very small (13). |

### 3. Benefit v risk of PJP prophylaxis

**Patients:** Children up to 19 years of age with solid malignancies undergoing chemotherapy+/- radiotherapy with a low risk of PJP

**Intervention:** does PJP prophylaxis with

1. co-trimoxazole
2. aerosolized pentamidine
3. atovaquone or
4. dapsone

**Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)

**Control:** compared with no prophylaxis/ alternative regimens

### Studies of alternatives to co-trimoxazole

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug/Regime** | **Paper** | **Design** | **Study population** | **Results** | **Summary** |
| **Dapsone** | (56)  Ebenshade et al 2011 | Retrospective review | 167 paediatric patients (≤22y) treated for haematological malignancies or aplastic anaemia | Symptomatic methemoglobinemia documented in 19.8%  Higher dosing increased risk  Cytochrome b5 reductase activity did not differ by methemoglobinemia status.  No patient developed PJP | Risk of methemoglobinemia found exceeds likely risk of PJP in solid tumour patients.  Study population was not solid tumours but underlying malignancy is unlikely to affect risk of drug side effect.  Risk of methemoglobinemia was related to dapsone dosing but efficacy in preventing PJP was not (although numbers were too small to adequately assess the latter). Possible that less frequent dapsone dosing may be safer and equally as effective. |
| **Co-trimoxazole versus atovaquone** | (57)  Colby et al 1999 | Prospective randomized trial.  Prophylaxis given from day -5 to day -1 and then resumed on neutrophil count recovery.  Both drugs given 3d/week post transplant.  Not blinded. | 39 adult patients undergoing PBSC for haematological and solid malignancies | High incidence of adverse effects in co-trimoxazole group (40%) led to early discontinuation of trial  None of 16 patients treated with atovaquone suffered adverse events  No PJP in either group | Atovaquone seemed to be well tolerated in the 16 adult patients undergoing PBSC in this study. High incidence of adverse reactions to co-trimoxazole.  Rate of side effects to co-trimoxazole in adults known to be much higher than in children.  Study not powered to look at efficacy of atovaquone versus co-trimoxazole, only the toxicity and safety of both treatments.  Study is probably not relevant to children with solid malignancies, as the underlying diagnoses, treatment regimens and risk of adverse effects differ substantially. |

### 4. Use of lymphocyte/CD4 counts as a marker of risk

**Patients:** Children up to 19 years of age with solid malignancies undergoing chemotherapy+/- radiotherapy

**Intervention:** can lymphocyte and/or CD4 counts

**Outcome**: predict risk of PJP?

**Control:** none

Table 6: CD4 counts and PJP

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Paper** | **Design** | **Study population** | **Results** | **Summary** |
| (32)  Overgaard & Helweg-Larsen 2007 | Retrospective study to describe risk factors associated with PJP in HIV negative patients | 50 cases of histologically and micoroscopy +/- PCR confirmed PJP identified in one institution over 3y period. Only 11 children 0-17y | Major predisposing factor was haematological malignancy, especially NHL (n=15) and ALL (n=6).  All 6 ALL patients were not taking prophylaxis at the time.  76% patients had received steroids, median time of treatment 12 weeks.  72% received chemotherapy.  Lymphocyte counts were available for all patients but CD4 counts for only 17 (34%).  Lymphopaenia (<1 x 109 cells/litre) detected in 78% before onset or during initiation of PJP therapy.  Median CD4 count 280 x 106/litre. Only 52% <300, and 70% <400. 3 patients had CD4 counts >500. | All patients identified with PJP had established risk factors, including steroid therapy (76%), haematological malignancy and chemotherapy (72%).  Relation between CD4 counts and risk of PJP is less obvious compared to HIV positive patients.  Number of children included in this study (11) is too small to meaningfully address the clinical question above. Results have not been separated for adults and children. |

### 5. Corticosteroids and brain tumours

**Patients:** Children up to 19 years of age with brain tumours undergoing treatment with corticosteroids

**Intervention:** does PJP prophylaxis

**Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)

**Control:** compared with no prophylaxis.

No directly relevant studies found. See [table 1](#_Table_1:_PJP_4) for background risk of PJP in brain tumours.

Henson et al 1991 & Sepkowitz 1992 (25,26) and Green et al 2007 – Cochrane review (19) for side effects of co-trimoxazole in children.

6. Temozolomide

**Patients:** Children up to 19 years of age with solid malignancies undergoing treatment with temozolomide

**Intervention:** does PJP prophylaxis

**Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)

**Control:** compared with no prophylaxis.

No relevant studies found

### 7. Rituximab and other immunomodulating agents

**Patients:** Children up to 19 years of age with solid malignancies undergoing treatment with immunomodulating agents

**Intervention:** does PJP prophylaxis

**Outcome**: offer more benefit (prevention of PJP) than risk (side effects/cost/inconvenience)

**Control:** compared with no prophylaxis.

No relevant studies found

### 8. Underlying lung pathology

**Patients:** Children up to 19 years of age with solid malignancies and underlying chronic lung disease

**Intervention:** undergoing chemotherapy +/- radiotherapy

**Outcome**: what is the risk of PJP?

**Control:** compared to children up to 19 years of age with solid malignancies but healthy lungs

Studies of PJP and underlying lung pathology

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Paper** | **Design** | **Study population** | **Results** | **Summary** |
| (10)  Maini et al 2013 | Retrospective analysis of multiple national data sources | All inpatient admissions to NHS hospitals in England where PJP infection was coded between 2000-2010. HIV infected patients excluded. Laboratory confirmed cases extracted from LabBase2 (HPA’s national communicable diseases database for England, Wales and N Ireland). Death certificate data where PJP coded as cause or contributory cause of death | Number of inpatient admissions where PJP coded increased from 157 to 352/year over the study period, an average annual increase of 9% (p<0.001).  Most (40.6%) had a haematologic malignancy  17.5% had pre-existing lung disease (included TB, COPD, CF, bronchiectasis, asthma and interstitial lung disease).  There was also an increasing trend in rates of microbiologically confirmed cases. However hospital admission data yielded 2258 cases but LabBase2 found only 765. This difference may reflect underreporting by laboratories, or diagnosis by clinical and radiological findings or by immunofluorescence in the cytology department without microbiological confirmation.  Unable to say whether increased number of cases is due to increased testing as the laboratory surveillance system captures positive samples only, not the total number of samples submitted. | Increased incidence of PJP in HIV negative patients between the years 2000-2010. Observed across all age groups, but especially in over 60s.  Identification of a new group at risk for PJP: patients with pre-existing lung disease. Age range of this sub-group not given.  Does not provide information on severity of lung disease.  NB – Does mild asthma increase the risk of PJP? |

### 9. Previous PJP

**Patients:** Children up to 19 years of age with solid malignancies who have had previous PJP infection

**Intervention:** undergoing chemotherapy +/- radiotherapy

**Outcome**: what is the risk of PJP?

**Control:** compared to children up to 19 years of age with solid malignancies who have had not had previous PJP infection

No relevant studies found

### 10. Myelosuppression with co-trimoxazole

a)

**Patients:** Children up to 19 years of age with malignancies undergoing chemotherapy +/- radiotherapy

**Intervention:** does PJP prophylaxis with co-trimoxazole

**Outcome**: cause clinically significant myelosuppression

**Control:** compared with no prophylaxis.

b)

**Patients:** Children up to 19 years of age with malignancies undergoing chemotherapy +/- radiotherapy

**Intervention:** does PJP prophylaxis with twice weekly co-trimoxazole

**Outcome**: cause clinically significant myelosuppression

**Control:** compared with thrice weekly or daily co-trimoxazole.

See also under q 2 references (14,23,71) [Studies on PJP prophylaxis efficacy](#_Studies_on_PJP) and [Studies of different co-trimoxazole regimens](#_Studies_of_different_1)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Paper** | **Design** | **Study population** | **results** | **Summary** |
| (60)  Fontanet et al 2011 | Retrospective case control | 17 adult patients undergoing HSCT receiving continuous prophylaxis with co-trimoxazole compared with 49 matched controlled who received interrupted prophylaxis | No differences in time to neutrophil and platelet engraftment found (p= 0.9 and 0.6 respectively). No cases of PJP infection | No differences observed in speed of myeloid and platelet engraftment on comparing patients receiving continued with those receiving interrupted prophylaxis  Insufficiently powered study to detect small differences |

### 11. Methotrexate (mtx)

**Patients:** Children up to 19 years of age with malignancies undergoing treatment with methotrexate

**Intervention:** does PJP prophylaxis with co-trimoxazole

**Outcome**: cause clinically significant increased rates of methotrexate toxicity

**Control:** compared with no prophylaxis.

Studies of methotrexate and co-trimoxazole

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Paper** | **Design** | **Study population** | **results** | **Summary** |
| (58)  Ferrazzini et al 1990 | Pharmacokinetic study of mtx given iv or orally, once with and once without co-trimoxazole. | 9 children (2-11y) with ALL on maintenance therapy. | Increase in free mtx fraction in the serum during co-trimoxazole therapy in all patients from 37.4 +/- 11% to 52.2 +/- 6.4% (p<0.01)  Plasma clearance of total mtx before and during co-trimoxazole administration did not change significantly but there was a significant decrease in the plasma clearance of free mtx.  Consistent decrease in renal clearance of free mtx with co-trimoxazole (p<0.05)  Elimination half life of free mtx was not significantly different without or without the antibiotic  Elimination half life of free mtx in the oral studies did not differ from that in during iv therapy  Correlation between serum concentrations of co-trimoxazole and percentage of decrease in renal clearance of free mtx (r=0.91, p<0.05)  No changes in creatinine clearance. | Mean 66% increase in systemic exposure to free mtx when co-administered with co-trimoxazole.  Since the free mtx fraction enters cells and exerts the antileukaemic and toxic effects, children exposed to both drugs may be at risk of increased mtx toxicity, including myelosuppression. However this study did not assess myelosuppression directly. |
| (59)  Relling et al 1994 | Retrospective analysis of clinical and pharmacokinetic variables associated with high-risk mtx concentrations | 134 children entrolled on the St. Jude Total Therapy Study XII for newly diagnosed ALL.  Data analysed for 66 patients with high risk mtx levels at 42h after high dose mtx | Most important covariates of high risk mtx concentrations were mtx area under the curve (or end of infusion concentration), low urine pH and occurrence of emesis during mtx infusion.  The concurrent use of co-trimoxazole did not correlate with high risk mtx levels.  All patients were treated with co-trimoxazole 3 days/week (mon, tues, wed). *Estimated* approximately half the children in the study received co-trimoxazole on the same day at high dose mtx but all would have received it within the same week. | Small numbers of patients may mean that significant correlations between toxic mtx levels and concurrent use of co-trimoxazole may have been missed.  Current doses of high dose mtx used in ALL and osteosarcoma protocols are much higher (5g/m2 and 12g/m2 respectively compared to 0.9-3.7g/m2 used in this study) |

### 12. Potential for development of resistant isolates

**Patients:** Children up to 19 years of age with malignancies

**Intervention:** does PJP prophylaxis with co-trimoxazole

**Outcome**: cause increased rates of resistant strains of PJP

**Control:** compared with no prophylaxis.

No relevant studies found

### 13. G6PD deficiency

**Patients:** Children up to 19 years of age with malignancies and G6PD deficiency

**Intervention:** does PJP prophylaxis with co-trimoxazole

**Outcome**: cause haemolysis

**Control:** compared with no prophylaxis.

No relevant studies found

## Appendix E: Grading the Quality of Evidence

**Assessing the quality of the identified evidence**

The lead author assessed the quality of the evidence for each outcome identified in the literature review using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria.

**GRADE Profiles/ Grading the Quality of Evidence**

The main criteria considered in the rating of the evidence are summarized below. The ratings for each component were summed to obtain an overall assessment for each outcome.

**Description of quality elements in GRADE profile** (Source: Adapted from BMJ 2008 diagnostic GRADE (74–76) )

|  |  |
| --- | --- |
| **Quality element** | **Description** |
| Study limitations/ risk of bias | Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. |
| Inconsistency | Unexplained heterogeneity of results |
| Indirectness | Differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made. |
| Imprecision | Studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold. |
| Publication Bias | Systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. |
| Large Effect | Large effect size may increase the quality level of evidence |
| Plausible confounding | May reduce the effect or suggest a spurious effect |
| Dose Response Gradient | Presence of such a gradient increases confidence in the findings and should raise the rating of the quality of evidence. |

￼**Levels of quality elements in GRADE**

|  |  |
| --- | --- |
| Level | Description |
| None | There are no serious issues with the evidence |
| Serious | The issues are serious enough to downgrade the outcome evidence by one level |
| Very serious | The issues are serious enough to downgrade the outcome evidence by 2 levels |

**Overall quality of outcome evidence in GRADE**

￼

|  |  |
| --- | --- |
| Level | Description |
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | Further research in very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain |

**Grading the quality of clinical evidence**

The overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs, prospective diagnostic cross sectional or cohort studies start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.

1. The rating was then downgraded or upgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias were rated down -1 or -2 points respectively.
2. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
3. The reasons or criteria used for downgrading were specified in the footnotes.

## Appendix F: GRADE profiles for outcomes identified from the literature review:

| 1. Outcome: PJP infection in children receiving co-trimoxazole prophylaxis undergoing treatment for solid tumours | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Ref | No. of studies | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias |
|
| Cochrane systematic review 2007(19) | 4 | RCT | Serious:  not all studies clear allocation concelament | Not serious | Serious:  studies in adults and children being treated for Leukaemia | not serious | undetected |
| Harris et al 1980(71) | 1 | cohort | very serious:  observational not randomised or concealed | not serious | Serious:  included ALL patients | not serious:  calculated confidence interval 0-1.6% proportion of PJP cases on prophylaxis (binomial exact model) | undetected |
| Wilber et al 1980 (23) | 1 | cohort | very serious | not serious:  not randomised or controlled. Prophylaxis given at attending oncologists discretion. | Serious:  most patients in the study had ALL, not solid tumours | Serious:  evidence of efficacy provided by decline in yearly PJP rate at the same institution and comparison with historical data. Imprecise | undetected |

| 1. Outcome: PJP infection in children receiving co-trimoxazole prophylaxis undergoing treatment for solid tumours – continued | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref | Large effect | Plausible confounding | Dose response gradient | Summary of Findings | | | | | Quality |
| Cotrimoxazole events | No. of patients | Placebo/ no prophylaxis events | No. of patients | Pooled effect |
| Cochrane systematic review 2007(19) | very large | no | no | 0 | 276 | 26 | 252 | 0.08 (0.02-0.38) | high |
| Harris et al 1980(71) | large | no | no | 0 | 229 | 5 | 10 | n/a | low |
| Wilber et al 1980 (23) | large | no | no | 1 | 786 | n/a | n/a | n/a | low |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 2. Outcome: Prevalence of PJP infection in children undergoing treatment for solid tumours | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | |
| Brown et al 2013 (68) | cohort | very serious:  observational, not randomised | very serious:  all patients given prophylaxis but duration and drug regimens varied | not serious | not serious | |
| Cyklis & Zielinska 1983 (24) | cohort | very serious:  some diagnoses of PCP were made by cysts on throat swab only and no clinical symptoms (Ie carriage only). Unknown number within NHL patients in this group. | very serious:  some cases diagnosed on clinical and radiological grounds, plus cysts on throat swab. Others diagnosed by throat swab alone. | Serious:  historical population given historical treatment protocols | very serious:  diagnosis of PCP very imprecise | |
| Henson et al 1991 (26) | cohort | Serious:  incomplete follow up of patients. Some cases of PJP may have been missed | not serious | very serious:  Only adults >20 years | Serious:  Incomplete follow up, uncertain denominator | |
| hughes et al 1973(22) | cohort | Serious:  unknown if the study population is representative of the paediatric oncology as a whole and if cases were missed | not serious | Serious:  historical population given historical treatment protocols | not serious | |
| Hughes et al 1975 (13) | cohort | not serious | not serious | Serious:  Only children with ALL. All were treated with cranial irradiation and on protocols that vary from those used today | not serious | |
| 2. Outcome: Prevalence of PJP infection in children undergoing treatment for solid tumours | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | |
| Perera et al 1970 (21) | cohort | Serious:  Significance of cases discovered at autopsy only not clear | not serious | Serious:  Historical study, children treated with protocols that vary from those used today | not serious | |
| Peters & Prakash 1987 (69) | Cohort | Not serious | Not serious | Very serious:  Only 4 children included in the study, for whom the underlying diagnoses were not given | Very serious:  No specific data on incidence or risks of PJP for children. No information on whether prophylaxis was used. | |
| Sedaghatian & Singer 1972 (70) | Cohort | Serious:  Indication for autopsy and autopsy rates not given | Not serious | Very serious:  includes some patients with leukaemia. Includes some patients with only a few isolated organisms found at autopsy of unknown clinical significance. None of the patients were diagnosed or treated for PJP pre-death. All the solid tumour patients had disseminated tumour at autopsy. | Very serious:  Not clear whether the patients died of PJP or their primary malignant disease. Prevalence rates for children undergoing autopsy, not for all patients treated for malignancy or dying of malignancy and its associated complications. Indications for autopsy not given. | |
| Sepkowitz 1992 (25) | Cohort | Not serious | Not serious | Very serious:  most patients in the study were adults. Within the PJP attack rate for brain tumours the number of children included is not given. | Not serious | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 2. Outcome: Prevalence of PJP infection in children undergoing treatment for solid tumours | | | | | |
| Ref | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Brown et al 2013 (68) | undetected | n/a | no | n/a | Very low |
| Cyklis & Zielinska 1983 (24) | undetected | n/a | would reduce demonstrated effect:  inclusion of PCP carriers (throat swab positive only) | n/a | Very low |
| Henson et al 1991 (26) | undetected | n/a | would reduce demonstrated effect:  incomplete follow up may have some missed some cases of PJP | n/a | Very low |
| hughes et al 1973(22) | undetected | n/a | no | n/a | Very low |
| Hughes et al 1975 (13) | undetected | large | no | Yes:  more intensive chemotherapy regimens are associated with higher risk of PJP | moderate |
| Perera et al 1970 (21) | undetected | n/a | Would reduce demonstrated effect:  Unclear significance of cases discovered at autopsy only | n/a | moderate |
| Peters & Prakash 1987 (69) | Undetected | n/a | Would reduced demonstrated effect:  Not known if prophylaxis was given to any of the groups of patients | n/a | Very low |
| 2. Outcome: Prevalence of PJP infection in children undergoing treatment for solid tumours | | | | | |
| Ref | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Sedaghatian & Singer 1972 (70) | Undetected | n/a | Would reduce demonstrated effect:  Possible that those children referred for autopsy may have had higher rates of PJP. | n/a | Very low |
| Sepkowitz 1992 (25) | Undetected | n/a | Would reduce demonstrated effect | n/a | Low |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 3. Outcome: Incidence of PJP infection in children undergoing treatment for solid tumours receiving co-trimoxazole 3 days per week v 2 days per week v one day per week | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Caselli et al 2004  (16) | Cohort | Very serious:  Lack of randomisation and lack of concealment allocation | Not serious | Serious:  Includes large number of haematological malignancies | Not serious:  Calculated confidence interval for the once weekly group = 0-0.5% | Undetected | n/a | No | No | Very low |
| Hughes et al 1987 (8) | RCT, not blinded | Not serious | Not serious | Serious:  All patients with ALL, not solid malignancies | Not serious | Undetected | Large | No | n/a | high |
| Lindemulder & albano 2007 (14) | Cohort | Serious:  Mixed, small (n=13) control group. No randomisation | Not serious | Serious:  Most of the patients in the study had leukaemia | Not serious | Undetected | Very large | No | n/a | High |
| Ohata et al 2009 (15) | Cohort | Serious:  Not comparative or controlled, small numbers | Not serious | Serious:  Included patients with haematological malignancies, histiocytosis, immunodeficiency and metabolic disease and patients undergoing HSCT. Only 102 solid tumour patients (53%) | Serious  Small numbers, n=181 | Undetected | No | No | n/a | low |

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| 4. Outcome: Effectiveness of pentamidine in preventing PJP infection in children undergoing treatment for solid tumours | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision |
| DeMasi et al 2013 (50) | Cohort | Serious:  Not comparative or controlled, Data collected retrospectively | Not serious | Serious:  Only 33% of paitents had a solid malignancy | Serious  Small numbers, n=137 |
| Kim et al 2008 (51) | cohort | Serious:  Not comparative or controlled. Data collected retrospectively | not serious | Serious:  50% patients leukaemia, 50% solid tumours | not serious |
| Mustafa et al 1994(52) | Cohort | Serious:  Historical controls only. Small numbers | Not serious | Serious:  Included only 9 patients with solid tumours (15%). Only children >3y | Serious:  Small numbers, n=60 |
| Orgel & Rushing 2014 (53) | Cohort | Very serious:  not comparative or controlled. Younger patients more likely to be given iv pentamidine. Choice of therapy was by practioner preference then midway through the study period an institutional practice guideline was implemented | Not serious | Serious:  Half the cohort had ALL | Serious:  Scarcity of events preluded statistical power to perform a direct comparison |
| Orgel & Rushing 2014 (53) | Cohort | Very serious:  not comparative or controlled. Younger patients more likely to be given iv pentamidine. Choice of therapy was by practioner preference then midway through the study period an institutional practice guideline was implemented | Not serious | Serious:  Half the cohort had ALL | Serious:  Scarcity of events preluded statistical power to perform a direct comparison |

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| 4. Outcome: Effectiveness of pentamidine in preventing PJP infection in children undergoing treatment for solid tumours | | | | | |
| Ref | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| DeMasi et al 2013 (50) | Undetected | No | No | n/a | low |
| Kim et al 2008 (51) | Undetected | no | no | n/a | low |
| Mustafa et al 1994(52) | Undetected | No | No | n/a | Very low |
| Orgel & Rushing 2014 (53) | undectected | No:  Very few patients experienced breakthrough PJP infection but there was no control group for comparison | n/a | n/a | low |

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| 5. Outcome: Effectiveness of atovaquone in preventing PJP in paediatric patients undergoing treatment for solid tumours | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Madden et al 2007 (73) | Cohort | Serious:  Retrospective, not comparative or controlled | Not serious | Serious:  Only patients with AML or ALL | Serious:  Small numbers, n=86. incidence of PJP = 0 (95% CI 0-1.74 per 100 person-years by Poisson exact statistics) | Undetected | Large:  if compared to historical controls (Hughes et al 1977), where 21% patients receiving placebo developed PJP, this is a large effect. | Would increase demonstrated effect:  more intensive treatment given to this cohort of patients than to historical control so effect may be greater as background risk of PJP may be higher | n/a | moderate |

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| 6. Outcome: Comparison of effectiveness of co-trimoxazole, dapsone, pentamidine and atovoquone in preventing PJP in paediatric patients undergoing treatment for solid tumours | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Prasad et al 2008 (55) | Cohort | Serious:  Retrospective, not comparative, controlled or randomised | Not serious | Serious:  Most patients had haematological malignancies (72.6%) | Serious:  Results not statistically significant for dapsone and pentamidine, especiallly the latter. The rate of PCP was lowest for patients receiving TMP-SMZ (rate, 95% confidence interval: 0.004/person–year, [ 0.004, 0.012]), and was significantly lower than dapsone (0.03/person–year, [ 0.03, 0.08]) and intravenous pentamidine (0.17/person–year, [ 0.04, 0.38]). | Undetected | No | Would suggest spurious effect:  Numbers are small in the dapsone, pentamidine and atovaquone groups so incidence of PJP may differ due to difference in underlying diagnosis and treatment intensity rather than prophylactic regimen | n/a | low |

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| 7. Outcome: Side effects of dapsone (risk versus benefit) in the prevention of PJP in paediatric patients undergoing treatment for solid tumours | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Esbenshade et al 2011 (56) | cohort | Not serious | Not serious | Not serious:  although patients in the study had haematological malignancies, the underlying diagnosis is unlikely to affect the risk of the side effect (methemoglobinemia) being assessed in this study | Not serious | undetected | Large:  19.8% patients treated with dapsone suffered confirmed methemoglobinemia. This is likely to exceed the background risk of PJP in paediatric solid tumour patients. Dapsone is probably effective since none of the patients developed PJP. However there was no control group. | No | Yes:  risk of methemoglobinaemia was related to increased dapsone levels. Efficacy was not affected by drug levels. | moderate |

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| 8. Outcome: Atovaquone versus co-trimoxazole for the prevention of PJP in paediatric patients undergoing treatment for solid tumours | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Colby et al 1999 (57) | RCT:  Prospective but not blinded | Serious:  Treatment allocation not blinded | Not serious | Very serious:  all adult patients undergoing autologous peripheral blood stem cell transplantation. Study discontinued early because of high incidence of side effects due to co-trimoxazole. Co-trimoxazole is known to be better tolerated in children (Cochrane review 2007(77)) | Serious:  small numbers of patients as study discontinued early, n=39. Study not powered to look at efficacy of atovaquone, only toxicity and safety. | Undetected | No | No | no | low |

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| 9. Outcome: Use of CD4 or lymphocyte counts to predict risk of PJP in paediatric patients undergoing treatment for solid tumours | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Overgaard & Helweg-Larsen 2007 (32) | Cohort | Serious:  Retrospective, not comparative, controlled or randomised. | Not serious | Very serious:  only 11 (22%) patients included were children. Most diagnoses were of haematological maligancies. Inflammatory diseases, organ transplants and other non-malignant diagnoses were included. | Serious:  no control group or denominator given. CD4 counts only available for 17 (34%) of total cohort, Not known how many of these were children. | Undetected | No | Would suggest spurious effect:  Underlying diagnoses and treatments were hugely varied | No | low |

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| 10. Does underlying lung pathology increase the risk of PJP in paediatric patients undergoing treatment for solid tumours? | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | quality |
| Maini et al 2013  (10) | Cohort | Serious:  retrospective analysis of data. Increased number of PJP cases identified may be due to increased testing. Total number of samples sent to labs for possible PJP not known. Paediatric population at risk may not be identified as they are already taking prophylaxis. | Serious:  Hospital admission data yielded many more cases than laboratory confirmed data (2258 versus 765). Not known how many cases may have been confirmed by cytology or by clinical and radiological findings as this data was not collected. | Serious:  patients with pre-existing lung disease identified as a group at risk for PJP but the age range for this group is not given. | Very serious:  no information on the severity of the lung disease. Not known whether increased risk applies to children with mild asthma for example. | Undetected | Large:  17.5% of patients identified with PJP had pre-existing lung disease. | Would increase demonstrated effect:  Paediatric population at risk may not be identified as they may already be taking prophylaxis | n/a | low |

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| 11. Outcome: Myelosuppression with co-trimoxazole | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | Quality |
| Lindemulder & Albano 2007(14) | Cohort | Serious:  Mixed, small (n=13) control group. No randomisation | Not serious | Serious:  only the subgroup of patients with ALL or lymphoblastic lymphoma were assessed for neutropaenia on maintenance therapy days | Serious:  numbers in the group given an alternative to co-trimoxazole small (n=13) and not uniform (pentamidine or dapsone). No control group. | Undetected | No | No | n/a | Low |
| Ohata et al 2009 (15) | Cohort | Serious:  Not comparative or controlled, small numbers | Not serious | Serious:  included patients with haematological malignancies, histiocytosis, immunodeficiency and metabolic disease patients undergoing HSCT. Only 102 solid tumour patients (53%). Myelosuppression as an outcome not directly or prospectively measured, only recorded as a reason for discontinuing co-trimoxazole. | Serious:  small number of patients, n=181. Only 1 discontinued co-trimoxazole due to myelosuppression, with no information regarding the certainty that the drug was the cause of the myelosuppression. In addition reasons for discontinuing co-trimoxazole were not clearly documented in 10 cases. Myelosuppression not directly or prospectively measured. | Undetected | No | Would suggest spurious effect:  no information regarding the certainty that the drug was the cause of the myelosuppression. In addition reasons for discontinuing co-trimoxazole were not clearly documented in 10 cases. | n/a | Very low |
| 11. Outcome: Myelosuppression with co-trimoxazole | | | | | | | | | | |
| Ref | Study Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Plausible confounding | Dose response gradient | quality |
| Wilber et al 1980 (23) | Cohort | Very serious:  not randomised or controlled. Prophylaxis given at attending oncologists discretion. Adverse events recorded by attending physician, not verified. | Not serious | Serious:  most patients in the study had ALL, not solid tumours. Daily prophylaxis with co-trimoxazole given. | Serious:  Detection of adverse reactions depended on the assessment recorded by the attending physician. Relationship between haematological abnormalities and cotrimoxazole not verified. | Undetected | Large | Would suggest spurious effect:  data not prospectively collected. Review of medical records may have missed cases with myelosuppression. Many other drugs given concurrently with cotrimoxazole. Detection of adverse reactions depended on the assessment recorded by the attending physician. | n/a | Very low |

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| 12. Outcome: Increased methotrexate toxicity with co-trimoxazole | | | | | | | | |
| Ref | Study Design | Risk of bias | | Inconsistency | | Indirectness | Imprecision | |
| Ferrazzini et al 1990 (58) | Cohort | Not serious | | Not serious | | Serious:  ALL patients on maintenance only. Showed increase in systemic exposure to free methotrexate when co-administered with co-trimoxazole but did not assess consequent toxicity or myelosuppression. | Not serious:  Increase in free mtx fraction in the serum during co-trimoxazole therapy in all patients from 37.4 +/- 11% to 52.2 +/- 6.4% (p<0.01) | |
| Relling et al 1994 (59) | Cohort | Serious:  Retrospective | | Not serious | | Serious:  ALL patients undergoing high dose methotrexate. Current doses of mtx used in ALL and osteosarcoma protocols are much higher (5g/m2 and 12g/m2 respectively compared to 0.9-3.7g/m2 used in this study) | Serious:  small numbers of patients (n=66) may mean that significant correlations between toxic mtx levels and concurrent use of cotrimoxazole may have been missed. Concurrent use of contrimoxazole was estimated as it was prescribed 3 days/week (mon, tues, wed) so it was supposed that was that half the children received cotrimoxazole on the same day as high dose mtx but this may not be true. | |
| 12. Outcome: Increased methotrexate toxicity with co-trimoxazole | | | | | | | | |
| Ref | Publication bias | | Large effect | | Plausible confounding | | Dose response gradient | quality |
| Ferrazzini et al 1990 (58) | Undetected | | No | | No | | No | moderate |
| Relling et al 1994 (59) | Undetected | | No | | Would suggest spurious effect:  Concurrent use of contrimoxazole was estimated as it was prescribed 3 days/week (mon, tues, wed) so it was supposed that was that half the children received cotrimoxazole on the same day as high dose mtx but this may not be true. Nonetheless all patients would have received cotrimoxazole within the same week and there may not be any difference in the increased mtx toxicity afforded by the antibiotic whether it is given on the same day or, for example, the day before. | | No | low |

## Appendix G: Consensus Survey & Results

The following six statements were circulated to all members of the CCLG and the GDG and 55 responses were received. Respondents included paediatric oncologists, a paediatric infectious disease physician, a medical microbiologist, a paediatric advanced nurse practioner and paediatric pharmacists.

Respondents were asked to choose between the following choices for each statement:

*I support the statement*

*I would support the statement with modification\**

*I do not support the statement\**

*I do not have the experience in this area to be able to comment*

*\*If you have answered ‘I would support the statement with modification’ or ‘I do not support the statement’ please add comments below:*

**Results:**

1. PJP prophylaxis should be offered to all solid tumour patients undergoing treatment that is likely to render them lymphopaenic, unless there are clear contraindications\*.

\**For example allergy and concurrent high dose methotrexate*

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| **Answer choices** | **Responses** | |
| I support the statement | 42 | 76.4% |
| I would support the statement with modification\* | 5 | 9% |
| I do not support the statement\* | 3 | 5.5% |
| I do not have the experience in this area to be able to comment | 5 | 9% |
| Total | 55 |  |

2. For patients intolerant of co-trimoxazole the need for any prophylaxis at all should be re-evaluated on an individual basis *because alternatives are associated with increased toxicity and expense.*

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| **Answer choices** | **Responses** | |
| I support the statement | 44 | 80% |
| I would support the statement with modification\* | 4 | 7.3% |
| I do not support the statement\* | 5 | 9% |
| I do not have the experience in this area to be able to comment | 2 | 3.6% |
| Total | 55 |  |

3. Where 2nd line prophylaxis is required intravenous or inhaled pentamidine is recommended**.**

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| **Answer choices** | **Responses** | **%** |
| I support the statement | 26 | 48.2% |
| I would support the statement with modification\* | 9 | 16.7% |
| I do not support the statement\* | 10 | 18.5% |
| I do not have the experience in this area to be able to comment | 9 | 16.7% |
| Total | 54 |  |

4. In children undergoing autologous stem cell transplant, recommence co-trimoxazole prophylaxis once neutrophil count is >1 x109/litre

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| **Answer choices** | **Responses** | **%** |
| I support the statement | 29 | 53.7% |
| I would support the statement with modification\* | 7 | 13% |
| I do not support the statement\* | 5 | 9.3% |
| I do not have the experience in this area to be able to comment | 13 | 24.1% |
| Total | 54 |  |

5. In children undergoing autologous stem cell transplant continue prophylaxis until 6 months post stem cell transplant

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| **Answer choices** | **Responses** | **%** |
| I support the statement | 35 | 63.6% |
| I would support the statement with modification\* | 9 | 16.4% |
| I do not support the statement\* | 2 | 3.6% |
| I do not have the experience in this area to be able to comment | 9 | 16.4% |
| Total | 55 |  |

6. Children who are immunocompromised due to treatment for a solid malignancy should receive prophylaxis against PJP from the start of treatment until 3 months after the end of treatment as long as lymphocyte count has returned to normal.

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| **Answer choices** | **Responses** | **%** |
| I support the statement | 33 | 61.1% |
| I would support the statement with modification\* | 10 | 18.5% |
| I do not support the statement\* | 3 | 5.6% |
| I do not have the experience in this area to be able to comment | 8 | 14.8% |
| Total | 54 |  |

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1. Strength of Recommendations based on GRADE system and Delphi Process. (78,79) [↑](#footnote-ref-1)
2. *Pneumocystis* species demonstrate a high degree of host species specificity. Those infecting humans have been named *P. jirovecii*, whilst *P. carinii* refers to those infecting rats. [↑](#footnote-ref-2)
3. This figure may not be reliable, see section on RMS. [↑](#footnote-ref-3)
4. Lymphopaenia following radiotherapy was first described in the early 20th century only a few years after x-rays were discovered. The radiation field need not include the bone marrow or lymphoid tissues to exert this effect as cranial irradiation in children with ALL can cause a 60% or more depletion in lymphocyte count (80). Recently Yovino et al have created a mathematical model to estimate the radiation doses to circulating cells during radiotherapy (RT) for high grade glioma (HGG)(81). They concluded that standard treatment plans for brain tumours deliver potentially lymphotoxic radiation doses to the entire circulating blood pool. The mean radiation dose to circulating lymphocytes was estimated at 2Gy and nearly all the circulating blood receives at least 0.5Gy. Lymphocytes are highly sensitive to radiation, nonetheless limited field RT alone is usually not a significant factor in the development of clinically relevant lymphopaenia (82). It is only when this treatment modality is combined with chemotherapy and/or corticosteroids that the risk of opportunistic infection emerges (41,42). [↑](#footnote-ref-4)