ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients

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The 5th European Conference on Infections in Leukaemia (ECIL-5) meeting aimed to establish evidence-based recommendations for the prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP) in non-HIV-infected patients with an underlying haematological condition, including allogeneic HSCT recipients. Recommendations were based on the grading system of the IDSA. Trimethoprim/sulfamethoxazole given 2–3 times weekly is the drug of choice for the primary prophylaxis of PCP in adults (**A-II**) and children (**A-I**) and should be given during the entire period at risk. Recent data indicate that children may benefit equally from a once-weekly regimen (**B-II**). All other drugs, including pentamidine, atovaquone and dapsone, are considered second-line alternatives when trimethoprim/sulfamethoxazole is poorly tolerated or contraindicated. The main indications of PCP prophylaxis are ALL, allogeneic HSCT, treatment with alemtuzumab, fludarabine/cyclophosphamide/rituximab combinations, >4 weeks of treatment with corticosteroids and well-defined primary immune deficiencies in children. Additional indications are proposed depending on the treatment regimen.

Introduction

Pneumocystis jirovecii pneumonia (PCP) is a life-threatening disease in immunocompromised patients. Hence, adequate prophylaxis is critical in high-risk conditions. This implies both the early recognition of patients at risk as well as using the drug of choice, including adequate dose, route of administration and duration of prophylaxis. Large, prospective, randomized trials have provided solid information on the optimal prophylactic strategy in HIV-infected patients, whereas data on PCP prophylaxis in haematology populations are often retrospective in nature and frequently based on historical controls. During the 5th European Conference on Infections in Leukaemia (ECIL-5) meeting (19–21 September 2013, Nice, France), we developed guidelines for prophylaxis of PCP in HIV-negative haematology patients. This paper presents these recommendations, both for adult and paediatric patients.

Methodology

Search criteria

A systematic literature review was performed using a search strategy in the PubMed database for English language literature up to August 2013 and updated in September 2015, based on the following MeSH terms: 'Pneumocystis OR Pneumocystis carinii OR Pneumocystis jirovecii AND pneumonia'; and 'pneumonia AND epidemiology OR risk factors OR haematological malignancies OR haematopoietic stem cell transplantation'. A restricted group reviewed the published literature. Their proposals were discussed in the plenary session at the meeting, until consensus was reached. Recommendations were graded according to the IDSA–US Public Health Service Grading System recommendations for ranking.[1] A summarizing slide set was made available following ECIL-5 at www.kobe.fr/ecil on 28 March 2014.

Preventing exposure

Most cases of PCP occur from reactivation of latent infection, although cases of person-to-person transmission have been reported.[2–4] Few healthcare facilities require respiratory precautions with respect to patients infected with PCP, but it seems reasonable that severely immunocompromised patients should avoid contact with patients with documented PCP (**C-III**).

Preventing PCP in adults

Indications for prophylaxis

The ECIL recommended indications for PCP prophylaxis in patients with an underlying haematological condition are summarized in Table 1. This is based on the risk factors that were described in greater detail in the introductory paper.[1]

Choice of drugs (Table 2)

Trimethoprim/sulfamethoxazole

At present, trimethoprim/sulfamethoxazole is the drug of choice for the primary chemoprevention of PCP. In a Cochrane meta-analysis (including 1155 adult patients with acute leukaemia and recipients of an HSCT and solid organ transplant), the incidence of PCP was reduced by 91% [relative risk (RR) 0.09] compared with placebo, no treatment or treatment with antimicrobial agents showing no activity against P. jirovecii (e.g. quinolones).[5,6] The number needed to treat to prevent one case of PCP was 15 patients.[6] In addition, PCP-related mortality was significantly reduced by 83% (RR 0.17).[6] These beneficial results are in line with the well-documented efficacy of trimethoprim/sulfamethoxazole in preventing PCP in HIV-infected patients in which trimethoprim/sulfamethoxazole also showed a significant beneficial effect in preventing death (RR 0.69). However, trimethoprim/sulfamethoxazole prophylaxis did not markedly reduce all-cause mortality in haematology populations.[6] Nevertheless, given the more severe course of PCP and the higher PCP-related mortality rates, it is likely that trimethoprim/sulfamethoxazole prophylaxis can save lives in other immunocompromised groups as well. In addition, trimethoprim/sulfamethoxazole, though inferior to quinolones, also significantly reduced the incidence of bacterial infections compared with placebo or no treatment[6] and may also be active against toxoplasmosis, listeriosis and nocardiosis, depending on the dose of the drug.

Table 1. ECIL guidelines in haematology patients at risk of Pneumocystis pneumonia: indication and duration of prophylaxis

Indication for prophylaxis	Adults		Children	
	disease/condition	duration of prophylaxis	disease/condition	duration of prophylaxis
Main (A)	ALL	from induction to end of maintenance	ALL	from induction to end of maintenance
	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing
	alemtuzumab	>6 months after completion of treatment	alemtuzumab	life-long or until restoration of underlying defect
	fludarabine/cyclophosphamide/rituximab	≥6 months after completion of treatment	SCID, WAS, X-linked agammaglobulinaemia, HLA II combined immunodeficiency	
	steroids (>20 mg/day prednisone for 4 weeks)		steroids (>0.4 mg/kg or 16 mg/day for ≥1 month)	
Optional (B)	Lymphoma treated with R-CHOP14 or escalated BEACOPP		AML	duration of chemotherapy
	nucleoside analogues (fludarabine, cladribine, mycophenolate mofetil)		solid tumours	duration of chemotherapy
	radiotherapy for brain tumours/metastasis + high-dose steroids			

HLA, human leucocyte antigen; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome.

Table 2. Main characteristics of the drugs available for second-line prophylaxis of *Pneumocystis* pneumonia

Characteristic	Pentamidine, 300 mg	Dapsone, 100 mg	Atovaquone, 1500 mg
Route of administration	inhalation (intravenous)	oral	oral solution with fatty meal
Frequency of administration	monthly	daily	daily
During neutropenia/pre-engraftment	yes	yes	yes
Special equipment or trained personnel needed	yes	no	no
Anti-*Toxoplasma* activity[a]	no	yes, if combined with pyrimethamine	uncertain[b]
Antibacterial activity	no	no	no
Use in glucose-6-phosphate dehydrogenase deficiency	yes	no	yes
Particular toxicity	respiratory	haemolytic anaemia, methaemoglobinaemia	gastrointestinal
Cost	low	low	high

[a]In all situations (especially with pentamidine or atovaquone) where PCP prophylaxis does not cover the risk of *Toxoplasma* reactivation in high-risk patients (e.g. allogeneic HSCT recipients with a positive pre-transplant serology), regular screening with blood PCR is recommended.
[b]Atovaquone is used for second-line treatment of (ocular) toxoplasmosis, but breakthrough cases have been reported in patients given atovaquone prophylaxis.[42,43] The cause of failure may be variable intestinal absorption.[44]

Side effects of trimethoprim/sulfamethoxazole (at doses routinely used for PCP prophylaxis) include fever, drug sensitivity rash [resembling cutaneous graft-versus-host disease (GVHD)], headache, nausea, vomiting, neutropenia (simultaneous administration of folinic acid or leucovorin may reduce the incidence), pancytopenia, meningitis, nephrotoxicity (dose adjustments are needed for a creatinine clearance <30 mL/min), hepatitis, hypoglycaemia, hyperkalaemia and anaphylaxis. Trimethoprim/sulfamethoxazole occasionally causes haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency. However, the toxicity of trimethoprim/sulfamethoxazole is often overemphasized in comparison with its efficacy and depends on the dose given and the duration of prophylaxis. An analysis of four trials comparing trimethoprim/sulfamethoxazole prophylaxis versus placebo or no intervention (including 470 patients) showed no significant difference in the adverse event rate between both groups (RR 1.01).[6] In the aforementioned meta-analysis, severe adverse events requiring permanent discontinuation occurred in only 3.1% of adults and included leukopenia, thrombocytopenia and/or severe skin reactions.[6]

Multiple dosing regimens have been studied using both single-strength (80/400 mg) as well as double-strength (160/800 mg) tablets, although there is no compelling evidence to indicate that efficacy differs.[7] However, in countries with a high rate of seropositivity for *Toxoplasma gondii*, daily dosing may be preferred (**B-III**). There are no comparative studies on when to start and how long to continue primary prophylaxis. Given the potential for marrow toxicity, it is advised not to start trimethoprim/sulfamethoxazole prophylaxis during the pre-engraftment period in HSCT recipients (with the possible exception of the conditioning period) (**B-III**). Primary prophylaxis is usually prescribed throughout the period of treatment-induced immunosuppression or until the CD4+ cell count increases to >200 cells/mm^3 and, for allogeneic HSCT recipients, from engraftment until ≥6 months after transplant or longer in patients who continue to receive immunosuppressive drugs and/or have chronic GVHD (**B-III**). Of note, there is no convincing evidence that prophylaxis can be stopped safely when the CD4+ cell count normalizes (as is the case in HIV infection), probably because other risk factors persist.

Recommendation (Table 3). Trimethoprim/sulfamethoxazole is the preferred drug for the primary prophylaxis of *Pneumocystis* infections in adults (**A-II**). The recommended dose is either a single-strength (80/400 mg) tablet daily or a double-strength tablet (160/800 mg) daily or three times weekly (**B-II**).

It should be noted that this recommendation has never been validated (for haematology patients) in well-designed, properly executed randomized controlled prophylaxis trials, making 'level I evidence' recommendations inadmissible. The meta-analysis included smaller studies, all published before the PCR era, in which patients were given a variety of different dosing regimens for varied durations. Data are lacking on the actual risk of PCP for a broad range of haematological conditions (including AML, cerebral lymphoma, indolent lymphoproliferative disorders, haemophagocytic syndrome and autoimmune cytopenia). In addition, there have been important changes in medical practice over the last two decades that have likely placed more patients at risk of PCP. These changes include the use of lymphocyte-depleting substances (e.g. purine analogues, rituximab, alemtuzumab and bendamustine), T cell-depleting procedures (e.g. CD34 selection) and delayed T cell recovery following transplantation (e.g. use of antithymocyte globulin, cord blood transplants and haplo-identical transplants). Moreover, non-neutropenic patients receiving corticosteroids for a prolonged period of time (e.g. prednisone equivalent of ≥20 mg/day for >4 weeks) or treated with biological modifiers (e.g. anti-TNF-α) carry a substantial risk and may equally be good candidates for PCP prophylaxis. Future research should focus on: (i) the incidence of PCP in these 'new' risk groups; (ii) the role of prophylaxis with trimethoprim/sulfamethoxazole; (iii) better delineation of the duration of primary prophylaxis; (iv) documentation of the actual adverse drug reaction rate; and (v) the development of resistance and occurrence of breakthrough infections.

Adverse reactions may prompt temporary or permanent discontinuation of trimethoprim/sulfamethoxazole. The actual rate of adverse events in haematology patients remains unknown, but high rates (31%–56%) of early withdrawal have been reported for HSCT recipients. Of note, reintroduction of the drug after recovery or after reduction of other marrow-toxic agents

Table 3. Summary of the ECIL guidelines about choice of drugs and doses for PCP prophylaxis in haematology patients

	Adults		Children	
	drug grading	dose	drug grading	dose
First-line choice				
trimethoprim/sulfamethoxazole; all other alternatives are inferior (**A-II**)	**A-II**	one single-strength (80/400 mg) tablet/day or one double-strength tablet (160/800 mg)/day or thrice a week: **B-II**	**A-I**	150/750 mg/m^2/day in 1 or 2 doses/day or same dose 2 or 3 days/week: **A-I** 150/750 mg/m^2/day once a week: **B-II**
Second-line choice[a]				
dapsone	**A-II**	50 mg×2/day: **B-II**	**C-II**	2–4 mg/kg/day
atovaquone	**B-II**	1500 mg/day: **B-II**	**B-II**	30 mg/kg/day if >24 months of age 45 mg/kg/day if 4–24 months of age
pentamidine aerosols	**A-II**	300 mg once/month: **B-II**	**B-II**	300 mg once/month (age >5 years)
pentamidine intravenously	no data	—	**C-II**	4 mg/kg every 4 weeks

[a]Only in case of intolerance or severe adverse effects due to trimethoprim/sulfamethoxazole.

(e.g. ganciclovir) may prove worthwhile for patients with mild marrow toxicity.

Alternative agents for PCP prophylaxis include aerosolized or intravenous pentamidine, dapsone and atovaquone. However, none of these agents has prospectively been compared with trimethoprim/sulfamethoxazole in a randomized trial of first-line prophylaxis in haematology. Consequently, the use of pentamidine, dapsone and atovaquone should be limited to second-line prophylaxis for those patients who cannot tolerate trimethoprim/sulfamethoxazole. However, given its superior effectiveness, every effort should be made to maintain prophylaxis with trimethoprim/sulfamethoxazole.

Pentamidine

Following reports of effective PCP prophylaxis with aerosolized pentamidine in HIV infection and the success in 13 HSCT recipients,[8] the toxicity, safety and feasibility of using the drug was prospectively evaluated in 31 allogeneic and 12 autologous HSCT recipients.[9] Inhalations of pentamidine isethionate (60 mg via Respirgard II®) were given at day −3 and at day +14. From day +30 onwards, 300 mg was given every 4 weeks for 6 months. During the 6 month study period, there were no cases of pulmonary or extrapulmonary *Pneumocystis* infection in this small study. Treatment was discontinued in ~10% of cases because of poor compliance or side effects, usually cough, excessive salivation or sore throat. Inhalation on day 14 after HSCT proved particularly impracticable for patients with mucositis. Machado *et al.*[10] compared a retrospective cohort of 38 HSCT recipients who had received trimethoprim/sulfamethoxazole with a prospective cohort of 40 patients who received 300 mg aerosolized pentamidine every 3 weeks from day +21 until 6 months after all immunosuppressive drugs had been stopped. Three patients, all of whom had received trimethoprim/sulfamethoxazole, developed PCP. There were no discontinuations of aerosolized pentamidine because of adverse events, although bronchospasm, cough and nausea were seen in 2.5%, 7.5% and 5%, respectively. In summary, no cases of PCP were reported in these three small, uncontrolled

series totalling 96 HSCT patients who had received aerosolized pentamidine as primary prophylaxis. In addition, there were few adverse reactions, all of which were manageable, compliance was excellent and prophylaxis could be started early after transplant, even before engraftment.

However, these positive findings differ substantially from the conclusions of a large US retrospective cohort study that analysed the efficacy of three first-line prophylactic regimens [trimethoprim/sulfamethoxazole at 160/800 mg twice daily, three times weekly (n=105), aerosolized pentamidine at 150 mg every 2 weeks or 400 mg every 4 weeks (n=44) or dapsone at 100 mg daily (n=31); 147 patients received more than one regimen]. Treatment was given for a year to 327 evaluable adult HSCT recipients and eight cases (2.4%) of PCP were detected.[11] However, patients receiving only aerosolized pentamidine had a significantly higher probability of developing PCP (9.1%) than did those receiving only trimethoprim/sulfamethoxazole (0%) (OR 23.4 relative to trimethoprim/sulfamethoxazole). Although the patients who received only aerosolized pentamidine had a significantly lower probability of treatment-related toxicity (7.5% discontinuations due to toxicity) than those receiving trimethoprim/sulfamethoxazole (35.4% discontinuation) (OR 0.19), their probability of developing serious non-PCP, non-viral infections was increased (OR 2.2), as well as their probability of dying within a year of HSCT (OR 5.2), even after adjusting for gender and the type of transplant.

More recently, a retrospective analysis assessed the role of second-line aerosolized pentamidine in 439 allogeneic HSCT recipients in whom first-line trimethoprim/sulfamethoxazole prophylaxis was discontinued because of allergy or low blood counts.[12] The incidence of PCP was 2.7% and although about one in four patients reported toxicity, <5% of them had to stop pentamidine due to an adverse reaction.

However, there are several important caveats to be taken into consideration. Firstly, these studies were retrospective. Moreover:

- Cases of toxoplasmosis have been described, especially in countries with high rates of *Toxoplasma* seropositivity (Table 2).

- Also, more extrapulmonary *Pneumocystis* infections have been reported in patients with HIV infection who were receiving pentamidine prophylaxis.
- Radiographic patterns other than interstitial infiltrates are often seen in PCP under pentamidine prophylaxis, which could lead to delayed diagnosis and therapy.
- Twice-monthly administration of pentamidine was more effective than once monthly in patients with HIV infection who needed secondary prophylaxis.
- The success of pentamidine prophylaxis depends on adherence to a strict protocol as the drug should be administered in a separate room. Side effects such as coughing and wheezing can be prevented or ameliorated by administering β-adrenergic agonists. Most studies have used a jet nebulizer such as Respirgard II, which produces particles with a mass mean aerodynamic diameter of <1 μm, whereas other nebulizers create larger particles that are unable to reach the alveoli and may be less effective.
- There are no data on the intravenous use of pentamidine in adults.

Recommendation (Table 3). Although less effective than trimethoprim/sulfamethoxazole for first-line prophylaxis of PCP (**A-II**), aerosolized pentamidine is a well-tolerated and valid alternative for preventing PCP in adult patients who are intolerant of trimethoprim/sulfamethoxazole (**A-II**). The recommended dose is 300 mg given once a month (**B-II**). Aerosolized pentamidine delivery should be performed using well-studied equipment (**B-III**).

Dapsone

In 1998, Hughes[13] reviewed >40 studies on the use of dapsone to prevent PCP in patients with HIV infection. However, only three studies, all non-randomized, compared dapsone with no prophylaxis.

Data on the use of dapsone in haematology are scarce and only available for HSCT recipients. One retrospective study analysed a cohort of 646 transplant recipients[14] given trimethoprim/sulfamethoxazole as the drug of choice for primary *Pneumocystis* prevention. However, dapsone was given at least once to 111 patients due to allergy or clinical intolerance ('the dapsone cohort') at a dose of 50 mg twice daily, thrice weekly for ≥6 months. Eight of 10 patients who developed PCP were in the dapsone cohort that had an overall incidence of 7.2% compared with 0.37% of patients who only received trimethoprim/sulfamethoxazole (P<0.001). A second, retrospective matched case–control study was reported by the same group and compared a cohort of 155 allogeneic HSCT recipients who received daily dapsone (50 mg twice daily) as second-line PCP prophylaxis with a cohort of 310 control patients who received only standard trimethoprim/sulfamethoxazole post-transplant.[15] Two patients (1.3%) in the dapsone group developed PCP versus none in the control group (P=0.11). This incidence is lower than that previously reported with intermittent dosing, suggesting that daily dosing might be more effective. Patients in the dapsone cohort had a higher transfusion requirement compared with those in the control group, but whether dapsone was the cause remains contentious since treatment was switched to dapsone in most cases because of poor marrow function and intolerance only led to permanent discontinuation or temporary suspension of therapy in 10% of cases. Finally, a trend towards more breakthrough infections by organisms potentially preventable by trimethoprim/sulfamethoxazole but not covered by dapsone (e.g. *Nocardia*, *Toxoplasma*, *Streptococcus pneumoniae* and *Haemophilus* species) was noted.

Dapsone causes dose-related haemolytic anaemia and methaemoglobinaemia and should not be given to patients with glucose-6-phosphate dehydrogenase deficiency. Common toxicities unrelated to dose include neutropenia, rash, nausea and a sulfone syndrome (fever, rash, lymphadenopathy, hepatitis and methaemoglobinaemia). It should also be noted that a substantial number of patients allergic to trimethoprim/sulfamethoxazole will also be intolerant of dapsone and the drug should not be used as an alternative for patients with severe or life-threatening trimethoprim/sulfamethoxazole toxicities.

Recommendation (Table 3). Although less effective than trimethoprim/sulfamethoxazole for first-line prophylaxis of PCP (**A-II**), dapsone is a valid alternative for preventing PCP in adult HSCT recipients who are intolerant of trimethoprim/sulfamethoxazole (**A-II**). The recommended dose is 50 mg given twice daily (**B-II**).

Atovaquone

Atovaquone suspension at 1500 mg was compared with dapsone at 100 mg, both given once daily,[16] and with aerosolized pentamidine given 300 mg once a month[17] in two large, randomized, open-label multicentre studies for patients with HIV infection who could not tolerate trimethoprim, sulphonamides or both. The RR of developing PCP in the atovaquone group versus the dapsone group was 0.85 (P=0.20). There was no difference in mortality between the two groups and there was no significant difference in discontinuations due to intolerance or adverse events, although atovaquone was generally better tolerated than dapsone. In the second study, atovaquone given at 750 or 1500 mg, both once daily, were compared with aerosolized pentamidine.[17] The ITT analysis showed no statistically significant differences in the incidence of PCP or in mortality, but atovaquone was less well tolerated. Failure of low-dose atovaquone to prevent PCP has also been reported in transplant recipients, possibly because the achievable serum levels at a dose of 750 mg fall below the MIC for rodent *P. jirovecii*.[18]

A prospective, randomized, controlled, open-label study of 39 autologous HSCT recipients compared the effects of primary prophylaxis with atovaquone at 1500 mg plus ofloxacin at 400 mg (n=20) versus double-strength trimethoprim/sulfamethoxazole (n=19).[19] Drugs were administered daily from day −5 until day −1 and then restarted after neutrophil recovery 3 days a week until day +100 post-transplant. There were no documented cases of PCP. However, significantly more patients who were receiving trimethoprim/sulfamethoxazole discontinued prophylaxis prematurely due to intolerance (P<0.003).

Common toxicities of atovaquone include rash, headache and gastrointestinal disturbances. Marrow toxicity is uncommon. Since the drug is not well absorbed unless ingested with fatty food, atovaquone might be less preferable to patients with gastrointestinal complaints, including gut GVHD.

Recommendation (Table 3). Although less effective than trimethoprim/sulfamethoxazole for first-line prophylaxis of PCP (**A-II**), atovaquone is a well-tolerated agent and valid alternative for preventing PCP in adult HSCT patients (data limited to autologous

transplants) who are intolerant of trimethoprim/sulfamethoxazole (**B-II**). The recommended dose is 1500 mg daily (**B-II**).

In conclusion, aerosolized pentamidine, dapsone and atovaquone are valid second-line options for patients who have to stop taking trimethoprim/sulfamethoxazole prophylaxis. The final choice may depend on drug-specific characteristics, including route and frequency of administration (and hence patient compliance), marrow toxicity, additional prophylactic coverage, availability, specific toxicities and cost (see Table 2).

Echinocandins

Echinocandins exhibit *in vitro* activity against *P. jirovecii* cysts, but are less active against the trophic forms.[20] These drugs also show some activity in animal models of PCP in combination with other anti-*Pneumocystis* drugs,[21,22] but there are, as yet, no prospective studies of prophylaxis of PCP in immunocompromised patients.

Preventing recurrence

Recurrent PCP is rare provided that secondary prophylaxis is continued until the end of immunosuppression.

Preventing PCP in paediatric patients

Trimethoprim/sulfamethoxazole

The efficacy of trimethoprim/sulfamethoxazole was demonstrated in prospective and retrospective studies. In a prospective, randomized study, trimethoprim/sulfamethoxazole 150/750 mg/m^2/day was superior to placebo in preventing PCP.[23] Subsequent work showed that trimethoprim/sulfamethoxazole was equally effective as daily dosing when given for 3 days a week.[24] This regimen has since become the standard because toxicity was reduced. The efficacy of trimethoprim/sulfamethoxazole was confirmed in two retrospective studies in which PCP was reported only in patients who were not receiving trimethoprim/sulfamethoxazole prophylaxis.[25,26] Recently, lower doses of trimethoprim/sulfamethoxazole (150/750 mg/m^2/day given on 2 days a week, whether on consecutive days or not) also proved to be effective in preventing PCP.[27–29] In addition, a retrospective analysis of 2466 patients (1373 with acute leukaemia or lymphoma and 1093 with a solid tumour) showed that even a once-weekly regimen was as effective as the drug given two or three times weekly.[25] Although the cumulative dose of trimethoprim/sulfamethoxazole might exceed the standard daily dose (300/2500 mg/m^2/day), this regimen is easy to administer for prolonged periods and patient compliance is improved. The optimal duration of prophylaxis has never been formally investigated, but a recent European survey noted that most centres reported giving prophylaxis during the entire course of chemotherapy until 6 weeks, and even up to 6 months, after stopping chemotherapy.[26]

Alternative drugs for PCP prophylaxis

Data on alternative drugs to trimethoprim/sulfamethoxazole (pentamidine, atovaquone and dapsone) are limited. Pentamidine can be administered intravenously in children at the dose of 4 mg/kg every 3–4 weeks or by inhalation at the dose of 150 mg (<4 years) or 300 mg (≥4 years) every 4 weeks. Failure of intravenous pentamidine prophylaxis in preventing PCP has been reported in 3 of 232

(1.3%) patients and in 2 of 12 (16%) patients,[30,31] whereas several authors reported no failures with aerosolized pentamidine.[32–34] The side effects of pentamidine aerosol such as bronchospasm, cough, vomiting and nausea occurred in up to 10% of cases.[32] If patients with HIV infection are included, pentamidine by inhalation is considered more effective than when given intravenously.[35,36] In two retrospective studies involving 86 and 5 paediatric patients, respectively, atovaquone at 30–40 mg/kg/day orally prevented PCP without significant effects.[31,37] Studies in children with HIV infection showed that atovaquone is well tolerated, even in infants of ≤3 months.[38] The use of dapsone at 1 mg/kg daily in paediatric haematology is limited to 36 patients reported by Prasad *et al.*[31] One patient failed prophylaxis and developed PCP. In 94 children with HIV infection, no significant difference was observed in PCP breakthrough with a dose of 1 mg/kg/day versus 2 mg/kg/day versus 4 mg/kg/week.[39] The main side effects of dapsone are haemolytic anaemia with or without glucose-6-phosphate dehydrogenase deficiency and methaemoglobinaemia that can affect up to 20% of children especially with a dose >2 mg/kg/day.[40,41]

Recommendations for children (Tables 1 and 3)

Omitting prophylaxis is the major factor contributing to development of PCP in at-risk patients (**A-I**). Poor compliance has also been reported as a cause of failure of PCP prophylaxis in children. Trimethoprim/sulfamethoxazole is the agent of choice for primary prophylaxis in paediatric haematology (**A-I**). The recommended dose is 150/750 mg/m^2/day, given in one or two administrations per day (**A-I**). Intermittent weekly administration of trimethoprim/sulfamethoxazole is as effective as daily trimethoprim/sulfamethoxazole (**A-I**). A lower dose of trimethoprim/sulfamethoxazole given 1 or 2 days a week is as effective as given 3 days a week (**B-II**). Aerosolized pentamidine, dapsone or atovaquone are alternative choices in case of intolerance, marrow toxicity or adverse effects due to trimethoprim/sulfamethoxazole. There is more evidence to support the use of aerosolized pentamidine (**B-II**) or atovaquone (**B-II**) than the use of dapsone (**C-II**). Intravenous pentamidine, though well tolerated, is less effective, with the risk of breakthrough PCP (**C-II**). PCP prophylaxis is recommended during the entire period of chemotherapy and up to 6 weeks to 6 months after the end of therapy (**B-II**). In HSCT recipients, PCP prophylaxis is recommended from engraftment until a protective immune recovery is achieved (**B-II**).

Conclusions

PCP prophylaxis is of utmost importance for certain patients with haematological disorders. Primary prophylaxis with trimethoprim/sulfamethoxazole is highly effective and only limited by intolerance that may necessitate resort to alternative drugs. Future research should focus on better risk assessment, more effective prophylaxis and treatment of patients treated with new therapeutic compounds, including monoclonal antibodies, targeted therapies and novel approaches to HSCT.

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References

1 Cordonnier C, Cesaro S, Maschmeyer G et al. Pneumocystis jirovecii pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother 2016; **71**: 2379–85.

2 Manoloff ES, Francioli P, Taffe P et al. Risk for Pneumocystis carinii transmission among patients with pneumonia: a molecular epidemiology study. Emerg Infect Dis 2003; **9**: 132–4.

3 Miller RF, Ambrose HE, Novelli V et al. Probable mother-to-infant transmission of Pneumocystis carinii f. sp. hominis infection. J Clin Microbiol 2002; **40**: 1555–7.

4 Vargas SL, Ponce CA, Gigliotti F et al. Transmission of Pneumocystis carinii DNA from a patient with P. carinii pneumonia to immunocompetent contact health care workers. J Clin Microbiol 2000; **38**: 1536–8.

5 Green H, Paul M, Vidal L et al. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2007; **82**: 1052–9.

6 Green H, Paul M, Vidal L et al. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev 2007; issue 3: CD005590.

7 Di Cocco P, Orlando G, Bonanni L et al. A systematic review of two different trimetoprim-sulfamethoxazole regimens used to prevent Pneumocystis jirovecii and no prophylaxis at all in transplant recipients: appraising the evidence. Transplant Proc 2009; **41**: 1201–3.

8 Mahon FX, Sadoun A, Benz-Lemoine E et al. Possible prevention of Pneumocystis carinii pneumonia by pentamidine aerosol after bone marrow transplantation. Bone Marrow Transplant 1991; **8**: 64–5.

9 Link H, Vohringer HF, Wingen F et al. Pentamidine aerosol for prophylaxis of Pneumocystis carinii pneumonia after BMT. Bone Marrow Transplant 1993; **11**: 403–6.

10 Machado CM, Macedo MC, Medeiros RS et al. Primary Pneumocystis carinii prophylaxis with aerosolized pentamidine after bone marrow transplantation. Acta Haematol 1998; **99**: 54–6.

11 Vasconcelles MJ, Bernardo MV, King C et al. Aerosolized pentamidine as Pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant 2000; **6**: 35–43.

12 Marras TK, Sanders K, Lipton JH et al. Aerosolized pentamidine prophylaxis for Pneumocystis carinii pneumonia after allogeneic marrow transplantation. Transpl Infect Dis 2002; **4**: 66–74.

13 Hughes WT. Use of dapsone in the prevention and treatment of Pneumocystis carinii pneumonia: a review. Clin Infect Dis 1998; **27**: 191–204.

14 Souza JP, Boeckh M, Gooley TA et al. High rates of Pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. Clin Infect Dis 1999; **29**: 1467–71.

15 Sangiolo D, Storer B, Nash R et al. Toxicity and efficacy of daily dapsone as Pneumocystis jiroveci prophylaxis after hematopoietic stem cell transplantation: a case–control study. Biol Blood Marrow Transplant 2005; **11**: 521–9.

16 El-Sadr WM, Murphy RL, Yurik TM et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. N Engl J Med 1998; **339**: 1889–95.

17 Chan C, Montaner J, Lefebvre EA et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis 1999; **180**: 369–76.

18 Rodriguez M, Sifri CD, Fishman JA. Failure of low-dose atovaquone prophylaxis against Pneumocystis jiroveci infection in transplant recipients. Clin Infect Dis 2004; **38**: e76–8.

19 Colby C, McAfee S, Sackstein R et al. A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999; **24**: 897–902.

20 Finkelman M. Pneumocystis jirovecii infection: cell wall (1-3)-β-D-glucan biology and diagnostic utility. Crit Rev Microbiol 2010; **36**: 271–81.

21 Cushion MT, Linke MJ, Ashbaugh A et al. Echinocandin treatment of Pneumocystis pneumonia in rodent models depletes cysts leaving trophic burdens that cannot transmit the infection. PLoS One 2010; **5**: e8524.

22 Lobo ML, Esteves F, de Sousa B et al. Therapeutic potential of caspofungin combined with trimethoprim-sulfamethoxazole for Pneumocystis pneumonia: a pilot study in mice. PLoS One 2013; **8**: e70619.

23 Hughes W, Kuhn S, Chaudhary S *et al*. Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 1977; **297**: 1419–26.

24 Hughes WT, Rivera GK, Schell MJ *et al*. Successful intermittent chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 1987; **316**: 1627–32.

25 Caselli D, Petris MG, Rondelli R *et al*. Single-day trimethoprim/sulfamethoxazole prophylaxis for *Pneumocystis* pneumonia in children with cancer. *J Pediatr* 2013; **164**: 389–92 e1.

26 Levinsen M, Shabaneh D, Bohnstedt C *et al*. *Pneumocystis jiroveci* pneumonia prophylaxis during maintenance therapy influences methotrexate/6-mercaptopurine dosing but not event-free survival for childhood acute lymphoblastic leukemia. *Eur J Haematol* 2012; **88**: 78–86.

27 Agrawal AK, Chang PP, Feusner J. Twice weekly *Pneumocystis jiroveci* pneumonia prophylaxis with trimethoprim-sulfamethoxazole in pediatric patients with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2011; **33**: e1–4.

28 Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for *Pneumocystis carinii* (*jiroveci*) pneumonia in pediatric oncology patients. *Pediatrics* 2007; **120**: e47–51.

29 Ohata Y, Ohta H, Hashii Y *et al*. Intermittent oral trimethoprim/sulfamethoxazole on two non-consecutive days per week is effective as *Pneumocystis jiroveci* pneumonia prophylaxis in pediatric patients receiving chemotherapy or hematopoietic stem cell transplantation. *Pediatr Blood Cancer* 2009; **52**: 142–4.

30 Kim SY, Dabb AA, Glenn DJ *et al*. Intravenous pentamidine is effective as second line *Pneumocystis* pneumonia prophylaxis in pediatric oncology patients. *Pediatr Blood Cancer* 2008; **50**: 779–83.

31 Prasad P, Nania JJ, Shankar SM. *Pneumocystis* pneumonia in children receiving chemotherapy. *Pediatr Blood Cancer* 2008; **50**: 896–8.

32 Mustafa MM, Pappo A, Cash J *et al*. Aerosolized pentamidine for the prevention of *Pneumocystis carinii* pneumonia in children with cancer intolerant or allergic to trimethoprim/sulfamethoxazole. *J Clin Oncol* 1994; **12**: 258–61.

33 O'Sullivan BP, Spaulding R. The use of aerosolized pentamidine for prophylaxis of *Pneumocystis carinii* pneumonia in children with leukemia. *Pediatr Pulmonol* 1994; **18**: 228–31.

34 Weinthal J, Frost JD, Briones G *et al*. Successful *Pneumocystis carinii* pneumonia prophylaxis using aerosolized pentamidine in children with acute leukemia. *J Clin Oncol* 1994; **12**: 136–40.

35 Cheval P, Kinzonzi P, Allaert-Cheval C. Principal clinical manifestations during the course of disease caused by the human immunodeficiency virus (HIV) in Pointe-Noire (Republic of Congo). (307 cases hospitalized during 2 years at the medical service of the Regional Hospital of the Army). *Med Trop (Mars)* 1993; **53**: 225–39.

36 Weintrub PS, Wara DW, Duliege AM. Failure of intravenous pentamidine prophylaxis for *Pneumocystis carinii* pneumonia. *J Pediatr* 1993; **122**: 163–4.

37 Madden RM, Pui CH, Hughes WT *et al*. Prophylaxis of *Pneumocystis carinii* pneumonia with atovaquone in children with leukemia. *Cancer* 2007; **109**: 1654–8.

38 Hughes W, Dorenbaum A, Yogev R *et al*. Phase I safety and pharmacokinetics study of micronized atovaquone in human immunodeficiency virus-infected infants and children. Pediatric AIDS Clinical Trials Group. *Antimicrob Agents Chemother* 1998; **42**: 1315–8.

39 McIntosh K, Cooper E, Xu J *et al*. Toxicity and efficacy of daily vs. weekly dapsone for prevention of *Pneumocystis carinii* pneumonia in children infected with human immunodeficiency virus. ACTG 179 Study Team. AIDS Clinical Trials Group. *Pediatr Infect Dis J* 1999; **18**: 432–9.

40 Esbenshade AJ, Ho RH, Shintani A *et al*. Dapsone-induced methemoglobinemia: a dose-related occurrence? *Cancer* 2011; **117**: 3485–92.

41 Williams S, MacDonald P, Hoyer JD *et al*. Methemoglobinemia in children with acute lymphoblastic leukemia (ALL) receiving dapsone for *Pneumocystis carinii* pneumonia (PCP) prophylaxis: a correlation with cytochrome b5 reductase (Cb5R) enzyme levels. *Pediatr Blood Cancer* 2005; **44**: 55–62.

42 Garcia de la Fuente I, Ansari M, Rougemont AL *et al*. Acute disseminated fatal toxoplasmosis after haploidentical stem cell transplantation despite atovaquone prophylaxis in a young man. *Pediatr Infect Dis J* 2010; **29**: 1059–60.

43 Megged O, Shalit I, Yaniv I *et al*. Breakthrough cerebral toxoplasmosis in a patient receiving atovaquone prophylaxis after a hematopoietic stem cell transplantation. *Pediatr Transplant* 2008; **12**: 902–5.

44 Derouin F. Anti-toxoplasmosis drugs. *Curr Opin Investig Drugs* 2001; **2**: 1368–74.