

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

MS KAREN FRANCES URBANCIC (Orcid ID : 0000-0002-9275-578X)

Article type : Short Communication

Dapsone safety in haematology patients: pathways to optimising *Pneumocystis jirovecii* pneumonia prophylaxis in haematology malignancy and transplant recipients.

Short running title: Dapsone safety in haematology patients

Authors: Urbancic K. F^{1,2,3,4}, Pisasale D¹, Wight J⁵, Trubiano J. A^{2,3,4}

Affiliations:

¹Pharmacy Department, Austin Health, Heidelberg, VIC, Australia

²Infectious Diseases Department and Centre for Antibiotic Allergy and Research, Austin Health, Heidelberg, VIC, Australia

³National Centre for Infections in Cancer, National Health and Medical Research Council Centre of Research Excellence, Peter MacCallum Cancer Centre, Department of Oncology, University of Melbourne, Parkville, VIC, Australia

⁴Department of Medicine, University of Melbourne, Parkville, VIC Australia

⁵Clinical Haematology Department, Austin Health, Heidelberg, VIC, Australia

Corresponding author:

Karen F Urbancic, BPharm (Hons) MClinPharm

Departments of Pharmacy and Infectious Diseases, Austin Health

Melbourne, VIC, Australia

Email: karen.urbancic@austin.org.au

Tel: +61-3-94966676 Fax: +61-3-94966677

Funding Information:

K.F.U is supported by a National Health and Medical Research Council (NHMRC) postgraduate research scholarship (APP1133479) and J.A.T by a NHMRC Early Careers Fellowship (APP1139902).

Disclosures:

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/tid.12968](https://doi.org/10.1111/tid.12968)

This article is protected by copyright. All rights reserved

31 K.F.U has sat on an advisory board for Merck Sharp & Dohme. The other authors have no conflicts of
32 interest to declare.

33 **Abstract:**

34 Dapsone may be used for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in haematology
35 patients receiving immunosuppressive therapy or after hematopoietic stem cell transplant (HSCT) in
36 the setting of trimethoprim-sulfamethoxazole (TMP-SMX) adverse drug reaction (ADR) history.
37 Dapsone-induced haematological toxicities such as oxidative haemolysis may limit use in these
38 patients and modern assessments of dapsone allergy cross-reactivity in non-HIV patients with a
39 sulphonamide allergy are largely absent. The aim of this single-centre, retrospective study was to
40 describe dapsone usage in haematology patients requiring PJP prophylaxis, including HSCT
41 recipients, over a 12-month period in terms of indications, incidence of dapsone-attributed oxidative
42 haemolysis, and immune cross-reactivity in those previously labelled with a sulphonamide allergy, as
43 well as describing potential opportunities for first-line TMP-SMX PJP prophylaxis reintroduction. Out
44 of 24 patients meeting the study inclusion criteria, 12 (50%) were receiving dapsone PJP prophylaxis
45 post-HSCT. No cases of breakthrough PJP infection were noted. Sixteen patients (67%) were initiated
46 on dapsone to avoid the perceived risk of further myelosuppression with TMP-SMX and 5 patients
47 (21%) due to prior delayed immune-mediated allergy to TMP-SMX. None experienced rash with
48 dapsone therapy. Six patients (25%) were successfully rechallenged on TMP-SMX, including one
49 patient with prior TMP-SMX-associated rash. Four (17%) patients had confirmed oxidative
50 haemolysis, all resulting in dapsone cessation. Dapsone PJP prophylaxis in haematology patients was
51 effective and safe, with non-life threatening dapsone-related haemolysis noted in a small number.
52 An absence of sulphonamide allergy cross-reactivity was noted, suggesting greater TMP-SMX
53 rechallenges or desensitisation could be considered in those receiving dapsone.

54 **Keywords:** dapsone, adverse drug reactions, *Pneumocystis jirovecii* pneumonia, haematopoietic
55 stem cell transplantation

56 **Introduction:**
57 Dapsone is recommended as a second-line agent for *Pneumocystis jirovecii* pneumonia (PJP)
58 prophylaxis in the setting of a trimethoprim-sulfamethoxazole (TMP-SMX) adverse drug reactions
59 (ADR) history^{1, 2}. Whilst reports of dapsone cross-reactivity in TMP-SMX allergic patients is up to
60 20%³⁻⁵, modern assessments of dapsone tolerability in non-HIV patients with an antibiotic
61 sulphonamide allergy are largely absent. Dapsone is associated with haematological ADRs including
62 oxidative haemolysis, particularly in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients
63 and at higher doses^{6, 7}. Incidence may be higher in haematology patients due to limited bone
marrow reserve. Screening of patients for G6PD deficiency is recommended prior to

64 commencement^{1, 2}. Here, we describe dapsone usage in our cohort of patients with haematological
65 conditions requiring PJP prophylaxis, including haematopoietic stem cell transplant (HSCT)
66 recipients, to better understand its real-world safety profile and indications for use, immune cross-
67 reactivity in those previously labelled as sulphonamide allergic, and subsequently potential
68 opportunities for conversion to first-line PJP prophylaxis with TMP-SMX.

69 **Patients and Methods:**

70 This was a retrospective study of patients with haematological conditions, including HSCT recipients
71 (autologous and allogeneic) at Austin Health (Melbourne, AUS), receiving dapsone PJP prophylaxis.
72 Haematology patients were identified from dispensing records if they had received dapsone
73 between 1 November 2016 and 31 October 2017 inclusive. Patients were excluded if they received
74 less than 7 days of dapsone or were not followed up by the Austin Health Haematology unit. Data
75 collected included: patient characteristics, allergy history, dapsone course details, haemoglobin pre-
76 and during dapsone course, G6PD levels (if tested), presence of oxidative haemolysis as documented
77 in patient notes and/or on blood film, and management of cases. Cases with documented oxidative
78 haemolysis were independently reviewed by a haematopathologist not involved in the original
79 diagnosis (JW). Haemolysis was deemed dapsone-related if it was temporally related, resolved with
80 cessation, and there were no other obvious causes. Common TMP-SMX ADRs were categorized as
81 either Type-A (non-immune-mediated) or Type-B (immune-mediated) according to standard
82 definitions⁸. Following accurate TMP-SMX ADR phenotyping, patients could undergo either TMP-
83 SMX rechallenge, desensitization or continued avoidance as per our previously published protocol,
84 developed in consultation with an external expert who leads an international antibiotic allergy
85 service⁹. Patients with a history of mild delayed TMP-SMX hypersensitivity (Type-B), real/perceived
86 myelosuppression risk, or other Type-A TMP-SMX ADR could undergo rechallenge with a single oral
87 dose (TMP-SMX; 160mg-800mg OR 80mg-400mg)⁹. This study was approved by the Austin Human
88 Research Ethics Committee (LNR17/Austin/312).

89 **Results:**

90 Twenty-six patients received dapsone PJP prophylaxis during the study period, with 24 meeting
91 inclusion/exclusion criteria. The median age was 59 (IQR 49,69) years, the majority male (54%), and
92 9 (38%), 8 (33%) and 3 (13%) were receiving PJP prophylaxis for allogeneic HSCT, high-dose
93 corticosteroid therapy, and autologous HSCT respectively. Remaining indications for PJP prophylaxis
94 included receipt of ALL chemotherapy (1, 4%), or cladribine therapy (1, 4%), low lymphocyte CD4
95 count (1, 4%), and secondary prophylaxis for prior PJP infection (1, 4%). Dapsone 100mg daily was
96 prescribed in the majority of cases (23, 96%), with one patient receiving the combination of dapsone

97 50mg daily plus weekly pyrimethamine for concurrent toxoplasmosis prophylaxis. Patients received
98 dapsone for a median (IQR) of 67 days (30, 175). Only 42% (10/24) had G6PD assay performed, with
99 none found to be deficient. No cases of breakthrough PJP infection were diagnosed during the study
100 period.

101 Sixteen patients (67%) were initiated on dapsone PJP prophylaxis to avoid the perceived risk of
102 further myelosuppression with TMP-SMX. Five patients (21%) had a history of mild delayed immune-
103 mediated allergy (Type-B ADR) to TMP-SMX. None experienced rash with dapsone therapy, and one
104 patient was later successfully rechallenged with TMP-SMX without rash recurrence. Three patients
105 (13%) had documented other intolerances to TMP-SMX (Type-A ADR) including hyperkalaemia and
106 nausea. Of the 24 patients receiving dapsone, 6 (25%) were rechallenged on TMP-SMX during the
107 study period, all successfully.

108 Four (17%) patients, 3 female and 1 male, were identified with confirmed oxidative haemolysis
109 during dapsone therapy. The onset of haemolysis was detected after a median (IQR) of 48 (33, 64)
110 days. Haemoglobin (Hb) changes from baseline are summarised in **Table 1**. Although the median
111 (IQR) Hb level did not change from baseline compared to during dapsone therapy for the whole
112 cohort, (95 [86,106] vs 95 [88,108]; $P = 0.69$), the patients with dapsone-related haemolysis had
113 reductions in Hb during dapsone therapy (19 to 27%). Two of these patients had a substantial
114 increase in their transfusion requirements attributable to haemolysis occurring concomitantly with
115 their pre-existing bone marrow failure. Only 1 out of 4 had G6PD assay performed, which was
116 normal. All of these patients subsequently ceased dapsone and 2 underwent TMP-SMX rechallenge
117 without subsequent ADR. The remaining 2 patients were assessed as not requiring ongoing PJP
118 prophylaxis.

119 **Discussion:**

120 Whilst limited by a short follow-up period and small patient numbers, we observed no episodes of
121 PJP infection with dapsone in our cohort of patients with haematological conditions, including post-
122 HSCT. A lack of immune-mediated ADR cross-reactivity in those with reported prior sulphonamide
123 ADR was also noted, reduced significantly from the up to 20% previously reported in HIV
124 populations³⁻⁵. Although the reported incidence of dapsone-induced haematological toxicities is
125 approximately 4% in HIV patients³, this is likely underestimated due to the ability of normal marrow
126 to compensate for haemolysis. In those with compromised bone marrow function, such as HSCT
127 recipients, up to 20-fold higher rates have been reported and may occur despite normal G6PD
128 activity¹⁰. We observed a small but significant number of patients with dapsone-related oxidative
129 haemolysis within the first 1-2 months, leading to the risk and expense of potentially avoidable

130 blood transfusions. A higher reported incidence in other transplant cohorts, too, has resulted in
131 greater hospitalisation and transfusion requirements¹¹.

132 G6PD deficiency is estimated to affect 400 million people worldwide and most commonly affects
133 African, Asian, Mediterranean and Middle Eastern ethnicities¹². In Australia, the only available data
134 are limited to a cohort of southern European decent, reporting a 2.9% incidence of G6PD
135 deficiency¹³. We observed suboptimal G6PD screening in our dapsone patient cohort, with less than
136 half undergoing documented testing during dapsone therapy. Although it is unclear from
137 retrospective review of the clinical notes, we postulate that testing may have been avoided by some
138 clinicians due to G6PD not being an absolute predictor for haemolysis in haematology patients.
139 Nonetheless, low uptake of screening makes it difficult to determine the contribution of G6PD
140 deficiency to oxidative haemolysis observed in our patients, and whether cases could have been
141 avoided.

142 In our patient cohort, dapsone 100mg per day dosing was utilised in accordance with Australian and
143 European PJP prophylaxis guidelines in patients with haematology malignancies^{1, 2}. Although dose
144 reductions or intermittent dose regimens may be employed with dapsone in order to mitigate
145 haematological toxicities¹⁴, a higher incidence of breakthrough PJP infection has been previously
146 noted in HSCT recipients utilising lower dapsone dosing¹⁵, suggesting dapsone dose reductions may
147 compromise efficacy.

148 The avoidance of TMP-SMX for reasons of myelosuppression also appears unfounded, as rates of
149 leukopenia in solid organ transplant cohorts when TMP-SMX is employed as prophylaxis have been
150 reported at less than 2%^{16, 17}. Modern studies have suggested that TMP-SMX therapy when
151 employed as prophylaxis in haematological malignancy does not impact on the degree or duration of
152 neutropenia¹⁸. A recent Cochrane review of PJP prophylaxis in the non-HIV setting found no
153 difference in adverse events requiring discontinuation when comparing TMP-SMX to no treatment
154 or placebo¹⁹. Therefore, for those with mild delayed TMP-SMX allergy, TMP-SMX rechallenge or
155 desensitisation should be considered in the peri-transplant period or at commencement of induction
156 chemotherapy, as an alternative to dapsone in accordance with previously published protocols⁹.

157 This study highlights that although dapsone is an alternative agent in PJP prophylaxis, it requires
158 careful monitoring of oxidative haemolysis, irrespective of G6PD status. Deployment of dapsone at
159 the first instance may be avoided in the majority of cases via rechallenge with the first-line agent,
160 TMP-SMX, especially in the peri-transplant period.

161 **References:**

- 162 1. Cooley L, Dendle C, Wolf J et al. Consensus guidelines for diagnosis, prophylaxis and
163 management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid
164 malignancies, 2014. *Intern Med J* 2014; 44: 1350-63.
- 165 2. Maertens J, Cesaro S, Maschmeyer G et al. ECIL guidelines for preventing *Pneumocystis*
166 *jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant
167 recipients. *J Antimicrob Chemother* 2016; 71: 2397-404.
- 168 3. Beumont MG, Graziani A, Ubel PA, MacGregor RR. Safety of dapsone as *Pneumocystis carinii*
169 pneumonia prophylaxis in human immunodeficiency virus-infected patients with allergy to
170 trimethoprim/sulfamethoxazole. *Am J Med* 1996; 100: 611-6.
- 171 4. Carr A, Penny R, Cooper DA. Efficacy and safety of rechallenge with low-dose trimethoprim-
172 sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; 7: 65-71.
- 173 5. Jorde UP, Horowitz HW, Wormser GP. Utility of dapsone for prophylaxis of *Pneumocystis*
174 *carinii* pneumonia in trimethoprim-sulfamethoxazole-intolerant, HIV-infected individuals. *AIDS* 1993;
175 7: 355-9.
- 176 6. Hughes WT. Use of Dapsone in the Prevention and Treatment of *Pneumocystis carinii*
177 Pneumonia: A Review. *Clin Infect Dis* 1998; 27: 191-204.
- 178 7. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: Overview and update. *J Am Acad*
179 *Dermatol* 2001; 45: 420-34.
- 180 8. Rawlins MD, Thompson TJ. *Textbook of adverse drug reactions*. Oxford: Oxford University
181 Press, 1977.
- 182 9. Urbancic KF, Ierino F, Phillips E, Mount PF, Mahony A, Trubiano JA. Taking the challenge: A
183 protocolized approach to optimize *Pneumocystis pneumonia* prophylaxis in renal transplant
184 recipients. *Am J Transplant* 2018; 18: 462-6.
- 185 10. Olteanu H, Harrington AM, George B, Hari PN, Bredeson C, Kroft SH. High prevalence of
186 Dapsone-induced oxidant hemolysis in North American SCT recipients without glucose-6-phosphate-
187 dehydrogenase deficiency. *Bone Marrow Transplant* 2012; 47: 399-403.
- 188 11. Mitsides N, Green D, Middleton R et al. Dapsone-induced methemoglobinemia in renal
189 transplant recipients: more prevalent than previously thought. *Transpl Infect Dis* 2014; 16: 37-43.
- 190 12. Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-
191 phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis*
192 2009; 42: 267-78.
- 193 13. Smith MB. The incidence of glucose 6 phosphate dehydrogenase deficiency in a population
194 of Greek, Italian and Yugoslav origin in Australia. *Med J Aust* 1976; 2: 485-6.

- 195 14. Antibiotic Expert Group. *Therapeutic guideline: antibiotic. Version 15 ed.* Melbourne:
196 Therapeutic Guidelines Limited, 2014.
- 197 15. Souza JP, Boeckh M, Gooley TA, Flowers ME, Crawford SW. High rates of *Pneumocystis*
198 *carinii* pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone
199 prophylaxis. *Clin Infect Dis* 1999; 29: 1467-71.
- 200 16. Mitsides N, Greenan K, Green D et al. Complications and outcomes of trimethoprim-
201 sulphamethoxazole as chemoprophylaxis for pneumocystis pneumonia in renal transplant recipients.
202 *Nephrology (Carlton)* 2014; 19: 157-63.
- 203 17. Zmarlicka M, Martin ST, Cardwell SM, Nailor MD. Tolerability of low-dose
204 sulfamethoxazole/trimethoprim for *Pneumocystis jirovecii* pneumonia prophylaxis in kidney
205 transplant recipients. *Prog Transplant* 2015; 25: 210-6.
- 206 18. Fontanet A, Chalandon Y, Roosnek E, Mohty B, Passweg JR. Cotrimoxazole myelotoxicity in
207 hematopoietic SCT recipients: time for reappraisal. *Bone Marrow Transplant* 2011; 46: 1272-3.
- 208 19. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for *Pneumocystis pneumonia* (PCP)
209 in non-HIV immunocompromised patients. *Cochrane Database Syst Rev* 2014; 10: CD005590.
- 210

Table 1: Dapsone patient demographics and course observations

Patient	Gender	Haematological condition	PJP prophylaxis indication	Reason for avoiding TMP-SMX	Dapsone daily dose	Dapsone duration (days)	G6PD	Hb baseline (g/L)	Hb during dapsone (g/L)	Haemolysis noted	TMP-SMX rechallenge
1	F	Red cell aplasia	HD corticosteroids	Leukopenia	100mg	34	NA	100	73	Yes	Success
2	F	AA	AlloSCT	Leukopenia	100mg	71	NA	75	58	Yes	NP
3	F	MM	HD corticosteroids	TMP-SMX Type-B ADR, rash	100mg	28	Normal	116	94	Yes	NP
4	M	MF	HD corticosteroids	Leukopenia	100mg	17	NA	101	82	No	NP
5	M	MM	HD corticosteroids	TMP-SMX Type-A ADR, hyperkalaemia	100mg	444	Normal	141	115	No	NP
6	M	MDS	AlloSCT	TMP-SMX Type-A ADR, nausea	100mg	172	NA	124	104	No	NP
7	F	MM	HD corticosteroids	TMP-SMX Type-B ADR, rash	100mg	42	NA	104	90	No	NP

8	F	Lymphoma	CD4 lymphopenia	Leukopenia	100mg	32	NA	100	87	No	NP
9	F	AML	AlloSCT	Leukopenia	100mg	34	NA	84	79	No	NP
10	F	Lymphoma	AutoSCT	Leukopenia	100mg	12	NA	91	88	No	NP
11	M	ALL	AlloSCT	Leukopenia	100mg	82	Normal	112	111	No	NP
12	M	Lymphoma	AlloSCT	Leukopenia	100mg	182	Normal	93	95	No	NP
13	M	Lymphoma	HD corticosteroids	Leukopenia	100mg	30	Normal	88	92	No	NP
14	M	MM	AlloSCT	TMP-SMX Type-B ADR, rash	100mg	22	NA	91	97	No	Success
15	F	MF	AlloSCT	Leukopenia	50mg [^]	326	Normal	82	88	No	NP
16	F	MM	AutoSCT	TMP-SMX Type-B ADR, rash	100mg	809	NA	96	104	No	NP
17	M	AML	AlloSCT	TMP-SMX Type-A ADR, nausea	100mg	389	NA	132	151	No	NP
18	M	ALL	ALL chemotherapy	Leukopenia	100mg	8	NA	87	103	No	Success
19	M	MM	AutoSCT	TMP-SMX Type-B ADR,	100mg	117	NA	111	134	No	NP

				itch							
20	M	Lymphoma	HD corticosteroids	Leukopenia	100mg	62	NA	71	87	Yes	Success
21	F	MM	HD corticosteroids	Leukopenia	100mg	193	Normal	72	89	No	NP
22	F	Langerhans cell histiocytosis	Cladribine	Leukopenia	100mg	13	Normal	86	107	No	Success
23	M	AML	AlloSCT	Leukopenia	100mg	110	Normal	104	136	No	Success
24	M	Jak2-positive myeloproliferative disorder	Previous PJP	Leukopenia	100mg	81	Normal	74	116	No	NP

^dapson 50mg daily administered plus weekly pyrimethamine/folinic acid for concurrent toxoplasmosis prophylaxis.

Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; alloSCT, allogeneic stem cell transplant; AA, aplastic anaemia; autoSCT, autologous stem cell transplant; G6PD, glucose-6-phosphate dehydrogenase; Hb, haemoglobin; HD, high dose; MM, multiple myeloma; MDS, myelodysplastic syndrome; MF, myelofibrosis; NP, not performed; PJP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim-sulfamethoxazole.

Definitions: **Type-A** – Non-immune pharmacologically predictable adverse drug reaction (e.g. nausea, vomiting, diarrhoea, mild creatine rise due to competitive tubular excretion); **Type-B** – Immune-mediated adverse drug reaction