Date: October 21, 2015

Title: Antimicrobial prophylaxis for pneumocystis jiroveci pneumonia (PCP) after solid organ transplantation (SOT)

Clinical Question

P	*(Population/Problem)*	In pediatric solid organ transplant recipients
I	*(Intervention)*	which pneumocystis jiroveci prophylactic agent, dose and duration
C	*(Comparison)*	compared to available alternatives
O	*(Outcome)*	results in the greatest risk reduction for pneumocystis infection?

Target Population for the Recommendation

Children 0-18 years of age that have received a solid organ transplant

Recommendations

It is strongly recommended that trimethoprim/sulfamethoxazole (TMP-SMX) be utilized as the primary agent for PCP prophylaxis in pediatric SOT patients (Stern 2014 [1a]; Gabardi 2012 [4a]; Olsen 2012 [4b]; Souza 1999 [4b]; Vasconcelles 2000 [4b]; Martin 2013 [5a]).

It is recommended that the doses, alternative agents, range of duration and reasons for re-initiation of PCP prophylaxis in pediatric SOT patients presented in Table 1 be utilized in the majority of situations. (Mustafa 1994 [3b]; Ebenshade 2011 [4a]; Gabardi 2012 [4a]; Madden 2007 [4a]; Naik 2008 [4a]; Nathan 1994 [4a]; Clark, 2015 [4b]; Kim 2008 [4b]; Marras 2002 [4b]; Mitsides 2014 [4b]; Saukkonen 1996 [4b]; Souza 1999 [4b]; Vasconcelles 2000 [4b]; Fishman 2001 [5a]; Martin 2013 [5a]; Siberry 2007 [5a]).

> **Note:** There is insufficient evidence and a lack of consensus to make a recommendation regarding a precise duration of therapy for PCP prophylaxis in pediatric heart, liver, or kidney transplant recipients (Gordon 1999 [4a]; Wang 2012 [4a]; de Boer 2011 [4b]; Martin 2013 [5a]; Rodriguez 2004 [5a]).

It is recommended that PCP prophylaxis be considered in patients being treated for acute cellular or humoral rejection episodes, those with concomitant/recurrent CMV infection, those experiencing prolonged neutropenia, those who need significantly increased immunosuppression and for those with clinical or laboratory evidence of immunodeficiency (Wang 2012 [4a]; Martin 2013 [5a]; Rodriguez 2004 [5a]).

Table 1

Organ	Primary Agent	Dose	Alternative Agents[1]	Duration	Reasons for Re-initiation[3]
Heart	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/day daily or TIW (Max TMP 160mg/day)	Atovaquone Dapsone Pentamidine[2]	While on steroids (6-24 months)	Treatment for acute rejection (e.g., ATG)
Kidney	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/day daily or TIW (Max TMP 160mg/day)	Atovaquone Dapsone Pentamidine[2]	3-6 months	Treatment for acute cellular or humoral rejection (e.g., ATG, bolus corticosteroids), recurrent/active CMV infection, prolonged neutropenia
Liver	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/day daily or TIW (Max TMP 160mg/day)	Atovaquone Dapsone Pentamidine[2]	6-12 months	Treatment for acute cellular or humoral rejection (e.g., ATG, bolus corticosteroids), recurrent/active CMV infection, prolonged neutropenia
Lung	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/day daily or TIW (Max TMP 160mg/day)	Atovaquone Dapsone Pentamidine[2]	Lifelong	N/A
Small Bowel	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/day daily or TIW (Max TMP 160mg/day)	Atovaquone Dapsone Pentamidine[2]	Lifelong	N/A

Note: 1. Agents are listed alphabetically. See discussion for additional information regarding organ-specific preferred alternative agent.
2. Inhaled pentamidine is not recommended in patients < 6 years old.
3. See discussion for additional information regarding indications for re-initiation of PCP prophylaxis.

Discussion/Synthesis of Evidence related to the recommendations

Preferred agent: Trimethoprim/sulfamethoxazole is considered the prophylactic agent of choice given its cost, coverage, side effects and efficacy compared to alternatives shown in various studies including all SOT (Stern 2014 [1a]; Gabardi 2012 [4a]; Souza 1999 [4b]; Vasconcelles 2000 [4b]; Olsen 2012 [4b]; Martin 2013 [5a]).

Dosing: Various TMP-SMX dosing regimens are reported in the literature and no specific regimen has been reported to be superior over another. Standard dosing is based upon the trimethoprim component and generally is 5mg TMP/kg/day, or 150mg TMP/m^2/day. Dose may be administered orally 3 days a week or daily, 7 days a week (Red Book 2015 [5a]; Lexicomp 2014 [5a]; Kelly 2013 [5a]). The recommended maximum dose suggested of 160mg/day is thought to lead to fewer side effects compared to higher doses (Ioannidis 1996 [1b]).

Alternative agents: All listed alternative agents should be considered second line and used for those patients that are intolerant of TMP-SMX. There is insufficient evidence to recommend one alternative agent over another for use in the SOT population. The majority of evidence is extrapolated from pediatric HIV patients, pediatric oncology patients and adult transplant recipients. When a second line prophylactic agent is needed, choice of agent should be made on a case-by-case basis. Additionally, the spectrum of activity of these alternative agents is limited largely to PCP and other non-bacterial organisms; they are not appropriate for use as single-agent bacterial prophylaxis. Factors affecting choice of specific agents are listed below:

Atovaquone has been found to have similar efficacy for PCP prevention as TMP-SMX and is well tolerated. Retrospective and prospective studies in adult organ transplant patients (Gabardi 2012 [4a]) and pediatric leukemia patients (Madden 2007 [4a]) found no increased risk or incidence of PCP with atovaquone. Other considerations include dosage form and economic impact. Atovaquone is available only as a suspension and should be taken with a meal. As of January 1, 2015, per the CCHMC pharmacy, the approximate wholesale price of one-month supply of daily single-strength TMP-SMX is $23, while one-month supply of atovaquone is $2,190, dapsone is $39 and pentamidine is $119. In short, atovaquone is effective and safe but expensive (Siberry 2007 [5a]).

Dapsone has been shown to be effective for PCP prevention in immune compromised hosts, with retrospective studies in BMT patients reporting from no increased risk of PCP up to an OR of 18.8 versus TMP-SMX (Souza 1999 [4b]; Vasconcelles 2000 [4b]). Switching from TMP-SMX to dapsone is not recommended for patients that developed severe side effects on TMP-SMX, including desquamation, neutropenia, severe nephritis or hepatitis and/or known G6PD deficiency (Fishman 2001 [5a]). Dapsone side effects include hemolytic anemia and methemoglobinemia. Retrospective studies report an incidence of methemoglobinemia of 19.8% – 46% (Ebenshade 2011 [4a]; Mitsides 2014 [4b]). Dapsone-related toxicities coupled with metabolism via the hepatic cytochrome P450 CYP3A system limits its utility in liver transplant recipients (Fishman 2001 [5a]). The prevalence of dapsone-induced anemia in lung transplant patients is 5-fold higher than that reported in adult HIV patients, and may limit its utility in this patient group as well (Naik 2008 [4a]). Dapsone is effective and inexpensive but associated with more serious adverse effects than atovaquone (Siberry 2007 [5a]).

Pentamidine rates of breakthrough infection have been shown to be variable depending on the population studied and route of administration, but with an overall assessment of a higher incidence of breakthrough infection compared to TMP-SMX or dapsone (Martin 2013 [5a]). Past retrospective studies in pediatric oncology patients treated with IV pentamidine found a PCP rate of 1.3%, increased to 6.5% in infants <2 years old (Kim 2008 [4b]), while a similar group given inhaled pentamidine reported zero cases of PCP (Mustafa 1994 [3b]). A 2015 retrospective study of the CCHMC experience with IV pentamidine reported a breakthrough rate of 0.3%, which is comparable to or better than the breakthrough rates of other second line agents (Clark, 2015 [4b]). Additional retrospective studies of inhaled pentamidine in adult BMT patients found rates of 2.7-9.1% (Vasconcelles 2000 [4b]; Marras 2002 [4b]). Conversely, a retrospective review of 35 adult liver and kidney transplant recipients given inhaled pentamidine reported no cases of PCP during 4.3 and 5.7 months of administration, respectively (Saukkonen 1996 [4b]). While a retrospective study in

nine adult lung transplant patients receiving inhaled pentamidine reported no cases of PCP (Nathan 1994 [4a]), there is insufficient evidence to recommend its use in the lung transplant population.

Duration: In most SOT patients, the risk for PCP infection is generally considered highest within the first 2-6 months, although this varies with each organ (De Boer 2011 [4b]; Martin 2013 [5a]; Rodriguez 2004 [5a]). Most of the literature supports PCP prophylaxis in all SOT recipients for a duration of 6 to 12 months post-transplantation. Much of the data and recommendations on PCP infection following organ transplant are retrospective or based on extrapolation from patients with other immunocompromising etiologies; therefore, there is no consensus recommendation on precise duration of therapy for liver, kidney, or heart solid organ transplant. Lung and small bowel transplant recipients should receive lifelong prophylaxis, as their risk for PCP does not diminish post-transplantation (Wang 2012 [4a]; Gordon 1999 [4a]; Martin 2013 [5a]). Other patients that should be considered for life-long PCP prophylaxis include those with a history of prior PCP infection or chronic CMV disease (Martin 2013 [5a]).

Re-initiation of PCP prophylaxis: Recommendations regarding re-initiation are based on known risk factors and suggested indications. Minimal data are available with respect to organ specific recommendations; therefore, local consensus recommendations vary between organs. With respect to treatment for humoral rejection, plasma exchange has not been directly linked to PCP infection; therefore therapeutic plasma exchange alone is not an indication for re-initiation of prophylaxis. Other causes of increased immunosuppression include, but are not limited to, the administration of corticosteroids, rituximab, bortezomib, alemtuzumab and TNF-alpha inhibitors such as infliximab and etanercept. The duration of prophylaxis should depend on the overall degree of immunosuppression (Wang 2012 [4a]; Martin 2013 [5a]; Rodriguez 2004 [5a]).

In determining the strength of the recommendation, the development group made a considered judgment in a consensus process which was reflective of critically appraised evidence, clinical experience, and these dimensions:			
Given the dimensions below and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statement above reflect the strength of the recommendation as judged by the development group. (Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)			
1. Grade of the Body of Evidence	☒ High	☐ Moderate	☐ Low
Rationale: The majority of pediatric SOT literature included consists of retrospective studies conducted at single institutions. However, a large systematic review/meta-analysis of adult and pediatric patients, immunocompromised for a variety of reasons, and a prospective cohort in pediatric oncology patients are included. These studies were consistent with the lower quality evidence documented in the pediatric SOT population of direct interest, with respect to the strong recommendation made within this Statement regarding the primary agent for prophylaxis.			
2. Safety/Harm (Side Effects and Risks)	☒ Minimal	☐ Moderate	☐ Serious
Rationale: Thrice weekly TMP-SMX dosing with a maximum of 160mg significantly minimizes adverse effects, when compared with other TMP-SMX regimens.			
3. Health benefit to patient	☒ Significant	☐ Moderate	☐ Minimal
Rationale: PCP infections lead to significant morbidity and mortality in SOT patients.			
4. Burden to adhere to recommendation	☒ Low	☐ Unable to determine	☐ High
Rationale: Studies did not specifically address adherence. However, our consensus group believes the overall burden of adherence to be low.			
5. Cost-effectiveness to healthcare system	☒ Cost-effective	☐ Inconclusive	☐ Not cost-effective
Rationale: While only one study included addressed cost-effectiveness, this study clearly demonstrated that PCP prophylaxis with thrice weekly TMP-SMX was cost-effective.			
6. Directness of the evidence for this target population	☐ Directly relates	☒ Some concern of directness	☐ Indirectly relates
Rationale: The majority of studies were in adult solid organ transplant patients. Pediatric studies included mostly contained data from other immunocompromised patients at risk for PCP (e.g., oncology, BMT and HIV patients).			
7. Impact on morbidity/mortality or quality of life	☒ High	☐ Medium	☐ Low
Rationale: Prevention of PCP infections in SOT is necessary, as these lead to significant morbidity and mortality.			

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IMPLEMENTATION

Applicability & Feasibility Issues
Adoption of the recommendation will involve approval through appropriate organizational structures that oversee practice changes in the Integrated Solid Organ Transplant Program (ISOT).

Relevant CCHMC Tools
None were found

Outcome Measures and Process Measures
Outcome data that may be collected are rates of PCP infection among pediatric SOT recipients. In addition, adverse events to medications used for PCP prophylaxis should be collected to evaluate any negative impact of the practice change.

Process measures may include percentage of SOT patients receiving preferred PCP prophylactic regimen, as well as percentage of patients re-initiated on PCP prophylaxis after a documented episode of rejection.

SUPPORTING INFORMATION

Background/Purpose of BESt Development
The overall goal of the ISOT is to ensure the best possible outcome as defined by patient experience and value for the children who undergo SOT by acquisition and application of new discoveries and/or by improvement of the health care delivery system to provide the best possible care. Solid organ transplant patients are at risk for opportunistic infections, including PCP. In order to provide consistent care to our SOT patients, ISOT requested the development of a standardized recommendation for PCP prophylaxis in SOT patients at CCHMC.

Definitions
aOR: Adjusted odds ratio
ALL: Acute lymphocytic leukemia
AP: Aerosolized pentamidine
ATG: Anti-thymocyte globulin
BID: Twice daily
BMT: Bone marrow transplantation
CMV: Cytomegalovirus
DS: Double strength (160mg/800mg)
HA: Hemolytic anemia
HIV: Human Immunodeficiency Virus
IV: Intravenous
MHgb: Methemoglobinemia
NNT: Number needed to treat
OR: Odds ratio
PCP: *Pneumocystis jiroveci* pneumonia
RR: Relative risk
RCT: Randomized controlled trial
SOT: Solid organ transplant
TMP-SMX: Trimethoprim/sulfamethoxazole
TIW: Thrice weekly

Search Strategy & Evidence Table – *See Appendix*

Group/Team Members

Multidisciplinary Team

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Other BESt Development Support

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Conflicts of Interest were declared for each team member and:

☒ No financial or intellectual conflicts of interest were found.
☒ The following conflicts of interest were disclosed:

Note: Full tables of the LEGEND evidence evaluation system are available in separate documents:

- *Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality (abbreviated table below)*
- *Grading a Body of Evidence to Answer a Clinical Question*
- *Judging the Strength of a Recommendation (dimensions table below and Rationale)*

Table of Evidence Levels *(see note above)*:

Quality level	*Definition*
1a† or 1b†	*Systematic review, meta-analysis, or meta-synthesis of multiple studies*
2a or 2b	*Best study design for domain*
3a or 3b	*Fair study design for domain*
4a or 4b	*Weak study design for domain*
5a or 5b	*General review, expert opinion, case report, consensus report, or guideline*
5	*Local Consensus*

†a = good quality study; b = lesser quality study

Table of Language and Definitions for Recommendation Strength *(see note above)*:

Language for Strength	*Definition*
It is strongly recommended that… *It is strongly recommended that… not…*	*When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly outweigh risks and burdens. (or visa-versa for negative recommendations)*
It is recommended that… *It is recommended that… not…*	*When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.*
There is insufficient evidence and a lack of consensus to make a recommendation…	

Please cite as: Paulsen, G., Cincinnati Children's Hospital Medical Center: Best Evidence Statement Antimicrobial prophylaxis for pneumocystis jiroveci pneumonia (PCP) after solid organ transplantation (SOT), http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/recommendations/default/, BESt 206, pages 1-12, 10/21/15.

This Best Evidence Statement has been reviewed against quality criteria by two independent reviewers from the CCHMC Evidence Collaboration. Conflict of interest declaration forms are filed with the CCHMC EBDM group.
The BESt will be removed from the Cincinnati Children's website, if content has not been revised within five years from the most recent publication date. A revision of the BESt may be initiated at any point that evidence indicates a critical change is needed.

Review History

Date	*Event*	*Outcome*
10/21/15	Original Publication	New BESt developed and published

For more information about CCHMC Best Evidence Statements and the development process, contact the Evidence Collaboration at EBDMinfo@cchmc.org.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

APPENDIX: EVIDENCE SEARCH STRATEGY, RESULTS, & EVIDENCE TABLE

Criteria for considering studies for this review

Types of Studies
All studies, review articles, meta-analysis and guidelines including pediatric or adult transplant/immune compromised patients receiving PCP prophylaxis

Types of Participants
Pediatric or adult transplant/immune compromised patients

Types of Interventions
PCP prophylaxis

Types of Outcomes
Safety and efficacy

Exclusion Criteria, if any
NA

Search Strategy

Search Databases	Search Terms	Limits, Filters, & Search Date Parameters	Date of Most Recent Search
☒ MedLine *via PubMed*	• PCP • Pneumocystis • Prophylaxis • Solid organ transplant • Pediatric • Child • Pneumocystis jiroveci pneumonia (PJP)	Publication Dates or Search Dates: • 1980 – 02/2015 ☒ English Language ☐ Pediatric Evidence Only: • X ☒ Other Limits or Filters: • Human	02/25/2015
☐ CINAHL	• X	Publication Dates or Search Dates: • mm/yyyy to mm/yyyy ☐ English Language ☐ Pediatric Evidence Only: • X ☐ Other: • X	
☒ Cochrane Database for Systematic Reviews	• PCP • Pneumocystis • Prophylaxis • Solid organ transplant • Pediatric • Child • Pneumocystis jiroveci pneumonia (PJP)	Publication Dates or Search Dates: • 1980 to 08/2015 ☐ English Language ☐ Pediatric Evidence Only: • X ☐ Other: • X	08/12/2015
☐ PsychInfo	• X	Publication Dates or Search Dates: • mm/yyyy to mm/yyyy ☐ English Language ☐ Pediatric Evidence Only: • X ☐ Other: • X	
☐ Other:	• X	Publication Dates or Search Dates: • mm/yyyy to mm/yyyy ☐ English Language ☐ Pediatric Evidence Only: • X ☐ Other: • X	

Search Results & Methods

The initial search for evidence identified 102 articles.
24 articles met the inclusion criteria above.

Evidence Table for Included Articles

Study Citation	Study Type	N Sample Size	Setting/Patients	Intervention/Comparison Groups	Outcomes
	Results			**Conclusions**	**Evidence Level**
Stern et al. (2014)	Systematic Review	13 RCT's or quasi-RCTs	13 trials between '74-'08; 1412 patients, 520 were peds with ALL.	TMP-SMX vs. inhaled pentamidine vs. dapsone	• PCP Infection
	• 85% reduction in PCP with TMP-SMX prophylaxis (RR 0.15). Event rate of 6.2% in control group. Thrice weekly similar efficacy as daily.			• PCP prophylaxis with TMP-SMX is highly effective among non-HIV immunocompromised patients, NNT of 19 patients	1a
Ioannidis et al. (1996)	Meta-analysis	6583 35 RCT	Adult HIV primary and secondary prophylaxis		• Efficacy and Safety
	• The risk of discontinuing TMP-SMX because of side effects decreased by 43% (95% CI, 30% to 54%) if 1 DS tablet was given TIW instead of daily. • TMP-SMX is almost universally effective for patients who tolerated the drug. Failure rates (per 100 person-years) were highest with 2 DS/day-5.9 (95% CI, 4.4 to 7.7), 1 DS/day-0.5 (95% CI, 0 to 2.9), and 1 DS TIW or 1 SS/day-1.8 (95% CI, 1 to 3.3).			• TMP-SMX is the superior regimen. Low doses improve tolerance without losing effectiveness	1b
Mustafa et al (1994)	Prospective, Cohort	60	Pediatric chemotherapy patients	Aerosolized pentamidine 200mg/m2 every 4 weeks in patients intolerant to TMP-SMX	• PCP infection
	• Adverse reactions in 10%, including bronchospasm, cough, vomiting and nausea. Severe in 2. Pentamidine discontinued in 5% due to toxicity. No PCP cases in 21,600 patient-days.			• Inhaled pentamidine appears to be well tolerated and effective in children with malignancy	3b
Gabardi et al. (2012)	Retrospective, Cohort	185	Adult renal transplant. Single center	25 Renal SOT with atovaquone x12 months vs 160 with TMP-SMZ x 12 months.	• PCP infection
	• No PCP infection in either group. More leukopenia in TMP-SMX group requiring dose reduction, and 41/160 discontinued TMP-SMX vs 0/25.			• Atovaquone prophylaxis has similar efficacy to TMP-SMX. Cost/mo: $1500 vs $20. Dapsone $39/mo., pentamidine $100/mo.	4a
Madden et al. (2007)	Retrospective, Cohort	86	Pediatric, oncology patients.	Daily atovaquone for those intolerant of TMP-SMX	• PCP infection
	• No PCP in any patient, upper limit of 95% CI was 1.74 per 100 person-years			• Atovaquone is efficacious alternative in pediatric leukemia patients.	4a
Wang et al. (2012)	Retrospective, Case series	1241	Adult kidney, pancreas, liver, and lung; single institution	Evaluated characteristics of SOT recipients diagnosed with PCP	• Risk factors and duration
	• PCP diagnosis in 1.1% (14/1241) of total population screened with the highest incidence of PCP in lung or heart/lung (5.8%, 6/104) • All incidences of PCP in liver transplant occurred within 7 months of transplantation (none had received prophylaxis) • PCP occurred in lung transplant patients a median of 1069 days post-transplant (range 645-1583 days) • Prior to PCP diagnosis, 64% were either treated for acute rejection (diagnosed median of 59 days prior to PCP) or had CMV viremia (diagnosis median of 204 days prior to PCP)			• Life-long prophylaxis recommended in lung transplant patients • Reinstitute prophylaxis in patients with acute rejection and/or CMV disease for a period of time based on overall degree of immunosuppression	4a

Gordon et al. (1999)	Retrospective, Case series	1299	Adult kidney, kidney-pancreas, heart, lung, liver; single institution	Review cases of PCP to determine the appropriate duration of prophylaxis	• Duration
	• No patients developed PCP while receiving prophylaxis • Overall incidence of 4.8 cases per 1000 person transplant years (PTY) with highest rate in lung transplant of 22 per 1000 PTY • Incidence rate for all SOT during first year post-transplant was 14.5 cases per 1000 PTY vs. 1.9 cases per 1000 PTY in subsequent years • Incidence of PCP in lung transplant recipients did not decline after the first year post-transplant (26 per 1000 PTY vs. 19.6 per 1000 PTY) • Mean cost of hospitalization for PCP was $25,000 per case ($200,000 total). Thrice-weekly TMP-SMX therapy cost $30 per year per patient.			• Highest risk of PCP in SOT recipients within the first year post-transplant • Lung transplant patients have the highest risk of developing PCP • Extending prophylaxis beyond one year (indefinitely) in lung transplant patients is warranted • PCP prophylaxis with TMP-SMX is cost-effective if it prevents all cases of PCP	4a
Nathan et al. (1994)	Retrospective, Case series	9	Adult lung transplant (8 single, 1 double); Single institution	Pentamidine 300mg aerosolized monthly (of note, pts were subsequently switched to PO TMP/SMX)	• PCP infection and safety
	• Pts received aerosolized pentamidine for 10 months (range 4-21 months) and none developed an episode of PCP • 2/9 (22.2%) patients developed cough or bronchospasm (1 was recurrent and led to discontinuation of pentamidine)			• Suggest that inhaled pentamidine is a safe and effective alternative form of PCP prophylaxis, and may be used in patients intolerant to TMP-SMX	4a
Naik et al. (2008)	Retrospective Observational	44	Adult lung transplant recipients receiving dapsone for PCP prophylaxis	Dapsone 100mg/day	• Safety
	• 10 (22.7%) patients had hemolytic anemia (HA); all with normal G6PD enzyme levels • OR for hemolysis was 4.75 (95% CI 1.07-21.03) for each 1mg/dL increase in SCr • HA occurred within 5 months of dapsone 100mg/day initiation in all patients (range 46-156 days) 7 patients (70%) received transfusions. One (10%) patient was admitted for symptomatic anemia			• Presence of HA in lung transplant recipients is 5x higher than the reported rate in HIV patients • Dosing reductions may be considered in renal failure	4a
Esbenshade et al. (2011)	Retrospective, Cohort	167	Pediatric malignancy on dapsone. Single center	32 with confirmed MHgb vs 131 with no event, all on dapsone.	• Harm
	• Dose-dependent MHgb occurred in 32/167 (19.8%). Mean duration of dapsone to MHgb was 67d. No PCP with 213.4 patient years of follow-up.			• Higher dapsone dose (>2mg/kg/day) is associated with increased MHgb risk	4a
De Boer et al. (2011)	Retrospective, Case-control	149	Adult renal transplant. Single center.	50 renal SOT w/PCP diagnosis vs. 99 control renal SOT patients	• Risk factors, adjusted OR for PCP infection
	• Multivariate: CMV Infection (aOR 3.0, CI 1.2-7.9), Rejection (aOR 5.8, 1.9-18). 6 mo prophylaxis with frequency of 1% = NNT 24. 6 mo + Rejection risk with 1yr prophylaxis, frequency of 1% = NNT 32			• 6 months prophylaxis for all renal transplant and 12 months for age > 55 years or rejection treatment = low PCP incidence and optimal TMP-SMX toxicity	4b
Marras et al. (2002)	Retrospective, Cohort	192	Adult BMT patients	Inhaled pentamidine to those intolerant of TMP-SMX.	• PCP infection
	• PCP breakthrough rate of 2.7%. • 192 patients received aerosolized pentamidine over 1114 patient-months.			• AP is effective and well-tolerated second-line agent for PCP prophylaxis after BMT	4b

Mitsides et al. (2014)	Retrospective, Observational	26	Adult renal transplant. Single center.	Dapsone 50-100mg once daily	• Harm
	• 12/26 (46%) developed MHgb. • 12 with MHgb vs 14 w/o MHgb. 23/26 were on dapsone after intolerance to TMP-SMX			• High prevalence of dapsone associated side effects (MHgb) in adult renal transplant patients.	4b
Saukkonen et al. (1996)	Retrospective, Cohort	35	Adult liver or kidney transplant recipients intolerant of TMP-SMX.	Aerosolized pentamidine 300mg monthly in patients intolerant to TMP-SMX	• PCP infection
	• Liver recipients given monthly AP for 4.3 months, kidney recipients for 5.7 months. • No PCP cases. Adverse events of bronchospasm, dyspnea, cough, nausea			• AP is well tolerated and an effective alternative to TMP-SMX in adult liver and kidney recipients	4b
Souza et al. (1999)	Retrospective, Cohort	646	Adult BMT patients. Single center	Dapsone 50mg BID thrice weekly vs. TMP-SMX 160mg-800mg BID twice weekly	• PCP infection
	• 8 PCP cases in dapsone (4.8/100 person-years) vs 2 in TMP group (0.28/100 person-years). Dapsone RR of 18.8. • 111 Dapsone (3d/wk) vs 535 TMP (2d/wk) patients			• Dapsone 3 days per week is associated with higher rates of PCP than TMP-SMX at 2 day per week.	4b
Kim et al. (2008)	Retrospective, Observational	232	Pediatric oncology patients. Single center	Monthly IV pentamidine 4mg/kg	• PCP infection
	• PCP infection rate of 1.3% (0.18%/patient-month of treatment). BMT rate was 1.9%. Infant (<2 yo) rate of 6.5%			• IV pentamidine is efficacious in pediatric oncology/BMT patients; but less effective in <2 yo. Other options should be considered in that group.	4b
Clark et al. (2015)	Retrospective, Observational	333	Pediatric oncology (n=287) & SOT patients. Single center	Monthly IV pentamidine 4mg/kg	• PCP infection
	• PCP infection rate of 0.3% (1/333). Adverse events leading to discontinuation in 6% (20/333), most common event was tachycardia. Toxoplasmosis developed in 0.6% (2/333).			• IV pentamidine is safe and effective as second-line PCP prophylaxis in pediatric transplant patients with a PCP breakthrough rate of 0.3%	4b
Vasconcelles et al. (2000)	Retrospective, Cohort	327	Adult BMT. Single center	Aerosolized pentamidine (AP) 150mg every 2 weeks or 300mg per month, (TMP-SMX) 160/800mg orally BID 3 times per week, or dapsone 100mg orally each day	• PCP infection
	• PCP OR for AP 23.4, 4/44, 9.1% of AP patients OR dapsone not significant, 1/31, 3.2% of dapsone patients. PCP TMP-SMX 0/105 patients.			• AP is associated with less toxicity, but inferior to TMP-SMX in PCP prophylaxis in post-BMT; also associated with higher mortality.	4b
Olsen et al. (1993)	Prospective Randomized	58	Adult cardiac transplant	TMP-SMX (160mg-800mg) BID thrice weekly vs. daily vs. no treatment	• PCP infection
	• No patients on TMP-SMX (either regimen) developed PCP; 7/17 on no prophylaxis developed PCP			• TMP-SMX prophylaxis is safe and effective when administered at least thrice weekly x 4 months	4b
Fishman (2001)	Review Article	NA	Solid-organ and BMT patients	Prevention and treatment of opportunistic infections	• Opportunistic infections
				• TMP-SMX is the agent of choice • IV and inhaled pentamidine is associated with breakthrough infection in 10% • Dapsone toxicities may limit utility in liver recipients	5a
Kelly et al. (2013)	Guideline	NA	Pediatric liver transplant	Long-term medical management after pediatric liver transplant	
				• Give at least 6 months prophylaxis with TMP-SMX	5a

Study Citation	Study Type	N Sample Size	Setting/Patients	Conclusions	Outcomes/ Evidence Level
Rodriguez et al. (2004)	Review Article	NA	HIV-negative immunocompromised patient	• Risk of PCP post-SOT greatest between 2-6 months (longer with lung), during prolonged neutropenia, and during intensified immunosuppression • TMP-SMX is the agent of choice • In SOT population, TMP-SMX intolerance may predict dapsone intolerance. Dapsone is not recommended in patients with severe TMP-SMX ADE	5a
Martin et al. (2013)	American Society of Transplantation Guidelines	NA	Solid organ transplant	• TMP-SMX is first-line agent • Life-long prophylaxis recommended for, lung transplant, small bowel transplant and any patient with a history of prior PCP infection or chronic CMV disease • Prophylaxis is recommended for all SOT recipients from 6-12 months	5a
Siberry et al. (2013)	Guideline	NA	Pediatric HIV and HIV-exposed patients	•Second line PCP prophylaxis is atovaquone (AI) or dapsone (BI). Inhaled pentamidine for those that cannot take TMP-SMX, atovaquone or dapsone (BI). IV pentamidine only if no other options (BII).	• PCP infection 5a
Red Book Online (2015)	Dosing Reference	NA	HIV-exposed/positive	•Infants > 4 weeks: TMP-SMX 150mg TMP/m^2/day or 5mg TMP/kg/day in divided doses twice a day, 3 times per week on consecutive days OR 150mg TMP/m^2/day as a single daily dose, 3 times per week on consecutive days or 150mg TMP/m^2/day in divided doses, twice a day, and administered 7 days per week or 150mg TMP/m^2/day in divided doses twice a day, and administered 3 times per week on alternate days	5a
Lexicomp Online (2014)	Dosing Reference	NA	HIV-exposed/positive	• Infants > 4 weeks: TMP-SMX 150mg TMP/m^2/day or 5mg TMP/kg/day for 3-7 days of every week; total daily dose may be given in divided doses every 12 hours for 3 consecutive or alternating days, in divided doses every 12 hours every day or as a single daily dose for 3 consecutive days • Adolescents: 80-160mg TMP daily or alternatively, 160mg TMP 3 times weekly	5a