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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Primary Agent</th>
<th>Dose</th>
<th>Alternative Agents</th>
<th>Duration</th>
<th>Reasons for Re-initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>5mg TMP/kg/day or TIW (Max TMP 160mg/day)</td>
<td>Atovaquone, Dapsone, Pentamidine</td>
<td>While on steroids (6-24 months)</td>
<td>Treatment for acute rejection (e.g., ATG)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>5mg TMP/kg/day or TIW (Max TMP 160mg/day)</td>
<td>Atovaquone, Dapsone, Pentamidine</td>
<td>3-6 months</td>
<td>Treatment for acute cellular or humoral rejection (e.g., ATG, bolus corticosteroids), recurrent/active CMV infection, prolonged neutropenia</td>
</tr>
<tr>
<td>Liver</td>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>5mg TMP/kg/day or TIW (Max TMP 160mg/day)</td>
<td>Atovaquone, Dapsone, Pentamidine</td>
<td>6-12 months</td>
<td>Treatment for acute cellular or humoral rejection (e.g., ATG, bolus corticosteroids), recurrent/active CMV infection, prolonged neutropenia</td>
</tr>
<tr>
<td>Lung</td>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>5mg TMP/kg/day or TIW (Max TMP 160mg/day)</td>
<td>Atovaquone, Dapsone, Pentamidine</td>
<td>Lifelong</td>
<td>N/A</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>5mg TMP/kg/day or TIW (Max TMP 160mg/day)</td>
<td>Atovaquone, Dapsone, Pentamidine</td>
<td>Lifelong</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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 (Ster 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/m²/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]).

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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:

| 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. |
Reference List


Infectious Disease/Pneumocystis Jiroveci Pneumonia (PCP)/Antimicrobial Prophylaxis


Vasconcelles MJ, Bernardo MV, King C, Weller EA, Antin JH. (2000) 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. Biology of Blood and Marrow Transplantation. 6(1): p. 35-43. [4b]


**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
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Team Members/Co-Authors: Leanna Darland, PharmD, Pharmacy Clinical Specialist – Lung Transplant

Other BEST Development Support
Content Reviewers: Christopher Towe, MD; Marc Schecter, MD; Clifford Chin, MD; Thomas Ryan, MD; John Bucuvalas, MD; David Hooper, MD

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):

<table>
<thead>
<tr>
<th>Quality level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a† or 1b†</td>
<td>Systematic review, meta-analysis, or meta-synthesis of multiple studies</td>
</tr>
<tr>
<td>2a or 2b</td>
<td>Best study design for domain</td>
</tr>
<tr>
<td>3a or 3b</td>
<td>Fair study design for domain</td>
</tr>
<tr>
<td>4a or 4b</td>
<td>Weak study design for domain</td>
</tr>
<tr>
<td>5a or 5b</td>
<td>General review, expert opinion, case report, consensus report, or guideline</td>
</tr>
<tr>
<td>5</td>
<td>Local Consensus</td>
</tr>
</tbody>
</table>

†a = good quality study; b = lesser quality study
Table of Language and Definitions for Recommendation Strength *(see note above)*:

<table>
<thead>
<tr>
<th>Language for Strength</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is strongly recommended that...</td>
<td>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)</td>
</tr>
<tr>
<td>It is strongly recommended that... not...</td>
<td></td>
</tr>
<tr>
<td>It is recommended that...</td>
<td>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.</td>
</tr>
<tr>
<td>It is recommended that... not...</td>
<td></td>
</tr>
<tr>
<td>There is insufficient evidence and a lack of consensus to make a recommendation...</td>
<td></td>
</tr>
</tbody>
</table>
### Search Strategy

<table>
<thead>
<tr>
<th>Search Databases</th>
<th>Search Terms</th>
<th>Limits, Filters, &amp; Search Date Parameters</th>
<th>Date of Most Recent Search</th>
</tr>
</thead>
</table>
| **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

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Study Type</th>
<th>N Sample Size</th>
<th>Setting/Patients</th>
<th>Intervention/Comparison Groups</th>
<th>Outcomes</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al. (2014)</td>
<td>Systematic Review</td>
<td>13 RCT’s or quasi-RCTs</td>
<td>13 trials between ‘74-’08; 1412 patients, 520 were peds with ALL.</td>
<td>TMP-SMX vs. inhaled pentamidine vs. dapsone</td>
<td>• 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.</td>
<td>1a</td>
</tr>
<tr>
<td>Ioannidis et al. (1996)</td>
<td>Meta-analysis</td>
<td>6583 RCTs</td>
<td>Adult HIV primary and secondary prophylaxis</td>
<td></td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>Mustafa et al. (1994)</td>
<td>Prospective, Cohort</td>
<td>60 Pediatric chemotherapy patients</td>
<td>Aerosolized pentamidine 200mg/m2 every 4 weeks in patients intolerant to TMP-SMX</td>
<td>• 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabardi et al. (2012)</td>
<td>Retrospective, Cohort</td>
<td>185 Adult renal transplant. Single center</td>
<td>25 Renal SOT with atovaquone x12 months vs 160 with TMP-SMX x 12 months.</td>
<td>• No PCP infection in either group. More leukopenia in TMP-SMX group requiring dose reduction, and 41/160 discontinued TMP-SMX vs 0/25.</td>
<td>• Atovaquone prophylaxis has similar efficacy to TMP-SMX. Cost/mo: $1500 vs $20. Dapsone $39/mo., pentamidine $100/mo.</td>
<td>4a</td>
</tr>
<tr>
<td>Madden et al. (2007)</td>
<td>Retrospective, Cohort</td>
<td>86 Pediatric, oncology patients</td>
<td>Daily atovaquone for those intolerant of TMP-SMX</td>
<td>• No PCP in any patient, upper limit of 95% CI was 1.74 per 100 person-years</td>
<td>• Atovaquone is efficacious alternative in pediatric leukemia patients.</td>
<td>4a</td>
</tr>
<tr>
<td>Wang et al. (2012)</td>
<td>Retrospective, Case series</td>
<td>1241 Adult kidney, pancreas, liver, and lung; single institution</td>
<td>Evaluated characteristics of SOT recipients diagnosed with PCP</td>
<td>• 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)</td>
<td>• Life-long prophylaxis recommended in lung transplant patients • Reinstitution prophylaxis in patients with acute rejection and/or CMV disease for a period of time based on overall degree of immunosuppression</td>
<td>4a</td>
</tr>
<tr>
<td>Best Evidence Statement – BEST</td>
<td>Duration</td>
<td>PCP infection and safety</td>
<td>Safety</td>
<td>Harm</td>
<td>Risk factors, adjusted OR for PCP infection</td>
<td>PCP infection</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Gordon et al. (1999)</td>
<td>Retrospective, Case series</td>
<td>1299</td>
<td>Adult kidney, kidney-pancreas, heart, lung, liver; single institution</td>
<td>Review cases of PCP to determine the appropriate duration of prophylaxis</td>
<td>Highest risk of PCP in SOT recipients within the first year post-transplant</td>
<td>PCP prophylaxis with TMP-SMX is cost-effective if it prevents all cases of PCP</td>
</tr>
<tr>
<td>Nathan et al. (1994)</td>
<td>Retrospective, Case series</td>
<td>9</td>
<td>Adult lung transplant (8 single, 1 double); Single institution</td>
<td>Pentamidine 300mg aerosolized monthly (of note, pts were subsequently switched to PO TMP/SMX)</td>
<td>Suggest that inhaled pentamidine is a safe and effective alternative form of PCP prophylaxis, and may be used in patients intolerant to TMP-SMX</td>
<td></td>
</tr>
<tr>
<td>Naik et al. (2008)</td>
<td>Retrospective Observational</td>
<td>44</td>
<td>Adult lung transplant recipients receiving dapsone for PCP prophylaxis</td>
<td>Dapsone 100mg/day</td>
<td>Presence of HA in lung transplant recipients is 5x higher than the reported rate in HIV patients</td>
<td>Dosing reductions may be considered in renal failure</td>
</tr>
<tr>
<td>Esbenshade et al. (2011)</td>
<td>Retrospective, Cohort</td>
<td>167</td>
<td>Pediatric malignancy on dapsone; Single center</td>
<td>32 with confirmed MHgb vs 131 with no event, all on dapsone.</td>
<td>Higher dapsone dose (&gt;2mg/kg/day) is associated with increased MHgb risk</td>
<td></td>
</tr>
<tr>
<td>De Boer et al. (2011)</td>
<td>Retrospective, Case-control</td>
<td>149</td>
<td>Adult renal transplant. Single center.</td>
<td>50 renal SOT w/PCP diagnosis vs. 99 control renal SOT patients</td>
<td>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</td>
<td>6 months prophylaxis for all renal transplant and 12 months for age &gt; 55 years or rejection treatment = low PCP incidence and optimal TMP-SMX toxicity</td>
</tr>
<tr>
<td>Marras et al. (2002)</td>
<td>Retrospective, Cohort</td>
<td>192</td>
<td>Adult BMT patients</td>
<td>Inhaled pentamidine to those intolerant of TMP-SMX.</td>
<td>AP is effective and well-tolerated second-line agent for PCP prophylaxis after BMT</td>
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</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Infectious Disease/Pneumocystis Jiroveci Pneumonia (PCP)/Antimicrobial Prophylaxis/BEST 206

Copyright © 2015 Cincinnati Children’s Hospital Medical Center; all rights reserved.
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Type</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Prophylaxis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsides et al. (2014)</td>
<td>Retrospective, Observational</td>
<td>26 Adult renal transplant. Single center.</td>
<td>Dapsone 50-100mg once daily</td>
<td>• Harm</td>
<td></td>
</tr>
<tr>
<td>• 12/26 (46%) developed MHgb. • 12 with MHgb vs 14 w/o MHgb. 23/26 were on dapsone after intolerance to TMP-SMX</td>
<td>• High prevalence of dapsone associated side effects (MHgb) in adult renal transplant patients.</td>
<td>4b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saukkonen et al. (1996)</td>
<td>Retrospective, Cohort</td>
<td>35 Adult liver or kidney transplant recipients intolerant of TMP-SMX.</td>
<td>Aerosolized pentamidine 300mg monthly in patients intolerant to TMP-SMX</td>
<td>• PCP infection</td>
<td></td>
</tr>
<tr>
<td>• 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</td>
<td>• AP is well tolerated and an effective alternative to TMP-SMX in adult liver and kidney recipients</td>
<td>4b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Souza et al. (1999)</td>
<td>Retrospective, Cohort</td>
<td>646 Adult BMT patients. Single center</td>
<td>Dapsone 50mg BiD thrice weekly vs. TMP-SMX 160mg-800mg BID twice weekly</td>
<td>• PCP infection</td>
<td></td>
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<tr>
<td>• 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</td>
<td>• Dapsone 3 days per week is associated with higher rates of PCP than TMP-SMX at 2 day per week.</td>
<td>4b</td>
<td></td>
<td></td>
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<tr>
<td>Kim et al. (2008)</td>
<td>Retrospective, Observational</td>
<td>232 Pediatric oncology patients. Single center</td>
<td>Monthly IV pentamidine 4mg/kg</td>
<td>• PCP infection</td>
<td></td>
</tr>
<tr>
<td>• PCP infection rate of 1.3% (0.18%/patient-month of treatment). BMT rate was 1.9%. Infant (&lt;2 yo) rate of 6.5%</td>
<td>• IV pentamidine is efficacious in pediatric oncology/BMT patients; but less effective in &lt;2 yo. Other options should be considered in that group.</td>
<td>4b</td>
<td></td>
<td></td>
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<tr>
<td>Clark et al. (2015)</td>
<td>Retrospective, Observational</td>
<td>333 Pediatric oncology (n=287) &amp; SOT patients. Single center</td>
<td>Monthly IV pentamidine 4mg/kg</td>
<td>• PCP infection</td>
<td></td>
</tr>
<tr>
<td>• 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).</td>
<td>• IV pentamidine is safe and effective as second-line PCP prophylaxis in pediatric transplant patients with a PCP breakthrough rate of 0.3%</td>
<td>4b</td>
<td></td>
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<tr>
<td>Vasconcelles et al. (2000)</td>
<td>Retrospective, Cohort</td>
<td>327 Adult BMT. Single center</td>
<td>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</td>
<td>• PCP infection</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td>• AP is associated with less toxicity, but inferior to TMP-SMX in PCP prophylaxis in post-BMT; also associated with higher mortality.</td>
<td>4b</td>
<td></td>
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<tr>
<td>Olsen et al. (1993)</td>
<td>Prospective Randomized</td>
<td>58 Adult cardiac transplant</td>
<td>TMP-SMX (160mg-800mg) BID thrice weekly vs. daily vs. no treatment</td>
<td>• PCP infection</td>
<td></td>
</tr>
<tr>
<td>• No patients on TMP-SMX (either regimen) developed PCP; 7/17 on no prophylaxis developed PCP</td>
<td>• TMP-SMX prophylaxis is safe and effective when administered at least thrice weekly x 4 months</td>
<td>4b</td>
<td></td>
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<tr>
<td>Fishman (2001)</td>
<td>Review Article</td>
<td>NA Solid-organ and BMT patients</td>
<td>Prevention and treatment of opportunistic infections</td>
<td>• Opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>• 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</td>
<td>5a</td>
<td></td>
<td></td>
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<tr>
<td>Kelly et al. (2013)</td>
<td>Guideline</td>
<td>NA Pediatric liver transplant</td>
<td>Long-term medical management after pediatric liver transplant</td>
<td>• Give at least 6 months prophylaxis with TMP-SMX</td>
<td>5a</td>
</tr>
<tr>
<td>Study Citation</td>
<td>Study Type</td>
<td>N Sample Size</td>
<td>Setting/Patients</td>
<td>Conclusions</td>
<td>Outcomes/ Evidence Level</td>
</tr>
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</tbody>
</table>
| 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                      |