Health Policy & Clinical Effectiveness Program

Evidence-Based Care Guideline

Pneumocystis Carinii Pneumonia Prophylaxis following Solid Organ Transplants*

Original Publication Date: 01-12-01
Reviewed and Revised 01-07

Target Population

Inclusion: These guidelines are intended for use in the following types of transplant patients from 0 to 18 years of age.

- Patients receiving prophylaxis to prevent primary infection following solid organ transplant (from transplantation to 6-12 months following transplantation depending on level of immunosuppression)
- Patients that experience graft rejection or Graft versus Host Disease > than 1 year following transplantation

Exclusion: These guidelines are not intended for use in the following types of transplantation patients.

- Patients presenting with prior history of PCP
- Patients with PCP (see disease definition)
- Patients requiring marked alterations in routine prophylaxis due to significant complications of illness
- Patients experiencing immunosuppression for reasons other than transplantation

Introduction

References in parentheses ( ) Evidence strengths in [ ] (See last page for definitions)

Infection remains a significant cause of morbidity and mortality in patients following solid organ transplant. Significant infection has been described to occur in up to 50% of patients *(Tolkoff-Rubin, 2000 [S]).* Infection following blood and marrow transplants accounts for 20 to 40% of morbidity and mortality *(Tutschka, 1988 [S]).* Pneumocystis (jiroveci) Carinii Pneumonia (PCP) is one of these significant infections.

The purpose of this guideline is to a) examine the published incidence of Pneumocystis Carinii Pneumonia (PCP) in patients undergoing heart, kidney, or liver transplants and b) develop recommendations for primary prophylaxis for these post transplant patients based on the best scientific evidence available, taking into consideration age of the recipient, prior exposure to the pathogen, type of transplant, degree of immunosuppression, and post transplant interval. Where evidence was minimal or non-existent, literature from pediatric and adult Human Immunodeficiency Virus (HIV) population was reviewed and evidence extrapolated as appropriate.

Disease Definition:
The recommendations of this evidence based clinical practice guideline address prophylaxis and not treatment options. PCP is diagnosed by identifying trophozoites, cyst walls or nuclear components from the organism in tissue or fluid obtained from the lower respiratory tract of an individual with clinical and/or radiographic respiratory disease. This is an indication to discontinue prophylaxis and begin a therapeutic regimen.

Etiology

Epidemiology: Pneumocystis carinii is a single cell organism more closely resembling fungi than protozoa. Although the route of infection acquisition is not entirely clear, experimental evidence supports airborne transmission. In solid organ and blood and marrow transplant recipients it is unclear whether symptomatic disease results from reactivation of quiescent infection or primary infection. Although rare reports of disseminated disease exist, infection occurs almost exclusively in the lung, where the organism causes a severe reactive and desquamative pneumonitis *(Hughes, 1998 [O]; Walzer, 2000 [O]).*

The overall incidence of PCP in solid organ transplant recipients not on prophylaxis is 4.9% (Table 1).

Table 1: Incidence of PCP without & with prophylaxis

Organ	Range	Range
	Without prophylaxis ^	With TMP/Sulfa Prophylaxis *
Heart/Lung & Lung	9-88%^	0%*
Heart	1.3-41%^^	0%**
Liver	9-13%^^^	<1.0%***
Kidney	0.6-24%^^^^	0.0%****
Blood & Marrow	5-15%^^^^^	0.1%*****

Without: *(Kramer, 1992 [D]; Gryzan, 1988 [D] ^); (Olsen, 1993 [B] ^^); (Colombo, 1992 [D]^^^); (Lufft, 1996 [D], Branten, 1995 [D] ^^^^); (Krowka, 1985 [S]^^^^); (Gordon, 1999 [D]^^,^^^,^^^^)*
With: *(Kramer, 1992 [D]*); (Olsen, 1993 [B]**); (Saukkonen, 1996 [D];Torres-Cisneros,1996 [C]; Singh, 1996 [C]***) (Fox, 1990 [B]; Branten, 1995 [D]****). (Colby, 1999 [B]; Hoyle, 1994 [D]*****); (Gordon, 1999 [D]**, ***,****)*

[a] Please cite as: **Infection Prophylaxis – PCP Clinical Effectiveness Team, Cincinnati Children's Hospital Medical Center:** Evidence-based care guideline for Pneumocystis Carnii Pneumonia Prophylaxis following Solid Organ Transplants, http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based /PCP-Transplant, Guideline 15, pages 1-9, January 2007.

The incidence is less for recipients on prophylaxis. The reported incidence of PCP in patients following solid organ, blood and marrow transplants varies in part due to discrepancies in definitions of clinical disease, use of different prophylactic regimens, and duration and timing of the surveillance.

Timing of Infection:

Based on available evidence it appears that PCP rarely develops in the first month following transplantation *(Gordon, 1999 [D]).*

Risk Factors:

1. The primary risk factor for PCP in transplant patients is immunosuppression. Risk for PCP increases with heightened immunosuppression associated with treatment of acute or chronic rejection or graft versus host disease *(Kramer, 1992 [D]; Lufft 1996 [D];Radisic 2003 [D]).*

Note: Heightened immunosuppression may include but is not limited to high dose corticosteroids *(Llufft, 1996 [D])* antibody therapy with OKT3 *(Kramer 1992[D])* or antithymocyte globulin *(Janner 1996 [D]; Radisic 2003 [D]).*

2. Risk for PCP is increased when the CD4+ T-lymphocyte count is < 200-500/μL or total lymphocytes are < 15% *(CDC, 1999 HIV guideline; Mansharamani, 2000 [C]; Castagnola, 1995 BMT case report).*

3. Direct exposure of immunocompromised patients to others with active PCP may increase the risk of developing PCP *(Chave, 1991 [D])*

Guideline Recommendations

Prophylaxis

1. It is recommended that the initiation of prophylaxis be considered within the first month after transplantation and continued for a minimum period of 6 months for solid organ *(Gordon, 1999 [D]; Fishman, 1998 [S]; Rubin, 1981 [S])*.

2. It is recommended that in addition to the initial prophylaxis period, re-initiation of prophylaxis be considered for solid organ and blood and marrow transplant recipients during periods of either rejection or Graft versus Host Disease therapy because of heightened immunosuppression *(Gordon, 1999 [D]; Kramer, 1992 [D])*.

3. It is recommended that trimethoprim-sulfamethoxazole (TMP-SMX) be considered as first-line therapy in the prophylaxis of PCP in these transplant recipient populations. TMP-SMX has been demonstrated in studies to be more efficacious than either dapsone and aerosolized pentamidine, although many of these studies have been completed in the HIV patient population *(AAP Red Book 2000 [E], Ioannidis 1996 [M], Dykewicz, 1999 CDC/MMWR [E], Vasconcelles 2000 [D]; Wazir 2004 [S])*.

The recommended dose of TMP-SMX is 5 mg/kg/day (based on the trimethoprim component, maximum daily dose 320 mg) given on a thrice- weekly schedule such as Monday-Wednesday-Friday, or on three consecutive days per week (see Table 2).

Note 1: TMP-SMX has been shown to prevent PCP in solid organ, blood and marrow transplant recipients *(Olsen, 1993 [B]; Kramer, 1992 [D]; Elinder,1992 [D]; Gordon, 1999,[D]; Hughes, 1987 [B]; Torre-Cisnernos, 1996 [C]; USPHS Guideline, 1997 [O])* and when given three times per week, toxicity is decreased *(Ioannidis, 1996 [M];Bozzette, 2-1995 [B]).*

Note 2: In addition to preventing PCP, TMP-SMX may also prevent most nocardia and toxoplasmosis infections *(Gordon, 1999 [D]; Fishman, 1998 [S]; USPHS guideline, 1997 [E]).*

4. It is recommended that aerosolized pentamidine be considered as alternative prophylactic therapy in transplant recipients who have myelosuppression or who have experienced an allergic reaction to TMP-SMX *(Saukkonen, 1996 [D]; Link, 1993 [C])* for children six years of age or older. For the purpose of these guidelines, myelosuppression is defined as an absolute neutrophil count < 1000.

Another alternative may be dapsone for children >1 month to six years who may be unable to tolerate the administration of an aerosolized treatment *(Dykewicz, 1999 CDC/MMWR [E]; Maltezou, 1997 [D])* (see Table 2).

Note: Dapsone and aerosolized pentamidine have been shown to be equally efficacious for the prevention of PCP *(Hughes, 1988 [S]; Ioannides, 1996 [M]; Slavin, 1992 [B]*. However, the risk for severe side effects is four fold greater with dapsone than with pentamidine *(Ioannides, 1996 [M]).* The adverse effects with dapsone are not shown as different when compared to TMP-SMX *(Ioannidis, 1996 [M]; Mallolas, 1993 [B]; Vasconcelles, 2000 [D]).* Dapsone is less expensive compared to aerosolized pentamidine.

It is recommended that *intravenous* pentamidine be considered for use in patients with myelosuppression (ANC <1000) or who have experienced adverse reactions with either TMP-SMX or dapsone *(Gupta, 1997 [O]; Lidman, 1993 [D])*. Effective dosing may not be achieved with aerosolized pentamidine in children < 6 years of age *(CDC/MMWR 1995 [E]; Hand, 1994 [C])* (see Table 2).

Note: Severe adverse effects from the use of intravenous Pentamidine for PCP prophylaxis are uncommon. Mild adverse effects are primarily infusion related (e.g. rash puritis). More significant adverse effects including hypoglycemia and pancreatitis have been reported with daily intravenous use but are rare with prophylactic use *(Lidman,1993 [D]; Gupta, 1997 [O]).*

6. If all recommended regimens are not tolerated atovaquone might be considered for prophylaxis *(AAP 2000 Red Book [E]).*

Note: Although atovaquone has been shown to be effective in the prophylaxis of PCP in adolescent and

adult HIV population *(El-Sadr, 1998 [A])* there is little known of its use in children *(Hughes, 1998 [S]; Meyers, 2001 [C]).*

7. It is recognized that randomized trials of PCP prophylaxis have not been conducted against current immunosuppression therapies. However, it remains local expert opinion that prophylaxis for PCP still be considered following solid organ transplant *(local expert consensus [E]).*

Table 2: Medications and Prophylactic Dosages

Medication	Pediatric Dose	Adult Dose/ Pediatric Maximum Dose
TMP-SMX	5 mg/kg/day TMP component 3X/wk	320 mg TMP/day 3X/wk
Dapsone (for ≥ 1 month of age)	2 mg/kg once daily or 4 mg/kg once every week	100 mg/day 200 mg/week
Aerosolized Pentamidine (for ≥ 6 years of age)	300 mg monthly via Respirgard II inhaler	300 mg monthly via Respirgard II inhaler
Intravenous Pentamidine (for < 6 years of age)	4 mg/kg monthly	4 mg/kg monthly (no maximum single dose)

(*Hughes, 1998 [S]; Mcintosh, 1999 [C]; CDC/MMWR 1995 [E]).*

Clinical Surveillance for PCP

1. It is recommended that recipients of solid organ, blood and marrow transplants at risk for PCP be monitored for hypoxemia and changes on chest radiograph if tachypnea, dyspnea, or cough develop, regardless of the presence or absence of other findings (*Janner, 1996 [D]; Fishman, 1998 [S]).*

Note 1: Oxygen saturations < 90% or chest radiograph findings consistent with PCP may indicate reason for suspicion of *Pneumocystis carinii (Janner, 1996 [D]; Olson, 1993 [B])*.

Note 2: Individuals with confirmed PCP often have abnormal findings on chest radiograph *(Egan, 1996 [D]; Fishman, 1998 [S])*; only 3.5% of confirmed cases of PCP are associated with normal chest radiographs *(Gordon, 1999 [D]).*

Note 3: Radiographic findings associated with PCP may vary widely. They may be alveolar or interstitial in nature, and most often they are diffuse, bilateral, symmetric and reticular in appearance. However, atypical patterns may include isolated lobar disease, focal parenchymal lesions, cavitary or military patterns, endobronchial lesions or pleural effusions *(Kuhlman, 1996 [S]).*

Note 4: Fever and/or auscultory findings of pneumonia may be minimal *(Janner, 1996 [D]; Gordon, 1999 [D]).*

Laboratory Assessment for PCP

1. It is recommended that individuals who are suspected to have PCP have tissue or fluid obtained from the lower respiratory tract for pathologic evaluation. Bronchoscopy with bronchoalveolar lavage (BAL) should be strongly considered, as children frequently cannot expectorate true lower respiratory specimens.

Note 1: The diagnostic sensitivity is greater for BAL (95-100%) *(von Eiff, 1995 [D]; Fraser, 1996, [C])* than for sputum specimens (50-60%) *(Metersky, 1998 [D])*; therefore, a sputum negative for *P. carinii* does not rule out the diagnosis of PCP.

Note 2: Transbronchial lung biopsy does not significantly increase the diagnostic sensitivity for PCP *(Fraser, 1996 [C])*; however, open lung biopsy may be required in 1-5% of cases *(Yale, 1996 [D]; Thomas, 1998 [S]).*

2. It is recommended that Grocott's Methenamine Silver (GMS) staining be utilized when a BAL specimen is obtained.

Note 1: GMS staining of BAL specimens is associated with 97% sensitivity for PCP diagnosis *(Baughman, 1989 [C]).* (See Table 3)

Table 3: Laboratory Screening Sensitivity & Specificity

Test	Sensitivity	Specificity
GMS	97%	96%
PCR (nested & single)	100%	90-97%
Fluorescent Antibody	97%	98%

(Baughman, 1989 [C]; Sing, 2000 [C])

Note 2: The polymerase chain reaction (PCR) is a tool for Pneumocystis detection, found in one study to be the most sensitive method for detecting low levels of Pneumocystis carnii typical of BAL and sputum samples *(Pinlaor 2004 [C]).* However, the clinical utility of PCP PCR needs to be validated and it is not widely available.

Note 3: In contrast to PCR or fluorescent antibody staining, GMS may also be more clinically useful by detecting etiologic agents other than Pneumocystis, including yeasts, pseudohyphae and true hyphae. In some cases, even bacteria can be visualized with the GMS stain. In addition, routine staining provides a more rapid response time as compared to PCR testing *(Armbruster, 1995 [C]; Sing, 2000 [C]); (Pinlaor 2004 [C]).*

Infection Prophylaxis - PCP
Clinical Effectiveness Team Members 2000

Brett Loechelt, M.D.	(Blood & Marrow)
James Acton, M.D.	(Pulmonology)
John Bucuvales, M.D	(Liver)
Beverly Connelly, M.D.	(Infectious Disease)
Stephen Guthery, M.D.	(Fellow)
Robert Spicer, M.D.	(Heart)
Paul Steele, M.D.	(Pathology)
Fred Strife, M.D.	(Kidney)
David Witte, M.D.	(Pathology)
Stavra Xanthakos, M.D.	(Chief Resident)

Patient Services

Tamara Hutson, Pharm D	(Pharmacy)
Joyce Slusher, R.N.	(Transplant Coordinator)
Rhonda Struck, R.N.	(T5A - Director)
Karen Uzark, PhD, CPNP	(Heart Center)
Carla Wallace, Pharm D	(Pharmacy)

2006 Revision

CHMC Physicians

Peter Manning , MD	(Cardiac Surgery)
Catherine Dent, MD	(Cardiac ICU/Transplant)
William Border, MD	(Cardiology)
James Spaeth MD	(Anesthesia)
Michael Alice Moga, MD	(Cardiology/Fellow)
Jeffrey Anderson, MD	(Cardiology/Fellow)
Pirooz Eghtesady, MD	(Cardiac Surgery/Transplant)
Jens Goebel, MD	(Nephrology/Transplant)
Kathleen Campbell, MD	(Liver Transplant)

Patient Services

Karen Uzark, PhD, CPNP	(Cardiology/Transplant)
Joyce Slusher, CPNP	(Cardiology/Transplant)
Christa Barlow, CNP	(Cardiac Surgery)
Melissa Magness, RN	(Cardiac ICU)
Tammy Lingsch, RN	(A6 Central)
Cynthia Wedekind, Pharm D	(Clinical Pharmacy)
Jenni Raake, RRT	(Respiratory Care)
Shawna Kirkendall, RN	(Manager, A 6 Central)

Clinical Effectiveness

Eloise Clark, MPH
Danette Stanko, MA, MPH, Epidemiologist
Kate Rich, Lead Decision Support Analyst
Carol Frese, RN, Medical Reviewer
Eduardo Mendez, RN, MPH, Director, Evidence-Based Care
Edward Donovan, MD, Medical Director, Clinical Effectiveness

Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices.

To select evidence for critical appraisal by the group for the update of this guideline, the Medline, EmBase and the Cochrane databases were searched. Evidence from 2000 and before was verified for inclusion in the guidelines. Evidence from 2001 to the present was reviewed for relevance to the clinical topics/questions to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to pneumocystis carnii pneumonia and solid organ transplant and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. April 2000 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

CCHMC Grading Scale			
M	Meta-analysis or Systematic Review	O	Other evidence
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
S	Review article	X	No evidence

Experience with the implementation of earlier publications of this guideline has provided learnings which have been incorporated into this revision.

Once the guideline has been in place for three years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

The guideline has been reviewed and approved by clinical experts not involved in the development process, distributed to senior management, and other parties as appropriate to their intended purposes.

The guideline was developed without external funding.

Copies of this Evidence-based Care Guideline (EBCG) and its any available implementation tools are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm Examples of approved uses of the EBCG include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care guidelines;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the EBCG may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This guideline 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 guideline is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about these guidelines and their supporting evidences contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4770 or thc@cchmc.org .

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Note: Some references included in this listing are not cited in the guidelines and are included for those interested in pursuing a further in-depth review of these subjects.

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