

***Pneumocystis jirovecii* infections  
in (non HIV-infected) adult and pediatric  
hematology patients:  
*Part B: Clinical aspects*  
“risk factors, presentation and prevention”  
Focus on pneumonia**

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# Pneumocystis infections

## Epidemiology (I)

- First reported as a cause of pneumonia in premature and malnourished children following world war II (Giese 1953)
- 1960's and 1970's: primarily diagnosed among patients with hematologic malignancies (Hughes 1975)
- 1980's: dramatically increased prevalence during HIV epidemic
  - But significant reduction following routine prophylaxis in HIV-infected patients
- A cause of pneumonia in patients with non-HIV types of immunodeficiencies not receiving prophylaxis:
  - Children with ALL: 16% and higher (Hughes 1975)
  - Primary or secondary central nervous system tumors (Henson 1991)
  - Allogeneic HSCT: 5-15% (Meyers 1982)
  - Solid organ transplantation: 5-15% (highest in lung and heart-lung transplants) (Gryzan 1988)
  - Immunosuppressive drugs, esp. glucocorticoids in combination with cytotoxic agents (e.g. cyclophosphamide)



# Pneumocystis infections

## Epidemiology (II)

- Transmission by airborne route
- Acquisition in humans most likely by person-to-person spread (Thomas 2004)
- Nearly universal seropositivity in immunocompetent children 2 years of age (Vargas 2001)
- Primary infection is generally asymptomatic or a mild, self-limiting upper respiratory tract infection
- Mortality: up to 50% in patients with lymphoid malignancies (Sepkowitz 1993)
- Pneumocystis *jirovecii* Pneumonia (PjP) may develop while tapering immunosuppression (steroids) or during maintenance chemotherapy for ALL (Wu 2004)



# PjP in adult patients with hematological disorders



# Risk factors for PjP in adult patients with hematological disorders

## 1. Classical risk factors:

- Use of corticosteroids
- Cytomegalovirus infection
- Treatment of graft rejection or graft-versus-host disease (GvHD)
- Lymphocytopenia
- Low CD4 cell count (no threshold value identified in non-HIV)
  
- Lymphoid malignancies, esp. ALL
  
- Allogeneic HSCT:
  - impaired thymic function<sup>1</sup> (→age) and CD45RA+CD31+CD4+ T cell numbers

<sup>1</sup>Schürmann 2013



# Risk factors for PjP in adult patients with hematological disorders

## 2. Newly identified risk factors:

- Co-existing pulmonary HSV and/or CMV infection
- Pre-existing lung disease<sup>2</sup>
- *Pneumocystis jirovecii* carriage
- Patient-to-patient transmission
- Genetic risk factors<sup>3</sup>:
  - Dectin-1 polymorphisms<sup>4</sup>
- Use of cytokine antibodies: adalimumab<sup>5</sup>, etanercept
- Lymphocyte depleting agents: alemtuzumab<sup>6</sup>, rituximab, fludarabine (FCR!)<sup>7</sup>
- Use of temozolomide



# CLINICAL PRESENTATION OF PjP IN NON-HIV+ PATIENTS

PjP symptoms classically include **fever, cough, dyspnea, and interstitial pneumonia**. However:

- fever may be absent or minimal at the beginning, and especially in case of use of steroids or antipyretic drug
- respiratory symptoms may be minimal until advanced disease
- chest-X ray may be normal for several days (*Pagano 2002, De Castro 2005, Torres 2006, Vogel 2007, Monnet 2008, Toper 2011, Ainoda 2012, Martin-Garrido 2013*)

Rare extra-pulmonary Pj infections, including diffuse, multi-visceral forms, have been reported almost exclusively in AIDS patients and before the era of PCR (*Ng VL, 1997*)



# MAIN DIFFERENCES ON CLINICAL PRESENTATION OF PjP BETWEEN HIV<sup>+</sup> AND NON-HIV<sup>+</sup> PATIENTS

	HIV <sup>+</sup>	Non-HIV <sup>+</sup>	References
PjP may reveal the underlying disease	Yes	Exceptional (3 cases of ATLL due to HTLV infection, revealed by PjP)	Moryiama 1988, Elias 2011
Pts. received corticosteroids before the diagnosis of PjP	No	Yes (90%), mostly during tapering or after stopping	Sepkowitz 1993, Mansharamani 2000, Toper 2005, Mc Kinnel 2012, Martin-Garrido 2013
Onset Duration of symptoms before diagnosis	Progressive Long (3-5 weeks)	Acute Short (4-8 days)	Monnet 2008, Tasaka 2010, Hardak 2010
Hypoxemia	Mild	Often severe	Kovacs 1984, Limper 1989, Mansharamani 2000
LDH elevation: - Specificity and sensitivity - Levels	Good High	Low Moderate	McKinnell 2012 , Vogel2011
Characteristics of BAL fluid	High number of cysts Few neutrophils	Low number of cysts Many neutrophils	Kovacs 1984, Limper 1989, Monnet 2008
Mortality rate	17-30%	28-53% Especially high after HSCT	Ewig 1995, Pagano 2002, Torres 2006, Toper 2011, Ainoda 2012, Martin-Garrido 2013,



# CLINICAL PRESENTATION OF PjP IN NON-HIV<sup>+</sup> PATIENTS

## Co-infections

- Co-infections are frequent, between 28 to 71% , especially in the lungs  
They are due to multiple pathogens: *S aureus*, Gram-negative bacteria, *Aspergillus sp.*, CMV...
- In allogeneic HSCT recipients, PjP is associated with CMV pneumonia in half of the cases



*Ewig 1995, Yale 1996, Torres 2006, Toper 2011*

# IMAGING IN PjP IN NON-HIV<sup>+</sup> PATIENTS (1/3)

Although a presentation of diffuse interstitial pneumonia is highly evocative of PjP in patients at risk, no aspect is specific.

## Main imaging patterns:

- ***bilateral interstitial pneumonia*** (60-80%)
- less frequently: ***alveolar*** (10-20%) or ***alveolo-interstitial*** pattern (10-20%)

## Rarely:

- spontaneous ***pneumothorax*** complicating cystic lesions, especially in HSCT recipients (*Kovacs 1984, Chow 1993, Torres 2006, Hardak 2010*)
- ***pleural effusion***, up to 39% of HSCT recipients (*Torres 2006*)



# IMAGING IN Pj PNEUMONIA IN NON-HIV<sup>+</sup> PATIENTS (2/3)

## ***Multislice chest CT: gold standard, but lacks specificity***

- Extensive ground glass opacities (GGO) in 80-90%, diffuse in more than half of the cases, frequent apical predominance or mosaic pattern (*Vogel 2007, Hardak 2010, Kanne 2012,*)
- Consolidations (22-48%) more common than in HIV<sup>+</sup> patients, often well demarcated (*Vogel 2007, Tasaka 2010*)
- thin-walled solitary or multiple cysts on the GGO background in around 10%, sometimes reversible (*Tasaka 2010, Kanne J2012, Lu 2012*)
- Interlobular septal thickening
- Solitary, or multiple small (< 1 cm) nodules (11-31%) *Vogel 2007, Hardak 2010, Tasaka 2010*), mass lesion in granulomatous forms
- Lymph node enlargement (15%) (*Vogel 2007*)
- Reversed halo sign reported (*Otera 2010, Marchiori 2012*)



# IMAGING OF PJP IN NON-HIV<sup>+</sup> PATIENTS (3/3)

## ***FDG-PET:***

Diffuse, increased FDG uptake of the lungs

Few data available in non-HIV<sup>+</sup> patients (*Win Z. 2005, Nakazato T. 2010*)

Marginal use for routine practice



# THE KEY ROLE OF BAL IN DIAGNOSING PjP

- **Case definition:** Clinical and radiological finding of lung infiltrates with or without fever

*and*

Evidence of cysts or trophozoites documented by classical stainings (toluidine blue, calcofluor white, or Gomori methenamine silver or Giemsa) or immunofluorescence (IF) in respiratory specimens (BAL, induced sputum, nasal swab, or lung biopsy). However, qPCR is a more sensitive diagnostic tool to evidence the presence of Pj compared to IF and classical stainings.

- BAL is the gold standard for the diagnosis of PjP.
- Performing BAL should not be delayed, especially not given the more rapid deterioration and poorer outcome of PjP in hematology patients compared to HIV+ patients (Ainoda 2012).
- Diagnosis of PjP in children is usually established by the same diagnostic methods and stainings in children as in adults (reviewed in Pyrgos V 2009 and Shankar SM 2007). However, literature on PCR is poor in children, allowing no specific recommendation for result interpretation.



## PRACTICAL CONSIDERATIONS ON BAL IN DIAGNOSING PjP

Treating patients for 3 days with TMP-SMX on the basis of clinical suspicion does not substantially affect the performance of microscopic examination (staining and IF) nor the sensitivity of qPCR in BAL.

This should not be used as an excuse for not performing BAL in at-risk patients with a clinical suspicion.



# General comments

- While awaiting validation of qPCR compared with IF on BAL fluid, clearly identifying a threshold of positivity, centers should not give up on performing standard tests on BAL fluid, including IF and staining.
- In a patient receiving TMP-SMX prophylaxis with excellent compliance, the presence of PjP is highly unlikely.



# SIGNIFICANCE OF A NEGATIVE qPCR IN RESPIRATORY SAMPLES

- Clinical symptoms and/or imaging findings consistent with PjP should not be the only criteria to consider Pj as the cause of the pneumonia, as other pathogens can mimic PjP (bacteria, virus,...)
- qPCR in BAL has an excellent negative predictive value to rule out the diagnosis of PjP.
- However, negative qPCR results on other respiratory specimens do not rule out the diagnosis





# SIGNIFICANCE OF A POSITIVE qPCR IN RESPIRATORY SAMPLES

- When only qPCR is positive in respiratory samples (with negative stainings and negative IF):
  - although a positive qPCR *provides a high level of suspicion of infection*, this is not always associated with PjP, especially not if the fungal load is low and if serum  $\beta$ -D glucan is negative (it may be carriage and cases of spontaneous resolution have been reported).
  - if serum  $\beta$ -D glucan is positive, and/or if the fungal load is high (no threshold available), this increases further the level of suspicion for PjP
- The positive predictive value of qPCR is not yet clearly determined and likely varies with (1) site of respiratory sample, (2) fungal load and (3) immune status. More prospective studies are needed!
- However, a positive qPCR may be predictive of later development of PjP in patients at risk (*Mori S 2009*) and should at least trigger prophylaxis in patients with risk factors for PjP.



# Preventing exposure

- Clinical and molecular data confirm that inter-human transmission of *P jirovecii* is possible, particularly to lymphopenic transplant recipients

(J Gea-Banacloche 2009)

- Few healthcare facilities mandate respiratory precautions with respect to patients infected with PjP.

## Expert opinion

- Severely immunocompromised patients should avoid exposure to patients with documented PjP.
- Infected patients should be preferably hospitalized in single rooms.



# PcP prophylaxis: available recommendations

- *Guidelines for preventing infectious complications among **hematopoietic cell transplant** recipients: a global perspective.*
  - Tomblyn 2009
    - *Regionally limited or rare infections: prevention after hematopoietic cell transplantation.* Gea-Banacloche J et al. Bone Marrow Transplantation 2009
- *Prevention and treatment of **cancer-related** infections.*
  - Baden 2012
- *Primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with **hematological malignancies and solid tumors**. Guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology*
  - Neumann 2013
- *The official American Thoracic Society Statement*
  - Limper 2011



## A global perspective

Recommendations of the CIBMTR, the NMDP, the EBMT, the ASBMT, the CBMTG, the IDSA, the SHEA, the AMMI, and the CDC

### Recommendation for adults:

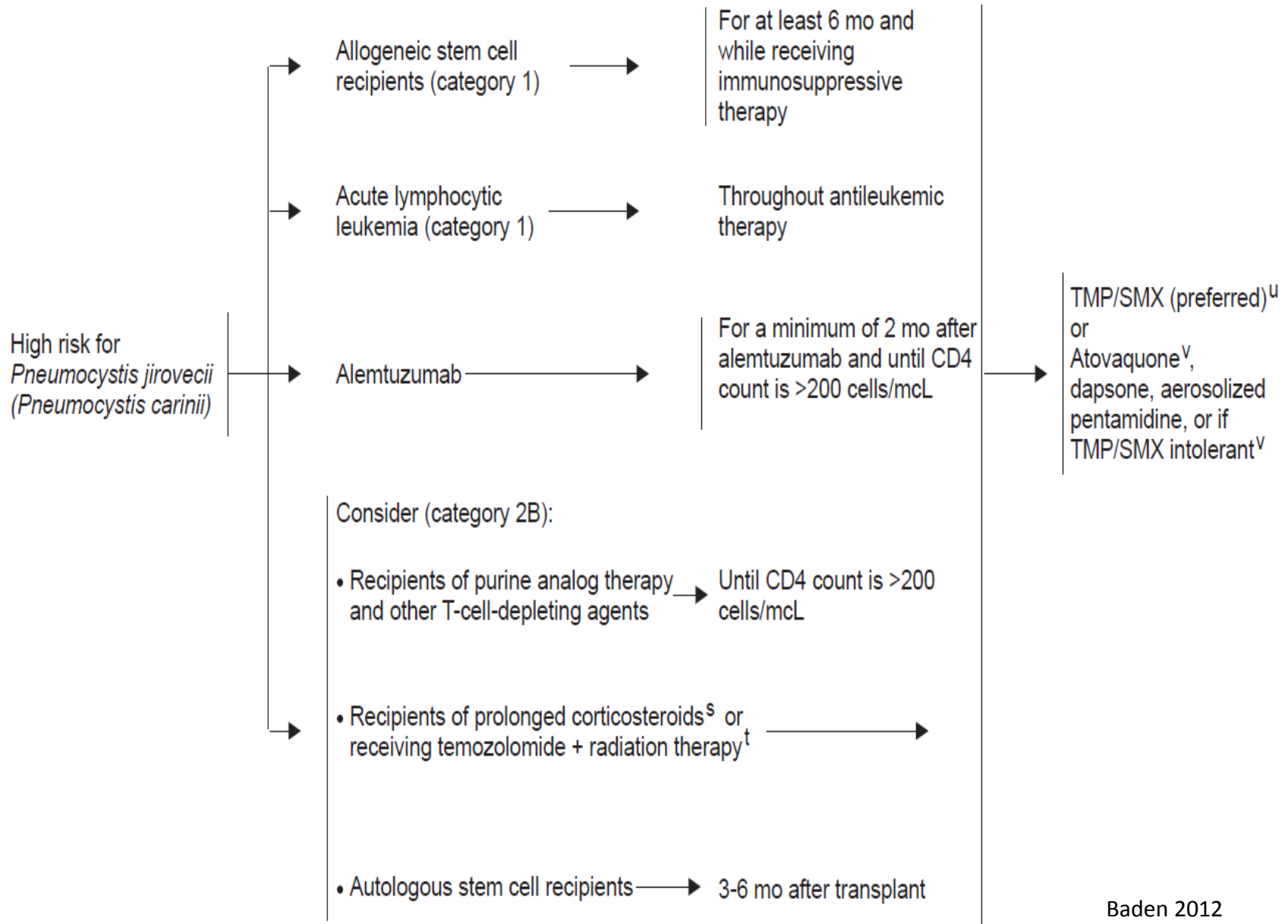
Pathogen: *Pneumocystis jiroveci*

<i>Indication</i>	<i>First choice</i>	<i>Alternatives</i>
Prophylaxis among (a) all allogeneic HCT recipients (AII); or (b) autologous HCT recipients with underlying hematological malignancies, those receiving intense conditioning regimens or graft manipulation, or those who have recently received purine analogs (BIII) <sup>481</sup>	Trimethoprim–sulfamethoxazole (AII)  <i>Adult/adolescents:</i> 1 double-strength (160/800 mg) tablet orally daily; or 1 single-strength (80/400 mg) tablet orally daily; or 1 double-strength tablet orally thrice per week	<i>Adult/adolescents</i> Dapsone, 50 mg orally twice per day or 100 mg orally daily (CII) Atovaquone, 750 mg twice daily or 1500 mg once daily, orally (CII) Pentamidine, 300 mg every 3–4 weeks by Respigard II nebulizer (CII)



A= should always be offered/B=should generally be offered/C=optional

# NCCN guidelines



# Guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology

Infection risk	Disease/therapy	Level of evidence
Strong evidence for increased risk <sup>a</sup> <ul style="list-style-type: none"><li>- ALL</li><li>- Prolonged CD4 &lt;200/<math>\mu</math>l</li><li>- Long-term steroids<sup>b</sup></li></ul>	TMP/SMX for the duration of therapy or until CD4 > 200/ $\mu$ l	A-I
Risk status not entirely conclusive <ul style="list-style-type: none"><li>- R-CHOP; BEACOPP<sup>esc</sup></li><li>- Prolonged neutropenia</li><li>- Acute myeloid leukemia</li><li>- High dose cytarabine</li></ul>	TMP/SMX for the duration of therapy	C-III
Consider PCP prophylaxis when recommended by the manufacturer (for example temozolamide and radiation)		

# *The official American Thoracic Society Statement*

- “In patients with hematologic malignancies receiving cytotoxic chemotherapies, ....., we recommend prophylaxis during the period of immune suppression with either:
  - TMP-SMX dosed as one double strength tablet or one single-strength tablet given once a day, or one double-strength tablet taken three times per week (AI); or
  - Atovaquone 1,500 mg/day given as two daily divided doses (AI); or
  - Dapsone 50 mg twice daily or 100 mg/day (AI)
  - Alternative regimens include dapson (50 mg/d) plus pyrimethamine (50 mg/wk) plus leucovorin (25 mg/wk), or dapson (200 mg/wk) plus pyrimethamine (75 mg/wk) plus leucovorin (25 mg/wk) (BII).”
  - Remarks:
    - Aerosolized pentamidine (300 mg once a month) is very rarely used and is generally discouraged
    - Double-strength TMP-SMX may be associated with lesser occurrence of bacterial infections
    - In non-HIV patients, consider prophylaxis during time periods where prednisone dose exceeds 20 mg/day for greater than 1 month, especially if patient has associated T cell defects, or is receiving other cytotoxic drugs or anti-TNF agents.
    - Some experts also recommend monitoring CD4 counts in patients without AIDS, using the threshold of 200 CD4 cells/ $\mu$ L.



# CDC Grading system used at ECIL 5

Quality of Evidence	Strength of Recommendation
I Evidence from $\geq 1$ properly randomized, controlled trial.	A <b>Good</b> evidence to support a recommendation for or against use
II Evidence from $\geq 1$ well-designed clinical trial, without randomization: from cohort or case-controlled analytic studies (preferably from $> 1$ center); from multiple time-series studies; or from dramatic results from uncontrolled experiments.	B <b>Moderate</b> evidence to support a recommendation for or against use
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C <b>Poor</b> evidence to support a recommendation





# PjP prophylaxis: main questions

- Does PjP prophylaxis reduce the incidence of PjP?
- Does PjP prophylaxis reduce PjP-related mortality?
- Does PjP prophylaxis reduce all-cause mortality?
- Is PjP prophylaxis safe and/or well-tolerated?
- Does PjP prophylaxis reduce the incidence of other infections?



# Problems encountered

- Data from many (most) studies are outdated
- Very few prospective, well-executed, controlled studies with sufficient numbers of patients
- Difficulties comparing study results because of different doses and duration of prophylaxis
- Assumptions made from the HIV-population (e.g. CD4 count  $< 200/\mu\text{L}$ ), but outcome in non-HIV-infected patients is generally worse than in HIV-infected patients (with cancer patients having the worst outcome, including higher rates of hospitalization, ICU admissions and mortality).



# Trimethoprim-sulfamethoxazole (TMP-SMX)

## Main data source:

- The Cochrane collaboration analysis by Green et al. published in The Cochrane Library 2011 (Issue 1); review content assessed as up-to-date December 6, 2010.

## Main characteristics of the studies included:

- 11 trials included 1155 patients (520 children) (1974-1997)
- Criteria:
  - RCT or quasi-RCTs
  - Excluding HIV-infected patients
  - Only trials pre-defining PjP as an outcome
  - All agents effective against *Pneumocystis* in vitro: TMP-SMX; pentamidine; atovaquone; dapsone; pyrimethamine; clindamycin; mycophenolate



# TMP-SMX: effect of the intervention

Documented PjP infection	91% reduction in PjP infections in the TMP-SMX group RR 0.09 (95% CI 0.02-0.32); NNT 15 (95% CI 13-20) No cases of PjP in the prophylaxis arm by ITT. In hematological cancer patients (adults and children), the RR was 0.05 (95% CI 0.01-0.39)
PjP-related mortality	83 % reduction of PjP-related mortality in the TMP-SMX group RR 0.17 (95% CI 0.03-0.94)
All-cause mortality (not reported in all studies)	No significant difference in all-cause mortality RR 0.81 (95% CI 0.27-2.37)
Adverse events	No significant difference in any AE when comparing TMP-SMX with placebo/no treatment Overall, SAE requiring discontinuation (leukopenia, thrombocytopenia, severe dermatologic reactions): 3.1% of adults and 0% of children Most frequent AE is (prolonged) leukopenia
Other infections	More infections in the TMP-SMX group compared to the quinolone groups
Bacterial infections	TMP-SMX reduces the incidence of bacterial infections by 74% compared to placebo/no treatment (RR 0.26, 95% CI 0.11-0.59) but there are more bacterial infections in the TMP-SMX group compared to quinolone
Resistance development	TMP-SMX is associated with increased bacterial resistance rates during treatment

# TMP-SMX: dose

- **Dose**: no evidence that the efficacy differs when using a single-strength tablet (80/400 mg), given once daily, versus a double-strength tablet (160/800 mg), given either daily or thrice a week:
  - Meta-analysis from Cochrane group
  - Supportive data from HIV-infected patients
  - *A systematic review of two different trimethoprim-sulfamethoxazole regimens used to prevent Pneumocystis jirovecii and no prophylaxis at all in transplant recipients: appraising the evidence.* (Di Cocco 2009) Low-dose (80/400 mg daily or 160/800 mg every other day) versus full-dose (160/800 mg daily):
    - 4 studies included: solid organ transplantation only and low patient numbers
    - Incidence of PjP: full-dose 0% versus low-dose 1% versus no prophylaxis 11% ( $p < 0.001$ )



# TMP-SMX: duration

- **Duration**: there are no comparative studies addressing the question when to start and how long to administer primary prophylaxis. Some general comments about HSCT recipients:
  - It is recommended to start TMP-SMX after engraftment
  - It is recommended to give PjP prophylaxis for as long as the patient receives immunosuppressive drugs (maybe even a few weeks longer)/is considered immunocompromised
  - CD4 count is no substitute for stopping anti-Pj prophylaxis ; a threshold of 200 cells (often used in HIV+ patients) has not been validated in non-HIV patients
  - In Toxoplasma-seropositive recipients, stopping TMP-SMX may render patients at risk for reactivation and should be combined with a Toxo monitoring strategy (e.g. blood PCR)



# Aerosolized pentamidine (1)

- **Possible prevention of PjP by pentamidine aerosol after bone marrow transplantation.** Mahon 1991: 13 BMT recipients
  - **Pentamidine aerosol for prophylaxis of PjP after BMT.** Link 1993.
    - Prospective trial in 31 allogeneic and 12 autologous BM Transplants (BMT)
    - Aim: evaluate toxicity, safety, practicability and resorption of drug
    - 60 mg given at day -3 and day +14; starting at Week 4: 300 mg given every 4 weeks for 6 months
    - No cases of PjP
    - Cough 19%, salivation 9.6% and sore throat 5.7%
    - Pentamidine detected in serum of 33-54% of patients (median levels 7.5-9 ng/mL)
  - **Primary *Pneumocystis carinii* prophylaxis with aerosolized pentamidine after BMT.** Machado 1998
    - Retrospective chart review of 38 BMT recipients which had received TMP-SMX (during conditioning and twice a week from day +50 till 6 mo. after stop of all IS drugs): 31.5 % of these patients discontinued TMP at least once.
    - Prospective: next 40 patients received aerosolized pentamidine 300 mg (20 min) every 3 weeks from day + 21 till 6 mo. after stop of all IS drugs
    - 3 patients receiving TMP-SMX developed PjP vs. 0 patients in the AP group (p=0.11)
    - No patient discontinued AP because of adverse reactions, although there was bronchospasm (2.5%), cough (7.5%) and nausea (5%)
    - Emergence of toxoplasmosis: 5 cases in the AP group vs. 0 in the TMP-SMX group (p=0.031)
- : **Totaling 96 BMT recipients: no cases of PjP**



# Aerosolized pentamidine (2)

- ***Aerosolized pentamidine as *Pneumocystis* prophylaxis after BMT is inferior to other regimens and is associated with decreased survival and increased risk of other infections. Vasconcelles 2000***
  - Retrospective cohort study in 327 evaluable adult patients undergoing BMT (48.6% related, 9.5% unrelated, and 40.7% autologous) for various hematological malignancies.
  - All patients received TMP-SMX 160/800 BID from -6 to pre-BMT; PjP prophylaxis was reinstalled at day +30 and continued for 1 year post-BMT:
    - AP 150 mg/2 weeks or 300 mg/4 weeks (N=44)
    - TMP-SMX 160/800 mg BID 3 times a week (N=105)
    - Dapsone 100 mg QD (N=31)
    - More than one regimen (N=147)
  - PjP was documented in 2.4% of evaluable patients (all allogeneic transplants)
    - AP 150 mg/2 weeks or 300 mg/4 weeks: 4 cases (9.1%): Odds Ratio relative to TMP 23.4 (consistent with randomized data in HIV patients)
    - TMP-SMX 160/800 mg BID 3 times a week: 0 cases
    - Dapsone 100 mg QD: 1 case (3.2%)
    - More than one regimen: 2 cases (1.4%)
  - AP patients had significantly lower probabilities of treatment-related toxicities than those receiving TMP (OR 0.19), but higher probabilities of acquiring other serious non-PjP infections (OR 2.2) and higher probability of dying by 1 year post-BMT (OR 5.2)





## Aerosolized pentamidine (3)

- ***Aerosolized pentamidine prophylaxis for *Pneumocystis carinii* pneumonia after allogeneic marrow transplantation. Marras 2002***
  - Retrospective analysis of 506 allogeneic transplants. 1<sup>st</sup> line prophylaxis is TMP-SMX (320/1600 mg) 2 tablet on 2 consecutive days/week (later changed to one tablet three times weekly) for 1 year post-BMT (or as long as immunosuppressive therapy is given). TMP-SMX is substituted by AP (second-line prophylaxis) in case of intolerance/toxicity: 60 mg every 2 weeks (1990-1992); 300 mg every 4 weeks (1992-1999); 300 mg twice monthly (1999-2000) for ‘high risk’ (calcineurin inhibitors plus steroids) patients.
  - AP is an effective and well-tolerated (3% discontinuation due to toxicity) second-line agent for PjP prophylaxis post BMT.
  - Role of well-studied equipment (nebulizer) and dose schedules



## Aerosolized pentamidine: of note... (4)

- Excessive cases of toxoplasmosis have been described in AP-treated patients, underscoring once more the importance of selecting TMP-SMX for primary prophylaxis, especially in allogeneic HSCT recipients who are seropositive for *Toxoplasma* before transplantation.
- AP prophylaxis has been associated with extrapulmonary *Pj infection* in HIV+ patients, and with non-interstitial infiltrates, possibly leading to delayed diagnosis.
- Twice monthly AP administration was more effective than once monthly in HIV-infected patients needing secondary prophylaxis.
- The success rate depends on the adherence to a strict protocol: AP should be administered in individual rooms. Side effects such as coughing and wheezing can be prevented or diminished by the pre-administration of beta-adrenergic agonists. Most studies have used a jet-nebulizer (Respigard II), producing particles with a mass mean aerodynamic diameter of  $<1 \mu\text{m}$ ; other nebulizers producing larger particles unable to reach the alveoli may be less effective.
- There are no data on intravenous use of pentamidine in adults.
- Only data available for stem cell transplant recipients



# Dapsone

## *Use of dapsone in the prevention and treatment of Pneumocystis carinii pneumonia: a review.* Hughes 1998

- Data come from > 40 prophylaxis studies performed in HIV-positive patients
- Dosage schemes:
  - Dapsone 50 mg BID or 100 mg once a day
  - Dapsone 50 mg QD + pyrimethamine 50 mg once a week plus leucovorin 25 mg once a week
  - Dapsone 200 mg + pyrimethamine 75 mg plus leucovorin 25 mg once a week
- Heterogeneity is high; only 3 studies compared dapsone with no prophylaxis, but none was randomized. Dapsone reduces the incidence of PjP in HIV-positive patients.

	No prophylaxis		Dapsone	
	# patients	% PjP	# patients	% PjP
Metroka et al.	23	100	173	1 (100 mg qd)
Lucas et al.	46	35	16	6.3 (100 mg once a week)
Penco et al.	10	80	10	1 (50 mg twice weekly)

# Dapsone in HIV+ patients

- ***Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients***  
Bucher 1997
  - Dapsone/pyrimethamine versus aerosolized pentamidine: RR 0.90 (95% CI 0.71-1.15)
  - TMP-SMX versus aerosolized pentamidine: RR 0.59 (95% CI 0.45-0.76)
  - TMP-SMX versus dapsone/pyrimethamine: RR 0.49 (95% CI 0.26-0.92)



# Dapsone in HSCT recipients

- ***High rates of *Pneumocystis carinii* pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis***

Souza 1999.

- Retrospective cohort study (USA, Seattle) of all allogeneic blood and marrow transplants 9/1993-12/1996
- Dapsone cohort: all patients who received at least one dose of dapsone
- TMP-SMX given pre-transplant and resumed after transplant (at neutrophil recovery or day 30) for at least 6 months: 160/800 BID two days a week (longer in case of extensive cGvHD or continued IS). In patients with allergies/intolerance, dapsone is given at 50 mg BID 3 times/week for 6 months or longer.
- N = 646 patients; 111 patients received at least one dose of dapsone pre- or post-transplant
- 10 patients developed PjP: 8 from the dapsone cohort; 2 from the TMP-SMX cohort
- PjP was observed in 0.37% of patients in the TMP-SMX cohort and in 7.2% of patients in the dapsone cohort: RR 18.8 (95% CI 4-88.6)
  - On the basis of these results, daily dosing is recommended
  - Screening for glucose-6-phosphate dehydrogenase deficiency is advised



# Dapsone in HSCT recipients

- ***Toxicity and efficacy of daily dapsone as *Pneumocystis jiroveci* prophylaxis after hematopoietic stem cell transplantation: a case-control study*** Sangiolo 2005
  - Retrospective matched control study (USA, Seattle) on 155 allogeneic HSCT recipients between 1998-2001 who received **daily** dapsone as PjP prophylaxis for more than 1 week. Each case was matched with two control patients who received standard TMP-SMX.
  - Dapsone results in higher transfusion requirement compared to controls
  - Two of 115 dapsone patients developed PjP versus 0 of 310 control patients (p=0.11)
    - Efficacy of daily dosing = TMP-SMX group
    - Higher transfusion need is due to underlying condition of poor marrow reserve, not due to dapsone
    - Dapsone intolerance leading to drug discontinuation or temporary suspension occurred in 10% of patients
    - A trend towards more breakthrough infections of organisms not covered by dapsone (*Nocardia*, *Toxoplasma*, *Streptococcus pneumoniae* and *Haemophilus* species)



# Atovaquone

- ***A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation.***  
Colby 1994
  - Prospective, open label, randomized trial in 39 autologous HSCT recipients
  - Atovaquone suspension 1500 mg with a meal (N=20) versus TMP-SMX 160/800 mg (N=19) from -5 until -1 and resumed 3 days per week after engraftment until day +100
  - No difference in time to engraftment
  - No documented cases of PjP
  - Significantly more TMP-SMX discontinuations due to toxicity ( $p < 0.003$ )
- ***Failure of low-dose atovaquone prophylaxis against Pneumocystis jiroveci infection in transplant recipients*** Rodriguez 2004
  - Dose of atovaquone (liquid suspension) should be at least 1500 mg, taken with a high-fat meal. Lower doses (750 mg qd or 1500 mg thrice weekly) is inferior to daily 1500 mg. Serum levels achieved with a dose of 750 mg QD fall below the MIC of atovaquone for rodent *Pneumocystis carinii*.



# Echinocandins

- Echinocandins are active, *in vitro*, against *Pneumocystis jirovecii*.
- No data on the prophylactic use of these drugs in hematology.
- Caution: breakthrough cases of PjP have been described in patients treated empirically with caspofungin.





# Comparing second-line choices

Characteristic	Pentamidine 300 mg	Dapsone 100 mg	Atovaquone 1500 mg
Route of administration	Inhalation (intravenous)	Oral	Oral solution with fatty meal
Frequency of administration	Monthly	Daily	Daily
During neutropenia/pre-engraftment	Yes	Yes	Yes
Special equipment or trained personnel needed	Yes	No	No
Anti-Toxoplasma activity	No*	Yes, if combined with pyrimethamine	Uncertain*
Antibacterial activity	No	No	No
Use in G6PD deficiency	Yes	No	Yes
Main toxicity	Respiratory	Hemolytic anemia Methemoglobinemia	Gastrointestinal
Cost	Low	Low	High



\* In all situations – especially with Pentamidine and Atovaquone, - where PjP prophylaxis does not cover the risk of toxoplasma reactivation in high-risk patients (eg. allogeneic HSCT recipients with a positive pre-transplant serology) regular screening with blood PCR is recommended

**PjP in pediatric patients  
with (onco)-hematological disorders**



# Risk factors for PjP in pediatric onco-hematology patients

Author/year	Risk factors
Kim SY, 2008	Hematopoietic stem cell transplant (HSCT) Cancer chemotherapy
Poulsen A, 2001	ALL
Pyrgos V, 2009 (Review)	<u>Corticosteroid therapy</u> (0,4 mg/kg/d, or 16 mg/d for $\geq 1$ month) <u>Acute leukemia, lymphoma</u> Lymphopenia associated to fludarabine, Temozolomide, Alemtuzumab <u>HSCT, solid organ transplant (SOT)</u> <u>Primary immunodeficiency</u> (SCID, WAS, X-linked Hyper IgM, X-linked agammaglobulinemia) Anti-TNF therapy (rheumatic diseases)
Saltzman RW, 2010	ALL, maintenance chemotherapy included HSCT, solid organ transplant (SOT) Solid tumour Primary immunodeficiency SAA/ congenital errors

# Standard Recommendation for PjP Prophylaxis Based on American Academy of Pediatrics Guidelines \*

**Preferred regimen:** TMP/SMX (150/750mg/m<sup>2</sup>/d), BID, 3 times per week on consecutive days

**Alternative regimens:**

- TMP/SMX (150/750mg/m<sup>2</sup>/d)/Q24, 3 times per week on consecutive days
- TMP/SMX (150/750mg/m<sup>2</sup>/d), BID, daily
- TMP/SMX (150/750mg/m<sup>2</sup>/d), BID, 3 times per week on alternating days
  
- Dapsone (> 1mo of age) 2 mg/kg (max 100 mg) Qday or 4 mg/kg (max 200 mg) Qweek
- Inhaled pentamidine (> 5 y of age) 300mg Qmonth aerosolized with respigard II Nebulizer
- Atovaquone (1 to 3 mo and > 24 mo) 30 mg/kg Qday
- Atovaquone (4 to 24 mo) 45 mg/kg Qday

•American Academy of Pediatrics. *Pneumocystis jiroveci* infections. In: Pickering LK, Baker CT, Long SS, et al. eds. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: AAP; 2009:540.



# PjP Prophylaxis in pediatric onco-hematological patients: TMP/SMX

## Literature review

Author/year	Type of study	N° pts	Underlying disease	Prophylaxis	Duration of prophylaxis	Incidence PjP	Mortality PjP	Notes
Hughes, 1977	Prospect. Randomized Vs. placebo	80/80	Cancer pts	TMP/SMX 150/750 mg/m <sup>2</sup> /d, daily	339/382	17 vs 0		Less infections in TMP/SMX group
Hughes, 1987	Prospect. Randomized	92/74	ALL	TMP/SMX 150/750 mg/m <sup>2</sup> /d, Daily vs 3-d/w	332/369	0/0		Less fungal infections in the 3-d/w group
Lindemulder S, 2007	Retrospecti.	482	Leukemia / lymphoma	TMP/SMX , 5 mg/kg/d of TMP BID on 2 consecutive d/wk	556 average patient-days	0		
Ohata, 2009	Retrospect.	145	AL/cancer/ HSCT	TMP/SMX , 5 mg/kg/d of TMP BID on 2 non-consecutive d/wk	197	0		
Agrawal AK, 2011	Retrospect.	87	ALL	TMP/SMX 150/750 mg/m <sup>2</sup> /d, BID, 2 consecutive days of week	649 average patient-days	0		4 pts switched to Pentamidin for BM toxicity
Levinsen M, 2012	Retrospect.	447	ALL	120 pts. TMP/SMX for 2-7 d/wk 287 pts. No prophyl. 40 received TMP/SMX intermittent	Throughout maintenance therapy (2 to 2.5 yr after diagnosis)	10 Pts PjP All cases in patients not receiving prophylaxis.	0	TMP/SMX(2-7) group received lower oral 6MP doses than no-prophylaxis group

# Single-day Trimethoprim/Sulfamethoxazole prophylaxis for PjP in children with cancer(I)

Observational study in 20 Italian pediatric centers

Period: 2009-2011

2466 patients, 1373 leukemia/lymphoma, 1093 solid tumour

Prophylaxis with oral trimethoprim-sulphamethoxazole (160/800) suspension or tablets

Prophylaxis regimen	N° Centres	N° pts	Trimethoprim equivalent dose/week	PjP cases	note
3-day/w	11	1371 (55.6%)	15 mg/kg	0	
2-day/w	6	406 (16.5%)	10-20 mg/kg	2	Both patients withdrew prophylaxis
1-day/w	3	689 (27.9%)	5-10 mg/kg	0	



# Single-day Trimethoprim/Sulfamethoxazole prophylaxis for PjP in children with cancer(II)

**Period: 2009-2011**

PjP : overall 3-year cumulative incidence 0,09%

“ “ 2-day regimen: 0,51%

**Previous period: 2000-2008**

PjP : 8 cases, all after withdrawal of prophylaxis for patient/parent decision (3) or toxicity (3)

Comments:

- a) Single-day regimen is as efficacious as 2 or 3 day regimen of prophylaxis
- b) Non-compliance to prophylaxis is the main cause of PjP pneumonia in pediatric patients



# Pentamidine for PjP Prophylaxis in pediatric onco-hematological patients

## Literature review

Author/ year	Type of study	N° pts	Underlying disease	Prophylaxis	Duration of prophylaxis	Incidence of PjP	Notes
Kim SY, 2008	Retrospect.	232	Hematological- oncological malignancies	IV penta (4 mg/kg every 4 wk)		3 pts (1.3%), 2 after HSCT and were under the age of 2  Mortality: 0	Pentamidin used for TMP/SMX BM suppression or allergy  No pts D/C pentamidine for intolerance
Milstone AM, 2006	Case report	1	Leukemia	IV penta		1  Mortality : 1	Pentamidine used for TMP/SMX intolerance
Mustafa MM, 1994			Hematological or oncological malignancies	AP	12 – 25 months	0	Use of Pentamidin for TMP/SMX intolerance  AE: 79 (10%) of the 720 treatments: bronchospasm 23, cough i40, vomiting 10, and nausea 6
O'Sullivan BP, 1994	Retrospect.	9	Leukemia	AP	average of 8.11 +/- 4.1 months per child	0	moderate coughing in 1 pts 5 pts with medical history suggestive of reactive airways disease were pretreated with inhaled albuterol
Weinthal J, 1994	Retrospecti ve analysis	22	ALL	AP 300 mg /m (< 4 y, 150 mg)	460 average patient-days	0	Patients intolerant of TMP-SMZ



# PjP Prophylaxis in pediatric onco-hematological patients: other drugs

## Literature review

Author/year	Type of study	N° pts	Underlying disease	Prophylaxis	Duration of prophylaxis	Incidence PjP	Mortality PjP	Notes
Prasad P, 2008	Retrospect.	223	A cute leukemia, solid tumours, LH/LNH, HSCT	143 pts TMP/SMX (5 mg/ kg TMP, BID , 2 or 3 d/wk); 36 pts dapsone (1mg/kg/d) 21 pts inhaled pentamidine (300 mg every 4 wk) 12 pts i.v. pentamidine (4 mg/kg every 4 wk) 5 pts oral Atovaquone (40 mg/kg/d) 6 pts no prophylaxis	205 person–years/ TMP-SMX; 37 person–years dapsone; 15.5 person–years aerosolized pentamidine 11.7 person–years for intravenous Pentamidine 9.5 person–years for Atovaquone	4 cases: 2/iv. pentam; 1/ TMP/SMX; 1 on dapsone.	2	Rate of breakthrough infection/ person–year lower with TMP-SMZ
Madden RM, 2007	Retrospect.	86	ALL/AML	Atovaquone (30 mg/kg once daily)	ALL: median 584 d; AML: median 204 d	0	0	Use for intolerance to TMP/SMX

# Patients with hematological disorders who need PJP prophylaxis: ECIL recommendations

## Standard indications (A)

- All allogeneic stem cell transplant recipients
- All acute lymphocytic leukemia patients
- Alemtuzumab use
- Fludarabine-cyclophosphamide-rituximab
- Steroid-therapy (prednisone > 0.4 mg/kg/day or 16 mg/d for  $\geq 1$  month in children and > 20 mg/day for 7 weeks in adults)
- Primary immunodeficiency: SCID, WAS, X-linked hyper IgM, X-linked agammaglobulinemia, HLA class II combined immunodeficiency

## Optional (B)

- R-CHOP14 and escalated BEACOPP
- Nucleoside analogs
- Autologous stem cell transplantation



# ECIL recommendations for PjP prophylaxis in adults: drugs

- First-line prophylaxis
  - TMP-SMX : A-II
    - Dose: one single-strength (80/400 mg) tablet daily *or* a double-strength tablet (160/800 mg) daily *or* thrice a week: B-II
  - All other drugs are inferior to TMP-SMX as first-line agents and are therefore not recommended: A-II
- Second-line prophylaxis
  - Aerosolized Pentamidine: A-II
    - Dose: 300 mg once a month: B-II
  - Dapsone 100 mg qd: A-II
  - Atovaquone 1500 mg qd: B-II



# ECIL recommendations for PjP prophylaxis in children

- 1) Omitting prophylaxis is the major risk factor for PjP in patient at risk. A-I
- 2) TMX/SMP is the first choice for primary prophylaxis of PjP in pediatric onco-hematological patients. A-I
- 3) The recommended dose of TMP/SMX is 150/750mg/m<sup>2</sup>d, given in 1 or 2 administrations per day, for 1-3 times/week . A-II
- 4) Aerosolized Pentamidin (BII) or Atovaquone (BII) or dapsone (CII) are alternative choices in case of intolerance or SAE due to TMX/SMP.
- 5) Intravenous pentamidine is well tolerated but less effective with the risk of breakthrough PjP. C-II
- 6) In HSCT pediatric patients , PjP prophylaxis is recommended for the period of immunosuppression following engraftment . B-II



# Summary of ECIL 5 guidelines for PjP prophylaxis:

## (1) Choice of drugs and doses

	Adults		Children	
	Drug	Dose	Drug	Dose
<b>First-line choice</b>				
TMP-SMX <i>All other alternative is inferior (All)</i>	A-II	one single-strength (80/400 mg) tablet/d or a double-strength tablet (160/800 mg)/d or thrice a week: B-II	A-I	150/750 mg/m <sup>2</sup> /d in 1 or 2 doses/d or same dose 2 or 3 days/week : A-I 150/750 mg/m <sup>2</sup> /d once a week: B-II
<b>Second-line choice*</b>				
Dapsone	A-II	100 mg qd	C-II	2-4 mg/kg/d
Atovaquone	B-II	1500 mg qd	B-II	30 mg/kg/d 45 mg/kg/d (age 4-24 months)
Pentamidine IV	No data	-	C-II	4mg/kg every 4 weeks
Pentamidine aerosols	A-II	300 mg once/month: B-II	B-II	300 mg once/month (age > 5 years)

\* Only in case of intolerance or SAE due to TMP-SMX

# Summary of ECIL 5 guidelines for PjP prophylaxis:

## (2) Indications and duration

Indication	Adults		Children	
	Disease/condition	Duration	Disease/condition	Duration
Main (A)	Acute lymphoblastic leukemia	From induction to end of maintenance	Acute lymphoblastic leukemia	From induction to end of maintenance
	Allogeneic HSCT	From engraftment to $\geq 6$ months, and as long as IS is ongoing	Allogeneic HSCT	From engraftment to $\geq 6$ months, and as long as IS is ongoing
	Alemtuzumab		Alemtuzumab	
	Fludarabine/Cyclophosphamide/Rituximab		SCID, WAS, X-linked hyper IgM, X-linked $\alpha$ globulinemia, HLA II combined immunodeficiency	Life-long or until restoration of underlying defect
	Steroids (> 20mg/d prednisone for 7 weeks)		Steroids (>0,4 mg/kg or 16 mg/d for $\geq 1$ month)	
Optional (B)	Lymphoma treated with R-CHOP14 or Escalated BEACOPP		AML	All duration of chemo
	Nucleoside analogs		Solid tumors	All duration of chemo
	Autologous HSCT	3-6 months		