Pediatrik Kılavuzlar

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Hacettepe Üniversitesi

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Hacettepe Pediatrik Onkoloji & Pediatrik İnfeksiyon Hastalıkları

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Çocuk ve erişkin

Lösemi-lenfoma sıklığı
Daha yoğun tedavi protokolleri
Hematopoetik ve immün sistem daha immatür
Solid tümörlerde de yoğun tedaviler

Sonuç olarak;
Çocuklarda myelosupresyon daha sıktır!

Nötropenik hastada ateş

Bir kez aksiller >38°C

En az bir saat süreyle aksiller >37.5°C

Flora 2004;9(2):73-105

Bir kez oral 38.3 ^{0}C

Bir saat ara ile oral 2 kez >= 38 ^{0}C

COG Guidelines 2004

Nötropeni

MNS < 500/mm3

MNS 500-1000/mm3 olup, 24-48 saat'te 500/mm3'un altına düşmesinin beklendiği durumlar;

Flora 2004;9(2):73-105

ANS (PMN+band)

Ağır	< 200 /ul
Orta	200-500 /ul
Hafif	500-1000 /ul

COG Guidelines 2004

Yüksek riskli durumlar

- MNS < 100/mm^3 olması
- Beklenen nötropeni süresinin (> 10 gün) uzun olması
- Primer hastalığın lösemi olması (özellikle indüksiyon tedavisi sırasında)
- Hastalığın remisyonda olmaması
- Yüksek doz kemoterapi alan hastalar
- Ağır mukozit varlığı
- Renal, kardiyak ve hepatik fonksiyon bozuklukları
- Şok, hipotansiyon, solunum sıkıntısı ve mental durum değişikliği
- Pnömoni
- Tiflitis

MNS: Mutlak nötrofil sayısı.

Empirik monoterapi

Daha sık tercih edilir oldu!

Çünkü;

- Gram negatif infeksiyonların sıklığında azalma
- Yeni ilaçlar
  - ✓ 3-4. jenerasyon antipsödomonal sefalosproinler
  - ✓ Karbapenemler
  - ✓B-laktam/β-laktamaz inbitörü
- Düşük toksisite
- Ucuz
- Uygulama kolaylığı

Glikopeptid içeren kombinasyonlar

- Kateter ilişkili infeksiyonlar
- MRSA veya penisilin dirençli pnömokok kolonizasyonu
- Gram-pozitif bakterilerin kan kültüründe üremesi
- Hipotansiyon, kardiyovasküler bozukluk
- Yoğun kemoterapi (örneğin; belirgin mukozal hasar yapan yüksek doz Ara-C)
- Ağır mukozit varlığı

Antifungal tedavi

- ✓Ateşi düşmeyen hastalarda 5-7 günde
- ✓Progresif bozulanlarda 3. gün gibi erken dönemde başlanabilmektedir (Nadir)
- ✓Renal problemi olmayan veya risk içermeyen hastalarda amfoterisin-B
- ✓Riskli vakalarda lipid formulasyonları kullanılmaktadır.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

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Original Article

Clinical practice guidelines for children with cancer presenting with fever to the emergency room

Samart Pakakasama,[1] Kulvadee Surayuthpreecha,[2] Uthen Pandee,[3] Usanarat Anurathapan,[1] Vimolratne Maleewan,[2] Umaporn Udomsubpayakul,[5] Punnee Butthep,[4] Pitak Santanirand,[4] Nongnuch Sirachainan[1] and Suradej Hongeng[1]

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Table 2 Comparison of adverse outcomes between intervention and control groups

Adverse outcomes	Intervention group ($n = 170$)		Control group ($n = 138$)		P
	ANC < 500/mm^3 ($n = 157$)	500/mm^3 ≤ ANC < 1000/mm^3 ($n = 13$)	ANC < 500/mm^3 ($n = 124$)	500/mm^3 ≤ ANC < 1000/mm^3 ($n = 14$)	
Septic shock (n)	6	0	14	1	0.011
ICU admission (n)	5	0	12	1	0.016
Death	0	0	7	2	0.001

ANC, absolute neutrophil count; ICU, intensive care unit.

The occurrence of septic shock, ICU admission, and death were significantly reduced from 26.8% to 6.5%.

Time for paediatric febrile neutropenia guidelines – children are not little adults (EJC, 2011) ; WHY?

(1) Konakçı/Çevre;

Farklı kanserler, farklı tedaviler (daha yoğun), daha çok komplikasyona, daha sık nötropeni, farklı bağışıklık sistemi, ko-morbidite, beslenme, obezite, yaşam yarzı, kreş, okul, viral enfeksiyon (2) Risk stratification;

MASCC erişkinler için, çocuklarda risk tahmin kuralları

(3) Değerlendirme

Hikaye, FM, Kan kültürleri, tek kan kültürü epizodların %10'unu kaçırabilir, galactomannan testi ?

(4) Tedavi

Pediatri doz ve ilaç onayları (e.g Piperasillin-tazobaktam >2 yaş; Kistik fibrozis için sipro)

(5) Ailevi ve psikososyal faktörler

pagepress

Pediatric Reports 2011; volume 3:e7

Guidelines for the management of bacterial and fungal infections during chemotherapy for pediatric acute leukemia or solid tumors: what is available in 2010?

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ferences as regards pharmacology of drugs, epidemiology and, sometimes, clinical features of infectious complications during antineoplastic chemotherapy.

In the following paragraphs we will summarize guidelines provided for the management of infectious complications in adults with cancer by different international Societies, i.e. the European Conference for Infections in Leukaemia (ECIL) (available at http://www.ichs.org), Infectious Diseases Society of America (IDSA),[3]) British Committee for Standards in Haematology (BCSH),[4] German Society for Hematology and Oncology (DGHO),[5-7] National Comprehensive Cancer Network (NCCN, available at http://www.nccn.org), and will comment on how much they may be translated in the management of pediatric patients, mainly using as a base an epidemiological and clinical "common sense".

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Key words: pediatric leukemia, pediatric solid tumor, bacterial and fungal infections.

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Pediatrik Kılavuz sayısı eksik mi?

- Pediatrik klinik çalışma sayısının azlığı (Usulünce yapılmış, vaka sayısı uygun, vb.)
- Antibakteriyal proflaksi için Çift kör, plasebo kontrollü 1 çalışma var (173 hasta, 2003)
- Persistan ateşi olan FEN hastalarında empirik antifungal tedavi, ilk çalışma (163 hasta, 2010)
- Sonuç: farmakolojik, epidemiyolojik ve klinik farklılıklar olduğu zaman bile Erişkin Kılavuzları kullanılıyor

Erişkin kılavuzlar

- ECIL, European Conference for Infections in Leukemia (www.ichs.org)
- IDSA, Infectious Diseases Society of America
- BCSH, British committee for standards in leukemia
- DGHO, German Society for Hematology and Oncology
- NCCN, National comprehensive cancer network, (www.nccn.org)

Erişkin kılavuzlar'dan pediatriye çıkarımlar: Proflaksi

1. Önlemeyi düşündüğünüz olayın tedavisi kolay mı?

   Evet: Proflaksi gereksiz **Hayır: Proflaksi gerekli**

2. Olay ağır bir olay mı?

   Evet: Proflaksi gerekli Hayır: Proflaksi gereksiz

3. Proflaksinin yan etkileri ağır mı? (Direnç dahil)

   Evet: Proflaksi verme Hayır: Proflaksi ver

4. "NNT, Number of patients needed to treat to prevent one event"

   Bunun için **standard yok**, değişken

Table 1. Guidelines for the administration of prophylaxis in adults receiving antineoplastic chemotherapy

Group and year of publication	Antibacterial prophylaxis			Antifungal prophylaxis		
	Patients' population	Drug	Notes	Patients' population	Drug and level of evidence	Notes
ECIL 2007, 2009	Acute leukemia	Levofloxacin: highly recommended		Acute leukemia, myelodisplastic syndrome	Posaconazole: highly recommended Nebuized liposomal amphotericin B+ oral fluconazole: recommended Voriconazole/echinocandis: not enough data	No use of empirical triazoles, therapeutic drug monitoring recommended
IDSA 2002	Fluoroquinolone or trimethoprim-sulphametoxazole: not recommended for routine use; revision foreseen			Fluconazole or itraconazole: not recommended for routine use		
BCSH 2006, 2008	Acute myelogenous leukemia	Not recommended	No improvement in the prognosis of underlying disease, development of resistance	High risk patients (not further specified)	Itraconazole Revision foreseen	
NCCN 2009	Low risk	None	Standard chemotherapy Neutropenia anticipated < 7 days Neutropenua anticipated < 7 days	Low risk	None	Standard chemotherapy
	Intermediate risk	Consider fluoroquinolone or none	Neutropenua anticipated 7-10 days Administration of purine analog Lymphoma	Intermediate risk	Fluconazole, or liposomal amphotericin B	Especially in acute lymphobastic leukemia
	High risk	Consider fluoroquinolone	Neutropenia in acute leukemia or myelodisplastic syndrome Neutropenia anticipated > 10 days	High risk	Posaconazole, voriconazole, or liposomal amphotericin B	Especially in acute myelogenous leukemia or myelodisplastic syndrome
DHGO 2006	Recommended revision of prophylactic procedures in the wake of development of resistance to antibiotics			Acute myelogenous leukemia, myelodisplastic syndrome	Posaconazole: higly recommended Nebulized liposomal amphotericin B + fluconazole: moderately recommended	

Antibakteriyal proflaksi

- Antibakteriyal proflaksi için Çift kör, plasebo kontrollü pediatrik 1 çalışma var (173 hasta, 2003)
  - Lösemi/lenfoma grubunda etkili; koruyucu etki - %17
  - Solid tümörlerde etkin değil; NNT 6 hasta
- Erişkinlerde florokinolonlarla antibakteriyal proflaksi sadece ECIL ve NCCN kılavuzlarında tavsiye ediliyor. Diğerlerinde yok.

Antifungal proflaksi

- Çocuklarda çalışma yok
- İspatlamış ve olası **invaziv fungal enfeksiyon** proflaksisinde Posakonazol ECIL, DGHO, NCCN'de önemle tavsiye ediliyor. Nebulize Lip-Amfoterisin B + flukonazol ECIL ve DGHO'da daha düşük düzeyde tavsiye ediliyor
- Çocuklarda ALL'de NNT 13-25 arasında olacak ve ayrıca Posakonazol dozu çocuklarda bilinmiyor ve Posakonazol çocuk için zor (Yağlı yemek, asidik içecek, daha düşük doz sorunluluğu?, N/G tüp gerekebilir gibi..)
- Çocuklarda Lipozomal amfoterisin B çalışması için 5 yıl gerekiyor, buda değerlendirme etkinliğini gölgeliyor
- Nebulizerların uygun kullanılması sorunu
- Sekonder proflaksi (rölapsların engellenmesi) Bilinmiyor!

Antibakteriyal tedavi

- Oral vs intravenöz; lösemi vs solid
- Yüksek risklilerde “front-line” monoterapi (psödomonas beta laktamlar; seftazidim, sefepim, piperasilin-tazobaktam)
- Düşük risklilerde ciprofloksasin+amoksisilin klavulanat (özellikle solid tümörler)
- Başlangıçta aminoglikozid kullanımı seftriakson’lu kombinasyonlarda psödomonas için, veya lokal epidemiyolojik özelliklere göre değişir.
- FUO için empirik aminoglukozid verilmişse, 3 gün (3 doz?)’la sınırlandırılır
- Glikopeptidler: Tüm kılavuzlarda başlangıç empirik ya da persistan ateş tedavisinde rutin önerilmiyor! Mikrobiyolojik dökümentasyon, klinik bulgular (ör, deri/yumuşak doku infeksiyonları, sentral venöz kateter infeksiyonları
- ÇOCUKLARDA FARKLI BİR ÖNERİ İÇİN YETERLİ VERİ YOK!

Empirik antifungal tedavi

- Persistan ateşi olan FEN hastada empirik antifungal tedavi, ilk çalışma (163 hasta, 2010)
- Lipozomal amfoterisin B vs Caspofungin
- Genellikle hiçbir ilaç birbirine üstün değil ve öyle olunca hangisinin daha az toksik olduğuna bakılıyor.
- IDSA ve NCCN hala 5 gün persistan ateşi olanta empirik antifungal'ı öneriyor; DGHO bakılmamış, BSCH tavsiye etmiyor. ECIL ise bunu düşük düzeyde tavsiye ediyor ve sadece rutin CT ve serum galaktomannan'ın bakılamadığı yerlerde tavsiye ediyor. Bu tavsiyeler Pediatrik hastalar içinde geçerlidir.
- Bu nedenle Pre-emptif tedavi kavramı gelişti (Fungal hastalık kanıtlanmamış fakat düşündüren nedenler var!)
  - AC CT, serum/BAL galaktomannan, serum glucan, sitolojik hif gösterilmesi, Balgam/BAL sıvısı pozitif kültür
- Pre-emptif vs empirik ???? (Hem erişkinlerde hem çocuklarda)

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

Clinical Infectious Diseases 2011;52(4):e56–e93

"What has not changed is the indication for immediate empirical antibiotic therapy. It remains true that all patients who present with fever and neutropenia should be treated swiftly and broadly with antibiotics to treat both gram-positive and gram-negative pathogens."

Cultures

In pediatric patients weighing <40 kg, proportionately smaller volumes of blood culture samples are suggested. Some centers limit blood draws to no more than 1% of a patient's total blood volume. Because total blood volume is approximately 70 mL/kg, the total sample limit would be 7 mL for a 10-kg patient and 28 mL for a 40-kg patient

Unexplained Fever in Low-Risk Patients

A number of studies, primarily involving pediatric patients, have supported the simpler alternative of stopping antibiotic therapy altogether before attaining the endpoint of an ANC >500 cells/mm3 if cultures are negative at 48 h and patients remain afebrile for at least 24 h

Fluoroquinolones prohylaxis

Some clinicians are reluctant to routinely use fluoroquinolones in children because of preclinical studies in animals that have suggested musculoskeletal toxicity. Large surveys of fluoroquinolone use in children who do not have cancer have not identified serious problems, although the drugs may be associated with more musculoskeletal adverse effects, compared with other classes of antibiotics. High-quality clinical trials have not assessed the risk-benefit ratio of fluoroquinolone prophylaxis in children, **but it may be reasonable to use the drugs in very high-risk situations, such as allogeneic transplantation or induction therapy for acute leukemia.**

A second large randomized trial of levofloxacin prophylaxis examined only lower-risk patients with solid tumors or lymphoma and showed a 33% reduction in febrile episodes per chemotherapy cycle with prophylaxis but no effect on documented infections. Given the low rate of fever in the placebo arm, **up to 71 patients per chemotherapy cycle would be necessary to prevent one febrile neutropenic episode, without any impact on all-cause mortality. Therefore, routine use of fluoroquinolone chemoprophylaxis in low-risk patient populations is not recommended.**

Support Care Cancer
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REVIEW ARTICLE

Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children—a systematic review of prospective trials

A. Manji · J. Beyene · L. L. Dupuis · R. Phillips · T. Lehrnbecher · L. Sung

Received: 7 September 2011 /Accepted: 21 February 2012

Abstract
Background There is no consensus on whether therapeutic intensity can be reduced safely in children with low-risk febrile neutropenia (FN). Our primary objective was to determine whether there is a difference in efficacy between outpatient and inpatient management of children with low-risk FN. Our secondary objective was to compare oral and parenteral antibiotic therapy in this population.
Methods We performed electronic searches of Ovid Medline, EMBASE, and the Cochrane Central Register of Controlled Trials, and limited studies to prospective pediatric trials in low-risk FN. Percentages were used as the effect measure.
Results From 7,281 reviewed articles, 16 were included in the meta-analysis. Treatment failure, including antibiotic modification, was less likely to occur in the outpatient setting compared with the inpatient setting (15% versus 28%, $P=0.04$) but was not significantly different between oral and parenteral antibiotic regimens (20% versus 22%, $P=0.68$). Of the 953 episodes treated in the outpatient setting and 676 episodes treated with oral antibiotics, none were associated with infection-related mortality.
Conclusion Based on the combination of results from all prospective studies to date, outpatient and oral antibiotic management of low-risk FN are effective in children and should be incorporated into clinical care where feasible.

Keywords Cancer · Children · Febrile · Meta-analysis · Neutropenia

Fig. 1 Flow diagram of trial identification and selection

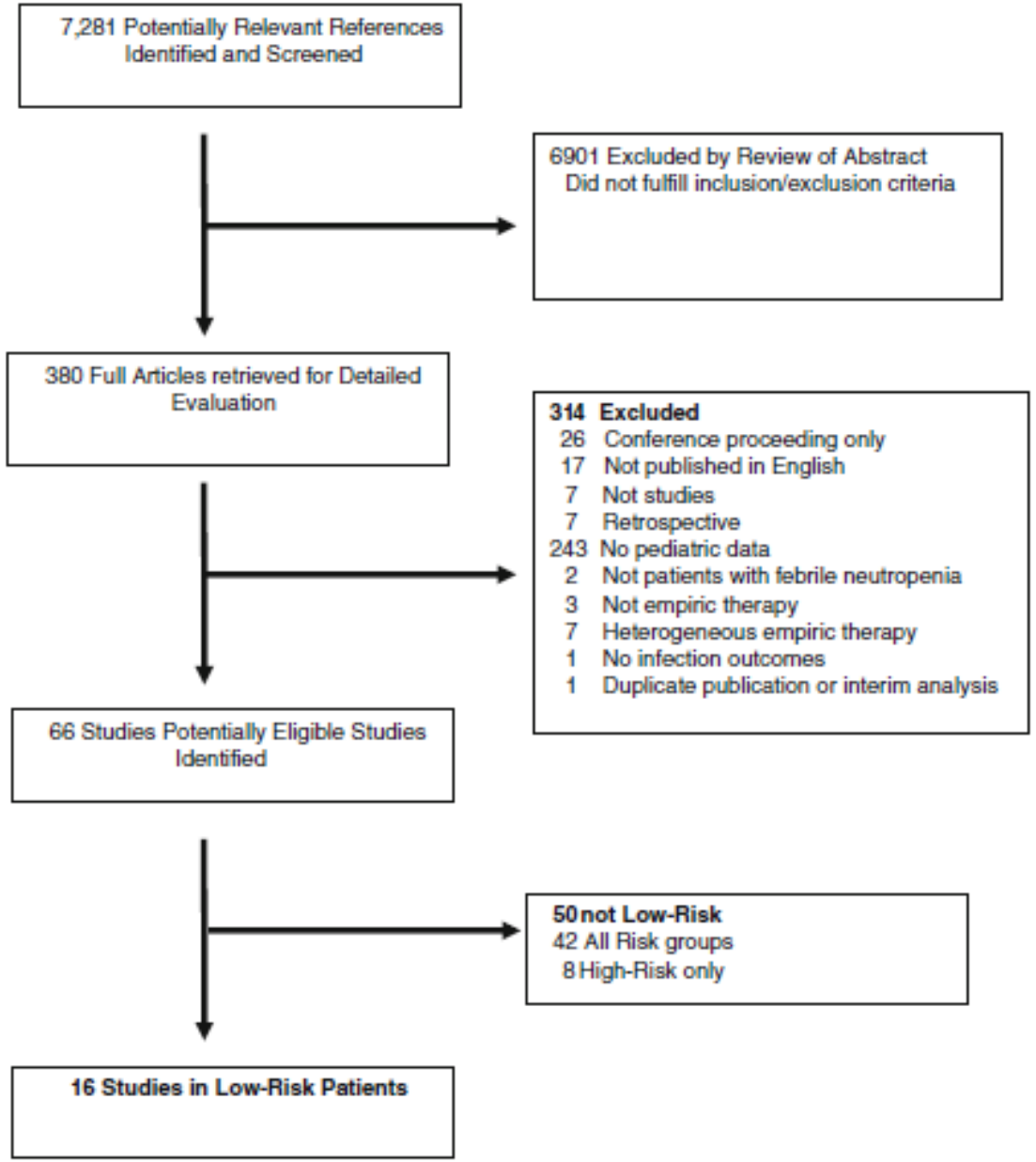


Table 1 Characteristics of included studies: prospective studies of initial empiric regimens for children with low-risk fever and neutropenia

Author	Year	RCT	Setting	Route	Drug (s)	FN episodes	Mean or median* age	Unexplained fever (%)	L&L[a] (%)	ANC<100[b] (%)
Cagol [9]	2009	Y	In	PO	Cipro, Amox-Clav	43	7.9	88	9	NR
			In	IV	Cefepime	48	7.6	92	10	NR
Gupta [17]	2009	Y	Out	PO	Oflox, Amox-Clav	62	8.3*	27	31	21
			Out	IV	CTX, AMK	61	7.8*	26	36	33
Kutluk [24]	2004	Y	In	IV	Cefepime	25	6*	NR	NR	NR
			In	IV	Meropenem	24	9*	NR	NR	NR
Paganini [31]	2003	Y	Out	IV	CTX, AMK	89	6.9*	31	71	47
			Out	sdPO	CTX, AMK: Cipro	88	8.2*	25	56	50
Duzova [13]	2001	Y	In	IV	Meropenem	45	7	NR	60	42
			In	IV	Piperacillin, AMK	45	8.4	NR	64	51
Paganini [32]	2001	Y	sdOut	sdPO	CTX, AMK: Cipro	48	5*	31	42	23
			sdOut	sdPO	CTX, AMK: Cefixime	45	6*	33	49	31
Petrilli [34]	2000	Y	Out	PO	Cipro	68	10.3*	41	6	NR
			Out	IV	CTX	70	9.8	32	3	NR
Mullen [28]	1999	Y	Out	IV	CTZ	33	9.6	97	NR	55
			Out	sdPO	CTZ, Cipro	40	9.8	82	NR	65
Shrestha [41]	2009	N	In	PO	Oflox, Amox-Clav	54	7.2	83	74	0
Petrilli [33]	2007	N	Out	PO	Gatifloxacin	201	10.8	51	15	NR
Abbas [1]	2003	N	Out	IV	CTX, AMK	68	4.7	47	100	10
Aquino [5]	2000	N	sdOut	sdPO	CTZ, Cipro	45	6.5	87	69	40
Bartolozzi [6]	1997	N	In	IV	CTX	33	6.3	91	0	NR
Malik [26]	1997	N	Out	PO	Oflox	91	9.2	84	48	27
Mustafa [29]	1996	N	Out	IV	CTX	19	7.5	74	68	NR
Kaplinsky [21]	1994	N	Out	IV	CTX	50	NR	NR	56	NR

NR not reported; *RCT* randomized controlled trial; *In* inpatient; *Out* outpatient; *sdOut* step-down outpatient; *IV* intravenous therapy; *PO* oral therapy; *sdPO* step-down oral therapy; *CTX* ceftriaxone; *CTZ* ceftazidime; *AMK* amikacin; *Cipro* ciprofloxacin; *Oflox* ofloxacin; *Amox-Clav* amoxicillin-clavulanate

[a] Percentage of patients with leukemia and lymphoma

[b] Percentage of patients with absolute neutrophil count <100 per microliter at presentation

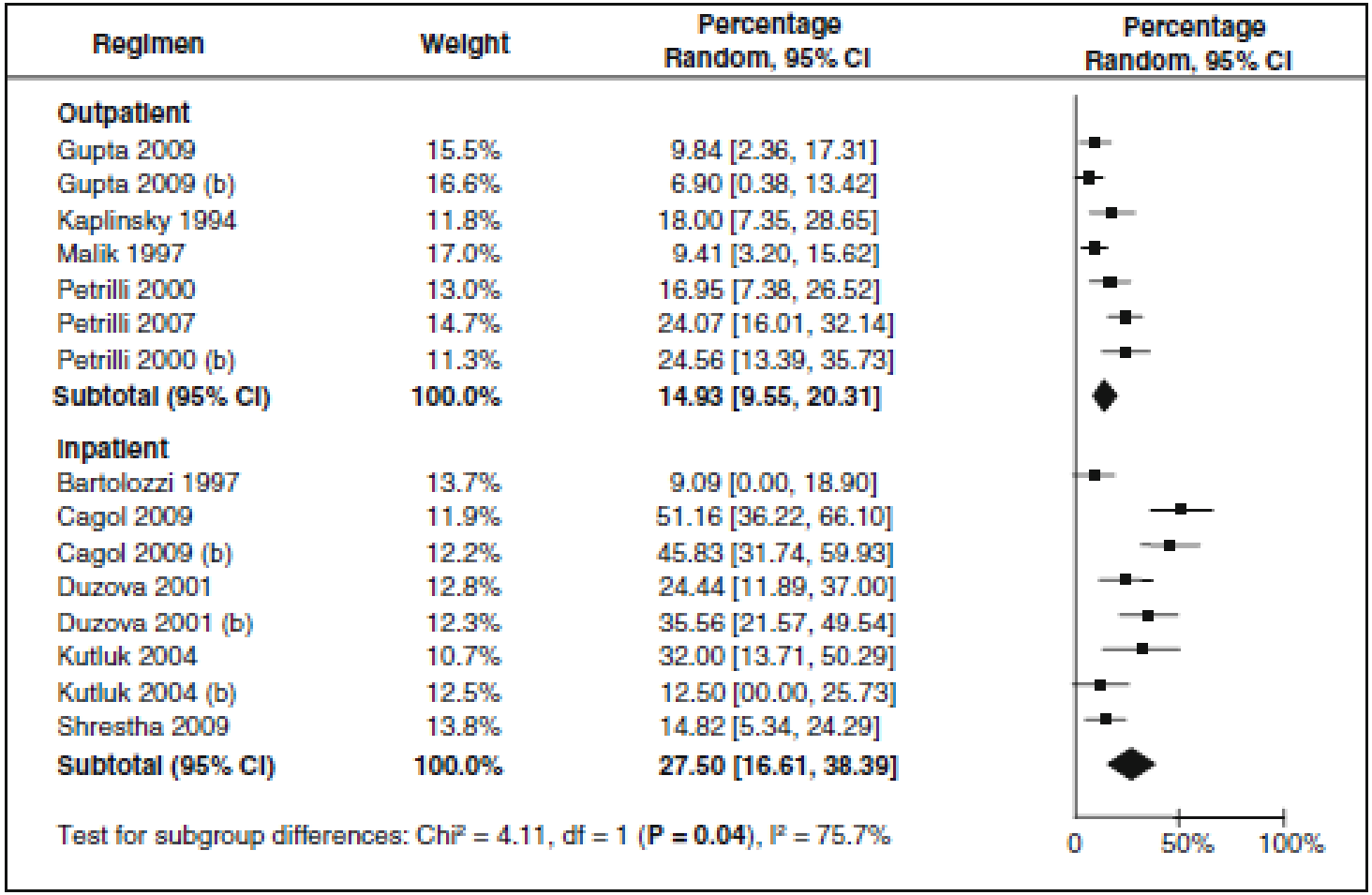


Fig. 2 Forest plot of treatment failure, including antibiotic modification, comparing outpatient with inpatient empiric regimens. *Squares* indicate percentages with horizontal lines representing 95% CIs. *Diamonds* represent overall percentages from the meta-analysis with corresponding 95% CIs. A test for heterogeneity [19] across subgroup results was used to determine if outcomes were modified based upon treatment setting or route of administration

ECIL 4 – Pediatric Group Considerations for Fungal Diseases and Antifungal Treatment in Children

Elio Castagnola (Italy); Simone Cesaro (Italy); Jean-Hugues Dalle (France); Dan Engelhard (Israel); William Hope (United Kingdom); Thomas Lehrnbecher (Germany); Emmanuel Roilides (Greece); Jan Styczynski (Poland), Adilia Warris (The Netherlands)

Co-ordinator: Andreas H. Groll (Germany)

Meeting: September 8-10th, 2011
Final version: Jan 19th, 2012

Incidence, probable/proven IFD in children

Ref	Patients studied	IFD incidence	Evidence
Kobayashi et al. (Japan) 2008.	334 Hem. malignancies, HSCT and others	AML 11.7%; alloHSCT 8.1%; ALL 2.0%; sporadic in solid tumors moulds >> yeast	II retro-spective
Kaya et al. (Turkey) 2009	155 AL during intensive chemotherapy	AML 12,4; ALL 8,4 yeast >> moulds	II retro-spective
Castagnola et al. (Italy) 2010	240 AML	10% of all courses; recurrent AML: 15% moulds >> yeast	II retro-spective
Hale et al. (AUS) 2010	Acute leukemia / HSCT patients	Recurrent leukemia 21%; ALL 18.5%; alloHSCT 15.2%; AML 8.8%; yeast >> moulds	II retro-spective
Mor et al. (Israel) 2011	1047 HSCT and heme/onc patients	AML 13.6%; ALL 5.9%; alloHSCT 3.9%; autoHSCT 3.0%; solid tumors 1.6%; lymphoma 0.8% moulds >> yeast	II retro-spective

Mortality, probable/proven IFD in children

Ref	Patients studied	Mortality rate (% of infected patients)	Evidence
Kobayashi et al. (Japan) 2008.	hematologic malignancies, HSCT and others	48.2% overall*	II retrospective
Kaya et al. (Turkey) 2009	AL during intensive chemotherapy	4.7% overall	II retrospective
Castagnola et al. (Italy) 2010	AML	20%overall	II retrospective
Hale et al. (AUS) 2010	Acute leukemia / HSCT patients	22% in yeast, 50% in mould infections	II retrospective
Mor et al. (Israel) 2011	HSCT and hematology/oncology patients	21.7% overall	II retrospective

*in invasive pulmonary aspergillosis – the mortality was above 70%

Stratification of Risk of IFDs in Pediatric Cancer / HSCT Patients

Risk stratum	Patient population
High risk (≥ 10 %)	-acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HSCT
Low risk (≤5 %) *	-acute lymphoblastic leukemia ** -non-*Hodgkin* lymphoma's -autologous HSCT
Sporadic occurrence *	-pediatric solid tumors -brain tumors -*Hodgkin's* lymphoma

* consider that low and sporadic risk is not equal to no risk
** depending on the protocol and additional risk factors, risk for IFD may exceed 10 %

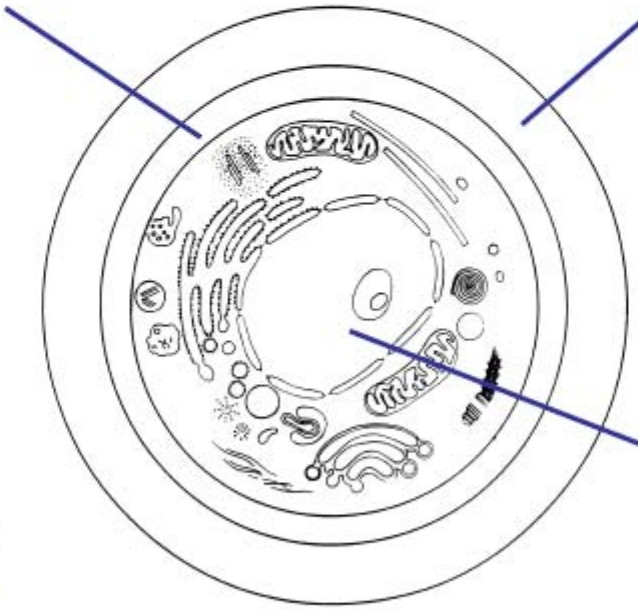
Groll et al. 1999; Hovi et al. 2000; Lin et al. 2001; Benjamin et al. 2002; Zaoutis et al. 2004; Zaoutis et al. 2005; Zaoutis et al. 2006; Rosen et al. 2005; Kobayashi et al. 2008; Kaya et al. 2009; Castagnola et al. 2010; Hale et al. 2010; Mor et al. 2011

Antifungal Drugs: Pediatric Approval Status

Cell membrane

- **Polyenes**
  - > DAMB
  - > LAMB
  - > ABLC
  - > ABCD

- **Triazoles**
  - > Fluconazole
  - > Itraconazole *
  - > Voriconazole
  - > Posaconazole *



Cell wall

- **Echinocandins**
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin *

Nucleic acid synthesis

- > Flucytosine

* *not approved in pediatric patients*

Pediatric PK: Getting Dosages Right

Agent	Dosage*	Comment	PK References
Fluconazole	8-12 mg/kg/d qd iv/po	Optimal dose uncertain	Lee 1992; Brammer 1994;
Itraconazole	5 mg/kg/d bid po	Limited data, not licensed	De Repentigny 1998; Groll 2002
Posaconazole	600-800 mg/d (tid, bid/qid) po	Only >13 yrs, not licensed	Krishna 2007
Voriconazole	8-14 mg/kg/d bid iv 400 mg/d bid po	Optimal dose uncertain, and age-dependent	Walsh 2004; Karlsson 2009
Anidulafungin	1.5 (d1:3) mg/kg/d iv	Studies under way, not licensed	Benjamin 2006
Caspofungin	50 (d1:70) mg/m²/d iv	Robust dataset and models	Walsh 2005; Neely 2009
Micafungin	1-4 mg/kg/d iv	Robust dataset and models	Seibel 2005; Hope 2007
Liposomal amphotericin B	3->5 mg/kg/d iv	Weight-based dosage inferred without robust PK	Hong 2006
Amphotericin B Lipid Complex	5 mg/kg/d iv	Limited PK data in children	Walsh 1997

** Dosages may vary according to indication*

Randomized trials on IFD prophylaxis with inclusion of pediatric patients

- One randomized, double-blind study in 882 HSCT patients included 84 children <16 yrs, comparing micafungin vs. fluconazole (separately analyzed) (van Burik 2004); in another study in 600 HSCT recipients, comparing fluconazole vs. voriconazole, 51 children > 2 yrs were enroled (Wingard; Blood 2010) (children not separately analyzed)

- Other studies included only few children, were observational, or also included superficial infections in the efficacy assessments

Recommendation for primary antifungal chemoprophylaxis in children undergoing <u>allogeneic</u> HSCT: Neutropenic Phase

- Primary prophylaxis against IFDs is recommended during the neutropenic phase until engraftment (BII)
- *Options include (alphabetical order)*
  - *fluconazole (AI) (active only against yeast)*
  - *Itraconazole (BI), TDM recommended*
  - *liposomal amphotericin (CIII)*
  - *micafungin (CI)*
  - *Voriconazole (BI), TDM recommended*
  - *other options include aerosolized LAMB and posaconazole +TDM (no grading)*

TDM, therapeutic drug monitoring

Recommendation for primary antifungal chemoprophylaxis in children undergoing allogeneic HSCT: Post engraftment phase

- No GVHD, standard immunosuppression:
  - continue antifungal prophylaxis until immune recovery (no grading)
- GVHD, augmented immunosuppression
  - primary prophylaxis against mold and yeast infections is recommended (AII); options include
    - itraconazole (CII), TDM recommended
    - posaconazole (BI for children >12 years), TDM recommended
    - voriconazole (BI), TDM recommended

  other options include liposomal amphotericin B and micafungin (no grading)

TDM, therapeutic drug monitoring

Recommendation for primary antifungal chemoprophylaxis in pediatric leukemia patients

- Primary antifungal prophylaxis against IFDs should be considered in high risk patients (BII)
- Options include
  - fluconazole (CI) (active only against yeast)
  - itraconazole (BI), TDM recommended
  - liposomal amphotericin (BII)
  - Posaconazole (BI for children >12 years), TDM recommended
  - other options include voriconazole +TDM, micafungin, and aerosolized liposomal amphotericin B (no grading)
  - note: caution should be used with the concurrent use of itraconazole, posaconazole, voriconazole with vincristin

TDM, therapeutic drug monitoring

Pediatric Dosages / Key References

Agent	Dosage for Prophylaxis	Key References
Fluconazole	8-12 mg/kg/d qd iv/po (max. 400mg/d)	Lee 1992; Brammer 1994; Ninane 1994; Novelli 1999; Goodman 1992; Slavin 1995; Marr 2000; Menichetti 1994; Rotstein 1999
Itraconazole	5 mg/kg/d bid po +TDM	De Repentigny 1998; Groll 2002; Foot 1999 Menichetti 1999; Harousseau 2000; Marr 2004; Winston 2003
Posaconazole	600 mg/d tid po +TDM	Krishna 2007; Cornely 2007; Ullmann 2007
Voriconazole	<13 yrs 14 mg/kg/d bid / >12 yrs 400 mg/d bid iv; 400 mg/d bid po (all) +TDM	Walsh 2004; Karlsson 2009; Molina 2011 Wingard 2010; Marks 2011
Micafungin	1 mg/kg (>=50kg: 50 mg) qd iv	Seibel 2005; Hope 2007; Arrieta 2011; Van Burik 2006
Liposomal amphotericin B	1 mg/kg or 2.5 mg/kg twice weekly iv	Ringden 1997; Hong 2006; Kolve 2009; Bochennek 2011; Tollemar 1993; Kelsey 1999; Penack 2006

Key references include:
Pediatric PK , safety, and efficacy data, if available
Pivotal adult phase II I clinical trials

Galactomannan

Recommendations

- When GM in serum is used for screening for invasive mold infection in children with hematological malignancies/undergoing HSCT, the assay has a sensitivity and specificity profile that is similar to that observed in adults. Despite a number of limitations of the available pediatric data (wide variations amongst the studies regarding cut-off, definition of positivity etc), prospective monitoring of GM in serum every three to four days in children at high risk for IFD is reasonable for early diagnosis of invasive aspergillosis (AII)

- Although the optimal cut-off value of GM in the serum of children is not well defined, published data support the use of a threshold of an optical density index 0.5. (serum specimens) (BIII)

Recommendations

- The very limited published data support the value of GM in the diagnosis of pulmonary aspergillosis (GM in BAL; cut-off 1) and central nervous system aspergillosis (GM in CSF; cut-off 0.5) in children (BIII)
- Systemic mold-active prophylaxis may decrease the performance of the test (BIII).

β D Glukan

Recommendations

- Although BG testing has been shown to be useful in diagnosing IFD in adult patients, data are too limited to make any recommendations on BG testing in children

Analysis of imaging

- Limited data on imaging studies in children with underlying malignancies and persistent febrile neutropenia
- None of these studies were designed to evaluate the impact of CT imaging on the decision to withhold or to initiate antifungal therapy
- In contrast to adult patients, typical signs of IFD (e.g., halo sign, air crescent sign, and cavities) are not seen in the majority of children
- Radiographic findings in immunocompromised children with invasive pulmonary fungal disease are often unspecific, in particular in the younger age group (e.g., < 5-year of age): multiple nodules or fluffy masses and infiltrates which look like mass lesions were the two basic types of involvement

Taccone 1993; Archibald 2001; Burgos 2008

Recommendations

- In high-risk children with persistent febrile neutropenia that persists beyond 96 hours or with focal clinical findings, imaging studies (e.g., CT-scan of the lung or adequate imaging of the symptomatic region) should be performed (BII)

- In chest X ray and/or CT scan, typical signs of invasive pulmonary fungal disease are often missing, in particular in the younger age group. In contrast, even atypical pulmonary infiltrates (e.g., fluffy masses) may support the diagnosis of invasive pulmonary fungal disease in a patient at high risk

  → further diagnostic work-up (e.g., BAL, biopsy) should be considered **and mold-active** antifungal treatment should be initiated (BII)

Management of persistently or recurrently febrile neutropenic children:

Empiric / pre-emptive therapy

Analysis

- To date, no study compared empirical antifungal therapy with no therapy in children with persistent febrile neutropenia

- 3 prospective randomized trials in children
  - *Prentice et al* 1997
    - AmB-D (1 mg/kg) vs L-AmB (1mg/kg) vs L-AmB (3 mg/kg)
    - n=204, >60% children with leukemia
  - *Sanders et al* 2000
    - AmB-D (0.8 mg/kg) vs ABCD* 4mg/kg
    - n=49, >60% children with leukemia/HSCT
  - *Maertens et al* 2010
    - L-AmB (3 mg/kg) vs Caspo (50 mg/m^2 after loading day 1)
    - n=82, >70% children with leukemia/HSCT

*not licensed for this indication in children

Prentice 1997; Sanders 2000; Maertens 2010

Recommendations

- In neutropenic children with acute leukemia/allogeneic HSCT, empirical antifungal treatment, if chosen as strategy, should be initiated after 96 hours of fever with unclear etiology that is unresponsive to broad-spectrum antibacterial agents (BII)
- Both caspofungin (50 mg/m^2/day, day 1 70 mg/m^2; max 70 mg/d) and liposomal amphotericin B (1-3 mg/kg/d*), which are approved for this indication in children of all ages, can be recommended for empirical antifungal therapy in children (AI)

  * L-AmB is approved for empirical therapy in some countries at the dosage of 3 mg/kg/d, in others at dosages between 1 and 3 mg/kg/d
- Although there are no adult or pediatric data to recommend a specific empirical antifungal agent for patients already receiving mold-active antifungal prophylaxis, however, switching to a different class of mold-active antifungal agent seems reasonable (no rating due to no data) Patients receiving antifungal prophylaxis without mold activity (e.g. fluconazole) should be given either caspofungin or L-AmB for empirical therapy as described above (no rating due to the lack of data)
- Empirical antifungal treatment should be continued until resolution of neutropenia (BII)
- Although there are no data on pre-emptive antifungal strategies in children, it may be an alternative to the empirical antifungal approach (no rating)

Suggested diagnostic and therapeutic algorithm for children with persistent febrile neutropenia

Diagnostic work-up to include blood cultures, serum GM (>1x), and chest CT (other imaging as indicated)

- Work-up negative:

  Continue mold-active antifungal prophylaxis or start mold-active empirical antifungal therapy

- Positive blood cultures:

  Treat according to species identified and *in vitro* susceptibility

- GM positive (>1x), chest CT negative:

  Start pre-emptive antifungal therapy (change of class if on mold-active prophylaxis)

- Positive chest CT / positive imaging:

  Start pre-emptive therapy (change of class if on mold-active prophylaxis) and pursue invasive diagnostic procedure

- If proven IFD: treat according to species / *in vitro* susceptibility

Treatment of Established Invasive Fungal Infections

Recommendations:
1st line Therapy of Invasive Aspergillosis

Antifungal therapy: *

ABLC	B II[1]
Liposomal AmB	B I [1]
Voriconazole i.v.	A I [1]
Combination therapy	C III

[1] voriconazole should be preferred in CNS infection.
[2] oral voriconazole should be used in presence of renal failure because of potential for accumulation of the cyclodextrin excipient

* *in alphabetical order*

Recommendations: Candidemia and Invasive Candidiasis

Management includes antifungal therapy, control of underlying condition(s), surgery, removal of central venous line (no grading)

Antifungal therapy: *

Amphotericin B Lipid Complex	C II
Caspofungin [2]	B II
Fluconazole [2]	B II
Liposomal Amphotericin B	B II
Micafungin [1,2]	B II
Voriconazole [2]	B II

[1] note EMA Black Box Warning for micafungin; implications for other echinocandins not clear

[2] C.krusei is inherently resistant to fluconazole; C.glabrata has variable susceptibility to fluconazole, and treatment with fluconazole is not advised; echinocandins have higher MICs against C.parapsilosis, however, the clinical implications are unknown.

* *in alphabetical order*

Pediatric Dosages / Key References

Agent	Dosage for Treatment	Key References *
Fluconazole	8-12 mg/kg/d qd iv/po	Lee 1992; Brammer 1994; Novelli 1999 Rex 1994; Anaissie 1996; Rex 2003;
Itraconazole	5 mg/kg/d bid po +TDM	De Repentigny 1998; Groll 2002; Foot 1999 Denning 1994; Caillot 2001
Posaconazole	800 mg/d (bid/qid) po +TDM in children > 12 years	Krishna 2007; Lehrnbecher 2010; Cesaro 2011; Walsh 2007
Voriconazole	<13 yrs 14 mg/kg/d bid / >12 yrs 400 mg/d bid iv; 400 mg/d bid po (all) +TDM	Walsh 2004; Karlsson 2009; Walsh 2002; Herbrecht 2002; Kullberg 2005
Caspofungin	50 (d1:70) mg/m^2 qd iv Maximum: 70 mg QD	Walsh 2005; Neely 2009; Zaoutis 2009; Zaoutis 2009; Mora-Duarte 2002; Maertens 2004; Pappas 2007; Betts 2009
Micafungin	2-4 mg/kg qd iv	Seibel 2005; Hope 2007; Arrieta 2010; Queiroz-Telles 2008; Denning 2006; Kuse 2007; Pappas 2007
Liposomal amphotericin B	3 (->5) mg/kg qd iv	Hong 2006; Queiroz-Telles 2008; Kolve 2009; Cornely 2007; Kuse 2007
Amphotericin B Lipid Complex	5 mg/kg qd iv	Walsh 1997; Walsh 1999; Wiley 2005; Walsh 1998

** Pediatric PK , safety, and efficacy data, if available Pivotal adult phase II Iclinical trials*

ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Paediatric Population

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