Appendix 3. Pediatric and Adult Studies that Evaluated the Proportion of Positive Blood Cultures Identified only by Peripheral Culture

Study	Pediatric or Adult	Number of Paired Blood Cultures	Contaminates Deleted	Proportion Positive Only in Peripheral Culture (%)
Handrup 2010[40]	Pediatric	68	No	7/51 (13.7)
Scheinemann 2010[35]	Pediatric	318	Yes	28/228 (12.3)
Chen 2009[37]	Adult	2775	No	68/533 (12.8)
Raad 2004[39]	Both pediatric and adult	6138	No	191/1010 (18.9)
Adamkiewickz 1999[38]	Pediatric	176	No	6/21 (28.6)
DesJardin 1999[36]	Adult	552	Yes	5/46 (10.9)
Barriga 1997[41]	Both pediatric and adult	143	No	7/44 (15.9)

Appendix 4. Efficacy and Safety of Initial Empiric Antibiotic Regimens in Children with Fever and Neutropenia Reported in All Prospective Trials*

	APP ± BLI Monotherapy	APP ± BLI and Aminoglycoside	Ceftazidime Monotherapy	Ceftazidime and Aminoglycoside	FGC Monotherapy	FGC and Aminoglycoside	Carbapenem
Citations	150-153	65,154-168	165,169-175	66,164,172,176-181	66,147,149,168,170, 173,175,181-185	183,184	61,65,150,152,166,167,176,182,183,186-188
Number of Studies***	4	13	7	10	11	2	10
Number of Patients***	210	1092	406	805	517	167	572
Percentage treatment failure including modification (95% CI)	34 (27,41)	41 (32, 50)	43 (28, 58)	32 (19, 45)	39 (35, 44)	40 (27, 52)	36 (26, 45)
Percentage infection-related mortality (95% CI)	2 (0, 3)	1 (0, 2)	1 (0, 2)	2 (1, 3)	1 (0, 2)	1 (0, 2)	1 (0, 1)
Percentage overall mortality (95% CI)	2 (0, 4)	4 (2, 7)	1 (0, 2)	3 (2, 4)	2 (0, 3)	1 (0, 2)	1 (0, 2)
Mean days of fever (95% CI)	3.1 (2.8, 3.5)	3.5 (2.9, 4.2)	2.8 (1.7, 3.9)	3.1 (2.3, 3.9)	3.0 (2.4, 3.7)		3.5 (2.7, 4.3)
Percentage recurrent infection** (95% CI)		12 (8,16)	3 (0, 5)	2 (0, 6)	12 (0, 24)	5 (0, 10)	3 (0, 8)
Percentage sepsis (95% CI)		3 (1, 6)	4 (0, 7)	2 (0, 6)	16 (0, 39)		5 (0, 10)
Percentage secondary infection** (95% CI)	10 (3, 18)	5 (2, 8)	4 (2, 6)	4 (2, 6)	4 (1, 7)		2 (0, 4)
Percentage adverse events causing antibiotic discontinuation (95% CI)	1 (0, 3)	0 (0, 1)	1 (0, 3)	1 (0, 2)	1 (0, 2)	1 (0, 3)	1 (0, 3)

Abbreviations: APP – anti-pseudomonal penicillin; BLI – beta lactamase inhibitor; FGC – fourth generation cephalosporin, CI – confidence interval

* If outcome is missing, no studies reported on that outcome.
** Recurrent infection defined as reappearance of fever or infection after initial resolution; secondary infection defined as development of a new infection during ongoing treatment.
*** Maximum number of studies and patients reporting any outcome. Not all outcomes were reported for each study.

Appendix 5. Prospective Studies that Compared Initial or Step-down Outpatient Management with Inpatient Management in Children with Low-Risk Fever and Neutropenia*

Number of Regimens	Number of Patients and Effect** (95% CI)		Comparison	Quality	Importance
	Inpatient [156,182,185,189,190]	Outpatient [174,186-188,191-197]			
Treatment Failure Including Modification					
8 inpatient: 7 outpatient	317 27% (17, 38)	478 15% (10, 20)	P=0.04	Moderate	Critical
Infection-related Mortality					
6 inpatient: 16 outpatient	227 1% (0, 3)	953 0%	P=0.49	Moderate	Critical
Overall Mortality					
6 inpatient: 14 outpatient	227 1% (0, 3)	837 0%	P=0.48	Moderate	Critical
Days of Fever					
1 inpatient: 12 outpatient	33 2.6 (2.4, 2.8)	642 2.3 (1.9, 2.6)	P=0.12	Low	Important
Adverse Events - Antibiotic Discontinuation					
3 inpatient: 6 outpatient	124 2% (0, 5)	253 1% (0, 2)	P=0.39	Moderate	Important

Abbreviation: CI – confidence interval
* Based upon all prospective trials conducted in pediatrics including randomized controlled trials (RCTs).
** Effect is percentage for all outcomes except duration of fever where the mean is presented.

Limitations refer to factors that decrease the quality of evidence supporting a recommendation. Directness refers to whether the trials studied the same population, intervention and outcomes. All estimates are limited by a lack of RCTs and indirect comparisons. For quality, observational studies can provide moderate or strong evidence in unusual circumstances. Importance refers to whether the outcomes are crucial to decision making.

Appendix 6. Prospective Studies that Compared Initial or Step-down Oral with Parenteral Antibiotic Management in Children with Low-Risk Fever and Neutropenia*

Number of Regimens	Number of Patients and Effect** (95% CI)		Comparison	Quality	Importance
	Parenteral 156,174,182,185-187,189,191,193,195,197	Oral 174,182,186-188,190,192,194,196,197			
Treatment Failure Including Modification					
9 parenteral: 6 oral	385 22% (14, 31)	410 20% (11, 29)	P=0.68	Moderate	Critical
Infection-related Mortality					
11 parenteral: 11 oral	504 1% (0, 2)	676 0%	P=0.71	Moderate	Critical
Overall Mortality					
10 parenteral: 10 oral	447 1% (0, 2)	617 0%	P=0.70	Moderate	Critical
Days of Fever					
6 parenteral: 7 oral	289 2.5 (1.9, 3.0)	386 2.1 (1.6, 2.7)	P=0.39	Moderate	Important
Recurrent Infection					
2 parenteral: 3 oral	69 3% (0, 8)	138 0%	P=0.31	Low	Important
Sepsis					
5 parenteral: 7 oral	267 0%	528 1% (0, 2)	P=0.73	Moderate	Critical
Secondary Infection					
1 parenteral: 4 oral	19 0%	339 4% (0, 8)	P=0.90	Low	Critical
Adverse Events - Antibiotic Discontinuation					
5 parenteral: 4 oral	201 1% (0, 3)	176 2% (0, 3)	P=0.73	Moderate	Important
Readmission					
6 parenteral: 9 oral	324 8% (2, 15)	672 7% (4, 11)	P=0.80	Moderate	Important

Abbreviation: CI – confidence interval

* Based upon all prospective trials conducted in pediatrics including randomized controlled trials (RCTs).

** Effect is percentage for all outcomes except duration of fever where the mean is presented.

Limitations refer to factors that decrease the quality of evidence supporting a recommendation. Directness refers to whether the trials studied the same population, intervention and outcomes. All estimates are limited by few RCTs and mainly indirect comparisons. For quality, observational studies can provide moderate or strong evidence in unusual circumstances. Importance refers to whether the outcomes are crucial to decision making.

Appendix 7. Pediatric Studies that Evaluated Fever and Neutropenia Outcomes of Antibiotic Discontinuation by Bone Marrow Recovery Requirements

Number of Studies by Design N=10	Number of Episodes	Marrow Recovery Requirements among All Studies (Not Stratified by Design)*	Proportion of Patients with Recurrent Fever (95% CI)
Randomized trial (n=1)[78]	1,167	Requirement for evidence of marrow recovery explicitly stated (n=2)	1% (0.1 to 5)
Prospective cohort studies (n=3)[79-81]		Requirement for marrow recovery not clear (n=7)	5% (3 to 9)
Retrospective cohort studies (n=6)[76,82-86]		No requirement for evidence of marrow recovery explicitly stated (n=4)	14% (5 to 36)**

Abbreviation: CI – confidence interval
* Discontinuation rules all required negative blood cultures (48 – 72 hours incubation), and patients to be afebrile between 24 and 48 hours.
**Significant heterogeneity

Appendix 8. Studies Evaluating Serum Galactomannan for Diagnosis of Invasive Fungal Disease

Author	Number of patients	Number of samples	Median Age in Years (range)	Number							Sensitivity	Specificity	Quality
				Proven IFD	Probable IFD	Controls	True positive	False positive	True negative	False negative			
Steinbach [116]	64	826	8 (0.8-19.5)		1	63	0 (0%)	8 (13%)	55 (87%)	1 (100%)	98%	87%	Low
Hayden [117]	56	990	NR (0.25-18)	17		39	11 (65%)	5 (13%)	34 (87%)	6 (35%)	65%	87%	Moderate
Armenian [118]	68	1086	11.1 (0.4-22.2)	0	3	45	NR						Low
Castagnola [119]	119 (195 episodes)	1798	9.5 (0.1-20)	NR									Moderate
Rohrlich [113]	37	413	8.5* (0.4-18)		10	27	10 (28%)	0 (0%)	2 (100%)	25 (72%)	29%	100%	Low
Challier [120]	20	NR	not specified	4	8	8	11 (92%)	0 (0%)	8 (100%)	1 (8%)	92%	100%	Low
Sulahian [198]	347	2376	14.5 (6-25) for IA	9		338	9 (100%)	34 (10%)	304 (90%)	0 (0%)	100%	90%	Moderate
Herbrecht [199]	48 episodes	NR	<18	NR									Low
Hovi [115]	98 (117 episodes)	932	6.5* (1-16.5)	2		97	1 (100%)	6 (6%)	91 (94%)	0 (0%)	100%	94%	Low
El-Mahallawy [114]	91	NR	6 (2-18)	15	13	63	22 (78%)	32 (51%)	31 (49%)	6 (22%)	79%	49%	Low

Abbreviations: IFD – invasive fungal disease; IA – invasive aspergillosis; NR – not reported
*Mean and not median reported

Appendix 9. Prospective Trials Evaluating Empiric Antifungal Therapy in Persistently Neutropenic Children with Fever

Author	Composite Endpoint for Efficacy	Results by Endpoint	Overall efficacy	Safety
Maertens[143]		Caspofungin vs LAmB		Caspofungin vs LAmB
	Successful treatment of any baseline invasive fungal disease	0/1 vs 0/0	Caspofungin 46%	Serious adverse events: 2% vs 12% Discontinuation of study drug due to adverse events: 4% vs 12%
	Survival 7 days after antifungal treatment	56/56 (100%) vs 25/25 (100%)	LAmB 32%	Clinical adverse events: 48% vs 46%
	No premature discontinuation of study drug	51/56 (91%) vs 21/25 (84%)		
	Resolution of fever >48 hours during neutropenia	27/56 (48%) vs 9/25 (36%)		
	No breakthrough invasive fungal disease	56/56 (100%) vs 24/25 (96%)		
Sandler[144]		ABCD vs AmB-D		ABCD vs AmB-D
	Survival 7 days after last dose of study drug		ABCD 18/26 (69%)	Renal toxicity*: 3/25 (12%) vs 11/21 (52%) (P<0.003)
	No breakthrough invasive fungal disease	24/25 (96%) vs 19/21 (90%)		Serum creatinine change from baseline to day 7: 0.1 vs 0.19 mg/dL (P<0.001)
	No premature discontinuation of study drug		AmB-D 9/22 (41%)	Serum creatinine change from baseline to end of therapy: 0.07 vs 0.28 mg/dL (P<0.001)
	Defervescence	Time to defervescence similar (data not reported; P=0.65)	(P=0.051)	Infusion-related chills: 78% vs 50% Hypoxia: 4% vs 0% Hypokalemia: 52% vs 55%
Prentice[142]		AmB-D vs LAmB1** vs LAmB3**		AmB-D vs LAmB1 vs LAmB3
	Minimum of 3 consecutive days without fever (<38°C) which continued until study end (recovery of neutrophils)	26/61 (43%) vs 18/70 (26%) vs 24/71 (34%)	AmB-D 31/61 (51%) LAmB1 45/70 (64%)	Severe adverse event related to drug: 8% vs 1% vs 1% (P=0.06) Nephrotoxicity***: 21% vs 8% vs 11% (P=0.1)
	No addition of antifungal therapy other than AmB	59/61 (97%) vs 66/70 (94%) vs 70/71(99%)	LAmB3 45/71 (63%)	Hypokalemia: 26% vs 10% vs 11% (P=0.02)
	No breakthrough invasive fungal disease	60/61 (98%) vs 67/70 (96%) vs 70/71(99%)	(P=0.22)	

Abbreviations: LAmB - liposomal amphotericin B, Ambisome®; ABCD – Amphotericin B Colloidal Dispersion, Amphotec®; AmB-D – amphotericin B deoxycholate
*Defined by a doubling of baseline serum creatinine, an increase of creatinine by 1 mg/dL, or a 50% decrease of calculated creatinine clearance;
**Dosage of 1 mg/kg/d (LAmB1) or 3 mg/kg/kg (LAmB3); ***Defined as 100% increase of baseline creatinine