SIOP PODC Supportive Care Education

Presentation Date: 13th March 2015

Recording Link at www.cure4kids.org:

https://www.cure4kids.org/ums/home/conference_rooms/enter.php?room=p6p3ejxppjh

CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF PEDIATRIC FEVER AND NEUTROPENIA

Clinical Practice Guidelines for the Management of Pediatric Fever and Neutropenia

Full guidelines may be found at
http://www.sickkids.ca/HaematologyOncology/IPFNG/

Citation: Lehrnbecher et al. JCO 2012;30(35):4427-38

Lillian Sung MD,
Associate Professor
Division of Haematology/Oncology
The Hospital for Sick Children
March 13, 2015

collaboration excellence innovation integrity

SickKids

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Rationale for FN Guidelines

Fever and neutropenia (FN) common

- Lack of guidelines focused on children
- Children have unique issues compared to adults

International Pediatric Fever and Neutropenia Guideline Panel

- Formed October 2010
- Oncology, infectious disease, nursing, pharmacy, patient advocate
- 10 different countries

Name	Country	Profession	Discipline
Sarah Alexander	Canada	Physician	Oncology
Frank Alvaro	Australia	Physician	Oncology
Fabianne Carlesse	Brazil	Physician	Infectious disease
Elio Castagnola	Italy	Physician	Infectious disease
Bonnie Davis	Canada	Patient advocate	
Lee Dupuis	Canada	Pharmacist	Oncology
Brian Fisher	US	Physician	Infectious disease
Faith Gibson	UK	Nurse	Oncology
Andreas Groll	Germany	Physician	Oncology, ID
Aditya Gaur	US	Physician	Infectious disease
Ajay Gupta	India	Physician	Oncology
Hana Hakim	US	Physician	Infectious disease
Rejin Kebudi	Turkey	Physician	Oncology
Thomas Lehrnbecher	Germany	Physician	Oncology
Sérgio Petrilli	Brazil	Physician	Oncology
Bob Phillips	UK	Physician	Oncology
Maria Santolaya	Chile	Physician	Infectious disease
William Steinbach	US	Physician	Infectious disease
Lillian Sung	Canada	Physician	Oncology, ID
Milena Villarroel	Chile	Physician	Oncology
Theo Zaoutis	US	Physician	Infectious disease

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Methods

- Appraisal of Guidelines for Research & Evaluation II (AGREE II) framework

- Divided into working groups:
  - Developed the key clinical questions
  - Identified and rated the importance of outcomes
  - Conducted systematic reviews

- GRADE approach to:
  - Generate summaries
  - Classify evidence as high, moderate, low or very low

Grading Recommendations

Guyatt Chest 2006

Grade of Recommendation:		Methodological Quality of:	
Description	**Benefit vs Risk and Burdens**	**Supporting Evidence**	**Implications**
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very lowquality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Definitions

Fever

- Single oral temperature measurement of >38.3°C or a temperature of >38.0°C sustained over one hour

Neutropenia

- ANC of <500 cells/uL or an ANC that is expected to decrease to <500 cells/uL during next 48 hours

Freifeld CID 2010

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Initial Risk Stratification and Evaluation Health Questions

What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low-risk or high-risk for poor outcomes?

What clinical, laboratory and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?

Validated Risk Stratification Strategy

- 23 different risk strategies have been derived
  - Address variable outcomes using variable predictive elements
  - Common themes:
    - Broadly similar definitions of adverse outcome
    - Use of patient-specific and episode-specific clinical or laboratory features

- 6 subject to validation

Phillips PlosOne 2012

	Rackoff (1996)	Alexander (2002)	Rondinelli (2006)	PINDA (2001)	Ammann (2003)	SPOG (2010)
Patient and disease related factors	None	AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement	2 points for central venous catheter, 1 point for age ≤5 years	Relapsed leukemia, chemotherapy within 7 days of episode	Bone marrow involvement, central venous catheter, pre-B-cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode specific factors	Absolute monocyte count	Hypotension, tachypnea/hypoxia <94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, clinical reason for in-patient treatment	4.5 points for clinical site of infection,2.5 points for no URTI, 1 point each for fever >38.5°C, hemoglobin ≤70g/L	CRP ≥90 mg/L, hypotension, platelets ≤50 g/L	Absence of clinical signs of viral infection, CRP >50 mg/L, white blood cell count ≤500/uL, hemoglobin >100 g/L	5 points for hemoglobin ≥90 g/L, 3 points each for white blood cell count <300/uL, platelet <50 g/L
Rule formulation	Absolute monocyte count ≥ 100/uL= low-risk of bacteremia	Absence of any risk factor = low-risk of serious medical complication	Total score <6 = low-risk of serious infectious complication	Zero factors or only platelets or <D7 from chemotherapy = low-risk of invasive bacterial infection	Three or fewer risk factors = low-risk of significant infection	Total score <9 = low-risk of adverse FN outcome

Initial Risk Stratification Recommendation Summary

Risk Stratification

Adopt a validated risk stratification strategy and incorporate it into routine clinical management

(Strong recommendation, low quality evidence).

Initial Evaluation

Peripheral blood cultures

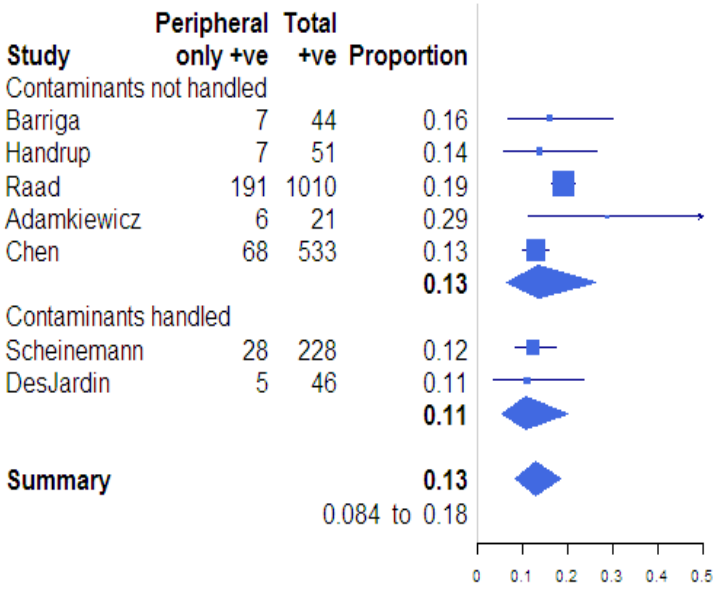
Routine CXR

Peripheral Blood Cultures for FN

- Many/most children have a central line
- Routine to take only central cultures in some settings
  - Approach to peripheral blood culture varies widely
- Systematic review of studies examining contribution of peripheral and central samples
- 7 studies included – 1,933 episodes of bacteremia
- Examined proportion of bacteremia detected only by peripheral sample

Synthesis

- 13% of positive blood cultures are detected by only the peripheral blood samples
- Will not detect these if omit peripheral blood cultures



Rodriguez Support Care Cancer 2012

Routine CXR

- Concern that neutropenia may reduce signs of pneumonia
- Systematic review of signs/symptoms
- 2057 articles screened to include 4 studies
- Probability of abnormal CXR very low if no signs or symptoms

Initial Evaluation Recommendation Summary

Evaluation
Obtain blood cultures at the onset of FN from all lumens of central venous catheters (Strong recommendation, low evidence).
Consider peripheral blood culture concurrent with obtaining central venous catheter cultures (Weak recommendation, low quality evidence).
Obtain chest radiography only in symptomatic patients (Strong recommendation, moderate evidence).

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Initial Treatment Health Questions

What empiric antibiotics are appropriate for children with high-risk FN?

Overview Empiric Therapy

- Influenced by patient characteristics, clinical presentation, local infrastructure, drug availability and costs and local resistance patterns

- Coverage - Gram-negative organisms in all patients and viridans group streptococci and *Pseudomonas aeruginosa* in high-risk FN

- Overall goal to provide coverage for virulent organisms while minimizing exposure to unnecessary antibiotics

Monotherapy vs Combination Therapy

- Original regimens combination therapy
- Two meta-analyses RCTs compared monotherapy versus aminoglycoside-containing regimens
- Non-inferiority of monotherapy regimens and higher toxicity with combination regimens
- Primarily adult trials

Furno Lancet Inf 2002
Paul BMJ 2003

Empiric Anti-pseudomonal Penicillin with an Aminoglycoside versus Anti-pseudomonal Penicillin Monotherapy (N=19)

	APP with Aminoglycoside			APP Monotherapy			*P* Value
	No. regimens	No. patients/ episodes	Percentage with Outcome (95% CI)	No. regimens	No. patients/ episodes	Percentage with Outcome (95% CI)	
Treatment failure including modification	12	1039	41 (32, 50)	4	210	34 (27, 41)	0.23
Overall mortality	9	699	4.2 (1.8, 6.6)	3	145	1.6 (0.0, 3.6)	0.10
Infection-related mortality	13	1092	1.3 (0.42, 2.3)	4	210	1.6 (0.0, 3.2)	0.83
Adverse events causing antibiotic discontinuation	3	201	0.40 (0.0, 1.3)	3	142	0.92 (0.0, 2.5)	0.57

Manji PIDJ 2012

Role of Empiric Vancomycin

- RCTs studying glycopeptides as part of the initial empirical treatment of febrile neutropenic patients with a beta-lactam with or without an aminoglycoside

- 14 RCTs with 2,413 patients

Vardakas Lancet Infect 2005

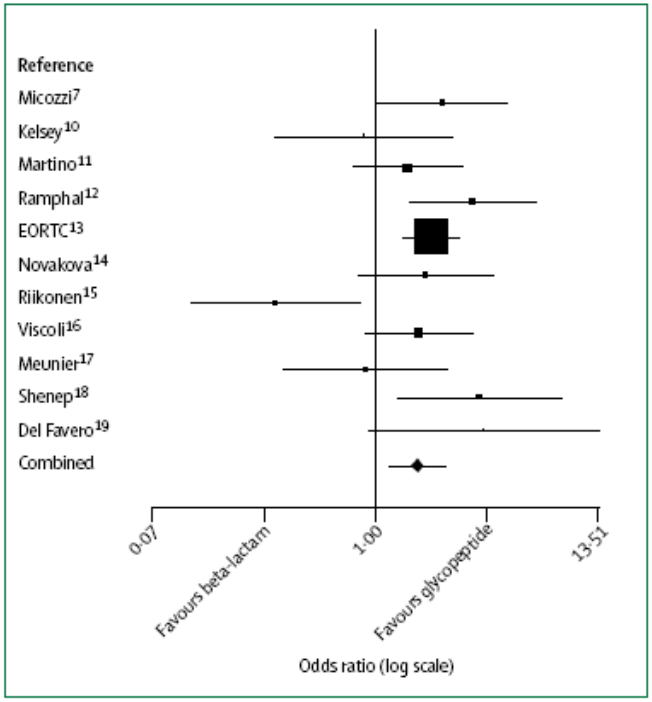


Figure 1: Odds ratios of treatment success (without modification of the empirical regimen) with the inclusion, or not, of a glycopeptide as part of the empirical regimen of febrile neutropenic patients
Vertical line="no difference" point between the compared groups. Square=odds ratio; the size of each square denotes the proportion of information given by each trial. Diamond=pooled odds ratio for all randomised controlled trials. Horizontal lines=95% CI.

When addition of any antibiotic classified as failure, addition of glycopeptides associated with more success
OR 1.63; 95% CI (1.17, 2.28)

Glycopeptide Meta-analysis

Addition of glycopeptide:

- If delayed addition of vancomycin not considered failure (i.e. for Gram positive blood culture)
  - No difference in success
  - OR 1.02 (95% CI 0.71, 1.46)
- More adverse effects
  - OR 4.98 (95% CI 2.91, 8.55)
- More nephrotoxicity
  - OR 2.10 (95% CI 1.12, 3.95)

Initial Treatment Recommendation Summary

Treatment
High-Risk FN
Use monotherapy with an anti-pseudomonal *β*-lactam or a carbapenem as empiric therapy in pediatric high-risk FN (Strong recommendation, high quality evidence).
Reserve addition of a second Gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (Strong recommendation, moderate quality evidence).

Monotherapy Regimens Studied in Children

Anti-pseudomonal penicillins

- Piperacillin-tazobactam, ticarcillin-clavulinic acid

Anti-pseudomonal cephalosporins

- Cefepime

Carbapenems

- Meropenem, imipenem

Overview

- Rationale for FN guideline development
- Methodology
- Areas for discussion
  - Risk Stratification and Evaluation at Initial Presentation of Pediatric Fever and Neutropenia
  - Initial Treatment of Pediatric Fever and Neutropenia
  - Approach to Empiric Antifungal Therapy

Empiric Antifungal Treatment Health Question

When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?

Empiric Antifungal Therapy for FN

- Adult guidelines recommend empiric antifungal therapy be initiated in neutropenic patients after 96 hours of fever in the setting of broad-spectrum antibiotics.

- Data specific to children are lacking and in the absence of additional data, reasonable to recommend a similar approach in children

Empiric Antifungal Therapy Trials in Children

Three RCTs 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

Empiric Antifungal Therapy in Children: Efficacy

Prentice	**AmB-D**	**L-AmB 1**	**L-AmB 3**	
Efficacy*	51%	64%	63%	(NS)
Breakthrough IFD	1 (*C.alb*)	3 (2 *C.alb*,1 IA)	1 (IA)	
Sanders	**AmB-D**	**ABCD**		
Efficacy	41%	69%		(NS)
Breakthrough IFD	2 (IA, yeast)	1 (Fusarium)		
Maertens		**L-AmB**	**Caspo**	
Efficacy		32%	46%	(NS)
Breakthrough IFD		1 (IA)	0	

*All studies used composite endpoints for efficacy

Conclusion:

- L-AmB = Caspo; L-AmB slighty better than AmB-D
- Similar to adult trials

Empiric Antifungal Therapy in Children: Safety

Prentice	**AmB-D**	**L-AmB1**	**L-AmB 3**
Nephrotoxicity (creatinine)	21%	8 %	11 %
Hypokalemia	26%	10 %	11 %
Sanders	**AmB-D**	**ABCD**	
Nephrotoxicity (creatinine)	9%	0	
Hypokalemia	55%	52 %	
Infusion related (e.g, chills)	50%	78 %	
Maertens		**L-AmB**	**Caspo**
Tachycardia		11.5%	1.8 %
Hypokalemia		11.5 %	3.6 %
Discontinued due to AEs		11.5 %	3.6 %

Conclusion:

- Caspo better tolerated than L-Am-B
- L-AmB better tolerated than AmB-D

Empiric Antifungal Treatment Recommendation Summary

Treatment
Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy (Strong recommendation, high quality evidence).

Conclusions

- Clinical practice guidelines optimally developed by international panel
- Provided recommendations for risk stratification, initial therapy and empiric antifungal treatment
- Guideline will be updated early 2016

Acknowledgements

International Pediatric Fever and Neutropenia Guideline Panel members

Bob Phillips (Leeds, UK)

Thomas Lehrnbecher (Frankfurt, Germany)

Tanya Hesser

CIHR meeting grant

CIHR New Investigator Award

CIHR IRSC

National Cancer Institute of Canada | Institut national du cancer du Canada

Canadian Cancer Society | Société canadienne du cancer

Childhood Cancer Foundation Candlelighters Canada

Thank you!