Outpatient Management of F&N in Paediatric Oncology Patients

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POGO
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F&N: What's the risk?

1-3%

65.5 Million

Basu et al, JCO 2005

Mueller et al, BMC Cancer, 2015

Risk Stratification Algorithms

Table 3. Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

Schema-Related Factors	Rackoff[4]	Alexander[5]	Rondinelli[6]	Santolaya[7]	Ammann[8]	Ammann[9]
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 or hypoxia < 94%; new CXR changes; altered mental status; severe mucositis, vomiting, or abdominal pain; focal infection; other clinical reason for inpatient 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/μL, hemoglobin > 100 g/L	5 points for hemoglobin ≥ 90 g/L, 3 points each for white blood cell count < 300/μL, platelet < 50 g/L
Rule formulation	Absolute monocyte count ≥ 100/μL = low risk of bacteremia; HSCT = high risk	Absence of any risk factor = low risk of serious medical complication; HSCT = high risk	Total score < 6 = low risk of serious infectious complication; HSCT = high risk	Zero risk factors or only low platelets or only < 7 days from chemotherapy = low risk of invasive bacterial infection	Three or fewer risk factors = low-risk of significant infection; HSCT = high risk	Total score < 9 = low risk of adverse FN outcome; HSCT = high risk
Demonstrated to be valid*	USA, Madsen[10]	United Kingdom, Dommett[11], Arif[12]	Brazil, Rondinelli[6]	South America, Santolaya[13]	Europe, Ammann,[9] Macher,[14] Arif[12]	Europe, Miedema[15]

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CRP, C-reactive protein; CXR, chest radiography; HSCT, hematopoietic stem-cell transplantation; URTI, upper respiratory tract infection.

*Valid refers to clinically adequate discrimination of a group at low risk of complications.

Lehrnbecher et al, JCO, 2017

Adult Guidelines: Flowers et al, JCO, 2013

Table 3. MASCC Scoring System to Identify Patients With Cancer and Febrile Neutropenia at Low Risk of Medical Complications*

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms†	5
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease‡	4
Solid tumor or hematologic malignancy with no previous fungal infection§	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms†	3
Outpatient status	3
Age < 60 years	2

Abbreviation: MASCC, Multinational Association for Supportive Care in Cancer.

*Maximum score is 26; scores ≥ 21 indicate a low risk for medical complications. Data adapted.[12,127]

†Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5), moderate symptoms (score of 3), and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

‡Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, or need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

§Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

Table 4. Additional Specific Clinical Criteria* That Exclude Oncology Patients With FN From Initial Outpatient Care Even With a MASCC Score ≥ 21

Category	Criteria
Cardiovascular	Presyncope/witnessed syncope
	Accelerated hypertension
	New onset or worsening of hypotension
	Uncontrolled heart failure, arrhythmias, or angina
	Clinically relevant bleeding
	Pericardial effusion
Hematologic	Severe thrombocytopenia (platelets < 10,000/μL)
	Anemia (Hb < 7 g/dL or Hct < 21%)
	ANC < 100/μL of expected duration ≥ 7 days
	Deep venous thrombosis or pulmonary embolism
GI	Unable to swallow oral medications
	Intractable nausea and/or vomiting
	New onset or clinically relevant worsening of diarrhea
	Melena, hematochezia (nonhemorrhoidal), or hematemesis
	Abdominal pain
	Ascites
Hepatic	Impaired hepatic function (aminotransferase values > 5× ULN) or clinically relevant worsening of aminotransferase values
	Bilirubin > 2.0 or clinically relevant increase in bilirubin
Infectious	Presence of a clear anatomic site of infection (eg, symptoms of pneumonia, cellulitis, abdominal infection, positive imaging, or microbial laboratory findings)†
	Any evidence of severe sepsis‡
	Allergies to antimicrobials used for outpatients
	Antibiotics ≤ 72 hours before presentation
	Intravascular catheter infection
Neurologic	Altered mental status/sensorium or seizures
	Presence of or concern for CNS infection or noninfectious meningitis
	Presence of or concern for spinal cord compression
	New or worsening neurologic deficit
Pulmonary/thorax	Tachypnea or hypopnea
	Hypoxemia, hypercarbia
	Pneumothorax or pleural effusion
	Presence of cavitary lung nodule or imaging findings suggestive of an active intrathoracic process
Renal	Impaired renal function (creatinine clearance ≤ 30 mL/min) or oliguria or clinically relevant worsening renal function (as determined by the treating physician)
	New onset of gross hematuria
	Urinary obstruction or nephrolithiasis
	Clinically relevant dehydration
	Clinically relevant electrolyte abnormalities, acidosis or alkalosis (requiring medical intervention)
Other significant comorbidity	Presence of a major abnormality in regard to: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, laboratory data, or imaging data
	Any relevant clinical worsening (as determined by the treating physician) of: organ dysfunction, comorbid condition, vital signs, clinical signs or symptoms, laboratory data, or imaging data
	Pregnant or nursing
	Need for IV pain control
	Fractures, injuries, or need for emergent radiation therapy

Inpt vs Outpt: Teuffel et al, Annals Oncol, 2011

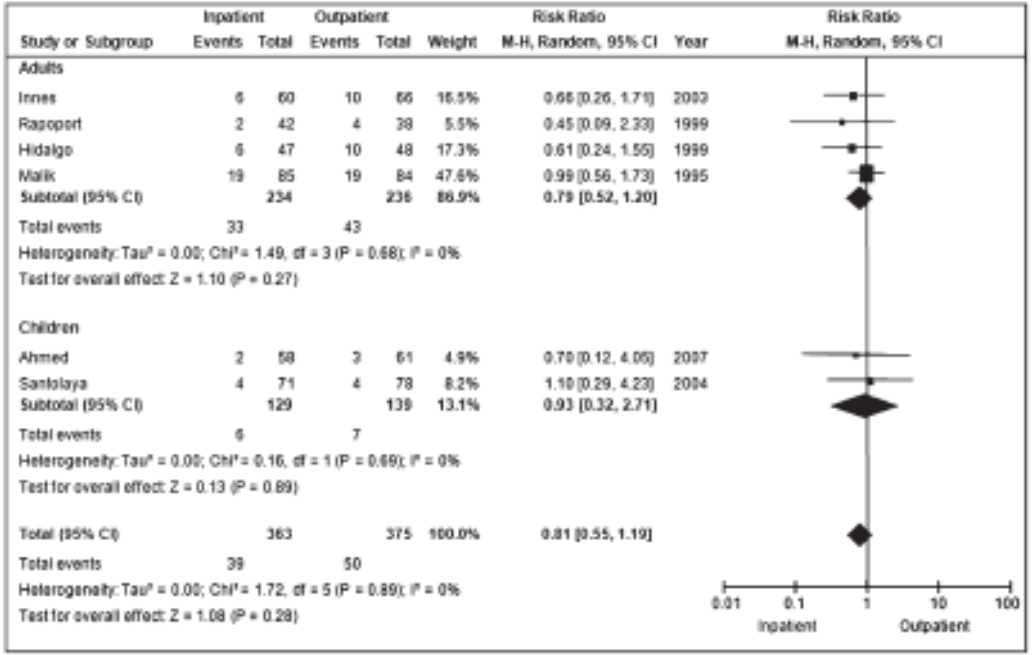
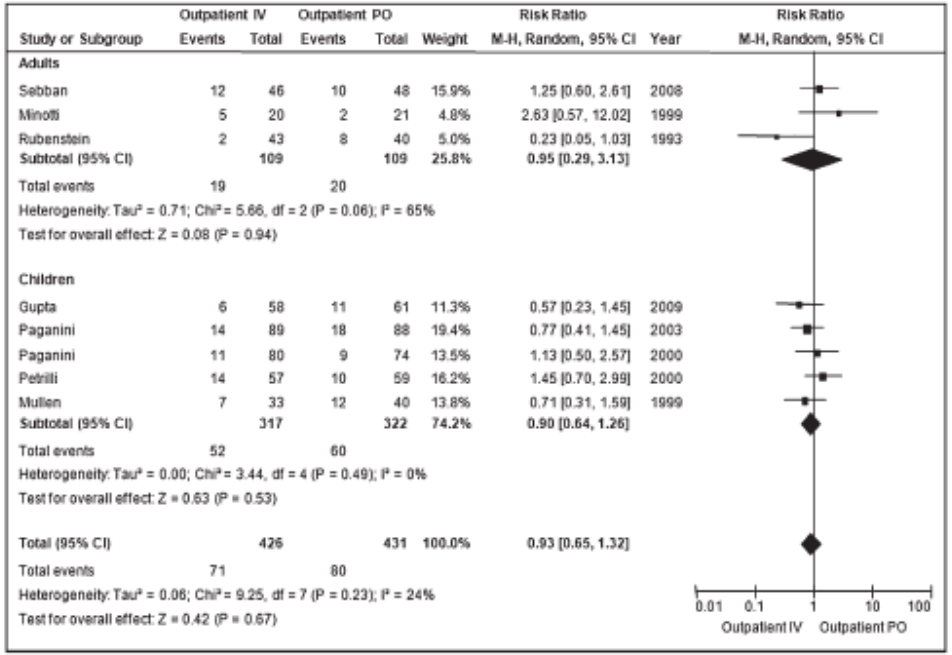


Figure 2. Inpatient versus outpatient—Forest plot of treatment failure. Squares to the left of the vertical line indicate a decreased risk of developing treatment failure in patients receiving inpatient management. Horizontal lines through the squares represent 95% confidence intervals (CIs). The diamonds represent the overall risk ratio (RR) from the meta-analyses and the corresponding 95% CIs.

Overall mortality 1.8%:
Inpatient- 7/365
Outpatient- 6/377
RR 1.11 (p=.83)

Outpt IV vs PO: Teuffel et al, Annals Oncol, 2011



Study or Subgroup	Outpatient IV Events	Total	Outpatient PO Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Adults								
Sebban	12	46	10	48	15.9%	1.25 [0.60, 2.61]	2008	
Minotti	5	20	2	21	4.8%	2.63 [0.57, 12.02]	1999	
Rubenstein	2	43	8	40	5.0%	0.23 [0.05, 1.03]	1993	
Subtotal (95% CI)		**109**		**109**	**25.8%**	**0.95 [0.29, 3.13]**		
Total events	19		20					
Heterogeneity: Tau² = 0.71; Chi² = 5.66, df = 2 (P = 0.06); I² = 65%								
Test for overall effect: Z = 0.08 (P = 0.94)								
Children								
Gupta	6	58	11	61	11.3%	0.57 [0.23, 1.45]	2009	
Paganini	14	89	18	88	19.4%	0.77 [0.41, 1.45]	2003	
Paganini	11	80	9	74	13.5%	1.13 [0.50, 2.57]	2000	
Petrilli	14	57	10	59	16.2%	1.45 [0.70, 2.99]	2000	
Mullen	7	33	12	40	13.8%	0.71 [0.31, 1.59]	1999	
Subtotal (95% CI)		**317**		**322**	**74.2%**	**0.90 [0.64, 1.26]**		
Total events	52		60					
Heterogeneity: Tau² = 0.00; Chi² = 3.44, df = 4 (P = 0.49); I² = 0%								
Test for overall effect: Z = 0.63 (P = 0.53)								
Total (95% CI)		**426**		**431**	**100.0%**	**0.93 [0.65, 1.32]**		
Total events	71		80					
Heterogeneity: Tau² = 0.06; Chi² = 9.25, df = 7 (P = 0.23); I² = 24%								
Test for overall effect: Z = 0.42 (P = 0.67)								

Figure 3. Intravenous versus oral treatment in ambulatory care—Forest plot of treatment failure. Squares to the left of the vertical line indicate a decreased risk in developing treatment failure in patients receiving intravenous antibiotics. Horizontal lines through the squares represent 95% CIs. The diamonds represent the overall risk ratio (RR) from the meta-analyses and the corresponding 95% confidence intervals. p.o. = oral.

No deaths, n=816 episodes. Trend to inferiority for po outpt therapy for readmit (RR .52, p=.08)

Paediatric Guidelines: Lehrnbecher et al, JCO, 2012

Table 1. Overall Summary of Recommendations*

Initial Presentation of FN		
Risk Stratification	Evaluation	Treatment
Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)	Obtain blood cultures at onset of FN from all lumens of central venous catheters (1C) Consider peripheral-blood cultures concurrent with obtaining central venous catheter cultures (2C) Consider urinalysis and urine culture in patients where clean-catch, midstream specimen is readily available (2C) Obtain chest radiography only in symptomatic patients (1B)	High-risk FN: Use monotherapy with antipseudomonal β-lactam or carbapenem as empiric therapy in pediatric high-risk FN (1A) Reserve addition of second Gram-negative agent or glycopeptide for patients who are clinically unstable, when resistant infection is suspected, or for centers with high rate of resistant pathogens (1B) Low-risk FN: In children with low-risk FN, consider initial or step-down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B) In children with low-risk FN, consider oral antibiotic administration if child is able to tolerate this route of administration reliably (2B)

Updates: Lehrnbecher et al, JCO, 2017

A7. In low-risk FN:		
A7a. Consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (weak recommendation, moderate-quality evidence).	None	It is a weak recommendation because institutions must have the infrastructure in place to safely implement outpatient management. Clinical outcomes were similar between strategies and thus, resources and preferences are important considerations.
A7b. Consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (weak recommendation, moderate-quality evidence).	None	It is a weak recommendation because readmission may be higher among outpatients treated with oral *v* parenteral therapy, and other outcomes were similar. Thus, resources and preferences are important considerations.

NO CHANGES

Table 2. Research Gaps

Initial presentation
- Optimal temperature threshold to define fever
- New serum biomarkers as diagnostic and monitoring aids
- Impact of viral diagnosis and the role of systemic viruses on management of FN
- Appropriate monitoring and follow-up for outpatient therapy
- Optimal choice of empirical antibiotics in low-risk FN

Patient and Provider Preferences: Sung et al, JCO, 2004

- All outcomes being equal, what percentage of patients and providers preferred outpatient therapy?
  - Patients/parents: 53%
  - Providers: 71%
- What were predictors of initial choice of therapy?
  - Patients/parents: higher comfort ranking (QoL), lower fear ranking
  - Providers: lower fear/anxiety ranking, no association with comfort
- What clinical outcome most predicted switch of therapy?
  - Agreement on this one: increasing risk of death

Satellite Manual States:

- Outpatient management may be considered in select patients who are considered low risk (see section *4.1.4)* . Significant resources are required to maintain an outpatient program and it is **neither expected nor encouraged** in the satellite care setting.
- If there is particular interest in developing such an outpatient program in the satellite setting program, the plan by which it will be set up must be developed in consultation with collaborating tertiary centre(s) and reviewed with the POGO medical director.

SickKids Out Patient Management Criteria

- Deemed low risk
- Access to hospital
  - Within 1 hour of hospital
  - Access to car 24 hours per day
- Communication
  - Working telephone
- Thermometer
  - Have working thermometer
- Caregiver
  - Available at home 24 hours per day
  - Available for daily contact
  - Agrees to follow up clinic visits
- Child
  - Able to tolerate oral meds (tabs- levoflox; susp- amox/clav + cipro)
  - Stays home from school/daycare
- Adherence
  - History of compliance/adherence to other outpatient treatment

Parent Information

What will happen if my child can receive treatment for Fever & Neutropenia at home?

In the Emergency Department or the Haematology/Oncology Clinic:

1. Your child will receive one dose of IV antibiotic.
2. Your child will receive one dose of the 1 or 2 types of oral antibiotics that will be given at home.
3. Your child will then be discharged home on oral antibiotics under the care of at least one parent (or alternate) who can stay with your child at home (not in daycare or school).
4. Before you leave the Emergency Department, you will be given:
    a. A 72-hour supply of the 1 or 2 antibiotics to be given by mouth or by enteral tube
    b. A Temperature Diary & Medication Calendar
    c. An appointment for a follow-up appointment in the clinic

What you need to do if your child is being managed at home:

1. Record each time you give your child their antibiotic on the Medication Calendar.
2. Take your child's temperature every 4 hours and record it in the Temperature Diary.
3. Bring your child to the Haematology/Oncology Clinic to be evaluated by the primary team on Monday, Wednesday and Friday until treatment for febrile neutropenia is stopped by your child's doctor or nurse practitioner.
4. Between the hours of 8:00 in the morning and 12 noon, on days that you do not come to clinic, call your child's Contact Nurse daily (Monday through Friday) or the Haematology/Oncology Fellow-on-call at 416-813-7500 (weekends).
5. If your child looks ill at any time, if your child throws up the antibiotic or if you have concerns about your child, call your child's **Contact Nurse** (Monday through Friday, between the hours of 8:00 in the morning and 5:00 in the afternoon) or the **Haematology/Oncology Fellow-on-Call** at 416-813-7500 (after 5:00 in the afternoon or anytime on the weekends).

Daily Assessments on Outpatient FN Protocol:

Questions for Parent Caregiver

1. Review temperatures over last 24 hours with parent/caregiver.
2. Were there any episodes of fever?
   Fever = 38.3°C or more by mouth one time *or* 38°C or more by mouth for 1 hour or more OR 37.8°C or more axillary one time *or* is 37.5°C or more axillary for 1 hour or more.
3. Has acetaminophen (Tylenol®, Tempra®) been given in the last 24 hours?
4. Has there been any emesis?
5. Is the child eating and drinking?
6. Have all doses of antibiotics (either levofloxacin or ciprofloxacin plus amoxicillin/clavulanic acid) been given in the last 24 hours? Were any doses vomited, and if so, were they repeated?
7. How many levofloxacin doses does the family have left? Is this enough to last until their next clinic appointment? OR When family seen in clinic, do they need a script for levofloxacin?
8. Are there any new symptoms (i.e.: cough, runny nose, diarrhea) or if already present are they improving or worsening?
9. Does the child look worse than when last seen in the hospital?
10. Is an adult still able to be at home 24 hours/day with the child?
11. Remind the family of their next scheduled clinic appointment (that is, next Monday, Wednesday or Friday, whichever is soonest).

Reasons for reassessment in clinic or ER earlier than scheduled:

A. Inability to tolerate medications
B. Family not giving antibiotics as prescribed and/or not taking and recording temperature as required.
C. Positive culture results
D. Clinical deterioration
E. Recurrent or persistent fever after 5 or more days of oral antibiotic administration regardless of clinical status

Audit (year 1): Inpatients – Low Risk

- 22 admitted
- Reasons for admission of low risk FN patients:

Can't swallow tablets	9
Family preference/request	4
Unable to determine	3
Concerns re follow up	2
Confusion re process	2
Unreliable access to car	1
Concurrent procedure	1

Audit (year 1): Outpatients-Low Risk

- 8 patients
- Age range: 3.8 to 17.8 yrs
- No misadventure
- Deviations from guideline:
  - Length of time from home to hospital: 123 min
  - No intention for follow-up in clinic
  - Discharge on non-protocol antibiotics
  - Lack of documentation re materials/instructions and follow-up

Discussion Points as related to Satellite care

- Follow up ability during clinic closures or afterhours; recommendations require q2 day clinic assessment
- Daily results follow up after hours and weekends
- Communication between Peds oncology team, Peds inpatient unit and Pediatrician on call.
- Admitting institution for ongoing fever beyond 5 days