Management of Febrile Neutropenia in Children

APPHON-ROHPPA 2014

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Thank you

Objectives

- Recognise the importance of febrile neutropenia
- Understand the risks of febrile neutropenia
- Be familiar with APPHON Guidelines
- Be familiar with updated algorithms & orders
- Know the timeframes for treatment

Febrile neutropenia

Febrile Neutropenia

- Commonest oncologic emergency
- Infection:
  - Important
  - 2nd commonest cause of death
- Causes "angst" amongst care teams

Why?

- Reduced resistance to infection e.g.
  - Impaired physical barriers
  - Impaired immune responses
  - Myelosuppression
  - Altered flora
  - Malnutrition
  - Implanted devices

Risks

- Infection
- Sepsis
- **DEATH**

- Literature reviews:
  - ~ 5-10% risk of bacteremia
  - ~10-20% have sepsis (+/- bacteremia)
  - ~1% risk of death (with treatment)

Who are at risk?

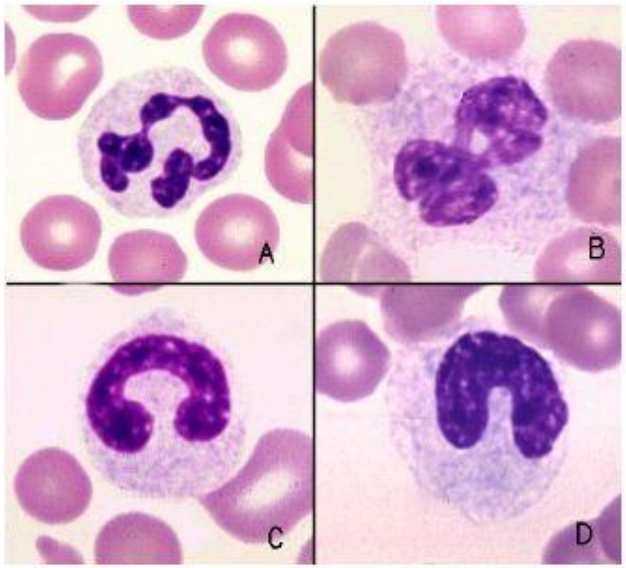
- Active chemotherapy
- Post HSCT +/- GVHD
- Other immunosuppressed patients e.g.
  - Solid organ transplants
  - Other immunosuppression
  - Immunodeficiency
- Neutropenia – other causes e.g.
  - Congenital/acquired neutropenia

Definitions:

- Fever:
  - Oral/tympanic
    - 38.3°C & over - 1 reading
    - 38°C & over - 2 readings 1 hour apart
  - Axillary
    - 37.8°C & over - 1 reading
    - 37.5°C & over - 2 readings 1 hour apart

Definitions:

- Neutropenia:
  - Absolute neutrophil count (ANC)
    - **< 0.5 x 10^9/L**
    - **Expected to fall to <0.5 within 72h**
  - ANC = Neutrophils + Bands



Clinical Presentation – FEVER!

UNSTABLE/SICK/SEPTIC

- Septic
- Clammy/flushed/cold
- Tachycardic/shut down
- Rigors (e.g. with line flush)
- Irritable
- Listless

OTHER SIGNS/SYMPTOMS

- Mucositis
- Abdo pain
- Diarrhoea
- Rashes/Cellulitis
- Dysuria
- Cough/Rhinorrhea etc.

- **NO RECTAL EXAMS**
- **NO RECTAL TEMPS**

Beware

- Unstable/Sick/Septic child
  - Can be septic without positive cultures
    - Hypotensive, shut-down, needing fluid resuscitation
- Profound or prolonged Neutropenia
  - $<0.1 \times 10^9/L$
- Afebrile Sepsis

- **Cannot make pus without neutrophils**

Clinical Assessment

HISTORY

- Current symptoms
- Date of last chemo cycle
- Duration of symptoms
- Exposure to infections e.g.
  - RTI
  - Chickenpox
- Recent antibiotics

EXAMINATION

- Ears and Throat
- Mouth
- Skin
- Perineum
- CVL site
- Wound sites
- Conscious state

APPHON Guidelines

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www.apphon-rohppa.com

Guidelines

- Evidence-based
  - International Recommendations
  - Endorsed by C17 Canadian Centres
  - Adapted to local needs
    - Practices
    - Models of care
    - Microbiology patterns

- Guidelines **AUGMENT** good clinical practice

Applicability

- **Active cancer patients**
  - Known or suspected malignancy
  - Receiving antineoplastics
  - Up to 3m post cancer Rx
- **Post HSCT**
  - Up to 3m post HSCT (regardless of counts)
  - Active GVHD on immunosuppression

- Other neutropenias/immunosuppressed

Assessment & Management

Immediate Management 1

- **Be IN HOSPITAL within 1 hour of fever**
  - Home – hospital
- **Be ASSESSED within 1 hour of arrival**
  - **Immediate access of CVL**
    - Do not wait for anaesthetic cream
    - Peripheral access if can't do CVL
  - **Draw CBC & Cultures within 30 minutes of arrival**
    - CBC & differential STAT
    - Aerobic blood cultures
      - Anaerobic if indicated (e.g. severe typhlitis)

Immediate Management 2

- Airway
- Breathing
- Circulation

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- **Antibiotics**
  - **Give within 1 hour of arrival**
    - Don't delay if CBC not yet reported
  - **Give prior to patient transfer**
  - **Give prior to blood products**

Immediate Management 3

- Investigations
  - Biochemistry
  - Cultures as indicated
  - CXR if clinically indicated
- IV Fluids
  - 1.5 x maintenance & reassess carefully
- Blood products
  - Hb <70 g/L
  - Plts <20 x 10^9/L
- Stop ongoing chemotherapy
- Acetaminophen prn – No NSAIDs

Immediate management 4

- **Contact on-call paediatric oncologist to discuss**

Empiric Antibiotic Therapy

- Need to cover appropriate organisms
  - Gram negative
    - Pseudomonas
    - E coli
    - Klebsiella
  - Gram positive
    - Strep viridans spp
    - Staphylococci
  - Fungi
  - Viruses

Which antibiotic?

- Comprehensive meta-analyses
  - ~11% had documented bacteremia
    - Gram +ve commoner than Gram –ve
      - ~15% pseudomonas infection
  - Monotherapy not inferior to Dual therapy
    - Use antipseudomonal penicillin or cephalosporin
    - Also active vs Gram +ve
    - Empiric aminoglycosides - ↑ toxicity (NNH ~31 (nephro))
      - Added aminoglycosides only better if proven Gram -ve infection
    - Need to adjust depending on:
      - Local practices
      - Microbiologic surveillance patterns

Risk Grouping

- “high” and “low” risk removed
- New grouping:
  - Unstable Child
  - All other patients
    - “special” or “individual” circumstances

Unstable Patient

- Triple antibiotic coverage
  - Piperacillin-tazobactam
    - (Ceftazidime if allergic)
  - Tobramycin
  - Vancomycin

All Other Patients

- Monotherapy
  - Piperacillin-tazobactam
    - (Ceftazidime if allergic)

Special/Individual cases

ALL OTHER PATIENTS

- Monotherapy
  - Piperacillin-Tazobactam
    - (ceftazidime if allergic)

SPECIAL CASES

- Add Vancomycin if:
  - **AML**
  - **Infant < 1y on ALL protocol**
  - **HSCT <3m**
  - **HSCT – active GVHD**
  - **Burkitt's Gp C in induction**
  - **Down Syndrome**
  - **Severe mucositis**

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Guideline Algorithm

ALGORITHM FOR THE EMPIRIC MANAGEMENT OF FEBRILE NEUTROPENIA

IWK Health Centre

Pediatric Hematologist/Oncologist
902-470-8888 or
902-470-5888 (toll free)

STABLE PATIENT

YES

Piperacillin-Tazobactam**

If any of the following...

- HSCT less than 100 days and/or active GVHD*
- AML
- Infant less than 12 months with ALL
- Down syndrome
- Burkitt's Lymphoma Group C Induction
- Mucositis

Treat with Piperacillin-Tazobactam ** AND Vancomycin

Call Pediatric Oncologist

After 48 hours, is patient clinically well and afebrile (in the previous 24 hours) with negative cultures and ANC rising?

YES

Stop all antibiotics

If positive culture, continue 10 days from 1st negative culture using broad spectrum appropriate antibiotics****

NO

Piperacillin-Tazobactam** AND Tobramycin*** AND Vancomycin AND call Pediatric Oncologist

At 48 hours, is patient clinically well and afebrile in the previous 24 hours with negative cultures?

NO

YES

Stop Tobramycin

At 72 hours, is patient remaining clinically well with negative cultures and afebrile in the previous 24 hours?

NO

YES

Stop Vancomycin

At 96 hours, is patient remaining clinically well, afebrile in the previous 24 hours with negative cultures from the last fever and ANC 0.5 x 10^9/L and rising?

NO

YES

Consider stopping all antibiotics in consultation with Pediatric Oncologist

Continue antibiotics as per clinical judgment and call Pediatric Oncologist

If positive culture, continue 10 days from 1st negative culture using broad spectrum appropriate antibiotics****

* HSCT = Hematopoietic stem cell transplant and GVHD = Graft vs Host Disease

**If penicillin ALLERGIC or clearing Methotrexate use ceftAZIDime instead of Piperacillin-Tazobactam.

*** Any patient with hearing loss (sensorineural hearing loss 30 dBHL or greater at one or more frequencies between 250 Hz-4000 Hz) or renal impairment (i.e. GFR 60 mL/min/1.73m^2 or less, serum creatinine 1.5 times upper limit of normal for age AVOID aminoglycoside and contact pediatric hematologist/oncologist or infectious disease specialist. In these cases antibiotics of choice are meropenem (60 - 120mg/kg/day IV q8h maximum 6 g/day) AND vancomycin.

****Redraw culture from all lumens to ensure negative before discontinuation of antibiotics.

Patient: _____
Age _____ Wt: _____ kg Date of Wt (dd/mm/yyyy) _____
Height _____ Body Surface Area _____
Allergies: _____

The following orders will be carried out by a licensed healthcare professional **ONLY ON THE AUTHORITY OF AN APPROVED PRESCRIBER. Where choice occurs, check as appropriate.**
***For definition of fever neutropenia refer to Guidelines for Management of Fever with Neutropenia, IWK/APPHON Guidelines.**

Required Evaluations	Daily CBC and Differential Daily Na, K, Cl, BUN, Creatinine Blood cultures from central line (all lumens) prior to administration of antibiotics Blood cultures from peripheral site (if doesn't have a central line) prior to administration of antibiotics Repeat blood cultures once daily, if temperature is greater than or equal to 38.3° and/or appears sick
Please check as appropriate	
Optional Evaluations	□ Urinalysis □ Urine Culture □ NPA swab for; □ Influenza, □ RSV, □ Adenovirus, □ Other _____ □ Chest X-ray □ Other: _____
Vital Signs	At least every hour until stable, then q4h and within 30 minutes prior to leaving the hospital

- **Unstable patients require TRIPLE antibiotic therapy. Start antibiotics immediately on arrival.**
- **For management of patients see algorithm on reverse of form.**
- **In a stable patient if CBC and differential results cannot be obtained within 1 hour of hospital arrival start antibiotics regardless.**
- **Alternate antibiotics between lumens.**

		Treatment
●	**Hydration**	IV D5W+ 0.9% NaCl at 1 ½ x maintenance per hour = _____ mL/hour (up to 150 ml/hour) or oral equivalent
●	□ **NO Penicillin Allergy**	Pipercillin-Tazobactam _____ mg IV q8h (240 mg pipercillin/kg/day) (max 4g/dose)
	□ **Penicillin Allergy**	ceftAZIDime _____ mg IV q8h (150 mg/kg/day) (maximum 6 g/day)
□	□ **Under 12 years of age**	Vancomycin _____ mg IV q6h (50 mg/kg/day) (maximum 4 g/day before levels) Trough levels pre 3rd or 4th dose (target 5−15 micrograms/mL)
	□ **12 years and older**	Vancomycin 1 gram IV q12h (Infuse over at least 90 minutes). Trough levels pre 4th or 5th dose (target 5−15 micrograms/mL)
□	□ **1 month* of age up to 6 years**	Tobramycin _____ mg IV q24h (10 mg/kg/day) (maximum 400 mg/day before levels) Peak level with 1st dose 30 minutes after 30 minute infusion (target 15-25 micrograms/mL)
	□ **6 years and older**	Tobramycin _____ mg IV q24h (8 mg/kg/day) (maximum 400 mg/day before levels) Peak level with 1st dose 30 minutes after 30 minute infusion (target 15-25 micrograms/mL)

*For neonate dosing refer to the IWK Health Centre Formulary if available otherwise use neonatal dosing reference.
Please fax completed order to (902)470-7208.

Call the oncologist:

- Basic Centre
  - Call immediately
    - Immediate management
    - Arrange transfer to appropriate centre
- Intermediate Centre
  - Call immediately
    - Immediate management
    - Arrange admission to appropriate centre
- AdvancedCentre
  - Call within 24h to discuss managment

Next Steps

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Positive blood cultures

- Treat with appropriate antibiotics
  - Keep broad spectrum if still neutropenic
  - Consult Infectious Diseases
  - Treat 10-14 days from 1st negative culture
  - Repeated positive cultures
    - Consider CVL infection
    - ?removal

Initially Stable patient

- Continue antibiotics x 48 hours
  - Cultures negative
  - Afebrile & well
  - Rising ANC

  - Stop antibiotics and discharge

Initially Unstable patient

- Continue triple antibiotics x 48h
  - If afebrile, well, cultures negative
    - Stop tobramycin
- Continue double antibiotics x 24h
  - If afebrile, well
    - Stop vancomycin
- Continue single antibiotic x 24h
  - If afebrile, well, count rising (~0.5 x 10^9/L)
    - Stop piperacillin-tazobactam

Persistently febrile patient

- **Discuss with paediatric oncologist**
  - If stable – continue single antibiotic
  - If febrile >3 days –consider adding other antibiotic
  - If febrile > 5 days – consider empiric antifungal
- If clinical condition changes
  - Treat as clinically appropriate

Other non-empiric issues

Fungal infection

- Prophylaxis
  - Incorporated into some protocols (e.g. AML)
- Empiric Antifungal therapy
  - Used in febrile neutropenia
  - If > 5 days persistent fever/unwell
    - Amphotericin B (usually liposomal (AmBisome®))
  - Needs work-up too
- **Discuss with paediatric oncologist**

Viral infection

- Herpes simplex/Varicella zoster
  - New or recurrent outbreak
    - HD IV Aciclovir (30-50 mg/Kg ÷ q8h)
      - Never start with oral aciclovir

- Influenza A
  - Consider Oseltamivir (Tamiflu®)

Pneumocystis jirovekii

- All patients on prophylaxis
  - Cotrimoxazole
  - Pentamidine
  - Atovaquone
- Suspect if:
  - Tachypnoea
  - Hypoxia
  - Bilateral infiltrates
  - Prolonged immunosuppression
- Rx – Cotrimoxazole HD
  - 15-20 mg/Kg TMP component ÷ q6h

Off-treatment patients – to 3m

- Neutropenic or low IgG (e.g. post rituximab)
  - As febrile neutropenia
  - Monotherapy - piperacillin-tazobactam
- Non-neutropenic but unwell
  - Obtain blood culture
  - Monotherapy - piperacillin-tazobactam
- Non-neutropenic, well, but has CVL
  - Obtain blood culture
  - Monotherapy - Ceftriaxone (may be outpatient)
- Non-neutropenic, well, no CVL
  - Treat as any other child

Remember:

- **GUILTY – until proven innocent**

References

- Lehrnbrecher T et al. 2012: J Clin oncol, 30, 1-12. Guidelines for the management of fever and neutropenia in chidren with cancer and/or undergoing hematopietic stem cell transplantation
- Manji a et al. 2012: pediatr inf dis J, 31, 353-359. A meta-analysis of antipseudomonal penicillins and cephalosporins in pediatric patients with fever and neutropenia
- Furno P et al. 2002: Lancet Infect dis, 2, 231-242. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis
- Paul M et al. 2014: cochrane Database of systematic Reviews, issue 2. beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia

Questions?