Management of Febrile Neutropenia in Children

APPHON-ROHPPA 2014
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
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)
    - $< 0.5 \times 10^9/L$
    - 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/Rhinorrrhea 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
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

- 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
Immediate Management 2

- Airway
- Breathing
- Circulation

- 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

- 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
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
Special/Individual cases

ALL OTHER PATIENTS

- Monotherapy
  - Piperacillin-Tazobactam
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Guideline Algorithm
ALGORITHM FOR THE EMPIRIC MANAGEMENT OF FEBRILE NEUTROPENIA

YES

STABLE PATIENT

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
- Mucoats
Treat with Piperacillin-Tazobactam ** AND Vancomycin

Call Pediatric Oncologist

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

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

YES

Stop all antibiotics

NO

Piperacillin-Tazobactam** AND Tobramycin***
AND Vancomycin

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

YES

Stop Tobramycin

NO

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

YES

Stop Vancomycin

NO

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***

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?

YES

Consider stopping all antibiotics in consultation with Pediatric Oncologist

NO

Consider stopping all antibiotics in consultation with Pediatric Oncologist

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* 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 dB HL 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.

Pediatric Hematologist/Oncologist
902-470-8888 or 902-470-5888 (toll free)
Patient: ___________________ 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/APPON Guidelines.

<table>
<thead>
<tr>
<th>Required Evaluations</th>
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<tbody>
<tr>
<td>Daily CBC and Differential</td>
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<tr>
<td>Daily Na, K, Cl, BUN, Creatinine</td>
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<tr>
<td>Blood cultures from central line (all lumens) prior to administration of antibiotics</td>
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<tr>
<td>Blood cultures from peripheral site (if it doesn’t have a central line) prior to administration of antibiotics</td>
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<tr>
<td>Repeat blood cultures once daily, if temperature is greater than or equal to 38.3°C and/or appears sick</td>
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<tr>
<th>Optional Evaluations</th>
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<tbody>
<tr>
<td>✣ Urinalysis</td>
</tr>
<tr>
<td>✣ Urine Culture</td>
</tr>
<tr>
<td>✣ NPA swab for;</td>
</tr>
<tr>
<td>✣ Influenza, ✣ RSV; ✣ Adenovirus, ✣ Other</td>
</tr>
<tr>
<td>✣ Chest X-ray</td>
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<tr>
<td>✣ Other: ____________________</td>
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<th>Vital Signs</th>
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<td>At least every hour until stable, then q4h and within 30 minutes prior to leaving the hospital</td>
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- 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.

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

- **Advanced Centre**
  - Call within 24h to discuss management
Next Steps
ALGORITHM FOR THE EMPIRIC MANAGEMENT OF FEVERILE NEUTROPENIA

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

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

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

NO

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

YES

Stop Tobramycin

NO

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

YES

Stop Vancomycin

NO

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?

YES

Consider stopping all antibiotics in consultation with Pediatric Oncologist

NO

Piperacillin-Tazobactam**

AND Tobramycin***

AND Vancomycin

AND call Pediatric Oncologist

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

- Treat with appropriate antibiotics
  - Keep broad spectrum if still neutropenic
  - Consult Infectious Diseases
  - Treat 10-14 days from 1\textsuperscript{st} 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 10⁹/L)
    - Stop piperacillin-tazobactam
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


- 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?