NEUTROPENIC FEVER: NO PATHOGENS BUT STILL ANTIBIOTICS?

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Royal Melbourne Hospital
National Centre for Infections in Cancer
WHICH
GHOST INFECTION
do you have?
DISCLOSURES

Educational and research grants from MSD, Gilead Sciences, Pfizer.
# FEVER AND NEUTROPENIA (FN)

<table>
<thead>
<tr>
<th>Population</th>
<th>Micro Dx</th>
<th>Bacteria</th>
<th>Fungal</th>
<th>Viral</th>
<th>Mycobact</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT</td>
<td>79%</td>
<td>47%</td>
<td>11%</td>
<td>40%</td>
<td>2</td>
<td>Safdar et al, Medicine 2007</td>
</tr>
<tr>
<td>Allo HCT</td>
<td>96%</td>
<td>71%</td>
<td>5%</td>
<td>4%</td>
<td>0</td>
<td>Martin-Pena A et al, Clin Transplant 2011</td>
</tr>
<tr>
<td>Auto HCT</td>
<td>75%</td>
<td>36%</td>
<td>3.5%</td>
<td>15.5%</td>
<td>0</td>
<td>Marchesi F et al, Int J Molec Sci 2019</td>
</tr>
<tr>
<td>Auto HCT</td>
<td>48%</td>
<td>46%</td>
<td>0%</td>
<td>4%</td>
<td>0</td>
<td>Gil L et al, Infection 2007</td>
</tr>
<tr>
<td>Adult HM</td>
<td>63%</td>
<td>33%</td>
<td>0%</td>
<td>30%</td>
<td>0</td>
<td>Ohrmalm L et al, PLOSone 2012</td>
</tr>
<tr>
<td>Adult ALL</td>
<td>70%</td>
<td>23%</td>
<td>4.3%</td>
<td>1%</td>
<td>0</td>
<td>Di Blasi R et al, Ann Haematol 2018</td>
</tr>
<tr>
<td>Child cancer</td>
<td>51%</td>
<td>6%</td>
<td>0%</td>
<td>41%</td>
<td>0</td>
<td>Soderman M et al, PLOSone 2016</td>
</tr>
<tr>
<td>Child cancer</td>
<td>25%</td>
<td>50%</td>
<td>34%</td>
<td>14%</td>
<td>0</td>
<td>Hakim et al, J Ped Hematol Oncol 2009</td>
</tr>
</tbody>
</table>
FEVER AND NEUTROPENIA ..... BUT NO MICROBIOLOGY

Median duration of fever: 7-9 days HCT

GIT Translocation

Organisms not treated by routine antibiotics

- **Bacterial:** Stenotrophomonas, Burkholderia, Elizabethkingia, Nocardia, Rhodococcus, Legionella, Mycoplasma, Mycobacteria, Listeria
- **Fungal:** Wide spectrum including *Cryptococcus*
- **Viral:** in patients not routinely tested
- **Parasite:** *Strongyloides, Toxoplasma*

GUT TRANSLOCATION HAEMATOLOGIC MALIGNANCY (HM)

94 patients with 176 episodes fever

Bacterial infection in 59.6%

Blood samples days 0, 1, 2 and 6 after fever
  • Endotoxin in 40% regardless aetiology
  • TNF-α in 61%
  • IL-6 in 94%

Initial TNF-α and IL-6 levels were significantly higher in patients with Gram-negative bacteraemia than other causes of fever \((P < 0.001)\)

Failing mucosal barrier allows endogenous bacterial products/bacteria to reach the circulation

Microbial Translocation Contribute to Febrile Episodes in Adults with Chemotherapy-Induced Neutropenia

Michelle Wong1, Bablia Barqashi2, Lars Öhrmalm1, Thomas Tolfvenstam1, Piotr Nowak2,3

1 Department of Medicine, Söders, Infectious Disease Unit, Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden, 2 Department of Laboratory medicine, Division of Microbiology, Karolinska Institute, Huddinge, Sweden, 3 Department of Medicine, Huddinge, Infectious Disease Unit, Karolinska Institute, Karolinska University Hospital, Huddinge, Sweden

Endotoxin levels

A

n=42

Endotoxin concentration (pg/ml)

n=103

n=37

n=28

n=38

\* \( p<0.05 \)\n
\*** \( p<0.0001 \)

B

Endotoxin concentration (pg/ml)

** \( p<0.05 \)\n
*** \( p<0.0001 \)

ESCMID eLibrary

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Wong M et al PLOS One 2013:8:E68056
16 S rRNA BLOOD TESTING

Paediatric patients with fever and neutropenia (n=111), 16S rRNA gene amplification and sequencing

Positive blood cultures: 17
  • Bacterial DNA detected in 9/11 blood culture-positive episodes identical to the cultured isolates.

Negative blood cultures: 94
  • Bacterial DNA in 20 episodes (21 bacterial sequences)

18/20 in patients on antibiotics
  • Species by partial 16S rRNA gene sequencing:
    • Pseudomonas spp. (n = 6), Acinetobacter spp. (n = 5)
    • Escherichia spp. (n = 3); Moraxella spp. (n = 3)
    • Staphylococcus spp. (n = 2); Neisseria spp. (n = 1); Bacillus spp. (n = 1)
OPEN

Metagenomic analysis of bloodstream infections in patients with acute leukemia and therapy-induced neutropenia

P. Gyarmati\textsuperscript{1,2}, C. Kjellander\textsuperscript{3}, C. Aust\textsuperscript{4}, Y. Song\textsuperscript{5}, L. Öhrmalm\textsuperscript{6} & C. G. Giske\textsuperscript{1,2}

Received: 07 January 2016
Accepted: 08 March 2016
Published: 21 March 2016
METAGENOMIC SEQUENCING

9 patients with acute leukemia and suspected BSI at 3 time points:

- At onset fever and neutropenia before antibiotics, persistent fever, 5-7 days of antibiotics

Shotgun metagenomic sequencing of bacterial, fungal, viral pathogens and antimicrobial resistance genes

Average 33.5 million reads/sample. Decreased white blood cell counts associated with the presence of microbial DNA, and inversely proportional to the number of sequencing reads

METAGENOMICS

Significant reduction in bacteria after antibiotic treatment

**Bacteria:** *Propionibacterium acnes*, *Corynebacterium* spp, *Staphylococcus* spp, *Neisseria* spp, *Dolosigranulum* pigrim

**Viral:** mostly bacteriophages, Torque Teno Virus, Merkel cell PV, hepatitis C, HHV6

**Fungal:** *Fusarium oxysporum* (all time points), *Aspergillus*, *Malassezia*

TIMING AND FUNGAL ORGANISMS

**FUNGI**

- **Aspergillus species**: 9/27
- **Fusarium oxysporum**: 3/27
- **Malessezia globosa**: 2/9
- **Botryotinia fuckeliana**: 1/9
- **Melampsora larici-populina**: 1/7
- **Coprinopsis cinerea**: 4/7

**All samples**: 13/27

**Fever onset**: 3/9

**Persistent fever**: 5/7

**Follow up**: 5/11

CASE ONE

44-year-old with refractory AML

- Prior Azacitidine, FLAG
- Complicated by *E-coli* septicaemia and liver abscess on ciprofloxacin 500mg BD, abscess decreasing
- Chronically neutropenic: ANC 0.0 x 10⁹/L to 0.8 x 10⁹/L for 4 months

7+3 re-induction chemotherapy

- Neutropenic fevers on day 3: meropenem (penicillin allergy)
- Persistent fever and pleuritic chest pain day 10 (still neutropenic)

CTPA performed and blood cultures flagged positive 2 days later
CASE ONE

*Stenotrophomonas maltophilia*

IV cotrimoxazole 15mg/kg/day and moxifloxacin 400mg daily. Hickman line was removed

Prophylactic posaconazole changed to ambisome 5mg/kg daily based on radiology

Progressive sepsis day 15. ICU admission and bronchoscopy. Bronchial washings and multiple tracheal aspirates

- All cultured *Stenotrophomonas maltophilia*
- No positive fungal culture, Aspergillus GM or aspergillus PCR

Bacteraemic for 7 days. He continued to deteriorate, and was palliated

GRAM NEGATIVE INFECTION

Non-fermenting environmental organisms

Intrinsic and acquired antibiotic resistance:

- Intrinsic β-lactamases
- Efflux pump systems
- Enzymatic modifications
- Changes in the outer membrane
- Target site modification

Abbott IJ and Peleg AY. Semin Respir Crit Care Med 2015;36:99–110
## Antimicrobial Resistance

<table>
<thead>
<tr>
<th></th>
<th>S. maltophilia</th>
<th>B. cepacia complex</th>
<th>A. xylosoxidans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EUCAST</td>
<td>CLSI</td>
<td>EUCAST</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Ticarcillin–clavulanate</td>
<td>–</td>
<td>–</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>R</td>
<td>R</td>
<td>–</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
<td>R</td>
<td>–</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
<td>–</td>
<td>n/r</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>R</td>
<td>R</td>
<td>n/r</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>R</td>
<td>R</td>
<td>–</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>–</td>
<td>n/r</td>
<td>R</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Minocycline/Tigecycline</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Colistin</td>
<td>–</td>
<td>–</td>
<td>R</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbott IJ and Peleg AY. Semin Respir Crit Care Med 2015;36:99–110
### STENOTROPHOMONAS BSI IN CANCER: CATHETER RELATED VS OTHER

<table>
<thead>
<tr>
<th>Condition</th>
<th>Catheter-related n=53</th>
<th>Other n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia</td>
<td>19%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>38%</td>
<td>17%</td>
<td>0.02</td>
</tr>
<tr>
<td>Neutropenic at onset BSI</td>
<td>23%</td>
<td>81%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay during BSI</td>
<td>6%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation at onset</td>
<td>4%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11%</td>
<td>85%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breakthrough bacteremia</td>
<td>36%</td>
<td>83%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ciprofloxacin resistant</td>
<td>17%</td>
<td>51%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BSI: blood stream infection; ICU: intensive care unit

### OUTCOME STENOTROPHOMONAS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definite CR-BSI (n = 53) (%)</th>
<th>Secondary BSI (n = 47) (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>47 (89)</td>
<td>14 (30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Response among patients in whom catheters were removed</td>
<td>39/41 (95)</td>
<td>9/16 (56)</td>
<td>.001</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>6 (11)</td>
<td>33 (70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>6 (11)</td>
<td>30 (64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death attributed to <em>S. maltophilia</em> bacteremia</td>
<td>6 (11)</td>
<td>27 (57)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
CASE 3

59-year-old undergoing unrelated donor HCT

JAK2 positive myelofibrosis, prior ruxolitinib

Persistent fever, pancytopenia, hepatitis day 12

Trans-jugular liver biopsy: haemorrhagic shock and oliguric renal failure

Insertion of a tunnelled dialysis catheter on day 26

Persistent fever and neutropenia
CASE 3: *M. ABSCESSUS COMPLEX*

*M. abscessus/cheloneae* MALDI-TOF day 30
ITS sequencing: *M. abscessus complex*
Empiric: amikacin, cefoxitin, imipenem, clarithromycin
Debridement of catheter tract after neutrophil recovery
Susceptibility testing by microbroth dilution

Susceptible: Amikacin, Tigecycline
Intermediate: Cefoxitin, Imipenem
Resistant: trimethoprim/sulfamethoxazole, ciprofloxacin, moxifloxacin, doxycycline linezolid.
Inducible clarithromycin resistance. Mediated by mutations in *erm* gene in *M. abscessus* subsp. *abscessus* and subsp. *bolletii* but not in *M. abscessus* subsp. *massiliense*
RAPIDLY GROWING MYCOBACTERIA BSI

116 patients with cancer

- CVC in 111 (96%) patients; CVC was removed from 87 (79%) patients
- Eighty-five patients (73%) also received antibiotics
- \textit{M. chelonae} mitral valve endocarditis. Median treatment 4-6 weeks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>52 (10–81)</td>
</tr>
<tr>
<td>Sex, male:female ratio</td>
<td>67.49 (58:42)</td>
</tr>
<tr>
<td>Underlying cancer</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>70 (60)</td>
</tr>
<tr>
<td>Solid</td>
<td>46 (40)</td>
</tr>
<tr>
<td>HSCT</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>33 (28)</td>
</tr>
<tr>
<td>Autologous</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>29 (25)</td>
</tr>
<tr>
<td>GVHD</td>
<td>19 (16)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chemotherapy in month before bacteremia</td>
<td>84 (72)</td>
</tr>
<tr>
<td>Corticosteroids in month before bacteremia</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>104 (90)</td>
</tr>
<tr>
<td>&gt;600 mg (30-day cumulative dose of prednisone equivalent)</td>
<td>22 (21)</td>
</tr>
<tr>
<td>&lt;600 mg (30-day cumulative dose of prednisone equivalent)</td>
<td>82 (79)</td>
</tr>
<tr>
<td>Radiation therapy in month before bacteremia</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Surgery in month before bacteremia</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Hemodialysis at time of bacteremia</td>
<td>4 (3)</td>
</tr>
<tr>
<td>TPN at time of bacteremia</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Neutropenia at time of bacteremia</td>
<td>23 (20)</td>
</tr>
<tr>
<td>Fever at time of bacteremia</td>
<td>76 (66)</td>
</tr>
<tr>
<td>Hypothermia at time of bacteremia</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>111 (95)</td>
</tr>
</tbody>
</table>
159 neutropenic patients with haematological malignancy

35/159 (22%) ≥ one virus in blood

On multivariate analysis associations with virus in blood
- Fever
- CLL
- Not autologous SCT
- Steroids
- Lower CD4 (median 38)
- Steroids
- Monoclonal Antibody

Virus NPA: 18%

Overall number with viral detection: 35%

Ohrmalm L et al PLOS one 2012:7:e36543
CMV REACTIVATION IN AUTOLOGOUS STEM CELL TRANSPLANT

Up to 41% CMV seropositive patients with prospective monitoring
Up to 12% with clinically driven diagnostic strategy

- Risks
  CD34+ selected autografts, total body irradiation, prior Alemtuzumab, Fludarabine, Bortezomib

- Possible risks
  Prior Rituximab, T-cell lymphomas, pretransplant HBcAb, end organ disease 9.2% (lymphoma, myeloma),

In non-transplant patients 2-67%

- Putative risk factors
  High-dose steroids, advanced disease, poor performance status, Alemtuzumab, Fludarabine, Bortezomib, Rituximab

STRONGYLOIDES

Association with HTLV-1 infection and adult T cell leukaemia

- Small survey fever and neutropenia after chemotherapy in Australia
- 2/6 indigenous patients had positive stool cultures

<table>
<thead>
<tr>
<th>HTLV-1</th>
<th>Sensitivity</th>
<th>Cases n/N</th>
<th>Controls n/N</th>
<th>OR (95% BC)</th>
<th>OR (95% BC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nero FA et al. (1986)</td>
<td>High</td>
<td>22/84</td>
<td>20/100</td>
<td>1.44 (0.73 - 2.79)</td>
<td></td>
</tr>
<tr>
<td>Chiff JP et al. (2000)</td>
<td>Moderate</td>
<td>11/91</td>
<td>1/93</td>
<td>2.92 (1.08 - 11.9)</td>
<td></td>
</tr>
<tr>
<td>Couto et al. (2004)</td>
<td>High</td>
<td>27/81</td>
<td>33/253</td>
<td>4.95 (2.47 - 11.0)</td>
<td></td>
</tr>
<tr>
<td>Einsiedel L et al. (2010)</td>
<td>High</td>
<td>37/78</td>
<td>23/967</td>
<td>1.92 (1.12 - 3.32)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>105/220</td>
<td>277/2288</td>
<td>2.48 (0.70 - 9.03)</td>
<td></td>
</tr>
</tbody>
</table>

Immigrants and refugees
CASE 5

57yo IgG kappa myeloma
Induction: lenalidomide, dexamethasone
Autologous HCT and maintenance lenalidomide
Relapse: carfilzomib, thalidomide & dexamethasone trial

Post-cycle 5 ...ANC=0.4, Temp 38.5
Increasing lethargy and malaise
Piperacillin-tazobactam and discharge on amoxycillin-clavulanate for presumed pneumonia
FACIAL RASH ALSO NOTED

Recalled when blood cultures flagged positive with a yeast
CASE 5

Histology facial biopsy organisms consistent with Cryptococcus

Lumbar Puncture
- Opening pressure 20cm
- Protein 1.37 g/L
- Glucose <0.3 mmol/L
- Culture: Cryptococcus neoformans
- CrAg: positive, titre > 1:2560
- Serum CrAg positive, titre: 1:20480
CRYPTOCOCCOSIS

- Increased risk of cryptococcus in myeloma and other haematological malignancies including CLL well described

- Progressive/end stage disease with significant effect from both myeloma and multiple lines of treatment

- Proteosome inhibitors (Carfilzomib, Bortezomib)
  - Increased risk of viral infections due to T cell depletion
  - Increased rate of herpes zoster & influenza
  - High rates of pneumonia in clinical trials
  - Not recognised to increase risk of cryptococcosis

BRUTON’S TYROSINE KINASE INHIBITOR AND INVASIVE FUNGAL INFECTION (IFI)

IFI in CLL/lymphoma with ibrutinib
- PJP, Cryptococcosis, mould infection early after starting ibrutinib
- Aggressive, unusual course, disseminated

Mouse model
- More severe IA with BTK knockout

Human monocytes and aspergillus
- Ibrutinib impairs in activation, neutrophil attraction and TNF production

IMAGING IN NEUTROPENIC FEVER

- Patients frequently do not have localising signs
- Reliant on microbiology and imaging to localise infection
- Conventional CT scanning is not “high yield”
  - 52% sensitivity, 43% specificity
  - No functional component
  - Issues with differentiating cancer from infection

Gafter-Gvili A et al. Leukemia research. 2013
PET AND INVASIVE FUNGAL INFECTION

Retrospective review of 30 cases of IFI on FDG-PET/CT
- Hepatosplenic candidiasis - not evident on CT
- Invasive pulmonary aspergillosis - not evident on CT

Case-control study in 113 with NF
- Less antifungals started
- More antifungals ceased
- Cost savings of $7445 - $14,455 AUD (2012) per patient

FDG-avidity in liver pre and post treatment for hepatosplenic candidiasis

Allogeneic or Autologous Transplants AML/ALL

Fever and neutropenia continues at 72 hours or recurs after afebrile Blood PCR and blood culture

Randomised to FDG-PET/CT or standard CT arm

Yield of multiplex blood PCR compared to blood culture

IMAGING RESULTS IN REAL TIME
Impact on outcomes
- Proportion with diagnosis
- Change in management
- Proportion on antifungals
- Cost of care
- ICU admission
- Length of hospital stay
CONCLUSION

“...for high-risk patients with persistent fever and neutropenia, continued antibiotic therapy along with empirical antifungal therapy starting 4 to 7 days after initiation of antibiotic therapy is recommended.”

- Continue antibiotics
- Look for pathogens not covered by antibiotics including viruses
- Investigate: CT scan, PET/CT scan, bronchoscopy
- Multiplex PCR
- Promise of metagenomics
21st ICHS Symposium on
Infections in the Immunocompromised Host

7–9 June, 2020
Melbourne, Australia

www.ichs2020.com