Neutropenic fever and non-infectious causes: no pathogens, but still antibiotics?

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• Shionogi: Consultancy
Antibiotics the bad, the good and the ugly
In retrospective studies disruption of microbiota has been associated with adverse disease outcomes.

Shono et al., Nature Reviews, 2017
Taur et al., Virulence, 2016

Non-relapse mortality at 1 year after HCT With Early VRE bacteremia

Probability of non-relapse mortality after HCT

Papanicolaou et al, Clin Infect Dis 2019
Duration of Empiric Antibiotic Therapy in Granulocytopenic Patients with Cancer

After 7 days of Keflin, carbenicillin, gentamicin (KCG) randomized to continue until neutrophil recovery (ANC>500) or stop 0/16 patients that stopped abx developed infection 7/17 (41%) developed infectious sequelae, 2 ultimately fatal
Recommendations for antibiotic duration for fever and neutropenia

**IDSA**
- Maintain Abx until neutrophil recovery (ANC≥0.5x10^9/L)

**ECIL-4**
- Discontinue after ≥72 hours of Abx irrespective of ANC count if:
  - Afebrile ≥72 hours
  - Clinically stable
  - Restart Abx if fever recurs

What if fever and neutropenia persists, and a non-infectious cause of fever is identified?

Freifeld A et al Clinical Infectious Diseases 2011;52(4):e56–93
Damage response is a cause of fever during mucositis

Baseline

Phase I:
Initiation
[0-2 days]

Phase II & III:
Primary Damage Response & Signal Transduction
[2-10 days]

Phase IV
Ulceration
[10-15 days]

Phase V
Healing
[14-20 days]

Adapted from Sonis, Nature Reviews, 2004
Practice Changing Treatments in AML

- **Allogeneic Transplant**
- **7+3** (1970)
- **Ara-C Consol** (1990)
- **Dauno Intensification**
- **Liposomal chemo for sAML**
- **IDH2i**
- **FLT3i** (2000)
- **Anti-CD33** (2010)
- ??

References:
- Thomas et al. NEJM, 1979; Mayer et al. NEJM, 1994;
- Fernandez et al. NEJM, 2009; Stone et al. NEJM 2017
Immune based therapy: CAR T-cell generation and mechanism of action
Case 1

• 66 year old male with Interstitial Lung Disease, Pre B-ALL in 2016
• s/p hyper-CVAD, IT MTX, Blinatumomab- progression of disease
• S/p CAR-T cells in 2017-with remission
• MDS→AML in early 2018
• s/p azacitidine and venetoclax- prolonged neutropenia
• August 2019: pneumonia with ESBL E.coli, CRE colonization, parainfluenza virus
Multiple admissions for fever over next 3 months

Can we stop antibiotics?

<table>
<thead>
<tr>
<th>Date</th>
<th>Antimicrobial Treatment</th>
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<tbody>
<tr>
<td>Nov 6-9</td>
<td>Meropenem</td>
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<tr>
<td>Nov 10-19</td>
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<tr>
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Fever due to underlying disease

Can we stop antibiotics?

Fever curve

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Case 2

• 44 year old with AML
• Induction chemotherapy with 7+3
• Day 7: Fever → piperacillin-tazobactam
• Day 14: Bone marrow aspirate: 66% Blasts
• Day 18: Recurrent fever → vancomycin added
• Day 22: Transaminitis, persistent daily fevers (up to 39.3°C)
The patient looks well

Multiple blood cultures (-)
CT chest/abdomen/pelvis (-)
ALT 1,966/AST 1,750
Ferritin 53,000
Soluble IL2 receptor 2,717 (high)
Triglycerides 47

Do you continue antibiotics?
Hemophagocytic Lymphohistiocytosis (HLH)

ALT 1,966
AST 1,750
Ferritin 53,000
Soluble IL2 receptor 2,717
Triglycerides 47

Started on Etoposide, Dexamethasone
Fever resolved
She remains neutropenic

Do you continue antibiotics?
Non infectious causes of fever

• Fever and pulmonary infiltrates
  • Idiopathic pneumonitis syndrome
  • Diffuse alveolar hemorrhage
  • Organizing pneumonia

Fever and multi-organ involvement
• Sweet’s syndrome
• Differentiation syndrome
• Engraftment syndrome
• Cytokine release syndrome
Case 1

- 66 yo woman with h/o AML in CR1, D#21 s/p MUD HCT. Course c/b grade III aGVHD of skin.
- Presents with fever, cough and severe hypoxemia
- Peripheral ID w/u is negative
- Patient is intubated for hypoxemia
- Bronchoscopy with BAL is performed
  - Microbiologic studies negative
- What is the diagnosis?
Idiopathic Pneumonia Syndrome - definition

- Widespread alveolar injury
  - Multilobar opacities
  - Sx and signs of PNA
  - Hypoxemia and/or new or increased restrictive pulmonary physiology
- Absence of active lower respiratory tract infection
  - Negative tests of bacteria, viruses, fungi on blood, sputum, BAL, lung biopsy
- No alternative explanation, such as
  - CHF
  - Fluid overload
Case 2

• 23 yo woman with AML is day # 15 s/p DUCBT develops hypoxemic respiratory failure. She has cough, but denies hemoptysis despite being asked about it at least 10 times (does this r/o DAH?).
• Chest imaging is obtained
• Labs notable for
  • PLT = 23
• What should you do next?

• Bronchoscopy with BAL is performed
Sweet’s syndrome

Acute onset of painful erythematous plaques or nodules

Dermal neutrophilic infiltrate without evidence of vasculitis on histopathological examination

Temperature >38°C
Periorbital and preseptal involvement with Sweet’s syndrome
Lung involvement with Sweet’s syndrome
Anticancer drugs associated with Sweet’s syndrome

- GCSF
- Bortezumab
- Azacitidine
- Decitibine
- Imatinib
- Lenalidomide
- All Trans-retinoic acid
Differentiation syndrome

Develops 2-21 days post induction with ATRA

• 25% incidence
• Fever, peripheral edema, pulmonary infiltrates, renal/hepatic failure, serositis with effusions

Treatment

• Dexamethasone
• Hold ATRA
Cytokine release syndrome after CAR-T cells and Blinatumomab

Frey NV et al, Hematology 2016

CRS Grading

Grade 1
- Fever
- Constitutional symptoms

Grade 2
- Hypotension responding to fluids, low dose vasopressors
- Grade 2 organ toxicities

Grade 3
- Shock requiring high dose multiple vasopressors
- Hypoacia requiring ≥ 40 % FiO2
- Grade 3 organ toxicities, grade 4 transaminases

Grade 4
- Mechanical ventilation
- Grade 4 organ toxicities (e.g., transaminases)
ATG - Serum Sickness

Classic presentation:
• 1-2 weeks after exposure
• Fevers, arthralgias, headache, edema, GI symptoms, and rash

1. Rabbit ATG is recognized by our immune systems as foreign
2. Primary immunization occurs (if this is first exposure), resulting in plasma cell secretion of immunoglobulins specific to r-ATG
3. Immunoglobulins bind to r-ATG resulting in immune complexes (antibody-antigen complexes)
4. Immune complexes deposit in tissues and blood vessels
5. Complement activation results in release of cytokines and neutrophil recruitment
Engraftment syndrome has a range of severity.
To give or NOT to give Antibiotics

Continue antibiotics

High risk for infection

Sepsis may be fatal

Sense of “safety”

What’s the big deal?

Stop all antibiotics if alternative diagnosis

Avoid “collateral damage”

Selection of MDR organisms, C-difficile etc

Programmatic: Hospital resistance, cost etc

Knowledge gap

Knowledge gap
The treatment landscape in hematologic malignancies is rapidly changing

Less mucositis
Targeted therapies
Immune deregulation
Prolonged cytopenia
“Surprising” infections

• Rapid diagnostics
• Surrogate markers?
• Close clinical monitoring
• Randomized clinical trials lacking
• Share experiences?
We need, real time assessment, non-invasive, integrating multiple data, and rapid decision making
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The Medical Tricorder

https://en.wikipedia.org/wiki/Tricorder
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