Infections in Bone Marrow Transplantation

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Introduction

- Infection is a common complication of bone marrow transplantation
  - Significant morbidity & mortality
- Higher risk groups
  - Allogenic BMT
  - Extensive pre-transplant immunosuppression
  - Grade III-IV GVHD / extensive cGVHD
  - HLA-mismatched donor
  - Delayed or failed engraftment
Critical role of BMT Nurses & Allied Health in management of post-HSCT infections

**Diagnosis**
- Symptom awareness
- Good rapport with patient, family & carers
- Timely sampling for microbiological diagnosis without delaying treatment

**Treatment**
- Administer life-saving treatment
- Awareness of potential for drug interactions & allergies
- Vigilance in side-effects monitoring

**Prevention**
- Meticulous hand hygiene & line care
- Infection control guideline implementation
- Patient education
- Vaccinations
Talk outline

- Pathogenesis of infections in BMT recipients
- Types of post-transplant infections
- Spotlight on 4 common post-transplant infectious syndromes
- Infection prevention
Pathogenesis of infections in BMT
Pathogens

Host immunity

EQUILIBRIUM
HOST PATHOGEN(S)

EQUILIBRIUM?
Sources of infection in HSCT recipients

Opportunistic
- Exposure to microbes that do not cause disease in normal hosts – establishes infection

Reactivation
- Latent infection
- Reactivates with immunosuppression

Nosocomial
- Devices – lines, catheters
- Transfusion products – including donor-derived
- Person-to-person transmission – HCW, visitors
- Environmental – air, food & water, fomites

Sources:
- Aspergillus
- Nocardia
- Scedosporium
- CMV
- EBV
- HSV
- Hepatitis B
- Tuberculosis
- Toxoplasmosis
- Strongyloides
- Staph. aureus
- Coag –ve Staph
- C. difficile
- Influenza / RSV
- CMV
Common things occur commonly…

- BMT recipients also get normal “community-acquired” infections
  - Viral URTI
  - Community-acquired pneumonia
  - Cellulitis
  - Urinary tract infections
- Often more severe due to immunosuppression
- Can be forgotten in protocol-driven empirical treatment
EQUILIBRIUM?

HOST

PATHOGEN(S)
Host Immune system

Components

- Leukocytes (WBC)
  - Neutrophils
  - Lymphocytes – T & B cells
  - Eosinophils
- Antibodies
Adaptive Immunity: Antibodies and Immunodeficiencies

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition.


FIGURE 5-1
# Host Immune system

<table>
<thead>
<tr>
<th>Components</th>
<th>Natural physical barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (WBC)</td>
<td>Skin</td>
</tr>
<tr>
<td>- Neutrophils</td>
<td>- Gut endothelium</td>
</tr>
<tr>
<td>- Lymphocytes – T &amp; B cells</td>
<td>- Genitourinary tract</td>
</tr>
<tr>
<td>- Eosinophils</td>
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<tr>
<td>Antibodies</td>
<td></td>
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<tr>
<td>Complement</td>
<td></td>
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<tr>
<td>Spleen &amp; lymphoid tissue</td>
<td></td>
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</tbody>
</table>

- Skin
- Gut endothelium
- Genitourinary tract
Bacteria

Gram +ve
- S. aureus
- Coagulase –ve Staph
- Streptococci

Gram –ve
- E. coli
- Klebsiella
- Pseudomonas

Anaerobic
- Bacteroides
Bacteria

Gram +ve
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Gram –ve
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Anaerobic
- Bacteroides

Encapsulated bacteria
- Strep. pneumoniae
- Neisseria meningitidis
- Haemophilus influenzae

Significantly ↑ risk in hyposplenism
Bacteria

Mycobacteria & Nocardia

Mycobacteria
- Tuberculosis (*Mycobacterium tuberculosis*)
- MAC (*M. avium* complex)

Weakly acid-fast
- Nocardia

Photo: Concord Microbiology Laboratory
Bacteria

Mycobacteria & Nocardia

Viruses

Herpes Viruses
- CMV
- EBV
- HSV
- HHV-6, 7

Respiratory viruses

Polyoma viruses
- JC Virus
- BK Virus
Bacteria

Mycobacteria & Nocardia

Viruses

Yeast
- Candida
- Cryptococcus
- Malassezia

Filamentous fungi
- Aspergillus
- Zygomycetes
- Lomentospora prolificans (prev Scedosporium prolificans)

Dimorphic fungi
- Histoplasmosis
- Coccidiomycosis

Pneumocystis jirovecii (PCP, PJP)
Bacteria

Mycobacteria & Nocardia

Viruses

Fungi

Parasites

Protozoa
- Giardia
- Cryptosporidium
- Toxoplasma gondii
- Malaria (Plasmodium)

Helminths (worms)
- Strongyloides
Timing of infections post-HSCT
Immune cell recovery post-myeloablative BMT

Phase I: Pre-engraftment

Graft-versus-host-disease: Acute

Neutropenia, barrier breakdown (mucositis, central venous access devices)
Gram-negative bacilli
Gram-positive organisms
Gastrointestinal Streptococcus species

Phase II: Post-engraftment

Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire

Encapsulated bacteria

Phase III: Late phase

Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies

Varicella zoster virus

Other viruses eg, HHV6

EBV PTLD

Aspergillus species

Candida species

Pneumocystis

Case 1: Febrile neutropaenia
Case 1

- 16yo girl D7 salvage chemotherapy for AML
- Neutropaenic (0.5), temp 38.5
- Hickmanns line – exit site unremarkable
- Tazocin + gentamicin commenced as per protocol, post BCs
- Blood cultures taken
  - Peripheral: 1/2 bottles – yeast (12hrs)
  - Hickmanns culture 2/2 – yeast (4hrs)
Case 1

- Yeast identified as *Candida krusei*
  - **Empirical echinocandin**
    (e.g. anidulafungin, caspofungin)
- Daily BCs – persistent *candidaemia* for 8 days
- Hickmans removed at day 6
- Investigations for other sites of infection:
  - Echocardiogram – no endocarditis
  - Abdominal imaging – NAD
  - Eye check – *endophthalmitis*
- Intravitreal voriconazole + 6 weeks IV echinocandin
Endogenous *Candida* endophthalmitis with multiple focal white lesions within the choroid and extension of the two largest lesions through the retina into the vitreous.

*Courtesy of Carol Kauffman, MD.*
Line-related infections

- Simultaneous paired BCs are useful
  - Aim same volume in each BC
  - Do not exceed max volume
  - Time to positivity $\geq$ 2hr difference
- Line removal is key to optimising source control
  - Timing can be tricky due to pancytopaenia
- S. aureus & Candida spp. are highly associated with metastatic sites of infection
  - Infected sites can be asymptomatic e.g. endophthalmitis
Case 2: Post-transplant diarrhoea
Case 2

- 45yo woman D30 MUD post allogenic BMT for AML
  - 10/10 human matched unrelated donor (MUD)
  - Cyclophosphamide / total body irradiation conditioning

- Tacrolimus & methotrexate
- Prompt engraftment at D21
- Presents to clinic for review, not feeling well
- 2x courses broad spectrum antibiotics for febrile neutropaenia – no cause identified
- Profuse diarrhoea – 10x day

Post-transplant diarrhoea

**Infectious**
- Neutropaenia colitis
  - Translocation of gut flora
  - +/- bacteraemia
- Clostridium difficile
- Enterovirus
- Adenovirus
- CMV
- Parasites
  - Giardia / Cryptosporidium
  - Amoebic dysentery

**Non-infectious**
- Drug toxicity
- Acute gut GVHD
Case 2

- Bacterial stool culture – ve
- Stool ova, cyst & parasites – ve
- Empirical tazocin → meropenem
- Worsening abdominal pain
  - AXR – toxic megacolon

Source: UpToDate
Photo by: J T Lamont, MD
Case 2

- C. difficile PCR – positive
- Meropenem ceased
- Oral vancomycin 125mg qid + rectal vancomycin retention enema
- Failed to respond – for consideration of colectomy
**Clostridium difficile**

- Gut commensal
  - Commonly isolated from faeces of children <2yo; significance uncertain but only if asymptomatic
- Overgrowth occurs with antibiotic use
- Hand hygiene
  - Alcohol hand-rubs are insufficient - spores resistant
  - Require soap & water
- **Oral** metronidazole – first line treatment
  - Oral vancomycin if severe

Source: Todar’s Online Textbook of Bacteriology
Case 2a

- 45yo woman D30 MUD post allogenic BMT for AML
- Profuse diarrhoea 10x/day
- Bacterial stool culture –ve
- Stool ova, cyst & parasites -ve
- C. difficile PCR -ve
- Peripheral blood CMV PCR – below detectable limit

- Gastroenterology consult
  - Colonoscopy – no macroscopic abnormality
  - Random biopsies taken
Case 2a

Colonic biopsy histology
Source: eMedicine

- Treatment
  - IV ganciclovir for 3 weeks (induction)
  - PO valganciclovir (consolidation)
CMV disease

- General pop latent infection rate ≈ 60%
- Modes of acquisition in BMT recipients:
  - Endogenous reactivation
  - Exogenous – donor derived, transfusion product
- Presentations e.g.
  - Pneumonitis
  - Viraemia
  - Hepatitis
  - Endophthalmitis

NB. End-organ CMV disease can still occur without high peripheral blood viral load
Case 3: Respiratory infiltrates
Case 3

- 25yo man MUD allogenic BMT for ALL
- Delayed engraftment at D35
- Fevers at Day 50
- CT Chest:
  LUQ lesion with ‘halo sign’

Case 3

- FNA lesion
- Hyphae seen
- Culture = *Aspergillus fumigatus*
- Commenced on voriconazole

Source: Mycology Online, University of Adelaide
Fungal differential diagnoses

Zygomycetes  “Lid pushers”
• Empirical therapy requires liposomal amphotericin

Mucor spp
Saksenaea vasiformis
Fungal differential diagnoses

Lomentospora prolificans
(previously Scedosporium prolificans)
• Extensively resistant to most antifungal classes
Infection control

- Critical on the haematology unit!
- No flowers
- Visitors with URTI symptoms or fevers not to enter unit
- Droplet precautions for respiratory viruses
Case 4

- 15yo man allogenic MUD BMT for anaplastic large cell lymphoma
- Engraftment at D21, complicated by:
  - grade II GVHD – steroids
- Day 110 – developed fevers & seizures

Source: Kerl et al, Transplant Infectious Diseases 2015 17: 119-124
Cerebral toxoplasmosis

- CSF
  - mild mononuclear pleocytosis
  - toxoplasmosis PCR +ve
- Brain biopsy +ve immunohistochemistry for *T. gondii*
- Immunosuppression reduced
- Antibiotics - pyrimethamine + sulfadiazine
Neurological infections

Patterns:
- Meningitis – headache, neck stiffness
- Encephalitis – confusion
- Space-occupying lesion
BMT CNS infection differentials

Order of likelihood depends on clinical syndrome & imaging:

- Encapsulated bacteria
- Listeria
- Toxoplasmosis
- Nocardia
- Fungal
- HHV6
- JC Virus – progressive multifocal leukoencephalopathy (PML)
- HSV
- Infectious mimics – cerebral involvement of primary disease or post-transplant lymphoma
Conclusions
Broader healthcare challenges

- Increasing prevalence of MROs
  - **MRSA** – Methicillin-resistant Staph. aureus
    - VISA – vancomycin-intermediate
    - VRSA - vancomycin-resistant
  - **VRE** – vancomycin-resistant Enterococci
  - **CRE** – carbapenem-resistant Enterobacteriaceae
- Periodic nation-wide antibiotic shortages
- Costs of antimicrobials
Take home messages

- Humans are highly vulnerable without immunity
- BMT recipients at risk of a myriad of infections
  - Broad range of differential
  - Presentation may be non-specific / atypical
- Clues from history & examination are critical to guide investigations
- Diagnostic sample is crucial, but intervention can be high risk due to cytopaenias
- BMT Nurses play a critical role in reducing infections post BMT