APPROACH TO PREVENTION AND MANAGEMENT OF INFECTIOUS COMPLICATIONS IN HEMATOLOGIC MALIGNANCY PATIENTS

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From a TB Sanitorium to a Comprehensive Cancer Center
DISCLOSURE

- Research Support: Merck
- Consultant: Merck
- Ad board: Merck, Janssen, Clinigen
- Investigator: Merck, Gilead, Ansun, AiCuris, Shire/Takeda, Chimerix,
Outline

- Epidemiology

  Risk factors; disease and therapy based

- Prophylactic approach

- Management of infectious syndromes
Epidemiology

- Infection risk dependent on type of HM
- Disease status – initial diagnosis vs. relapsed disease
- Therapeutic intervention for the HM
- Type of infection: risk dependent on the immune deficit (neutropenia, lymphopenia, hypogammaglobulinemia, etc.)
- Prior exposure history; occupation, travel, residence, habits
Risk Factors – disease based

• **Neutropenia** (duration and severity)
  – MDS/ AML
  – ALL
  – Multiple myeloma

• **Lymphopenia and hypogammaglobulinemia:**
  – Lymphoma
  – CLL
  – Multiple myeloma
Risk factors – therapy based

- Cytotoxic chemotherapy: induction for AML/ALL
- Bispecific T-cell engagers (Bite antibodies): ALL
- Monoclonal antibodies: Rituxan, Brentuximab (ADC): Lymphomas
- Small molecules:
  - Bruton tyrosine kinase inhibitor, Ibrutinib: multiple disease groups
  - Tyrosine kinase inhibitors, Janus kinase inhibitors: CML/myeloproliferative disorders
- Immune checkpoint inhibitors
- CAR T cellular therapy: Lymphoma and ALL
Cytotoxic chemotherapy

- AML: various regimens used based on disease status; newly diagnosed, refractory or relapsed disease or based on cytogenetics

- Neutropenia is the main issue: bacterial and fungal infections

- Mucositis: risk for microbial translocation

- ALL: mostly in the context of induction therapy (such as hyper-CVAD), steroid use during different phases of therapy
Bispecific T-cell engagers

- **Blinotumumab**: target is CD19
  - Infection rates lower than conventional chemotherapy
  - Blood stream infection concern with continuous infusion
  - Cytokine storm – capillary leak with ARDS like presentation, CNS toxicity.

- **Inotuzumab**: Not yet FDA approved

  - [https://doi.org/10.1016/j.cmi.2018.02.003](https://doi.org/10.1016/j.cmi.2018.02.003)
### Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Blinatumomab Group (N = 267)</th>
<th>Chemotherapy Group (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>263 (98.5)</td>
<td>108 (99.1)</td>
</tr>
<tr>
<td>Event leading to premature discontinuation of trial treatment</td>
<td>33 (12.4)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>165 (61.8)</td>
<td>49 (45.0)</td>
</tr>
<tr>
<td>Fatal serious adverse event</td>
<td>51 (19.1)</td>
<td>19 (17.4)</td>
</tr>
<tr>
<td>Any adverse event of grade ≥3</td>
<td>231 (86.5)</td>
<td>100 (91.7)</td>
</tr>
<tr>
<td>Grade ≥3 adverse event of interest reported in at least 3% of patients in either group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>101 (37.8)</td>
<td>63 (57.8)</td>
</tr>
<tr>
<td>Infection</td>
<td>91 (34.1)</td>
<td>57 (52.3)</td>
</tr>
<tr>
<td>Elevated liver enzyme</td>
<td>34 (12.7)</td>
<td>16 (14.7)</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>25 (9.4)</td>
<td>9 (8.3)</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>13 (4.9)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>9 (3.4)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (1.5)</td>
<td>4 (3.7)</td>
</tr>
</tbody>
</table>

## Small Molecule Kinase Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor (Company)</th>
<th>Mechanism</th>
<th>Kinase(s)</th>
<th>Clinical Use</th>
<th>Year</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica; Pharmacycics and Johnson &amp; Johnson)</td>
<td>TKI</td>
<td>Bruteon kinase</td>
<td>MCL, CLL, WM</td>
<td>2013</td>
<td>Reported SSTIs; no evidence of Olb</td>
</tr>
<tr>
<td>Idelalisib (Zydelig; Gilead)</td>
<td>Lipid kinase inhibitor</td>
<td>PI3Kδ</td>
<td>Small lymphocytic lymphoma, NHL, CLL</td>
<td>2014</td>
<td>Black-box warning for serious infections in 21% of patients receiving monotherapy, including CMV reactivation, PJP</td>
</tr>
<tr>
<td>Dasatinib (Sprycel; Bristol-Myers Squibb)</td>
<td>TKI</td>
<td>BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2, PDGFRβ</td>
<td>Ph⁺ CML, ALL</td>
<td>2006</td>
<td>Bacterial infections, including sepsis, pneumonia, several cases of PJP, possible fungal pneumonia, candidemia, and CMV reactivation</td>
</tr>
<tr>
<td>Ruxolitinib (Jakafi; Incyte)</td>
<td>TKI</td>
<td>JAK1/2</td>
<td>Myelofibrosis, PV</td>
<td>2011</td>
<td>Warning box: serious bacterial (UTI), mycobacterial, fungal, viral (VZV, PML) infections</td>
</tr>
<tr>
<td>Ponatinib (Iclusig; Ariad)</td>
<td>Multiple TKIs</td>
<td>BCR-Abl, BCR-Abl T315I, VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, Flt3</td>
<td>Ph⁺ CML or ALL</td>
<td>2012</td>
<td>No evidence of Ol; occasional febrile neutropenia and sepsis</td>
</tr>
</tbody>
</table>

Ibrutinib

- Used in CLL, lymphoma’s (including PCNSL), post HCT for GVHD

- BTK inhibitor (BTK is critical for neutrophil innate immune response to aspergillus)

- In a PCNSL study of 18 patients (using upfront Ibrutinib followed by Ibrutinib + Temozolamide, Dexamethasone and Rituxan – TEDDI-r):
  - 7/18 (38%) developed invasive aspergillosis, with 2 developing CNS involvement

- In another study rate of invasive fungal infection reported at 5-10% (similar to allogeneic HCT); tends to occur early after starting ibrutinib.
  - Other risk factors: > 3 prior therapies and use of steroids

PCNSL – Ibrutinib based regimen and Aspergillosis

Figure 1. Ibrutinib-chemotherapy cytotoxicity models and DA-TEDDi-R Schema

Ibrutinib and timing to development of infection

BTK and Aspergillosis

Immune checkpoint inhibitors (ICI)

- Infectious disease encountered in the context of management of ICI related toxicities: SJS, pneumonitis
  - high dose steroid use and
  - Inhibitors of TNF-alpha
CAR T cellular therapy

• Pre CAR-T- Infusion: factors associated with infection

• In a step wise multivariable model of baseline features, following were associated with higher risk of infection:
  • Diagnosis of ALL
  • >4 prior antitumor regimens
  • Level 3 CAR T cell load

Post CAR-T-I factors associated with infection

- Only factor associated with increased risk for infection in MV model was:

- The “severity of CRS”

- Increased hazard for infection - 3.4 (p<0.001) by increase each CRS severity category (grades 0 vs. 1-3 vs. 4-5)

  - Hill JA et al. Blood 2018
**Table 3. Comparison of Early Versus Late Infections After Chimeric antigen receptor T-cell infusion**

<table>
<thead>
<tr>
<th></th>
<th>Earlya (Day 0–30) (n = 53)</th>
<th></th>
<th>Late (Day 31–180) (n = 32)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infections, No.</td>
<td>Patients, No. (%)</td>
<td>Infections, No.</td>
</tr>
<tr>
<td>Any infection</td>
<td>26</td>
<td>22 (42)c</td>
<td>15</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodstream</td>
<td>8</td>
<td>7 (13)</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial site</td>
<td>9</td>
<td>9 (17)</td>
<td>4</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td>1</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Mold</td>
<td>3</td>
<td>3 (6)</td>
<td>1</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory virus</td>
<td>3</td>
<td>3 (6)</td>
<td>8</td>
</tr>
<tr>
<td>Other virus</td>
<td>2</td>
<td>2 (4)</td>
<td>1</td>
</tr>
</tbody>
</table>

aDay 0 was the day of Chimeric antigen receptor T-cell infusion (CTI).
bPatients with complete remission after CTI.
cTwo patients had >1 infection.
dThree patients had >1 infection.
### Risk factors/ Predictors of infection

Park JH et al. Clin Infect Dis. 2018

#### Table 4. Univariate and Multivariate Cox Models for Predictors of Infection and Bloodstream Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predictors of Infection</th>
<th>Predictors of Bloodstream Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>PValue</td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td>1.04 (.43–2.39)</td>
<td>.92</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.29 (1.51–3.00)</td>
<td>.57</td>
</tr>
<tr>
<td>Prior chemotherapy (≥3 lines)</td>
<td>0.86 (0.38–2.03)</td>
<td>.72</td>
</tr>
<tr>
<td>Prior allogeneic HSCT</td>
<td>0.77 (0.30–1.79)</td>
<td>.55</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cy 1.5 g/m²</td>
<td>1.00 (—)</td>
<td>...</td>
</tr>
<tr>
<td>Cy 3.0 g/m²</td>
<td>0.47 (0.18–1.36)</td>
<td>.16</td>
</tr>
<tr>
<td>Cy/Flu or Cy/Clo</td>
<td>1.41 (0.49–4.21)</td>
<td>.52</td>
</tr>
<tr>
<td>Morphologic disease (≥5% blasts or extramedullary disease)</td>
<td>1.76 (0.74–4.72)</td>
<td>.21</td>
</tr>
<tr>
<td>CAR T-cell dose (3 × 10⁹/kg vs 1 × 10⁶/kg)</td>
<td>0.44 (0.19–1.01)</td>
<td>.05</td>
</tr>
<tr>
<td>Hypogammaglobulinemia (IgG &lt;600 mg/dL)</td>
<td>1.10 (0.32–5.66)</td>
<td>.89</td>
</tr>
<tr>
<td>CRS grade ≥3*</td>
<td>2.64 (1.11–6.03)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Analyzed as a time-dependent predictor. All the analysis time was CRS grade 3-4.

Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; Clo, clofarabine; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G.
CI of infection vs. CRS grade

Figure 2. Cumulative incidence of infection after chimeric antigen receptor T-cell infusion (CTI) and cytokine release syndrome (CRS). A, Cumulative incidence of any infection in patients by CRS grade. B, Cumulative incidence of bloodstream infection by CRS grade. Note that all the analysis time was CRS grade 3–4.
Neutropenic fever
Antibiotic Prophylaxis

- Many studies have demonstrated a decreased incidence of bacteremia and neutropenic fever, but no single study has demonstrated a survival benefit.


- The downside of antibacterial prophylaxis is the selection and emergence of resistant bacteria and the increased incidence and virulence of other infectious diseases, e.g., *Clostridium difficile* enterocolitis and invasive fungal infection.

- The IDSA Fever and Neutropenic Guidelines panel recommends that “routine prophylaxis…be avoided”.

- We recommend fluoroquinolone in only high-risk patients.

Taplitz RA et al. JCO. 2018. https://doi.org/10.1093/cid/ciy381
Bucaneve et al. Cochrane Database Syst Rev. 2005, CD004386
General principles of empiric treatment

- Awareness of institutional epidemiology
- Choice should be guided by local antibiogram
- Choice should address knowledge of colonization with MDRO’s
- Higher rates of FQ resistant and MDRO infections – in the setting of prophylaxis

- Initial regimen should be broad with antimicrobial having anti-pseudomonal coverage (e.g., pip/tazobactam, carbapenems, 3rd generation cephalosporins)
- In cases suspected to have gram + infections consider vancomycin
- Persistent fever: consider fungal infection and institute empiric antifungal agent
Neutropenic Fever

- Risk stratification (low vs. high) - starting point for management

- Assessment of risk for complications of severe infection at presentation with fever – helps determining:
  - type of empirical antibiotics (oral vs. iv),
  - setting (OP vs. IP) and
  - duration of antibiotics
Neutropenic Fever Risk Assessment

- High risk:
  - prolonged neutropenia (>7 days),
  - profound neutropenia (<100/ mm3 following cytotoxic chemotherapy),
  - and or significant co-morbid conditions, including hypotension, pneumonia, new onset abdominal pain or neurologic changes.

- High risk patients should be hospitalized for management
Neutropenic Fever
Risk Assessment

• Low Risk
• ANC > 100 cells/mm³
• neutropenia anticipated to last < 7 days
• No IV catheter site infection
• No appearance of illness (no localizing s/s)
• No co-morbid conditions or complications (shock, hypoxia, pneumonia or other deep-organ dysfunction, vomiting or diarrhea)

• Low risk patients are candidates for oral therapy
Neutropenic Fever Risk Assessment – MASCC score
(Multinational association for supportive care in cancer score).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Point score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of illness</td>
<td></td>
</tr>
<tr>
<td>No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection in hematologic tumor</td>
<td>4</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Aged &lt;60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. Scoring system for risk of complications among febrile neutropenic patients, based on the Multinational Association for Supportive Care in Cancer predictive model [6].
## Neutropenic Fever Risk Assessment

**Table 3. Medical complications in 72 febrile neutropenic patients with bacteremia due to a single pathogen, according to pathogen and Multinational Association for Supportive Care in Cancer (MASCC) score.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No (%) of patients, by class of pathogen and risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram-negative</td>
</tr>
<tr>
<td></td>
<td>Low risk (n = 13)</td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
</tr>
<tr>
<td>Without complications</td>
<td></td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Low-risk was defined as an MASCC score of ≥21; high-risk was defined as a score of <21. *P* < .001 for comparison of the death rates among low-risk versus high-risk patients with bacteremia due to gram-negative pathogen. *P* < .001 for comparison of the death rates among high-risk patients with bacteremia due to gram-negative pathogen versus high-risk patients with bacteremia due to gram-positive pathogen.
Neutropenic fever
Empiric antibiotic Therapy

• Duration of antibiotic therapy:

• In those with documented infection, it will depend on the organism and site of infection. Continue for at least the duration of neutropenia (until ANC >500) or no longer clinically necessary

• Unexplained fever – continue initial regimen if stable until there are signs of marrow recovery (ANC > 500)

• Recent reports from Europe suggest discontinuation of empiric antibiotics in pts with resolution of fever and any signs or symptoms of infection
Central venous catheter tunnel infections
Indwelling Catheters
Catheter related infection: Indications for CVC removal

- **Exit site infection**
  - Usually can be treated without removing catheter.
- **Tunnel infection**
  - Will almost always require removal.
- **Catheter-associated sepsis**
  - Should be removed if the following organisms are isolated:
    - *Candida* sp., *Fusarium* sp.
    - *Corynebacterium JK, Bacillus species*
    - Mycobacterium (esp. *M. fortuitum, M. chelonae*), *Pseudomonas aeruginosa*
    - *Staphylococcus aureus* (including MRSA)
    - Enterococci (esp. VRE)
- Or pt has one of the following:
  - Septic thrombophlebitis
  - Septic emboli
  - Persistent bacteremia or fevers
  - Endocarditis
  - Pocket-space abscess (in PAC pocket)
Catheter Related Infection

• Duration of antibiotics:

• Uncomplicated infection: 14 days

• Complicated infections such as
  • deep tissue infection
  • endocarditis
  • septic emboli
  • septic thrombophlebitis, or
  • persistent fungemia or bacteremia occurring >72 hr after removal of catheter: 4-6 weeks
Non-Infectious Causes for Fever

- Acalculous cholecystitis
- Adrenal Insufficiency
- Blood product transfusion related
- Cytokine mediated
- Drug fever
- Fibroproliferative phase of ARDS
- Gout

- CCM 2008:36:1330-49

- Serotonin syndrome – mydriasis, diaphoresis, autonomic instability, agitation, clonus, hyperreflexia
Gastrointestinal infections

• Neutropenic enterocolitis or typhlitis
• Clostridium difficile colitis
• Viral infections: CMV colitis (has been observed with TKI’s such as Dasatinib), consider norovirus/rotavirus in unabated diarrhea
• Protozoal infections: in the appropriate epidemiologic setting

• Stool test – PCR based (biofire panel), antigen based or cytotoxin assay
• C. difficile: first line – oral vancomycin
Typhlitis with Clostridial Myonecrosis
Case

- 62 year old male with h/o NHL with prolonged neutropenia after targeted chemotherapy, receiving Voriconazole 200 mg BID, admitted with fever to 102 F, cough with right sided chest discomfort, and hemoptysis. He had a CT scan of the chest that revealed a consolidation in right lung. Bronchoscopy was non-diagnostic, and had negative fungal serologic markers (serum and BAL fluid). Microbiologic evaluation was negative. He continues to spike on Meropenem.

- Next step:
  1. CT guided biopsy
  2. Empiric antifungal therapy with Echinocandin
  3. Empiric therapy with lipid or liposomal amphotericin
  4. Posaconazole
Case continued

• Patient was continued on Voriconazole and biopsy held due to severe thrombocytopenia. Patient had low grade intermittent fever on therapy. Vancomycin was added. CT scan done 10 days later shows increase in size of the infiltrate.

• Next Step:
  – 1. CT guided biopsy of the mass
  – 2. Repeat BAL
  – 3. Change Voriconazole to liposomal amphotericin (and since 5/2015 – Isavuconazole)
  – 4. Add Gentamicin
Imaging and pathology
Case

- 45 year male with refractory AML with profound neutropenia after an experimental clinical trial for months. He has been on posaconazole prophylaxis 300 mg once daily, levaquin 500 mg once daily, protonix 40 mg once daily, metoprolol 25 mg QD.
- He reports injury to left shin, and subsequently developed a painful lesions on left thigh and over next 7 days on arms and face. He has been having fever for 7 days.
- Apart from skin lesions and fever he denies of any other symptoms
Epidemiology of IFI and troubling trends

- Invasive aspergillosis most common (ahead of *Candida* spp.)
- Breakthrough infections with mucormycosis and uncommon molds in those on triazole prophylaxis
- Azole resistant aspergillosis – in context of azole prophylaxis and agricultural use
- Echinocandin resistance in *C. glabrata* and break through infection with *Trichosporon* spp., and mucormycosis
- Emergence of uncommon mold such as *Fusarium* spp.

Lancet Infect Dis. 2017;17(12)
J Infect Dis. 2017;216:53:s436-44
Azole Resistance through TR34/L98H or TR46/Y121F/T289A mutations

Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al).

Diagnostic work up

- Depends on the suspected site of infection
- Sino-pulmonary:
  - Sputum – usually not present during neutropenic phase
  - Imaging
  - Bronchoscopy with bronchoscopic alveolar lavage
  - Biopsy – CT guided transthoracic needle biopsy, and if non-diagnostic may require open lung biopsy
  - Sinus biopsy (not a swab)

- Other sites: CNS, visceral organs, osteoarticular
Diagnostic testing for IFI

- Aspergillus galactomannan (serum/ BAL fluid/ CSF) – limitation is false negative test in patients on anti-mold prophylaxis

- Beta 1, 3 D-glucan test (serum/ CSF) – moderate sensitivity/ poor specificity. High false + in patients on dialysis, post-operative, gut mucositis, use of IVIg in preceding 4 weeks.

- Pneumocystis: induced sputum or BAL for DFA/ cytology or PCR

- Serum cryptococcal antigen, Histoplasma antigen and others based on epidemiologic exposure history

- Certain molds grow on blood culture – fusarium, scedosporium and acremonium

- Imaging: lung – nodular, patchy to interstitial infiltrates, sinusitis, brain lesions, etc.

- Biopsy: skin lesions, lung infiltrate, or lesions in other organs
Diffuse infiltrates/Nodular lesion
Invasive Fungal Sinusitis
Fungal Lesions

1. Acremonium
2. Mucor
3 & 4. Fusarium
Antifungal agents

- **POLYENES** - Inserts into fungal cytoplasmic membrane by binding to sterols (ergosterol) increased membrane permeability. Fungicidal
  - Amphotericin B

- **AZOLES** - Inhibits C-14α demethylation of lanosterol by binding to one of the cytochrome P-450 enzymes leading to accumulation of C-14α methylsterols and reduced ergosterol (essential for fungal cytoplasmic membrane). Fungistatic.
  - Isavuconazole, Voriconazole, Fluconazole, Itraconazole

- **NUCLEOSIDE ANALOG** - Inhibitor of thymidylate synthetase which interferes with DNA synthesis. Fungicidal.
  - Flucytosine

- **ECHINOCANDINS** - Inhibits 1,3-β-D-glucan synthase, an enzyme essential for cell wall synthesis. Fungicidal to yeasts; fungistatic for molds
  - Caspofungin, Micafungin and Anidulafungin
Antifungal Prophylaxis

• High risk:
  
  – Prophylaxis against Candida infections recommended such as HCT or those undergoing intensive chemotherapy for AML (Fluconazole, micafungin, posaconazole, voriconazole, and caspofungin)

  – Prophylaxis against invasive aspergillus infection with Posaconazole should be considered in select patients undergoing intensive chemotherapy for AML/ MDS in whom risk of IA without prophylaxis is high
Invasive Mold Infection Algorithm

Symptomatic Patient (i.e. cough, fever, pleuritic chest pain, sinus congestion or HA)

CT scan chest/sinuses

(+)

Isavuconazole or L-AmB and diagnostic workup

BAL, tissue, or sinus culture and cytology KOH

(-)

Septate, acute branching*

Continue ISA or AmB

Can change to VCZ

Broad aseptate, right angle branching

Continue L-AmB or Isavuconazole

GM serology

(+)*

Triazole

Continue Isa or AmB

(-)

PCZ, posaconazole; VCZ, voriconazole

*Combination therapy suggested
Invasive Candidiasis Algorithm

Febrile Immunocompromised Host

Blood Culture Yeast +

Hemodynamically Stable

Prior Prophylaxis?

No

Fluconazole

Yes

If Azole, use EC
If EC, use AmB

Hemodynamically Unstable

Prior Prophylaxis?

No

EC or AmB

Yes

If Azole, use EC
If EC, use AmB

EC: echinocandin, AmB: Amphotericin B
Isavuconazole vs Voriconazole in Invasive Aspergillosis

• Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Isavuconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
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• ITT Pop:

<table>
<thead>
<tr>
<th>N</th>
<th>258</th>
<th>258</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>48 (18.6%)</td>
<td>52 (20.2%)</td>
</tr>
</tbody>
</table>

• mITT Pop:

<table>
<thead>
<tr>
<th>N</th>
<th>143</th>
<th>149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success Rate</td>
<td>50 (35.0%)</td>
<td>47 (36.4%)</td>
</tr>
</tbody>
</table>

Isavuconazole vs Ampho B-Based Treatment of Mucormycosis

- **Endpoint**
  - Isavuconazole
  - Ampho B*

- **Mortality**
  - 7/21 (33.3%)
  - 13/33 (39.4%)

- **Success**
  - 6/19 (31.6%)

*matched controls from Fungiscope Registry

Role of Combination Therapy: Invasive Aspergillosis

- Generally reserved for mold infections in patients at highest risk for treatment failure

- Important that treatment is for PROVEN OR PROBABLE invasive fungal infection

- Bedside decision

- Consider toxicity and drug interactions

## Combination Antifungal Therapy for Invasive Aspergillosis

### Mortality

<table>
<thead>
<tr>
<th>Group</th>
<th>Monotherapy (Voriconazole)</th>
<th>Combination (Vori + Anidula)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 6-week mortality</td>
<td>39/142 (27.5%)</td>
<td>26/135 (19.3%)</td>
<td>0.087</td>
</tr>
<tr>
<td>Subgroup* 6-wk mortality</td>
<td>30/110 (27.3%)</td>
<td>17/108 (15.7%)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*IA diagnosis established by radiographic findings and maximum galactomannan positivity.

Combination Antifungal Therapy for Invasive Aspergillosis

Figure 1. (a) Kaplan-Meier survival curves for the overall modified intent-to-treat population (MITT) (circles represent censored data), and (b) overall mortality in the MITT population with p-value using mortality estimates adjusted for randomisation strata.

Figure 2. Outcomes in patients with probable invasive aspergillosis (IA), based on a positive bronchoalveolar lavage or serum galactomannan test. (a) Kaplan-Meier survival curves (circles represent censored data), (b) all-cause mortality rate at week 6 with p-value using mortality estimates adjusted for randomisation strata.
Treatment effect on follow up imaging

- Follow up imaging suggested no sooner than 2 weeks after initial imaging (unless interval worsening)
Pneumonia: antimicrobial therapy

- In neutropenic patient with first fever episode; therapy as for neutropenic fever is justified

- Empiric therapy should address typical/ atypical bacterial pathogens, and if indicated for MRSA, pseudomonas.

- Fungal pathogens: based on risk determination and type of fungus: Voriconazole vs. lipid or liposomal amphotericin B vs. Isavuconazole

- Pneumocystis: Bactrim (alternatives include mepron, clindamycin+primaquine, dapsone and pentamidine)

- Viral: Influenza: Oseltamivir or Zanamavir (with or without adamantanes), for HSV – acyclovir and CMV – ganciclovir or foscarnet
Viral Infections
Herpesvirus infections

- **Common characteristics:**
  - Almost universal acquisition prior to adulthood.
  - Lifelong latent infection (“latency”).
  - Reactivation occurs during immunosuppression.

- **Clinical syndromes:**
  - HSV: mucositis, cutaneous, esophagitis, pneumonitis, encephalitis, disseminated
  - CMV: Interstitial pneumonitis (IP), colitis, hepatitis, CNS involvement, retinitis
  - VZV: cutaneous (dermatomal), visceral, disseminated.
  - HHV-6: culture negative fever, encephalitis, hepatitis, pneumonitis. Uncommon in the non-HCT patients
Rash - VZV
HSV and VZV lesions

- HSV
- VZV
- Atypical VZV
- Atypical VZV
HSV/ VZV

- **HSV**: can occur with any of the regimens – neutropenia/ mucositis
  - Prophylaxis – Acyclovir or Valtrex
  - Treatment – higher doses of acyclovir, in situation of acyclovir resistant infection; foscarinet or cidofovir

- **VZV**: mostly in the context of cellular immune deficiency – more common in lymphoid malignancies/ myeloma (especially those treated with proteasome inhibitors)
  - Classic: dermatomal
  - Multi-dermatomal
  - Disseminated and in some dissemination to the visceral organs – high mortality

**Management:**
- Prophylaxis: Oral Valtrex/ acyclovir
- Treatment : in uncomplicated infection – oral Valtrex or acyclovir
- Intravenous in complicated cases and in those with ophthalmic or CNS involvement
- Vaccination: no data (except for after autologous HCT)
HBV

- Reactivation can lead to asymptomatic increase in LFT to fulminant liver failure
- Concern in those with carrier state or active infection
- Can occur even after a resolved infection (HBsAg neg, HBsAB total +, HBcAb + and PCR neg)
- Risk highest in patients with lymphoid malignancies (in the context of treatment with rituxan and similar therapies, ibrutinib and others)
- Hepatology or infectious disease consult
- Treatment: antiviral prophylaxis prior to start (or concurrent) of chemotherapy/SMKI/ICI
Community Respiratory Viruses

- Respiratory Syncitial Virus (RSV) – no role of Ribavirin
- Parainfluenza: no approved agents
- Influenza: Oseltamivir, Baloxavir (newest agent approved)
- Rhinovirus
- Human metapneumovirus
- Rhinovirus
- Adenovirus
- Coronavirus
Diagnosis

• Specimen: nasal wash, NP swab (lower yield), BAL, tracheal aspirate
  
  – RT-PCR (Biofire)

  – Fluorescent antigen detection-DFA (Influenza, RSV, PIV, Adenovirus)
Parasitic infections

- Screen for Strongyloides in persons from endemic areas – (especially in those with HTLV related lymphomas)
- Often eosinophilia is present (although this could be elevated with lymphoma)
- Stool screen or serology
Neurologic

• Meningitis: bacterial, fungal, bacterial, viral, non-infectious (NSAIDS, Bactrim related, etc.)

• Encephalitis: herpes viruses (HHV6, HSV, EBV, CMV), West Nile virus, Enteroviruses, JC virus related PML (reactivation with biologic agents, Rituxan)

• Brain abscess/ lesions: bacterial, fungal (mold, cryptococcus), Nocardia, AFB, etc.

• Diagnostic work-up: 1. Imaging: CT, MRI, 2. CSF analysis; cell count, protein, glucose, PCR – pathogen specific, cultures, 3. Brain biopsy; cultures, histology, may use universal PCR, 4. EEG
Conclusion

- Risk adapted antimicrobial prophylaxis
- Routine antibacterial prophylaxis with fluoroquinolone should be approached with caution – suggested for high risk pts only
- Antifungal prophylaxis – suggested for AML/MDS, ?pts on ibrutinib, ALL patients undergoing induction chemotherapy
- Antiviral prophylaxis: for HSV, VZV, those with HBV infection or past exposure
- Pneumocystis prophylaxis: recommended in patients receiving various Mab’s, T cell depleting regimens, SMKI’s, steroid use, and after induction chemotherapy
Acknowledgements

- City of Hope patients (and their families) and the organizing team (Steven T. Rosen, Larry Kwak, Amrita Krishnan, Guido Marcucci, Jasmine Zain & Dr. Stephen J. Forman)
3. Ito JI et al. Leuk & Lymphoma. 2010. 51 (9): 1623-1631