Causes of Death

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February, 2012
Overview

- Attribution of COD important for research purposes
- Frequently not correctly coded or completely reported
- Source of confusion
Causes of Death (COD)

Transplant can be lethal

Sometimes
100-day Mortality after Autologous Transplants, 2008-2009

- Early Disease
- Intermediate/Advance Disease
- Sensitive
- Resistant
- Unknown
- Other

Mortality, %

CIBMTR
100-day Mortality after HLA-identical Sibling Transplants, 2008-2009

Mortality, %

- Early Disease
- Intermediate Disease
- Advanced Disease
- Chronic Phase
- Accelerated Phase
- Blast Phase
- Other

Disease Types:
- AML
- ALL
- CML
- MDS/MPS
- Aplastic Anemia
- Immune Deficiency

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100-day Mortality after Unrelated Donor Transplants, 2008-2009

- Early Disease
- Intermediate Disease
- Advanced Disease
- Chronic Phase
- Accelerated Phase
- Blast Phase
- Other

Mortality, %

AML | ALL | CML | MDS/MPS | Aplastic Anemia | Immune Deficiency
Causes of Death after Transplants performed in 2008-2009

Unrelated Donor

- Primary Disease: 33%
- New Malignancy: 1%
- GVHD: 15%
- Infection: 16%
- Organ Failure: 6%
- Other: 29%

HLA-identical Sibling

- Primary Disease: 47%
- New Malignancy: 1%
- GVHD: 14%
- Infection: 12%
- Organ Failure: 4%
- Other: 21%

Autologous

- Primary Disease: 73%
- New Malignancy: 1%
- Infection: 8%
- Organ Failure: 2%
- Other: 16%
Probability of Survival after Allogeneic Transplants for SAA, 2000-2009
- By Donor Type and Age -

- ≤ 20y, Sibling Donor (N=1,191)
- > 20y, Sibling Donor (N=1,256)
- ≤ 20y, Unrelated Donor (N=574)
- > 20y, Unrelated Donor (N=550)

P < 0.0001
Why do we care about COD?

- Although the data is sometimes hard to capture, for some studies very valuable
- Example: GWAS study to evaluate genetic profiles that may contribute to non-relapse mortality after HCT
- If well-recorded, helps investigators understand distribution of non-relapse mortality after HCT
Take Home Points (I)

- Consider and report *all* causes and contributing causes of death
- Make best effort to report primary COD
- Read and interpret autopsy results
- Communicate and clarify with team leader/physicians
Take Home Points (II)

- *Cause* of death must occur before the death
- Recurrence need not be primary or *only* cause of death
- Think through the “chain” of events
- What are those ‘900’ numbers *really* for?
Common “Myth” regarding reporting COD

- Presence of disease takes precedence as cause of death
  - Historically, this was common practice in HCT
- Transplant is evolving
- New environment of transplantation with reduced intensity conditioning and conversion of some diseases to chronic conditions
Underlying Cause of Death

- World Health Organization defines as “the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence, which produced fatal injury.”

- Best medical opinion
Consider and Report All Causes

- All causes/contributing causes are important:
  - Understand and analyze causes
  - Double-check with other parts of form
- If relapse occurs, report coincidental causes—infecction, organ failure, etc.
- If graft failure as COD, should report another cause as contributing, like infection
Communication with Team Leader

- They know the patient and course of illness
  - Provide information (in hand)
  - Guidance by CRP/DM
- Consistency in reporting within team
- Save time and effort
- CIBMTR can help, but handicapped by remoteness
- Examples
Interpret Autopsy Results (I)

- Correct patients?
- Read summary (compare to prior causes)
- Look for discussion regarding status of disease for which transplant performed:
  - relapse
  - marrow results for heme malignancies
  - disease sites for lymphoma
Interpret Autopsy Results (II)

- Look for findings in organs evaluated
- Review chimerism results, last disease assessment
- Discuss with team leader
  - Discrepancies
Autopsy Examples
How to Handle “New” Autopsy Finding

- EG, Cause of death (or contributing causes) may change after an autopsy is performed

- Example: Bone marrow at autopsy demonstrates recurrent CLL, not appreciated before death

- Record the recurrence as the date of death, and report as such
Example

- Young alloHCT recipient with AML, 90+% blasts in BM at HCT and history of leukemia cutis.
- Dies at day 15 after alloHCT
- Before death has fungal skin infection and requires dialysis for renal failure
- Reported COD by center is renal failure
Autopsy review

- Gross description with substantial skin sloughing, fungus reported by culture
- BM without blasts (NED), skin with reported Sweet Syndrome (neutrophilic dermatitis)
- Likely COD?
Do you like to avoid queries from CIBMTR about submitted data??

- Be thorough when completing the forms
  - Multiple fields across forms may be relevant
- Provide an autopsy report if one is available
  - Still need to do best to report appropriate COD, autopsy report helps us sort out the chain
“Timing” the Cause of Death

- Most causes of death precede the death!
- However, research data demonstrates many causes of death not further described in preceding sections of research inserts:
  - GVHD as a COD, but no GVHD information completed
  - Infection reported as COD, no infection listed on last research insert
  - Disease reported as COD, disease insert not completed or states CR as last known status
- Consistency is important
Report in All Appropriate Places on Insert

- 20-25% of patients with a secondary COD as IPN do not have an IPN section completed on a research insert, or have answered “no”

- 15% of patients with a research insert reporting secondary malignancy as the COD have an answer of “no” for the post-transplant malignancy

- Reg-research discrepancy may explain?
Report consistently

- If patient dies of “GVHD”
  - Should be noted as having GVHD on the CRF or the post-TED!
  - GVHD should be listed as “still occurring at time of last report”
  - Severity should be appropriate (grade I aGVHD of skin only??)
- If GVHD is mild and there is another contributing cause, consider whether the other is the primary COD
Other inconsistencies

- If patient dies of sepsis (organism identified), what COD to report?:
  - Organ failure or Infection?
  - Sepsis and MOF can be a COD, but the root cause is really infection, so should be reported as such, with the organism identified if on CRF track.
“Chain” of Events

- Think through the ‘chain’ or sequence of events leading to death

- Goal is to track back to the ‘root cause’ of death eg; organ failure should have a listed cause

- Try to identify which event(s) is/are a consequence and which event is/may be an underlying cause
Recurrence as Cause of Death

- Recurrence is common, may or may not be the primary causes of death:
  - acute leukemia
  - indolent lymphoma
  - accidental death
- Important to understand in the chain of events leading to death
- If present, should always be reported, regardless of role in death
Chain of Events (I)

- Graft failure
- Aspergillus infection of brain
Chain of Events (II)

- Acute myelogenous leukemia (relapse treated with DLI)
- Acute GVHD
- Pneumocystis pneumonia
Chain of Events (III)

- Patient dies with following conditions:
  - Recurrence of disease
  - Kidney failure and ARDS
  - Suspected sepsis syndrome
  - Organism not identified
Chain of Events (IV)

- Patient with lymphoma persistent, but not progressive
- Develops pneumonia
- Bacteremia
Examples

- Patient dies of pulmonary embolism

- Code as? :
  - Pulmonary toxicity
  - Vascular thromboembolic
Examples

- Patient celebrates 2 year anniversary from alloHCT for CML with African Safari. He had low level cytogenetic evidence of disease, on TKI.
- While taking a short hike, he stumbles upon a lion finishing a meal of fresh gazelle and experiences an MI with ventricular tachycardia and dies
- Cause of death?
Examples

- Allo BMT for AML, relapse 1 year later, treated with induction chemotherapy
- Dies 24 days into therapy, Candida and ARDS at autopsy, no evidence of AML
- Cause of death?
Examples

- Patient has AML, develops aGHVD, placed on immunosuppressives
- Subsequently develops EBV lymphoma and PCP pneumonia
- Cause of death?
What Do I Do with ‘900’ Numbers?

- 1-900-UNKNOWN
- 1-900-ASK CIBMTR
- Make attempt to place in appropriate organ or toxicity category
- Myocardial infarction is cardiac
- Stroke is neurologic
- Provide as much detail as required
One-year survival after myeloablative conditioning for acute leukemias in any remission phase, CML or MDS, age <50 years, by year of transplant and graft source, 1988-2009
More Help

- CIBMTR
- National Association of Medical Examiners www.thename.com
- National Center for Health Statistics www.cdc.gov/nchs
How do I know they are dead?

- Several national death index search engines associated with genealogy applications
  - Google “death index search”
- National death index searches that use the SSDI have an inherent delay of 18 mos to 2 years before reports are updated
Where do I put it?

SURVIVAL

2. Survival status at latest follow-up:
   - Alive
   - Dead
   Latest follow-up:
   YYY  MM  DD
   Date of death

5. Main cause of death (check only one main cause):
   - Relapse/Progression/Persistent disease
   - HSCT related causes (check as many as appropriate):
     - GVHD
     - Cardiac toxicity
     - Infection
     - Pulmonary toxicity
     - Rejection/Poor graft function
     - VOD
     - Other
     - New malignancy
     - Other
     - Unknown
4. Cause of death: 📚

Codes for cause of death are listed on the following page. If a code for “other, specify” (29, 39, 89, 109, 129, or 900) is entered, specify the cause in the space provided.

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<tr>
<td>10</td>
<td>Graft rejection or failure</td>
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<tr>
<td>20</td>
<td>Organism not identified</td>
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<tr>
<td>21</td>
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<td>Fungal</td>
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<tr>
<td>23</td>
<td>Viral</td>
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<td>Protozoal</td>
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<tr>
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<td>Other infection, specify</td>
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<tr>
<td>90</td>
<td>Secondary malignancy (new malignancy post-HSCT)</td>
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<tr>
<td>100</td>
<td>Hemorrhage, not otherwise specified</td>
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<tr>
<td>101</td>
<td>Pulmonary</td>
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<tr>
<td>102</td>
<td>Intracranial</td>
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<tr>
<td>103</td>
<td>Gastrointestinal</td>
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<td>Hemorrhagic cystitis</td>
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<td>109</td>
<td>Other hemorrhage, specify</td>
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<td>110</td>
<td>Accidental death</td>
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<td>Suicide</td>
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<td>Vascular, not otherwise specified</td>
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<td>121</td>
<td>Thromboembolic</td>
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<td>122</td>
<td>Disseminated intravascular coagulation (DIC)</td>
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<tr>
<td>123</td>
<td>Thrombotic thrombocytopenic purpura (HUS / TTP)</td>
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<td>129</td>
<td>Other vascular, specify</td>
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<td>140</td>
<td>Prior malignancy (prior to HSCT, and reported on baseline form at history of malignancy)</td>
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<tr>
<td>900</td>
<td>Other cause, specify</td>
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</table>

Infection (other than idiopathic pneumonia syndrome (IPS))

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<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>30</td>
<td>IPS, Idiopathic</td>
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<tr>
<td>31</td>
<td>IPS, viral, cytomegalovirus (CMV)</td>
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<tr>
<td>32</td>
<td>IPS, viral, other</td>
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<td>39</td>
<td>Other IPS, specify</td>
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</tbody>
</table>

Idiopathic pneumonia syndrome (IPS) / IPn

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>40</td>
<td>Adult Respiratory Distress Syndrome (ARDS) (other than IPS)</td>
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<tr>
<td>50</td>
<td>Acute GVHD</td>
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<tr>
<td>60</td>
<td>Chronic GVHD</td>
</tr>
</tbody>
</table>

Recurrence / persistence / progression of disease reported for first HSCT

<table>
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<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>70</td>
<td>Acute GVHD</td>
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</tbody>
</table>

Organ failure (not due to GVHD or infection)

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>80</td>
<td>Organ failure, not otherwise specified</td>
</tr>
<tr>
<td>81</td>
<td>Liver (not VOD)</td>
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<tr>
<td>82</td>
<td>Veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS)</td>
</tr>
<tr>
<td>83</td>
<td>Cardiac</td>
</tr>
<tr>
<td>84</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>85</td>
<td>Central nervous system (CNS)</td>
</tr>
<tr>
<td>86</td>
<td>Renal</td>
</tr>
<tr>
<td>87</td>
<td>Gastrointestinal (GI) (not liver)</td>
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<tr>
<td>88</td>
<td>Multiple organ failure, specify</td>
</tr>
<tr>
<td>89</td>
<td>Other organ failure, specify</td>
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</table>
Questions?