Cross Canada Rounds, October 2016

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Case

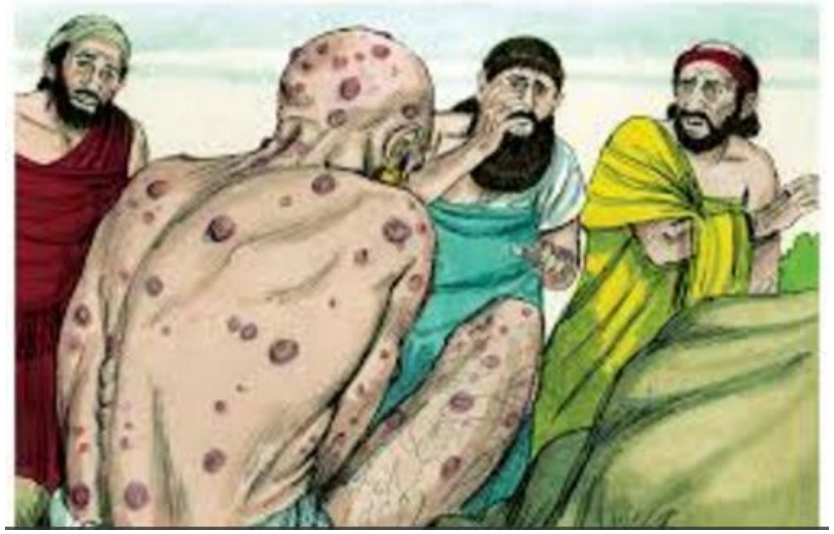
- 9 year old boy
- Day +33 BMT for Hyper IgE Syndrome
- New dry cough
- worsening hypoxemia
- diffuse infiltrates on x-ray

What differential diagnoses would you consider?

- **Infectious**
  - CMV, PJP, Respiratory viruses, Legionella spp, Mycoplasma pneumoniae, TB, NTM, fungal infections
- Acute GVHD
  - Less commonly directly affects the lung
- ARDS
- Drug reaction
- Congestive heart failure
- Diffuse alveolar hemorrhage
  - Less common in allogenic than autologous HSCT
- Idiopathic pneumonia syndrome

Small aside about HIES

- AKA Job's syndrome
- "So went Satan forth from the presence of the Lord and smote Job with sore boils from the sole of his foot unto his crown" (Job, II, 7)



http://distantshores.org/resources/illustrations/sweet-publishing/job

Experience of HSCT in HIES:

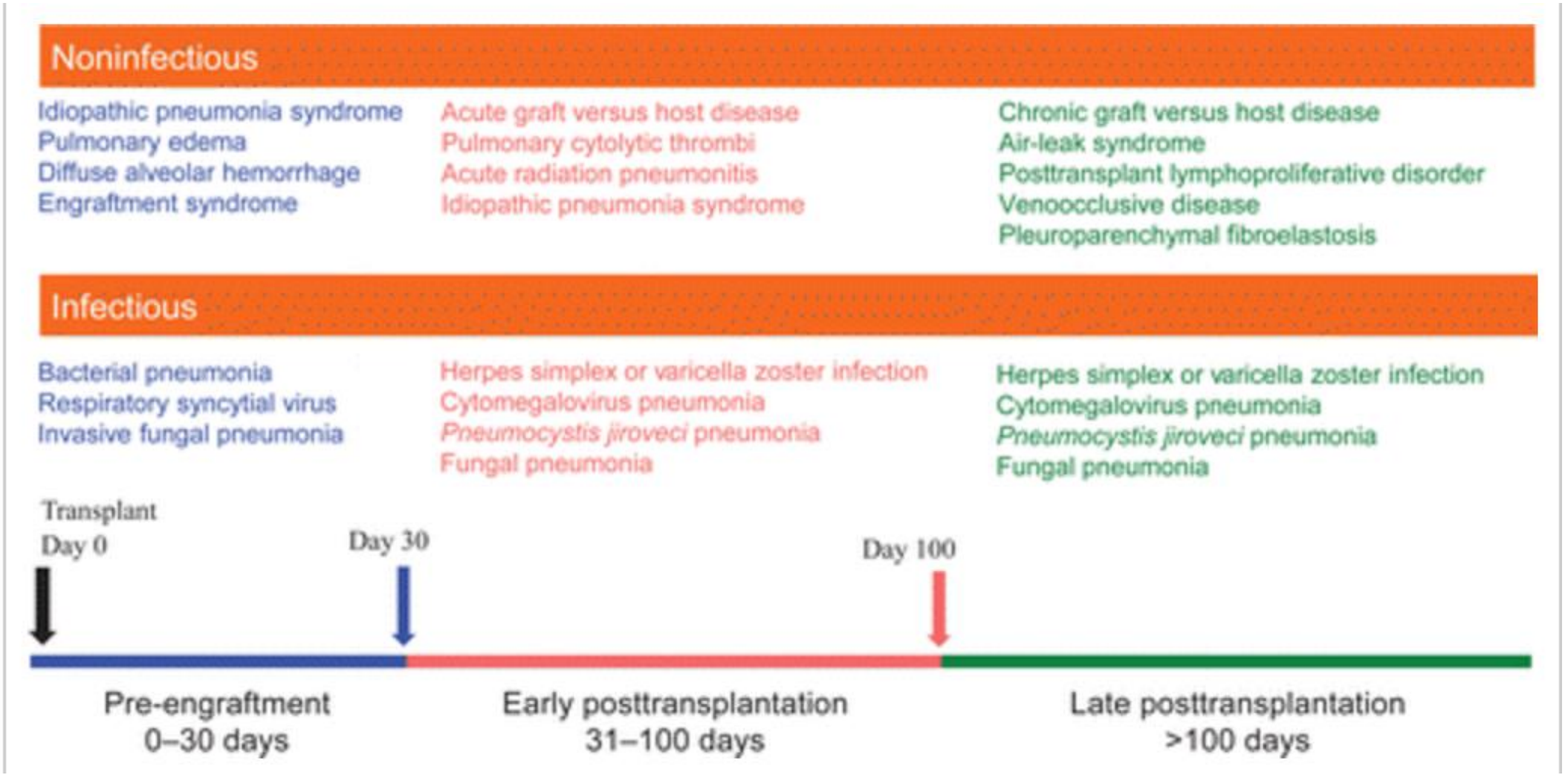
- Only reported in rare cases
- Results have been mixed

Table 1 Clinical features of patients with AD-HIES who underwent HSCT in the present and previous reports

	patient 1[7]	patient 2[5]	patient 3[6]	patient 4[6]	patient 5[8]	present case 1	present case 2
Age at HSCT (yr	46	7	15	16	14	8	22
Sex	M	F	M	M	F	F	M
Genotype	N.D.	N.D.	R382Q/W	R382W/W	V713L/W	V637M/W	T620S/W
Before HSCT							
HIES score	−	−	77	79	64	69	72
Skin abscesses	+	+	+	+	+	+	+
Pulmonary abnormalities	−	Pneumatocele	−	Bronchiectasis Pneumatocele	Pneumatocele	Pneumatocele Lobectomy	Pneumatocele Lobectomy
Indication for HSCT	NHL	Increasing severity of infection	NHL	NHL	Increasing severity of infection	Increasing severity of infection	Increasing severity of infection
Donor type	HLA-matched sibling	HLA-11/12 matched unrelated donor	HLA-matched sibling	HLA-matched sibling	Haploidentical father	HLA-matched unrelated	HLA-matched sibling
Source of HSC	PBSCT	BMT	BMT	BMT	T-cell depleted HSCT	BMT	BMT
Conditioning regimen	MAC	MAC	MAC	MAC	RIC	RIC	RIC
GVHD (acute/chronic)	IS teparing → +/−	−/+	−/−	−/−	−/−	+/−	−/−
Donor chimerism	N.D.	donor	donor	donor	donor	donor	mixed
IgE (IU/ml) (before/after)	8000/6.4	1500/2000	50000/107	20000/14	4300/25	3357/83	7706/1300
Follow-up period (years)	0.5	2	14	10	3.5	8	10
Current status	died from pulmonary complication of HSCT	staphylococcal and pseudomonal skin sepsis	non-immunologic manifestations resolved	well	infection-free	recurrent pulmonary aspergillosis	recurrent pneumatocele

N.D. Not determined, *NHL* non-Hodgkin lymphoma, *MAC* myeloablative conditioning regimen, *RIC* reduced intensity conditioning regimen, *PBSCT* peripheral blood stem cell transplantation, *BMT* bone marrow transplantation, *IS* immunosuppressants

Diagnosis: idiopathic pneumonia syndrome



Chi et al. 2013. Chest; 144 (6)

Idiopathic pneumonia syndrome

Epidemiology

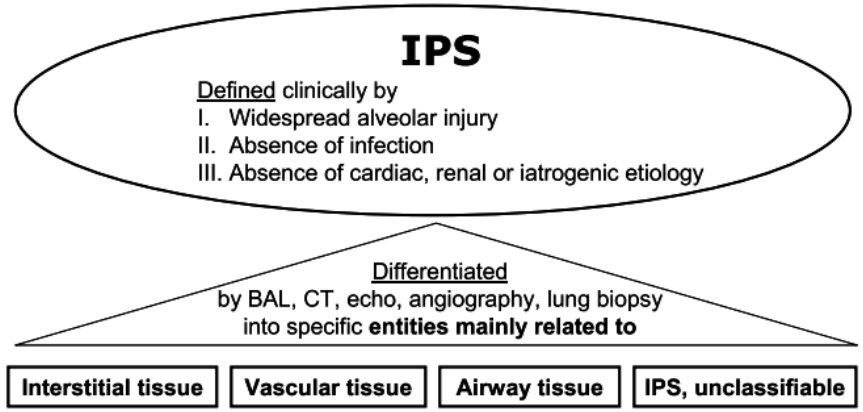
- Incidence in allogenic HSCT is 4-12%
- Generally occurs within 4 months from transplant
  - Median time of onset is 19 days post BMT
  - Less common in patients undergoing autologous transplantation
- 2/3 of patients develop respiratory failure requiring mechanical ventilation
- Mortality is extremely high – estimated between 50-75%
  - May be slightly lower in more recent studies

Definition

- **Evidence of widespread alveolar injury**
  - Multilobar infiltrates on CXR or CT chest
  - Symptoms and signs of pneumonia (cough, dyspnoea, tachypnoea, crackles)
  - Evidence of abnormal pulmonary physiology – increased A-a gradient, abnormal PFTs
- **Absence of infection based on**:
  - Alveolar lavage cultures negative for bacterial and non-bacterial microorganism
    - Including NTM, TB, Atypical organisms, Nocardia (by culture or PCR)
    - Viruses and fungi, including CMV and RSV
  - Consider testing for HMNV, rhinovirus, coronavirus and HHV6 by PCR
  - Serum and BAL galactomannan
  - Biopsy if patient stable enough (transbronchial or open)
- **Absence of cardiac dysfunction, acute renal failure, fluid overload**

New definition from ATS includes many disease entities (2011)

- ARDS
- Capillary leak syndrome
- Diffuse alveolar hemorrhage
- Peri-engraftment respiratory distress syndrome (PERDS)



Panoskaltsis-Mortari. AJRCCM. 2011; 183

Clinical presentation

- Dyspnoea
- Fever
- non-productive cough
- Increasing oxygen requirements
- Diffuse radiographic infiltrates
- Pathology: no definite histopathological diagnosis
  - DAD, other interstitial pneumonitis
  - Rarely obtained because patients unwell

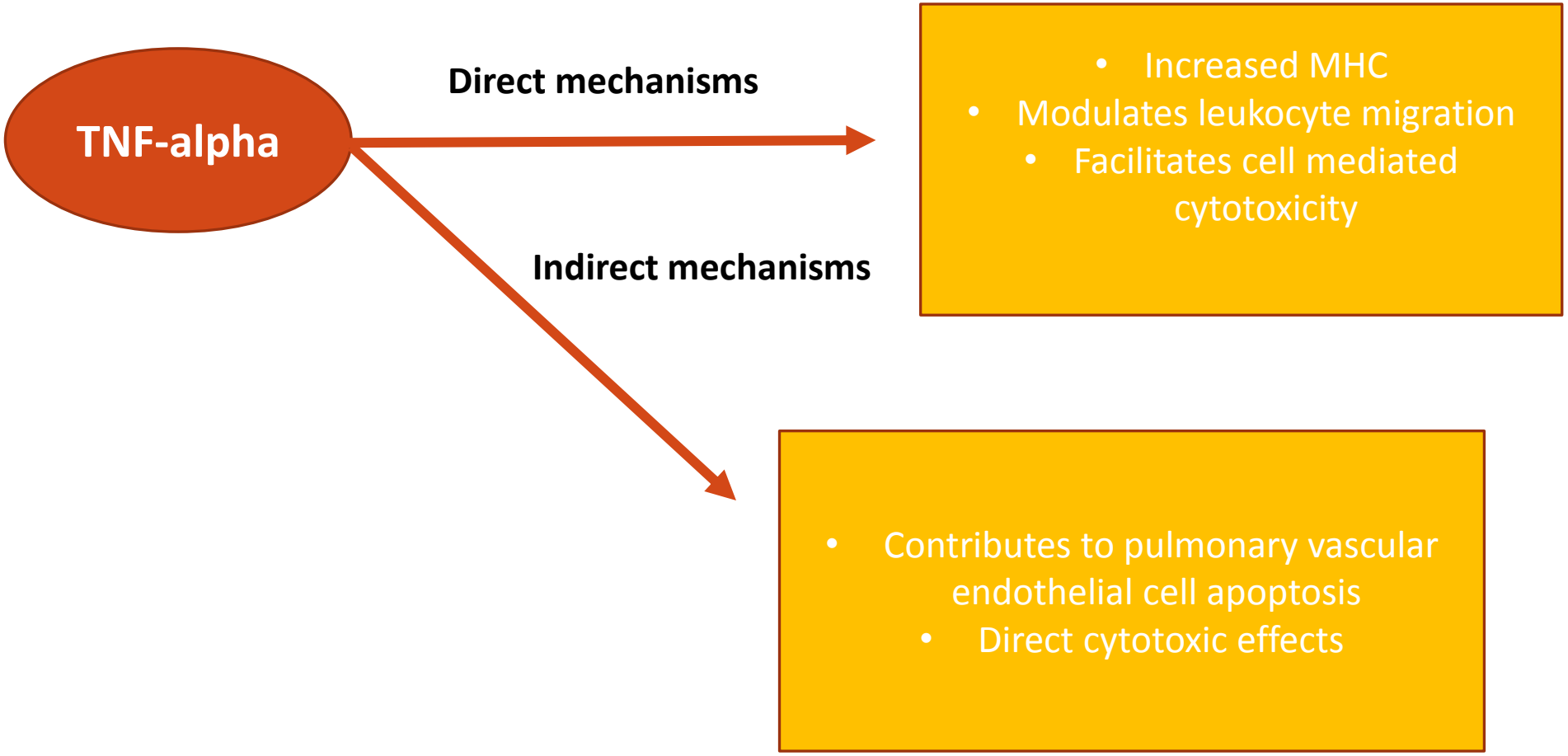
Proposed risk factors

Intensity of conditioning regimen
- non-myeloablative has lower incidence
- Associated with the use of busulfan

- Older age
- Use of total body irradiation
- Primary diagnosis other than leukemia
- Poor pre-transplantation performance status
- Presence of GVHD
  - Suggests a role for alloreactive T-cell injury
- ? Occult infection
- Previous hisotry viral pneumonitis – only identified in children

Chi et al. Chest. 2013; 144 (6)

Proposed pathophysiology



Panoskaltsis-Mortari et al. 2010. Am J Respir Crit Care Med; 183

Treatment

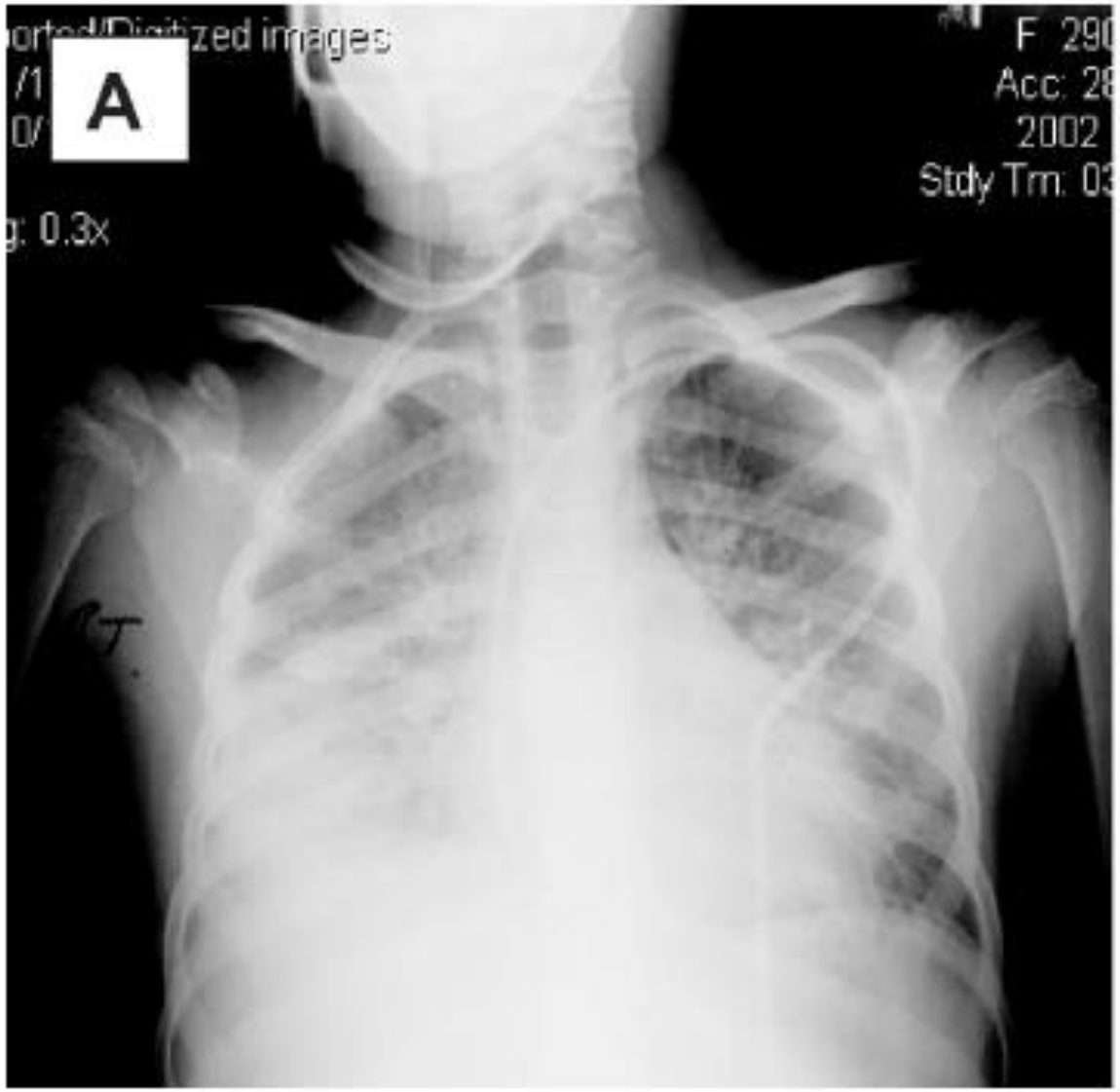
- Respiratory support
- Corticosteroids
  - No difference between high (> 4mg/kg) and low (</= 2 mg/kg) dose steroids (methylprednisolone equivalents)
- Prognosis remains poor despite supportive measures and glucocorticoids
  - in one series of 81 patients, mortality was 75% despite high dose glucocorticoid therapy

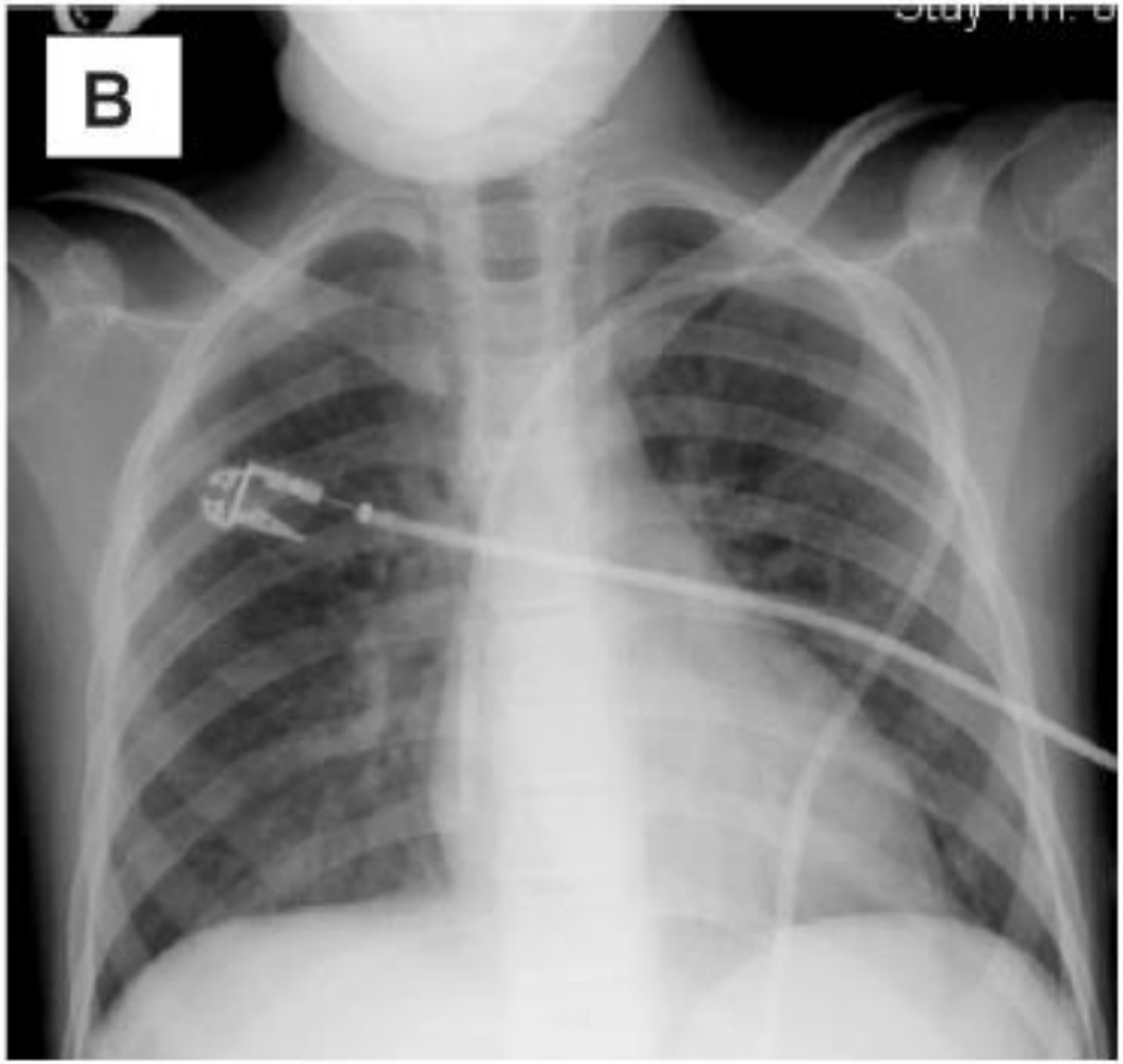
Fukida et al. Blood 2003;102

Use of Etanercept in IPS

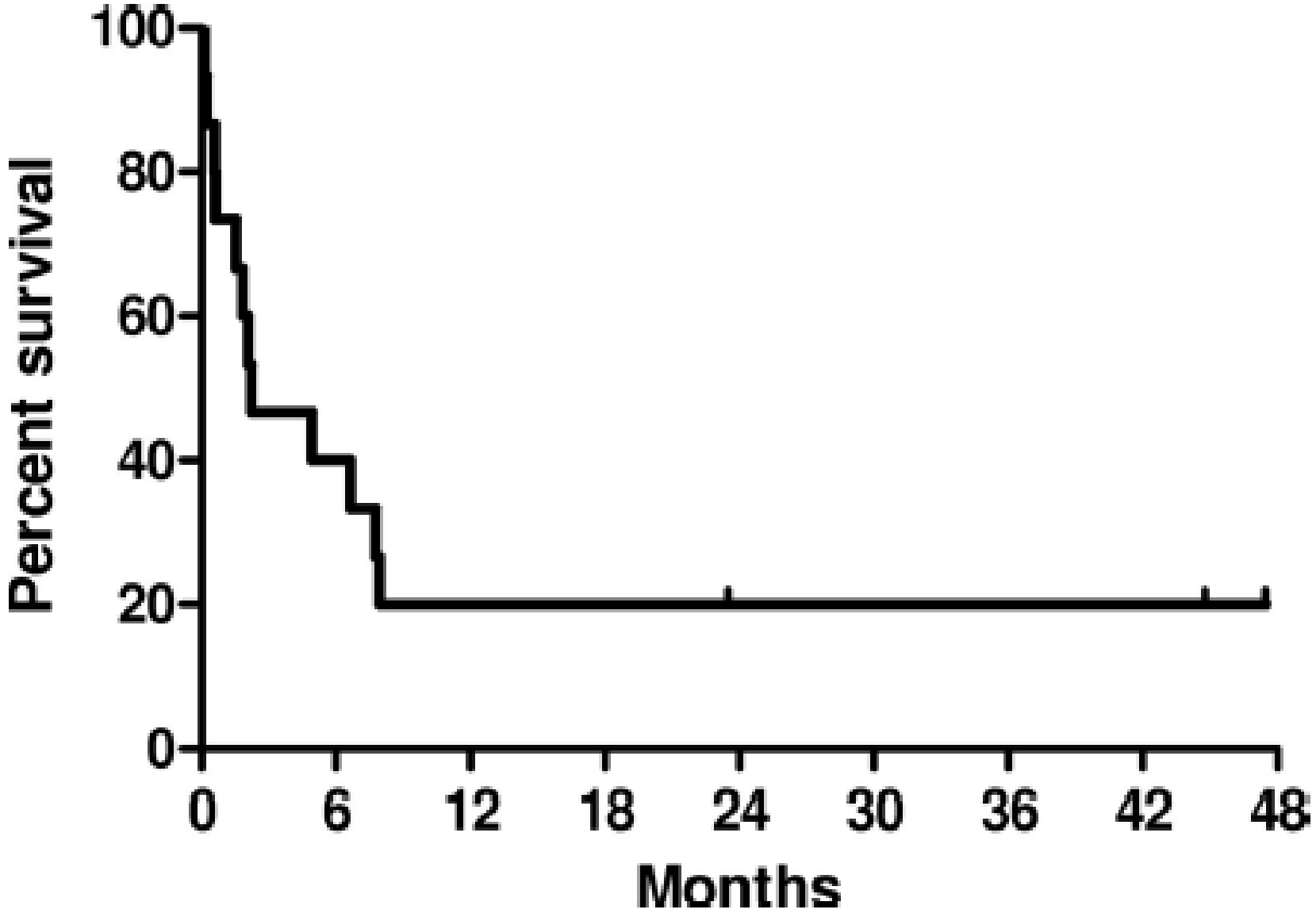
- 15 patients post allogenic stem cell transplant
  - Treated with corticosteroids and etanercept 0.4 mg/kg twice weekly x 8 doses
  - 10 patients had a response within 3-18 days
  - Survival rate at 28 days was 73%
  - Response defined as ability to discontinue all supplemental oxygen support within the study period (28 days)
  - Time to response was defined as first of 3 consecutive days with an SpO2 > 93%
- Patients who did not respond tended to be started later

Yanik et al. Blood. 2008; 112



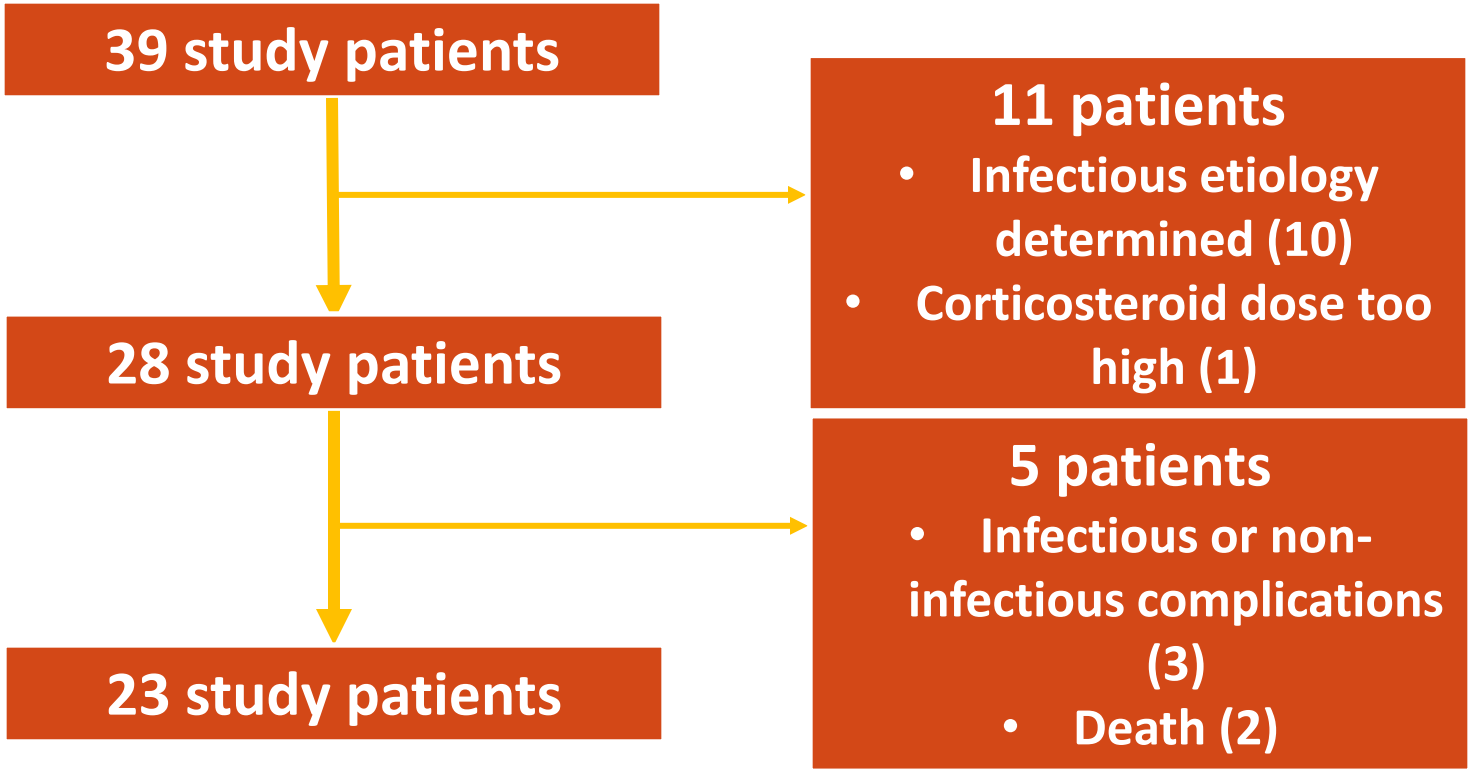


Yanik et al. Blood. 2008; 112



Yanik et al. Blood. 2008; 112

Use of Etanercept in Pediatric Patients



Yanik et al. Blood. 2015; 21

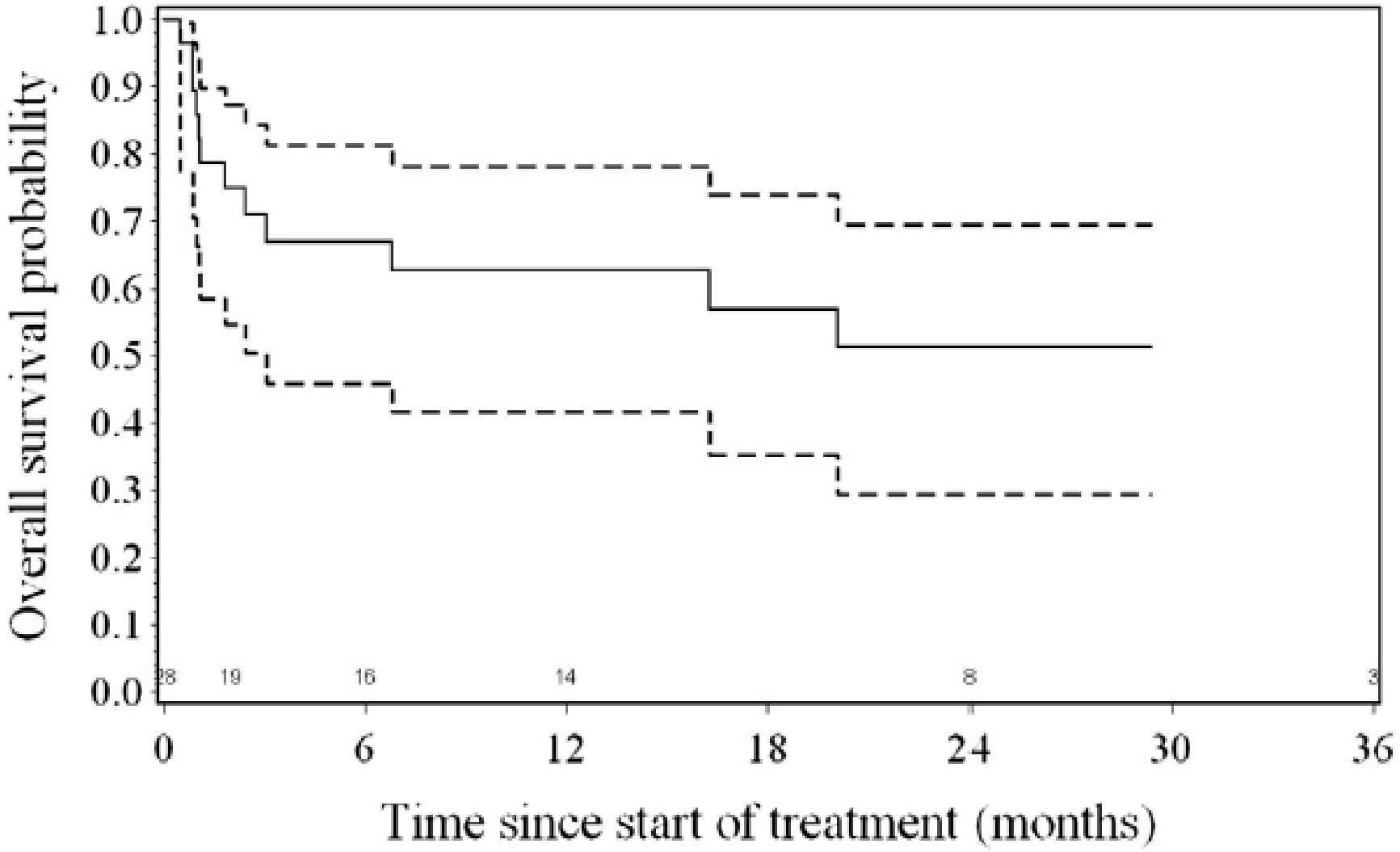
Use of Etanercept in Pediatric Patients

- Median duration of pre-therapy supplemental oxygen was 2 days, median FiO_2 0.45
  - 17 patients required mechanical ventilation at day 0
- Median time to onset of therapy was 20 days
- Primary endpoint = survival at 28 days plus discontinuation of oxygen > 72 hours

Yanik et al. Blood. 2015; 21

Results

- Early closure was recommended
  - Primary endpoint achieved in 20/28 patients
- Median time to complete response 10 days, median 3 doses
- 2 of 8 non-responders had clinical improvement
- Better response in patients who were less sick at enrollment
  - $FiO_2 < 0.45$
  - Off mechanical ventilation



Yanik et al. Blood. 2015; 21

Differences between Peds and Adult studies

- Source of bone marrow cells different
  - Most adults – peripheral cells
  - Most children – bone marrow or cord cells
- Adult trial underpowered
  - Stopped due to poor patient accrual
- More pediatric patients completed the 8 doses of Etanercept

Take home points

- Idiopathic pneumonia syndrome is a relatively common complication of bone marrow transplant
- Mortality is very high
- Early recognition is important for better outcomes
  - Patients started late did worse
  - Patients who were sicker did worse
- Etanercept may represent a new treatment modality in eligable patients

Thank you for your attention