



Pulmonary Complications of Bone Marrow Transplantation:

When infection isn't the answer

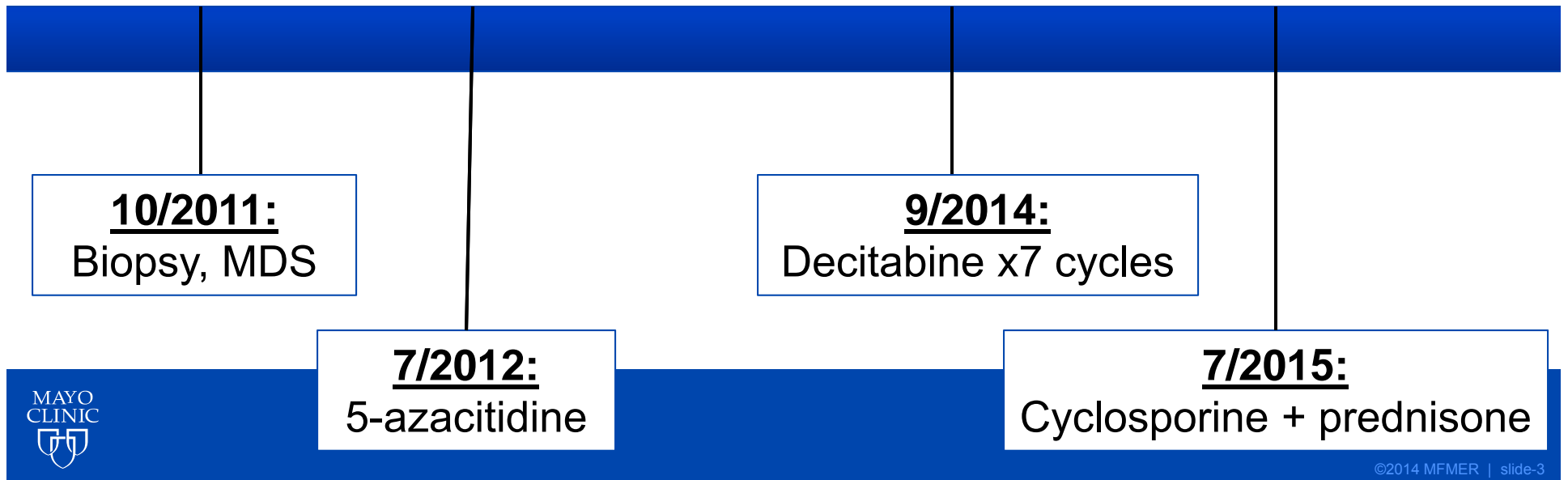
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Objectives

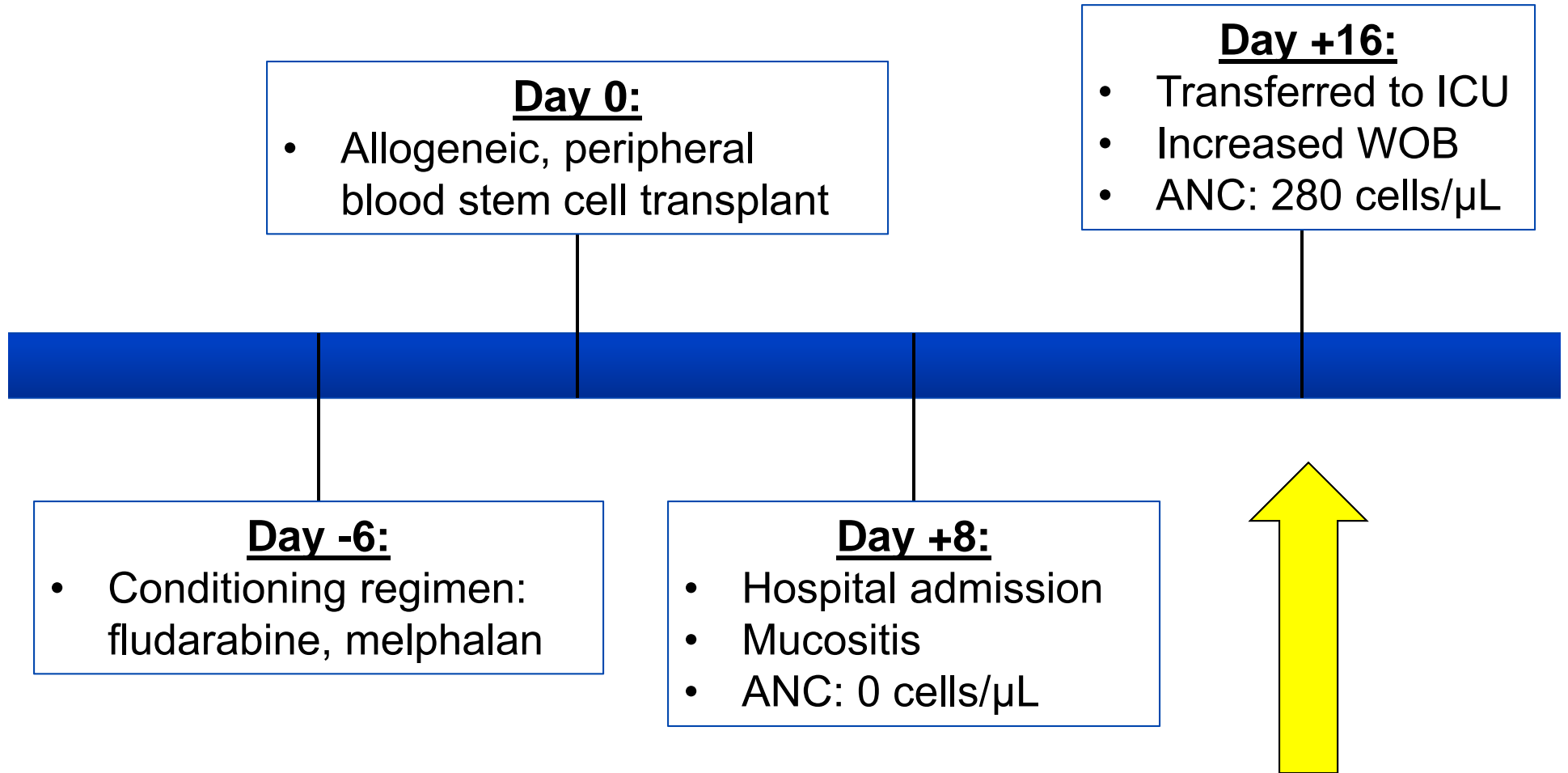
- List the American Thoracic Society diagnostic criteria for idiopathic pneumonia syndrome
- Identify key clinical differences between diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome, and non-cardiogenic capillary leak syndrome
- Determine the role of corticosteroid therapy in treatment of diffuse alveolar hemorrhage

65 y/o M with respiratory distress

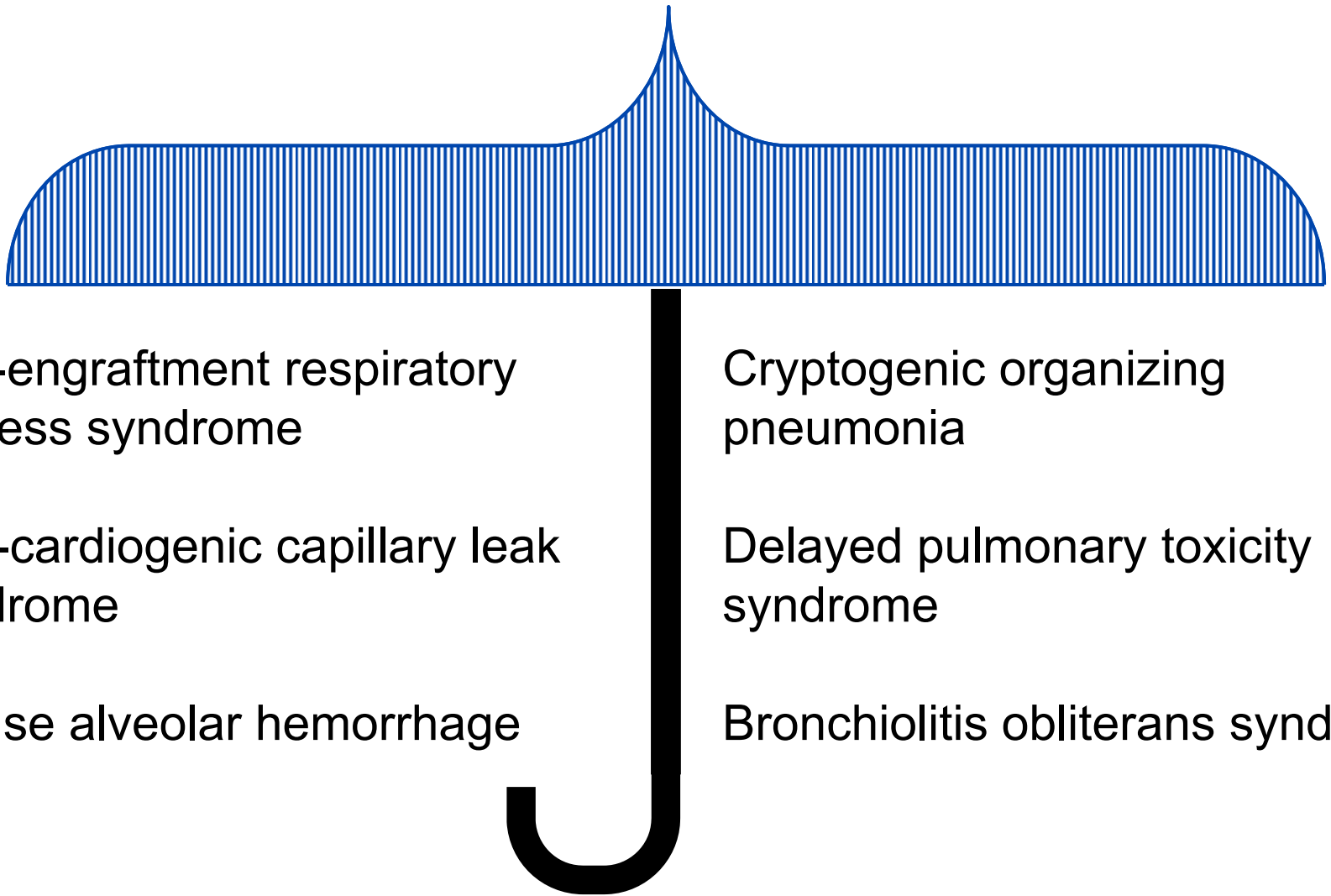
- Past Medical History:
 - Type II Diabetes Mellitus
 - Atrial fibrillation
 - Anxiety/depression
 - Myelodysplastic syndrome (MDS)



History of Present Illness



Idiopathic Pneumonia Syndrome



Peri-engraftment respiratory distress syndrome

Non-cardiogenic capillary leak syndrome

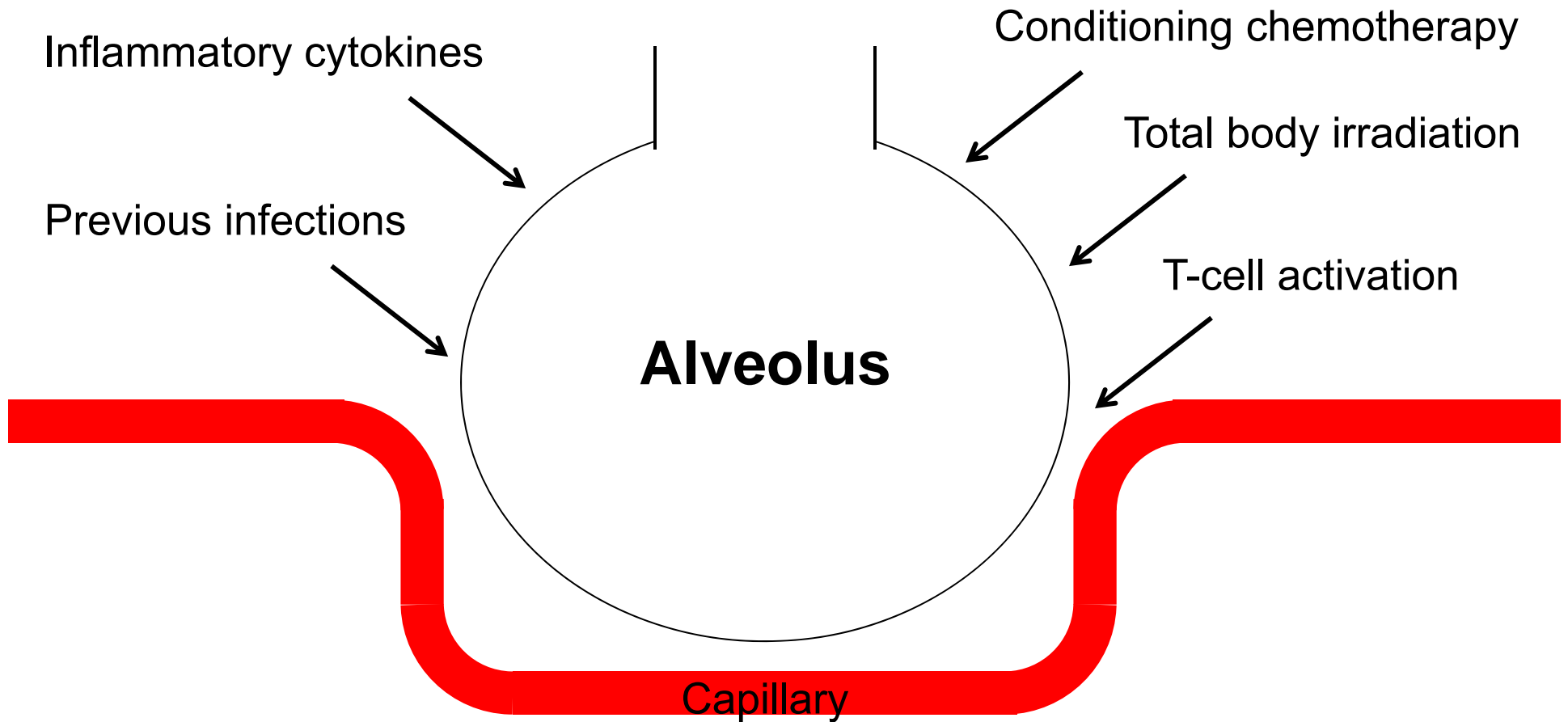
Diffuse alveolar hemorrhage

Cryptogenic organizing pneumonia

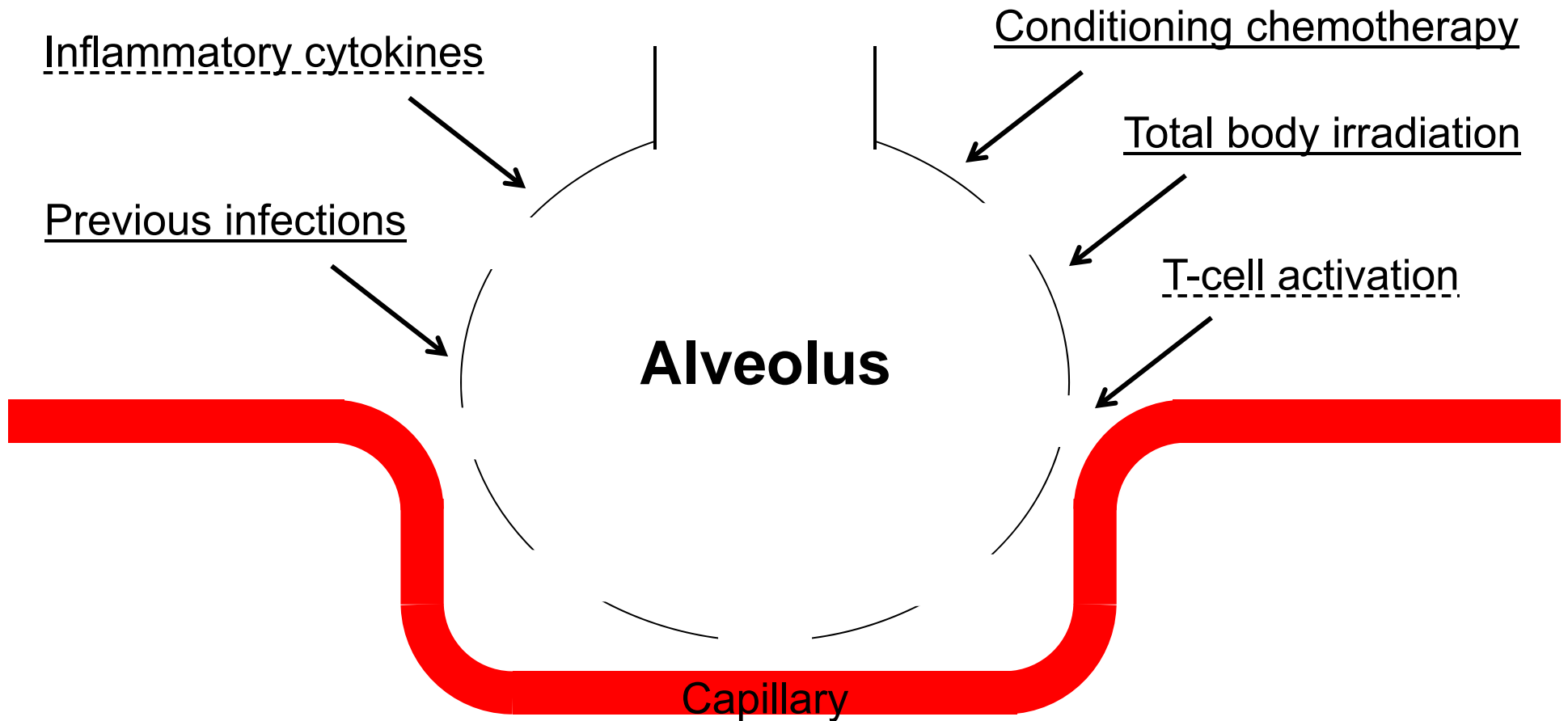
Delayed pulmonary toxicity syndrome

Bronchiolitis obliterans syndrome

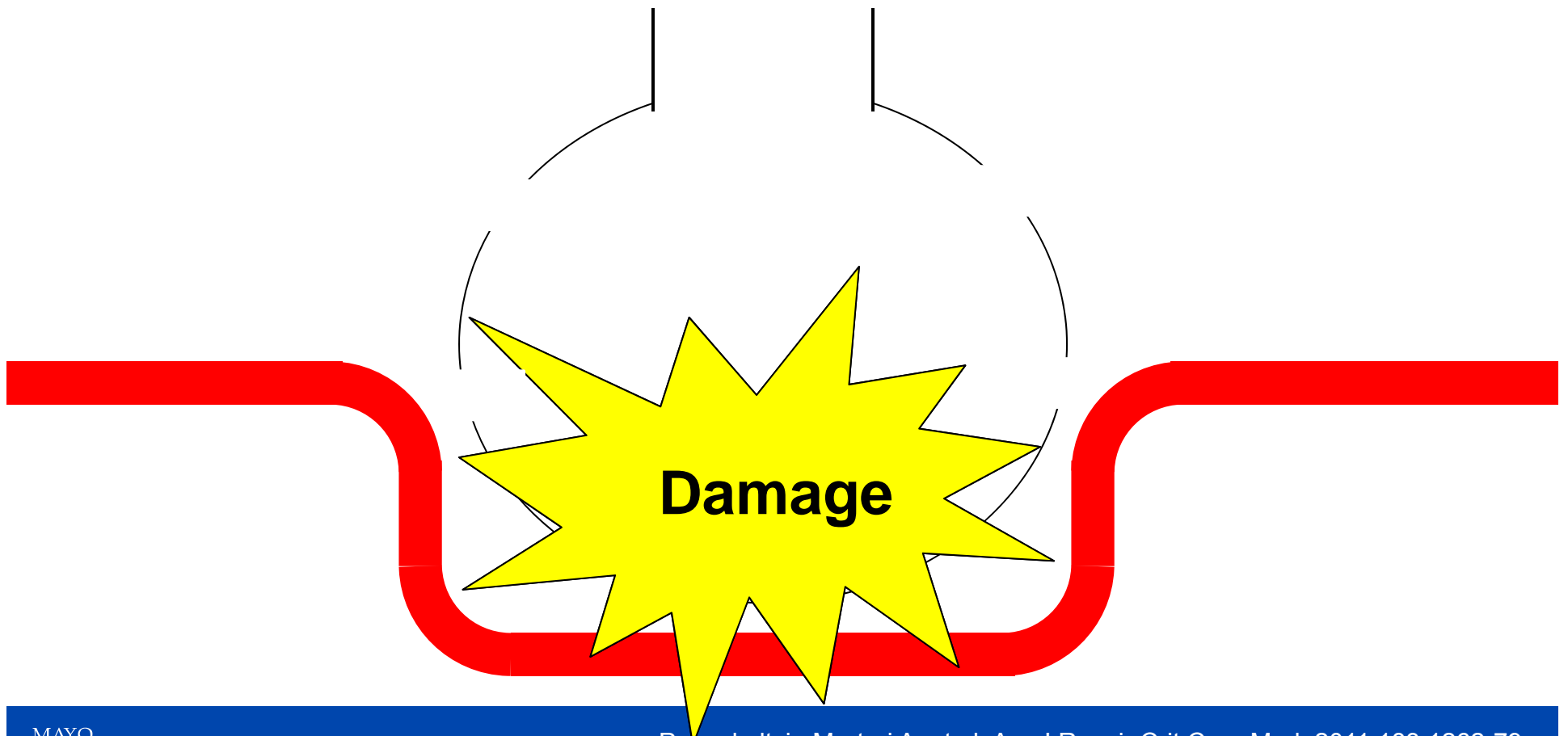
Pathophysiology



Pathophysiology, Example: DAH



Pathophysiology



IPS: American Thoracic Society Definition

1. Evidence of widespread alveolar injury
2. Absence of infection
3. Absence of cardiac dysfunction, acute decline in renal function as a sole explanation

Where do we go from here?

Back to the Case

- Vital signs
 - T 39.0°C
 - SaO₂: 88%
 - RR: 28
 - HR: 112 bpm
 - BP: 151/72 mmHg
- Physical exam: notable for bilateral lower extremity edema
- Blood cultures, tracheal secretions pending
- Chest x-ray

Bilateral, Multi-lobar Pulmonary Infiltrates



Back to the Case

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- Physical exam: notable for bilateral lower extremity edema
- Blood cultures, tracheal secretions pending
- Chest x-ray
- Considering CT chest, BAL

Respiratory distress in a BMT patient

Infection?

- Work-up ongoing
- Initiated on broad spectrum antibiotics

Timeline

Days 1-30:

- Diffuse alveolar hemorrhage
- Peri-engraftment respiratory distress syndrome
- Non-cardiogenic capillary leak syndrome

Days 100+:

- Delayed pulmonary toxicity syndrome
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia

DAH:

- Fever +/-
- Hemoptysis (~60%)
- Diagnosis: BAL
 - Progressively bloody return
 - >20% Hemosiderin-laden macrophages

Respiratory distress

PERDS:

- Fever
- Cutaneous rash
- Days surrounding engraftment

CLS:

- i.e., pulmonary edema
- Weight gain
- Peripheral edema
- Responsive to diuresis



Back to the Case: What's the Verdict?

- PERDS

- Previous day, first detectable ANC
- No rash on physical exam

- CLS

- Down 2kg from admission
- Peripheral edema on physical exam

- DAH

- Progressively bloody return on BAL
- 26% hemosiderin-laden macrophages

Diffuse Alveolar Hemorrhage

- Epidemiology:
 - Median onset day +19 (range, day +5-34)
 - 5-12% incidence in BMT population
 - Reported 21-day mortality 60-100%
- Risk factors:
 - Age >40 years
 - Full-intensity conditioning regimen, total body irradiation
 - Underlying acute leukemia or MDS
 - Type of transplant?
- PT/PTT, thrombocytopenia are NOT risk factors

Diffuse Alveolar Hemorrhage

Use of Corticosteroids in Bone Marrow Transplant Patients

Treatment Outline

1. Steroids
2. Steroids
3. Steroids

Diffuse Alveolar Hemorrhage

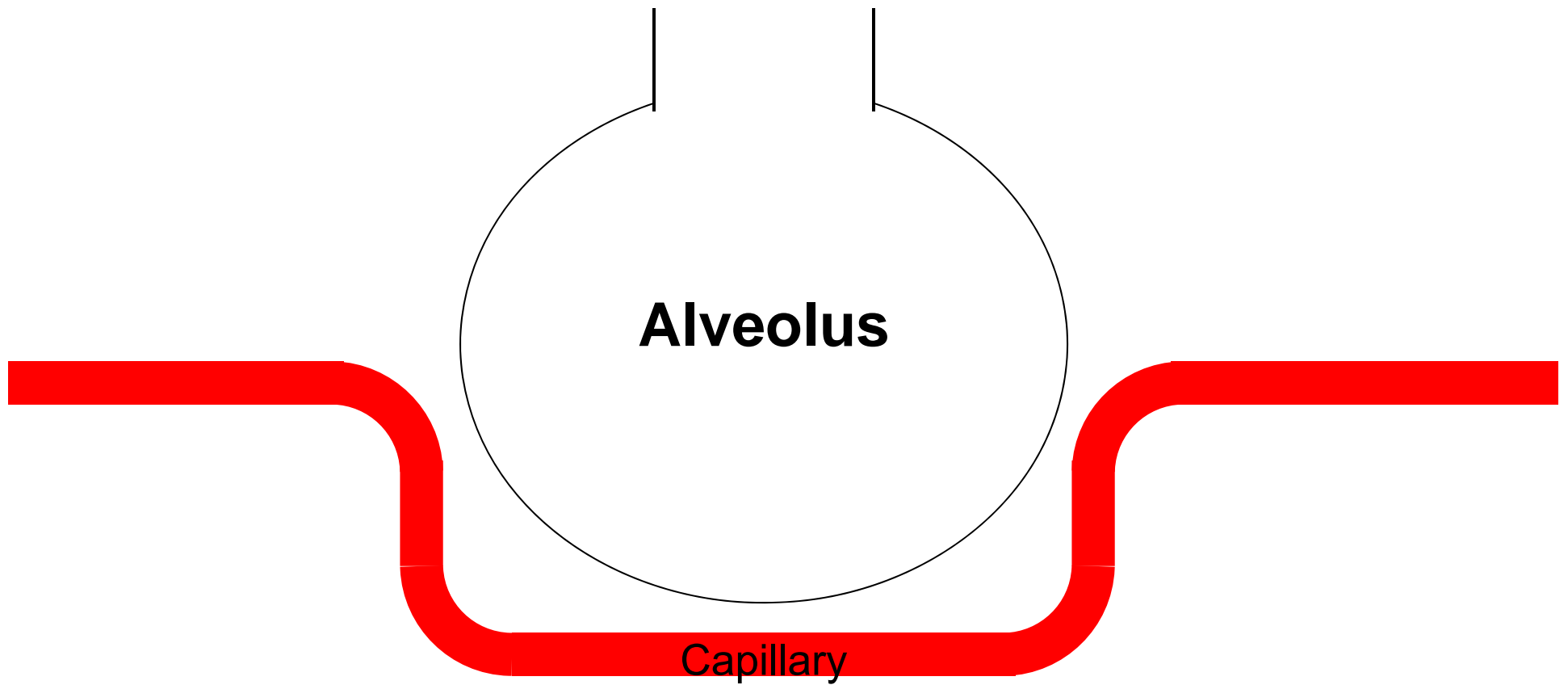
Immune Mediated

- ANCA-associated vasculitis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Antiphospholipid antibody syndrome

Non-Immune Mediated

- Infection
- Trauma
- Coagulopathy
- Left ventricular dysfunction

Pathophysiology



Treatment Outline

1. Steroids
2. Steroids
3. Steroids
4. Others?
 - Management of coagulopathy
 - rVIIa
 - Etanercept

Let's take a walk down memory lane...

Metcalfe, et al.

- Retrospective cohort, descriptive analysis
- Patient population
 - January 3, 1985 – November 9, 1990
 - 603 BMT patients reviewed for DAH diagnosis
- Treatment (N = 63; 3 groups)
 - No steroids
 - Low-dose: $\leq 30\text{mg}$ methylprednisolone or equivalent
 - High-dose: $> 30\text{mg}$ methylprednisolone or equivalent (125-250mg q6h)

Mortality

#1	No steroids (N = 12)	Low-dose (N = 10)	High-dose (N = 43)	P-value
Death prior to discharge	11	9	29	P < 0.05



90%

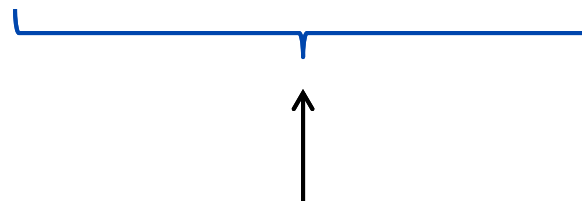


67%

Mortality

#1	No steroids (N = 12)	Low-dose (N = 10)	High-dose (N = 43)	P-value
Death prior to discharge	11	9	29	P < 0.05

#2	No steroids (N = 12)	Low-dose (N = 10)	High-dose (N = 43)	P-value
Death (at study conclusion?)	11	9	35	Not evaluated

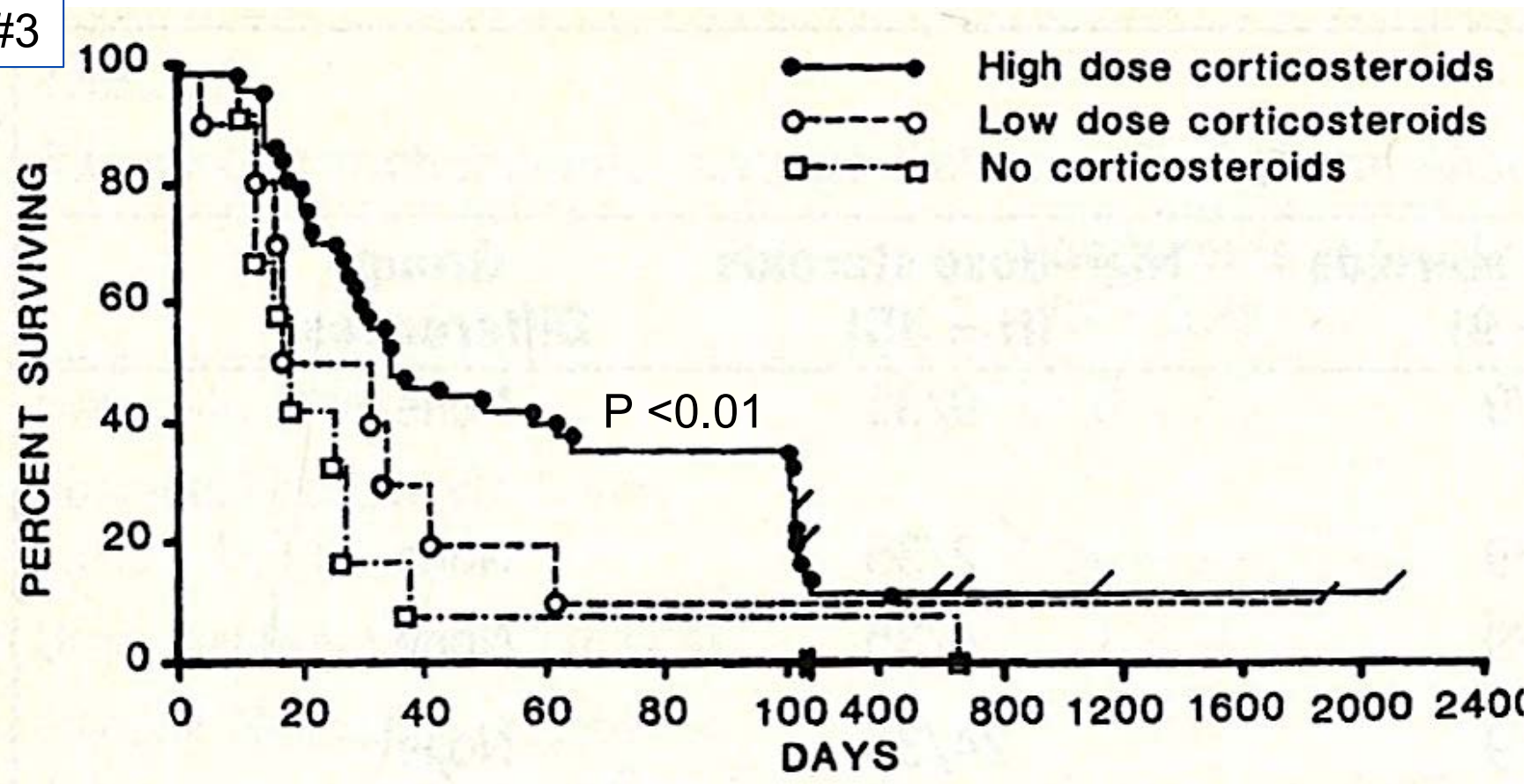


90%

81%

Mortality: Kaplan-Meier Curve

#3



Study Conclusions

- Three different representations of mortality
 - Somewhat contradicting, confusing
 - Statistical methods unclear
- Difficult to interpret
 - Only available data
 - Doesn't seem harmful? – ADE not well reported
 - Let's go with it...

Raptis, et al.

- Retrospective case-series
- Patient population
 - September 1993 – January 1998
 - 74 BMT patients evaluated, 4 with DAH
- Treatment

Case	#1	#2	#3	#4
Methylprednisolone regimen	1g daily	1g daily	2g x1, 1g daily	0.5g daily

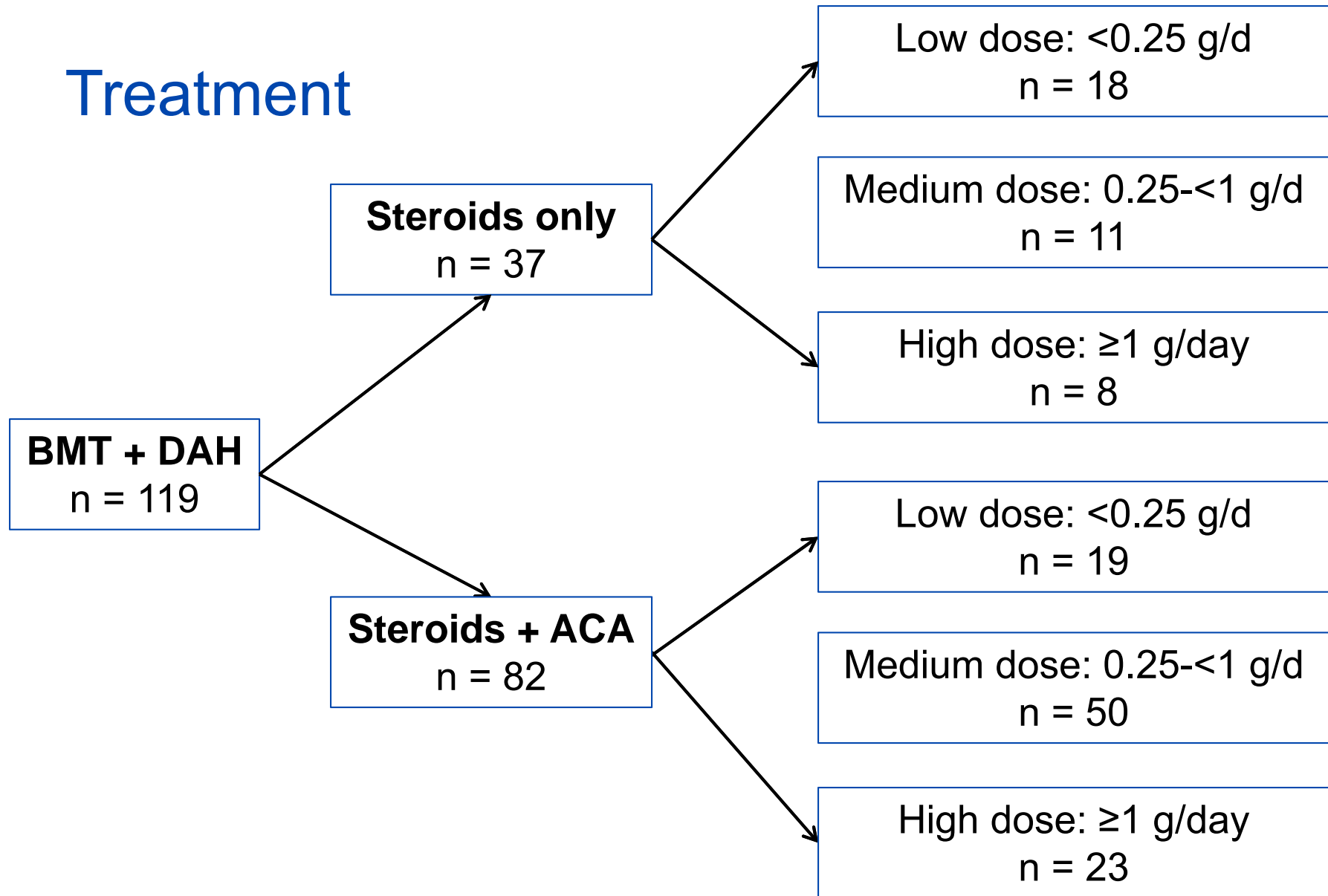
Study Conclusions

- 50% mortality due to DAH-related complications
- Authors' perspective:
 - DAH is life-threatening
 - Potentially reversible with high-dose steroid treatment
- Even smaller population
- Again, doesn't seem harmful?

Rathi, et al.

- Retrospective cohort, descriptive analysis
- Inclusion:
 - October 2007 – June 2011
 - BMT patients w/ DAH that received steroids +/- aminocaproic acid
- Exclusion:
 - Age <18 years
 - Steroids +/- aminocaproic acid for non-DAH illnesses

Treatment



Mortality

Outcomes	Low-dose	Medium-dose	High-dose	P-value
<i>Steroids only</i>	n = 18	n = 11	n = 23	
Mortality – n (%)				
ICU	4 (22.4)	7 (63.6)	6 (75)	0.02
Hospital	9 (50)	9 (81.8)	8 (100)	0.02
<i>Steroids + ACA</i>	n = 19	n = 40	n = 23	
Mortality – n (%)				
ICU	6 (31.6)	23 (57.5)	15 (65.2)	0.07
Hospital	13 (68.4)	33 (82.5)	18 (78.3)	0.45

*No difference when evaluating 30-d, 60-d, and 100-d mortality between steroid doses

A Closer Look...

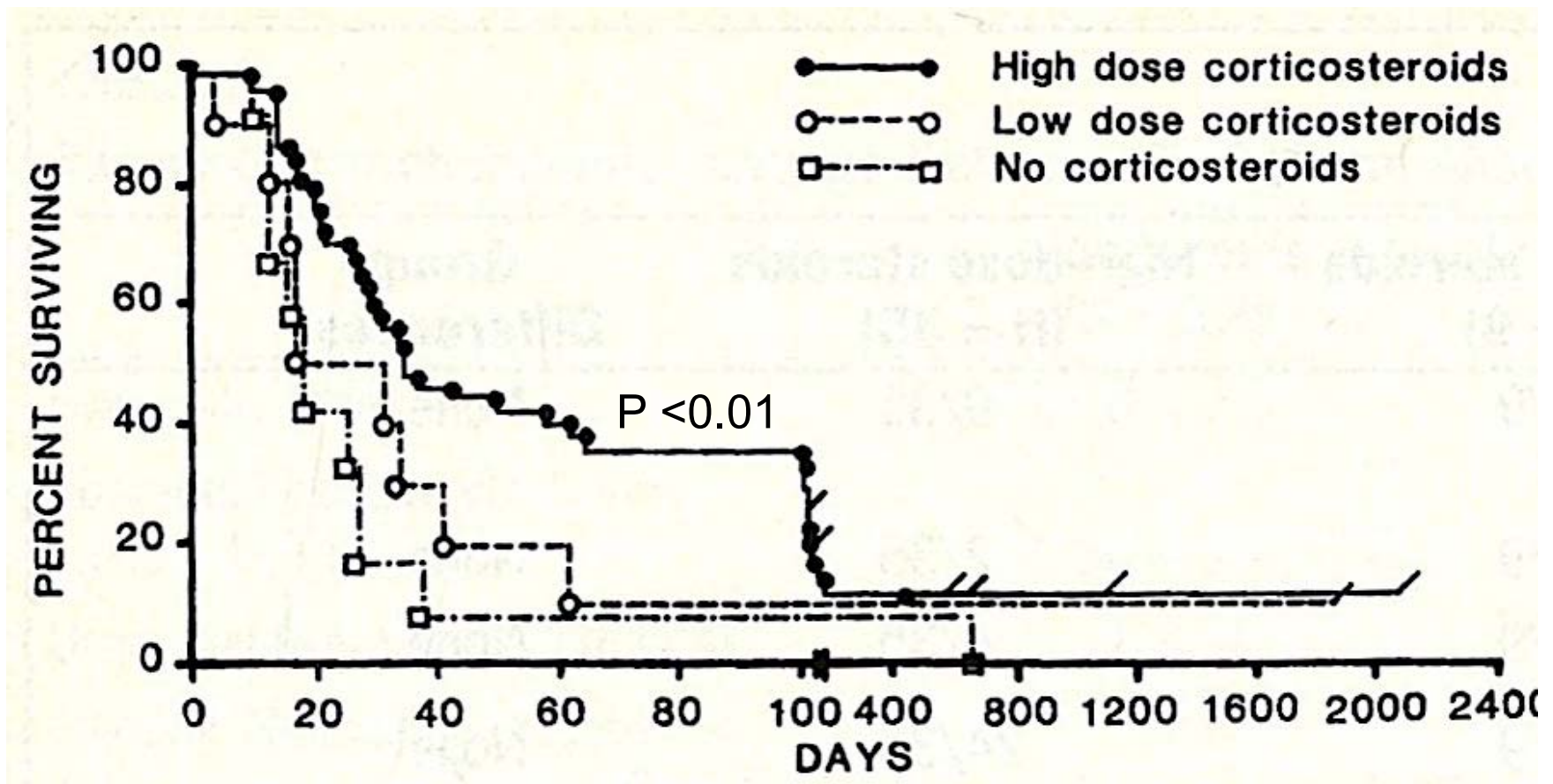
Variables	ICU Mortality			Hospital Mortality		
	OR	95% CI	P-value	OR	95% CI	P-value
Steroids + ACA vs. steroids alone	0.81	0.29-2.27	0.69	1.02	0.38-2.75	0.96
Medium-dose vs. low-dose steroids	3.93	1.31-11.77	0.01	2.91	1.03-8.21	0.04
High-dose vs. low-dose steroids	4.79	1.45-15.90	0.01	2.99	0.87-10.34	0.08

*No difference when evaluating 30-d, 60-d, and 100-d mortality between groups

Study Conclusions

- Strongest study published – both size, design
 - Limitations still exist
- No benefit conferred with ACA
 - Makes sense, DAH not thought to be a result of coagulopathy
- Medium-, high-dose steroids potentially harmful
- No benefit in any group beyond hospital stay

Mortality: Kaplan-Meier Curve



Study Conclusions

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Harmful Effects of Steroids

- Not well described in aforementioned literature
- Infection
- Blood glucose control
- Delirium
- Myopathy
- Concurrent use of paralytic

Clinical Practice

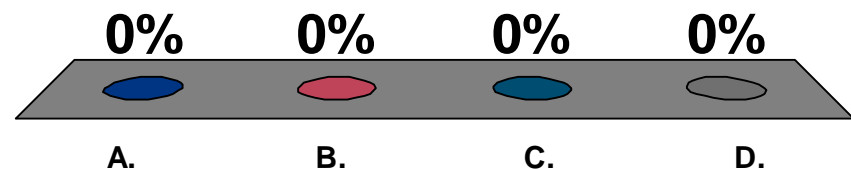
- Clinicians recognize high risk for mortality
- Data scarce, conflicting
- Mayo Clinic – Rochester practice
 - Supportive cares + steroids
 - Methylprednisolone 250mg q6h x4-5 days followed by taper
 - Monitor for ADE, check in the ‘con’ column for considering short course
- Should practice shift away from the use of high-dose steroids?

Conclusion

- ✓ List the American Thoracic Society diagnostic criteria for idiopathic pneumonia syndrome
- ✓ Identify key clinical differences between diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome, and non-cardiogenic capillary leak syndrome
- ✓ Determine the role of corticosteroid therapy in treatment of diffuse alveolar hemorrhage

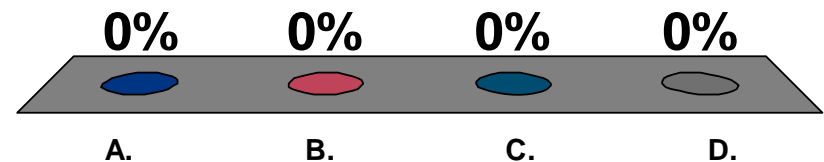
Which of the following is true?

- A. Use of aminocaproic acid for the treatment of DAH is the standard of care as it has been shown to significantly reduce 60-d mortality
- B. Mortality associated with DAH s/p BMT is reported to be <10%
- C. Treatment of DAH with steroids is controversial as studies have shown both positive and negative results
- D. None of the above are true



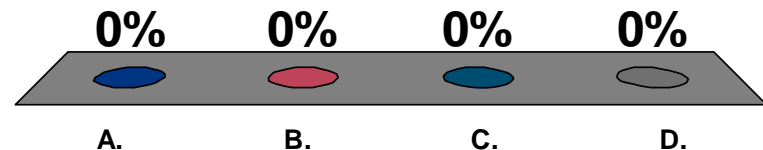
JW is a 38y/o M s/p allogeneic PBSCT in the setting of ALL. He presents to the ICU day +14 with acute respiratory distress, a fever, and a diffuse cutaneous rash. What non-infectious pulmonary complication s/p BMT might JW be experiencing?

- A. Diffuse alveolar hemorrhage
- B. Cryptogenic organizing pneumonia
- C. Non-cardiogenic capillary leak syndrome
- D. Peri-engraftment respiratory distress syndrome



RM is a 66 y/o F s/p autologous PBSCT in the setting of MDS. She presents to the ICU day +20 with acute respiratory distress and was found to have DAH requiring intubation and subsequent paralysis. Which of the following would be a reason to consider avoiding use of steroids?

- A. Advanced age
- B. Use of paralytic
- C. BMT associated DAH is a non-immune mediated process
- D. Timing of DAH onset





Questions & Discussion