

It's Easy to Spot When You Know What to Look for: Nonalcoholic Wernicke Encephalopathy In Medically Ill

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January 2021



Disclosure

Consulting agreement (Celgene USA)



Learning Objectives

Objective 1: Improved knowledge of clinical risk factors for neurologic thiamine deficiency

Objective 2: Improved recognition of neuroimaging clues to thiamine deficiency

Objective 3: Better understanding of the physiology of neurologic thiamine deficiency and supplementation

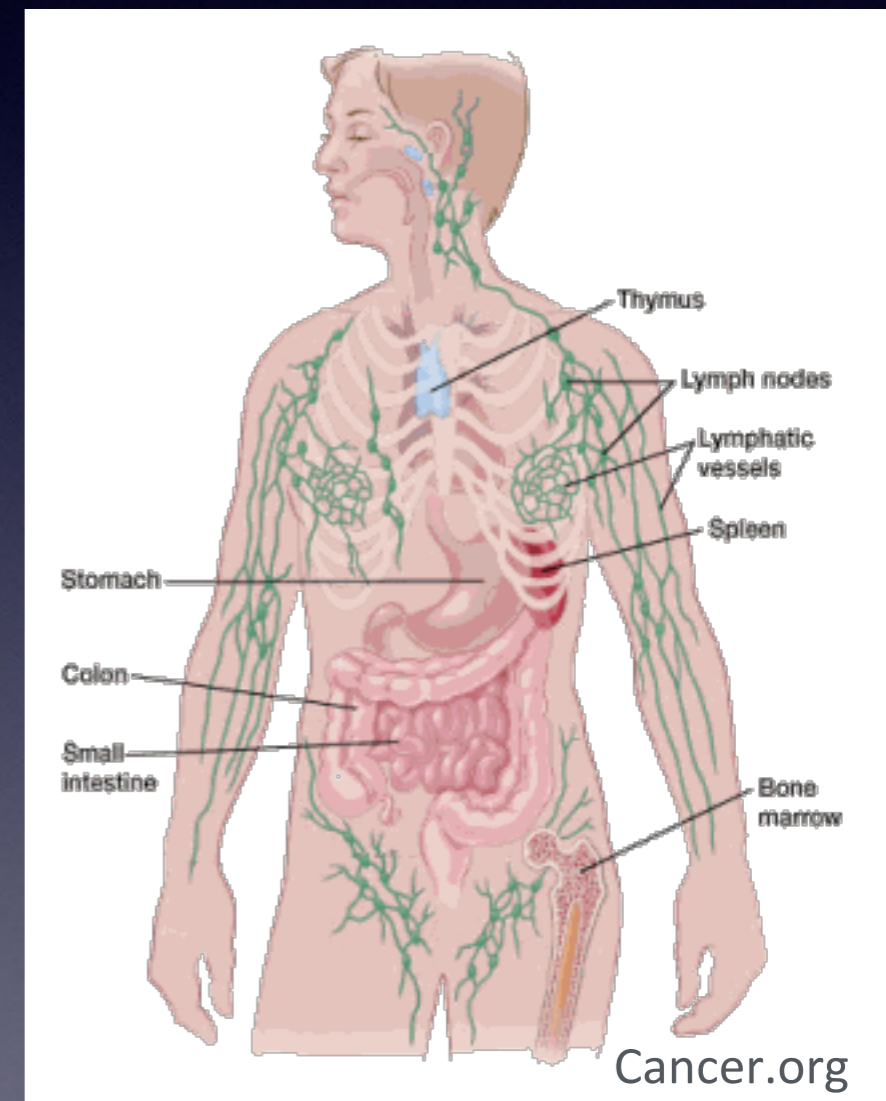


Clinical Vignette



Clinical Vignette

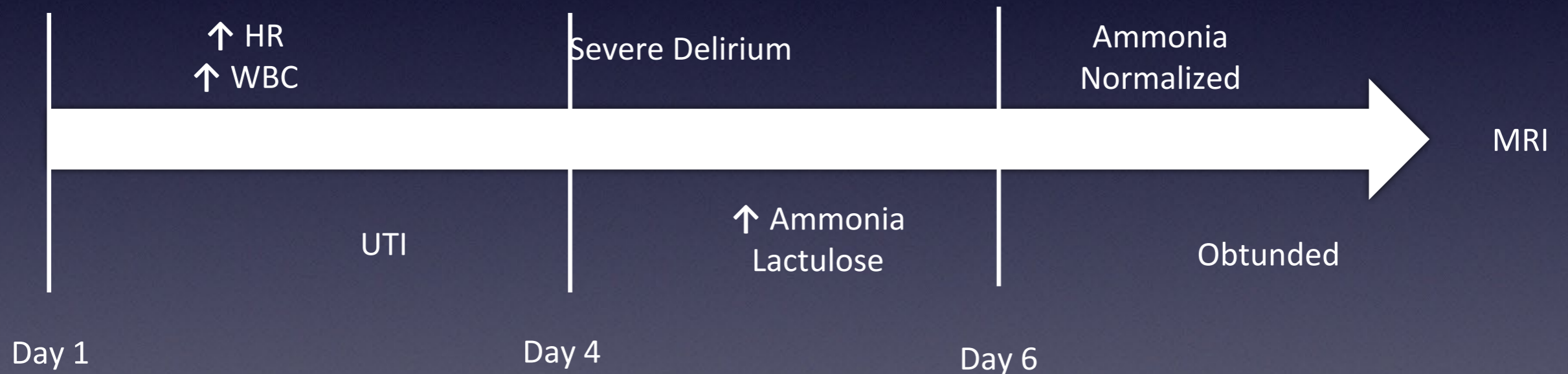
- 61F Non-Hodgkin Lymphoma
- Curative intent treatment 5 years ago
- Recurrence 6 months ago
- Radiation to pelvis + immunotherapy



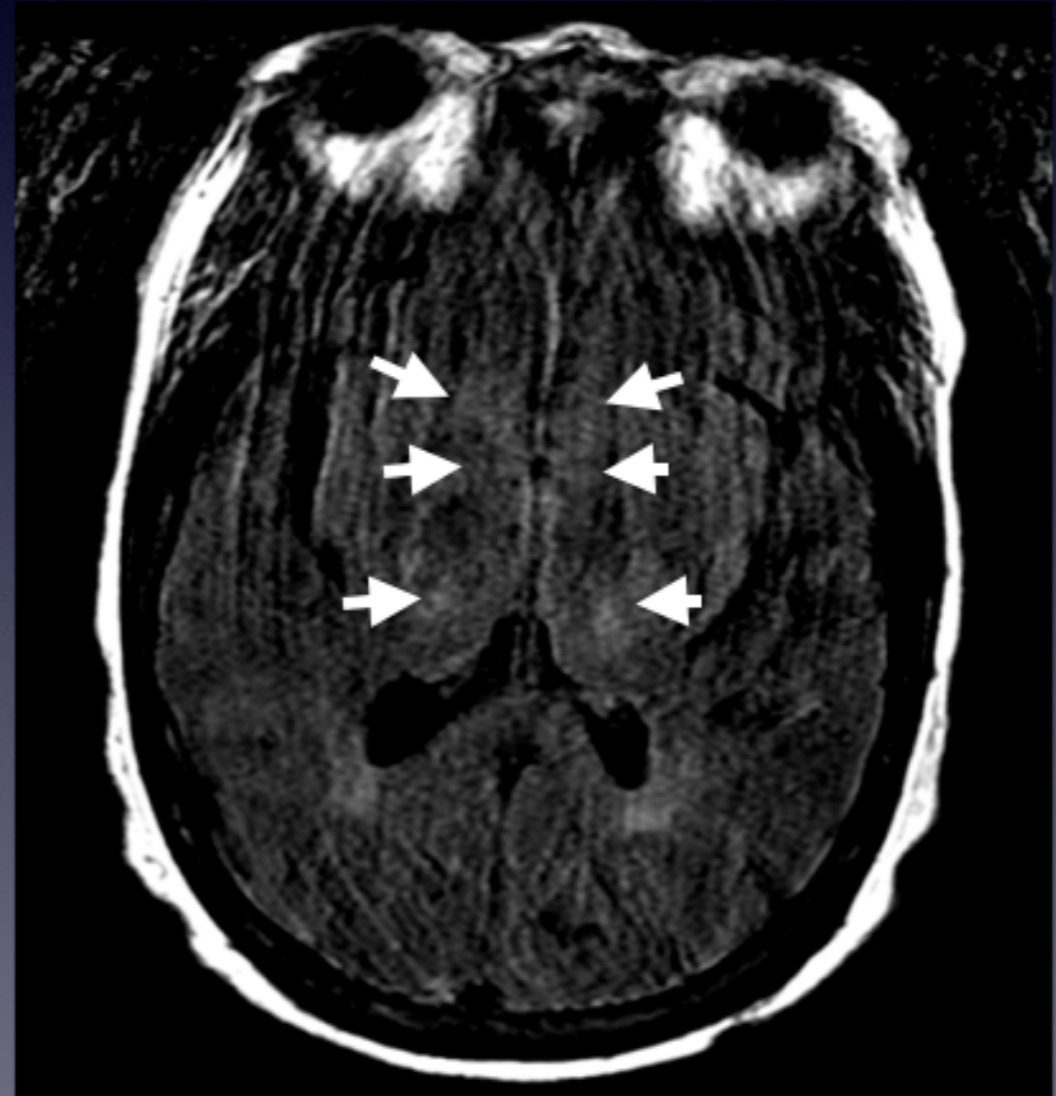
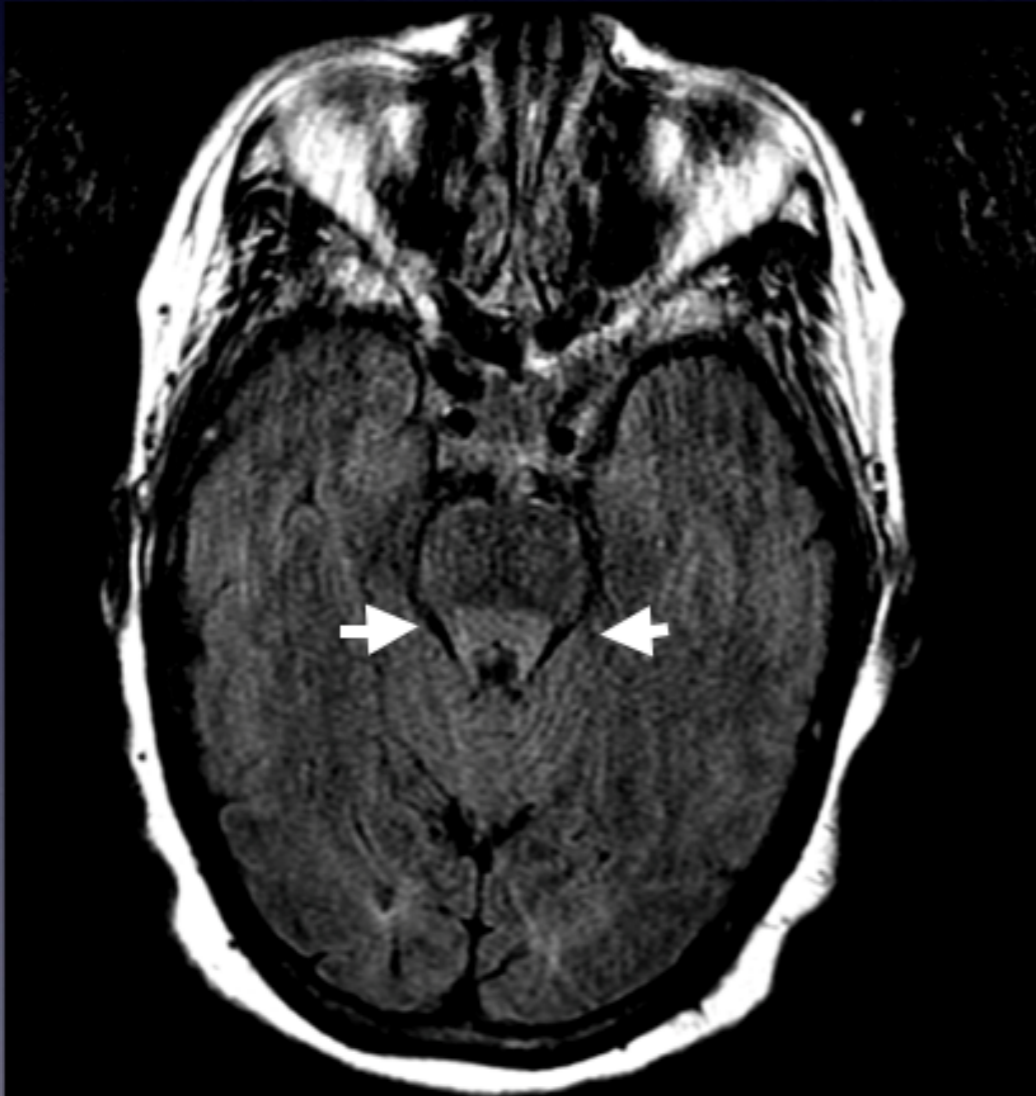
Clinical Vignette



Clinical Vignette

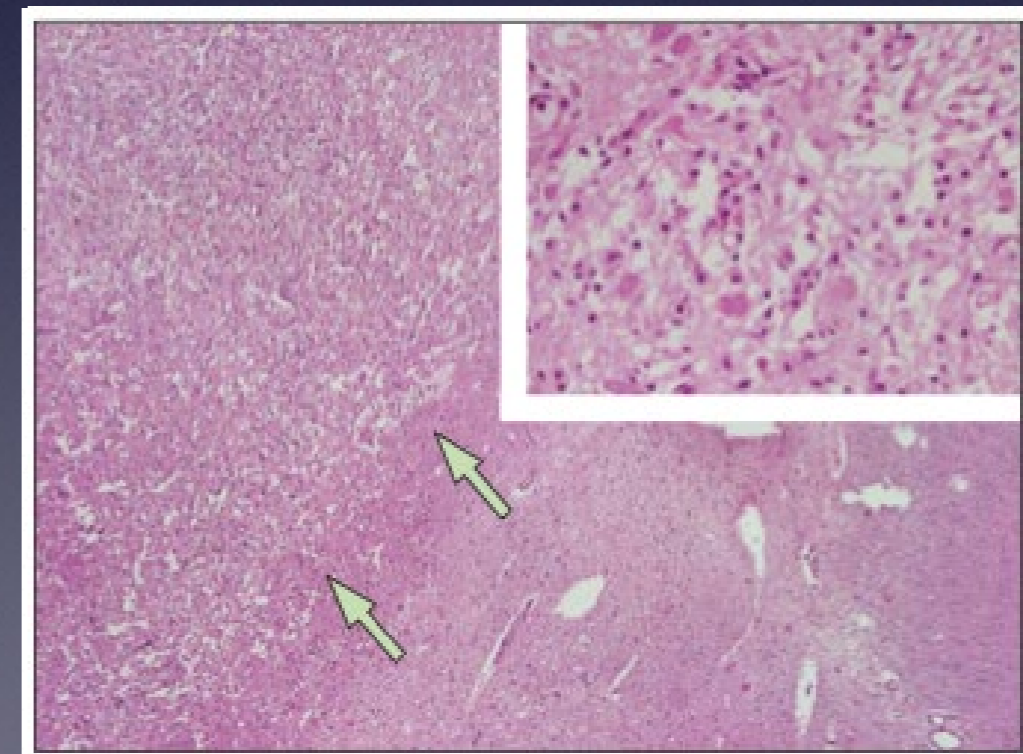


Clinical Vignette



Background: Wernicke-Korsakoff Syndrome

- Neuropsychiatric syndrome
- Thiamine deficiency (vitamin B1)
- Characteristic histopathology
- Mammillary bodies, grey matter around 3rd/4th ventricle, cerebral aqueduct



Thiamine (Vitamin B1)

- Essential nutrient
- Stored in liver (2-3 wks)
- Role in energy metabolism
- Co-Factor: Krebs Cycle



Vitamin A	10%	15%
Vitamin C	10%	10%
Calcium	10%	25%
Iron	25%	25%
Vitamin D	10%	25%
Thiamin	25%	30%
Riboflavin	25%	35%
Niacin	25%	25%
Vitamin B ₆	25%	25%
Folic Acid	50%	50%
Vitamin B ₁₂	25%	35%
Phosphorus	8%	20%
Magnesium	6%	10%
Zinc	25%	30%

* Amount in cereal. A serving of cereal plus skim milk provides 1.5g total fat, less than 5mg cholesterol, 220mg sodium, 320mg potassium, 28g total carbohydrate (15g sugars, 12g other carbohydrate), and 7g protein.

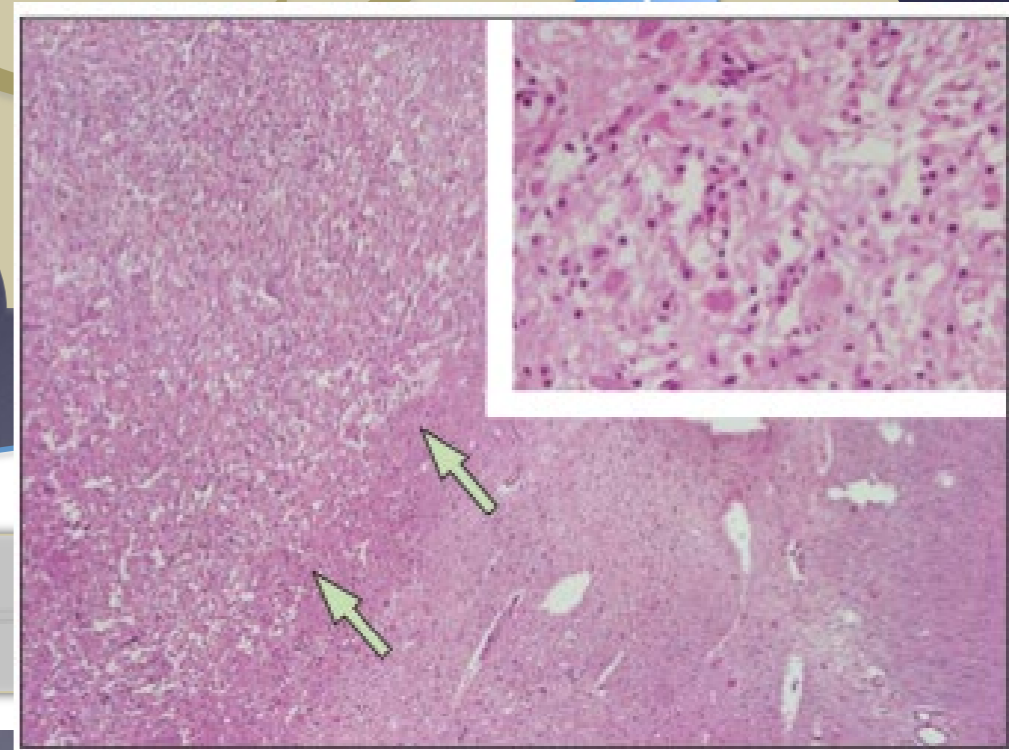
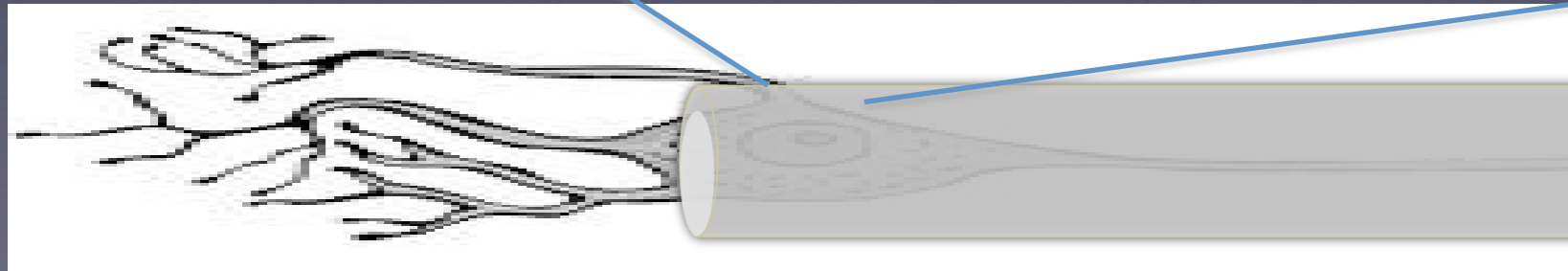
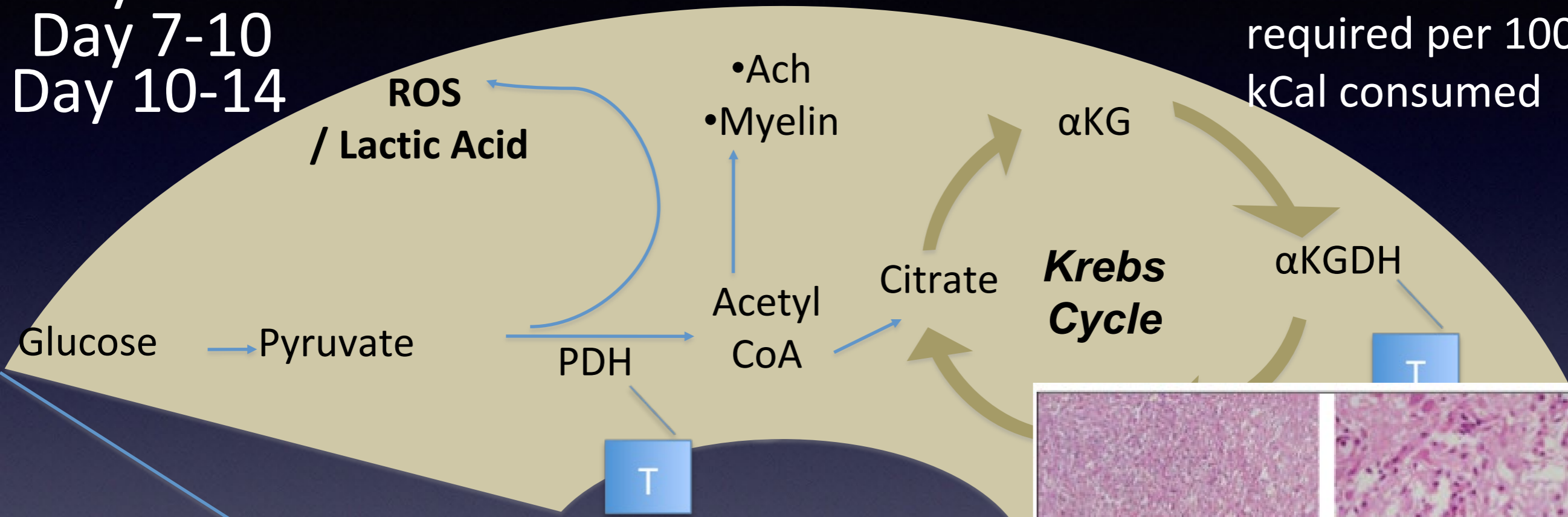
** Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

		Calories	2,000	2,500
Total Fat	Less than		65g	80g
Sat Fat	Less than		20g	25g
Cholesterol	Less than		300mg	300mg
Sodium	Less than		2,400mg	2,400mg
Potassium			3,500mg	3,500mg
Total Carbohydrate			300g	300g
Dietary Fiber			25g	25g

Krebs Cycle

Day 4 -7
Day 7-10
Day 10-14

0.33 mg thiamine
required per 1000
kCal consumed



Classical Descriptions

- Wernicke Encephalopathy
- Korsakoff Syndrome

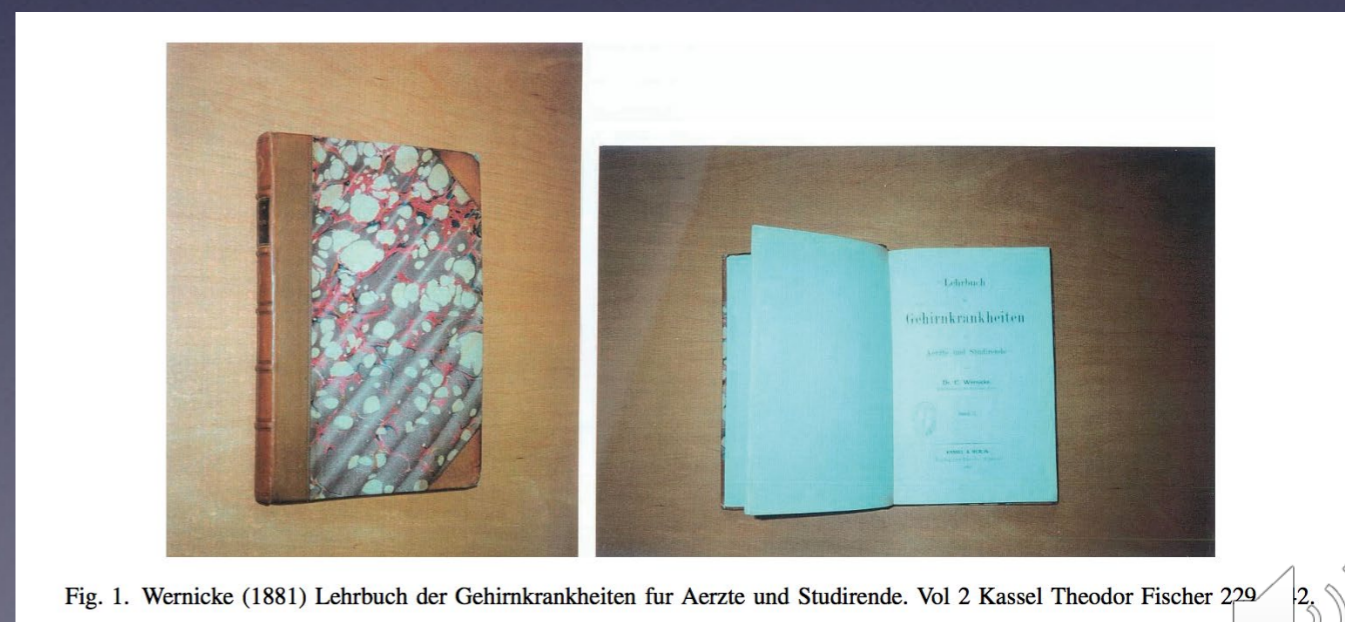
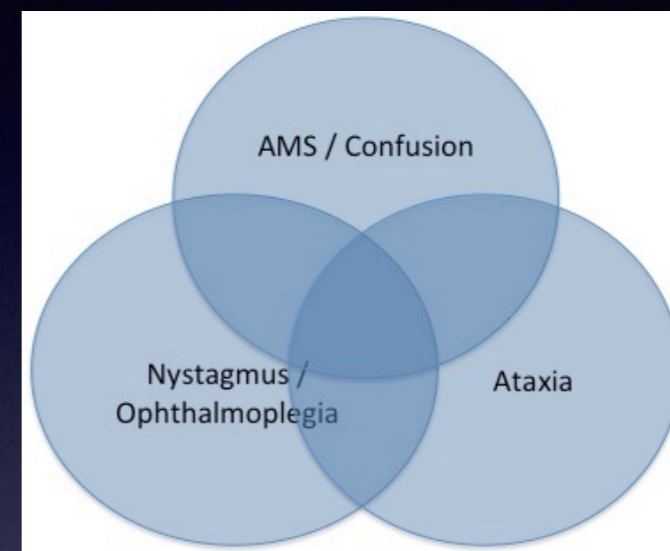


Fig. 1. Wernicke (1881) Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende. Vol 2 Kassel Theodor Fischer 229

- Mild Memory Impairment
- Attention Impairment
- Hallucinations

3 Signs:
10%

Abrupt onset of
confusion

- Fatigue, Apathy
- Weakness
- Emotional Changes
- Fear, Apprehension

2 Signs: 28%
1 Sign: 37%
0 Signs: 19%

- Diplopia / Nystagmus
- Vision Changes

- Unsteadiness Ataxia
- Dysdiadochokinesia
- Dysmetria



Diagnosing WKS

J Neurol Neurosurg Psychiatry. 1997 Jan;62(1):51-60.

Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy.

Caine D, Halliday GM, Kril JJ, Harper CG.

Neuropsychology Unit, Royal Prince Alfred Hospital, Camperdown, Australia.

(1) Dietary Deficiency

(2) Ocular Signs

(3) Cerebellar Signs

(4) AMS or Mild Memory Impairment

≥ 2 of 4 criteria \rightarrow Diagnosis

Sensitivity 85% Specificity 100%



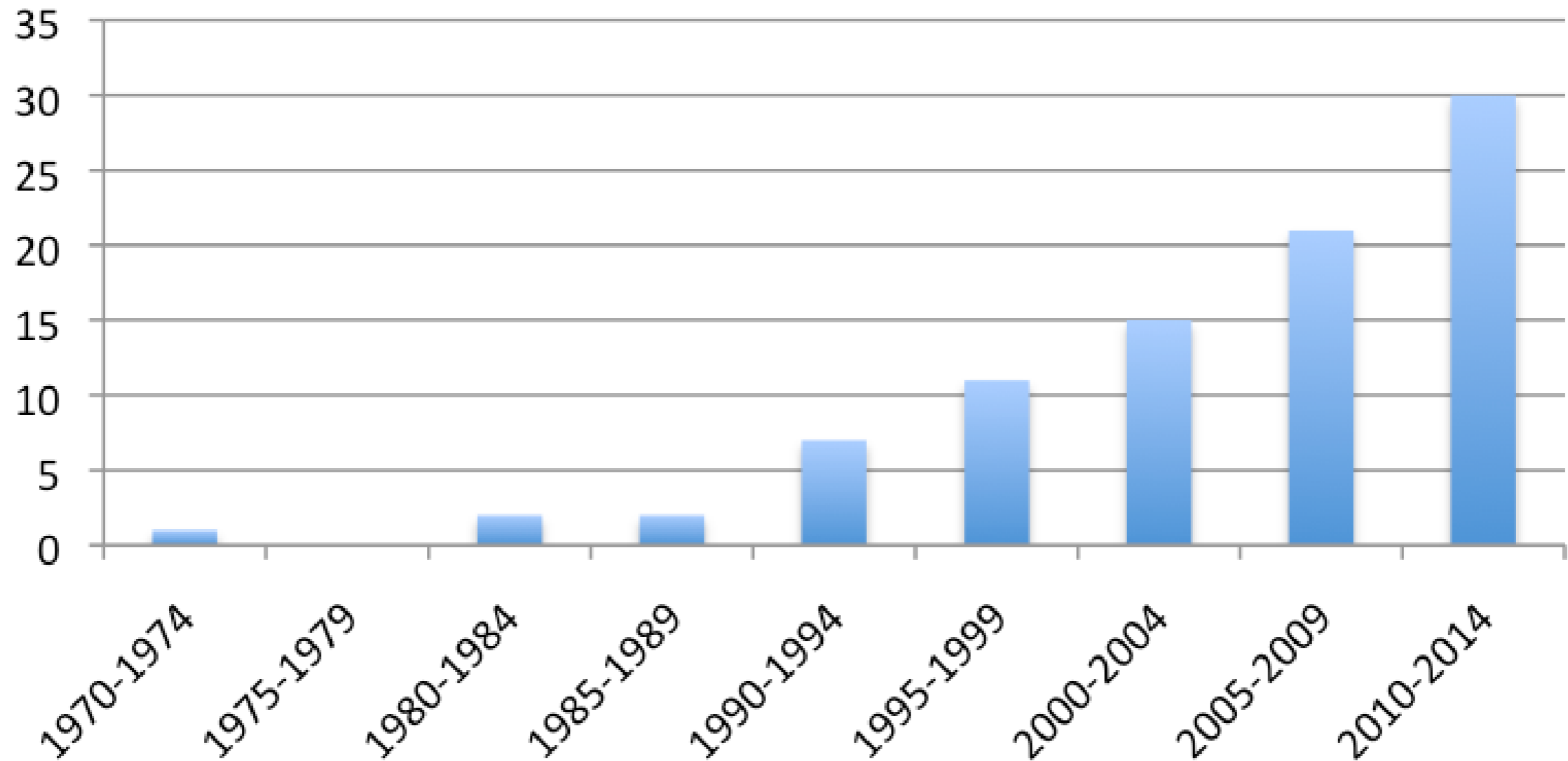
Epidemiology

- Prevalence of Wernicke Encephalopathy
 - Alcohol-use disorder: 12%
 - General Population: 2%
 - HIV/AIDS: 10%
 - Bone Marrow Transplant: 6-33%
- Case reports:
 - Crohn's, Pancreatitis, Anorexia nervosa, Hyperemesis gravidarum, Total parenteral nutrition, Thyrotoxicosis, Cancer



WKS in Cancer

Articles Identified



Mechanisms of Nonalcoholic Thiamine Deficiency

- ↓ Availability
- Impaired Utilization
- ↑ Usage
- ↑ Losses



Mechanisms of Nonalcoholic Thiamine Deficiency

- ↓ Availability

Etiology	Clinical Examples
<u>Starvation</u>	Anorexia nervosa Hunger strike GI obstruction Chemotherapy Systemic illness
<u>Malnutrition</u>	Anorexia nervosa Hunger strike Fad dieting Bariatric surgery Homebound elderly TPN (if not supplemented)
<u>Malabsorption</u>	Bariatric surgery Crohn's disease
<u>Vomiting</u>	Hyperemesis gravidarum Chemotherapy-induced Status post-abdominal surgery GI obstruction Pancreatitis Bariatric surgery



Mechanisms of Nonalcoholic Thiamine Deficiency

- Impaired Utilization

Etiology	Clinical Examples
Decreased enzyme activity	<u>Co-factor deficiency</u> Malignancy <u>Chemotherapy-induced</u>



Mechanisms of Nonalcoholic Thiamine Deficiency

- ↑Usage

Etiology	Clinical Examples
<u>Hypermetabolic state</u>	Thyrototoxicosis Systemic illness Infection/sepsis Pregnancy
<u>Excess glucose metabolism</u>	Following rapid infusion of glucose Seizures Alcohol withdrawal
<u>Rapid cell turnover/high cell density</u>	Hematological malignancy Fast-growing tumor



Mechanisms of Nonalcoholic Thiamine Deficiency

- ↑ Losses

Etiology	Clinical Examples
Iatrogenic	Hemodialysis

Isenberg-Grzeda E, Kutner H, Nicolson SE. Wernicke-Korsokoff Syndrome: Under-recognized and under-treated. *Psychosomatics* 2012; 53: 507–516. PubMed ID: 23157990.



TD in Cancer

Psycho-Oncology

Psycho-Oncology (2016)

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/pon.4155

High rate of thiamine deficiency among inpatients with cancer referred for psychiatric consultation: results of a single site prevalence study

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Abstract

Objective: Thiamine deficiency (TD) is increasingly recognized in medically ill patients. The prevalence of TD among cancer patients is unknown. This study aims to characterize the prevalence of TD among inpatients with cancer.

Methods: Retrospective chart review of patients admitted to a large cancer center who were referred for psychiatric consultation and whose serum thiamine concentration was measured. Patients with alcohol use were excluded.

Results: Among 217 patients with various cancer types, TD was found in 55.3%. Risk factors included fluorouracil-based chemotherapy, significant weight loss, and undergoing active cancer treatment. Almost all patients were normal weight, overweight, or obese, and few had concomitant vitamin B12 or folate deficiency. A total of 17.5% were receiving multivitamin supplementation. Nearly half (49.8%) did not receive empiric treatment with thiamine and among those who did, treatment delay



Prescribing Thiamine

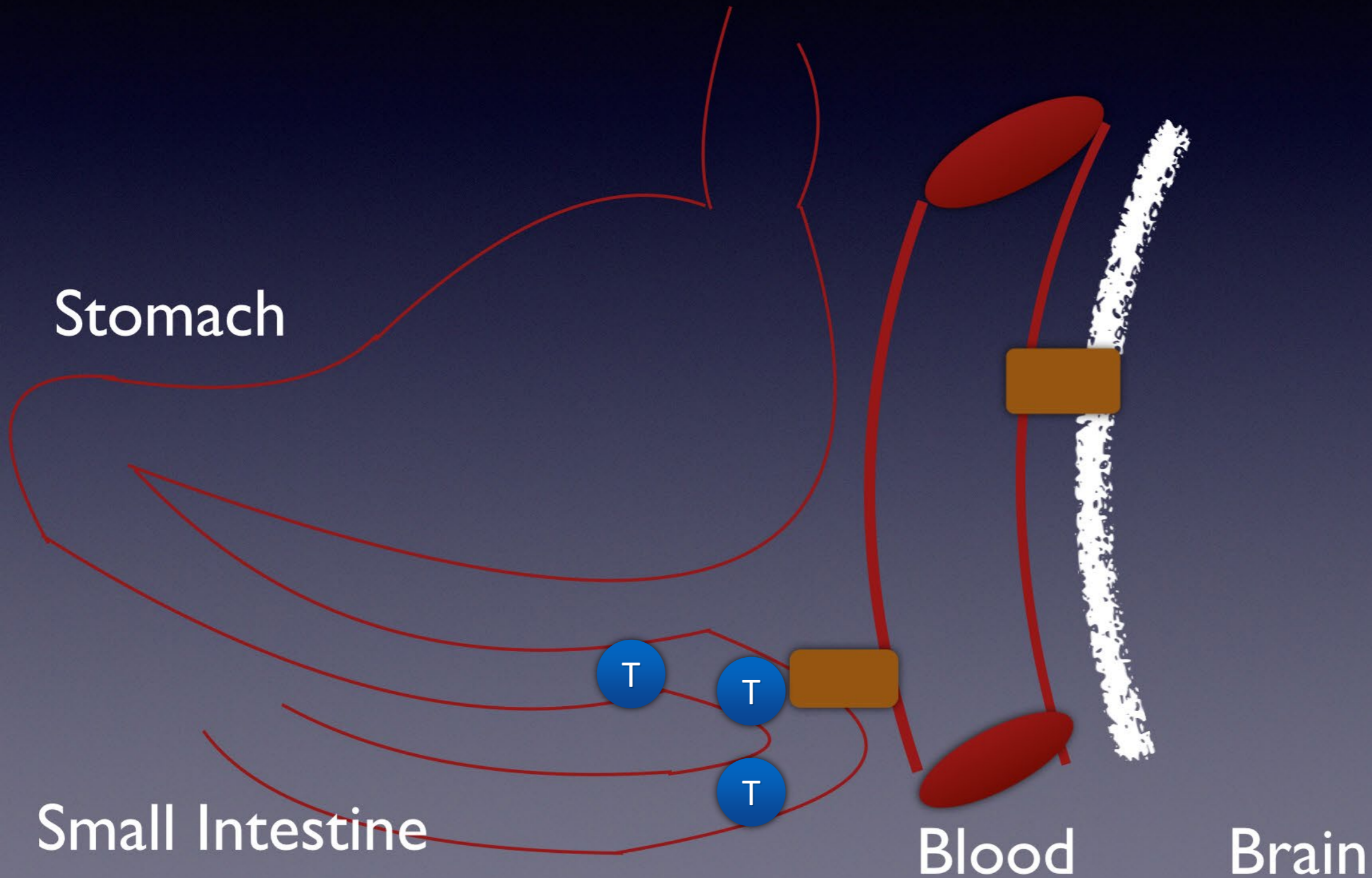


Principles of Prescribing 1

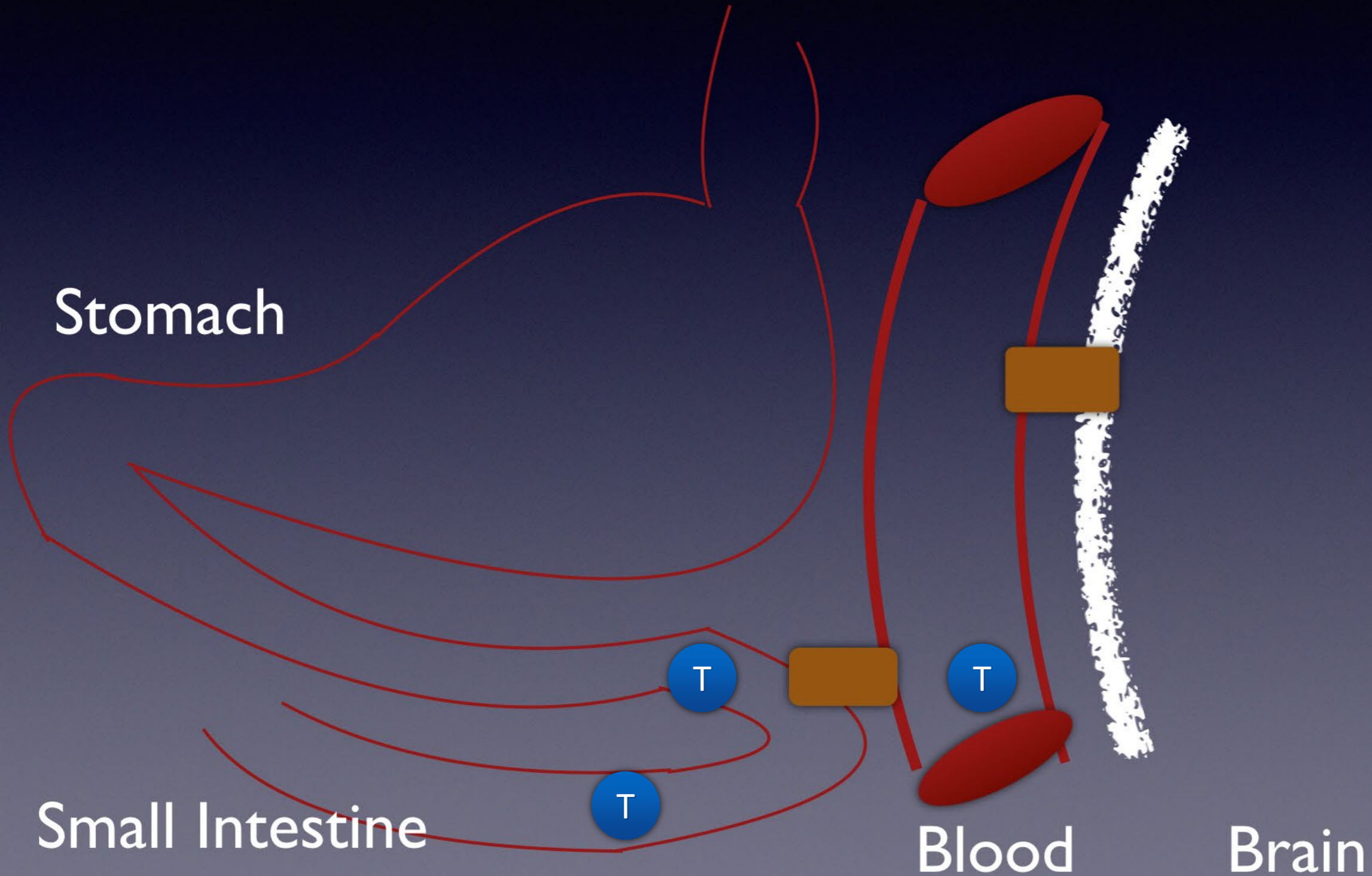
- Half-life of i.v. thiamine is short (96 minutes)
- Therefore, use BID or TID dosing



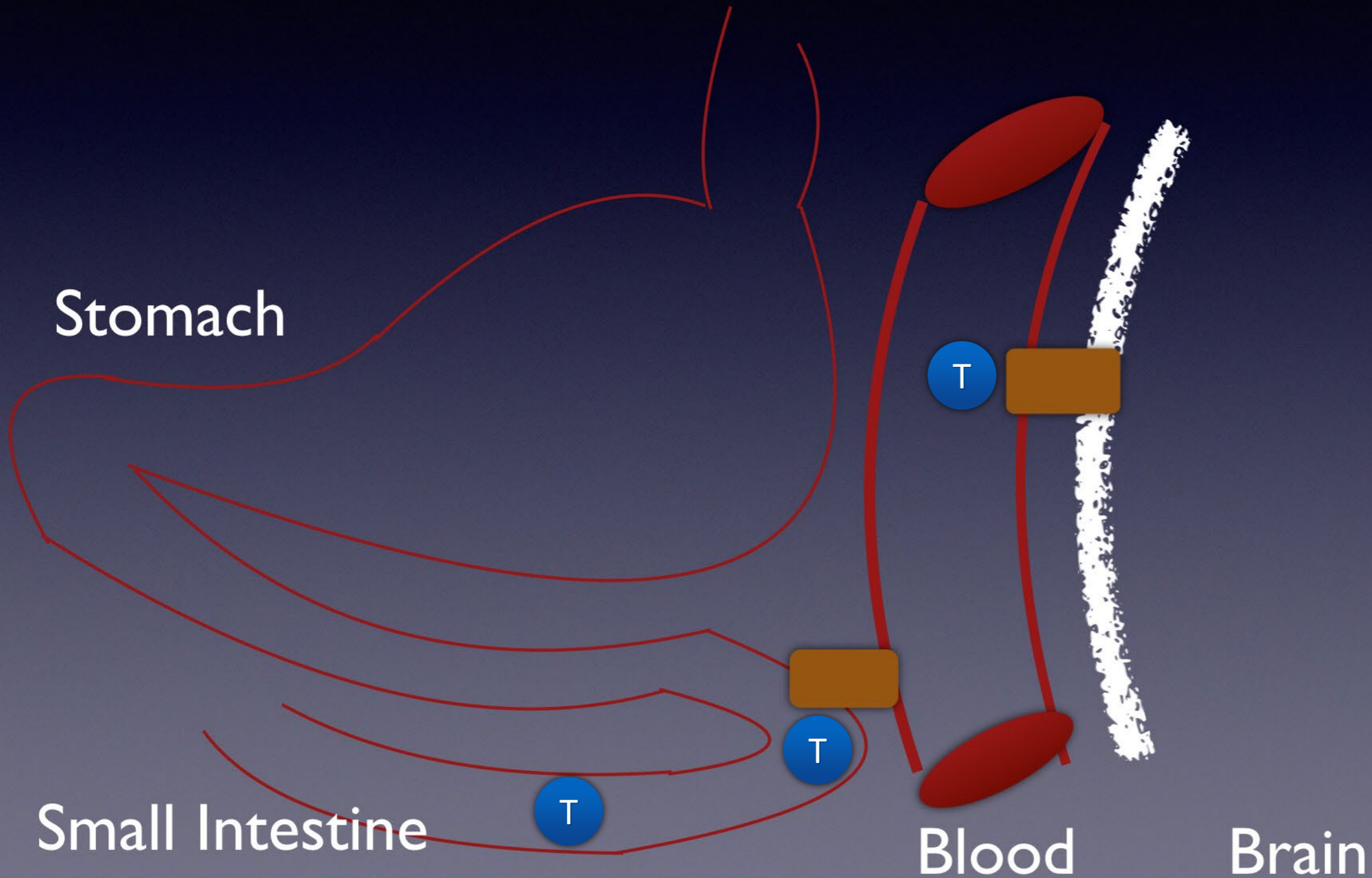
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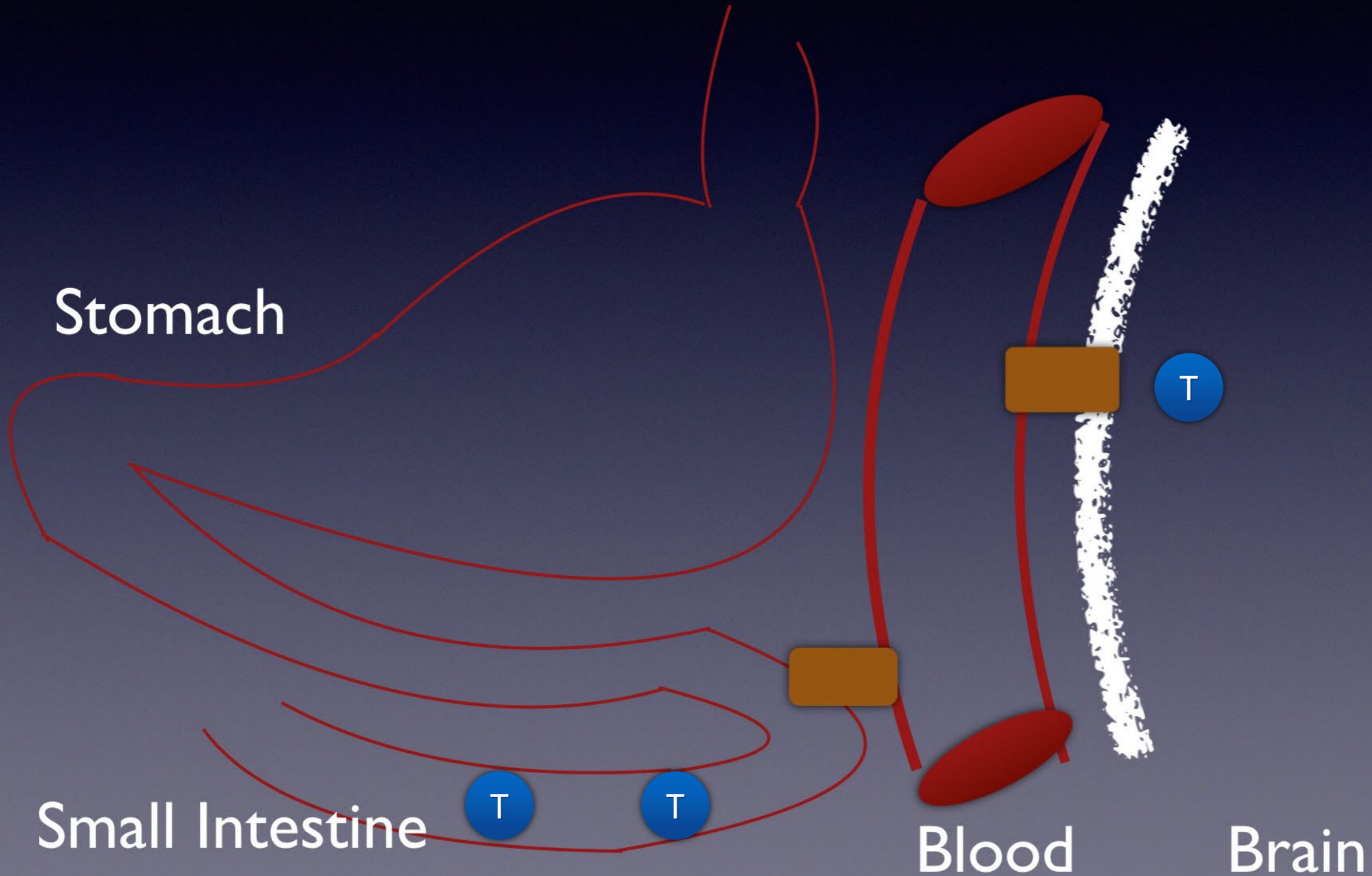
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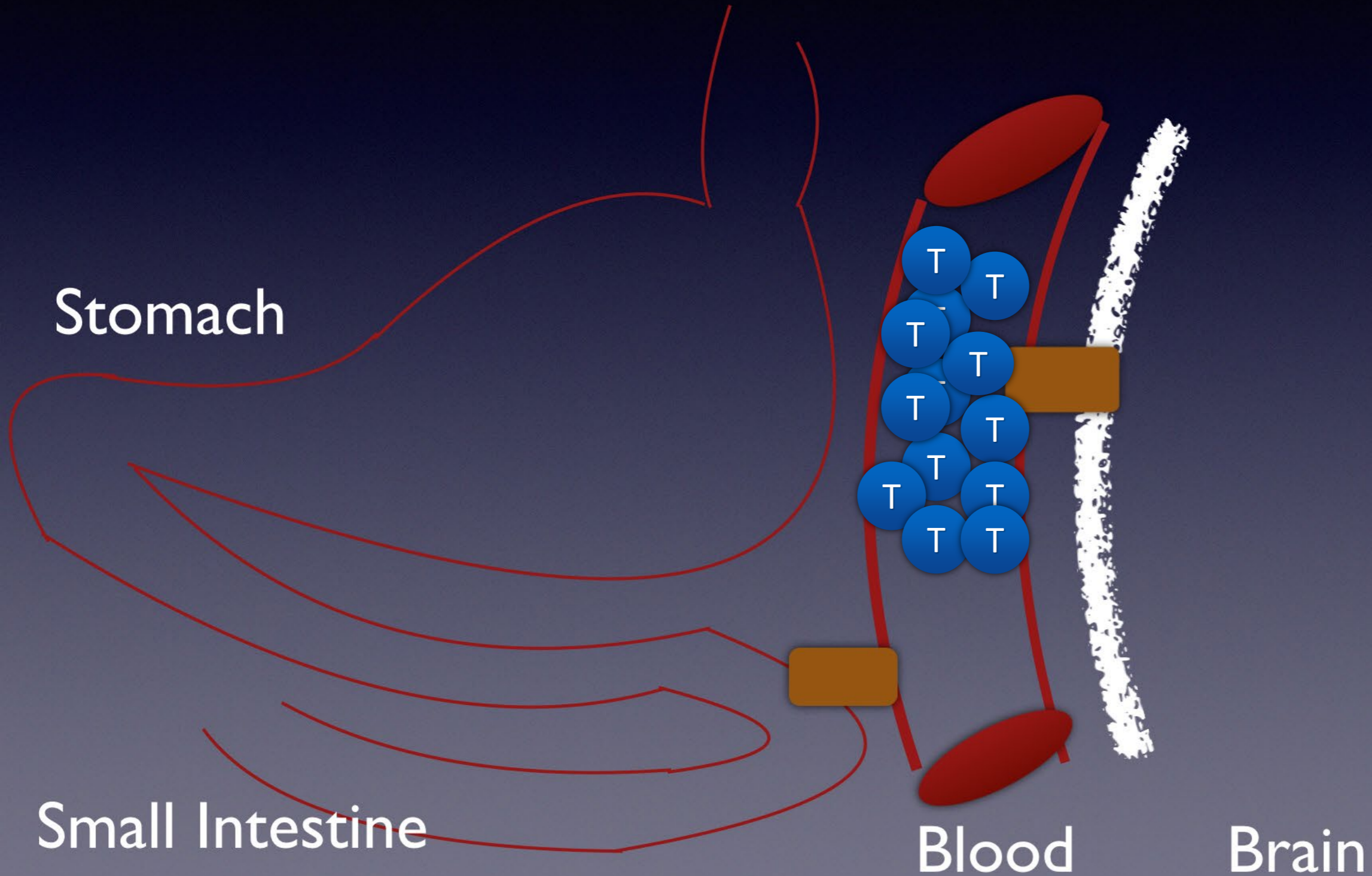
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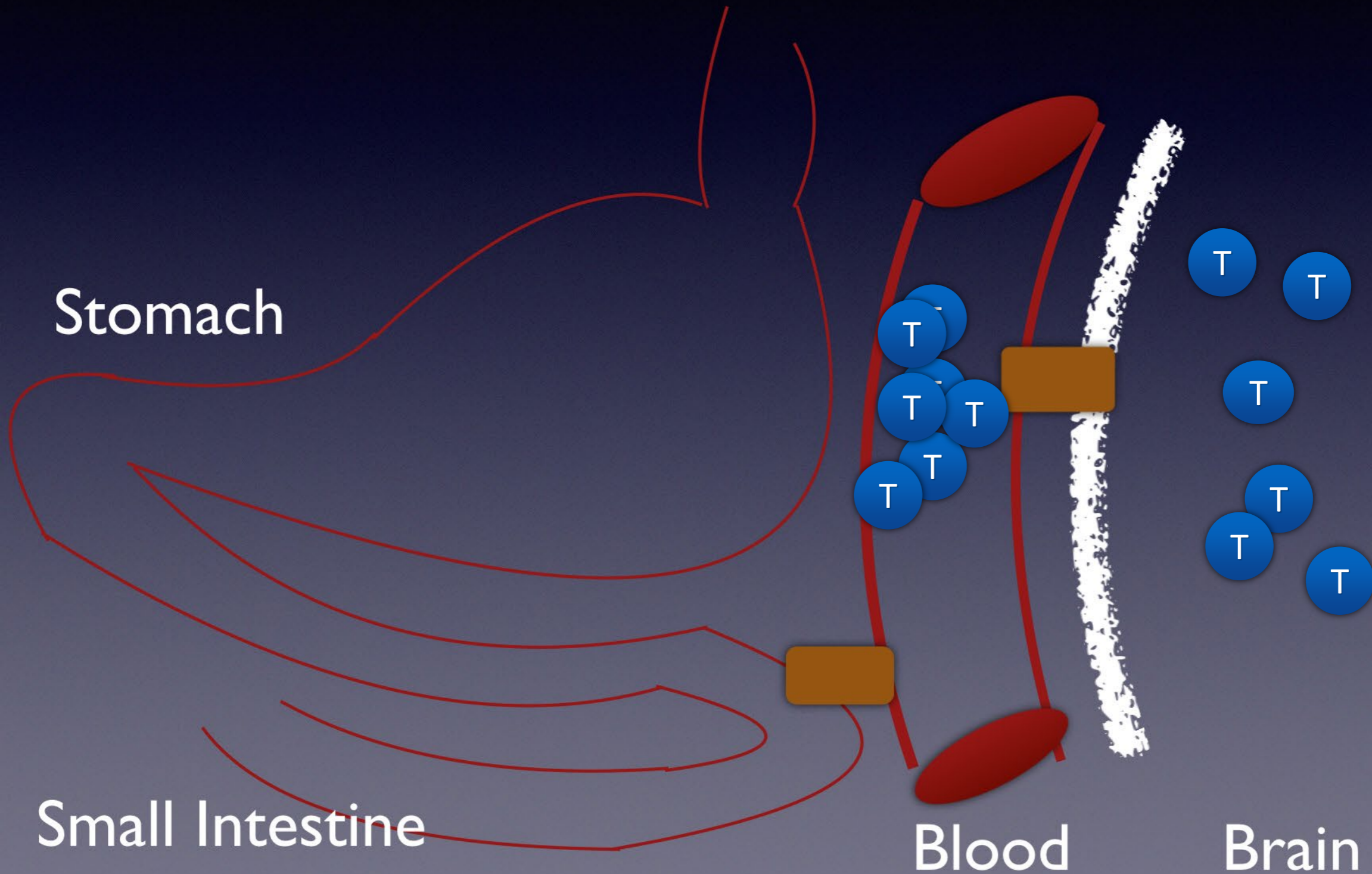
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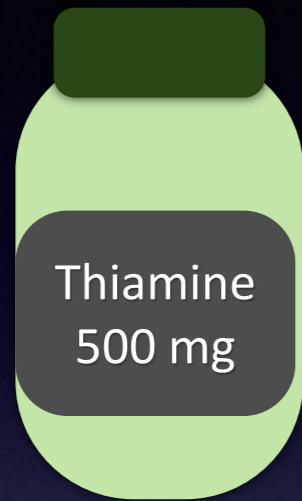
Principles of Prescribing 2



Principles of Prescribing 2



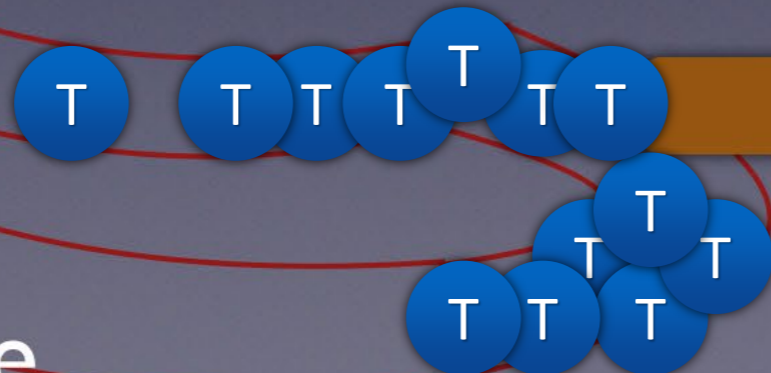
Principles of Prescribing 2



Stomach



Small Intestine

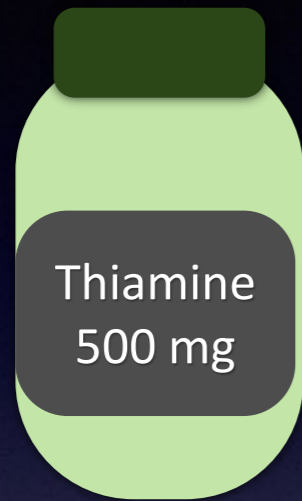


Blood

Brain



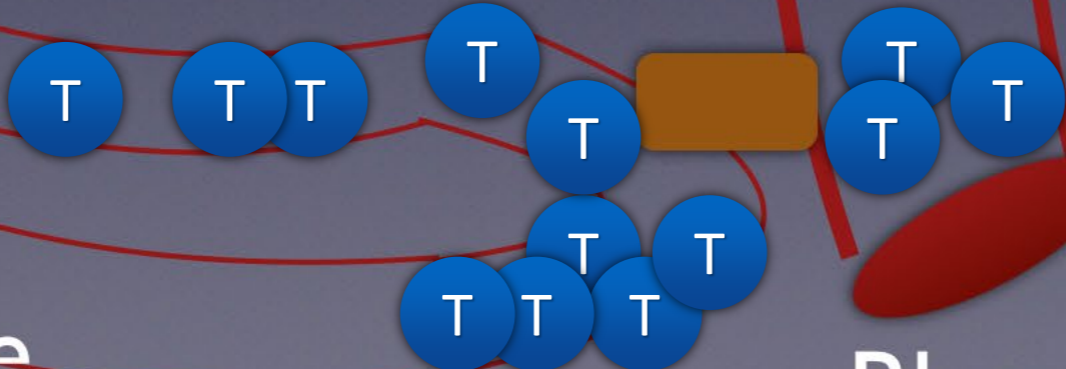
Principles of Prescribing 2



Stomach



Small Intestine



Blood

Brain



Principles of Prescribing 2



Stomach



Blood

Brain

Small Intestine



Principles of Prescribing 2



Stomach



Small Intestine

Blood

Brain



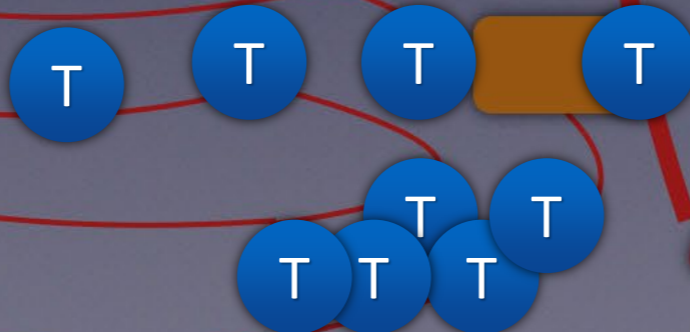
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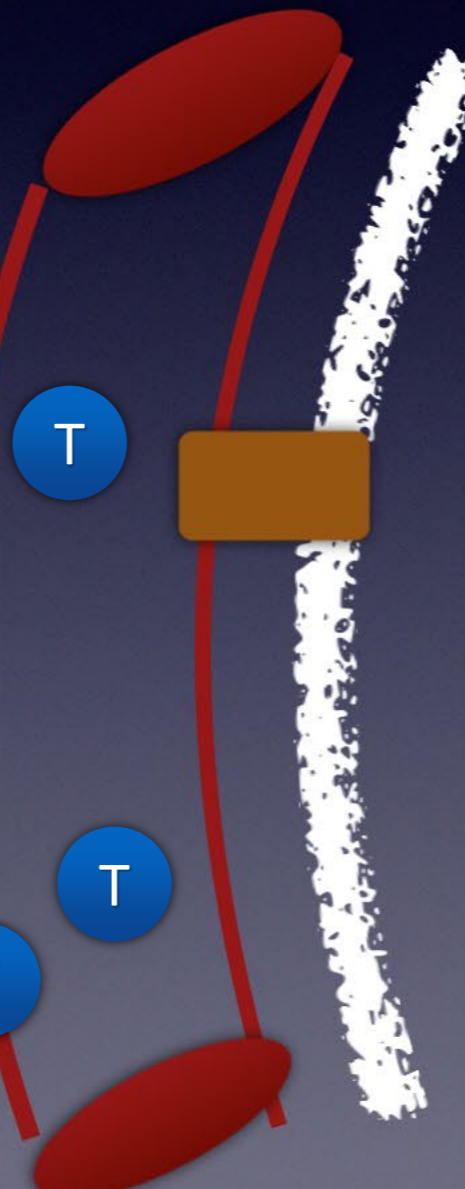
Stomach



Small Intestine



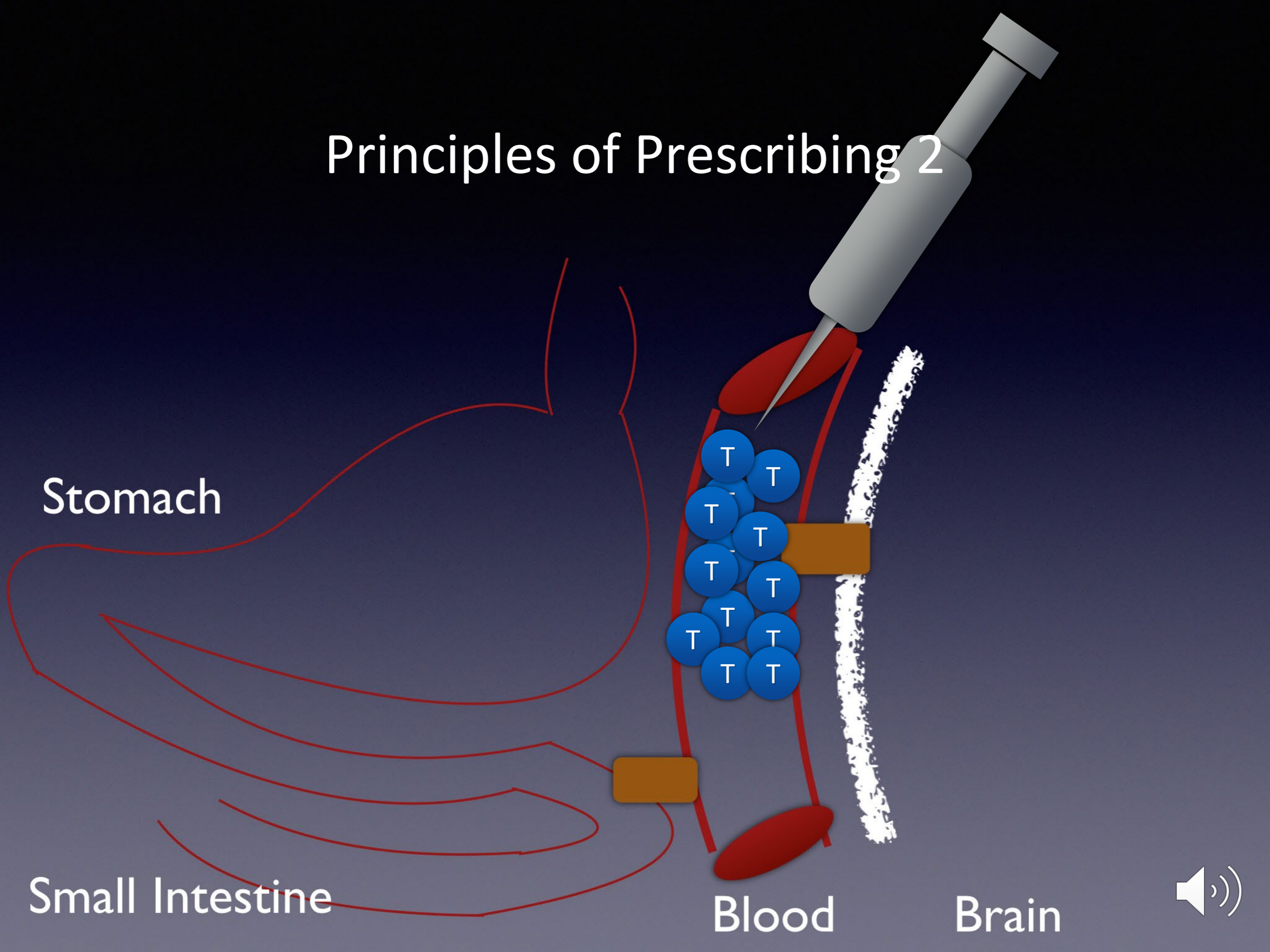
Blood



Brain



Principles of Prescribing 2



Stomach

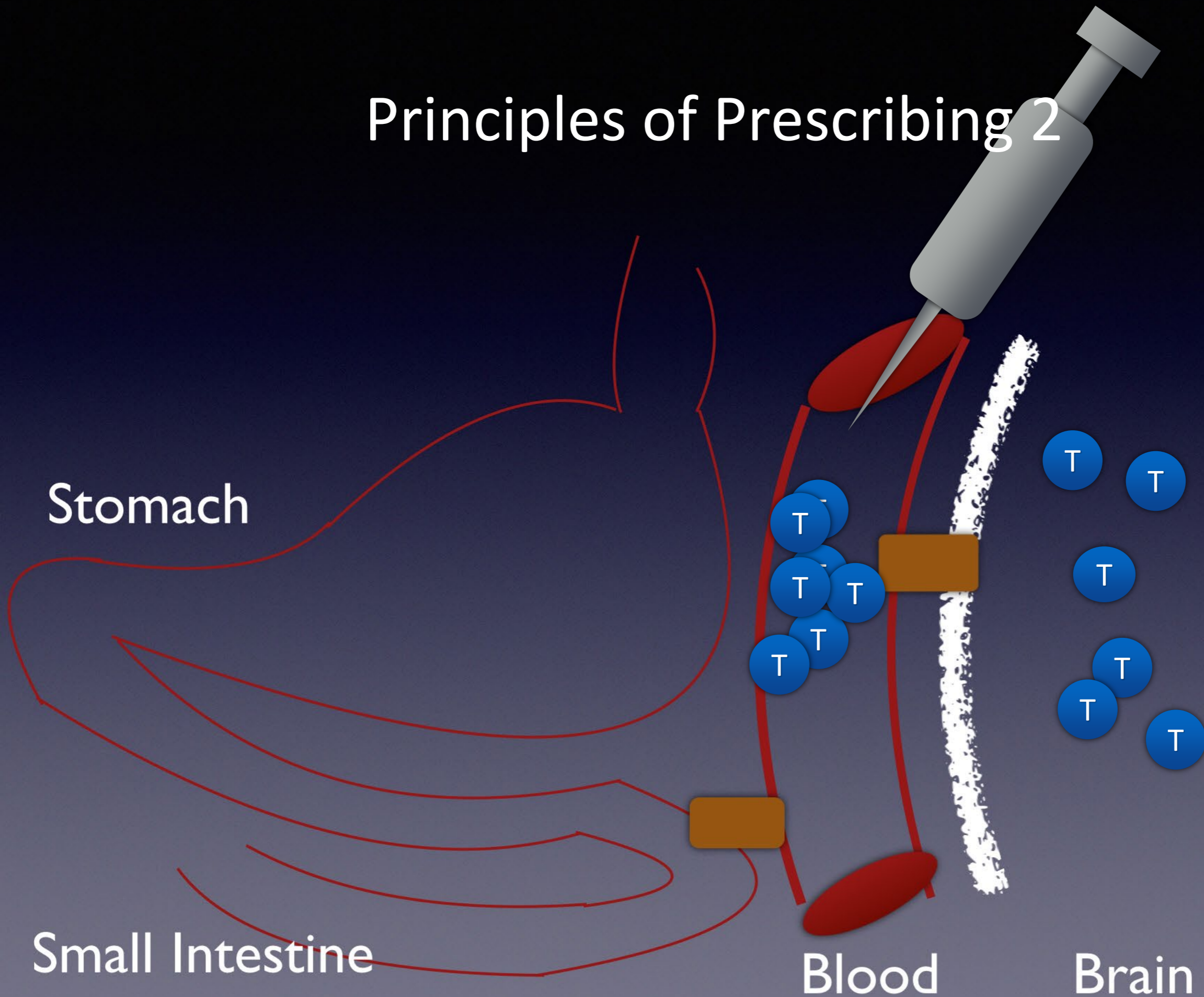
Small Intestine

Blood

Brain



Principles of Prescribing 2

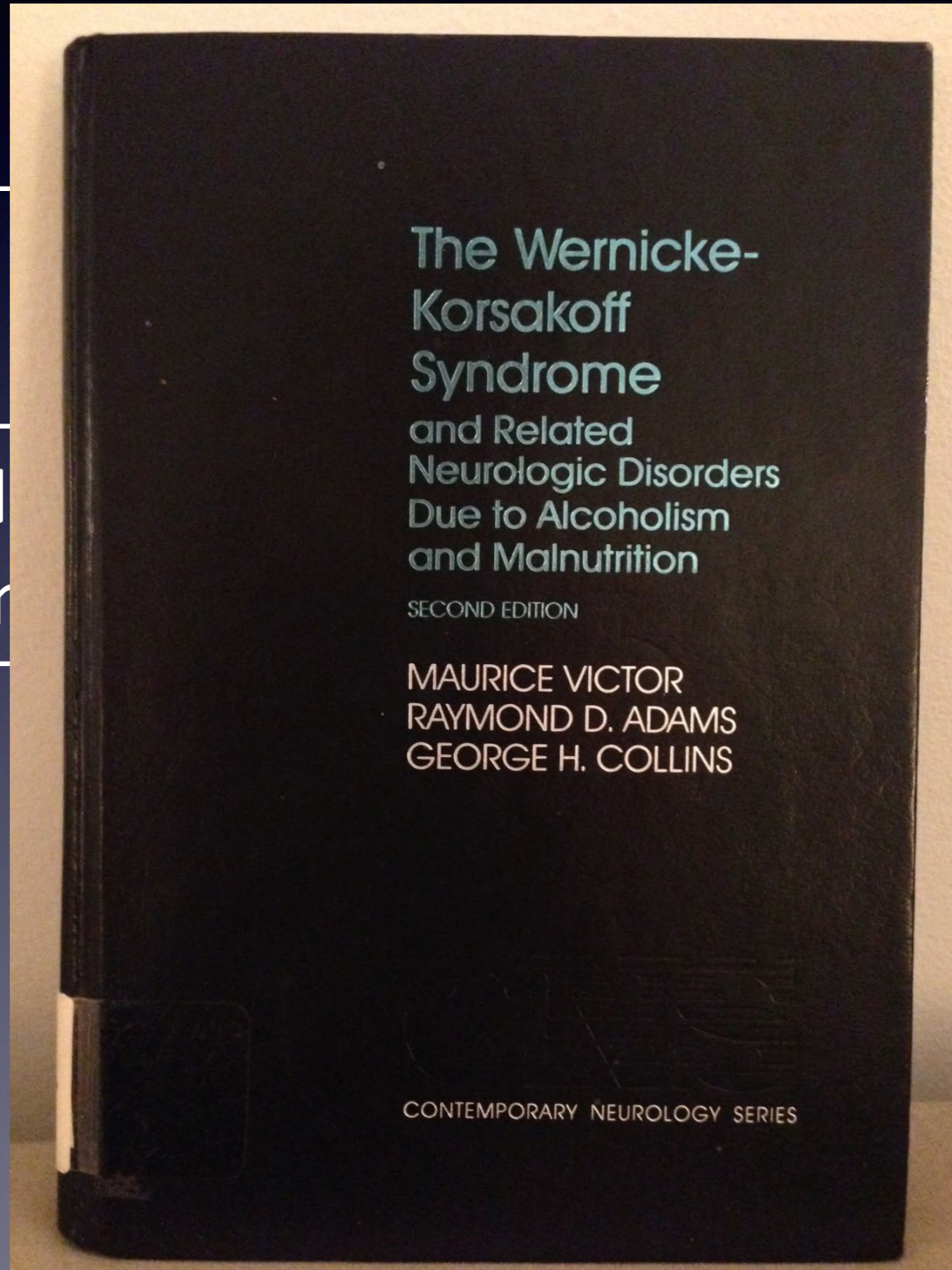


Principles of Prescribing 3

1. Prevention of WE in at-risk patients
2. Treatment of WE



Dosing



Back vitamin B1 (common name) e

beriberi
10-20 mg IM tid x2wk
Info: follow w/ 5-30 mg PO qd x1mo; give intradermal skin test before use if hypersensitivity risk (IM/IV)

wet beriberi w/ CHF
10-30 mg IV tid
Info: give intradermal skin test before use if hypersensitivity risk (IM/IV)

Wernicke encephalopathy
100 mg IV x1
Info: followed by 50-100 mg IM/IV qd; give intradermal skin test before use if hypersensitivity risk (IM/IV)

dietary supplementation
individualize dose
Info: see Dietary Reference Intakes: Vitamin B1 (thiamine) table

+ ☆ ✍ ☎ 🏠



Dosing

- Parenteral >> oral
- 200mg >> 100mg, 50mg, 20mg, 5mg
- BID or TID >> Once Daily



Dosing

	Dose	Route	Frequency	Duration
North America	50 -100 mg	im/iv	Daily	3 days
UK	500 mg	iv	TID	3 days ++
Europe	200 mg	iv	TID	Until Resolves



Original Research Reports

Nonalcoholic Thiamine-Related Encephalopathy (Wernicke-Korsakoff Syndrome) Among Inpatients With Cancer: A Series of 18 Cases

Elie Isenberg-Grzeda, M.D., C.M., F.R.C.P.C., Yesne Alici, M.D., Vaios Hatzoglou, M.D.,
Christian Nelson, Ph.D., William Breitbart, M.D.



Gaps in The Literature

- Limited literature on cancer-related WKS
- Small sample sizes (n=1)
- Aim: Describe WKS in nonalcoholic cancer patients



Methods:

- Setting: MSKCC inpatients
 - July 2013 - December 2014
- Patient Sample: Adults
 - Diagnosed by operational criteria (2 of 4 features, Caine et al., 1997)
 - +1 supporting feature: MRI, Serum thiamine, Response to Tx



Methods:

- Exclusion Criteria:
 - Current alcohol use
 - Clinical presentation better explained by other diagnosis
 - Lack of supporting feature



Results: Sample

34 patient identified for possible inclusion

- Alcohol Use: 0
- Lacking Supportive Feature: 3
- Better Explanation for AMS: 13

18 patients included



Results: Demographics 1

- N=18
- Age (mean \pm SD; range): 64 \pm 13; 31-80 yr
- Female: 33%
- Hematologic Malignancy: 39% (N=7)
- 1-year mortality: 50%



Results: Demographics 2

- All patients undergoing treatment within past month
 - Chemotherapy: 72%
 - Surgery: 33%
 - Radiation: 22%



Usual Suspects??

- Few patients were underweight (n=4, 22%)
- Concurrent Vitamin Deficiency:
 - Vitamin B12 deficiency (0/15)
 - Folate deficiency (1/13)
- Prescribed multivitamin (n=4, 22%)



Results: Phenomenology

- Cerebellar
- Ocular
- Cognitive



Phenomenology: Cerebellar Signs

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total	
Unsteadiness	+		+		+				+											4
Impaired Coordination				+			+													2
Ataxic gait						+														1
Dysdiadochokinesia							+													1
Any Cerebellar Signs	+		+	+	+	+	+		+											7



Phenomenology: Ocular Signs

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total
Blurry Vision	+	+		+															3
Ophthalmoplegia																			0
Nystagmus																			0
Diplopia																			0
Any Ocular Signs	+	+		+															3



Phenomenology: Cognitive Signs

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Total
Change in Alertness	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	16
Attention Impairment	+	+	+	+	+	+	+		+	+		+	+	+	+		+	+	15
STM Impairment	+		+	+	+	+	+	+		+		+	+		+		+	+	13
Disorientation	+	+		+	+	+		+	+	+	+		+		+	+			12
"Confusion"		+		+	+	+			+	+	+		+		+	+		+	11
Sleep-Wake Alteration					+	+			+	+	+		+					+	7
Disorganized Thinking		+			+	+	+		+									+	6
Hallucinations		+		+							+		+						4
Any Cognitive Symptoms	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18



Triad vs. Operational Criteria

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular	+	+		+														
Cerebellar	+		+	+	+	+	+		+									
Altered Mental Status	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+



Triad vs. Operational Criteria

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular	+	+		+														
Cerebellar	+		+	+	+	+	+		+									
Altered Mental Status	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular	+	+		+														
Cerebellar	+		+	+	+	+	+		+									
Altered Mental Status or Mild Memory Impairment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nutritional Deficiency	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+



Treatment



- All patients received thiamine 500 mg iv TID
- Delay in treatment
- Mean =18d (SD=18d, range 2-58)



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
Blurry Vision																		
Cerebellar Signs:																		
Unsteadiness																		
Cognitive Signs:																		
"Confusion"																		
Hypoarousal																		
Hyperarousal																		
Sleep-Wake Reversal																		
Disorientation																		
STM Impairment																		
Attention Impairment																		
Disorganized Thinking																		
"Other" Signs																		
Dysarthria																		
Apathy / Depression																		
Mood Lability																		
Follow-Up Period (days)																		



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
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Disorientation																		
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Attention Impairment																		
Disorganized Thinking																		
"Other" Signs																		
Dysarthria																		
Apathy / Depression																		
Mood Lability																		
Follow-Up Period (days)	52	393	2	16	13	11	14	3	6	44	12	298	186	70	24	3	4	4



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
Blurry Vision	3	3		-														
Cerebellar Signs:																		
Unsteadiness	-	-							-									
Cognitive Signs:																		
"Confusion"		17		-	2	2			-	4	-		13		1	1		2
Hypoarousal	2	3	1	4		2	3	3	4		4				1	1	4	
Hyperarousal		8			2	2				4	10		6					1
Sleep-Wake Reversal						2			-	4	-		6				4	
Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
STM Impairment	-	-		-	-	-	-	3		-			-		-		-	-
Attention Impairment	-	-	1	-	-	-	3			-		7	6	-	1		4	20
Disorganized Thinking		17			2	2	3		-									20
"Other" Signs																		
Dysarthria						2	3		3									
Apathy / Depression	2	10	2											6				
Mood Lability	2	10								4								2
Follow-Up Period (days)	52	393	2	16	13	11	14	3	6	44	12	298	186	70	24	3	4	42



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
Blurry Vision	3	3		-														
Cerebellar Signs:																		
Unsteadiness	-	-							-									
Cognitive Signs:																		
"Confusion"		17		-	2	2			-	4	-		13		1	1		2
Hypoarousal	2	3	1	4		2	3	3	4		4				1	1	4	
Hyperarousal		8			2	2				4	10		6					1
Sleep-Wake Reversal						2			-	4	-		6				4	
Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
STM Impairment	-	-		-	-	-	-	3		-			-	-	-		-	-
Attention Impairment	-	-	1	-	-	-	3			-		7	6	-	1		4	20
Disorganized Thinking		17			2	2	3		-									20
"Other" Signs																		
Dysarthria						2	3		3									
Apathy / Depression	2	10	2											6				
Mood Lability	2	10								4								2
Follow-Up Period (days)	52	393	2	16	13	11	14	3	6	44	12	298	186	70	24	3	4	42



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
Blurry Vision	3	3		-														
Cerebellar Signs:																		
Unsteadiness	-	-							-									
Cognitive Signs:																		
"Confusion"		17		-	2	2			-	4	-		13		1	1		2
Hypoarousal	2	3	1	4		2	3	3	4		4				1	1	4	
Hyperarousal		8			2	2				4	10		6					1
Sleep-Wake Reversal						2			-	4	-		6				4	
Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
STM Impairment	-	-		-	-	-	-	3		-			-	-	-		-	-
Attention Impairment	-	-	1	-	-	-	3			-		7	6	-	1		4	20
Disorganized Thinking		17			2	2	3		-									20
"Other" Signs																		
Dysarthria						2	3		3									
Apathy / Depression	2	10	2											6				
Mood Lability	2	10								4								2
Follow-Up Period (days)	52	393	2	16	13	11	14	3	6	44	12	298	186	70	24	3	4	42



Symptom Resolution

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular Signs:																		
Blurry Vision	3	3		-														
Cerebellar Signs:																		
Unsteadiness	-	-							-									
Cognitive Signs:																		
"Confusion"		17		-	2	2			-	4	-		13		1	1		2
Hypoarousal	2	3	1	4		2	3	3	4		4				1	1	4	
Hyperarousal		8			2	2				4	10		6					1
Sleep-Wake Reversal						2			-	4	-		6				4	
Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
STM Impairment	-	-		-	-	-	-	3		-		-	-		-		-	-
Attention Impairment	-	-	1	-	-	-	3			-		7	6	-	1		4	20
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Disorientation	-	17		-	2	2	3	3	-	4	12	-		-	1			
STM Impairment	-	-		-	-	-	-	3		-		-	-	-		-	-	
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STM Impairment	-	-		-	-	-	-	3		-		-	-		-		-	-
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Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
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Hyperarousal		8			2	2				4	10		6					1
Sleep-Wake Reversal						2			-	4	-		6				4	
Disorientation	-	17		-	2	2	3	3	-	4	12		-		-	1		
STM Impairment	-	-		-	-	-	-	3		-		-	-		-		-	-
Attention Impairment	-	-	1	-	-	-	3			-		7	6	-	1		4	20
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Treatment



- All patients received thiamine 500 mg iv TID
- Delay in treatment: 18 days (2-58 +/- 18d)



Summary - 1

- Risk Factors:
 - Cancer patients have many risk factors
 - Not the “usual suspects”
 - Many had normal B12 / Folate
 - Most were not underweight / low BMI
 - Some were even taking multivitamins



Summary - 2

- Diagnosis:
 - Triad is not reliable
 - Operational criteria may have high sensitivity



Summary - 3

- Other Important Findings:
 - Diagnostic and treatment delay
 - Significant morbidity



Questions?

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