

Managing Multiple Complications in Multiple Myeloma

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Presenter Disclosure

- **Faculty / Speaker's name:** Isanne Schacter
- **Relationships with commercial interests:**
 - **Grants/Research Support:** None
 - **Speakers Bureau/Honoraria:** Astra-Zeneca
 - **Consulting Fees:** None
 - **Other:** None

Mitigating Potential Bias

- **Not applicable**

Learning Objectives

- Describe the mechanism of hypothyroidism in the context of immunomodulatory drug use, and how to treat appropriately
- Describe the mechanism of hyperglycemia and diabetes mellitus in a patient treated with high dose glucocorticoids, and how to treat accordingly

Learning Objectives (Cont.)

- Describe the mechanism of hypercalcemia in the setting of multiple myeloma
- List treatment options for acute hypercalcemia

Case 1

- 67 year old female with multiple myeloma
- Treated with lenalidomide and Dexamethasone
- Mild symptoms of ~2.5 lb weight gain, constipation, cold intolerance and dry skin
- “Routine bloodwork” by family MD reveals:
 - TSH of 10.2 mU/L (N)
 - Free T3 of 1.8 pmol/L (N)
 - Free T4 of 6.7 pmol/L
- **What is the diagnosis?**



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What Is the Differential Diagnosis?

- Primary hypothyroidism
 - Autoimmune (Hashimoto's)
 - Iatrogenic
 - Thyroidectomy
 - Radioiodine therapy
 - External irradiation
 - Iodine deficiency OR excess
 - Infiltrative disease
 - Drugs
 - Thionamides
 - Lithium
 - Amiodarone
 - Tyrosine kinase inhibitors
 - Chemotherapy agents (i.e. thalidomide, lenalidomide)

Symptoms of Hypothyroidism:



- Fatigue
- Cold Intolerance
- Loss of Eyebrow Hair
- Sleep Problems
- Muscle Aches
- Infertility
- Slow Heart Beat
- Weight Gain
- Constipation
- Headaches
- Depression
- Dizziness
- Brain Fog
- Arthritis
- Brittle Nails
- Heavy Menstrual Periods

Mechanism of Action

- Uncertain
 - ?Inhibition of thyroid hormone secretion
 - ?Reduction of iodide uptake into follicular cells
 - ?antiangiogenic function: decreased blood flow to thyroid
 - ?Autoimmune thyroiditis
 - Deregulation of cytokines
 - Direct effect on T lymphocytes
 - ?Direct toxic effects

How Commonly Does this Occur?

- AZ Badros et al, Am J Med 2002:
 - In pts receiving thalidomide:
 - 20% had a TSH > 5 mU/L
 - 7% had a TSH > 10 mU/L
 - In pts receiving lenalidomide
 - 5-10% rate of hypothyroidism

Management

- Treat just like any other case of hypothyroidism!
 - Starting dose levothyroxine ~ 1.6 mcg/kg/day
 - Adjust according to repeats TFTs, with the aim of bringing TSH into the euthyroid range
- Monitoring
 - A Giagounidis et al., Ann Hematol 2008
 - Recommend baseline TSH before starting treatment
 - Q 2-3 months checks while receiving treatment

Case 2

- 67 yo previously healthy female with multiple myeloma
- Treated with Lenalidomide and Dexamethasone
- After one month, she complains of increasing polyuria and polydipsia as well as blurry vision
- RBG on blood work found to be 15.7 mmol/L
- Subsequent HbA1c = 9.4%

- **What is the diagnosis?**



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What Is the Differential Diagnosis?

- Likely underlying Type 2 diabetes not previously diagnosed
 - HbA1c is fairly high, likely reflects insidious process
 - All patients > 40 years old should be screened for DM2 before initiation of steroids
- “Unmasking of type 2 diabetes”
 - i.e. NOT de novo
 - Dose-dependent, usually mild increase in FBG and greater increase in post-prandial values

1. Olefsky HM et al. *Effects of glucocorticoids on carbohydrate metabolism*. Am J Med Sci. 1976
2. Gurwitz JH, et al. *Glucocorticoids and the risk for initiation of hypoglycemic therapy*. Arch Intern Med. 1994.

Mechanism

- Multifactorial
 - Increased hepatic gluconeogenesis
 - Decreased glucose uptake in adipose tissue
 - Alteration of receptor and post-receptor functions
- Gurwitz, JH, et al. Arch Intern Med, 1994.
 - Relative risk of new-onset diabetes rose progressively with GC dose from 1.8 (equivalent of < 10 mg/day prednisone) to 10.3 (equivalent of > 30 mg/day prednisone)
 - **Same risk factors as other patients with DM2**

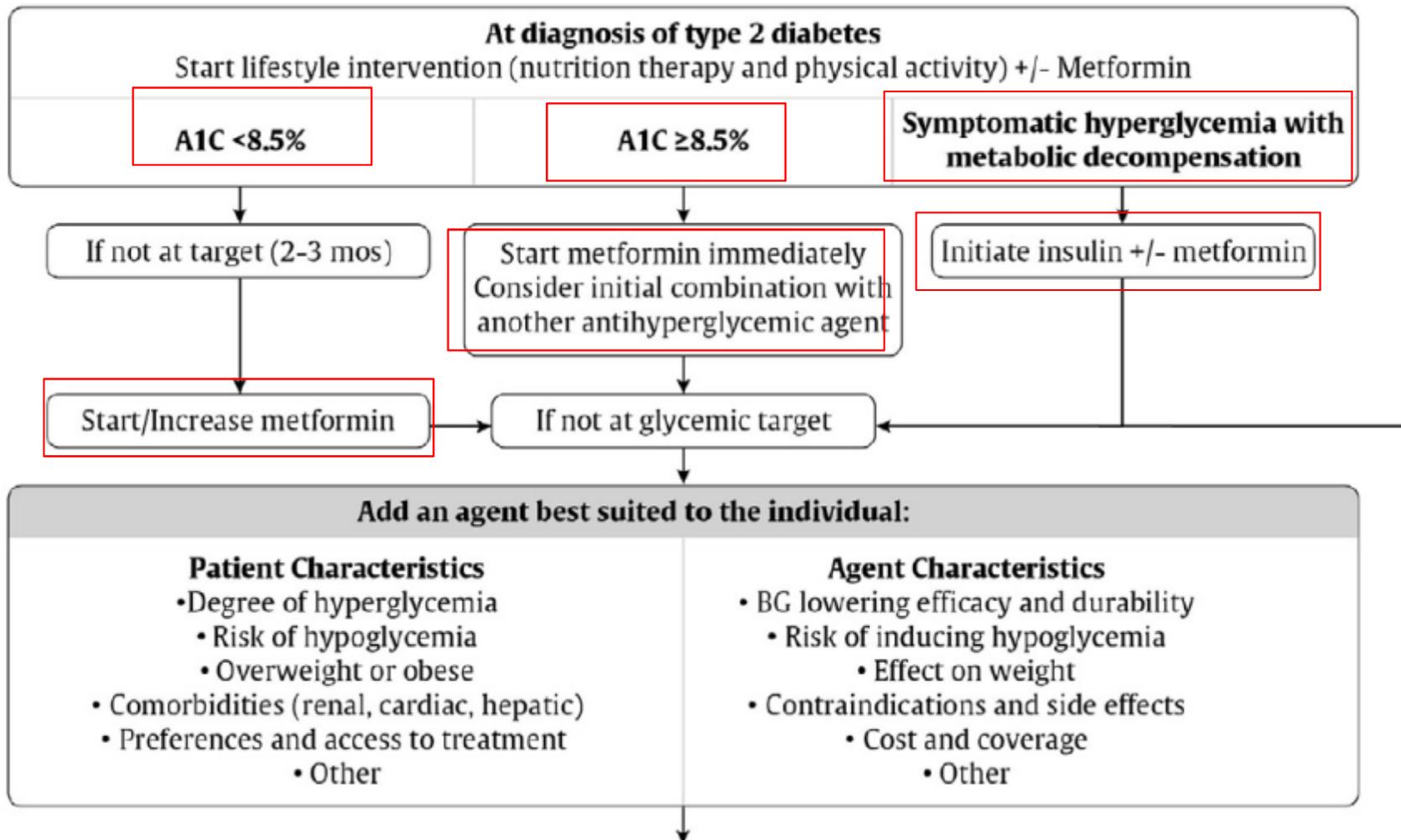
1. Schacke H, et al. *Mechanisms involved in the side effects of glucocorticoids*. Pharmacol Ther. 2002.
2. Hirsch IB, et al. *Diabetes management in special situations*. Endocrinol Metab Clin North Am. 1997.

How Would You Treat?

Treatment

- **Step 1**
 - **Initiate counseling re: diet and lifestyle choices to promote weight loss and normoglycemia**
 - Provide/arrange diabetes education, including SMBG (minimum BID; target FBG 4-7 mmol/L, 2 hour post prandial glucose < 10 mmol/L)
 - If not already taking, start on **metformin** 250 mg PO BID, with the aim of titrating up to a maximum dose of 1000 mg PO BID if tolerated/necessary
 - Monitor HbA1c q 3 months

CDA Clinical Practice Guidelines



Treatment (Cont.)

- Targets:
 - FBG (and pre-prandial BG) 4-7 mmol/L
 - 2 hour post-prandial BG < 10 mmol/L
- Shorter timeframe with steroids associated with chemotherapy
- **If not yet at target, what would you do?**
- **Step 2:**
 - If not within target at two weeks
 - Add additional OHA
 - Or proceed to insulin...

Treatment (Cont.)

- **Step 3**

- **If fasting blood glucose elevated (> 7 mmol/L)
ONLY:**

- **Initiate basal insulin**

- Start long-acting insulin (NPH/levemir/lantus) 10 units subcut at hs
- Increase dose by 1 unit q 1 night until FBG 4-7 mmol/L

- **Maintain metformin +/- other OHAs**

- **If daytime hypoglycemia, reduce dose of metformin/OHAs**

Treatment (Cont.)

- **Step 4**

- **If pre/post-prandial blood glucose values become elevated** (>7 mmol/L pre-prandial, or > 10 mmol/L 2 hours post-prandial):
 - **Add bolus insulin**
 - Add 10% of basal dose as bolus insulin pre meals (i.e. if 50 units NPH at hs, add 5 units rapid ac meals)
- **Stop secretagogues**
- **Maintain basal dose and metformin**

Treatment (Cont.)

- **Step 5**

- **If blood glucoses elevated all day long (i.e. pre-prandial BG values > 7 mmol/L and/or 2 hour post-prandial values > 10 mmol/L):**
 - **Initiate basal/bolus insulin**
 - Calculate Total Daily Dose (TDD) insulin as 0.3-0.5 units/kg x total body weight (kg)
 - » Administer 50% of TDD as basal insulin at hs
 - » Administer 50% of TDD distributed in split bolus doses (Novorapid/Humalog/Apidra) before each meal
- **Stop secretagogues**
- **Maintain metformin**

Treatment (Cont.)

- For **all** patients receiving insulin:
 - **Adjust basal insulin to target FBG of 4-7 mmol/L**
 - If fasting blood glucose < 7 mmol/L → reduce dose by 10%
 - **Adjust bolus insulin to target pre-prandial BG of 4-7 mmol/L of subsequent meal OR post-prandial BG of 5-10 mmol/L**
 - Give rapid acting insulin 0-10 minutes prior to eating meal
 - Patients should be counseled about the prevention, recognition, and treatment of hypoglycemia
 - *****Continue to monitor HbA1c q 3 months**

Screening

- Patients will require screening for microvascular complications as per other patients with DM2
 - Annual dilated eye examination to rule out diabetic retinopathy
 - Annual urinary albumin:creatinine ration to rule out diabetic nephropathy
 - Annual foot exam (with either monofilament or tuning fork) to rule out peripheral diabetic neuropathy

Screening (Cont.)

- If cessation of steroids
 - Hyperglycemia improves with reduction in dose of GC, and usually reverses when medication stopped
 - However, some patients develop persistent diabetes
 - Increased risk of development of diabetes in future
 - Should be screened annually

1. Miller SE, et al. *Clinical features of the diabetic syndrome appearing after steroid therapy*. Postgrad Med J. 1964.
2. Hricik DE, et al. *Effects of steroid withdrawal on posttransplant diabetes mellitus in cyclosporine-treated renal transplant recipients*. Transplantation. 1991.

Case 3

- 67 yo female with multiple myeloma
- Treated with Lenalidomide and Dexamethasone
- Increasingly lethargic, constipated, polyuria and polydipsia
- Unroutable by family
- Taken to local ER
- Routine blood work reveals a corrected calcium of **3.54** mmol/L
 - PTH within normal limits
- **What is the diagnosis?**



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Hypercalcemia of Malignancy

- 3 major mechanisms
 - Tumor secretion of parathyroid hormone-related protein (PTHrP)
 - Tumor production of 1,25-dihydroxyvitamin D (calcitriol)
 - **Osteolytic metastases with local release of cytokines (including osteoclast activating factors)**
- Osteoclast-induced bone resorption in discrete focal areas (lytic lesions) or throughout the skeleton

What Are the Typical Symptoms of Hypercalcemia?

Symptoms of Hypercalcemia

- Renal
 - Polyuria
 - Polydipsia
 - Nephrolithiasis
 - Nephrogenic DI
 - Acute and/or chronic KI
- GI
 - Anorexia, nausea, vomiting
 - Constipation
 - Pancreatitis
- MSK
 - Muscle weakness
 - Bone pain
 - Osteopenia/osteoporosis
- Neurologic
 - Decreased concentration
 - Confusion
 - Fatigue
 - Stupor
 - Coma
- Cardiac
 - QT interval shortening
 - Bradycardia
 - Hypertension

**“Bones, stones, groans, moans and
psychic overtones”**

How Should this Be Managed?

Management

- **Mild** (Ca < 3 mmol/L and asymptomatic or mildly symptomatic)
 - Avoid aggravating factors
 - HCTZ, lithium
 - Volume depletion
 - Prolonged bed rest or inactivity
 - High calcium diet (> 1000 mg/day)
 - Adequate hydration (6-8 glasses water/day)
 - Minimizes risk of nephrolithiasis

Management (Cont.)

- **Moderate/severe** hypercalcemia (Ca > 3 mmol/L and or symptomatic)
 - Require immediate attention
 - Volume expansion- IV NS at 200-300 cc/hr initially
 - Only once “juicy”, may use loop diuretic to increase calcium excretion

Other Agents

- Bisphosphonates
 - Pamidronate 30-90 mg IV x 1 (over 2 hours)
 - Zoledronate 4 mg IV x 1 (over 15 minutes)
 - Takes on average 2-4 days to reach full effect
 - Do not use if eGFR < ~30
- IV calcitonin
 - Tachyphylaxis
- Denosumab 60 mg subcut
 - No adjustment in CKD
- If refractory, hemodialysis

Other Agents (Cont.)

- Unfortunately, hypercalcemia unlikely to resolve until underlying mechanism resolves
- Therefore, many patients require ongoing and intermittent treatment with calcium-lowering agents

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Take Home Messages

- Treat hypothyroidism as per usual
- Treat diabetes as per usual
 - Tighter timeframe
 - Lower threshold to use insulin
- Treat acute hypercalcemia with fluids, fluids, fluids, then some lasix, and maybe a bisphosphonate
 - Remember alternatives in A/CKD

- Thank you!
- Any questions?



My Complication Had a Little Complication

Bad Things that Happen to Good People with
Multiple Myeloma

Dr. Mark Kristjanson

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 - **Consulting Fees:** Casey Hein & Associates
 - **Other:** N/A

Mitigating Potential Bias

- **Not Applicable**

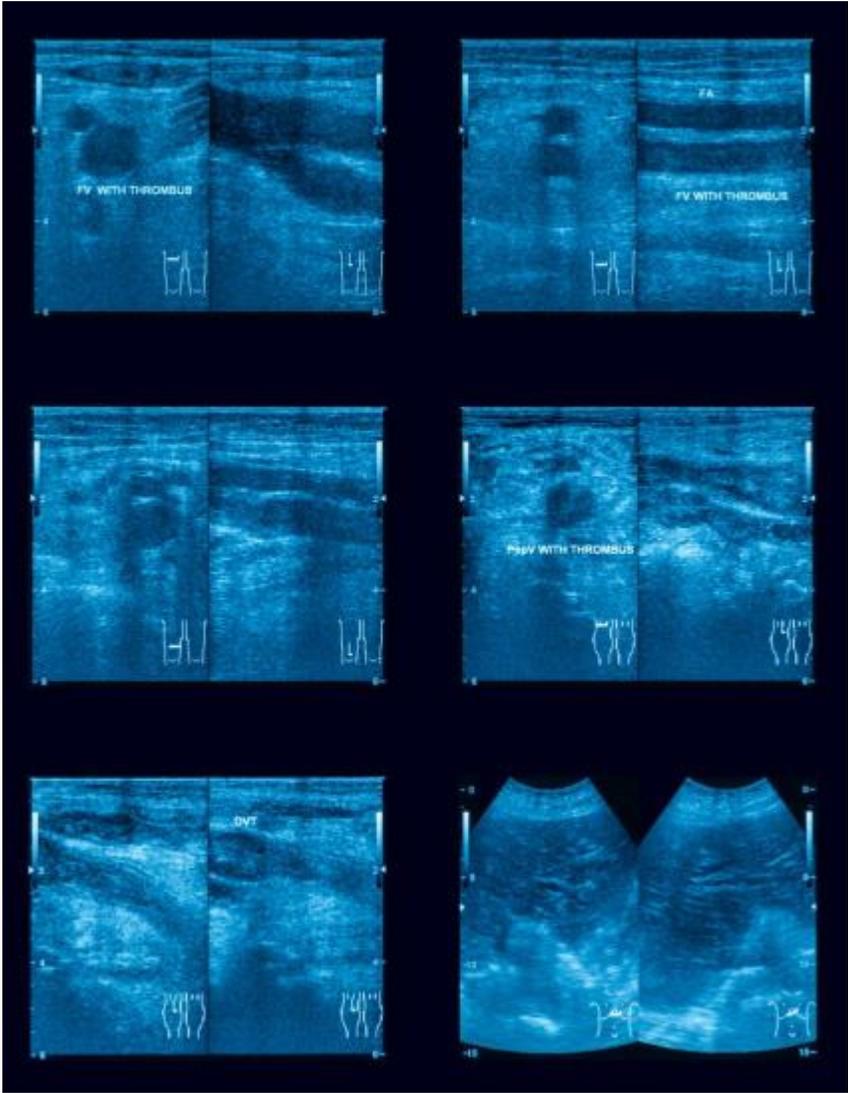
Learning Objectives

Describe the clinical presentation and management of each of these potential complications:

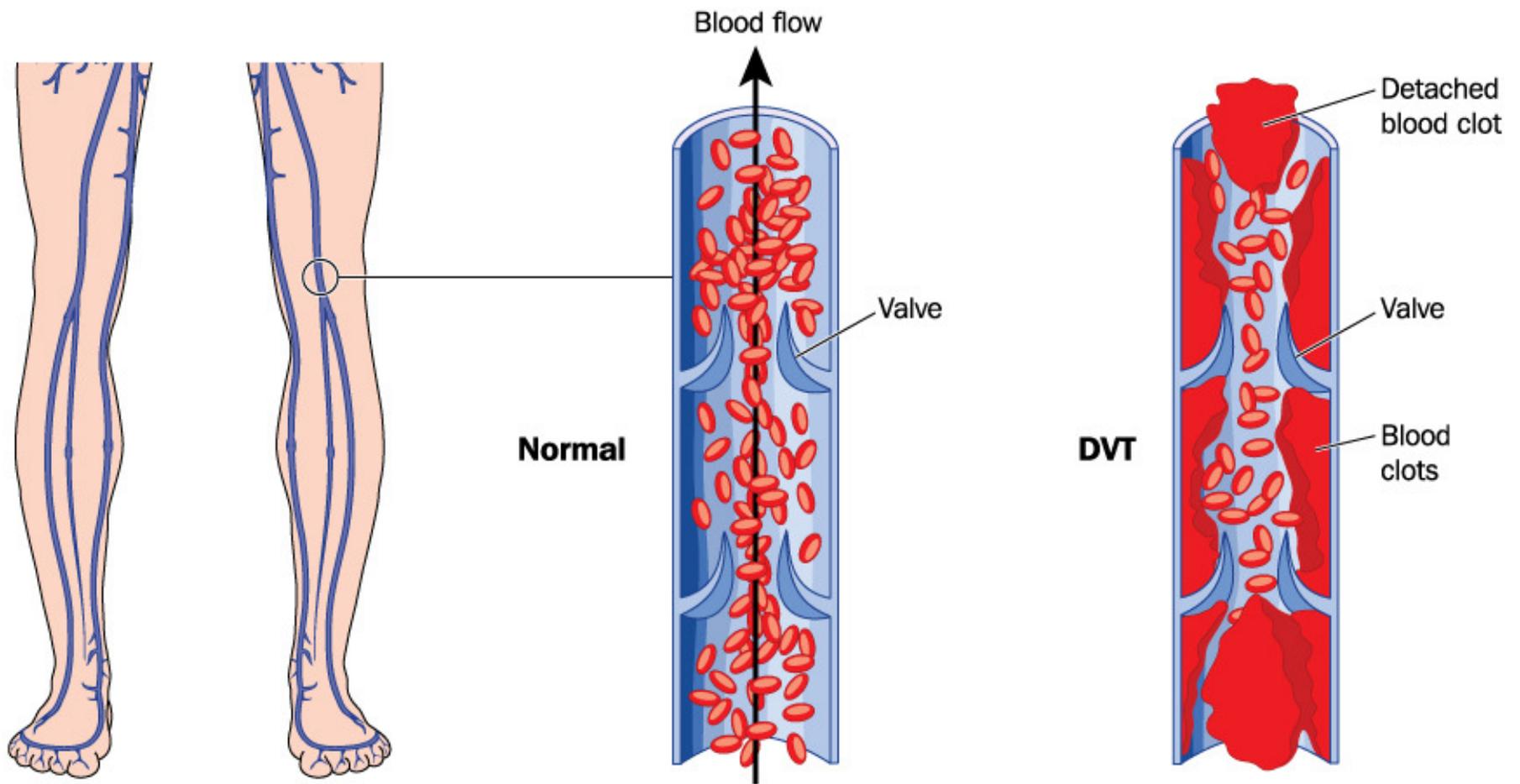
- VTE
- Herpes zoster (shingles)
- Heartburn (esp. from steroids)

Questions? – Any time

VTE

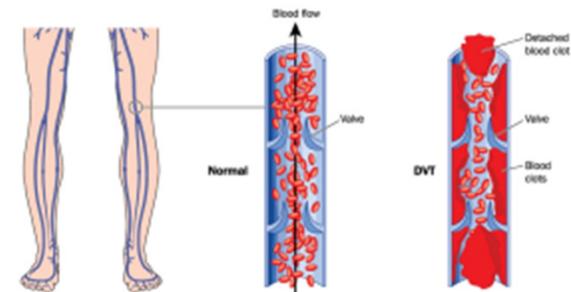


VTE



VTE – Risk Factors

- Increase in risk of VTE with MM highest in first year after diagnosis (HR 7.5)
- Immobilization e.g. pathologic #
- Renal disease
- Diabetes due to glucocorticoid use



VTE – Risk Factors (cont.)

- Acute infection due to immunosuppression,
- Erythropoietin
- CVAD
- Lenalidomide *plus* (e.g. len/dex; induction chemo)

VTE – Risk Factors (cont.)

- Brain
- Lung
- Prostate
- Kidney
- Ovary
- Adenocarcinoma of: pancreas; colon; stomach

VTE - Management

- CLOT* - randomized trial of 672 cancer patients with acute VTE
- 6 months of dalteparin vs. warfarin
- Significant reduction in the rate of recurrent VTE at six months (9 versus 17 %)

VTE – Management (Cont.)

- 200 international units/kg SQ once per day for the first month
- 150 international units/kg for the remaining five months)

VTE – Dalteparin vs Warfarin

- No significant differences in:
 - Major bleeding (6 versus 4 %)
 - Any bleeding (14 versus 19 %)
 - Overall mortality (39 versus 41 %)
- However, a post-hoc analysis mortality benefit with dalteparin in patients *without* metastatic disease (20 versus 36 percent)

VTE – How Long to Treat?

- Controversial
- Provoked - 3 months of blood thinner
- Catheter associated- as long as the catheter is in place or a minimum of 3 months.

VTE – How Long to Treat? (Cont.)

- Unprovoked (i.e. due to the myeloma):
 - at least 3 mo but more commonly 6 mo
 - then ***either*** continue LMWH ***or*** switch to an oral blood thinner for:
 - As long as cancer is considered "active"
 - or until prevention of clot is no longer meaningful goal.

VTE – Recurrence on treatment

- If on DOAC or warfarin – switch to LMWH
- If on therapeutic dose of LMWH – increase dose to 120 – 130% of therapeutic.
- Recurrence vs. post-phlebitic syndrome? Check D-dimer



Herpes Zoster

- For patients on bortezomib – prophylax with valacyclovir 500 mg od (or acyclovir 400 mg BID)
- Treatment:
 - Valacyclovir 1000 mg TID x 7 days;
 - Famcyclovir 500 mg TID x 7 days; or
 - Acyclovir 800 mg 5x/day x 7 days





Disseminated Shingles

- Hospitalize for IV acyclovir
- 5 to 10 mg/kg/dose every 8 hours for 2 to 7 days, follow with oral therapy to complete at least 10 days of therapy
- ID consult



Steroids & Tummy Aches



Steroid Gastropathy

- Do steroids cause ulcers? - not by themselves
- Combining a glucocorticoid with an NSAID (this includes ASA) raises x 4 the risk of upper GI injury (symptomatic or complicated ulcers)

Ann Rheum Dis. 2006;65(3):285–93. *Epub 2005 Aug 17*

Ann Intern Med. 1991;114(9):735.

Bonus content!
No extra charge



Estimating Fracture Risk with Bone Lesions

Mirels' Fracture Risk Calculator

Score	Site of lesion	Size of lesion	Nature of lesion	Pain
1	Upper limb	< 1/3 of cortex	Blastic	Mild
2	Lower limb	1/3 – 2/3	Mixed	Moderate
3	Trochanteric region	> 2/3 of cortex	Lytic	Functional

Mirels' Score

- 9 or greater: Fixation indicated
- 7 or less: manage using radiotherapy & drugs.
- 8: probability of fracture =15%; use clinical judgement

Take Home Messages

- Myeloma patients are at risk for VTE
- Dalteparin is first line tx
- Treat for 3 months (provoked)
- or for as long as disease active (unprovoked)

Take Home Messages

- Prophylax for shingles if on bortezomib
- Valacyclovir 1 g TID x 7d if one dermatome
- Cytoprotection if ASA + steroids
- Prophylactic fixation for Mirels' score 8 or more