CLINICAL CASES

Case: Ms. MC

Patient Profile

- 35-year-old female, accountant
- Non-smoker, does not drink alcoholic beverages
- Presents at the ER complaining of difficulty urinating
- Started to experience difficulty urinating about a year ago
  - Also increased frequency and pain
  - Febrile episodes; Tmax = 38.6°C

Ms. MC's History: 1 Year Ago

- Urinalysis: pyuria = 20-30 pus cells/hpf
- **Diagnosis**: urinary tract infection
- **Treatment**: 500 mg ciprofloxacin q 12 h x 7 days
  - Repeat urinalysis showed no infection

hpf = high power field

Discussion Questions

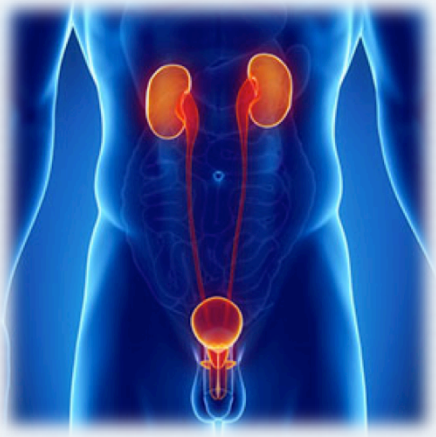
BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Signs and Symptoms of Interstitial Cystitis

- Chronic pelvic pain
- Pain between vagina and anus (women) or scrotum and anus (men)
- Persistent, urgent need to urinate
- Frequent urination – often small amounts – throughout the day and night
  - Up to 60 times/day
- Pain/discomfort while bladder fills
- Relief after urination
- Painful sexual intercourse



Mayo Clinic. Interstitial Cystitis. Available at: http://www.mayoclinic.org/diseases-conditions/interstitial-cystitis/basics/symptoms/con-20022439. Accessed March 24, 2015.

Burden of Interstitial Cystitis

- Frequent urination
- Bladder pain
- Decreased physical functioning
- Decreased ability to function in normal role
- Decreased vitality
- Decreased social functioning
- Decreased sexual functioning

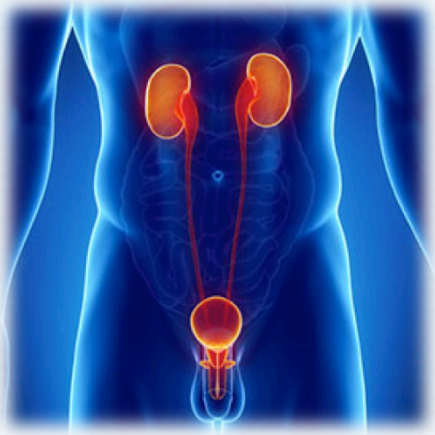
Quality of life of patients with interstitial cystitis is poorer than that of patients undergoing dialysis for ESRD

ESRD = end-stage renal disease

Hanno PM. *Rev Urol*. 2002;4(Suppl 1):S3-S8; Rothrock NE *et al. J Urol.* 2002;167:1763-7; Nickel JC *et al. J Urol*. 2007;177:1832-6.

Causes of Interstitial Cystitis (IC)

- Exact causes unknown
  - Likely involves many factors
  - May include autoimmune reaction, genetics, infection, or allergy
- Patients with IC may also have a defect in bladder epithelium
- May be a bladder manifestation of a more general inflammatory condition



Some IC symptoms resemble those of bacterial infection but urine cultures indicate no infection

Mayo Clinic. Interstitial Cystitis. Available at: http://www.mayoclinic.org/diseases-conditions/interstitial-cystitis/basics/causes/con-20022439. Accessed March 24, 2015; National Kidney and Urologic Diseases Information Clearinghouse. Interstitial Cystitis/Painful Bladder Syndrome. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/IC_PBS_T_508.pdf. Accessed March 24, 2015.

Ms. MC: Past Medical History

- Migraines since the age of 20
- Unremarkable gynecologic history
- Occasional dysmenorrhea
- Family history (mother) of hypertension

Ms. MC: 10 Months Ago…

- Experienced subrapubic pain
  - Intermittent and crampy
  - Increased frequency of urination
    - Nocturia: sometimes 3-4 times nightly
- Dyspareunia
- Symptoms resolved spontaneously after a few days so she did not consult her physician

Ms. MC: 7 Months Ago…

- Recurrence of suprapubic pain
- Radiating to lower abdomen
- Increased urinary frequency and nocturia
- Consulted physician
  - Urinalysis = normal
  - Treatment = analgesics (paracetamol, mefenamic acid)
    - Did not provide symptom relief

Ms. MC: Gynecological Consult

- 3 months ago
- Results unremarkable
  - Normal speculum and pelvic exams
  - Normal Pap smear

Ms. MC: Urology Consult

- 3 months ago
- Cystoscopy
  - Multiple submucosal hemorrhages over posterior wall of urinary bladder
  - Glomerulations
- Cystometry
  - Increase in pain during bladder filling; relieved with bladder emptying
- Bladder biopsy: no carcinomatous lesions

Ms. MC: History

- Patient continues to experience relentless pain over suprapubic area
  - Pain medications do not work
- Sleepless nights due to nocturia
- Reduced sex drive
- Depressed

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Diagnosis

- This patient has interstitial cystitis.

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Treatment of Interstitial Cystitis

Non-pharmacological	• Avoidance of trigger foods • Dietary supplementation • Stress relieving exercises • Transcutaneous nerve stimulations (TENS)
Oral medication	• Antihistamines • Antidepressants • Cimetidine • Sodium pentosanpolysulfate • L-arginine • Prelief • Oxybutinin • Antibiotics • Methenamine
Drugs for bladder instillation	• Hylauronic acid • Chondroitin sulfate • Dimethylsulfoxide (DMSO) • Intravesical heparin • Hydrodistension
Surgery	• Partial cystectomy • Augmentation cystoplasty • Urinary diversion

Jha S *et al. The Obstetrician and Gynecologist.* 2007;9:34-41.

Case Template: Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Ms. MC: Follow Up

- A full gynecologic and urologic examination and diagnostic tests were done

Case: Mr. AD

Mr. AD: History

- 38-year-old male journalist
- 8-year history of bowel problems
- Complains of intermittent abdominal cramping, bloating, and urgent loose stools
  - “Bad days" occur 2 or 3 times per week
- Describes lower abdominal cramping that is relieved after 1 or 2 loose stools
- Reports his symptoms are worse after eating
  - Significant impact on his personal and work life
- Avoids going to restaurants
  - Usually skips meals on work days to prevent an urgent need to use the bathroom while driving

Mr. AD: History

- Previous treatments: antispasmodics, a probiotic, and an antibiotic.
- Antidiarrheal agents sometimes provided transient relief but led to constipation
- Short course of amitriptyline: sedative side effects; medication was intolerable
- Denies rectal bleeding, fevers, or weight loss
- Thinks his mood affects his symptoms
  - Believes stress may be an exacerbating factor
- No family history of gastrointestinal diseases or cancer
- Has been trying to avoid fatty and greasy foods
  - Not sure if it has been helpful
- Wondering if there are any other options – including nonmedical strategies – to address his symptoms

Discussion Question

Which of the following would you use to make the diagnosis in Mr. AD? Why?

- Colonoscopy with biopsies
- Breath test for small intestinal bacterial overgrowth
- ROME III criteria
- Thyroid-stimulating hormone and celiac serologies

Mr. AD: Clinical Examination and Pain Assessment

- Good health
  - Mild obesity (body mass index = 29 kg/m^2)
- Clinical examination
  - Abdomen is soft, mildly tender diffusely with some mild distention
  - No organomegaly
- Previous laboratory results show no anemia
- Celiac serologies negative
- Colonoscopy (1 year ago): normal colonic and terminal ileal mucosa with normal random biopsies

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Rome III Diagnostic Criteria for Irritable Bowel Syndrome (IBS)

- Symptom onset ≥6 months prior to diagnosis
- Recurrent abdominal pain or discomfort ≥3 days per month in the last 3 months associated with ≥2 of the following:
  - Improvement with defecation
  - Onset associated with a change in stool frequency
  - Onset association with a change in stool form (appearance)
- ≥1 of the following symptoms on at least one quarter of occasions for subgroup identification:
  - Abnormal stool frequency (<3/week)
  - Abnormal stool form (lumpy/hard)
  - Abnormal stool passage (straining, incomplete evacuation)
  - Bloating or feeling of abdominal distension
  - Passage of mucous
  - Frequent, loose stools

Longstreth, GF *et al*. Functional bowel disorders. In: Drossman, DA; Corazziari, E; Delvaux, M *et al.*, editors. Rome III: the functional gastrointestinal disorders. 3rd ed. McLean, VA: Degnon; 2006. p. 487-555.

Rome III Diagnostic Criteria for Irritable Bowel Syndrome (IBS)

- Three subgroups of IBS:
  - IBS with diarrhea (IBS-D) (more common in men)
  - IBS with constipation (IBS-C) (more common in women)
  - IBS with mixed bowel habits

- Each group accounts for about one third of all patients.

Longstreth, GF *et al*. Functional bowel disorders. In: Drossman, DA; Corazziari, E; Delvaux, M *et al.*, editors. Rome III: the functional gastrointestinal disorders. 3rd ed. McLean, VA: Degnon; 2006. p. 487-555.

Mr. AD: What Is the Diagnosis?

- Patient fulfills Rome III criteria for **IBS**:
  - >6 months of recurrent abdominal pain/discomfort ≥3 days per month within the last 3 months
  - Pain/discomfort improves with defecation
  - Onset of symptoms associated with a change in frequency or form of stool
- Patient fulfills criteria for **IBS with diarrhea** (IBS-D):
  - Loose (mushy) or watery stools ≥25% of the time and hard or lumpy stools <25% of bowel movements
  - Also some classic IBS symptoms (bloating, urgency, heightened gastrocolic reflex)

Mr. AD: What Is the Diagnosis?

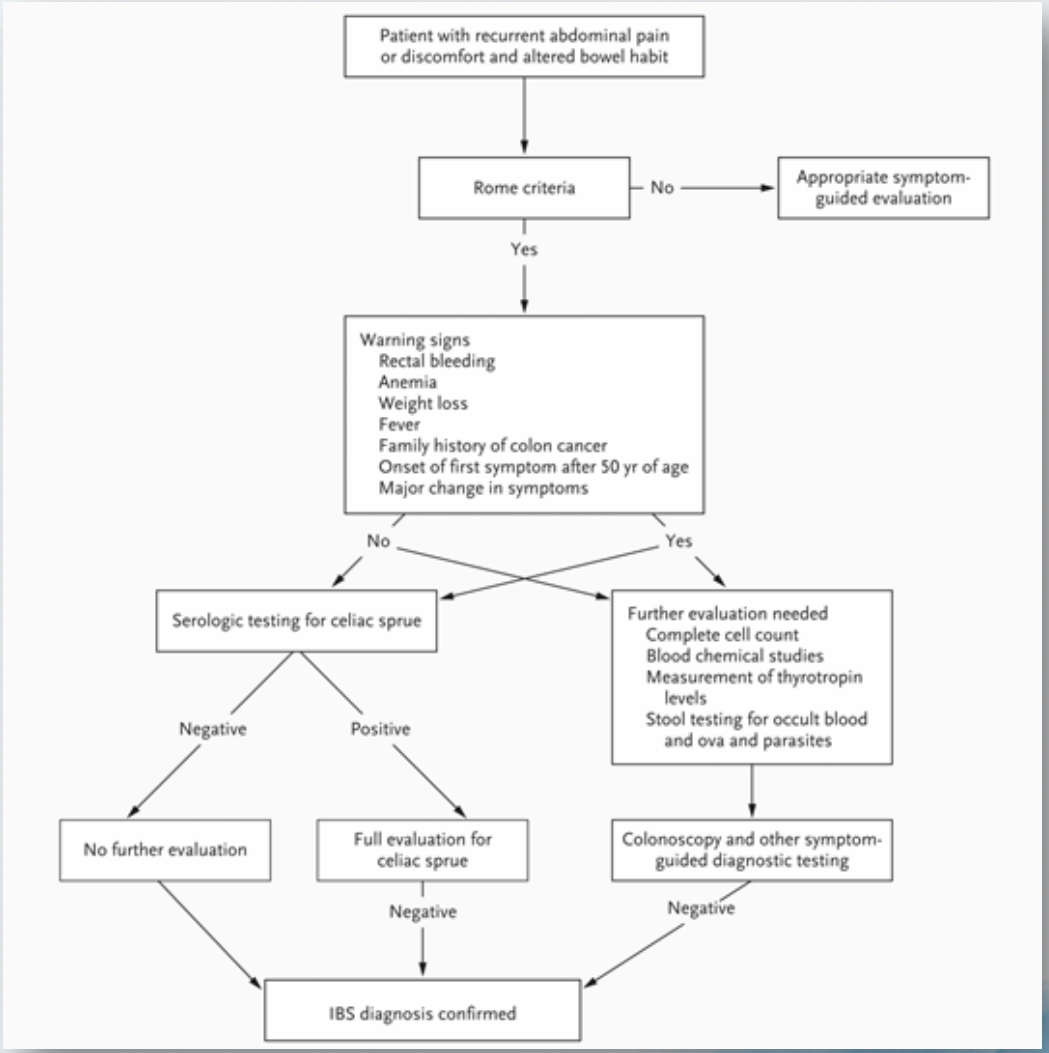
Mr. AD was diagnosed with irritable bowel syndrome with diarrhea (IBS-D)

Irritable Bowel Syndrome (IBS)

- ≤20% of adults experience symptoms compatible with IBS
- Defined by recurring abdominal pain with altered bowel habits
  - No structural or easily identifiable biochemical abnormality
- Possible factors in IBS pathogenesis:
  - Disturbances in motility
  - Brain-gut axis
  - Genetic factors
  - Impaired gut barrier function
  - Mucosal immunologic function
  - Gut microbiome
  - Psychosocial factors

Lacy BE. Available at: http://www.medscape.org/viewarticle/750958. Accessed June 15, 2015.

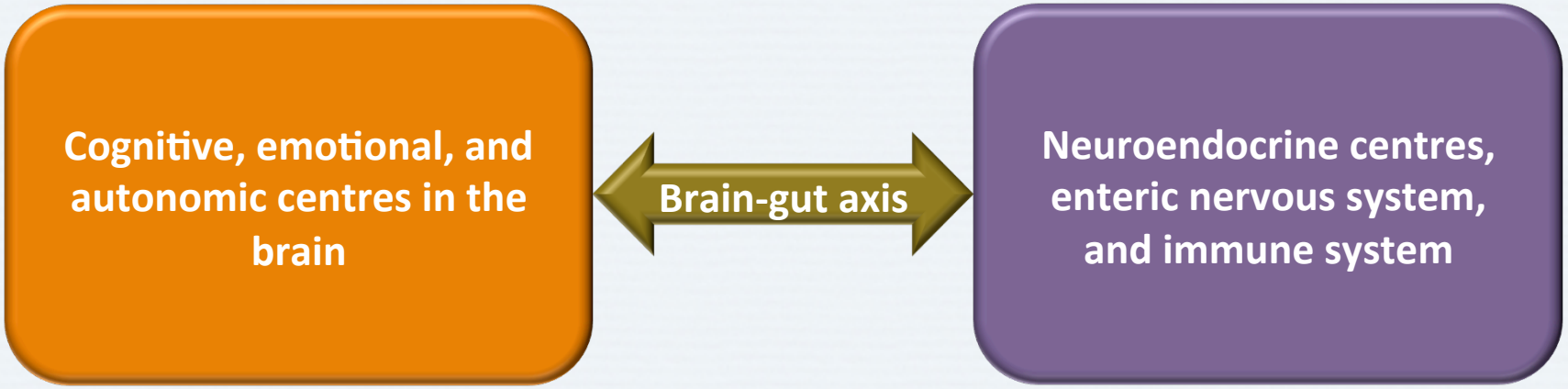
Differential Diagnosis of Irritable Bowel Syndrome (IBS)



IBS = irritable bowel syndrome

Mayer EA. *N Engl J Med*. 2008;358:1692-9.

Brain-Gut Axis in Visceral Pain



Altered brain-gut interactions can contribute to autonomic dysregulation of the gut and associated pain and perceptual changes in visceral disorders

Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care*. 2012;6(1):17-26.

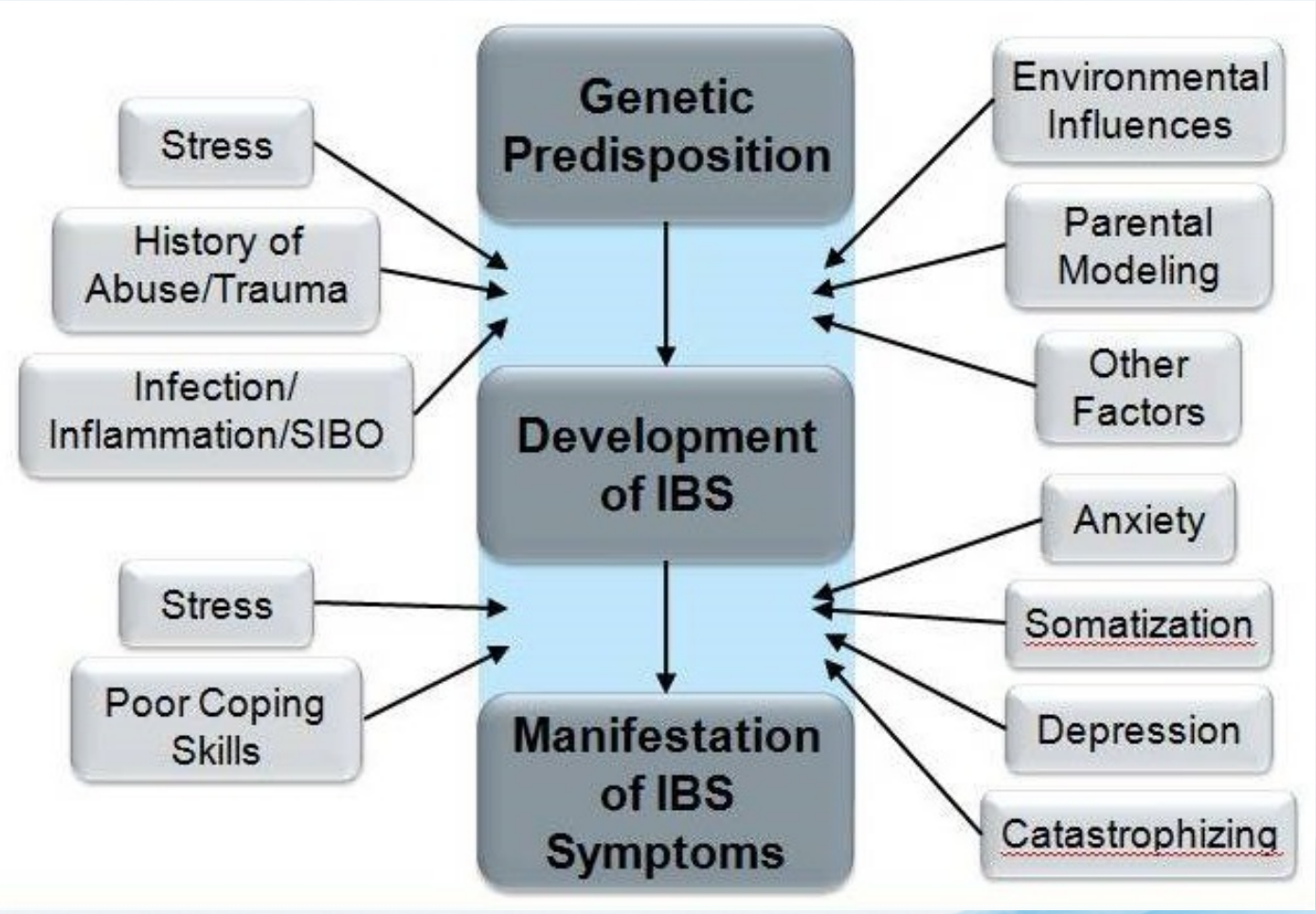
Discussion Question

What would you tell this Mr. AD is the cause of his IBS symptoms?

- Underlying anxiety and depression
- History of sexual abuse
- Malabsorption
- Genetic predisposition in the face of an insult

IBS = irritable bowel syndrome

Putative Model of IBS Development



IBS = irritable bowel syndrome

Lacy BE. Available at: http://www.medscape.org/viewarticle/750958. Accessed June 15, 2015.

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

What is the best treatment for IBS ?

IBS = irritable bowel syndrome

Multimodal Approach to IBS Treatment

The multiple symptoms of IBS require a multidisciplinary approach to treatment, including medications, diet and nonpharmacological methods

IBS = irritable bowel syndrome

Lacy BE. Available at: http://www.medscape.org/viewarticle/750958. Accessed June 15, 2015.

Discussion Question

The prescription of which of the following agents for Mr. AD would be based on high-quality randomized trials demonstrating efficacy?

- Loperamide
- Diphenoxylate
- Alosetron
- Octreotide

Evidence-Based Treatments for IBS-D

Drug	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency
Alosteron	+	+	+	+	
Antibiotics (rifaximin)	+		+		
Antidepressants	+	+			
Loperamide				+	+
Antispasmodics	+/-	+			
Probiotics (bifidobacteria, some combinations)	+	+	+		

IBS-D = irritable bowel syndrome with diarrhea

American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD *et al. Am J Gastroenterol.* 2009;104 Suppl 1:S1-35.

Medications for Diarrhea in IBS-D

Drug	Side Effects	Evidence		FDA Approved	
		For Symptom	For IBS	For Symptom	For IBS
Loperamide	Constipation	+++	-	Yes	No
Amitriptyline		++	+	No	No
Desipramine		++	+	No	No
SSRIs	Sexual dysfunction, headache, nausea, sedation, insomnia, sweating, withdrawal symptoms				
Paroxetine		-	+	No	No
Citalopram		+	+	No	No
Fluoxetine		+	-	No	No

IBS-D = irritable bowel syndrome with diarrhea; SSRI = selective serotonin reuptake inhibitor

Mayer EA. *N Engl J Med*. 2008;358:1692-9.

Medications for Constipation in IBS-C

Drug	Side Effects	Evidence		FDA Approved	
		For Symptom	For IBS	For Symptom	For IBS
Laxatives and Secretory Stimulators					
Polyethylene glycol 3350	Diarrhea, bloating, cramping	+++	-		
Lactulose	Diarrhea, bloating, cramping	+++	-		
Lubiprostone	Nausea, diarrhea, headache, abdominal pain and discomfort	+++	-	Yes	No
Prokinetics					
Tegaserod	Initial diarrhea, abdominal pain, cardiovascular ischemia (rare)	+++	+++	Yes	Yes

IBS-C = irritable bowel syndrome with constipation

Mayer EA. *N Engl J Med*. 2008;358:1692-9.

Abdominal Pain in IBS

- Antispasmodics (hyoscyamine, mebeverine) have been used to treat pain
  - No data from high quality RCTs of effectiveness in reducing pain or global symptoms
- Tricyclic antidepressants commonly used
  - Often in low doses (*e.g.*, 10-75 mg amitriptyline)
- Several small, randomized, controlled trials suggest SSRIs may have beneficial effects in patients with IBS
  - Especially effective in improving general well-being
  - Some studies indicate positive effects on abdominal pain
- High prevalence of coexisting anxiety in patients with IBS
  - Benzodiazepines are **not** recommended for long-term therapy
    - Risk of habituation and potential for dependency

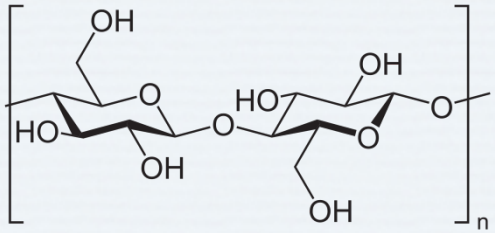
IBS = irritable bowel syndrome; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor

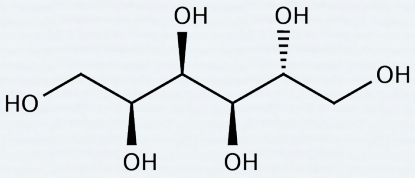
Mayer EA. *N Engl J Med*. 2008;358:1692-9.

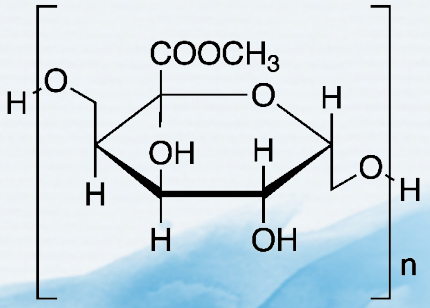
Discussion Question

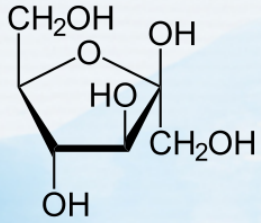
Which of the following would you limit if you were to recommend a FODMAP-restricted diet for this patient?

- Fructose, lactose, cellulose
- Fructose, fructans, pectins
- Fructose, cellulose, pectins
- Sorbitol, fructans, raffinose









FODMAP = Fermentable Oligo-Di-Monosaccharides and Polyols

Low FODMAPs: A Dietary Approach to IBS

- FODMAPs = poorly absorbed, short-chain carbohydrates
- Highly fermentable by gut bacteria
- Fermentation → gas and increased fluid load
  - Secondary luminal distension + peristalsis in distal small bowel and proximal colon → diarrhea, bloating, cramping

Evidence suggests a FODMAP-reduced diet may provide a 20% therapeutic advantage over a standard diet

FODMAP = Fermentable Oligo-Di-Monosaccharides and Polyols; IBS = irritable bowel syndrome

Catsos P. IBS – Free at Last!: A Revolutionary, New Step-by-Step Method for Those Who Have Tried Everything. Control IBS Symptoms by Limiting FODMAPS Carbohydrates in Your Diet. Portland, Maine: Pond Cove Press; 2009.

FODMAP Dietary Recommendations

FODMAP	Fructose	Polyols	Lactose	Fructans, Galactans
High FODMAP	Apples, pears, watermelon, honey, fruit juices, dried fruits, high-fructose corn syrup	Sugar, alcohols,* stone fruits, avocado, mushrooms, cauliflower	Milk,† yogurt, soft cheeses (ricotta, cottage)	Wheat, rye, garlic, onions, artichokes, asparagus, inulin, soy, leeks, legumes, lentils, cabbage, Brussels sprouts, broccoli
Alternative Lower FODMAP	Citrus, berries, bananas, grapes, honeydew, cantaloupe, kiwifruit	Sweeteners, including sugar, glucose, other artificial sweeteners not ending in "ol" (sucralose, aspartame are good)	Lactose-free dairy products, rice milk, hard cheeses	Starches (rice, corn, potato, and quinoa), vegetables (winter squash, lettuce, spinach, cucumbers, bell peppers, green beans, tomato, eggplant)

*Sorbitol, maltitol, mannitol, xylitol, isomalt †Cow, goat, sheep

FODMAP = Fermentable Oligo-Di-Monosaccharides and Polyols

Catsos P. IBS--Free at Last!: A Revolutionary, New Step-by-Step Method for Those Who Have Tried Everything. Control IBS Symptoms by Limiting FODMAPS Carbohydrates in Your Diet. Portland, Maine: Pond Cove Press; 2009.

Cognitive Behavioral Therapy (CBT) for IBS

- Best studied psychological treatment for IBS
- Cognitive techniques (group or individual, 4 to 15 sessions) aim to change catastrophic or maladaptive thinking patterns underlying the perception of somatic symptoms
- Behavioral techniques aim to modify dysfunctional behaviors through relaxation techniques, contingency management (rewarding healthy behaviors), or assertion training
- Some RCTs have also shown reductions in IBS symptoms with the use of gut-directed hypnosis

IBS = irritable bowel syndrome; RCT = randomized controlled trial

Mayer EA. *N Engl J Med*. 2008;358:1692-9.

Mr. AD: Therapeutic Approach

- A lot of Mr. AD's first visit was spent reviewing the etiology, pathophysiology, and treatment of IBS with him
- A low-FODMAP diet administered under the guidance of a registered dietician who is familiar with this diet was recommended
- He was referred for cognitive behavioral therapy
- He was also seen by a psychiatrist for hypnotherapy

Case Template: Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Mr. AD: Follow-up

6 weeks

- Mr. AD states that he feels 40%-45% better

3 months

- Mr. AD notes a 70%-75% improvement in his symptoms

Mr. AD: Case Conclusion

- Mr. AD's presentation represents moderately severe IBS-D because his symptoms are longstanding and lifestyle altering, but they are not incapacitating.
- He has tried multiple medications in the past, including antispasmodics and antidiarrheal medications, but ultimately did not find them helpful.
- Often in these types of cases a low-dose TCA would be recommended, but he has been intolerant to these medications in the past.
- He has also tried a probiotic and possibly rifaximin for his IBS-D without much success.
- Given his lack of response and intolerance to multiple medications, he was motivated to follow through with diet modification and cognitive behavioral therapy for his IBS symptoms.

IBS-D = irritable bowel syndrome with diarrhea; TCA = tricyclic antidepressant

Mr. AD: Case Conclusion cont'd

- While it is natural for providers to initially presume that the complexity of the low-FODMAP diet guarantees patient non-adherence, patients with IBS often desire a more holistic approach to their care.
- They often are interested in learning about dietary interventions, especially when symptom onset is related to eating a meal.
- Such patients are often already on highly restrictive diets; they are therefore highly motivated to follow structured, evidence-based dietary interventions.

The treatment of IBS-D requires a multifaceted approach that includes finding the optimal combination of the pharmacotherapeutic, dietary, and behavioral treatments.

FODMAP = Fermentable Oligo-Di-Monosaccharides and Polyols; IBS-D = irritable bowel syndrome with diarrhea

Red Flags for Differential Diagnosis in IBS

- Symptom onset after age 50 years
- No rectal bleeding
- No significant changes in blood tests (*e.g.*, unexplained iron deficiency anemia)
- No fever
- No unexplained weight loss
- No abdominal mass
- No family history of cancer, gastrointestinal disease
- No evidence of inflammatory, anatomic, metabolic, or neoplastic process

IBS = irritable bowel syndrome

Chey WD *et al. JAMA*. 2015;313:949-58.

Case: Mrs. RL

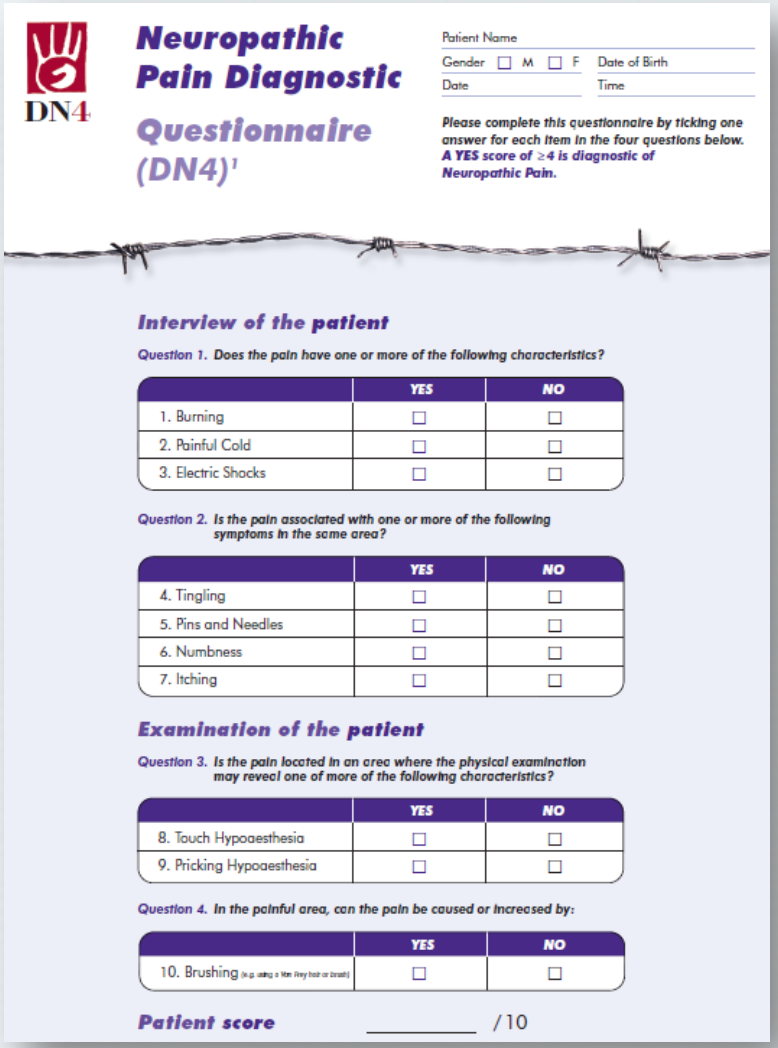
Mrs. RL: Profile

- 33-year-old female housewife
- Complains of vulvar discomfort described as burning
  - Has been occurring for the last 9 months

Mrs. RL: Physical Exam

- No sign of vaginal infection (*e.g.*, herpes, candidiasis), inflammation (*e.g.*, lichen sclerosis), or neoplasia
- Cotton swab touching 6 vestibular sites was described as painful
- Brush allodynia positive for most painful vestibule area
- DN4 questionnaire score = 5/10

DN4



Neuropathic Pain Diagnostic Questionnaire (DN4)[1]

DN4

Patient Name

Gender ☐ M ☐ F Date of Birth

Date Time

Please complete this questionnaire by ticking one answer for each item in the four questions below. A YES score of ≥4 is diagnostic of Neuropathic Pain.

Interview of the patient

Question 1. Does the pain have one or more of the following characteristics?

	YES	NO
1. Burning	☐	☐
2. Painful Cold	☐	☐
3. Electric Shocks	☐	☐

Question 2. Is the pain associated with one or more of the following symptoms in the same area?

	YES	NO
4. Tingling	☐	☐
5. Pins and Needles	☐	☐
6. Numbness	☐	☐
7. Itching	☐	☐

Examination of the patient

Question 3. Is the pain located in an area where the physical examination may reveal one of more of the following characteristics?

	YES	NO
8. Touch Hypoaesthesia	☐	☐
9. Pricking Hypoaesthesia	☐	☐

Question 4. In the painful area, can the pain be caused or increased by:

	YES	NO
10. Brushing (e.g. using a fine fluffy hair or brush)	☐	☐

Patient score _____ /10

- Completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 2 pain questions (7 items)
- 2 skin sensitivity tests (3 items)
- **Score ≥4 is an indicator for neuropathic pain**
- Validated

DN4 = Douleur neuropathique en 4 questions

Bouhassira D *et al. Pain* 2005; 114(1-2):29-36.

Mrs. RL: History

- Mrs. RL admits she suffers from anxiety
- She is also having marital difficulties

Medical history

- Interstitial cystitis (painful bladder, frequency, urgency, nocturia with no known cause)
- Fibromyalgia

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

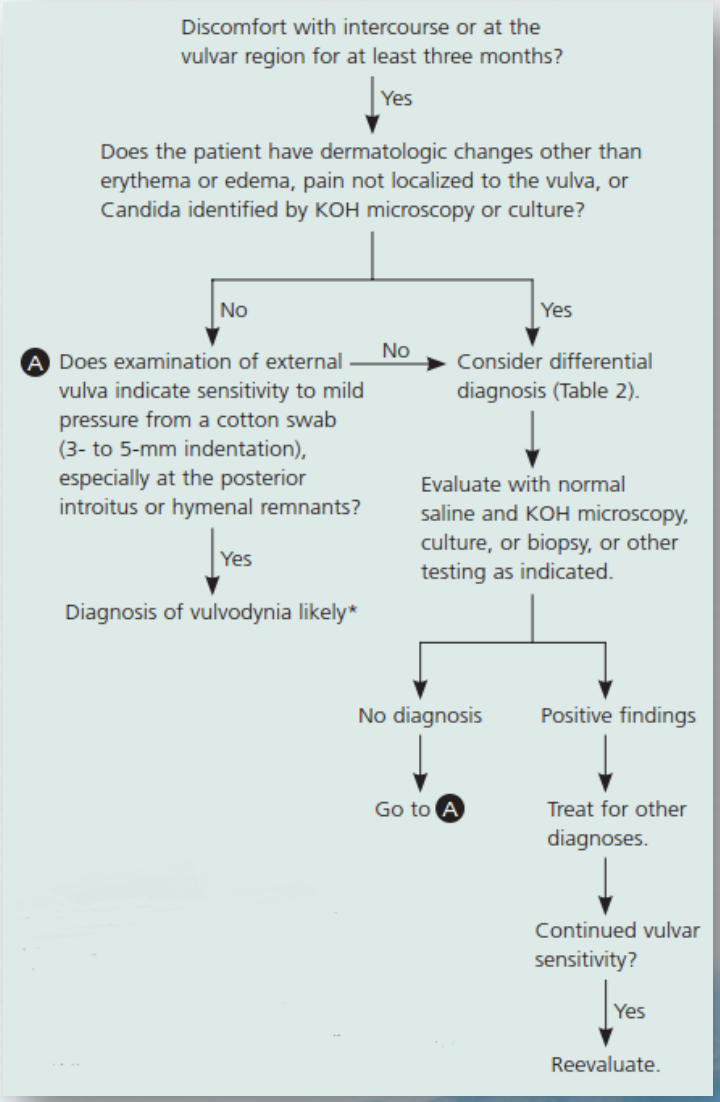
Mrs. RL: Further Tests/Examinations

- ***Dermatological examination***: no evidence of edema, erythema, pallor, or hyperpigmentation
- ***Neurological examination***: No evidence of hypoesthesia in pudental nerve distribution, but brush allodynia (+) and pinprick hyperalgesia (+) in the vulvar region, posterior introitus
- ***Gynecological examination***: No evidence of tumor, infection

Further Tests/Examinations - Results

- Vaginal smear test: negative for neoplastic changes
- Vaginal wet mount, KOH stain, fungal culture and Gram stain: negative for Candidiasis/yeast or bacterial infection

Differential Diagnosis of Vulvar Pain and Dyspareunia



Reed BD. *Am Fam Physician*. 2006;73(7):1231-8.

ISSVD Vulvodynia Pattern Questionnaire

What are your symptoms? (circle all that apply)

burning	stinging	rawness	irritation
soreness	itching	stabbing	knife-like
paper-cuts	aching		
other	_____		

Which of the following produces pain?

Sexual intercourse

If yes,

With penetration

During intercourse

After intercourse

With all partners

Insertion of tampon

Tight clothing or blue jeans

Which of the following problems do you have? (circle)

Fibromyalgia	High blood pressure
Frequent headaches	Angina pectoris/heart attacks
Frequent urinary tract infections	Diabetes mellitus
Chronic fatigue syndrome	Genital herpes
Low energy levels	Thyroid disease
Depression	Sinus problems/hay fever
Difficulty sleeping	Allergies to medications
Weight gain or loss of more than ten pounds unintentionally in the past six months	
Back pain	TMJ syndrome (temporomandibular joint)
Pelvic pain	

Full questionnaire

ISVVD = International Society for the Study of Vulvovaginal Disease

Available at: https://netforum.avectra.com/temp/ClientImages/ISSVD/3ef9c6ea-aac7-4d2b-a37f-058ef9f11a67.pdf. Accessed March 24, 2015.

Vulval Pain Functional Questionnaire

1. Because of my pelvic pain
   - ☐ 3 I can't wear tight-fitting clothing like pantyhose that puts any pressure over my painful area.
   - ☐ 2 I can wear closer fitting clothing as long as it only puts a little bit of pressure over my painful area.
   - ☐ 1 I can wear whatever I like most of the time, but every now and then I feel pelvic pain caused by pressure from my clothing.
   - ☐ 0 I can wear whatever I like; I never have pelvic pain because of clothing.

3. My pelvic pain
   - ☐ 3 Gets worse when I sit, so it hurts too much to sit any longer than 30 minutes at a time.
   - ☐ 2 Gets worse when I sit. I can sit for longer than 30 minutes at a time, but it is so painful that it is difficult to do my job or sit long enough to watch a movie.
   - ☐ 1 Occasionally gets worse when I sit, but most of the time sitting is comfortable.
   - ☐ 0 My pain does not get worse with sitting, I can sit as long as I want to.
   - ☐ 0 I have trouble sitting for very long because of another medical problem, but pelvic pain doesn't make it hard to sit.

6. Because of my pelvic pain
   - ☐ 3 I don't get together with my friends or go out to parties or events.
   - ☐ 2 I only get together with my friends or go out to parties or events every now and then.
   - ☐ 1 I usually will go out with friends or to events if I want to, but every now and then I don't because of the pain.
   - ☐ 0 I get together with friends or go to events whenever I want, pelvic pain does not get in the way

10. Because of my pelvic pain
    - ☐ 3 It hurts too much for my partner to touch me sexually even if the touching doesn't go in my vagina.
    - ☐ 2 My partner can touch me sexually outside the vagina if we are very careful
    - ☐ 1 It doesn't usually hurt for my partner to touch me sexually outside the vagina, but every now and then it does hurt
    - ☐ 0 It never hurts for my partner to touch me sexually outside the vagina
    - ☐ 0 This question does not apply to me because I don't have a sexual partner.
    - ☐ 0 Specifically, I won't get involved with a partner because I worry about pelvic pain during sex.

Available at: http://www.medstarhealth.org/content/uploads/sites/8/2015/02/PMandR_VulvarPainQuestionnaire111910.pdf. Accessed March 24, 2015.

Full questionnaire

Vulval Pain Questionnaire

Indicate the effect which the following have on your discomfort:
[On the list, circle the best treatments and underline the worst treatments]

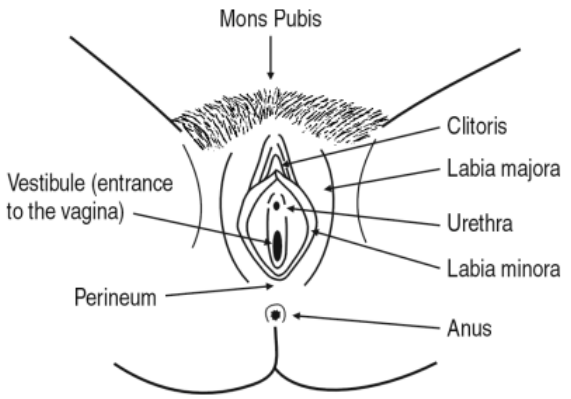
Heat (like a hot bath)	Relief	No change	Worsens
Cold (like a cool compress)	Relief	No change	Worsens
Sexual activity - (does not have to be intercourse)	Relief	No change	Worsens
Underwear	Relief	No change	Worsens
Friction (rubbing or scratching)	Relie		
Other	Relie		

My discomfort usually causes

- ❑ NO interference with daily routine or planned activities
- ❑ SOME interference with daily routine or planned activities
- ❑ An interruption in daily routine or planned activities
- ❑ Confinement to bed
- ❑ The pursuit of immediate medical attention

Please mark the squares which best show the location of your symptoms

- ❑ Mons pubis area
- ❑ Clitoris
- ❑ Labia majora
- ❑ Labia minora
- ❑ Urethra (bladder opening)
- ❑ Vestibule (inside vulva)
- ❑ Vagina (within the vestibule)
- ❑ Perineum
- ❑ Anal area



Full questionnaire

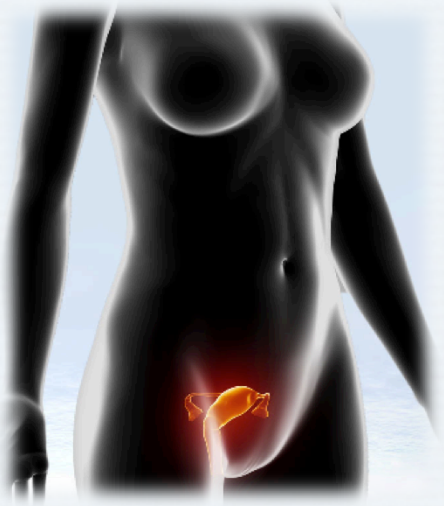
Available at: http://www.vulvalpainsociety.org/vps/images/pdf/vulval_pain_questionnaire_final_for_bssvd.pdf. Accessed March 24, 2015.

Discussion Question

WHAT WOULD BE YOUR DIAGNOSIS FOR THIS PATIENT?

Signs and Symptoms of Vulvodynia

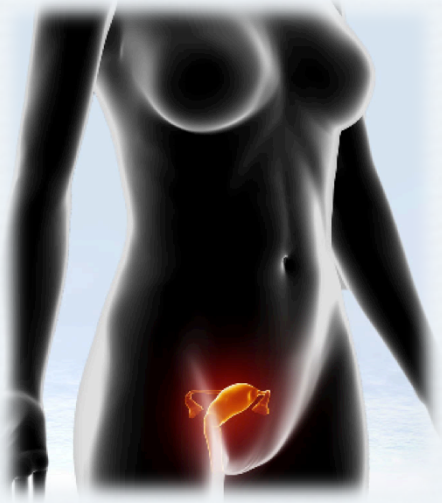
- Pain in genital area:
  - Burning
  - Soreness
  - Stinging
  - Rawness
  - Painful intercourse
  - Throbbing
  - Itching
- Occasional or constant pain that can last for month or years



Mayo Clinic. Vulvodynia. Available at: http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/symptoms/con-20020326. Accessed March 24, 2015.

Causes of Vulvodynia

- Exact causes unknown
- Possible contributors:
  - Injury to or irritation of nerves of vulvar region
  - Past vaginal infections
  - Allergies or sensitive skin
  - Hormonal changes
- Some women with vulvodynia have a history of sexual abuse



Most women with vulvodynia have no known causes

Mayo Clinic. Vulvodynia. Available at: http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/causes/con-20020326. Accessed March 24, 2015.

Burden of Vulvodynia

- Chronic vulvar discomfort
- Common descriptors:
  - Itching
  - Burning
  - Periodic knife-like or sharp pain
  - Excessive pain on contact to the genital area
- Compromises ability of sufferers to enjoy life
- Quality of life is lower than in kidney transplant recipients

Many women with vulvodynia feel out of control of their lives, and vulvodynia has a severe negative impact on their sex lives

Harlow BL, Vazquez G. *J Womens Health (Larchmt)*. 2009;18:1333-40; Arnold LD *et al. Obstet Gynecol. 2006*;107:617-24; Xie Y *et al. Curr Med Res Opin.* 2012;28(4):601-8.

Vulvodynia: Factors Affecting Pain

Factors that Exacerbate Pain	Factors that Relieve Pain
• Intercourse • Tight clothes • Partner touch • Riding a bicycle • Use of tampons • Prolonged sitting	• Loose clothing • Not wearing underwear • Applying ice to the area • Being distracted • Lying down

Reed BD. *Am Fam Physician*. 2006;73:1231-8.

Comorbidities of Vulvodynia

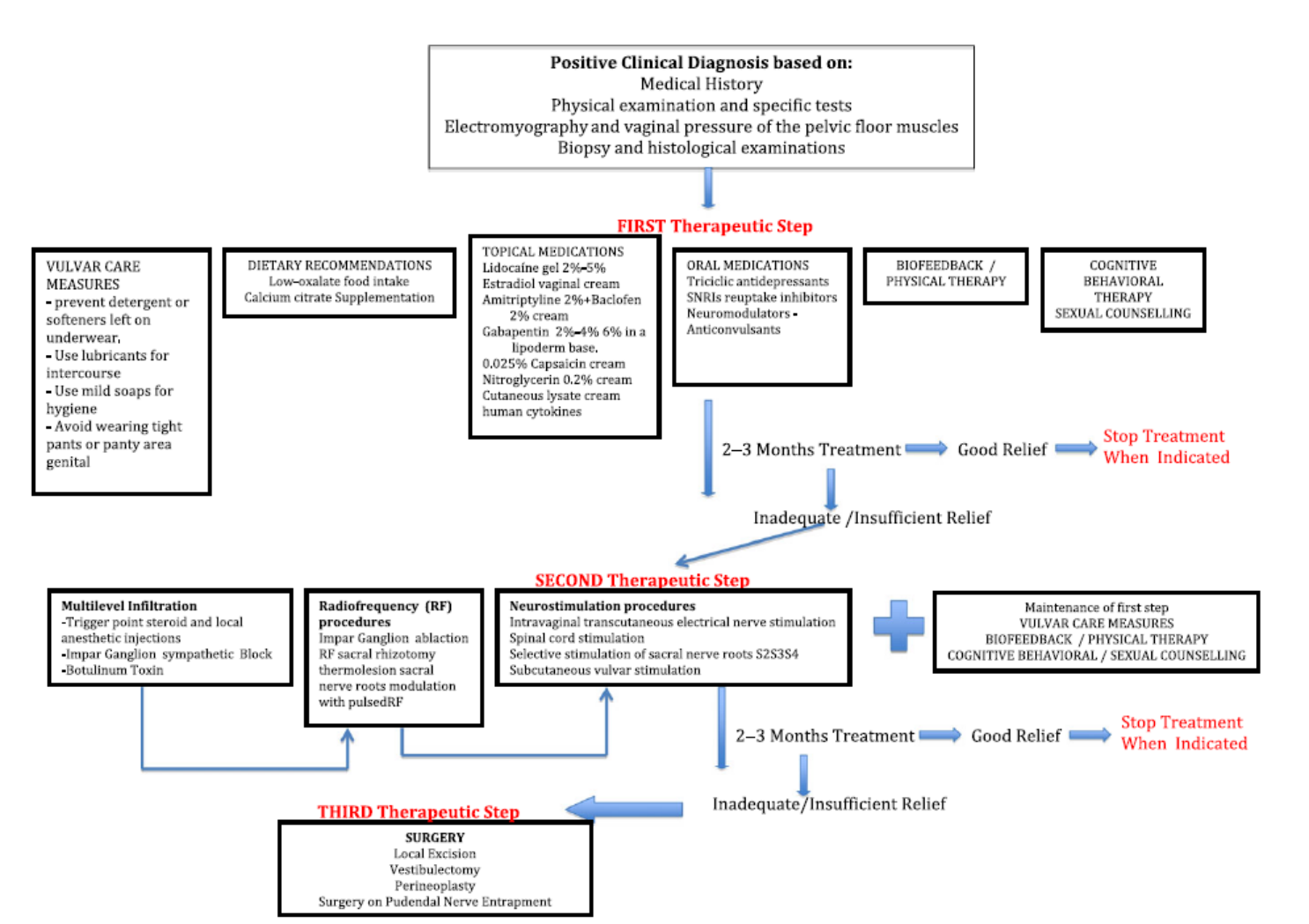
- Psychological distress
- Fibromyalgia
- Irritable bowel syndrome
- Repeated yeast infections
- Chronic fatigue syndrome
- Dyspareunia
- Interstitial cystitis

Arnold LD *et al. Obstet Gynecol. 2006*;107:617-24; Reed BD *et al. Obstet Gynecol*. 2012;120:145-51.

Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Proposed Treatment Algorithm for Vulvodynia



De Andres J*et al. Pain Pract*. 2015 Jan 12. doi: 10.1111/papr.12274. [Epub ahead of print]

Treatment Options for Vulvodynia

- Oral pharmacological therapies
  - Amitriptyline, calcium citrate, desipramine, gabapentin, paroxetine, venlafaxine
- Topical therapies
  - Lidocaine, avoidance of irritants
- Dietary changes
  - Low oxalate diet
- Surgical therapy
  - Perineoplasty, vestibulectomy
- Other therapies
  - Biofeedback, physical therapy, cognitive behavioral therapy

Reed BD. *Am Fam Physician*. 2006;73(7):1231-8.

Oral Therapies for Vulvodynia

Drug	Proposed Mechanism	Side Effects	Evidence
Amitriptyline	Decreases neuronal hypersensitivity	Dry mouth, fatigue (often transient), constipation, weight gain (uncommon)	Case reports Retrospective reports
Calcium citrate	Decreases oxalate deposition in tissues	Minimal	Case reports Anecdotal reports
Desipramine	Decreases neuronal hypersensitivity	Same as amitriptyline but less common	None. Based on similarity to amitriptyline.
Gabapentin	Decreases neuronal hypersensitivity	Headaches, nausea, vomiting, fatigue, dizziness (often transient or mild)	Case reports
Paroxetine	Decreases neuronal hypersensitivity	Rarely fatigue, anorgasmia, or weight gain	Case report
Venlafaxine	Decreases neuronal hypersensitivity	Anorgasmia, GI side effects, anxiety	Used in other painful neuropathies

GI = gastrointestinal

Reed BD. *Am Fam Physician*. 2006;73(7):1231-8.

Mrs. RL: Treatment

- ***Oral medication***: amytriptyline titrated up to 50 mg/night
- ***Topical treatment***: Emla cream, max: 12 hours/day
- ***Cognitive behavioral therapy***

Mrs. RL: Follow up

- After 3 months of treatment, Mrs. RL reported good relief and the medications were tapered off gradually.

Case Template: Discussion Question

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

Case: Mr. Ali

Mr. Ali: Profile

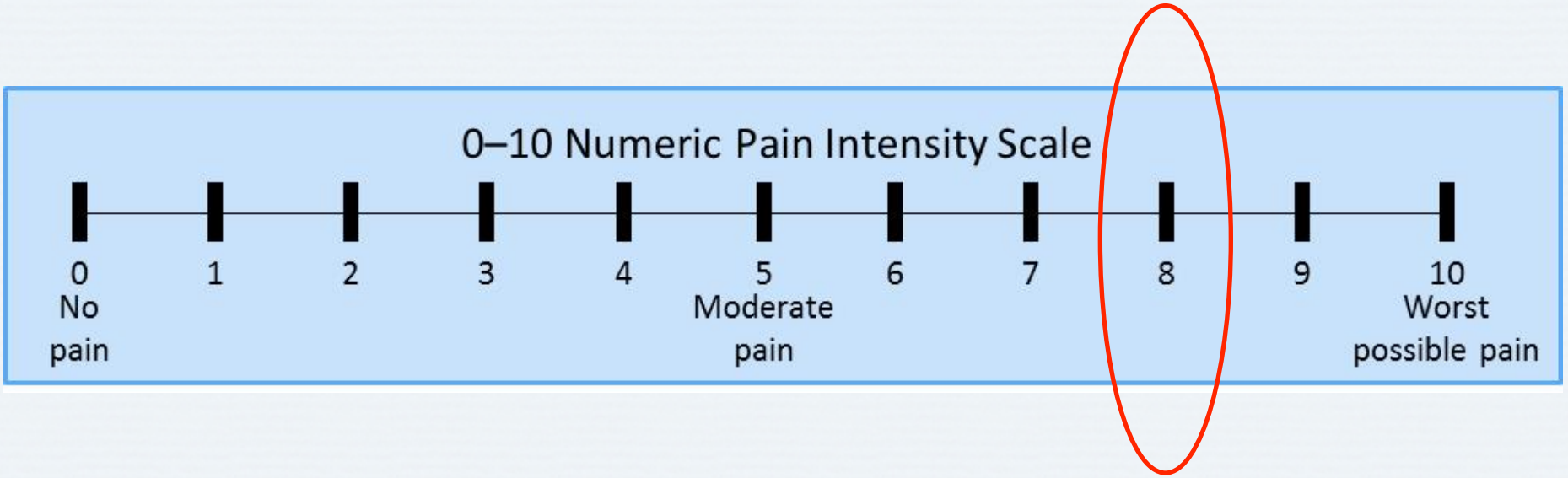
- 29-year-old male, soldier
- No history of any comorbidities
- Heavy smoker
- Experienced shortness of breath and chest and throat pain during military training

Mr. Ali: Physical Examination

- Heart rate = 110 beats/min
- Blood pressure = 90/45 mmHg
- VAS = 8/10
- Diffuse chest pain
- On and off pain in left arm
- Sweating, pallor
- No GI tract signs or symptoms

GI = gastrointestinal; VAS = visual analog scale

Visual Analog Scale (VAS) for Pain



The patient's pain score is 8

Discussion Questions

BASED ON THE CASE PRESENTATION, WHAT WOULD YOU CONSIDER IN YOUR DIFFERENTIAL DIAGNOSIS?

Mr. Ali: Diagnosis

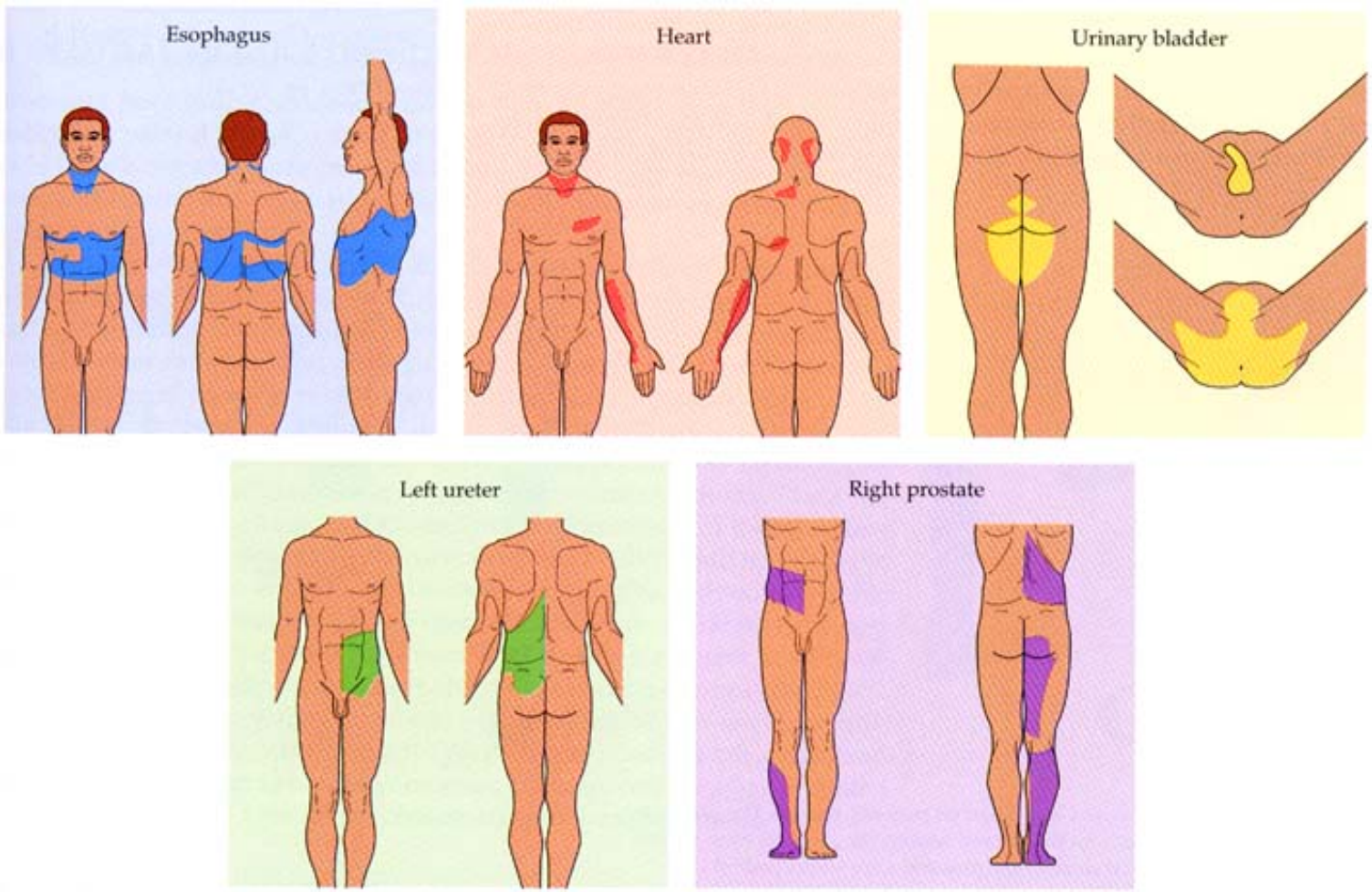
- Inferior wall myocardial infarction

Somatic vs. Visceral Pain

Somatic	Visceral
• Pain originating from skin/skeletal muscle • Evoked by tissue injury • Can always be stimulated by mechanical injury • Can be superficial (skin, muscle) or deep (joints, tendons, bones) • Nociceptors are involved • Sharp, precise; often well localized • Usually described as throbbing or aching • Never referred	• Pain originating from organs • Not always evoked by tissue injury • Primarily stimulated by inflammation, distention and ischemia, not mechanical injury • Involves hollow organ and smooth muscle nociceptors sensitive to stretching, hypoxia, and inflammation • Usually referred, dull, poorly localized, vague, and diffuse • Often referred to somatic regions • May be associated with autonomic symptoms (*e.g.*, pallor, sweating, nausea, blood pressure and heart rate changes

McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006; Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care.* 2012;6(1):17-26.

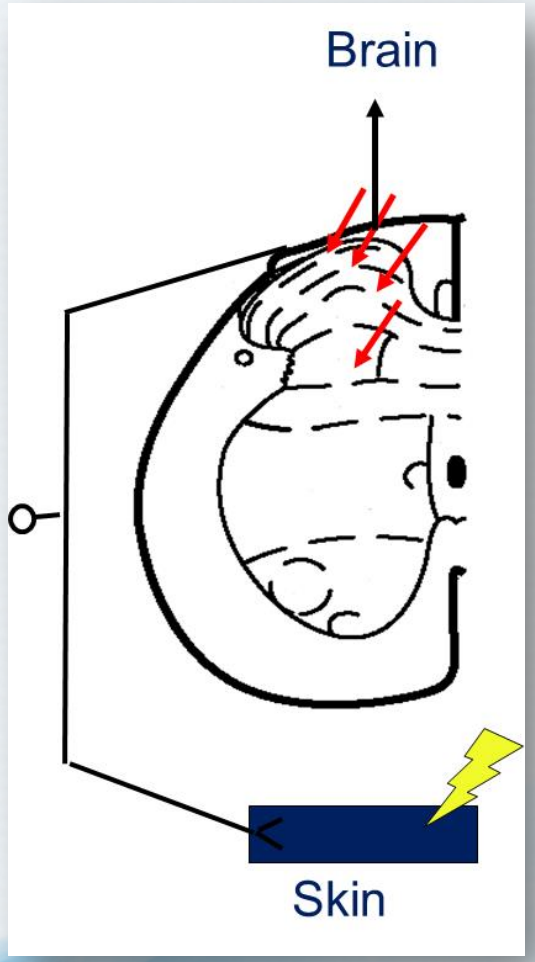
Visceral Pain



Pain Transmission through Sensory Somatic Afferents

Skin Nociceptors

- Aβ (large myelinated)
  - CV= 30-100 m/s, ~25% of total
- Aδ (small myelinated)
  - CV= 6-30 m/s
- C fiber (small unmyelinated)
  - CV= 1-2.5 m/s
- Terminations: Lamina I, IIo, III and V



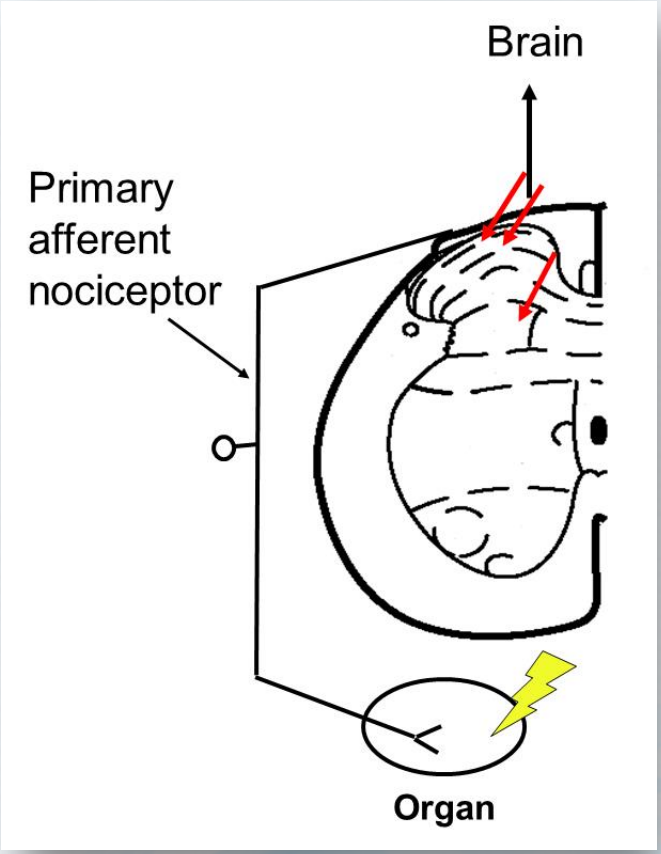
CV = conduction velocity

Procacci P *et al.* Visceral Sensation. In: Cervero, F.; Morrison, JFB., editors. Progress in Pain Research. Elsevier; Amsterdam: 1986. p. 21-8, p. 39.

Pain Transmission through Sensory Visceral Afferents

Visceral nociceptors

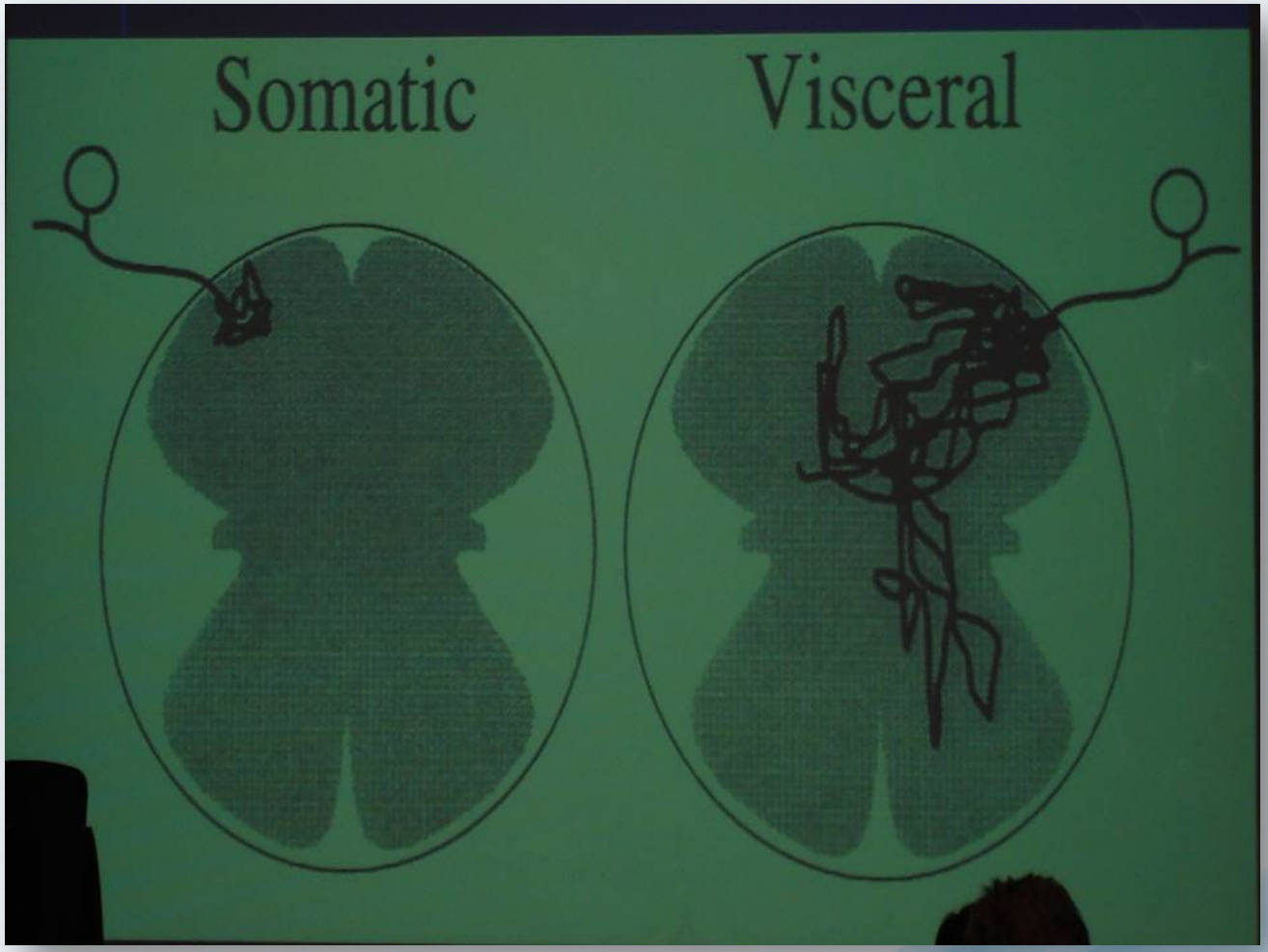
- Aδ (small myelinated)
  - CV = 6-30 m/s
- C fiber (small unmyelinated)
  - CV= 1-2.5 m/s
- Terminations:
  - Lamina I, IIo, V



CV = conduction velocity

Procacci P *et al.* Visceral Sensation. In: Cervero, F.; Morrison, JFB., editors. Progress in Pain Research. Elsevier; Amsterdam: 1986. p. 21-8, p. 39.

Somatic vs. Visceral Pain



Procacci P *et al.* Visceral Sensation. In: Cervero, F.; Morrison, JFB., editors. Progress in Pain Research. Elsevier; Amsterdam: 1986. p. 21-8, p. 39; Ness, TJ. Historical and Clinical Perspectives. In: Gebhart, GF., editor. Visceral Pain, Progress in Pain Research and Management. IASP Press; Seattle: 1995. p. 3-23.

Visceral Pain

- Higher brain centers get "**confused**" between somatic and visceral origin
  - Myocardial pain (T1-T5) refers to anterior chest wall and down to the medial aspect of the arm (T1-T2)
  - Diaphragmatic and biliary tract pain travels through the PN to terminate at C3-C4
    - Pain is referred to dermatomes in the neck and shoulder

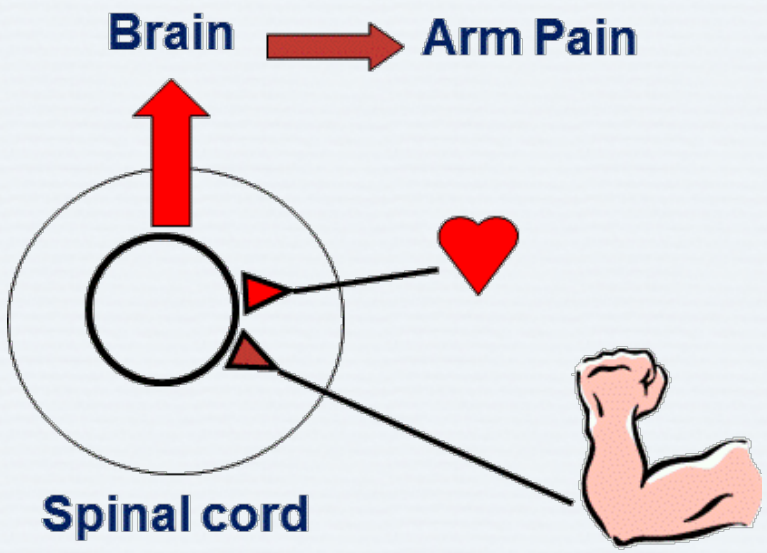
NOT all visceral pain is referred

PN = phrenic nerve

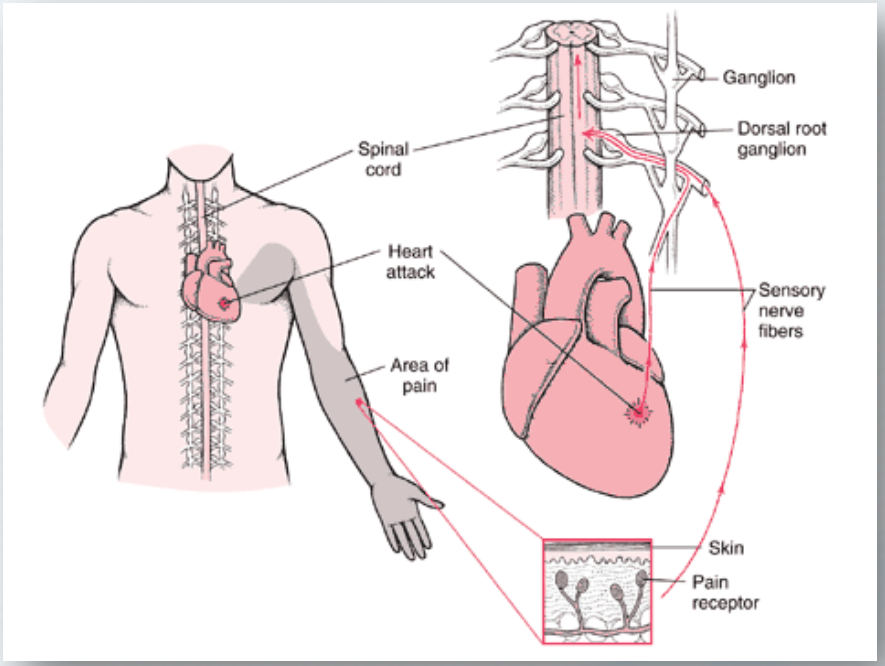
Gebhart GF. *Gut*. 2000;47(Suppl 4):iv54–5. discussion iv8; Ness TJ, Gebhart GF. *J Neurophysiol.* 1991;66:20-8.

Referred Pain: Viscerosomatic Convergence

Viscerosomatic convergence:
Primary afferents from myocardium and somatic region of left arm converge on same projection neuron in spinal cord



Myocardial Infarction



Discussion Questions

WHAT FURTHER HISTORY WOULD YOU LIKE TO KNOW?

WHAT TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Mr. Ali: Investigation

- Lab tests: Troponin 1 increased from 0.24 to 1.19 in 24 h (N:0-0.1)
- Normal X-ray
- ECG: sinus rhythm, abnormal T: ischemia
- CT Scan
- Angiography

Mr. Ali: Lab Reports (over 24 h)

Referred By:

Reviewed Date : 26/12/2014 03:29 AM

Reporting Date: 26/12/2014 03:29 AM

Request Date: 26/12/2014 02:50 AM

Clinical Chemistry Report

Test	Result		Unit	Reference Range
BUN	19		mg/dL	(8 - 24)
Creatinine, serum	1.10		mg/dL	(0.80 - 1.30)
Blood Glucose	122		mg/dL	Fasting -: 70 - 99 Random : Less Than 140 2Hours PostPrandial:Less Than 140
Total Bilirubin	0.20		mg/dL	(0.00 - 1.00)
Alkaline phosphatase	91		U/L	(50 - 136)
S.G.P.T. (ALT)	56		U/L	(20 - 65)
S.G.O.T. (AST)	22		U/L	(0 - 37)
Total Protein	6.9		g/dL	(6.2 - 8.2)
Albumin	3.8		g/dL	(3.2 - 5.0)
Globulin	3.1		g/dL	(2.3 - 4.0)
Calcium	8.50		mg/dL	(8.50 - 10.50)
Sodium	139		mmol/L	(136 - 145)
Potassium	3.9		mmol/L	(3.5 - 5.5)
Chloride	102		mEq/L	(98 - 107)
Total CO2	25.60		mmol/L	(21.00 - 32.00)
CI	82		U/L	(39 - 308)
CK - MB	16		U/L	(0 - 25)
LDH	159		U/L	(85 - 227)
CRP Extended Range	4.70	H	mg/L	(0.00 - 3.00)
Troponin I	0.24	H	ng/mL	(0.00 - 0.10)

Comments :

TROPONIN RESULT INFORMED TO ZUBAIDA

Referred By:

Reviewed Date : 27/12/2014 06:31 AM

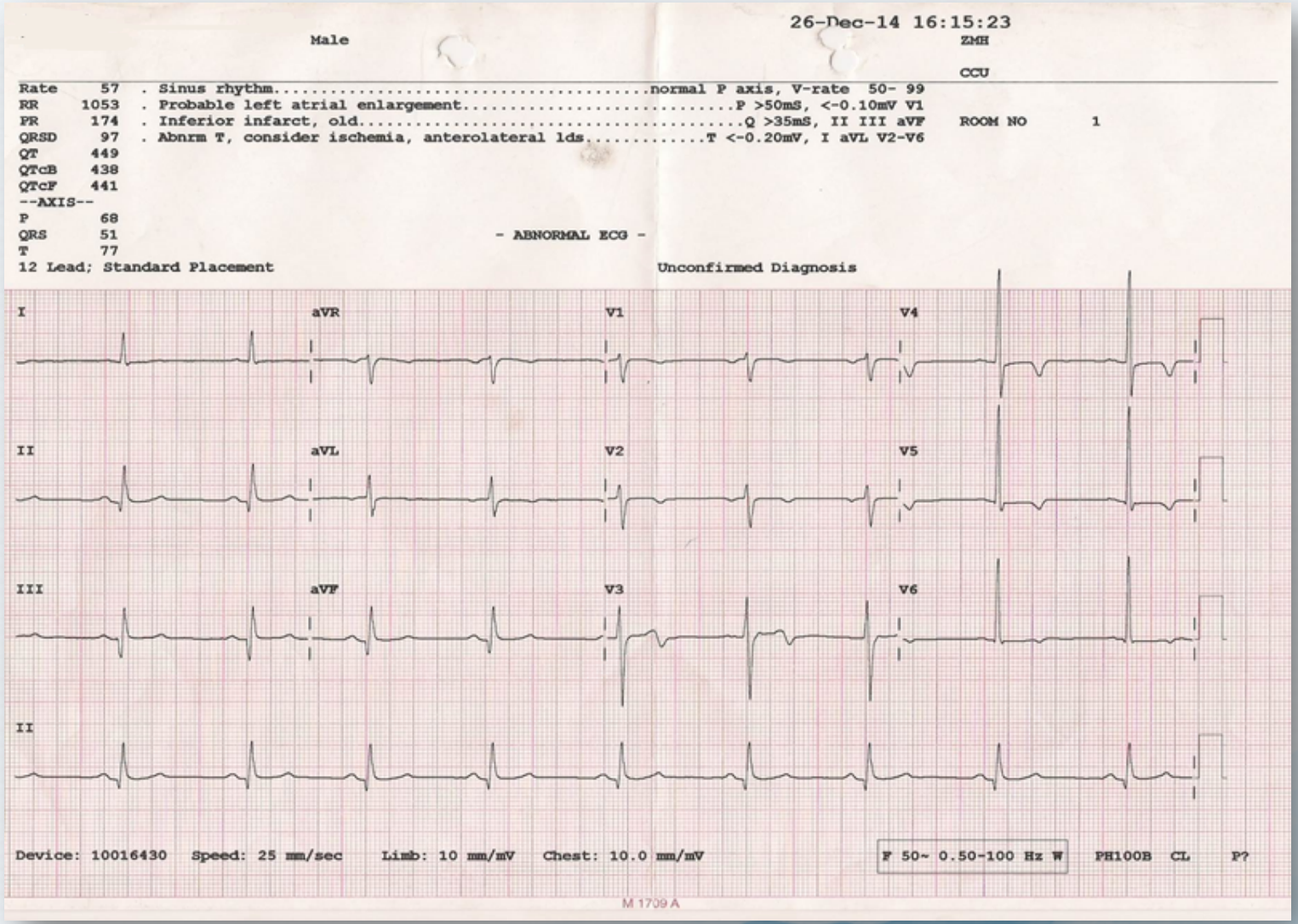
Reporting Date: 27/12/2014 06:31 AM

Request Date: 27/12/2014 12:58 AM

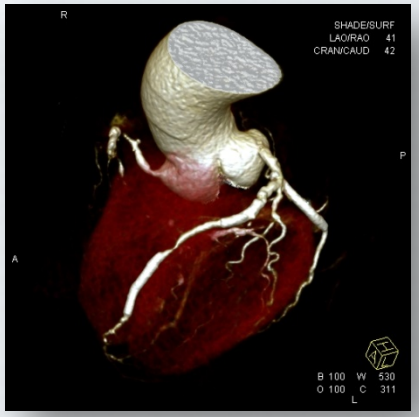
Clinical Chemistry Report

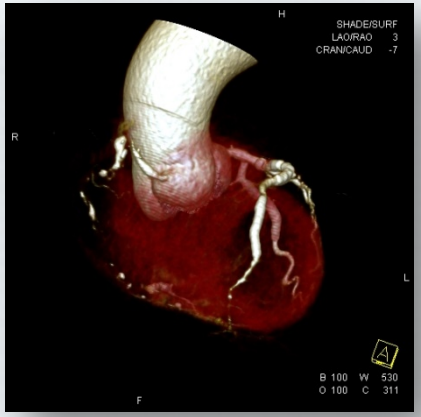
Test	Result		Unit	Reference Range
BUN	14		mg/dL	(8 - 24)
Creatinine, serum	0.90		mg/dL	(0.80 - 1.30)
Blood Glucose	90		mg/dL	Fasting -: 70 - 99 Random : Less Than 140 2Hours PostPrandial:Less Than 140
Total Bilirubin	0.50		mg/dL	(0.00 - 1.00)
Alkaline phosphatase	80		U/L	(50 - 136)
S.G.P.T. (ALT)	52		U/L	(20 - 65)
S.G.O.T. (AST)	24		U/L	(0 - 37)
Total Protein	6.6		g/dL	(6.2 - 8.2)
Albumin	3.6		g/dL	(3.2 - 5.0)
Globulin	3.0		g/dL	(2.3 - 4.0)
Calcium	8.60		mg/dL	(8.50 - 10.50)
Sodium	139		mmol/L	(136 - 145)
Potassium	4.1		mmol/L	(3.5 - 5.5)
Chloride	105		mEq/L	(98 - 107)
Total CO2	27.50		mmol/L	(21.00 - 32.00)
CI	106		U/L	(39 - 308)
CK - MB	18		U/L	(0 - 25)
LDH	153		U/L	(85 - 227)
Phosphorus	4.2		mg/dL	(2.5 - 4.9)
Magnesium	1.80		mg/dL	(1.60 - 2.40)
CRP Extended Range	4.00	H	mg/L	(0.00 - 3.00)
Troponin I	1.19	H	ng/mL	(0.00 - 0.10)

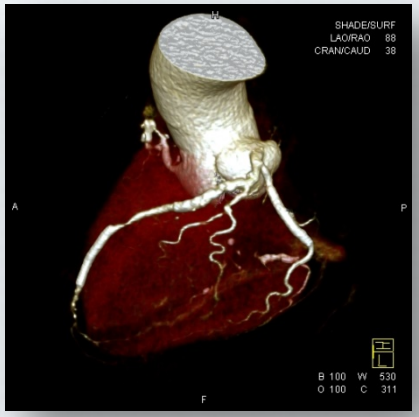
Mr. Ali: ECG

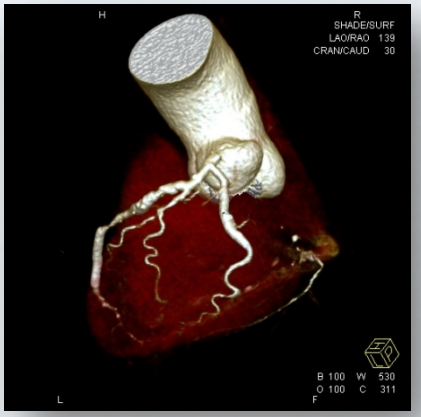

Male
26-Dec-14 16:15:23
ZMH
CCU
Rate 57 . Sinus rhythm.....normal P axis, V-rate 50- 99
RR 1053 . Probable left atrial enlargement.....P >50mS, <-0.10mV V1
PR 174 . Inferior infarct, old.....Q >35mS, II III aVF
QRSD 97 . Abnrm T, consider ischemia, anterolateral lds.....T <-0.20mV, I aVL V2-V6
QT 449
QTcB 438
QTcF 441
--AXIS--
P 68
QRS 51
T 77
ROOM NO 1
- ABNORMAL ECG -
12 Lead; Standard Placement
Unconfirmed Diagnosis
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Device: 10016430 Speed: 25 mm/sec Limb: 10 mm/mV Chest: 10.0 mm/mV
F 50~ 0.50-100 Hz W PH100B CL P?
M 1709 A

Mr. Ali: CT Scan

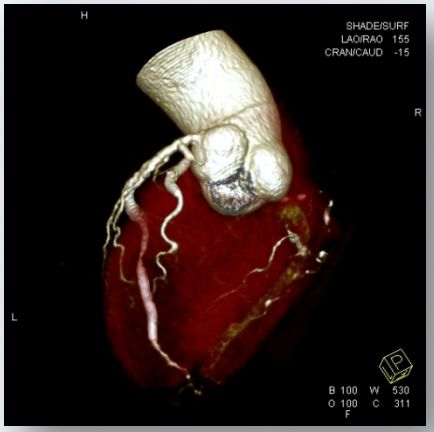


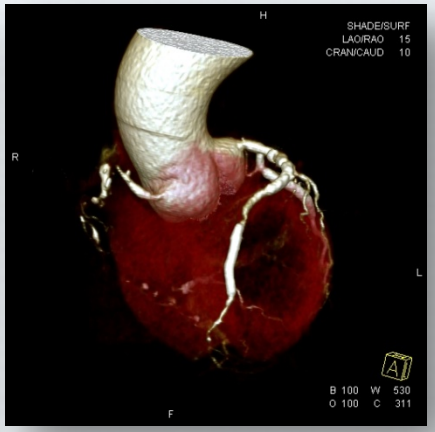


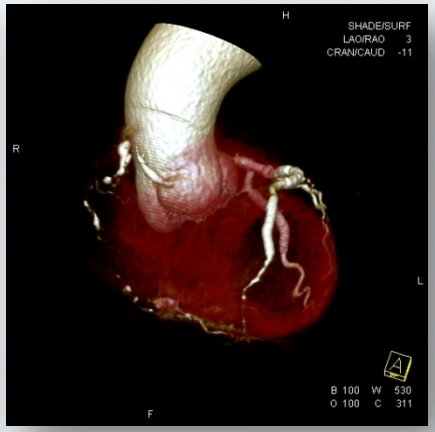


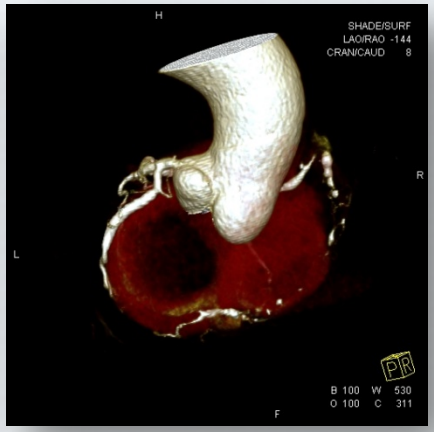


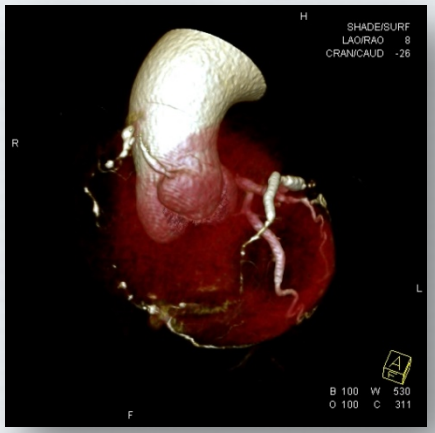
Mr. Ali: CT Scan



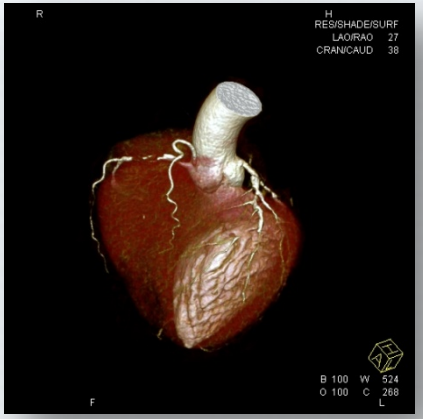


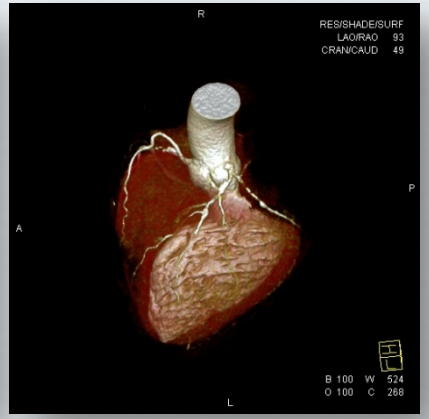


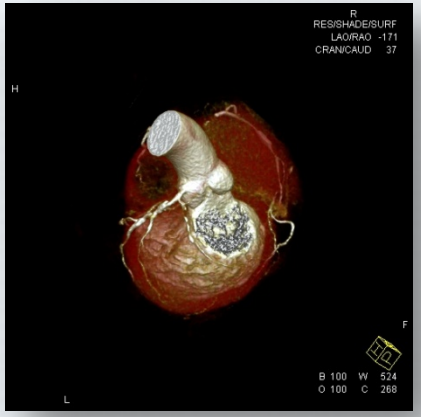


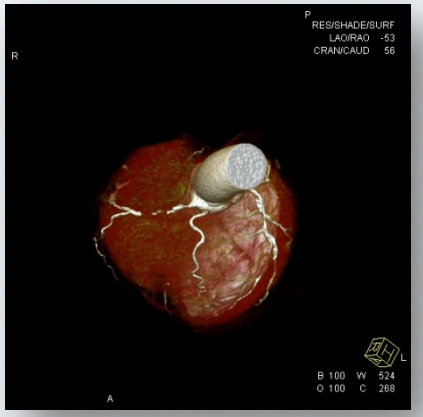


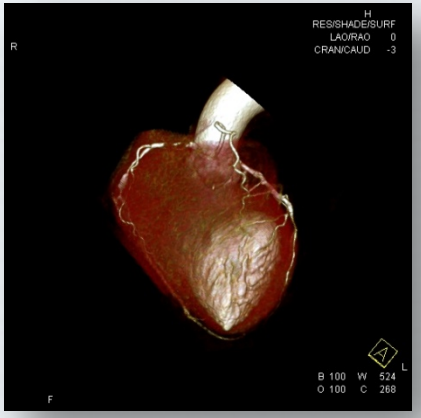
Mr. Ali: CT Scan

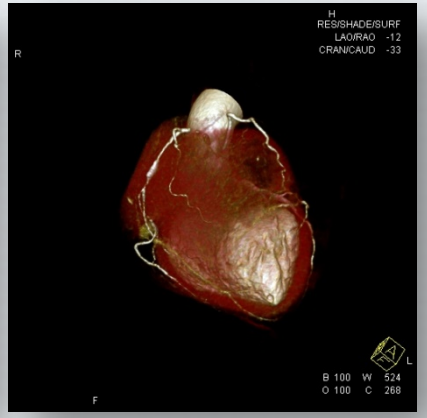


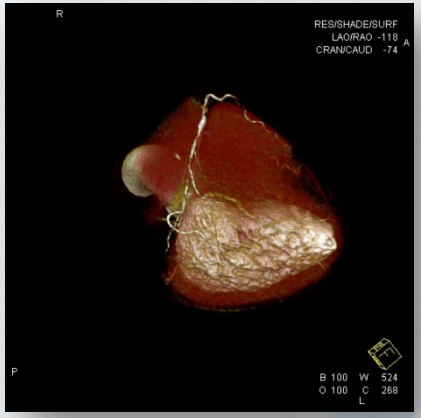


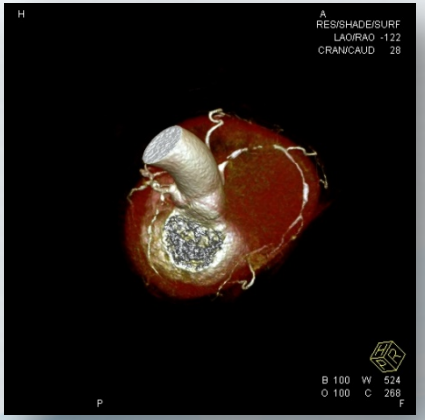




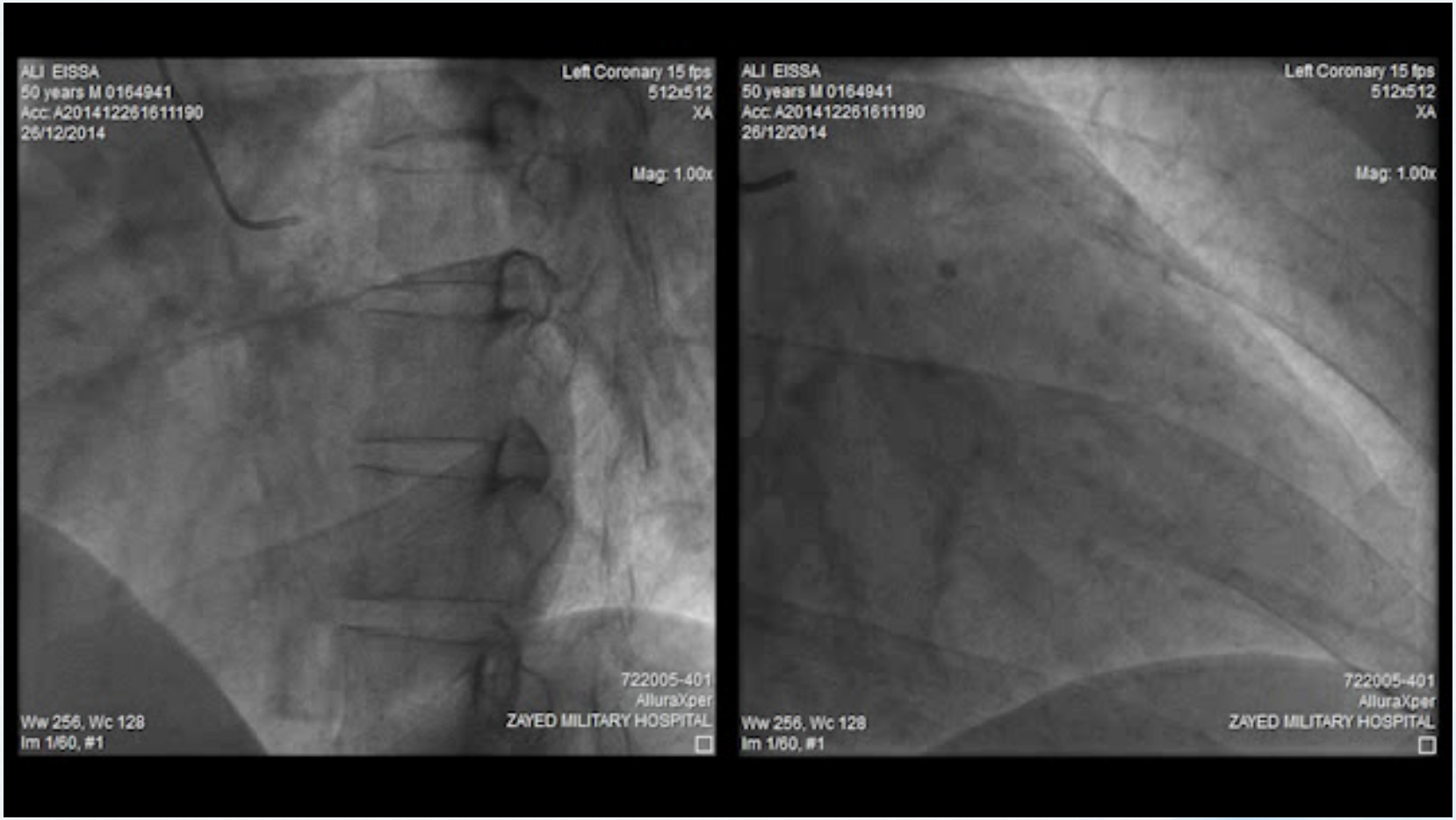








Mr. Ali: Angiography



Discussion Question

WHAT TREATMENT STRATEGY WOULD YOU RECOMMEND?

Mr. Ali: Treatment

- Heparin
- Nitroglycerin
- Stenting

Discussion Questions

WHAT OTHER TESTS OR EXAMINATIONS WOULD YOU CONDUCT?

Mr. Ali: Further Testing and Follow-up

- Clinical
- Biological
- Electrical
- Echography

WOULD YOU MAKE ANY CHANGES TO THERAPY OR CONDUCT FURTHER INVESTIGATIONS?

References

American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD *et al*. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol.* 2009;104 Suppl 1:S1-35.

Arnold LD, Bachmann GA, Rosen R *et al.* Vulvodynia: characteristics and associations with comorbidities and quality of life. *Obstet Gynecol.* 2006;107:617-24.

Bouhassira D *et al.* Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.

Catsos P. IBS – Free at Last!: A Revolutionary, New Step-by-Step Method for Those Who Have Tried Everything. Control IBS Symptoms by Limiting FODMAPS Carbohydrates in Your Diet. Portland, Maine: Pond Cove Press; 2009.

Cervero F. Somatic and visceral inputs to the thoracic spinal cord of the cat: effects of noxious stimulation of the biliary system. *J Physiol*. 1983;337:51–67.

De Andres J, Sanchis-Lopez N, Asensio-Samper JM *et al.* vulvodynia-an evidence-based literature review and proposed treatment algorithm. *Pain Pract.* 2015 Jan 12. doi: 10.1111/papr.12274. [Epub ahead of print]

Gebhart GF. Visceral pain-peripheral sensitisation. *Gut*. 2000;47(Suppl 4):iv54–5. discussion iv8.

Hanno PM. Interstitial cystitis – epidemiology, diagnostic criteria, clinical markers. *Rev Urol.* 2002;4(Suppl 1):S3-S8.

Harlow BL, Vazquez G. Self-reported vulvar pain characteristics and their association with clinically confirmed vestibulodynia. *J Womens Health (Larchmt).* 2009;18:1333-40.

ISSVD Vulvodynia Pattern Questionnaire. Available at: https://netforum.avectra.com/temp/ClientImages/ISSVD/3ef9c6ea-aac7-4d2b-a37f-058ef9f11a67.pdf. Accessed March 24, 2015.

Jha S, Parsons M, Toozs-Hobson P. Painful bladder syndrome and interstitial cystitis. *The Obstetrician and Gynecologist*. 2007;9:34-41.

Lacy BE. A 42-year-old woman presents for second opinion: nonconstipation IBS – case study approach. Available at: http://www.medscape.org/viewarticle/750958. Accessed June 15, 2015.

Longstreth GF *et al.* Functional bowel disorders. In: Drossman, DA.; Corazziari, E.; Delvaux, M., et al., editors. Rome III: the functional gastrointestinal disorders. 3rd ed.. McLean, VA: Degnon; 2006. p. 487-555.

Mayer EA. Irritable bowel syndrome. *N Engl J Med*. 2008;358:1692-9.

Mayo Clinic. Interstitial Cystitis. Available at: http://www.mayoclinic.org/diseases-conditions/interstitial-cystitis/basics/causes/con-20022439. Accessed March 24, 2015.

References

Mayo Clinic. Vulvodynia. Available at: http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/symptoms/con-20020326. Accessed March 24, 20.

Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. *Gastroenterology*. 1995;109:40-52.

National Kidney and Urologic Diseases Information Clearinghouse. Interstitial Cystitis/Painful Bladder Syndrome. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/IC_PBS_T_508.pdf. Accessed March 24, 2015.

Ness TJ, Gebhart GF. Interactions between visceral and cutaneous nociception in the rat. I. Noxious cutaneous stimuli inhibit visceral nociceptive neurons and reflexes. *J Neurophysiol.* 1991;66:20-8.

Ness, TJ. Historical and Clinical Perspectives. In: Gebhart, GF., editor. Visceral Pain, Progress in Pain Research and Management. IASP Press; Seattle: 1995. p. 3-23.

Nickel JC, Tripp D, Teal V *et al.* Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. *J Urol*. 2007;177:1832-6.

Payne CK, Joyce GF, Wise M *et al.* Interstitial cystitis and painful bladder syndrome. *J Urol*. 2007;177:2042-9.

Procacci P, Zoppi M, Maresca M. Visceral Sensation. In: Cervero, F.; Morrison, JFB., editors. Progress in Pain Research. Elsevier; Amsterdam: 1986. p. 21-8, p. 39.

Reed BD, Harlow SD, Sen A *et al.* Relationship between vulvodynia and chronic comorbid pain conditions. *Obstet Gynecol*. 2012;120:145-51.

Reed BD. Vulvodynia: diagnosis and management. *Am Fam Physician*. 2006;73(7):1231-8.

Rothrock NE, Lutgendorf SK, Hoffman A, Kreder KJ. Depressive symptoms and quality of life in patients with interstitial cystitis. *J Urol.* 2002;167:1763-7.

Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. *Curr Opin Support Palliat Care.* 2012;6(1):17-26.

Vulval Pain Functional Questionnaire. Available at: http://www.medstarhealth.org/content/uploads/sites/8/2015/02/PMandR_VulvarPainQuestionnaire111910.pdf. Accessed March 24, 2015.

Vulval Pain Questionnaire. Available at: http://www.vulvalpainsociety.org/vps/images/pdf/vulval_pain_questionnaire_final_for_bssvd.pdf. Accessed March 24, 2015.

Xie Y, Shi L, Xiong X *et al.* Economic burden and quality of life of vulvodynia in the United States. *Curr Med Res Opin*. 2012;28(4):601-8.