

Idiopathic Venous Thromboembolism and Screening for Occult Malignancy

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CASE:

- 45 yr old female admitted for PE
- No pregnancy, immobilization, long trips, family history of clots or estrogen use.
- Smoker
- Discharged on lovenox and coumadin from hospital and she arrives at UHC clinic

- NOW WHAT?

Goals:

- What is the connection between DVT/PE and cancer?
- Which DVT/PE admissions/clinic patients should I work up for cancer?
- How should I screen them?

Outline:

- History
- Definitions
- Epidemiology of VTE and Malignancy
- Screening for Occult Malignancy
- Recommendations

History

- Armand Trousseau (1801-1867)
 - French internist University of Paris
 - First Tracheostomy
 - First Thoracentesis
 - Described Hemochromatosis

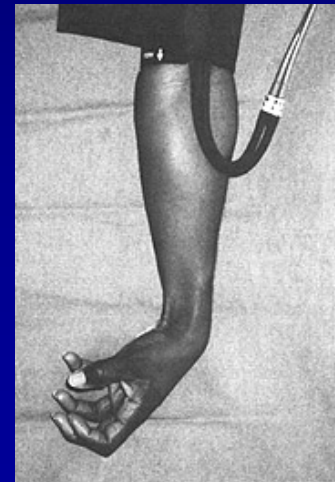


Trousseau Eponyms

Trousseau's Sign:

Carpal spasm in hypocalcemia with blood pressure cuff at 300mmHg for 3 minutes.

sacré bleu!



Trousseau Eponyms

Trousseau's Spot:

Red streak seen on scratching the skin in acute meningitis.

SO RARE I COULDN'T FIND IT ON
GOOGLE IMAGES!!!

Trousseau's Syndrome

- Superficial migratory thrombophlebitis
- “Phlegmasia Alba Dolens”



Initially described as an association with occult visceral malignancy, most commonly pancreatic

Trousseau's Syndrome

- Over the years has been broadened to include any instance of cancer associated with arterial and venous clots
- Useful definition: **unexplained thrombotic events that precede the diagnosis of an occult visceral malignancy or appear concomitantly with the tumor.**

The End of Trousseau

- January 1, 1867 Trousseau noticed a phlebitis in his own left upper extremity. He told his student at that time,
- “I am lost: the phlebitis that has just appeared tonight leaves me no doubt about the nature of my illness.”
- He died of gastric carcinoma several months later...



Outline

- History of VenousThromboEmbolicism (VTE) and Cancer
- **Definitions**
- Epidemiology of VTE and Malignancy
- Screening for Occult Malignancy
- Recommendations

Definitions:

- Venous Thromboembolism (VTE)
 - Blood clot formation in venous circulation
- Types of VTE:
 - Migratory Superficial Thrombophlebitis
 - Deep Venous Thrombosis (DVT)
 - Pulmonary Embolism (PE)
- Primary (idiopathic) or Secondary

Definitions:

- **Secondary VTE: A predisposing condition.**
 - Pregnant
 - On estrogen or SERM
 - Surgery within last 6 weeks
 - Bed Ridden (stroke, paraplegic etc.)
 - Inherited Thrombophilia
 - Known Malignancy

Definitions:

- **Primary or Idiopathic VTE (iVTE):**
 - Venous thromboembolic event with no known predisposing condition.
 - NOT Pregnant
 - NOT On estrogen or SERM
 - NO Surgery within last 6 weeks
 - NOT Bed Ridden (stroke, paraplegic etc.)
 - NO Inherited Thrombophilia
 - NO Known Malignancy

Definitions:

- iVTE is a risk factor for occult malignancy!

Outline

- History of VenousThromboEmbolicism (VTE) and Cancer
- Definitions
- **Epidemiology**
- Screening for Occult Malignancy
- Recommendations

Epidemiology

- Cancer is an independent risk factor for VTE as well as Recurrent VTE. Why?
 - Biologic mediators including TF, TNF alpha, selectins, mucin
 - Chemotherapy leading to vessel damage
 - Indwelling catheters
 - Venous compression by tumors

Epidemiology

- Those with Cancer are at high risk for VTE
- Blom et al 2005 JAMA
 - 3220 patients at AC clinic in Netherlands
 - Risk of VTE higher in cancer vs non cancer cohort **OR of 6.7**
 - Those with metastatic disease had **OR of 19.8**

Epidemiology

- VTE in cancer patients = poor prognosis
- Chew et al Arch Int Med 2006
 - 235,000 cancer cases with 2 year follow up
 - Adjusted for age, stage, race those who had VTE had **decreased survival** for all cancer types Hazard Ratios 1.6 to 4.2
 - VTE much more common in metastatic disease with Metastatic Pancreatic CA (20% in first yr)

Epidemiology

- Risk of VTE depends on cancer type
- Levitan et al 1999 review of medicare records (8 million medicare patients)
- Looked at those patients with cancer who were admitted with VTE

Epidemiology

- Types of Cancers Associated with VTE
 - Absolute (reflects most common cancers)
 - Relative (reflects thrombogenicity of specific tumor?)

Site	No. of Patients with DVT/PE	No. of Patients with Cancer	Rate of DVT/PE per 10,000 Patients
Head/neck	35	20,924	16
Bladder	180	74,517	22
Breast	469	186,273	22
Esophagus	64	14,742	43
Uterus	226	11,606	44
Cervix	53	10,236	49
Prostate	1,230	218,743	55
Lung	1,504	232,764	61
Rectal	417	65,837	62
Liver	121	22,938	69
Colon	1,320	168,832	76
Leukemia	591	47,234	81
Renal	278	34,376	84
Stomach	280	32,655	85
Lymphoma	537	52,042	98
Pancreas	488	41,551	110
Brain	184	13,529	117
Ovary	327	26,406	120

Abbreviations: DVT/PE = deep vein thrombosis and/or pulmonary embolism.

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Epidemiology

- To Summarize:
 - VTE more common in cancer patients
 - VTE more common in metastatic disease
 - VTE poor prognosis in cancer patients
 - VTE more prevalent in Ovarian, Brain, Pancreas, Lymphoma, Lung and GI

Epidemiology

- Those with Cancer get VTE but **The Reverse is Also True:**
- Those with VTE (particularly idiopathic VTE) get Cancer...

Epidemiology

iVTE and Occult Malignancy

- Approximately 10% of those with first iVTE are diagnosed with cancer within 2 years of iVTE diagnosis
- Standardized Incidence Ratio (SIR) for development of cancer 2.1 to 4.6

Epidemiology

iVTE and Occult Malignancy

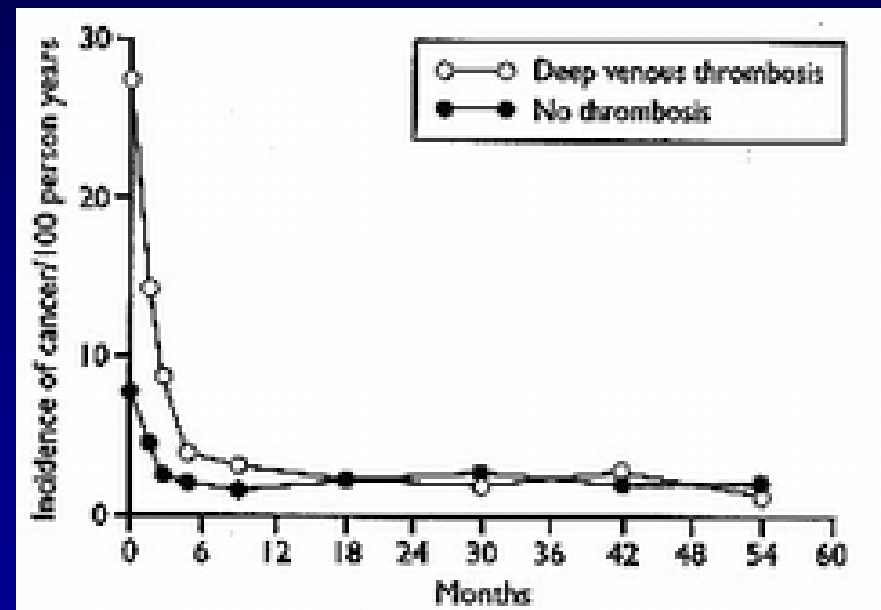
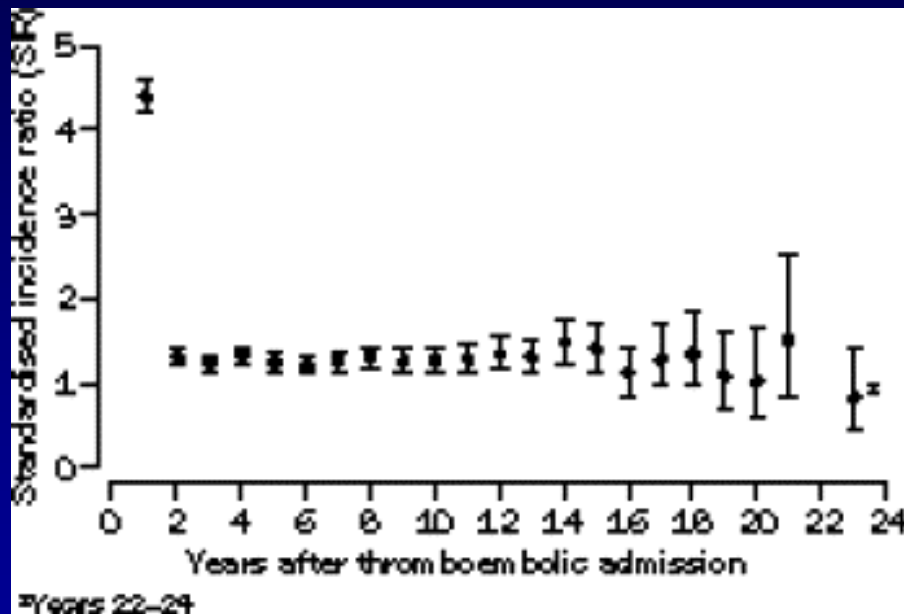
- **Murchison et al, 2004**
 - Scottish Population based Retrospective Cohort Study
 - 59,534 inpatients diagnosed with idiopathic VTE followed over 19 years
 - Excluded recent surgeries, pregnancy and cancers diagnosed within 1 mo of VTE but could not exclude thrombophilia

Epidemiology

iVTE and Occult Malignancy

- **Murchison et al, 2004**
 - 7.5% diagnosed with malignancy
 - SIR of 2.9 for all cancers 1 to 12 months following iVTE diagnosis
 - SIR fell rapidly back to baseline incidence after approximately 2 years
 - Highest SIR (4.0 – 6.0) for Ovarian, Hodgkins, Pancreatic, Kidney

Cancer Risk Decreases with Time after iVTE Diagnosis



From Baron, 2000 and Nordstrom 1994

Epidemiology

iVTE and Occult Malignancy

- Those with iVTE are more likely than secondary VTE to develop cancer.
- Prandoni, 1992 NEJM
 - Prospective cohort of 250 patients with DVT (105 with secondary DVT and 145 with iDVT)
 - At 2 year follow up, 7.6% of the iDVT patients developed cancer vs 1.9% ($p < 0.043$)
 - Of patients with iDVT, 17% of those that had VTE recurrences had malignancy.

Epidemiology

iVTE and Occult Malignancy

- To Summarize:
 - iVTE have SIR 2.1 to 4.6 for cancer
 - Strongest association 1-12mo post VTE
 - Association weakens after 2 years
 - Recurrent iVTE are at even higher risk
 - iVTE have 3-4 times the risk of secondary VTE for developing cancer

Outline

- History of Venous Thromboembolism (VTE) and Cancer
- Definitions
- Epidemiology of VTE and Malignancy
- **Screening for Occult Malignancy**
- Recommendations

Cancer Screening in Idiopathic VTE

- Knowing that iVTE is such a big risk factor for occult malignancy... Question:
- Should we routinely screen this unique population for cancer?
- How aggressive should we screen?

Cancer Screening in Idiopathic VTE

- Several Retrospective and Prospective Cohort Studies:
 - Nordstrom 1994
 - Cornuz 1996
 - Med Monreal 1993
 - Monreal 2004
- Prospective Randomized Trials:
 - Piccioli, 2004

Nordstrom 1994

- Nordstrom BMJ 1994

- 3795 patients without known malignancy had venography: 1383 +DVT, 2412 –DVT
- Those with +DVT were more likely to develop cancer in 6 month follow up than those without ($p < 0.0001$)
- Drawback: not prescreened for secondary causes of VTE

Nordstrom 1994

- In 66 DVT+ patients who developed cancer during follow up, 38/66 (58%) diagnosed by H&P, Labs, CXR
- Only 2 of remaining 28 would have benefited from aggressive screening
- “screening all patients with deep venous thrombosis for cancer would not be cost effective.

Cornuz 1996

- Retrospective Cohort
- 986 patients with no risk factors for VTE who had BLE US for suspected DVT
- 142 + DVT
- 16 with cancer at time of DVT (12%)

Cornuz 1996

- All 16 patients had abnormal results on at least 1 of 4 categories of clinical exam
 - History
 - Physical
 - Basic Labs
 - Chest Xray

Cornuz 1996

- **Points to take home**
 - H&P and screening labs/cxr can be very powerful if your H&P is thorough and you know what you are looking for...
 - 4/16 cancers were early Stage!
 - Conclusion: No more screening necessary than the thorough H&P, Chem18, CBC, CXR

Monreal, Chest 1993

- Prospective study of 78 patients with iPE
- Aggressive screening of all patients: H&P, ESR, BMP, LFT, CBC, peripheral smear, SPEP, LDH, CEA
- EGD, Abd US and CXR were offered to all patients
- If history of bowel changes or CEA got colonoscopy

Monreal, Chest 1993

- Malignancy in 9/78 (11.5%)
- 7 at time of PE hospitalization (6/7 no symptoms)

Table 1—Clinical Characteristics of the Nine Patients With PE in Whom a Malignancy Was Found

Patient No./ Sex/Age, yr	Risk Factor	Symptoms of Cancer	Time of Diagnosis	Abnormal Findings*	Site of Cancer
1/F/81	Idiopathic	No	1 wk	Anemia	Colon
2/F/68	Idiopathic	No	1 wk	ALT, AST	Liver
3/F/49	Idiopathic	No	1 wk	Pelvic mass	Ovary
4/M/82	Idiopathic	No	1 wk	Rectal examination	Prostate
5/M/70	Leg varicosities	Yes	2 wk	Lumbar pain	Prostate
6/F/85	Postoperative	No	2 wk	Breast node	Breast
7/M/44	Idiopathic	No	4 wk	CEA	Colon
8/F/59	Idiopathic	No	5 mo	Dysphagia	Esophagus
9/M/60	Postoperative	No	21 mo	Bleeding	Colon

*ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen.

Monreal Chest 1993

- Aggressive screening is not without risk:
- One gentleman with prostate node had AC held for prostate biopsy...
- Died of massive PE days later

Monreal Chest 1993

- Points to take home
 - 8/9 patients had abnormalities in basic labs, CEA or physical exam

Monreal, 2004

- Prospective cohort follow up study
- 864 patients with DVT
- **Routine Screen:**
 - H&P, CBC, Chem18, **ESR**, UA, **SPEP**, CXR
- **Additional Limited Workup:**
 - CEA, CA-125 (females), PSA (males)
 - General Abd US

Monreal, 2004

864 patients with DVT

Routine Exam / Labs / CXR

167 high risk

(127 on H&P, 40 on labs / cxr)

697 neg routine screen

133 neg

Limited Screen

54 high risk

13 with cancer

14 developed cancer during follow up

34 with cancer (20.4%)

Monreal, 2004

- Routine H&P, labs and CXR sensitivity of 55.7% (34/61)
- Limited work up 13 of remaining 27 sensitivity of 48.1%
- Routine H&P, labs, CXR AND abd US, PSA, CA125 and CEA sensitivity of 77%

Monreal, 2004

- LOW specificity, what does this mean?
- Every woman who had + abd US or CA-125 got a CT Abd/Pelv and/or **XLAP!**

Table 2 Type of abnormalities at the diagnostic work-up that led to the suspicion of occult cancer in the 830 patients without cancer at the routine examination

Type of abnormality	Patients (N)	Patients with cancer [N (%)]	Sites of cancer
CA-125 levels	21	3 (14)*	Ovary (2), uterus*
PSA levels	14	7 (50)	Prostate (7)
CEA levels	8	–	
Abdominal ultrasound	13	5 (38)	Ovary, uterus, pancreas, bladder, biliary system

*Two patients had both increased CA-125 levels and abnormal abdominal ultrasonography.

Screening Summary

- Thorough H&P, CBC, CMP and CXR catches 60-100% of cancers
- No good prospective data for further screening with CT, endoscopy, tumor markers
- Need a randomized controlled trial!

Piccioli, 2004

- Prospective Randomized Clinical Trial
- Study Population: **IDIOPATHIC VTE**
 - No malignancy, leg trauma, recent surgery or immobilization (6mo), iVTE in 1st deg relative, thrombocytosis, AT-III, Prot C or S, lupus AC, estrogen use, pregnancy, recent childbirth.

Piccioli, 2004

- Randomized to Extensive workup or Control (follow up)
- Extensive Malignancy Workup:
 - US abd/pelv, CT abd/pelv, EGD, Colonoscopy, Hemeoccult, Sputum cytology, CEA, AFP, CA-125, Pap, Mammography, TAUS prostate, PSA. (within 4 weeks of DVT)

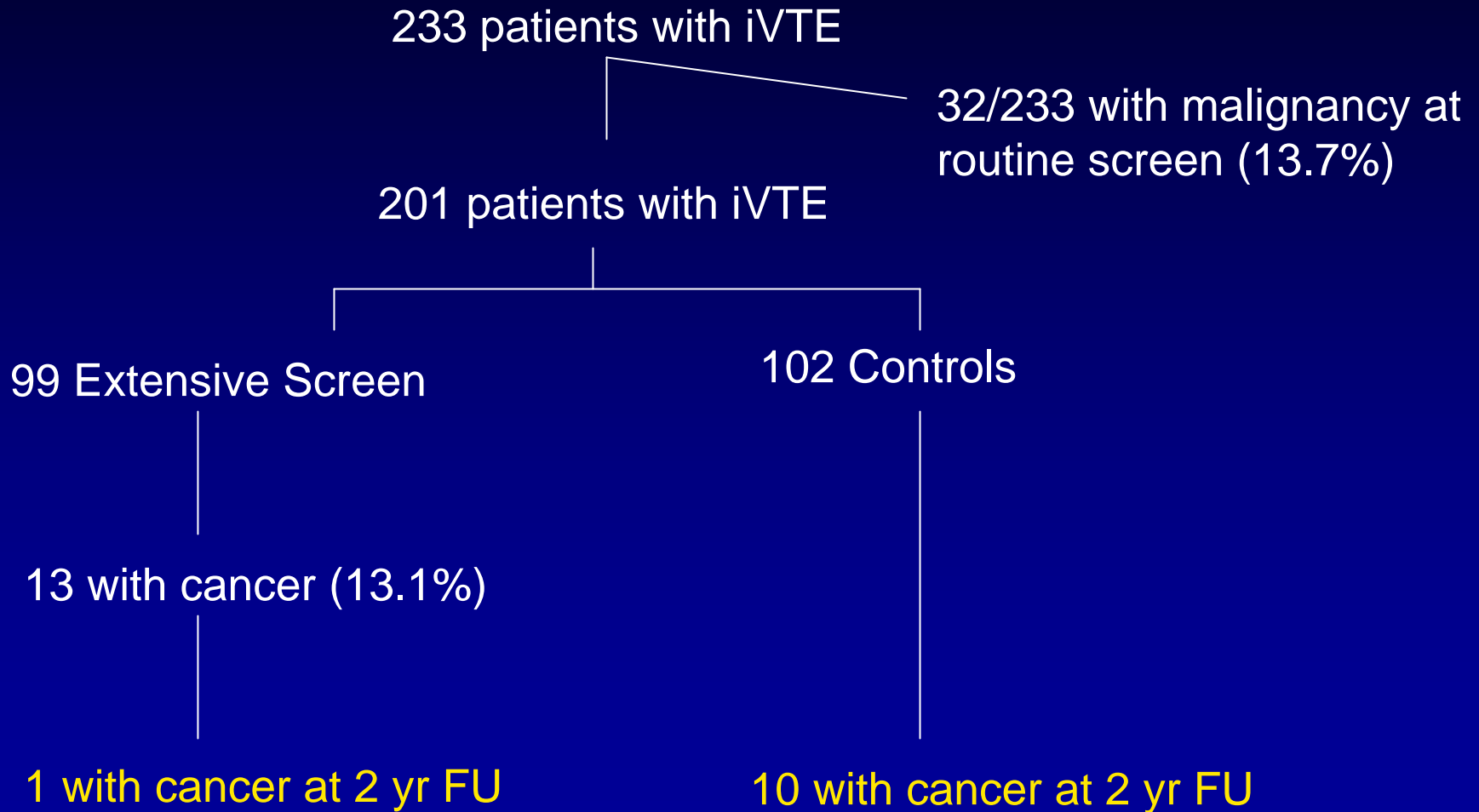
Piccioli, 2004

- Follow up at 3,12,24 months
- Primary Outcome: **CANCER RELATED MORTALITY!!!**
 - defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer

Piccioli, 2004

- 1020 patients referred for study with acute DVT or PE
- 681 had secondary VTE
- 138 excluded because of prior VTE or malignancy diagnosed at presentation by routine labs, cxr, H&P
- **TOTAL of 201 patients included in study**
 - 99 to extensive screening, 102 controls

Piccioli, 2004



Piccioli, 2004

- **Results:**

- Mean time to diagnosis 1 month vs 11.6 months (P<0.001)
- 9/14 patients in extensive screen with T1 or T2 without mets vs 2/10 in control (P<0.05)
- Primary endpoint (cancer related mortality) was not met. Trend toward decreased mortality (2/99 vs 4/102) not significant.
- Despite 80% getting full screens, **NO PROCEDURE RELATED COMPLICATIONS**

Piccioli, 2004

- Why did this study fail to support it's primary outcome?
 - Type II error (insufficient power)
 - Initially calculated a need for 1000 patients
 - Lost accrual secondary to ethics questions
 - Contamination in control group (docs ordered a lot of screening tests in control group)

Piccioli, 2004

- **Highest Yield Tests:**
 - CT scan of Chest, Abdomen and Pelvis would have found 12 of the 14 cancers
 - CEA, PSA, CA125, AFP and Hemeoccult would have found 10/14 but had 39 false +

Outline

- History of VenousThromboEmbolicism (VTE) and Cancer
- Definitions
- Epidemiology
- Screening for Occult Malignancy
- **Recommendations**

Recommendations

- There are no consensus guidelines
- For first DVT/PE:
 - Screen for secondary cause
 - Do thorough initial malignancy screen
 - H&P (tailored to cancer: breast, pelvic, testicular, rectal)
 - Workup any abnormalities aggressively
 - CBC, CMP, Ca, Hemeoccult, UA
 - PA lat CXR

Recommendations (H&P)

- Tailor your H&P to cancer screening:
 - Weight Loss
 - Change in bowel/bladder
 - Fatigue
 - Unusual pain (especially skeletal)
 - Unusual bleeding
 - Cough (recent change if chronic)
 - New or unusual headache (brain CA?)

Recommendations (H&P)

- Tailor your physical exam to cancer screening
 - Lymph Node Chains (including inguinal)
 - Abdominal exam
 - Breast exam
 - Testicular exam
 - Prostate exam
 - Pelvic exam
 - Oral exam
 - Skin

Recommendations

- For **Idiopathic DVT/PE**, especially **Recurrent iVTE**, there is debate on whether to aggressively screen using:
 - PSA, CA-125, CEA and AFP
 - Abd US or CT chest/abd/pelv
 - EGD and Colonoscopy

Recommendations

- **My Two Cents:**
 - For anyone with new VTE
 - Thrombophilia workup
 - H&P and routine screen (UA!)
 - Get those cancer screening tests that are appropriate for age (colonoscopy, PAP, mammo)
 - If history or sx of GERD get EGD
 - For iVTE get a CT chest/abd/pelvis
 - For Recurrent iVTE: Piccioli's screen

Possible Screening Strategy Based on Pretest Probability

- Any DVT/PE
 - Increased Risk
 - Routine Labs, UA, H&P, Hemeoccult and CXR, and cancer screening appropriate for age (colonoscopy, mammography, PAP, PSA)
- Idiopathic DVT/PE
 - High Risk
 - Above workup including CT of Chest, Abdomen and Pelvis
- Recurrent DVT/PE
 - Very High Risk
 - Piccioli's Complete workup including tumor markers, EGD, Colonoscopy

CASE:

- 45 yr old female admitted for PE
- No pregnancy, immobilization, long trips, family history of clots or estrogen use.
- Smoker
- Discharged on lovenox and coumadin from hospital and she arrives at UHC clinic

- NOW WHAT?

CASE:

- **NOW WHAT?**

- Rule out thrombophilia
- Review routine screen
 - Chest ct done, routine labs normal
 - Ensure no H&P abnormalities
 - Pelvic, PAP, Breast exam, Lymph Nodes
 - Get routine screens: mammography indicated
- Because idiopathic, it would be reasonable to add CT abdomen and pelvis

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