Diagnostic strategy in the emergency department

Spells as an example

Daniël C. Knockaert
General internal medicine
University hospital Leuven

Spells: definition

- Symptom(s) and/or signs : lightheadedness, dizziness, weakness, lethargy, headache, perspiration, flush or pallor, palpitations, vague chest discomfort, tremor, nausea, anxiety, blood pressure changes,…… (e.g. hot flash of the menopausal woman)
- Sudden onset
- Recurrent
- Self-limited , mostly short duration
- Stereotypic

Periodic/episodic phenomenon

Spells: literature

- Syncope
- Dizziness
- Flush
- Urticaria /angioedema
- Abdominal pain (“the non surgical acute abdomen”)
- FUO (recurrent FUO)

Spells: *diagnostic approach*

"The effective diagnostician is the one who makes least mistakes in delaying with common conditions, not the one who makes occasional brilliant guesses" .

However, pay enough attention to the rare causes which may be life-threatening.

Know the typical heuristics in diagnostic reasoning which lead to wrong diagnoses

Recurrent left upper abdominal pain

- 43 yrs old man
- Repeated attacks of severe left upper abdominal pain radiating to the back, duration 6-12 h
- Clearly linked to alcohol intake

Differential diagnostic suggestions?

Diagnostic step(s)

Suspected symtomatic ureteropelvic junction narrowing

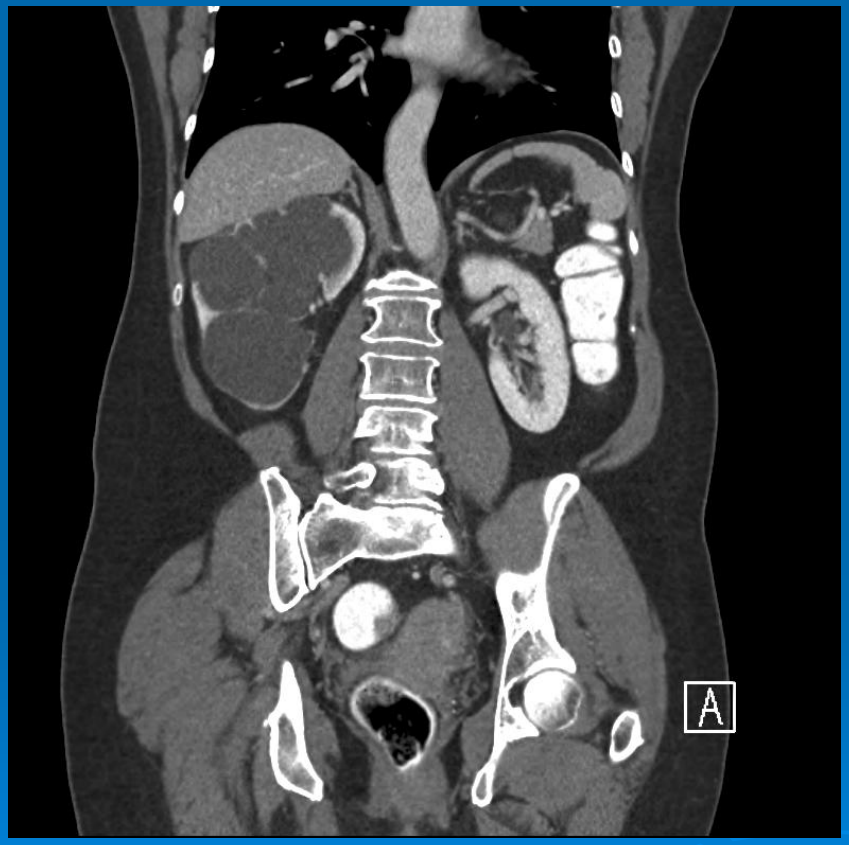
Diagnostic test

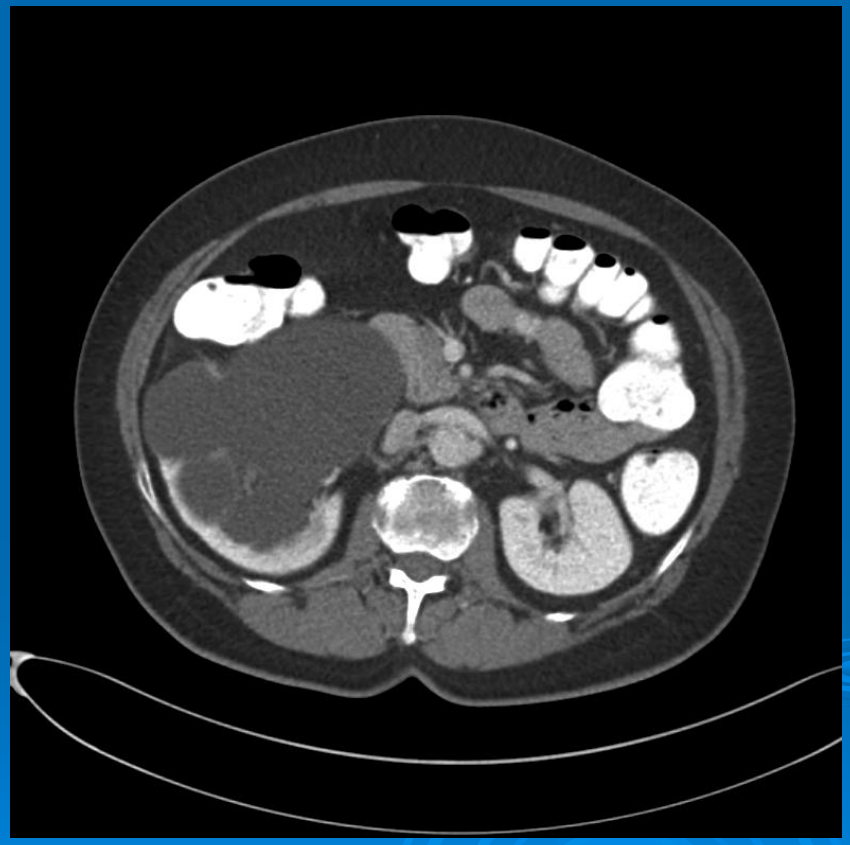
IV urography or CT scan with lasix wash out

Recurrent right abdominal pain

- 58 yr old woman
- Repeated bouts of right sided abdominal and loin pain since several years
- Much better after stopping her “evening” glass of porto
- Now again crises related to renewed porto drink
- No urinary complaints
- Physcial exam: tender right loin region
- Creatinin value: normal
- Urinalysis: normal

“Porto” kidney





ureteropelvic junction narrowing

ME ♀ 67 yrs old

- episodic tachycardia and light headedness, no flush nor pallor,
- History of difficult to control arterial hypertension
- “adenoma” of the left surrenal gland (known since years)

→ Phaeochromocytoma ?

ME ♀ 67 yrs old: outpatient data

- → Urinary catecholamins: nl
- → Chromogranin 191 µg/l (40 – 170)
- → 5HIAA: sky high

and now???

come to the emergency department during a new attack

→ Repeated measurement of urinary catecholamins during attack: again normal

→ Serotonin blood level during attack: normal

Fals positive 5HIAA value due to ibuprofen

Slighly increased chromogranin due to omeprazole

Typical problems with laboratory test for pheochromcytoma and carcinoid syndrome

Table 4.—**Spell Phenotypes: Medications and Foods That May Interfere With Laboratory Evaluation***

Pheochromocytoma

- May cause false-positive results in 24-hour urinary studies of metanephrines and catecholamines
  - Tricyclic antidepressants
  - Labetalol
  - Levodopa
  - Drugs containing catecholamines
  - Ethanol
  - Sotolal hydrochloride
  - Withdrawal from clonidine hydrochloride and other drugs
  - Amphetamines
  - Methyldopa
  - Benzodiazepines
- Cause false-negative results
  - Metyrosine
  - Methylglucamine†

Carcinoid syndrome

- Cause false-positive results in 24-hour urinary studies of 5-HIAA
  - Foods—bananas, plantain, pineapple, kiwi, avocados, nuts
  - Cough syrups containing guaifenesin (for example, Robitussin)
  - Acetaminophen
  - Naproxen
  - Melphalan and fluorouracil
- Cause false-negative results
  - Aspirin
  - Levodopa
  - Phenothiazines

Mast cell disease

- May interfere with the measurements of histamine and histamine metabolites
  - Antihistamines

Mayo Clinic Proc 1995; 70: 757

BW ♂ 60 yrs old

High fever; 3d later shock, easily reversed with massive fluid therapy

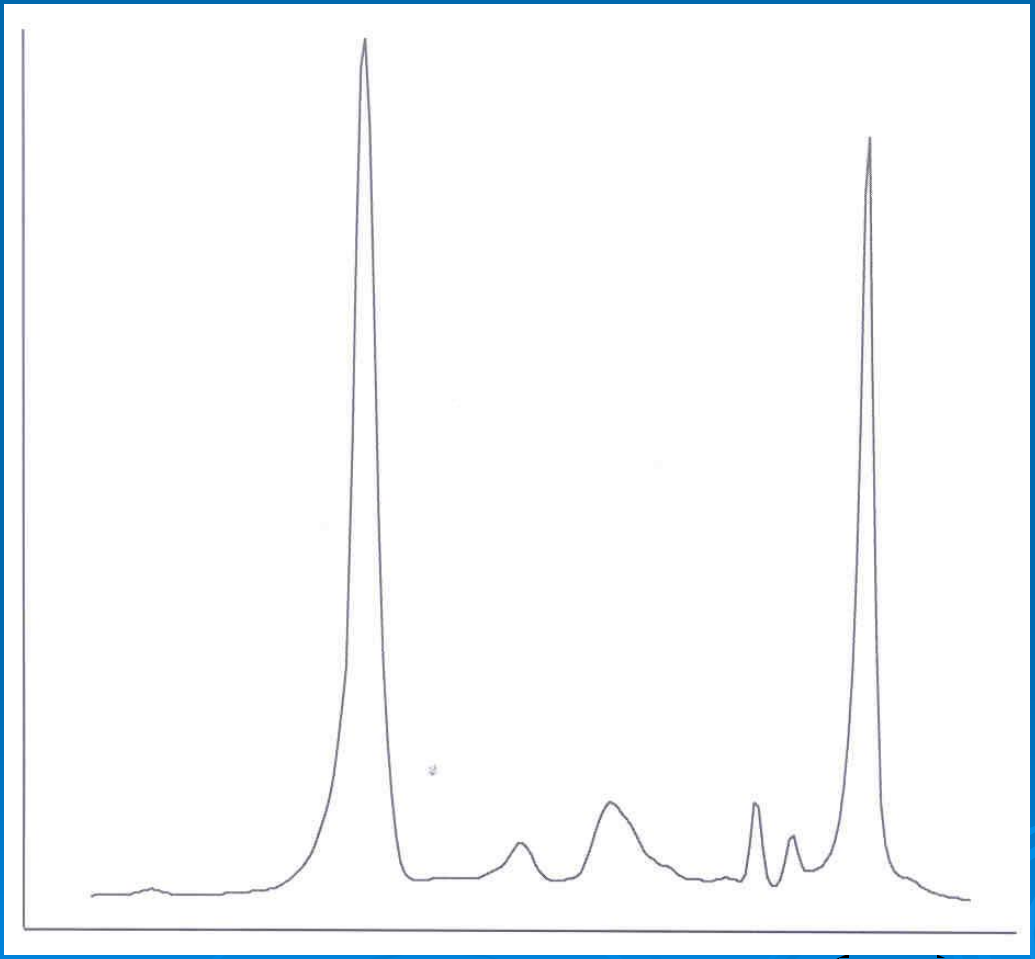
10 months later : again shock, again easily reversed:

4 months later: again same story

1 month later: again same story: referral

	h o	h24	h48
• Hgb	22,7 g/dl	16,3 g/dl	10,9
• Htc	0,65	0,47	0,32
• Ureum	102	95	50
• Creatinine	1,5	1,64	0,83
• Alb	35 g/l	24 g/l	31 g/l

A (simple) diagnostic test?



Systemic capillary leak syndrome

- Recurrent attacks of impressive hypovolemic shock
- Triphasic clinical course
  - ***Prodromal phase*** (hours to days) of malaise, abdominal discomfort, thirst, sometimes fever
  - ***Extravastion (capillary leak) phase*** (1 to 4 days): hypotension, increased hematocrit and hypoalbuminemia, weight gain and oedema (palpebral, peripheral, intestinal, ascites, pleural and pericardial, even muscular resulting in compartment syndrome
  - ***Recovery phase*** (polyuria and risk of pulmonary oedema)

- Clue: hemoconcentration without obvious fluid loss
- Important tests: paraprotein screening and complement levels

- Pathophysiology: transient capillary hyperpermeability (extravasation of albumin-rich plasma)

- Treatment: fluid resucitation, corticosteroids (0,5mg/kg), high dose iv Ig?
- Prophylactic treatment : β-2 agonists (terbutaline, salbutamol) and theopylline.

Diagnostic strategies

- Possibilistic approach: “lists”
- Causal reasoning (based on anatomy, pathophysiology)
- Deterministic reasoning
  - Flow charts
  - Pattern recognition (requires quite a lot of experience)
- Probabilistic reasoning

*The possibilistic diagnostic approach of **syncope***

Cardiac causes

- Structural cardiac or cardiopulmonary disease (aortic stenosis, mitral stenosis, pulmonary stenosis, left atrial myxoma, aortic dissection, acute myocardial infarction, cardiac tamponade, pulmonary embolism, obstructive cardiomyopathy)
- Cardiac arrhythmias (tachyarrhythmias, bradyarrhythmias)
- Neurally mediated syncopal syndrome (includes neurocardiogenic or vasovagal syncope, carotid sinus syncope, and situational syncope)
- Orthostatic (or postural) hypotension

Metabolic causes

- Hypoxia
- Hypoglycaemia
- Hyperventilation

Psychiatric causes

- Somatisation disorders
- Hysteria
- Panic
- Fright

Neurological causes

- Seizure disorders
- Transient ischaemic attacks
- Subclavian steal syndrome
- Normal pressure hydrocephalus

BMJ 2004; 329:336

Cardiac or Cardiopulmonary Causes

- Arrhythmias
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy
- Aortic dissection
- Myocardial ischemia
- Pericardial tamponade
- Pulmonary embolism
- Pulmonary hypertension

Noncardiac Causes (baroreceptor reflex disturbances)

- Neurally mediated reflex syndromes
  - Vasovagal faint
  - Micturition or defecation syncope
  - Postprandial hypotension
- Orthostatic hypotension
- Cerebrovascular steal

Conditions frequently misdiagnosed as syncope

- Hypoglycemia
- Epilepsy
- Cataplexy
- Vertebrobasilar transient ischemic attacks

The possibilistic diagnostic approach of dizziness

TABLE 4. Final Diagnoses for 907 Patients Presenting to the Emergency Department With Dizziness[a]

Diagnosis[b]	Patients, No. (%)
Serious neurologic diseases	49 (5)
Ischemic stroke	24 (3)
Transient ischemic attack	8 (1)
Brain neoplasm	6 (1)
Intracerebral hemorrhage	5 (1)
Seizure	4 (<1)
Demyelinating disease	2 (<1)
Subarachnoid hemorrhage	0
Subdural hemorrhage	0
Epidural hemorrhage	0
Brain abscess/meningitis	0
Peripheral neurologic diseases	294 (32)
Peripheral vertigo NOS	185 (20)
BPPV	78 (9)
Vestibular neuronitis	27 (3)
Meniere disease	4 (<1)
Other neurologic diseases	388 (43)
Dizziness NOS	199 (22)
Orthostasis/near syncope	121 (13)
Migraine	37 (4)
Syncope	20 (2)
Concussion	11 (1)
Gait disorder NOS	0
Psychiatric conditions	22 (2)
Psychiatric disorder NOS	22 (2)
Serious cardiac diseases	35 (4)
Arrhythmia	22 (2)
Hypertensive emergency	10 (1)
Acute coronary syndrome	2 (<1)
Heart failure exacerbation	1 (<1)
Stable angina	0
Other medical conditions	119 (13)
Drug or substance ingestion/withdrawal	46 (5)
Systemic infection	34 (4)
Electrolyte disorder	14 (2)
Other	11 (1)
Anemia or gastrointestinal bleeding	10 (1)
Hypoglycemia	4 (0.4)

Mayo clin Proc 2012;87:1080

*The possibilistic diagnostic approach of **flush***

Flushing caused by systemic diseases
- Carcinoid syndrome
- Mastocytosis
- Medullary thyroid carcinoma
- Pancreatic carcinoma
- Phaeochromocytoma
- Renal cell carcinoma

Neurological flushing
- Anxiety
- Brain tumours
- Migraine
- Parkinson's disease
- Spinal-cord lesions

Flushing reactions related to alcohol and drugs
- Aromatase inhibitors
- Bromocriptine
- Calcium-channel blockers
- Cephalosporins
- Cholinergic drugs
- Chlorpropamide
- Ketoconazole
- Metronidazole
- Nicotinic acid

Opiates
- Luteinising hormone-releasing hormone agonists or antagonists
- Anti-oestrogens, SERMs
- Aromatase inhibitors

Flushing associated with eating and food additives
- Auriculotemporal
- Dumping syndrome
- Gustatory
- Hot beverages
- Monosodium glutamate
- Sodium nitrite
- Sulphites

Lancet 2002;360:1852

Differential diagnosis of flushing

Autonomic-mediated	Vasodilator-mediated
Thermoregulatory flushing	Rosacea
Fever	Medications (ie, calcium channel blockers, nicotinic acid)
Exercise	Food ingestion
Heat exposure (environmental or ingestion)	Alcohol
Menopause	Carcinoid syndrome
Emotional flushing	Systemic mastocytosis
Neurologic	Pheochromocytoma
CNS tumor	Medullary thyroid carcinoma
Autonomic epilepsy	Serotonin syndrome
Cluster headache	Anaphylaxis
Spinal cord injury	VIPoma
Parkinson's disease	Renal cell carcinoma
Multiple sclerosis	Dumping syndrome
Autonomic hyperreflexia/orthostatic hypotension	Sarcoidosis
Auriculotemporal (Frey) syndrome	Hyperthyroidism
Trigeminal neuralgia	Bronchogenic carcinoma
Migraine	Androgen deficiency in men

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*The possibilistic diagnostic approach of **recurrent FUO***

TABLE 1 Infections Reported as Causes of Recurrent FUO

Chronic prostatitis
Recurrent cholangitis (Caroli's disease)
Otitis media/mastoiditis
Brucellosis
Dental abscess
Sinusitis
Yersinia enterocolitica
Rat bite fever (*Spirillum minor, Streptobacillus moniliformis*)
Melioidosis
Q-fever
Relapsing fever (*Borrelia* sp.)
Trypanosomiasis
Whipple disease
Epstein Barr virus infection
Toxoplasmosis

TABLE 2 Neoplastic Diseases Reported as Causes of Recurrent FUO

Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Malignant histiocytosis
Angioimmunoblastic lymphadenopathy
Craniopharyngioma
Schnitzler syndrome
Artrial myxoma
Hepatocellular carcinoma

Systemic inflammatory diseases reported as causes of recurrent FUO

- Adult onset Still's diseas,
- Behçet's disease
- Relapsing polychondritis

TABLE 3 Miscellaneous Conditions Reported as Causes of Recurrent FUO[a]

Addison's disease
Aorta-enteric fistula
Brewer's yeast ingestion
Castleman's disease
Cirrhosis (68)
Cholesterol embolism
Chronic fatigue syndrome (2)
Crohn's disease
Cryopyrin-associated periodic syndromes
Muckle-Well's disease (urticaria, deafness, and ayloidosis)
Familial cold autoinflammatory syndrome (familial cold urticaria)
Neonatal onset multisystem inflammatory disease or chronic infantile neurologic, cutaneous and articular syndrome
Cyclic neutropenia
Erdheim-Chester disease (58)
Drug fever
Fabry disease
Factitious fever
Familial Mediterranean fever
Periodic fever, aphtous stomatitis, pharyngitis (cervical) adenitis
Gaucher's disease
Gout
Granulomatous hepatitis
Habitual hyperthermia
Hemolytic anemia (69)
HIDS (hyper IgD syndrome)
Hypersensitivity pneumonitis
Hypothalamic hypopituitarism
Hypertriglyceridemia
Idiopathic granulomatosis
Inflammatory pseudotumor of lymph nodes
Lung embolism
Mastocytosis (70)
Metal fume fever
Milk protein allergy
Poikilothermia
Polymer fume fever
Pseudogout
Ratke's cleft cyst
Rosai-Dorfman syndrome (21)
Seizures
TNF-receptor-1-associated periodic syndrome (familial Hibernian fever)

Spells: the possibilistic approach

Table 1.—**Differential Diagnosis of Spells**

Endocrine
- Pheochromocytoma
- Thyrotoxicosis
- Primary hypogonadism (for example, menopausal syndrome
- Medullary thyroid carcinoma
- Pancreatic tumors (for example, insulinoma)
- Hypoglycemia
- Carbohydrate intolerance
- "Hyperadrenergic spells"

Cardiovascular
- Labile essential hypertension
- Cardiovascular deconditioning
- Pulmonary edema
- Syncope
- Orthostatic hypotension
- Baroreflex dysfunction
- Paroxysmal cardiac arrhythmia
- Angina
- Renovascular disease

Psychologic
- Anxiety and panic attacks
- Somatization disorder
- Hyperventilation

Pharmacologic
- Withdrawal of adrenergic inhibitor
- Monoamine oxidase inhibitor treatment and tyramine (in foods) or sympathomimetic drugs
- Sympathomimetic ingestion
- Illegal drug ingestion (for example, cocaine, PCP, LSD)*
- Chlorpropamide-alcohol flush
- Vancomycin ("red man syndrome")

Neurologic
- Postural orthostatic tachycardia syndrome
- Autonomic neuropathy
- Migraine headache
- Seizure disorders
- Diencephalic epilepsy (autonomic seizures)
- Fatal familial insomnia
- Stroke
- Cerebrovascular insufficiency

Other
- Mastocytosis—systemic or activation disorder
- Environmental allergies
- Carcinoid syndrome
- Recurrent idiopathic anaphylaxis
- Unexplained flushing spells
- Polycythemia vera
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)

Mayo Clinic Proceedings 1995;70:757

Spells

The subspecialty possibilistic approach

- Cardiovascular
  - Cardiac (rythm-conduction abnormalities, myxoma,…)
  - Cardiovascular (baroreceptor-vasomotor)
  - Lung embolism
- Neurologic (epilepsy, migraine,….)
- Endocrinologic (hypogonadism, hypoglycemia, pheochromocytoma, NET,…)
- Psychologic/psychiatric (panic attack, somatization disorder, simulation,….)
- Pharmacologic/toxic (medication, drugs, toxins)
  - recreational drugs (cocaine, amfetamines, ….)
  - medication (MAO blockers and tyramine in food, metronidazole and alcohol, nicotinic acid, nitrates…)
  - toxins (glue sniffers, metal fume fever in welders, lead poisoning….)
- Allergic/immunologic (food and other (pseudo) allergies, extrinsic allergic alveolitis, C1 inhibitor deficiency, mastocytosis,…..
- Metabolic (porfyria, periodic paralysis…..)

be aware of the availibility heuristic: considering the diagnosis that springs to mind by recalling past cases

Diagnostic methods

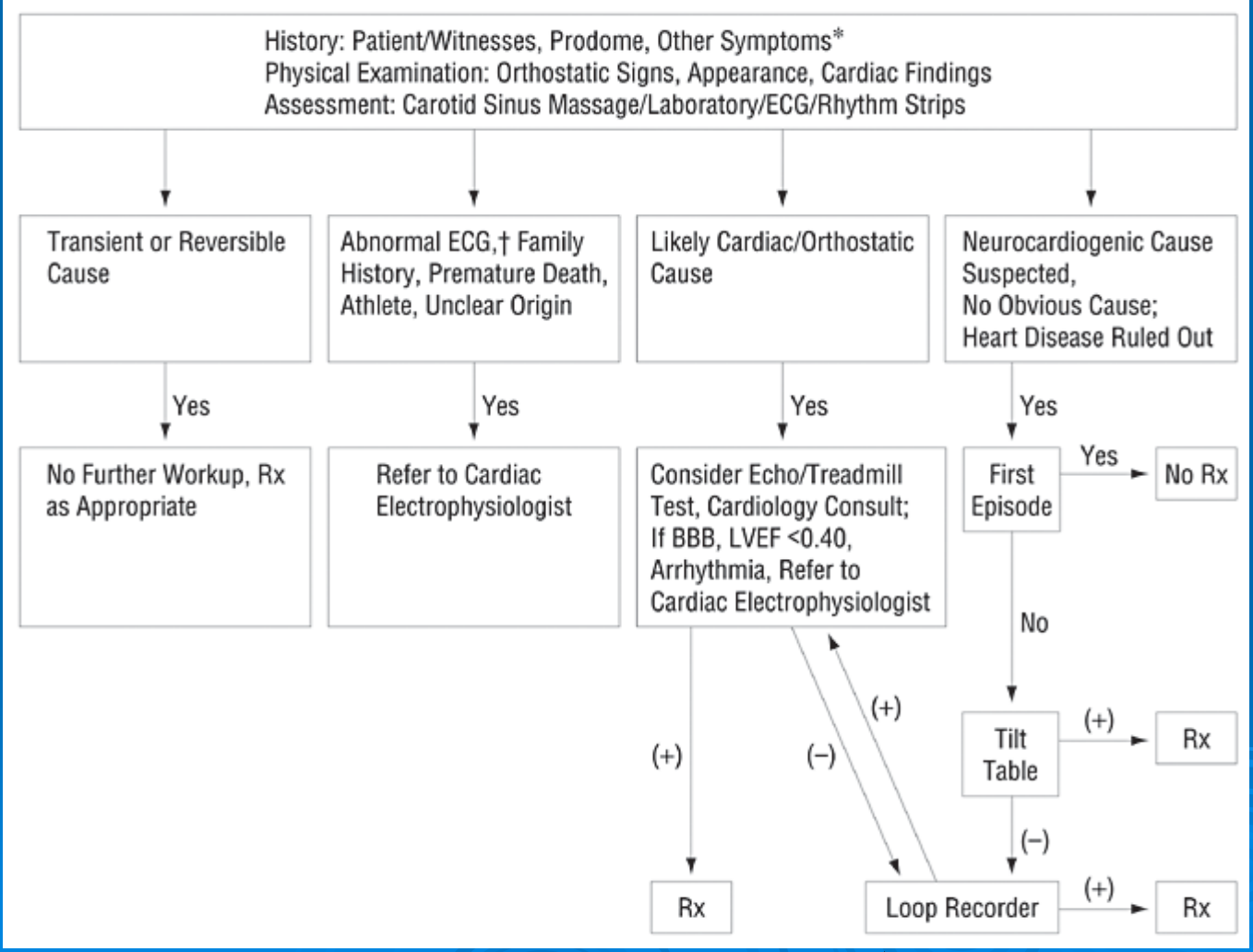
- Possibilistic approach: “lists”
- Causal reasoning (based on pathophysiology, anatomy,)

  Profound hypokaliemia: periodic paralysis
- Deterministic reasoning
  - Flow charts
  - Pattern recognition (requires quite a lot of experience)
- Probabilistic reasoning

Diagnostic methods

- Possibilistic approach: “lists”
- Causal reasoning (based on anatomy, pathophysiology)
- Deterministic reasoning
  - Flow charts
  - Pattern recognition (requires quite a lot of experience)
- Probabilistic reasoning

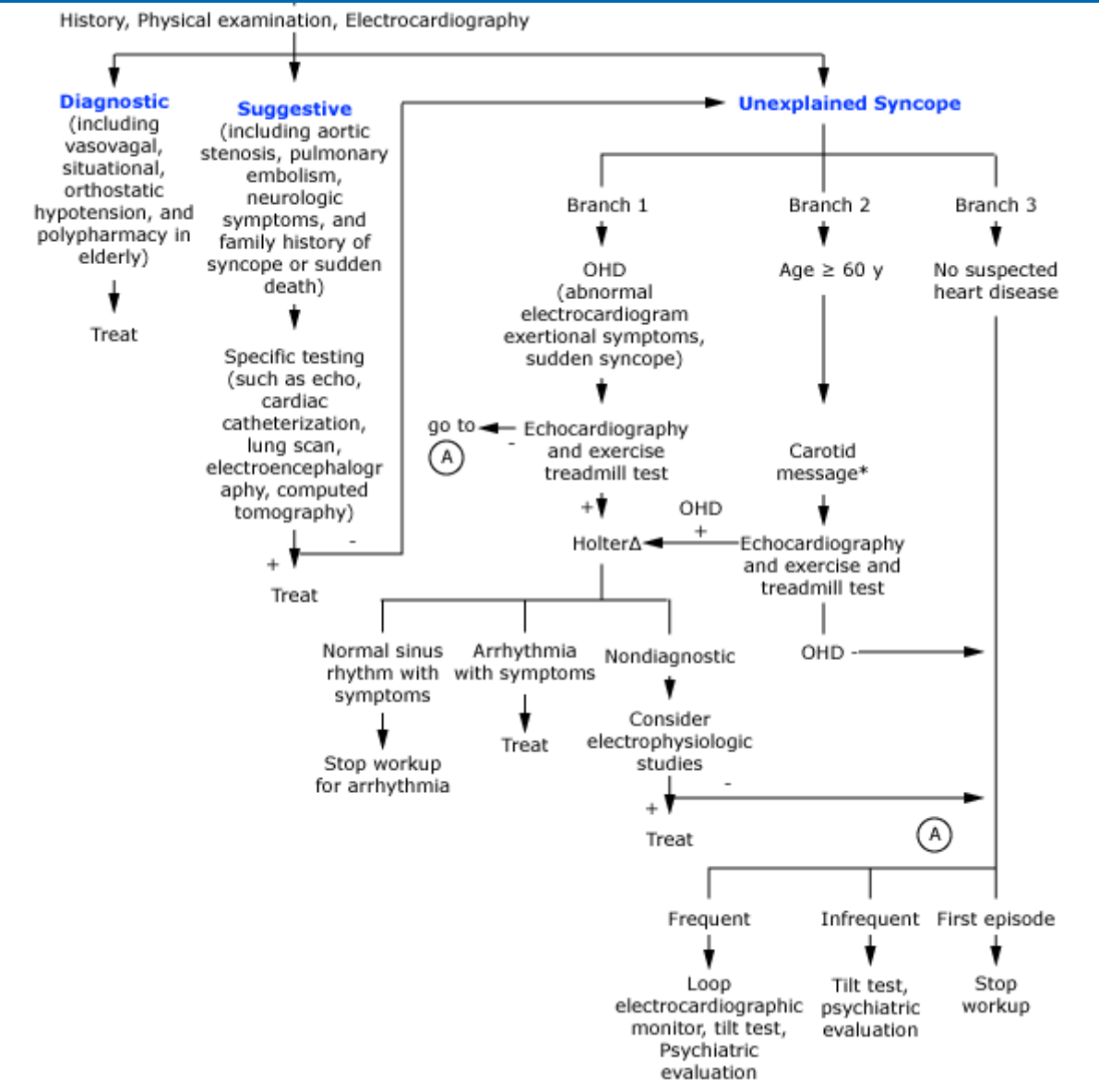
Deterministic reasoning: "flow charts"
the syncope example



Arch Int Med 2003; 163:151

Deterministic reasoning: “flow charts”

the syncope example



Diagnostic methods

- Possibilistic approach: “lists”
- Causal reasoning (based on anatomy, pathophysiology)
- Deterministic reasoning
  - Flow charts
  - Pattern recognition (requires quite a lot of experience)
- Probabilistic reasoning

Deterministic reasoning: pattern recognition

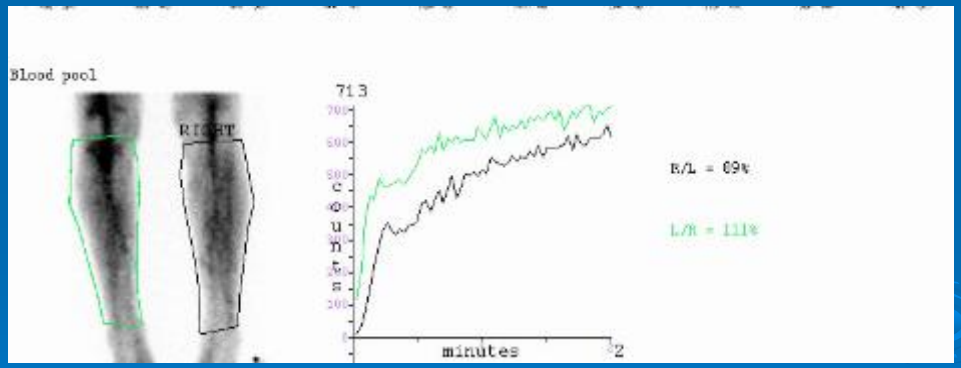
Episodic fever

accompanied with urticaria

Bone pain (limbs mostly)

X-rays: osteosclerosis

Bone scintigraphy



Diagnosis? which further tests?

Deterministic reasoning: pattern recognition

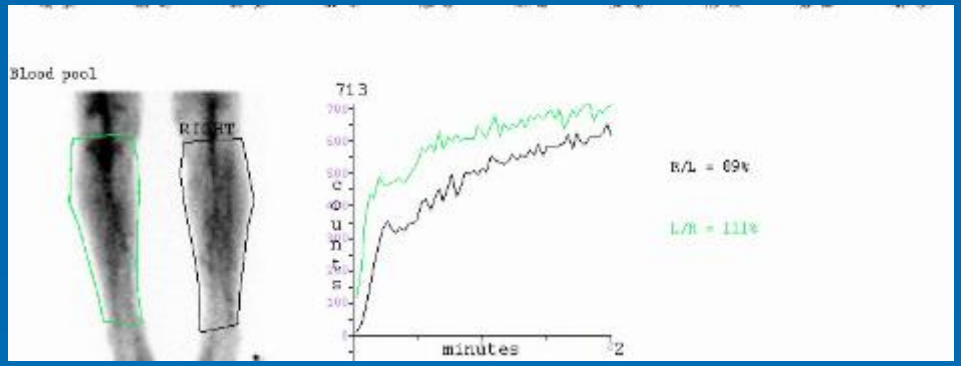
Episodic fever

accompanied with urticaria

Bone pain

X-rays: osteosclerosis

Bone scintigraphy



IgM paraprotein

Schnitzler syndrome

Deterministic reasoning: pattern recognition

Knowledge of rare diseases is limited just due to their rarity

be aware of

the “availibility heuristic” the diagnosis that springs to mind by recalling past cases

“premature closure” *narrow minded belief in a single diagnosis due to too much confidence in the result of tests even when they do not fit in the leading hypothesis (eg incidentaloma)*

Diagnostic methods

- Possibilistic approach: “lists”
- Causal reasoning (based on anatomy, pathophysiology)
- Deterministic reasoning
  - Flow charts
  - Pattern recognition (requires quite a lot of experience)
- Probabilistic reasoning: “art and science”

Pretest probability based on literature data adjusted for the individual patiënt based on age, gender, ethnicity and on the art of history taking and physical exam…

Posttest probablility based on test characteristics (sensitivity, specificity, positive and negative predictive value , likelihood ratios….): “the science”

Be aware of the limited sensitivity of a number of tests in patients presenting very early after onset of complaints (e. g. sensitivity of ultrasonography for cholecystitis)

Se → ”snout”; Sp → “spin”

History of spells

- Sequence of symptoms
  - Chest discomfort followed by panic attack symtoms: think about acute coronary syndromes and lung embolism,……
  - Palpitations followed by panic attack symptoms: think about primary arythmia
- Precipitating factors
  - Food, medications, drugs,…..
  - Physical effort
  - Environment
- Correct description, if possible by proxy

  flush or pallor, which kind of palpitations, …..
- Duration
- Frequency
- Medications and substance abuse

e.g. ACE inhibitors and angio-oedema risk

Physical exam

- Blood pressure check for orthostatic changes
- Lung ausculation: wheezing?
- Skin: café au lait? Neurofibromatosis (pheochromocytoma)
  pigmentation: mastocytosis
- Thyroid gland
- Neurologic exam

Spell “phenotype”

- Sharply defined, based on the most pertinent components of history and physical exam
  - Syncope, presyncope, dizziness, vertigo, epilepsy,…?
  - Flush or pallor
  - Hyper- or hypotension
  - In case of palpitations evidence for arythmia
  - Chest discomfort suggestive for acute coronary syndrome or not
  - ……

Useful tests in case of spells

- Serial hematocrit level (increased value points to fluid shift and possible anafylactoid mecahnism/angioedema)
- K: periodic paralysis syndromes
- Phosfate: decreased in case of panic attack (due to acute respiratory alcalosis)
- Glucose (sometimes also HGBA1c, (pro)insuline, C-peptide,)
- ABG: be aware of the posthypocapnic hypoxemia and increased lactate value in case of psychogenic hyperventilation/panic attack
- d-dimer
- TSH

- ECG
- Neuro-imaging and EEG in selected cases

Probabilistic diagnostic strategy

Put forward a leading hypothesis (based on history, physical exam, routine tests,….)

be aware of *the framing effect* (selecting only those elements which fit in your hypothesis because you are familiar with those elements), a particular risk for subspecialists confronted with atypical problems

be aware of the red herring when formulating your leading hypothesis

a strong but misleading clue, a wrong track

Probabilistic diagnostic strategy

Put forward a leading hypothesis (based on history, physical exam, routine tests,….)

be aware of *the framing effect* (selecting only those elements which fit in your hypothesis), a particular risk for subspecialists confronted with atypical problems

be aware of the red herring phenomenon when formulating your leading hypothesis

a strong but misleading clue, a wrong track

Try to confirm your hyothesis by (positive) highly specific test *(Spin)* but

be aware of the *anchoring heuristic* ("stick" to the first hypothesis, relying on initial impressions)

be aware of *premature closure:* *(due to too much confidence in the results of tests even when they do not fit in the leading hypothesis : eg incidentaloma of the surrenal gland and a history of palpitations*

“Premature closure” in case of (pre)syncope/dizziness

carotid sinus hypersensitivity as cause

Table 2. Prevalence of CSH in Study Group and Subsample With No Prior Falls, Syncope, or Dizziness*

Variable	Study Group (n = 272)	Subsample With No Prior Falls, Syncope, or Dizziness (n = 80)
CSH	107/272 (39)	28 (35)
Cardioinhibitory CSH	6/107 (6)	2/28 (7)
Vasodepressor CSH	42/107 (39)	8/28 (29)
Mixed CSH	59/107 (55)	18/28 (64)
Symptoms with CSH	43/107 (40)	10/28 (36)
Syncope	18/43 (42)	4/10 (40)
Presyncope/dizziness	25/43 (58)	6/10 (60)
RR interval post-CSM, median (range), ms	1701 (633-11264)	1676 (633-8637)
Maximum delta RR, median (range), ms	766 (29-10021)	783 (29-7798)
SBP nadir, mean ± SD, mm Hg	83 ± 28	85 ± 27
Maximum fall in SBP during CSM, mean ± SD, mm Hg	47 ± 20	45 ± 17

Abbreviations: CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; ms, milliseconds; SBP, systolic blood pressure.
*Data are given as number/total number (percentage) of patients unless otherwise specified.

Carotid sinus massage

Se: 41%

Sp: 64%

PPV: 73%

NPPV: 32%

Arch Int Med 2006; 166:515

Selected tests in case of spells

- Consider measurement of urinary catecholamins or 5 HIAA
- Consider paraproteïn screening(above the age of 40 yrs)
- Consider measurement of complement levels
- Consider measurement of tryptase value
- Consider chromogranine (Se 56-100% in case of carcinoidsyndrome, poor specificity ,may be increased in case of kidney failure, liver disease, IBD, prolonged PPI therapy…)
- Consider porfyrin screen
- (calcitonin)

Probabilistic diagnostic strategy

- Leading hypothesis (based on history, physical exam, routine tests,….)
- Alternative hypotheses
  Rule out by (negative) highly sensitive tests (*Snout*)
- Other unlikely hypotheses
  Hold off on testing in the initial investigation

Differential diagnosis of spells

the most frequent causes

- Panic attack/ hyperventilation
- Atypical migraine
- Presyncope/orthostatic intolerance
- Somatization/simulation
- Medication induced anaphylactoid reaction
- Food allergy/intolerance
- Hypoglycemia
- Perimenopausal symptoms
- Epilepsy
- Illegal drug ingestion

Differential diagnosis of spells

Conditions That Can Mimic Epileptic Seizures

Table 1. Conditions That Can Mimic Epileptic Seizures.

Diagnosis	Important Clinical Features
Hyperventilation	Anxiety and overbreathing evident; often perioral cyanosis, hand paresthesias, and carpopedal spasm are present; environmental trigger may be evident
Migraine	Slow progression of neurologic symptoms; visual symptoms prominent; basilar migraine has unusual features, including confusion, stupor, bilateral blindness; headache may be minimal or absent
Panic attack	Abrupt onset with intense feeling of dread or fear; often sense of impending death or inability to breathe; prominent autonomic features (e.g., tachycardia, sweating, nausea); lasts longer (5–30 min) than typical seizure; no loss of consciousness
Psychogenic seizures	Psychiatric history; patient usually motionless with eyes closed at onset; fluttering eye movements and forceful eye closure common; out-of-phase, thrashing limb movements and pelvic thrusting common; urinary incontinence unusual; refractory to treatment
Syncope	Precipitating circumstances usually identifiable; prodrome of wooziness but no aura or unilateral symptoms; loss of consciousness brief (<20 sec), with rapid return to normal; a few muscle jerks ("convulsive syncope") can occur at end because of hypoxia
Transient global amnesia	Isolated amnesic syndrome; prolonged duration (several hours); no alteration of consciousness; no confusion, weakness, or aphasia; persistent memory gap during period of attack; recurrence unusual
Transient ischemic attack	Sudden onset without progression of symptoms; variable symptoms related to brain and vascular anatomy; negative features (e.g., weakness, loss of sensation, aphasia) predominate

French J and Pedley T. N Engl J Med 2008;359:166-176

The NEW ENGLAND JOURNAL of MEDICINE

Differential diagnosis/rarities

- Phaeochromocytoma
- Carcinoid and other NET
- Mastocytosis
- Hereditary angioedema
- Paraprotein associated syndromes

  acquired C1 inhibitor deficiëntie, systemic capillary leak syndrome, Schnitzler syndrome
- Periodic paralysis
- Porfyria

Further testing

"Look where the money is" " look for clues"

age: <40 yrs : think about unusual or delayed presentation of classical hereditary syndromes (diagnostic delay of hereditary angio-oedema was 10 yrs in 2005, 22 yrs in 1977)

> 40 yrs: be aware of paraprotein associated syndromes

(acquired C1 inhibitor deficiëntie, systemic capillary leak syndrome, Schnitzler syndrome)

Important clues in recurrent “medical” acute abdomen

- Family history
  Heredidary angio-oedema, FMF, (porfyria)
- Ethnicity
  FMF (particularly Armenian, Turkish, Arabs, Jewish, less frequently North-African descent)
  Sickle cell crisis
- Older age
  Monoclonal gammopathy associated pathology
- Atopic constitution
  Food and drug allergy

What to do for unexplained cases?

Instructions to measure heart rate and if possible blood pressure during attack

Readmission with a plan for appropriate testing based upon the most probable and prognostically important entities.

Spells: a pathophysiologic classification

- **Reflex disturbances**
  - Baroreceptor
    - Syncope (vasovagal, vagovagal, orthostatic,….)
    - Postural tachycardia syndrome)
  - Lung embolism
  - Panic attack (psychogenic hyperventilation)
- "Electrophysiologic" (abnormal cellular depolarisation, ion channelopathology)
  - Cardiac arythmia → syncope (light headedness)
  - Epilepsy
  - Migraine, trigeminus neuralgia, cluster headache
  - Periodic paralysis syndromes (potassium channelopathies)
- Mediator release (endocrinologic)
    - Hypogonadism (menopauze, andropauze)
    - Hypoglycemia
    - Feochromocytoma
    - Carcinoid syndrome
    - NET (neuroendocrine tumors)
    - Medullary thyroid carcinoma
    - Dumping syndrome

Spells: a pathophysiologic classification

- "Immunologic"
  - Hereditary C1- inhibitor deficiency
  - Mastocytosis
  - (Pseudo) allergens (EAA, food allergy, NSAID/aspirin induced angiooedema)
  - Paraprotein related
    - acquired C1- inhibitor deficiency
    - Systemic capillary leak syndrome
    - Schnitzler syndrome

- Exogen/environmental substances
  - glue sniffers, metal/polymer fume, lead poisoning,……
  - drugs (niacine flush, nitrates, furadantine,…)
  - recreational drugs

    glue sniffers, cannabinoied hyperemesis syndrome, cocain induced chest pain,….
- Metabolic
  - Porfyria
  - Rabdomyolysis (glycogen storage diseases, fat chain oxidation diseases, ….)

Hypoglycemia

- The Whipple triade (1938) is still required
  - Hypoglycemia
  - + clinical symptoms
  - + reversal of symptoms with glucose