Pruritus in systemic diseases

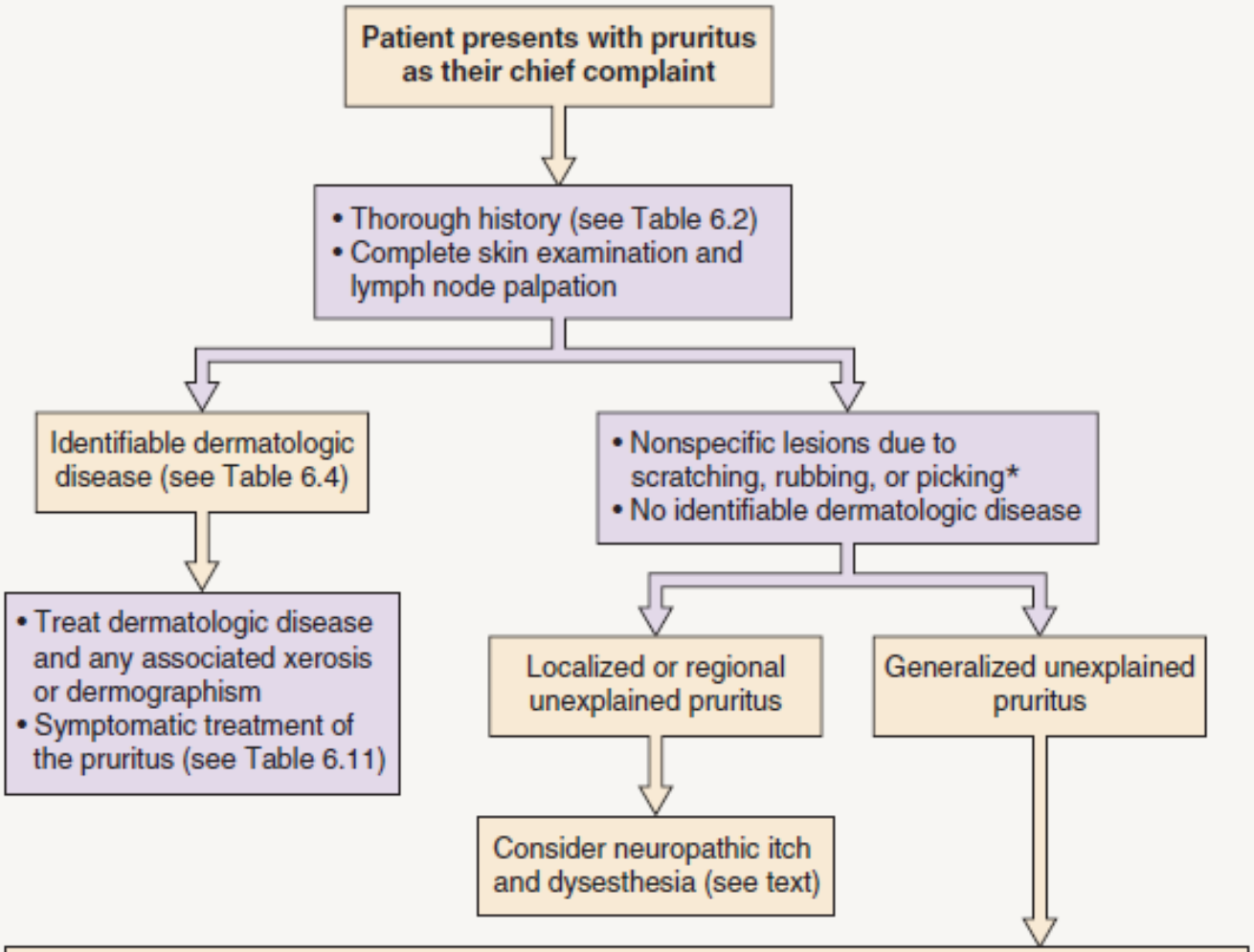
M.S.Ansari M.D
Tehran University of Medical Sciences

INTRODUCTION

- an unpleasant sensation that elicits a desire to scratch
- the most common skin-related symptom
- underlying systemic disease in ~10–25%
  - hepatic, renal, or thyroid dysfunction; lymphoma, myeloproliferative neoplasms (e.g. polycythemia vera), and chronic lymphocytic leukemia;HIV or parasitic infections; and neuropsychiatric disorders

PREVALENCE OF PRURITUS IN SELECTED CONDITIONS	
Disorder	**Reported prevalence of pruritus**
Atopic dermatitis	100% (diagnostic criterion)
Lichen planus	~95%
Psoriasis	≤85%
End-stage renal disease on hemodialysis	25–30% (previously 60–80%)
Primary biliary cirrhosis	80% (presenting symptom in 25–70%)
Hepatitis C viral infection	15%
Cutaneous T-cell lymphoma	60–80% overall; >90% in Sézary syndrome
Polycythemia vera	30–50%
Hodgkin disease	15–30%
Non-Hodgkin lymphoma	2–10%
Leukemias	<5%
Herpes zoster	≤60%
Postherpetic neuralgia	≤30%
Pregnancy	20%

A SIMPLIFIED APPROACH TO THE PATIENT WITH PRURITUS



*May include prurigo nodularis, prurigo simplex, linear excoriations, lichen simplex chronicus

EVALUATION OF THE PATIENT

- chronic, progressive generalized pruritus without primary skin lesions raises suspicion of an underlying systemic disease
- Careful and complete examination of the skin, nails, scalp, hair, mucous membranes
- palpation of major peripheral lymph node groups

LABORATORY AND RADIOGRAPHIC EVALUATION IN PATIENTS WITH PRURITUS OF UNKNOWN ETIOLOGY

Basic initial evaluation

- Complete blood cell count (CBC) with differential and platelet count
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Creatinine, blood urea nitrogen, electrolytes
- Liver transaminases, alkaline phosphatase, bilirubin
- Lactate dehydrogenase (LDH)
- Fasting glucose
- Thyroid stimulating hormone (TSH) ± free thyroxine

Skin biopsy
- Routine histology (if skin lesions are present)
- Direct immunofluorescence studies*

Other laboratory tests
- Serum total and/or allergen-specific IgE
- Serum ferritin, iron, total iron binding capacity
- Hemoglobin A1c
- Parathyroid function (calcium, phosphate and parathyroid hormone levels)
- Stool for ova/parasites and/or occult blood
- Viral hepatitis panel (including hepatitis B and C viruses)
- HIV testing
- Anti-tissue transglutaminase ± epidermal transglutaminase IgA antibodies**
- Anti-BP180 and anti-BP230 bullous pemphigoid IgG antibodies
- Anti-mitochondrial and anti-smooth muscle antibodies
- Serum tryptase, histamine, and/or chromogranin-A levels
- Urinalysis with sediment evaluation
- 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite) and porphyrins
- Serum protein electrophoresis, serum immunofixation electrophoresis

Radiographic studies
- Chest X-ray or CT scan
- Abdominal and pelvic ultrasonography or CT scan
- Lymph node ultrasonography
- Spinal X-ray or MRI (for regional pruritus)

Other investigations
- Patch testing
- Prick testing for major atopy and relevant occupational allergens
- Age-appropriate cancer screening (in conjunction with primary care physician)
- If hydroxyethyl starch (HES)-induced pruritus is suspected, electron microscopy of a biopsy sample from normal-appearing skin

PRURITUS IN SPECIFIC LOCATIONS

- Scalp Pruritus
- middle-aged individuals during periods of stress and fatigue

PRURITUS IN SPECIFIC LOCATIONS

Pruritus ani

- male : female ratio of ~4 : 1
- onset is typically insidious
- primary (idiopathic) or secondary
  - excessive coffee intake, poor personal hygiene, psychiatric disorders.
  - chronic diarrhea, fecal incontinence/anal seepage, hemorrhoids, anal fissures or fistulas, rectal prolapse
  - primary cutaneous disorders
  - sexually transmitted diseases, infestations (e.g. pinworms), previous radiation therapy, and neoplasms(e.g. anal cancer)
  - Neuropathic
    - compression or irritation of lumbosacral nerves from prolapsed intervertebral discs, vertebral body fractures, or osteophytic processes
- anxiety and depression may be aggravating factors

PRURITUS IN SPECIFIC LOCATIONS

Pruritus ani

- In patients receiving chronic antibiotic therapy who have liquid stools with a pH of 8–10, *Lactobacillus replacement therapy is recommended.*
- Mild cases
  - sitz baths, cool compresses, and water-moistened, fragrance-free toilet paper
  - The area is should be dried with blotting or a fan
  - avoidance of rubbing and alkaline soaps
  - zinc oxide
  - A mild corticosteroid cream
  - Topical calcineurin inhibitors, including use on a rotational basis with topical corticosteroids

PRURITUS IN SPECIFIC LOCATIONS

Pruritus vulvae and scroti

- psychogenic in only 1–10% of patients.
- worse at night, lichenification
- *Acute pruritus of the vulva or scrotum*
  - candidiasis, allergic or irritant contact dermatitis
- *Chronic pruritus in these sites may be caused by*
  - dermatoses ,malignancy (e.g. extramammary Paget disease, squamous cell carcinoma), or atrophic vulvovaginitis,lumbosacral radiculopathy
- irritation related to cleansing and toilet habits needs to be addressed

Aquagenic Pruritus

- usually secondary
- stinging sensations within 30 minutes of water contact, irrespective of its temperature or salinity, and lasts for up to 2 hours
- symptoms begin on the lower extremities and then generalize, with sparing of the head, palms, soles, and mucosae
  - PUVA
  - Capsaicin cream (0.025–0.1%) applied 3–6 times daily for ≥4 weeks
  - oral cyproheptadine,cimetidine, and cholestyramine: minimal effectiveness

DIFFERENTIAL DIAGNOSIS OF PRURITUS OR PRICKLING SENSATIONS PROVOKED BY WATER CONTACT

Disease-associated skin findings typically evident at time of visit

- Polycythemia vera* (ruddy complexion)
- Mastocytosis (cutaneous lesions, positive Darier's sign)
- Hypereosinophilic syndrome (cutaneous lesions in >50% of patients)
- Hemochromatosis (diffuse hyperpigmentation)

Urticaria by history and/or challenge

- Dermographism
- Cold urticaria
- Cholinergic urticaria (with hot water exposure)
- Aquagenic urticaria

Skin findings (other than those due to scratching) typically absent

- Hodgkin disease
- Myelodysplastic syndromes
- Essential thrombocythemia
- Testosterone-induced erythrocytosis
- Drug-related (e.g. antimalarials, bupropion, clomipramine)
- Aquagenic pruritus of the elderly (xerosis may be subtle)
- Primary (idiopathic) aquagenic pruritus

*Aspirin doses up to 300–500 mg 1–3 times daily may provide partial relief; improvement of aquagenic pruritus with selective serotonin reuptake inhibitors (SSRIs) has been reported.

Table 6.5 Differential diagnosis of pruritus or prickling sensations provoked by water contact. A possible relationship with lactose intolerance in a subset of patients has also been reported.

Renal

- advanced chronic kidney disease
- localized (back) or generalized
- intensity and distribution often vary over time(evening and night)
- independent predictor of mortality in dialysis patients
- sleep disturbances, depression, and impaired quality of life
- rare in children
- CAPD less or equally affected compared to hemodialysis
- usually peaks in the evening after 2 days without dialysis, is relatively high during dialysis, and is lowest the following day

Renal

- no relationship between plasma histamine levels and the severity of pruritus: antihistamines are ineffective
- higher serum levels of calcium, phosphate, PTH:no correlation
- Peripheral neuropathy
- xerosis

Renal

- Xerosis :gentle skin care and emollients
- pramoxine, corticosteroids, tacrolimus, or capsaicin
- Antihistamines: sedative effects
- hyperparathyroidism should be treated if present.
- The quality of dialysis
- itch persists,
  - gabapentin (100–300 mg orally) after each dialysis session
  - low-dose pregabalin equally effective.
  - Phototherapy
  - The μ-opioid receptor antagonist naltrexone (25–100 mg orally daily) or κ-opioid receptor agonist nalfurafine
  - renal transplantation

THERAPEUTIC LADDER FOR RENAL PRURITUS
Topical medications
• Capsaicin (0.025% three to five times daily) (2)
• γ-linolenic acid (2.2% four times daily) (1)
• Pramoxine (1)
• Cromolyn sodium (4% cream twice daily) (1)
Systemic medications and phototherapy
First-line for persistent moderate-to-severe pruritus
• Gabapentin (100–300 mg po†) (1)
• Pregabalin (25–75 mg po†) (1)
• UVB broadband or narrowband phototherapy (1)
Second-line for persistent moderate-to-severe pruritus
• Naltrexone (25–100 mg po daily) (2)
• Nalfurafine* (2.5–5 mcg po or iv†) (1)
Additional options
• Activated charcoal (6 g po daily) (1)
• Montelukast (10 mg po daily) (1)
• Cromolyn sodium (100–135 mg po 3–4 times daily) (1)
• Thalidomide (100 mg po daily) (1)
• Ketotifen (1–2 mg po daily) (2)
• Doxepin (10–20 mg po daily) (1)
• Sertraline (25–100 mg po daily) (2)
• Pentoxifylline (600 mg iv†) (3)
• Lidocaine (200 mg iv daily) (3)
• Erythropoietin (36 U/kg sc three times a week) (3)
• Cholestyramine (4–16 g po daily in divided doses) (2)
†Typically administered post hemodialysis; daily or every other day administration of gabapentin/pregabalin has also been reported.
*Kappa-opioid receptor agonist; available in Japan.

Table 6.6 Therapeutic ladder for renal pruritus. In addition, the quality of dialysis should be evaluated (see text) and the parathyroid hormone (PTH) level assessed, with treatment of hyperparathyroidism if present. Ondansetron was found to have no benefit over placebo in randomized controlled trials, and antihistamines have marginal efficacy. Acupuncture, omega-3 fatty acid supplementation, and oral turmeric have been reported to have benefit, and

Cholestatic

- any liver disease
  - primary biliary cholangitis primary sclerosing cholangitis, obstructive choledocholithiasis,carcinoma of the bile duct, cholestasis,chronic hepatitis C viral infection, and other forms of viral hepatitis
- generalized, migratory, and not relieved by scratching
- worse on the hands, feet, and regions constricted by clothing
- most pronounced at night
- an early symptom ,develops years before
- Lysophosphatidic acid

Cholestatic

- In intrahepatic cholestasis of pregnancy :ursodeoxycholic acid (UDCA)
- first-line treatment
  - cholestyramine, binds bile acids
- second-line
  - Rifampin,reducing ATX expression
- liver transplantation

TREATMENT OPTIONS FOR HEPATIC OR CHOLESTATIC PRURITUS		
1st line	Cholestyramine*	• 4–16 g po daily • Improvement may be temporary • Only FDA-approved medication for cholestatic pruritus.
1st line for ICP	Ursodeoxycholic acid (ursodiol)*	• 13–15 mg/kg or 1 g po daily
2nd line	Rifampin*	• 300–600 mg po daily (depending upon serum bilirubin level) • Increases hepatic metabolism of bile salts
3rd line	Naloxone*	• 0.2 mcg/kg/min iv infusion, preceded by 0.4 mg iv bolus (continue treatment with oral naltrexone) • μ-opioid receptor antagonist
	Naltrexone*	• 25 mg po twice daily [day 1], then 50 mg po daily • μ-opioid receptor antagonist
	Nalfurafine*	• 2.5–5 mcg po daily • κ-opioid receptor agonist available in Japan
4th line	Sertraline*	• 50–100 mg po daily • Selective serotonin reuptake inhibitor

Additional medical options	
Phototherapy	• Especially broadband- or narrowband-UVB • Can be used in combination with other treatments for an additive effect
Bright light therapy	• 10 000 lux reflected toward the eyes for up to 60 minutes twice daily
Nalmefene*	• Escalating twice daily po dose: 2 mg [day 1], 5 mg [day 2], 10 mg [day 3], then 20 mg; further increases as needed to maximum of 120 mg • μ-opioid receptor antagonist
Butorphanol nasal spray	• 1–2 mg (1 to 2 puffs) daily • κ-opioid receptor agonist and μ-opioid receptor antagonist
Ondansetron	• 4–8 mg iv or 4–24 mg po daily (equivocal effects in controlled studies) • 5-HT_3 receptor antagonist
Paroxetine	• 10–20 mg po daily • Selective serotonin reuptake inhibitor
Dronabinol	• 5 mg po nightly • Cannabinoid B1 receptor agonist
Phenobarbital	• 2–5 mg/kg po daily
Stanozolol	• 5 mg po daily
Propofol*	• 10–15 mg iv (bolus), 1 mg/kg/h (infusion)
Lidocaine	• 100 mg iv daily
Thalidomide	• 100 mg po daily
Procedural interventions	
Nasobiliary drainage	• Quick relief of pruritus; possible complications include cholangitis and pancreatitis
Other methods to removal putative circulating pruritic factors	• Plasmapheresis, plasma separation and anion adsorption • Extracorporeal albumin dialysis (e.g. MARS [molecular adsorbents recirculating system])

*Benefit confirmed in controlled clinical trials.

Table 6.7 Treatment options for hepatic or cholestatic pruritus. Antihistamines have limited therapeutic benefit other than their sedating properties, and gabapentin did not have a therapeutic advantage over placebo in a controlled study. Ileal bile transporter inhibition (e.g. with GSK2330672) is currently under investigation and was shown to be of benefit for primary biliary cholangitis in a randomized controlled trial. General measures for pruritus management are

Hematologic

Iron deficiency

- generalized
- localized pruritus
  - perianal or vulvar region
- improvement with iron supplementation
- iron deficiency can be a sign of polycythemia vera and other malignancies or systemic diseases

Hematologic

Polycythemia vera

- Aquagenic pruritus may precede several years and eventually affects ~30–50%
- activation and agonist hypersensitivity in basophiles
- Platelet aggregation :release of serotonin and histamine
- Oral aspirin (81–500 mg one to three times a day; current recommendation is daily low dose)
  - relief from pruritus for 12–24 hours.
- phototherapy
- SSRIs
- the JAK inhibitor ruxolitinib
- intramuscular interferon-α (good efficacy)
- oral H1- or H2-receptor antagonists (variable results)

Malignancy

- any malignancy
  - association is not as strong in solid tumors
- "paraneoplastic itch" as a systemic reaction to the presence of a tumor or a hematological malignancy
  - myeloproliferative neoplasms(e.g. polycythemia vera > essential thrombocythemia), Hodgkin disease, and non-Hodgkin lymphomas
- persistent unexplained pruritus or failure of generalized pruritus to respond to conventional therapy
  - evaluation for an underlying malignancy, including a complete blood count and hepatic panel
  - slightly increased risk for a future diagnosis of malignancy
    - hematologic malignancy ,bile duct carcinoma
- advanced disease or early sign(years before)
- intensity do not correlate with the extent of tumor

Malignancy

- toxic products from necrotic tumor cells
- production of chemical mediators
- allergic reactions to tumor-specific antigens
- increased proteolytic activity, and histamine release
- treatment with surgery, radiotherapy, cytotoxic chemotherapy, or targeted tumor therapy
  - Traditional antihistamines are largely ineffective.
  - Paroxetine , low dose mirtazapine ,aprepitant

Hodgkin disease

- primary symptom: up to five years
- nocturnal generalized pruritus
  - lower extremities and is occasionally accompanied with ichthyosiform skin changes
- Severe, persistent pruritus is predictive of a poor prognosis
- more severe in older patients
- Recurrence
- Production of IL-5 by Reed–Sternberg cells :eosinophilia
- release of histamine (from basophiles),
- leukopeptidases,or bradykinin.
- Hepatic involvement
- topical corticosteroids
- oral mirtazapine (7.5–30 mg/day)
- aprepitant, an NK1 receptor antagonist

Non-Hodgkin lymphoma

- less prevalent :10% of patients

Leukemia

- not a common symptom
- usually generalized.
- Chronic lymphocytic leukemia (CLL)
  - exaggerated reactions to insect bites

Endocrine Pruritus

Thyroid disease

- Severe generalized pruritus :presenting symptom of hyperthyroidism
  - direct effect of thyroid hormone on the skin
- Localized or generalized pruritus: hypothyroidism
  - Dry skin

Diabetes mellitus

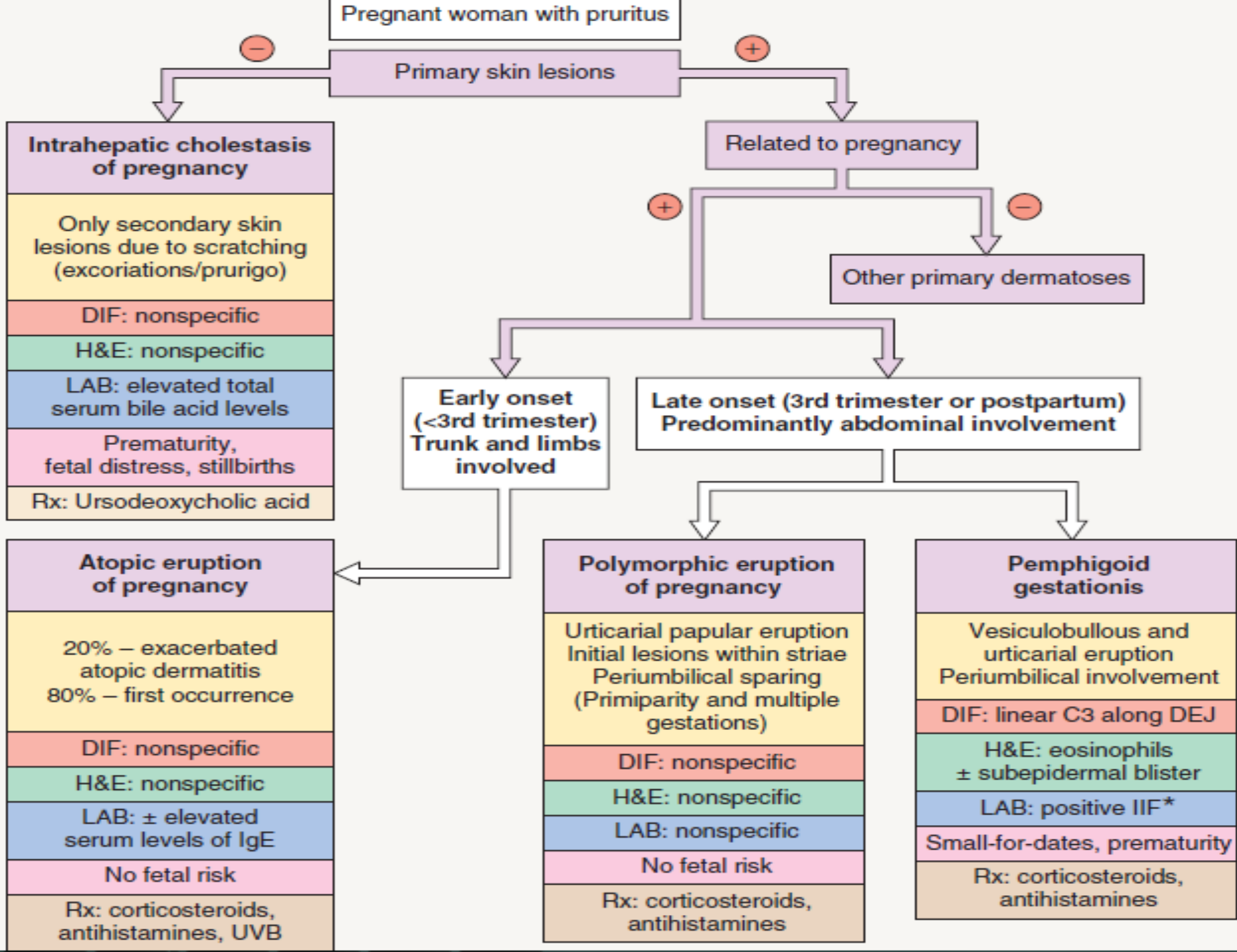
- Generalized pruritus :presenting symptom of diabetes mellitus
- localized pruritus, especially in the genital and perianal areas
  - diabetic women and associated with poor glycemic control
  - Candidiasis
- Diabetic neuropathy

Systemic rheumatic disease

- common symptom of dermatomyositis, systemic sclerosis (scleroderma), and primary Sjögren's syndrome
- Dermatomyositis:
  - intense pruritus, affects their quality of life
  - An increase in interleukin-31

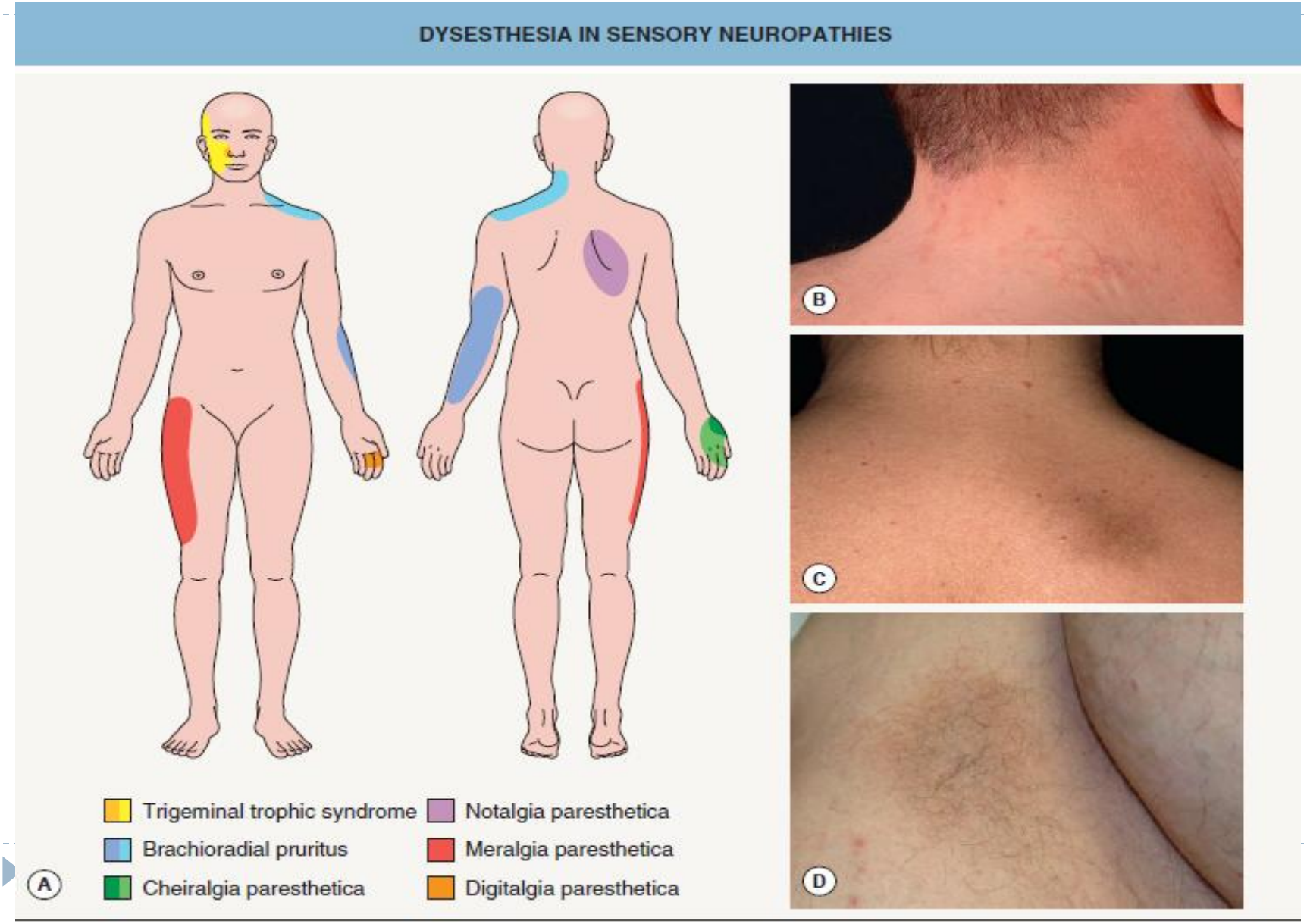
HIV Infection and AIDS

- initial presenting symptom
- Severe, treatment-resistant pruritus correlation with increased HIV viral load
- Markedly elevated IgE levels, peripheral hypereosinophilia, and a Th2-type cytokine profile
- Topical corticosteroids and antihistamines (anti-eosinophilic potential)
- UVB
- Thalidomide (100–300 mg/day)


Pregnant woman with pruritus
Primary skin lesions
−
+
Intrahepatic cholestasis of pregnancy
Only secondary skin lesions due to scratching (excoriations/prurigo)
DIF: nonspecific
H&E: nonspecific
LAB: elevated total serum bile acid levels
Prematurity, fetal distress, stillbirths
Rx: Ursodeoxycholic acid
Related to pregnancy
+
−
Other primary dermatoses
Early onset (<3rd trimester) Trunk and limbs involved
Late onset (3rd trimester or postpartum) Predominantly abdominal involvement
Atopic eruption of pregnancy
20% – exacerbated atopic dermatitis
80% – first occurrence
DIF: nonspecific
H&E: nonspecific
LAB: ± elevated serum levels of IgE
No fetal risk
Rx: corticosteroids, antihistamines, UVB
Polymorphic eruption of pregnancy
Urticarial papular eruption
Initial lesions within striae
Periumbilical sparing
(Primiparity and multiple gestations)
DIF: nonspecific
H&E: nonspecific
LAB: nonspecific
No fetal risk
Rx: corticosteroids, antihistamines
Pemphigoid gestationis
Vesiculobullous and urticarial eruption
Periumbilical involvement
DIF: linear C3 along DEJ
H&E: eosinophils ± subepidermal blister
LAB: positive IIF*
Small-for-dates, prematurity
Rx: corticosteroids, antihistamines

- history of identical skin findings in past pregnancies (recurrence) suggests ICP
- Abdominal location of skin lesions is characteristic of pemphigoid gestationis and PEP,
- Involvement of the trunk and extremities of AEP
- predominant involvement of the extremities of ICP

NEUROLOGIC ETIOLOGIES OF PRURITUS AND DYSESTHESIA



NEUROLOGIC ETIOLOGIES OF PRURITUS AND DYSESTHESIA

- Secondary skin lesions
  - excoriations, crusted papules, hyperpigmentation, lichenification
- topical capsaicin (0.025–0.3%) 3–6 times daily for ≥4–6 weeks
- capsaicin 8% patch
- topical anesthetics (e.g. pramoxine, lidocaine), topical
- corticosteroids, oral gabapentin/pregabalin, and acupuncture
- spinal imaging
- physical therapy, nerve blocks, and surgical decompression

multiple sclerosis

- recurrent and severe episodes of generalized pruritus
- to activation of artificial synapses in areas of demyelination
- paroxysmal pruritus :carbamazepine

neuropathies

- Diabetes
- infection,
- autoimmune disorders
- Fabry disease
- Cerebrovascular accidents
- trigeminal trophic syndrome

Psychogenic itch

Psychogenic excoriation

- pick and scratch normal skin
- scattered,linear, crusted lesions anywhere on the body
  - within reach of the patient
  - almost often confined to the extremities
- Psychologic stress
- mood and anxiety disorders
- depression or bipolar disorder

Delusional infestation

Drug use

- opioids,
- cocaine
- amphetamines

TREATMENT

General Measures

- wearing soft breathable clothing (i.e. no wool or rough fabrics), cool environment
- avoiding excessive bathing (lukewarm baths or showers with mild synthetic detergents
- using emollients on a daily basis with application immediately after bathing,
- Elderly patients
  - full bathing to once or twice weekly, with interim sponge bathing of odorous regions
- interrupting the itch–scratch cycle,
  - application of a cold washcloth or gentle pressure
- Controlled physical exercise, relaxation therapy, and minimization of exposure to dust and heat as well as of stress and anxiety

TREATMENT

Topical Treatment

- corticosteroids, coal tars, counterirritants (e.g. menthol, camphor, capsaicin)
- Topical anesthetic agents (e.g. lidocaine/prilocaine)
  - decrease pain and pruritic sensations
- Capsaicin
  - Concentrations 0.025–0.3%, and it needs to be applied three to six times daily
  - notalgia paresthetica ,brachioradial,aquagenic pruritus, and pruritus associated with chronic renal disease
  - side effects of stinging, burning, pain, erythema, and irritation:localized pruritus.
- Topical tacrolimus and pimecrolimus
  - anti-inflammatory and antipruritic effects
  - anogenital pruritus, psychogenic pruritus, chronic graft-versus-host disease

TREATMENT

Systemic treatment

- Antihistamines
  - Urticaria, mastocytosis
  - first generation (sedating): pruritus at night
- Opioid receptor antagonists
  - naltrexone, naloxone:mu-opioid receptor antagonists
  - cholestasis, chronic urticaria, epidural morphine administration,aquagenic pruritus
- Opioid receptor agonists
  - butorphanol and nalfurafine:kappa-opioid receptor agonists
  - intranasal butorphanol :intractable pruritus due to infammatory skin disease or systemic disorders
  - chronic kidney disease

TREATMENT

Systemic treatment

- Antidepressants
  - mirtazapine, doxepin
  - Chronic pruritus related to malignancies, cholestasis, and chronic kidney disease
- Anticonvulsants
  - gabapentin and pregabalin
  - Brachioradial pruritus and notalgia paresthetica, idiopathic pruritus

Thanks for your attention