The flushing patient: Differential diagnosis, workup, and treatment

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Cutaneous flushing—a common presenting complaint to dermatologists, allergists, internists, and family practitioners—results from changes in cutaneous blood flow triggered by multiple conditions. Most cases are caused by very common, benign diseases, such as rosacea or climacterum, that are readily apparent after a thorough taking of history and physical examination. However, in some cases, accurate diagnosis requires further laboratory, radiologic, or histopathologic studies to differentiate several important clinicopathologic entities. In particular, the serious diagnoses of carcinoid syndrome, pheochromocytoma, mastocytosis, and anaphylaxis need to be excluded by laboratory studies. If this work-up is unrevealing, rare causes, such as medullary carcinoma of the thyroid, pancreatic cell tumor, renal carcinoma, and others, should be considered. (J Am Acad Dermatol 2006;55:193-208.)

Learning objective: At the completion of this learning activity, participants should be familiar with the mechanisms of flushing, its clinical differential diagnosis, the approach to establish a definitive diagnosis, and management of various conditions that produce flushing.

The phenomenon of cutaneous flushing has fascinated human beings since prehistoric times, as evidenced by numerous archaeologic artifacts that depict erythema in the classic blush area. The term *flush* itself was pioneered in 1882 by Dr. E. J. Tilt, who proposed a short and expressive word for this phenomenon. The conceptual framework for flushing reactions was developed over the past 2 centuries by many investigators, starting in 1829 with Burgess, but a more detailed mechanistic understanding came mainly in the latter part of the 20th century, owing to major advances in pharmacology and physiology.[1] The mechanisms of flushing reactions are pharmacologically and physiologically heterogeneous. Table I provides a list of pharmacologic mediators of flushing in various conditions. Flushing may result from agents that act directly on the vascular smooth muscle or may be mediated by vasomotor nerves. Vasomotor nerves may lead to flushing owing to events at both peripheral and central sites.[1-10]

Abbreviations used:

CS:	carcinoid syndrome
5-HIAA:	5-hydroxyindoleoacetic acid
5-HT:	5-hydroxytryptamine
MCT:	medullary carcinoma of the thyroid
NSAID:	nonsteroidal anti-inflammatory drug
TMEP:	telangiectasia macularis eruptiva perstans
VIP:	vasoactive intestinal polypeptide

Flushing may be defined as a sensation of warmth accompanied by visible reddening of the skin.[4] Normally, it is part of a coordinated physiologic thermoregulatory response to hyperthermia and results from increased cutaneous blood flow caused by transient vasodilation.[1,4] Flushing is usually most prominent in the classic "blush area," which includes the face, neck, upper portion of the chest, and upper limbs. Such predilection stems from the increased relative volume of visible superficial cutaneous vasculature in these regions, as well as qualitative differences in skin vascular response and vascular regulation compared with other body areas.[1,4,9]

Flushing can be episodic or constant. Episodic attacks are generally mediated by release of endogenous vasoactive mediators or by drugs.[4] Repetitive episodes over long periods (persistent flushing) may produce fixed facial erythema with telangiectases and a cyanotic tinge. This appearance is due to the development of large cutaneous blood vessels that contain slow-flowing deoxygenated blood.[4]

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Table I. Pharmacologic mediators of flushing

Foods, beverages, alcohol
Tyramine, histamine, sulfites, nitrites, alcohol, aldehyde, higher chain alcohols, monosodium glutamate, capsaicin, cigua toxin (fish)
Climacterium
Estrogen fluctuations
Carcinoid syndrome
5-HT (no flushing but diarrhea), substance P, histamine, catecholamines, prostaglandins, kallikrein, kinins, tachykinins, neurotensin, neuropeptide K, VIP, gastrin-related peptide, motilin
Pheochromocytoma
Catecholamines (epinephrine, norepinephrine, dopamine), VIP, calcitonin-gene-related peptide, adrenomedullin
Mastocytosis
Histamine, prostaglandin D2, leukotrienes, tumor necrosis factor α, vascular endothelial growth factor, interleukins, heparin, acid hydrolases
Anaphylaxis
Histamine, other mast cell and basophil mediators, as above for mastocytosis
Medullary carcinoma of the thyroid
Calcitonin, prostaglandins, histamine, substance P, levodopa, ketacalcin, adrenocorticotropic hormone, corticotropin-releasing hormone
Pancreatic cell carcinoma
VIP, prostaglandin, gastric inhibitory polypeptide
Renal cell carcinoma
Prostaglandins, pituitary down-regulation
Neurologic
Substance P, catecholamines

Table II. Differential diagnosis of flushing

Common causes
Benign cutaneous flushing
Emotion
Temperature
Food or beverage
Rosacea
Climacteric flushing
Fever
Alcohol
Uncommon, serious causes
Carcinoid
Pheochromocytoma
Mastocytosis
Anaphylaxis
Other causes
Medullary thyroid carcinoma
Pancreatic cell tumor (VIP tumor)
Renal cell carcinoma
Fish ingestion
Histamine
Ciguatera
Psychiatric or anxiety disorders
Idiopathic flushing
Neurologic
Parkinson's
Migraine
Multiple sclerosis
Trigeminal nerve damage
Horner syndrome
Frey syndrome
Autonomic epilepsy
Autonomic hyperreflexia
Orthostatic hypotension
Streeten syndrome
Medications (see Table IV)
Very rare causes
Sarcoid, mitral stenosis, dumping syndrome, male androgen deficiency, arsenic intoxication, POEMS syndrome, basophilic granulocytic leukemia, bronchogenic carcinoma, malignant histiocytoma, malignant neuroblastoma, malignant ganglioneuroma, peri-aortic surgery, Leigh syndrome, Rovsing syndrome

The differential diagnosis of flushing is extensive and comprises various benign and malignant entities (Tables II and III; Fig 1). Fever, hyperthermia, emotional blushing, menopause, and rosacea are by far the most common reasons for the flush reactions. With the exception of carcinoids, flushing due to tumors is rare and tends to occur in advanced stages. The following discussion focuses on the common and rare, benign and malignant causes of flushing, their diagnosis, differential diagnosis, and management.

FEVER

Fever is the most common cause of "hot flushes," particularly when associated with night sweats.[1] This elevation in body temperature can be easily diagnosed by taking the oral temperature during an attack and should prompt a fever workup, which may reveal an infectious or noninfectious cause.[11] Fevers generally are treated with antipyretics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

BENIGN CUTANEOUS FLUSHING

Benign cutaneous flushing is a large rubric that includes hyperthermia (from causes other than fever) and emotional flushing. It is triggered by emotion, exercise, temperature changes, and foods or beverages, especially spicy foods.[2] Associated findings may include a feeling of warmth and cognitive dysfunction. Benign cutaneous flushing affects women more often than men and, since it does not