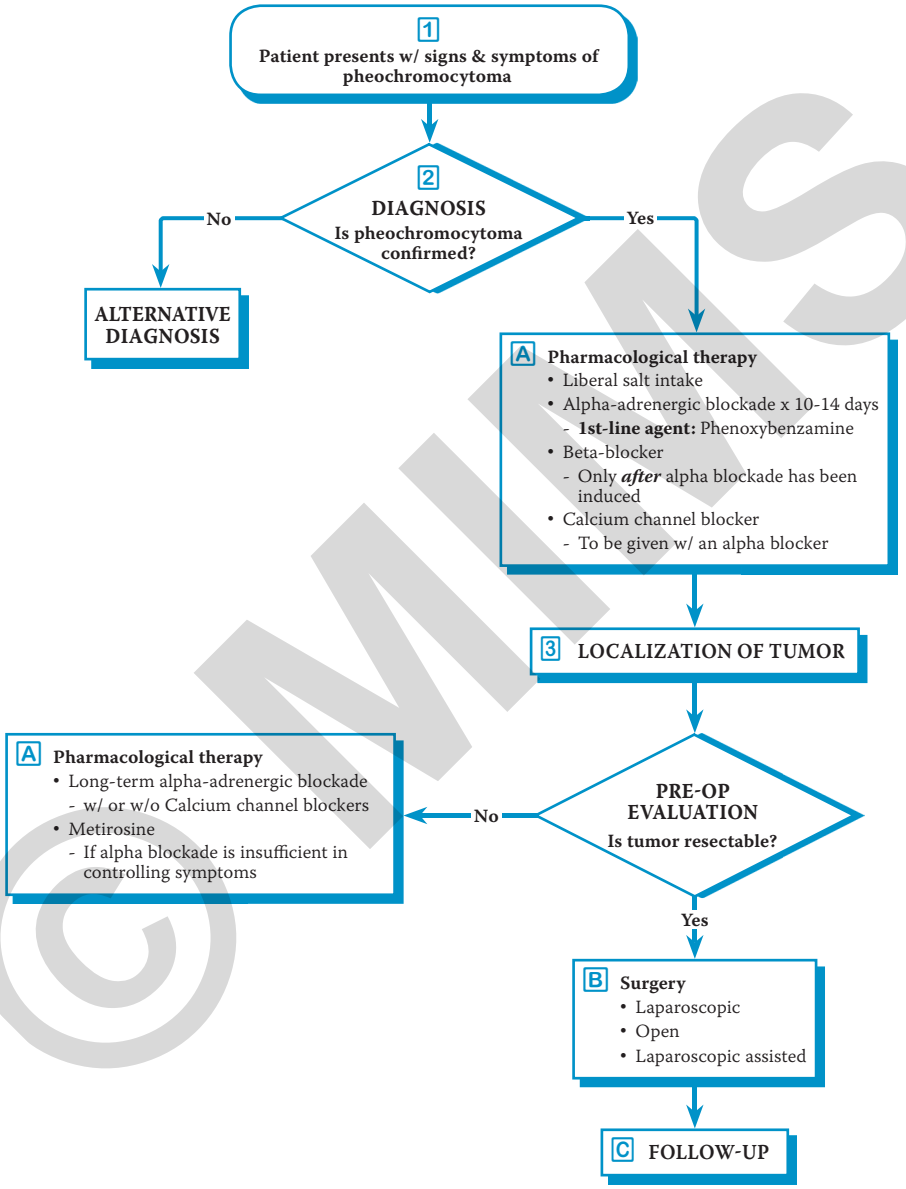
Pheochromocytoma (1 of 6)



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Specific prescribing information may be found in the latest MIMS.

1 SIGNS & SYMPTOMS OF PHEOCHROMOCYTOMA

- Pheochromocytoma can occur at any age
  - Usually occurs during young to mid-adult life
- 10% of patients are asymptomatic

Majority of patients present w/ ≥1 of the following:

- Hypertension resistant to standard antihypertensive treatment
  - May be associated w/ headaches, excessive sweating &/or palpitations
- Hypertensive crisis w/ malignant hypertension, hypertensive encephalopathy, aortic dissection or myocardial infarction (MI)
- Paroxysmal symptoms which suggest seizure disorder, anxiety attacks or hyperventilation
  - Occurs in half of patients
  - Usually sudden in onset but variable in length (eg min-several hr)
  - Associated w/ headache, sweating, palpitations, apprehension, chest or abdomen pain, N/V
  - Pallor may occur
  - Very high BP usually w/ tachycardia

Other Symptoms

- Increased metabolic rate
  - Mild-moderate wt loss
- Orthostatic hypotension
  - Results from decreased plasma volume & dulled sympathetic reflexes
- Cardiac symptoms
  - Sinus tachycardia, sinus bradycardia & other arrhythmias
  - Acute MI or angina may occur even in the absence of coronary artery disease
  - ECG changes
  - Cardiomyopathy
- Multi-organ system failure w/ noncardiogenic pulmonary edema
- Carbohydrate intolerance
- Elevated hematocrit secondary to decreased plasma volume
- Hypercalcemia
- Fever, elevated erythrocyte sedimentation rate (ESR)
- Polyuria, occasionally rhabdomyolysis w/ myoglobinuric renal failure
- Hypokalemia

2 DIAGNOSIS

- Evaluation using liquid chromatography w/ mass chromatography is preferred over laboratory methods
- Blood for plasma metanephrine measurement should be obtained w/ patient in supine position, w/ subsequent extractions done in the same position

Plasma Metanephrine

- Diagnostic test of choice
  - More suitable for high risk patients w/ a hereditary predisposition
  - Normal plasma levels excludes the diagnosis
  - Elevated plasma levels confirm the diagnosis
- Clonidine suppression test
  - Maybe done when plasma total cathecholamines concentration is elevated but not diagnostic
  - May distinguish elevated norepinephrine levels secondary to sympathetic nerves vs true pheochromocytoma
  - Failure to suppress norepinephrine levels by 50% suggests pheochromocytoma
- Glucagon stimulation test
  - Performed when plasma metanephrine levels are high but catecholamines are either normal or only moderately high
  - A 3-fold rise in norepinephrine levels in response to glucagon signify pheochromocytoma
  - Rarely used

Urine Biochemical Tests

- Alternative for excluding pheochromocytoma
  - May be preferred in those at low risk for pheochromocytoma

Accuracy is improved if at least 2 of the following are measured from urine sample:

- Unconjugated (free) catecholamines
  - **Normal range:** 590-885 nmol/24 hr (100-150 mcg/24 hr)
  - **Diagnostic range:** >1480 nmol/24 hr (>250 mcg/24 hr), or 2-fold elevation from normal level
  - Epinephrine should also be measured & may be high if multiple endocrine neoplastics (MEN) adrenal lesion is present
- Metanephrine/Normetanephrine
  - **Upper limit of normal range:** 7 micromol/24 hr (1.3 mg/24 hr)
  - **Diagnostic range:** Normetanephrine (>900 mcg/24 hr); Metanephrine (>400 mcg/24 hr)

24-Hr Urine Sample

- Analysis of urine sample should be done when patient is symptomatic eg hypertensive or during a crisis
- Full 24-hr sample is preferred
- Cr_{Cl} should be measured to assess adequacy of collection
- If possible, patient is at rest, not taking medication & no recent exposure to radiographic contrast media
- Acidify & refrigerate urine during & after collection
- Tests may need to be repeated during attacks to exclude diagnosis
  - Pharmacologic tests may be helpful in difficult cases

2 LOCALIZATION OF TUMOR

- Once patient is diagnosed tumor localization & search for possible metastases should be undertaken
  - Maybe adrenal or extra-adrenal (paraganglioma)
  - Patient can be prepared pharmacologically at the same time
- CT scan & MRI are 1st-line diagnostic tools
  - Both provide localization & metastatic assessment
  - CT scan is preferred over MRI as 1st-line diagnostic tool for imaging of the thorax, abdomen & pelvic area
  - MRI is used best for detection of tumors in the skull base & neck, patients w/ contraindications for contrast dyes & radiation, & for patients w/ artifacts seen in CT

Anatomic Imaging

Magnetic Resonance Imaging

- Identify intraadrenal lesions
- Identify extraadrenal lesions in the abdomen
  - Look for von Hippel-Lindau disease neurofibromatosis or multiple endocrine neoplasia type 2 (MEN-II) if bilateral or extra-adrenal
- Detect intracardiac, juxtacardiac, juxtavascular pheochromocytoma
  - Reduces cardiac and respiratory motion-induced artifacts
- Initial evaluation for children, pregnant women or in cases of contrast allergy

CT Scan

- Detects adrenal pheochromocytoma of ≥0.5-1 cm or metastatic pheochromocytoma of ≥1-2 cm
- Extraadrenal tumors w/in the abdomen & pelvis (inital CT should visualize these areas); chest & neck
- Spiral CT preferred for small thoracic tumors
- CT w/ contrast can aggravate or precipitate crisis
  - Some consider CT as the most useful method to locate pheochromocytoma

Abdominal Aortography

- May be used to identify extraadrenal tumors in the abdomen since they are usually supplied by a large aberrant artery
- Alpha-adrenergic blockade must be completed before attempting aortography

Functional Imaging

Functional imaging techniques are not recommended as 1st-line procedures for localizing pheochromocytoma

Metaiodobenzylguanidine (MIBG) Scintigraphy

- May use I^{131} and I^{123}
  - I^{123} is superior to I^{131}, but is not approved by USFDA
- Useful in detecting recurrent or metastatic pheochromocytoma, tumors w/ fibrosis, extranodal tumors, tumors in unusual location or in areas w/ distorted anatomy
- Indicated when abdominal imaging results are negative, or if found pheochromocytoma is >10 cm in diameter

Positron Emission Tomography (PET) Imaging

- Advantages include low radiation exposure and superior spatial resolution
- Imaging is carried out immediately
  - Unlikely delays in scintigraphy
- Provides accurate information regarding the number & location of metastatic lesions
- Preferred over MIBG scintigraphy for patients w/ known metastatic lesions
- Limited availability among various centers
- Procedure is expensive

Somatostatin Receptor Scintigraphy

- Detects malignant/metastatic tumors better than primary/benign tumors
- Low sensitivity

A PHARMACOLOGICAL THERAPY

Alpha-Adrenergic Blockade

- First-line therapy used to minimize complications prior to surgery

Phenoxybenzamine

- **Action:** Powerful irreversible alpha-adrenergic blocker of the alpha receptors in the smooth muscles
- **Effects:** Oral administration results in an onset of action w/in a few hr & persists for up to 3-4 days
  - Used to control the hypertension caused by excessive catecholamine release by pheochromocytoma

A PHARMACOLOGICAL THERAPY (CONT'D)

Alpha-Adrenergic Blockade (Cont'd)

Selective Alpha$_1$-Antagonists[1]

- Eg Doxazosin
- **Action:** Selective blockade of alpha$_1$-adrenoreceptors
- **Effects:** Limited use in pheochromocytoma, Phenoxybenzamine is more effective
- May be used to treat individual paroxysms
- May also may be used to treat hypertension while pheochromocytoma workup is ongoing
  - Better tolerated than Phenoxybenzamine
  - Prevent serious pressor crisis if pheochromocytoma is present

Beta-Blockers

- Eg Propranolol, Atenolol
- Administer only after alpha blockade has been induced
  - W/o alpha blockade paradox increase in BP may occur
- **Action:** Competitive antagonists of catecholamines at beta-adrenergic receptors
- **Effects:** Used to treat tachycardia that may develop w/ alpha blockade
  - Assist in preventing catecholamine-induced arrhythmias
- Low doses are usually sufficient

Calcium Channel Blockers

- Eg Nifedipine, Amlodipine
- Used as add-on treatment to alpha-adrenergic receptor blockers to further improve cardiovascular function peri-operatively
- **Action:** Blocks slow calcium channels to prevent calcium ion flow into the cell
- **Effects:** Vasodilatation, reduced afterload, peripheral resistance & blood pressure

Metirosine (Metyrosine)

- **Action:** Inhibits tyrosine hydroxylase which inhibits synthesis of catecholamines by the tumor
- **Effects:** Simplifies chronic management
- Should be used if other agents are ineffective or when tumor destruction will be marked

[1]Many selective alpha$_1$ antagonists are available. Please see the latest MIMS for specific formulations.

B SURGERY

- Treatment of choice for most cases of pheochromocytoma
- Should be performed in experienced centers
- It is microscopically difficult to determine if pheochromocytoma is malignant
- Each pheochromocytoma should be regarded as potentially malignant during surgery
  - The entire gland & the surrounding tissues must be removed to prevent recurrence of local disease
- Preoperative pharmacologic management involves alpha & beta adrenergic blockade to control blood pressure & prevent hypertensive crisis during the surgical procedure
  - A high-sodium diet w/ increased fluid intake is recommended pre-op to prevent post-operative volume depletion

C FOLLOW-UP

- Measure catecholamine excretion 1-2 wk after surgery
  - Ensures complete tumor removal
- Catecholamine excretion should be measured yrly or more often if symptoms reappear
- Genetic testing should be considered in patients w/ pheochromocytoma to determine presence of disease-causing germ-line mutations, mutations that may lead to metastatic diseases, and to identify possible risk of inheritance

Dosage Guidelines

BETA-BLOCKER[1]		
Drug	**Dosage**	**Remarks**
Propranolol	**Initial dose:** 10 mg PO 6-8 hrly May increase as needed to control pulse rate	**Adverse Reactions** • CV effects (bradycardia, hypotension in patients w/ preexisting CV disorders: heart block, heart failure); CNS effects (depression, dizziness, sleep disturbances); Other effects (bronchospasm, fatigue) • May interfere w/ carbohydrate & lipid metabolism, rash **Special Instructions** • Use w/ caution in patients w/ asthma, chronic obstructive pulmonary disease (COPD), DM

[1]Many beta-blockers are available. Please see the latest MIMS for specific formulations.

OTHER ANTIHYPERTENSIVES		
Drug	**Dosage**	**Remarks**
Alpha-Adrenoreceptor Antagonist		
Doxazosin (Doxazosine)	**Initial dose:** 1 mg PO 24 hrly x 1-2 wk May increase dose to 2 mg PO 24 hrly for additional 1-2 wk **Maintenance dose:** 2-4 mg PO 24 hrly **Max dose:** 16 mg/day	**Adverse Reactions** • Neurologic effects (ataxia, kinetic disorders, hypertonia); GI effects (dry mouth, abdominal pain, diarrhea, nausea); CV effects (chest pain, hypotension, palpitation, orthostatic hypotension, arrhythmia); Resp effects (dyspnea, influenza-like symptoms, rhinitis, epistaxis); Other effects (fatigue, headache, muscle cramps, sexual dysfunction, polyuria) **Special Instructions** • Use w/ caution in patients w/ renal/hepatic impairment, prostatic carcinoma, orthostatic hypotension • Avoid use prior to driving or performing hazardous tasks for 24 hr after initiation of therapy
Imidazoline Derivative		
Phentolamine	***For hypertension in pheochromocytoma:*** **Adult:** 2-5 mg IV May repeat as needed **Childn:** 1 mg IV/IM 1-2 hr prior to surgery **During surgery:** 1 mg IV as needed	**Adverse Reactions** • CV effects (tachycardia, orthostatic hypotension, anginal pain, arrhythmias); GI effects (diarrhea, N/V); Other effects (flushing, sweating, weakness, dizziness, nasal congestion) **Special Instructions** • Monitor BP while on therapy • Contraindicated in patients w/ renal impairment, coronary/cerebral arteriosclerosis

Dosage Guidelines

OTHER ANTIHYPERTENSIVES (CONT'D)		
Drug	**Dosage**	**Remarks**
Other Peripheral Vasodilators		
Phenoxybenzamine	***For hypertension in pheochromocytoma:*** **Adult:** **Initial dose:** 10 mg PO 12-24 hrly May increase slowly to 1-2 mg/kg/day in 2 divided doses if needed **Childn:** **Initial dose:** 0.2 mg/kg PO 24 hrly May increase by 0.2 mg/kg increments **Maintenance:** 0.4-1.2 mg/kg/day PO 6-8 hrly ***Operative cover in pheochromocytoma:*** **Adult:** 1 mg/kg/day IV in 200 ml NaCl 0.9% infused over ≥2 hr	**Adverse Reactions** • CNS effects (confusion, drowsiness, convulsions); GI effects (dry mouth, slight GI irritation); CV effects (postural hypotension, compensatory tachycardia); Other effects (nasal congestion, miosis, fatigue) **Special Instructions** • Use w/ caution in patients w/ CV disease, cerebrovascular disease, renal impairment, respiratory infections & in patients where fall in BP could be dangerous • Doses should be increased slowly w/ close monitoring of upright & supine BP

TYROSINE HYDROXYLASE INHIBITOR		
Drug	**Dosage**	**Remarks**
Metirosine (Metyrosine)	**Initial dose:** 250 mg PO 6 hrly Increase dose based on patient response by 250-500 mg/day **Max dose:** 4 g/day **Pre-op management:** Administer for 5-7 days	**Adverse Reactions** • CNS effects (sedation, trismus, parkinsonism, anxiety, depression, psychiatric disorders, disorientation, confusion); GI effects (diarrhea, decreased salivation, dry mouth, N/V, abdominal pain) **Special Instructions** • Should be used only when other agents are ineffective or when tumor manipulation will be marked • To avoid crystalluria patients need to have fluid intake of ≥2 L/day. Examine urine regularly for crystals • Alpha-adrenergic blockers & beta-blockers may also used in combination to control symptoms • If used for pre-op, ECG & BP should be monitored continuously during surgery - Arrhythmia & hypotension may occur - Blood volume must be maintained before & after surgery

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.