Danylo Halytsky Lviv National Medical University
Department of Surgery №2

«APPROVED»

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on Scientific and Pedagogical work
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Methodical recommendations for independent work
"SURGERY"
Second (master`s) level of higher education
Field of Knowlendge 22 "Healthcare"
Specialty 222 «Medicine»
Faculty of Foreigh Students, year: Medicine, 5th year

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Head of the Department
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Approved
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Minutes No 3 dated "__" April 2023
Head of the Board

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Preface

In modern conditions, student independence becomes a necessary quality of personality.

Independent work of students is a planned cognitive, organizational and methodological activity, which is carried out without the direct help of the teacher, to achieve results. As a form of organization of individual study of educational material by students outside the classroom, it is the main means of mastering educational material in time free from compulsory subjects.

Independent work is intended for better mastering of the course, expansion and supplementation of lecture material. The teacher provides the student with recommended literature, basic and additional, and, while studying certain topics, specifies it on the list.

The purpose of independent work of students:

• development of creative abilities and activation of students' mental activity;

• formation of students' need for continuous self-replenishment of knowledge;

• development of moral and volitional efforts;

• independent work of students as a result of their moral and volitional efforts.

Independent work as a type of educational activity will be effective under the following conditions:

if this work is clearly organized by the teacher;

if it is a component of the educational process, and not an episodic phenomenon;

if the independent work of students is subject to pedagogical control (assessment and correction of knowledge).

The success of independent work of students is determined primarily by their readiness for such educational activities. In essence, independent work involves maximum activity of students in various aspects: the organization of mental work, the search for harmony, the desire to make meaning beliefs.

The organization of independent work of students in the subject should be carried out in compliance with a number of requirements, including the following:

- substantiation of the need for tasks in general and a specific task in particular, which requires the identification and promotion of positive motives for students;

- openness and general visibility of tasks. All students must know the content of the task, be able to compare the tasks performed in one and in different groups, analyze the correctness and usefulness of the work performed, the relevance of the grades (adequacy of assessment);

- providing detailed methodological recommendations for the performance of work;

- enabling students to perform creative work that corresponds to the conditional-professional level of knowledge acquisition, without limiting them to the performance of standard tasks.

Implementation of an individual approach for independent work. Individual tasks can be performed at the request of all students or some of them (who are creatively gifted, demanding, have extensive practical experience). Individualization of independent work promotes self-realization of the student, revealing in him such facets of the personality which help professional development.

To implement independent work in the process of studying the subject, students perform a set of tasks of different types of appropriate levels of difficulty.

The results of the study of the effectiveness of independent work of students in the educational process allow us to express the following assumptions:

1. The main source of theoretical information for the student is a syllabus of lectures.

2. The duration of the student's work in the library with educational literature decreases, which is often explained by the increase in the workload in the classroom, the increase in the number of tasks and the need to study and work at the same time.

3. The cost of time to perform traditional types of tasks for the processing of theoretical information (analysis, comparisons, answers to questions, explanations, etc.) is reduced. At the same time, the weight of time and productivity of tasks that provide algorithmic-effective and creative levels of knowledge acquisition increases.

To control students' knowledge are used:

a) oral answers to theoretical questions;

b) written works.

Completion of independent tasks is a prerequisite for admission to the final test.

The organization and methods of independent work of students must be subject to certain requirements:

1) development of motivational attitude in students.

2) regularity and continuity.

3) consistency in work.

4) proper planning of independent work, rational use of time.

5) the use of appropriate methods, techniques and techniques.

6) guidance from teachers. The main forms of management of independent work of students are the definition of program requirements for the study of academic disciplines; orientation of students in the list of literature; conducting group and individual consultations; organization of special classes on methods of studying scientific and educational literature, methods of taking notes; preparation of educational and methodical literature, recommendations, monuments, etc.

Independent work of students is provided by a system of teaching aids provided for the study of a particular discipline:

• basic literature (textbook, lecture notes, teaching and methodical manuals);

• additional literature (scientific, professional, monographic, periodical);

• methodical materials (methodical instructions on performance of independent work of students).

Independent work on mastering educational material in a particular discipline can be performed in the library, classrooms, computer classes (laboratories), as well as at home.

The success of independent work of students is determined primarily by their readiness for such educational activities. In essence, independent work involves maximum activity of students in various aspects: the organization of mental work, the search for harmony, the desire to make meaning beliefs.

The teacher is not limited in the choice of other tasks for independent work, provided that the content of the task corresponds to the working curriculum of the discipline.

When drawing up the agenda, anticipating their participation in all major activities carried out in the higher education institution, the student must focus on the curriculum, plans and schedule. Independent tasks can be performed in a workbook, cards, landscape sheets, Word documents.

Instructions for organizing independent work of students.

Independent work is carried out for the purpose of working off and mastering of the educational material defined for independent employment; preparation for future classes and control measures; formation of students' culture of mental work, independence and initiative in the search and acquisition of knowledge. The content of the student's independent work is determined by the work program of the discipline, the relevant methodological material, tasks and instructions of the teacher.

The student's independent work in this discipline is provided by appropriate information and methodological tools (textbooks, teaching aids, lecture notes, guidelines for organizing independent work and individual tasks), provided by the work program of the discipline.

In addition, for the quality organization of independent work of the student there is appropriate scientific and periodical literature. The student's independent

work on the study of educational material in a particular discipline can take place in the library, classrooms, computer classes and more.

The student is directly responsible for the quality of independent work.

TOPICS OF STUDENTS' SELF-TRAINING WORK (INCLUDING INDIVIDUAL WORK) OF DISCIPLINE "SURGERY"

№o/o	KIND OF WORK	HOURS	FORM OF CONTROL
1	**Preparation for practical classes. Preparation and training of practical skills.**	**16**	The current control on practical lessons
2	**Working up of the topic, not included into thematic plan.**	**44**	Independent written processing of the thopic. Defence of the written work.
1. Surgical pathology of the diaphragm. 2. Surgical diseases of the adrenal glands. 3. Surgical complications of diabetes. Diabetic foot syndrome. 4. Neuroendocrine tumors of the pancreas. 5. Surgical diseases of the parathyroid glands. 6. Minimally invasive surgical technologies in angiology. 7. Etiology, pathogenesis, diagnosis and treatment of lymphedema. 8. Wounds and closed injuries of the abdomen, pelvis and pelvic organs. 9. Infectious complications of combat injuries. 10. Gunshot wounds. 11. Combined radiation and chemical damage. Thermal damage.			
3	**Individual independent student's work**	**14**	The current control on practical classes, defence of the history of disease
3.1 Review of the scientific literature of your choice on the topic of the thematic plan of the discipline with a report in class			
3.2 Participation in writing a scientific article on the topic of the thematic plan of the discipline with a report in class			
3.3 Writing a medical history			
Total		**74**	

Information block

1. Diaphragm Disorders

Background

The diaphragm is the dome-shaped muscle that separates the thoracic and abdominal cavities; it is the major muscle of respiration. Dysfunction of the diaphragm may be an asymptomatic incidental finding, or it may be associated with dyspnea, decreased exercise tolerance, sleep disturbances, respiratory failure, and death. [1, 2, 3, 4]

Diaphragmatic dysfunction may result from disease processes in the central nervous system, the phrenic nerves, the neuromuscular junction, or anatomically. Dysfunction may range in severity from a partial loss of muscle contraction to complete paralysis, and it may involve one or both hemidiaphragms.

The diagnosis and management of unilateral and bilateral diaphragm dysfunction may be challenging for the clinician because of its relative rarity and subtle clinical manifestations, and it is likely underdiagnosed. [5] The workup for suspected diaphragm dysfunction includes chest radiography, pulmonary function testing, fluoroscopy, phrenic nerve conduction studies (NCS), needle electromyogram (EMG) of the diaphragm, and transdiaphragmatic pressure measurements. Each modality has strengths and weaknesses, but all of these produce false-positive and false-negative findings. [6]

Pathophysiology

Disorders of neuromusculature

During normal respiration, the brainstem sends action potentials to the third through fifth cervical spine levels, which then give off dorsal rami that join to form the phrenic nerves bilaterally. The phrenic nerves then traverse the neck and thorax and innervate the diaphragm. The successful impulse of respiratory stimulus from the brain to the diaphragm can be compromised by an interruption of the phrenic nerve at any point along this course.

Traumatic injury to the head or brainstem prevents nerve signals from reaching the phrenic nerve. Generally, injuries that affect the brain and brainstem are catastrophic, with the chance of survival being poor. [7] Other etiologies of

central nervous system damage that may affect the brainstem include multiple sclerosis, stroke, Arnold-Chiari malformations, and poliomyelitis.

Injuries or disease processes that affect the phrenic nerves along their course are well described and impair the transmission of action potentials from the brainstem to the diaphragm. Numerous clinical entities can affect the phrenic nerve directly, including trauma, external compression from a tumor, cardiac or thoracic surgery, chiropractic cervical spine manipulation, radiation therapy, demyelinating diseases (eg, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, Charcot-Marie-Tooth), uremia, lead neuropathy, and postinfectious neuropathies.

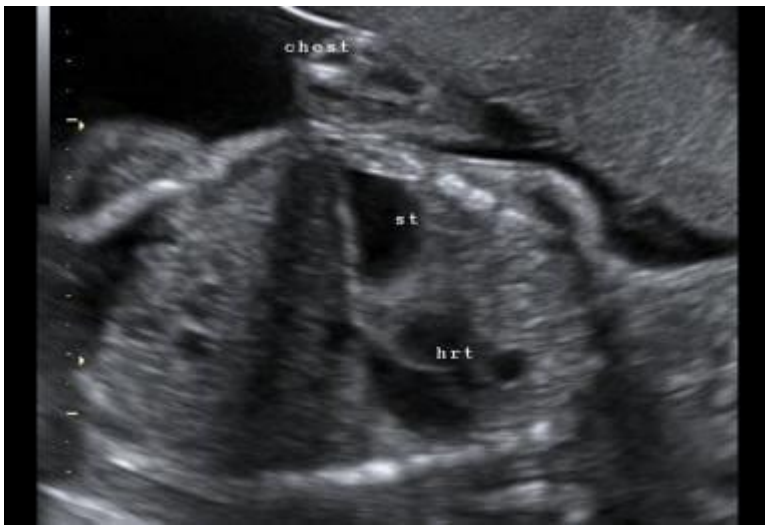
Diseases of the neuromuscular junction can inhibit the production, release, or binding of neurotransmitters at phrenic-diaphragmatic synapses. These processes include myasthenia gravis, Lambert-Eaton syndrome, botulism, organophosphate poisoning.

Diseases that affect the muscle fibers of the diaphragm may result in decreased muscle strength resulting in a decreased ability to generate transdiaphragmatic pressure gradients and thereby less negative maximal inspiratory pressures. These processes include muscular dystrophies, glucocorticoid myopathy, statin myopathy, malnutrition, thyroid disorders, and disuse atrophy in mechanically ventilated patients. [8, 9, 10]

Disorders of anatomy

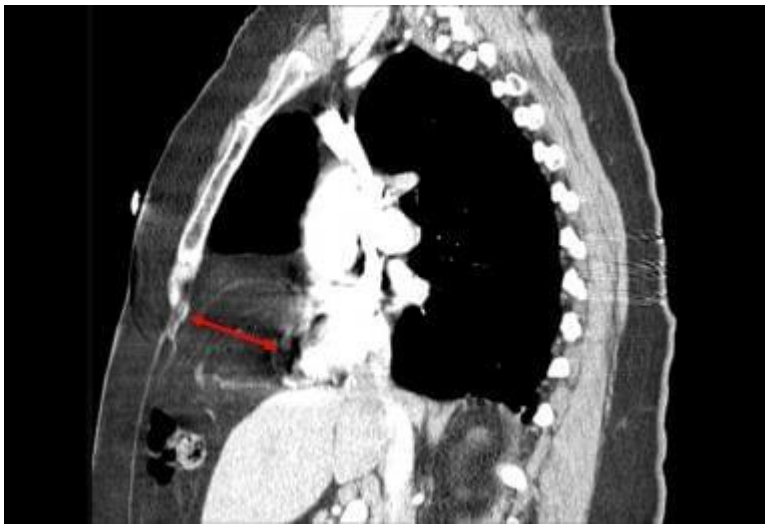
Anatomic disorders of the diaphragm are typically classified into two broad categories, congenital and acquired.

Congenital diaphragmatic hernias occur when the muscular entities of the diaphragm do not develop normally, usually resulting in displacement of the abdominal components into the thorax (see the image below). [11] The underlying etiologies of these diaphragmatic hernias are not well understood, but a number of studies implicate abnormalities of the retinoid system which may result from maternal vitamin A deficiency. [12, 13, 7]



Diaphragm Disorders (Diaphragmatic dysfunction). Congenital diaphragmatic hernia is shown in this coronal obstetric ultrasound (the patient's head is to the right of the image; the thorax is center, and the abdomen is left). The stomach (st) and heart (hrt) are both within the thorax. Courtesy of Wikipedia (https://en.wikipedia.org/wiki/File:Cdh0002.jpg), author Dr Laughlin Dawes.

Congenital diaphragmatic hernias are classified by the position of the defect. Bochdalek hernias, which represent between 80% and 90% of congenital diaphragmatic hernias, are posterolateral defects of the diaphragm that result in either failure in the development of the pleuroperitoneal folds or improper or absent migration of the diaphragmatic musculature. [14, 15, 16] Morgagni hernias involve the anterior portion of the diaphragm (see the following image). Congenital diaphragmatic hernias involving the central portion of the diaphragm are rare.



Diaphragm Disorders (Diaphragmatic dysfunction). Sagittal computed tomography scan of the chest with intravenous contrast demonstrates a Morgagni hernia (red arrow) containing abdominal fat. Courtesy of Wikipedia (https://en.wikipedia.org/wiki/File:Morgagni_Hernia.PNG), author Jason Robert Young, MD.

The most common cause of acquired diaphragmatic disorders is trauma. [17, 18] Traumatic diaphragmatic rupture can occur secondary to both blunt and penetrating trauma. Up to 65% of diaphragmatic ruptures are a result of penetrating injury from stab or gunshot wounds. The remainder of traumatic diaphragmatic injury is blunt trauma sustained from motor vehicle accidents, falls, or direct impacts. Left-sided rupture is more common, occurring in 65%-75% of blunt trauma cases. [19, 20, 21]

Etiology

The etiology of diaphragmatic dysfunction is most easily separated into anatomic, neurologic, neuromuscular junction, and myopathic disorders.

Anatomic defects include the following:

- Congenital defects: Bochdalek hernia, Morgagni hernia, eventration of the diaphragm, and diaphragmatic agenesis
- Acquired defects: Blunt traumatic rupture, penetrating injuries, and iatrogenic injury during surgery or other invasive procedures

Neurologic defects are include the following:

- Brainstem stroke
- Spinal cord disorders: Trauma to the cervical spinal cord, syringomyelia, poliomyelitis, anterior horn cell disease
- Cervical spondylosis
- Cervical chiropractic manipulation [22]
- Trauma to the phrenic nerve from surgery, [23] radiation, [24] or a tumor
- Guillain-Barré syndrome [25]
- Diabetic neuropathy
- Alcoholic neuropathy

- Viral and postviral neuropathy (polio, West Nile virus, herpes zoster, human immunodeficiency virus [26])
- Heavy metal toxicity (lead, arsenic) [27]
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Connective-tissue disease (eg, systemic lupus erythematosus [SLE], rheumatoid arthritis)

Myopathic causes of diaphragmatic paralysis are include the following:

- Disuse atrophy due to mechanical ventilation [9]
- Malnutrition
- Electrolyte disturbances (hypophosphatemia, hypokalemia, hypocalcemia) [28]
- Limb-girdle dystrophy
- Hyperthyroidism or hypothyroidism
- Acid maltase deficiency
- SLE
- Dermatomyositis
- Mixed connective-tissue disease
- Amyloidosis
- Myasthenia gravis
- Muscular disorders: Myotonic dystrophies, Duchenne muscular dystrophy, and metabolic myopathies

Epidemiology

The exact frequency of diaphragmatic disorders is not known and is difficult to estimate. It is likely that diaphragmatic disorders are underdiagnosed due to subtle clinical findings and varying etiologies. However, the incidence of many specific causes of diaphragmatic disorders is known.

For example, congenital diaphragmatic hernia (CDH) affects 1 in 3500 live-born infants. [29] Coronary artery bypass grafting (CABG) surgery is associated with lesions of the phrenic nerves resulting in postoperative diaphragmatic

paralysis, with reported incidences varying from 1% to 5%, with some reports as high as 60%. Internal mammary artery harvesting and the use of frozen slurry during cardiac surgery increase the risk of phrenic nerve injury. [5, 30, 31] Up to 25% of patients with Guillain-Barre disease will develop diaphragmatic weakness requiring mechanical ventilation. [25]

Prognosis

The prognostic and clinical evolution of diaphragm dysfunction are variable and related to the underlying etiology and the extent of the dysfunction.

Patients with congenital diaphragmatic hernias generally present in the neonatal period, with associated postsurgical survival rates of 60%-80%. Despite improvements in surgical correction over the years, complications and comorbidities still affect 20%-40% of the treated children. These include both surgical complications (recurrence, postoperative adhesions and obstruction, stenosis, strictures, and recurrent fistulae) as well as pulmonary problems (chronic lung disease, obstructive and restrictive pulmonary dysfunction), gastrointestinal problems (dysphagia, gastroesophageal reflux, impaired intestinal motility), and failure to thrive. [29]

Patients with diaphragmatic disorders due to transient neuropathies such as postviral neuropathy or Guillain-Barré syndrome as well as patients with iatrogenic phrenic nerve injury from cardiac or thyroid surgery generally have a favorable prognosis, with functional recovery in up to 69% of patients within 2 years. [32, 30, 33]

In the intensive care unit, ventilator-induced diaphragm dysfunction is a negative prognostic marker, with clinical impact on the weaning outcome, length of mechanical ventilation, survival, and long-term outcome. [34, 35] The mechanisms underlying this process include weakness of the diaphragm from defective contractility and reduced diaphragm muscle mass, as well as oxidative loads, structural damage, and muscle fiber remodeling. [34, 36]

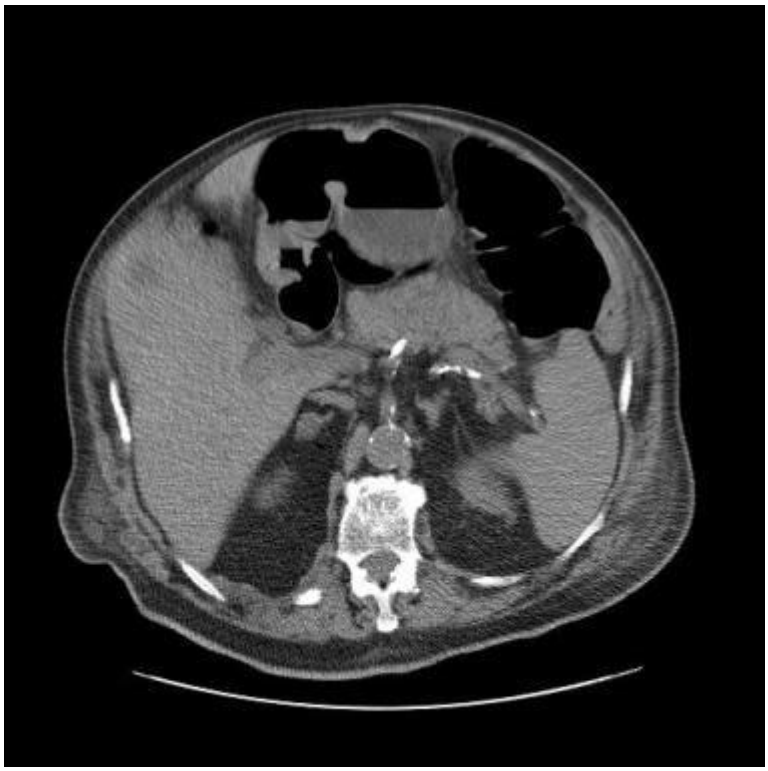
Persons with high cervical spine fractures generally fare worse than individuals with transient neuropathies. Trauma to the cervical spine at C1-C2 results in complete diaphragmatic paralysis. Trauma to C3 and C4 may lead to

substantial loss of diaphragm function whereas trauma to C4 and C5 are much less likely to require ventilatory support.[7] In the context of degenerative myopathies or neurologic diseases, respiratory muscle weakness frequently progresses relentlessly with the underlying disease and may progress to fulminate respiratory failure. Patients with amyotrophic lateral sclerosis have universally fatal outcomes, but respiratory muscle strength has been demonstrated to be a predictive marker for prognosis.

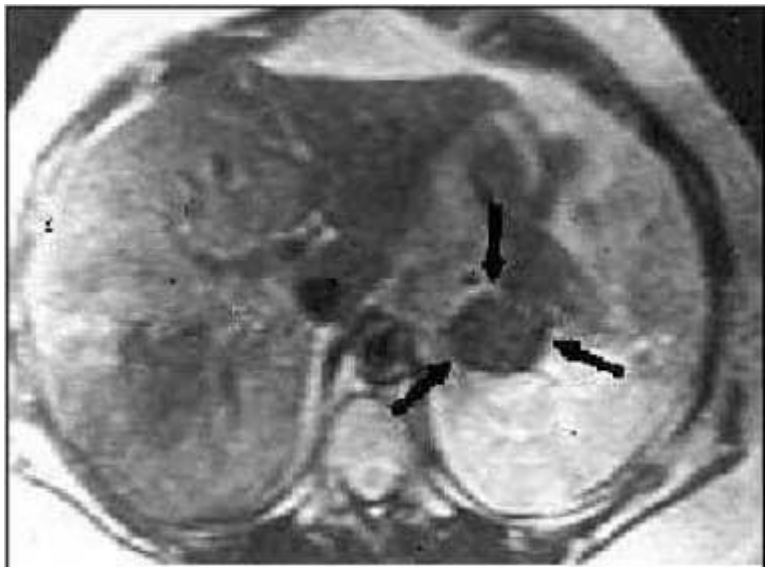
2. Adrenal disease

Practice Essentials

Tumors of the adrenal cortex are reported in 2% of all autopsies, with the most common lesion being a benign adenoma (see the first image below). The common major pathologic entities of the adrenal gland that require surgical intervention are primary hyperaldosteronism (ie, Conn syndrome, see the second image below), Cushing syndrome, pheochromocytoma, neuroblastoma, and adrenocortical carcinoma. However, many adrenal glands are removed en bloc as part of a radical nephrectomy for renal cell carcinoma.



Homogeneous, well-defined, 7-HU ovoid mass is seen in the right adrenal gland; this finding is diagnostic of a benign adrenal adenoma.



Magnetic resonance imaging (MRI) scan in a patient with Conn syndrome showing a left adrenal adenoma.

Background

Frequently, lesions metastatic to the adrenal gland necessitate adrenalectomy, and reports exist of adrenal excision for symptomatic adrenal cysts. The workup of adrenal disorders requiring surgical intervention has undergone a revolution with the tremendous advances in hormonal research, as well as in radiographic techniques and localization. In general, neoplastic lesions of the adrenal gland may be classified with the tumor, node, metastases (TNM) staging system, as follows:

- Tumor
    - T1 - Tumor confined to adrenal gland and less than 5 cm
    - T2 - Tumor confined to adrenal gland and greater than 5 cm
    - T3 - Tumor invasion into periadrenal fat
    - T4 - Tumor invasion of adjacent organs
- Node
    - N0 - Negative lymph nodes
    - N1 - Positive lymph nodes
- Metastases
    - M0 - No metastases
    - M1 - Distant metastases

Table. TNM Staging System for Neoplastic Lesions of the Adrenal Gland (Open Table in a new window)

Stage	TNM
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 or T1-2, N1, M0
Stage IV	Any T, N, M1, or T3-4, N1, M0

History of the Procedure

The adrenal gland is crucial to endocrine homeostasis, and maladies associated with it result in several recognized syndromes. Understanding of the adrenal glands began in 1805, when Currier first delineated the anatomic structure of the medulla and cortex. Addison later described the clinical effects of adrenal insufficiency in 1855. Thomas Addison first described the association of hypertensive episodes with adrenal tumors in 1886. Medical and surgical management of pheochromocytoma was first described in the United States by Mayo [1] and remained relatively unchanged until the 1960s, when Crout et al elucidated the biochemical pathways and diagnostic catecholamine studies, allowing diagnostic ability prior to exploration. [2]

Problem

Primary hyperaldosteronism

First described in 1955 by Jerome Conn, the hallmarks of primary hyperaldosteronism are hypertension, hypokalemia, hypernatremia, and elevated urine aldosterone levels (with salt repletion), as well as decreased renin activity and alkalosis with increased urinary potassium excretion. Primary

hyperaldosteronism can be secondary to an adrenal adenoma or secondary to bilateral adrenal hyperplasia. Differentiating between these two disease processes is important because they can be treated differently. The patient's renin level should also be checked to rule out causes of secondary hyperaldosteronism, such as renal artery stenosis. The renin level is elevated in persons with renal artery stenosis, whereas the renin level is suppressed in those with primary hyperaldosteronism.

Cushing syndrome

The diagnosis of Cushing syndrome is made based on abnormalities of urinary and plasma cortisol and/or adrenocorticotropic hormone (ACTH). The syndrome typically is attributed to central, hypothalamic, or pituitary excess secretion of ACTH (Cushing disease), primary adrenal hypercorticalism, or ectopic secretion of ACTH.

Pheochromocytoma

These tumors arise from chromaffin cells of the adrenal medulla. Ten percent of cases may be familial, and 10% might be bilateral or in extra-adrenal locations. If the tumor arises from a site other than the adrenal, it is termed a paraganglionoma. Paraganglionomas have been reported in locations from the neck to the pelvis. While pheochromocytoma follows the "rule of 10s," with only 10% of cases involving malignant tumors, 50% of cases of paraganglionomas have reported malignancies. Pheochromocytomas also can be a part of an endocrine syndrome such as multiple endocrine neoplasia (MEN) IIa, MEN IIb, von Hippel-Lindau disease, or von Recklinghausen disease.

Neuroblastoma

Neuroblastomas arise from sympathetic neuroblasts and occur almost exclusively in the pediatric population. Neuroblastoma represents the most common extracranial solid tumor in children, and approximately one third of neuroblastomas arise in the adrenal gland. Surgery of neuroblastoma is an important element in diagnosis, staging, and treatment of children with neuroblastoma. Surgery is curative therapy for patients with stage I and early stage

II disease, with a reported 2-year survival rate of 89%. [3] Reviews regarding safety reveal a low complication rate, commonly less than 10%. Advanced-stage tumors usually require a combination of surgery, chemotherapy, and/or radiation therapy to provide a complete response.

Myelolipoma

Adrenal myelolipomas are rare benign masses that consist of fat and hematopoietic cells. They are hormonally inactive. These masses are typically asymptomatic, but some are associated with flank or abdominal pain. Adrenal myelolipomas can often be diagnosed with imaging studies. On CT scans, myelolipomas appear as well-circumscribed massed with a negative attenuation consistent with fat. Should the diagnosis still be in doubt, obtaining an image-guided needle biopsy can be helpful. As myelolipomas are benign lesions with no hormonal activity, most physicians recommend observation unless symptoms occur or the tumor begins to grow during observation.

Adrenocortical carcinoma

Adrenocortical carcinoma is a rare disease with a poor prognosis. Up to 80% of adrenal carcinomas are functional and secrete multiple hormones.

Pathophysiology

Primary hyperaldosteronism

The hallmarks of primary hyperaldosteronism are hypertension, hypokalemia, hypernatremia, and elevated urine aldosterone levels (with salt repletion), as well as decreased renin activity and alkalosis with increased urinary potassium excretion. The most common causes of aldosterone overproduction are idiopathic adrenal hyperplasia, followed by adenomas, and then (rarely) adrenal carcinoma. Of the benign adenomas, approximately 60% are unilateral (typically managed surgically), while 40% are bilateral lesions that are treated medically with spironolactone, unless marked asymmetry of aldosterone production is present. In this case, the dominant gland often is excised, unless bilateral disease that is uncontrollable by medical therapy exists.

Cushing syndrome

The syndrome typically is attributed to central, hypothalamic, or pituitary excess secretion of ACTH (Cushing disease), primary adrenal hypercorticalism, or ectopic secretion of ACTH.

Pheochromocytoma

These tumors arise from chromaffin cells of the adrenal medulla. Presentation of the pheochromocytoma varies with the production of active metabolites. Most commonly, episodic alpha-adrenergic hypersecretion leads to intermittent malignant hypertension.

Neuroblastoma

Neuroblastomas arise from sympathetic neuroblasts and occur almost exclusively in the pediatric population. Neuroblastoma represents the most common extracranial solid tumor in children, and approximately one third of neuroblastomas arise in the adrenal gland. They are rapidly growing tumors and may be metabolically active; however, the more common presentation is from mass effect.

Adrenocortical carcinoma

As the name implies, adrenocortical carcinoma arises from the cortex. The adrenal cortex in made up of 3 distinct zones: glomerulosa (outer), fasciculata (middle), and reticularis (inner). These 3 zones are responsible for aldosterone, cortisol, and sex steroid production, respectively. Up to 80% of adrenal carcinomas are functional and secrete multiple hormones. The most common hormones secreted are glucosteroids, followed by androgens, estradiol, and, finally, aldosterone. Adrenal carcinomas can be subclassified according to their ability to produce adrenal hormones.

Etiology

Primary hyperaldosteronism

The most common causes of aldosterone overproduction are idiopathic adrenal hyperplasia, followed by adenomas, and then (rarely) adrenal carcinoma. Of the benign adenomas, approximately 60% are unilateral (and typically managed surgically), while 40% are bilateral lesions.

Cushing syndrome

See Cushing syndrome in Pathophysiology.

Pheochromocytoma

See Pheochromocytoma in Pathophysiology.

Neuroblastoma

Neuroblastomas arise from sympathetic neuroblasts and occur almost exclusively in the pediatric population. Approximately one third of neuroblastomas arise in the adrenal gland.

Myelolipoma

Many theories have been proposed as to the etiology of myelolipomas. The most widely accepted theory is adrenocortical cell metaplasia and growth due to an insult to the adrenal gland (eg, infection, ischemia).

Adrenocortical carcinoma

See Adrenocortical carcinoma in Pathophysiology.

Epidemiology

United States statistics

In the United States, tumors of the adrenal cortex are reported in 2% of all autopsies, with the most common lesion being a benign adenoma. The incidence of adrenal carcinoma is estimated to be 1 case per 1.7 million, and it accounts for 0.02% of all cancers.

Presentation

Primary hyperaldosteronism

Presentation of primary hyperaldosteronism includes hypertension, hypokalemia, hypernatremia, and elevated urine aldosterone levels (with salt repletion), as well as decreased renin activity and alkalosis with increased urinary potassium excretion.

Cushing syndrome

The clinical presentation of Cushing syndrome is hypertension, moon facies, abdominal striae, buffalo hump, muscle weakness, amenorrhea, decreased libido, osteoporosis, fatigue, hirsutism, and obesity.

Pheochromocytoma

Presentation of the pheochromocytoma varies with the production of active metabolites. Pheochromocytoma most often develops in young–to–middle-aged adults. The classic triad is episodic headache, tachycardia, and diaphoresis. The most common clinical sign of pheochromocytoma is hypertension. Persons with this condition may experience sustained hypertension, paroxysmal hypertension, or sustained hypertension with superimposed paroxysms. Other common signs are palpitations, anxiety, tremulousness, chest pain, and nausea and vomiting. A small group of these patients experience induced myocardiopathy due to sustained catecholamine release. They present with decreased cardiac function and congestive heart failure. Generally, the cardiomyopathy is reversible with the use of antiadrenergic blocking agents and alpha-methylparatyrosine, a catecholamine synthesis inhibitor.

Neuroblastoma

Neuroblastomas arise from sympathetic neuroblasts and occur almost exclusively in the pediatric population. Neuroblastoma represents the most common extracranial solid tumor in children, and approximately one third of neuroblastomas arise in the adrenal gland. They are rapidly growing tumors and may be metabolically active; however, the more common presentation is from mass effect.

Adrenocortical carcinoma

These patients present with constitutional symptoms such as weight loss, fever, and malaise. Up to 80% of adrenocortical carcinomas are functional, and patients with these present with clinical signs of Cushing syndrome. An increase in sex steroid levels can result in oligomenorrhea, virilization, or feminization.

The most common presentation of adrenocortical carcinoma is that of an incidentaloma. At presentation, 19% have inferior vena cava (IVC) involvement and 32% have metastases.

Lesions metastatic to the adrenal gland

Adrenal masses thought to arise from distant metastases include melanoma, lung cancer, renal cell carcinoma, and breast cancer. These should be discussed with the primary service taking care of these lesions, but these adrenal masses are often amenable to laparoscopic adrenalectomy.

Indications

In deciding whether adrenalectomy is indicated for a newly discovered adrenal mass, one must ascertain whether the mass is functional and if it has signs of malignancy. Except for bilateral adrenal hyperplasia, which can be treated medically with spironolactone, most functional masses should be surgically removed.

Signs of malignancy

Signs of malignancy are based on tumor size, radiographic findings, and history of carcinoma.

Tumor size

Studies have shown that adrenal masses larger than 6 cm have a much greater chance of malignancy. Because CT scans tend to underestimate the size of the tumor by more than 20%, the cutoff on CT scan for an adrenal mass should be 4-6 cm. Therefore, adrenal masses larger than 4-6 cm on CT scan are considered high risk for cancer and should be surgically removed.

Radiographic findings

Adrenocortical carcinomas and pheochromocytomas have been shown to be hyperintense on MRI T2–weighted images. If the intensity of the adrenal lesion relative to the liver or spleen on an MRI T2–weighted image is less than 80%, the lesion is more likely to be a cortical adenoma. CT scan findings suggestive of an adrenocortical carcinoma include lesions that have irregular margins, are heterogeneous, and have high densities on noncontrast images. Necrosis and calcification are also more commonly associated with adrenal carcinoma. Most adenomas are lipid rich and have densities of less than 10 Hounsfield units. Furthermore, the density of adenomas on delayed contrast images is reduced by at least 60%, unlike adrenocortical carcinomas. Finally, nuclear scans such as

metaiodobenzylguanidine (MIBG) and NP-59 (131-6-β-iodomethylnorcholesterol) can help to identify pheochromocytomas and adrenocorticalcarcinomas, respectively.

History of carcinoma

Patients with a history of carcinoma and a newly discovered adrenal mass have a 32%-73% chance of having metastasis to the adrenal gland. The most common cancers that metastasize to the adrenal glands are melanoma, lung cancer, breast cancer, and renal cancer. Biopsy of an adrenal lesion is appropriate in a patient with a history of cancer. If the biopsy sample is positive for metastasis, the decision of whether to give chemotherapy, with or without adrenalectomy, should be further explored. In most settings, adrenalectomy would not be indicated in the presence of metastases. Metastatic disease, unless part of a research protocol, is a contraindication to adrenal surgery.

Adrenal incidentalomas

Attention must be given to the increasing diagnosis of the adrenal incidentaloma, which refers to a clinically inapparent adrenal mass that is discovered with some form of imaging study performed for an indication not related to adrenal disease. Estimates of the prevalence of adrenal incidentalomas range from 0.1%-4.3%. Current National Institutes of Health (NIH) recommendations dictate that patients with such a diagnosis should undergo hormonal evaluation, including an overnight dexamethasone suppression test, plasma-free metanephrine study, and a study of plasma aldosterone level–plasma renin activity ratio. [4] In general, adrenal incidentalomas associated with abnormal hormonal findings should undergo surgical adrenalectomy. Masses larger than 6 cm are associated with a 25% risk of malignancy, and these should also be treated surgically.

If a mass is nonfunctional and has no signs of malignancy (ie, >6 cm), the patient can be monitored and observed. The patient should undergo CT scanning every 6 months and an annual endocrine evaluation for 4 years. If the mass grows or affects endocrine function, it should be removed. Some clinicians now believe

that if the mass is stable as revealed by CT scan at 3 and 12 months and is not functional, routine follow-up is not required.

Relevant Anatomy

Before describing surgical technique, understanding the anatomy of the adrenal glands is essential. The adrenal glands, also known as suprarenal glands, belong to the endocrine system. They are a pair of triangular-shaped glands, each about 2 in. long and 1 in. wide. The suprarenal glands are responsible for the release of hormones that regulate metabolism, immune system function, and the salt-water balance in the bloodstream; they also aid in the body's response to stress.

Both adrenals are located on the superior posterior aspect of the kidneys in the retroperitoneum. The right adrenal is covered anteriorly by the liver and has a short vein typically draining directly into the inferior vena cava (IVC). The left adrenal is covered anteriorly by the pancreas and spleen. In general, the surgical approach is dependent on the primary adrenal lesion, the size of the lesion, the side of the lesion, and the habitus and health of the patient, as well as surgeon preference and familiarity.

Prognosis

Primary hyperaldosteronism

The surgical removal of the adrenal gland and adenoma provides excellent results, with most patients being cured.

Pheochromocytoma

Long-term cures are rare in cases of malignant pheochromocytomas. In cases of metastatic disease, 5-year survival rates as high as 36% have been reported.

Neuroblastoma

Surgery of neuroblastoma is an important element in diagnosis, staging, and treatment of children with neuroblastoma. Surgery is curative therapy for people with stage I and early stage II disease, with a reported 2-year survival rate of 89%. Reviews regarding safety reveal a low complication rate, most commonly less than

10%. Advanced-stage tumors usually require a combination of surgery, chemotherapy, and/or radiation therapy to provide a complete response.

Adrenocortical carcinoma

At presentation, 19% of patients had IVC involvement and 32% had metastases. The median time of survival was 17 months, and evaluation of factors affecting survival reveal benefit to the following characteristics: age younger than 54 years, absence of metastasis, and nonfunctional tumors.[5] Another study at Memorial Sloan-Kettering reviewed 115 patients and revealed overall median survival to be 38 months, with a 5-year survival rate of 37%. Patients with stage I or II disease fared better, with a 5-year survival rate of 60%, while patients with stage III and IV disease had a 5-year survival rate of 10%.

Complications of adrenal surgery

The keys to adrenal surgery are exposure and dissecting the body away from the tumor. Most preventable complications arise from failure to strictly adhere to these principles. Certainly, the most troublesome complication occurs from avulsion of the short right adrenal vein. Manual compression and good exposure allow the avulsed area of the cava to be partially occluded with sponge sticks, and the vein stump may be grasped with an Allis forceps and subsequently suture ligated. In addition, on the right side, the accessory hepatic veins can be avulsed and are handled using a similar manner of vascular control and then ligation.

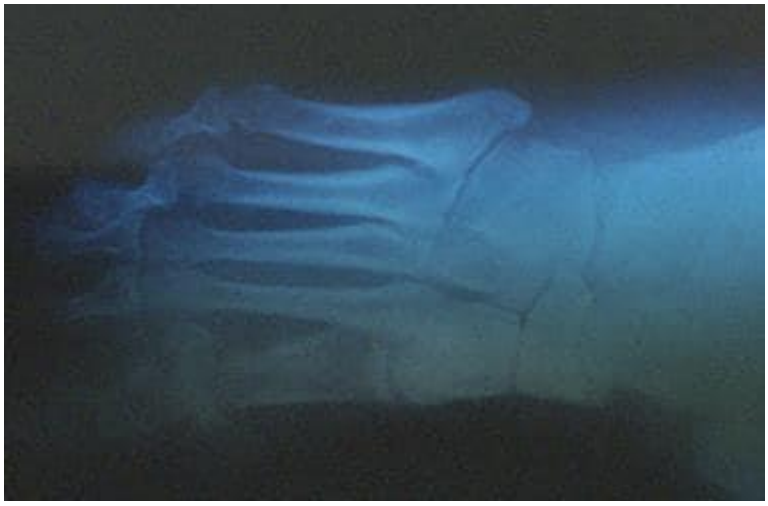
On the left side, complications typically involve splenic laceration or damage to the tail of the pancreas. Dissection superiorly on either adrenal involves the possibility of entering the pleura, with subsequent pneumothorax. Finally, being aware of the possible need for postoperative supplementation of glucocorticoids and mineralocorticoids in the patient with complex and/or bilateral disease is essential.

3. Surgical complications of diabetes. Diabetic foot syndrome.

Practice Essentials

Compromise of the blood supply from microvascular disease, often in association with lack of sensation because of neuropathy, predisposes persons with diabetes mellitus to foot infections. These infections span the spectrum from simple, superficial cellulitis to chronic osteomyelitis.

The radiograph below demonstrates a foot lesion in a patient with diabetes.



Chronic diabetic ulceration with underlying osteomyelitis. Plain film radiograph exhibiting cortical disruption at the medial aspect of the first MTP joint.

Signs and symptoms

Diabetic foot infections typically take one of the following forms:

- Cellulitis
- Deep-skin and soft-tissue infections
- Acute osteomyelitis
- Chronic osteomyelitis

Cellulitis

- Tender, erythematous, nonraised skin lesions are present, sometimes with lymphangitis
- Lymphangitis suggests group A streptococcal infection
- Bullae are typical of *Staphylococcus aureus* infection, but occasionally occur with group A streptococci

· No ulcer or wound exudate is present

Deep-skin and soft-tissue infections

- The patient may be acutely ill, with painful induration of the soft tissues in the extremity
- Wound discharge is usually not present
- In mixed infections that may involve anaerobes, crepitation may be noted over the afflicted area
- Extreme pain and tenderness may indicate compartment syndrome or clostridial infection (ie, gas gangrene)
- The tissues are not tense, and bullae may be present
- Discharge, if present, is often foul

Acute osteomyelitis

- Unless peripheral neuropathy is present, the patient has pain at the site of the involved bone
- Usually, fever and regional adenopathy are absent

Chronic osteomyelitis

- The patient's temperature is usually less than 102°F
- Discharge is commonly foul
- No lymphangitis is observed
- Pain may or may not be present, depending on the degree of peripheral neuropathy
- Deep, penetrating ulcers and deep sinus tracts (diagnostic of chronic osteomyelitis) are usually located between the toes or on the plantar surface of the foot
- The medial malleoli, shins, or heels are not usually sites of involvement

Diagnosis

Cellulitis

- The WBC and ESR are slightly or moderately elevated, but these elevations are not diagnostic
- Blood culture results are usually negative; if positive, they usually indicate the presence of group A or group B streptococci

Cultures of skin via aspiration or biopsy are generally unrewarding; aspiration of a sample from the leading edge of the erythematous border has a low yield (likely < 5%) but may be used if the likely organism must be identified on initial presentation

Skin and soft-tissue infections

- The WBC and ESR are mildly or moderately elevated
- If bullae are present, Gram stain and culture results from aspirated exudate from a bullous lesion may help identify the pathogen
- Blood culture results may be positive
- In suspected deep soft-tissue infection, plain radiography, CT, or MRI may be performed to evaluate for compartment syndrome or for gas or a foreign body in the deep tissues [1]; excessive gas signifies a mixed aerobic-anaerobic infection, in contrast to gas gangrene (clostridial myonecrosis)
- Gram stains and/or cultures of samples aspirated from deep-skin and soft-tissue infections may be used to identify the organism

Acute osteomyelitis

- The WBC usually reveals leukocytosis, and the ESR is moderately or highly elevated [2]
- Blood culture results are usually negative; when positive, the findings most frequently indicate the presence of *S aureus*
- For affected long bones, plain radiographic findings generally become abnormal after 10-14 days; soft-tissue swelling and periosteal elevation are the earliest signs
- Bone scans are preferred to gallium or indium scans; bone-scan findings are positive within 24 hours
- Bone biopsy is not necessary

Chronic osteomyelitis

- The WBC is often within the reference range; the ESR is usually very highly elevated and may exceed 100 mm/hr [2]; the platelet count is also often elevated

- Blood culture results are usually negative
- Plain radiographic findings are invariably abnormal
- Bone scans are usually unnecessary unless diagnostic confusion exists with another disorder (eg, bone tumor); an MRI scan would also be helpful in such a situation
- Bone biopsy performed under aseptic conditions in the operating room is the preferred way to identify the causative pathogen
- Important pathogens include *Bacteroides fragilis, E coli, Proteus mirabilis, and Klebsiella pneumoniae; Pseudomonas aeruginosa* is usually not the causative organism

Management

Treatment of diabetic foot infections varies by type, as follows:

- Cellulitis – Most responsive to antibiotics
- Deep skin and soft-tissue infections – Usually curable, but additional debridement is usually indicated
- Acute osteomyelitis – Infecting microorganisms and the likelihood of successful treatment with antimicrobial therapy are essentially the same as in patients without diabetes
- Chronic osteomyelitis – Surgical debridement is essential, in addition to antibiotics; amputation may be necessary

See Treatment and Medication for more detail.

Background

Foot infections are the most common problems in persons with diabetes. These individuals are predisposed to foot infections because of a compromised vascular supply secondary to diabetes. Local trauma and/or pressure (often in association with lack of sensation because of neuropathy), in addition to microvascular disease, may result in various diabetic foot infections that run the spectrum from simple, superficial cellulitis to chronic osteomyelitis.

The radiograph below demonstrates a foot lesion in a patient with diabetes.

Infections in patients with diabetes are difficult to treat because these individuals have impaired microvascular circulation, which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues. In addition, diabetic individuals can not only have a combined infection involving bone and soft tissue called fetid foot, a severe and extensive, chronic soft-tissue and bone infection that causes a foul exudate, but they may also have peripheral vascular disease that involves the large vessels, as well as microvascular and capillary disease that results in peripheral vascular disease with gangrene. [3, 4, 5, 6, 7]

Except for chronic osteomyelitis, infections in patients with diabetes are caused by the same microorganisms that can infect the extremities of persons without diabetes. Gas gangrene is conspicuous because of its low incidence in patients with diabetes, but deep-skin and soft-tissue infections, which are due to gas-producing organisms, frequently occur in patients with these infections.

In general, foot infections in persons with diabetes become more severe and take longer to cure than do equivalent infections in persons without diabetes.

Staging in diabetic foot infections is applicable only in cases of chronic osteomyelitis that require surgery.

Go to Type 1 Diabetes Mellitus,Type 2 Diabetes Mellitus, and Diabetic Ulcers to see more complete information on these topics.

Pathophysiology

In chronic osteomyelitis, a sequestrum and involucrum form; these represent islands of infected bone. Bone fragments that are isolated have no blood supply.

Bacteremia may accompany cellulitis, skin or soft-tissue infections, and/or acute osteomyelitis, but this is not a complication per se. If chronic osteomyelitis is left untreated for years, it may lead to complications such as amyloidosis or squamous cell carcinoma at the site of drainage through the skin. Bacteremia and septic shock rarely, if ever, occur as a result of chronic osteomyelitis.

Research indicates that when present in *Staphylococcus aureus*, the prophage ROSA-like inhibits the bacterium from infecting diabetic foot ulcers and

also prevents *S aureus* from replicating inside osteoblasts, diminishing cell damage to these lesions. [8]

Etiology

Diabetes mellitus is a disorder that primarily affects the microvascular circulation. In the extremities, microvascular disease due to "sugar-coated capillaries" limits the blood supply to the superficial and deep structures. Pressure due to ill-fitting shoes or trauma further compromises the local blood supply at the microvascular level, predisposing the patient to infection, which may involve the skin, soft tissues, bone, or all of these combined.

Diabetes also accelerates macrovascular disease, which is evident clinically as accelerating atherosclerosis and/or peripheral vascular disease. Most diabetic foot infections occur in the setting of good dorsalis pedis pulses; this finding indicates that the primary problem in diabetic foot infections is microvascular compromise.

Impaired microvascular circulation hinders white blood cell migration into the area of infection and limits the ability of antibiotics to reach the site of infection in an effective concentration. Diabetic neuropathy may be encountered in conjunction with vasculopathy. This may allow for incidental trauma that goes unrecognized (eg, blistering, penetrating foreign body). Go to Diabetic Neuropathy for more complete information on this topic.

Microbial characteristics

The microbiologic features of diabetic foot infections vary according to the tissue infected. In patients with diabetes, superficial skin infections, such as cellulitis, are caused by the same organisms as those in healthy hosts, namely group A streptococci and *S aureus*. In unusual epidemiologic circumstances, however, organisms such as *Pasteurella multocida* (eg, from dog or cat bites or scratches) may be noted and should always be considered. Group B streptococcal cellulitis is uncommon in healthy hosts but not uncommon in patients with diabetes. In diabetic individuals, group B streptococci may cause urinary tract infections and catheter-associated bacteriuria in addition to cellulitis, skin and/or

soft-tissue infections, and chronic osteomyelitis. Such infections may be complicated by bacteremia.

Furthermore, as previously mentioned, deep soft-tissue infections in diabetic persons can be associated with gas-producing, gram-negative bacilli. Clinically, these infections appear as necrotizing fasciitis, compartment syndrome, or myositis. Gas gangrene is uncommon in persons with diabetes.

Acute osteomyelitis usually occurs as a result of foot trauma in an individual with diabetes. The distribution of organisms is the same as that in an individual without diabetes who has acute osteomyelitis. In chronic osteomyelitis, however, the pathogens include group A and group B streptococci, aerobic gram-negative bacilli, and *Bacteroides fragilis*.

Other pathogens implicated in chronic osteomyelitis in patients with diabetes include *B fragilis*, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.

Pseudomonas aeruginosa is generally not a pathogen in chronic osteomyelitis in these individuals. Although *P aeruginosa* is frequently cultured from samples obtained from a draining sinus tract or deep penetrating ulcers in patients with diabetes, these organisms are superficial colonizers and are generally not the cause of the bone infection.

Because *Pseudomonas* organisms are water-borne, superficial ulcers may be contaminated by bacteria in wet socks or dressings. To the authors' knowledge, however, no well-documented cases of biopsy-proven *P aeruginosa* infection have been reported in patients with chronic osteomyelitis.

Fetid foot represents a combined deep-skin and soft-tissue infection caused by pathogens involved in chronic osteomyelitis.

Epidemiology

Globally, diabetic foot infections are the most common skeletal and soft-tissue infections in patients with diabetes. The incidence of diabetic foot infections is similar to that of diabetes in various ethnic groups and most frequently affect elderly patients. There are no significant differences between the sexes.

Mortality is not common, except in unusual circumstances. The mortality risk is highest in patients with chronic osteomyelitis and in those with acute necrotizing soft-tissue infections.

A prospective cohort study by Lynar et al indicated that in patients with diabetic foot infections, the mortality risk is increased in those who are undergoing hemodialysis or of older age. The 1-year, cumulative mortality risk in patients receiving hemodialysis was determined to be 24.5%. [9]

Prognosis

The prognosis for cases of cellulitis, skin and/or soft-tissue infections, and acute osteomyelitis depends on the adequacy of antimicrobial therapy and surgical debridement. For cases of chronic osteomyelitis, the prognosis is directly related to the vascular supply in the affected limb and the adequacy of surgical debridement.

In a German study, nearly 250 patients with diabetic foot ulcers were evaluated and followed over time. Major adverse risk factors for long-term limb salvage included the presence of significant peripheral artery disease and renal insufficiency. [10]

A study by Chammas et al indicated that ischemic heart disease is the primary cause of premature death in patients with diabetic foot ulcer, finding it to be the major source of mortality on postmortem examination in 62.5% of 243 diabetic foot ulcer patients. The study also found that in patients with diabetic foot ulcer, the mean age of death from ischemic heart disease, as derived from postmortem examination, was 5 years below that of controls. Patients with neuropathic foot ulcers were determined to have the highest risk of premature death from ischemic heart disease. [11]

A study by Chen et al indicated that following hospital treatment for diabetic foot ulcer, invasive systemic infection associated with the ulcer (DFU-ISI) is an important late complication that increases mortality risk. In the study's patients, methicillin-resistant *Staphylococcus aureus* (MRSA) gave rise to 57% of the ISIs. Using Cox regression modeling, the investigators found that complicated ulcer healing and the presence of MRSA in the initial ulcer culture predicted the

development of DFU-ISIs (hazard ratios of 3.812 and 2.030, respectively), with the hazard ratio for mortality risk in association with DFU-ISIs being 1.987. [12]

Patient Education

Patients with diabetes must be careful to avoid foot trauma and to properly care for their feet to minimize the possibility of infection. In addition, they must understand that chronic osteomyelitis cannot be cured with antibiotics alone and that adequate surgical debridement is necessary.

Patients who are unwilling to undergo the surgical procedure must understand the long-term complications of chronic osteomyelitis. They should be advised that if the infection is not adequately treated with sufficient surgical debridement and/or amputation, systemic complications, including bacteremia and/or systemic infection, amyloidosis, and squamous cell carcinoma at the affected site, may occur over time.

Long-term suppressive therapy may decrease the incidence of septic complications, but it does not affect the long-term complications, which may include amyloidosis or squamous cell carcinoma at the drainage site.

4. Neuroendocrine tumors of the pancreas.

Practice Essentials

Neoplasms of the endocrine pancreas can be divided into functional and nonfunctional varieties. Most pancreatic endocrine neoplasms discovered clinically are functional—that is, they secrete one or more hormonal products into the blood, which leads to a recognizable clinical syndrome. [1]

The first report of a hormone-producing pancreatic tumor syndrome was published in 1927, when Wilder et al described insulinoma syndrome in a patient with a metastatic islet cell tumor who had hyperinsulinism and hypoglycemia. [2] Subsequently, four other classic pancreatic endocrine tumor syndromes have been described. The first is Zollinger-Ellison syndrome (also termed gastrinoma syndrome), described by Zollinger and Ellison in 1955. [3]

The second type comprises a group of three tumor syndromes: Verner-Morrison syndrome, WDHA (watery diarrhea, hypokalemia, and achlorhydria)

syndrome, and pancreatic cholera (also termed vasoactive intestinal peptide [VIP]–releasing tumor or VIPoma); these were described by Verner and Morrison in 1958. [4]

The third is glucagonoma syndrome, described by Mallinson et al in 1974. The fourth is somatostatinoma syndrome, described by Ganda et al and Larsson et al in 1977. [5, 6]

Several other rare clinical syndromes have been proposed as possible functional endocrine syndromes associated with pancreatic neoplasms. These include the following:

- Calcitoninoma [7, 8]
- Parathyrinoma [9]
- Growth hormone–releasing factor–secreting tumor (GRFoma)
- Adrenocorticotropin hormone–secreting tumor (ACTHoma)
- Neurotensinoma [10]

Patients with pancreatic neoplasms that have the histologic characteristics of a pancreatic endocrine tumor but no associated elevation in plasma hormone levels (excluding the pancreatic polypeptide level) and those without a recognizable clinical syndrome are considered to have nonfunctional pancreatic endocrine tumors. A subset of these patients have neoplasms that secrete pancreatic polypeptide (ie, PPomas). Pancreatic polypeptide (PP) is a product that appears to be a marker for pancreatic endocrine tumors, but it is not a mediator of any specific PP-related clinical syndrome. [11] Other nonfunctional pancreatic endocrine tumors likely secrete unknown products that are of little or no clinical significance.

Each of the classic pancreatic endocrine tumor syndromes is discussed in detail in the following articles:

- Insulinoma
- Gastrinoma
- Zollinger-Ellison Syndrome
- VIPomas
- WDHA Syndrome

- Glucagonoma
- Somatostatinomas

For discussion of other conditions with which pancreatic endocrine tumors are associated, see the following:

- Multiple Endocrine Neoplasia Type 1 (MEN1)
- von Hippel-Lindau Disease

Background

Pathophysiology

The cells in pancreatic endocrine neoplasms are termed amine precursor uptake and decarboxylation (APUD) cells because they have a high amine content, are capable of amine precursor uptake, and contain an amino acid decarboxylase.[12] Pearse first used the term APUD in 1968 to unify a group of functionally and structurally similar neuroendocrine cells that are present throughout the body.[13] APUD cells were once believed to originate from the embryologic neural crest, but current evidence suggests that these cells—and thus endocrine tumors of the pancreas and other endocrine tumors of the upper gastrointestinal tract (eg, carcinoid tumors)—actually develop from the embryologic endoderm.[14]

Although the term islet cell tumor is often used to identify neoplasms of the endocrine pancreas, this is a misnomer because many pancreatic neuroendocrine tumors do not develop directly from islet cells.[15] Instead, the tumors arise from APUD stem cells, which are pluripotential neuroendocrine cells located within the ductular epithelium of the exocrine pancreas and elsewhere in the distal foregut.[16] The fact that many gastrinomas and somatostatinomas are found close to, but not within, the pancreatic parenchyma supports the notion of the possible extrapancreatic development of these neoplasms.[17]

Functional pancreatic endocrine neoplasms cause physiologic derangements related to the normal action of the hormonal product that the tumors overproduce. Thus, patients with an insulin-secreting tumor (ie, insulinoma) have the pathophysiologic manifestations of hypoglycemia; patients with a gastrin-secreting

tumor (ie, gastrinoma) have hypersecretion of gastric acid, which often leads to the development of peptic ulcers (ie, Zollinger-Ellison syndrome); and so on. In contrast, patients with nonfunctional pancreatic endocrine neoplasms typically present later in the course of their disease, when their tumors begin to cause symptoms related to a mass effect.

Epidemiology

United States

Neoplasms of the endocrine pancreas occur in two distinct epidemiologic groups. Solitary tumors that develop in patients without a significant personal or family history of endocrine disorders are characterized as the sporadic form. The second form affects kindreds with the multiple endocrine neoplasia type 1 (MEN 1) syndrome in a pattern of autosomal dominant inheritance. [18] Approximately 80% of individuals with MEN 1 syndrome have one or more pancreatic neoplasms in their lifetime; gastrinoma and insulinoma are the most commonly identified lesions. [19]

Clinically recognized neoplasms of the endocrine pancreas are rare, with an overall annual incidence in the United States of 3-10 cases per million persons. [20, 21] However, the much higher prevalence of these tumors in unselected autopsy specimens, 0.5-1.5%, reflects the indolent nature of many of these tumors. [22, 23]

Insulinomas and gastrinomas occur with roughly equal annual incidences; together they account for more than half of all clinically apparent pancreatic endocrine tumors. [23] VIPomas are one-eighth and glucagonomas are one-seventeenth as common, whereas somatostatinomas are even more rare. [20] Nonfunctional tumors account for 14-48% of all recognized neoplasms of the endocrine pancreas. [24, 25]

Mortality/Morbidity

Functional neoplasms of the endocrine pancreas can produce the following morbidity as a result of their excess hormonal production:

- If untreated, patients with insulinoma can have hypoglycemic seizures and even frank coma. [26]
- Prior to the development of effective antisecretory medications (eg, histamine 2 blockers, proton pump inhibitors), patients with gastrinoma often had life-threatening gastrointestinal bleeding from peptic ulcers.
- Untreated patients with VIPoma can become severely dehydrated from diarrhea, and fatal cardiac arrhythmias can develop secondary to associated hypokalemia.
- Glucagonomas can cause diabetes, wasting, stomatitis, and other features similar to severe nutritional deficiency.

Late in the course of pancreatic endocrine neoplasms, the growth of the tumor can result in the following morbidity related to the mass effects of the disease:

- Patients with tumors in the pancreatic head occasionally have biliary obstruction, pancreatic obstruction, or both.
- Chronic abdominal pain can occur because of the compressive effects of a large intra-abdominal mass or obstructive pancreatitis.

Because of the relative rarity of pancreatic endocrine tumors in the general population, accurate rates of morbidity and mortality for persons with these lesions are difficult to determine. However, both the survival and the quality of life of patients with neoplasms of the endocrine pancreas are generally improving as a result of improvements in the modalities used to diagnose and treat these lesions (also see Prognosis).

Race-, Sex-, and Age-related Demographics

Sporadic and inherited forms of pancreatic endocrine tumors appear to occur with equal frequency among the different racial groups in the United States.

Neoplasms of the endocrine pancreas seem to have a slightly higher incidence in women than in men. [27, 18, 28] As would be expected in patients with a genetic disorder of autosomal dominant inheritance, no significant sex predilection

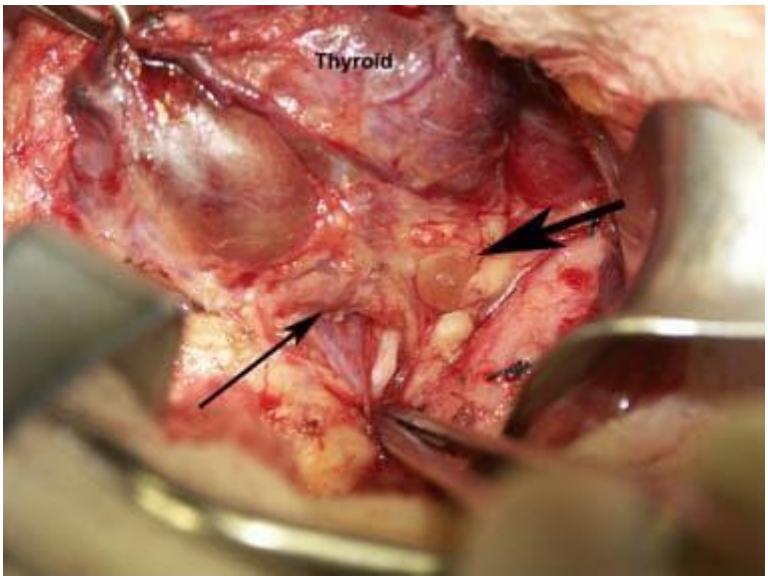
is observed among patients with pancreatic endocrine tumors as part of MEN1 syndrome. [17]

Patients with sporadic pancreatic endocrine tumors present most commonly at the age of 30-50 years. [29] In contrast, patients with pancreatic endocrine tumors that develop as part of MEN1 syndrome tend to present when younger, commonly at age 10-30 years. [18]

5. Surgical diseases of the parathyroid glands.

Practice Essentials

Through their secretion of parathyroid hormone (PTH), the parathyroid glands are primarily responsible for maintaining extracellular calcium concentrations. Hyperparathyroidism is a disease characterized by excessive secretion of parathyroid hormone, an 84–amino acid polypeptide hormone. The secretion of parathyroid hormone is regulated directly by the plasma concentration of ionized calcium. See the image below.



Normal parathyroid glands as seen during a thyroidectomy. The large arrow points to the superior parathyroid. The thinner arrow points to the inferior parathyroid. The forceps points toward the recurrent laryngeal nerve. The patient's head is toward the top right.

The main effects of parathyroid hormone are to increase the concentration of plasma calcium by increasing the release of calcium and phosphate from bone matrix, increasing calcium reabsorption by the kidney, and increasing renal

production of 1,25-dihydroxyvitamin D-3 (calcitriol), which increases intestinal absorption of calcium. Thus, overproduction of parathyroid hormone results in elevated levels of plasma calcium. Parathyroid hormone also causes phosphaturia, thereby decreasing serum phosphate levels. Hyperparathyroidism is usually subdivided into primary, secondary, and tertiary hyperparathyroidism.

Signs and symptoms of hyperparathyroidism

Primary hyperparathyroidism

Skeletal manifestations include a selective cortical bone loss. Bone and joint pain, pseudogout, and chondrocalcinosis have also been reported.

Renal manifestations include the following:

- Polyuria
- Kidney stones
- Hypercalciuria
- Nephrocalcinosis (rarely)

Gastrointestinal manifestations include the following:

- Vague abdominal pain
- Anorexia
- Nausea
- Vomiting
- Constipation
- Peptic ulcer disease
- Acute pancreatitis

Neuromuscular and psychological manifestations include the following:

- Fatigue
- Muscle weakness
- Depression
- Inability to concentrate
- Memory problems or subtle deficits

Cardiovascular manifestations include the following [1] :

- Hypertension

- Bradycardia
- Shortened QT interval
- Left ventricular hypertrophy

Workup in hyperparathyroidism

Primary hyperparathyroidism

Testing of the intact parathyroid hormone level is the core of the diagnosis. An elevated intact parathyroid hormone level with an elevated ionized serum calcium level is diagnostic of primary hyperparathyroidism. A 24-hour urine calcium measurement is necessary to rule out familial benign (hypocalciuric) hypercalcemia (FHH).

Ultrasonography of the neck is a safe and widely used technique for localization of abnormal parathyroid glands.

Secondary hyperparathyroidism

The serum level of parathyroid hormone, calcium, phosphorus, and 25-hydroxyvitamin D should be measured. Patients with secondary hyperparathyroidism usually have low-normal calcium and elevated parathyroid hormone. The serum phosphorus level may vary based on the etiology, trending towards higher values with reduced kidney function and lower values with vitamin D deficiency.

Ultrasonography may reveal thyroid pathology that was previously not recognized and that should be dealt with at the time of neck exploration.

Management of hyperparathyroidism

Primary hyperparathyroidism

Surgical excision of abnormal parathyroid glands offers the only permanent, curative treatment for primary hyperparathyroidism.

Secondary hyperparathyroidism

Unlike primary hyperparathyroidism, medical management is the mainstay of treatment for secondary hyperparathyroidism.

Nonsurgical options for the management of secondary hyperparathyroidism in chronic kidney disease (CKD) include the following:

- Dietary phosphorus restriction
- Phosphate binders
- Vitamin D and its analogs
- Calcimimetics

Tertiary hyperparathyroidism

Total parathyroidectomy with autotransplantation or subtotal parathyroidectomy is indicated.

Anatomy and Embryology

Usually, 4 parathyroid glands are situated posterior to the thyroid gland. A small number of patients have 3, 5, or, occasionally, more glands. The glands are identified based on their location as right or left and superior or inferior.

The inferior glands are derived from the third pharyngeal pouch. This structure is also the embryologic origin of the thymus. Therefore, the inferior glands originate more cephalad than the superior glands, but they migrate along with the thymus to finally become situated more inferiorly than the superior glands. Because of their embryologic association with the thymus, the inferior glands are often found adjacent to or within the thymus. They are usually located near the inferior pole of the thyroid.

The superior glands are more consistent in location, usually found just superior to the intersection of the inferior thyroid artery and the recurrent laryngeal nerve. The superior glands are derived embryologically from the fourth pharyngeal pouch. This structure also gives rise to the C cells of the thyroid gland. Because of their embryologic origin, the superior glands are occasionally found within the substance of the thyroid gland. Ectopic locations of parathyroid glands are discussed in more detail in Surgical care in Primary Hyperparathyroidism.

Primary Hyperparathyroidism

Definition of problem

Primary hyperparathyroidism is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis.

Frequency

Primary hyperparathyroidism is more common in women, the incidence being 66 per 100,000 person-years in females, and 25 per 100,000 person-years in males. In a large study of 3.5 million enrollees in Kaiser Permanente of southern California, the incidence fluctuated over time but was not seen to decrease substantially. On the contrary, the prevalence of primary hyperparathyroidism saw a substantial increase in this population.[2] The mean age at diagnosis has remained between 52 and 56 years.

Etiology

In approximately 85% of cases, primary hyperparathyroidism is caused by a single adenoma. In 15% of cases, multiple glands are involved (ie, either multiple adenomas or hyperplasia).[3] Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma. The etiology of adenomas or hyperplasia remains unknown in most cases. Familial cases can occur as either part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), hyperparathyroid-jaw tumor (HPT-JT) syndrome, or familial isolated hyperparathyroidism (FIHPT). Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism also belong to this category. The molecular genetic basis of MEN 1 is an inactivating mutation of the *MEN1* gene, located on chromosome band 11q13. MEN 2a is caused by a germline mutation of the *Ret* proto-oncogene on chromosome 10.[4] Germline mutation of *HRPT2* localized on chromosome arm 1q is responsible for HPT-JT, while FIHPT is genetically heterogeneous.

Pathophysiology

In primary hyperparathyroidism due to adenomas, the normal feedback on parathyroid hormone production by extracellular calcium seems to be lost, resulting in a change in the set point. However, this is not the case in primary hyperparathyroidism from parathyroid hyperplasia. An increase in the cell numbers is probably the cause.

The chronic excessive resorption of calcium from bone caused by excessive parathyroid hormone can result in osteopenia. In severe cases, this may result in osteitis fibrosa cystica, which is characterized by subperiosteal resorption of the

distal phalanges, tapering of the distal clavicles, salt-and-pepper appearance of the skull, and brown tumors of the long bones. This is not commonly seen now. In addition, the chronically increased excretion of calcium in the urine can predispose to the formation of renal stones.

The other symptoms of hyperparathyroidism are due to the hypercalcemia itself and are not specific to hyperparathyroidism. These can include muscle weakness, fatigue, volume depletion, nausea and vomiting, and in severe cases, coma and death. Neuropsychiatric manifestations are particularly common and may include depression, confusion, or subtle deficits that are often characterized poorly and may not be noted by the patient (or may be attributed to aging). Increased calcium can increase gastric acid secretion, and persons with hyperparathyroidism may have a higher prevalence of peptic ulcer disease. Rare cases of pancreatitis have also been attributed to hypercalcemia.

A prospective cohort study by Ejlsmark-Svensson et al reported that in patients with primary hyperparathyroidism, quality-of-life questionnaire scores were significantly lower in association with moderate-severe hypercalcemia than in relation to mild hypercalcemia. However, quality of life did not seem to be related to the presence of organ-related manifestations of primary hyperparathyroidism, such as osteoporosis, renal calcifications, and renal function impairment. [5] This suggests that hypercalcemia is the primary driver of an impaired quality of life.

Clinical presentation

History

The clinical syndrome of primary hyperparathyroidism can be easily remembered as "bones, stones, abdominal groans, and psychic moans." With the introduction of routine measurement of blood calcium in the early 1970s, the most common clinical presentation of primary hyperparathyroidism changed from severe bone disease or kidney stones to asymptomatic hypercalcemia. [6]

Skeletal manifestations of primary hyperparathyroidism include primarily a selective cortical bone loss. Bone and joint pain, pseudogout, and chondrocalcinosis have also been reported. In the early clinical descriptions of

primary hyperparathyroidism, some patients developed a peculiar type of bone disease known as osteitis fibrosa cystica, which was characterized by increased generalized osteoclastic bone resorption. Radiographic plain film changes associated with osteitis fibrosa cystica include subperiosteal resorption in the phalanges and a finding known as salt and pepper skull. This presentation is rarely seen today except in medically underserved populations.

Renal manifestations include polyuria, kidney stones, hypercalciuria, and, rarely, nephrocalcinosis.

Gastrointestinal manifestations include vague abdominal pain, anorexia, nausea, vomiting, constipation, peptic ulcer disease, and acute pancreatitis.

Neuromuscular and psychological manifestations include fatigue, muscle weakness, depression, inability to concentrate, and memory problems or subtle deficits that are often characterized poorly and may not be noted by the patient, a common description being “brain fog." These symptoms are often attributed to aging, and some patients are diagnosed with chronic fatigue syndrome or fibromyalgia.

Cardiovascular manifestations include hypertension, bradycardia, shortened QT interval, and left ventricular hypertrophy. [1]

Physical

Physical examination findings are usually noncontributory. Examination may reveal muscle weakness and depression. A palpable neck mass is not usually expected with hyperparathyroidism, although in rare cases, it may indicate parathyroid cancer. A previously undiagnosed thyroid nodule is much more commonly the source of a palpable nodule.

Diagnostic considerations

The causes of hypercalcemia that result in a concomitantly elevated parathyroid hormone level are few. These include familial benign (hypocalciuric) hypercalcemia (FHH) (see Related disorders), lithium-induced hypercalcemia, and tertiary hyperparathyroidism. A minority of patients (ie, 10-15%) with hyperparathyroidism have parathyroid hormone levels that are within the reference

range but are inappropriately high in the presence of elevated serum calcium concentrations. A subset of patients has normal calcium levels with elevated parathyroid hormone, so-called normocalcemic hyperparathyroidism. However, when considering this diagnosis, all potential causes of secondary hyperparathyroidism (eg, low calcium intake, gastrointestinal disorders, renal insufficiency, vitamin D deficiency, hypercalciuria of renal origin) should be excluded. Patients with normal calcium levels and elevated parathyroid hormone levels in the absence of an identifiable secondary cause should be monitored for progression to hypercalcemia.

Secondary and tertiary hyperparathyroidism are typically diagnosed based on their clinical context. Cancer-induced hypercalcemia is associated with a low parathyroid hormone level but possibly a high parathyroid hormone–related peptide level.

Workup

Laboratory studies

Total serum calcium and albumin levels or ionized calcium levels should be measured. Hypercalcemia should be documented on more than one occasion before a diagnostic workup is undertaken.

Testing of the intact parathyroid hormone level is the core of the diagnosis. An elevated intact parathyroid hormone level with an elevated ionized serum calcium level is diagnostic of primary hyperparathyroidism. A 24-hour urine calcium measurement is necessary to rule out FHH.

Older assays measured fragments of the parathyroid hormone molecule, such as the C-terminal or mid region of parathyroid hormone. These first-generation assays are considered obsolete for the clinical practice. Second-generation parathyroid hormone assays, globally called "intact" parathyroid hormone assays, and third-generation parathyroid hormone assays called "whole" or "biointact" parathyroid hormone assays use two different antibodies against two different segments of parathyroid hormone. Second- and third-generation parathyroid hormone assays are producing far more clinically satisfying data than

the first-generation assays but have some limitations that continue to be assessed in several studies.

Other laboratory findings in primary hyperparathyroidism include mild hyperchloremic acidosis, hypophosphatemia, and mild to moderate increase in urinary calcium excretion rate.

Vitamin D levels should be measured in the evaluation of primary hyperparathyroidism. Vitamin D deficiency (a 25-hydroxyvitamin D level of less than 20 ng per milliliter) can cause secondary hyperparathyroidism, and repletion of vitamin D deficiency can help to reduce parathyroid hormone levels. [7] In most studies, increasing serum 25-hydroxyvitamin D stores to at least 37.5 ng per milliliter is sufficient for parathyroid hormone suppression and prevention of secondary hyperparathyroidism in persons with normal renal function (although some studies have suggested increasing stores to 50 ng per milliliter). [8]

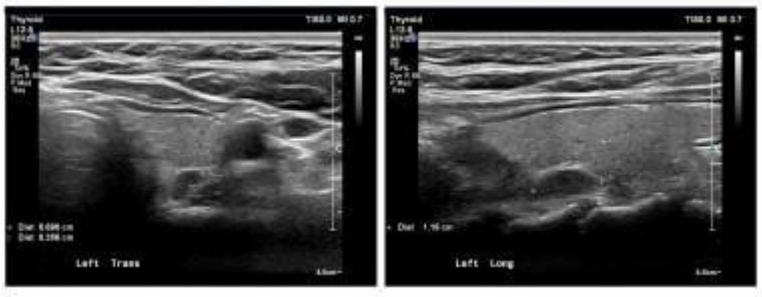
Imaging studies

Imaging studies are not used to make the diagnosis of primary hyperparathyroidism (which is based on laboratory data) or to make a decision about whether to pursue surgical therapy (which is based on clinical criteria). Imaging studies are used to guide the surgeon once surgical therapy has been decided. If a limited parathyroid exploration is to be attempted, a localizing study is necessary. Other uses of imaging studies in the initial evaluation of a patient with primary hyperparathyroidism are controversial (see Choice of surgical treatment, below).

For many patients, the recommendation remains for complete parathyroid exploration with resection of all involved glands. Many surgeons agree that imaging studies are not required when this surgical treatment is chosen. However, in patients who have recurrent or persistent hyperparathyroidism after a previous surgical exploration, an imaging test to localize involved glands is definitely indicated.

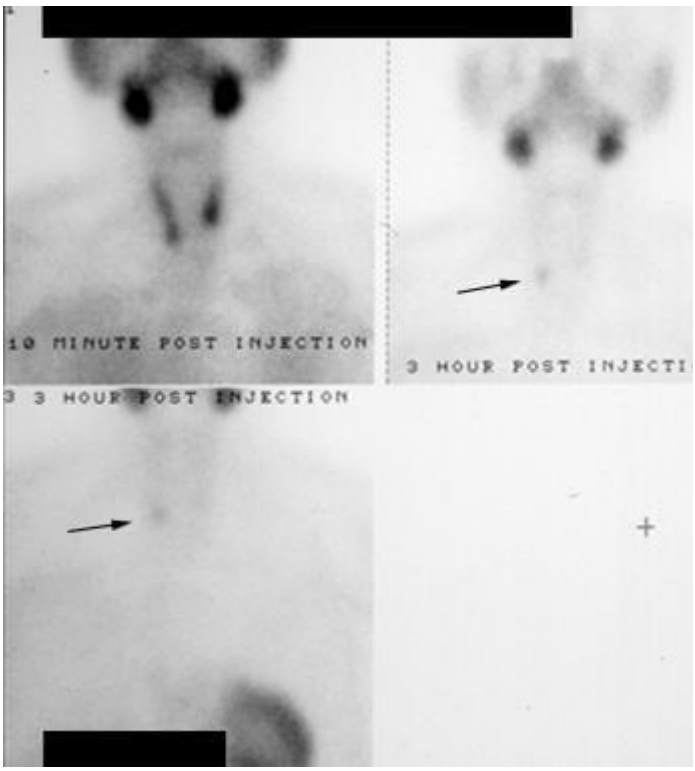
Ultrasonography of the neck is a safe and widely used technique for localization of abnormal parathyroid glands. It is capable of a high degree of

accuracy, but it is operator dependent and its reported accuracy has varied widely in the literature. One advantage of neck ultrasonography is that it can be performed rapidly by the clinician at the time of the initial evaluation. Studies of clinician-performed ultrasonography show accuracy rates that compare favorably with the accuracy of traditional radiology departments, in the vicinity of 75-80%. [9, 10, 11, 12] Ultrasonography, like nuclear medicine scanning, has not been reliable in detecting multigland disease.



The panels show a transverse and longitudinal (sagittal) view of a left superior parathyroid adenoma on ultrasonography. The caliper marks designate the adenoma. Adenomas are typically homogeneous and hypoechoic.

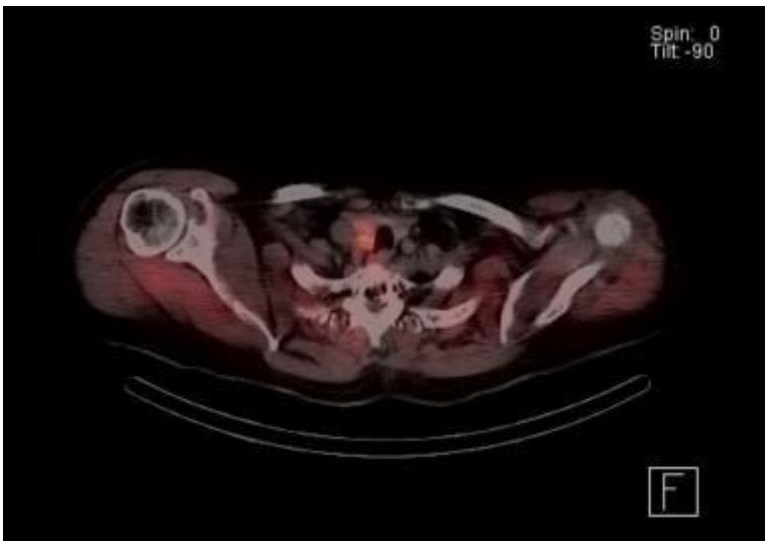
Nuclear medicine scanning with radiolabeled sestamibi is also a widely used technique. Sestamibi is commonly used in cardiac imaging and was found serendipitously to accumulate in parathyroid adenomas. This radionuclide is concentrated in thyroid and parathyroid tissue but usually washes out of normal thyroid tissue in under an hour. It persists in abnormal parathyroid tissue. See the image below.



Hyperparathyroidism. Technetium-99m (99mTc) sestamibi radionuclide scan. The early image (top left) shows uptake in the salivary glands and thyroid. The later images (right and bottom) show washout from the thyroid but persistence in the region of the right inferior thyroid lobe (arrows). This proved to be a right parathyroid adenoma.

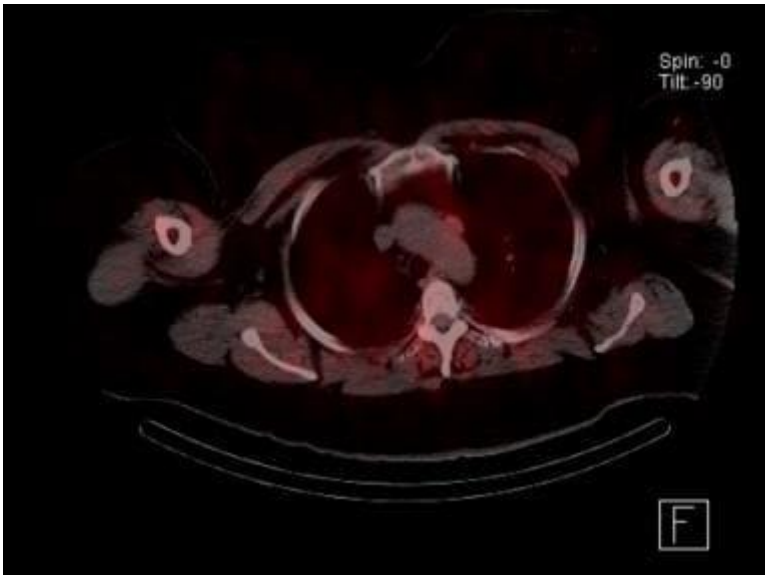
View Media Gallery

On delayed images, an abnormal parathyroid is seen as a persistent focus of activity. The scan's sensitivity for detecting solitary adenomas has varied widely in the literature but generally is reported as 60-90%. The main weakness of this test is in diagnosing multiglandular disease. In this case, sensitivity drops to approximately 50%. [3] Most modern sestamibi scans are performed with single-photon computed tomography (SPECT). This technique (see the image below) combines the detection of the radioactivity with the detailed imaging of CT scanning, allowing better sensitivity and more precise anatomic localization than standard planar imaging (as shown above).



Sestamibi parathyroid scan with SPECT scan. The orange indicates radionuclide accumulation. The findings indicate the presence of a right-sided parathyroid adenoma just behind the thyroid lobe. At exploration, this patient was found to have adjacent double adenomas on the right.

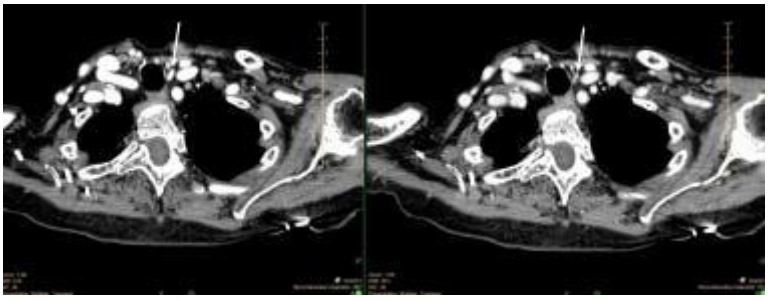
One major advantage of the sestamibi parathyroid scan is the ability to detect ectopic parathyroid glands, particularly in the mediastinum.



Sestamibi parathyroid scan with SPECT scan showing an ectopic mediastinal parathyroid adenoma adjacent to the aortic arch. This patient had undergone a failed neck exploration. A transthoracic, robotic excision was curative.

The use of four-dimensional (4D) CT scanning for parathyroid localization is increasing. [13] The study can be done either without contrast or with

dynamic contrast imaging. Parathyroid adenomas enhance brightly with contrast due to their high vascularity, and then the contrast quickly washes out. Four-dimensional CT scan studies have shown sensitivity rates as high as 88%.[14, 15] The largest retrospective study available at the time of this writing reported an overall sensitivity of 79%.[16] Like other imaging studies, 4D-CT scanning is less sensitive in detecting multiglandular disease (43-67%[17, 18]) than single-gland disease (92-94%[19, 20]). Some studies have argued that a two-phase CT scan is as effective as the 4D modality in the localization of the parathyroids, including in cases of small adenomas, reoperation, and multiglandular disease, with less radiation exposure for the patient.[21]) However, while the two-phase technique does lower radiation exposure, this is probably at the cost of optimal accuracy.[22, 20]



A small, left inferior parathyroid adenoma as demonstrated on a 4D-CT scan. The left panel is a single image from the early contrast phase showing intense enhancement. The right panel shows rapid washout of contrast. The white arrows point to the adenoma.

Magnetic resonance imaging (MRI) has not commonly been used for parathyroid localization in most centers, and studies regarding this modality have generally been small and have all utilized contrast. Newer techniques, conceptually similar to the 4D-CT scanning, are being developed that may increase the sensitivity of MRI and expand its usefulness.[23, 24, 25]

Dual-energy radiographic absorptiometry is a useful tool to demonstrate the skeletal involvement in primary hyperparathyroidism. Note that hyperparathyroidism preferentially affects the cortical bone at the radius (distal third). In cases of severe primary hyperparathyroidism, skeletal radiographs show

pathognomonic changes such as salt-and-pepper degranulation in the skull and subperiosteal bone resorption in the phalanges. However, plain radiographs are generally not useful for routine employment in the diagnosis and treatment of hyperparathyroidism.

A study by Thimmappa et al suggested that imaging studies can be used in place of intraoperative parathyroid assays (discussed below) to predict cure in surgery for primary hyperparathyroidism. The investigators described the following protocol [26] :

- Two preoperative localization studies, including one with surgeon-performed ultrasonography, are performed
- Preoperative vitamin D levels are assessed, with supplementation provided as indicated

The report contended that in select patients with strong corroboration between the two localization studies and intraoperative findings that are consistent with these studies, intraoperative parathyroid assays may not be required, with the study finding that cure rates in patients in whom this protocol was employed equaled those attained using parathyroid assays. [26]

Procedures

Bilateral internal jugular vein sampling is used to help localize ectopic parathyroid adenomas, usually in cases of failed surgical exploration when standard imaging techniques have not been helpful. This technique should generally be reserved for centers with specialists and for highly selected patients.

Treatment

Surgical excision of abnormal parathyroid glands (see below for details of surgical treatment) offers the only permanent, curative treatment for primary hyperparathyroidism. There is universal agreement that surgical treatment should be offered to all patients with symptomatic disease. The authors would note, however, that symptoms are often dismissed by both physicians and patients; fatigue is an extremely common symptom that is often ignored, especially

in the elderly, who commonly attribute it to aging or other causes. Some controversy exists regarding the optimal management of asymptomatic patients.

Guidelines for the management of asymptomatic primary hyperparathyroidism were updated in 2013 by the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism. Indications for surgery include the following [27] :

- Serum calcium >1 mg/dL above the upper limit of the reference range
- Bone mineral density T-score at or below -2.5 (in perimenopausal or postmenopausal women and in men aged 50 years or older) at the lumbar spine, total hip, femoral neck, or distal 1/3 radius
- Vertebral fracture as evidenced via radiography or vertebral fracture assessment (VFA)
- Creatinine clearance of < 60 cc/min
- Twenty-four–hour urinary calcium excretion >400 mg/day and increased stone risk as assessed through biochemical stone risk analysis.
- Presence of nephrolithiasis or nephrocalcinosis as determined using radiography, ultrasonography, or CT scanning
- Age younger than 50 years

Some clinicians advocate surgical therapy in all patients with primary hyperparathyroidism, modified only for those patients who are not able to tolerate surgery. They argue that the operation is generally well tolerated, that such treatment prevents complications (eg, osteoporosis), and that it may reverse symptoms that patients often do not realize they have (eg, fatigue, mild depression). In addition, the monitoring of asymptomatic patients is expensive and cumbersome. This more liberal approach has been articulated by an expert group convened by the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons. They concluded that "...operative management should be considered and recommended for all asymptomatic patients with PHPT [primary hyperparathyroidism] who have a reasonable life expectancy and suitable operative and anesthesia risk factors." [28] This proactive approach, as

with all parathyroidectomies, should depend on the availability of an experienced, well-trained surgeon.

A survey study by Sharata et al of primary care providers in the United States found that only a minority of respondents showed firm familiarity with management strategies for primary hyperparathyroidism. The investigators found that 31% of the 109 clinicians who responded to the survey were familiar with the whole range of criteria regarding surgical intervention in asymptomatic patients and that 34% were able to accurately identify correct surveillance testing for patients being observed. Among patients under observation, only 16% underwent proper surveillance studies. [29]

Management of severe hypercalcemia in the acute setting

Reduction of elevated serum calcium can be accomplished by the use of intravascular volume expansion with sodium chloride and loop diuretics such as furosemide once the intravascular volume is restored. Drugs such as calcitonin and IV bisphosphonate have been used as a temporary measure prior to surgical treatment.

Nonsurgical care and long-term monitoring

Asymptomatic patients who do not undergo surgery require long-term monitoring. Recommendations include assessing for overt signs and symptoms of hyperparathyroidism annually, annual serum calcium and creatinine testing, and bone mineral density (spine, hip, and forearm) evaluation every 1-2 years. [27]

Patients with primary hyperparathyroidism should maintain a moderate daily elemental calcium intake of 800-1000 mg and a vitamin D intake appropriate for their age and sex. Maintaining good hydration, participation in regular exercise activity, and avoidance of immobilization and certain medications (such as thiazides, diuretics, and lithium) are desirable.

Pharmacotherapy

Estrogen therapy in postmenopausal women has been shown to cause a small reduction in serum calcium (0.5-1 mg/dL) without a change in parathyroid hormone. Estrogen also has beneficial effects of lumbar spine and femoral neck

bone mineral density (BMD). However, due to risks associated with estrogen replacement, it should not be used for the sole purpose of treating primary hyperparathyroidism.

Selective estrogen receptor modulators such as raloxifene have been shown to cause a decrease in serum calcium of the same magnitude observed with estrogen.

Bisphosphonates, in particular alendronate, has been shown to improve the BMD at the spine and hip BMD in patients with primary hyperparathyroidism. [30, 31] No significant change in parathyroid hormone, calcium, or 24-hour urinary calcium has been reported. Treatment with a bisphosphonate such as alendronate can be considered in patients with primary hyperparathyroidism and low BMD who cannot, or will not, undergo surgery.

Calcimimetic drugs activate the calcium-sensing receptor and inhibit parathyroid cell function. [32, 33] Treatment with cinacalcet resulted in reduction without normalization of parathyroid hormone levels, reduction and even normalization of serum calcium, but no increase in BMD was observed.

Other treatments

Percutaneous alcohol injection, ablation with ultrasound energy, and other percutaneous ablation techniques of the parathyroid gland have been suggested as alternative treatments in patients with primary hyperparathyroidism who cannot or will not undergo surgery. Although studies of these techniques continue, their routine use cannot yet be supported.

Surgical care

Surgical treatment should be offered to most patients with primary hyperparathyroidism. The historical criterion-standard operative approach is complete neck exploration with identification of all parathyroid glands and removal of all abnormal glands. Approximately 85% of cases of primary hyperparathyroidism are caused by a single adenoma. Therefore, most patients who undergo full neck exploration to evaluate all parathyroids endure some unnecessary dissection. Rather than explore all parathyroid glands, a newer

technique, directed parathyroidectomy, has evolved. This technique relies on preoperative imaging studies to localize the abnormal gland. The surgeon then removes only that gland, without visualizing the other glands.

With modern imaging techniques, an abnormal parathyroid may be detected preoperatively in 70-80% of cases. However, no current imaging study is reliable for detecting multiple abnormal glands.[3] Therefore, an additional method is required to confirm that no other abnormal glands are present after excision of the imaged lesion. For this purpose, most centers use the intraoperative parathyroid hormone assay.[3, 34, 35] Because the plasma half-life of parathyroid hormone is only approximately 4 minutes, the level falls quickly after resection of the source. If the level fails to fall after resection of the identified abnormal gland, the procedure is extended to allow for further exploration. However, the intraoperative parathyroid hormone assay is usually available only in centers that perform a high volume of parathyroidectomies.

A few authors have advocated radio-guided parathyroidectomy, detecting the labeled sestamibi in the abnormal gland using a handheld probe. Most centers have abandoned this technique because if the gland labels well with sestamibi, allowing for adequate preoperative imaging, use of the handheld probe intraoperatively is unnecessary in most cases.

Greene et al examined trends in surgeons' use of bilateral versus limited exploration for parathyroidectomy between 1998 and 2008.[36] Surveying 256 surgeons (members of the American Association of Endocrine Surgeons and the American College of Surgeons), who together accounted for 46% of parathyroid operations in the United States, the investigators found that in 2008, 10% of surgeons employed bilateral neck exploration, 68% used limited exploration, and 22% used both of these exploration techniques in their practice. In 1998, the statistics for surgeons using bilateral, limited, or both types of exploration were 74%, 11%, and 15%, respectively. The study indicated that the physicians who are most likely to use limited exploration are endocrine surgeons, surgeons with a high-volume practice, and surgeons whose mentors used limited exploration.

The authors also found that in 2008, half of the general surgeons surveyed never monitored parathyroid hormone intraoperatively (whether using bilateral or limited exploration), while the same held true for less than 10% of the endocrine surgeons. In addition, there was great variation "among subsets of surgeons in operative volumes, indications for bilateral neck exploration, [follow-up] care, expertise with [ultrasonography] and sestamibi, and perceptions of cure and complication rates." Greene and his coauthors concluded that because of the many differences that exist in the surgical management of hyperparathyroidism, best-practice guidelines may need to be defined.

For familial diseases, such as MEN 1, total parathyroidectomy is performed along with cervical thymectomy and autotransplantation to the forearm. Cryopreservation of some parathyroid tissue is also recommended. [37]

Parathyroidectomy is usually well tolerated. The main risks are injury to the recurrent laryngeal nerves and hypoparathyroidism due to resection or devascularization of all parathyroid glands. Although local anesthesia has been used successfully for this procedure, especially in the directed approaches during which a single adenoma is localized preoperatively, general anesthesia is used most commonly. In patients in whom hypercalcemia (and, therefore, dehydration) has been severe, special attention must be directed to perioperatively restoring the fluid balance. Neck mobility must be assessed to ensure proper positioning in the operating room.

Technique for full neck exploration with identification of all parathyroid glands

The most critical aspect to ensure success in this operation is identification of all 4 parathyroid glands and removal of all abnormal glands. In the case of 4-gland hyperplasia, a 3.5-gland (subtotal) parathyroidectomy is performed. Approximately 50-70 mg of the most normal-appearing tissue is left behind. A nonabsorbable suture is left as a tag to identify the gland should reoperation be necessary.

The patient is placed in the lawn-chair position with the neck extended over a transversely placed shoulder roll. This position allows full exposure of anterior neck structures and improves venous drainage.

A low transverse incision placed within a skin crease provides the best cosmetic result. The length of the incision must be adequate to allow thorough exploration of all potential locations of the parathyroid glands; however, given the elasticity of the neck skin flaps, a 2- to 5-cm incision usually allows safe identification of important structures.

After hemostasis of the skin incision is obtained, subplatysmal flaps are developed superiorly to the notch of the thyroid cartilage and inferiorly to the flat portion of the manubrium. The sternohyoid and sternothyroid (strap) muscles are separated in the midline to expose the thyroid gland. If preoperative localization studies suggest a parathyroid adenoma, that side is approached first.

Frequently, a middle thyroid vein may require ligation to ensure adequate mobilization of the thyroid lobe. The thyroid lobe is elevated off the common carotid artery and retracted medially. The inferior thyroid artery is identified after blunt and sharp dissection of the areolar tissue anteriorly and medially to the common carotid artery and posteromedially to the thyroid lobe. The recurrent laryngeal nerve is identified next, inferior and lateral to the lower lobe of the thyroid gland.

The intersection of the inferior thyroid artery and the recurrent laryngeal nerve is an important landmark because most parathyroid glands, superior and inferior, are located within 2 cm of this area. The superior parathyroid glands are located dorsal to the upper two thirds of the thyroid lobe and posterior to the recurrent laryngeal nerve. The inferior glands, which are less consistent in location, can usually be found inferior to the inferior thyroid artery and ventral to the recurrent laryngeal nerve. They are usually within 1 cm of the inferior lobe of the thyroid gland.

Occasionally, not all parathyroid glands can be identified. In such instances, the usual locations are reexamined first because most parathyroid glands are

located in typical areas. If parathyroid glands are not identified in those locations, then a systematic search is performed, taking into consideration the path of descent of superior and inferior parathyroid glands.

Inferior glands may be located in the thyrothymic ligament. They may be difficult to identify, especially after division of the inferior thyroid vein, a maneuver that allows the gland to retract into the superior mediastinum. Another location for ectopic inferior parathyroid glands is the thymus. If an inferior gland cannot be located, a cervical thymectomy can be performed, elevating as much thymic tissue superiorly from the mediastinum as can be done safely.

Superior parathyroid glands are usually dorsal to the upper two thirds of the thyroid gland. Occasionally, these glands are adjacent to the superior thyroid vessels. Other locations include the carotid sheath or posterior to the esophagus or pharynx (retroesophageal). Finally, both superior and inferior parathyroid glands may be located aberrantly within the capsule of the thyroid gland. Some surgeons perform a thyroid lobectomy on the side of the missing abnormal gland after an exhaustive search is made in the aforementioned locations. Median sternotomy should generally not be performed during the initial neck exploration for hyperparathyroidism.

Abnormally enlarged glands are excised after confirmation of the normal size of other glands. During excision, avoiding capsular rupture of the abnormal gland is important because this may be associated with implantation of parathyroid cells in the operative site and subsequent parathyromatosis. Parathyroids may be identified by highly experienced surgeons based on appearance and location. If necessary, identification of the parathyroid glands should be confirmed histologically by frozen section examination. In cases of total parathyroidectomy with autotransplantation, parathyroid tissue should be cryopreserved for future autotransplantation in case the initial transplant does not function adequately.

Technique for directed parathyroidectomy

In many respects, the operative technique is similar to that described above for a complete parathyroid exploration. Differences are noted below.

Adequate imaging of the abnormal gland prior to surgery is essential. In addition, arrangements for intraoperative measurement of parathyroid hormone should be confirmed. [3] A line for sampling of peripheral venous blood should be established. Often, the distal saphenous vein provides the most convenient access.

Some surgeons modify the location of the incision based on the preoperative location of the adenoma. This author prefers a small incision (ie, ~2 cm) in the standard location for a collar incision. This incision can be readily extended should extensive exploration prove necessary.

A baseline parathyroid hormone level is drawn immediately prior to skin incision. Following identification and dissection of the adenoma, a preexcision level is drawn. Manipulation of the gland occasionally causes significant increases, sometimes of more than 10-fold, in the parathyroid hormone level. Following excision of the gland, parathyroid hormone levels are drawn at 5 minutes and 10 minutes postexcision. Criteria for adequate excision are either a 50% drop in parathyroid hormone from the baseline level to the 10-minute postexcision level or a 50% drop in parathyroid hormone from the preexcision level at 10 minutes and a postexcision level below the baseline level. [38]

The incision may be closed while the last parathyroid hormone levels are being processed, but the patient should remain under anesthesia, and the sterile field maintained until the parathyroid hormone assay results are known.

If a directed parathyroidectomy is performed successfully, most of these patients may be safely discharged the day of surgery.

Complications and postoperative care

For a full parathyroid exploration, postoperative hypoparathyroidism and hypocalcemia are concerns, but they are extremely uncommon after a directed parathyroidectomy and limited neck exploration. Hypocalcemia is more common after bilateral parathyroid exploration, especially when subtotal parathyroidectomy is performed. The nadir of serum calcium usually occurs 24-72 hours postoperatively. Many patients become hypocalcemic, but few become symptomatic. On the other hand, even when a limited exploration has been done,

mild symptoms of hypocalcemia can occur in the first few days after parathyroidectomy in the absence of verifiable hypocalcemia. Because of this, some practitioners routinely administer oral calcium supplements postoperatively.

Hypocalcemia after parathyroid surgery may be due to hungry bone syndrome where calcium and phosphorus are rapidly deposited in the bone. This is characterized by hypoparathyroidism and transient, but occasionally severe, hypocalcemia until the normal glands regain sensitivity.

If hypoparathyroidism persists, oral supplementation with calcium and vitamin D is required. Calcium citrate or calcium carbonate may be started at 400-600 mg of elemental calcium four times per day. Some patients require substantially more. Calcitriol is started at 0.5 mcg twice daily and increased as required. Patients in whom total parathyroidectomy and autotransplantation is performed can be expected to require temporary calcium supplementation.

If a recurrent laryngeal nerve is transected during parathyroidectomy, immediate repair is indicated. If the recurrent nerve is not known to be injured intraoperatively but dysfunction is suggested because the patient has developed new hoarseness, expectant management is chosen initially since most patients recover nerve function over a few weeks to months. Laryngoscopy is indicated to document both dysfunction and recovery of function.

A potential life-threatening emergency in the postoperative period is the development of an expanding hematoma in the pretracheal space. This complication must be recognized and treated immediately by opening the wound and evacuating the hematoma. If untreated, laryngeal edema may progress rapidly, causing airway obstruction. Moreover, the edema may prevent endotracheal intubation, and opening of the wound should precede any intubation attempt.

Most small hematomas do not require treatment. A subplatysmal fluid collection may occasionally form, and these are usually treated adequately with a single aspiration. In a few cases, aspiration may need to be repeated. Rarely, a drain may need to be placed for recurrent fluid collections.

Treatment outcomes

Cure rates after surgery for primary hyperparathyroidism are very high in expert hands, approximately 97-98%. [39] A cure is generally defined as normalized serum calcium. Parathyroid hormone levels, however, may be elevated postoperatively in as many as 20-40% of patients. If the serum calcium remains within the reference range, this elevated state does not usually suggest persistent disease but may indicate a higher risk of recurrence. [40, 41, 42, 43, 44, 45, 46, 47] Many patients with primary hyperparathyroidism have vitamin D deficiency, and replacement may correct the elevated parathyroid hormone concentration. [48] There is also some weak evidence that calcium supplementation may decrease an isolated elevation in parathyroid hormone after parathyroidectomy. [46]

Quality of life has been shown repeatedly to be improved after parathyroidectomy. [49, 5] Notably, quality of life has also been found to undergo measurable improvement in "asymptomatic" patients, which underscores the fact that some mild symptoms may go unnoticed by patients and clinicians. [50]

A systematic literature review by Livschitz et al indicated that in patients with primary hyperparathyroidism, sustained improvement in quality of life can be achieved through parathyroidectomy. Quality of life was evaluated using such tools as the 36-Item Short Form Health Survey and the Parathyroidectomy Assessment of Symptoms score, with a median follow-up period of 1 year. In 27 out of 31 studies (87%), scores revealed significant, long-term improvement in quality of life, with the other reports showing mixed results. [51]

Follow-up

Patients are seen 1-2 weeks postoperatively, and serum calcium, 25-hydroxyvitamin D levels, and parathyroid hormone levels are obtained. Vitamin D deficiency is particularly common in patients with hyperparathyroidism. Many practitioners routinely add calcium and vitamin D supplementation postoperatively to help restore bone loss and supplement poor dietary intake.

Analysis has shown that the recurrence rate after successful parathyroidectomy is approximately 10-15% with long-term follow-up, which is

much higher than had historically been thought.[52, 53] Long-term follow-up is therefore recommended, with annual calcium and parathyroid hormone determinations.

Secondary Hyperparathyroidism

Definition of problem

Secondary hyperparathyroidism is the overproduction of parathyroid hormone secondary to hypocalcemia, typically as a result of vitamin D deficiency and/or chronic kidney disease (CKD).[54]

Frequency

Vitamin D deficiency has been estimated to affect approximately 40% of US adults, according to data from the National Health and Nutrition Examination Survey (NHANES).[55]. Deficiency of the vitamin in adults has been attributed to decreases in sun exposure, changes in dietary intake, gastrointestinal disorders such as malabsorption syndromes and pancreatic insufficiency, and liver failure with decreased hydroxylation. In CKD, secondary hyperparathyroidism is common and varies based on estimated glomerular filtration rate (eGFR). In milder forms of CKD, elevations in parathyroid hormone levels occur in about 10% of patients, with the prevalence increasing to 90% of individuals with severe CKD who are approaching the need for dialysis therapy.[56]

Etiology

Secondary hyperparathyroidism results from a chronic stimulus of the parathyroid gland to release parathyroid hormone. Parathyroid hormone release is increased in the setting of hypocalcemia and hyperphosphatemia and is decreased by fibroblast growth factor 23 (FGF-23).

Parathyroid hormone acts on bone to release calcium into the blood and activates 1 alpha hydroxylation in the kidney to form 1,25-dihydroxvitamin D, which in turn increases calcium absorption in the gastrointestinal tract. The rise in calcium detected by the calcium-sensing receptor on the parathyroid gland reduces the stimulus for parathyroid hormone excretion.

Pathophysiology

Calcium and phosphorous homeostasis is tightly regulated between bone, the kidney, and the parathyroid gland. Key modulators of calcium and phosphorous include FGF-23, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and parathyroid hormone. FGF-23 is released from bone due to increasing serum phosphorus levels and acts in the kidney to increase phosphorous excretion and decrease 1 alpha hydroxylation of 25-hydroxyvitamin D. FGF-23, along with serum phosphorous, also decreases parathyroid hormone secretion, to maintain calcium and phosphorous balance. In CKD, stages 3-5 (eGFR < 59 mL/min), FGF-23 levels increase, initially leading to phosphaturia and decreased parathyroid hormone excretion. As the CKD progresses, there is a resistance in the kidney and parathyroid gland to FGF-23 and a deficiency in the kidney of 1 alpha hydroxylation of vitamin D, both of which contribute to reduced phosphorous excretion. The deficiency of 1,25-dihydroxyvitamin D, along with the decreased phosphorus excretion, results in hypocalcemia and hyperphosphatemia, thereby maintaining stimulation of parathyroid hormone synthesis and parathyroid gland hyperplasia.

Clinical presentation

Because virtually all patients with CKD have hyperparathyroidism to some degree, there is not a unique clinical presentation that is a hallmark of secondary hyperparathyroidism. Often, secondary hyperparathyroidism is discovered on routine laboratory testing when monitoring individuals with CKD. In patients with secondary hyperparathyroidism due to vitamin D deficiency, the symptoms result mainly from the vitamin deficiency (and include increased fracture risk in osteomalacia, and, rarely, myopathy). In advanced cases of secondary hyperparathyroidism, some patients may have bone pain.

Workup

Laboratory studies

The serum level of parathyroid hormone, calcium, phosphorus, and 25-hydroxyvitamin D should be measured. Patients with secondary hyperparathyroidism usually have low-normal calcium and elevated parathyroid

hormone. The serum phosphorus level may vary based on the etiology, trending towards higher values with reduced kidney function and lower values with vitamin D deficiency.

Vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 12 ng/mL. A level of 12-20 ng/mL may be considered insufficiency of vitamin D, and a level of 20 ng/mL or greater can be considered to indicate sufficient vitamin D. [57]

Imaging studies

Since all parathyroid glands will be affected in secondary hyperparathyroidism, localizing studies are not necessary, although they are increasingly being performed. Ultrasonography is noninvasive and may reveal thyroid pathology that was previously not recognized and that should be dealt with at the time of neck exploration. Bone density may be determined to assess the severity of bone disease. Radiographs of sites of bone pain are reasonable but seldom necessary. Hand radiographs may show characteristic subperiosteal erosions.

Treatment

Medical care

Unlike primary hyperparathyroidism, medical management is the mainstay of treatment for secondary hyperparathyroidism.

Correcting vitamin D deficiency may be achieved using cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2). Recommended therapy for patients with vitamin D deficiency is 50,000 IU of vitamin D2 or D3 once a week for 8 weeks and then supplementation with 800 IU daily indefinitely.

For patients with CKD, the National Kidney Foundation (NKF) published clinical practice guidelines as part of its Kidney Disease Outcomes Quality Initiative (KDOQI). In general, it has been recommended to reduce parathyroid hormone levels to within a range that supports normal bone turnover and minimizes ectopic calcification.

The following is a list of current nonsurgical treatment options for management of secondary hyperparathyroidism in CKD:

- Dietary phosphorus restriction may be initiated if parathyroid hormone is elevated despite sufficient 25-hydroxyvitamin D (>20 ng/mL).
- Phosphate binders may be considered if hyperphosphatemia persists despite dietary phosphate restriction. These include calcium-based phosphate binders such as calcium carbonate or calcium acetate and non–calcium-based phosphate binders such as sevelamer hydrochloride, lanthanum carbonate, ferric citrate, or sucroferric oxyhydroxide.
- Non–calcium-based binders are generally preferred for use over calcium-based binders due to concern that excess calcium supplementation may increase coronary artery calcification and cardiovascular risk. [58]
- Vitamin D and its analogs may be used—including calcitriol and analogs of calcitriol such as calcifediol, paricalcitol, doxercalciferol, maxacalcitol, and falecalcitriol—to treat hypocalcemia and secondary hyperparathyroidism. [59] Treatment with calcimimetics such as cinacalcet leads to significant improvements in biochemical parameters, but patient-based benefits have not yet been demonstrated.
- The newest class of drugs to reduce the parathyroid hormone level, the aforementioned calcimimetics—which includes etelcalcetide (Parsabiv) and cinacalcet (Sensipar)—binds to and activates the calcium-sensing receptor. Activation of this receptor on parathyroid chief cells decreases parathyroid hormone secretion. Etelcalcetide can be administered intravenously at the end of hemodialysis sessions. Its approval was based on randomized, double-blind trials that compared the drug to placebo and cinacalcet. Patients in both studies were on hemodialysis and had moderate to severe secondary hyperparathyroidism. Those taking etelcalcetide had a significantly greater chance of reaching the primary efficacy endpoint (>30% reduction from baseline in mean predialysis parathyroid concentration at 20-27 weeks) than did patients receiving placebo (74-75.3%

vs 8.3-9.6%, respectively). [54] When compared with cinacalcet, etelcalcetide was superior in decreasing parathyroid hormone levels over the span of 26 weeks. [60]

- The EVOLVE (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) trial was one of the first large-scale, randomized controlled trials in patients with ESRD to examine the treatment of secondary hyperparathyroidism with cinacalcet vs placebo along with standard of care phosphorous binders and vitamin D analogs. Hyperphosphatemia and hyperparathyroidism have been associated with increased risk of death in ESRD patients and this trial was designed to see if there was a mortality benefit in the use of the noncalcium/non–vitamin D analog cinacalcet in the ESRD population. The results of the trial demonstrated that cinacalcet did not result in improved mortality or improve cardiovascular endpoints. The use of cinacalcet did reduce the need for parathyroidectomy for refractory hyperparathyroidism. Of note, there was an increased risk of serious adverse events, namely hypocalcemia, with the use of cinacalcet. In conclusion, despite aggressive management of secondary hyperparathyroidism that is associated with increased mortality in ESRD patients, cinacalcet did not offer a cardiovascular or mortality benefit in this population of patients. [61]

Surgical care

Indications for surgery include bone pain or fracture, pruritus, calciphylaxis (see Related Disorders), and extraskeletal nonvascular calcifications with elevated parathyroid hormone levels despite appropriate medical therapy. Parathyroidectomy can be considered in patients with severe hyperparathyroidism (persistent serum levels of intact parathyroid hormone greater than 800 pg/mL [88.0pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that is refractory to medical therapy.

A study by Hsu et al indicated that in patients with severe secondary hyperparathyroidism resulting from end-stage renal disease, parathyroidectomy

reduces the risk of peripheral arterial disease. In the end-stage renal disease patients who underwent parathyroidectomy (947 patients, 5.08-year follow-up), the incidence density rate of peripheral arterial disease was 12.26 per 1000 person-years, compared with 24.09 per 1000 person-years in those who did not undergo the surgery (3746 patients, 4.52-year follow-up). [62]

Mortality has been shown to be reduced in dialysis patients who undergo parathyroidectomy for severe secondary hyperparathyroidism.

Surgical treatment of severe secondary hyperparathyroidism may also improve quality of life. In a meta-analysis of patients with secondary hyperparathyroidism treated with cinacalcet or parathyroidectomy, quality of life was seen to improve after surgical treatment but not with medical therapy. [63] However, available studies into quality of life in such cases are observational, and randomized, comparative data are not available.

Surgical technique

The general surgical technique in secondary hyperparathyroidism involves complete parathyroid exploration, as described previously for primary hyperparathyroidism. All four glands must be exposed, and biopsies are taken if needed to ensure correct identification. In most cases, diffuse hyperplasia is encountered, although the size of the glands can be significantly heterogeneous.

The treatment procedure of choice is either total parathyroidectomy with autotransplantation or subtotal parathyroidectomy. In a study by Rothmund et al, a randomized, controlled trial of total versus subtotal parathyroidectomy for secondary hyperparathyroidism, the investigators found that four of 17 subjects treated with subtotal parathyroidectomy developed recurrent hypercalcemia, with two requiring reexploration. None of the subjects treated with total parathyroidectomy developed recurrent hypercalcemia. [64] A subtotal parathyroidectomy has the advantage of less dramatic postoperative hypocalcemia. However, reoperative neck exploration is required in the case of recurrence, which can be very difficult. Another approach is to perform total parathyroidectomy without autotransplantation. Good results have been reported, but at present this

procedure should be considered investigational and should be reserved only for patients in whom future transplantation is not an option. [65, 66, 67]

Parathyroid autotransplantation is usually performed after a total parathyroidectomy. Briefly, about 100 mg of parathyroid tissue is cut into approximately 12-20 pieces, each of which measures about 1 x 1 mm. These are inserted into pockets in the forearm, either in the subcutaneous tissue or the musculature (the forearm being chosen primarily for convenience). After surgery, blood draws from the antecubital fossa above the transplantation site can be compared with blood drawn from the contralateral side to assess graft function. The site may be marked with a polypropylene suture on the fascia for localization later, if necessary. We also use clips to facilitate localization with ultrasonography. Parathyroid tissue may also be cryopreserved in case the primary autotransplant fails.

Most patients require admission after subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Hypocalcemia is to be expected and is often severe, especially in persons who have had a history of very high parathyroid hormone levels for many years. Although hypocalcemia is usually more severe after total parathyroidectomy with autotransplantation, it can occur after subtotal parathyroidectomy as well. A constant calcium infusion is often required, and oral calcium and calcitriol requirements can be quite high. The target calcium level should typically be below the normal range but above the level at which the patient is symptomatic. The patient can be discharged when he or she is able to maintain a safe calcium level on oral supplements. Typically, the patient can be weaned off of these over a period of weeks to a few months.

Outcome and prognosis

Medical treatment of secondary hyperparathyroidism is successful in most patients. Patients who require parathyroidectomy have approximately a 10% risk of recurrent or persistent disease. This may be due to a hyperfunctioning or missed neck gland or hyperplasia of the autograft. Occasionally, a patient has persistent hypoparathyroidism after operation. If tissue has been cryopreserved,

transplantation may reverse hypoparathyroidism. If hypoparathyroidism is permanent, lifelong calcium and calcitriol supplementation is necessary.

Tertiary Hyperparathyroidism

Definition of problem

Tertiary hyperparathyroidism is a state of excessive secretion of parathyroid hormone after longstanding secondary hyperparathyroidism and resulting in hypercalcemia. Some authorities reserve the term for secondary hyperparathyroidism that persists after successful renal transplantation.

Etiology

Tertiary disease is characterized by the development of autonomous hypersecretion of parathyroid hormone causing hypercalcemia. The etiology is unknown but may be due to monoclonal expansion of parathyroid cells (nodule formation within hyperplastic glands). A change may occur in the set point of the calcium-sensing mechanism to hypercalcemic levels. Four-gland involvement occurs in most patients.

Pathophysiology

Tertiary hyperparathyroidism is observed most commonly in patients with chronic secondary hyperparathyroidism who have been on dialysis therapy for years. The hypertrophied parathyroid glands enlarge over time and continue to oversecrete parathyroid hormone, despite serum calcium levels that are within the reference range or even elevated. In these cases, the hypertrophied glands become autonomic and cause hypercalcemia, even after withdrawal of calcium and active vitamin D therapy. They also may become resistant to calcimimetic treatment. [68, 69] This type of tertiary disease is particularly dangerous because the phosphate level is often elevated. If the calcium value multiplied by the phosphate value yields a high product, diffuse calcinosis may occur.

Clinical presentation

The clinical manifestations of tertiary hyperparathyroidism are related to the effects of hypercalcemia and hyperphosphatemia, including bone pain, pruritus, fatigue, lethargy, and increased risk for fractures.

Treatment

Total parathyroidectomy with autotransplantation or subtotal parathyroidectomy is indicated.

Related Disorders

Familial benign (hypocalciuric) hypercalcemia

Familial benign (hypocalciuric) hypercalcemia (FHH) is caused by a loss-of-function mutation of one allele of the gene for the calcium-sensing receptor (*CaR*). It causes hypercalcemia, hypophosphatemia, and hypermagnesemia. The parathyroid hormone level is usually within the reference range or is mildly elevated. It can be distinguished from primary hyperparathyroidism by low 24-hour urinary calcium excretion. Persons with FHH are asymptomatic. Parathyroidectomy is not indicated.

Hypercalcemia of malignancy

This disorder is usually caused by tumor release of a hormone called parathyroid hormone -related peptide. Less commonly, hypercalcemia of malignancy is caused by local osteolytic lesions and, rarely, by overproduction of 1,25-dihydroxyvitamin D. This disorder is the most common cause of hypercalcemia in hospitalized patients. The hypercalcemia of malignancy results in a low or undetectable intact parathyroid hormone level. Usually, it is easily distinguished from hyperparathyroidism. Only a few cases of ectopic production of true parathyroid hormone are reported in the literature.

Calciphylaxis

Calciphylaxis, also known as uremic gangrene syndrome, is a rare disorder observed in patients with CKD, typically ESRD, and secondary or tertiary hyperparathyroidism. It is characterized by ischemic necrosis of the skin due to calcium phosphate crystal deposition and subsequent inflammation in small-to-medium–sized vessels. The exact mechanism is unknown because the product of the calcium value multiplied by the phosphate value is often near the reference range. The disease is often fatal. There is some evidence that the use of sodium thiosulfate, a chelator of calcium and iron, may improve wound healing and

outcomes in patients with calciphylaxis.[70] Total parathyroidectomy may also reverse the necrosis and is occasionally done emergently.

Practice Essentials

Hypoparathyroidism is a condition of parathyroid hormone (PTH) deficiency. Primary hypoparathyroidism is a state of inadequate PTH activity. In the absence of adequate PTH activity, the ionized calcium concentration in the extracellular fluid falls below the reference range. Primary hypoparathyroidism, the subject of this article, is a syndrome resulting from iatrogenic causes or one of many rare diseases.[1, 2, 3]

Secondary hypoparathyroidism is a physiologic state in which PTH levels are low in response to a primary process that causes hypercalcemia. The primary processes that lead to hypercalcemia are discussed in other articles.

Treatment of patients with hypoparathyroidism involves correcting the hypocalcemia by administering calcium and vitamin D.[4] Recombinant human PTH (rhPTH[1-84], Natpara) is commercially available in the United States and is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

Signs and symptom of hypoparathyroidism

Signs and symptoms of hypoparathyroidism can include the following:

- Muscle cramps involving the lower back, legs, and feet are common in patients with hypoparathyroidism and hypocalcemia
- Increased neuromuscular irritability from hypoparathyroidism-induced hypocalcemia can be found at beside by eliciting the Chvostek and Trousseau signs
- Hypocalcemia of primary hypoparathyroidism may cause extrapyramidal choreoathetoid syndromes in patients with basal ganglia calcifications[5]
- Parkinsonism, dystonia, hemiballismus, and oculogyric crises may occur in approximately 5% of patients with idiopathic hypoparathyroidism[6]
- Spastic paraplegia, ataxia, dysphagia, and dysarthria have been documented in association with hypoparathyroidism-induced hypocalcemia

- Emotional instability, anxiety, depression, confusion, hallucinations, and psychosis have been described in patients with hypoparathyroidism when the calcium level is low
- Chronic hypocalcemia, as observed in primary hypoparathyroidism, is associated with ocular cataracts, abnormal dentition, and dry, puffy, coarse skin
- In severe hypocalcemia, a prolongation of the QT interval is observed on electrocardiography (ECG), and congestive heart failure may develop
- In patients with autoimmune polyglandular syndrome, idiopathic hypoparathyroidism is associated with adrenal insufficiency and moniliasis

Workup in hypoparathyroidism

Laboratory tests in the workup of hypoparathyroidism include parathyroid and hormone studies, with primary hypoparathyroidism being defined by a low concentration of PTH with a concomitant low calcium level.

Moreover, measurement of 25-hydroxy vitamin D is important to exclude vitamin D deficiency as a cause of hypocalcemia.

Serum magnesium is measured because hypomagnesemia may cause PTH deficiency and subsequent hypocalcemia.

Also, serum phosphorus levels are tested because PTH is a phosphaturic hormone; in its absence, phosphorus levels in the blood rise.

Management of hypoparathyroidism

Treatment of patients with hypoparathyroidism involves correcting the hypocalcemia by administering calcium and vitamin D. [4]

A diet rich in calcium content (ie, emphasizing dairy products) is recommended for patients with primary hypoparathyroidism.

Patients undergoing parathyroidectomy for parathyroid hyperplasia are at high risk of developing permanent primary hypoparathyroidism. Patients may be treated with an autotransplant of a segment of parathyroid gland to prevent hypoparathyroidism. [7] This autotransplant is usually placed subcutaneously in the

forearm or in the neck. If the autotransplantation fails, patients receive the same treatment that is administered to other patients with hypoparathyroidism.

Pathophysiology

The ionized calcium concentration in the extracellular fluid (ECF) remains nearly constant, at a level of approximately 1 mM. Ionized calcium in the ECF is in equilibrium with ionized calcium in storage pools such as bone, proteins in the circulation, and within the intracellular fluid. The intracellular fluid concentration of calcium is more than 10,000-fold lower than in the ECF. The maintenance of ionized calcium concentrations in the intracellular and extracellular fluids is highly regulated and modulates the functions of bone, renal tubular cells, clotting factors, adhesion molecules, excitable tissues, and a myriad of intracellular processes.

An extracellular calcium-sensing receptor has been isolated from parathyroid, kidney, and brain cells. The extracellular calcium-sensing receptor is G protein coupled. Mutations in the extracellular calcium-sensing receptor have been demonstrated to result in hypercalcemic or hypocalcemic states. Normally, the extracellular calcium-sensing receptor is extremely sensitive and responds to changes in the ECF calcium ion concentration of as small as 2%.

In parathyroid cells, the extracellular calcium-sensing receptor regulates the secretion of PTH. Inactivating mutations of the extracellular calcium-sensing receptor lead to hypercalcemia, as observed in familial hypocalciuric hypercalcemia (heterozygous mutation) and neonatal severe hyperparathyroidism (homozygous mutation). Conversely, activating mutations of the extracellular calcium-sensing receptor lead to hypocalcemia, as observed in some families with autosomal-dominant hypocalcemia.

The intracellular mechanism(s) whereby activation of the extracellular calcium-sensing receptor leads to inhibition of PTH exocytosis is unknown. Because pertussis toxin blocks the inhibition of cyclic adenosine monophosphate (cAMP), but not PTH, in response to a high ECF ionized calcium concentration, cAMP is probably not an important second messenger for the extracellular

calcium-sensing receptor. Candidate second messengers include protein kinase C, phospholipase A2, and intracellular calcium.

Conversely, a fall in ECF ionized calcium concentration leads to exocytosis of PTH. PTH has the overall effect of returning the ECF ionized calcium concentration to the reference range by its effects on the kidneys and the skeleton.

PTH activates osteoclasts. Osteoclast activation results in bone resorption and a release of ionized calcium into the ECF. Evidence suggests that small pulse doses of PTH activate osteoblasts, with ensuing bone deposition. The effect of PTH on osteoclasts seems more important than the effect on osteoblasts.

PTH inhibits the proximal tubular transport of phosphate from the lumen to the interstitium. In conditions of primary PTH excess, hypophosphatemia tends to occur. Conversely, in hypoparathyroidism, the phosphate concentration in the plasma is within the reference range or slightly elevated.

PTH has a calcium-retaining effect on the distal tubule. The PTH-mediated calcium reabsorption is independent of any effects on sodium or water reabsorption. This effect of PTH is important in hypoparathyroidism because, in the absence of this distal tubular calcium reabsorption, the kidneys waste calcium. This depletes the ECF ionized calcium and increases the urinary calcium concentration.

PTH stimulates renal 1-alpha-hydroxylase, the enzyme that synthesizes formation of 1,25-dihydroxy vitamin D; 1,25-dihydroxy vitamin D allows for better dietary calcium absorption. Thus, 1,25-dihydroxy vitamin D has a synergistic effect with PTH; both contribute to a rise in the ECF ionized calcium concentration.

In the absence of PTH, bone resorption, phosphaturic effect, renal distal tubular calcium reabsorption, and 1,25-dihydroxy vitamin D–mediated dietary calcium absorption cannot occur. Therefore, the consequence of PTH deficiency is hypocalcemia.

Epidemiology

Hypoparathyroidism has an estimated prevalence in the United States of 37 per 100,000 person-years. In Denmark, it is estimated to be 22 per 100,000 person-years. [8]

Age-related demographics

A study by Powers et al found 74% of US hypoparathyroid patients to be aged 45 years or older. [9]

Sex-related demographics

In the United States, 75% of hypoparathyroidism cases are in females and 25% in males. [1] Similarly, in an Italian study, Cipriani et al found the rate of hospitalizations for hypoparathyroidism in women and men to be 72.2% and 27.8%, respectively.

6. Minimally invasive surgical technologies in angiology.

Angiology (from Greek ἀγγεῖον, angeīon, "vessel"; and -λογία, -logia) is the medical specialty dedicated to studying the circulatory system and of the lymphatic system, i.e., arteries, veins and lymphatic vessels.

In the UK, this field is more often termed angiology, and in the United States the term vascular medicine is more frequent. The field of vascular medicine (angiology) is the field that deals with preventing, diagnosing and treating vascular and blood vessel related diseases.

Overview

In minimally invasive surgery, doctors use a variety of techniques to operate with less damage to the body than with open surgery. In general, minimally invasive surgery is associated with less pain, a shorter hospital stay and fewer complications.

Laparoscopy — surgery done through one or more small incisions, using small tubes and tiny cameras and surgical instruments — was one of the first types of minimally invasive surgery. Another type of minimally invasive surgery is robotic surgery. It provides a magnified, 3D view of the surgical site and helps the surgeon operate with precision, flexibility and control.

Continual innovations in minimally invasive surgery make it beneficial for people with a wide range of conditions. If you need surgery and think you may be a candidate for this approach, talk with your doctor.

Types of minimally invasive surgery

Surgeons perform many minimally invasive surgeries on specific parts of the body, including:

- Adrenalectomy to remove one or both adrenal glands
- Brain surgery
- Colectomy to remove parts of a diseased colon
- Gallbladder surgery (cholecystectomy) to relieve pain caused by gallstones
- Heart surgery
- Hiatal hernia repair, sometimes called anti-reflux surgery, to relieve gastroesophageal reflux disease (GERD)
- Kidney transplant
- Nephrectomy (kidney removal)
- Spine surgery
- Splenectomy to remove the spleen

Minimally invasive surgery can also be used for more general surgeries, including the following:

- Cancer surgery, for example, to destroy a tumor
- Colon and rectal surgery
- Endovascular surgery to treat or repair an aneurysm
- Gastroenterologic surgery, including for gastric bypass
- Gynecologic surgery
- Neurosurgery
- Orthopedic surgery
- Otolaryngology (ear, nose and throat surgery) head and neck surgery
- Thoracic surgery, such as video-assisted thoracoscopic surgery (VATS)
- Urologic surgery

Robotic heart surgery – What you should know and what you should ask

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Types

1. Minimally invasive heart surgery
2. Robotic hysterectomy
3. Robotic myomectomy
4. Robotic surgery

Why it's done

Minimally invasive surgery emerged in the 1980s as a safe and effective technique to meet the surgical needs of many people. In the last 20 years, many surgeons have come to prefer it to traditional (open) surgery, which requires larger incisions and, usually, a longer hospital stay.

Since then the use of minimally invasive surgery has expanded widely in many surgical specialties, including colon surgery and lung surgery. Talk with your doctor about whether you would be a good candidate for this surgical approach.

Risks

Minimally invasive surgery uses smaller surgical incisions, and it's generally less risky than traditional surgery. But even with minimally invasive surgery, there are risks of complications with anesthesia, bleeding and infection.

7. **Etiology, pathogenesis, diagnosis and treatment of lymphedema.**

Practice Essentials

Lymphedema (see the image below) is an abnormal collection of protein-rich fluid in the interstitium resulting from obstruction of lymphatic drainage. Lymphatic obstruction causes an increase in the protein content of the

extravascular tissue, with subsequent retention of water and swelling of the soft tissue. The increase in the extravascular protein stimulates proliferation of fibroblasts, organization of the fluid, and the development of a nonpitting swelling of the affected extremity.

Signs and symptoms

Signs and symptoms of lymphedema include the following:

- Chronic swelling of an extremity preceded lymphedema
- Primarily lower extremity involvement (80%) but can also involve the upper extremities, face, genitalia, and trunk
- Fevers, chills, and generalized weakness
- Fatigue related to the size and weight of the extremity
- Embarrassment in public
- Severe impairment of daily activities
- Recurrent bacterial or fungal infections
- Recurrent episodes of cellulitis, lymphangitis, fissuring, ulcerations, and/or verrucous changes

See Clinical Presentation for more detail.

Diagnosis

Examination in a patient with lymphedema may reveal the following findings:

- Nontender, pitting edema of the affected area, most commonly in the distal extremities; over time, radial enlargement of the area, progressing to a nonpitting edema
- Erythema of the affected area and thickening of the skin, which appears as peau d'orange skin and woody edema
- Elephantiasis nostra verrucosa (with long-term involvement): An area of cobble-stoned, hyperkeratotic, papillomatous plaques most commonly seen on the shins; the plaques can be covered with a loosely adherent crust, can be weepy or oozing a clear or yellow fluid, and/or can have a foul-smelling

odor. Lymphedema from Kaposi sarcoma so severe as to be evident as elephantiasis nostras verrucose may occur. [1]

- Fissuring, ulcerations, skin breakdown, and lymphorrhea
- Superinfection: Common and can manifest as impetigo with yellow crusts
- Positive Stemmer sign (inability to pinch the dorsal aspect of skin between the first and second toes)
- Detection of early mild arm lymphedema may be facilitated by using cutaneous palpation in combination with determining the tissue dielectric constant, which evaluates local tissue water in the skin and upper subcutis, measured from fixed measurement sites. [2]

Other associated physical findings specific for the cause of secondary lymphedema and genetic disorders involving lymphedema may be noted upon examination.

Testing

In general, analysis of blood, urine, or tissue is not needed to make the diagnosis of lymphedema. Such tests, however, help to define the underlying causes of lower extremity edema when the etiology is unclear.

If a renal or hepatic etiology is suspected, obtain the following laboratory tests:

- Liver function tests
- Blood urea nitrogen/creatinine levels
- Urinalysis

If a neoplasm is suspected, obtain results for specific markers. Obtain a complete blood count with differential if an infectious etiology is being considered.

Imaging studies

Imaging is not necessary to make the diagnosis of lymphedema, but it can be used to confirm it, to assess the extent of involvement, and to determine therapeutic intervention. Such studies may include the following:

- Plain radiographs: To exclude abnormalities of the bone
- Computed tomography scanning: When malignancy is suspected

- Magnetic resonance imaging: When malignancy is suspected or to show lymph trunk anatomy and causes of obstructive secondary lymphedema
- Ultrasonography: To evaluate the lymphatic and venous systems
- Fluorescence microlymphography: To demonstrate a lack of microlymphatics
- Lymphoscintigraphy: Criterion standard for evaluation of the lymphatic system

Procedures

Perform a biopsy if the diagnosis is not clinically apparent, if areas of chronic lymphedema look suspicious, or if areas of chronic ulceration exist.

See Workup for more detail.

Management

The goal of lymphedema therapy is to restore function, reduce physical and psychologic suffering, and prevent the development of infection. In secondary lymphedema, the underlying etiology (ie, neoplasm, infection) should also be properly treated, in order to relieve the lymphatic obstruction.

Pharmacotherapy

The following medications are used in to manage lymphedema:

- Benzopyrones (eg, coumarin, flavonoids)
- Retinoidlike agents (eg, acitretin, topical tazarotene)
- Anthelmintic agents (eg, albendazole)
- Topical skin products (eg, ammonium lactate lotion, topical urea)
- Antibiotics (eg, cefazolin, clindamycin, penicillin G)

Nonpharmacotherapy

Conservative measures for managing lymphedema include the following:

- Maintenance of appropriate hygiene and skin care
- Use of complex physical therapy (first-line treatment) [3] and compression stockings
- Weight loss (if overweight)
- Avoiding trauma

- Avoiding constrictive clothing
- Elevating affected limb

Surgical option

Surgical treatment is palliative, not curative, and it does not obviate the need for continued medical therapy. Procedures are divided into physiologic (to improve lymphatic drainage) and excisional (removal of the affected tissues to reduce the lymphedema-related load) surgeries.

Surgical intervention is reserved for patients who do not improve with conservative measures or for cases in which the extremity is so large that it impairs daily activities and prevents successful conservative management.

Background

Lymphedema is an abnormal collection of protein-rich fluid in the interstitium resulting from obstruction of lymphatic drainage. Lymphatic obstruction causes an increase in the protein content of the extravascular tissue, with subsequent retention of water and swelling of the soft tissue. The increase in the extravascular protein stimulates proliferation of fibroblasts, organization of the fluid, and the development of a nonpitting swelling of the affected extremity (see the image below). (See Pathophysiology and Etiology.)

Fibrosis also obstructs the lymphatic channels and leads to increased protein concentration in the tissues, continuing this cycle. Lymphedema most commonly affects the extremities, but it can involve the face, genitalia, or trunk. (See Etiology, Pathophysiology, and Presentation.)

In addition to causing soft tissue swelling, lymphedema opens channels in the integument and allows bacteria to enter the subcuticular space, which overwhelms host defenses and leads to cellulitis of the extremity. (See Pathophysiology, Prognosis, Treatment, and Medication.)

Lymphedema is classified into primary and secondary forms. Primary lymphedema (which results from genetic factors) is caused by abnormalities in the lymphatic system that are present at birth, although not always clinically evident until later in life. Primary lymphedema can also be associated with various

cutaneous syndromes. The three categories of primary lymphedema are as follows (see Etiology and Workup):

- Congenital lymphedema (Milroy disease)
- Lymphedema praecox (Meige disease)
- Lymphedema tarda

Secondary lymphedema occurs as a result of obstruction of lymphatic flow by known mechanisms, including the following (see Etiology and Workup):

- Filariasis
- Silica
- Podoconiosis, which occurs in barefoot subsistence farmers after walking on red volcanic soil, mostly commonly in Ethiopia [4]
- Obstruction by a proximal mass
- Postsurgical mechanisms - Eg, mastectomy
- Fibrosis secondary to chronic infections
- Unilateral lower extremity edema (as a complication of non-Hodgkin lymphoma) [5]
- Massive obesity (termed massive localized lymphedema or obesity-related lymphedema) [6, 7]: The risk of lower extremity lymphedema has been correlated with body mass index (BMI), such that BMI less than 40 is 0%, BMI of 40-49 is 17%, BMI of 50-59 is 63%, BMI of 60-69 is 86%, BMI of 70-79 is 91%, and BMI of 80 or greater is 100%. [8]
- Edema (giant penile elephantiasis) after circumcision of the penis [9]

Pathophysiology

Normal lymphatic physiology

The normal function of the lymphatics is to return proteins, lipids, and water from the interstitium to the intravascular space; 40-50% of serum proteins are transported by this route each day. High hydrostatic pressures in arterial capillaries force proteinaceous fluid into the interstitium, resulting in increased interstitial oncotic pressure that draws in additional water.

Interstitial fluid normally contributes to the nourishment of tissues. About 90% of the fluid returns to the circulation via entry into venous capillaries. The remaining 10% is composed of high-molecular-weight proteins and their oncotically associated water, which are too large to readily pass through venous capillary walls. This leads to flow into the lymphatic capillaries, where pressures are typically subatmospheric and can accommodate the large size of the proteins and their accompanying water. The proteins then travel as lymph through numerous filtering lymph nodes on their way to join the venous circulation.

Disease-related changes in lymphatic flow and their effects

In a diseased state, the lymphatic transport capacity is reduced. Consequently, the normal volume of interstitial fluid formation exceeds the rate of lymphatic return, resulting in the stagnation of high-molecular-weight proteins in the interstitium. This usually occurs after flow has been reduced by 80% or more. The result, as compared with forms of edema that have much lower concentrations of protein, is high-protein edema, or lymphedema, with protein concentrations of 1.0-5.5 g/mL. This high oncotic pressure in the interstitium favors the accumulation of additional water.

Accumulation of interstitial fluid leads to massive dilatation of the remaining outflow tracts and valvular incompetence that causes reversal of flow from subcutaneous tissues into the dermal plexus. The lymphatic walls undergo fibrosis, and fibrinoid thrombi accumulate within the lumen, obliterating much of the remaining lymph channels. Spontaneous lymphovenous shunts may form. Lymph nodes harden and shrink, losing their normal architecture.

In the interstitium, protein and fluid accumulation initiates a marked inflammatory reaction. Macrophage activity is increased, resulting in destruction of elastic fibers and production of fibrosclerotic tissue. Fibroblasts migrate into the interstitium and deposit collagen. The result of this inflammatory reaction is a change from the initial pitting edema to the brawny nonpitting edema characteristic of lymphedema. Consequently, local immunologic surveillance is suppressed, and

chronic infections, as well as malignant degeneration to lymphangiosarcoma, may occur. [10]

Dermatologic pathology

The overlying skin becomes thickened and displays the typical peau d'orange (orange skin) appearance of congested dermal lymphatics.

Chronic lymphedema causes fissuring and impairment of the epidermis, allowing bacteria to enter and grow, and leading to lymphorrhea, the leakage of lymph onto the surface of the skin. With chronic lymphedema, the development of verrucous, cobblestone plaques, a condition known as elephantiasis nostra verrucosa (ENV), can occur.

Protein composition in lymphedema

A theory has also been proposed that chronic lymphedema changes the protein composition of lymph in affected areas. A decrease in alpha-2 globulin levels and an increase in the albumin-to-globulin ratio have been reported. This change in proteins and the resultant slowing of transport to the lymphoid tissue have been suggested to play a role in diminishing the effectiveness of immune surveillance and to prevent early detection of tumor-specific antigens.

Additionally, repeat episodes of chronic ulceration and healing may stimulate the proliferation of keratinocytes, which may contribute to neoplastic transformation.

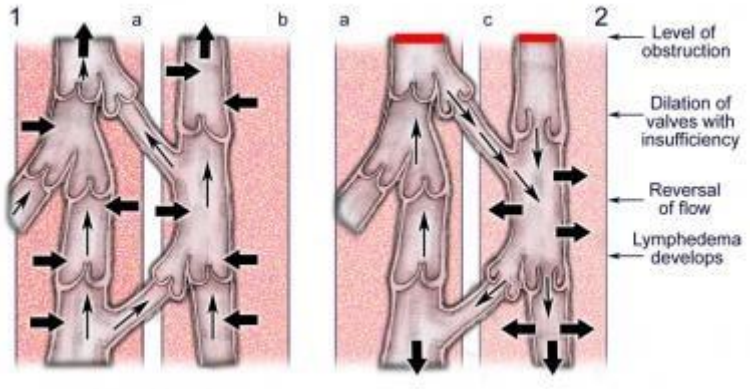
Etiology

Lymphedema is caused by a compromised lymphatic system that impedes and diminishes lymphatic return. In primary lymphedema, the failure is caused by congenital hypoplasia or aplasia of the peripheral lymphatics or by valvular incompetence. In secondary lymphedema, the lymphatic drainage is altered by an acquired blockade of the lymph nodes or by disruption of the local lymphatic channels caused by one of the following etiologies:

- Recurrent attacks of lymphangitis - A key type of this is cellulitis
- Malignancy
- Obesity

- Surgery

Whether the cause is acquired blockade of the lymph nodes or disruption of the local lymphatic channels, the result is a failure to drain protein-rich lymphatic fluid from the tissue, causing interstitial edema with swelling of the affected site. (See the image below.



(1) Normal lymphatic flow in (a) deep systems and (b) superficial systems. Note the small collateral vessels interconnecting the 2 systems. (2) Lymphedema develops from obstruction, dilation of valves, valvular insufficiency, and subsequent reversal of lymphatic flow.

Although etiology determines the classification of lymphedema as either primary or secondary, it rarely impacts the choice of treatment. [11]

Primary lymphedema

Lymphedema arising from a developmental abnormality of the lymphatic system is classified as primary lymphedema. [11] This form of the disease is divided into the following 3 main types, which are distinguished by their age of onset. (Connell et al proposed a classification system of the primary lymphatic dysplasias that is based on phenotype rather than age of onset. [12]) These types are as follows:

- Congenital lymphedema (Milroy disease)
- Lymphedema praecox (Meige disease)
- Lymphedema tarda

These conditions involve the lower extremities almost exclusively. All are caused by a congenital abnormality in the lymphatic system, although these defects may not always be clinically evident until later in life, when a triggering event or

worsening of the condition causes the lymphatic transport capacity to exceed the volume of interstitial fluid formation; in such cases, the patient is unable to maintain normal lymphatic flow.

Primary lymphedema also can be associated with other cutaneous and genetic disorders not among the 3 main, age-based categories.

Congenital lymphedema

Congenital lymphedema, or Milroy disease, accounts for 10-25% of all primary lymphedema cases. A familial, autosomal-dominant disorder, it is often caused by anaplastic lymphatic channels. The disorder manifests at birth or later, up to age 1 year. Females are affected twice as often as males, and the lower extremities are involved 3 times more frequently than the upper extremities. The edema is most commonly pitting and nonpainful. Patients may have bilateral lymphedema, and this form may improve spontaneously with increasing age. Unilateral lymphedema is not noted in Milroy disease, but if it were, it might spontaneously improve with age.

Congenital lymphedema has also been associated with cellulitis, prominent veins, intestinal lymphangiectasias, upturned toenails, and hydrocele.

Although congenital lymphedema is classically thought to be caused by the failure of lymphatic vessels to develop in utero, examination of patients with this disease by fluorescence microlymphangiography demonstrated a high rate of functional failure of the lymphatic system. [13, 14] Such failure may play a role in the development of edema.

Congenital lymphedema may be linked to a mutation that inactivates *VEGFR3*. This gene, which is expressed in adult lymphatic endothelial cells, has been mapped to the telomeric part of chromosome arm 5q in the region 5q34-q35. This region codes for a tyrosine kinase receptor specific for the function of the lymphatic vessels, and indeed, the receptor has been reported to be abnormally phosphorylated in patients with Milroy disease. [15, 16, 17, 18, 19, 20, 21]

Lymphedema praecox

Lymphedema praecox, also known as Meige disease, is the most common form of primary lymphedema. By definition, this disease becomes clinically evident after birth and before age 35 years. The condition accounts for 65-80% of all primary lymphedema cases and most often arises during puberty. About 70% of cases are unilateral, with the left lower extremity being involved more often than the right. Histologically, these patients are likely to demonstrate a hypoplastic pattern, with the lymphatics reduced in caliber and number.

Females are affected 4 times as often as males. The fact that lymphedema praecox usually manifests clinically around menarche suggests that estrogen may play a role in its pathogenesis.

Lymphedema tarda

Lymphedema tarda manifests later in life, usually in persons older than 35 years. It is thought to be caused by a defect in the lymphatic valves, resulting in incompetent valve function. Whether this defect is congenital or acquired is difficult to determine.

As the rarest form of primary lymphedema, this disease accounts for only 10% of cases. Histologically, patients are likely to demonstrate a hyperplastic pattern, with tortuous lymphatics increased in caliber and number.

Associated conditions

As mentioned, primary lymphedema is seen in association with various cutaneous and genetic disorders.

Distichiasis lymphedema syndrome is a form of hereditary early and late-onset lymphedema associated with distichiasis (double row of eyelashes). Affected persons usually manifest bilateral lower extremity lymphedema by age 8-30 years. Lymphatic vessels are usually larger in affected areas. It is a hereditary condition with an autosomal dominant pattern with variable penetrance. It reportedly is associated with a mutation in the *FOXC2* transcription factor. [22] Other associated anomalies may include vertebral abnormalities, spinal arachnoid cysts, hemangiomas, cleft palate, ptosis, short stature, webbed neck, strabismus, thoracic duct abnormalities, and microphthalmia.

Primary lymphedema has also been associated with yellow nail syndrome. This entity may be associated with recurrent pleural effusions and bronchiectasis.

Other genetic syndromes and cutaneous conditions associated with primary lymphedema include the following:

- Turner syndrome
- Noonan syndrome
- Klinefelter syndrome
- Neurofibromatosis type 1
- Hemangiomas
- Xanthomatosis
- Congenital absence of nails

One case reportedly occurred in association with CHARGE (coloboma, heart anomalies, choanal atresia, somatic and mental retardation, genitourinary anomalies, ear abnormalities) syndrome. [23]

Secondary lymphedema

Secondary Lymphedema is caused by an acquired defect in the lymphatic system and is commonly associated with obesity, infection, neoplasm, trauma, and therapeutic modalities. It may also be associated with intravenous drug abuse. [24] Puffy hand syndrome is associated with lymphedema-cellulitis-venous thrombosis of the hand in intravenous drug abusers.

Filariasis

The most common cause of secondary lymphedema worldwide is filariasis, a disease caused by a mosquito-borne nematode infection with the parasite *Wucheria bancrofti*. Commonly occurring in developing countries around the world, this infection results in permanent lymphedema of the limb. [25, 26, 27] The major immunological feature of lymphatic filariasis appears to be an antigen-specific Th2 response, with an expansion of interleukin 10 secreting $CD4^+$ T cells; such an immunological pattern involves a muted Th1 response. [28]

Malignancy and cancer treatment

In the industrialized world, the most common causes of secondary lymphedema are malignancy and its treatment. This means that the disease can arise from obstruction from metastatic cancer or primary lymphoma or can be secondary to radical lymph node dissection and excision.

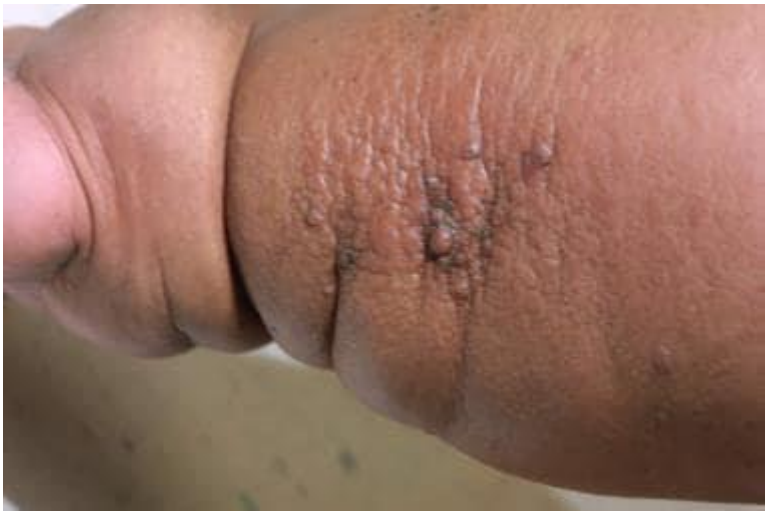
Although lymphatics are thought to regenerate after transection via surgery, when combined with radiotherapy to the area, the risk of lymphedema increases because of scarring and fibrosis of the tissue. The most commonly affected area is the axillary region after mastectomy and radical dissection for breast cancer.

Lymphedema can also be seen after regional dissection of pelvic, para-aortic, and neck lymph nodes. Other associated neoplastic diseases are Hodgkin lymphoma, metastatic prostate cancer, cervical cancer, breast cancer, Kaposi sarcoma, and melanoma.

The concept of Ruocco's immunocompromised cutaneous district may explain the association of lymphedema with opportunistic infections, including viral warts, tumors (including angiosarcoma, basal cell carcinoma, squamous cell carcinoma, and sebaceous carcinoma), and immune reactions. [29, 30]

Other causes

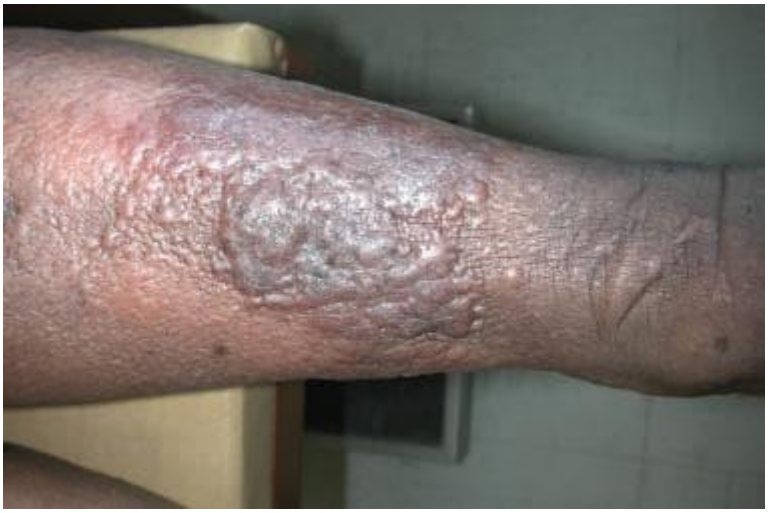
Morbid obesity frequently causes impairment of lymphatic return and commonly results in lymphedema, as shown in the image below. This entity can be termed massive localized lymphedema [6, 7] or obesity-related lymphedema.



Morbidly obese patient with lymphedema.

Lymphedema is also associated with the following etiologies (see the image below):

- Trauma
- Varicose vein surgery
- Congestive heart failure
- Portal hypertension
- Peripheral vascular surgery
- Lipectomy
- Burns
- Burn scar excision
- Insect bites
- Extrinsic pressure



Lymphedema in a patient with hypertension, diabetes, and impaired cardiac function.

Recurrent episodes of cellulitis or streptococcal lymphangitis have also been linked to the development of lymphedema.

Rarely, herpes simplex infection can cause lymphangitis and resultant lymphedema. In one reported case, a patient with herpetic whitlow presented with acquired lymphedema of the hand. [31]

The peptide adrenomedullin (AM) is encoded by the *ADM* gene. One report sought to determine if a deficiency in AM predisposes to secondary

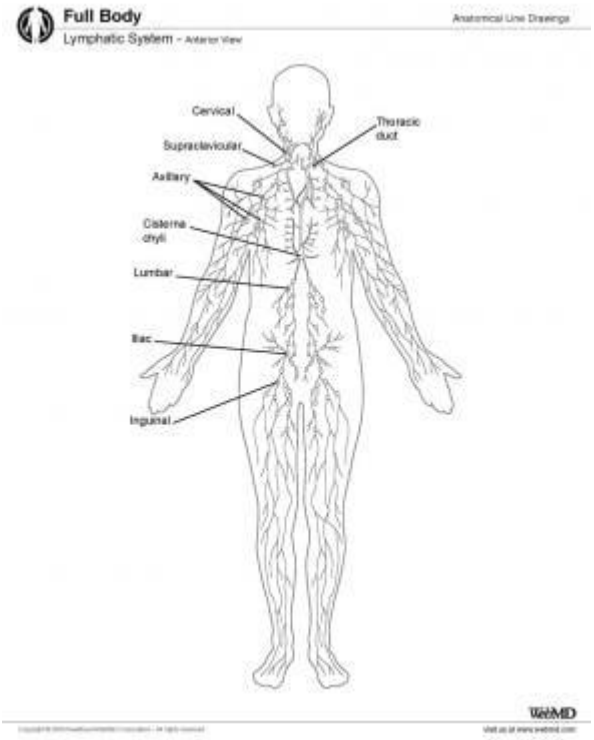
lymphedema. [32] Endogenous AM was determined to play an important role in secondary lymphedema pathogenesis.

Another interesting report [33] notes a 75-year-old woman with a monoclonal gammopathy of uncertain significance (MGUS) and rapidly progressive lipolymphedema. The researchers speculated that MGUS and lymphedema might be due to initial fibrogenesis worsening preexisting lipedema.

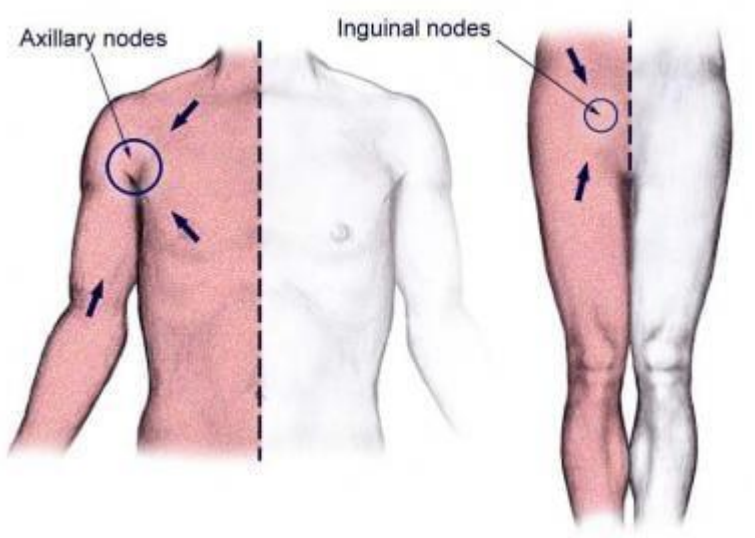
Anatomy

Before embarking on the treatment of lymphedema, a thorough knowledge of the relevant anatomy is essential. Blind-ended lymphatic capillaries arise within the interstitial spaces of the dermal papillae. These unvalved, superficial dermal lymphatics drain into interconnected subdermal channels, which parallel the superficial venous system. These subsequently drain into the deeper, epifascial system of valved trunks lined with smooth muscle cells and located just above the deep fascia of the extremity.

This system is responsible for the drainage of lymph from the skin and subcutaneous tissues. Valves provide for unidirectional flow towards regional lymph nodes and eventually the venous circulation in the neck. Flow is achieved by variations of tissue pressure through skeletal muscle contractions, pulsatile blood flow, and contractions of the spiral smooth muscle fibers surrounding larger lymphatic channels. (See the images below.)



Lymphatic system, anterior view.



The body quadrants of superficial lymph drainage.

A deeper-valved subfascial system of lymphatics is responsible for the drainage of lymph from the fascia, muscles, joints, ligaments, periosteum, and bone. This subfascial system parallels the deep venous system of the extremity.

The epifascial and subfascial systems normally function independently, although valved connections do exist in the popliteal, inguinal, antecubital, and axillary regions where lymph nodes form interconnected chains. These connections probably do not function under normal conditions; however, in lymphedema, some

reversed flow through perforators from the epifascial to the subfascial system may occur as a mechanism of decompression of the epifascial system.

However, the derangement in lymphedema is almost always exclusive to the epifascial lymphatic system, with the subfascial system being uninvolved. Thus, the surgical approaches to lymphedema focus on the epifascial system.

Epidemiology

Occurrence in the United States

In the United States, lymphedema most often occurs after breast cancer surgery, especially in patients who, after undergoing axillary lymphadenectomy, receive radiation therapy. Within this population, 10-40% develop some degree of ipsilateral upper extremity lymphedema. [11, 34]

Although not reported as often as postmastectomy-induced lymphedema, obesity is also one of the most common causes of lymphedema seen in practice today.

The primary lymphedemas occur in 1 of 10,000 individuals, with lymphedema praecox accounting for 80% of cases. The incidence of congenital lymphedema is unknown because most patients have been reported in small, case-based studies.

International occurrence

Worldwide, the most common cause of lymphedema is filariasis infection. More than 100 million people are affected in endemic areas worldwide. [11, 35]

Sex-related demographics

Primary lymphedema occurs most often in females. Lymphedema praecox, the most common primary form, affects 1 in 100,000 females and 1 in 400,000 males. Similarly, females account for 70-80% of cases of congenital lymphedema.

Age-related demographics

Secondary lymphedema can affect persons of any age group, with the onset being determined by the disease's primary cause. [36] Hereditary (primary) lymphedema can be divided into 3 groups based on the age of onset of clinical lymphedema, as follows:

- Congenital lymphedema - Usually manifests from birth to age 1 year
- Lymphedema praecox - Occurs between the ages of 1 and 35 years; it most commonly occurs in adolescents
- Lymphedema tarda - Manifests after age 35 years

Prognosis

The outcome for persons with lymphedema depends on its chronicity, the complications that result, and the underlying disease state that caused the lymphedema. (Primary lymphedema usually does not progress, with the condition stabilizing after several years of activity.)

Patients with chronic lymphedema for 10 years have a 10% risk of developing lymphangiosarcoma, the most dreaded complication of this disease. Patients with this tumor commonly present with a reddish purple discoloration or nodule that tends to form satellite lesions. It may be confused with Kaposi sarcoma or traumatic ecchymosis. This tumor is highly aggressive, requires radical amputation of the involved extremity, and has a very poor prognosis. [37, 38, 39, 40, 41, 42, 43]

The 5-year survival rate for lymphangiosarcoma is less than 10%, with the average survival following diagnosis being 19 months. This malignant degeneration is most commonly observed in patients with postmastectomy lymphedema (Stewart-Treves syndrome), in whom the incidence is estimated to be 0.5%. [44]

Other neoplasms identified in areas of chronic lymphedema are squamous cell carcinoma, Kaposi sarcoma, [42, 45] B-cell lymphoma, [46] and malignant fibrous histiocytoma.

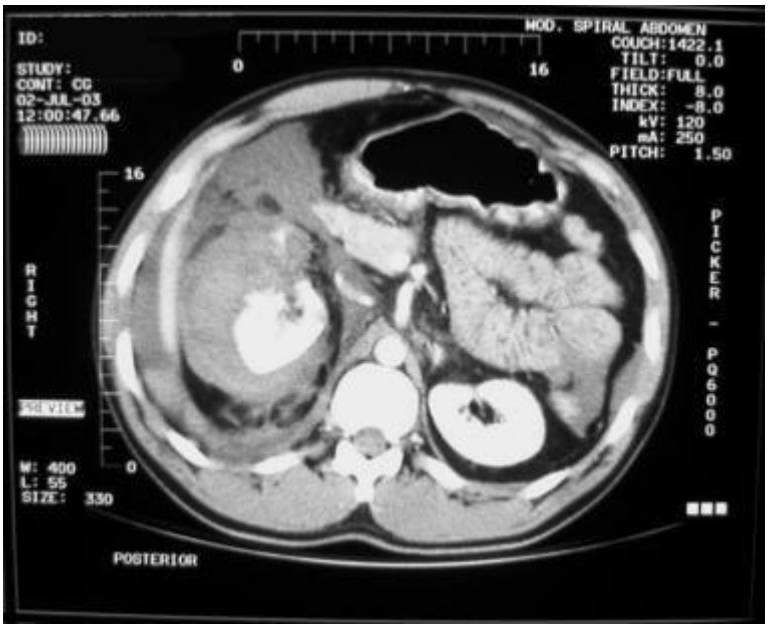
Complications of lymphedema also include recurrent bouts of cellulitis and/or lymphangitis, bacterial and fungal infections, lymphangio-adenitis, deep venous thrombosis, severe functional impairment, cosmetic embarrassment, and necessary amputation. Some patients may develop protein-losing enteropathy and visceral involvement. Chylous ascites and chylothorax can develop but are rare. Amyloidosis has been described as a complication of primary lymphedema. [47, 48]

Complications following surgery are common and include partial wound separation, seroma, hematoma, skin necrosis, and exacerbation of foot or hand edema.

8. Wounds and closed injuries of the abdomen, pelvis and pelvic organs.

Practice Essentials

Blunt abdominal trauma (see the image below) is a leading cause of morbidity and mortality among all age groups. Identification of serious intra-abdominal pathology is often challenging; many injuries may not manifest during the initial assessment and treatment period.



Blunt abdominal trauma. Right kidney injury with blood in perirenal space. Injury resulted from high-speed motor vehicle collision.

Signs and symptoms

The initial clinical assessment of patients with blunt abdominal trauma is often difficult and notably inaccurate. The most reliable signs and symptoms in alert patients are as follows:

- Pain
- Tenderness
- Gastrointestinal hemorrhage
- Hypovolemia

- Evidence of peritoneal irritation

However, large amounts of blood can accumulate in the peritoneal and pelvic cavities without any significant or early changes in the physical examination findings. Bradycardia may indicate the presence of free intraperitoneal blood.

On physical examination, the following injury patterns predict the potential for intra-abdominal trauma:

- Lap belt marks: Correlate with small intestine rupture
- Steering wheel–shaped contusions
- Ecchymosis involving the flanks (Grey Turner sign) or the umbilicus (Cullen sign): Indicates retroperitoneal hemorrhage, but is usually delayed for several hours to days
- Abdominal distention
- Auscultation of bowel sounds in the thorax: May indicate a diaphragmatic injury
- Abdominal bruit: May indicate underlying vascular disease or traumatic arteriovenous fistula
- Local or generalized tenderness, guarding, rigidity, or rebound tenderness: Suggests peritoneal injury
- Fullness and doughy consistency on palpation: May indicate intra-abdominal hemorrhage
- Crepitation or instability of the lower thoracic cage: Indicates the potential for splenic or hepatic injuries

See Clinical Presentation for more detail.

Diagnosis

Assessment of hemodynamic stability is the most important initial concern in the evaluation of a patient with blunt abdominal trauma. In the hemodynamically unstable patient, a rapid evaluation for hemoperitoneum can be accomplished by means of diagnostic peritoneal lavage (DPL) or the focused assessment with sonography for trauma (FAST). Radiographic studies of the

abdomen are indicated in stable patients when the physical examination findings are inconclusive.

Diagnostic peritoneal lavage

DPL is indicated for the following patients in the setting of blunt trauma:

- Patients with a spinal cord injury
- Those with multiple injuries and unexplained shock
- Obtunded patients with a possible abdominal injury
- Intoxicated patients in whom abdominal injury is suggested
- Patients with potential intra-abdominal injury who will undergo prolonged anesthesia for another procedure

FAST

Bedside ultrasonography is a rapid, portable, noninvasive, and accurate examination that can be performed by emergency clinicians and trauma surgeons to detect hemoperitoneum.

The current FAST examination protocol consists of 4 acoustic windows (pericardiac, perihepatic, perisplenic, pelvic) with the patient supine.

An examination is interpreted as positive if free fluid is found in any of the 4 acoustic windows, negative if no fluid is seen, and indeterminate if any of the windows cannot be adequately assessed.

Computed tomography

Computed tomography is the standard for detecting solid organ injuries. CT scans provide excellent imaging of the pancreas, duodenum, and genitourinary system.

CT scanning often provides the most detailed images of traumatic pathology and may assist in determination of operative intervention [1, 2, 3, 4] Unlike DPL or FAST, CT can determine the source of hemorrhage.

Management

Treatment of blunt abdominal trauma begins at the scene of the injury and is continued upon the patient’s arrival at the ED or trauma center. Management may involve nonoperative measures or surgical treatment, as appropriate.

Indications for laparotomy in a patient with blunt abdominal injury include the following:

- Signs of peritonitis
- Uncontrolled shock or hemorrhage
- Clinical deterioration during observation
- Hemoperitoneum findings on FAST or DPL

Nonoperative management

In blunt abdominal trauma, including severe solid organ injuries, selective nonoperative management has become the standard of care. Nonoperative management strategies are based on CT scan diagnosis and the hemodynamic stability of the patient, as follows:

- For the most part, pediatric patients can be resuscitated and treated nonoperatively; some pediatric surgeons often transfuse up to 40 mL/kg of blood products in an effort to stabilize a pediatric patient
- Hemodynamically stable adults with solid organ injuries, primarily those to the liver and spleen, may be candidates for nonoperative management
- Splenic artery embolotherapy, although not standard of care, may be used for adult blunt splenic injury
- Nonoperative management involves closely monitoring vital signs and frequently repeating the physical examination

See Treatment and Medication for more detail.

Pathophysiology

Intra-abdominal injuries secondary to blunt force are attributed to collisions between the injured person and the external environment and to acceleration or deceleration forces acting on the person’s internal organs. Blunt force injuries to the abdomen can generally be explained by 3 mechanisms.

The first mechanism is deceleration. Rapid deceleration causes differential movement among adjacent structures. As a result, shear forces are created and cause hollow, solid, visceral organs and vascular pedicles to tear, especially at relatively fixed points of attachment. For example, the distal aorta is attached to the

thoracic spine and decelerates much more quickly than the relatively mobile aortic arch. As a result, shear forces in the aorta may cause it to rupture. Similar situations can occur at the renal pedicles and at the cervicothoracic junction of the spinal cord.

Classic deceleration injuries include hepatic tear along the ligamentum teres and intimal injuries to the renal arteries. As bowel loops travel from their mesenteric attachments, thrombosis and mesenteric tears, with resultant splanchnic vessel injuries, can result.

The second mechanism involves crushing. Intra-abdominal contents are crushed between the anterior abdominal wall and the vertebral column or posterior thoracic cage. This produces a crushing effect, to which solid viscera (eg, spleen, liver, kidneys) are especially vulnerable.

The third mechanism is external compression, whether from direct blows or from external compression against a fixed object (eg, lap belt, spinal column). External compressive forces result in a sudden and dramatic rise in intra-abdominal pressure and culminate in rupture of a hollow viscous organ (ie, in accordance with the principles of Boyle law).

The liver and spleen seem to be the most frequently injured organs, though reports vary. The small and large intestines are the next most frequently injured organs. Recent studies show an increased number of hepatic injuries, perhaps reflecting increased use of CT scanning and concomitant identification of more injuries.

Etiology

Vehicular trauma is by far the leading cause of blunt abdominal trauma in the civilian population. Auto-to-auto and auto-to-pedestrian collisions have been cited as causes in 50-75% of cases. Other common etiologies include falls and industrial or recreational accidents. Rare causes of blunt abdominal injuries include iatrogenic trauma during cardiopulmonary resuscitation, manual thrusts to clear an airway, and the Heimlich maneuver.

Background

The care of the trauma patient is demanding and requires speed and efficiency. Evaluating patients who have sustained blunt abdominal trauma remains one of the most challenging and resource-intensive aspects of acute trauma care. [5, 6]

Blunt abdominal trauma is a leading cause of morbidity and mortality among all age groups. Identification of serious intra-abdominal pathology is often challenging. Many injuries may not manifest during the initial assessment and treatment period. Missed intra-abdominal injuries and concealed hemorrhage are frequent causes of increased morbidity and mortality, especially in patients who survive the initial phase after an injury.

Physical examination findings are notoriously unreliable. One reason is that mechanisms of injury often result in other associated injuries that may divert the physician's attention from potentially life-threatening intra-abdominal pathology. Other common reasons are an altered mental state and drug and alcohol intoxication.

Coordinating a trauma resuscitation demands a thorough understanding of the pathophysiology of trauma and shock, excellent clinical and diagnostic acumen, skill with complex procedures, compassion, and the ability to think rationally in a chaotic milieu.

Blunt abdominal trauma usually results from motor vehicle collisions (MVCs), assaults, recreational accidents, or falls. The most commonly injured organs are the spleen, liver, retroperitoneum, small bowel, kidneys (see the image below), bladder, colorectum, diaphragm, and pancreas. Men tend to be affected slightly more often than women.

For more information, see the following:

- Pediatric Abdominal Trauma
- Penetrating Abdominal Trauma
- Focused Assessment with Sonography in Trauma (FAST)
- Abdominal Vascular Injuries

Anatomy

The abdomen can be arbitrarily divided into 4 areas. The first is the intrathoracic abdomen, which is the portion of the upper abdomen that lies beneath the rib cage. Its contents include the diaphragm, liver, spleen, and stomach. The rib cage makes this area inaccessible to palpation and complete examination.

The second is the pelvic abdomen, which is defined by the bony pelvis. Its contents include the urinary bladder, urethra, rectum, small intestine, and, in females, ovaries, fallopian tubes, and uterus. Injury to these structures may be extraperitoneal in nature and therefore difficult to diagnose.

The third is the retroperitoneal abdomen, which contains the kidneys, ureters, pancreas, aorta, and vena cava. Injuries to these structures are very difficult to diagnose on the basis of physical examination findings. Evaluation of the structures in this region may require computed tomography (CT) scanning, angiography, and intravenous pyelography (IVP).

The fourth is the true abdomen, which contains the small and large intestines, the uterus (if gravid), and the bladder (when distended). Perforation of these organs is associated with significant physical findings and usually manifests with pain and tenderness from peritonitis. Plain x-ray films are helpful if free air is present. Additionally, diagnostic peritoneal lavage (DPL) is a useful adjunct.

Epidemiology

United States statistics

By nearly every measure, injury ranks as one of the most pressing health issues in the United States. More than 150,000 people die each year as a result of injuries, such as motor vehicle crashes, fires, falls, drowning, poisoning, suicide, and homicide. Injuries are the leading cause of death and disability for US children and young adults.

According to the 2000 statistics from the National Center for Injury Prevention and Control, trauma (unintentional and intentional) was the leading cause of death in persons aged 1-44 years. Further review of the data reveals that in those aged 15-25 years, 14,113 persons died from unintentional injuries, 73% of

which were related to vehicular trauma. In individuals aged 25-34 years, 57% of the 11,769 deaths reported were from motor vehicle collisions.

In 2001, approximately 30 million people visited emergency departments (EDs) for the treatment of nonfatal injuries, and more than 72,000 people were disabled by injuries. Injury imposes exceptional costs, both in health care dollars and in human losses, to society.

The true frequency of blunt abdominal trauma, however, is unknown. Data collected from trauma centers reflect patients who are transported to or seek care at these centers; these data may not reflect patients presenting to other facilities. The incidence of out-of-hospital deaths is unknown.

One review from the National Pediatric Trauma Registry by Cooper et al reported that 8% of patients (total=25,301) had abdominal injuries. Eighty-three percent of those injuries were from blunt mechanisms. Automobile-related injuries accounted for 59% of those injuries.[7] Similar reviews from adult trauma databases reflect that blunt trauma is the leading cause of intra-abdominal injury and that MVC is the leading mode of injury. Blunt injuries account for approximately two thirds of all injuries.

Hollow viscus trauma is more frequent in the presence of an associated, severe, solid organ injury, particularly to the pancreas. Approximately two thirds of patients with hollow viscus trauma are injured in MVCs.

International statistics

In 1990, approximately 5 million people died worldwide as a result of injury. The risk of death from injury varied strongly by region, age, and sex. Approximately 2 male deaths due to violence were reported for every female death. Injuries accounted for approximately 12.5% of all male deaths, compared with 7.4% of female deaths.

Globally, injury accounts for 10% of all deaths; however, injuries in sub-Saharan Africa are far more destructive than in other areas. In sub-Saharan Africa, the risk of death from trauma is highest in those aged 15-60 years, and the proportion of such deaths from trauma is higher than in any other region of the

world. South Africa, for instance, has a traffic death rate per unit of distance traveled that is surpassed only by those of Korea, Kenya, and Morocco.

Estimates indicate that by 2020, 8.4 million people will die yearly from injury, and injuries from traffic collisions will be the third most common cause of disability worldwide and the second most common cause in the developing world.

Data from the World Health Organization (WHO) indicate that falls from heights of less than 5 meters are the leading cause of injury, and automobile crashes are the next most frequent cause. These data reflect all injuries, not just blunt injuries to the abdomen.

A review from Singapore described trauma as the leading cause of death in those aged 1-44 years. Traffic accidents, stab wounds, and falls from heights were the leading modes of injury. Blunt abdominal trauma accounted for 79% of cases. [8]

A similar paper from India reported that blunt abdominal trauma is more frequent in males aged 21-30 years; the majority of patients were injured in automobile accidents. A German study indicated that, of patients with vertical deceleration injuries (ie, falls from heights), only 5.9% had blunt abdominal injuries.

Age-related differences in incidence

Most studies indicate that the peak incidence is in persons aged 14-30 years. A review of 19,261 patients with blunt abdominal trauma revealed equal incidence of hollow viscus injuries in both children (ie, ≤14 y) and adults.

Sex-related differences in incidence

According to national and international data, blunt abdominal trauma is more common in men. The male-to-female ratio is 60:40.

Prognosis

Overall prognosis for patients who sustain blunt abdominal trauma is favorable. Without statistics that indicate the number of out-of-hospital deaths and the total number of patients with blunt trauma to the abdomen, a description of the

specific prognosis for patients with intra-abdominal injuries is difficult. Mortality rates for hospitalized patients are approximately 5-10%.

The National Pediatric Trauma Registry reported that 9% of pediatric patients with blunt abdominal trauma died. Of these, only 22% were reported as having intra-abdominal injuries as the likely cause of death. [7]

A review from Australia of intestinal injuries in blunt trauma reported that 85% of injuries occurred from vehicular accidents. The mortality rate was 6%. In a large review of operating room deaths in which blunt trauma accounted for 61% of all injuries, abdominal trauma was the primary identified cause of death in 53.4% of cases.

Patient Education

Proper adjustment of restraints in motor vehicles is an important aspect of patient education. The following are key recommendations:

- Wear lap belts in conjunction with shoulder restraints.
- Adjust lap belts so that they fit snugly, and place them across the lower abdomen and below the iliac crests.
- Wear restraints even in vehicles equipped with supplemental vehicle restraints (eg, airbags).
- Adjust seats and steering wheels so that the distance between the abdominal wall and the steering wheel is as wide as possible while still allowing proper control of the vehicle.

Advise patients to practice defensive driving by observing speed limits and keeping a safe distance between them and other automobiles on the road.

9. Infectious complications of combat injuries.

Summary

Infections after combat trauma are common and complex, requiring a multidisciplinary approach to prevention and care.

Introduction

Infectious complications after battlefield injury are not a new phenomenon. The most ancient descriptions of war include attention to the resulting

complications and treatments, some of which are still applicable today [1•]. In the pre-antibiotic era, these infections were frequently fatal, but appropriate modern treatment approaches have markedly reduced the risk of morbidity and long-term disability or death. However, as mechanisms of injury, theaters of operation, and medical care itself evolve, there is real-time change in the types and microbiology of infectious disease complications, necessitating important adjustments in care. Infectious complications after combat trauma can be disastrous, resulting in amputation, loss of function, or death. Particular attention to infection control is required to avoid preventable infections.

Epidemiology

Soon after combat began in Operations Iraqi Freedom and Enduring Freedom (OIF, OEF), military physicians noted an unusual number of multidrug-resistant (MDR) organisms causing infections in casualties. The most notable of these was Acinetobacter baumannii-calcoaceticus (ABC), but MDR Pseudomonas aeruginosa, Klebsiella pneumoniae, and methicillin-resistant Staphylococcus aureus were also being recovered from infected casualties. An early report of ABC infections primarily in servicemembers injured in Iraq described >100 bloodstream infections caused by the organism, clearly the tip of the iceberg [2]. Reports increased of MDR ABC causing wound, burn, skin and soft tissue, bone, and respiratory infections, including those in exposed healthcare workers and patients who had not been deployed but were treated alongside returning combat casualties [3,4,5].

The source of these infections was not immediately clear. ABC is a hardy environmental organism and, given the extensive contamination of most battlefield injuries, it was postulated that soil and debris in the wound might be the source for colonization and infection. Pre-injury colonization was also considered as a possibility, especially considering the likelihood of some changes to the skin and gut microbiomes of servicemembers in hot, austere conditions. Both of these possibilities were studied, with no evidence that either contributed to MDR ABC or any other MDR gram-negative rod (GNR) infection in combat casualties

[6,7,8,9]. Instead, it became clear that nosocomial transmission within the chain of combat casualty care was the predominant mechanism for colonization and infection [10•, 12, 13]. Additionally, although these organisms were frequently found at the time of initial diagnosis of infection, they were predominantly replaced with Staphylococcus spp., especially S. aureus, by the time of relapsed or recurring infection [14, 15].

As the theater of combat operations shifted from Iraq to Afghanistan, the predominant organisms changed as well from ABC to other MDR GNR, especially extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli, Enterobacter spp., and K. pneumoniae. However, overall rates of colonization with any MDR GNR remained fairly stable at around 15% [16, 17]. In contrast to ABC, the role of other routes of transmission, especially the possibility of pre-injury colonization with these pathogens playing a role in later infection, is less clear. MDR GNRs were frequently isolated as community-acquired pathogens in local nationals admitted to deployed hospitals, similar to data seen with ABC in Iraq [11, 13]. However, there are also data to suggest that uninjured deployed personnel to that region are colonized with MDR E. coli at higher rates than US-based personnel; one evaluation revealed a 5.5-fold higher rate of colonization [18]. Severe, complex blast injuries in Afghanistan, particularly in the lushly vegetated southern Kandahar and Helmand provinces, were also found to be uniquely at risk for serious invasive fungal infections (IFI) with a wide variety of mold species [19•, 20]. Risk factors include dismounted blast injuries, above-the-knee amputations, and large-volume red cell transfusion requirements [21].

According to prospectively collected data from the TIDOS cohort enrolling trauma patients evacuated from combat theaters, 27% of casualties experience at least one infectious complication. This increases to 50% if only intensive care unit (ICU) patients are considered [22••]. The spectrum of these infections largely mirrors the anatomic distribution of combat injuries and the nosocomial infections common in trauma ICU populations. Wound/skin and soft tissue infections

occurred in 18% of the TIDOS cohort, followed by osteomyelitis (9%), bloodstream infections (9%), and pneumonia (4%), with higher rates in ICU compared to those in ward patients for all sites of infection. The median number of days from injury to infection diagnosis was as short as 3 for pneumonia, 6 for bloodstream infections, 12 for wounds, and 15 for osteomyelitis. In patients with open extremity fractures, approximately 15% developed osteomyelitis; in Gustilo type III tibial plateau fractures, deep wound infection (including osteomyelitis) rates ranged from 22 to 77% [14, 15, 23, 24]. Bloodstream infections are typically secondary; one evaluation of central line-associated bloodstream infections at a deployed hospital in Iraq found substantial variability (0 to 29 per 1000 device-days), not apparently related to census or staff turnover periods [25]. The most common organism isolated was S. aureus. Catheter-associated urinary tract infections in the same study remained stable over the course of a year and comparable to rates seen in US trauma ICUs. Healthcare-associated pneumonia in evacuated casualties from the 2009–2010 TIDOS cohort has also been evaluated; 9% of all patients and 18% of ICU patients developed pneumonia, with the majority being ventilator associated. Although the majority of isolates were GNR, S. aureus was the single most common isolate recovered (11%) [26]. Thermal injury was relatively common in the first 5–6 years of the conflict in Iraq, sustained by approximately 5% of casualties; 12% of these developed at least one episode of bacteremia [27]. Every anatomical site of trauma has its own unique infectious complications, and while an extensive discussion of these is outside the scope of this review, the Journal of Trauma published guidelines and entire supplements in 2008 and 2011 dedicated to prevention of infections associated with combat injuries, excellent resources for further information [28••, 29••].

Infections after combat trauma are by no means trivial events, but lead to serious complications of their own. Longer times to fracture union and higher rates of both reoperation and amputation have been seen in patients with deep wound infections/osteomyelitis [30]. Infections after combat-related amputation can also result in conversion to a more proximal amputation, which carries significant

additional morbidity and a decrease in functional outcomes. Additionally, compared to casualties without deep wound infections or osteomyelitis, those suffering these complications are less likely to return to duty, more likely to be rehospitalized, and fail limb salvage attempts [23, 30, 31]. Infection is the most common complication both before and after late amputation in limb salvage patients [32]. In those with invasive fungal infections, a crude mortality rate of 9% has been seen, along with high-level amputation (including hemipelvectomy and hip disarticulation) rates exceeding 20% [33]. In burn patients, death was more strongly associated with infection (most typically with K. pneumoniae, P. aeruginosa, or IFI) in combat casualties than it was in civilian patients in one autopsy study [34].

Prevention

First, it must be acknowledged that all infectious complications of medically attended trauma are by definition healthcare-associated infections, a reality which has been highlighted in recent conflicts by the clear evidence of nosocomial transmission of MDR organisms. The success of standardized, bundled approaches to infection prevention (IP) in the last decade, especially the reductions in central line-associated bloodstream infections and ventilator-associated pneumonias, has also underscored that such complications cannot be assumed to be inevitable or nonpreventable. Despite the challenges associated with IP in austere environments of care, simple measures have been proven effective in deployed hospitals. Hand hygiene adherence rates at Craig Joint Theater Hospital, Afghanistan, nearly tripled within 1 month of surveillance and increased access to alcohol-based hand rub [35]. Two- to fivefold reductions in ventilator-associated pneumonia (VAP) were seen there and at Balad Air Force Theater Hospital, Iraq, with promotion of hand hygiene, implementation of VAP bundles, antimicrobial stewardship, and attention to environmental disinfection [36•]. In Iraq, these measures also resulted in significant improvements in ABC susceptibilities to both amikacin and imipenem. In general, national guidelines to prevent specific infections and transmission of resistant infections should be followed throughout the course of

combat casualty care. Guidelines for the prevention of infections associated with combat casualties, published in 2011, emphasize attention to established IP measures, command support, and deployed IP expertise [37•].

The mainstay of preventing combat wound infections and osteomyelitis after open fracture is early and thorough debridement and irrigation. Removal of foreign material, organic contamination, and devitalized tissue should be performed as early after injury as possible. Current guidelines recommend normal saline without additives, delivered at low pressure. Sterile or even potable water can also be used if necessary. The recently published FLOW study concluded that normal saline alone was preferable to the use of saline with castile soap, regardless of delivery pressure [38•]. Operative debridement is also recommended to be performed as early as possible and repeated until wounds are clean and free of necrosis. This may require serial operative debridement in the first few days after a grossly contaminated injury. However, the timing of initial operative debridement has been an unresolved issue in civilian trauma literature. While early debridement has long been seen as the primary intervention to reduce infection risk, recent studies with a range of times to first debridement have not demonstrated any consistent increase in risk with delayed surgery up to 24 h after injury [39, 40•]. External fixation is preferred initially by the USA, with open reduction and internal fixation typically delayed until evacuation and stabilization of the patient. The British military recommends casting, also with good outcomes, although this may not be scalable to larger numbers of casualties or with longer evacuation times [41]. Penetrating fragments can often be left in situ and observed, particularly if there is no evidence of infection or small entry/exit wounds, and they do not penetrate the peritoneum, pleura, bone, or vascular spaces. Obtaining routine cultures of uninfected appearing wounds is not recommended.

Adjunctive antimicrobials are thought to play an important role in prevention of infection after combat-related injuries, as in civilian trauma. Clinical practice guidelines published in 2011 were endorsed by the Infectious Disease Society of America and the Surgical Infection Society (SIS); these remain the most

current guidelines focusing on antimicrobial use in battlefield injuries [28]. The choice of a prophylactic antibiotic has centered on the need to cover the staphylococcal and streptococcal species typically responsible for wound infections, and the need to limit antibiotic pressure driving resistance. High-dose cefazolin (2 g every 6 to 8 h) remains the agent of choice for most injury patterns, with metronidazole added in instances of hollow viscus injury or organic contamination of the brain or spinal cord (Table 1). As in the SIS civilian orthopedic trauma guidelines, neither extended-spectrum GNR coverage for high-risk open fractures nor penicillin for contaminated wounds is recommended [42]. A full discussion of the controversy surrounding the need for extended GNR coverage after open fracture is beyond the scope of this review. However, recent retrospective analysis of TIDOS data revealed additional risk of MDR isolate recovery with even cefazolin prophylaxis, with an OR of 3.5. This risk was increased further with the use of a fluoroquinolone (OR 5.4) [43]. The MDR ABC and ESBL-producing E. coli isolates seen in recent conflicts have typically been resistant to all agents but colistin and carbapenems, respectively; both of which are unattractive choices for prophylactic agents. This, together with the TIDOS data suggesting increased resistance with even fluoroquinolone use, provides additional reassurance that cefazolin alone is likely an appropriate strategy in this group. The duration of prophylaxis should be short (the maximum duration recommended for any extremity injury is 3 days) and not extended due to the presence of drains or fixators, or restarted after additional debridement. Point-of-injury antimicrobials should be administered on the battlefield if evacuation to surgical care is anticipated to be delayed, and evaluation of the need for tetanus vaccine and immunoglobulin must not be overlooked.

Since recognizing and characterizing the risk of IFI in a subset of combat-injured patients, in 2012, a DoD clinical practice guideline was published to address prevention and updated in 2015 [44, 45•]. These fungal pathogens originate in the environment of the injury and do not typically share the nosocomial route of transmission of the MDR GNR pathogens discussed above. In

contrast to some natural disaster-related experiences with IFI, where only one species is described, these present with a wide variety of fungal species [19, 46]. These are often polymicrobial including Aspergillus, Fusarium, and Mucorales spp. While having any IFI delays wound closure, times to eventual wound closure in combat casualties have been seen to be longest with growth of Mucorales spp. compared to other genera [47]. Again, the primary method for prevention is aggressive debridement; this remains the primary therapy even for established infection. Dilute Dakin's solution has an in vitro dose-related antifungal effect against multiple relevant species of molds, as well as limited toxicity in dilute concentrations [48]. These data have led to a recommendation for use in high-risk patients with battlefield injuries, even prior to the patient's evacuation. Although in combat casualties this diagnosis has been context-specific to southern Afghanistan, similar infections have been seen after numerous natural disasters involving high-energy, heavily contaminated injuries in extensively vegetated environments [46, 49, 50]. It is possible that these could be diagnosed in future conflicts in such environments with much more regularity, given that the modern chain of combat casualty care involves evacuation to hospitals with fungal culture and histopathology within days of injury. It is likely that these infections require not only a similar environment of injury but also a host with high-energy injuries, further predisposed by super-massive requirements for blood product transfusion [51]. Understanding the role of blood product transfusions, and transfusion-transmitted infections like CMV, in immune modulation and predisposition to infection remains challenging. This is particularly relevant in combat casualty care, where the use of fresh whole blood (FWB) has been associated with CMV, and rarely HTLV-1 and hepatitis C transmission, and where practices continue to change to include use of frozen and low-titer O− blood in theater [52,53,54].

Other adjunctive strategies for infection prevention via combat wound care have been the subject of considerable recent research. Topical antimicrobial therapy has long been an attractive target for both prevention and treatment of wound infections, given the potential for high local concentrations to overcome

biofilm activity and the absence of significant systemic absorption to drive major microbiome changes or toxicity. However, the literature has failed to conclusively demonstrate a clinical advantage to the use of antibiotic-impregnated beads or pouches, and recent efforts have not settled the question. The hypothetical advantages to topical therapy also prove to be limitations, since application methods that comprehensively and persistently cover irregular, complex wound surfaces are challenging, and penetration into tissue is limited. Appropriate injury management relies on keeping traumatic wounds free of blood and extravasated fluid, which clearly serve as growth media for bacteria, but in removing these fluids, any topical antimicrobials are also rapidly dispensed with. One recent evaluation of the use of a negative-pressure wound dressing (NWPD) along with antimicrobial-impregnated beads demonstrated that the wound dressing effectively obviated the effect of antimicrobial beads [55]. NWPD itself has been used increasingly, even in deployed hospitals and during aeromedical evacuation, and experience has demonstrated its feasibility in such settings. Its role in preventing infection is unclear, however. Some data suggest that there is an increased risk of S. aureus in the setting of NWPD, and others have raised concerns of local wound toxicity and effects on tissue appearance that make diagnosis of infection more challenging [56,57,58]. Finally, considerable efforts have gone into biomedical research investigating other novel therapies including gallium, blue and ultraviolet light, the development of biofilm-resistant surfaces for orthopedic hardware, and other materials used for dead space management and fracture stabilization [59,60,61,62]. Multiple federally funded translational studies remain underway.

Treatment

The treatment of infectious complications after combat trauma is specific to the host, the site of infection, and the microorganism(s) involved. Many infections are managed similarly to those seen after civilian trauma and should be treated according to relevant guidelines (e.g., catheter-associated bloodstream infections, ventilator-associated pneumonias). Wound infections and osteomyelitis constitute the majority of combat-related infections. The treatment of orthopedic infections

has frequently been the most individualized and most challenging. This is a result of the heterogeneous nature of these injuries, the typical need for ongoing orthopedic hardware and fracture fixation, multiple operative takebacks, the frequent involvement of biofilm, and the challenges associated with often prolonged and repeated courses of antimicrobials.

Surgical treatment for infected wounds is paramount and relies upon debridement of overtly infected and devitalized tissue, draining abscesses or infected hematomas, removal of residual foreign bodies, and ensuring adequate vascular supply. When the underlying bone is involved, removal of orthopedic hardware is preferred, though not always possible. Diagnosis of the infected wound or bone relies on the surgeon's direct visualization and obtaining diagnostic material. If there is suspicion for infection, adequate material for aerobic and anaerobic cultures should be obtained. In general, swabs should be avoided. Fluids should be aspirated into a syringe and capped, and multiple specimens of involved tissue should be obtained; yield increases with increasing number of specimens. While yeast will typically grow easily from standard bacterial cultures, mold will not. While occasionally a dressing change will reveal a wound visibly covered in mold, IFI should generally be suspected in high-risk patients in the setting of progressive, rapid wound necrosis. If IFI is suspected or proven, surgical debridement must be aggressive and frequent until wounds appear consistently healthy. Fungal cultures as well as histopathology to determine depth of invasion are essential to establish the diagnosis and optimize treatment. Mycobacteria have rarely been involved in combat-associated wound infections, and cultures for these organisms are indicated in chronic, nonhealing wounds [63].

Empiric therapy should be chosen based again upon the host, the site of infection, and the most likely pathogens involved. Accurate understanding of involved pathogens depends upon a current, context-specific antibiogram. The need for these has been highlighted even in the deployed environment, and given that predominant pathogens change over time and in different theaters of operation, it is impossible to give a standard regimen that will be appropriate in all future

combat casualties. In recent casualties from Afghanistan, ESBL-producing Enterobacteriaceae have been predominant, necessitating empiric use of carbapenems for many serious infections. Newer combination agents including ceftazidime/avibactam and ceftolozane/tazobactam have been developed for treatment of MDR GNR infections and may have an increasing role for treating combat casualties in the future, although experience is currently limited with this population [64]. Initial treatment for suspected IFI requires broad antimold coverage, as many species have been involved, including some (e.g., Aspergillus terreus, Fusarium spp.) resistant to amphotericin. Given the predominance of Mucorales spp. and other resistant molds, echinocandins are not recommended for treatment. Clinical practice guidelines recommend the use of both amphotericin and voriconazole, and experience is also growing with posaconazole and newer broad-spectrum antifungals like isavuconazole in this context, though these are not recommended as monotherapy initially. When culture results are available, empiric therapy for both bacterial and fungal infections should be directed against organisms isolated from wounds and felt to be responsible for infection. This can be easier said than done, however, given the often polymicrobial involvement of wounds in the first few weeks after injury. Early GNR predominance gives way to primarily staphylococci in well-established, relapsing infections, especially with lower-virulence pathogens like ABC. S. aureus, beta-hemolytic streptococci, Enterobacteriaceae, and P. aeruginosa are considered to be pathogens when isolated from a wound. Anaerobes are occasionally isolated; though, even in established infection, they are often resistant to agents used for treatment without apparent differences in outcomes [65]. Candida spp., when isolated in wounds, are usually also part of a polymicrobial infection and do not appear to have an impact on mortality [66]. Enterococci as well as lower-virulence GNR (Stenotrophomonas maltophilia and non-aeruginosa Pseudomonas spp.) infrequently contribute to long-term infectious complications, although they are often found with other pathogens; Enterococcus in particular has been shown to be present in a majority of mangled extremities during the first few days after injury [67]. Coagulase-

negative staphylococci are the single most frequently isolated organisms in the TIDOS cohort, and interpretation of their significance must take into account whether other organisms are also present, the size of the inoculum, whether they are repeatedly isolated, and perhaps most importantly, whether a device or hardware is involved.

Conclusions

Infectious complications after combat-related injury are common, affecting more than a quarter of all casualties, and are frequently caused by MDR pathogens transmitted within the chain of combat casualty care. These complications may cause delayed union of fractures, unplanned operative takebacks and rehospitalizations, failure of limb salvage, high-level amputations, prolonged ICU stays, and death. Prevention includes aggressive surgical management, judicious and brief use of antimicrobial prophylaxis, and systematic, command-supported efforts at IP. Treatment must take into account the overall clinical status of the patient, the anatomical site of infection, and the suspected and proven pathogens involved.

10.Gunshot wounds.

A gunshot wound (GSW) is a penetrating injury caused by a projectile (e.g. a bullet) from a gun (typically firearm or air gun).[11][12] Damages may include bleeding, bone fractures, organ damage, wound infection, loss of the ability to move part of the body and, in more severe cases, death.[2] Damage depends on the part of the body hit, the path the bullet follows through the body, and the type and speed of the bullet.[12] Long-term complications can include lead poisoning and post-traumatic stress disorder (PTSD).[1][2][13]

Factors that determine rates of gun violence vary by country.[5] These factors may include the illegal drug trade, easy access to firearms, substance misuse including alcohol, mental health problems, firearm laws, social attitudes, economic differences and occupations such as being a police officer.[5][6] Where guns are more common, altercations more often end in death.[14]

Before management begins it should be verified the area is safe.[9] This is followed by stopping major bleeding, then assessing and supporting the airway, breathing, and circulation.[9] Firearm laws, particularly background checks and permit to purchase, decrease the risk of death from firearms.[7] Safer firearm storage may decrease the risk of firearm-related deaths in children.[8]

In 2015, about a million gunshot wounds occurred from interpersonal violence.[10] In 2016, firearms resulted in 251,000 deaths globally, up from 209,000 in 1990.[5] Of these deaths 161,000 (64%) were the result of assault, 67,500 (27%) were the result of suicide, and 23,000 (9%) were accidents.[5] In the United States, guns resulted in about 40,000 deaths in 2017.[15] Firearm-related deaths are most common in males between the ages of 20 to 24 years.[5] Economic costs due to gunshot wounds have been estimated at US$140 billion a year in the United States.[16]

Signs and symptoms

Trauma from a gunshot wound varies widely based on the bullet, velocity, mass, entry point, trajectory, affected anatomy, and exit point. Gunshot wounds can be particularly devastating compared to other penetrating injuries because the trajectory and fragmentation of bullets can be unpredictable after entry. Moreover, gunshot wounds typically involve a large degree of nearby tissue disruption and destruction caused by the physical effects of the projectile correlated with the bullet velocity classification.[17]

The immediate damaging effect of a gunshot wound is typically severe bleeding with the potential for hypovolemic shock, a condition characterized by inadequate delivery of oxygen to vital organs.[18] In the case of traumatic hypovolemic shock, this failure of adequate oxygen delivery is due to blood loss, as blood is the means of delivering oxygen to the body's constituent parts. Devastating effects can result when a bullet strikes a vital organ such as the heart, lungs or liver, or damages a component of the central nervous system such as the spinal cord or brain.[18]

Common causes of death following gunshot injury include bleeding, low oxygen caused by pneumothorax, catastrophic injury to the heart and major blood vessels, and damage to the brain or central nervous system. Non-fatal gunshot wounds frequently have mild to severe long-lasting effects, typically some form of major disfigurement such as amputation because of a severe bone fracture and may cause permanent disability. A sudden blood gush may take effect immediately from a gunshot wound if a bullet directly damages larger blood vessels, especially arteries.

Pathophysiology

Femur shot with a .58 caliber Minié ball.

Femur shot with a 5.56 mm bullet.

The degree of tissue disruption caused by a projectile is related to the cavitation the projectile creates as it passes through tissue. A bullet with sufficient energy will have a cavitation effect in addition to the penetrating track injury. As the bullet passes through the tissue, initially crushing then lacerating, the space left forms a cavity; this is called the permanent cavity. Higher-velocity bullets create a pressure wave that forces the tissues away, creating not only a permanent cavity the size of the caliber of the bullet but a temporary cavity or secondary cavity, which is often many times larger than the bullet itself.[19] The temporary cavity is the radial stretching of tissue around the bullet's wound track, which momentarily leaves an empty space caused by high pressures surrounding the projectile that accelerate material away from its path.[18] The extent of cavitation, in turn, is related to the following characteristics of the projectile:

- Kinetic energy: KE = $1/2mv^2$ (where *m* is mass and *v* is velocity). This helps to explain why wounds produced by projectiles of higher mass and/or higher velocity produce greater tissue disruption than projectiles of lower mass and velocity. The velocity of the bullet is a more important determinant of tissue injury. Although both mass and velocity contribute to the overall energy of the projectile, the energy is proportional to the mass while proportional to the *square* of its velocity. As a result, for constant velocity, if the mass is doubled, the energy is doubled; however, if the velocity of the bullet is doubled, the energy increases four times. The initial velocity of a bullet is largely dependent on the firearm. The US military commonly uses 5.56-mm bullets, which have a relatively low mass as compared with other bullets; however, the speed of these bullets is relatively fast. As a result, they produce a larger amount of kinetic energy, which is transmitted to the tissues of the target.[19][20] The size of the temporary cavity is approximately proportional to the kinetic energy of the bullet and depends on the resistance of the tissue to stress.[18] Muzzle energy, which is based on muzzle velocity, is often used for ease of comparison.
- Yaw: Handgun bullets will generally travel in a relatively straight line or make one turn if a bone is hit. Upon travel through deeper tissue, high-energy rounds may become unstable as they decelerate, and may tumble (pitch and yaw) as the energy of the projectile is absorbed, causing stretching and tearing of the surrounding tissue.[19]
- Fragmentation: Most commonly, bullets do not fragment, and secondary damage from fragments of shattered bone is a more common complication than bullet fragments.[19]

Diagnosis

Classification

Gunshot wounds are classified according to the speed of the projectile using the Gustilo open fracture classification:

- Low-velocity: Less than 1,100 ft/s (340 m/s)

Low velocity wounds are typical of small caliber handguns and display wound patterns like Gustilo Anderson Type 1 or 2 wounds

- Medium-velocity: Between 1,200 ft/s (340 m/s) and 2,000 ft/s (610 m/s)

These are more typical of shotgun blasts or higher caliber handguns like magnums. The risk of infection from these types of wounds can vary depending on the type and pattern of bullets fired as well as the distance from the firearm.

- High-velocity: Between 2,000 ft/s (610 m/s) and 3,500 ft/s (1,100 m/s)

Usually caused by powerful assault or hunting rifles and usually display wound pattern similar to Gustilo Anderson Type 3 wounds. The risk of infection is especially high due to the large area of injury and destroyed tissue.[21]

Bullets from handguns are sometimes less than 1,000 ft/s (300 m/s) but with modern pistol loads, they usually are slightly above 1,000 ft/s (300 m/s), while bullets from most modern rifles exceed 2,500 ft/s (760 m/s). One recently developed class of firearm projectiles is the hyper-velocity bullet, such cartridges are usually either wildcats made for achieving such high speed or purpose-built factory ammunition with the same goal in mind. Examples of hyper velocity cartridges include the .220 Swift, .17 Remington and .17 Mach IV cartridges. The US military commonly uses 5.56mm bullets, which have a relatively low mass as compared with other bullets (40-62 grains); however, the speed of these bullets is relatively fast (Approximately 2,800 ft/s (850 m/s), placing them in the high velocity category). As a result, they produce a larger amount of kinetic energy, which is transmitted to the tissues of the target.[19] However, one must remember that high kinetic energy does not necessarily equate to high stopping power, as incapacitation usually results from remote wounding effects such as bleeding, rather than raw energy transfer. High energy does indeed result in more tissue disruption, which plays a role in incapacitation, but other factors such as wound size and shot placement play as big of, if not a bigger role in stopping power and thus, effectiveness. Muzzle velocity does not consider the effect of aerodynamic drag on the flight of the bullet for the sake of ease of comparison.

Prevention

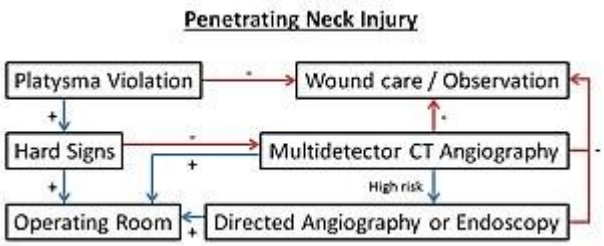
Medical organizations in the United States recommend a criminal background check being held before a person buys a gun and that a person who has convictions for crimes of violence should not be permitted to buy a gun.[15] Safe storage of firearms is recommended, as well as better mental health care and removal of guns from those at risk of suicide.[15] In an effort to prevent mass shootings greater regulations on guns that can rapidly fire many bullets is recommended.[15]

ManagementInitial assessment for a gunshot wound is approached in the same way as other acute trauma using the advanced trauma life support (ATLS) protocol.[22] These include:

- A) Airway - Assess and protect airway and potentially the cervical spine
- B) Breathing - Maintain adequate ventilation and oxygenation
- C) Circulation - Assess for and control bleeding to maintain organ perfusion including focused assessment with sonography for trauma (FAST)
- D) Disability - Perform basic neurological exam including Glasgow Coma Scale (GCS)
- E) Exposure - Expose entire body and search for any missed injuries, entry points, and exit points while maintaining body temperature

Depending on the extent of injury, management can range from urgent surgical intervention to observation. As such, any history from the scene such as gun type, shots fired, shot direction and distance, blood loss on scene, and pre-hospital vitals signs can be very helpful in directing management. Unstable people with signs of bleeding that cannot be controlled during the initial evaluation require immediate surgical exploration in the operating room.[22] Otherwise, management protocols are generally dictated by anatomic entry point and anticipated trajectory.

Neck



Penetrating neck injury protocol.[23]

A gunshot wound to the neck can be particularly dangerous because of the high number of vital anatomical structures contained within a small space. The neck contains the larynx, trachea, pharynx, esophagus, vasculature (carotid, subclavian, and vertebral arteries; jugular, brachiocephalic, and vertebral veins; thyroid vessels), and nervous system anatomy (spinal cord, cranial nerves, peripheral nerves, sympathetic chain, brachial plexus). Gunshots to the neck can thus cause severe bleeding, airway compromise, and nervous system injury.[24]

Initial assessment of a gunshot wound to the neck involves non-probing inspection of whether the injury is a penetrating neck injury (PNI), classified by violation of the platysma muscle.[24] If the platysma is intact, the wound is considered superficial and only requires local wound care. If the injury is a PNI, surgery should be consulted immediately while the case is being managed. Of note, wounds should not be explored on the field or in the emergency department given the risk of exacerbating the wound.

Due to the advances in diagnostic imaging, management of PNI has been shifting from a "zone-based" approach, which uses anatomical site of injury to guide decisions, to a "no-zone" approach which uses a symptom-based algorithm.[25] The no-zone approach uses a hard signs and imaging system to guide next steps. Hard signs include airway compromise, unresponsive shock, diminished pulses, uncontrolled bleeding, expanding hematoma, bruits/thrill, air bubbling from wound or extensive subcutaneous air, stridor/hoarseness, neurological deficits.[25] If any hard signs are present, immediate surgical exploration and repair is pursued alongside airway and bleeding control. If there are no hard signs, the person receives a multi-detector CT angiography for better diagnosis. A directed angiography or endoscopy may be warranted in a high-risk

trajectory for the gunshot. A positive finding on CT leads to operative exploration. If negative, the person may be observed with local wound care.[25]

Chest

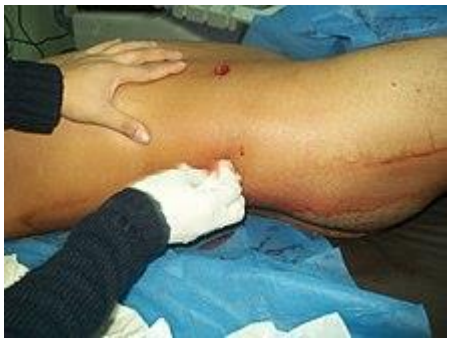
Important anatomy in the chest includes the chest wall, ribs, spine, spinal cord, intercostal neurovascular bundles, lungs, bronchi, heart, aorta, major vessels, esophagus, thoracic duct, and diaphragm. Gunshots to the chest can thus cause severe bleeding (hemothorax), respiratory compromise (pneumothorax, hemothorax, pulmonary contusion, tracheobronchial injury), cardiac injury (pericardial tamponade), esophageal injury, and nervous system injury.[26]

Initial workup as outlined in the Workup section is particularly important with gunshot wounds to the chest because of the high risk for direct injury to the lungs, heart, and major vessels. Important notes for the initial workup specific for chest injuries are as follows. In people with pericardial tamponade or tension pneumothorax, the chest should be evacuated or decompressed if possible prior to attempting tracheal intubation because the positive pressure ventilation can cause hypotention or cardiovascular collapse.[27] Those with signs of a tension pneumothorax (asymmetric breathing, unstable blood flow, respiratory distress) should immediately receive a chest tube (> French 36) or needle decompression if chest tube placement is delayed.[27] FAST exam should include extended views into the chest to evaluate for hemopericardium, pneumothorax, hemothorax, and peritoneal fluid.[27]

Those with cardiac tamponade, uncontrolled bleeding, or a persistent air leak from a chest tube all require surgery.[28] Cardiac tamponade can be identified on FAST exam. Blood loss warranting surgery is 1–1.5 L of immediate chest tube drainage or ongoing bleeding of 200-300 mL/hr.[28][29] Persistent air leak is suggestive of tracheobronchial injury which will not heal without surgical intervention.[28] Depending on the severity of the person's condition and if cardiac arrest is recent or imminent, the person may require surgical intervention in the emergency department, otherwise known as an emergency department thoracotomy (EDT).[30]

However, not all gunshot to the chest require surgery. Asymptomatic people with a normal chest X-ray can be observed with a repeat exam and imaging after 6 hours to ensure no delayed development of pneumothorax or hemothorax.[27] If a person only has a pneumothorax or hemothorax, a chest tube is usually sufficient for management unless there is large volume bleeding or persistent air leak as noted above.[27] Additional imaging after initial chest X-ray and ultrasound can be useful in guiding next steps for stable people. Common imaging modalities include chest CT, formal echocardiography, angiography, esophagoscopy, esophagography, and bronchoscopy depending on the signs and symptoms.[31]

Abdomen



Abdominal gunshot wound

Important anatomy in the abdomen includes the stomach, small bowel, colon, liver, spleen, pancreas, kidneys, spine, diaphragm, descending aorta, and other abdominal vessels and nerves. Gunshots to the abdomen can thus cause severe bleeding, release of bowel contents, peritonitis, organ rupture, respiratory compromise, and neurological deficits.

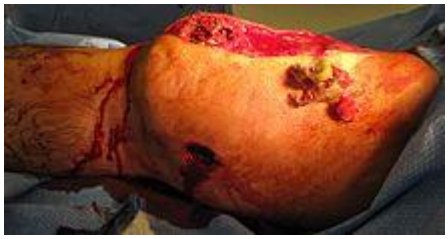
The most important initial evaluation of a gunshot wound to the abdomen is whether there is uncontrolled bleeding, inflammation of the peritoneum, or spillage of bowel contents. If any of these are present, the person should be transferred immediately to the operating room for laparotomy.[32] If it is difficult to evaluate for those indications because the person is unresponsive or incomprehensible, it is up to the surgeon's discretion whether to pursue laparotomy, exploratory laparoscopy, or alternative investigative tools.

Although all people with abdominal gunshot wounds were taken to the operating room in the past, practice has shifted in recent years with the advances in

imaging to non-operative approaches in more stable people.[33] If the person's vital signs are stable without indication for immediate surgery, imaging is done to determine the extent of injury.[33] Ultrasound (FAST) and help identify intra-abdominal bleeding and X-rays can help determine bullet trajectory and fragmentation.[33] However, the best and preferred mode of imaging is high-resolution multi-detector CT (MDCT) with IV, oral, and sometimes rectal contrast.[33] Severity of injury found on imaging will determine whether the surgeon takes an operative or close observational approach.

Diagnostic peritoneal lavage (DPL) has become largely obsolete with the advances in MDCT, with use limited to centers without access to CT to guide requirement for urgent transfer for operation.[33]

Extremities



Acute penetrating trauma from a close-range shotgun blast injury to knee. Birdshot pellets are visible in the wound, within the shattered patella. The powder wad from the shotgun shell has been extracted from the wound, and is visible at the upper right of the image.

The four main components of extremities are bones, vessels, nerves, and soft tissues. Gunshot wounds can thus cause severe bleeding, fractures, nerve deficits, and soft tissue damage. The Mangled Extremity Severity Score (MESS) is used to classify the severity of injury and evaluates for severity of skeletal and/or soft tissue injury, limb ischemia, shock, and age.[34] Depending on the extent of injury, management can range from superficial wound care to limb amputation.

Vital sign stability and vascular assessment are the most important determinants of management in extremity injuries. As with other traumatic cases, those with uncontrolled bleeding require immediate surgical intervention.[22] If surgical intervention is not readily available and direct pressure is insufficient to

control bleeding, tourniquets or direct clamping of visible vessels may be used temporarily to slow active bleeding.[35] People with hard signs of vascular injury also require immediate surgical intervention. Hard signs include active bleeding, expanding or pulsatile hematoma, bruit/thrill, absent distal pulses and signs of extremity ischemia.[36]

For stable people without hard signs of vascular injury, an injured extremity index (IEI) should be calculated by comparing the blood pressure in the injured limb compared to an uninjured limb in order to further evaluate for potential vascular injury.[37] If the IEI or clinical signs are suggestive of vascular injury, the person may undergo surgery or receive further imaging including CT angiography or conventional arteriography.

In addition to vascular management, people must be evaluated for bone, soft tissue, and nerve injury. Plain films can be used for fractures alongside CTs for soft tissue assessment. Fractures must be debrided and stabilized, nerves repaired when possible, and soft tissue debrided and covered.[38] This process can often require multiple procedures over time depending on the severity of injury.

Epidemiology

In 2015, about a million gunshot wounds occurred from interpersonal violence.[10] Firearms, globally in 2016, resulted in 251,000 deaths up from 209,000 in 1990.[5] Of these deaths 161,000 (64%) were the result of assault, 67,500 (27%) were the result of suicide, and 23,000 were accidents.[5] Firearm related deaths are most common in males between the ages of 20 to 24 years.[5]

The countries with the greatest number of deaths from firearms are Brazil, United States, Mexico, Colombia, Venezuela, Guatemala and South Africa which make up just over half the total.[5] In the United States in 2015 about half of the 44,000 people who died by suicide did so with a gun.[39]

As of 2016, the countries with the highest rates of gun violence per capita were El Salvador, Venezuela, and Guatemala with 40.3, 34.8, and 26.8 violent gun deaths per 100,000 people respectively.[40] The countries with the lowest rates of

were Singapore, Japan, and South Korea with 0.03, 0.04, and 0.05 violent gun deaths per 100,000 people respectively.[40]

Canada

In 2016, about 893 people died due to gunshot wounds in Canada (2.1 per 100,000).[5] About 80% were suicides, 12% were assaults, and 4% percent were an accident.[41]

United States

In 2017, there were 39,773 deaths in the United States as a result gunshot wounds.[15] Of these 60% were suicides, 37% were homicides, 1.4% were by law enforcement, 1.2% were accidents, and 0.9% were from an unknown cause.[15] This is up from 37,200 deaths in 2016 due to a gunshot wound (10.6 per 100,000).[5] With respect to those that pertain to interpersonal violence, it had the 31st highest rate in the world with 3.85 deaths per 100,000 people in 2016.[40] The majority of all homicides and suicides are firearm-related, and the majority of firearm-related deaths are the result of murder and suicide.[42] When sorted by GDP, however, the United States has a much higher violent gun death rate compared to other developed countries, with over 10 times the number of firearms assault deaths than the next four highest GDP countries combined.[43] Gunshot violence is the third most costly cause of injury and the fourth most expensive form of hospitalization in the United States.[44]

History

Until the 1880s, the standard practice for treating a gunshot wound called for physicians to insert their unsterilized fingers into the wound to probe and locate the path of the bullet.[45] Standard surgical theory such as opening abdominal cavities to repair gunshot wounds,[46] germ theory, and Joseph Lister's technique for antiseptic surgery using diluted carbolic acid, had not yet been accepted as standard practice. For example, sixteen doctors attended to President James A. Garfield after he was shot in 1881, and most probed the wound with their fingers or dirty instruments.[47] Historians agree that massive infection was a significant factor in Garfield's death.[45][48]

At almost the same time, in Tombstone, Arizona Territory, on 13 July 1881, George E. Goodfellow performed the first laparotomy to treat an abdominal gunshot wound.[49]:M-9 Goodfellow pioneered the use of sterile techniques in treating gunshot wounds,[50] washing the person's wound and his hands with lye soap or whisky, and his patient, unlike the President, recovered.[51] He became America's leading authority on gunshot wounds[52] and is credited as the United States' first civilian trauma surgeon.[53]

Mid-nineteenth-century handguns such as the Colt revolvers used during the American Civil War had muzzle velocities of just 230–260 m/s and their powder and ball predecessors had velocities of 167 m/s or less. Unlike today's high-velocity bullets, nineteenth-century balls produced almost little or no cavitation and, being slower moving, they were liable to lodge in unusual locations at odds with their trajectory.[54]

Wilhelm Röntgen's discovery of X-rays in 1895 led to the use of radiographs to locate bullets in wounded soldiers.[55]

Survival rates for gunshot wounds improved among US military personnel during the Korean and Vietnam Wars, due in part to helicopter evacuation, along with improvements in resuscitation and battlefield medicine.[55][56] Similar improvements were seen in US trauma practices during the Iraq War.[57] Some military trauma care practices are disseminated by citizen soldiers who return to civilian practice.[55][58][59] One such practice is to transfer major trauma cases to an operating theater as soon as possible, to stop internal bleeding. Within the United States, the survival rate for gunshot wounds has increased, leading to apparent declines in the gun death rate in states that have stable rates of gunshot hospitalizations.

11. Combined radiation and chemical damage. Thermal damage.

What Are the Different Types of Burns?

A burn injury usually results from an energy transfer to the body. There are many types of burns caused by thermal, radiation, chemical, or electrical contact.

- **Thermal burns:** Burns due to external heat sources which raise the temperature of the skin and tissues and cause tissue cell death or charring. Hot metals, scalding liquids, steam, and flames, when coming in contact with the skin, can cause thermal burns.
- **Radiation burns:** Burns due to prolonged exposure to ultraviolet rays of the sun, or to other sources of radiation such as x-ray
- **Chemical burns:** Burns due to strong acids, alkalies, detergents, or solvents coming into contact with the skin and/or eyes
- **Electrical burns:** Burns from electrical current, either alternating current (AC) or direct current (DC)

The Effects of Burns

A severe burn can be a seriously devastating injury—not only physically but emotionally. It can affect not only to the burn victim, but the entire family. Persons with severe burns may be left with a loss of certain physical abilities, disfigurement, loss of a limb, loss of mobility, scarring, and infection. In addition, severe burns are capable of penetrating deep skin layers, causing muscle or tissue damage that may affect every system of the body.

Burns can also cause emotional problems such as depression, nightmares, or flashbacks from the traumatizing event. The loss of a friend or family member and possessions in the fire may add grief to the emotional strain of a burn.

Burns are classified as first-, second-, or third-degree, depending on how deep and severe they penetrate the skin's surface.

- **First-degree (superficial) burns**

  First-degree burns affect only the epidermis, or outer layer of skin. The burn site is red, painful, dry, and with no blisters. Mild sunburn is an example. Long-term tissue damage is rare and usually consists of an increase or decrease in the skin color.
- **Second-degree -(partial thickness) burns**

  Second-degree burns involve the epidermis and part of the dermis layer of skin. The burn site appears red, blistered, and may be swollen and painful.

- **Third-degree (full thickness) burns**

  Third-degree burns destroy the epidermis and dermis. Third-degree burns may also damage the underlying bones, muscles, and tendons. The burn site appears white or charred. There is no sensation in the area since the nerve endings are destroyed.

Burns affecting 10 percent of a child's body and those affecting 15 to 20 percent of an adult's body are considered to be major injuries and require hospitalization and extensive rehabilitation.

Burn Rehabilitation Team

Because so many functions and systems of the body can be affected by severe burns, the need for rehabilitation becomes even more crucial.

Many hospitals have a specialized burn unit or center and some facilities are designated solely for the rehabilitation of burn patients. Burn patients need the highly specialized services of medical specialists who work together on a multidisciplinary team, including any of the following:

- Physiatrists
- Plastic surgeons
- Internists
- Orthopaedic surgeons
- Infection disease specialists
- Rehabilitation nurses who specialize in burn care
- Psychologists/psychiatrists
- Physical therapists
- Occupational therapists
- Respiratory therapists
- Dietitians
- Social workers
- Case managers
- Recreation therapists
- Vocational counselors

The burn rehabilitation program

Burn rehabilitation begins during the acute treatment phase and may last days to months to years, depending on the extent of the burn. Rehabilitation is designed to meet each patient's specific needs; therefore, each program is different. The goals of a burn rehabilitation program include helping the patient return to the highest level of function and independence possible, while improving the overall quality of life - physically, emotionally, and socially.

In order to help reach these goals, burn rehabilitation programs may include the following:

- Complex wound care
- Pain management
- Physical therapy for positioning, splinting, and exercise
- Occupational therapy for assistance with activities of daily living (ADLs)
- Cosmetic reconstruction and skin grafting
- Counseling to deal with common emotional responses during convalescence, such as depression, grieving, anxiety, guilt, and insomnia
- Patient and family education and counseling
- Nutritional counseling

Advances in the understanding and treatment of burns, state-of-the-art burn units and facilities, comprehensive burn rehabilitation services, and integrated medical care have all contributed to the increase in survival rate and recovery of burn patients.

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