



Donovanosis

Granuloma inguinale is a chronic bacterial infection that frequently is associated with other sexually transmitted diseases. Granuloma inguinale is characterized by intracellular inclusions in macrophages referred to as Donovan bodies. Granuloma inguinale usually affects the skin and mucous membranes in the genital region, where it results in nodular lesions that evolve into ulcers. The ulcers progressively expand and are locally destructive

The intracellular organism responsible for granuloma inguinale was initially described by Donovan over a century ago, and subsequently, the bacterium was classified in 1913 as *Calymmatobacterium granulomatis*. Although Anderson suggested that the organism be eponymously named *Donovania granulomatosis*, Carter et al discovered that the molecular structure of the causative organism was similar to *Klebsiella* species and reclassified the gram-negative pleomorphic bacillus as *Klebsiella granulomatis*.^{1,2}

The mode of transmission of granuloma inguinale primarily occurs through sexual contact; however, it is hypothesized to have low infectious capabilities because repeated exposure is necessary for clinical infection to occur. Additionally, granuloma inguinale may also be obtained through the fecal route or by passage through an infected birth canal.

History

Although the exact incubation period for granuloma inguinale is unknown, it ranges from a day to a year, with the median time being 50 days. [3](#)

Physical

Morphology

The 4 main types of cutaneous lesions are as follows:

- Nodular: The initial granuloma inguinale lesion is a papule or nodule that arises at the site of inoculation. The nodule is soft, often pruritic and erythematous, and eventually ulcerates. A nodule may be mistaken for a lymph node [ie, pseudobubo].
- Ulcerovegetative (most common): These granuloma inguinale lesions develop from nodular lesions and consist of large, usually painless, expanding, suppurative ulcers. The ulcers have clean, friable bases with distinct, raised, rolled margins and have a tendency to bleed easily. The ulcers are "beefy red" and slowly expand centrifugally, eventually becoming more granulomatous with serpiginous borders. They are commonly located in the skin folds, and autoinoculation is a common feature, resulting in lesions on adjacent skin. Ulcers often become secondarily infected with other types of bacteria and emit a putrid odor.
- Cicatricial: Dry ulcers evolve into cicatricial plaques and may be associated with [lymphedema](#).
- Hypertrophic or verrucous (relatively rare): This proliferative reaction, with the formation of large vegetating masses, may resemble [genital warts](#).

Elephantiasislike swelling of the external genitalia is a frequent complication and is found most often in infected females in the late stage of granuloma inguinale.

- The most common locations of granuloma inguinale lesions in men are the sulcocranal and balanopreputial regions, as well as the anus.

- In women, granuloma inguinale lesions occur on the labia minora, the mons veneris, the fourchette, and/or the cervix. Cervical involvement occurs in 10% of cases.
- Children are frequently infected via contact with an adult; however, this is not necessarily the result of sexual abuse. ³

Extragenital involvement

- Extragenital involvement occurs in 6% of granuloma inguinale cases.
- Autoinoculation or direct extension may lead to involvement of the lips, oral/gastrointestinal mucosa, scalp, abdomen, arms, legs, and bones.
- Lymphadenopathy does not occur as a result of the primary infection with *Klebsiella granulomatis*, but, rather, it occurs from secondary bacterial infections. Pseudobuboes resemble lymph nodes, but they are just nodular lesions.
- Disseminated lesions associated with systemic symptoms are frequently reported in endemic regions. ³ Hematogenous dissemination to the spleen, lungs, liver, bones, and the orbits may occur and occasionally results in death.

Causes

Granuloma inguinale is caused by *Klebsiella granulomatis*, a gram-negative pleomorphic bacillus formerly known as *Calymma tobacterium granulomatis*.

Laboratory Studies

- Although isolation of *Klebsiella granulomatis* has been reported, the organism is extremely fastidious and culture is beyond the capability of most laboratories. The easiest method to visualize the organism is via smears from the base of the ulcer. The organisms are seen within the cytoplasm of histiocytes. Characteristically, they exhibit bipolar staining, which has been likened to a safety-pin appearance, and are referred to as Donovan bodies. The organisms can occasionally be identified in tissue biopsy specimens with the use of special stains.
- If a quick diagnosis is necessary, a smear can be performed. First, a cotton swab is gently rolled over the ulcer so as not to cause bleeding. The swab is then rolled over a glass slide. The slide is allowed to air dry and is then stained with Giemsa stain or pinacyanol to demonstrate Donovan bodies.
- Alternatively, a crush preparation can be performed. A small piece of tissue should be obtained from the ulcer edge or base via punch biopsy, curettage, or a thin wedge resection. Next, the tissue is crushed between 2 glass slides, separated, and then air dried. A

Wright-Giemsa, Warthin-Starry, toluidine blue, or Leishman stain may be used to demonstrate the Donovan bodies.

- Lastly, a tissue biopsy specimen can be obtained; however, the organisms may be difficult to find in early or secondarily infected lesions, or on routine stained sections with hematoxylin and eosin. Thin, paraffin-embedded sections stained with Giemsa or silver stain may facilitate identification of the rod-shaped, encapsulated organisms within the macrophages.

- Polymerase chain reaction techniques may be more sensitive ; however, they are currently only used for scientific research.

- An indirect immunofluorescent technique is available to test serum; however, it is not accurate enough for confirmatory diagnosis.

- Culture of *Klebsiella granulomatis* from feces has been reported using a monocyte co-culture system and a modified *Chlamydia* culture.

- Papanicolaou smears may identify Donovan bodies in patients undergoing routine cervical cytological screening.

Imaging Studies

- If bony involvement is suspected in granuloma inguinale, radiography or other imaging studies are indicated.

Other Tests

- Testing for other sexually transmitted diseases is warranted because multiple coexisting infections are common.

Histologic Findings

The epidermis displays acanthosis at the ulcer edge, with pseudoepitheliomatous hyperplasia variably present. A dense dermal infiltrate of histiocytes and plasma cells is present, with a scattering of small neutrophilic abscesses. The macrophages are large and vacuolated, and they contain intracellular bacilli (ie, Donovan bodies), which are best visualized using special stains such as a Warthin-Starry, Wright-Giemsa, or Leishman stain. *Klebsiella granulomatis* does not stain well with hematoxylin and eosin.

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Medical Care

The recommended antibiotic for granuloma inguinale is either trimethoprim/sulfamethoxazole [7](#) or doxycycline. Alternatives include ciprofloxacin, erythromycin, or azithromycin.

[8](#)

The antibiotic should be given for at least a 3-week course and continued until reepithelialization of the ulcer occurs and any signs of the disease have resolved. If the granuloma inguinale ulcers do not respond within the first days of therapy, add an aminoglycoside (eg, gentamicin at 1 mg/kg IV q8h). Relapse of granuloma inguinale may occur up to 18 months after treatment. In some countries, tetracycline is no longer recommended, owing to bacterial resistance.

[9](#)

Special considerations

Pregnancy is a relative contraindication for the use of sulfonamides. In pregnant and lactating women with granuloma inguinale, the Centers for Disease Control and Prevention [10](#) recommends erythromycin with or without a parenteral aminoglycoside; however, recent data suggest erythromycin may increase the risk of congenital malformation.

[11](#)

Doxycycline and ciprofloxacin are contraindicated in pregnancy.

HIV-associated granuloma inguinale may take longer to heal, and the addition of a parenteral aminoglycoside to the regimen is highly recommended. [12](#)

Sexual contacts within 60 days prior to the onset of the patient's symptoms of granuloma inguinale should be examined and offered therapy.

Surgical Care

coadministration; sulfonamides may increase free methotrexate concentrations; TMP-SMZ may interfere with Jaffe alkaline picrate reaction for creatinine, causing overestimation of creatinine value

Documented hypersensitivity; megaloblastic anemia due to folate deficiency; pregnant patients; nursing mothers; age <2 mo

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Discontinue at first appearance of rash or sign of adverse reaction; Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias have rarely occurred; pseudomembranous colitis caused by *Clostridium difficile* has been reported; sulfonamide hypersensitivity reactions may cause cough, shortness of breath, and pulmonary infiltrates

Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (elderly persons, alcoholic patients, anticonvulsant therapy, malabsorption, malnutrition) and those with severe allergies or bronchial asthma; dose-related hemolysis may occur in patients with G-6-PD deficiency

Obtain CBC count frequently and discontinue therapy if significant hematologic changes occur; may cause bone marrow suppression (if signs occur, give 5-15 mg/d leucovorin); patients with AIDS may not tolerate or respond to TMP-SMZ in same manner as non-AIDS patients; give fluids to prevent crystalluria and stone formation

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Doxycycline (Adoxa, Doryx, Vibramycin, Periostat)

Bacteriostatic tetracycline antibiotic that inhibits protein synthesis and thus bacterial growth by

Ciprofloxacin (Cipro)

Bactericidal fluoroquinolone antibiotic that inhibits the bacterial enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination.

Adult

750 mg PO bid for at least 3 wk

Pediatric

<18 years: Not recommended
>18 years: Administer as in adults

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Multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, didanosine, other highly buffered drugs or products containing calcium, iron, or zinc may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones; phenytoin serum levels may be altered (increased or decreased); probenecid may increase serum concentrations; may increase toxicity of theophylline, caffeine, tizanidine, glyburide, methotrexate, cyclosporine, and digoxin (monitor theophylline and digoxin levels); may increase effects of warfarin (monitor PT); metoclopramide accelerates absorption of oral ciprofloxacin; NSAIDs (but not acetyl salicylic acid) with very high doses of fluoroquinolones may provoke convulsions

Documented hypersensitivity; use with tizanidine

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

In prolonged therapy, perform periodic evaluations of organ system functions (eg, renal, hepatic, hematopoietic); adjust dose in renal function impairment; superinfections with drug-resistant bacteria may occur with prolonged or repeated antibiotic therapy; avoid excessive sunlight due to risk of phototoxicity; crystalluria may occur if urine is alkaline or concentrated; CNS may be affected, resulting in nervousness, agitation, insomnia, anxiety, nightmares, or paranoia

Erythromycin (E-Mycin, Ery-Tab, Eryc)

Macrolide antibiotic that inhibits bacterial protein synthesis by binding to 50S ribosomal subunits of susceptible organisms; may be bacteriocidal or bacteriostatic depending on concentration and type of microorganism.

Adult

500 mg PO qid for at least 3 wk

Pediatric

30-50 mg/kg/d PO divided q6-8h for at least 3 wk

Coadministration may increase toxicity of theophylline and digoxin; may potentiate anticoagulant effects of oral anticoagulants; because erythromycin is an inhibitor of cytochrome P450 3A (CYP3A), the following drug levels may rise, causing increased risk of toxicity: ergotamine, dihydroergotamine, benzodiazepines (eg, triazolam, alprazolam, midazolam), HMG-CoA reductase inhibitors (eg, lovastatin, simvastatin), sildenafil, cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine; additional drug interactions exist with hexobarbital, phenytoin, valproate, terfenadine, and astemizole

When coadministered with cisapride, terfenadine, or astemizole, rare cases of serious cardiovascular adverse events, including ECG QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed and fatalities have been reported

Documented hypersensitivity; coadministration of terfenadine, astemizole, pimozide, or cisapride

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution with impaired hepatic function; estolate formulation may cause cholestatic jaundice; adverse gastrointestinal effects are common; discontinue use if nausea, vomiting, malaise, abdominal colic, or fever occur; risk of superinfection; may aggravate weakness in patients with myasthenia gravis; possible increased risk of infantile hypertrophic pyloric stenosis in infants that have consumed erythromycin

Azithromycin (Zithromax)

Azalide antibiotic (subclass of macrolide antibiotics) that inhibits bacterial protein synthesis by binding 50S ribosomal subunits of susceptible organisms; may be bacteriocidal or bacteriostatic depending on concentration and type of microorganism.

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Adult

1 g PO qwk for at least 3 wk

Pediatric

<16 years: Not established

>16 years: Administer as in adults