

Virginia Department of Health
Glanders: Guidance for Healthcare Providers
Key Medical and Public Health Interventions
after Identification of a Suspected Case

Table of Contents

1. Epidemiology	1
2. Clinical Manifestations	2
3. Specimen Collection and Laboratory Testing	2
4. Diagnosis.....	5
5. Treatment.....	5
6. Postexposure Prophylaxis	6
7. Vaccination	7
8. Infection Control.....	7
9. Decontamination.....	7
10. Postmortem Practices	7
11. Public Health Measures.....	7
12. References and Resources	8

1. Epidemiology

Glanders is a zoonotic disease caused by the bacterium *Burkholderia mallei* (formerly *Pseudomonas mallei*). Glanders is primarily a disease of equids (e.g., horses, donkeys and mules), but other animals (e.g., dogs, cats, sheep, goats, bears, wolves) can become infected if they come into contact with infected equids or consume their meat. Transmission from infected animals to humans is rare, and human-to-human transmission has also been identified rarely (and never in the United States), suggesting that glanders is not easily transmissible from animal to human or from human to human. Human infection occurs through direct mucous membrane contact with infected animal materials, direct contact of abraded or lacerated skin with infected animal materials, or inhalation of infective aerosols; person-to-person transmission might potentially occur through sex or direct care of infected patients. Laboratory-associated infections may occur through direct mucous membrane or skin contact with *B. mallei* cultures or through inhalation of infective aerosols.

Glanders is endemic in animals in portions of the Middle East, Asia, Africa, and Central and South America, although very few cases occur each year. No naturally-occurring cases of equine or human glanders have been reported in the United States since the 1940s. Persons who care for infected animals or handle infected specimens are at increased risk of becoming infected, including veterinarians, horse caretakers, laboratorians, equine butchers and abattoir workers. Laboratory-acquired glanders infections in humans in the United States have occasionally been reported; more often these infections have been a result of exposure to *B. mallei* cultures, rather than to clinical specimens.

If a case of glanders is suspected, it is critical to identify the individual’s occupation (e.g., laboratory worker, veterinarian, or any job involving equids) and travel history to assess possible exposures. If the patient’s history does not indicate a possible source of exposure, bioterrorism should be suspected. If used for bioterrorism, the bacteria would most likely be delivered as an aerosol. *B.*

mallei is designated as a Category B bioterrorism agent (i.e., moderate ease of transmission and morbidity with a lower rate of mortality than category A agents) and is specifically designated as a select agent, which means that it could be developed as a bioterrorism agent and that possession could pose a severe threat to human or animal health and use or transfer of this organism requires registration with CDC or USDA.

2. Clinical Manifestations

The clinical spectrum of human glanders is wide, ranging from asymptomatic infection to life-threatening septicemia and varies depending on the mode of infection, dose, and host factors. Illness can generally be characterized into 1 of 4 clinical syndromes: localized, pulmonary, septicemic, or chronic.

Localized Form

- Incubation Period: 1–5 days
- Signs and symptoms of localized cutaneous infections might be limited to a cutaneous nodule at the site of inoculation; other symptoms might include lymphangitis (common), nodule deterioration leading to ulcer, fever, rigors, fatigue, headache or myalgia. Signs and symptoms of localized mucous membrane infection might involve eyes, nose, or oral cavity, depending on the site of inoculation. Ulcerating granulomatous reactions can occur; mucopurulent nasal or ocular discharges are often present; other signs and symptoms, such as fever, rigors, fatigue, headache or myalgia, may or may not be present. With treatment, the fatality rate of localized infection is 20%.

Pulmonary Form

- Incubation Period: 10–14 days (could be as short as 1–2 days)
- Signs and symptoms might include cough, fever, dyspnea, mucopurulent discharge, pulmonary abscesses, pleural effusions, skin abscesses after several months or symptoms as described below for septicemia. Chest radiographs might show lobar pneumonia, bronchopneumonia or nodular densities; consolidation might be present.

Septicemic Form

- Incubation Period: 1–4 weeks
- Signs and symptoms of the septicemic form of glanders might occur at any point in the illness and are consistent with a typical sepsis syndrome. Multiple abscesses involving spleen, liver and lungs or granulomatous or necrotizing lesions in any organ might occur. Jaundice, diarrhea or a generalized papular rash that progresses to a pustular rash might occur. Untreated infection will usually develop into either the septicemic or chronic form. Untreated septicemia is usually fatal within 7–10 days. Note: blood cultures often remain negative.

Chronic Form

- Signs and symptoms might include multiple abscesses within muscles or skin of the arms and legs or in the lungs, liver or spleen. Characterized by remission and exacerbation and might persist for years. If untreated, the fatality rate for the chronic form is 50%–70%.

3. Specimen Collection and Laboratory Testing

Protocols for sentinel clinical laboratories are no longer posted on the CDC website. The American Society for Microbiology (ASM) has agreed to take the lead in the development and dissemination of

sentinel laboratory information. The most current ASM guidelines for specimen collection and laboratory testing are available at <http://www.asm.org/index.php/guidelines/sentinel-guidelines>. For additional laboratory guidance, refer to the CDC Infectious Diseases Test Directory or CDC's Biosafety in Microbiological and Biomedical Laboratories (5th edition) (see References).

Because *B. mallei* is highly infectious in the laboratory, laboratory personnel **must** be alerted when glanders is suspected to ensure safe and appropriate specimen processing. Consultation with the state public health laboratory, Division of Consolidated Laboratory Services (DCLS), is **strongly recommended**. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.

When *B. mallei* is suspected, it is recommended that laboratory work be performed using biosafety level (BSL) 3 precautions or BSL 2 with BSL 3 precautions (which includes wearing gowns, gloves and respiratory protection). All patient specimens and culture isolates should be handled while wearing gloves and PPE in a BSC. Subcultures should be performed in a Class II biosafety cabinet (BSC). Plates should be taped shut when incubating. All further testing should be performed only in the BSC while wearing gloves to protect from infections through the skin. Any procedure that can generate an aerosol, such as preparing standard inoculums for identification systems, must be performed in a BSL 2 BSC with BSL 3 precautions. Centrifugation and vortexing should be avoided. It is recommended that if *B. pseudomallei* or *B. mallei* is suspected, samples should be transferred to a BSL 3 facility as soon as possible.

Because *B. mallei* is rarely isolated in the United States, its characteristics are unfamiliar to many clinical microbiologists. Commercial bacterial identification systems might misidentify *B. mallei*. Therefore, any isolate should be referred to DCLS if it meets a combination of the criteria outlined below for suspected *B. mallei* based on clinical suspicion or available laboratory testing:

- Any clinical suspicion of suspected *B. mallei* infection
- Colony morphology on sheep blood agar: at 24 hours of incubation, there is poor growth; at 48 hours of incubation, colonies appear smooth, gray, or translucent. *B. mallei* will grow without any inhibition around the colistin or polymyxin B disk.
- Gram stain morphology: Gram negative, faintly staining, straight or slightly curved coccobacilli
- Oxidase test: variable (e.g., positive or negative test result)
- Motility test: nonmotile. Note: the motility test should only be performed if the laboratory has the appropriate motility media; a wet preparation of any suspected *B. mallei* isolate should **not** be performed.
- Growth at 42 degrees Celsius on sheep blood agar: very light growth at 72 hours
- Triple Sugar Iron (TSI): nonfermenter

Instructions for sample collection and submission for laboratory testing are shown in Table 1. Consultation with DCLS is required before specimen collection and submission. For additional laboratory guidance, refer to the CDC Infectious Diseases Test Directory (available at <http://www.cdc.gov/laboratory/specimen-submission/list.html>) or the American Society for Microbiology sentinel laboratory guide: American Society for Microbiology (ASM). Sentinel Level Clinical Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases. Glanders: *Burkholderia mallei* and Melioidosis: *Burkholderia pseudomallei*. Revised October 2014. Available at <http://www.asm.org/images/PSAB/Burkholderia101714.pdf>

Table 1. Sample Collection Instructions for Testing Suspected Glanders*

Test	Acceptable samples	Amount	Instructions
<i>Burkholderia mallei</i> identification and genotyping (at DCLS and CDC)	Blood (for culture)	10 mL	Collect before antibiotic use if possible. Use blood isolator tube. If isolator tube is not available, then blood culture should be incubated on the instrument at the local lab and then the isolate should be forwarded if it “flags” positive. Ship isolate at room temperature. Transport to lab within 16 hours.
	Blood (for tests other than culture)	2 mL (or more)	Collect blood in red top or purple top (EDTA) blood tube. Ship refrigerated with cold packs. Transport to lab as soon as possible.
	Urine	10 mL (or more)	Collect in sterile screw-capped container or sterile urine container. Ship refrigerated with cold packs. Transport to lab as soon as possible.
	Abscess, tissue aspirate, or purulent discharge	3 mL, or as much material as possible (avoid swabs)	Aspirate with a syringe and transfer material to a sterile screw-capped leak-proof container, if possible. Aspirate can remain in collection syringe if needle is removed and syringe is capped to prevent leakage. Ship refrigerated with cold packs. Transport to lab as soon as possible.
	Sputum or bronchoscopically obtained specimens	3 mL (or more)	Collect in sterile screw-capped leak-proof container. Ship refrigerated with cold packs. Transport to lab as soon as possible.
	Tissue biopsy	1 gram	Collect in sterile container. Moisten sample with sterile broth or saline. Ship refrigerated with cold packs. Transport to lab as soon as possible.
	Culture isolate	n/a	Contact DCLS (Microbiology Reference Laboratory or Bioterrorism Coordinator) directly when a suspected isolate is identified*. Send culture on an agar slant, not a plate. Agar slants should be shipped at room temperature. Transport to lab as soon as possible.
<i>Burkholderia mallei</i> molecular detection (PCR at CDC and DCLS)	Testing at DCLS: Whole blood, serum or isolate. Testing at CDC: Whole blood, serum, urine, abscess, sputum or tissue	0.5 – 1mL (or more)	Whole blood specimens should be collected in purple top (EDTA) or light-blue top (sodium citrate) tube; green top (heparin) tube is <u>not</u> acceptable. Other specimens should be collected as described above or below. Agar slants should be shipped at room temperature and clinical specimens should be shipped refrigerated with cold packs. Transport to lab as soon as possible.
	Serum	2mL (or more)	Collect acute and convalescent serum (>14 days apart) in red top or tiger top tube. Remove serum and place in sterile tube. Acute and convalescent specimens can be shipped together (freeze acute specimen until convalescent specimen has been collected and is ready for shipment; ship both specimens on dry ice); if shipping separately, ship refrigerated with cold packs.
	Culture isolate	n/a	Contact DCLS (Microbiology Reference Laboratory or Bioterrorism Coordinator) directly when a suspected isolate is identified*. Send culture on an agar slant, not a plate or blood culture bottle. Agar slants should be shipped at room temperature. Transport to lab as soon as possible.

*If glanders is suspected, notify the local health department immediately to discuss the case and laboratory testing (see www.vdh.virginia.gov/LHD/index.htm). Specimens should be sent to Division of Consolidated Laboratory Services (DCLS) after LHD has been consulted and testing has been approved by LHD/DCLS. The DCLS Emergency Duty Officer can be reached 24/7 at (804) 335-4617. In addition to specimens, the DCLS Blood and Body Fluid Submission Form should be completed with the appropriate test request.

4. Diagnosis

There is currently no CDC case definition for glanders. Isolation of *B. mallei* from a clinical sample with definitive identification at DCLS and/or CDC in conjunction with clinically compatible signs and symptoms should guide treatment and public health measures. Blood cultures often remain negative, even in patients with septicemia.

5. Treatment

In 2010, the US Public Health Emergency Medical Countermeasures Enterprise held a workshop for subject matter experts to develop consensus recommendations for treatment and postexposure prophylaxis against *B. pseudomallei* and *B. mallei* (Lipsitz 2012). The recommendations focus primarily on treatment of melioidosis caused by *B. pseudomallei*; however, experts agreed that recommendations would be similar for glanders because antibiotic susceptibility profiles for *B. mallei* resemble those of *B. pseudomallei* and clinical experience with melioidosis treatment might be applicable to glanders. Of note, *B. pseudomallei* is naturally resistant to many antimicrobial drugs, and this resistance must be taken into account when selecting the appropriate treatment. Treatment of both glanders and melioidosis consists of an intensive phase with intravenous therapy lasting for at least 10–14 days (Table 2) and an eradication phase with oral therapy to reduce the chances of relapse (Table 3).

Table 2. Initial intensive-phase therapy for *Burkholderia pseudomallei* and *B. mallei* infections during a public health emergency*

Patient Group	Drug	Regimen for Suspected or Confirmed Clinical Cases (10-14 day duration) [†]
With no complications	Ceftazidime	50 mg/kg /(up to 2 g) intravenous every 8 hours or 6 g/d by continuous infusion after a 2-g bolus
With neuromelioidosis or persistent bacteremia or in intensive care unit	Meropenem	25 mg/kg /(up to 1 g) intravenous every 8 hours

*Adapted from Lipsitz R, Garges S, Aurigemma R, et al. Workshop on treatment of and postexposure prophylaxis for *Burkholderia pseudomallei* and *B. mallei* infection, 2010. *Emerg Infect Dis*. 2012; 18 (12). Online report available at http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm (accessed February 20, 2014).

[†]Duration of intensive therapy is generally 10–14 days; however, >4 weeks of parenteral therapy may be necessary in cases of more severe disease (e.g., septic shock, deep seated or organ abscesses, extensive lung disease, osteomyelitis, septic arthritis, or neurologic melioidosis). Consider adding trimethoprim-sulfamethoxazole for patients with severe infection involving the brain, prostate, or other privileged site (same dosing as described for eradication therapy below. Can be administered by intravenous infusion over 30–60 min every 12 hours, or nasogastric, or oral, as appropriate). If trimethoprim-sulfamethoxazole is included, continue for the entire duration of the intensive phase. Switching to meropenem is indicated if patient condition worsens while receiving ceftazidime (e.g., organ failure, development of a new focus of infection during treatment, or if repeat blood cultures remain positive). Depending on the severity of infection, the dose for patients >3 mo can be <40 mg/kg/; not to exceed 2 g/dose.

Table 3. Oral eradication-phase therapy for *Burkholderia pseudomallei* and *B. mallei* infections during a public health emergency*

Drug	Patient Group	Regimen for Suspected or Confirmed Clinical Cases (minimum 12-week duration) [†]
Trimethoprim-sulfamethoxazole [§]	Adult, >60 kg	160 mg/800 mg tablets: 2 tablets every 12 hours
	Adult, 40–60 kg	80 mg/400 mg tablets: 3 tablets every 12 hours
	Adult, <40 kg	160 mg/800 mg tablets: 1 tablet every 12 hours

		or 80 mg/400 mg tablets: 2 tablets every 12 hours
	Child	8 mg/40 mg/kg; maximum dose 320 mg/1,600 mg every 12 hours
<u>or</u>		
Amoxicillin/clavulanic acid (co-amoxiclav)	Adult, ≥60 kg	500 mg/125 mg tablets: 3 tablets every 8 hours [¶]
	Adult, <60 kg	500 mg/125 mg tablets: 2 tablets every 8 hours [¶]
	Child	20 mg/5 mg/kg every 8 hours; maximum dose 1,000 mg/250 mg every 8 hours

* For additional information on dosing, please consult the package inserts. Adapted from Lipsitz R, Garges S, Aurigemma R, et al. Workshop on treatment of and postexposure prophylaxis for *Burkholderia pseudomallei* and *B. mallei* infection, 2010. Emerg Infect Dis. 2012; 18 (12). Online report available at http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm (accessed February 20, 2014).

[†]Recommended duration of therapy is a minimum of 12 weeks.

[§]If the organism is susceptible and the patient does not have a documented allergy to it, oral trimethoprim-sulfamethoxazole is the agent of first choice. If the organism is resistant to trimethoprim-sulfamethoxazole or the patient is intolerant, the second-line choice is co-amoxiclav. Co-amoxiclav is available in different ratios and formulations, depending on the source country. Co-amoxiclav at a ratio of 4:1 is preferred to ensure there is sufficient clavulanate (Cheng AC, 2008 cited in Lipsitz R et al, 2012). Preparations of co-amoxiclav are available in the United States, with ratios of amoxicillin to clavulanic acid ranging from 2:1 to 16:1, as follows: 22:1 (Augmentin 250 mg), 4:1 (Augmentin 125 mg and 250 mg suspension, Augmentin 125 mg and 250 mg chewable tablet, Augmentin 500 mg.), 7:1 (Augmentin 200 mg and 400 mg suspension, Augmentin 400 mg chewable tablet, Augmentin 875 mg oral tablet), 14:1 (Augmentin ES-600, Amoclan 600 mg suspension) and 16:1 (Augmentin XR).

[¶]Weight-based dosage based on 20 mg/5 mg/kg/dose.

6. Postexposure Prophylaxis

Consensus postexposure prophylaxis recommendations for *B. mallei* and *B. pseudomallei* are based on the 2010 workshop held by the US Public Health Emergency Medical Countermeasures Enterprise (Lipsitz 2012) and are summarized in Table 4. As with glanders eradication-phase oral treatment recommendations, trimethoprim-sulfamethoxazole is the agent of first choice for glanders prophylaxis.

Table 4. Postexposure prophylaxis for *Burkholderia pseudomallei* and *B. mallei* infections during a public health emergency*[†]

Drug	Patient Group	Regimen for Suspected or Confirmed Clinical Cases (21-day duration)
Trimethoprim-sulfamethoxazole	Adult, >60 kg	160 mg/800 mg tablets: 2 tablets every 12 hours
	Adult, 40–60 kg	80 mg/400 mg tablets: 3 tablets every 12 hours
	Adult, <40 kg	160 mg/800 mg tablets: 1 tablet every 12 hours
		or 80 mg/400 mg tablets: 2 tablets every 12 hours
	Child	8 mg/40 mg/kg; maximum dose 320 mg/1,600 mg every 12 hours
<u>or</u>		
Amoxicillin/clavulanic acid (co-amoxiclav)	Adult, ≥60 kg	500 mg/125 mg tablets: 3 tablets every 8 hours [§]
	Adult, <60 kg	500 mg/125 mg tablets: 2 tablets every 8 hours [§]
	Child	20 mg/5 mg/kg every 8 hours; maximum dose 1,000 mg/250 mg every 8 hours

*For additional information on dosing, please consult the package inserts. Adapted from Lipsitz R, Garges S, Aurigemma R, et al. Workshop on treatment of and postexposure prophylaxis for *Burkholderia pseudomallei* and *B. mallei* infection, 2010. Emerg Infect Dis. 2012; 18 (12). Online report available at http://wwwnc.cdc.gov/eid/article/18/12/12-0638_article.htm (accessed February 20, 2014).

†Duration of postexposure prophylaxis is 21 days. If the organism is susceptible and the patient does not have a documented allergy to it, oral trimethoprim-sulfamethoxazole is the agent of first choice. If the organism is resistant to trimethoprim-sulfamethoxazole or the patient is intolerant, the second-line choice is co-amoxiclav.

§Weight-based dosage based on 20 mg/5 mg/kg/dose.

7. Vaccination

No vaccine is available to prevent glanders in humans. Prevention of glanders focuses on controlling the disease in equids through early detection, humane culling and safe removal of infected carcasses and taking precautions to prevent exposures in the laboratory.

8. Infection Control

For infection control, standard precautions are adequate for most patients with suspected glanders. Additional precautions may be necessary depending on the form of disease or the specific area(s) of the body involved. For example, for patients with draining cutaneous lesions or mucopurulent nasal discharge, contact precautions are indicated.

9. Decontamination

Under favorable, natural conditions (i.e., warm and moist environments), *B. mallei* may survive for up to several months, but most infectivity may be lost after a few weeks. *B. mallei* is sensitive to heat, desiccation, ultraviolet radiation and disinfection with common disinfectants including benzalkonium chloride, 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, iodine, mercuric chloride in alcohol and potassium permanganate.

Potentially contaminated material should be cleaned with ~5,000 ppm diluted bleach solution. If using 5.25% sodium hypochlorite, mix 1 part bleach to 9 parts water or 1 ¾ cups bleach per gallon of water; if using 8.25% (concentrated) sodium hypochlorite, mix 1 part bleach to 15 parts water or ~1 cup of bleach per gallon of water. Hospital rooms of patients with glanders should receive terminal cleaning consistent with standard precautions, and clothing or linens contaminated with body fluids should be disinfected according to hospital protocol.

10. Postmortem Practices

If glanders is suspected as a cause of death, the district Office of the Chief Medical Examiner (OCME) should be immediately notified (<http://www.vdh.virginia.gov/medExam/ContactUs.htm>).

Consultation should occur to determine if an autopsy should be conducted, the parties responsible for conducting the autopsy, and proper personal protective procedures to follow.

11. Public Health Measures

- Suspected or confirmed glanders cases should be reported immediately to the local health department. See <http://www.vdh.virginia.gov/LHD/index.htm>.

- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of the agent and other studies after consultation and approval. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.
- Designated public health authority should begin an epidemiologic investigation.
 - Collect detailed information from the patient to attempt to identify the source of the exposure.
 - Investigate contacts of the case-patient for compatible illness to investigate a potential common exposure.
 - Notify Virginia Department of Agriculture and Consumer Services (VDACS) if animal exposures are identified.
 - Implement control measures to prevent disease and additional exposures. For laboratorians or others potentially exposed who might have worked with the agent before identification, postexposure prophylaxis and monitoring might be recommended based on a risk assessment.
 - VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

12. References and Resources

American Society for Microbiology (ASM). Sentinel Level Clinical Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases. Glanders: *Burkholderia mallei* and Melioidosis: *Burkholderia pseudomallei*. Revised October 2014. Available at <http://www.asm.org/images/PSAB/Burkholderia101714.pdf> (accessed December 8, 2014).

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