



Complete Summary

GUIDELINE TITLE

Tularemia as a biological weapon. Medical and public health management.

BIBLIOGRAPHIC SOURCE(S)

Dennis DT, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Layton M, Lillibridge SR, McDade JE, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Tularemia as a biological weapon: medical and public health management. JAMA 2001 Jun 6;285(21):2763-73. [102 references]

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SCOPE

DISEASE/CONDITION(S)

Exposure to or infection with tularemia (*Francisella tularensis*)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology

Pathology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of tularemia as a biological weapon against a civilian population

TARGET POPULATION

Adults, pregnant women, children, and immunosuppressed persons exposed to or infected with tularemia as a biological weapon

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Assessment of clinical findings and epidemiological features
2. Collection of specimens of respiratory secretions and blood followed by alert of laboratory to the need for special diagnostic and safety procedures
3. Reporting to local or state public health authorities suspicion of inhalational tularemia so timely epidemiological and environmental investigations can be made
4. Clinical microbiology laboratory studies: gram stain of respiratory secretions and culture of pharyngeal washings, sputum specimens, fasting gastric aspirates or occasionally blood for growth of *Francisella tularensis*
5. Additional laboratory studies:
 - Examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains
 - Antigen detection assays, polymerase chain reaction, enzyme-linked immunoassays, immunoblotting, pulsed-field gel electrophoresis, and other specialized techniques to identify *Francisella tularensis* and to characterize strains (usually only performed in research and reference laboratories)

Vaccination

1. Live vaccine strain only for laboratory personnel routinely working with *Francisella tularensis*

Note: Postexposure vaccination is considered but not recommended

Treatment

Tularemia infection in the contained casualty setting:

1. Preferred therapy: Streptomycin or gentamicin (adults, children, pregnant women, immunosuppressed persons)
2. Alternative therapy: doxycycline, chloramphenicol, ciprofloxacin (adults, children); doxycycline or ciprofloxacin (pregnant women)

Note: Use of beta-lactam and macrolide antibiotics is discussed but not recommended.

Tularemia infection in mass casualty setting or postexposure prophylaxis:

1. Preferred therapy: doxycycline or ciprofloxacin (adults, children, pregnant women); streptomycin or gentamicin (immunosuppressed persons)

Infection Control

1. Standard hospital precautions
2. Precautions for microbiology laboratory personnel: biological safety level-2 conditions (routine diagnostic procedures); biological safety level-3 conditions (centrifuging, grinding, vigorous shaking, growing cultures in volume, animal studies)
3. Autopsy precautions

Environmental Decontamination and Protection

MAJOR OUTCOMES CONSIDERED

Therapeutic efficacy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE databases from January 1966 to October 2000 were searched using the Medical Subject Headings *Francisella tularensis*, *Pasteurella tularensis*, biological

weapon, biological terrorism, bioterrorism, biological warfare, and biowarfare. Review of the bibliographies of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other published and unpublished references and sources for review.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group were asked to make written comments on this first draft in May 1999. Subsequent revised drafts were reviewed and edited until full consensus of the working group was achieved.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

In 1969, a World Health Organization expert committee estimated that an aerosol dispersal of 50 kg of virulent *F tularensis* over a metropolitan area with 5 million inhabitants would result in 250000 incapacitating casualties, including 19000 deaths. Illness would be expected to persist for several weeks and disease relapses to occur during the ensuing weeks or months. It was assumed that

vaccinated individuals would be only partially protected against an aerosol exposure. Referring to this model, the Centers for Disease Control and Prevention (CDC) recently examined the expected economic impact of bioterrorist attacks and estimated the total base costs to society of an *F tularensis* aerosol attack to be \$5.4 billion for every 100000 persons exposed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnosis

Tularemia in humans occurs infrequently, resulting in a low index of diagnostic suspicion among clinicians and laboratorians. Since rapid diagnostic testing for tularemia is not widely available, the first indication of intentional tularemia might follow recognition by public health authorities of a clustering of acute, severe respiratory illness with unusual epidemiological features (see "Diagnosis of Inhalational Tularemia Following Use of a Biological Weapon" below). Suspicion of tularemia might be triggered in alert clinicians encountering patients with findings of atypical pneumonia, pleuritis, and hilar lymphadenopathy. Identification of *Francisella tularensis* in clinical specimens may be missed or delayed for days or weeks when procedures for routine microbiological screening of bacterial pathogens are followed, and it is unlikely that a serendipitous laboratory identification would be the sentinel event that alerted authorities to a major bioterrorism action.

Diagnosis of Inhalational Tularemia Following Use of a Biological Weapon

Clinical Findings

Sudden onset of acute febrile illness, progressing in some patients to pharyngitis, bronchiolitis, pneumonitis, pleuritis, hilar lymphadenitis. Complications of overwhelming untreated infection may lead to sepsis and inflammatory response syndrome.

Epidemiology

Point-source outbreak pattern; likely urban, nonagricultural setting. Unexpected severe respiratory illness in otherwise healthy persons. Risk related to degree of exposure with no differences in susceptibility by age or sex.

Microbiology

Small, gram-negative coccobacilli in direct stain of respiratory secretions. Sputum, tracheobronchial secretions, and blood should be cultured using cysteine-enriched medium. Antimicrobial susceptibility of isolates should be determined. Direct fluorescent antibody stain is first-line, rapid identification procedure at reference laboratories. Polymerase chain reaction and antigen detection procedures may also provide rapid identification. Microagglutination assay can detect serum antibodies beginning 10 days after illness onset. Virulence testing and molecular genetic characterizations are performed at specialized laboratories.

Pathology

Histological findings of acute suppurative necrosis followed by granulomatous reactions. Target organs include lungs, lymph nodes, spleen, liver, and kidney.

Radiology

Peribronchial infiltrates to bronchopneumonia in 1 or more lobes, often accompanied by pleural effusion and enlarged hilar nodes. Signs may be absent or minimal, with only 1 or several small, discrete pulmonary infiltrates, or scattered granulomatous lesions of lung parenchyma or pleura.

Physicians who suspect inhalational tularemia should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures. *Francisella tularensis* may be identified by direct examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains. By light microscopy, the organism is characterized by its small size (0.2 micrometers X 0.2-0.7 micrometers), pleomorphism, and faint staining. It does not show the bipolar staining characteristics of *Yersinia pestis*, the agent of plague, and is easily distinguished from the large gram-positive rods characteristic of vegetative forms of *Bacillus anthracis* (see Figure 3 in the original guideline document). Microscopic demonstration of *Francisella tularensis* using fluorescent-labeled antibodies is a rapid diagnostic procedure performed in designated reference laboratories in the National Public Health Laboratory Network; test results can be made available within several hours of receiving the appropriate specimens if the laboratory is alerted and prepared. Suspicion of inhalational tularemia must be promptly reported to local or state public health authorities so timely epidemiological and environmental investigations can be made (see below).

Clinicians Caring for Patients With Suspected Tularemia Should Immediately Contact Their:

1. Hospital epidemiologist or infection control practitioner
2. Local or state health departments

Consult the local telephone operator, the telephone directory under "governmental listings," or the Internet at <http://www.cdc.gov/other.htm#states> or <http://www.astho.org/state.html>.

If the local and state health departments are unavailable, contact the [Centers for Disease Control and Prevention](#) or (970) 221-6400.

Growth of *Francisella tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. *Francisella tularensis* can be grown from pharyngeal washings, sputum specimens, and even fasting gastric aspirates in a high proportion of patients with inhalational tularemia. It is only occasionally isolated from the blood. *Francisella tularensis* grows best in cysteine-enriched broth and thioglycollate broth and on cysteine heart blood agar, buffered charcoal-yeast agar, and chocolate agar. Selective agar (such as chocolate agar selective for *Neisseria gonorrhoea* isolation) may be useful when culturing materials from nonsterile sites, such as sputum. Inoculated media should be incubated at 37°C. Although growth may be visible as early as 24 to 48 hours after inoculation, growth may be delayed and cultures should be held for at least 10 days before discarding. Under ideal conditions, bacterial colonies on cysteine-enriched agar are typically 1 mm in diameter after 24 to 48 hours of incubation and 3 to 5 mm in diameter by 96 hours. On cysteine heart agar, *Francisella tularensis* colonies are characteristically opalescent and do not discolor the medium (see Figure 4 in the original guideline document).

Antigen detection assays, polymerase chain reaction, enzyme-linked immunoassays, immunoblotting, pulsed-field gel electrophoresis, and other specialized techniques may be used to identify *Francisella tularensis* and to characterize strains. These procedures are usually performed only in research and reference laboratories, however. In laboratories where advanced methods are established, results of antigen detection and polymerase chain reaction analyses can be obtained within several hours of receipt of isolates. Typically, serum antibody titers do not attain diagnostic levels until 10 or more days after onset of illness, and serology would provide minimal useful information for managing an outbreak. Serological confirmation of cases, however, may be of value for forensic or epidemiological purposes. Most laboratories use tube agglutination or microagglutination tests that detect combined immunoglobulin M and immunoglobulin G. A 4-fold change in titer between acute and convalescent serum specimens, a single titer of at least 1:160 for tube agglutination or 1:128 for microagglutination is diagnostic for *Francisella tularensis* infection. Information on reference diagnostic testing and shipping/handling of specimens can be obtained from state public health laboratories and from the Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC), Fort Collins, CO; telephone: (970) 221-6400; e-mail: dvbid@cdc.gov.

Vaccination

In the United States, a live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratorians routinely working with *Francisella tularensis*; until recently, this vaccine was available as an investigational new drug. It is currently under review by the U.S. Food and Drug Administration (FDA), and its future availability is undetermined.

Correlates of protective immunity appear about 2 weeks following natural infection or vaccination. Given the short incubation period of tularemia and incomplete protection of current vaccines against inhalational tularemia, vaccination is not recommended for postexposure prophylaxis. The working group recommends use of the live vaccine strain only for laboratory personnel routinely working with *Francisella tularensis*.

Treatment

Contained Casualty Situation

Adults. In a contained casualty situation, in which logistics permit individual medical management, the working group recommends parenteral antimicrobial therapy for tularemia (see Table 2 in the original guideline document). Streptomycin is the drug of choice. Gentamicin, which is more widely available and may be used intravenously, is an acceptable alternative. Treatment with aminoglycosides should be continued for 10 days. Tetracyclines and chloramphenicol are also used to treat tularemia; however, relapses and primary treatment failures occur at a higher rate with these bacteriostatic agents than with aminoglycosides, and they should be given for at least 14 days to reduce chance of relapse. Fluoroquinolones, which have intracellular activity, are promising candidates for treating tularemia. Ciprofloxacin, which is not labeled for use in tularemia, has been shown to be active against *Francisella tularensis* in vitro and in animals and has been used to successfully treat tularemia in both adults and children. Treatment with ciprofloxacin should be continued for 10 days. In persons beginning treatment with parenteral doxycycline, ciprofloxacin, or chloramphenicol, therapy can be switched to oral antibiotic administration when clinically indicated. Very limited experiences in treating tularemia patients with beta-lactam and macrolide antibiotics have been reported, and treatment failures have occurred. Use of beta-lactam and macrolide antibiotics in treating tularemia is neither FDA-approved nor recommended by the working group.

Children. In children, streptomycin or gentamicin is recommended by the working group as first-line treatment in a contained casualty situation (see Table 2 in the original guideline document). Doxycycline, ciprofloxacin (≤ 1 g/d), and chloramphenicol can be used as alternatives to aminoglycosides. Fluoroquinolones have been reported to cause cartilage damage in immature animals and are not FDA-approved for use in children. However, short courses of these agents have not been associated with arthropathy in pediatric patients, and the potential risks of their use must be weighed against their benefits in treating serious infections.

Mass Casualty Situation

Doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment in the mass casualty setting, for both adults and children (see Table 3 in the original guideline document). The ciprofloxacin dosage for children should not exceed 1 g/d. In a mass casualty situation, the working group believes the benefits to children from short courses of doxycycline or fluoroquinolones (see Table 3 in the original guideline document) outweigh the risks of their use.

Since it is unknown whether drug-resistant organisms might be used in a bioterrorist event, antimicrobial susceptibility testing of isolates should be conducted quickly and treatments altered according to test results and clinical responses.

Antibiotics for treating patients infected with tularemia in a bioterrorism scenario are included in a national pharmaceutical stockpile maintained by the Centers for Disease Control and Prevention, as are ventilators and other emergency

equipment needed to respond to situations of large numbers of critically ill persons that strip local and state resources.

Management of Special Groups

Pregnant Women. In a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat tularemia in pregnant women (see Table 2 in the original guideline document). Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women (see Table 3 in the original guideline document).

Immunosuppressed Persons. There is scant experience in treating tularemia in immunocompromised patients. However, considering the greater occurrence in immunocompetent patients of tularemia relapses and treatment failures following use of bacteriostatic antimicrobial agents compared with aminoglycosides, streptomycin or gentamicin should be used when possible to treat patients with known immune dysfunction in either contained casualty or mass casualty situations (see Table 2 in the original guideline document).

Postexposure Antibiotic Recommendations

In the unlikely event that authorities quickly become aware that a *Francisella tularensis* biological weapon has been used and are able to identify and reach exposed persons during the early incubation period, the working group recommends that exposed persons be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin (see Table 3 in the original guideline document). In a circumstance in which the weapon attack has been covert and the event is discovered only after persons start to become ill, persons potentially exposed should be instructed to begin a fever watch. Persons who develop an otherwise unexplained fever or flulike illness within 14 days of presumed exposure should begin treatment as outlined in Table 2 and Table 3 of the original guideline document.

In the laboratory, persons who have had potentially infective exposures to *Francisella tularensis* should be administered oral postexposure antibiotic prophylaxis if the risk of infection is high (e.g., spill, centrifuge accident, or needlestick). If the risk is low, exposed persons can be placed on a fever watch and treated if they develop symptoms.

Postexposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended since human-to-human transmission of *Francisella tularensis* is not known to occur.

Infection Control

Isolation is not recommended for tularemia patients, given the lack of human-to-human transmission. In hospitals, standard precautions are recommended by the working group for treatment of patients with tularemia.

Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety level 2 (BSL-2) conditions. Examination of cultures in which *Francisella tularensis* is suspected should be carried out in a biological safety cabinet. Manipulation of cultures and other activities involving infectious materials with a potential for aerosol or droplet production (centrifuging, grinding, vigorous shaking, growing cultures in volume, animal studies) require biological safety level-3 (BSL-3) conditions. When *Francisella tularensis* is presumptively identified in a routine biological safety level-2 clinical laboratory (level A), specimens should be forwarded to a biological safety level-3 laboratory (level B) (e.g., a state public health laboratory) for confirmation of agent and other studies, such as antimicrobial susceptibility testing. Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to cause aerosols, such as bone sawing, should be avoided. Clothing or linens contaminated with body fluids of patients infected with *Francisella tularensis* should be disinfected per standard precautions protocols.

Environmental Decontamination and Protection

Under natural conditions, *Francisella tularensis* may survive for extended periods in a cold, moist environment. The working group lacks information on survival of intentionally dispersed particles but would expect a short half-life due to desiccation, solar radiation, oxidation and other environmental factors, and a very limited risk from secondary dispersal. In circumstances of a laboratory spill or intentional use in which authorities are concerned about an environmental risk (e.g., inanimate surfaces wet with material thought to contain *Francisella tularensis*), decontamination can be achieved by spraying the suspected contaminant with a 10% bleach solution (1 part household bleach and 9 parts water). After 10 minutes, a 70% solution of alcohol can be used to further clean the area and reduce the corrosive action of the bleach. Soap water can be used to flush away less hazardous contaminations. Persons with direct exposure to powder or liquid aerosols containing *Francisella tularensis* should wash body surfaces and clothing with soap water. Standard levels of chlorine in municipal water sources should protect against waterborne infection. Following an urban release, the risk to humans of acquiring tularemia from infected animals or arthropod bites is considered minimal and could be reduced by educating the public on simple avoidance of sick or dead animals and on personal protective measures against biting arthropods.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Diagnostic and management recommendations in the setting of a biological tularemia attack are consensus recommendations of the Working Group based on the best available evidence (see also "Qualifying Statements" and the "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Improved diagnosis, management and containment of tularemia following a bioterrorist attack

POTENTIAL HARMS

- Children. Fluoroquinolones have been reported to cause cartilage damage in immature animals and are not FDA-approved for use in children. However, short courses of these agents have not been associated with arthropathy in pediatric patients, and the potential risks of their use must be weighed against their benefits in treating serious infections.
- Pregnant Women. In a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat tularemia in pregnant women. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- In some instances, the indications, dosages, and other information in this article are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA nor of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.
- The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Dennis DT, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Layton M, Lillibridge SR, McDade JE, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Tonat K. Tularemia as a biological weapon: medical and public health management. JAMA 2001 Jun 6;285(21):2763-73. [102 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 June 6

GUIDELINE DEVELOPER(S)

Center for Biosecurity - Academic Institution

GUIDELINE DEVELOPER COMMENT

The working group comprised 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions, including:

- National Center for Infectious Diseases, Centers for Disease Control and Prevention
- Center for Civilian Biodefense Strategies, and Public Health, Johns Hopkins University Schools of Medicine
- Viral and Rickettsial Diseases Laboratory, California Department of Health Services
- US Army Medical Research Institute of Infectious Diseases
- Bureau of Communicable Disease, New York City Health Department

- Kroll Associates
- ican Inc
- Office of Emergency Preparedness, Department of Health and Human Services

SOURCE(S) OF FUNDING

Funding for this study primarily was provided by each participant's institution or agency. The Johns Hopkins Center for Civilian Biodefense Strategies provided travel funds for 5 members of the group.

GUIDELINE COMMITTEE

Working Group on Civilian Biodefense

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: David T. Dennis, MD, MPH; Thomas V. Inglesby, MD; Donald A. Henderson, MD, MPH; John G. Bartlett, MD; Michael S. Ascher, MD; Edward Eitzen, MD, MPH; Anne D. Fine, MD; Arthur M. Friedlander, MD; Jerome Hauer, MHS; Marcelle Layton, MD; Scott R. Lillibridge, MD; Joseph E. McDade, PhD; Michael T. Osterholm, PhD, MPH; Tara O'Toole, MD, MPH; Gerald Parker, PhD, DVM; Trish M. Perl, MD, MSc; Philip K. Russell, MD; Kevin Tonat, DrPH, MPH for the Working Group on Civilian Biodefense

Ex Officio Participants in the Working Group on Civilian Biodefense: George Counts, MD; Margaret Hamburg, MD; Robert Knouss, MD; Brian Malkin, Esq; Stuart Nightingale, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Journal of the American Medical Association Web site.

Full text available in:

- [HTML Format](#)
- [Portable Document Format \(PDF\)](#)

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on November 1, 2001.

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