VERMONT
DEPARTMENT OF HEALTH

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HEALTH SURVEILLANCE DIVISION

MULTIDRUG-RESISTANT ORGANISM (MDRO) PROTOCOL

Author: Nancy Thayer	Date Created: October 2009	Last Updated: June 2016

OBJECTIVE

To provide clinical information on reportable communicable diseases, prescribe standardized investigational measures, identify procedural guidance to insure consistency in management, data collection, and reporting of disease, and implement interventions to prevent further disease transmission.

I. DESCRIPTION

For epidemiologic purposes, multidrug-resistant organisms (MDROs) are defined as microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Although the names of certain MDROs describe resistance to only one agent, these pathogens are frequently resistant to most available antimicrobial agents. The most commonly recognized resistant organisms are methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).

In most instances, MDRO infections have clinical manifestations that are similar to infections caused by susceptible microorganisms. However, options for treating patients with these infections are often extremely limited. For example, until recently, only vancomycin provided effective therapy for potentially life-threatening MRSA infections. Although new antimicrobials have become available for treatment, resistance to each new agent has already emerged in clinical isolates.

In 2002, vancomycin-resistant *Staphylococcus aureus* (VRSA) was first reported in the US. This organism was not only resistant to methicillin (in fact, oxacillin) but also to vancomycin, previously the only antibiotic to which it had been sensitive. Concern was that additional cases would occur and treatment options would be unavailable. There was concern that should a person be co-infected with VRE and MRSA, VRSA would develop. All six VRSA infections reported in the US contained the same resistance gene found in VRE. Nationwide surveillance for vancomycin resistance continues to watch for this serious consequence.

In 2009, infection with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* was recognized as an organism of emerging importance, challenging health-care settings. Currently, carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is the species of CRE most commonly encountered in the United States. CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters). During January-June 2010, three *Enterobacteriaceae* isolates carrying a newly described resistance mechanism, the New Delhi metallo-beta-lactamase (NDM-1) were identified from three U.S. states at the CDC antimicrobial susceptibility laboratory. See http://www.cdc.gov/hai/organisms/cre/index.html Surveillance has demonstrated identification of this organism throughout the US, See: http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html#CREmap

A retrospective review of clinical microbiology data by Vermont hospitals in 2010 revealed previously unrecognized CRE cases in more than one facility. Clinical laboratories will be requested to report future suspected cases. This is an effort to prevent emergence of an MDRO becoming endemic. The first carbapenem-resistant *Klebsiella pneumoniae* in Vermont was identified in 2014.

The MDROs reportable in Vermont are

- Carbapenem-resistant or Carbapenemase-producing *Enterobacteriaceae* (CRE) – considered reportable under Chapter II of the Vermont Communicable Disease Regulations (sections 4-203, 4-204) For complete list of organisms, see: http://www.healthvermont.gov/advisory/2012/documents/092012_hai.pdf
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staphylococcus aureus* Infection (VRSA)

II. INCUBATION PERIOD

MDROs have incubation periods consistent with the isolated organisms; this can be within days of contact.

III. COMMUNICABLE PERIOD

While the organism is viable (on hosts or fomites) the organism can be passed to others. Persons can be infected, or colonized, with the organism. Infection is an acute infectious process, i.e., inflammation AND purulence, occurring at the site of the positive culture. Colonization is isolation of the organism in culture without signs of infection at the site.

IV. MODE OF TRANSMISSION

Epidemiologic evidence suggests MDROs are transmitted from one person to another hand-to-hand. Hands are easily contaminated during the process of care-giving or from contact with environmental surfaces in close proximity to the patient. Contact Precautions are indicated when caring for the individual in a hospital setting.

V. SIGNS AND SYMPTOMS

Signs of infection are varied and are the same as in drug-sensitive infections.

IV. CASE DEFINITION

CONFIRMED CASE- Carbapenem-resistant *Enterobacteriaceae* (CRE)
SEE. HTTP://WWW.CDC.GOV/HAI/ORGANISMS/CRE/CRE-TOOLKIT/RCREPREVENTION-APPENDIXA.HTML

Isolation of genus enterobacteriaecea using current Clinical and Laboratory Standards Institute (CLSI) guidelines for detection of carbapenemase production

Nonsusceptible to one of the following carbapenems: doripenem, meropenem, or imipenem

AND

Positive for carbapenemase production

2012 interpretive criteria for susceptibility and resistance

	Disk Diffusion (mm)			MIC (µg/mL)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Doripenem	≥23	20-22	≤19	≤1	2	≥4
Ertapenem	≥23	20-22	≤19	≤0.5	0.1	≥2
Imipenem	≥23	20-22	≤19	≤1	2	≥4
Meropenem	≥23	20-22	≤19	≤1	2	≥4

CONFIRMED CASE – STREPTOCOCCUS PNEUMONIAE – DRUG-RESISTANT

Isolation of *Streptococcus pneumoniae* with intermediate or high-level resistance to at least one

antimicrobial agent currently approved for use in treating pneumococcal infection (e.g., penicillins, cephalosporins) from a normally sterile site, including blood, CSF, synovial, pericardial, pleural or peritoneal fluid, tissue biopsy or surgical wound. Indicate resistance to penicillin and/or ceftriaxone.

CONFIRMED CASE – VRE NOTE: AS OF MARCH 26, 2015 VRE IS NO LONGER REPORTABLE

Receipt of laboratory report with isolate from any site, of *Enterococcus* resistant to vancomycin, in person with identifiable county of residence.

CONFIRMED CASE – VRSA/VISA

All isolated strains of *Staphylococcus aureus* with a MIC ≥4 μg/mL using interpretive criteria defined by the Clinical Laboratory Standards Institute should be considered candidate strains for reduced vancomycin susceptibility. **Isolates must be confirmed by CDC before reported into NNDSS.**

Vancomycin-intermediate (VISA) (vancomycin MIC 4-8 μg/mL)
Vancomycin-resistant (VRSA) (vancomycin MIC ≥16 μg/mL)

VII. LABORATORY TESTING

These organisms are isolated by taking a bacterial culture of a clinical specimen. Screening cultures are often taken for MRSA and VRE. MRSA is usually colonized in the anterior nares, but can be harbored in other sites, especially site of indwelling lines, e.g., tracheotomies; VRE is commonly colonized in the peri-anal area, but can reside in chronic wounds.

Carbapenem-resistant *Enterobacteriaceae* (CRE)

A difficulty in detecting CRE is the fact that some strains that harbor the carbapenemase enzyme have minimal inhibitory concentrations (MICs) that are elevated but still within the susceptible range for carbapenems. Because these strains are susceptible to carbapenems, they are not identified as potential clinical or infection control risks using current susceptibility testing guidelines. CLSI published a recommendation that carbapenem-susceptible *Enterobacteriaceae* with elevated MICs or reduced disk diffusion zone sizes be tested for the presence of carbapenemases using the modified Hodge test (MHT). The MHT is a phenotypic test used to detect carbapenemases in isolates demonstrating elevated but susceptible carbapenem MICs and has demonstrated sensitivity and specificity exceeding 90% in identifying carbapenemase-producing *Enterobacteriaceae*. If the MHT reveals the presence of a carbapenemase, CLSI recommends that a comment be added to the microbiology report to inform clinicians and infection preventionists. Because treatment information on MHT-positive, carbapenem-susceptible isolates is limited, CLSI guidelines do not recommend any changes regarding the reporting of susceptibility results themselves. Strains of *Enterobacteriaceae* that test intermediate or resistant to carbapenems should be reported as such and do not need to be subjected to the MHT.

VIII. CASE-CONTACT INVESTIGATION

A. VRE See: http://www.cdc.gov/HAI/organisms/vre/vre.html
NOTE: AS OF MARCH 26, 2015 VRE IS NO LONGER REPORTABLE

1. Receive report from reporting hospital laboratory.
2. Gather demographic information as available.
3. Central Office enters into NBS when case classification is complete.
4. Enter and send confirmed cases electronically to CDC.
5. Make Out-of-State cases “not-a-case” and send reciprocal notification to state.
6. If person has had positive culture result sent to VDH, attach to previous report; do not initiate new report.

7. If organism is isolated from blood, complete Bacterial Meningitis, Other form; specify *Enterococcus* as other bacterial species.

B. VISA/VRSA (NOTE – MRSA, i.e., resistant to oxacillin, but sensitive to vancomycin is NOT reportable in Vermont) See: http://www.cdc.gov/HAI/organisms/visa_vrsa/visa_vrsa.html

1. Receive report from reporting laboratory or Hospital Preventionist. If report comes to District Office, notify Central Office promptly.
2. Gather MIC values.
3. Confirm diagnosis; have isolate forwarded to VDHL.
   See: http://www.cdc.gov/ncidod/dhqp/pdf/ar/VRSA_testing_algo09v4.pdf
4. Gather information on patient as available on generic form.
5. See CDC: Investigation and control of vancomycin-intermediate and resistant *Staphylococcus aureus* (VISA/VRSA) http://www.cdc.gov/ncidod/dhqp/pdf/ar/visa_vrsa_guide.pdf
6. Central Office will report suspected cases promptly to CDC @ 800-893-0485.
7. Contact investigation is indicated in any cases of VRSA. Anterior nares culture may be indicated for case/close contacts as determined by individual circumstances.

C. CRE See: http://www.cdc.gov/hai/organisms/cre/index.html
http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf

1. Receive report form laboratory or facility with suspected or confirmed CRE. *Klebsiella* species and *Escherichia coli (E. coli)* are examples of Enterobacteriaceae, a normal part of the human gut bacteria that can become carbapenem-resistant.
2. Instruct laboratories to alert epidemiology and infection control staff members if CRE is identified. See http://www.healthvermont.gov/advisory/2012/documents/092012_hai.pdf
3. When a CRE is identified in a patient (infection or colonization) with a history of an overnight stay in a healthcare facility (within the last 6 months) outside the United States, send the isolate to a reference laboratory for confirmatory susceptibility testing and test to determine the carbapenem resistance mechanism; at a minimum, this should include evaluation for KPC and NDM carbapenemases. See worksheet and checklist.
4. Advise that patients colonized or infected with CRE should be placed on Contact Precautions.
5. When a case of healthcare-associated CRE is identified, facilities should conduct a single round of active surveillance testing of patients with epidemiologic links to the CRE case (e.g., those patients in the same unit or patients who have been cared for by the same health-care personnel). See specimen collection instructions. Collection kits are available in the District Offices. Provide facilities with collection kits when indicated.
6. Because the prevalence of CRE is low, routine microbiologic surveillance of persons admitted, such as that performed in some facilities to detect carriage of MRSA, is not recommended.
7. Clinicians should be aware of the possibility of CRE in patients who have received medical care in India and Pakistan. For patients admitted to healthcare facilities in the United States after recently being hospitalized (within the last 6 months) in countries outside the United States, consider each of the following:
   - Perform rectal screening cultures to detect CRE colonization.
   - Place patients on Contact Precautions while awaiting the results of these screening cultures.
8. See: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm
9. See: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html

IX. TREATMENT AND PROPHYLAXIS

Treatment for specific antibiotic resistant infections is complex and best supervised by someone familiar with infectious conditions and pharmacology. Often the hospital formulary dictates which antibiotics are recommended in certain settings. Specific information of treatment is beyond the scope of this text.

Decolonization entails treatment of persons colonized (not infected) with, usually MRSA, to eradicate carriage of that organism. Decolonization of persons carrying MRSA in their nares has proved possible with several regimens that include topical mupirocin alone or in combination with orally administered antibiotics (e.g., rifampin in combination with trimethoprim-sulfamethoxazole or ciprofloxacin) plus the use of an antimicrobial soap for bathing. Decolonization regimens are not sufficiently effective to warrant routine use.

X. COMPLICATIONS

Complications that occur are often from delay of effective antibiotic administration. If first-line antibiotics are initiated and the patient does not respond, an interruption in effective treatment can cause a delay in recovery, and sometimes untoward sequelae. Prolonged hospitalization is not uncommon.

XI. IMMUNIZATION

Emerging antimicrobial resistance emphasizes the need to prevent pneumococcal infections using immunization strategies. A vaccine-efficacy trial has demonstrated a 57% reduction in pneumococcal acute otitis media infections in children. Use of appropriate immunization could decrease the need for, and dependence on, antibiotics, and hence the prevalence of antibiotic resistant *Streptococcus pneumoniae*.

The first polysaccharide (14-valent) pneumococcal vaccine was licensed in the US in 1977. The current 23-valent polysaccharide vaccine first became available in 1992. The first conjugate vaccine became available in 2000. It is estimated that appropriate vaccine use could reduce deaths related to invasive disease by half.

There are no vaccines for either *Staphylococcus* or *Enterococcus*.

XI. SCHOOL AND CHILDCARE FACILITY MEASURES

For MRSA - NOTE – not reportable as individual case in Vermont.

Suspected outbreaks of MRSA in school settings should be reported to the District Health Office.

See VDH website
http://www.healthvermont.gov/prevent/MRSA.aspx
See informational booklet
http://www.healthvermont.gov/prevent/documents/MRSAbooklet_pgs.pdf
See CDC: http://www.cdc.gov/ncidod/dhqp/ar_mrsa_in_schools.html

XIII. INSTITUTIONAL SETTINGS

See: http://www.cdc.gov/ncidod/dhqp/ar_multidrugFAQ.html
http://www.cdc.gov/drugresistance/DiseasesConnectedAR.html

Hospitals and other residential setting, e.g., correctional facilities, group home, shelters, and other places where people congregate in close proximity are places where transmission of multi-drug resistant organisms can be transmitted from person-to-person. Hand hygiene and good personal hygiene are important barriers to transmission.

XIV. PREVENTION MEASURES

Efforts toward prevention of resistance emphasize appropriate use of antibiotics. Efforts to prevent transmission of infections with resistant organisms emphasize hand hygiene and personal hygiene and responsibility. Physicians should only prescribe antibiotic therapy when likely to be beneficial to the patient, and for the appropriate dose and duration.

One vaccine can be used in the arsenal of prevention of one specific infection. Pneumococcal vaccine decreases the number of pneumococcal infections, and along with that the number of resistant pneumococcal infections. Parents of infants under 24 months of age, persons over 65 years of age and other persons at greater risk of developing invasive disease should discuss pneumococcal vaccine with their medical care provider.

XV. ISOLATION & QUARANTINE

Contact Precautions are indicated when caring for hospitalized persons with MDRO infections.

XVI. VOLUNTARY COMPLIANCE

Persons identified with MDRO infections should be asked to avoid exposing others to potentially infectious body fluids.

XVII. HEALTH ORDERS

Seeking of Health Orders is not anticipated. However, there have been previous incidents of MRSA community clusters associated with tattooing for which orders were considered.

XVIII. COMMUNITY MITIGATION

Community mitigation would most likely not be a factor in MDRO infection.

XIX. BORDER ISSUES

MDROs are unlikely to be a factor at the Vermont–Canadian Border.

XX. REPORTING

Report vancomycin-resistant *Enterococcus* through NBS as indicated.

Vancomycin-resistant (or intermediate, reduced-susceptibility) *Staphylococcus aureus* is a significant finding. The isolation of *S. aureus* with confirmed or presumptive vancomycin resistance should be reported immediately to the VDH Infectious Disease Epidemiology Section and the CDC the Division of Healthcare Quality Promotion, National Center for Infectious Diseases @ 800-893-0485.

As of January 28, 2013 the Division of Healthcare Quality Promotion has created a dedicated email address and phone number for health departments to use to request CDC's input on healthcare-associated infection (HAI) response activities including potential HAI outbreaks and patient notifications related to HAIs (e.g., infection control breaches).

Healthcare outbreak phone number: 404-578-4027
Healthcare outbreak email address: haioutbreak@cdc.gov

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XXI. HEALTH ALERT NETWORK ALERTS

Forward CDC Health Alerts as indicated.

XXII. REFERENCES

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H. CDC. Facility Guidance for Control of Carbapenem- Resistant *Enterobacteriaceae* (CRE). November 2015. http://www.cdc.gov/hai/pdfs/cre/CRE-guidance-508.pdf

I.

Subject to change periodically--consult with
Epidemiology at the Vermont Department of Health for updates: **1-800-640-4374**

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