Clinical Bulletin: DxWound ermA and ermB Tests

Description

Antibiotic resistance is considered by the CDC to be a major public health threat in the United States.[1] Patients with antibiotic resistant infections have higher morbidity and mortality, including longer hospital stays with increased costs to the healthcare system.[1] To help mitigate the consequences of antibiotic resistance, the CDC has called for improved antibiotic stewardship and the development of new diagnostic tests.[1]

Antibiotic resistance genes are genes present in bacteria that mediate resistance to a specific antibiotic or class of antibiotics. DxWound tests for several antibiotic resistance genes associated with bacteria that typically cause skin and soft tissue infections (SSTIs), including the erythromycin-resistance rRNA methylase (*erm*) genes *ermA* and *ermB*. The *ermA* and *ermB* genes have been found in *Staphylococcus*, *Streptococcus*, *Enterococcus*, and a broad range of other bacterial genera (See Table 1).[2,3] Organisms that express *ermA* and/or *ermB* are considered to be "MLS_B-resistant". They mediate resistance to macrolides (e.g. azithromycin), clindamycin and quinupristin/dalfopristin.[2,4]

Indications for Ordering

The DxWound *ermA* and *ermB* tests are ordered based on the clinician's determination of medical necessity. Tests for *ermA* and *ermB* can be useful for any patient suspected of having a skin and soft tissue infection (SSTI) caused by *Staphylococcus*, *Streptococcus*, or *Enterococcus* and for which a macrolide, clindamycin or quinupristin/dalfopristin may be considered. The presence of *ermA* or *ermB* may indicate resistance to macrolides, clindamycin or quinupristin/dalfopristin.[2,4] Testing for *ermA* and *ermB* genes may help clinicians rapidly target antibiotic therapy.

Methodology

DxWound tests analyze DNA using real-time polymerase chain reaction (PCR) technology. The tests are performed on a swab sample taken directly from the site of infection without need for bacterial growth. The process is simple. First, cleanse and debride the wound as necessary. The Levine technique is then suggested for collection of the sample. The swab sample is collected in a solution that kills microorganisms at the same time as protecting microbial DNA, essentially preserving the wound microbiome in time at the point of specimen collection. DNA is detected directly from the patient specimen without culture enrichment. All DxWound tests have ≥95% accuracy and ≥99% reproducibility. The accuracy and reproducibility of DxWound tests were defined by either comparison to culture reports for wound samples and/or by correct identification of known organisms or antibiotic resistance genes in reference samples obtained from the FDA-CDC antimicrobial resistance isolate bank, commercial vendors, and research laboratories. For more information, please refer to the Technical Specifications bulletin.

Clinical Use

Macrolides, clindamycin and quinupristin/dalfopristin may be used to treat infections caused by various *Staphylococcus* or *Streptococcus* species. However, resistance to these antibiotics has been growing. For example, Erythromycin-Resistant Group A *Streptococcus* and Clindamycin-Resistant Group B *Streptococcus* have been identified as antibiotic resistance threats in the United States by the CDC.[1]

The erm enzymes are the most common and best studied resistance mechanism against macrolides, clindamycin and quinupristin/dalfopristin.[4] Macrolide antibiotics, such as azithromycin, as well as the structurally unrelated clindamycin and quinupristin/dalfopristin, bind to the 50S ribosomal subunit of the bacterial rRNA complex, thereby inhibiting protein synthesis.[3] The *erm* genes encode adenine-N^6 methyltransferases, which add one or two methyl groups to a single adenine in 23S rRNA of the 50S ribosomal subunit. This modification reduces the binding of macrolides, clindamycin and quinupristin/dalfopristin to the 50S ribosomal subunit resulting in resistance.[3]

Test Interpretation

These genetic tests identify if *ermA* and/or *ermB* genes are present. The *ermA* and *ermB* genes have a broad host range and have been associated with multiple bacterial genera (see Table 1).[2,3]

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Table 1. Bacterial Genera Associated with ermA and ermB Genes (**DxWound Test Offerings in Bold**).[2,3]

Gene	Genera
ermA	*Actinobacillus*, ***Bacteroides***, *Helcococcus, Peptostreptococcus*, ***Prevotella***, ***Staphylococcus***, ***Streptococcus***
ermB	***Acinetobacter***, *Actinobacillus, Aerococcus, Arcanobacterium, Bacillus*, ***Bacteroides***, ***Citrobacter***, ***Clostridium***, *Corynebacterium*, ***Enterobacter***, ***Enterococcus***, ***Escherichia***, *Eubacterium, Fusobacterium, Gemella, Haemophilus, Klebsiella, Lactobacillus, Micrococcus, Neisseria, Pantoeae, Pediococcus, Peptostreptococcus, Porphyromonas*, ***Proteus***, ***Pseudomonas***, *Rothia, Ruminococcus, Serratia*, ***Staphylococcus***, ***Streptococcus***, *Treponema, Wolinella*

Although these genes have been reported in a wide range of diverse organisms, most data on their prevalence and clinical impact have only involved *Staphylococcus*, *Streptococcus*, and *Enterococcus*. Pilot study data of DxWound samples indicate a strong association between the *ermA* and *ermB* genes with aerobic Gram-positive cocci, including *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae* (Group B), and *Streptococcus pyogenes* (Group A).[5]

The association of *ermA* and *Staphylococcus aureus* is highly likely when they are co-detected. If samples are positive for *ermA*, *S. aureus*, and coagulase-negative *Staphylococcus* species (CoNS), the probability of *S. aureus* being a carrier of *ermA* is 81% vs. 32% for CoNS.[5] In the absence of *S. aureus*, an association of *ermA* with a CoNS or a beta-hemolytic *Streptococcus* (Group A *Streptococcus pyogenes* or Group B *Streptococcus agalactiae*) is likely. In case of co-detection of *ermA*, a CoNS, and a beta-hemolytic *Streptococcus*, the CoNS has more than 50% chance to be a carrier.[5] The *ermA* gene is not often identified in *Enterococcus*. See Table 2 for additional information for *ermA* test interpretation.

Table 2. DxWound ermA Test Interpretation[6,7]

DxWound Test Results	Potential Organism Present*	Common Antibiotic Coverage	
		Oral	IV
ermA + *Streptococcus pyogenes* or *Streptococcus agalactiae*	MLS_B-Resistant Streptococcus**	Amoxicillin, Amox-Clav, Cephalexin, Linezolid#	Cefazolin, Ceftriaxone, Penicillin G, Vancomycin#
ermA + *Staphylococcus* species	MLS_B-Resistant *Staphylococcus* species	Cephalexin, Dicloxacillin, Trimethoprim-Sulfamethoxazole	Cefazolin, Nafcillin, Oxacillin, Vancomycin#
ermA + *mecA* + *Staphylococcus* species	MLS_B-Resistant Methicillin-Resistant *Staphylococcus* species	Doxycycline, Linezolid, Minocycline, TMP-SMX	Daptomycin, Linezolid, Vancomycin#

Abbreviation: MLS_B, Macrolide-Lincosamide-Streptogramin B.

*ermA can also be found in a broad range of other bacterial genera (see Table 1).

**Erythromycin-resistant Group A Streptococcus and clindamycin-resistant Group B Streptococcus are identified as antibiotic resistance threats in the United States by the CDC.

#Possible alternative If the patient has a true penicillin allergy

The association of *ermB* and *Enterococcus* is highly likely and consistent with the high prevalence of *ermB* in *Enterococcus* species reported in the literature. There are other potential carriers of *ermB* (see Table 1) but the probability of these species carrying *ermB* in pilot study data was small. See Table 3 for additional information for *ermB* test interpretation.

Table 3. DxWound *ermB* Test Interpretation[6,7]

DxWound Test Results&	Potential Organism Present*	Common Antibiotic Coverage	
		Oral	IV
ermB + *Streptococcus pyogenes* or *agalactiae*	MLS_B-Resistant** Streptococcus	Amoxicillin, Amox-Clav, Cephalexin, Linezolid#	Cefazolin, Ceftriaxone, Penicillin G, Vancomycin#
ermB + *Staphylococcus* species	MLS_B-Resistant Staphylococcus	Cephalexin, Dicloxacillin, Trimethoprim-Sulfamethoxazole	Cefazolin, Nafcillin, Oxacillin, Vancomycin#
ermB + *mecA* + *Staphylococcus* species	MLS_B-Resistant Methicillin-Resistant Staphylococcus species	Doxycycline, Linezolid, Minocycline, TMP-SMX	Daptomycin, Linezolid, Vancomycin#

Abbreviation: MLS_B, Macrolide-Lincosamide-Streptogramin B.

**ermB* can also be found in a broad range of other bacterial genera (see Table 1).

**Erythromycin-resistant Group A *Streptococcus* and clindamycin-resistant Group B *Streptococcus* are identified as antibiotic resistance threats in the United States by the CDC.

& Interpret with caution as ermB is commonly identified in Enterococcus species

#Possible alternative if patient has a true penicillin allergy

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Limitations

- These tests detect the presence of genes and do not detect whether the genes are expressed
- These tests do not detect all known antibiotic resistance mechanisms, nor do they identify which species is associated with *ermA* or *ermB*
- It is possible that *ermA* or *ermB* is associated with an organism that is not included in these tests
- The DxWound Genetic Analysis Report does not make recommendations for treatment. All test results should be evaluated in the context of the patient's individual clinical presentation

Technical Assistance

For technical assistance with interpretation or to speak with one of our clinical support specialists, scientists or clinical pharmacists, please call Client Services at 877-866-0603, Monday–Friday 5:00am to 5:00 pm (Pacific Time).

Reporting

All test results are reported, generally, within 1 business day of specimen receipt. These results are available in the online portal as a DxWound Report.

How to Order

Using a CogenDx test requisition (paper or electronic), medically necessary tests are ordered by individual test based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider. Submit swab specimen in the collection device provided according to the directions in the Specimen Collection Manual. A completed Documentation for DxWound Testing form is required with each order.

References

1. Centers for Disease Control and Prevention, Antibiotic Resistance Threats in the United States, 2013.
2. Roberts MC. Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. *FEMS Microbiol Lett*. 2008; 282(2): 147-59.
3. Roberts MC, Sutcliffe J, Courvalin P, Jensen LB, Rood J, Seppala H. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resistance determinants. *Antimicrob Agents Chemother*. 1999; 43(12): 2823-30.
4. Fyfe C, Grossman TH, Kerstein K, Sutcliffe J. Resistance to Macrolide Antibiotics in Public Health Pathogens. *Cold Spring Harb Perspect Med*. 2016; 6(10).
5. Data on file, Millennium Health, LLC. 12-18-17.
6. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014; 59(2): e10-52
7. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012; 54(12): e132-73.

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Contact CogenDx to learn more.

Client Services: **877.866.0603**

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