

Clinical Bulletin: Antibiotic Resistance Gene 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). The detection of these genes suggests the presence of bacteria that may be resistant to specific antibiotics or classes of antibiotics (Table 1).

Table 1. Antibiotic Resistance Genes and Associated Antibiotic Classes

Antibiotic Resistance Genes		Antibiotics That May Be Impacted by Resistance Gene									
Resistance Type	Genes	Penicillins	Cephalosporins	Aztreonam	Carbapenems	Macrolides	Clindamycin	Vancomycin	Quinolones	TMP/SMX	Tetracyclines
Oxacillin/Methicillin Resistance ^{2,4}	<i>mecA</i>	X	X†	X	X	-	-	-	-	-	-
Carbapenemase ^{5,7}	IMP	X	X	-	X	-	-	-	-	-	-
	KPC	X	X	X	X	-	-	-	-	-	-
	NDM	X	X	X	X	-	-	-	-	-	-
	OXA-48	X	X	-	X	-	-	-	-	-	-
	SME	X	X	X	X	-	-	-	-	-	-
	VIM	X	X	-	X	-	-	-	-	-	-
Extended Spectrum β-Lactamase ⁸	CTX-M	X	X ^Y	X	-	-	-	-	-	-	-
	SHV	X	X ^Y	X	-	-	-	-	-	-	-
Macrolide/Clindamycin Resistance ^{9,10}	<i>ermA</i>	-	-	-	-	X	X	-	-	-	-
	<i>ermB</i>	-	-	-	-	X	X	-	-	-	-
Vancomycin Resistance ^{11,12}	<i>vanA</i>	-	-	-	-	-	-	X	-	-	-
	<i>vanB</i>	-	-	-	-	-	-	X	-	-	-

X = Drug class potentially affected; - = No known effect on drug class; † = Except Ceftaroline⁴; Y = except cephamycins

Indications for Ordering

DxWound can be used for any patient suspected of having a SSTI or with clinical signs of a SSTI. Testing for antibiotic resistance genes may help clinicians quickly 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 (for more information, please refer to the Technical Specifications bulletin). Table 2 shows the antibiotic resistance genes and alleles included in DxWound.

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All DxWound tests have $\geq 95\%$ accuracy and $\geq 99\%$ reproducibility. Accuracy and reproducibility were established by testing reference specimens with characterized organisms or antibiotic resistance genes obtained from multiple sources including the FDA-CDC antimicrobial resistance isolate bank, commercial vendors, and other laboratories.

Clinical Use

The failure of empiric therapy is a concern in treatment of SSTIs. One study suggested that as many as 16.6% of acute SSTIs, 34.1% of chronic or ulcerative infections, and 26.7% of surgical site infections had initial treatment failure. It has been shown that antimicrobial therapy which is not targeted to the causative pathogen within 48 hours of presentation is an independent risk factor for treatment failure.¹³ This type of data contributed to the U.S. Food and Drug Administration (FDA)'s decision to revise its guidance for the evaluation of clinical response to skin infections to earlier time points of 48 to 72 hours after initiation of therapy.¹³ DxWound tests for several antibiotic resistance genes associated with bacteria that typically cause SSTIs. Clinicians can use these results to help them quickly target antibiotic therapy, ideally within that important 48 hour window.

MecA gene

The *mecA* gene is associated with *Staphylococcus* species, including *Staphylococcus aureus*, *Staphylococcus lugdunensis* and *Staphylococcus epidermidis*.² The *mecA* gene mediates oxacillin/methicillin resistance and is associated with resistance to most β -lactams with the exception of cephalosporins with anti-MRSA activity.^{2,4} Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major public health threat.¹ For more information, please see the clinical bulletin titled "DxWound *Staphylococcus* tests."

Carbapenemase genes

The carbapenemase genes generally mediate resistance to β -lactams, including carbapenems.⁵⁻⁷ The carbapenemase genes included in DxWound have been found in *Acinetobacter*, *Pseudomonas*^{14,15}, and Enterobacteriaceae,^{6,16-19} such as *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, and *Serratia marcescens*. The DxWound carbapenemase genes have also been found less frequently in other bacteria genera.^{14,15,20} Carbapenemase-producing organisms are rare but considered a major public health threat.¹

Extended-spectrum β -lactamase (ESBL) genes

The ESBL genes included in DxWound are commonly associated with Enterobacteriaceae, such as *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, and *Serratia marcescens*, but have also been found in other bacteria genera.^{17,18,20-22} The ESBL genes generally confer resistance to β -lactams except carbapenems.⁸ ESBL-producing Enterobacteriaceae are a major public health threat.¹

Test Interpretation

These tests indicate whether specific antibiotic resistance genes are detected in the wound specimen. The DxWound report provides information about the association of the detected antibiotic resistance gene to the specific antibiotic or antibiotic classes that may be affected. In addition, the report indicates when a potential antibiotic resistant organism may be present, based on the detection of specific organisms with the antibiotic resistance genes. For example, when *mecA* and *Staphylococcus aureus* are both detected, then MRSA may be present. In another example, when KPC and either *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*,

Table 2. Antibiotic Resistance Genes included in DxWound

Gene	Alleles Tested	Resistance Type
<i>mecA</i>	<i>mecA</i>	Oxacillin/Methicillin Resistance ^{2,4}
IMP	IMP-1,-3,-4,-6,-10,-25,-26	Carbapenemase ⁵⁻⁷
KPC	KPC-1 through -11	
NDM	NDM-1, -2	
OXA-48 group	OXA-48, -162, -163, -181	
SME	SME-1, -2, -3	
VIM	VIM-1 through -26 (except -7, -21, -22)	Extended Spectrum β -Lactamase (ESBL) ⁸
CTX-M	CTX-M groups -1 (37 alleles) and -9 (40 alleles)	
SHV	All known alleles	Macrolide/Clindamycin Resistance ^{9,10}
<i>ermA</i> , <i>ermB</i>	<i>ermA</i> , <i>ermB</i>	
<i>vanA</i> , <i>vanB</i>	<i>vanA</i> , <i>vanB</i>	Vancomycin Resistance ^{11,12}

Erm genes

ermA and *ermB* genes have been found in *Staphylococcus*, *Streptococcus*, *Enterococcus*, and in a broad range of other bacterial genera.^{9,23} They mediate resistance to macrolides (e.g. azithromycin) and clindamycin.^{9,10} Clindamycin-resistant group B *Streptococcus* and erythromycin-resistant group A *Streptococcus* are public health threats.¹ For *ermB* testing, in order to identify potential clindamycin-resistant group B *Streptococcus* and erythromycin-resistant group A *Streptococcus*, *Enterococcus faecium* and *Enterococcus faecalis* tests may also be useful, since *ermB* is commonly found in *Enterococcus* species.

vanA and *vanB*

vanA and *vanB* mediate resistance to vancomycin and are associated with *Enterococcus* and very rarely with *Staphylococcus* species.^{11,12} Vancomycin-resistant *Enterococcus* (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA) are public health threats.¹

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Escherichia coli, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis/vulgaris* or *Serratia marcescens* are detected, carbapenem-resistant Enterobacteriaceae may be present.

Clinically, these test results may help clinicians quickly target antibiotic therapy. It is important to note that these tests do not detect all known antibiotic resistance mechanisms, nor do they definitively identify which organism is associated with the antibiotic resistance gene.

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 with which organism an antibiotic resistance gene is associated. It is possible that an antibiotic resistance gene is associated with an organism that is not included in the test.
- Antibiotic resistance gene-organism associations are dependent on published data; unrecognized gene-organism associations may exist.
- *Acinetobacter baumannii* has a high frequency of multidrug-resistance, usually caused by mechanisms not detected by this test.
- The SHV test does not differentiate between narrow-spectrum and extended-spectrum β -lactamase genes.
- The ability to detect target organisms depends on the proper collection and handling of the wound swab specimen. Variation in specimen quality may occur due to poor collection technique, lack of bioburden, or substances applied to the SSTI/wound that interfere with the test, as well as specimen contamination due to non-sterile procedures.
- 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 5:00pm (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.

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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.



Contact CogenDx to learn more.

Client Services: (877) 866-0603

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