Multidrug-Resistant Enterococcal Infections

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You have asked…

I have isolated a multidrug-resistant *Enterococcus* species. What's next?

The expert says…

Enterococci are gram-positive bacteria that are widely found in all types of animals and in the environment. They are ubiquitous members of the commensal microbiota and are typically harmless inhabitants of various body sites—particularly the intestinal tract. However, enterococci are opportunistic pathogens that can cause a wide range of signs if the circumstances are advantageous.

Although enterococci are relatively easy to isolate, determination of clinical relevance may be a challenge. In addition, enterococci are inherently resistant to many antimicrobials, including penicillin, clindamycin, trimethoprim–sulfamethoxazole, and low levels of aminoglycosides, and they are poorly responsive to cephalosporins and fluoroquinolones in vivo.

Enterococci may also acquire resistance to many other antimicrobials, resulting in multidrug-resistant strains with limited treatment options. For example, vancomycin-resistant enterococci (VRE) are of particular concern in human healthcare. VRE can be isolated from companion animals,[1,2] but clinically relevant infections are rarely reported. However, even vancomycin-susceptible enterococci may be resistant to a wide range of antimicrobials, leaving few viable treatment options in some cases.

When addressing with a potential enterococcal infection, a few questions should be considered.

Is this *Enterococcus* species relevant?

Determining whether treatment is needed for an infection with an *Enterococcus* species is an important first step, but the answer is not always clear. Enterococci are common inhabitants of different body sites and have relatively limited virulence. It is impossible to give absolute guidance, but general considerations are presented in **Table** 1, next page.

VRE = vancomycin-resistant enterococci

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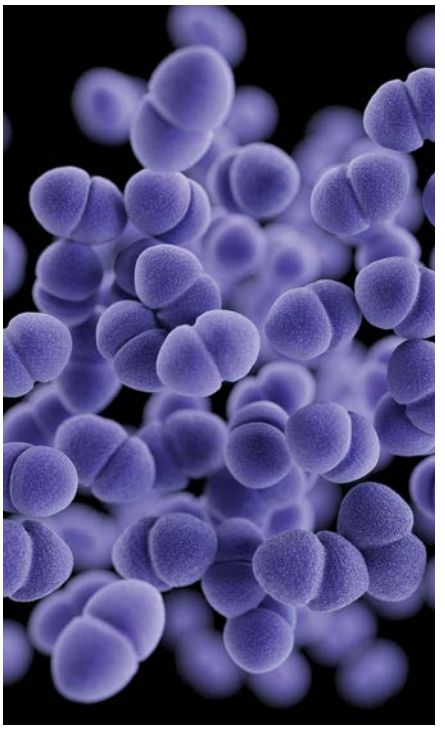

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Find More

Bridge the Gap
Map the isolation process with **Isolation of *Enterococcus* spp**, an algorithm on page 12 of the March 2015 issue of *Plumb's Therapeutics Brief*.

Table. General Considerations for Treatment Decisions

Indication for treatment	■ Isolation of *E faecium* or *E faecalis* from a normally sterile site with clear evidence of an infection and without isolation of any other bacterium, particularly in a hospitalized or otherwise compromised patient.
May be no indication for treatment	■ Isolation of an *Enterococcus* spp other than *E faecium* or *E faecalis*. ■ Concurrent isolation of an *Enterococcus* spp and a more convincing pathogen (eg, *Escherichia coli*).
Likely no indication for treatment	■ Isolation of *Enterococcus* spp from an external body site (eg, skin, nasal passages). ■ Isolation of *Enterococcus* spp from a fecal sample. ■ Isolation of *Enterococcus* spp in the absence of evidence of disease (eg, subclinical bacteriuria). ■ Isolation of *Enterococcus* spp with other diagnostic tests (eg, cytology) that do not support the presence of a bacterial infection or infection by a gram-positive coccus.

The two main pathogenic enterococcal spp are *E faecium* and *E faecalis*. A variety of other species can be encountered, but the clinical relevance of those species is variable. Some have been associated with disease in humans or animals (eg, *E casseliflavus, E avium, E durans, E gallinarum*) but not all enterococci are recognized as being clinically important. Enterococci other than *E faecium* and *E faecalis* should not be dismissed, but additional thought should be given to their clinical relevance when they are isolated.

It is important to remember the degree of antimicrobial resistance has no impact on the decision to treat. Highly resistant isolates are no more inherently virulent than susceptible isolates. If a susceptible *Enterococcus* spp would be considered clinically irrelevant, the same would apply to a multidrug-resistant isolate from the same sample.

What are the available antimicrobial options?

Results of culture and susceptibility testing will guide treatment. Clinical and Laboratory Standards Institute (CLSI) guidelines dictate that laboratories should not report susceptibility results for drugs to which enterococci are inherently resistant or where there is poor efficacy in vivo (ie, penicillin, clindamycin, trimethoprim-sulfamethoxazole, cephalosporins, low-level aminoglycosides),[3] so susceptibility panels may contain few drugs.

Ampicillin or amoxicillin are the drugs of choice in isolates susceptible to these drugs. While enterococci have inherent low-level aminoglycoside resistance, aminoglycosides may be useful in combination with amoxicillin or ampicillin when isolates do not demonstrate high-level aminoglycoside resistance. Combination therapy can be effective because bacterial cell wall damage from ampicillin or amoxicillin facilitates entrance of the aminoglycoside into the cell, even if the isolate is resistant to ampicillin/amoxicillin and gentamicin individually.

Many laboratories report whether the isolate is susceptible to high-level gentamicin (or gentamicin/ampicillin synergy), and this combination is a good option when amoxicillin or ampicillin resistance is reported and when other options are limited.

Fluoroquinolones tend to work poorly for systemic enterococcal infections and are typically not recommended for infections other than those in the urinary tract. Recently, breakpoints for ciprofloxacin and levofloxacin for the treatment of urinary tract infections in humans were proposed,[4] and this drug class may be useful in animals. However, efficacy data are lacking. *E faecium*—but not *E faecalis*—is also inherently resistant to carbapenems, which further reduces treatment options.

Chloramphenicol may be useful in some situations, such as when the isolate is susceptible in vitro. Patient and owner safety must be addressed when considering this drug, which can be an effective option in situations where other drugs are limited and owners can properly handle the drug. Additional options may be available for urinary tract infections, such as nitrofurantoin and fosfomycin.

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In rare cases, isolates may be resistant to all commonly used drugs and susceptible only to drugs such as vancomycin or linezolid. There are ethical debates about the use of these types of drugs in animals because of the need to balance public health with animal health and welfare. These drugs should be rarely needed and rarely used, and careful consideration should be made before using them (see **Checklist for Use of Vancomycin or Linezolid).**

The public health implications of *rare* and *appropriate* use of these drugs are likely inconsequential, but some potential for resistance exists with any use of an antimicrobial, so the concerns should not be dismissed.

Use of these drugs is prohibited in some countries. In addition, some veterinary facilities voluntarily prohibit use of these drugs or restrict their use to situations where a detailed set of criteria have been fulfilled—typically with approval by an infectious disease expert.

How do I manage this resistant infection?

The general approach to treatment of a resistant enterococcal infection is no different than treating an infection caused by a susceptible isolate. Resistant pathogens can be associated with worse outcomes, but that is typically because of the failure of empiric antimicrobial therapy. After the cause is known and an appropriate antimicrobial has been identified (if a viable antimicrobial option can be found), there should be no difference in prognosis and management for resistant versus susceptible pathogens.

While resistant strains may need different antimicrobials, resistance should not impact other aspects, such as duration of treatment and whether other measures (eg, surgery) are required.

Additional considerations

Enterococci are important hospital-associated pathogens in humans,[5,6] and they can cause significant problems in healthcare facilities because of susceptible populations.

Enterococci are also able to persist in the environment better than some other pathogens[7] and can commonly be found in veterinary hospitals,[8,9] although they are readily inactivated by proper disinfection.

Enterococci are transmitted by direct and indirect contact, not airborne or aerosol routes, so proper use of standard practices (ie, personal protective equipment, hand hygiene, environmental cleaning and disinfection) should minimize risk of transmission.

Although objective data are lacking, it is reasonable to use enhanced infection control practices for animals with multidrug-resistant enterococcal infections when they are in the clinic. This would include physical separation (isolation or using other housing and handling practices) and use of personal protective equipment, hand hygiene, cleaning, and disinfection to minimize the risk for direct or indirect exposure.

There are limited concerns about zoonotic transmission of enterococci. While clear evidence of human–animal

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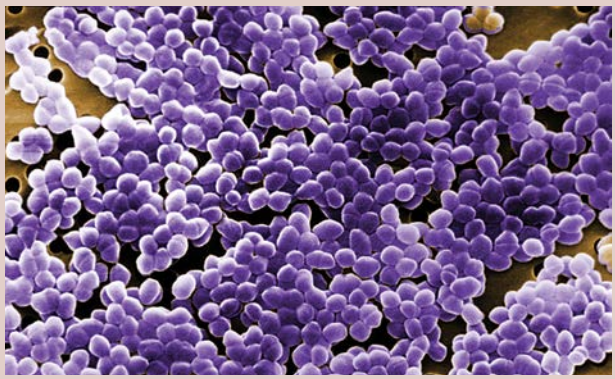
Checklist for Use of Vancomycin or Linezolid

- Is there convincing evidence that the *Enterococcus* species is causing disease?
- Are there other treatment approaches that could be used (eg, topical therapy, local antimicrobials, surgery)?
- Is this a survivable infection?
- Is the isolate resistant to all other options?
- Have I discussed the case with an expert in infectious disease to ensure treatment is required and there are no other viable treatment options?
- Is there an underlying disease process that can and will be addressed?



transmission is lacking, molecular studies have identified the same types of enterococci in humans and animals,[2,10] suggesting that there may be some risk. However, enterococci are shed by virtually all animals (meaning human exposure would be high), so the risk must be low considering the lack of convincing evidence that animals are a relevant source of human infection.

The potential for zoonotic infection should not be dismissed, particularly for humans at increased risk for infection (eg, the young, the elderly, pregnant women, immunocompromised persons) are present, but routine infection control and hygiene practices should minimize any risk. ■ cb

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For Animals Only

Rapinovet™ (propofol) Anesthetic Injection

Emulsion for intravenous use in dogs and cats.

BRIEF SUMMARY: Before using Rapinovet™ (propofol), please consult the product insert, a summary of which follows:

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

WARNINGS: Induction of anesthesia with Rapinovet™ injection is frequently associated with apnea and respiratory depression. Hypotension and oxygen desaturation can occur also, especially following rapid bolus administration. Apnea is observed less frequently following maintenance doses of Rapinovet™ injection when given as the sole maintenance agent, or when a maintenance dose is administered during inhalant anesthesia.

When using Rapinovet™ injection, patients should be continuously monitored, and facilities for the maintenance of a patent airway, artificial ventilation, and oxygen supplementation must be immediately available. The clinical use of propofol without available supplemental oxygen and artificial ventilation has not been adequately evaluated and is not recommended.

SIDE EFFECTS: The primary side effect of Rapinovet™ injection in dogs is respiratory depression and apnea. Apnea was observed in 20% of the dog cases in the clinical trial. Apnea was observed in 1.4% of the cat cases in the clinical trial. All apnea cases responded satisfactorily to oxygen supplementation and/or controlled ventilation.

The primary side effect of Rapinovet™ injection in cats is paddling during recovery. Paddling was observed in 11% of the cat cases in the clinical trial.

Other transient side effects in dogs or cats are observed infrequently or rarely:

• **Respiratory:** panting, reverse sneezing, cyanosis • **Musculoskeletal:** paddling during recovery, tremors, tenseness, movements, fasciculations • **Cardiovascular:** bradycardia, hypotension, cyanosis, tachycardia, premature ventricular contractions • **Central Nervous System:** excitation, opisthotonus, seizure • **Injection Site:** pain during injection • **Gastrointestinal:** emesis/retching • **Other:** rubbing at face or nose during recovery, vocalization during recovery, chewing or licking the injection site during recovery.

PRECAUTIONS:

1. Rapinovet™ injection contains no antimicrobial preservatives. Strict aseptic techniques must always be maintained during handling since the vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis, and/or life-threatening illness. Do not use if contamination is suspected.

2. When using Rapinovet™ injection, patients should be continuously monitored, and facilities for the maintenance of a patent airway, artificial ventilation, and oxygen supplementation must be immediately available. The clinical use of propofol without available supplemental oxygen and artificial ventilation has not been adequately evaluated and is not recommended.

3. Anesthesia effects: Careful monitoring of the patient is necessary when using Rapinovet™ injection as a maintenance anesthetic due to the possibility of rapid arousal. Apnea may occur following maintenance doses of Rapinovet™ injection.

4. Physiological effects: During induction of anesthesia, mild hypotension and increased heart rate may occur when Rapinovet™ injection is used alone.

5. Premedicants: Premedicants may increase the anesthetic or sedative effect of Rapinovet™ injection and result in more pronounced changes in systolic, diastolic, and mean arterial blood pressures. The use of ketamine (an approved compound for restraint in cats) is not recommended as a preanesthetic prior to propofol due to an increased number of patients experiencing apnea.

6. Breeding Animals: Adequate data concerning the safe use of Rapinovet™ injection in pregnant, lactating, and breeding dogs and cats have not been obtained. Propofol crosses the placenta, and as with other general anesthetic agents, the administration of propofol may be associated with neonatal depression.

7. Puppies and Kittens: The use of propofol has not been evaluated in puppies or kittens.

8. Compromised or debilitated dogs and cats: Doses may need adjustment for geriatric or debilitated patients. The administration of Rapinovet™ injection to patients with renal failure and/or hepatic failure has not been evaluated. As with other anesthetic agents, caution should be exercised in dogs or cats with cardiac, respiratory, renal or hepatic impairment, or in hypovolemic or debilitated dogs and cats.

9. Sighthounds: Rapinovet™ injection induction followed by inhalant anesthetic agents produced satisfactory anesthesia and recovery times in sighthounds. Propofol alone in 6 greyhounds and 7 non-greyhounds showed satisfactory, but longer recovery times in the greyhounds (averages of 47 and 18 minutes, respectively).[2] In a propofol pharmacokinetics study, greyhounds had higher propofol levels in plasma, a lower volume of distribution, slower total body clearance rates, and longer recovery times than did mixed-breed dogs. The elimination half-life was similar in both groups.[3]

10. Arrhythmogenicity: In one study in dogs, propofol increased myocardial sensitivity to the development of epinephrine-induced ventricular arrhythmias in a manner similar to other anesthetics.[4]

11. Consecutive day treatment: Heinz bodies increased dramatically in cats following repeat administration of propofol on consecutive days and were associated with decreases in RBC count and hematocrit. Large numbers of Heinz bodies can lead to hemolytic anemia.[5,6] In one study in cats, treatment with propofol once a day for 3 days led to a marked increase in Heinz bodies. Treatment for 5 or more consecutive days resulted in generalized malaise and/or facial edema; clinical signs of illness resolved within 24 to 48 hours after cessation of propofol.

12. Concurrent Medication: No significant adverse interactions with commonly used drugs have been observed.

13. Perivascular Administration: Perivascular administration does not produce local tissue reaction.

CONTRAINDICTIONS: Rapinovet™ injection is contraindicated in dogs and cats with a known hypersensitivity to propofol or its components, or when general anesthesia or sedation are contraindicated.

HUMAN USER SAFETY: Not for human use. Keep out of reach of children.

Rapinovet™ injection should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting. Rare cases of self-administration of propofol have been reported, including dose-related fatalities.

The material safety data sheet (MSDS) contains more detailed occupational safety information. For customer service, and/or a copy of the MSDS, call 1-800-633-3796. To report adverse effects, call 1-800-422-9874.

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