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Clinical Microbiology Portal's March Hot Topic

Laboratory Support of Infection Control Initiatives: Should We be Doing More or Less?

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Introduction

- One of the biggest current challenges in the field of infection prevention is the control of multidrug-resistant organism infections
- One approach to reducing the risk of these infections is to measure the prevalence of asymptomatic colonization by these organisms (the reservoir) in your patient population; active surveillance
- Active surveillance means specimens will be sent to the laboratory with instructions to look for a certain resistant bacterial phenotype
- This presentation will show several ways laboratories can detect MDROs for active surveillance programs

Learning objectives

- Participants will be able to:
  - **List** the multidrug resistant organisms (MDRO) that are of significance in hospital infection control
  - **State** the rationale for active surveillance for MDROs
  - **Distinguish** the advantages and disadvantages of the current methods for screening for MDROs
  - **Select** the best screening method for MDROs in their laboratory and hospital setting

Disclaimers

- Dr. Van Enk has no financial interest in any product, instrument or technique discussed in this presentation.
- Any mention or illustration of a commercial product does not imply endorsement of the product
- The information presented is the sole opinion of the presenter. ASM reviews the presentations for overall appropriateness but this review is not an endorsement by the Society of the content.

Limitations

- This presentation will focus on the “more” of the question “more or less”
- Assumes that a decision has been made to do active surveillance testing and the laboratory must decide which method to use
- A later Hot Topic presentation may focus on the “less” issues of designing an active surveillance program
  - Should active surveillance be done, when and for how long, to whom, which and how many MDROs should be looked for, how many body sites should be sampled, does the patient need to give consent, does the hospital have the right to screen asymptomatic patients, who pays for screening, are there unintended negative consequences of active surveillance programs, and so on

Outline

- What are multidrug resistant organisms?
- Why are they important?
- Why screen asymptomatic people for them?
- What methods can we use to detect them in specimens?
- What are the advantages and disadvantages of the methods?
- Which method should I use in my laboratory?

What are multidrug resistant organisms?

- The definition of a multidrug resistant organism is surprisingly unclear and will always be tentative
  - Resistant to at least two complete classes of antibiotics (for example, all beta-lactams or all aminoglycosides)
  - Resistant to the drug of choice (methicillin-resistant *S. aureus* or vancomycin-resistant enterococci)
  - May not be antibiotic resistant but just hard to kill for other reasons (*Clostridium difficile*)
  - Epidemiologically significant in your population
  - Must be pathogens in humans

What are multidrug resistant organisms?

- There is a consensus around which should be considered MDRO, at least for now
- Methicillin-resistant *Staphylococcus aureus*; MRSA
- Vancomycin-resistant enterococci (by the vanA mechanism); VRE
- Extended-spectrum beta-lactamase-producing enteric Gram negatives; ESBL
- Carbapenem-resistant Gram negatives; KPC
- Highly resistant *Acinetobacter* and *Pseudomonas*, other non-fermenter strains
- *Clostridium difficile*

Why are MDROs important?

- Many studies show that when patients get MDRO infections, bad things happen
  - Patient outcomes are worse; acuity, mortality, length of stay, complications, toxicity of alternative antibiotics required
  - Cost per episode of care is increased; antibiotic costs, length of stay, cost of special precautions
- MDROs are transmissible; their presence in some patients poses a risk to other patients
  - Transmission is theoretically preventable if you know their source

How common are MDROs and what is their reservoir?

- Most multidrug resistant bacteria are strains of bacteria that are normal human flora, but they happen to be resistant phenotypes
  - MRSA, VRE, enteric Gram negatives, *C. difficile*
- The Gram negative non-fermenter MDROs typically have an environmental source like water or soil but can cause outbreaks in hospitals
  - *Acinetobacter, Pseudomonas, Stenotrophomonas*

How common are MDROs and where are they?

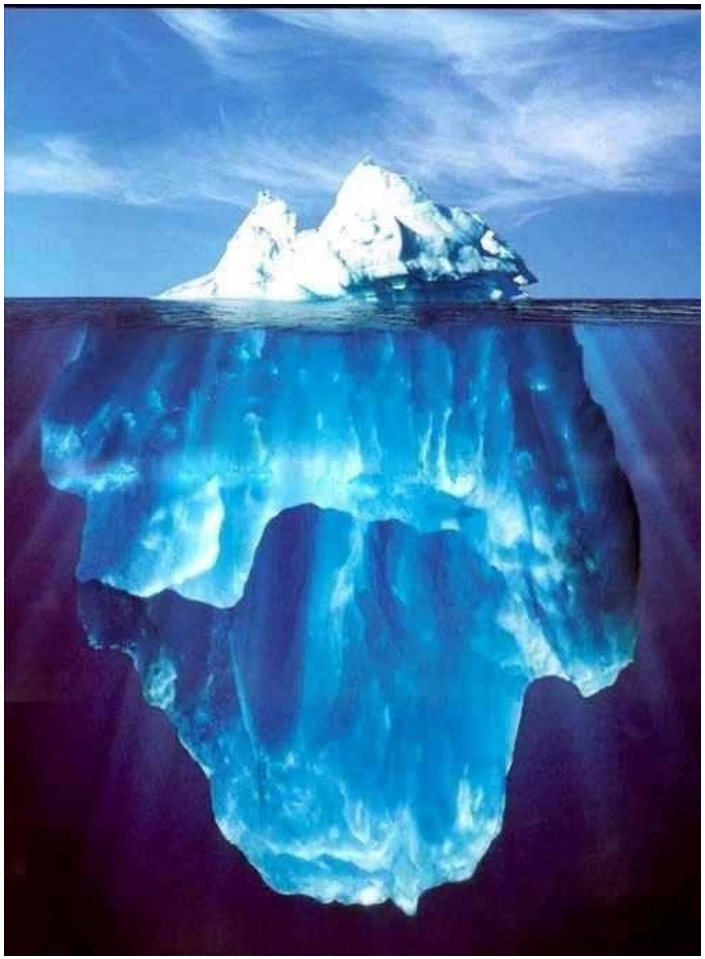
- MRSA can be carried in the nose of 5% of the population
- VRE can be carried in the GI tract of 5% of the population
- *C. difficile* is carried in the GI tract of 1-3% of the population
- Prevalence of MDRO enteric Gram negatives is less understood (one study found ESBL-producers in 8.2% of stool specimens)
- Prevalence varies with the population, hospitalization increases the prevalence of MDRO colonization
- The resistant phenotype may not be predominant in the specimen; you have to use sensitive and selective testing to find it

Why screen asymptomatic people for multidrug resistant organisms?

- Patients who are known to carry an MDRO are placed in special precautions to reduce the risk of spreading the MDRO to others
  - Usually **Contact Precautions** (private room, staff wear gloves and gowns, room is cleaned differently)
  - Special precautions can be used proactively or reactively (put patients in precautions until test is negative or put them in when test is positive)
- The longer a MDRO-carrying patient is not in special precautions, the higher the risk of spread
- **Time is risk; a fast result is worth more than a slow one**

Why screen asymptomatic people for multidrug resistant organisms?

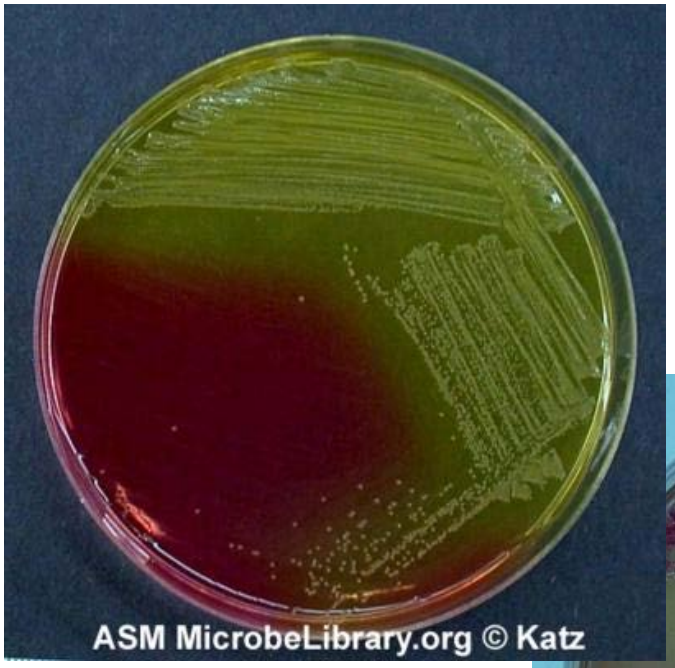
- You cannot tell if a noninfected patient is colonized with an MDRO unless you test them
- Colonized patients are the reservoir for MDRO strains that may later cause infections
  - Infected patients are the tip of the iceberg, colonized patients are the rest of the iceberg

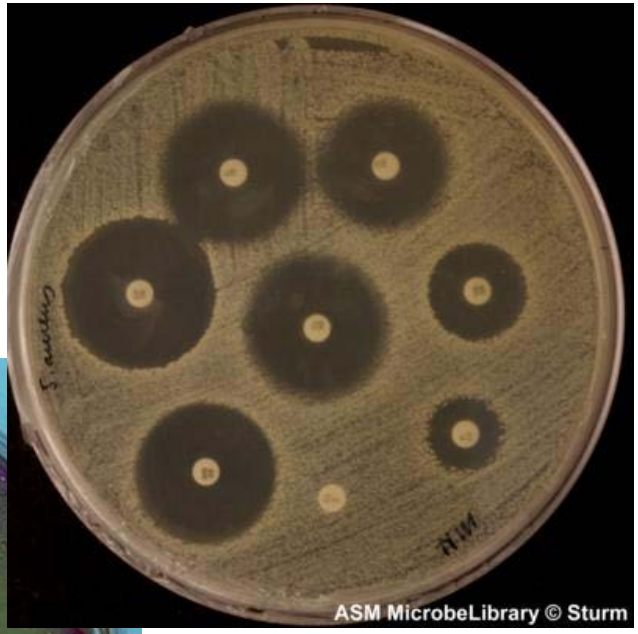


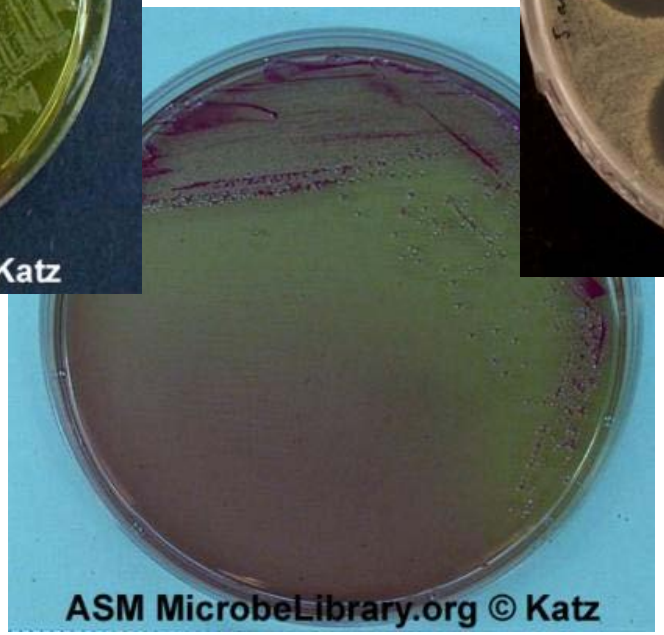
What methods can we use to detect them in specimens?

- Routine cultures
- Selective screening culture
- Molecular tests

Using routine cultures to assess the prevalence of MDROs







Using routine cultures to assess the prevalence of MDROs

- All of the current multidrug-resistant organisms are considered pathogens if they are recovered from specimens from infections
- Using your normal work-up procedures, they would be identified and susceptibility testing done, so you would detect them
- In some ways incidence in cultures is a more meaningful measure of risk because it measures both incidence and virulence
- Does not require purchase and QC testing of new culture media or equipment
- Routine cultures are billable and reimbursable

Using routine cultures to assess the prevalence of MDROs

- Routine culture does not select for the MDRO
  - You would find it only if it were the predominant strain in the specimen
  - If it were hiding in low numbers in the primary streak area, or below your work-up limit, you would miss it
- Culturing infections is not assessing colonization
  - Routine culture specimens (blood, sputum, urine, wounds) are usually not the place where MDROs colonize (nose, stool)
- Measuring MDRO prevalence in routine cultures is a good place to start and meaningful if the prevalence is low but may not be enough

Using selective screening media to assess the prevalence of MDROs

- To properly measure the reservoir of MDRO in an asymptomatic patient population, you have to sample the sites of the body where they colonize and use a sensitive method to pick up the resistant phenotype
  - Exclude the susceptible strains of the desired species
  - Exclude resistant strains of other species (the test must tell you both the identification and the susceptibility)
- Speed and accuracy are both needed (in microbiology, they often conflict)

Chromogenic Agar

- Chromogenic agars are designed to give an **identification by a color reaction** of the colonies and **select for the resistant phenotype** by including the resistant antibiotic in the medium
  - Only the resistant organisms grow and the color tells you what species it is
  - Can be used like a primary plate; streak the original specimen

Commercial chromogenic agar products

- CHROMagar™
  - Developed in Europe, sold in the US by Becton, Dickinson and Company
  - Products for MRSA (cefoxitin, in nares swabs), VRE (includes vanA and vanB, in stool), KPC (in stool, urine), ESBL (in stool, urine), and CTX (third generation cephalosporins, in stool, urine)
- ChromID™
  - bioMérieux
  - Products for MRSA (nose, throat, perineum, wound, groin), VRE (rectal or stool), ESBL (rectal, urine, respiratory), C. difficile (stool)

Commercial chromogenic agar products

- HardyCHROM™
  - Hardy Diagnostics
  - Products for MRSA (nares only), VRE, ESBL, Carbapenemase

- Denim Blue Agar and new Brilliance™ MRSA Agar
  - Oxoid, distributed by Thermo Fisher
  - For MRSA

Commercial chromogenic agar products

- Things to note
  - Cost; list price of one vendor is about $2.50 per plate, but the plate includes culture, identification and susceptibility test
  - Color reactions; identification depends on the color of the colony (may be a problem for color-blind people)
  - All chromogenic plates are incubated at 35-37° C in air for 18-24 hours, do not use CO_2, do not incubate longer or you will get break-through growth
  - Not all plates are approved for all specimens
  - VRE plates pick up both vanA and vanB strains

How good are chromogenic agar products for active surveillance?

- What is the “gold standard” for detecting colonization?
  - Most studies use some sort of broth-enrichment culture to establish 100% sensitivity
- Published studies on chromogenic media generally show sensitivity and specificity in the 95-100% range for the approved specimen sources
- They all seem to work very well for their intended purpose when used as directed
- The question is whether they are fast enough, or would a faster result add value in your setting

Nucleic acid amplification (PCR) methods

- Nucleic acid amplification methods use the polymerase chain reaction (PCR) method to detect target DNA sequences in the specimen without the need for growth of the organism
  - Two targets; one to establish the organism's identity and another to detect the resistant gene
  - Provides a **faster** result; as short as 45 minutes
  - Theoretically 100% sensitive, but one study showed an actual limit of detection of VRE in stool of about 100 organisms, one company claims to detect 5 MRSA organisms
- Following are commercial PCR tests, this presentation will not discuss designing your own PCR test

Nucleic acid amplification (PCR) commercial products

- BD GeneOhm™
  - Becton-Dickinson
  - Products for MRSA (nasal swabs) and *C. difficile* toxin B (stool), VRE test in development
- Xpert®
  - Cepheid
  - Products for MRSA, C. difficile , VRE (vanA only)
- LightCycler® MRSA Advanced Test
  - Roche
  - Detects MRSA in nasal swabs

Nucleic acid amplification (PCR) commercial products

- Things to note
  - All require some sort of instrument to run the test
  - No current systems detect Gram negative MDROs
  - Test systems vary in test menu, time to result, cost of instrument ($27,000-$35,000), cost per test ($25-$42), service contract cost, reagent rental agreements, difficulty to run, number of controls, effect of batching tests
  - Instrument platforms can also run other billable tests that reduce the instrument cost per test

How good are PCR tests for MDROs?

- All evaluations show both false positive and false negatives compared to culture, but it is unclear what those mean (which is the gold standard?)
- Most studies compare PCR to chromogenic media
- Most studies have evaluated the PCR MRSA tests
- All evaluation studies show the commercial PCR tests to be highly sensitive and specific when used for their intended purpose and using the approved specimens
- Direct comparisons of the GeneOhm and Xpert MRSA tests show that they are equivalent

How good are PCR tests for MDROs?

- A weakness of all PCR tests is that they detect only **one genotype**, not all possible resistant phenotypes
  - If alternative resistance mechanisms exist, they will not detect them (true ESBL versus high ampC, true mecA versus high beta lactamase, how many carbapenemases are there?)
  - If alternative target DNA sequences exist or emerge by mutation, they may not detect them, giving a false-negative
  - If the resistant gene is present but not transcribed, the test will be false-positive

Which method should I use in my laboratory?

- If routine cultures do not show any MDROs or very few and not related, routine culture might be good enough to establish a low risk in your setting
- If you regularly find MDROs in your routine cultures, their incidence is increasing, and the infections are epidemiologically related, you probably need to do a risk assessment using active surveillance
- If your active surveillance program is temporary and limited, to spot-check a population, chromogenic media will tell you what you want to know with a much lower up-front investment
- If your active surveillance program is large and will be continued forever, a PCR method is probably required

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We encourage you to log in, submit your questions, and participate in the live event. No question will go unanswered!

Follow these instructions to log in and submit your question:

1. Open http://clinmicro.asm.org/.
2. Click on the blue "Hot Topics" icon to the bottom-center of the page.
3. Once the Blog page has opened, click the "Login" link at the very top right of the screen.
4. If you have login credentials with ASM, enter them here to log in. If you do not, click the "Register Your UserID…" box on the bottom-left side of the page. Follow the instructions to complete the registration. You will be asked to enter your email address. This step is important as it will verify whether you have an existing account with ASM.
5. Once you have completed your registration and logged in, you should be returned back to the Hot Topics Blog. If not, repeat steps one and two.

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