Of Dogs and Men: A case study in Methicillin-resistant *Staphylococcus aureus* [MRSA]

AAVMC / APTR One Health Case Studies Initiative

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STUDENT CASE MATERIALS:

Case scenario

A healthy, adult male presents to the primary care professional for laboratory testing associated with recurrent skin infections. The doctor obtains a swab from the perineal area by gently lifting the patient's tail…..yes, tail. The patient is Rusty, a 6 year-old, Golden Retriever, whose family is experiencing recurrent episodes of pyoderma associated with MRSA.

Learning Objectives

Participation in this case will enable the student to:

- Describe laboratory methods used to differentiate *Staphylococcus aureus* from other bacteria
- Understand the mechanism conferring the antimicrobial resistance associated with MRSA
- Describe the laboratory methods used to differentiate methicillin-resistant *Staphylococcus aureus* (MRSA) from methicillin-susceptible *Staphylococcus aureus* (MSSA)
- Evaluate and discuss approaches to MRSA infection control in humans and pets (dogs) in a household experiencing recurrent MRSA infections

Preparatory materials (See Note in Facilitator's Guide)

Students should carefully read through the following materials prior to class discussion:

1) Becker K, Skov R, von Eiff C. (2015) Staphylococcus, Micrococcus, and Other Catalase-Positive Cocci. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, 11th Edition*. ASM Press, Washington, DC. p 354-382.

2) Que Y and Moreillon P. (2010) Staphylococcus aureus (Including Staphylococcal Toxic Shock). *In* Mandell GL, Bennett JE, Dolin R (ed), *Principles and Practice of Infectious Diseases, 7th Edition.* Churchill Livingstone Elsevier, Philadelphia, PA. p 2543-2578.

A) Songer JG, Post KW (2005) The Genus *Staphylococcus. Veterinary Microbiology: Bacterial and Fungal Agents of Animal Diseases*. Elsevier-Saunders, St. Louis, MO. p 35-41.

B) Weese, JS (2012) Staphylococcal Infections. *In* Greene CE (ed), *Infectious Diseases of the Dog and Cat, 4th Edition.* Elsevier Saunders, St. Louis, MO. p 340-348.

Students will find additional recommended references within the case study. These references are not required but should serve as supplemental materials that can be used to address specific questions.

Background

The Problem

Staphylococcus aureus is an opportunistic pathogen of both humans and animals. In humans, clinical presentations can range from toxin-mediated food poisoning (Fetsch, 2014) to endocarditis (Hoen, 2013) to skin / soft tissue infections [SSTI] (Frazee, 2005). Population surveys estimate that 30-35% of people in the United States are asymptomatically colonized with *Staphylococcus aureus* (Graham, 2006). This means that it may be found on body surfaces, such as the nares, axilla or groin, but does not cause any disease state.

In animals, *Staphylococcus aureus* also causes a wide variety of clinical syndromes, including orthopedic implant infections, mastitis, pyoderma and also asymptomatic carriage (Leonard, 2008). *Staphylococcus aureus* carriage in dogs was shown to occur with a frequency of less than 10% (Boost, 2008).

The (Other) Problem

In 1929, Dr. Alexander Fleming described a substance produced by *Penicillium* mold that would revolutionize modern medicine. "Penicillin", as he termed it, produced a strong inhibitory/lytic effect against many bacterial species *in vitro*, most notably, the pyogenic cocci (*Staphylococcus*).

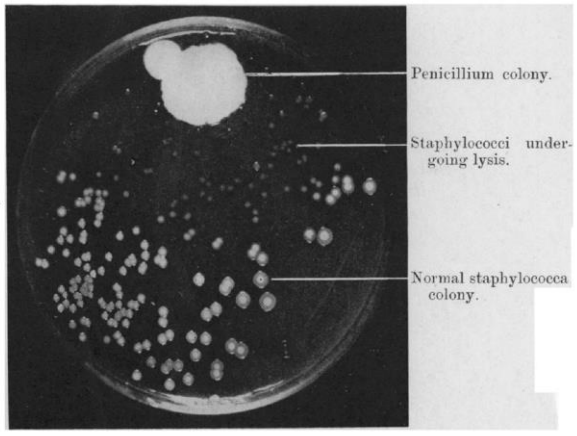

FIG. 1.—Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a penicillium colony.

Image from: Fleming A (1929) On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of *B. influenza*. British Journal of Experimental Pathology; 10.

However, within a short span of time, penicillin-resistant *Staphylococcus aureus* were being isolated from clinical infections. (Rammelkamp, 1942). For many years, penicillin resistant *S. aureus* was a major problem in human medicine. Then a new antimicrobial agent, methicillin, was discovered, and it was hoped that this agent would represent a cure for staphylococcal infections and end the ongoing outbreaks and epidemics. However, reports of methicillin resistant staphylococci began to emerge *within one year* of the drug being introduced into clinical use. (Jevons, 1961) Initially, MRSA infection was strongly associated with recent hospitalization (Hospital-associated MRSA or HA-MRSA), but in the 1980s / 1990s reports of MRSA *not* associated with hospitalization started to appear. These MRSA strains were distinctly different from HA-MRSA and were called Community-acquired MRSA (CA-MRSA) (Chambers, 2001). Many of the CA-strain types carried additional virulence or toxin genes and were associated with community-acquired skin and soft tissue infections, but also severe invasive disease, such as necrotizing pneumonia. The CA-MRSA was causing disease in previously healthy individuals and children. Fast-forward to 2013, the Centers for Disease Control and Prevention has classified methicillin-resistant *Staphylococcus aureus* as a "Serious Threat" to public health causing an estimated 80,000 infections and 11,000 deaths annually in the United States. (CDC, 2013)

While the role of pets in transmitting MRSA is largely unknown, one study demonstrated that MRSA carriage in healthy dogs was low (Vengust, 2006). However, there have been several case reports in which dogs have been colonized with a MRSA strain that was indistinguishable from the strain causing human disease (Cefai, 1994; Manian, 2003; Rutland, 2009; van Duijkeren, 2005). In many of these cases, the direction of transmission was considered bi-directional. That said, in households of individuals with recurrent MRSA infection, any reservoir for MRSA is often feared, even if the source of the reservoir is indeed the index patient.

Laboratory workup / clinical management of recurrent skin infections within a household

In cases of recurrent skin infections where MRSA is suspected, there are three primary questions that should be cooperatively addressed by the laboratory / attending physician / veterinarian.

1. Is *Staphylococcus aureus* involved?
2. If so, is the particular *Staphylococcus aureus* methicillin-resistant?
3. If so, how will MRSA be managed in this particular household?

Part 1: Is *Staphylococcus aureus* involved?

You are the working in the microbiology laboratory that has received Rusty's perineal swab. You must determine if Rusty is colonized with Staphylococcus aureus. The recommended references should guide your answers to the following:

References:

1. Becker K, Skov R, von Eiff C (2015) Staphylococcus, Micrococcus, and Other Catalase-Positive Cocci. *In* Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), *Manual of Clinical Microbiology, 11th Edition*. ASM Press, Washington, DC. p 354-382.

2. Songer JG, Post KW (2005) The Genus *Staphylococcus. Veterinary Microbiology: Bacterial and Fungal Agents of Animal Diseases*. Elsevier-Saunders, St. Louis, MO. p 35-41.

Questions:

1. What type of culture medium is frequently used to cultivate *S. aureus* in clinical laboratories?
2. What is the phenotypic appearance of *Staphylococcus aureus* on a blood agar plate?
3. What are the gram stain characteristics of *Staphylococcus aureus?*
4. What laboratory tests could be used to differentiate *Staphylococcus aureus* from other bacteria, including other *Staphylococcus* spp.?
    a. Which particular bacterium could easily be misidentified as *Staphylococcus aureus* in this scenario? How would you differentiate the two organisms?
5. Design a flow chart to be used in the microbiology lab to aid in identification of *Staphylococcus aureus.*

Part 2: Is the particular *Staphylococcus aureus* methicillin-resistant?

You are able to isolate Staphylococcus aureus from Rusty's specimen. You must now determine if the particular isolate is methicillin-resistant. The recommended references should guide your answers to the following:

References:

1. Chambers HF (2006) General Principles of Antimicrobial Therapy. In *Goodman and Gilman's: The Pharmacological Basis of Therapeutics 11th edition.* McGraw-Hill, New York, NY. Pg. 1095-1099.

2. Que Y and Moreillon P. (2010) Staphylococcus aureus (Including Staphylococcal Toxic Shock). *In* Mandell GL, Bennett JE, Dolin R (ed), *Principles and Practice of Infectious Diseases, 7th Edition.* Churchill Livingstone Elsevier, Philadelphia, PA. p 2543-2578.

3. Boerlin P and White DG (2013) Antimicrobial Resistance and Its Epidemiology. *In Giguere S, Prescott JF, Dowling PM (ed), Antimicrobial Therapy in Veterinary Medicine, 5th edition.* Wiley Blackwell, Ames, IA. Pg. 21-40.

4. CLSI. *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Fourth Edition.* CLSI document VET01-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

5. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement.* CLSI document M100-S25. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

6. Centers for Disease Control and Prevention - Methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Laboratory Testing for MRSA. Accessed 2 Sept 2015 at: http://www.cdc.gov/mrsa/lab/index.html#a2

From the reading:

1. Define "antibiotic resistance" in technical terms. Answers to a) and b) below should be included in your definition.
    a. How do antibiotics exert their effects on bacteria?
    b. How is the drug-pathogen relationship altered when a resistance mechanism is present?
2. Define "antibiotic resistance" in a tweet that could be understood by a non-technical audience.
3. Through words and/or pictures, describe the specific antimicrobial resistance mechanism associated with MRSA.
4. Describe 3 tests that can be used to detect methicillin resistance.

Part 3: How will MRSA be managed in this particular household?

While there are guidelines in managing recurrent MRSA (Lui, 2011), many of the recommendations are based on relatively weak evidence. The evidence for the role of pets in MRSA transmission is equally unclear. Due to the equivocal nature of evidence in managing recurrent MRSA in households with a pet, a "one-health" approach of both human and veterinary medical perspectives is most likely to result in an optimal outcome.

You are now the clinician on Rusty's case. Using the provided references, defend a medical plan for this household. You should specifically address the scientific support for or against the following measures:

a. Personal hygiene
b. Environmental hygiene
c. Decolonization
    a. Humans
    b. Rusty
d. Bacterial monitoring (cultures)
    a. Humans
    b. Rusty

References:

1. Catry B, van Duijkeren E, Pomba MC *et al* (2010) Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health. Epidemiology and Infection, 138.
2. Centers for Disease Control and Prevention - Methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Accessed 2 Sept 2015 at: http://www.cdc.gov/mrsa/
3. Cohn LA, Middleton JR. (2010) A veterinary perspective on methicillin-resistant staphylococci. Journal of Veterinary Emergency and Critical Care, 20.
4. Cookson B, Bonten MJM, MacKenzie FM *et al.* (2011) Meticllin-resistant *Staphylococcus aureus* (MRSA): screening and decolonization. International Journal of Antimicrobial Agents, 37.
5. Ellis MW, Schlett CD, Millar EV *et al.* (2014) Hygiene strategies to prevent methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections: a cluster-randomized controlled trial among high-risk military trainees. Clinical Infectious Diseases, 58.
6. Fritz SA, Hogan PG, Hayek G *et al.* (2012) Household versus individual approaches to eradication of community-associated *Staphylococcus aureus* in children: a randomized trial. Clinical Infectious Diseases, 54.
7. Fritz SA, Hogan PG, Singh LN *et al.* (2014) Contamination of environmental surfaces with *Staphylococcus aureus* in households with children infected with methicillin-resistant *S. aureus.* JAMA Pediatrics; 168.
8. Liu C, Bayer A, Cosgrove SE *et al.* (2011) Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clinical Infectious Diseases, 52.
9. Weese JS. (2011) Methicillin-resistant staphylococcal infections in pets. European Journal of Companion Animal Practice, 21.

Other References

Boost MV, O'Donoghue MM, James A (2007) Prevalence of *Staphylococcus aureus* carriage among dogs and their owners. Epidemiology and Infection, 136.

Cefai C, Ashurst S, Owens C. (1994) Human carriage of methicillin-resistant *Staphylococcus aureus* linked with a pet dog. The Lancet, 344.

Centers for Disease Control and Prevention (2013) Antibiotic resistance threats in the United States. Accessed 18 Aug 2015 at: http://www.cdc.gov/drugresistance/threat-report-2013/

Chambers HF. (2001) The changing epidemiology of *Staphylococcus aureus*? Emerging Infectious Diseases, 7.

Fetsch A, Contzen M, Hartelt K *et al.* (2014) *Staphylococcus aureus* food-poisoning outbreak associated with the consumption of ice-cream. International Journal of Food Microbiology, 187.

Frazee BW, Lynn J, Charlebois ED *et al.* (2005) High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. Annals of Emergency Medicine, 45.

Graham PL, Lin SX, Larson EL (2006) A U.S. population-based survey of *Staphylococcus aureus* colonization. Annals of Internal Medicine, 144.

Hoen B, Duval X. (2013) Infective Endocarditis. The New England Journal of Medicine, 368.

Jevons MP. (1961) Celbenin-resistant staphylococci. British Medical Journal, 1.

Leonard FC, Markey BK. (2008) Meticillin-resistant *Staphylococcus aureus* in animals: a review. The Veterinary Journal, 175.

Liu C, Bayer A, Cosgrove SE *et al.* (2011) Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clinical Infectious Diseases, 52.

Manian FA. (2003) Asymptomatic nasal carriage of mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. Clinical Infectious Diseases, 36.

Rammelkamp CH and Maxon T. (1942) Resistance of *Staphylococcus aureus* to the action of penicillin. Experimental Biology and Medicine, 51.

Rutland BE, Weese JS, Bolin C *et al.* (2009) Human-to-Dog transmission of methicillin-resistant *Staphylococcus aureus.* Emerging Infectious Diseases, 15.

Van Duijkeren E, Wolfhagen MJHM, Heck MEOC, Wannet WJB (2005) Transmission of a Panton-Valentine leucocidin-positive, methicillin-resistant *Staphylococcus aureus* strain between humans and a dog. Journal of Clinical Microbiology, 43.

Vengust M, Anderson MEC, Rousseau J, Weese JS (2006) Methicillin-resistant staphylococcal colonization in clinically normal dogs and horses in the community. Letters in Applied Microbiology, 43.

About the Authors

Brian Lubbers is an assistant professor at the Kansas State University College of Veterinary Medicine. After earning a Doctor of Veterinary Medicine from Kansas State University, he spent 3 years in private veterinary practice with an emphasis on food animal medicine and herd health. He returned to Kansas State University to earn a PhD in Microbiology. In 2011, he was certified as a Diplomate of the American College of Veterinary Pharmacologists.

Dr. Lubbers currently serves as the director of clinical microbiology and microbial surveillance sections of the Kansas State Veterinary Diagnostic Laboratory. His primary teaching responsibilities are in the food animal medicine, pharmacology and diagnostic medicine courses of the veterinary curriculum with a particular emphasis on diagnostic testing and therapy of bacterial diseases of animals.

Carey-Ann Burnham is an Associate Professor of Pathology & Immunology, Molecular Microbiology and Pediatrics at Washington University School of Medicine in St. Louis, and the Medical Director of Clinical Microbiology for Barnes Jewish Hospital in St. Louis. Burnham earned a PhD in Medical Sciences with a focus in microbial pathogenesis at the University of Alberta in Edmonton, Alberta, Canada and then completed a fellowship in Medical and Public Health Microbiology under the direction of Dr. Mike Dunne at Washington University.

Burnham is currently the director of Washington University's Clinical Microbiology Fellowship and she is the founder and co-editor of Medical Microbiology Question of the Day (pathquestions.com). Burnham's research interests are in the development of new diagnostic assays to improve the health of patients with infectious diseases, and the transmission and epidemiology of multi-drug resistant bacteria, including *Staphylococcus aureus*, *Clostridium difficile* and the Carbapenem-Resistant *Enterobacteriaceae*.