IAPO-Interamerican Association of
Pediatric Otorhinolaryngology

Methicillin-Resistant Staphylococcus aureus (MRSA)

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On 17th October 2007, The Washington Post published this:
"A Dangerous germ that has been spreading around the country causes more life-threatening infections than public health authorities had thought and it's killing more people in the United States each year than the AIDS virus, federal health officials reported yesterday".
I think it will be interesting that the use of the antibiotics is one of the reasons further on in this article where the researchers calculate that Methicillin-Resistant *Staphylococcus aureus* (MRSA) was striking nearly 32 out of every 100,000 Americans, so it was killing more than 18,000 Americans last year whereas AIDS killed only 12,000.
So this is a big deal, this is not just a small thing. In Pediatric ENT, the community of acquired MRSA has been steadily growing.
In 1999 it was 0% in our hospital, and it went up to 65% of neck abscess/head due to MRSA by 2004.
And whereas it has typically been reported in the skin and soft tissues, at our institution, otorrhea accounted for almost 1/3 of the Pediatric Otolaryngology isolates of MRSA.
This otorrhea is infectious otorrhea that starts first in the middle ear. So, by design, you must have a tympanostomy tube (TT) in place or a chronic perforation in order to have MRSA otorrhea.
It is felt that MRSA otorrhea is often secondary to a distant reservoir, such as the nasopharynx or the nasal vestibule, and this becomes very important later on, as we discuss treatment options.
As it has been emphasized today, the most significant risk factor for the development of MRSA otorrhea is the previous use of systemic antibiotics for any type of otorrhea.
This was published by Joseph Dohar in 2005, and later we are going to the Dohar's "Do's and Don'ts". We all know this is being a very frustrating disease process, but we can take this child with MRSA otorrhea, we can treat them for 6 weeks with intravenous Vancomycin, and we can get the otorrhea to stop – likely for about 5 days, and then, once again you have the child with a draining ear.
As it has been stated, MRSA was first identified in 1961, and it's the mecA gene that codes for the altered penicillin-binding protein that results in the infection. MRSA tends to affect skin, soft tissue and surgical sites.
Back in 1975, when it was only hospital-acquired, MRSA was the infectious cause in only 2.4% of the nosocomial, or hospital-acquired, infections. MRSA then grew to almost 50% of all nosocomial infections by 2004.

It has been noted that transmission of MRSA can be from athletes sharing towels or benches or other infected items, by going to a nursing home and coming into contact with infected items, or even by being children of health care providers having contact with the parent who could bring the infection home.

MRSA, as you can see, stays alive on inanimate objects, and it's often passed along by airborne transmission. Because the nasal cavity is considered the primary reservoir, whenever there is an MRSA identified patient, we use gowns, gloves, masks to prevent the health care work from carrying it between patients, we try to keep any open wound covered, and even having exam rooms with laminar airflow is being considered for MRSA infected patients to try and decrease the spread of the bacterial infection. At Denver Children's Hospital we have seen an increase in the incidence from 2000 when it was less than 5%., to 2004 when the MRSA infection rate was 16%, and in 2005 it was actually over 25%. This is the percentage of all *Staphylococcus aureus* cases that are at Children's Hospital which are MRSA positive.

If we then look at MRSA positive cases, it can be seen that a MRSA infection is certainly resistant to the beta-lactams such as penicillin, dicloxacillin and cephalexin as expected. MRSA infections are systematically in-vitro sensitive to the trimethoprim/sulfa drugs, but mostly resistant to the macrolides. Clindamycin sensitivity is not much over 50% and for Denver, fortunately, MRSA infections are still 100% sensitive to vancomycin.

Looking more closely at systemic treatment for MRSA infection, the susceptibility to many antibiotics has decreased over time. From 1996 to 2001 a decrease in macrolide sensitity was noted from 75% to less than 50%, from 100% to 80% in the quinolones and down to about 84% with clindamycin.

There has been no change in the sensitivity levels, however, for gentamicin, rifampin, tetracyclines, sulfa drugs or vancomycin. A very brief pharmacy lecture here to explain this phenomena. **Beta-Lactam types of antibiotics such as penicillins or cephalosporings work on a pharmacokinetic principle**. **Pharmacokinetics are based on the time spent above the minimum inhibitory concentration line.** As a time based treatment, the antibiotic concentration needs to be above the minimum inhibiotory concentration for 40 to 50% of the dosage interval in order to kill the bacteria in question. On the other hand, the **quinolones, the aminoglycosides and the macrolides are a pharmacodynamic process.** And they **depend upon area under the minimum inhibitory concentration curve – not how much time is spent, but the actual area** – and so **increased concentrations of a pharmacodynamic antibiotic will cause a big increase in the area, and so you can overpower and infection,** even if the minimal inhibitory concentration (MIC) may be very high. Therefore, there can still be effective use of these antibiotics by highly increasing their concentrations and using them topically where there is no concern for systemic toxicity.

So because, for example, in the fluoroquinolone you have 200 micrograms per milliliter within each drop, there has been less than 1% resistance develop clinically, or *in-vivo* to MRSA infections, even in the *in-vitro* MIC levels would indicate the bacteria would be resistance to the antibiotic.

So if we look at **treatment strategies for MRSA otorrhea, we note that if we were to create ear drops under a MIC or pharmacokinetic type of antibacterial strategy, we cannot get the dose high enough to have enough time under the curve, so they are not effective. This would be antibiotics such as the beta-lactam dependent penicillin and cephalosporins, but if we use a drop that has a pharmacodynamic strategy, where it's the time spent in the area under the curve (versus the MIC ratio), than we can have medication that is still effective, such as a quinolone.**

Treatment

The first thing to do in MRSA management is to **treat the source site of the infection**, so we need to treat the infection reservoir. Because this is usually the nasopharynx or the nares, topical treatment is commonly started in the **nose**, but you actually need to also inspect the rest of the patient. I recently had a child who had severe neck extension as a mucopolissacaridosis patient and her MRSA was coming from her **neck folds**. So we would had to treat the neck fold location in order to get her otorrhea to decrease. Other common locations may be the **feet**, or in **any other areas that is moist and where the Staphylococcus aureus likes to grow.** The next step in treating a MRSA draining ear infection then, is to treat the otorrhea. A culture of a chronic draining ear is needed to determine which bacteria is causing in the infection. Once MRSA is identified, sensitivities are not particularly helpful as they only measure MIC's of systemically tolerated doses of antibiotics. If ototopical and other types of topical treatments are going to be used for this infection, the concentration used is so many times higher than the MIC that the information of sensitivity is not helpful. The culture does determine whether or not it is a MRSA infection.

And here come Dr. Dohar's publication "Dohar's Do's and Do Nots".

- **DO NOT use systemic antibiotics**. Dr. Dohar very much emphasizes not to chase an otorrhea infection with systemic antibiotics. Just because MIC is good for bactrim, linezolid or vancomycin, it's the use of these systemic antibiotics that results in the MRSA overgrowth and probable persistence of a MRSA biofilm which is not susceptible to oral antibiotics.
- **DO NOT overoperate**. He feels that very much—that MRSA otorrhea is not a surgical disease, and so the use of the tympanomastoidectomy again would get you only very temporary resolution of your MRSA otorrhea.
- **DO identify the reservoir of colonization and treat it**.

In order to rid the patient of the MRSA infection, it is necessary to restore the homeostasis within the nasal cavity. Stated otherwise, you want to have the good bacteria restored therefore a technique maybe used in the future will be adding the good bacteria back into the nasal cavity. Also we need to have the time for this infection to disappear, biofilm bacteria grow slowly. So you can see that we need to use topical antibiotics such as the quinolone or mupirocin, and we need to eliminate the barriers that keep the topical antibiotic from the reservoir or source of the infection that is contributing to the middle-ear infection.

Just a little bit on that mupirocin, which is brand name in the US as Bactroban. Mupirocin is a naturally-occurring antibiotic that is produced by fermentation

using the organisms *Pseudomonas aeruginosa fluorescens*. It inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase.
This is a very unique type of antibacterial activity and it has a wide range of gram-positive activity including the MRSA and other types of gram-negative bacteria.
So, in the Reservoir-Type Management, if you were to look at mupirocin, you can use it as an ointment in the nasal vestibule, or you can mix it into saline spray and spray that up into the nasopharynx in order to get it back to where it needs to go, and it can also be used topically on the skin if there's a different site reservoir.
For aminoglycosides, we've now used the Tobi-nebs® for patients with Cystic Fibrosis for topical treatment in the lungs, or for sinusitis, either with the face mask and the closed mouth breathing or the new actual specific sinus mask for a delivery of the tobramycin nebulizers to the area of the reservoir.
To speak to the direct otorrhea management, quinolone drops can be used successfully for MRSA otorrhea even if the sensitivities obtained with a culture would say that the MRSA infection is resistant. Remember that by using a high concentration drop we overwhelm the MIC levels. This means that the drop needs to reach the middle ear where the otorrhea is originating and that the drop needs to be safe to the inner ear as the middle ear drop will have access through the round window membrane. Fluoquinolones are safe and effective but aminoglycosides are ototoxic.
A helpful technique to get the drop down to the middle ear can be the use of an Oto-wick®. Otowick is typically a solid expanding sponge, but there is a second type that is made with a fenestration through it, which allows you to be able to use the Oto-wick® along with the hearing aids, so that you don't decrease these kids hearing. It does seem that many children with MRSA otorrhea also have other chronicle illnesses and they need to use the hearing aids in order to communicate. Thet fenestration allows for some sound conduction to with the delivery process of the antibacterial drop down the walls of the sponge.
So, in conclusion, **DO NOT use any systemic antibiotics for otorrhea in general** as this just selects out for MRSA otorrhea, **DO use topical applications of antibiotics** that work by pharmacodynamics such as the quinolones, aminoglycosides and mupirocin, and use medications that are safe for the site of application.

Recommended readings

1. Coticchia JM, Dohar JE Methicillin-Resistant *Staphylococcus aureus* Otorrhea after Tympanostomy Tube placement. Arch Otolaryngol HNS 2005:131;868-873.
2. Klevens RM, etal. Invasive Methicillin-Resistant *Staphylococcus aureus* Iinfections in the United States. JAMA 2007:298;1763-1772.
3. Vlasteraskos PV etal. Biofilms in Ear, Nose and Throat Infections: How Important are They? Laryngoscope, 2007:117;668-673.