

TITLE: Antibiotics 2005 - An Update

SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology

DATE: December 22, 2004

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Introduction

Infections of the head and neck are a varied group of infections, with overlapping symptoms and etiologic factors. Often otolaryngologists are consulted for management of these various infections, and the management may be surgical or medical. Infections in the head and neck range from harmless to life threatening. As a specialist, the head and neck surgeon must be familiar with these infections, and with the best choices for antimicrobial treatment to maximize patient outcomes. In addition, specialists must be able to quickly recognize these dangerous infections and administer aggressive management to help diminish poor patient outcomes. This paper is a review of current available antimicrobials, the fluoroquinolone safety profile in children, antibiotic resistance mechanisms and the treatment of methicillin resistant *Staphylococcus aureus*.

Antimicrobial Agents

In general, the current armamentarium of antibiotics is derived from chemicals created by bacteria and fungi which function in inhibiting growth of other organisms. These main functional groups have been modified to increase their activity against a broader range of organisms and decrease their side effect profiles.

Cell wall inhibitors:

Penicillins

Penicillin was first isolated from the fungus *Penicillium notatum* in 1929 by Fleming. Since that time, the B-lactam antibiotics have become the most commonly used antibiotic class. They are the least toxic of all antibiotic choices and can be taken orally, IM or IV.

Penicillin V is an acid-stable form of penicillin most commonly used for oral infections. Penicillin G is given IV or IM. The IV form has a half-life of 4 hours and must be given several times per day to maintain therapeutic concentrations. The penicillins are used for treatment of

oral infections as they have activity against anaerobic gram-positive cocci such as Peptococcus. They generally have activity against group A, B-hemolytic Strep., group B streptococci, Gram positive Bacilli such as diphtheria, anthrax, and listeria, syphilis, Borrelia (relapsing fever and Lyme disease), and Pasteurella multocida.

The major limiting factor for the use of penicillins is the high incidence of reported allergy (5%). A maculopapular rash is the most common side effect. Up to 50% of patients will not have a recurrent rash with subsequent penicillin exposure. There is a high incidence (50-100%) of rash formation in patients with mononucleosis taking amoxicillin. Anaphylactic reactions occur in 1/10000 patients. Symptoms range from urticaria to anaphylactic shock. All other beta lactams should be avoided in these patients.

Resistance of Strep pneumo to penicillin has been increasing. Currently only 60% of S. pneumo strains are susceptible to penicillin, with 20% showing intermediate susceptibility and 20% showing high resistance. Strep pneumo resistance is related to a decrease binding affinity of penicillin to penicillin binding proteins (PBP) responsible for the formation of peptidoglycan. Six PBPs have been characterized. Studies with radio-labeled penicillin show that intermediate susceptibility strains have at least one PBP with decreased affinity. The most common cause for resistance is the alteration of PBP 2b. Inoculation of intermediate resistant strains with higher concentrations of penicillin results in saturation of the PBPs, even those with decreased affinity.

Semisynthetic penicillins such as methicillin, nafcillin, and dicloxacillin were created by the alteration of the B-lactam ring to protect it from penicillinase producing staphylococci. Methicillin-resistant Staphylococcus aureus is an increasingly common pathogen. MRSA bacteria are resistant to all other semisynthetic penicillins and cephalosporins. Methicillin is used infrequently because it causes interstitial nephritis. Nafcillin is generally used IV due to poor absorption PO and IM.

The aminopenicillins such as ampicillin and amoxicillin are extended-spectrum penicillins. They are generally active against Haemophilus influenzae, Escherichia coli, Salmonella, and Shigella species. Addition of sulbactam to ampicillin (Unasyn) and clavulanic acid to amoxicillin (Augmentin) gives activity against beta-lactamase-producing organisms such as H. influenzae, S. aureus, Klebsiella, Proteus, and M. catarrhalis. When using these drugs, neutropenia and mild hepatotoxicity are possible adverse side effects, and LFTs as well as CBCs should be checked periodically when starting long term therapy with these drugs.

Antipseudomonal penicillins such as carbenicillin, ticarcillin, azlocillin, mezlocillin and piperacillin are generally used for treatment of Pseudomonal infections. They also have effectiveness against H. influenza, Neisseria, Salmonella, Clostridium, Actinomyces, and some oral flora. Piperacillin and Azlocillin are the most effective against Pseudomonas. Timentin (Ticarcillin combined with clavulanic acid) is a parenteral preparation that extends activity against B-lactamase-producing S. Aureus, and H. influenzae, as well as E. coli, Klebsiella, and Proteus. GI absorption is low and IV therapy is the most common form. Platelet aggregation problems, hepatic toxicity, and neutropenia are the common adverse reactions in patients.

Imipenem is a carbapenem that binds to different penicillin-binding proteins than the

antimicrobials (PBP 1a, 1b, 2) mentioned before, allowing for very close inhibitory and cidal concentrations. It is usually combined with cilastatin (Primaxin) which inhibits the half-life of the proximal renal tubular brush border enzyme, dehydropeptidase-I increasing imipenem absorption. Primaxin has the widest spectrum of activity of any B-lactam antibiotic. Most Staphylococci, enterobacteriaceae, Pseudomonas, H. influenzae, N. gonorrhoea, Bacteroides, Peptococcus, and Eikenella are susceptible to Primaxin. Primaxin should be used with other agents when treating pseudomonas infections. Monitoring chemistries and CBCs are appropriate for patients on Primaxin.

Aztreonam is a monobactam antibiotic with a narrow range of antimicrobial activity. It is not active against gram positives or anaerobes but has high activity against aerobic gram negative rods. It is also active against B-lactamase-producing organisms. Penicillin-allergic patients are generally not allergic to aztreonam. As a result, it is often used to treat penicillin-allergic patients with sepsis in combination with vancomycin or clindamycin.

Cephalosporins

The cephalosporins were discovered in 1948 by E. P. Abraham when he extracted cephalosporin C from *Cephalosporium acremonium*, a fungus isolated from a sewage outlet in Sardinia. Cephalosporin C is an acid-stable molecule with antibacterial activity from which other cephalosporins are synthesized. Cephalosporins are the most frequently prescribed class of antibiotics. The toxicities and adverse reactions of the cephalosporins are similar to those of the penicillins.

The first-generation cephalosporins are characterized by gram-positive activity, including B-lactamase-producing *Staphylococcus aureus* and streptococci. It should be noted that Methicillin-resistant *Staph. aureus*, *S. epidermidis* and enterococci are resistant to all cephalosporins. First-generation cephalosporins have some activity against a limited number of *E. coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. Anaerobic gram-positive cocci and rods are also susceptible to these cephalosporins.

The first-generation cephalosporins are Cephalexin, Cephalothin, Cephapirin, Cefazolin, and Cephadrine. Cefazolin is the most commonly used first-generation cephalosporin with a half-life of 2-hours because of its rapid excretion by the kidneys. The other first-generations have similar efficacy to Cephalexin, but must be dosed more often, and are therefore not as common.

The second-generation cephalosporins are used for broader gram-negative control, including coverage for B-lactamase-producing *H. influenzae*. They are less effective than the first-generations in covering *Staph. aureus* and other gram-positive organisms. Caution should be used when administering cefamandole, cefotetan, and cefmetazole as the N-methylthiotetrazole side chain may result in a disulfiram reaction and a vitamin K reversible coagulopathy.

The second-generation cephalosporins are Cefoxitin, Cefamandole, Cefaclor, and Cefuroxime. Cefoxitin is unique among the second-generation cephalosporins because it is

active against *B. fragilis* group, but has poor gram-positive activity. Its greatest utility is in the use against mixed gram-negative aerobic and anaerobic infections, such as intra-abdominal infections. Cefaclor is an oral second-generation cephalosporin with greater activity against *H. influenzae* than cephalexin. Cefuroxime is similar to cefamandole, but does not have the N-methylthiotetrazole side chain responsible for disulfiram reactions.

Third-generation cephalosporins display an extended gram-negative spectrum at the expense of decreased activity against gram-positive bacteria. They are often used for treating gram-negative sepsis, as several cross the blood-brain barrier (cefotaxime, ceftizoxime, ceftriaxone). These drugs are also used in treating pseudomonal infections (cefoperazone, cefpiramide, cefsulodin, ceftazidime). Cefoperazone, cefmenoxime, and moxalactam are associated with coagulation problems and disulfiram reactions. Moxalactam is associated with a ten- to one hundred-fold risk of hemorrhagic complications, so bleeding complications should be suspected when using this drug.

The fourth generation cephalosporin currently on the market is cefepime. It has the broadest spectrum activity of all the cephalosporins. It has activity against gram-negative organisms, especially pseudomonas, yet keeps activity against gram-positives including *Staph. aureus*. It is an excellent drug in the treatment of hospital-acquired pneumonias. Cefepime penetrates the blood-brain barrier and is eliminated in urine. Adverse reactions are similar to the above cephalosporins.

Vancomycin

Vancomycin is a tricyclic glucopeptide bactericidal antibiotic that interferes with the second stage of cell wall synthesis. It also interferes with RNA synthesis and disrupts the cytoplasmic membrane. Vancomycin is used in the treatment of gram-positive infections and is most effective against *Staph.* and *Strep.* infections. Almost all gram-negative organisms are resistant to the antibiotic. Vancomycin is not normally absorbed by the GI tract and is generally given IV except in the treatment of *C. difficile* colitis. It is given IV over 30-60 minutes to avoid "red man syndrome", which is hypotension and a maculopapular rash of the face, arms, and trunk. This is treated with steroids, antihistamines, and IV fluids. Vancomycin penetrates most tissues well, including the blood-brain barrier. It is excreted by the kidneys and dose adjustments must be made for renal failure. In addition to red man's syndrome, it is extremely ototoxic. Renal toxicity occurs less frequently with vancomycin than with the aminoglycosides. Vancomycin must be given IV and can cause thrombophlebitis when given through peripheral IVs. Its use has been associated with neutropenia.

Bacitracin

Bacitracin is a polypeptide originally isolated from a comminuted leg fracture wound. The polypeptide is produced by *Bacillus subtilis* and it inhibits the regeneration of phospholipids receptors involved in peptidoglycan synthesis. It can only be used topically because it is nephrotoxic when ingested. It has a wide spectrum for most gram positives and negatives. It has been named as one of the top ten allergens implicated in contact dermatitis.

Polymyxin

Polymyxin is a decapeptide produced by *Bacillus polymyxa* which saponifies bacterial phospholipid membranes. It has very good gram negative coverage, including pseudomonas but has less gram positive coverage than bacitracin. Commercially, polymyxin, bacitracin and neomycin are sold as over the counter anti-bacterial creams (triple antibiotic ointment).

Protein Synthesis Inhibitors:

Aminoglycosides

Aminoglycosides are bactericidal antibiotics that interfere with protein synthesis by causing misreading of the genetic message and stimulation of faulty production of RNA. In addition, they inhibit cell respiration and cause potassium leakage of cell membranes. Aminoglycosides have an oxygen-dependent transport system and are therefore ineffective against anaerobic bacteria. These antibiotics are used against gram-negative aerobic and facultative bacteria and *Staph. aureus*.

There are three principal toxicities of aminoglycosides: Nephrotoxicity, ototoxicity, and neurotoxicity. Nephrotoxicity occurs as a result of proximal tubular damage and glomerular dysfunction. Persons with kidney disease and taking other nephrotoxic agents should avoid this medication. Ototoxicity, be it cochlear or vestibular, may be caused by all aminoglycosides. Drug accumulates in the perilymph and endolymph and destroys hair cells in the organ of corti and the ampullae causing permanent ototoxicity. It should also be noted that loop diuretics predispose patients to streptomycin ototoxicity. Neurotoxicity is rare and is seen mostly in patients with myasthenia gravis.

Streptomycin is the drug of choice for tularemia and the plague. It is considered primarily an anti-TB drug. Neomycin is generally used topically during preoperative regimens for bowel surgery because of poor GI absorption. Gentamycin is the most frequently used parenteral aminoglycoside because of its activity against *P. aeruginosa*, and low cost. Tobramycin is similar to gentamycin but is less nephrotoxic and ototoxic.

Tetracyclines

Tetracyclines are bacteriostatic antibiotics that inhibit protein synthesis by binding to the 30S ribosome and preventing binding of tRNA to mRNA. They are generally effective in treating staphylococci, anaerobic infections, enterobacteriaceae, brucella, rickettsia, Chlamydia, mycoplasma, legionella, and *Borrelia burgdoferi*. They are ineffective in treating most streptococci, clostridium, peptostreptococcus, and lactobacillus infections. Tetracyclines are absorbed by the proximal small bowel. Absorption is inhibited by ingestion with divalent and trivalent cations. Tetracyclines also need an acidic environment to be absorbed. For this reason, they should not be taken with milk, antacids, ferrous sulfate, cimetidine, or other B-blockers. Doxycycline is almost completely absorbed in the duodenum and is less affected by foods and divalent and trivalent cations. Tetracyclines penetrate most tissues including those found in the CNS. All tetracyclines except doxycycline should be avoided in renal failure.

Toxicity of tetracyclines includes hypersensitivity reactions, GI symptoms, pseudomembranous colitis, Candida superinfection, and photosensitivity reactions. Excessive doses in pregnancy can cause a fatal hepatotoxicity consisting of fatty infiltration. In addition, tetracyclines deposit in calcifying bones and teeth causing permanent discoloration when given to children under the age of 7. Tetracyclines have caused benign intracranial hypertension, neuromuscular blockade in myasthenia gravis, and transitory myopia.

Tetracycline, minocycline, doxycycline, and demeclocycline all have similar efficacy and antimicrobial spectrums. Doxycycline, as mentioned above, is not affected by foods for absorption and can be given with caution to patients with renal failure.

Macrolides

Erythromycin, azithromycin, and clarithromycin are the macrolides most commonly used. They are bacteriostatic antibiotics that interfere with protein synthesis by binding to the 50S ribosome. They are active against Staph. aureus, Strep. Pyogenes, Strep. Pneumoniae, Bacillus anthracis, Listeria monocytogenes, the gram-positive anaerobes commonly found in the mouth, and H. influenzae. Erythromycin is the drug of choice in treatment of Bordetella pertussis, Campylobacter jejuni, Corynebacterium diphtheriae, H. ducreyi (chancroid), and pneumonias caused by L. pneumophila and Mycoplasma pneumoniae.

Erythromycin resistance is mediated by an energy dependant efflux system (msrA) or by alteration of the 50S ribosome. Ribosomal alteration changes the binding site of macrolides, lincosamides, chloramphenicol and streptogramins so that they no longer interfere with protein production. The macrolide-lincosamide-streptogramin_B (MLS_B) resistance phenotype is expressed from the ermA or ermC genes. MLS_B resistance is important in determining treatment with any of these antibiotics. MLS_B resistance can be induced in some strains of bacteria when there are low concentrations of related agents. Inducible MLS_B resistance can be determined by placing erythromycin and clindamycin impregnated disks in close proximity on agar plates. Low levels of erythromycin can induce resistance to clindamycin, changing the pattern of bacterial growth on the plate to a D-shaped clearing instead of a circle.

Erythromycin frequently causes gastrointestinal disturbances because of its direct stimulatory effects on smooth muscles of the GI tract. This is less common with azithromycin and clarithromycin. Large doses of IV erythromycin have caused transient ototoxicity. Care should be taken when administering erythromycin with prednisone, theophylline, carbamazepine, cyclosporine and warfarin as it can affect metabolism and excretion.

Lincosamides

Lincomycin and clindamycin compose this group of antibiotics. They are bacteriostatic antibiotics that inhibit protein synthesis by attaching to the 50S ribosome. They are active against most gram-positive cocci, including Staph. aureus. They are very active against anaerobes, and for this reason are excellent in the treatment of infections of the head and neck. Clindamycin has excellent oral absorption and is metabolized by the liver. It can be used at full doses in mild renal insufficiency but should be halved in anuric patients. The main toxicity with clindamycin use is the development of pseudomembranous colitis caused by the toxin C.

difficile. This is treated by immediate discontinuation of the drug and oral vancomycin or metronidazole oral or IV.

MLS_B inducible resistance is clinically important because its prevalence is increasing. At UTMB, up to 10% of outpatients and 6% of TDC inmates with *S. aureus* infections show MLS_B inducible resistance.

Chloramphenicol

Chloramphenicol has a wide-spectrum of bacteriostatic activity. Given the fact that chloramphenicol has the potential for fatal bone marrow toxicity, indications for chloramphenicol are limited. There are many effective and safe alternative therapies, however. In addition, chloramphenicol interferes with vitamin K synthesis, iron and vitamin B12 therapy in deficient patients, and can cause Jarisch-Herxheimer reactions. Its indications are limited to brain abscess with penicillin therapy, meningitis with *H. influenzae*, typhoid fever, rickettsial diseases, and acute melioidosis. Its use in head and neck infections is limited.

Sulfonamides and Related Drugs

Bacteria synthesize folate using two enzymes not present in humans: tetrahydroptericoic acid synthetase and dihydrofolate reductase. Sulfonamides act as competitive inhibitors of dihydroptericoic acid synthetase and are metabolized by the enzyme to inactive analogues. Trimethoprim interferes with dihydrofolate reductase by the same mechanism.

Although sulfonamides display a broad antibacterial spectrum, many susceptible organisms have developed a resistance. They can be active against *Staph. aureus*, *S. saprophyticus*, *Clostridia* species, *Neisseria* species, *H. influenzae*, and many gram-negative enterics. Sulfamethoxazole is usually combined with trimethoprim into the formulation cotrimoxazole (Bactrim). They are synergistic, and organisms that are resistant to one of the two may be susceptible to the combination. Renal toxicity, hepatic toxicity, GI distress, aplastic anemia, and rare cardiomyopathy have been associated with its use.

There are large numbers of commercially available preparations containing sulfonamide. Sulfamylon cream is used topically in burn patients. Carbonic anhydrase inhibition with this drug can cause metabolic acidosis. Sulfacetamide eye drops are available for bacterial conjunctivitis. Bactrim is useful for UTIs, gram-negative sepsis, bacterial pneumonias, and otitis media. Bactrim is considered combination therapy in patients with MRSA infections.

Metronidazole

Metronidazole inhibits anaerobic bacteria and protozoa. The exact mechanism is not understood, but it is believed that it interferes with the synthesis of DNA. It penetrates all tissues including those found in the CNS. A reversible peripheral neuropathy may develop with prolonged use, and GI symptoms including furred tongue and metallic taste are common. It produces a disulfiram reaction when alcohol is used, and it interferes in the metabolism of warfarin. It is commonly used in the treatment of intra-abdominal infections, oral infections, and mixed infections where anaerobic organisms are suspected.

Quinolones

Norfloxacin, ciprofloxacin, and ofloxacin are the most commonly used quinolones. They inhibit type 2 topoisomerase, a DNA gyrase involved in the supertwisting of bacterial DNA molecules, replication, and repair. These enzymes are present in mammalian organisms, but the quinolones selectively inhibit bacteria. They are bactericidal, and bacteriostatic under anaerobic conditions.

Quinolones have a broad range of activity. They are effective against *P. aeruginosa*, Staph., Strep. and the respiratory pathogens including *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, and *L. pneumophila*. They are also effective against Rickettsial diseases and enteric pathogens. They demonstrate synergy when used with B-lactams, aminoglycosides, and rifampin.

Ciprofloxacin may cause fever, rash, GI complaints, and in one to four percent of people, mild neurological complaints such as insomnia, anxiety, and depression. Animal studies have suggested that chronic therapy may cause phototoxicity, arthritis, and cataract formation.

Use in children has been cautioned due to questions of joint toxicity. Animal studies show that arthritis can be induced in young rats and dogs with all the fluoroquinolones. The extent of arthritis is dose and species-dependant. Despite reservations about joint damage, fluoroquinolones are still prescribed to children in the acute setting. Other populations of patients with cystic fibrosis and those at risk for chronic or recurrent UTI's have been treated with long term doses. Reviewed data from these subgroups of patients, along with prospective trials by Bayer indicate that the safety profile of fluoroquinolones shows no significant difference when compared to control groups. Bayer indicates that arthralgias occur in 1% of patients treated but the symptoms are self-limited and resolve when the agent is discontinued. Several other studies suggest the incidence of adverse effects of ciprofloxacin in children is not different that that from adults. Currently the FDA has not approved ciprofloxacin for use in children except for the treatment of anthrax.

Oxazolidinones

Linezolid is the first of a new class of antibiotics, oxazolidinones, which has activity against a broad spectrum of gram-positive bacteria, including MSSA and MRSA. The mechanism of action of linezolid is unique in its ability to inhibit the initiation complex of bacterial protein synthesis. This is unlike other inhibitors of protein synthesis which interfere with protein synthesis in the elongation or termination stages. The final result is prevention of a functional 70S initiation complex. In a study done by the Shriners Hospital for Children in Galveston, (Hegggers, et al 2002) 95% of MRSA, MRSE treated with linezolid were susceptible.

The main advantages of linezolid are its broad spectrum gram positive coverage and its availability in an oral form. Oral linezolid is 100% bioavailable, making it possible to treat MRSA/MRSE infections on an outpatient basis. The main disadvantage is cost, with daily dosing ranging about \$100-150/day. Dosage is 400-600mg BID. The most common side effects are headache, diarrhea, and thrombocytopenia.

Mupirocin

Mupirocin (Bactroban) is a topical antibiotic derived from *Pseudomonas fluorescens*. It binds isoleucyl transfer-RNA synthetase and prevents isoleucine incorporation into the amino acid chain. It is active against gram positives, including MRSA. It has been indicated in the treatment of impetigo and to reduce the carriage of MRSA in the anterior nares.

Prevalence and Treatment of MRSA

MRSA was first noted in the 1960's shortly after methicillin was introduced in 1959. Since then, it has spread nosocomially around the world. There are currently five strains of MRSA worldwide, three of which can be traced back to the original isolates from Denmark and England in the 1960's. There has been a sharp rise in MRSA infections during the 1990's. One hospital noted a 22-57% rise in MRSA over a 6 year period. By 2002, approximately 50-60% of hospitalized patients with staph infections were infected with MRSA. At UTMB, 47-71% of all *S. aureus* isolates are MRSA.

MRSA is defined by an oxacillin MIC ≥ 4 ug/ml. The mechanism of resistance is related to the presence of the *mec* gene on the staphylococcal chromosomal cassette. The *mec* gene is necessary for methicillin resistance. Horizontal transfer of the gene into known MSSA strains, converts the strains to MRSA in all cases.

The *mec* gene consists of a structural gene and two key regulatory genes. The *mecA* gene codes for the PBP 2a protein which has decreased binding affinity for penicillins. PBP 2a is able to construct an altered, but functional peptidoglycan wall in the presence of penicillins despite the inactivity of the other PBPs. The *mecR1-mecI* gene is a negative regulator of *mecA*. Mutations in this gene are seen in highly resistant strains of MRSA.

There are five types of *mec*. Types I, II, and III are found in healthcare associated (HA) MRSA strains while type IV is found in community acquired (CA) strains. HA-MRSA is usually multi-drug resistant and is more likely to cause systemic infections related to indwelling catheters and prosthetic devices. It is spread by direct contact, so rigorous hand washing and isolation techniques are critical in preventing its spread. CA-MRSA is usually found in younger populations and is more likely to cause skin and soft tissue infections. It is not typically multi-drug resistant. High risk populations for CA-MRSA include athletes, children, Native Americans, aborigines, homosexual males, drug users and inmates.

Fear of vancomycin resistant strains has been increasing with sporadic reports of vancomycin intermediate susceptible strains (VISA) and some vancomycin resistant strains. The mechanism for VISA strains is probably due to production of a thicker peptidoglycan wall which decreases vancomycin delivery to the periplasmic space. The VRSA strains have been reported in patients with chronic leg ulcers and documented VRE infections. Resistance may be due to an alteration of the terminal peptide on vancomycin's target site.

New agents that have been approved for treatment of MRSA skin infections include linezolid, Quinupristin-dalfopristin, Daptomycin and Lysostaphin. Linezolid was discussed

earlier in this paper. Quinipristin-dalfopristin is a streptomycin A and B dimer that binds the 50S ribosome. It is synergistic with beta-lactams and shows an additive effect with vancomycin. Daptomycin is a cyclic lipopeptide that disrupts cell membrane function that has been shown to be equally effective as vancomycin in the treatment of soft tissue infections. Lysostaphin is an enzyme produced by *Staphylococcus simulans* that cleaves the pentaglycine cross links found in *S. aureus*. It is synergistic with beta-lactams. These new agents should be reserved for situations in which treatment with vancomycin is not an option due to patient intolerance or unavailability.

Conclusion

Infections of the head and neck are varied in etiology and severity. While the most common infectious agents are viral, the otolaryngologist should be able to recognize bacterial infections and start effective therapy with antimicrobials. As resistance patterns develop in the near future, first line therapy will evolve. The fluid and varied nature of head and neck infections demand periodic review of the subject by physicians treating these infections.

Reference

- 1) Boyce, John M. Epidemiology; prevention; and control of methicillin-resistant *Staphylococcus aureus* in adults. *Up To Date* (12.3). 2004.
- 2) Lowy, Franklin D. Treatment of Methicillin-Resistant *Staphylococcus aureus* Infection in Adults. *Up To Date* (12.3). 2004.
- 3) Lowy, Franklin D. Mechanisms of Antibiotic Resistance in *Staphylococcus aureus*. *Up To Date* (12.3). 2004.
- 4) Richard, Grady. Safety profile of quinolone antibiotics in the pediatric population. *The Pediatric Infectious Disease Journal*. 22(12): p1128-1132: 2003.
- 5) Fiebelkorn, K. R., Crawford, S.A., McElmeel, M.L., and Jorgensen J.H. Practical Disk Diffusion Method for Detection of Inducible Clindamycin Resistance in *Staphylococcus aureus* and Coagulase-Negative Staphylococci. *Journal of Clinical Microbiology*. 41(10): p4740-4744: 2003.
- 6) Kiri, N. Archer, G. and Climo, M. W. Combinations of Lysostaphin with Beta-Lactams are Synergistic against Oxacillin-Resistant *Staphylococcus epidermidis*. *Antimicrobial Agents and Chemotherapy*. 46(6): p2017-2020: 2002.
- 7) Patron, R.L., Climo, M. W., Goldstein, B. P., and Archer, G. L. Lysostaphin Treatment of Experimental Aortic Valve Endocarditis Caused by a *Staphylococcal aureus* Isolate with Reduced Susceptibility to Vancomycin. *Antimicrobial Agents and Chemotherapy*. 43(7): p1754-1755: 1999.
- 8) Spann, C. T., Tutrone, W. D., Weinberg, J. M., Scheinfeld, N., and Ross, B.
- 9) Topical Antibacterial Agents for Wound Care: A Primer. *Dermatologic Surgery*. 29(6): p620-626: 2003.
- 10) Jacob, S. E., and James, W. D. From Road Rash to Top Allergen in a Flash: Bacitracin. *Dermatologic Surgery*. 30(4): p521-524: 2004.
- 11) Eliopoulos, G. M. Current and New Antimicrobial Agents. *American Heart Journal*. 147(4): p587-592: 2004.
- 12) Patron, R.L., Climo, M. W., Goldstein, B. P., and Archer, G. L. Lysostaphin Treatment of Experimental Aortic Valve Endocarditis Caused by a *Staphylococcal aureus* Isolate with Reduced Susceptibility to Vancomycin. *Antimicrobial Agents and Chemotherapy*. 43(7): p1754-1755: 1999.
- 13) Spann, C. T., Tutrone, W. D., Weinberg, J. M., Scheinfeld, N., and Ross, B.
- 14) Topical Antibacterial Agents for Wound Care: A Primer. *Dermatologic Surgery*. 29(6): p620-626: 2003.
- 15) Jacob, S. E., and James, W. D. From Road Rash to Top Allergen in a Flash: Bacitracin. *Dermatologic Surgery*. 30(4): p521-524: 2004.
- 16) Eliopoulos, G. M. Current and New Antimicrobial Agents. *American Heart Journal*. 147(4): p587-592: 2004.