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From the dawn of modern medicine the understanding of infectious disease and how to treat it has been an integral part of our craft. Many thousands of scientist-physicians struggled to learn the secrets of the diseases that plagued their patients. Their work brought a new era of clarity and promise. When penicillin was discovered our world was changed forever. Suddenly, it was possible not only to diagnose disease and predict its course, but to halt its progression. Multiple classes of antibiotics were discovered as the microbiology of disease came into focus. Medical treatment of disease changed dramatically. Today, a wealth of information is available to guide the use of antibiotics in infectious disease.

ANTIBIOTICS

The practice of Otolaryngology--HNS requires a clear understanding of many diseases specific to the head and neck, as well as a thorough knowledge of the antibiotic armamentarium. The antibiotics are divided into families of drugs that act in a similar ways to attack the bacterial pathogen. These families include penicillins, cephalosporins, macrolides, aminoglycosides, sulfonamides, flouroquinolones, and "other" drugs such as vancomycin and clindamycin.

Penicillins are fermentation products of *Penicillium* mold. The drugs are characterized by a Beta-lactam nucleus attached to a thiazolidine ring. Different penicillins with different spectra of effectiveness are created when changes are made to the side chains attached to the ring. Alteration of the Beta-lactam nucleus results in loss of the compound's antibiotic potential. Penicillins act to inhibit bacterial replication by interfering with the final step of cell wall synthesis. As a result of this action (or perhaps by an other, unknown mechanism) the bacterial cell's enzymatic regulatory system is deregulated and lytic enzymes are produced that result in autolysis. Bacteria that do not have such an enzymatic pathway tend to be more resistant to penicillin's action. Thus, penicillins can be either bacteriostatic or bacteriocidal. The penicillins are excreted in their original form by the kidney. The drug Probenecid has been used to slow excretion allowing for higher and longer serum drug concentration. Most penicillins are destroyed by stomach acid, thus they should be taken on an empty stomach. Tissue penetration is generally good. Antibiotic concentrations are generally higher in areas of inflammation and enable CSF and middle ear penetration.

Many patients report they are “allergic” to penicillins. Hypersensitivity is known to occur in approximately 5% of the population. A rash is the most common reaction. This symptom may be treated with antihistamines, but usually results in discontinuing the antibiotic. This may recur in only 50% of patients with repeated exposure. Penicillin-induced rash in the face of mononucleosis is not a contraindication for further use. Only 5% of patients who are sensitive to penicillin can be expected to be sensitive to cephalosporin antibiotics. Anaphylaxis is a rare occurrence (1 in 10,000) is more common with IV dosing. Beta-lactam antibiotics (cephalosporins and carbapenems) should not be used in penicillin-allergic patients unless there are no other good alternatives. Penicillin desensitization can be undertaken with the patient in the intensive care unit under continuous monitoring.

B-lactam antibiotic use has led to the emergence of multiple resistant strains of bacteria. There are several methods for bacteria to become resistance to the antibiotic's effects. Intrinsic resistance is the particular makeup of the bacteria which prevents drug binding of cell proteins or penetration of the cell wall. This likely accounts for the penicillins' lack of activity against *Legionella*, *Mycobacterium*, fungi, *Chlamydia*, and *rickettsia* families. Production of enzymes that inactivate penicillin is the most common method of resistance. It is propagated via plasmid or chromosome transmission. Beta-lactamase and penicillinase are enzymes produced by resistant bacteria that cleave the beta-lactam ring and inactivate penicillins. These enzymes have been shown to be produced by *H. influenzae*, *M. catarrhalis*, *S. aureus*, many anaerobes and gram-negative organisms. Penicillinase is specific to *S. aureus*. Resistant *S. aureus* is especially virulent as it proliferates the enzyme and releases it into the milieu. This destroys the antibiotic before it reaches the cell and provides protection for any other sensitive organisms in the vicinity. Of note, penicillinase is not effective against the semisynthetic (antistaphylococcal) penicillins or cephalosporins. *S. pneumoniae* resistance is entirely different and is mediated by alteration in cell binding sites. Intermediately-resistant strains are still sensitive to higher concentrations of antibiotic.

Antistaphylococcal penicillins are semisynthetic penicillins which have been found to be especially effective against penicillin-resistant *S. aureus* or *S. epidermidis* infections. (*S. aureus* resistant to this group of drugs is known as “methicillin-resistant *S. aureus*” (MRSA) and is resistant to all penicillins). This class includes methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin. Of these antibiotics, dicloxacillin achieves the highest serum levels. These drugs are generally less effective against organisms that are penicillin sensitive. These antibiotics are commonly used when skin flora are the suspected pathogens.

The aminopenicillins have an extended spectrum when compared with penicillin. This class includes ampicillin, amoxicillin, and bacampicillin. They cover all bacteria sensitive to penicillin (pneumococcal, streptococcal, actinomycosis, and about half of the anaerobic organisms of the oral and upper respiratory tract) as well as increased efficacy in treating resistant Streptococci, pneumococcus (except highly-resistant), *H. influenzae* (5-55% of cultured strains currently found to be resistant), *Proteus*, and many coliforms. These drugs are typically less effective against beta-lactamase (and penicillinase) producing microbes. Ampicillin, when given per os, is destroyed by stomach acid. Amoxicillin and bacampicillin, however, may be taken at mealtime. Serum and middle ear levels are highest with these agents. There is evidence that high levels of amoxicillin can be effective against intermediate-resistant *S. pneumo*. The side effect profile is somewhat different for these antimicrobials. They generally cause much

more diarrhea and may cause rash in 50% of patients with mononucleosis who are treated with amoxicillin. Yogurt or Bacid is often prescribed concurrent with aminopenicillins in an attempt to ameliorate the GI side effects.

The augmented penicillins include amoxicillin + clavulanate (Augmentin), ampicillin + sulbactam (Unasyn), Ticarcillin + clavulanate (Timentin), Piperacillin + tazobactam (Zosyn). The additives are substances that are weakly antimicrobial by themselves, but when combined with a penicillin serve to irreversibly bind the beta-lactamase enzyme. This action reverses resistance trends in *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *B. fragilis*. The augmented ticarcillin and piperacillin add pseudomonas coverage. As pneumococcal resistance is mediated by penicillinase (not a beta-lactamase) the augmented penicillins are no more effective against penicillin-resistant *S. pneumoniae*. The side effects are similar to those of the aminopenicillins.

The antipseudomonas penicillins include ticarcillin, mezlocillin, and piperacillin. These drugs are less active against gram-positive bacteria than are the aminopenicillins. Despite their extended spectrum, they are inactivated by beta-lactamase and therefore offer no advantage over other penicillins for non-pseudomonas infections. Synergy has been noted when antipseudomonas penicillins are combined with aminoglycosides. Ticarcillin is known to cause platelet dysfunction and may exacerbate congestive heart failure with its high NaCl content.

Cephalosporins are semisynthetic beta-lactam antimicrobials which are derived from *Cephalosporium acremonium*. Their mechanism of action is essentially the same as that of penicillin. Resistance to cephalosporins is mediated by enzymes that destroy the beta-lactam core. The chemical structure of this drug makes it less susceptible to penicillinase. These drugs achieve wide distribution in the body, but do not cross the blood-brain barrier even in the setting of meningeal inflammation (some of the later generation agents are exceptions to this). Cephalosporins are metabolized in the liver and excreted by the kidney. As with penicillin, Probenecid may be used to increase serum levels and decrease kidney excretion. This is accomplished by competing for protein binding sites and decreasing tubular secretion. The broad spectrum of this class can lead to opportunistic bacterial/yeast/fungus overgrowth (candidiasis, *C. difficile* infections). Non-Clostridium diarrhea is also common. The cephalosporins are subdivided into “generations” which are grouped according to their spectrum. In general, the earlier generations cover most gram-positive bacteria and few gram-negative organisms. Later generations cover progressively more gram-negative and fewer gram-positive bacteria.

The first generation agents include cefadroxil, cefazolin, cephalexin. Their spectrum includes most gram-positive cocci (GAS, *S. pneumo.*, *S. aureus* (except MRSA which is resistant to all cephalosporins), as well as gram-negatives like *E. coli*, *Proteus*, and *Klebsiella*. These drugs are commonly used for treatment of *S. aureus* infections and for surgical prophylaxis (skin flora).

Second generation cephalosporins are effective against the bacteria commonly found in otitis media and sinusitis, including ampicillin-resistant *H. influenzae* and intermediate-resistant *S. pneumo.* They generally have good CSF penetration. 2nd generation equivalents from the 3rd generation include cefepime (Vantin), ceftazidime (Omnicef). Their activity is equivalent to

cefuroxime (Ceftin) and can all be used as an alternative to Augmentin. It is less effective against *S. aureus* than the 1st generation cephalosporins.

Third generation cephalosporins cover more gram-negative bacteria than the earlier classes, but lose much of their effectiveness against gram-positive microbes. They are especially useful in identified beta-lactamase positive *H. influenzae* infections, as well as against *M. catarrhalis*, *N. gonorrhoea*, and *N. meningitidis*. Ceftriaxone (Rocephin) and ceftotaxime (Claforan) are effective against *S. pneumo.* (even highly-resistant forms), as well as *H. influenzae*, and *N. meningitidis*. These agents can be used against high-level, multi-drug resistant pneumococcal infections in combination with Vancomycin. A single dose of Rocephin (IM) has been shown effective in common otitis media. Ceftazidime (Fortaz) is the most effective of all beta-lactam antibiotics against *P. aeruginosa* and is considered an alternative to Gentamicin.

The carbapenem class includes imipenem-cilastin (Primaxin) and meropenem (Merrem). These are broad-spectrum beta-lactam antibiotics which cover nearly all bacteria with the exception of MRSA and *C. difficile*. Side effects include hypersensitivity reactions and seizures. Meropenem is considered less prone to cause seizure activity. These drugs are useful in critical patients with serious mixed infections. Aztreonam (Azactam) is a mono-bactam antibiotic that can be used in penicillin-allergic patients for gram-negative infections and can be substituted for aminoglycosides.

Macrolides are derived from *Streptomyces erythreus* (erythromycin is a natural product). These drugs bind the 50s subunit of bacterial ribosomes which results in inhibition of protein synthesis. Microbes develop resistance by altering target sites, altering the antibiotic, or changing transfer kinetics. Macrolides are especially useful for their excellent penetration of oropharyngeal secretions and tissues. These drugs are effective in the treatment of atypical infections (*Chlamydia*, *Mycoplasma*), Staphylococcal infections (MRSA is resistant), Strep. (including resistant strains), *Bordetella pertussis*, *H. influenzae*, and *M. catarrhalis*. Their spectrum makes them useful in treating GAS pharyngitis, AOM with resistant bacteria, and sinusitis. Bactrim, clarithromycin, and azithromycin are all as effective as Augmentin in the treatment of AOM. Clarithromycin has been shown to have equal efficacy to that of Augmentin in sinusitis, but necessitates just as long a course (10-14 days). Azithromycin is a good alternative for treating sinusitis as it requires only a 3-5 day course (500mg per day). Side effects are rare with macrolide use. Ototoxicity has been documented with prolonged use and high peak levels.

Clindamycin is derived from *Streptomyces Lincolnensis*. The mechanism of action, like the macrolide class, is inhibition of protein synthesis by binding to the 50s ribosomal subunit. It has a wide distribution, but does not cross the blood-brain barrier. The drug is concentrated in the bone, respiratory tissues, mucus, and saliva. The oral form results in only 25-50% of serum levels when administered parenterally. At lower concentrations the drug is bacteriostatic, but bacteriocidal at higher concentration. Resistance is mediated by decreased permeability of the drug into the cell and alteration of binding sites on the 50s ribosome subunit. Side effects include nausea/vomiting, and pseudomembranous colitis. The spectrum of action is primarily against gram-positive bacteria and anaerobes (especially *B. fragilis*). It has little activity against gram-negative microbes. The drug is useful in chronically draining ears, contaminated neck

wounds, chronic tonsillitis and deep neck abscesses. It is superior to penicillin in clearing pharyngitis/tonsillitis. Some strains of MRSA are sensitive to clindamycin.

Vancomycin is a glycopeptide produced by *Streptomyces Orientalis*. It is bacteriocidal and acts by inhibiting cell wall replication. Parenteral vancomycin is eliminated by the kidneys. The oral form is not absorbed and is primarily for treatment of *C. difficile*. Vancomycin is a highly-effective agent to treat gram-positive infection. It is one of the few antibiotics that have activity against MRSA, and multi-drug resistant, highly-resistant Pneumococci. When used in combination with gentamicin there is a notable synergy in addition to increased risk of ototoxicity. Side effects include red-man syndrome (chills, fever, rash and flushing) and development of resistant enterococcus.

Metronidazole (Flagyl) is an important antibiotic that provides significant efficacy in treating anaerobic and parasitic infections. The mechanism of action includes intracellular chemical reactions that produce DNA-toxic substances within the cell resulting in bacteriocidal effect. Metronidazole reaches good levels in nearly all body tissues, including the CSF, saliva, bone, and abscesses. Bioavailability studies show equal efficacy with oral and intravenous dosing. The oral form is used to treat *C. difficile* colitis. Other uses include deep neck infections, brain abscesses or difficult anaerobic infections. Side effects can include nervous system deficiencies, but are rare. When taken with alcohol the drug results in a disulphram-like effect.

Aminoglycosides are produced by *Streptomyces* and *Micromonospora* species. They act by binding to ribosomes and interfering with bacterial protein synthesis. They are bacteriocidal. These drugs are given IM or IV, though parenteral administration gives more consistent and higher serum drug levels. Aminoglycosides have poor penetration into CSF, but cross the placenta. They are excreted, unchanged, in the urine. These antimicrobials are effective in the treatment of gram-negative bacilli, especially *P. aeruginosa*. Resistance is mediated via bacterial enzymes that modify the antibiotic resulting in the inability to bind to the target ribosomes. Toxicities include damage to the kidneys (elevated trough levels), inner ear (concentrated in perilymph with prolonged use and elevated peak levels), and neuromuscular blockade.

Sulfonamides are effective against *H. influenzae*, and *M. catarrhalis*, but generally not effective against other microbes. It is often combined with other antibiotics. When combined with erythromycin (Pediozole) is it as effective as ampicillin in the treatment of otitis media. Bactrim is the combination of a sulfonamide with trimethoprim. These drugs act at different points of the protein synthesis chain. Used together, their actions are synergistic. Bactrim is more effective against beta-lactamase producing *H. influenzae* and *M. catarrhalis* than ampicillin. Sulfa allergies can result in life-threatening reactions (TENS).

Flouroquinolones are broad spectrum antibiotics effective against gram-positive bacteria, gram-negative bacteria, atypical bacteria, and pseudomonas. Ciprofloxacin is the most effective oral agent to treat *P. aeruginosa*. Ciprofloxacin and ofloxacin ototopicals are extremely effective in treatment of mastoiditis and otitis media (via PET). Ototoxicity is not a part of the side effect profile. Levofloxacin is active against GAS, *S. pneumo.* (including penicillin-resistant strains), *S. aureus* (including MRSA), *H. influenzae*, and *M. catarrhalis* (including beta-lactamase producing strains). The newer flouroquinolones show a spectrum similar to levofloxacin, but

with increased anaerobic and decreased pseudomonas coverage. The flouoroquinolones are well absorbed by mouth (bioavailability is equal to that of parenteral dosing) with wide distribution, including the CSF. It is long-acting and requires only once-a-day dosing. Side effects include drug interactions, tendon toxicity, and questionable bone growth impairment (animal studies only).

SELECTED INFECTIOUS DISEASES

Rhinosinusitis is one of the most common medical problems in America. The mechanism for this disease is thought to be the blockage of the osteomeatal complex leading to stasis of nasal secretions and subsequent infection. First line treatment for simple rhinosinusitis is similar to that of otitis media (amoxicillin/Bactrim) as the same microorganisms are implicated—*S. pneumo.*, *M. catarrhalis*, and *H. influenzae*. Second line antibiotics include Augmentin, clarithromycin, cefuroxime, Pediazole. Adjuvant therapies can include nasal irrigation, nasal steroids (shown to increase effectiveness of antibiotics), and decongestants. One study looking at the differences in outcome, etc. between first and second-line antibiotics was the cost of the treatments. Chronic sinusitis is characterized by a mixture of microorganisms, including anaerobes. Treatment is best undertaken with clindamycin or Augmentin. Polyposis often cultures positive for *P. aeruginosa* and is therefore commonly treated with Cipro or other antipseudomonas drugs. Finally, patients with recurrent sinusitis after FESS have been shown to grow a wide variety of microbes (37.9% gram-positive cocci, 14.8% gram-negative rods, and 1.7% fungal elements, 30% negative cultures). *Pseudomonas* was isolated in 7.2% of cultures and 12% of these were resistant to Cipro. 90% of patients that grew gram-negative bacteria were noted to have multiple recurrent infections. Given the spectrum of possible agents in FESS patients, it is wise to implement culture-directed antibiotic therapy. Topical antimicrobials have also been shown to be of some use, though this is still under study. Hypertonic saline irrigations have also been shown to be effective treatment in patients with patent ostia.

Pharyngitis is most commonly of concern when it is caused by Group A Streptococcus (GAS). GAS is the most common bacterial cause of this acute pharyngitis (15-30% in children, 5-10% in adults). Physical examination often reveals tonsillopharyngeal exudates (though not as florid as with Mono) with anterior cervical lymphadenitis. Treatment traditionally has called for penicillin/erythromycin as first line treatment (still shown effective in patients >12 years old or ill for >2 days). The advent of increasingly resistant organisms have resulted in recommendations for use of a second generation cephalosporin or clindamycin. This argument is based on two hypotheses: beta-lactamases proliferated by *S. aureus* and other resistant organisms may inactivate penicillin before it is able to have effect against GAS; or normal flora (alpha-streptococci) is decimated by penicillins, but are preserved by cephalosporins. Diphtheria, though rare, can also cause pharyngitis. Viral infections are likely responsible for the majority of all cases of pharyngitis. Infectious mononucleosis is an important entity. It is caused by the Epstein-Barr virus and affects 15-24 year-old patients predominately. The disease is characterized by a prodrome followed by sore throat, high fever and lymphadenitis (often pronounced). Splenomegaly is seen in 50% of patients. Treatment is supportive with care taken to avoid prescribing amoxicillin which causes rash in 50% of patients with Mononucleosis.

Otitis media has been the subject of multiple studies and continues to be a topic of considerable discussion. Three bacteria are primarily responsible for middle ear infections. These include *Strept. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. In recent studies of large numbers of children *S. pneumoniae* showed resistance to penicillin in 5-61% of patients, *H. influenzae* showed 5-55% resistance to amoxicillin, and *M. catarrhalis* showed >75% resistance to all penicillins. Recommended treatment is amoxicillin (80-90mg/kg/day as higher doses seem to overcome some resistance patterns) or Bactrim (penicillin-allergic). Second-line agents (Augmentin, ceftriaxone, quinolones) should be used if one is practicing in an area of high resistance, or after failure of a first-line agent. Serious otologic infections should be treated with vancomycin. If the infection is involving areas that are poorly penetrated by vancomycin (i.e. CSF), cefotaxime or ceftriaxone should be added. Prophylaxis has been evaluated for those with recurrent infections. A recent study showed that prophylaxis with amoxicillin (once-daily dosing) decreased the incidence of MEE, AOM, and OME without evidence of bacterial resistance. Several recent meta-analyses have shown questionable efficacy of antibiotic treatment for AOM in children. These studies are flawed by differing entrance criteria and definitions of resolution—most authors feel they do not provide convincing evidence. Most agree that the serious complications of untreated AOM necessitate active treatment of this disease.

Suppurative otitis is often associated with chronic ear disease. In one study cultures grow 27% *P. aeruginosa*, and 24% *S. aureus*. *Proteus* and fungal agents have also been identified. Treatment is debridement followed by ototopical antimicrobials. Ototopicals that cover *Pseudomonas* and *S. aureus* are indicated. These include polymyxin (or gent) with neomycin, or cipro/ofloxacin (good for use with TM that is not intact). Aspergillus fungal otitis externa can be treated with topical acetic acid (ototoxic), boric acid, merthiolate, iodine, or gentian violet (ototoxic). Topical Lotrimin (clotrimazole) is used for candidiasis.

Sialadenitis can be caused by different organisms depending on which gland is involved. One study cultured drainage from acutely infected salivary glands. Their results helped to clarify the microbiology of acute suppurative sialadenitis. Their results showed:

	Anaerobic	Aerobic	Mixed
Parotid	41%	35%	25%
Submaxillary	33%	44%	22%
Sublingual	33%	33%	33%

The most common aerobes isolated were *S. aureus* and *H. influenzae*. The anaerobes were predominately gram-negative bacilli. Antimicrobial treatment for acute sialadenitis may include Augmentin, clindamycin, or a cephalosporin combined with metronidazole.

Deep neck abscesses are usually caused by a mixture of organisms which may include anaerobes, Staph, Strept., and *Pseudomonas*. Treatment is incision and drainage followed by clindamycin and gentamicin, or ceftazidime combined with metronidazole.

Bacterial resistance to antibiotics has become an increasing problem in the era of “big gun” antibiotics and patients who expect a prescription for every illness. Precise use of antibiotics is seldom practiced as physicians opt for drugs that will cover “everything.”

Moreover, doctors often find themselves treating illnesses that are likely not bacterial. These factors have created an evolutionary pressure that has resulted in the most common pathogens of otitis media, sinusitis, and pharyngitis developing resistance to antibiotics that were extremely effective just 10-20 years ago. The development of MRSA, VRE, and the like may very well be precursors to a time when there will be infections we cannot treat with antibiotics. If we are to avoid a return to the time when we must stand helpless against infectious disease we must understand the illnesses we diagnose and treat them appropriately.

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