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Adverse effects of Antibiotics in the Geriatric Patient Population

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Elderly patients have several unique issues related to antibiotic therapy. In addition to age-associated physiological changes and drug-drug interactions, adverse drug reactions are also a noteworthy concern specific to this population. By using evidence-based medicine, pharmacists can help identify, prevent and resolve adverse drug related problems in the elderly. Common adverse effects seen in the elderly on antibiotics include: dizziness, renal toxicity, hyperkalemia, blood dyscrasias, seizures, esophageal ulceration and acute liver injury.[1]

Aminoglycosides-renal and auditory toxicity

Aminoglycosides are associated with potentially irreversible nephrotoxicity and ototoxicity. Risk factors for these adverse effects include: older age, higher dosages, longer duration of therapy, renal insufficiency and concomitant medications that also have a higher risk of renal or auditory toxicity (eg amphotericin B, cyclosporine, vancomycin, contrast agents and loop diuretics).[1,2]

Dizziness, including vertigo, has been associated with antibiotics that affect the inner ear, such as aminoglycosides. Considering that this toxicity of aminoglycosides often manifests with ineffective renal elimination, this can be problematic in the elderly, who have a notably higher incidence of renal impairment. Most importantly, dizziness is of concern since this is also a population where balance and stability are already problematic and fall risk should be minimized.

Trimethoprim and sulfamethoxazole-induced hyperkalemia and blood dyscrasias

The elderly population already has a high prevalence of renal impairment and cardiac disease. Trimethoprim can increase serum potassium levels by decreasing renal excretion. Hyperkalemia may also be of higher risk in those on angiotensin converting enzyme (ACE) inhibitors or potassium-sparing diuretics, agents that are prevalent with those of advanced age. The commonly prescribed combination antibiotic, trimethoprim and sulfamethoxazole, may also be of concern for the elderly in regards to folic acid deficiency. Folic acid deficiency is already a common vitamin deficiency in the elderly, and this can ultimately lead to megaloblastic anemia.[2]

Fluoroquinolone-related seizures and QT prolongation

This class of antibiotics has been associated with central nervous system (CNS) stimulatory effects and cardiac arrhythmias. Although seizures are rare, these agents should be used in caution for elderly patients or those with preexisting CNS disorders or epilepsy.[3] Advanced age, female gender and those with existing QT prolongation or known risk factors (i.e., concomitant medications that increase the QT interval) are at high risk for QT prolongation with fluoroquinolone therapy.[4] Some medications associated with QT prolongation include: antiarrhythmic drugs, certain nonsedating antihistamines, macrolides, certain psychotropic medications and certain gastric motility agents. Use of fluoroquinolones should be avoided in elderly patients that are at high risk for QT prolongation.

Doxycycline-related esophageal ulcerations & strictures

Since elderly patients are more likely to have comorbidities related to esophageal damage (i.e., gastroesophogeal reflux disease) and use medications that can cause esophageal damage (i.e., aspirin, bisphosphonates, nonsteroidal anti-inflammatory drugs), doxycycline poses an increased threat for esophageal ulcerations and strictures. Administering

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doxycycline with 8 oz. of water and instructing elderly patients to sit up for 30 minutes can help reduce the risk of esophageal irritation and ulceration.[1,2]

Acute liver injury secondary to prolonged amoxicillin/clavulanate therapy

Amoxicillin/clavulanate therapy is an appropriate antimicrobial choice for outpatient management of community-acquired pneumonia in the elderly.[5] Some data suggest that advanced age and longer duration of therapy are predisposing risk factors. With prolonged therapy, hepatic function should be monitored more closely in the elderly population.[2,6]

In addition to risk for adverse effects, elderly patients have age-related physiological changes, polypharmacy and comorbidities that increase their risk of drug-related problems when administering antibiotics. *Clostridium difficile* infection (CDI) is a growing area of concern in this patient population, which has higher morbidity and mortality with CDI.[6] As healthcare providers, we play a key role in recognizing the potential for adverse-related drug reactions that are often seen with antibiotic therapy in the elderly population to mitigate these risks in our patients.

<Click here for references>

Reader Submitted Drug Information Question: Does tigecycline have a place in therapy for hospital-acquired pneumonia or ventilator-associated pneumonia?

Response by Sara Ingargiola PharmD Candidate; Torry Schilling, PharmD; Kathryn Samai, PharmD, BCPS

Tigecycline is a tetracycline derivative antibacterial agent. It inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking the entry of amino-acyl tRNA molecules, preventing the incorporation of amino acids into elongating peptide chains. Although tigecycline is generally considered to be bacteriostatic, it has demonstrated bactericidal activity against isolates of *Streptococcus pneumoniae* and *Legionella pneumophila*.[1]

Tigecycline is FDA approved in patients 18 years of age or older for the treatment of complicated skin and skin structure infections (SSSI) caused by susceptible organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-sensitive *Enterococcus faecalis*. In addition, it is indicated for the treatment of complicated intra-abdominal infections (cIAI) and community-acquired pneumonia (CAP) caused by susceptible organisms.[1]

To date, tigecycline does not have a place in therapy for hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) due to an increase in mortality that was observed when using tigecycline in these conditions. A search of the medical literature returned several supportive studies.

Freire, et al. (2010) conducted a phase 3, randomized, double-blind trial comparing tigecycline with imipenem/cilastatin for the treatment of HAP.[2] Patients were given an initial dose of 100 mg IV, followed by 50 mg IV every 12 hours. The tigecycline regimen was non-inferior to the imipenem/cilastatin group for non-VAP, but did not meet the statistical criteria of non-inferiority to the imipenem/cilastatin regimen in the VAP group.[2, 3] While it remains unclear why VAP patients treated with tigecycline had lower cure rates, one hypothesis is the lower AUC/MIC that was observed.[2] The traditional dose of tigecycline attained very low serum concentrations (0.655 mcg/mL in the steady state), raising some concerns regarding the use of this drug for the treatment of infections with secondary bacteremia.[3]

Gandjini, et al. (2012) also compared tigecycline to imipenem/cilastatin in HAP. This phase 2, multicenter, double-blind study compared higher doses of tigecycline. Patients received either tigecycline 75 mg IV every 12 hours, tigecycline 100 mg IV every 12 hours or an imipenem/cilastatin regimen. The authors noted improved efficacy in the patients who received the tigecycline 100 mg regimen; however, the sample size was too small to reach statistical

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significance. Due to enrollment challenges, this study was discontinued prior to planned full enrollment.[4]

The American Thoracic Society recommends the following regimen (Table 1) for treatment of early onset (within 4 days of hospitalization) HAP and VAP .[5]

Table 1: HAP and VAP early onset; Empiric therapy No multi-drug resistant risk factors (MDR)
Choose one of the following:
• ceftriaxone
• levofloxacin, moxifloxacin, or ciprofloxacin
• ampicillin/sulbactam
• ertapenem

The American Thoracic Society recommends the following regimen (Table 2) for late onset (≥ 5 days) HAP AND VAP.[5]

Table 2: HAP and VAP late onset; Empiric therapy Multi-drug resistant (MDR) risk factors	
Choose a combination of the following:	
antipseudomonal cephalosporin	• cefepime • ceftazidime
OR	
antipseudomonal carbepenem	• imipenem • meropenem
OR	
β-lactam / β-lactam inhibitor	• piperacillin-tazobactam
PLUS	
antipseudomonal floroquinolone	• ciprofloxacin • levofloxacin
OR	
aminoglycoside	• amikacin • gentamycin • tobramycin
PLUS	
If MRSA coverage needed	• linezolid • vancomycin

Based on the information about tigecycline and the current data from clinical trials, tigecycline should not be recommended for the treatment of HAP or VAP. There is a documented increase in the risk of mortality when using standard doses of tigecycline to treat HAP or VAP, as well as insufficient data to support higher tigecycline doses in these patients. More literature is needed to better assess tigecycline's role in the treatment of nosocomial pneumonias and whether or not a dosage increase is warranted.

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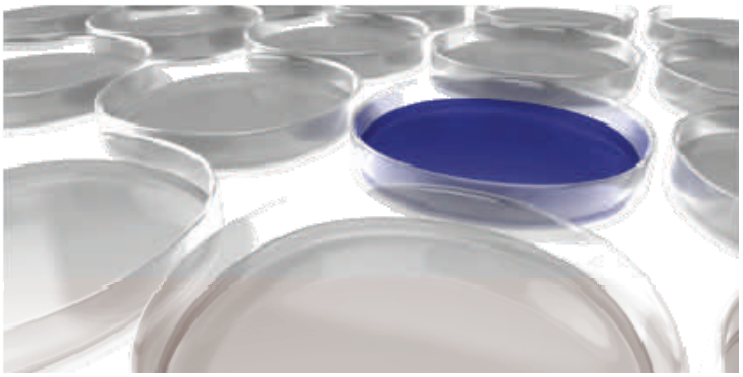

Evolving resistance trends for *Neisseria gonorrheae*

Lucas Reinhartz, PharmD Candidate; Michael Mueller, PhD

Gonorrhea remains the second most commonly reported sexually transmitted disease in the United States behind chlamydia.[1] Prevention and treatment of *N. gonorrheae,* through safe sex practices and antibiotics, can result in a decrease of male patients with epididymitis and female patients with pelvic inflammatory disease and the possibility of infertility. Historically, several different antibiotic classes have been used to treat *N. gonorrheae* including sulfonamides, penicillins, tetracyclines and fluoroquinolones, but all have been met with resistant strains. By the 1980s, sulfonamides, penicillin and tetracyclines were no longer seen as first-line options for treatment. In 2007, fluoroquinolone-resistant *N. gonorrheae* emerged in the United States which left cephalosporins as the only recommended antimicrobial class available for treatment.[2] Recently, the CDC's Gonococcal Isolate Surveillance Project (GISP) is showing an alarming trend of resistance, increased minimum inhibitory concentrations (MICs), and reduced susceptibility to the only orally available agent, cefixime.[3]

From January 2006 to August 2011, the percentages of isolates with elevated cefixime MICs (≥ 0.25 mcg/mL) have increased from 0.1% to 1.5%. Percentages of ceftriaxone

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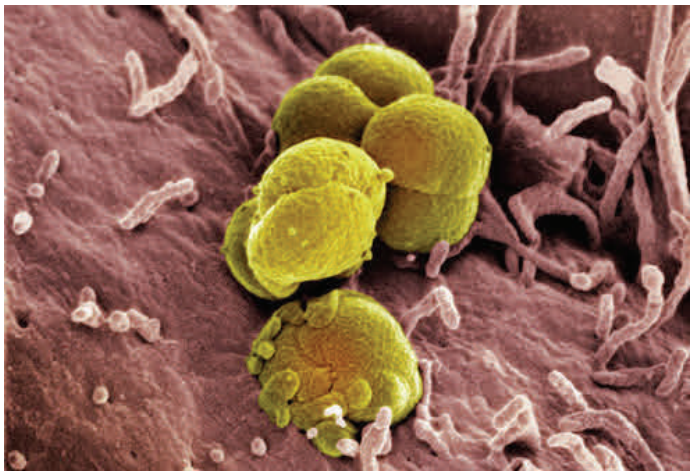
MIC elevations have also increased but very minimally as compared to cefixime, 0% to 0.4% in the same timeline.[4] The highest reported incidence of elevated MICs for cefixime and ceftriaxone isolates are in the Western United States and in men who have sex with men. In Europe, there have been several reports of gonorrhea treatment failure with cefixime.[5] This data is indicative of declining effectiveness of cefixime and therefore, as of August 2012 the CDC no longer recommends the routine use of cefixime as a first-line regimen for the treatment of *N. gonorrheae* in the United States. As cefixime is used less for treatment of *N. gonorrheae*, the increased usage of ceftriaxone will likely hasten the continued development of resistance patterns. With intramuscular ceftriaxone being the remaining critical treatment for *N. gonorrheae* and resistance beginning to emerge, there is an increased need for new treatment regimens for *N. gonorrheae*.



Based on the new data showing increased resistance for treatment of *N. gonorrheae*, the CDC has updated their recommendations from the 2010 Sexually Transmitted Diseases Treatment Guidelines. When looking at the treatment of uncomplicated urogenital, anorectal and pharyngeal gonorrhea, the CDC recommends combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days.[4] Patients with persistent infections despite treatment with the recommended combination therapy regimen should have cultures gathered with susceptibility testing of the *N. gonorrheae* isolates.

Despite changes to the guidelines, cefixime has not been fully removed from treatment regimens. Cefixime 400 mg orally plus either azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days can be used if ceftriaxone is not readily available. Azithromycin 2 g orally in a single dose should be the agent used if ceftriaxone cannot be given because of severe allergy. If a patient with gonorrhea is treated with an alternative regimen, the patient should return 1 week after treatment for a test-of-cure at the infected anatomic site.[4] Cases of treatment failure with either the first-line or alternative regimens should be reported to the CDC through the local or state health department. Sexual partners of patients with gonorrhea should be tested for *N. gonorrheae* and if detected should be treated with a recommended regimen.

<Click for references>

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