CHAPTER **16**

Common Antibiotics, Allergies, and Alternatives

Yusuf Opakunle, DPM

INTRODUCTION

An allergy is simply an unpleasant hypersensitivity of the immune system. Most allergies are benign and can be contained when detected early; however, a few could be debilitating and may even lead to death. Most common causes of allergic reactions include food, latex, pollen, dust, insect stings, and most importantly medications. Certain medications are well known to cause allergies such as antibiotics, anticoagulants, opioids, and diabetic agents (1). Approximately 4 per 1,000 emergency department visits in 2013-2014 were for adverse drug reactions, of which approximately 27.3% resulted in hospitalization (1). Another study reviewing International Classification of Disease, 9th edition, Clinical Modification codes during a 6 year period for identification of allergic drug reactions found 27% of the emergency department visits were for allergic drug reactions (2).

Hives and rash after taking a particular medication are common symptoms of an allergy. However, the most life-threatening condition of any allergy is called anaphylaxis shock, which affects multiple body organs (2). Epinephrine is the first line treatment for an anaphylaxis reaction (3). It is important for the podiatric physician to realize that a known drug side effect and drug toxicity are not the same as a drug allergy. The broad use of the word "allergy" is used by patients for any adverse drug reaction or drug-drug interaction. Further investigation by the physician is necessary. Nausea can be a known side effect of a drug and not an allergy. For example, constipation is a known side effect of opioid medications, therefore physicians must educate patients about known side effects of a drug versus true allergy. A true allergy occurs when the immune system recognizes a harmless substance as a foreign body, thereby triggering an immune response (4). A common immune reaction is the production of immunoglobulin E (IgE) that is specific to the particular drug called an allergen (3). The onset and symptoms of a drug allergy can be divided into 2 categories: Immediate reaction (from seconds to hours), which is IgE mediated, and delayed response (from hours to days or weeks), which is T cell dependent (4).

PENICILLIN/BETA-LACTAMASE

Arguably the most common drug allergy is penicillin (5). Penicillin and its derivatives are commonly the first line drugs for common bacterial infection, and surgical prophylaxis. They are also very affordable. All the drugs in the penicillin family contain the compound beta-lactamase, which is a known culprit for true penicillin allergy (5). Beta-lactam antibiotics include penicillins, cephalosporins, carbepenems, and monobactams (6). Beta-lactam is a cyclic amide with a 4-membered ring that inhibits cell wall synthesis in bacteria. It is very difficult for physicians to determine ahead of time which patients will develop an allergic reaction to beta-lactamase. An allergic reaction can happen within seconds or minutes of taking a medication although some may take hours, days or even weeks (6). It is a bigger challenge to determine the source of allergy when a reaction develops after completing the dose of medications or when the patient is taking multiple medications at once. Many people in the health care field will argue that a true penicillin allergy is rare. Hives, rash, and anaphylaxis are common allergic reactions to penicillin (5). Patients with a penicillin allergy are routinely not prescribed any medication in the beta-lactamase family. This is unfortunate because beta-lactamase penicillins and cephalosporins have excellent coverage against many penicillin sensitive organisms (7). Physicians tend to avoid cephalosporins in patients with penicillin allergy even though the cross-reactivity between cephalosporins and penicillin is low (8,9). It is even lower between carbapenems and penicillins (10). It is not uncommon to hear a patient say they had an allergic reaction as a child without knowing the exact reaction. The old adage "better safe than sorry" applies here. This has unintended consequences because the practitioner is forced to use other stronger broad-spectrum antibiotics, which over the years, has led to the development of methicillin resistant *Staphylococcus aureus* (MRSA) (11).

Skin sensitivity testing for penicillin allergies can help confirm a true allergy in patients with the presence of IgE mediated hypersenstivity (10), however no commercial skin test reagent is available. Testing is beneficial to patients because cephalosporins and penicillin derivatives such as augmentin are cheaper compared to other medications and thus help control health care cost (12). A common alternative for those with a true penicillin allergy is clindamycin. Clindamycin is the most commonly used prophylaxis in preoperative patients who have a penicillin allergy (13). Other alternatives depend on the organism and area of the body. Commonly used alternatives are vancomycin, sulfamethoxazole/trimethoprim (Bactrim), doxycycline, clindamycin, linezolid, synercid, and levofloxacin (14-16).

SULFA DRUGS

Sulfa drugs are any drugs containing sulfonamides. They are derivatives of para-amino benzoic acid (17). There are many groups of drugs that contain sulfa. Examples include antibiotics (sulfamethoxazole/trimethoprim), diuretics for high-blood pressure (hydrochlorothiazide, furosemide), sulfonylureas for reducing blood sugar in diabetes mellitus (glyburide), and dapsone for leprosy (18). Other drugs containing sulfa include burn creams and eye drops. Drugs containing sulfa were one of the earliest drugs used against bacterial infections. Antibiotic derivatives of sulfa drugs include septrin, gantanol, and bactrim. Bactrim is the most common drug used in patients with MRSA diabetic foot infection (19). Today, it is a commonly prescribed prophylactic drug for patients living with HIV/AIDS. These patients should be monitored because a retrospective cohort study showed that sulfamethoxazole/trimethoprim could cause reversible hyperkalemia in HIV patients (20). Trimethoprim works by inhibiting dihydrofolate reductase while sulfamethoxazole inhibits dihydropteroate synthase (21). Together they inhibit the production of folic acid in bacterial cells thereby making it bactericidal. Bactrim has excellent coverage for gram-positive cocci (*Staphylococcus aureus* and *Streptococcus agalactiae*, not active against Enterococcus), and gram-negative rods (*Escherichia coli*, not active against *Pseudomonas spp* or Anaerobes) (21).

It should be noted that nausea, diarrhea, vomiting, and rash are common side effects of sulfa drugs (21) and these should not be mistaken for an allergic reaction. Other adverse drug reactions include cytopenia and hepatotoxicity (22). A true allergic reaction to sulfa drugs occurs when the sulfonamide molecule is metabolized by the body, and the molecule binds to proteins in the human body thereby producing large molecules (23). This large molecule serves as an allergen that triggers the body's immune response leading to rash, hives, and swelling of the mucous membrane and lips with difficulty breathing. In severe cases, patients can have an anaphylactic reaction which could be life threatening (23). A common misconception is mistaking a sulfa allergy for a sulfite allergy. These two are mutually exclusive, and patients must be educated. Sulfonamides and sulfa are chemically different, and both can cause an allergic reaction independently. Sulfite is found naturally in wine and used as a preservative in some foods (processed foods) (23). Alternatives to sulfa drugs for gram-positive coverage is augmentin in patients without history of MRSA; clindamycin, levofloxacin, or doxycycline should be utilized in patients with an active MRSA infection or history of MRSA.

VANCOMYCIN

Vancomycin is a glycopeptide produced by *Streptococcus orientalis* (24). It is bactericidal, and it works by inhibiting cell wall synthesis in bacteria. It has excellent gram-positive coverage (24). Vancomycin is widely used as the first-choice drug in the treatment of MRSA (25). It is also the drug of choice for patients with penicillin allergies or patients that have failed treatment with penicillins or cephalosporins. Vancomycin is widely used intravenously however oral vancomycin is available and used for the treatment of *Clostridium difficile* (c diff) (26). A known adverse reaction from vancomycin is red man syndrome (RMS) (25), with an incidence between 3.7 and 47% (27). This occurs when vancomycin is rapidly infused or administered over a short period of time (25). RMS does not involve any antibodies but rather a histamine release. This causes pruritis, erythema, and flushing usually affecting the face and neck (27). Treatment involves steroids and antihistamines (27). Histamine receptor blocker can help reduce the occurrence of RMS (25). The upper body is more likely to be affected than the lower body (24). RMS can be reduced by slow infusion of vancomycin over several hours (27). Other side effects of vancomycin include muscle spasms, dyspnea, and hypotension (24). Peaks and troughs are routinely ordered for vancomycin and the trough value is used to measure toxicity (28). Increased vancomycin use and higher trough concentration can lead to nephrotoxicity (28,29). It must be noted that other antibiotics such as ciprofloxacin, amphotericin B, and rifampin can also lead to RMS (25). Although rare, a true allergy to vancomycin can initially present as RMS and then progress to anaphylaxis (30). Therefore, it is important for health care professionals to recognize it early and treat it accordingly. Alternative treatments for MRSA in patients with a vancomycin allergy include bactrim, doxycycline, linezolid, daptomycin, tigercycline, and synercid.

CLINDAMYCIN

Clindamycin is an antibiotic with gram-positive and anaerobic coverage, which is also sensitive to MRSA with good bone and joint coverage (31). Clindamycin is produced by the bacterium Streptomyces lincolnensis (32) and it is available in both oral and parenteral forms. Clindamycin is the drug of choice for surgical prophylaxis in patients with a penicillin allergy. It works by stopping the translocation of ribosomes, thereby inhibiting protein synthesis (32) and making it bacteriostatic (32). Clindamycin also has an antitoxin effect against strains of staphylococcus and streptococcus that produce toxins; this mechanism is not clearly understood

(33). Therefore, clindamycin is often used in suspected and confirmed cases of toxic-shock syndrome (33). A major adverse effect of clindamycin is the development of pseudomembranous enterocolitis, which is diarrhea caused by outgrowth of *Clostridium difficile* (34). Other side effects include nausea, vomiting, joint pain, and abdominal pain (35). The incidence of allergies caused by clindamycin is low, but they do exist (36). The most common allergy for clindamycin is a delayed maculopapular exanthema, which generally presents about a week after drug initiation (37). This can be a problem in patients starting multiple medications at the same time. Other allergic reactions include anaphylactic shock, Sweets syndrome, and bullous eruptions. Alternatives to a clindamycin allergy include synercid, linezolid, metronidazole, imipenem, vancomycin, bactrim, and doxycycline.

FLUOROQUINOLONES

Fluoroquinolones are a family of antibiotics with excellent gram-positive and gram-negative coverage (38). They are unique because of the antipseudomonal coverage and excellent bone penetration with the oral form (39). Fluoroquinolones are derived from synthetic fluorinated analogs of nalidixic acid. The mechanism of action is targeting topoisomerase IV in gram-positive organisms thereby separating catenated DNA molecules that result from DNA replications (39). In gram-negative organisms, it works by targeting DNA gyrase thereby inhibiting DNA supercoiling (uncoils DNA) and making it bactericidal (39). Studies have shown that mutation of gyrA can confer resistance (39,40). Ciprofloxacin is arguably one of the most prescribed fluoroquinolons for gram-negative coverage especially for *Pseudomonas spp* due to his bioavailability in oral form (38). Levofloxacin and moxifloxacin are becoming common, secondary to the rise of community-acquired MRSA and community-acquired pneumonia infection (41). Fluoroquinolones are also used to treat complicated or recurrent urinary tract infections, pneumonia and severe diabetic foot infections involving bone and joints (39,42).

This group of drugs should never be used as a first line treatment for routine skin and soft tissue infections due to severe side effects and black box warning. Known side effects include cartilage damage in children younger than 18 years, irreversible peripheral neuropathy, prolonged QT interval, hepatic toxicity, and the black box warning of increased risk of Achilles tendon rupture (42,43). Fluoroquinolones are used when other treatment options have failed and careful consideration should be given when prescribing this class of drug. Reported allergies to fluoroquinolones include urticarial, anaphylactic shock, erythema, rash (44) and the most common being delayed maculo papular exanthema (45). Alternatives to fluoroquinolones include linezolid, bactrim, aztreonam, and pipercillin-tazobactam

METRONIDAZOLE

Metronidazole, widely known as flagyl, is an imidazole with exceptional anaerobic coverage (46). It is available in both oral and parenteral forms (47). Anaerobes are unicellular or multicellular organisms that thrive in environments with little or no oxygen. Examples include *bacteroides spp, clostridia spp, peptococcus spp,* and *peptostreptococcus spp*. Metronidazole works by inhibiting the DNA of bacteria cells by disrupting nucleic acid synthesis (47). It is important to note that metronidazole functions in a partially reduced state, which only happens in anaerobic cells. Anaerobic organisms can cause gas gangrene in diabetic foot infections, which are seen on radiographs as diffuse soft-tissue emphysema. Gas gangrene is a surgical emergency and immediate incision and drainage is required. Metronidazole is a remarkable drug used to cover anaerobes in diabetic foot infection (47). It is also used to treat diarrhea associated with *Clostridium difficile* (46,). A known side effect when using metronidazole is a disulfiram-like reaction when taken with alcohol. Patients should be advised to avoid alcohol when taking any medication especially metronidazole (47). Other side effects include nausea, headache, loss of appetite, metallic taste, and stomach upset (48). To prevent stomach upset, patients should be advised to take the medication with food or a glass of milk. Neurotoxicity secondary to metronidazole has been reported in a few case reports (48-50). A true allergic reaction to metronidazole is rare. Alternatives to metronidazole are clindamycin, linezolid, synercid, cefoxitin, and cefmetazole

TETRACYCLINE

Tetracyclines are broad spectrum antibiotics active against gram-positive and gram-negative organisms. It was originally made from the bacteria Streptomyces (51), and works by binding reversibly to the 30s subunit of ribosomes thereby inhibiting protein synthesis (52). Consequently, it has a bacteriostatic effect. Tetracyclines are sensitive to atypical pathogens such as treponema spp, rickettsia spp, borrelia spp, borrelia burgdorferi, vibrio cholera, and mycoplasma pneumonia. The two most common derivatives of tetracycline are doxycycline and minocycline (53). However, a newer generation of tetracycline is tigecycline, which is indicated for severe soft tissue and bone infections (54,55). Doxycycline is routinely prescribed to patients with diabetic foot infections that are resistant to penicillin.

Known side effects to tetracycline include vomiting, diarrhea, rash, black hairy tongue, and sore throat. Other notable side effects include tooth discoloration in children (56, 57). Tetracycline is contraindicated in pregnant women because it can cross the placenta and be toxic to fetal tissues (57). Reversible Fanconi syndrome has been associated in patients who take outdated medication (58). A true allergy to tetracycline is rare but allergic reaction can include rash, skin lesions, and itching (59). Alternatives to tetracycline include penicillin (if sensitive), bactrim, vancomycin, and ciprofloxacin.

Important factors to consider when deciding alternatives to antibiotics, is to look at the sensitivity report and also the history of susceptibility or resistance of the patient. Alternatives to a medication should only be prescribed for well-defined indications.

REFERENCES

1. Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug events, 2013-2014. JAMA 2016;31:2115.
2. Saff RR, Camargo CA Jr, Clark S, Rudders SA, Long AA, et al. Utility of ICD-9-CM codes for identification of allergic drug reactions. J Allergy Clinical Immunol Pract 2016;4:114-9.
3. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Ellis A, et al. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol 2015;115:341-84.
4. Campbell RL, Li JT, Nicklas RA, Sadosty AT. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol 2014;113:599-608.
5. Shehab N, Patel PR, SrinivasanA, Budnitz DS. Emergency department visits for antibiotic□ associated adverse events. Clin Infect Dis 2008;47:735-43.
6. Moreno E, Laffond E, Munoz-Bellido FJ, Gracia MT, Macias EM, Davila I. Using beta-lactam antibiotics in patients with a history of beta-lactam allergy: current concepts. Pol Arch Intern Med 2017;127:7-8.
7. Blumenthal KG, Shenoy ES, Huang M, Kuhlen JL, Ware WA, Parker RA, et al. The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive Staphylococcus Aureus bacteremia. PLoS ONE 2016;11:e0159406.
8. Caplinger C, Smith G, Remington R, et al. Evaluation of a computerized decision support intervention to decrease use of anti-pseudomonal carbapenems in penicillin allergic patients. Antibiotics 2016;5:7.
9. Blumenthal KG, Youngster I, Shenoy ES, Banerji A, Nelson SB. Tolerability of Cefazolin after immune-mediated hypersensitivity reactions to nafcillin in the outpatient setting. Antimicrob Agents Chemother 2014;58:3137-43.
10. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? Ann Pharmacother 2009;43:304-15.
11. Al-Ahmad M, Rodriguez-Bouza T. Drug allergy evaluation for betalactam hypersensitivity: Cross-reactivity with cephalosporines, carbapenems and negative predictive value. Asian Pac J Allergy Immunol 2017;10:12932.
12. Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. J Allergy Clin Immunol 1998;102:281-5.
13. Robertsson O, Thompson O, W-Dahl A, et al. Higher risk of revision for infection using systemic clindamycin prophylaxis than with cloxacillin. Acta Orthopaedica 2017;88:562-7.
14. Blumenthal KG, Shenoy ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015;115:294-300.
15. Shah NS, Ridgway JP, Pettit N, Fahrenbach J, Robicsek A. Documenting penicillin allergy: the impact of inconsistency. PLOS ONE 2016;11:e0150514.
16. Yayan J, Ghebremedhin B, Rasche Kurt. No outbreak of vancomycin and linezolid resistance in staphylococcal pneumonia over a 10-year period. PLoS ONE 2015;10:0138895.
17. Podnecky NL, Rhodes KA, Mima T, Drew HR, Chirakul S, Wuthiekanun, et al. Mechanisms of resistance to folate pathway inhibitors in burkholderia pseudomallei : deviation from the norm. mBio 2017;8:e01357-17.
18. Ponka D. Approach to managing patients with sulfa allergy: use of antibiotic and nonantibiotic sulfonamides. Can Fam Physician. 2006;52:1434-8.
19. Frei CR, Miller ML, Lewis JS, et al. Trimethoprim-Sulfamethoxazole or Clindamycin for community-associated MRSA (CA-MRSA) skin infections. J Am Board Family Med 2010;23:714-9.
20. Greenberg S, Reiser IW, Chou SY, et al. Trimethoprim-Sulfamethoxazole induces reversible hyperkalemia. Ann Internal Med 1993;119:291.
21. Gleckman R, Blagg N, Joubert DW. Trimethoprim: mechanisms of action, antimicrobial activity, bacterial resistance, pharmacokinetics, adverse reactions, and therapeutic indications. Pharmacotherapy 1981;1:14-9.
22. Cho SY, Kang CI, Kim J, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating stenotrophomonas maltophilia bacteremia? Antimicrobial Agents and Chemotherapy 2014;58:581-3.
23. Hemstreet BA,d Page RL. Sulfonamide allergies and outcomes related to use of potentially cross-reactive drugs in hospitalized patients. Pharmacotherapy 2006;26:551-7.
24. Bruniera FR, Ferreira FM, Saviolli LRM, et al. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci 2015;19:694-700.
25. Sivagnanam S, Deleu D. Red man syndrome. Crit Care 2003;7:119-20.
26. Vickers JR, Tillotson SG, Nathan R, et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis 2017;17:735-44.
27. Wazny LD, Daghigh B. Desensitization protocols for vancomycin hypersensitivity. Ann Pharmacother 2001;35:1458-64.
28. Horey A, Mergenhagen KA, Mattapallil A. The relationship of nephrotoxicity to vancomycin trough serum concentrations in a veteran's population: a retrospective analysis. Ann Pharmacother 2012;46:1477-83.
29. Pritchard L, Baker C, Leggett J, et al. Increasing Vancomycin serum trough concentrations and incidence of nephrotoxicity. Am J Med 2010;123:1143-9.
30. Hassaballa H, Mallick M, Orlowski J. Vancomycin anaphylaxis in a patient with vancomycin-induced red man syndrome. American J Therap 2000;7:319-20.
31. Bouazza N, Pestre V, Jullien V, et al. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Brit J Clin Pharmacol 2012;74:971-7.
32. Spízek J, Rezanka T. Lincomycin, clindamycin and their applications. Appl Microbiol Biotechnol 2004;64:455-64.
33. Schlievert PM, Kelly JA. Clindamycin-induced suppression of toxic-shock syndrome-associated exotoxin production. J Infect Dis 1984;149:471-7.
34. Büchler AC, Rampini SK, Stelling S, et al. Antibiotic susceptibility of Clostridium difficile is similar worldwide over two decades despite widespread use of broad-spectrum antibiotics: an analysis done at the University Hospital of Zurich. BMC Infect Dis 2014;14:607.

35. Smeets TJL, Jessurun N, Harmark L, Kardaun SH. Clindamycin-induced acute generalised exanthematous pustulosis: five cases and a review of the literature. Neth J Med 2016;74:421-8.
36. Chiou CS, Lin SM, Lin SP, et al. Clindamycin-induced anaphylactic shock during general anesthesia. J Chinese Med Assoc 2006;69:549-51.
37. Pereira N, Canelas MM, Santiago F, et al. Value of patch tests in clindamycin-related drug eruptions. Contact Dermatitis 2011;65:202-7.
38. Fu Y, Zhang W, Wang H, Zhao S, Chen Y, Meng F, et al. Specific patterns of gyrA mutations determine the resistance difference to ciprofloxacin and levofloxacin in Klebsiella pneumoniae and Escherichia coli. BMC Infectious Diseases 2013;13:8.
39. Grillon A, Schramm F, Kleinberg M, et al. Comparative activity of ciprofloxacin, levofloxacin and moxifloxacin against Klebsiella pneumoniae, Pseudomonas aeruginosa and Stenotrophomonas maltophilia assessed by minimum inhibitory concentrations and time-kill studies. PLOSoNE 2016;11:0156690.
40. Mustaev A, Malik M, Zhao X, et al. Fluoroquinolone-Gyrase-DNA complexes. J Biologic Chemistry 2014;289:12300-12.
41. Fernández TD, Ariza A, PalomaresF, et al. Hypersensitivity to fluoroquinolones. Medicine 2016;95:e3679.
42. Kim GK. The risk of fluoroquinolone-induced tendinopathy and tendon rupture: what does the clinician need to know? J Clin Aesthet Dermatol 2010;3:49-54.
43. Jones CS, Budnitz DS, Sorbello A, et al. US-based emergency department visits for fluoroquinolone- associated hypersensitivity reactions. Pharmacoepidemiol Drug Saf 2013;22:1099-106
44. Lobera T, Audicana MT, Alarcon E, et al. Allergy to quinolones: low cross-reactivity to levofloxacin. J Investig Allergol Clin Immunol 2010;20:607-11.
45. Nair PA. Ciprofloxacin induced bullous fixed drug reaction: three case reports. J Family Med Primary Care 2015;4:269.
46. Jarrad AM, Karoli T, Debnath A, Tay CY, Huang JX, Kaeslin G, et al. Metronidazole-triazole conjugates: activity against Clostridium difficile and parasites. Eur J Med Chem 2015;101:96-102.
47. Lofmark S, Edlung C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis 2010;50:S16-23.
48. Senthilkumaran S, Shah S, Balamurugan N, et al. Metronidazole encephalopathy: uncommon reaction to a common drug. Int J Crit Illn Inj Sci 2015;5:123-4.
49. Kim H, Kim YW, Kim SR, et al. Metronidazole-induced encephalopathy in a patient with infectious colitis: a case report. J Med Case Rep 2011;5:63.
50. Chandak C, Agarwal A, Shukla A et al. A case report of metronidazole induced neurotoxicity in liver abscess patient and the usefulness of MRI for its diagnosis. J Clin Diagnos Res 2016;10:1.
51. Wang S, Gao X, Gao Y, et al. Tetracycline resistance genes identified from distinct soil environments in China by functional metagenomics. Front Microbiol 2017;8:1406.
52. Gzyl KE and Wieden HJ. Tetracycline does not directly inhibit the function of bacterial elongation factor Tu. PLOSoNE 2017;12:0178523.
53. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 2006;58:256-65.
54. Kreis CA, RaschkeMJ, Roßlenbroich SB, et al. Therapy of intracellular Staphylococcus aureus by tigecyclin. BMC Infectious Diseases 2013;13:267.
55. Hoffmann M, DeMaio W, Jordan RA et al. Metabolism, excretion, and pharmacokinetics of [14c] tigecycline, a first-in-class glycylcycline antibiotic, after intravenous infusion to healthy male subjects. drug metabolism and disposition 2007;35:1543-53.
56. Sanchez AR, Rogers RS, Sheridan PJ. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. Int J Derm 2004;43:709-15.
57. Conchie JM, Munroe JD, Anderson DO. The Incidence of Staining of Permanent Teeth by the Tetracyclines. Can Med Assoc J 1970;103:351-6
58. Montoliu J, Carrera M, Darnell A, et al. Lactic acidosis and Fanconi's syndrome due to degraded tetracycline. BMJ 1981;283:1576-157.
59. Shapiro LE, Knowles SR and Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. Arch Derm1997;133:1224-30.

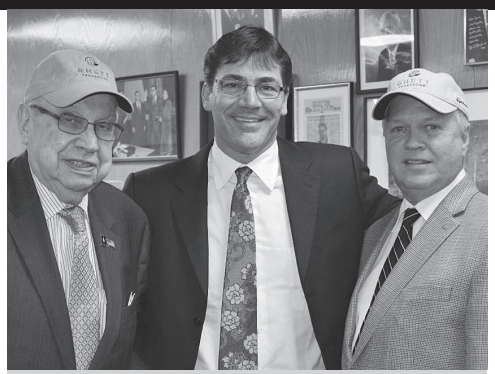
Giving Back.

Some End Their Professional Careers Without Giving Back.

Look What the Rhett Foundation has Done in Just a Few Short Months.

$100,000 to the Temple University School of Podiatric Medicine

Complimentary dermatology textbooks for all 3rd year residents



$100,000 to The New York College of Podiatric Medicine

Unlike businesses selling products and services, the Rhett Foundation supports solely to promote education. Here's more of what we've already done:

- APMA Corporate Diamond Partner
- AAPPM Corporate Partner
- Podiatry Institute Platinum Sponsor
- IFAF Diamond Sponsor
- NYSPMA Platinum Sponsor
- FPMA Annual Platinum Sponsor
- IPED Educational Platinum Sponsor
- Grant to the Goldfarb Foundation
- Numerous Additional Sponsorships Nationwide!

For the Advancement of Podiatric Medical Education

www.rhettfoundation.org
770-360-9811 • info@rhettfoundation.org

RHETT
FOUNDATION