ALLERGEN Focus

Focus On: Bacitracin Allergen of the Year 2003

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In 1997 the Food and Drug Administration gave indication to the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test for use as a valuable, first-line screening tool in the diagnosis of allergic contact dermatitis (ACD). Many dermatologists and allergists use this standard tool in their practices and refer to contact dermatitis referral centers when the T.R.U.E test fails to identify a relevant allergen. Specifically, the T.R.U.E. test screens for 46 distinct allergens in addition to the Balsam of Peru mixture, and is thought to adequately *identify an allergen in approximately 24.5%* of patients.[1]

This being said, many relevant allergens are not detected by use of this screening tool alone and, for this reason, "Allergen Focus" has been expanded to cover the notorious allergens of the year. ***This month, the column focuses on bacitracin.***

The contact dermatides include irritant contact dermatitis (ICD), contact urticaria (CU) and allergic contact dermatitis (ACD). ICD is the most common form, accounting for approximately 80% of environmental-occupational based dermatoses. CU (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis. The foremost example of this would be latex protein hypersensitivity. While this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key resources.[2,3,4]

ACD is a T-cell dependent delayed-type (Type IV) hypersensitivity reaction, which has a high impact both in terms of patient morbidity and economics. This type of hypersensitivity reaction is primarily instigated by small lipophilic chemicals (haptens) with a molecular weight less than 500 Daltons. These chemical allergens trigger a complex immunologic cascade, which leads to the clinical picture of ACD.

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CASE ILLUSTRATION

A 54-year-old man with a history of venous insufficiency and chronic exudative ulceration of the medial malleolus presented for evaluation of worsening pain and depth of his ulcer and increased intensity of peri-wound erythema.

HISTORY OF WOUND CARE

Wounds from injuries and diseases have plagued mankind since ancient times, and pulstaces (preparations derived from living matter) have been developed to apply to wounds to help heal them and to destroy infection. In fact wound closure was of extreme importance to the Egyptians because they felt it protected the soul and prevented the spirit from being exposed to "infernal beings".[5] As early as 1500 B.C., the Egyptians used a mixture of lard, honey and lint as an ointment for wounds. The honey was thought to function as a topical antiseptic, the lard as a functional barrier to pathogens, and the lint as a fibrous base to assist with wound closure.[5,6] The Egyptians were also the first to utilize essential oils including myrrh, lotus and sandalwood oils for purification rituals, and clove and lemon for prevention of infection.[7]

The protective effects of essential oils stood the test of time and became well utilized during the Middle Ages. For example, Doktor Schnabel von Rom ("Doctor Beak of Rome") was known to wear a special mask that had a long beak stuffed with herbs and spices to ward off plague.[8] In fact, the famous nursery rhyme "Ring around the rosie, a pocket full of posies, ashes, ashes, we all fall down" has often been sung as a reference to plague times with the posies representing the practice of carrying flowers to protect oneself from the disease.[9] It is also said that in the early 18th century, a band of robbers were known to steal from plague victims without ever contracting the disease. When four of the thieves were eventually

caught and put on trial in Marseilles, France, the magistrate proposed leniency in exchange for the thieves disclosing their secret for warding off the disease. The thieves [who were actually perfumers and spice traders] revealed that they would rub themselves with aromatic herbs such as cinnamon, clove and oregano to prevent infection as they stole from the dying and dead plague victims.[7] Interestingly, during these pre-modern times, the plague was reasoned to be due to 'God's wrath' rather than the sequelae of infection by a microbe.[8]

Despite Anton van Leeuwenhoek's discovery in 1675 of the first single-celled organisms, which he originally referred to as *animalcules,*[10] the practice of using chemistry to prevent infection by microbes did not take a stronghold until the late nineteenth century. The groundbreaking discoveries in the fields of microbiology and cellular pathology in the 19th century led to the development of a whole new era in wound care. Indeed, the idea that a microorganism was capable of destroying another microbiotic species was not established until the 1870s, when Louis Pasteur discovered the antagonistic effect of saprophytic (soil) bacteria on the growth of anthrax bacteria. This astute observation identified the potential to take advantage of 'anti' microbial interaction for therapeutic use.[11]

GRAM STAINING

In 1882, Hans Christian Gram, a Danish bacteriologist, developed a method (the Gram Stain) to distinguish and identify bacteria.[12] He built upon a method German Chemist Paul Ehrlich had previously worked on over a 30-year period using alkaline-aniline solutions to identify microorganisms. Gram's experiments centered around the use of Gentian violet and Lugol's iodine solution as he examined lung tissue from patients who had died from pneumonia. With these stains, he was able to differentiate between pneumococci (Gram positive) and *Klebsiella pneumoniae* (Gram negative).[13,14] In his initial publication, Gram stated "I have therefore published the method, although I am aware that as yet it is very defective and imperfect; but it is hoped that also in the hands of other investigations it will turn out to be useful."[14]

More than 200 years later, the Gram Stain remains the gold standard for the differentiation between organisms with a peptidoglycan-rich and lipid-poor cell wall (Gram-positive organisms) and organisms with lipid-rich cell walls (Gram-negative organisms). The main stain in this method is crystal violet, which when bound to iodine, forms a complex not easily removed by a mixture of ethanol and acetone (the decolorizer) in Gram-positive organisms because of their peptidoglycan-rich and lipid-poor cell wall. These bacteria thus appear under the microscope in purple-brown tones. Gram-negative organisms, on the other hand, do not to retain this dye after the decolorizer is added because their lipid-rich cell walls become dissolved by this solvent and the crystal-violet dye easily leaks out. Because Gram-negative organisms appear colorless after this process, a counter-stain of basic fuchin or safranin is often added to help easily identify these Gram-negative bacteria with a pinkish-red color.[12]

THEORY OF SELECTIVE TOXICITY

Of interest, having learned of Gram's advances in the field, Paul Ehrlich went on to develop his 'theory of selective toxicity' in 1906, which postulated that certain chemicals or organisms could either be toxic or harmless depending on the organism they came in contact with.[11] Many advances in sterile technique and antimicrobial therapeutics arose from this theory — for example, the use of surgical gauze pre-treated with carbolic acid (phenol) for the prevention of infection, which yielded a reduction in post-surgical mortality rate by 45%, as well as the use of dressings pre-treated with iodine to disinfect wounds.[5] This theory additionally contributed to the development of modern antibiotics.

HISTORY OF ANTIBIOTICS

It is in fact the Chinese who were the first known to use what is now referred to as 'antibiotics' more than 2,500 years ago, as they had realized that the application of moldy curd of soybeans successfully treated infections.[15] Of interest, Ernest Duchesne (circa 1897) was the first to observe that a biotic inhibitory effect [of *Penicillium glaucum*] in his dissertation for his doctorate degree.[16,17] His pivotal discovery was inspired through his observation of Arab stable boys who purposely stored saddles in dark, damp rooms to promote mold growth.[17] When he asked them why they performed this practice, they replied that the mold aided in healing the horses' saddle sores. Duchesne, intrigued that the mold could have a therapeutically beneficial effect on wounds (and presumably infections), prepared a solution with isolates from the mold and injected it into bacteremic guinea pigs and found that they all recovered.[17] When he submitted his dissertation on these observations to the Institut Pasteur in 1897, it did not even acknowledge receipt of his work because he was a 23-year-old *unknown*.[17]

Thirty-two years later in 1928, Scottish biologist Alexander Fleming [without knowledge of Duchesne's original work] came across what would become the world's first antibiotic when he returned to his lab after a holiday and noticed that many of his Staphylococcus culture dishes were contaminated with mold. He noted that there was an area around the mold colonies where the bacteria did not seem to grow. He proceeded to isolate the organism causing the mold [*Penicillium notatum*],[11] a discovery which led to the development of penicillin.[15]

Fleming was awarded the Nobel Prize in Medicine in 1945 along with two other scientists, Ernst Chain and Howard Florey, who together developed a purified form of penicillin.[16] Of interest, Fleming had also previously reported that a product in human tears could lyse bacterial cells, which he called lysozyme. This was the first example of an 'antibacterial agent' found in humans; unfortunately, lysozyme proved inefficacious as an antibacterial agent as it also destroyed nonpathogenic bacterial cells.[18]

These early discoveries proved to be catalysts for further advances in antibiotics. A soil microbiologist named Rene Dubos, recruited by the Rockefeller Institute in 1927 to find a soil microbe that could destroy the durable polysaccharide capsule of type III pneumococcal bacteria, isolated the capsule-degrading S III enzyme. Unfortunately, this discovery could not be used to treat sick patients as it was difficult to purify and detoxify. Dubos continued his search in the soil for other agents that could potentially treat other bacterial

infections including hemolytic streptococci, the Gram-positive bacteria of rheumatic fever that infected both Dubos and his first wife.[19] In 1939, he observed that the saprophyte *Bacillus brevi* could destroy most Gram-positive organisms.[11,19] One of the polypeptides in the active substance was a bacteriostatic agent named gramicidin (which Dubos' colleague Rollin Hotchkiss referred to as "the gentle protector"). Hotchkiss so named it as it inhibited cell growth in this subgroup of bacteria, while the other polypeptide tyrocidine ("roughneck") attacked the membranes of both Gram-positive and Gram-negative bacteria.[20] Intravenous administration of gramicidin proved to be too toxic for the treatment of systemic infections, but topical gramicidin proved to be highly efficacious in the treatment of wounds and ulcers during World War II, and is still used today in some current topical antibiotic ointments.[19]

The race was on to discover even more antibiotics, including ones with Gram-negative class bioactivity with the aim of conquering tuberculosis [a disease classified at the time under the umbrella category of the 'consumption' during the 19th and early 20th centuries], as it was a widespread public health concern, especially among the urban poor.[21] In 1944, two American microbiologists saw this dream to fruition; Selman Waksman and Albert Schatz isolated streptomycin from the actinomycete (a bacteria-like organism found in the soil), *Streptomyces griseus.*[2] Initially, only Selman Waksman was recognized as the discoverer of this antibiotic, but one of his graduate students Albert Schatz argued this crediting and filed a lawsuit against Waksman in 1950, asking for recognition for his role in the discovery as well as a portion of the royalties, a claim settled later, out-of-court.[21] Streptomycin, the first antibiotic in the aminoglycoside class, revolutionized the treatment of tuberculosis.[22] The clinical trial that studied streptomycin versus the current treatment standard of the time (bed rest) was interestingly also one of the first randomized controlled trials.[22] Selman Waksman, who also discovered neomycin, went on to be awarded the Nobel Prize in Medicine in 1952.[23]

TRIPLE ANTIBIOTIC THERAPY

Neomycin, an aminoglycoside produced by the growth of *Streptomyces fradieae*, is a common topical antibiotic effective against Gram-negative organisms including *Escherichia coli, Proteus sp., Klebsiella sp.*, and *Enterobacter.*[24,25] It works by binding with ribosomal RNA and inhibiting protein synthesis. Neomycin is commonly compounded with bacitracin in addition to polymyxin B sulfate for a broader antimicrobial action, together providing coverage against: *Staphylococcus aureus,* streptococci including *Streptococcus pneumonia, Escherichia coli, Haemophilus influenza, Klebsiella-Enterobacter* species, *Neisseria* species and *Pseudomonas aeruginosa*. Specifically, bacitracin, active primarily against Gram-positive organisms, interferes with the dephosphorylation of C55-isoprenyl pyrophosphate, thereby inhibiting the synthesis of the peptidoglycan bacterial cell wall.[26]

HISTORY OF BACITRACIN

In June 1943, the Tracey I strain of *Bacillus subtilis* was isolated from damaged tissue debrided from a compound fracture of a 7-year-old girl named Tracey.[27,28] This non-toxic and relatively heat-stable organism was found to have secreted into its growth medium a powerful antibiotic with a broad spectrum of action [aptly named 'bacitracin'].[28,29] In 1948, the Surgeon General's office requested interested parties to delineate specifications for the use of bacitracin especially in regards to potency and toxicity.[28,29] By the time everyone met in March 1948, 200 surgical infections had been locally treated with bacitracin with "favorable results" in 87% of these cases, many of which were resistant to penicillin.[28,29] "The dermatologists were particularly impressed with the high rate of cure and low incidence of allergic reactions to bacitracin [topically] as contrasted with penicillin and sulfonamides".[28]

The success of systemic bacitracin in the treatment of pneumonia, syphilis, amebiasis and neurologic infections were subsequently reported. As experience grew on using this antibiotic, it was noted that its systemic effectiveness against bacteria was in direct proportion to its concentration,[28,30] however, as higher doses were used, there became increasing evidence of nephrotoxicity.[29]

Because of its nephrotoxic profile, bacitracin was slated to become primarily a topical antibiotic and proceeded to be efficacious in the treatment of local skin and surgical infections, suppurative conjunctivitis and corneal ulcers.[31,32] Initial reports on topical use indicated a well tolerated safety profile without evidence of toxicity and minimal allergenicity.[27,29] Meleney et al did however warn that there was the potential for toxicity and hypersentivity with increased use.[29]

TRANSITION OF BACITRACIN TO ALLERGEN

Currently, bacitracin is readily available over the counter and in use in a wide variety of topical and ophthalmic antibacterial preparations, as well as in cosmetics and animal feed additives.[33,34] It is interesting to note that, because of the high sensitization rates to neomycin (which was reported to be as high as 34% in chronic venous insufficiency patients and rivaled nickel for the most common allergen in tested populations for the last 30 years),[35] there was a strong interest in finding an effective alternative. Bacitracin's reported lower rates of sensitization in comparison to neomycin (7.9% vs. 11.6%),[36] led it to quickly become one of the most prescribed topical agents in the United States,[34] with widespread use in emergency departments and operating rooms across America and Europe.[37]

In 1992, the U.S. Department of Health and Human Services reported that it had climbed to rank as the 7th most frequently prescribed medication among the 34 million injury-related ER visits.[34,38] This increase in utility paralleled its rise to the status of a top allergen.

Reporting on data from 1998 to 2000, the Mayo Clinic Contact Dermatitis Group reported bacitracin to be 8th most common allergen with 8.7% of 1,321 patients patch testing positive.[39] During the same time period, the North American Contact Dermatitis Group reported bacitracin to be the 9th most common allergen by revealing a positive patch test result in 9.2% of 5,812 patients tested between 1998 and 2000,[40] which was a significant increase from 1.5% and 7.8% of positive reactions in patients tested from 1989 to 1990 and 1992 to 1994, respectively.[41] Furthermore, in another study, 73 of 858 (8.5%) of patients studied between 1995 and 2001 had clinically relevant positive patch test results to bacitracin.[42]

This emerging data contrasted significantly with prior data such as the Bjorkner et al study published in 1973 in which only three out of 1,000 patients (0.3%) experienced ACD.[43] Additionally, because of the apparent increase in observed sensitization rates, it became named as the 2003 Allergen of the Year by the American Contact Dermatitis Society.[34]

ALLERGY TO BACITRACIN

Because of its increased use, bacitracin has proven to be a significant inducer of ACD, as well as anaphylactic-type reactions.[34] The clinical presentation of allergy to topical bacitracin is varied and may include acute vesicular dermatitis or gradually worsening chronic dermatitis.

Bacitracin also has been commonly used in the treatment of infected leg ulcers. Thus, it stands to reason that in a 2004 study on frequencies of contact sensitivity in chronic leg ulcer patients, bacitracin was found to be clinically relevant in 24% of patients (13/54),[44] which approaches the overwhelming levels of neomycin sensitivity seen the same patient population of 34% reported in a 1979 study.[35]

Due to the hands-on nature of nursing in wound care, bacitracin has become an occupational allergen as well. In fact, the National Occupational Exposure Survey (NOES) reported 117,226 individuals in 23 different occupations to potentially have had exposure to bacitracin, and of these, 83,072 were registered nurses.[45] As expected, nurses have the highest incidence of ACD to this allergen.[46]

Numerous cases of allergic contact dermatitis[31,47] and anaphylaxis[48,49] have been reported with the use of topical bacitracin. There have also been reports of allergy to both bacitracin and neomycin (which are chemically and structurally dissimilar) in the same patients, but instead of representing true cross-reactivity, this is likely to be concomitant sensitivity because of their simultaneous use in products.[47,50] There have also been case reports of simultaneous contact allergy to neomycin, bacitracin and polymyxin (components of Neosporin).[51,52] Bacitracin and polymyxin may represent true cross-reactivity as they are both from *Bacillus* strains, although their structures are different.[50]

In terms of anaphylaxis, which is an immediate-type hypersensitivity reaction mediated by IgE, compared to the delayed cell-mediated hypersensitivity of allergic contact dermatitis (ACD), more than 31 cases have been reported in the literature secondary to both intraoperative and topical use[32] with the first case reported in 1967.[49]

It has been postulated that anaphylactic type reactions occur after topical therapy when the substance is able to enter the systemic circulation, for example, through ulcerated skin, excoriations, or skin-graft donor sites,[48] and probably accounts for the paucity of anaphylactic reactions seen during closed patch testing with bacitracin on intact skin.

It is important to note that many of these cases had previously reported allergic manifestations after using bacitracin prior to the episode when anaphylaxis was induced.[31,48] Anaphylaxis has been reported in a patient presenting to the emer-

gency room after topical bacitracin application on his new tattoo,[53] which highlights its wide utility

Because of the increasing number of reports documenting bacitracin allergy and near-fatal anaphylactic reactions, an interest to research bacitracin arose. Smack et al developed a large-scale, double-blind, randomized controlled trial prospectively studying white petrolatum versus bacitracin in 922 patients with 1,249 surgical wounds. While four patients treated with bacitracin ointment developed ACD, there were no documented cases of ACD or anaphylaxis with the white petrolatum and no statistically significant increase in infection or adverse effect to wound healing.[54]

Despite the multiple case series and studies reporting ACD to bacitracin, dermatologists have continued to administer topical bacitracin after surgical procedures. In a survey that assessed bacitracin ointment use as part of their post-biopsy/surgical wound care, 57 out of 64 dermatologists (89% response rate) responded, and an overwhelming 75% reported to apply bacitracin as part of their aftercare protocol.[48] Interestingly, of more than 300 articles reviewed [in *Dermatologic Surgery,* the *Journal of the American Academy of Dermatology* and *Archives of Dermatology*], less than 7% contained recommendations concerning surgical wound aftercare.[55] Notably, the articles that did specify aftercare, the overwhelming majority (72%) referred to the use of bacitracin.[55] Of note, alternatives to topical bacitracin ointment for clean surgical wounds such as white petrolatum have been recommended for use, due to their improved safety profiles and cost effectiveness over bacitracin.[54,55,56]

TESTING FOR BACITRACIN

To investigate allergy to bacitracin, patch testing is performed to bacitracin 20% in petrolatum on unbroken skin, with evaluative readings performed at both 46 and 96 hours, because a delayed type hypersensitivity reaction is well-documented in the literature.[31] In patients who may have symptoms or a history of an immediate hypersensitivity reaction, it has been recommended that they be observed for at least 1 hour after the patches are applied and that adequate resuscitation equipment be readily available.[33]

A lower incidence of bacitracin ACD has been historically reported in the United States as compared to Europe. For example, a 1967 study from Finland of topical antibiotic sensitization reported bacitracin ACD in 7.8% of 17,500 patients[57] while 200 dermatologists in America reported bacitracin sensitivity to be very rare in 196258 and a 1973 study reported it to be 0.3%.[43] ***Katz et al hypothesized that this phenomenon may be explained by the fact that delayed readings were not being performed in the Unite States as often as they were in Europe in routine patch testing, which could translate into 50% of the cases in the United States being missed, because it may take 96 hours for the positive patch test reaction to develop to bacitracin.***[31] Furthermore, Katz et al questioned using zinc-bacitracin as a screening agent, as it may have missed bacitracin allergy because it may be not have been as strong of a sensitizer as bacitracin is alone.[31]

VALUE OF THIS PATIENT CASE

Our patient tested positive to bacitracin, and discontinuation of its use and appropriate wound care (with compression and alginate dressings) at the University of Miami Wound Cure Center led to resolution of his venous ulcer. On a clinical note, in the setting of chronic wounds, bacitracin allergy may be a factor in delayed or absent healing.[59] When topical antibiotic ointments induce ACD responses in surgical wounds, they often appear indurated and inflamed, and it is not uncommon for physicians to mechanically administer systemic antibiotics.[34] Albeit, they often do stop the topical application, and the patient subsequently improves. ■

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