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Pharmaceutical Care Across the Continuum

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Choosing formulary antimicrobials? Your expertise should be the key

Merely considering cost-effectiveness can undermine effective choices

Cutting the costs of wholesale antimicrobials may not be the best way to save money for hospital pharmacy directors under the gun to make formularies cost-effective. It's an especially difficult challenge in the area of antimicrobials, where the market offers widespread choices coupled with the ongoing threats of resistance and nosocomial infections.

But there may be a more important bottom line than the financial one, according to **Joseph Paladino**, PharmD, clinical associate professor at State University of New York in Buffalo. "The cost of medication contributes less than 8% to overall health care costs," says Paladino, co-author of a recent study on the influence of fluoroquinolone purchasing patterns on hospital antimicrobial expenditures and on *Pseudomonas aeruginosa* susceptibility.

> **"When hospitals make a choice to use one drug over another on the basis of saving money, they may not actually get lower expenditures."**

"Antimicrobials are 20% of that, so antimicrobials constitute 2% of overall health care costs," he says. "When we study the costs of treating an infected patient, the antimicrobial is 2.5% to 5% of treatment costs for a hospitalized patient. That is a small part of the overall treatment costs. So it is wrong to look only at the cost of the drug."

The fluoroquinolone study looked at the influence of using ofloxacin in place of ciprofloxacin on hospital fluoroquinolone expenditures and total antimicrobial expenditures. It also looked at how this affected the fluoroquinolone susceptibility of *P. aeruginosa.*

The study found that hospitals using ciprofloxacin as their primary fluoroquinolone experienced greater savings in antimicrobial expenditures than institutions primarily using ofloxacin. In addition, the use of ciprofloxacin was associated with lower rates of ciprofloxacin-resistant

P. aeruginosa despite the fact that ofloxacin has been marketed as a lower-cost alternative to ciprofloxacin.

"When hospitals make a choice to use one drug over another on the basis of saving money, they may not actually get lower expenditures," says Paladino. "Cost-shifting will occur as physicians turn to other medications. Also, using a less-effective medication will increase the chance of bacterial resistance, and that, in turn, causes a patient to stay sicker for a longer period of time, and that costs more money and potentially exposes them to more infections. Outpatients go back to the doctor and the pharmacy more often, and inpatients stay in the hospital longer. Also, there's an increase in mortality as well as morbidity, so the human cost is measurable."

Look for the true cost

Paladino says hospitals should look at the cost of treating the patient, not the cost of the drug. The appropriate outcome measure, he says, is how well the drug is working.

"The cheaper drug may have expensive side effects. Maybe it doesn't work as quickly, so the patient stays sicker longer and uses more health care. We need cost-effectiveness in the real sense. The difference between economics and mere cost-containment is based on patient outcomes, and we can put a figure on that. Failure is more expensive than success, and success rewards good patient care."

Another part of this equation, Paladino says, is the importance of optimizing doses for individual patients through the use of pharmacokinetics and pharmacodynamics.

"I think the future value of pharmacists is grounded in this clinical contribution, rather than distributive functions or warehouse stocking of drugs. Pharmacists must get into this for their own survival. If they believe their only job is to cut costs, they will be asked to cut more and more, and inevitably, the administrator is going to be disappointed when there is no more opportunity to cut costs. So this is for their own survival. Also, they are not demonstrating their value if they do this. The only way to show value is to show the positive impact of patient outcomes. We need to take clinical pharmacy to the bedside."

Develop an infection control plan

According to the Centers for Disease Control and Prevention in Atlanta, nosocomial infections affect some 2 million patients a year in acute care facilities in the United States at an annual patient care cost of more than $3 billion. Those infections are difficult to treat because the microorganisms that cause them are becoming increasingly resistant to traditional antimicrobial agents.

CDC epidemiologist **Lennox Archibald**, MD, says preventing the transmission of resistant pathogens in hospitals is crucial. "You need infection control guidelines to do this. Hospitals should have infection control committees with representatives from all departments: doctors, nurses, pharmacy, everyone. And there should be a concerted plan. The committee must identify common infections, develop surveillance methods, and get feedback to those who need to know."

Archibald cites a recent survey that found getting feedback to surgeons actually reduces surgical wound infections.

According to the CDC, studies indicate a third of nosocomial infections could be prevented by well-organized infection control programs, but only 6% to 9% actually are prevented. One of the stated goals of the CDC's hospital infections program is addressing the discrepancy between what can be prevented and what is being prevented.

"Another key is to avoid triggering events, exposures to certain antimicrobials," Archibald says. "Be sure to use the best specific antimicrobial. Be aware that the cheapest isn't necessarily the best. Consideration while prescribing is key. Don't give the patient an antibiotic if there is a

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chance the condition is caused by a virus."

Lance Peterson, MD, professor of medicine and pathology at Northwestern University in Chicago, says there are several considerations when choosing an antimicrobial.

"You need to decide which class to use and then which is the optimal agent. And that really depends on where you are, whether you are somewhere with high levels of resistance. You need to know how much resistance there is in your area. Then you must decide whether the infection is truly bacterial and pick the appropriate specific agent."

Experts say those factors also must be considered when choosing which antimicrobials to include in the formulary and which to cut.

Patient education also is important. Archibald says patients, especially parents concerned about their children, still pressure physicians to prescribe an antibiotic when it's not indicated. Pharmacists can help educate parents about resistance, he says.

Patients also need to know how important it is to take antimicrobials properly, as prescribed. They should be advised to take an entire prescription course and not save the medication to self-prescribe later.

New weapons in the arsenal

Bayer Corporation's Avelox (moxifloxacin hydrochloride) has been approved for use against respiratory tract infections, including acute bacterial exacerbations of common bronchitis, community-acquired pneumonia of mild to moderate severity, and acute bacterial sinusitis. The U.S. Food and Drug Administration approved Avelox on Dec. 13, 1999.

Bayer officials say the drug helps fill a void created by the pathogens' increased resistance to commonly prescribed antibiotics. For now, it will be used mainly in outpatient settings because there is not yet an IV formulation.

"Because of resistance to commonly used agents, there is growing concern about choosing the correct antimicrobial," says Peterson. "Practitioners are turning to quinolones when resistance is a factor. And the unique thing about Avelox is that it has two or three initial targets, which makes it harder for the organism to become resistant."

Peterson says quinolones are particularly appropriate for older patients who have underlying diseases or true bacterial pneumonia, as well as for patients in densely populated urban areas where there are high levels of resistance. He says if you are going to use a fluoroquinolone, Avelox is least likely to cause resistance, and it is up to physicians to help keep it that way.

"If you don't use it in patients who don't need antimicrobials, and you use the correct dose, and use it only where you are sure you have a bacterial infection, you will delay resistance. You can't prevent resistance, but you can delay it," he explains.

Avelox was studied in clinical trials involving nearly 8,000 patients. Bayer says the drug is safe and well-tolerated and does not cause photosensitivity or serious liver toxicity. The most common adverse reactions were nausea and diarrhea.

Avelox is contraindicated in patients with a known hypersensitivity to moxifloxacin or any quinolone antimicrobial. It also should be used with caution in patients with known or suspected nervous system disorders or predisposition to seizures.

The recommended dosage for Avelox is 400 mg daily for five or 10 days, depending on the specific infection. Bayer says it is not metabolized by the enzyme system that breaks down many other drugs and therefore can be taken safely with a wide variety of other medications. In addition, it has a half-life of 12 to 14 hours and does not need to be taken at any particular time, nor does it need to be taken with meals.

Peterson says the drug is a good candidate for a managed care formulary. "I don't think it is priced higher than other agents, and the data presented to the FDA suggest quinolones decrease mortality and hospitalization. The Avelox data also indicated lower hospitalization rates, and keeping patients out of the hospital decreases costs."

Last year, the FDA also approved the injectable antibiotic quinupristin-dalfopristin (Synercid I.V., Rhone-Poulenc Rorer) for use against serious infections associated with vancomycin-resistant *Enterococcus faecium* (VRE) bacteremia, making it the first streptogramin approved for marketing in the United States. Synercid works by inhibiting bacterial protein synthesis, thereby eradicating the infection.

The urgency of providing safe and effective treatment for VRE allowed quinupristin-dalfopristin to qualify for approval under the FDA's accelerated approval process. The agency based its decision on a surrogate marker — the drug's ability to clear VRE from the bloodstream —

rather than on the more rigorous requirement of clinical benefit.

Synercid also is labeled for use in the treatment of complicated skin and skin-structure infections caused by *Streptococcus pyogenes* and methicillin-susceptible *Staphylococcus aureus.*

The recommended dosage is 7.5 mg/kg administered every eight hours for treatment of VRE infections and every 12 hours for skin and skin-structure infections.

Quinupristin-dalfopristin first went before the FDA's anti-infective drugs advisory panel in 1998. The committee's deliberations emphasized the need for more antimicrobials active against VRE. The drug was studied worldwide in clinical trials and an FDA-sanctioned emergency-use program. Possible side effects include local irritation, muscle aches, and general malaise.

Gram-positive bacteria such as *E. faecium* and *S. aureus* are considered serious public health threats because of their resistance to commonly used antibiotics. In addition, they are among the most common causes of nosocomial infections.

He also says he's seen limiting resistance become a real priority for physicians and patients over the past five years, which is an accomplishment if you consider the time span.

"These organisms have been around for a very long time, and we've only had the ability to manage them for a short time. So things have changed a lot. Physicians and patients are much more aware of the issue and open to talking about it. I think things have changed a lot, and limiting resistance is now a priority and a major concern." ■

SOURCES

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ISMP, AHA lead national program on drug safety

Spotlight focusing on medication error

The president of the Institute for Safe Medication Practices (ISMP), **Michael Cohen**, MS, FASHP, says he's very happy that the issue of medication safety has come to the forefront of public knowledge, helped largely by headlines in major media outlets over the past few months.

Cohen was at the White House Dec. 7, along with American Hospital Association president **Dick Davidson**, to announce a joint national initiative to help hospitals assess and improve medication safety.

He explains that a series of events led up to the announcement, including a report by the Institute of Medicine that contained this headline-grabbing statistic: Up to 98,000 deaths a year in the United States are caused by errors, including medication mistakes and other adverse drug events. The report also estimated that medical errors cause more deaths than breast cancer, traffic accidents, and AIDS combined.

Captivating the national media

During the last few months, the statistics resulted in high-profile articles in *TIME* magazine, *The New York Times*, and the *Wall Street Journal*, among other mainstream news organizations.

Cohen says that report, along with several highly publicized hospital accidents, seemed to galvanize the public, the U.S. Congress, and several major foundations. All parties have agreed that preventing medication errors is a crucial component in improving health care.

That in and of itself is nothing new. Agencies such as ISMP, the National Patient Safety Partnership, and the Institute for Healthcare Improvement have been studying medication safety for quite some time. Cohen says pharmacists have always talked about medication errors among themselves, but they limited their conversations to health professionals, for fear of alarming the public or breaching confidentiality. In retrospect, he says, perhaps pharmacists did not do a good enough job of bringing the issue to the public.

"When we did talk to patients about medication errors, we were criticized by hospital administrators. They accused us of scaring patients, and

we bought into that. But now the medical establishment has gotten behind it and it has gelled all at once, and that is good news for all Americans."

"The issue of medication errors has been at the forefront in a lot of individual places, but the Institute of Medicine report pulled things together and served as a catalyst to unify all the agencies," says **Rick Wade**, AHA senior vice president. "We were presented with the opportunity to unveil something we'd been working on for months with ISMP. The timing was coincidental with the Institute of Medicine report. The White House was aware of what we were doing and asked us to join in the unity on a national scale."

The AHA takes action

The first step in that campaign came in the form of a letter Davidson sent to hospital CEOs, advising them of the joint initiative. The letter included successful practice recommendations compiled from several respected sources. It is posted on AHA's Web site at www.aha.org.

The recommendations include:

• fully implement unit dose systems that include systems for labeling and order screening;

• limit the variety of doses and equipment;

• develop special procedures and written protocols for high-alert drugs;

• ensure the availability of up-to-date drug information;

• educate all clinicians involved in the medication administration process about ordering, dispensing, administering, and monitoring medications;

• educate patients about their medications and how to use them safely;

• ensure the availability of pharmacy expertise by having a pharmacist on call if the pharmacy does not operate 24 hours a day. Also, make pharmacists more visible in patient care areas. Consider having them make rounds or enter orders directly into computer terminals on patient care units;

• standardize prescribing and communication practices.

Other recommendations focus on long-term changes that require substantial modifications to existing systems. Many focus on computerization in the physician order-entry and pharmacy dispensing processes, such as using machine-readable codes (i.e. bar coding) and computerized drug profiling in the pharmacy. One suggestion is instituting 24-hour pharmacy service.

Drug Safety Web Sites

- ❑ **American Hospital Association:** www.aha.org
- ❑ **American Society of Health-System Pharmacists:** www.ashp.org
- ❑ **Institute of Medicine:** www.national-academies.org
- ❑ **Institute for Safe Medication Practices:** www.ismp.org
- ❑ **National Coordinating Council on Medication Error Reporting and Prevention:** www.nccmerp.org
- ❑ **National Patient Safety Foundation:** www.npsf.org

To get started, the advisory suggests hospitals organize a senior management team consisting of the CEO, chief medical officer, chief nurse executive, director of pharmacy, risk manager, director of information systems, and others to review and discuss the recommendations.

The advisory also recommends hospitals review their policies and procedures for reporting and investigating errors and create a nonpunitive culture so errors can be thoroughly evaluated and corrected. Executive behavior also counts; leaders are advised to declare the goal of safety to be a specific priority and to keep the board and organized medical staff up-to-date on what actions they are taking.

The letter also advised CEOs to make sure their staff "is aware of the tremendous amount of information available from organizations like ISMP, the Institute for Healthcare Improvement, the FDA, the National Coordinating Council on Medication Error Reporting, The Massachusetts Hospital Association, The National Patient Safety Partnership, The National Patient Safety Foundation, The American Society of Health-System Pharmacists and the American Society for Healthcare Risk Management." **(Web sites for several of the organizations mentioned are listed in the box, above.)**

The initiative's next step is to develop a "Medication Safety Awareness Test" that surveys hospitals' current status and future progress on medication error prevention. Cohen says it will help hospital CEOs look at systems directly so they can assess risks. He hopes over time they will continue to reassess and make changes as needed.

"Hospitals in this country range from 10-bed facilities to the most sophisticated medical centers in the world," says Wade. "Information and tools vary. This self-assessment tool will be very useful to many members in helping them look at their strengths and weaknesses."

The ISMP / AHA campaign also aims to:

• track implementation of the practices for reducing and preventing errors within the hospital and health system field;

• work with national experts to develop a nonpunitive model for a medication error prevention process;

• serve as a clearinghouse of information and resources for the hospital field on medication errors.

"We think it is great news that we have a voice directly to hospital CEOs," says Cohen. "They have been contacting us and asking us to come out to their facilities. They want to know what to do about medication errors; it has become a major issue for them. We hope to communicate with CEOs on a regular basis to alert them to problems or discuss our thoughts on how to create a nonpunitive reporting system and how to process and analyze error reports."

As the partnership progresses, the model reporting system is going to be of crucial importance. The Institute of Medicine's report recommends the establishment of a mandatory standardized public reporting system for all errors leading to serious injury or death, in an effort to foster knowledge about treatments and systems that lead to such mistakes. Currently, about one-third of states have mandatory reporting systems. In addition, the IOM said those error reports should be available to the public.

Clearly, making such information public raises concerns about confidentiality, liability, and punishment, concerns Wade says must be addressed.

"There are criteria for mandatory reporting. It cannot be punitive or a conduit for malpractice lawyers to go trolling," he says. "In order for it to work, people must not be afraid to report. Our hospitals already know things happen that don't get reported because people are afraid of punishment. It also must include resources for analysis and the use of that analysis to help prevent future errors. It can't just collect information; it must include a timely way to look at that information and help at the point of patient care.

"Also, there must be an avenue for making this information available to the public in a way that informs people something is being done. That is what the public wants to know. People don't want to see lives ruined for a mistake, they want to know the mistake won't happen again."

The message in the Institute of Medicine's report is also clear: Punitive action and blaming individuals does not reduce medical errors. The only way to increase safety is to focus on hospital systems.

The report also recommends the creation of a patient safety center within the Department of Health and Human Services. The center would collect and distribute medical errors and models for the prevention of errors; it would be similar to the federal agencies that monitor airline and workplace safety.

The federal government already is taking some action. President Clinton's health care quality task force has been analyzing the Institute of Medicine study, and the White House has announced that the 300 private health plans participating in the Federal Employee Health Benefits program will be required to institute quality improvement and patient safety initiatives. Clinton also signed legislation providing $25 million for research to improve health care quality and prevent medical errors and directed his budget and health care advisors to develop quality and patient safety initiatives for this year's budget. In March, a national conference with state health officials is scheduled to convene to promote the best practices in preventing medical errors.

In his Rose Garden remarks in December, Clinton said, "Ensuring patient safety is not about fixing blame. It is about fixing problems in an increasingly complex system; about creating a culture of safety and an environment where medical errors are not tolerated."

Those were welcome words for Cohen. "There isn't one pharmacist who hasn't been aware of this problem," he says. "And we couldn't have gotten this far without the bravery of those who were willing to report errors. They did this for no other reason than pure altruism." ■

SOURCES

- **Michael R. Cohen**, RPh, MS, President, Institute for Safe Medication Practices, Warminster, PA. Telephone: (215) 947-7797.
- **Rick Wade**, Senior Vice President, American Hospital Association, Washington, DC. Telephone: (202) 638-1100.

Drug aids care of diabetic peripheral neuropathy

Case study coincides with Wyeth clinical trials

Eleven patients with diabetic peripheral neuropathy treated with Wyeth-Ayerst's antidepressant venlafaxine (Effexor) experienced nearly 100% pain reduction by 14 days, according to endocrinologists in private practice in Oklahoma.

Wyeth has been testing the drug for this indication and recently has begun Phase II trials, although no trial results are being disclosed, according to a company spokesperson. The drug was approved for depression in 1997. An indication for generalized anxiety disorder was added a year later.

The physicians report no side effects among the small population treated. Side effects have hampered effective treatment with traditional tricyclic antidepressive agents, says **Marion Parrott**, MD, vice president for clinical affairs for the American Diabetes Association.

"Neuropathy is very difficult to treat. At this point, treatment is trial and error," she says. "In the common foot pain, it can lead to foot ulcers and, in some cases, amputation. It can be extremely painful."

Endocrinologist **Jonathan Davis**, MD, in private practice in Edmond, OK, says one of his patients, a 41-year-old male with mild nocturia being treated with glipizide, developed severe burning paresthesia not relieved by codeine, acetaminophen, or amitriptyline. At five days on 75 mg of venlafaxine, 95% relief was reported.

Success leads to further study

Following the initial patient's success, Davis put four other patients (all men, ages 35 to 71) on 37.5 mg to 75 mg daily, resulting in 75% to 100% relief by 14 days.

"They had been [unsuccessfully] treated with oral agents . . . that are commonly used for neuropathy. It's unlikely pain relief was due to spontaneous remissions or placebo effect because neuropathy recurred when medication was stopped in two patients. It is also unlikely that the relief was due to mood alterations because the relief occurred too rapidly," says Davis.

Venlafaxine inhibits the reuptake of serotonin and norepinephrine and, to a small extent, dopamine. Unlike the tricyclics, the drug does not block muscarinic, histaminergic, or andrenergic receptors, which Parrott says lead to side effects such as dry mouth, hypertension, and dizziness, hampering treatment for neuropathy.

Topical pain medications and anti-seizure drugs also have been used for diabetic neuropathy.

Parrott says up to 60% of diabetics experience neuropathy due to elevated blood sugar, which is most commonly manifested as foot pain but also can result in unregulated blood pressure or heart rate, muscle weakness, tingling sensations in the extremities, stomach or bladder disorders, or sexual dysfunction. "The most important thing in the long run is to control the blood sugar," she says. "But that can be difficult. We know the bonding of glucose to the nerve tissue causes the pain and that antidepressants can raise the pain threshold."

Venlafaxine is cautioned for use in patients with high blood pressure, heart, liver, or kidney disease, and in patients with a history of seizures. ■

New FDA Approvals

These drugs and/or new indications have received final approval from the U.S. Food and Drug Administration:

✔ **Breast cancer therapy Ellence (epirubicin hydrochloride) by Pharmacia & Upjohn.** Indicated for adjunct therapy in cases of axillary node presence following surgical removal of primary breast cancer, approval of the injectable therapy followed two combination clinical trials resulting in heightened survival and decreased risk of relapse. The trials involved cycles of epirubicin in combination with fluorouracil and cyclophosphamide compared to the latter two drugs in combination with methotrexate.

✔ **Organ rejection treatment Rapamune (sirolimus) by Wyeth-Ayerst.** Indicated specifically for renal transplant therapy, approval is for combination use with cyclosporine and corticosteroids. The drug's mechanism inhibits the activation of kinase involved in cell cycle progression toward the suppression of cytokine-induced T-lymphocyte proliferation. Approval follows a placebo-controlled trial of 576

patients resulting in rejection rates of 30% on the combination vs. 47.7% in the placebo group. Adverse reactions from trials included increased cholesterol and triglyceride levels, hypertension, and rash. ■

IN THE PIPELINE

The following drugs are still in clinical trials:

✔ **Antiangiogenesis therapy Endostatin by EntreMed, Inc.** Following submission of an Investigational New Drug Application in June, the FDA has approved clinical trials for the drug, one of an emerging class of protein-derived therapies aimed at inhibiting the growth of blood vessels in cancerous tumors. Phase I trials are scheduled at Brigham and Women's Hospital, Massachusetts General, and at the universities of Texas and Wisconsin.

✔ **Ovarian cancer investigative treatment yttrium 90 radiolabeled CEA-Cide by Immunomedics, Inc.** The FDA has granted orphan drug status to the drug as clinical trials begin. The monoclonal antibody is formulated to treat carcinoembryonic antigen expressed in solid tumors. The drug is currently in trials involving colorectal, pancreatic, and thyroid cancers.

✔ **Epstein-Barr virus vaccine EBV by Aviron/ Smithkline Beecham.** Phase I trials have been completed for the IM injectable single surface antigen testing the safety of immunogenicity in 67 subjects. The trial showed high safety and tolerability levels in patients regardless of prior exposure.

✔ **Stem cell transplant antirejection treatment T cell-HDM by Eligix.** The FDA has approved Phase III trials for the drug, which is formulated to block the development of graft vs. host disease (GvHD) arising after leukocyte infusion. The drug works by depleting immune T cells causing GvHD. The treatment is planned for use in conjunction with donor leukocyte infusion procedures that induce remission in cases of leukemias and related hematologic malignancies after previous failure on chemotherapy or alpha interferon. ■

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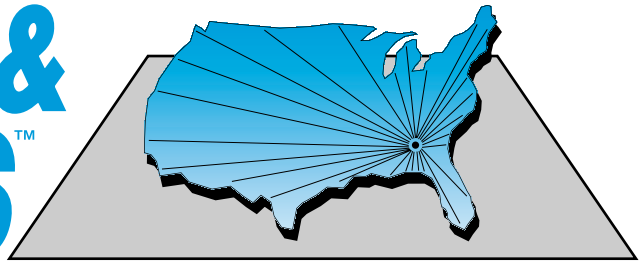

Understanding antimicrobial desensitization protocols

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Introduction

An understanding of the different types of hypersensitivity reactions is essential to proper usage of desensitization protocols. Hypersensitivity reactions are generally classified into four major categories: Types I, II, III, and IV.

The life-threatening reactions of the Type I hypersensitivity are often referred to as anaphylactic reactions. These reactions involve a typical immune response whereby an antigen enters the body and is identified as foreign. If the patient is antigen naïve, symptoms may not be expressed for one to two weeks, if at all. Otherwise, the reaction is immediate. In response to this antigen, humans will isolate each antigenic particle and present this antigen via antigen-presenting cells (usually macrophages or T lymphocytes) to T lymphocytes.

For Type I reactions, T lymphocytes initiate the clonal expansion of B lymphocytes into exaggerated immunoglobulin E (IgE)-producing plasma cells on primary exposure. On secondary exposure, IgE bound to mast cells and eosinophils attach to antigen, and mast cell degranulation ensues. Degranulation releases cytokines (cellular communicators) like chemotactic factors (such as NCF, LTB4, PAF, ECF-A) and spasmogens (histamine, SRS, PG, PAF), which result in the clinical picture of anaphylaxis.

Types II and III hypersensitivity reactions are mediated by IgF. Both of these reactions are more delayed in their presentation and are usually less severe than Type I reactions in that they do not cause immediate death. The mechanism of these reactions is related to antibody destruction of drug-bound to cell-bound or solubilized protein. This combination of drug and protein is called a hapten. For example, when IgG is formed against penicillin bound to a protein on a red blood cell's surface, the antibody destroys the cell causing hemolytic anemia.

Type II, III, and IV reactions occur on secondary exposure to a drug. Type IV reactions are usually less severe and often can be treated while the offending agent is continued.

Tolerance to an antigen is desirable when exposure is frequent or necessary. When a patient requires treatment with a pharmacological agent to which the patient is hypersensitive, tolerance may actually be critical to patient survival or cure of the infection. Immunologic tolerance to a drug (antigen or hapten) can be defined as one's ability to endure sustained exposure to the drug without adverse events. In a patient who has an "allergy" or "hypersensitivity" to a drug, tolerance can be achieved by decreasing the sensitivity of B or T lymphocytes.

Induction of tolerance in T or B lymphocytes can be achieved by four common methodologies. Clonal abortion is the loss of the specific B-lymphocyte clone that recognizes the antigen in question. This is easiest to achieve in a neonate for B lymphocytes when the B cells are less developed and less sensitive to antigen exposure. T lymphocytes respond equally well at all ages in life to clonal abortion. Clonal abortion is achieved by long-term, low-dose exposure of the antigen.

A second methodology is clonal exhaustion, which involves depletion of the clone's metabolic capabilities leading to cytokine and antibody depletion or exhaustion. Exhaustion can also be acquired again by long-term, low-dose exposure of the antigen.

Functional cell deletion is a recent phenomenon available due to molecular biology.

Table 1

Oral Penicillin Desensitization Protocol

Preparation of Oral Penicillin Desensitization Solutions

Solution 1	400,000 units/f mL	
Solution 2	[2 mL solution 1 + 14 mL sterile water]	10,000 units/mL
Solution 3	[2 mL solution 2 + 18 mL sterile water]	1,000 units/mL

Dosing and Administration Schedule

Time (in hours)	Penicillin (oral units)	Dose (mL)
0	100	0.1
0.25	200	0.2
0.5	400	0.4
0.75	800	0.8
1	1,600	1.6
1.25	3,200	3.2
1.5	6,400	6.4
1.75	12,000	12
2	25,000	25
2.25	50,000	50
2.5	100,000	100
2.75	200,000	200
3	400,000	400
3.25	800,000	800

Development of antibodies to specific cell lines (e.g. OKT3, OKT8) allows for the deletion of one or multiple cell lines within animals.

Finally, T-suppressor cell induction is also effective, but it is much slower than other methods. Induction of T-suppressor cells to a specific T lymphocyte's activity can suppress T-helper cells or B lymphocyte responses, yet it requires continued presence of the antigen and is also short-lived after antigen is removed.

A method not commonly used is blockage of antibody secretion by plasma cells. Suppression of both B and T lymphocytes is also obtained by the use of immunosuppressive agents. Cyclophosphamide would effectively induce tolerance by suppressing lymphocyte cellular function. However, in a patient with an infectious disease, the use of an immunosuppressive to induce tolerance to an anti-infective is undesirable.

An understanding of the pharmacodynamics of tolerance is critical for pharmacotherapeutic induction of tolerance or "desensitization." Administration of a slow upward titration of antigen controls mast cell degranulation. Degranulation should occur slowly, leading to milder or undetectable response to cytokine expression. This methodology induces T-suppressor cell induction and is probably the safest technique to use for most desensitizations. Methods that induce induction of B-lymphocyte tolerance can take four to 15 days and require two- to three-log higher doses of antigen. The duration of desensitization is at least as long as antigen presence with T-suppressor cell induction. In addition, T-lymphocyte tolerance persists longer than B-lymphocyte tolerance.

The goal of therapy is to block T-lymphocyte-dependent, B-lymphocyte response and exaggerated IgE expression. T-suppressor lymphocytes will also become class specific and prevent B-lymphocyte clonal expansion, antibody production, and thereby mast cell degranulation.

The desensitization protocols presented in this article deal primarily with IgE-mediated hypersensitivity reactions to common antimicrobial agents. It is not acceptable to extrapolate these published protocols to Type II and III reactions. Type IV reactions do not need desensitization.

Materials/methods

A MEDLINE search was performed using "antibiotics," "desensitization," and "protocol" as key terms. The identified articles were obtained, and a second search through their bibliographies was performed. All articles were then classified according to the class of antimicrobial agent and the route of administration for desensitization. For each reported class of antimicrobial, a desensitization protocol was identified or derived from these reports. When more than one desensitization protocol was

identified, all authors reviewed the protocols, and a consensus was reached about the most effective, safest, and most convenient protocol. In some instances, slight variations in the original protocol were made, primarily to simplify the preparation of desensitization solution(s).

Beta-lactam antibiotics (penicillins and cephalosporins)

Many desensitization protocols have been published for use in various patient populations with a positive penicillin skin test to the major (penicilloyl) or minor (penicilloic acid, penillic acid) determinants. Basic formulas for desensitization begin with very small oral dosages (i.e. 100 units of penicillin G, 60 mcg of carbenicilllin, 60 mcg of nafcillin; note that 1 mg penicillin G = 900-1050 penicillin G units [USP] [**see table 1**]) and double the dose every 15 minutes until 800,000 units is reached, then change to parenteral administration and advance until a full therapeutic dosage is achieved. Successful desensitization has been reported in 33 of 33 patients when using this approach.

Similar results have been reported when employing this protocol, with 25 of 26 patients successfully desensitized. The oral route is preferred, since a fatal reaction is extremely rare due to degradation of preformed conjugates before absorption and an incremental rise in blood levels resulting in univalent IgE interaction.

A rapid IV protocol for desensitization to a variety of penicillins and cephalosporins used an extremely small initial dosage (i.e. 0.5 mcg) infused over 20 minutes and increased the dose tenfold every 30 minutes until a full therapeutic dosage was reached.

Successful desensitization was achieved in 12 patients: four receiving ticarcillin, four receiving penicillin G, and one each receiving oxacillin, piperacillin, cefamandole and cephalothin. Two patients did experience delayed reactions requiring treatment with corticosteroids or antihistamines. However, no patient required cessation of the desired therapy (**table 2**).

A protocol effective for IV cefotaxime desensitization was used in one patient with severe lumbar osteomyelitis. The protocol began with a 1 mg / day dose that was doubled daily until a 2 g q12h schedule was achieved by day 14. This titration is unnecessarily slow, compared with penicillin protocols,

Table 2

Intravenous Penicillin Desensitization Protocol

Preparation of Intravenous Penicillin Densensitization Solutions

Solution 1	500 mg per 50 mL (a)(10 mg/mL)	
Solution 2	[5 mL solution 1 + 50 mL diluent]	0.9 mg/mL
Solution 3	[5 mL solution 2 + 50 mL diluent]	0.08 mg/mL
Solution 4	[5 mL solution 3 + 50 mL diluent]	0.007 mg/mL
Solution 5	[5 mL solution 4 + 50 mL diluent]	0.0007 mg/mL
Solution 6	[5 mL solution 5 + 50 mL diluent]	0.00006 mg/mL
Solution 7	[5 mL solution 6 + 50 mL diluent]	0.000006 mg/mL

(a) stock solution 1 prepared by solubilizing > 1 g of antibiotic with diluent to a final concentration of 10 mg/mL

Dosing and Administration Schedule

Solution (#)	Time (hr:min)	Concentration of infused solution (mg/mL)	Infusion rate (mL/hr)	Total dose delivered (mg)
7	0:0	0.000006	167	0.00033
6	0:20	0.00006	167	0.0033
5	0:40	0.0007	167	0.039
4	1:00	0.007	167	0.39
3	1:20	0.08	167	4.4
2	1:40	0.9	167	49.5
1(b)	2:00	10	150	500

(b) after solution 1 infused, patient can receive remainder of dose

because it does not correlate with the pharmacokinetic properties of the drug in question, and therefore a much faster desensitization should be possible.

Additionally, most patients requiring treatment with this or similar type agents could not wait for such a prolonged period of time to achieve a therapeutic dosing regimen.

Sulfonamides (trimethoprim-sulfamethoxazole)

Multiple reports address the issue of trimethoprim-sulfamethoxazole desensitization. As one would expect, the majority of concern for hypersensitivity and the need for such desensitization occurs most often in patients with HIV infection or AIDS, in which the frequency of allergic reactions to drugs is said to be increased.

Although differences do exist, most studies / case reports use serial dilutions, administered orally at various intervals. The largest report described desensitizing 22 patients using tenfold serial dilutions.

Nineteen patients were successfully desensitized. Three patients experienced nausea and / or chills, requiring cessation of the desensitization. These adverse events resolved upon treatment. Eighteen patients were evaluated long term, and of those, 15 tolerated for a mean of 14 months, until therapy was discontinued for reasons other than allergic reactions (**table 3**).

Only one case report was identified addressing IV desensitization. The patient tolerated the treatment doses but developed chills, rigor, and rash within hours of the full dose infusion of 240 / 1,200 mg.

No explanation was given regarding this delayed reaction. **Table 4** presents a slight modification, for solution preparation and administration purposes, of the protocol used in that case.

Table 3

Trimethoprim/Sulfamethoxazole Oral Desensitization Protocol

Preparation of Oral Desensitization Solutions

Solution 1	40/200 mg/5mL
Solution 2	[0.5 mL solution 1 + 4.5 mL sterile water] 4/20 mg/5mL
Solution 3	[0.5 mL solution 2 + 4.5 mL sterile water] 0.4/2 mg/5mL
Solution 4	[0.5 mL solution 3 + 4.5 mL sterile water] 0.04/0.2 mg/5mL
Solution 5	[0.5 mL solution 4 + 4.5 mL sterile water] 0.004/0.02 mg/ 5 mL

Dosing and Administration Schedule

Hours	Solution	Oral Dose	Dose (mL)
0	5	0.004/0.02 mg	5
1	4	0.04/0.2 mg	5
2	3	0.4/2 mg	5
3	2	4/20 mg	5
4	1	40/200 mg	5
5	*	160/800 mg	5

* commercially available tablet

Table 4

Trimethoprim/Sulamethoxazole Intravenous Desensitization Protocol

Minutes	Volume of Solution to be administered (mL)	Resulting IV Dose (mg)
0	0.2	0.16/0.8
20	2	1.6/8
40	10	8/40
60	20	16/80
80	100	80/400
100	170	136/680
120	300	240/1200

Table 5

Vancomycin Desensitization Protocol
Preparation of Desensitization Solutions

Solution 1	2 mg/mL (a) (2:1)
Solution 2	[25 mL solution 1 + 25 mL D5W] 1mg/mL (1:1)(b)
Solution 3	[5 mL solution 2 + 50 mL D5W] 0.09 mg/mL (1:10)(b)
Solution 4	[5 mL solution 3 +50 mL D5W] 0.008 mg/mL (1:100)(b)
Solution 5	[5 mL solution + 50 mL D5W] 0.0008 mg/mL (1:1000)(b)
Solution 6	[5 mL solution 5 +50 mL D5W] 0.00007 mg/mL (1:10,000)(b)

(a) Vancomycin 500 mg diluted in 250 mL of 5% dextrose in water (2 mg/mL).
(b) Approximate dilutions - 50 mL, rather than 45 mL, of diluent used to facilitate preparation (i.e. solution can be added to 50 mL minibag).

Dosing and Administration Schedule

Solution (#)	Time (hr:min)	Infusion Rate ML/hr (mL/min)	Volume Infused (mL)
6	0:0	60 (1)	15
5	0:15	15 (0.25)	3.75
5	0.30	30 (0.5)	7.5
5	0.45	60 (1)	15
4	1:0	15 (0.25)	3.75
4	1:15	30 (0.5)	7.5
4	1:30	60 (1)	15
3	2:0	15 (0.25)	3.75
3	2:15	30 (0.5)	7.5
3	2:30	60 (1)	15
2	3:0	15 (0.25)	3.75
2	3:15	30 (0.5)	7.5
2	3:30	60 (1)	15
1	3:45	225 (3.75)	225

Sulfadiazine

Only one case report on this desensitization was identified. The protocol used 1 mg, 10 mg, 100 mg, 500 mg, 1,000 mg, and 1,500 mg given every four hours orally. The patient experienced a recurrence in the maculoerythematous rash after 10 days of therapy. The rash was controlled with prednisone and the patient was able to continue therapy.

Vancomycin

For vancomycin, the first step should be to accurately classify the reaction as an allergic reaction in contrast to the more common "red-man syndrome." This syndrome is thought to be due to an infusion rate-dependent increase in histamine release, not immune mediated. Patients should not be labeled "vancomycin allergic" unless the possibility of red-man syndrome has been eliminated because vancomycin may be the only effective agent against some pathogens.

Several protocols have been used to date for this purpose. One described a rapid desensitization protocol applied to seven patients, five of whom required a modification (decrease fusion rate) in the protocol. Desensitization required two hours to several days and was successful for all patients. Slower protocols also have been used, with successful desensitization within four hours to nine days, depending upon the protocol used. A modification of these protocols, to facilitate solution preparation and administration, has been used in two patients, both of whom tolerated desensitization without adverse effects (**table 5**).

Aminoglycosides

An IV protocol was reported for tobramycin utilized in one cystic fibrosis patient. The first dose was 0.001 mg and was doubled every 30 minutes until a therapeutic dosage of 80 mg was obtained.

Pentamidine

Two reports of pentamidine desensitization were reviewed. Both used a serial dilution protocol. The starting dilution was 1:10,000 in the first, and 1:1,000 in the second report. Both patients were successfully treated, but they died shortly thereafter due to an underlying disorder (**table 6**).

Clindamycin

One report of clindamycin desensitization was identified. A female patient with HIV, diagnosed with toxoplasmosis encephalitis, experienced a cutaneous reaction to clindamycin. The maculopapular reaction was confirmed by rechallenge. Treatment with sulfadiazine had to be discontinued due to neutropenia.

Subsequently, clindamycin desensitization was attempted. The patient received 20 mg of oral clindamycin every eight hours, with the dose doubling every day, until a full therapeutic dose of 600 mg was achieved. The dose was then increased to 600 mg every six hours, which she had continued to tolerate at the time the report was published.

Anti-tubercular agents

Reactions to anti-tubercular agents have been a significant problem since the 1960s when these agents were first marketed. Rates of reaction as high as 17% have been observed with para-aminosalicylic acid (PAS). Streptomycin (1.2%-10.3%) and isoniazid (INH) (0.4%-1.5%) also have been frequently implicated. Overall, reaction rates of 4% to 5% are reported for all anti-tuberculars, which have led to drug discontinuation.

The onset of reactions, usually rash, is usually four to 24 hours after starting anti-tuberculars. Reactions as late as three to nine weeks also have been reported. Data on the patients reacting after two days suggest that they still could be having a Type I hypersensitivity reaction and could be candidates for desensitization. Measurement of IgE can be performed in these cases to verify the presence of a true Type I hypersensitivity.

However, most of these reactions are probably Type II or Type III reactions, which are not responsive to desensitization.

Rifampin also has been implicated as causing hypersensitivity reactions. However, caution is warranted in making the diagnosis of a hypersensitivity reaction because many noncompliant patients will have a flu-like syndrome associated with stopping and restarting rifampin. Fever and

Table 6

Pentamidine Desensitization Protocol

Preparation of Desensitization Solutions

Solution 1	0.8 mg/mL(a)	
Solution 2	[1 mL solution 1 + 9 mL D5W]	0.08 mg/mL
Solution 3	[1 mL solution 2 + 9 mL D5W]	0.008 mg/mL
Solution 4	[1 mL solution 3 + 9 mL D5W]	0.0008 mg/mL
Solution 5	[1 mL solution 4 + 9 mL D5W]	0.00008 mg/mL

(a) Pentamidine iseothionate 200 mg diluted in 250 mL of 5% dextrose in water (0.8 mg/mL)

Dosing and Administration Schedule

Time (Min)	Solution (#)	Dilution of solution	Volume of Infused (mL)	Pentamidine delivered (mg)
0	5	1:10,000	2	0.00016
15	4	1:1,000	2	0.0016
30	3	1:100	2	0.016
45	2	1:10	2	0.16
60	1	full strength	250 during 2 hrs.	200

(b) Infuse over 2 minutes. The line should be flushed following each administration to ensure complete delivery of medication.

Table 7

Antimicrobial Desensitization Protocol

Preparation of Desensitization Solutions

Solution 1	10 mg/mL (10:1)
Solution 2	[1 mL solution 1 + 9 mL diluent] 1 mg/mL (1:1)
Solution 3	[1 mL solution 2 + 9 mL diluent] 0.1 mg/mL (1:10)
Solution 4	[1 mL solution 1 + 9 mL diluent] 0.01 mg/mL (1:100)
Solution 5	[1 mL solution 1 + 9 mL diluent] 0.001 mg/mL (1:1000)
Solution 6	[1 mL solution 1 + 9 mL diluent] 0.0001 mg/mL (1:10,000)

Dosing and Administration Schedule

Solution (#)	Time (minutes)	Dilution of solution
6	0:0	1:10,000
5	0:30	1:1,000
4	1:0	1:100
3	1:30	1:10
2	2:0	1:1
1	2:30	10:1
-	3:00	Full therapeutic dose*

* Administer slowly; recommend over 2 hours

rash can mislead a diagnostician into thinking that the patient is allergic to the medication. It is also difficult to distinguish which of many antituberculars is the offending agent.

Discussion

The common theme in all desensitization protocols presented in this review is a three-step process. The first step it so confirm the lack of alternatives to treat the infectious disease of the patient. The second step is to determine the nature of the allergy. The desensitization process is the third and final step in these protocols.

Determining the nature of the allergy is performed by careful history of past exposures to the suspected agent, followed by a skin test, if necessary. Skin testing for IgE reactions is well-defined only for penicillin. The major determinant of penicillin (penicilloyl) is available commercially, and the minor determinants used are penicillin G and penicilloic acid, which is obtained by alkaline hydrolysis of penicillin G.

The first procedure in skin testing is the skin prick test. If this is negative, intradermal injections are placed on the anterior aspect of the forearm. The test is considered positive if the induration is greater than 5 mm after 15 to 20 minutes. A clinical caveat is to ensure that the patient is not taking a drug that would blunt the skin test reaction, such as corticosteroids or antihistamines. If the test is positive, desensitization should be initiated in a controlled environment, with cardiopulmonary resuscitation equipment and personnel available (preferably an intensive care unit) to treat any severe reaction that may occur.

Most protocols reviewed involved a serial dilution procedure to desensitization. Therefore, we propose a template desensitization protocol using tenfold serial dilutions. The recommended starting dilution is 1:10,000 and progressing toward a normal dose at intervals of 30 minutes (**table 7**). Desensitization should be initiated with oral doses whenever possible.

A missed dose during the procedure creates an ambiguous situation. It is unknown how many doses can be missed and what the consequences or risk for anaphylaxis are for a missed dose. Fortunately, Type I hypersensitivity reactions occur infrequently enough that an assessment of risk is almost impossible. Unfortunately, because of the low incidence of reactions, we do not have data to make recommendations. Therefore, a conservative approach should be taken. Begin the entire desensitization protocol at the beginning if there is a single missed dose.

It is noteworthy that a successful desensitization does not mean that the patient is free from future reactions to the same agent — only that the present course of therapy is unlikely to result in an immediate, life-threatening reaction.

[The American College of Allergy, Asthma & Immunology released a supplement to its journal that may be useful. The title is Disease Management of Drug Hypersensitivity: A Practice Parameter. *It is available for free at www.annallergy.org (December 1999 issue). The authors of the preceding article can be reached at the VA Medical Center in Sepulveda, CA, at (818) 891-7711.]* ■

New practice modes can involve pharmacists

Last fall, **Marc Silver**, MD, a cardiologist who runs the congestive heart failure (CHF) center at Christ Hospital in Chicago, invited cardiologists and primary care physicians from the entire Advocate Healthcare System in Oakbrook, IL, to spend a day talking about CHF and how care could be improved. About 100 people attended the "roundtable," which was held at nearby McDonald's corporate headquarters — Hamburger U.

"The purpose of the roundtable," explains Silver, "was to update everyone on where we stood with CHF initiatives across our system and to let them know how best to improve the outcomes of their patients with heart failure." While the cardiologist tried to get generalist physicians into the CHF treatment loop, many of the initiatives discussed can involve the hospital pharmacy department as well. Here are some highlights of the discussion and some suggestions on how to organize such an event in your facility.

✔ **Prevention:** Prevention is the "ultimate" solution and should be a daily practice. The presenters talked about the many secondary prevention measures. "We discussed preventing the diseases that cause CHF — diabetes and hypertension," says Silver. "We also talked about screening patients at high risk for developing CHF."

✔ **Using the systemwide resources at Advocate:** There are educational materials, home nursing, health advisors, support groups, and research and clinical trials. "We wanted to make sure cardiologists and primary care physicians alike know that there are CHF coordinators and CHF educational programs in place throughout this health system," says Silver. "We wanted to make sure they know that there's a lot of clinical research trials going on in CHF throughout the system, and they are available." Advocate also has a patient program called Health Advisor. Patients who sign up receive regular phone calls after discharge asking how their heart failure management is going. By virtue of those calls, Silver says, patients can improve their care at home.

✔ **Tidbits:** In this segment, the presenters talked about digoxin (Glaxo Wellcome's Lanoxin) and about spironolactone (Searle's Aldactone) and the Randomized Aldactone Evaluation Study (RALES) trial. They also discussed when to use angiotensin II receptor antagonists, the role of statins in CHF, salt restriction, and exercise. "These other modalities may be very helpful. Heart failure, like all chronic disease, is focused in the details."

✔ **Using beta blockers at target dose:** Clinical trials in more than 10,000 patients confirm that long-term treatment with beta blockers improves symptoms and clinical status and prevents hospitalization and death. This drug therapy can begin at the generalist's office visits. Doses are titrated slowly but progressively, with volume status evaluated.

✔ **Using ACE inhibitors at target dose:** All patients with CHF due to left ventricular dysfunction should receive an ACE inhibitor unless they have been shown to be intolerant, are elderly, or have a contraindication such as hypotension, renal insufficiency, hyperkalemia, or cough. ACE inhibitors also can decrease the risk of developing heart failure in asymptomatic patients with left ventricular dysfunction. Document their use (or adverse effect). Titrate up to target doses.

✔ **Using standing orders:** "A lot of the guidelines and consensus statements address outpatient care, but not so much that of inpatients," Silver says. "We decided to put our ideas into a set of working orders that tell people what steps to take to improve patient care." Standing orders for CHF patients are developed to make your life easier, to make documentation better, to guide proper therapy, and to help our patients. "We talked about the impetus to develop them, what they contain, and the importance of using them. We tried to get people to buy into using them in a consistent fashion and get their feedback on them."

✔ **Using the emergency department:** Estimates are that nearly half of the patients admitted can be safely discharged from the ED if the staff can be encouraged to use standing orders and work toward observation areas. Advocate's CHF orders initiate care right away in the ED — "It's fairly aggressive," he says. "In our Christ Hospital, where the CHF Institute is centered, we have a program in place to rapidly diurese people in the ED, and we're hoping to discharge at least 30% to 40% of patients who normally get admitted directly from the ED."

What's next? "The next step is to go back to each of the individual hospitals and revisit the same topics," Silver says. "We'll keep reinforcing them. Interest in this roundtable has been a very strong message from our system that CHF is a common problem that's not going away. In fact, the numbers are growing." ■