April 2014

BioSupply Trends

Special Focus: SAFETY

Quarterly

Safe Medicine

Policing the Supply Chain

Proactive Screening for Men's Health

Healthcare Quality: A New Way of Practicing Medicine

Growing Impact of Autoimmune Disease

Rare Adverse Effects of IG Therapy

Surviving Sepsis: Put Albumin to the Test? — Page 52

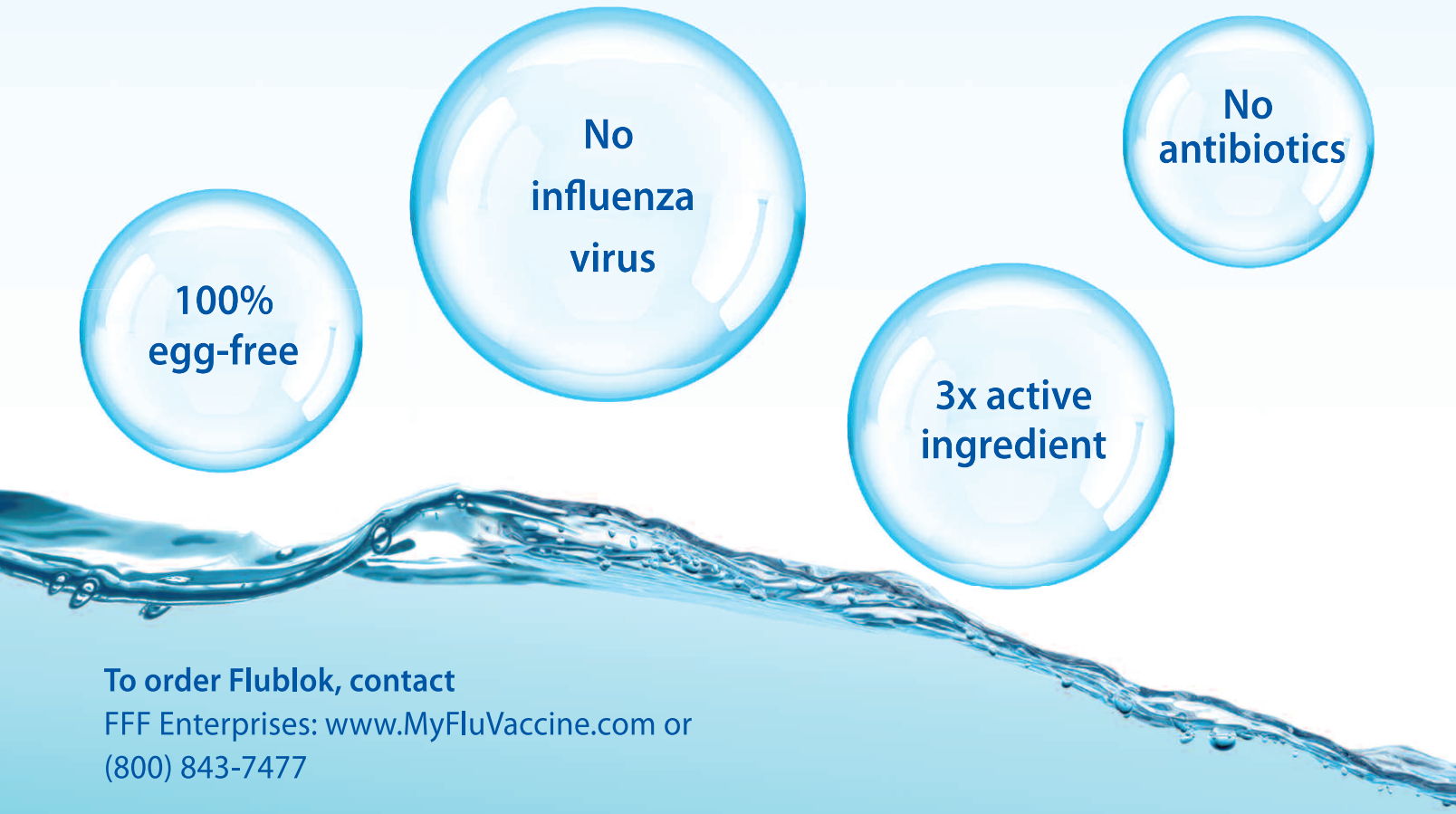
Flublok®

Influenza vaccine

Pure Simple Effective

ACIP recommended for ages 18-49

Also recommended for those with egg allergies



To order Flublok, contact
FFF Enterprises: www.MyFluVaccine.com or
(800) 843-7477

Protein Sciences
CORPORATION

Reimbursement Codes
CPT code: 90673
Q code: Q2033

Flublok (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok safely and effectively. See full prescribing information for Flublok available at www.Flublok.com.

INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

DOSAGE AND ADMINISTRATION

A single 0.5 mL dose for intramuscular injection.

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5mL single dose vials.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks.

ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (>37%); the most common (≥10%) solicited systemic adverse reactions were headache (>15%), fatigue (>15%) and myalgia (>11%).

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older.
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Issued: December 2012

Manufactured by:
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450
(203)686-0800 • www.proteinsciences.com

FB13017

www.Flublok.com

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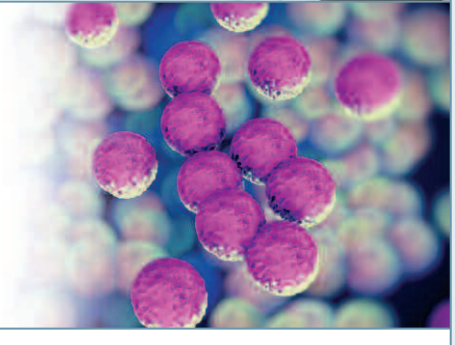

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BioSupply Trends Quarterly has a circulation of 40,000, with an approximate readership of more than 100,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

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Minimizing the Risks of Medicine

THE CHALLENGES SURROUNDING healthcare are likely to affect all of us at some time during our lives. Whether from lack of preventive care, inadequate quality of care, adverse reactions to medications, treatment with less-effective medicines or even the possibility of being treated with a counterfeit drug, the risks are worrisome. The good news is that new legislation aims to ensure better access to care, scientists are diligently researching new and improved treatments, and organizations worldwide are implementing safeguards to reduce the trafficking of compromised medicines. In this safety-themed issue of *BioSupply Trends Quarterly*, we take a look at some of these spiraling risks of healthcare.

Despite the availability of interventions, deaths from preventable illnesses continue to increase. This is especially true for men. As our article "Proactive Screening for Men's Health" points out, more men than women die of preventable causes due to lifestyle factors and because they "tend to wait until their condition is serious, even life-threatening" before they seek medical care. More men than women die of cancer, heart disease, accidental injury, respiratory disease, stroke, diabetes and suicide.

Of course, seeking treatment doesn't always result in good quality of care. The recent changes brought about by the implementation of the Affordable Care Act (ACA) should leave some patients wondering "whether the days of the kind and patient doctor are on their way out," says the author of our article "Practicing Medicine: A New Quality of Care." The intentions of the ACA's policies seem noble: to ensure thorough patient care and, ultimately, better coordinated care. But, the administrative burden imposed often results in physicians finding themselves with limited time for "real doctoring."

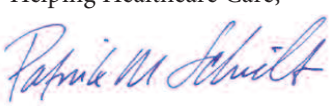
When it comes to safety and best manufacturing practices, medicines have come a long way, especially in the last several decades. For high-cost therapies like immune globulin (IG), this is markedly important. Manufacturing methods for IG have significantly improved, resulting in much lower incidences of severe adverse effects. But, as our article "Adverse Effects of Human Immunoglobulin Therapy" outlines, less common but more serious delayed reactions do still occur. What causes these adverse events and how to prevent and manage them are discussed.

As any experienced physician will tell you, it's not always a clear-cut decision which medicines should be used to treat patients. This is certainly the case for human albumin in the treatment of septic shock. Our article "Severe Sepsis: It's Time to Put Albumin to the Test" looks at some tantalizing research that strongly suggests use of human albumin to resuscitate patients in severe sepsis may cut mortality risk relative to saline, which is cheaper and very appealing to hospital pharmacists.

Finally, counterfeiting continues to plague the medical world, posing a dangerous threat to unsuspecting consumers. Our article "Supply Chain Safety: Where Are We Now?" examines the global impact of counterfeit medicines, estimating sales at $431 billion in 2012. Domestically, the U.S. has implemented new legislation to help track and trace drugs. Globally, INTERPOL is partnering with the world's largest pharmaceutical companies to combat the problem.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* and find it both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Artistic Director
Allan Bean

Graphic Artists
Allan Bean
Ben Drolet

Advertising Director
Cheryl Brooks

Contributing Writers
Keith Berman, MPH, MBA
Amy Ehlers, BS, PharmD, BCPS
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Amy Scanlin, MS
Carla Schick
E Richard Stiehm, MD
Jim Trageser

Proofreader
Jackie Logue

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Please direct editorial, advertising and marketing communications to
41093 County Center Drive
Temecula, CA 92591
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

CMS Postpones "Two Midnight" Rule

The Centers for Medicare & Medicaid Services (CMS) has delayed the new "two midnight" rule for Medicare hospital admissions until after Sept. 30. As part of Medicare's inpatient payment rule for 2014, the rule directs the agency's auditors to assume that a patient's hospital admission was reasonable and necessary if they were admitted to the hospital with proper documentation for more than a day — defined legally as spanning two midnights in a hospital bed.

The change was intended to address widespread complaints that Medicare's rules are too vague about when a moderately sick patient should be admitted for expensive inpatient care instead of outpatient observation. Hospitals have faced aggressive auditing over short inpatient stays, even though they say the rules didn't set clear standards. But, hospitals aren't happy with the new rules, either, because they are presumed to have made an error and provided medically unneeded care if an inpatient doesn't spend two midnights in a hospital bed.

This is the second delay in enforcing the two midnight rule, which was originally scheduled to go into effect on Oct. 1, 2013. CMS will continue to allow Medicare's administrative contractors to review short stays and deny payment if the patient record does not support medical necessity. However, those reviews are anticipated to be informative and will be limited to a sample of between 10 and 25 claims per hospital. ❖

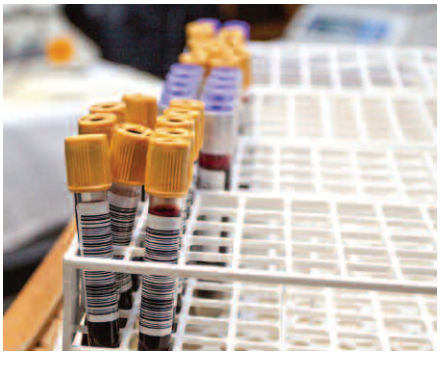
HHS Awards $150M to Grow Health Center Sites

In November, U.S. Health and Human Services Secretary Kathleen Sebelius announced that $150 million in awards will be issued under the Affordable Care Act (ACA) to support 236 new full-time health center delivery sites across the nation. This funding will help care for approximately 1.25 million additional patients.

Community health centers play a vital role in bringing healthcare services to neighborhoods with historically high uninsurance rates. Residents will have the ability to enroll in new coverage options available in the health insurance marketplaces under the ACA through expanded access to Medicaid in many states, new private health insurance options and tax credits. ❖

HHS Grants Patients' Access to Test Reports from Labs

As part of an ongoing effort to empower patients to be informed partners with their healthcare providers, the U.S. Department of Health and Human Services (HHS) ruled in February that laboratories are allowed to give patients or their designated representative a means of direct access to the patients' completed test reports upon their request. This ruling amends the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The new ruling also eliminates the exception under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule to the right of individuals to access their protected health information when it is held by a CLIA-certified or CLIA-exempt laboratory. Under the HIPAA Privacy Rule, patients and their personal representatives can view or be given a copy of the patients' personal health information, including an electronic copy, with limited exceptions, from the patient's physician. The new ruling from HHS now gives patients and their designated representatives the option to obtain their reports directly from the laboratory.



The final rule was issued by three agencies within HHS: the Centers for Medicare & Medicaid Services (CMS), which is responsible for laboratory regulation under CLIA; the Centers for Disease Control and Prevention, which provides scientific and technical advice to the CMS related to CLIA; and the Office for Civil Rights, which is responsible for enforcing the HIPAA Privacy Rule. ❖

HHS Awards $55.5M to Strengthen America's Healthcare Workforce

In December, the U.S. Department of Health and Human Services (HHS) announced $55.5 million in grants to support training for health professionals and bolster the size of the nation's healthcare workforce.

The grants, which total more than 270 that will be managed by HHS' Health Resources and Services Administration, will focus on health workforce needs, including nursing, public health, behavioral health, health workforce development and dentistry.

A majority of the funding, $45.4 million, will support nursing workforce expansion in the following six areas: increasing the number of nurse faculty by providing low-interest loans and loan cancellation; improving nursing diversity by expanding educational opportunities to students from disadvantaged backgrounds; increasing nurse anesthetists by providing traineeships to licensed registered nurses enrolled as full-time students in a master's or doctoral nurse anesthesia program; stimulating collaboration by bringing together nurses and other healthcare professionals to create and implement new practice models for providing care; supporting advanced nursing education by funding advanced nursing programs that support registered nurses in becoming nurse practitioners, nurse midwives and other practice nurses; and training doctoral-level psychologists to address the behavioral health needs of the underserved populations. An additional $3.1 million in funding will allow states to develop and implement innovative programs to assist areas where there are shortages in dental healthcare professionals. States must match at least 40 percent of the grant funding or provide equivalent support. ❖

Proposed New Standards for Insurers for 2015 Enrollment

According to a new proposal from the Centers for Medicare & Medicaid Services (CMS), insurers that want to sell plans through the federal exchanges for 2015 would have to do more to ensure members have access to an adequate network of providers. Under the proposal, participating health plans would be required to submit a list to CMS of all in-network providers and medical facilities covered under a plan, which would then be reviewed by CMS, in conjunction with state regulators, to ensure that there is "reasonable access" to all types of providers. Health insurance plans sold through the 2015 exchange would be required to include at least 30 percent of such providers in the territory covered, compared with the 20 percent that was required in 2014. If insurers fail to offer this level of access to essential community providers, they would need to provide an explanation to CMS as to why their health plan should still be sold on the exchange. CMS will then review their explanation to see if it is adequate.

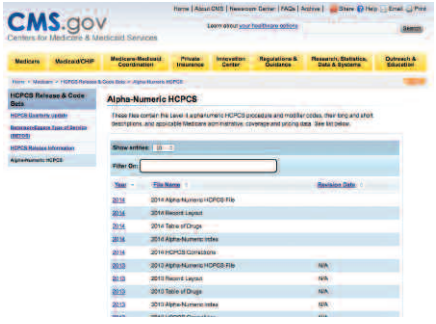
CMS is also considering requiring all exchange plans, or at least one plan at each level of coverage per insurer, to cover at least three primary care office visits per year prior to incurring any deductible. Timothy Jost, a healthcare expert at Washington and Lee University School of Law, suggests that "such a requirement may be a means of enticing younger, healthier individuals into the exchange by guaranteeing access to a certain level of free care even for high-deductible plans."

Participating insurers will need to submit plan details to CMS by June 27 for products they want to sell during the 2015 enrollment period. There will be two review periods over the summer, during which time federal officials will notify insurers about any deficiencies in their applications and allow them to submit changes. Signed agreements for products to be sold through HealthCare.gov must be finalized by Oct. 17. Open enrollment begins Nov. 15. ❖

CARLA SCHICK *is a staff writer for* BioSupply Trends Quarterly *magazine.*

Reimbursement FAQs

There's no doubt that complexity is the operational word for reimbursement, and this includes the rules and nuances that govern drugs and biologicals. This column summarizes some of the additional important issues that deserve attention in 2014. Even though some healthcare practitioners' sites may contract with an outside provider of billing services, it's incumbent on the providers and their office staffs to know the background information on the requirements of what's reimbursable. One of the best sources of information remains MLN Matters *publications, a free service provided by the Centers for Medicare & Medicaid Services. See the details for accessing* MLN Matters *newsletters at the end of the column.*



A New Set of Healthcare Common Procedure Coding System (HCPCS) Codes for Drugs, Biologicals and Immunologics

Although for several years HCPCS codes assigned to drugs and biologicals trended with the concept of using a generic description, the advent of newer biologicals and biosimilars has brought the assignment of brand-specific HCPCS codes into play. Not recognizing this and not incorporating this into physicians' billing for drugs and biologicals will drive a fatal blow to the reimbursement picture! These examples provide some background for practice sites to get started with.

A new HCPCS code for Neupogen (filgrastim) was released on Nov. 29, 2013, by the Centers for Medicare & Medicaid Services (CMS) as part of the HCPCS code set updates that became effective Jan. 1, 2014. The new HCPCS code for Neupogen is J1442 injection, filgrastim 1 mcg, and it replaces the old Neupogen HCPCS codes of J1440 for 300 mcgs and J1441 for 480 mcgs. The new code has a billing unit designation of 1 mcg. It's critical for healthcare providers to make sure billing unit conversion is working in their systems. The dose administered must be converted into billing units to be billed. For example:

Neupogen 300 mcg = 300/1 = 300 billing units of 1 mcg (the single use vial)

Neupogen 480 mcg = 480/1 = 480 billing units of 1 mcg (the prefilled syringe)

Granix (tbo-filgrastim) was approved as a new biologic product with its own labeled indications and not as a biosimilar. Effective Jan. 1, 2014, it has its own HCPCS code (J1446) and its own billing unit designation (5 mcg), as well as its own reimbursement rate and labeled indications. Using the HCPCS code, billing unit designation and applying the reimbursement rate for filgrastim is not appropriate for Granix. Continuing to use a miscellaneous code is not appropriate either and will result in zero reimbursement.

Key points to remember: Neupogen and Granix have different labelled indications, different HCPCS codes and different billing units assigned to them. Healthcare professionals should check their systems carefully to ensure they've captured these changes that were effective Jan. 1, 2014. ❖

Source: www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Alpha-Numeric-HCPCS.html

ICD-10 Coding System Transition

Several years ago, work began on changing the coding system used to describe diagnoses and procedures. The goal was to build increased complexity and specificity into the code sets. The mandatory launch of the new International Classification of Diseases, Tenth Revision (ICD-10), diagnosis code set, which will replace the current ICD-9 code set published in 1977, was scheduled for Oct. 1, 2014. However, on March 31, the Senate voted to pass a House-approved measure (HR 4302) that would delay the ICD-10 compliance deadline until 2015. As of this writing, it is expected that President Obama will sign the measure.

ICD-10 increases the number of diagnosis codes from 17,000 to 140,000. Although many sites perceive this as a huge and almost insurmountable burden, others are using it as an opportunity and strategic initiative to improve their practice site's performance under the new system. This clinically driven revenue cycle process will require training on and testing new systems that need to be ramped up in the next few months. Planning for the possible contingencies related to denied or delayed claims and productivity drops need to be factored in as well.

The Centers for Medicare & Medicaid Services has a website dedicated to providing agency-wide information and education on the ICD-10 implementation that includes a video providing a basic introduction to coding for ICD-10 at www.cms.gov/Medicare/Coding/ICD10/index.html?redirect=/ICD10/01_Overview.asp# 2014. ❖

New NDC Codes for Flebogamma 10% DIF Intravenous Immune Globulin (Human)

Recently, Grifols changed its NDC codes for Flebogamma 10% DIF intravenous immune globulin (human) to be in compliance with the U.S. Food and Drug Administration. The new NDC codes are as follow

Material	Description	Vial Label	Folding Carton
725943	FLEBOGAMMA 10% DIF 5 g	NDC 61953-0005-1	NDC 61953-0005-1
725975	FLEBOGAMMA 10% DIF 10 g	NDC 61953-0005-2	NDC 61953-0005-2
725976	FLEBOGAMMA 10% DIF 20 g	NDC 61953-0005-6	NDC 61953-0005-3

And, as new lots become available, new NDC codes will be assigned.

Mandatory Reporting of 8-Digit Clinical Trial Number

Items or services provided to Medicare patients in clinical trials that qualified for coverage as specified in the Medicare National Coverage Determination Manual (publication 100-03, section 310.1) may be eligible for reimbursement. Although reporting of the clinical trial identifier number has been encouraged on a voluntary basis since 2008, effective Jan. 1, the Centers for Medicare and Medicaid Services' (CMS) Change Request (CR) 8401 makes it mandatory to report a clinical trial number on these claims. The identifier number is not new; it's the same one that has been assigned by the National Library of Medicine (NLM) website at clinicaltrials.gov when a new study appears in the NLM Clinical Trials database. However, if providers still don't have the capacity to locate this number using the Internet, a generic 8-digit number (99999999) may be used only for the balance of 2014 following instructions in CR8401. The fields cannot be left blank; they must be populated for trial-related claims to process appropriately. Specifically, the clinical trial identifier number needs to be included if the beneficiary is enrolled in an approved clinical trial, *and* the claim is for the investigational item or service, *and/or* the costs are related to the investigational item or service, *and/or* the costs are related to routine care for the condition in the clinical trial. ❖

References

1. CMS Manual System Pub 100-04 Medicare Claims Processing: www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R2805CP.pdf.
2. Mandatory Reporting of an 8-Digit Clinical Trial Number on Claims: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM8401.pdf.
3. Centers for Medicare & Medicaid Services. Medicare Approved Facilities/Trials/Registries: www.cms.gov/Medicare/Medicare-General-Information/MedicareApprovedFacilitie/index.html.
4. MAC toll-free numbers: www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/provider-compliance-interactive-map/index.html.

BONNIE KIRSCHENBAUM , *MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.*

Annual Clotting Factor Furnishing Fee

Since Jan. 1, 2005, mobile medical application (MMA) rules require that a clotting factor furnishing fee be paid separately if providers furnish clotting factor, unless costs associated with furnishing the clotting factor are paid through another payment system. The Centers for Medicare & Medicaid includes the clotting factor furnishing fee in the published national payment limits for clotting factor billing codes. However, when it isn't included on the ASP Medicare Part B Drug Pricing File or the NOC Pricing File, the providers' carrier, FI, RHHI or A/B MAC must make payment for the clotting factor, as well as make payment for the furnishing fee. This fee is:

- Calendar year 2013: $0.188 per unit
- Calendar year 2014: $0.192 per unit

Source: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM8049.pdf

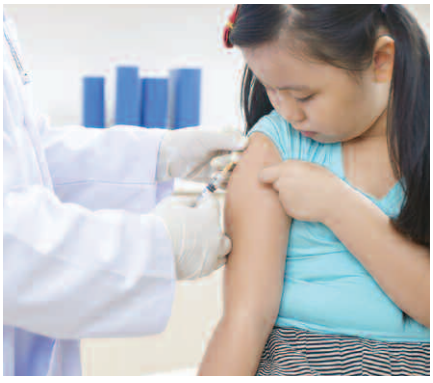
Ask Our Experts

Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.

Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

Research

Study Shows No Evidence Multiple Vaccines Raise Autism Risk



A new study conducted by the Centers for Disease Control and Prevention shows that the number of childhood vaccines administered, either in a single day or during the first two years of life, has no bearing on autism risk. The case-control study of more than 1,000 children showed there were no significant differences between those who did and those who did not have an autism spectrum disorder (ASD) in total antigens from vaccines received by age 2 years or in the maximum number of antigens received on a single day. In addition, increasing exposure to antibody-stimulating proteins or polysaccharides from vaccines from the age of 3 months to 2 years was not associated with the risk of developing an ASD.

In the study, investigators evaluated combined data from three managed care organizations for 256 children with an ASD and 752 age- and sex-matched healthy peers. All of the children were born between January 1994 and December 1999. Total cumulative exposure to antibody-stimulating proteins and polysaccharides was determined by adding together the antigen content of each vaccine received. The association between this exposure and ASD was determined at birth to 3 months, birth to 7 months and birth to 2 years. In addition, maximum number of antigens from vaccines received in a single day was determined. Further analysis evaluated the association between these exposures and the subcategories of autistic disorder or ASD with regression.

Results showed that the adjusted odds ratio of an ASD associated with each 25-unit increase in total antigen exposure was 0.999 for cumulative exposure to age 3 months, to age 7 months and to age 2 years. In other words, none of the associations was significant. There also was no risk for an ASD associated with single-day antigen exposure.

The investigators noted that the current routine vaccine schedule contains more childhood vaccines than were administered a couple of decades ago; however, the maximum number of antigens that a child could be exposed to by age 2 in 2013 is 315 compared with several thousands in the late 1990s. The study was published online March 29 in the *Journal of Pediatrics*. ❖

Medicines

FDA Grants Orphan Status to Diabetes Reversal Drug

DiaVacs' type 1 diabetes therapy DV-0100 has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA). The therapy uses a proprietary technology that is designed to halt the body's autoimmune reaction against the pancreatic islet cells that are responsible for producing insulin, allowing them to produce insulin normally and reversing the trajectory of the disease. It does this by taking the patient's own dendritic cells from their blood, modifying the cells through the use of small interfering oligonucleotides, and then vaccinating the patient with these modified cells under the skin with a small needle. The cells are absorbed and trafficked to the pancreatic lymph nodes, thereby inducing tolerance.

The therapy has been shown to be safe and effective in animal models of type 1 diabetes, and there has been no evidence of safety signals in human Phase I trials in patients with established type 1 diabetes for five years or longer. In some patients in the Phase I human trials, production of endogenous insulin was measured even after 10 years of disease. The company has initiated an FDA-approved Phase II human trial.

Orphan designation qualifies DV-0100 for seven years of marketing exclusivity in the U.S. if the company is the first to obtain marketing approval for this

product in type 1 diabetes. It also qualifies the company for certain tax credits and waivers for prescription drug user fees. ❖

Research

Single-Dose IVIG Results in Early Improvements in Sepsis Patients

A recent study conducted in Japan showed significant early post-administration improvements in sepsis patients who were given a single-dose administration of intravenous immune globulin (IVIG). The study analyzed 79 patients admitted to the intensive care unit (ICU) of tertiary care institutions due to severe sepsis or septic shock. Patients were randomly divided into a group that was administered standard divided doses of IVIG (5 g/day for three days, S group) or a group that was administered a standard single dose of IVIG (15 g/day for one day, H group). Freeze-dried sulfonated human IVIG was used. The longitudinal assessment of procalcitonin (PCT) levels, C-reactive protein (CRP) levels, white blood cell count, blood lactate levels, IL-6 levels, sequential organ failure assessment (SOFA) score and systemic inflammatory response syndrome (SIRS) was conducted, as well as mechanical ventilation duration (days), ICU stay (days), and 28-day and 90-day survival rates.

While the study showed no significant differences in PCT levels, CRP levels, and 28-day and 90-day survival rates between the two groups, patients in group H showed improvements in the various SIRS diagnostic criteria, IL-6 levels and blood lactate levels in the early stages after IVIG administration. In light of the non-recommendation of IVIG therapy in the Surviving Sepsis Campaign Guidelines 2012, the researchers say the findings of significant early post-administration improvements are noteworthy because IVIG's anti-inflammatory effects may account for the early reduction in IL-6 levels after treatment, and the accompanying improvements in microcirculation may improve blood lactate levels and reduce SOFA scores. However, they said the low dosages of IVIG in Japan may limit the anti-cytokine effects of this treatment, and, therefore, further studies are needed to determine appropriate treatment regimens of single-dose IVIG. ❖

Medicines

Pfizer Buys Rights to New Autoimmune Disease Therapy

Pfizer has paid $25 million for the license rights to an experimental, preclinical drug designed to replace pooled intravenous immune globulin (IVIG) therapy to treat autoimmune diseases. Currently, patients with certain autoimmune diseases receive IVIG infusions to bolster their antibody defense system in an effort to repel diseases. Gliknik's GL-2045 is a recombinant Fc fusion protein that may be used in much smaller quantities to provide the same or better therapeutic effects than IVIG therapy. It can be transfused in two days, and could potentially offer a major improvement in the lives of patients with autoimmune diseases. "GL-2045 is the first of several innovative drug candidates Gliknik is advancing for people with autoimmune diseases and cancer," said David Block, Gliknik's CEO. "We selected Pfizer as our partner to progress GL-2045 from among several interested and capable parties because of its exceptional development, manufacturing and commercial capabilities." ❖

Research

Vaccines May Reduce Risk of Strokes in Children

A new international study has found that vaccines may prevent the risk of strokes in children. In the study, kids who received some, few or no vaccines were nearly seven times more likely to have a stroke than kids who had all or most of their recommended shots. Leaders in the international study, titled *Vascular Effects of Infection in Pediatric Stroke*, interviewed the parents and guardians of 310 children who had a stroke and compared their findings with 289 children who hadn't experienced a stroke. Kids in both groups were around 7-and-a-half or 8 years old. The study, which included 40 centers on five continents, is the largest study on pediatric stroke ever funded by the National Institutes of Health.

Pediatric strokes are rare, affecting about five out of every 100,000. About half of these strokes are caused by blood clots, the focus of the study. Several vaccine-preventable bacterial diseases such as those caused by the bacteria pneumococcus or Haemophilus influenzae type b can lead to meningitis, an inflammation of the lining of the brain and spinal cord that also increases a child's risk of stroke. "The exciting thing about this study is that, with vaccination, it might prevent these strokes from happening," says neurologist M. Shazam Hussain, director of the stroke center at the Cleveland Clinic. ❖

Vaccines

Flu Vaccine Decreases Risk of Premature or Low-Birth-Weight Babies

Pregnant women who are vaccinated against the flu are significantly less likely to deliver premature or low-birth-weight babies compared with unvaccinated expectant mothers, according to a Canadian study. In the study, researchers looked at all women who delivered an infant at any hospital in the province of Nova Scotia during the two flu seasons immediately following the 2009 H1N1 pandemic. The researchers found that, overall, the odds of preterm birth (defined as deliveries at less than 37 weeks' gestation) and lower-birth-weight infants were lower among the babies of vaccinated women. "Both Canadian and World Health Organization guidelines now recommend routine seasonal influenza vaccination of all pregnant women in any trimester," said the study's first author, Alexandra Legge, a fourth-

year medical student at Dalhousie University in Halifax.

Based on more than 12,000 women in Nova Scotia who gave birth in the immediate aftermath of the H1N1 flu pandemic, the study adds to mounting evidence that the flu can have detrimental effects for both mothers and their babies. As women get closer to their due dates, their immune systems change, making them more vulnerable to serious illness from flu and other infections, which can put stress on the fetus. An earlier study from Nova Scotia showed that pregnant women who are admitted to the hospital with respiratory illnesses during flu season are more likely to deliver babies that are small for their gestational age or have a low birth weight. However, of the 12,233 women who gave birth to a live-born or stillborn infant between November 2010 and March 2012, only 16 percent received the flu vaccine during their pregnancy, the researchers said. And, while vaccination rates in pregnancy increased during H1N1 (government data suggest that 64 percent of pregnant women in Nova Scotia received the H1N1 vaccine during the pandemic), experts worry that it hasn't translated into higher rates of flu vaccination since. ❖

Did You Know?

A new study shows that autoimmune conditions such as rheumatoid arthritis and psoriasis are associated with high rates of depression, which suggests the impact on mental health, as well as the chronic pain and fatigue associated with the conditions, could be much larger than previously estimated.

— Arthritis Care and Research

Research

New Gene May Be an Effective Target for Autoimmune Disease Therapy

Researchers at King's College London have identified a new gene, PIM1, which could be an effective target for innovative treatments and therapies for psoriasis, an autoimmune disease. In the study, scientists injected the IL-22 cytokine, a protein that sends messages between cells, into models of normal human skin in mice. The changes that subsequently occurred in the skin were reminiscent of psoriasis. Injecting an antibody to block the IL-22 cytokine caused these changes to reverse. Then, using computer analysis (called integrative biology), they compared data from the human skin models with existing gene datasets and identified the gene PIM1 as one of the genes "switched on" by the presence of IL-22. Further, they showed that a small molecule drug blocking PIM1 was effective in models of psoriasis. They concluded that the link between the IL-22 cytokine, which causes inflammation, and subsequent changes in the PIM1 gene suggests a direct link between PIM1 and psoriasis.

"We have been able to confirm that the protein IL-22 causes inflammatory changes in human skin contributing to psoriasis," said Professor Frank Nestle from the St. John's Institute of Dermatology at Guy's and St. Thomas' NHS Foundation Trust and King's College London. "The most exciting part of the study was that detailed analysis of genes induced by IL-22 in skin allowed us to uncover a novel treatment target for this disease. We are hopeful that our research will lead to the development of new approaches for the treatment of this common and irritating skin condition." ❖

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Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including Privigen. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA, who have had hypersensitivity reactions. Patients with IgA deficiency and antibodies to IgA are at greater risk of severe hypersensitivity and anaphylactic reactions.

In patients at risk for developing acute renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine; discontinue if renal function deteriorates. Ensure that patients with preexisting renal insufficiency or otherwise predisposed are not volume-depleted and administer Privigen at the minimum rate of infusion practicable.

Thrombosis might occur with Privigen, even in the absence of known risk factors. Patients could also experience hyperproteinemia, increased serum viscosity, or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur—more frequently with high doses (2 g/kg) and/or rapid infusion.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to treatment. Risk factors include non-O blood group, underlying inflammation, and high doses. Closely monitor patients for hemolysis and hemolytic anemia. Consider the relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload. Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most common adverse reactions observed in >5% of subjects were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature.

In clinical studies of patients being treated with Privigen for chronic ITP, the most common adverse reactions seen in >5% of subjects were headache, elevated body temperature, positive DAT, anemia, nausea, epistaxis, vomiting, increases in conjugated and unconjugated bilirubin, decreased hematocrit, and increased blood lactate dehydrogenase. A serious adverse reaction was aseptic meningitis syndrome (AMS).

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing. Use in pregnant women only if clearly needed. In patients over 65 or in any patient at risk of developing renal insufficiency, do not exceed recommended dose and infuse Privigen at the minimum rate practicable.

Please see brief summary of prescribing information for Privigen, including boxed warning, on adjacent page.

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www.CSLBehring-us.com **www.Privigen.com**
PVG13-11-0038 12/2013

Privigen®
Immune Globulin Intravenous (Human), 10% Liquid

Initial U.S. Approval: 2007

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Privigen safely and effectively. See full prescribing information for Privigen.

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including Privigen. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Privigen does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer Privigen at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

----------INDICATIONS AND USAGE----------

Privigen is an Immune Globulin Intravenous (Human), 10% Liquid indicated for the treatment of:

- Primary humoral immunodeficiency (PI)
- Chronic immune thrombocytopenic purpura (ITP)

----------DOSAGE AND ADMINISTRATION----------

Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (as tolerated)
PI	200-800 mg/kg (2-8 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 8 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (10 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.005 mL/kg/min)	Increase to 4 mg/kg/min (0.04 mL/kg/min)

- Ensure that patients with pre-existing renal insufficiency are not volume depleted, and discontinue Privigen if renal function deteriorates.
- For patients at risk of renal dysfunction or thrombosis, administer Privigen at the minimum dose and infusion rate practicable.

----------DOSAGE FORMS AND STRENGTHS----------

Privigen is a liquid solution containing 10% IgG (0.1 g/mL).

----------CONTRAINDICATIONS ----------

- History of anaphylactic or severe systemic reaction to human immune globulin
- Hyperprolinemia (Privigen contains the stabilizer L-proline)
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity

----------WARNINGS AND PRECAUTIONS----------

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Thrombosis may occur with immune globulin products, including Privigen.
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur.
- Aseptic meningitis syndrome (AMS) may occur, especially with high doses or rapid infusion.
- Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to Privigen treatments. Risk factors for hemolysis include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.
- Privigen is made from human blood and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

----------ADVERSE REACTIONS----------

- **PI** – The most common adverse reactions, observed in >5% of study subjects, were headache, fatigue, nausea, chills, vomiting, back pain, pain, elevated body temperature, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/ effusion, influenza-like illness, pharyngolaryngeal pain, urticaria, and dizziness. Serious adverse reactions were hypersensitivity, chills, fatigue, dizziness, and increased body temperature.
- **Chronic ITP** – The most common adverse reactions, observed in >5% of study subjects, were headache, elevated body temperature, positive direct antiglobulin test (DAT), anemia, nausea, epistaxis, vomiting, blood bilirubin unconjugated increased, blood bilirubin conjugated increased, blood total bilirubin increased, hematocrit decreased, and blood lactate dehydrogenase increased. A serious adverse reaction was aseptic meningitis.

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

The passive transfer of antibodies may:

- Lead to misinterpretation of the results of serological testing.
- Interfere with the response to live virus vaccines.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed.
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Privigen at the minimum rate practicable.

Based on November 2013 revision.

Research

Tuberculosis Vaccine Effective as Treatment for MS

A recent study shows that a vaccine typically used to prevent tuberculosis in countries outside of the U.S. could also prevent multiple sclerosis (MS) in people who are in the beginning stages of the disease. In the study, researchers looked at 73 patients who showed early signs of MS, 33 of whom received one injection of the Bacille Calmette-Guerin (BCG) vaccine, while the others received a placebo. After six months of brain scans, all the participants received another MS drug called interferon beta-1a for one year, followed by whatever MS drug their neurologist prescribed. Immediately following the BCG vaccine,

all patients were evaluated for definite MS for five years. Six months into the study, patients who received the vaccine had a lower-than-average number of brain lesions (three) that are indicative of MS compared with the placebo group that had seven lesions. No major differences in side effects were noticed between the two groups by the end of the study. Altogether, 58 percent of the vaccinated group hadn't developed MS, which was almost twice that of the placebo group (30 percent). Typically, half of all patients in the early stage of MS, known as the clinically isolated syndrome, develop a clinically definite form of MS within two years of diagnosis, while 10 percent remain unchanged. The study was reported on in the Dec. 4 issue of *Neurology*. ❖

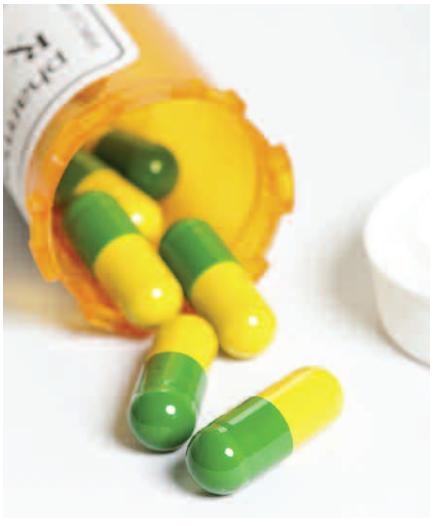
Research

Discharged Patients Who Skip Antibiotic Likely to Be Rehospitalized

A new study has found that patients who skip an antibiotic often used by hospitals to combat infection during patients' stays and prescribed to continue that fight after discharge are more likely to return to the hospital. The antibiotic, linezolid, is available in both oral and intravenous forms, and has received high marks for its ability to treat difficult infections, including ventilator-acquired pneumonia and skin and soft-tissue infections. The drug is given intravenously while the patients are hospitalized and then in pill form after discharge.

Published in *The American Journal of Managed Care*, the study was led by Margaret K. Pasquale, PhD, of Comprehensive Insights, a subsidiary of Humana Inc., which jointly funded the study with Pfizer Inc., marketer of linezolid. In the study, researchers used Humana's database to identify Medicare patients prescribed oral linezolid between June 1, 2007, and April 30, 2011. A total of 1,062 Medicare patients were identified, 16.5 percent who reversed a prescription for the drug. Among those reversing prescriptions, 73 percent received a different antibiotic and 27 percent received no antibiotic. But, the savings for this group overall was short-lived; infection-related hospitalizations were 14 percent higher for this group than for those who took linezolid as prescribed (23 percent vs. 9 percent), and the mean post-discharge cost was $1,280.93 higher than those who took the drug as directed.

Researchers speculated that high costs drive the decision to not fill prescriptions, as evidenced by the fact that the poorest patients were more likely to fill their orders for oral linezolid, since they had the lowest out-of-pocket costs. Oral linezolid is an expensive medication, and researchers found varying co-payment and co-insurance levels among the study population. The mean out-of-pocket cost for recipients with a co-payment was $7.05, while the mean out-of-pocket cost for those who paid a percent of co-insurance was $466.52. Of those patients whose out-of-pocket costs



exceeded $100, 27 percent did not fill the prescription. "If economic factors did indeed influence the decision to fill or reverse the linezolid prescription, then strategies to reduce member out-of-pocket costs (e.g., benefit design) for all health plan members could enable better member access and, in turn, reduce total healthcare costs," the researchers wrote. ❖

Research

Flu Vaccine May Work Better in Women

New research shows that women have a stronger immune response than men when given the flu vaccine, which may mean vaccinated women are better protected against catching the flu than vaccinated men. In the study, researchers examined the inflammatory responses of 53 women and 34 men following a flu vaccination. They found that men had a weaker response, or less inflammation in their bodies, than women after receiving the vaccine, and the response was weakest among some of the men who had the highest testosterone levels. The finding "reinforces the message that there are major differences between men and women in terms of their immune systems," said Mark Davis, one of the study's researchers and a professor of microbiology and immunology at Stanford School of Medicine. While this study didn't look directly at whether men and women have different levels of flu protection after vaccination, Davis said other studies suggest they do.

Why men and women have different levels of protection is unclear, but genetics are suspected. The researchers found that the vaccine activated certain genes, and this activation predicted who would have the weakest flu shot response. "There were a set of genes that were activated, or up-regulated, in men, and that showed the difference," said David Furman, a postdoctoral researcher in Davis' lab and first author on the study. "It turns out that those having the highest testosterone levels and the expression of these gene signatures" have a bad immune response to the vaccine. "It turns out that testosterone suppresses inflammation, and that inflammation can be a problem in lots of circumstances. It's a necessary part of immunity … but if it gets out of hand, it can kill you," explained Davis.

Davis hopes that their study will open the door for subsequent research in this area, including a study that might suggest ways of improving flu shots, perhaps by adding an ingredient to shots given to men. ❖

People and Places in the News

ALLIANCES

Clinical Research Advantage (CRA), the country's largest wholly owned network of clinical trial sites, has acquired the late phase division of Comprehensive Clinical Development to allow CRA to offer pharmaceutical sponsors and contract research organizations an across-the-board solution for their diverse **clinical research** needs. CRA includes 63 sites listed under "CRA" and "Radiant Research." Both brands are known as leaders in Stage II-IV clinical trials. CRA focuses on family practice and general medicine, while Radiant conducts multi-specialty and consumer trials.

Merck & Co. will work with Pfizer Inc., Amgen Inc. and Incyte Corp. to find the most-promising combination treatments for its top pipeline prospect, MK-3475, an immune system-based **cancer** medicine. The drug is one of a new class of experimental treatments called PD-1 inhibitors that use the body's own immune system to attack and kill tumors.

The U.S. National Institutes of Health and its foundation, the U.S. Food and Drug Administration and a pharmaceutical trade group, along with 10 major drugmakers and six disease-related foundations, will commit a combined $230 million to focus on complex chronic disorders: **Alzheimer's**, **type 2 diabetes** and the autoimmune disorders **rheumatoid arthritis** and **lupus**.

Several large European pharmaceutical companies are teaming up with universities, small- and medium-sized enterprises, patient groups and regulators to deliver new treatments for **systemic autoimmune disease**. The new collaborative effort, working under the name PRECISESADS, will study 2,000 patients living with systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, rheumatoid arthritis, primary antiphospholipid syndrome and mixed connective tissue disease, as well as 600 healthy controls, to identify overlapping clusters of individuals across these diseases that share recognizable molecular features and that consequently may benefit from treatments targeting these diseases. ❖

Did You Know?

The American Academy of HIV Medicine (AAHIVM), AIDS Community Research Initiative of America (ACRIA) and the American Geriatrics Society (AGS) have launched HIV-Age.org, an online site for clinicians seeking best practices for managing the care of older HIV patients. By 2015, half of the U.S. HIV population will be age 50 and older. Other individuals, such as patients, researchers, media and HIV advocates, will also find the content and resources useful in understanding the latest in managing the care of older Americans with HIV. The website is a continuation of the HIV and Aging Consensus Project, developed to assess how the presence of both HIV and common age-associated diseases alter the optimal treatment of HIV, as well as other co-existing medical conditions. As part of this project, in 2011, AAHIVM, AGS and ACRIA released the first clinical treatment strategies for managing older HIV patients: *Recommended Treatment Strategies for Clinicians Managing Older Patients with HIV.* The report, developed by a panel of experts with experience in the fields of HIV and geriatrics, provides guidance for HIV clinicians and other healthcare providers who treat, diagnose and refer older patients with HIV disease.

— American Academy of HIV Medicine

Guidelines

ACIP Revises Recommended Adult Immunization Schedule

In October, the Advisory Committee on Immunization Practices (ACIP) approved the Recommended Immunization Schedule for Adults Aged 19 Years or Older for 2014. The changes for 2014 are as follows:

• Adults who have had a successful hematopoietic stem cell transplant are recommended to receive a three-dose series of Haemophilus influenzae type B vaccine 6 months to 12 months after transplant regardless of prior Hib vaccination. Prior Hib vaccine guidance recommended that Hib vaccination of persons infected with human immunodeficiency (HIV) be considered, but updated guidance no longer recommends Hib vaccination of previously unvaccinated adults with HIV infection because their risk for Hib infection is low.

• Information on recombinant influenza vaccines (RIVs) and the use of RIVs and inactivated influenza vaccines (IIVs) among egg-allergic patients was added to the footnote and indicates that RIVs and IIVs can be used among persons with hives-only allergy to eggs. RIVs contain no egg protein and can be used among persons aged 18 years through 49 years who have egg allergy of any severity.

• The tetanus, diphtheria and pertussis (Td/Tdap) vaccine footnote was edited to harmonize language used in the pediatric immunization schedule. A single dose of Tdap vaccine is recommended for previously unvaccinated persons aged 11 years or older, and a Td booster should be administered every 10 years thereafter. Pregnant women are still recommended to receive one dose of Tdap vaccine during each pregnancy, preferably during 27 weeks' to 36 weeks' gestation, regardless of the interval since the prior dose of Tdap or Td vaccine.

• Information was added to the human papillomavirus (HPV) footnote to clarify the timing between the second and third doses and to harmonize language between the pediatric and adult immunization schedules; no changes in recommendations were made.

• The HPV vaccine and the zoster vaccine footnotes were simplified, with removal of the bullet regarding healthcare personnel (HCP). Being a healthcare worker is not a specific indication for these vaccines, but they should be given to HCP and others who meet age and other indications for these vaccines.

• Because pneumococcal conjugate vaccine PCV13 is recommended to be administered before the pneumococcal polysaccharide vaccine PPSV23 among persons for whom both vaccines are recommended, the PCV13 footnote now precedes the PPSV23 footnote and includes wording to remind providers of the appropriate order of these vaccines when both are indicated.

• The meningococcal vaccine footnote was edited to clarify which persons need either one or two doses of vaccine and to provide greater clarity regarding which patients should receive the meningococcal conjugate versus the meningococcal polysaccharide quadrivalent vaccines.

The full 2014 schedule is published in the *Annals of Internal Medicine*. This year, the figures, footnotes and tables are not being published in Centers for Disease Control and Prevention's (CDC's) *Morbidity and Mortality Weekly Report*, but will be posted and maintained on the CDC's website at www.cdc.gov/vaccines/schedules to facilitate updating the schedule during the year, if needed. ❖

Research

Vaccine Developed to Prevent the Return of Breast Cancer

Australian scientists have developed a vaccine that can prevent breast cancer from returning, and it is hoped that the vaccine will be on the market within five to 10 years. Trials of the vaccine in 31 women have shown it slashes the rate of breast cancer returning from 60 percent to just 12 percent over a 15-year period.

The team behind the discovery identified a protein called mucin 1 that is different on cancer cells than normal cells. Ninety percent of breast cancers carry the mucin 1 protein, which is also present in between 60 percent and 90 percent of many other types of cancer. The researchers then developed a sugar polymer, mannan, from baker's yeast that was able to bind to the mucin 1 protein and attached a cancer antigen into it. When it is injected into the body, it prompts the body's immune system to fight cancer cells.

In the mid 1990s, the researchers injected 16 women who had been treated for early breast cancer with the vaccine, and another 15 received a placebo. The women in the trial received an injection every two weeks for three months and received two boosters at six months and nine months when the treatment ceased. Fifteen years later, nine of the patients who received the placebo had seen their cancer return, while only two women who received the vaccine had a recurrence. And, the cancer took much longer to return in the women who received the vaccine — 118 months after their first surgery for the two vaccinated women compared with 65 months for those on the placebo.

A second trial of approximately 50 women is being planned and will involve women with matastatic cancer to see if it will work for them. Ascend Pharmaceuticals is looking for funding to run the second trial before proceeding to a full-blown clinical trial. The vaccine could also be useful in treating and preventing pancreatic, ovarian, colon and lung cancer. ❖

Vaccine Update

AC Immune has launched the world's first trial of a vaccine against a protein believed to cause **Alzheimer's**. Its ACI-35 vaccine aims to stimulate the immune system to produce antibodies that target the tau protein that forms twisted fibers and tangles inside the brain. The company has another vaccine, ACI-24, in Phase I/IIa clinical trials to prevent and clear amyloid plaques, another hallmark of the fatal brain-wasting disease.

A worldwide clinical trial that tests a newly developed **clostridium difficile (C-diff)** vaccine is seeking study participants. The Cdiffense vaccine, which was granted fast track approval by the U.S. Food and Drug Administration in 2010, is made by French pharamaceutical company Sanofi Pasteur. The study seeks to enroll 15,000 participants in 17 countries over the next four years. All participants must be 50 years or older who are deemed to be at high risk of developing C-diff, a deadly superbug. Participants will be separated into two groups. Group one will include former patients who have had at least two 72-hour hospital stays in the last 12 months and who have received systemic antibiotics during their stays. Group two will include anyone who anticipates hospitalization for a planned surgical procedure that involves certain areas of the body in the next 60 days and whose planned stay is for at least 72 hours. Those who participate will receive three doses of the vaccine or a placebo within a month's time. The study will follow up with each participant to see if they contracted C-diff after getting the vaccine. More information can be obtained by calling (877) 500-3788 or visiting www.cdiffense.org.

Researchers at the Instituto Gulbenkian de Ciência and Instituto de Tecnologia Química e Biológica in Portugal and colleagues from the Department of Biochemistry at the University of Washington and The Scripps Research Institute have designed a vaccine for the human-infecting **respiratory syncytial virus (RSV)**. The vaccine was tested in rhesus monkeys (which have a very similar immune system to humans), and proved to induce protective antibodies. Scientists have struggled to make a vaccine for the RSV for a long time without success because, like influenza, hepatitis C and HIV, these viruses change so fast that vaccines (and the immune memory they trigger) become obsolete very quickly. To create the new RSV vaccine, the researchers designed new protein scaffolds that induce epitope-specific neutralizing antibodies (antibodies capable of blocking the effects of the pathogen). According to the researchers, "The results provide proof of principle for epitope-focused and scaffold-based vaccine design, and encourage the evaluation and further development of these strategies for a variety of other vaccine targets, including antigenically highly variable pathogens such as human immunodeficiency virus and influenza." ❖

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Supply Chain Safety:
Where Are We Now?

New legislation, increased education, and high-tech tracking aim to curb the proliferation of compromised and counterfeit products in the pipeline.

By Trudie Mitschang

Supply chain safety made headlines in 2013, and not for positive reasons. In a well-publicized story, GlaxoSmithKline announced a recall of its asthma drug Ventolin after its contract manufacturer said that the syrup bottles might have been contaminated with glass particles. Also last year, *The New York Times* reported that the U.S. suffered shortages of injectable drugs due to quality failures at large manufacturers such as Hospira. And, in what "60 Minutes" described as "the worst pharmaceutical disaster in decades," 48 people died in a meningitis outbreak that was traced back to contaminated production in a Massachusetts compounding pharmacy.

While strides have been made in terms of improving the safety, efficacy and security of the pharmaceutical supply chain, there is still much work to be done. Millions of prescriptions are processed every year in the U.S., and simply keeping track of these legal medications is a daunting task. When you factor in the increasing numbers of illegally imported medicines and counterfeit drugs, it's easy to see how successfully policing the supply chain is easier said than done, especially when sales of counterfeit drugs continue to skyrocket.

According to the World Health Organization (WHO), global sales of counterfeit medicines in the marketplace and from online pharmacies represented an estimated $431 billion in 2012, and nearly 84 percent ($359 billion) had a direct impact on public health. Counterfeit formulations can range from random mixtures of inactive, ineffective preparations to harmful or even deadly concoctions, and all pose a very real threat to public health.[1]

"We've made progress in terms of awareness, but there is still a lot that needs to be done, including federal legislation and more education for both healthcare professionals and consumers," says Katherine Eban, investigative journalist and author of *Dangerous Doses*, an in-depth exposé on counterfeiting operations within the pharmaceutical supply chain. "Since my book was published, the FDA [U.S. Food and Drug Administration] has encouraged the industry to implement electronic pedigrees, but so far we're only seeing a response at the state level. Drug counterfeiting is a problem that is only going to get bigger as time goes on."

The Counterfeit Conspiracy

Federal officials document that, in recent years, many American consumers have purchased counterfeit versions of major brand-name drugs, including Adderall, Vicodin, Viagra and Xanax. Spurred by the success of these crimes, counterfeiters have begun feeding the pipeline with everything from counterfeit flu medications to cancer drugs. Counterfeit prescription drugs have become an exploding industry, with an estimated market worth $75 billion a year worldwide, fueled by online sales, global demand and skyrocketing profitability. Long the scourge of developing countries, fake drugs are now available at alarming rates within the United States.[2]

WHO defines counterfeit drugs as "those which are deliberately and fraudulently produced and/or mislabeled with respect to identity and/or source." Counterfeits are actually just one part of the broader problem of substandard pharmaceuticals, meaning products whose composition do not meet correct scientific specifications are consequently ineffective and often dangerous to the patient. The WHO fact sheet goes on to say that substandard medicines can result from many factors, including negligence, human error, insufficient resources or counterfeiting. Both branded and generic medicines can be considered counterfeit or substandard.

A drug may be considered counterfeit for many reasons, including:

- too much or not enough active ingredient
- no active ingredient
- the wrong active ingredient
- dangerous excipients and dyes
- the wrong ingredients but authentic packaging
- the correct ingredients but fake packaging
- the wrong ingredients, as well as fake packaging

While strides have been made in terms of improving the safety, efficacy and security of the pharmaceutical supply chain, there is still much work to be done.

In today's global marketplace, no one is truly safe from the effects of counterfeit drugs. It's a growing problem worldwide, with drug counterfeiters actively defrauding consumers and interfering with patient therapies that are necessary to alleviate suffering and save lives. Even if the ingredients are correct, counterfeit packaging may include mislabeling, false expiration dates and inaccurate information about dosage and origin.

While both industrialized and developing countries are impacted by drug counterfeiting, developing countries typically suffer the highest number of fatalities, in part because of the high number of pirated drugs that are being used to treat serious diseases like malaria, tuberculosis and HIV/AIDS. WHO estimates that nearly 200,000 people die each year because of fake malaria drugs. It is also estimated that between 1 percent and 10 percent of drugs sold around the world are counterfeits, up to as many as 50 percent in some countries.[3]

An Evolving Problem in North America

For decades, North America has seen the lion's share of counterfeits show up in the lifestyle rather than life-saving drug category. Among the most popular counterfeits is Pfizer's Viagra, now considered one of the most counterfeited drugs in the world. According to John Clark, vice president of global security for the company, about 60 different Pfizer medicines and products are currently being counterfeited around the world — everything from Lipitor to Centrum vitamins. Other popular counterfeits include diet pills, hair restoration pills and other "vanity" medications that become the entryway for criminals looking for easy money.[1]

In 2012, a counterfeit version of the cancer drug Avastin was widely distributed in the U.S., and a fake version of the attention deficit hyperactivity disorder drug Adderall, in high demand because of a shortage, arrived in the U.S. through unethical Internet pharmacies. Avastin is an injectable drug, used often in combination with chemotherapy, to treat patients with colon, lung and other cancers. In the U.S., a 400-milligram vial of the authentic drug — the size that was counterfeited — costs $2,400, according to Genentech. The counterfeit Avastin was made of salt, starch and other chemicals, and packaged in counterfeit boxes that included French writing and Roche's name. In the U.S., the genuine product's boxes are labeled in English and bear the Genentech imprint.[4]

In today's global marketplace, no one is truly safe from the effects of counterfeit drugs.

In early 2013, FDA warned doctors that a fake version of the cancer drug Altuzan was being distributed in the U.S. This particular counterfeit contained no active ingredients, making it potentially deadly for patients seeking life-saving therapies.[4]

In response to these and other crimes, the FDA stated in a letter to the healthcare community: "FDA is requesting that the medical practices stop administering drugs purchased from any foreign or unlicensed source. FDA urges the healthcare community to examine their purchasing practices to ensure that they buy directly from the manufacturer or from licensed wholesale drug distributors in the United States." The letter went on to admonish healthcare professionals, pharmacies and wholesalers/distributors of the role they play in protecting consumers from the threat of unsafe or ineffective products that may be stolen, counterfeit, contaminated or improperly stored and transported.[5]

New Legislation Promises to Track and Trace

In response to the alarming number of new counterfeits in the U.S. supply chain, the U.S. House of Representatives passed a new "track and trace" bill late last year. According to a news release from the U.S. Senate HELP committee, the Drug Quality and Security Act (H.R. 3204) is intended to help ensure the safety of compounded drugs and will track all prescription drugs from the manufacturer to the pharmacy.[6]

When it comes to compounded drugs, the proposed legislation distinguishes compounders engaged in traditional pharmacy practice from those making large volumes of compounded drugs without individual prescriptions; defines FDA's role in oversight of outsourcing facilities; offers providers and patients information about compounded drugs; and clarifies current federal law regarding pharmacy compounding.

More specifically, traditional pharmacies will continue to be primarily regulated by state boards of pharmacy. But, compounders who wish to practice outside the scope of traditional pharmacy practice can register as outsourcing facilities subject to FDA oversight in much the same way as traditional manufacturers. Providers and patients have the option of purchasing products from outsourcing facilities that comply with FDA quality standards.

As far as the track and trace proposal, the legislation develops a pathway to unit-level tracing in the next decade; strengthens licensure requirements for wholesale distributors and third-party logistics providers; and establishes nationwide drug serial numbers, currently a huge roadblock when it comes to tracking and tracing products in the supply chain.[6]

Creating a Global Initiative

In March 2013, INTERPOL, the world's largest police organization, announced that it will partner with 29 of the world's largest pharmaceutical companies to create an enhanced pharmaceutical crime program to combat counterfeit medicines.[7] "With no country, no drug, no medical product immune from counterfeiting, a global effort is needed to combat this threat, which puts the lives of millions of people at risk every single day," said INTERPOL Secretary General Ronald K. Noble. "This support from a group of 29 companies from the pharmaceutical industry forms a bridge between the public and private sectors and will assist INTERPOL and each of its 190 member countries to more effectively tackle the problem of medical product counterfeiting."

The three-year deal will see the creation of INTERPOL's Pharmaceutical Crime Program to further build on the work of its Medical Product Counterfeiting and Pharmaceutical Crime (MPCPC) unit. According to INTERPOL, an essential part of the program is to raise public awareness of the dangers of fake drugs, particularly for people buying medicines online. WHO estimates that in more than 50 percent of cases, medi-

cines purchased over the Internet from illegal sites that conceal their physical address have been found to be counterfeit, yet most consumers remain ignorant of this fact.

"In the case of drug counterfeiting, it can mean the difference between life and death for a patient," said Christopher Viehbacher, chief executive officer, Sanofi. "It is estimated that 10 percent of medicines are fake, and these figures can go up to 50 percent, particularly in some poorer countries. This is why it is so important that industry members partner with INTERPOL to coordinate law enforcement operations around the world so that we can help curtail the threat of counterfeit medicines online and at the retail level."

"Drug counterfeiters put at risk the health of patients around the world by producing substandard and sometimes lethal medicines," said John C. Lechleiter, PhD, chairman, president and chief executive officer of Eli Lilly and Company. "Putting an end to counterfeiting requires broad, coordinated action on a global scale. This new initiative between the pharmaceutical industry and INTERPOL is aimed at helping ensure that patients can trust in the safety and efficacy of the medicines they rely on."

The Consumer Component

Human behavior will always be a wild card when it comes to regulating pharmaceutical supply chain safety. While new initiatives, laws and systems are steps in the right direction, the problem of supply chain safety is not simply about supply; it's also about demand. As consumers continue to be enticed by the availability of hard-to-find drugs and gray market pricing available through fake online pharmacies, many will continue to make purchases outside of the secure supply chain, despite the inherent risks. From travelers restocking their medicine cabinets while on vacation to Internet shoppers hoping to score deep discounts on pricey lifestyle medications, purchasing products well below retail has a high level of consumer appeal. For many Americans, the decision to seek alternative methods of obtaining prescription medication is a simple one: It's the only way they can afford the drugs they need. According to the Centers for Disease Control and Prevention, 25 million Americans did not take prescribed medication in 2009 due to the high U.S. drug costs, and the Commonwealth Fund found that 48 million American adults didn't fill their prescription because of high drug costs in 2010. By contrast, drugs purchased online from other countries can cost anywhere between 80 percent and 90 percent less than those sold in reputable U.S. pharmacies.[8]

According to many industry experts, education about the risks associated with online transactions needs to significantly increase. For example, many U.S. consumers would avoid making a pharmaceutical purchase from a third world country for obvious reasons. But, those same consumers might feel very comfortable purchasing from neighboring Canada. Unfortunately, that confidence is falsely placed: A 2005 FDA drug bust examined nearly 4,000 packages at airports in New York, Miami and Los Angeles, and found that 85 percent of the drugs ordered from what customers believed were Canadian pharmacies actually came from 27 other countries. Not surprisingly, a number of the products were also found to be counterfeit.[9]

Human behavior will always be a wild card when it comes to regulating pharmaceutical supply chain safety.

The battle to secure the pharmaceutical supply chain is far from over, and despite some victories, there are no simple solutions to this widespread and multipronged problem. Organized efforts by pharmaceutical companies, government agencies and consumer groups will need to pursue increased education and more stringent legislation if we ever hope to curb the distribution and sale of compromised and counterfeited drugs. ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

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WHAT YOU SHOULD KNOW ABOUT
HEMOLYTIC DISEASE OF THE NEWBORN (HDN)



QUESTIONS AND ANSWERS

What is hemolytic disease of the newborn (HDN)?

If your body has produced antibodies to fight the antigens on your baby's red blood cells, a blood disorder called hemolytic disease of the newborn (HDN)—sometimes called rhesus (Rh) disease—can result. It is important to know that your body's production of these antibodies does not necessarily lead to HDN. But if it does, the results can be life-threatening, manifesting as anemia, jaundice, heart or liver problems, or mental retardation. Before any preventative treatment had been developed, HDN affected 1% of babies in second pregnancies born to Rh negative women in England and Wales.

What can happen if I have a different Rh blood group than my baby?

Having a different Rh blood group than your baby is only a potential problem if you are Rh negative and your baby is Rh positive. If a small amount of your baby's blood mixes with yours during pregnancy, your immune system may perceive this difference in blood type as a threat, producing antibodies that fight against your baby's blood. This process is called *sensitization* or *alloimmunization*, and once your body has made these antibodies, they cannot be removed. Sensitization is unlikely to affect your first pregnancy, but instead becomes a problem in any subsequent pregnancy if your baby is Rh positive. This is because the process of producing antibodies takes time. The initial antibodies you produce in your first pregnancy (IgM) cannot cross the placenta. These IgM antibodies are replaced by IgG antibodies—which can cross the placenta and adversely affect future pregnancies.

What are anti-D (RhD immunoglobulin) injections and when are they recommended?

Anti-D injections are given to pregnant women who are Rh negative as a means of preventing antibodies from forming against the baby's red blood cells. Anti-D injections are recommended after potentially sensitizing events that could result in a fetal/maternal hemorrhage: invasive procedures (amniocentesis), abdominal trauma, and delivery (C-section or vaginal).

If a patient fails to receive prophylactic RhD immunoglobulin at 28 weeks, when should she receive the first dose?

The dose should be given as soon as possible after it is recognized that the dose was missed. In such a case the second dose should be delayed until 6 weeks after the first dose.

COOMBS TEST

The Coombs test detects Rh incompatibility between mother and fetus.

To detect HDN, the presence of maternal anti-Rh immunoglobulin G (IgG) must be identified. In vivo, these antibodies destroy Rh positive fetal red blood cells (RBCs), but in vitro, they do not lyse cells or even cause agglutination, making them difficult to identify. Therefore, the Coombs test is used. This test uses antibodies that bind to human anti-D antibodies.

Reactions to Rh_0(D) immune globulin (human) are infrequent in Rh_0(D)-negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immunoglobulin is extremely rare, it has occurred.

Please see adjacent page for brief summary of full prescribing information.

Hyper**RHO**® S/D Full Dose

Rh_O(D) Immune Globulin (Human)

Solvent/Detergent Treated

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAMUSCULAR INJECTION ONLY

INDICATIONS AND USAGE

Pregnancy and Other Obstetric Conditions

Rh_O(D) Immune Globulin (Human) — Hyper**RHO**® S/D Full Dose is recommended for the prevention of Rh hemolytic disease of the newborn by its administration to the Rh_O(D) negative mother within 72 hours after birth of an Rh_O(D) positive infant, providing the following criteria are met:

1. The mother must be Rh_O(D) negative and must not already be sensitized to the Rh_O(D) factor.
2. Her child must be Rh_O(D) positive, and should have a negative direct antiglobulin test (see PRECAUTIONS).

If Hyper**RHO** S/D Full Dose is administered antepartum, it is essential that the mother receive another dose of Hyper**RHO** S/D Full Dose after delivery of an Rh_O(D) positive infant.

If the father can be determined to be Rh_O(D) negative, Hyper**RHO** S/D Full Dose need not be given.

Hyper**RHO** S/D Full Dose should be administered within 72 hours to all nonimmunized Rh_O(D) negative women who have undergone spontaneous or induced abortion, following ruptured tubal pregnancy, amniocentesis or abdominal trauma unless the blood group of the fetus or the father is known to be Rh_O(D) negative. If the fetal blood group cannot be determined, one must assume that it is Rh_O(D) positive, and Hyper**RHO** S/D Full Dose should be administered to the mother.

Transfusion

Hyper**RHO** S/D Full Dose may be used to prevent isoimmunization in Rh_O(D) negative individuals who have been transfused with Rh_O(D) positive red blood cells or blood components containing red blood cells.

CONTRAINDICATIONS

None known.

WARNINGS

HyperRHO** S/D Full Dose is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics Inc. [1-800-520-2807].**

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

NEVER ADMINISTER HYPER**RHO** S/D FULL DOSE INTRAVENOUSLY. INJECT ONLY INTRAMUSCULARLY. NEVER ADMINISTER TO THE NEONATE.

Rh_O(D) Immune Globulin (Human) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer Rh_O(D) Immune Globulin (Human) to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

PRECAUTIONS

General

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. If there is any doubt about the mother's Rh type, she should be given Rh_O(D) Immune Globulin (Human). A screening test to detect fetal red blood cells may be helpful in such cases.

If more than 15 mL of D-positive fetal red blood cells are present in the mother's circulation, more than a single dose of Hyper**RHO** S/D Full Dose is required. Failure to recognize this may result in the administration of an inadequate dose.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic reactions.

Drug Interactions

Other antibodies in the Rh_O(D) Immune Globulin (Human) preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Rh_O(D) Immune Globulin (Human) administration.

Drug/Laboratory Interactions

Babies born of women given Rh_O(D) Immune Globulin (Human) antepartum may have a weakly positive direct antiglobulin test at birth.

Passively acquired anti-Rh_O(D) may be detected in maternal serum if antibody screening tests are performed subsequent to antepartum or postpartum administration of Rh_O(D) Immune Globulin (Human).

Pregnancy Category C

Animal reproduction studies have not been conducted with Hyper**RHO** S/D Full Dose. It is also not known whether Hyper**RHO** S/D Full Dose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyper**RHO** S/D Full Dose should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Reactions to Rh_O(D) Immune Globulin (Human) are infrequent in Rh_O(D) negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immune globulin is extremely rare, it has occurred. Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_O(D) Immune Globulin (Human) following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

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Rare Adverse Effects of Human Immunoglobulin Therapy

Less-common adverse reactions to IG therapy are rare, but they are more severe.

By E Richard Stiehm, MD

Human immunoglobulin (IG) is used for IgG replacement therapy in primary and secondary immunodeficiency for prevention and treatment of certain infections, and as an immunomodulatory agent for autoimmune and inflammatory disorders. IG has a wide spectrum of antibodies to microbial and human antigens. Several high-titered IGs are also available enriched in antibodies to specific viruses or bacterial toxins. IG can be given intravenously (IVIG), intramuscularly (IGIM) or by subcutaneous infusions (SCIG).

Local adverse reactions such as persistent pain, bruising, swelling and erythema are rare with IVIG infusions but common (75 percent) with SCIG infusions. By contrast, adverse systemic reactions are rare with SCIG infusions but common with IVIG infusions, occurring in as often as 20 percent to 50 percent of patients and 5 percent to 15 percent of all IVIG infusions. Systemic adverse reactions can be immediate (60 percent of reactions) occurring within six hours of an infusion, delayed (40 percent of reactions) occurring six hours to one week after an infusion, and late (less than 1 percent of reactions) occurring weeks and months after an infusion. Immediate systemic reactions such as head and body aches, chills and fever are usually mild and readily treatable. Immediate anaphylactic and anaphylactoid reactions are uncommon. The most common delayed systemic reaction is persistent headache.

Less common but more serious delayed reactions include aseptic meningitis, renal failure, thromboembolism and hemolytic reactions. Late reactions are uncommon but often severe, and include lung disease, enteritis, dermatologic disorders and infectious diseases. The types, incidence, causes, prevention and management of these reactions are discussed.

Pathogenesis of Adverse Events

Adverse reactions may be due to the antigenicity of the IgG itself, large molecular weight IgG aggregates, the presence of an antibody to circulating microbial antigens or self antigens, complement activation or direct release of cytokines from mononuclear cells. The product may contain low molecular weight kinins or kallikreins or procoagulant factors not removed during fractionation.

The presence of these factors vary considerably from brand to brand and even lot to lot of the same product. The presence of factors in the product can sometimes be identified, e.g., high levels of IgA causing anaphylactic reactions, erythrocyte antibodies causing hemolytic reactions, or procoagulant activity causing thrombotic episodes (Table 1).

A search for the cause of a reaction is often unrewarding, although the product can be tested for erythrocyte antibodies, procoagulant activity and autoimmune antibodies. Post-infusion serum levels for tryptase, complement activation products or circulating immune complexes may help define the type of reaction that has occurred.

Adverse effects may occur with any IVIG product, so switching brands may not prevent another reaction.

Less Common Specific Adverse Reactions

Anaphylactic/anaphylactoid reactions. Anaphylaxis with urticaria, itching, flushing, chest tightness, dyspnea and wheezing, acute anxiety and circulatory collapse is most uncommon. This usually occurs shortly after the start of the infusion. Anaphylaxis usually occurs in patients with some ability to make antibody, notably non-immunodeficient patients, or immunodeficient patients that can make some antibody, e.g., selective IgA deficiency and common variable immunodeficiency. These reactions are treated with epinephrine, antihistamines, corticosteroids, fluids and oxygen as needed. No fatalities have been reported.

Anaphylactic reactions have not been reported with SCIG; indeed, patients with anaphylactic reactions to IVIG may tolerate slow SCIG.[1,2]

Anaphylactoid reactions resemble anaphylactic reactions but are not IgE mediated. They usually develop several hours after starting the infusion, and may not occur earlier or at all with subsequent infusions.

Serious side reactions are potentially life-threatening, and emphasize the necessity of close monitoring of patients during the infusions by trained personnel at a facility with emergency equipment and access to a facility near an emergency facility.

Anaphylaxis in IgA-deficient patients. Anaphylaxis following IVIG infusions may occur in patients with anti-IgA antibodies that react to the trace quantities of IgA found in most IVIG products.[3,4] Anti-IgA antibodies commonly develop in individuals with complete IgA deficiency who are exposed to IgA in IVIG or other blood products. These persons have some

Table 1. Factors in Some IG Products Associated with Adverse Effects

Microbial contamination (viruses, bacteria, endotoxins)
Immune complexes
Trace amounts of IgA
Low pH
Sugars: glucose, maltose, sucrose
High osmolality
High levels of sodium
Procoagulants
Vasoactive enzymes; kallikreins; others
Erythrocyte antibodies; Anti-A, -B, -D, -Kell; others
Antibodies to human leukocyte antigens
Antibodies to neutrophil or platelet antigens
Pathogenic autoimmune antibodies (e.g., antiphospholipid antibodies)
Procoagulant coagulation factors (Factor XIa)
Preservatives (thimerosal)

Table 2. Risk Factors for IG Adverse Effects

Infusion factors

1. Prior history of infusion reaction
2. First infusion
3. Large dose
4. Rapid dose
5. No pre-infusion or post-infusion hydration

Patient factors

1. Fever/infection at time of infusion
2. Autoimmunity
3. Older age
4. Immobility/air travel
5. Hypertension
6. Present or past cardiovascular disease
7. Diabetes
8. High lipids/cholesterol
9. Elevated serum proteins/gammopathy
10. Smoking
11. Prior/current thrombosis
12. Estrogen use
13. Hereditary hypercoagulable state (Factor V Leiden, prothrombin mutations, Protein C, S, or antithrombin III deficiencies)
14. Permanent indwelling venous catheter (i.e., Portacath)

antibody function; most have selective IgA deficiency or common variable immunodeficiency.[5,6] The anti-IgA antibodies are usually of the IgG class and only rarely of the IgE class, and either class of antibodies has been associated with rare anaphylactic reactions to IVIG. Indeed, most IVIG product brochures contain a warning of the risk of giving IVIG to patients with IgA deficiency. Note that IVIG therapy is not indicated as treatment for IgA deficiency without concomitant IgG antibody deficiency.[6]

Rachid and Bonilla found that anti-IgA antibodies are commonly present in normal individuals (2 percent to 7 percent) but are present in up to 30 percent of IgA-deficient individuals.[1] They identified only three reports of anaphylaxis associated with IgE anti-IgA antibodies, but identified 23 reports of anaphylaxis associated with IgG anti-IgA antibodies. Four other IgA-deficient patients had non-anaphylactic moderate systemic reactions. They also identified reports of 49 IgA-deficient patients with IgG anti-IgA antibodies who tolerated IG products.

Based on these studies, the consensus is that it is unnecessary to check IgA levels prior to an initial IVIG infusion for most patients. Nor is it necessary to measure anti-IgA antibodies in patients with IgA deficiency prior to IVIG infusions. Similar to other patients receiving their first IVIG infusion, premedication and a slow infusion rate should be used. Tests for IgA deficiency and anti-IgA antibodies should be sent in patients who experience a severe adverse reaction to IVIG. These patients (as well as other patients with a serious adverse reaction to IVIG) may be switched to SCIG infusions.[1,2] IgA-deficient patients and other patients with anaphylactic reactions to IVIG generally tolerate SCIG infusions well.[1,2]

Headaches/aseptic meningitis/central nervous system (CNS) complications. Headaches are a common complaint during or shortly after IVIG infusions. They often persist for several hours or even days. They may also have a delayed onset six to 12 hours after an infusion. Headaches are particularly common with high-dose IVIG therapy as used in neurologic or autoimmune diseases. Headaches usually subside within 24 hours and are responsive to analgesics. Occasionally, however, the headaches are associated with nausea and vomiting, muscle aches and prolonged malaise, and are refractory to non-narcotic analgesics.

Some headaches are persistent, severe and accompanied by neck stiffness, photophobia, fever and severe myalgia. Spinal puncture in early cases disclosed cerebrospinal fluid pleocytosis (both granulocytic and lymphocytic), elevated cerebral spinal fluid protein, and sterile viral or bacterial cultures, indicating a syndrome of aseptic meningitis. The first case of aseptic meningitis following IVIG was reported in 1988.[7] The onset is usually six hours to 24 hours after the infusion.[8] Patients with a history of migraine headaches are more susceptible to this complication.[9]

Aseptic meningitis is usually associated with high-dose IVIG therapy (1g/kg to 2 g/kg) for thrombocytopenia or neuromuscular diseases,[10,11] but has occasionally been observed in immunodeficient patients given standard doses.[12]

The cause of aseptic meningitis is not known, but its occurrence with high dose suggests that the CNS inflammatory response may result from small quantities of IgG in the cerebrospinal fluid, causing inflammation and osmotic shifts of the meninges. Some IVIG brands are more likely to cause aseptic meningitis for unknown reasons.

Jarius et al. have suggested that antineutrophil antibodies in some IVIG products may activate neutrophils in the CNS.[13]

Treatment consists of analgesics, antiemetics, and antimigraine therapy. Steroids or anti-TNF drugs can be used in severe cases. If IVIG must be continued, infusions should be given in smaller increments, with slower rates and with a different IVIG brand. Aseptic meningitis is very rare with SCIG.[14]

Other neurologic adverse events following IVIG infusions include encephalopathy, vasospasm, cerebral thrombosis, embolism, infarction and vasculitis.[15-20]

Renal complications. Renal insufficiency following IVIG is not uncommon, particularly in older individuals receiving high IVIG doses. Barton et al. in 1987 first reported renal failure after IVIG in a 39-year-old woman with lymphoma and cryoglobulinemia.[21] They postulated that immune complexes caused glomerular necrosis. Jordan in 1989 observed hematuria and proteinuria in three patients with glomerulonephritis given IVIG.[22] Schifferli et al. in 1991 observed an asymptomatic increase in serum creatinine in eight patients with chronic renal disease given IVIG.[23] Other patients have severe renal failure requiring dialysis.[24] Eighty-eight reports of renal failure or other features of renal dysfunction were reported to the U.S. Food and Drug Administration (FDA) from 1985 to 1998.[24] Most occurred in patients with pre-existing renal disease receiving a sucrose-containing IVIG product.

The first manifestation of renal toxicity is an increase of the BUN or creatinine, followed by oliguria and renal failure, peaking five to seven days following the infusions. This may be complicated by hemolysis, serum sickness, thrombosis, hyponatremia and hyperkalemia. The renal failure may require dialysis and renal transplantation.[24,25]

Nearly all such complications are associated with high-dose IVIG for hematologic or neurologic diseases in patients with pre-existing renal disease. Other risk factors include older age, diabetes, vascular disease and dysproteinemias such as multiple myeloma or cryoglobulinemia.

Most cases are attributable to the sugar stabilizers with the IVIG, particularly sucrose; the latter accounts for up to 88 percent of these reactions.[24] Maltose in IVIG has also been implicated.[26] Sucrose is not metabolized in the kidney; it localizes in the proximal tubule and causes swelling, osmotic nephrosis and injury to proximal renal tubules.[26-28] There is now an FDA black box warning on IVIG products containing sucrose.

Prevention and treatment include checking renal function prior to treatment, prehydration, avoiding volume depletion by diuretics, using slow infusion rates and limiting the IVIG dose to no more than 0.5 g/kg/day.

Thromboembolism. Thrombotic events associated with IVIG were first reported in 1986 by Woodruff et al. in four adults treated with IVIG for autoimmune thrombocytopenia.[29] Since then, multiple cases have been identified. The exact incidence is not known but may be as high as 10 percent in certain high-risk populations.[30,31] Patients receiving single IGIM injections, SCIG infusions and 5% IVIG for immunodeficiency are less likely to be affected, mostly because they receive low doses. Fatalities have been observed due to heart attacks, CNS thrombosis and veno-occlusive disease in transplant patients.[19,29-31]

Table 3. Minimizing Risk of Thrombosis for IVIG Infusions

1. Limit daily IVIG dose to 400 mg/kg to 500 mg/kg. If larger dose is needed, give repeat dose(s) on a subsequent day(s)
2. Consider pre-/post-infusion hydration
3. Use slow infusion rate, e.g., 50 mg/kg for first hour, 100 mg/kg/hour thereafter
4. Avoid "as tolerated" dose escalation
5. Premedicate with ASA or heparin/enoxaparin in high-risk patients
6. Test for hypercoagulable tests/viscosity/ dysproteinemias
7. Do Doppler tests for clots in bedridden patients

The thrombosis in 80 percent of reported cases is arterial (e.g., heart attack, stroke) occurring within hours or days of an infusion.[31-33]

Venous thrombosis (20 percent of cases) generally occurs days or weeks after an infusion (e.g., deep vein thrombosis, pulmonary embolism).

Local thrombosis at the site of infusion has been recorded.[34] CNS thromboses include cerebral sinus thrombosis and jugular vein thrombosis.[15,17-19] Thrombotic events have been listed as complications in several IVIG trials.[35-38]

Possible mechanisms are hyperviscosity, increased platelet count or adhesiveness, autoimmune procoagulant antibodies, or coagulation factors in the IVIG not removed by fractionation.[39-43] Certain IVIG brands with a high risk for thromboembolism contain activated factor XI. Several IVIG lots and a 16% product for subcutaneous use have been withdrawn from the U.S. market as a result of such procoagulant properties. New regulations may include routine testing for procoagulant properties.

Patient risk factors for thrombosis are multiple (Table 2). More than one risk factor multiplies the risk.[30] Preventive measures as listed in Table 3 include identifying high-risk patients, performing screening tests, prehydration and premedication such as aspirin and/or enoxaparin. Huang et al. reduced the rate of thrombosis associated with IVIG use in renal transplant recipients from nine in 275 infusions to none in 74 infusions using a protocol of pre-infusion hydration, aspirin/enoxaparin and slow infusion rate.[33] Tissue

plasminogen activator has been used in the treatment of thrombotic events.[44]

Hemolysis. IVIG administration may result in mild hemolytic reactions, usually due to the presence of anti-A or anti-B isoagglutinins or, less commonly, anti-D or anti-K antibodies.[45-51] These blood group antibodies often result in a slight degree of hemolysis, mild hyperbilirubinemia and a positive direct Coombs' test. These events are usually subclinical and thus overlooked. Isoagglutinin levels are variable in immunoglobulin preparations and are not routinely measured. Cross matching prior to IVIG is not usually done.

In some instances, significant hemolysis may occur with a fall in hemoglobin of 1 to 5 g/dL. Daw et al. recognized 16 cases of clinically significant hemolysis among 1,000 IVIG-treated adults (1.6 percent) given IVIG.[51] The decrease in hemoglobin was from 0.8 g/dL to 5.2 g/dL, and the cumulative dose of IVIG was 50 g to 350 g. Three patients required transfusions. Contributing factors included non-group O blood, female sex, a large cumulative IVIG dose and underlying inflammatory disease. Other risk factors that may contribute to clinically significant hemolysis include non-secretor status (with absence of circulating A and/or B substance),[51] high isoagglutinin titer in the IVIG product ,[51] and coadministration of products such as platelets or plasma containing additional isoagglutinins.[51]

Renal failure due to hemolysis and hemoglobinuria was reported, necessitating hemodialysis.[28] Fatal disseminated intravascular coagulation due to Rh immune globulin use for immune thrombocytopenia has also been reported.[52]

IVIG has also been used successfully for autoimmune hemolytic anemia, indicating its ability to result in a therapeutic Fc blockade overrides its potential for further hemolysis.[53]

Neutropenia. Transient asymptomatic neutropenia has followed IVIG administration. It generally occurs two to four days after an infusion, and lasts for less than a week.[54-56] No infectious complications have been reported.

One possible mechanism is granulocyte activation with increased adhesive molecule expression with increased margination.[57] Von Gunten et al. identified anti-Siglec-9 autoantibodies (anti-sialic acid-binding Ig-like lectin 9) in some batches of IVIG and suggest that these antibodies, in conjunction with proinflammatory cytokines such as granulocyte macrophage-colony stimulating factor and interferon-γ, may induce neutrophil death.[57]

Lassiter et al. reported prolonged neutropenia (lasting three weeks) in a premature infant given four infusions of IVIG for alloimmune thrombocytopenia.[58] They attributed this to anti-neutrophil antibodies present in the IVIG.

Pulmonary toxicity. Mild wheezing or dyspnea are not uncommon immediate reactions (Table 4). Serious but very rare pulmonary complications include pulmonary embolism, pulmonary edema, pleural effusion and transfusion-related lung injury associated with fever and hypotension.[59-61] The latter complication may be associated with neutrophil antibodies or human leukocyte antigen antibodies resulting in leukocyte aggregation in the lung.[61]

Hyponatremia. The plasma sodium may drop 10 mEq/L to 20 mEq/L shortly after an IVIG infusion. This hyponatremia is

Table 4. Adverse Effects Associated with Human Immunoglobulin Use

Mild adverse effects (common, usually immediate *)
Infusion site pain, swelling, erythema *
Headache *
Myalgia, back pain, arthralgia *
Fever, chills, flushing *
Anxiety, malaise, fatigue *
Nausea, vomiting *
Hypotension, hypertension, tachycardia *
Hyponatremia **
Neutropenia **
Direct Coombs' positivity **
Moderate adverse effects (less common, usually delayed **)
Persistent headache **
Aseptic meningitis **
Hemolytic anemia **
Serum sickness/arthritis **
Dermatologic complications **
Interference with vaccine effectiveness and/or immunodiagnosis ***
Severe adverse effects
Anaphylactic/anaphylactoid reaction *
Renal complications **
Pulmonary complications **
Thrombosis/embolism **
Colitis **
Bloodborne infectious diseases ***

* Immediate reaction—within six hours from onset of infusion
** Delayed reaction—six hours to one week after infusion
*** Late reaction—weeks to months after infusion

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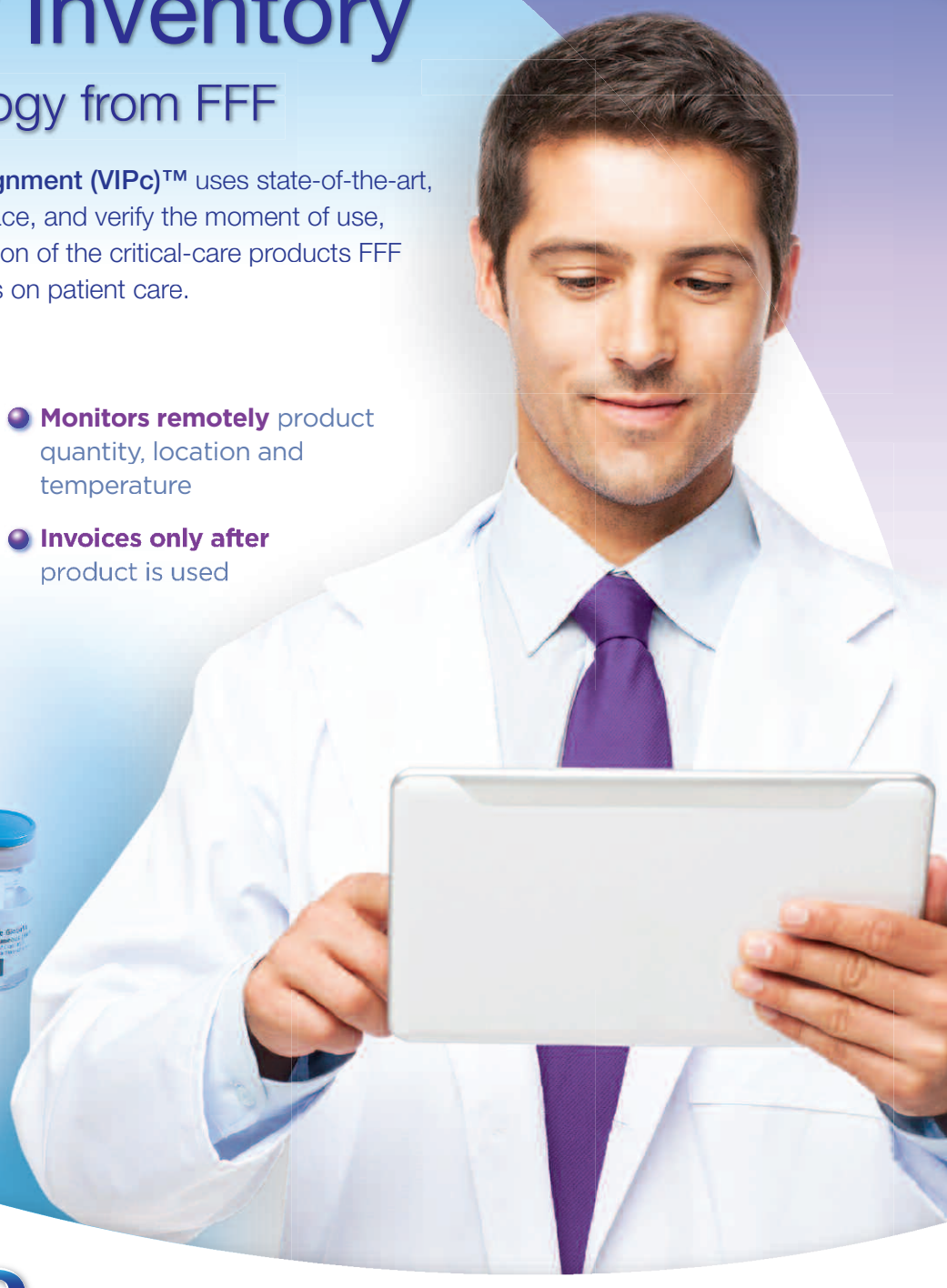

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usually dilutional and asymptomatic, and results from the large amount of sucrose or maltose present in the IVIG.[62,63] This increases the osmolality of the blood and results in an influx of fluid to the extracellular compartment, with dilution of the plasma volume, and a subsequent drop in sodium concentration.

The search for the cause of a reaction is often unrewarding, although the product can be tested for erythrocyte antibodies, procoagulant activity and autoimmune antibodies.

A similar fall in plasma sodium may result since the large amount of protein in the IVIG increases plasma volume without affecting the aqueous concentration, i.e., pseudohyponatremia.[64] In both dilutional hyponatremia and pseudohyponatremia, a true sodium deficiency does not exist, so additional sodium is not necessary and possibly detrimental.

Enterocolitis. Necrotizing enterocolitis in premature infants following IVIG for hemolytic disease of the newborn has been reported.[65,66] The hemolysis may aggravate the hypercoagulability of premature blood.

One case of reversible ileitis in an adult given IVIG for renal transplant neglect has also been reported.[67]

Infectious diseases. Hepatitis C infection following IVIG infusions given in the early 1990s was reported from several countries involving several IVIG and anti-D products.[68-72] These occurred after the FDA recommended that all donors positive for hepatitis C antibody be excluded from the donor plasma pools. Thus, the IVIG from these pools had no hepatitis C virus (HCV) antibodies to neutralize HCV in the HCV-antigen positive donors who escaped detection since they were in the seronegative window period during early infection. The hepatitis was of varying severity and sometimes fatal.[72] Other patients cleared their infection with or without antiviral agents.[71,72] Subsequently, new viral inactivation processes (solvent detergent, pasteurization) and polymerase chain reaction assays for HCV were adopted, and there have been no cases of hepatitis C from IVIG since 1996.[73]

Parvovirus B19 is not destroyed by solvent-detergent or heat treatment, so may appear in IG preparations. The parvovirus antibodies in these preparations probably prevent most clinical infection, although two cases have been reported.[74,75] Chronic parvovirus infection causing anemia is often treated with IVIG.[76]

Prion disease (e.g., variant Creutzfeldt-Jakob [mad cow] disease) has not been recorded as a result of IG therapy. A theoretical risk remains based on a case of its transmission by blood transfusion.[77] Tests for prions are in development, as are methods for their removal.[78,79]

Ziegner et al.[80] reported a series of immunodeficient patients with progressive neurodegeneration who had been exposed to IG preparations. None had proven prion disease.

No cases of HIV have been transmitted by IG products, probably because the fractionation process removes or inactivates this very labile virus.[74,78]

Dermatologic complications. Rare dermatologic complications following IVIG have been reported, including eczema,[81-83] alopecia,[84] erythema multiforme,[85] dyshidrosis,[86] and baboon syndrome.[87]

Other rare events. Single reports of adverse events include uveitis,[88] hypothermia,[89] non-infectious hepatitis[90] and serum sickness with arthritis.[91]

Interference with Immune Diagnosis, Vaccine Responsiveness and Endogenous IgG Synthesis

Recent IG therapy (within three to four months) may prevent an accurate assessment of baseline serum IgG levels (but not IgM, IgA or IgE levels). The antibodies in the administered IVIG also prevent the use of serum antibody levels to determine the presence of past infections. Further, the IVIG may interfere with the antibody response to administered vaccines, particularly live virus vaccines such as measles, varicella and shingles vaccines.[92]

Long-term administration of IG therapy inhibits endogenous IgG synthesis (if present initially) for several months after the IVIG is discontinued.[93,94] ❖

E RICHARD STIEHM, *MD, is professor of pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.*

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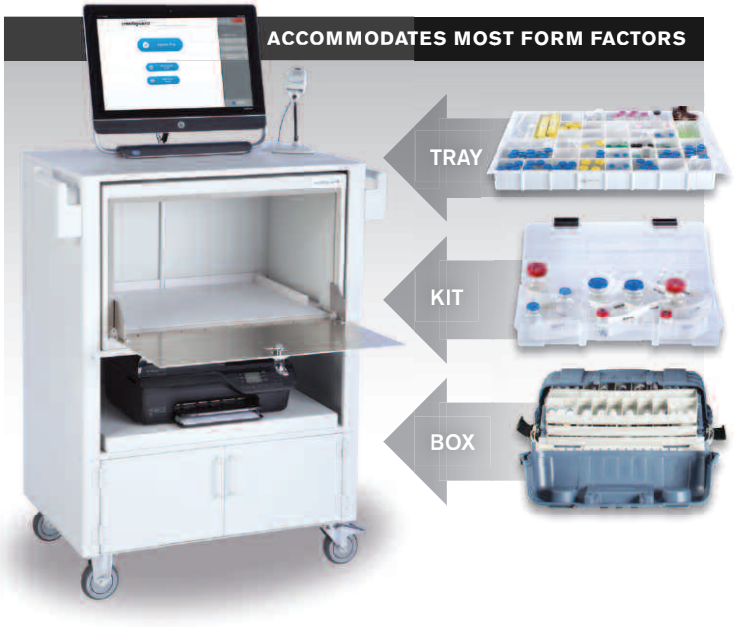

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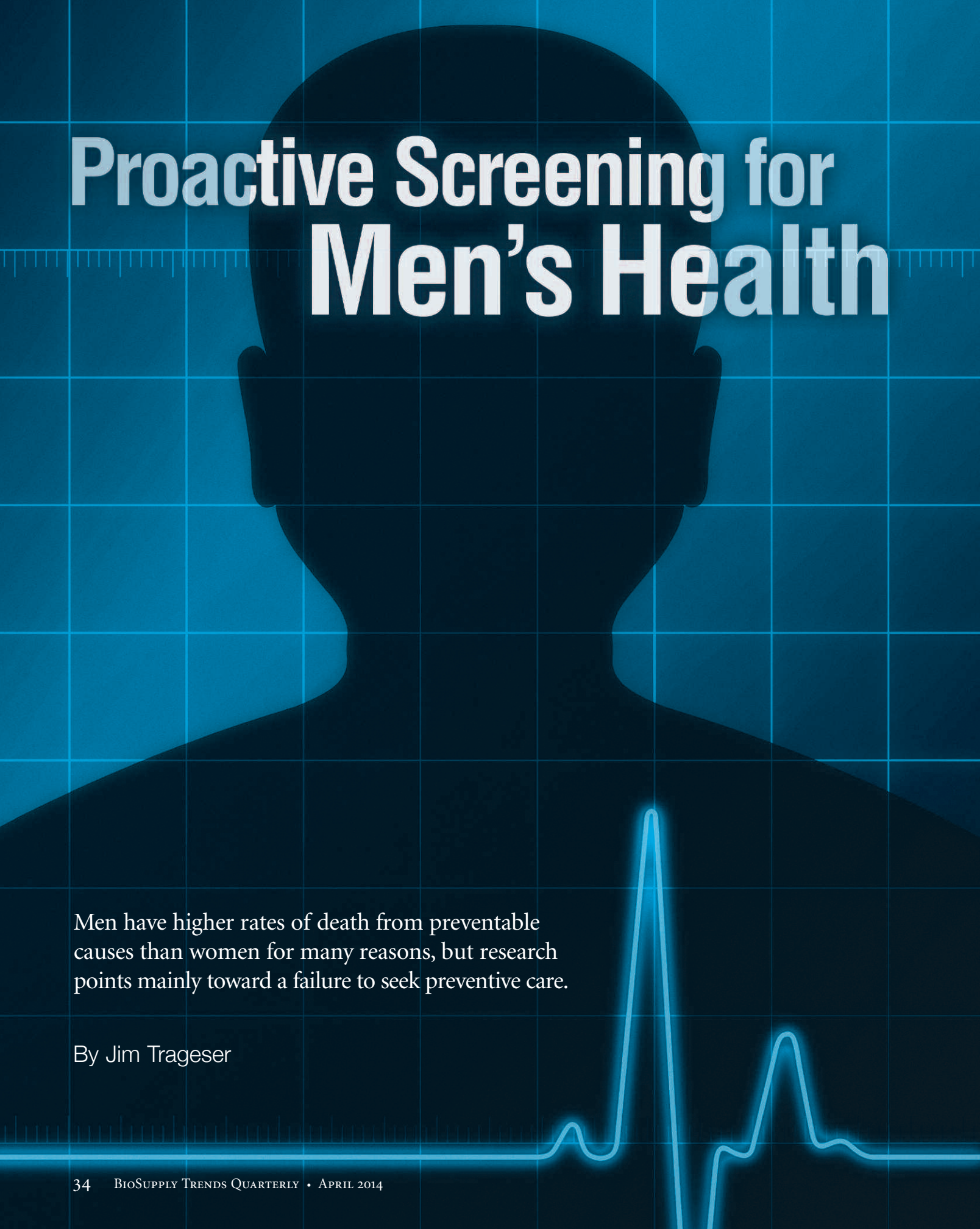

Proactive Screening for Men's Health

Men have higher rates of death from preventable causes than women for many reasons, but research points mainly toward a failure to seek preventive care.

By Jim Trageser

Medical professionals have long known what statisticians and researchers have documented throughout the past half-century: Men and women face significantly different health challenges over the course of their lives.

Part of it is biology: prostate cancer vs. cervical cancer, for instance. Individuals can't be killed by a body part they simply weren't born with. But, a significant portion of the differences in how and when men and women die, and from what causes, is likely based on behavioral differences. For instance, the rates of mouth, throat and lung cancers for men are much higher than for women[1] — based mostly on the fact that men have, historically, been much more likely to smoke or chew tobacco than women. When more women took up smoking in the 1970s as the social taboo against women smoking abated, the difference in rates between men's and women's smoking-related cancers narrowed.[2] And, men remain almost twice as likely as women to die from accidental injuries, as well as from suicide.[3] The former is likely due to more men holding dangerous jobs than women, while the latter is the subject of much study that has yet to yield any real insight.

How much behavioral differences that influence the mortality variance between men and women are based on socialization and how much on biology is probably a discussion for philosophers to have with psychiatrists. Still, beyond speculating on nature vs. nurture as to the root causes of the gender differential in morbidity, the fact remains that there is a wide gap between the sexes in cause and age of death. Overall today, cancer and morbidity rates are higher for men than for women throughout the developed world.[4] Additionally, men are at higher risk than women for heart disease.[2]

Perhaps not surprising given the above statistics, women are also more likely than men to take advantage of preventive care. A pair of studies from the early 1980s illustrated that women invested significantly more than men in healthcare in both dollars and time. The first, an economic study conducted by Jody Sindelar, noted that since the advent of modern medicine in the early 20th century, women have been more likely to avail themselves of medical care. This is true across socioeconomic groups and all time periods studied, and this persists even after accounting for childbearing care that would obviously not affect men.[5] The second, a medical study by L.M. Verbrugge, found that women are more likely to see a doctor for relatively mild symptoms, while men tend to wait until their condition is serious, even life-threatening.[6]

The Major Risks

Cancers and heart disease each account for roughly one-quarter of all deaths among men.[3] Lung cancer remains the most deadly form, followed by cancers of the prostate, colorectal system and liver.[7] Another 23 percent of all male deaths are classified as caused by "other" by the Centers for Disease Control and Prevention. Of the specified causes, accidental injury (including automotive crashes and workplace injuries) is the third-leading cause at 6.4 percent of all male deaths, followed by respiratory disease (5.5 percent), stroke (4.4 percent), diabetes (2.9 percent) and suicide (2.3 percent).

Cancer

Verbrugge's observation about how men and women are raised and taught to react to physical ailment may be most applicable to cancer: "Males may be socialized to ignore physical discomforts; thus, they are unaware of symptoms that females feel keenly. Also, men may be less willing and able to seek medical care for perceived symptoms. When diagnosis and treatment are finally obtained, men's conditions are probably more advanced and less amenable to control."[6]

Verbrugge takes care to note that this is only a hypothesis on her part, yet it is consistent with all the data on the gender differential in mortality. Survival rates for most types of cancer in large part correspond to how early the disease is detected. The sooner treatment begins, the more likely the patient is to beat the disease. Women develop cancer at rates comparable to men, but because they seek care sooner, they die from it later in life. Men, on the other hand, delay seeking treatment longer than women do, as the Verbrugge and Sindelar studies indicate, so their cancers are further along when treatment begins.

Overall today, cancer and morbidity rates are higher for men than for women throughout the developed world.

In taking action to prevent cancer, however, there should not be any objective obstacles to male and female participation rates. Tobacco use among men has fallen by a third since the 1960s, and lung cancer rates have fallen along with it.[8] Stopping smoking — and getting one's family and friends to stop smoking to reduce exposure to second-hand smoke — remains the single-most effective strategy to reduce the odds of developing lung, mouth and throat cancers.

Other effective preventions for cancer include maintaining a healthy, nutritious diet, which also forestalls cardiovascular disease.[9] A regular intake of fresh fruits and vegetables and

limiting fat and cholesterol are now believed to help prevent the development of colorectal, esophageal, kidney and pancreatic cancers, and possibly prostate cancer — all of which are linked to clinical obesity.[7]

With advances in our understanding of colorectal cancer, along with improved detection and treatment, it is now recommended that everyone undergo regular screenings at age 50. Pre-cancerous polyps on the walls of the large intestine can be detected and removed before they metastasize. Screenings are the single most effective method for preventing the disease.[10]

Screenings are the single most effective method for preventing colorectal cancer.

Prostate cancer is not so easily prevented. It is apparently stimulated by the presence of male hormones. While early prostate cancer and pre-cancerous cells can be detected through simple blood tests (the prostate-specific antigen or PSA test), many men who survive the generally slow-growing prostate cancer will have significantly diminished quality of life. There is one promising class of drug, however, known as alpha-reductase inhibitors, that appears to lower a man's risk of developing prostate cancer. Unfortunately, they carry the ominous side effect that if prostate cancer does arise during treatment, it will be a more serious and difficult type to treat. In addition, these inhibitors are associated with an increased risk of developing cardiovascular disease.[11] So, for now, there do not appear to be any effective methods of preventing prostate cancer — only regular screenings and treatment if the disease is found.

And, while the two most prevalent forms of skin cancer are also among the most common types of cancer that develop, carcinomas are easily treatable. Melanoma, conversely, is more dangerous and difficult to treat. However, like carcinomas, it can be prevented through the regular use of sunscreen. Regular examinations as part of an annual physical are recommended for those at risk of developing skin cancer.

Heart Disease and Stroke

Coronary and vascular disease progress far more slowly than do most cancers, with degradation measured in decades. But, the advancing of coronary or vascular disease, or increase in risk of a heart attack or stroke, is trackable from childhood on, with blood pressure readings and cholesterol levels fairly accurate gauges of risk.

Family history is perhaps the strongest indicator of risk for cardiovascular disease. The second strongest indicators are weight and fitness. The clinically obese are not only more prone to cancer, but are more likely to suffer a heart attack or stroke.[12] But, while diet and regular exercise are an important part of any cardiovascular disease prevention regimen, a physician's review of a patient's family history may also indicate the desirability of drug treatment.

Hypertension can be treated with a variety of classes of medications. In fact, most patients with high blood pressure can be prescribed a blood pressure control drug with acceptable side effects. High cholesterol also can be controlled with medication, often in conjunction with a blood pressure medication or blood thinners. And, of course, outpatient intervention to clear cholesterol-caused plaque from arteries is a last-resort tool available to prevent a heart attack.

While drugs may not address the root cause of high blood pressure or cholesterol, it is the blood pressure and cholesterol themselves that cause the systemic damage to the body. Therefore, relieving the symptoms *is* relieving the disease. Unfortunately, getting male patients to accept that they may need to take a maintenance prescription is — as the studies on male attitudes toward medical care show — perhaps the highest hurdle to treating their cardiovascular disease before it progresses.

Diabetes

Unlike with blood pressure and cholesterol, there is no prescription drug available to stop the advance of diabetes. The most effective method to prevent or at least delay the onset of type 2 diabetes is a combination of diet and exercise. The Mayo Clinic has a five-step program for those with a family history of diabetes,[13] and it revolves wholly around physical activity and better eating. Exercise not only promotes weight loss, but also makes the body more sensitive to insulin. Fiber and whole grains also improve the body's sugar control.

The Mayo Clinic also recommends regular screenings for diabetes for patients 45 and older with a history of diabetes in the family.

Suicide

Suicide is perhaps the most troubling cause of early mortality for physicians — or society — to address. As Catholic theologian and philosopher Father Ron Rolheiser wrote in one of his many columns on the subject: "Suicide remains widely misunderstood and generally leaves those who are left behind with a particularly devastating kind of grief. Among all deaths, suicide perhaps weighs heaviest on those left behind."[14]

While women remain more likely to attempt suicide, men are far more efficient at it.[15] Decades of study on the gender differential in suicide rates have yielded dozens, maybe

hundreds, of theories on the cause of this difference. Simultaneous medical research has found many promising treatments that have greatly helped untold numbers of patients — but almost no measurable impact on the overall rate of mortality, or on the ongoing gap between the numbers of men and women committing suicide.

Antidepressants have helped many patients. But, other patients have been found to react to some classes of these drugs by actually becoming more prone to suicide.[16] Psychotherapy has also proven effective for patients suffering from some specific types of mental illness.[17]

Still, as the National Institutes of Health points out, there is no surefire way to prevent individuals from taking their own life. However, it's noteworthy that most elderly victims of suicide met with their primary care physician within a year of their death, giving doctors a unique opportunity to offer preventive treatment.[17]

Improving Men's Attitudes Toward Healthcare

Male attitudes toward their health differ significantly from those of women. The reasons are complex and, at this time, not well understood — although many researchers suspect that the roots of the issue lie in the fact that men are generally uncomfortable admitting weakness or asking for help. The many jokes about men being lost and unwilling to stop to ask for directions are, after all, based on many real-life experiences common to most families.

Suicide is perhaps the most troubling cause of early mortality for physicians — or society — to address.

But, perhaps the military and professional sports offer a road map forward in getting men to move past their avoidance of seeking assistance. For instance, the National Football League (NFL), one of the most traditionally masculine of all sports, is currently struggling to address the prevalence of concussions and brain injury in its ranks. Football players — trained since childhood to "rub some dirt on it and get back in there" — are now working through their union to seek new rules that protect them and their place on the team (and, thus, paycheck) if they suffer a concussion in a game.

Another prime example is the United States Marine Corps, which prides itself on being the toughest of the tough. The Marine Corps now actively encourages its combat veterans to seek help if they show any symptoms of post-traumatic stress disorder (PTSD) when they return from the battlefield. Marines — as well as soldiers, sailors, airmen and Coast Guardsmen — are now able to receive confidential treatment for PTSD without worry about being branded a weakling or losing their next promotion.[18]

If Marines and NFL stars can be prodded to seek help without fear of being considered weak, there might yet be hope for physicians trying to get the rest of their male patients to get the preventive treatment they need to live longer, healthier lives. ❖

JIM TRAGESER *is a freelance journalist in the San Diego area.*

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Practicing Medicine: A New Quality of Care

The story of how one patient was diagnosed with a life-threatening condition illustrates how the changing healthcare landscape might affect the quality of physician care.

By Sue Romanick, MD

As I entered the exam room to meet Bob for the first time, I smiled with relief. Bob looked pleased to be in our clinic, appearing well-tanned and comfortable. I had already noted the priority that he had scrawled on the intake form for today's visit: "ear wax." I was relieved that this would be a straightforward visit. Because several patients that day had complex issues, I had already fallen behind in my schedule, and my staff had nervously pointed out that the waiting room was full. Yet, I must admit I was curious why Bob had come to me.

Bob knows I am a rheumatologist who deals with autoimmune disorders. Yet, he had insisted on seeing me when he made the appointment. His wife was already a patient, although they had been living in Hawaii for a few months. This visit was rather spur of the moment, so I was happy to help out.

After reviewing Bob's three detailed medical history forms, including his past medical history and medications, my examination confirmed that Bob, indeed, did have impacted ear wax in his right ear. There was no infection, and he appeared to be otherwise healthy. So, we discussed treatment options, and Bob opted for a simple, over-the-counter remedy.

Bob appeared pleased with my assessment. It felt like the visit was over, and I closed my laptop and moved toward the door. Little did I realize that a bombshell was about to drop. As my hand landed on the door handle, all of a sudden, Bob uttered words that have alarmed many a provider: "Doc?" he stated with hesitation and a meek, upward inflexion in his voice. "Can I ask you another question? I have this pain.…"

"Oh, and by the way…." How many times has a medical provider heard that? In truth, this can indicate a dangerous path depending on which fork in the road the provider takes. In the current healthcare environment, the right answer was to tell Bob to book another appointment. After all, providers get rated by patients these days. I knew it was unfair to keep my other patients waiting, and I sure didn't want a negative review. Even more importantly, I knew that health insurance companies rate their providers based on customer care, and they collect input from patients about how long their waits are. Yet, simply telling Bob to book another appointment was not the real me. It was not my style to send my patients out the door with a big question mark.

"Pain? Since when?" I asked, trying to hide the disappointment in my voice. My mind was reliving vignettes of life in slow motion. As Bob answered "three weeks," several vignettes played out in my mind, one of which was the "audit."

Audits: The Time Thief

I had to make a decision concerning Bob. My staff was getting impatient looks from the waiting room, and Bob had already used up his appointment time. Would I make Bob my priority or the other patients still waiting to be seen? I felt guilty for making the patients in the waiting room wait, and I felt equally guilty knowing that I would be keeping my own family waiting longer for me to get home that evening.

There is good reason for patients to question whether the days of the kind and patient doctor are on their way out. Being in private practice, I'm already overwhelmed by the impact of healthcare changes due to new regulations that are supposed to help patients get better medical care. The impact of these gradually adopted changes is being felt in full force by those of us in private practice in smaller clinics (and our numbers appear to be dropping like flies). In large institutions, the impact of these changes may be diluted through the higher numbers of administrative personnel. Yet, discussions with colleagues behind closed doors in both settings suggest a system both burdened and overwhelmed.

Many healthcare providers are dreading, rather than welcoming, the coming changes. For many years, doctors have peered down microscopes to learn why patients are sick and how best to help them. These days, the microscopes are turned around, and doctors are finding themselves subjects of magnification and scrutiny. These microscopes peer down on healthcare providers from different angles to judge their competency in areas unrelated to, and taking the focus away from, providing quality and effective medical care.

There is good reason for patients to question whether the days of the kind and patient doctor are on their way out.

It is unclear who is driving these changes in healthcare. But, insurance companies are playing a large role. These companies regularly perform audits on providers — audits that are conducted by nonmedical personnel who evaluate patients' healthcare records by systematically going through a list of bullet points to ensure benchmarks are met: "chief complaints" — how the reason(s) behind the medical visit are worded; "history of the presenting illness" — the list of descriptors in the story behind the medical problem; "review of systems" — how the rest of the patient's mind and body are doing; a review of medication and other allergies; up-to-date medication lists; past medical and family medical histories; social history; lifestyle issues; the physical examination; the complete medical assessment; and plans and recommendations that specifically document what was discussed, being sure that a recommendation for returning to the clinic was stated and documented. Whew! If the insurance administrator finds even small deficiencies in the audit, the provider may not be reimbursed what would have been customary payment for the visit, even if additional time was spent with the

patient to ensure he or she understood the tests, diagnoses or treatment.

Yet, to date, there has been insufficient evidence that these benchmarks tracked by the audits truly affect quality of patient care. Unbelievably, this shows clear lack of confidence in what providers have been taught in medical school. For providers, it is an apparent exercise in futility that requires even more administrative time, usually after hours or on weekends. Instead of taking their children to the park, providers are in their office wading through health-insurance-generated red tape. In fact, since my office changed from paper to electronic medical records, I am spending an extra two hours every work day trying to meet audit standards for charting. The current goal of recreating an office visit from the list of provided codes requires the coding skills of a librarian and the detailing ability of an accountant. This has nothing to do with real doctoring. It is time that is not reimbursed. And, it is time taken away from patient care.

Providers are finding it increasingly difficult to prescribe the best medication for patients without worrying about the patients' insurance companies denying reimbursement.

And, beware a new "time thief" on the horizon! In addition to providing information for the insurance audits, providers now have to participate in registries that require them to electronically send information about patients' private health information and treatment to a third party. This is not simply a point-and-click situation. This information must be entered into separate electronic documents. Currently, there is both a carrot-and-stick approach with some of the audits and registries. Not participating can lead to significant financial loss for providers, which translates to even lower reimbursement when reimbursements are already falling.

Why are these audits truly needed? A recent discussion with an employee of one of these companies revealed their real purpose is building profiles of providers and classifying them based on company criteria to determine how much a patient must pay out of pocket for treatment. For example, a provider who sees more challenging patients might be considered a more expensive provider. If so classified, the insurance company could force the patient to pay more out of pocket for a visit with that provider. So, if a patient has joint pain, the insurance company will steer that patient toward the "cheaper" doctor to both save the company money and to successfully make the patient feel he or she has saved money as well!

Obviously, the insurance company can save money if the patient chooses a cheaper doctor. And, obviously, patients will be tempted to choose a cheaper doctor. But what if a patient has medical issues that are challenging and require more complex, more comprehensive or more compassionate workup? Is it fair that the insurance companies are dictating how patients can choose their providers?

Gone are the good old days when a doctor could look each patient in the eye with sincere compassion and convey concern and empathy. Now, our eyes are trained on the computer screen.

Reimbursement: Cost vs. Care

With Bob's last-minute question still lingering, how my hand wanted to depress that door handle and keep moving! But my feet froze to the floor. Indeed, slowly and thoughtfully, I removed my hand from the door handle, and I turned to face him: "Pain where?" Bob answered timidly, motioning to where his liver should be: "Here. Right here."

I asked Bob: "How long have you had this pain?" He was a little noncommittal: "I've had it about three weeks, Doc. It's not too bad." As I stood there, I tried to build a quick mental list of pains that stick around for three weeks. I'd have preferred he had said three months or three days or even three hours. I could have more easily come up with explanations in each of those cases. Then, it would be easy for me to conduct the physical examination to address the usual diagnoses and to order the appropriate tests. But, the quick survey that flashed through my brain came up empty-handed and, instead, raised a red flag that something sinister was going on. I didn't know what, but I had to find out. I couldn't just send him home because the red flag would not leave my intuition.

Leaving the exam room door closed, I asked Bob to lie down on the exam table. What could be so elusive that, if serious, I could be missing on examination? I checked his breathing, blood pressure and pulse. They all checked out fine. His heart and lungs sounded normal. There was no swelling in a foot or leg. He was not uncomfortable when I pressed over his liver, nor over the rest of his abdomen. I was stymied.

Three weeks? Could this be a local infection? But, Bob had no fever, jaundice, rash, swelling or any other signs of serious nature. At this point, it would not be unusual for a provider to

order a test such as an ultrasound of the liver and gallbladder, or a flat plate (X-ray) of the abdomen. But, my intuition told me that a history of pain for specifically three weeks was unusual, especially over the liver. These usual tests for abdominal pain could turn out to be dead-ends. Something just didn't add up. So, I did the unusual, even though it could face scrutiny later.

Providers are finding it increasingly difficult to prescribe the best medication for patients without worrying about the patients' insurance companies denying reimbursement. That's why preauthorizations are necessary, but they are also potentially dangerous. I have been in my clinic on a Sunday to discover a non-urgent notice from an insurance company that a medication for which I had written an urgent prescription a few days before (a corticosteroid) had been denied to the patient. When I tried to contact the office number provided to get the necessary authorization, I was met with a recording saying that they were not open on Sundays. In my field, there are conditions like giant cell arteritis for which withholding this type of medication, prednisone, can lead to blindness. Furthermore, no other medication can be substituted, and it must be given in a timely fashion.

No one can dispute that the required preauthorizations, which involve filling out forms, copying portions of patient records, and spending excessive time on the phone waiting to speak to nonmedical and medical representatives of the insurance companies in order to get an OK for a diagnostic test or specific type of medication, pose a time and administrative burden on medical clinics. A simple understanding of basic human nature would reasonably predict that this burden would result in fewer tests and medications being ordered (and, therefore, decreased healthcare costs) simply because of the "nuisance factor" to providers. Preauthorizations should more aptly be named "deterrents." Unfortunately, these deterrents adversely affect the quality of healthcare.

Fortunately, in Bob's case, the direction I opted to take didn't require preauthorization. I have always learned a lot about patients at the bedside, even when others have opted for expensive tests. Asking Bob to lie back comfortably, I took the stethoscope and placed it gently just below Bob's ribs on the right side of his abdomen. I'm sure that some of my past mentors would have laughed when I did this. The liver itself, even when "sick," does not produce any unusual sounds. But, what I heard was astounding and unusual. It was as if one were listening to someone with a mouth full of food breathing slowly but noisily, in and out, through clenched teeth. But, in this case, Bob's mouth was nowhere near this area!

As soon as I heard this ugly noise, a light bulb went off. Bob had traveled from Hawaii three weeks before, which meant that he had been sitting in a plane for several hours — a set-up for a possible blood clot. But, while Bob had no health factors whatsoever for a blood clot, I could not deny that a blood clot that had originated from a leg during the trip and had traveled to his right lung could produce such a sound, audible only through a stethoscope. The good old-fashioned physical examination that cost nothing beyond the standard visit had to be believed. I called the emergency department and reported that I had an emergency for them. They were interested but not totally convinced as Bob had no other signs: no shortness of breath, no true chest pain, no cough, nor any swelling in either of his legs. On top of that, he was trim and fit. Was I sure? Or, could I be wrong?

Preauthorizations should more aptly be named "deterrents."

I explained to Bob that it was better to get checked out even if the odds were low. Two hours later, the emergency room physician called me personally. Bob's workup showed a surprisingly large blood clot in the right lung that would have killed him within 48 hours. It had been growing over three weeks. He was so fit that his body had been able to fully compensate for the increasing loss of lung function. He was admitted to the intensive care unit and started on blood thinners. A life had been saved.

"New and Improved" Quality of Healthcare

Of course, there is more to Bob's story. It seemed that Bob was not through stumping his doctors. He had returned to Hawaii after he was stabilized on his blood thinner medication for the blood clot in his lung. And, he had completed his blood-thinning treatments and had managed to stay out of medical clinics since his clot had resolved. But, almost exactly one year since he had first arrived in my office from Hawaii, he was back for a visit, this time presenting with the telltale look of worry in his eyes and explaining: "Doc, I have a pain in my stomach." Alas, this was not simply a matter of: "Here we go again!"

Surely, saving lives and limiting disability reflect the true quality of healthcare?

This time, when Bob announced abdominal pain, I feared the worst. In fact, I was not deterred by his bedside examination being completely normal. I tried to be extremely thorough. As before, I had to keep the next patient waiting longer while I spoke with a radiologist to schedule an urgent abdominal CT scan that afternoon.

Previously, I had wondered how his clot could have developed so easily without obvious risk factors. I was concerned that his blood could have developed a clotting problem due to some sort of tumor. Surprisingly, none of his doctors in the hospital or his family doctor had ever discussed this possibility with him. Even though it felt premature, I took extra time with Bob to explain why I needed him to see a cancer doctor. He was, of course, shocked that I brought this up so soon in our discussion. But, I knew intuitively that he could better cope with a bad diagnosis if we had the wheels of achieving wellness in motion. Later that evening, after hours, the radiologist phoned me. Bob had a tumor in his pancreas. This is one type of cancer that can cause the blood to clot unexpectedly. At least Bob was now linked to a cancer doctor in whom Bob knew I had full confidence. That softened the blow of a dreaded diagnosis and allowed Bob to start gaining some sense of control of a serious situation.

Bob's case is not isolated. Serious, unexpected medical diagnoses have been made in our clinic when only simple, routine appointments have been booked. It is increasingly difficult to keep all patients happy all the time, especially those who have difficulty waiting, and we make every effort to ensure patients' expectations for waiting are respected. Yet, had I been on time for some of these patients, I would have missed the unexpected findings in the patient before them that indicated a potentially life-threatening condition. I doubt Bob would disagree with this.

Surely, saving lives and limiting disability reflect the true quality of healthcare? Yet, the simple satisfaction of trying to be compassionate with one patient can be diminished by huge administrative demands imposed by insurance companies. And, there appears to be no way to communicate this to these companies. So, what's my take on where healthcare is going? It is increasingly difficult to be a compassionate and comprehensive physician when I have to keep an eye on the clock and both eyes focused on the computer screen, while keeping at least one eye on the financial bottom line — in a climate in which office expenses and demands on my free time are growing, especially while reimbursements and family time are decreasing. In this healthcare environment, the public should be increasingly concerned about physician burnout.

Some of us have a passion for helping patients, and this is the only thing that keeps us going. Yet, even we are struggling. We continue to hope that "new and improved" healthcare changes will eventually lead to improved medical care. But, this provider is skeptical and remains worried that some patients could end up dying because of it. Remember, we're in this together. Next patient, please! ❖

SUE ROMANICK, *MD, is board-certified, as well as recertified in both general internal medicine and rheumatology. She was involved with immunology research on cell clones at the German Cancer Research Institute in Heidelberg, Germany, and has worked in immunology and plasmapheresis at the University of California, San Francisco. Dr. Romanick is a public speaker and has spoken for the Arthritis Foundation, University of Washington and Overlake Hospital in Bellevue, Wash. She also has participated in lobbying efforts on Capitol Hill to support arthritis patients, both young and old, at the request of the American College of Rheumatology. She runs her own private practice clinic in Bellevue, Wash.*

Editor's note: The name of this patient has been changed to protect his privacy.

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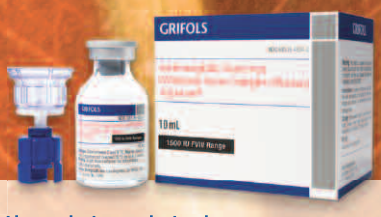

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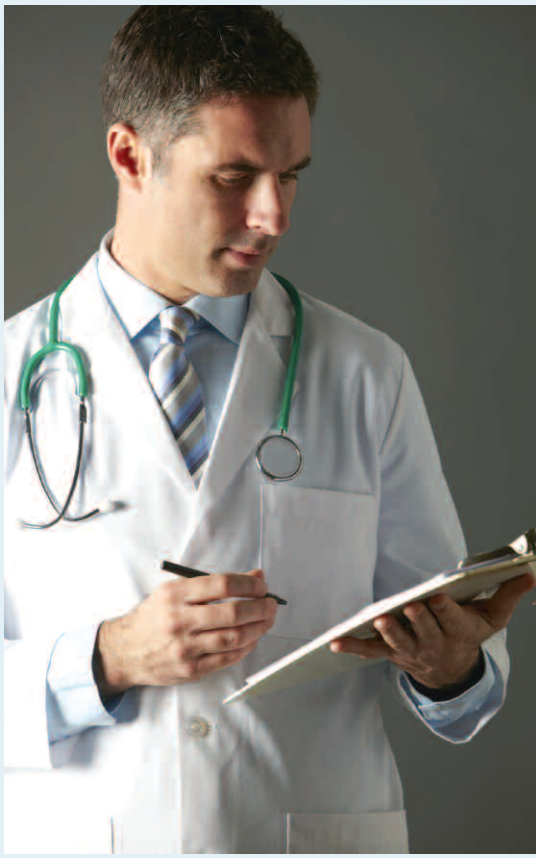

The Growing Impact

By Amy Scanlin, MS

Despite its increasing prevalence, autoimmunity is still not categorized as a "disease," and research to determine its cause remains hindered due to a lack of focus and funding.

Autoimmunity contributes to more than 100 serious chronic illnesses that involve almost every organ system in the human body. Some of these diseases are cited in the top-10 leading causes of death in women aged 65 and younger, and together, they represent the fourth-largest cause of disability among women in America.[1]

The National Institutes of Health's (NIH) Office of Research on Women's Health has named autoimmunity a major health issue that attacks women; 75 percent of autoimmune diseases (ADs) occur in women.[1] It is believed that women's enhanced immune systems make them more susceptible to ADs because, while enhanced immunity makes them more resistant to infection, it also exacerbates the autoimmune response that occurs when the body turns on itself and starts attacking healthy cells.

But, even with the staggering statistics surrounding autoimmunity, it has not yet been categorized as a disease. And despite the fact that the diseases believed to be caused by autoimmunity span many speciality areas, there has yet to be a determination that autoimmunity is the underlying cause.[1]

A Brief History

The idea of autoimmunity first came to light in the early 1900s, and the understanding that autoimmunity was in fact a feasible underlying cause for disease was recognized in the 1940s. The term AD was probably first recognized in a 1963 monograph and a subsequent international conference in 1965.[2] Fast-forward to 1998 when the NIH created the Autoimmune Diseases Coordinating Committee (ADCC) under the direction of the National Institute of Allergy and Infectious Diseases (NIAID).

In 1992, only 67 ADs had been identified.[3] Today, there are more than 100, and there are thought to be about 50 million Americans living with autoimmunity, 30 million of which are women. That number, unfortunately, is increasing, particularly within the past decade. According to the American Autoimmune Related Diseases Association (AARDA), while we don't know the reason for the increase, it is largely suspected to be due in part to environmental factors.[4]

ADs affect 5 percent to 10 percent of the developed world's population. The World Health Organization cites being too clean (also known as the hygiene hypothesis) as possibly impacting the prevalence of AD. "The mechanism by which an AD is triggered is still not known, but there is valid research supporting this 'too-clean' theory," says Virginia Ladd, president and executive director for AARDA. "For instance, some treatments for Crohn's and MS [multiple sclerosis] show the inflammatory response is reduced as the body goes after a parasite. Also, on the microbial theory, antibiotics clean out a lot of the good bacteria in the gut. We may have evolved so that our immune systems are decreasingly efficient."

ADs such as diabetes and MS are quite rare in less-developed areas of the world like Africa and Asia, and yet they are on the increase in societies that have a modern infrastructure.[3] Part of the reason is the health structure within less-developed nations and the diseases on which they are primarily focusing. In Africa, for instance, healthcare officials are so overwhelmed with diseases such as AIDS and malaria, they are not closely looking at ADs. However, says Dr. Noel Rose, director of the Johns Hopkins University's Center for Autoimmune Disease Research, "We have pretty good data from industrialized countries that are showing a true increase in AD, and we have been able to separate that true increase from a greater awareness of AD. After all, you diagnose what you are looking for. Data from Scandinavian countries such as Finland and Sweden — countries with a good national health scheme — are showing solid diagnostic measures. The consensus shows that AD rates are going up and at fairly significant rates. There is huge speculation, however, as to why."

Possible Theories of AD Development

Why so many people have multiple ADs and why they tend to run in families seems to point to genetics. Those who have a genetic predisposition to ADs will have a two- to five-times greater chance of developing one (or more) than those who have none.[5] It is estimated that about one-third of a person's risk of developing AD is due to hereditary factors, and the rest belongs to the environment. "We know in broad terms that there is a genetic component in every AD," says Dr. Rose.

Even with the staggering statistics surrounding autoimmunity, it has not yet been categorized as a disease.

In January 2012, the National Institute of Environmental Health Sciences reported that 32 million people in the U.S. have autoantibodies, most commonly antinuclear antibodies (ANA). Some who have ANA go on to develop ADs, and some do not.[4]

Finding genetic markers is an area of research that scientists are really excited about. "That is the real problem that is holding back progress," says Dr. Rose. "In most cases, we don't see a patient until the damage has been done, and you can't reverse that damage. What we want to do, and are slowly working our way toward, is finding early genetic markers that will allow us to begin to see patients earlier when AD may be reversible or even earlier before it develops to tell them of their risk.

Genetics, whether someone is high risk or low risk or somewhere in between on the scale, is the kind of information we'd like to be able to impart on patients. Susceptibility is not an all-or-nothing prospect. We can give patients advice when we know there is enough risk, and in certain groups where there is a pregenetic disposition, antibodies rise years before the disease presents. The type and number of antibodies are becoming predictive clues but are not at the clinical level yet."

One promising area that has provided a better understanding of why women tend to develop AD more than men is the link between the hormone estrogen and the immune response. The sex hormone estradiol has shown to induce a lupus-like disease in highly susceptible mice. Estradiol makes B cells that produce autoantibodies resistant to apoptosis — autoantibodies that normally destroy them. According to the study, when mice that were susceptible to lupus were treated with the hormone prolactin, "autoantibody-producing cells that are usually eliminated by the immune system survived, and the mice developed lupus symptoms."[6]

Currently, scientists are actively studying only 24 of the more than 100 ADs. This makes it harder to find a generalized way of connecting the diseases to one or some causal factors that would connect them into a disease category to better enable diagnoses and find treatments. A better understanding of ADs in the medical community can lead to earlier diagnosis and better management of symptoms, particularly through efforts such as community-based triage centers rather than emergency room visits and hospital stays.[7] This also affects funding; if ADs are not looked at in their totality, the impact of those diseases as a whole will be lessened and so, too, may the dollars put toward research.

Currently, scientists are actively studying only 24 of the more than 100 ADs.

There is a great focus in researching the etiology of autoimmune-related diseases, instead of a primary focus on treating a singular disease.[1] In 2003, etiology of AD received about 45.5 percent of research funding, followed by the study of genetic links (14.6 percent) and the environment (5.4 percent).[7]

While more crossover research among the different diseases is needed to confirm a causal link, one area that is being heavily investigated is the environment. Scientists are trying to determine if vaccines, female hormones, UVB radiation exposure, fetal blood cells, stress, vitamin D deficiency and toxins impact autoimmune prevalence.[4] Doctors know, for instance, that certain drugs such as procainamide and hydroxyzine can induce a lupus-like syndrome in genetically-susceptible individuals. When an individual is taken off the drug, the symptoms go away. As well, certain substances in the diet such as iodine can exacerbate thyroid disease. "If someone gets too much iodine in their diet, they are likely to develop AD of the thyroid," says Dr. Rose. "In our society, we have a diet heavy in fast food with lots of salt." Also, metals such as mercury, gold and silver can induce lymphocyte proliferation and subsequent autoimmunity. And, a selenium deficiency has been linked with autoimmune thyroiditis and cardiomyopathy, but improvements can be seen by some when taking selenium supplements.[7]

"We have a small list of exposures of things we know anything about," says Dr. Rose. "In some diseases like lupus, the effects of sun exposure is well-defined. We know of a few drugs where in a small percentage of people, they will trigger AD. That's probably in those who are genetically predisposed and the disease needed a little kick that the drug provides. We also have to put smoking on that list. We have lots of anecdotal information but don't have solid evidence yet as to these environmental risks. With the human genome project, it is possible that someday we will be able to have a more complete picture."

Scientists are also working to determine if infections and/or viruses may induce type 1 diabetes and MS, as well as lupus and rheumatoid arthritis.

Fiscal Impacts

In March 2011, the AARDA released a study on the fiscal burden of ADs. Because those diseases are not lumped together as one group, it is difficult to get a true cost for patients, insurance companies, federal government and research institutions. However, it is estimated that the 100-plus diseases together cost upward of $86 billion[1] to perhaps hundreds of billions of dollars in both direct and indirect costs.[7] And, some feel that number is too low, given the fact that the direct and indirect cost of the seven most common ADs (Crohn's, ulcerative colitis, lupus, MS, rheumatoid arthritis, psoriasis and scleroderma) reaches $50 billion alone.[3]

One reason the diseases are a funding challenge is because each disease is tracked independently, not collectively, under a nonexistent umbrella category of AD. So the true cost of ADs together is not actually known. The Agency for Healthcare Research and Quality also does not have codes for all the 100-plus individual ADs, making a thorough tracking of disease and costs nearly impossible.[4]

Additionally, because the totality of ADs is not documented, and thus its impact is not obviously significant, its funding for research falls short compared with diseases with a clearer impact. For example, the NIH estimates the direct cost for all ADs to be about $100 billion, while the costs of cancer are estimated to be about $57 billion, and heart disease and strokes about

$200 billion. Yet, research funding in the year 2003 equaled about $591 million for ADs, $6.1 billion for cancer and $2.1 billion for heart disease and strokes.[8] This number does not take into account funding from other sources such as the Centers for Disease Control and Prevention and the Department of Veterans Affairs. "Unfortunately, as a whole, AD [research] is very underfunded. Even within AD, we see most funding going to three or four diseases and not the rest," says Ladd of the AARDA.

Working with AD Patients

Patients often are misdiagnosed or not taken seriously when first presenting with symptoms that could be related to autoimmunity. This is because their symptoms are often vague and come and go, compounding the difficulty of diagnosis. A 2001 survey by the AARDA found that more than 45 percent of patients with ADs are first labeled as chronic complainers.[1] "Many times, it is such a long process to be diagnosed, they are just happy to have an answer," says Ladd. "I just spoke to one person with lupus who took eight years to be diagnosed because her doctor wouldn't send her to a specialist — she was too young, too stressed. … It took a car accident and an MRI where they saw that she'd had a stroke before she was sent to a specialist. And, it usually takes a specialist to diagnose AD. Generally, a family doctor just doesn't treat patients with those conditions."

Oftentimes, insurance becomes a barrier to referrals to specialists, and that may continue. According to Ladd, "Access to specialists is not part of the essential benefits plan in the Affordable Care Act. There is no definition of quality care, and it may be left to the states as to whether they want to include it."

ADs are not a single disease group, explains Ladd. They are different from patient to patient, and it is important to take patients through what an AD is, give them background on the disease, and how to cope with a chronic illness and overcome challenges. "Developing coping mechanisms is very important," says Dr. Rose. "AARDA does a great job of putting on forums across the country where we try to explain what an AD is and how it happens. We are trying to demystify medicine and let people know that this is not just some unnamed thing; it is a known entity, and medicine is looking at it."

"These treatments have become very sophisticated, and it takes a lot to follow the patients through them," says Ladd. "It can be a real challenge tackling AD, especially when more than one disease presents. It's a major problem! We don't have one center in the U.S. that specializes in AD. If you have cancer, you have a selection of oncology centers to go to, but with AD, there is not."

That means patients must take a more active role in managing their disease as they seek assistance from multiple specialists for each condition. "Patients tend to coordinate their own care, and sometimes one doctor treats with things another doctor may not. For instance, with diabetes, a doctor may not want a patient to take a corticosteroid because it gets their sugar out of balance, but a rheumatologist may want them to," says Ladd. It can get tricky. "It is difficult because we have a medical system based on specialities, and AD doesn't often fit into a speciality. If you have a disease, you want to go to the guy who knows the most about it."

Patients often are misdiagnosed or not taken seriously when first presenting with symptoms that could be related to autoimmunity.

There are many fine people working on the issue of AD, and that field of people is growing. "Johns Hopkins has Autoimmunity Day each year, and others are coming on board," says Ladd. "This year, the University of Michigan will sponsor a public forum in June for patients and physicians."

While there is still a long way to go toward understanding AD, a brighter future is surely ahead as we learn more about the triggers, treatment and how they all link together. ❖

AMY SCANLIN, *MS, is a freelance writer and editor specializing in medical and fitness topics.*

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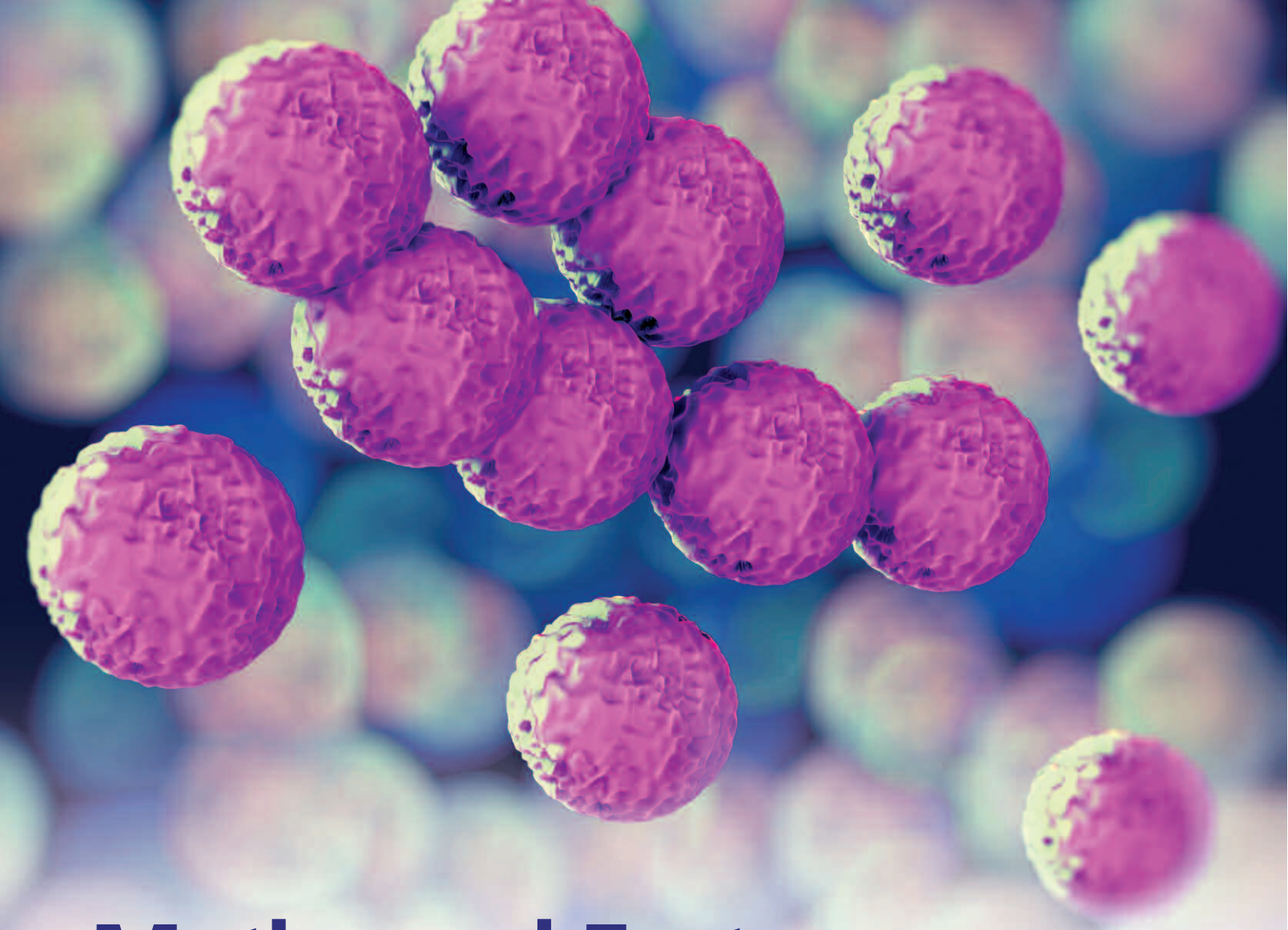

Myths and Facts: MRSA

By Ronale Tucker Rhodes, MS

While the incidence of the more deadly form of MRSA is declining, more needs to be understood about this infection so more cases can be prevented and those that occur can be properly diagnosed and successfully treated.

After a MRSA outbreak among Tampa Bay Buccaneers' players in October called into question whether the team would play the Philadelphia Eagles in the league's sixth scheduled game, a health specialist was called in to meet with the team, supervise the inspection of the facilities and conduct medical examinations. Just one day before the game, the specialist decided not to advise against the teams playing. With annual NFL revenues of $25 billion, this high-stakes decision to allow a third party to control the fate of a game shows how serious a risk MRSA, a sometimes-deadly infection, poses.

MRSA (methicillin-resistant Staphylococcus aureus) is a bacterium that causes infections in different parts of the body. Staphylococcus aureus, also known as staph, is one of the most common bacteria in the world that exists in the environment and in people's bodies.[1] The bacteria are commonly found on the skin and the noses of 25 percent to 30 percent of healthy people. Most of the time, this garden-variety staph does no harm, but when it does cause infection, it is easily treated with antibiotics. In the past few decades, the more dangerous form of staph, MRSA, has emerged. This form is referred to as a "superbug" because it is resistant to an entire class of antibiotics called beta-lactams, which includes methicillin and the more commonly prescribed penicillin, amoxicillin and oxacillin, among others, that are commonly used to treat bacterial infections. As such, MRSA is a serious infection, and the threat of contracting it causes fear in many. But, the fear about MRSA can be minimized by debunking the myths that create confusion about this sometimes deadly infection.

Separating Myth from Fact

Myth: The incidence of MRSA infection is rare.

Fact: Thirty years ago, MRSA accounted for 2 percent of staph infections. However, by 2003, 64 percent of staph infections were caused by MRSA. According to the Centers for Disease Control and Prevention (CDC), more than 94,000 people in the U.S. developed life-threatening infections caused by MRSA in 2005.[2] It is believed that MRSA developed due to overuse of antibiotics, especially in cases where the course of antibiotics was not finished, allowing the remaining bacteria to become familiar with the drug and develop resistance to it.[3]

Myth: MRSA can be contracted only in hospitals.

Fact: MRSA first appeared in the 1960s in hospitals in the U.S.[4] In 2005, 85 percent of MRSA cases were associated with healthcare facilities. However, there were also another 14 percent that occurred in individuals with no known exposure to healthcare.[2] Today, approximately 60 percent of MRSA cases occur in U.S. hospitals. But, a growing number of MRSA outbreaks are occurring in diverse types of people who are constantly in close contact such as team players of contact sports, dormitory residents, inmates and armed-services personnel.[5]

Myth: There is only one type of MRSA infection.

Fact: MRSA infections that occur in hospitals are referred to as hospital-associated MRSA (HA-MRSA), whereas those that occur in people who have not been hospitalized or who haven't had a medical procedure in the past year and are otherwise healthy are called community-associated MRSA (CA-MRSA) infections. Risk factors for an HA-MRSA infection include current or recent hospitalization, living in a nursing home or long-term antibiotic use. Risk factors for a CA-MRSA infection include having an underdeveloped or weakened immune system, playing contact sports, association with healthcare workers (family, friends, etc.) or living in crowded or unsanitary conditions.[6]

The number of CA-MRSA infections in the U.S. began increasing in the 1990s. Today, they comprise about 20 percent of all MRSA infections. CA-MRSA infections differ from HA-MRSA strains. CA-MRSA typically affects younger people (children under age 2 are especially susceptible), while HA-MRSA infections are more often found in older persons.[4] In a study of Minnesotans published in the *Journal of the American Medical Association*, the average age of people with MRSA in a hospital or healthcare facility is 68. But, the average age of a person with CA-MRSA is only 23.[7]

Today, approximately 60 percent of MRSA cases occur in U.S. hospitals.

In general, most CA-MRSA infections are mild skin and soft tissue infections, while most HA-MRSA infections are more serious and invasive (bloodstream infections, surgical site infections and pneumonia). CA-MRSA strains are also more susceptible to antibiotics than HA-MRSA strains, so there are more choices for treatment of CA-MRSA infections. However, CA-MRSA strains spread more rapidly in the community than do HA-MRSA strains because HA-MRSA is confined mostly to healthcare settings. CA-MRSA strains also appear to be more virulent than susceptible Staphylococcus aureus strains, whereas HA-MRSA strains are usually less so. In addition, there is increased mortality from HA-MRSA, usually due to delays in effective treatment and because the antibiotics available to treat HA-MRSA are less effective than those used to treat antibiotic-sensitive strains.

Although only about 1 percent of the U.S. population carries CA-MRSA, it is now the leading cause of pus-producing skin and soft tissue infections among adults.[4]

Myth: MRSA can be treated with antibiotics.

Fact: MRSA is most commonly resistant to antibiotics used to treat conventional staph infections, including beta-lactams (penicillins and cephalosporins), fluoroquinolones (e.g., levofloxacin) and macrolides (e.g., erythromycin and azithromycin). However, it can be treated with "last-resort" antibiotics such as clindamycin, vancomycin, linezolid and daptomycin (the last two of which are novel drugs approved to treat drug-resistant Staphylococcus aureus infections).[1] While these are all viable treatment options, they have their pros and cons. They are powerful drugs that have many side effects that

can be severe and long-lasting. They also can weaken the immune system and increase chances of recurring infections.[8]

Myth: MRSA infections are not serious.

Fact: While MRSA often first presents with mild symptoms that are easier to treat, MRSA can worsen and spread quickly, causing severe, long-lasting challenges that don't respond to standard treatments.[8] Symptoms that need immediate medical attention, especially when associated with skin infections, include fever, chills, low blood pressure, joint pains, severe headaches, shortness of breath and rash over most of the body. Occasionally, the infection can spread to almost any other organ in the body. MRSA that spreads to internal organs can cause complications such as endocarditis, necrotizing fasciitis, osteomyelitis and sepsis, which can be life-threatening.[9]

Myth: MRSA is not contagious.

Fact: MRSA is highly contagious, and anyone can get it. MRSA is spread very similarly to the way a cold is spread such as by touching someone or something that has staph bacteria on it and then touching the eyes, nose or any scrape or abrasion on the skin.

MRSA is highly contagious, and anyone can get it.

While controversial, there are two studies that indicate MRSA can be spread through the air. A June 2001 study published in *JAMA Otolaryngology Head and Neck Surgery* showed that MRSA could be acquired by medical staff and patients through the air in hospitals. The study was conducted in a hospital ward and found MRSA recirculating in the air, among the patients and on inanimate objects in the area, especially when there was movement in the patients' rooms. This study identified both colonized carriers and infected people as sources of risk.[8] A new study conducted by researchers at the University of Leeds in the United Kingdom used a biological aerosol chamber to replicate conditions in hospital rooms with one and two beds. Tiny aerosol droplets containing Staphylococcus aureus were released from a heated mannequin simulating the heat emitted by a human body. Petri dishes, placed where other patients' beds, bedside tables, chairs and washbasins might be located, were then checked to see where the bacteria landed and grew. It was determined that the bacteria were detected up to 11 feet away from the source inside the chamber.[10]

Myth: A MRSA infection is easily identified by its symptoms.

Fact: Most early-stage MRSA infections appear as skin infections. The types of skin infections include cellulitis, an infection of the skin or the fat and tissues that lie immediately beneath the skin, usually starting as red bumps in the skin with some areas resembling a bruise; boils, pus-filled infections of hair follicles; abscesses, collections of pus in or under the skin; sty, an infection of an oil gland of the eyelid; carbuncles, infections larger than an abscess, usually with several openings to the skin; impetigo, a skin infection with pus-filled blisters; and rash, with the skin appearing reddish or having red-colored areas.[9] However, these types of skin infections can often be mistaken for either spider bites or skin changes that occur with Lyme disease.[12]

Myth: If MRSA is suspected, testing is unnecessary.

Fact: Testing is always necessary because MRSA can be mistaken for other skin changes, which can result in the infection being treated with other agents such as dapsone (used for spider bites) that can cause a progression of the MRSA infection and even other complications.[12] In fact, it's common for doctors to prescribe a general broad spectrum antibiotic for anything that looks like a bacterial infection, and these often have no effect on MRSA and can actually make the condition worse.[8] To test for MRSA, a skin sample, a sample of pus from a wound, or blood, urine or biopsy material is sent to a lab and cultured for Staphylococcus aureus. If it tests positive, the bacteria are then exposed to different antibiotics, including methicillin. If the bacteria grow well in methicillin, the infection is diagnosed as MRSA. In 2008, a rapid blood test called the StaphSR assay that can detect the presence of MRSA genetic material in a blood sample in as little as two hours was approved by the U.S. Food and Drug Administration.[12]

Myth: MRSA infections occur only in humans.

Fact: Although rare, MRSA can be transferred between humans and pets. The first incidence of MRSA in a pet was recorded in 2007. Since then, it has been documented in dogs, cats and horses, but it is believed it may be found in other animals in the future. Animal care and treatments are similar to those in humans.[11]

Myth: MRSA is a growing threat.

Fact: A CDC study published in 2010 showed that the life-threatening HA-MRSA infections in healthcare settings are declining. Those that began in hospitals declined 28 percent from 2005 to 2008. Decreases in infection rates were more pronounced for patients with bloodstream infections. And, the study showed a 17 percent drop in invasive MRSA infections that were diagnosed before hospital admissions (community onset) in people with recent exposures to healthcare settings. The CDC study complements data from the National Healthcare Safety Network that found rates of MRSA bloodstream infections occurring in hospital patients fell nearly 50 percent from 1997 to 2007.[13]

On the other hand, CA-MRSA is now common and is a growing threat. Some have suggested that there is an epidemic of CA-MRSA in the U.S., and results of a 2012 meta-analysis of published studies revealed a dramatic increase in infections

over the past two decades, with CA-MRSA strains now endemic at unprecedented levels in many U.S. regions.[14]

Myth: MRSA can't be prevented.

Fact: MRSA can't always be prevented, but there are many ways to reduce the chances of contracting MRSA. The best way to avoid MRSA infection is to avoid making direct contact with skin, clothing and any items that have come in contact with either MRSA patients or MRSA carriers. Of course, infected individuals and carriers aren't immediately identifiable. Therefore, the next best way to foil infection is to treat and cover any skin breaks or wounds and to use excellent hygiene practices. These include hand-washing with soap after personal contact or toilet use, washing clothes that potentially come in contact with MRSA patients or carriers, and using disposable items when treating MRSA patients.[11] In fact, a study recently published in the *New England Journal of Medicine* found that "germ-killing soaps and ointments" used in ICUs reduced cases of MRSA by 40 percent.[6]

Myth: MRSA can't be cured.

Fact: MRSA can be successfully treated and, in many cases, infections do not reoccur. While MRSA is resistant to some antibiotics, there are other kinds of antibiotics that still work to treat it. Bactrim and vancomycin are often the first drugs used. Other options are clindamycin, minocycline, Tygacil, Cubicin, Zyvox and Synercid, some of which are only available intravenously. Unfortunately, there is emerging antibiotic resistance observed with some of these medications.[15] A study published in the *Journal of the American Medical Association* found that there is an increased risk of recurrent infection among recently hospitalized patients with healthcare-associated CA-MRSA infections. These patients had a 64 percent risk of infection at three months or less following discharge. There were also reports of a high risk of infection in discharged patients either infected or colonized with MRSA.[16]

In addition to antibiotics, healthcare providers may drain the infected area by inserting a needle or making a small cut in the skin to reduce the amount of infected material (pus), which will help the tissue to heal.[17]

There are some people who experience recurring infections of MRSA. However, data are sparse, and the rate in mild cases is thought to be very low. Some investigators report that patients may be carriers for up to 30 months, so it is possible for a carrier to have a contagious period for this length of time.[18]

Myth: You can't die from MRSA.

Fact: MRSA can be deadly. In 2005, a study published in the *Journal of the American Medical Association* found there were 94,360 cases of MRSA infection reported in the U.S. that were responsible for an estimated 18,650 deaths. Now, with the decline in HA-MRSA, CDC reports there are an estimated 10,800 deaths in the U.S. each year that are caused by staph, 5,500 of which are linked to MRSA.[6]

Dispelling the Myths Now

MRSA remains a major cause of healthcare-associated and, more recently, community-associated infections. While there has been a decline in HA-MRSA infections in the U.S., MRSA is still a very serious infection that can result in death. But, with early detection and testing, MRSA can be successfully treated. And, with good hygiene, MRSA can be prevented in many cases. Unfortunately, strains of staph continue to adapt and change over time, but researchers are tracking these changes to help identify the optimal treatments for patients. ❖

RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

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Surviving Sepsis: It's Time to Put Albumin to the Test

BY KEITH BERMAN, MPH, MBA

SPREAD OVER THE last 15 years are a pair of landmark trials and a number of smaller studies whose results suggest that use of human albumin as the initial resuscitation fluid in patients with severe sepsis or septic shock can importantly reduce its stubbornly high 30 percent death rate.

In a 1999 randomized trial of 126 patients with cirrhosis and spontaneous bacterial peritonitis — a condition that shares many features with the sepsis syndrome — mortality during hospitalization was dramatically lower in those who received albumin in addition to cefotaxime (10 percent vs. 29 percent, p = 0.01).[1] Then, in 2004, the Saline versus Albumin Fluid Evaluation (SAFE) study, organized by publicly financed hospitals in Australia and New Zealand, uncovered something unexpected: A subgroup analysis of more than 1,200 ICU patients with severe sepsis revealed a relative risk of death of 0.89 associated with resuscitation solely with 4% albumin instead of saline.[2] As this strong trend did not reach statistical significance, there were numerous calls for further clinical research.

Yet, here we find ourselves today with no new clinical research, no robust data to answer whether and to what extent albumin use may reduce mortality. The current Surviving Sepsis guideline continues to recommend crystalloids as the initial resuscitation fluid of choice. Albumin is suggested only for patients who "require substantial amounts of crystalloid," citing "the absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions" in this population.[3]

> "We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock."
>
> — 2012 Surviving Sepsis International Guidelines for Management of Severe Sepsis and Septic Shock

> "Until additional data are available, clinicians may consider albumin as a first-line resuscitation fluid for patients with sepsis."
>
> — The SAFE Investigators (2011)

But, meanwhile, recent new evidence has added weight to the hypothesis that albumin resuscitation instead of crystalloids can reduce the mortality burden from severe sepsis.

Albumin Does — and Doesn't — Spare Lives in Severe Sepsis

Meta-analysis of 17 sepsis trials. Seven years after publishing their landmark study, the SAFE investigators conducted a systematic review and meta-analysis to further explore whether albumin used in lieu of saline or other resuscitative fluids might confer a survival advantage in patients with sepsis.[4] Seventeen studies met the inclusion criteria. Overall, the use of albumin was associated with a reduction in mortality with a pooled estimate of the odds ratio of 0.82 (95 percent confidence interval [CI] 0.67 to 1.0, p = 0.047). Omitting the SAFE study still yielded a similar odds ratio of 0.84 (CI 0.59 to 1.18, p = 0.31). But further, separating eight small studies (totaling 383 participants) using concentrated albumin solutions from nine other studies (totaling 1,594 participants) that evaluated physiologic 4% to 5% albumin solutions revealed a sharp disparity in the effect of albumin concentration on mortality risk:

- *Concentrated (≥20 percent) albumin solutions:* A non-significant odds ratio of 1.08 favoring saline and other non-albumin solutions (95% CI 0.7 to 1.68, p = 0.73). A number of these, as well as other very recent trials,[5,6] stipulated very large doses or a rigid dosing regimen (e.g., dosing to a target circulating albumin level), independent of hemodynamic considerations.
- *Physiologic (4% to 5%) albumin solutions:* An odds ratio of 0.76 favoring iso-oncotic albumin solutions over saline and other non-albumin solutions with borderline statistical significance

(95% CI 0.61 to 0.95, p = 0.02). A survival advantage associated specifically with use of low-concentration albumin has also been documented in recent mouse models of severe sepsis, suggesting a dose-dependent effect.[7]

"The results of this meta-analysis suggest that resuscitation with albumin may result in lower mortality compared with resuscitation with other fluids. Until additional data are available, clinicians may consider albumin as a first line resuscitation fluid for patients with sepsis," the SAFE investigators concluded.

SAFE findings re-examined: a larger mortality treatment effect favoring albumin. In a post-hoc analysis of the severe sepsis subgroup, the SAFE investigators conducted a multivariate logistic regression analysis in 919 of the 1,218 patients for whom there were complete baseline data.[8] While assignment to albumin instead of saline was independently associated with a decreased odds ratio for death of 0.87 (95% CI 0.74 to 1.02, p = 0.09), after adjustment for baseline characteristics, the odds ratio favoring albumin resuscitation further decreased to 0.71 (95% CI 0.52 to 0.97, p = 0.03).

A second sub-analysis revealed that this impressive mortality reduction was very similar in albumin recipients whose pre-treatment baseline serum albumin concentration was ≤25 g/L or >25 g/L. If simple blood volume expansion is presumptively the key therapeutic effect of albumin in severe sepsis, why would more hypoalbuminemic patients not experience a larger mortality reduction benefit than those with relatively high baseline serum albumin levels? This similar mortality reduction trend — independent of baseline serum albumin level — suggests that albumin could be mediating pharmacologic actions entirely apart from its colloid properties.

Albumin Italian Outcome Sepsis (ALBIOS) study. In this newly published open-label study,[9] 100 Italian ICUs randomly assigned 1,818 patients with severe sepsis or septic shock to receive crystalloids only, or crystalloids plus 20% albumin on a daily basis, with the objective of maintaining serum albumin at 3.0 g/dL for 28 days or until ICU discharge. At 28 days after randomization, overall mortality in the two groups was the same — 32 percent and 31.8 percent. At 90 days, there was a small nonsignificant reduction in mortality (41.1 percent vs. 43.6 percent mortality) in the albumin group. A post hoc subgroup analysis of 1,121 patients in septic shock revealed that the relative risk of mortality was 0.87 favoring the albumin treatment group (95 percent CI, 0.77 to 0.99) at 90 days.

The ALBIOS investigators concluded that "the findings in our trial may appear to contradict those of the predefined subgroup analysis from the SAFE study, which suggested a survival advantage with an albumin-based strategy during severe sepsis." In reality, ALBIOS tested an entirely different hypothesis and a radically different dosing regimen from that of the SAFE study. ALBIOS trialists were rigidly required to dose 20% albumin to reach an arbitrary 3.0 g/dL serum level to address hypothetical "hypoalbuminemia" — regardless of the patient's hemodynamic status — for up to 28 days. On each day a patient's serum albumin level fell below 25 g/L, 300 mL of 20% albumin — the oncotic equivalent of 1,200 mL of 5% albumin — was infused.* Through day six, two-thirds of patients in the albumin group were still receiving large daily infusions of concentrated albumin, together with substantial volumes of crystalloids.

The results of this meta-analysis suggest that resuscitation with albumin may result in lower mortality compared with resuscitation with other fluids.

By contrast, blinded SAFE study clinicians decided when and how much fluid (albumin or saline) to administer based on each patient's clinical status and response to treatment. Following standard goal-directed sepsis management guidelines, SAFE study clinicians rapidly tapered their administration of albumin over the first three ICU days:

	4% albumin administered (mL)	% of patients given albumin
Day 1	1,339 ± 1,090	94.3%
Day 2	754 ± 1,069	57.7%
Day 3	283 ± 560	33.2%

** On days when the serum albumin level fell between 25 g/L and 30 g/L, 200 mL of 20% albumin was infused, without regard to the patient's hemodynamic status.*

Could repeated infusions of concentrated albumin by ALBIOS trialists to attain an arbitrary target serum level in all patients have adversely affected some patients, potentially countering its hemodynamic or other benefits in others? While this is not an answerable question, what is clear is that the ALBIOS results do not provide much insight into the life-saving potential of 5% albumin used early, appropriately and exclusively for early resuscitation of severe sepsis, in accordance with standard goal-directed principles of resuscitative fluid therapy.

Albumin in Sepsis Resuscitation: Costly or Cost-Effective?

Human albumin comprises more than one-half of plasma protein content in the circulation and performs an array of important physiologic functions. But confined to a bottle or flexible container, it is widely regarded as just another "volume expander." Even today, most specialists relegate albumin to the catch-all "resuscitative fluids" category occupied by balanced electrolyte solutions, hydroxyethyl starch products and lowly dollar-a-bag saline.

As long it is generally thought of and categorized as a simple resuscitative fluid, 5% albumin will continue to be perceived as an "expensive" alternative to crystalloids for resuscitation of severe sepsis and septic shock. Unsurprisingly, it is hard to find a published review paper, commentary, research article discussion that does not reference the "high cost" of albumin in considering resuscitative fluid options.

But suppose a larger trial were to actually confirm that resuscitation of severe sepsis patients with 5% albumin reduces mortality to a similar extent as the severe sepsis subgroup in the SAFE study? Would albumin resuscitation therapy still be "expensive" in relation to initial resuscitation with lower-cost saline? The answer can be found by simply modeling cost-effectiveness. In this scenario, the cost per life saved by using albumin in lieu of saline as the initial resuscitative fluid is around $7,000 (Table 1). The cost per quality-adjusted life year (QALY) would, of course, come in substantially lower. If one were to apply the adjusted odds ratio after considering differences in baseline factors (0.71),[8] which further favors albumin, the cost per life saved and cost per QALY go lower yet.

When albumin is examined as a potentially life-sparing therapeutic modality in this treatment setting, cost concerns based on comparing its per-liter cost to the cost of saline are obviously misplaced. The estimated cost per life saved,

Table 1. Hypothetical Cost Per Life Saved in Severe Sepsis Patients Resuscitated with 5% Human Albumin in Lieu of Saline (if the SAFE study outcome trend favoring albumin were to be affirmed by a robust adequately powered trial)

Study	Treatment arm – n	Mortality (%)	P value	Lives saved per 100 treated	Albumin cost	Nominal cost per life saved
SAFE Study[2]	4% albumin – 603	Albumin (30.7%)	0.09	4.6 lives	$336†	$7,300
	0.9% saline – 615	Saline (35.3%)				

† Assumes a mean of approximately two liters of 5% albumin at a cost of $42 per 250 mL unit (source: FFF Enterprises, Inc.)

both in absolute terms and relative to virtually any known life-saving treatment, is so low that it needs no further comment. Assuming a well-designed, adequately powered trial ultimately corroborates the SAFE study findings, albumin resuscitation as a means to reduce the death toll from severe sepsis would be remarkably cost-effective by any measure.

Albumin: From Fluid to Multifunctional Protein Therapeutic

Accumulating evidence now suggests that albumin is a human biologic with a spectrum of physiologic functions that may help protect and restore organ function and improve survival through mechanisms entirely unrelated to its role in regulating fluid compartmentalization:

- As the most abundant extracellular antioxidant in the human body, albumin functions as a potent antioxidant and free radical scavenger.
- Albumin binds and transports numerous endogenous and exogenous substances (e.g., bilirubin, hormones, metal ions, free fatty acids and enzymes), variously facilitating their physiologic function, detoxification and antioxidant protection.
- Albumin regulates microvascular permeability and supports endothelial stabilization.
- Albumin mediates anti-inflammatory activity.

Sepsis induces a complex inflammatory response, where severe oxidative stress, free radicals, endothelial dysfunction and other factors collectively can lead to multiple organ failure and death. Albumin is a potent multifunctional biologic that happens also to be the most abundant plasma protein. The prospect that there may be important survival benefit from administering iso-oncotic albumin to a severe sepsis patient whose circulating albumin level is low or whose functionality is overwhelmed by the disease process is certainly not far-fetched.

Is this not a golden opportunity for a team of investigators to design and seek NIH support for a U.S. prospective multicenter study?

A Golden Research Opportunity Awaits

Albumin is supplied by five manufacturers in the United States. It is a generic, low-priced biologic that is costly to produce. Either individually or acting collectively, these manufacturers simply cannot justify investing millions of dollars in a very large multicenter sepsis trial to try to confirm the strongly suggestive SAFE findings.

A decade ago, Australian and New Zealand government health authorities stepped up to conduct the 7,000-subject SAFE study. The SAFE investigators and numerous commenters have subsequently called for "further study" of the role of albumin resuscitation specifically in severe sepsis.

The U.S National Institutes of Health (NIH) annually disseminates $30 billion to support medical research. With the prospect to finally answer whether initial resuscitation with 5% albumin can meaningfully reduce the one-in-three death toll still exacted by severe sepsis and septic shock, is this not a golden opportunity for a team of investigators to design and seek NIH support for a U.S. prospective multicenter study? Inarguably, those would be research dollars well spent. ❖

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KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

Learning to Live with COPD

BY TRUDIE MITSCHANG

When Alice Dunkley was diagnosed with inherited chronic obstructive pulmonary disease (COPD), she was given less than five years to live. Twenty-six years later, this active grandmother continues to beat the odds.

ALICE DUNKLEY WAS only 36 when her family doctor discovered she'd lost 25 percent of her lung capacity and advised her to quit smoking right away. She complied, but five years later, she continued to suffer from shortness of breath and frequent respiratory infections. That's when a blood test determined the root of the problem: Alice had alpha-1 antitrypsin deficiency (Alpha-1), a genetic form of chronic obstructive pulmonary disease (COPD). Her doctor said her prognosis was dire; she was advised not to waste time planning for retirement — it was unlikely she'd live that long. "I was devastated," recalls Alice. "I went home and cried, and then I went into denial. But after about a week of feeling sorry for myself, I decided I either had two to five years to live, or two to five years to die. I decided to live."

Understanding COPD

COPD is one of the most common lung diseases. It is debilitating and incurable; patients require pulmonary and oxygen therapy, plus multiple prescription medications to retain a reasonable quality of life. "I started on Prolastin therapy and took antibiotics early on when I was sick or had an exacerbation," says Alice. "Eventually, I started using inhalers, and I also took prednisone and a mucus breaker."

After about a year on Prolastin injections, Alice's veins began to collapse. At that point, she had a port implanted in her chest to administer the medication, eventually learning to self-infuse, which she still does today.

In 1992, Alice took an early retirement under total disability. She spent two and a half years in pulmonary therapy that included education, exercise conditioning, breathing training and nutritional counseling. In time, Alice returned to her job part time, where she remained for 12-and-a-half more years. But, living with a rare disease often left Alice feeling very much alone. "My husband, Eugene, and I live in a very small town in upstate New York near the Adirondack Mountains," says Alice. "During the first five years following my diagnosis, I never met with a pulmonologist and never spoke to another Alpha-1 patient. In 1993, we drove to Minneapolis to attend a national support meeting, and it was unbelievable to sit in a room with 300 other patients and caregivers. I didn't feel alone anymore."

From Patient to Advocate

Alice returned from that meeting invigorated and inspired. With her husband and daughter's help, she founded a support group in her area, eventually pioneering meetings in Syracuse, Binghamton, Albany and Glen's Falls, N.Y.

A self-described "tough mountain girl," Alice has not only survived her hopeless prognosis, she has learned to thrive in spite of it. An active advocate for COPD awareness, Alice worked as a volunteer for the C.O.P.D. Information Line, where she eventually became a manager. "I have petitioned our governor for a COPD Awareness Month proclamation for the last three years, and have been active in the COPD Foundation, the Alpha-1 Association and the Alpha Net Foundation," she says.

Alice Dunkley defied her doctor's prognosis, and for 26 years, she has lived an active life despite her COPD diagnosis.

Alice believes the adage "knowledge is power," and that the key to self-empowerment lies in helping others. "I tell patients to always keep a positive attitude — seek support from family, your medical team or other people with COPD, especially Alpha-1 because it's so rare. But it doesn't have to be a death sentence. I'm proof of that." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

COPD: 5 Things Every Primary Care Physician Needs to Know

BY BARBARA P. YAWN, MD, MSC

1. **A diagnosis of COPD requires confirmation with pre- and post-bronchodilator spirometry testing.** Based on an appropriate history, you may be able to diagnose COPD using pre-bronchodilator spirometry alone — but you may then miss signs of adult-onset asthma. Post-bronchodilator testing is not that hard! The magic numbers are values for the FEV1 and the FVC; the FEV1/FVC should be ≤0.70.

2. **There are two new sets of COPD guidelines available.** One is jointly commissioned by the American College of Physicians (ACP), American Thoracic Society (ATS), American College of Chest Physicians and European Respiratory Society (2011),[1] and another is from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2011).[2] The ACP/ATS update stresses the importance of prescribing a long-acting bronchodilator for every patient who has COPD and an FEV1 of ≤60 percent of predicted. Keep in mind, the GOLD guidelines suggest that COPD treatment be selected based on a combination of spirometry results, symptom burden (using a measure such as the MRC breathlessness scale[3] or COPD Assessment Test)[4] and exacerbation rate.

3. **Inhaled corticosteroids (ICS) are used to decrease the risk of the next exacerbation.** ICS (or ICS/LABA combinations) are not to be used for all COPD patients, and the new GOLD guidelines suggest the step to start ICS should be based on history of exacerbation and not just an FEV1 of 50 percent of predicted. Up to 30 percent of patients with severe COPD (FEV1 from 30 percent to 49 percent of predicted) will not have an exacerbation over one to three years and should not be exposed to unnecessary use of ICSs.

4. **The hierarchy of therapy for COPD begins with short-acting bronchodilators, moves to long-acting bronchodilators and then to combinations of long-acting bronchodilators (e.g., LABA plus a long-acting antimuscarinic).** Following the patient's second exacerbation in any year, consider adding an ICS or phosphodiesterase (PDE)-4 inhibitor to their maintenance therapy. PDE-4 inhibitors are used in patients who have exacerbations and significant sputum production — the chronic bronchitis element of COPD. Low-dose theophylline can be a good adjunct for those with severe or very severe COPD.

5. **COPD exacerbations are managed with oral or systemic corticosteroids. It may take six to eight weeks for a return to baseline symptom level, functional status and lung function.** Exacerbations are clearly significant adverse events for patients with COPD. All patients should be seen for follow-up within three to seven days after hospitalization for an exacerbation or within two weeks after treatment as an outpatient. Readmission is best avoided through careful follow-up, appropriate therapy after hospital discharge, and a refresher course on appropriate medication use.

And, one for the road: Patient inhaler technique should be checked regularly, and at any visit that occurs longer than two weeks after a previous visit. Poor inhaler technique is common and leads to poor COPD control. Make sure patients know how to use the inhalers.[5] ❖

BARBARA P. YAWN, *MD, MSc, is the director of research at Olmsted Medical Center and an adjunct professor for the Department of Family and Community Health at the University of Minnesota. As a full-time family physician researcher, her areas of expertise include the diagnostic process, women's health, and asthma identification and management.*

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On the Frontlines of Flu Prevention

"I think people like to see their leader as a 'doer' — one who is actively engaged in a body of work that will help build success for the team and the company."

— Chris Woolway, U.S. Director, Sales & Marketing, Influenza, bioCSL

BY TRUDIE MITSCHANG

WHEN CHRIS WOOLWAY stepped into the role of U.S. director of sales and marketing for bioCSL last August, the company was in transition. As a global flu vaccine supplier, bioCSL (formerly CSL Biotherapies) had just announced the reshaping of a U.S. commercial organization dedicated to influenza vaccines, with a name change initiated in 2012 in Australia and implemented in February 2014 in the U.S. With U.S. corporate offices located in King of Prussia, Pa., bioCSL is a subsidiary of CSL Limited (CSL), based in Parkville, a suburb of Melbourne, Australia. From this base in Parkville, bioCSL operates one of the world's largest influenza vaccine manufacturing facilities for supply to global markets. CSL has nearly 50 years of experience in developing and manufacturing influenza vaccine. This long heritage underpins the company's commitment to safety, quality and reliability.

"This is a very unique opportunity. I've quickly built a focused sales and marketing force, supported by the mentorship of bioCSL Inc. President and Head of Global Commercial Influenza Operations Dr. Marie Mazur," says Woolway. "I've focused on building a team that is very talented and experienced in the vaccine space, which has accelerated our results. Importantly, we have been warmly received by our key customers, who recognize the focus that we have on excellence."

In September 2013, just one month after Woolway took his position, bioCSL became the first U.S. supplier to complete its 2013-2014 seasonal influenza vaccine delivery campaign, which consisted of more than 11 million doses of Afluria. Woolway attributes much of the credit for that achievement to the fact that bioCSL's facility focuses year-round exclusively on the early development and production of seasonal flu vaccine for the Northern and the Southern hemispheres. He also cites the important role operational excellence has played in the company's ongoing growth and expansion.

"This was a critical achievement, which was made possible by innovative approaches to our manufacturing, supply chain and cold-chain management activities," explains Woolway. "In 2009, bioCSL inaugurated a high-speed syringe filling and packaging line in its Kankakee, Ill., facility, with the objective to make its flu vaccine more rapidly available to U.S. healthcare providers. As a result, bioCSL was able to provide Afluria in a timely manner, which supported immunization efforts early in the season for the healthcare provider customers that we serve."

As U.S. Director of Sales & Marketing, Influenza, Chris Woolway is creating strategic partnerships to address industry challenges.

The Fluctuating State of the Flu Vaccine Business

Comfortable with his current role of "change agent," Woolway acknowledges that the flu vaccine industry is fraught with challenges, including issues of reimbursement, distribution and administration options; there are currently more than 20 different brands and presentations of flu vaccine, coupled with an ongoing debate over quadrivalent versus trivalent vaccine formulations. Additionally, there is the long-standing obstacle of consumer

perception and behavior; the fact is, the prime target age group of 18-to 64-year-olds simply does not believe they need a flu shot. "The 18-to 64-year-old population is the least immunized, with a vaccination rate of only about 30 percent," explains Woolway. "Yet, for the 2013-2014 influenza season, this was the group that was hardest hit in both hospitalizations and deaths by the H1N1 virus, a strain which everyone remembers as being the culprit of the 2009 pandemic."

Woolway affirms that increasing overall seasonal influenza vaccination rates is the most significant annual public health endeavor, noting that patient complacency continues to present a unique and daunting challenge within the flu vaccine supplier community and the medical community as a whole. "There is a very strong need as a supplier community to work as closely as we can to raise immunization rates in this country. We still have a significant amount of disease, and in the U.S., we are still seeing, on average, 36,000 deaths and 200,000 hospitalizations per year from flu-related complications," explains Woolway. "Those are big numbers, and I can't help but wonder if there is something those of us in the supplier community can do to change that."

On the Forefront of Prevention

Strategic partnerships play a large role in bioCSL's approach to addressing industry challenges. The company has aligned itself with immunization advocacy initiatives, as well as with key private national immunizers, and actively supports the National Adult and Influenza Immunization Summit in an effort to bolster vaccination rates. bioCSL selectively invests in life-cycle initiatives that are expected to provide differentiated product offerings, which might incite more Americans to get their seasonal flu shot, ultimately playing a role in reducing the burden of influenza. In an industry that has, in recent years, seen the introduction of differentiated products, bioCSL is pioneering a new mode of administration for our multi-dose vials via a needle-free injector system, which is partnered with PharmaJet Inc. "As we think about the future of the influenza vaccine industry, I think we are going to see a much more multidisciplinary approach to how suppliers address the market, especially as we think about the clinical, financial and operational imperatives of our customers. It used to be good enough to have a quality product delivered on or ahead of schedule, at a good price. Not in the future," says Woolway. "Suppliers will need to think carefully about how they relate to a spectrum of business partners and clinical constituents — there are opportunities that could come to fruition that might not even be on the radar today."

When it comes to leadership style, Woolway takes a "roll up your sleeves" attitude and approach, while striving to support individual development within his team. Committed to leading with vision and inspiration, he says a good leader is always tasked with helping the team understand the "why" behind any initiative, while clearly communicating the role that each team member contributes to the greater cause. "I think people like to see their leader as a 'doer' — one who is actively engaged in a body of work that will help build success for the team and the company," says Woolway. "Hard work and significant challenges don't scare me — in fact, they motivate me."

A second degree black belt, Woolway says the principles he's learned in Taekwondo greatly influence his business philosophy. "In martial arts, everybody goes into the ring understanding their skill sets, while also recognizing it's not just about imposing your plan of action, it's also about understanding your environment and how your competitor sizes up," he explains. "When you engage and find yourself in the heat of the battle, you have to get very clear on your objective. Is it to come out with a point? Is it to survive? You may go in with a particular game plan, but if it's not working, you need to be prepared to reassess and, possibly, change tactics. With the flu business, the ability to step back and reassess is very much a core competency." ❖

When it comes to leadership style, Woolway takes a "roll up your sleeves" attitude and approach, while striving to support individual development within his team.

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

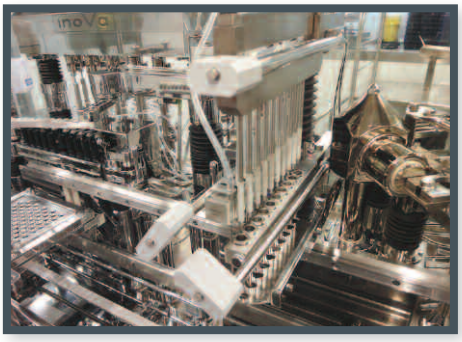
bioCSL™

Where delivering vaccines is our mission – protecting lives is our passion

bioCSL, previously CSL Biotherapies, understands the influenza vaccine business and our customers' needs for reliable, timely, and safe flu vaccine supplies. Our well-established parent, CSL Limited, has a global heritage of flu vaccine production without disruption for nearly five decades. Based in Melbourne, Australia, bioCSL provides influenza vaccine in both the Northern and Southern Hemispheres, inclusive of Australia, New Zealand, and more than 16 countries in Europe, South America and Asia.

Beginning with the 2007-2008 season, bioCSL has been contributing to the growing demand in the United States for reliable flu vaccine supply. bioCSL is ideally positioned as a reliable flu vaccine supplier for healthcare professionals who actively participate in flu vaccination campaigns for their patients each influenza season.

With a strong commitment to execute successful US influenza vaccine production and distribution campaigns, bioCSL offers several competitive advantages to US healthcare professionals in search of timely delivery of high-quality flu vaccines.



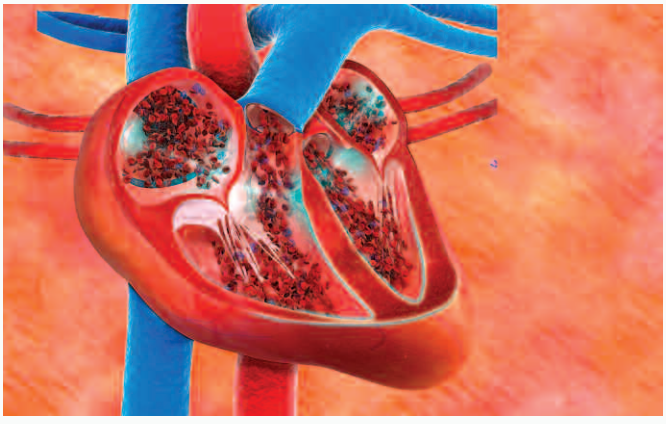
bioCSL has invested in one of the only high-speed pre-filled syringe filling lines in the US underscoring our commitment to the US influenza market.

Our well-established parent, CSL Limited, has a global heritage of flu vaccine production without disruption for nearly 50 years.

BioResearch

Summaries of up-to-date clinical research published internationally.

IVIG May Improve Left Ventricular Function and Reduce Episodes of Arrhythmia in Adults with Acute Fulminant Myocarditis



Chinese investigators conducted an observational retrospective case study of inpatients presenting at Guangdong General Hospital with acute fulminant myocarditis (AFM) between January 2001 and December 2010. Inclusion criteria included adult age over18 years, acute onset (duration less than three months) congestive heart failure and impaired left ventricular function following a recent viral illness. Of 58 enrolled patients, 32 were administered intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg for five days, along with other conventional therapies. The remaining patients, who were similar as a group with respect to baseline characteristics, received conventional therapies only.

The group receiving IVIG therapy had a higher left ventricular ejection fraction (LVEF) and a reduced left ventricular end-diastolic diameter (LVDD) compared with the non-IVIG therapy group four weeks subsequent to treatment (PLVEF = 0.011 and PLVDD = 0.048). While post-treatment incidence of ventricular tachycardia/ventricular fibrillation (VT/VF) and atrioventricular block (AVB) was reduced in the group receiving IVIG (PVT/VF = 0.025, PAVB = 0.003), no significant differences were seen in the non-IVIG group (PVT/VF = 0.564, PAVB = 0.083). Two and seven deaths occurred in the IVIG and non-IVIG groups, respectively (6% vs. 27%, P = 0.072).

The investigators concluded that IVIG therapy may be associated with improved recovery of left ventricular function and reduced episodes of fulminant arrhythmias.

Yu DQ, Wang Y, Ma GZ, et al. Intravenous immunoglobulin in the therapy of adult acute fulminant myocarditis: A retrospective study. Exp Ther Med *2014 Jan;7(1):97-102.*

Four-Factor Prothrombin Complex Concentrate Superior to Plasma for Warfarin Reversal Required Prior to Urgent Surgery

Historically, donor plasma has been the standard of care in the U.S. for vitamin K antagonist (VKA; e.g., warfarin) reversal prior to emergency surgery. In April 2013, the first nonactivated four-factor prothrombin complex concentrate (4F-PCC; Kcentra, CSL Behring) was approved for urgent VKA reversal in patients with acute major bleeding. A Phase IIIb randomized, prospective, open-label noninferiority clinical trial was designed to evaluate the efficacy and safety of 4F-PCC in comparison with plasma in patients requiring VKA reversal prior to an urgent surgery or other invasive procedure.

The efficacy analysis population comprised 168 patients, including 87 in the 4F-PCC arm and 81 in the plasma arm. Dosing of 4F-PCC (15, 35 or 50 units/kg) or plasma (10, 12 or 15 mL/kg) was based on baseline INR and weight. The co-primary endpoints were effective hemostasis and rapid INR reduction (≤1.3 at 0.5 hour after end of infusion).

Effective hemostasis was achieved in 89.7 percent of patients in the 4F-PCC group versus 75.3 percent in the plasma group, demonstrating both noninferiority and superiority of 4F-PCC over plasma. Rapid INR reduction was achieved in 55.2 percent of patients in the 4F-PCC group versus 9.9 percent in the plasma group, again demonstrating both noninferiority and superiority of 4F-PCC. Rates of mortality, serious adverse events and thromboembolic events were similar between the treatment groups. Significantly fewer fluid overload events occurred with 4F-PCC than with plasma (difference -9.1 percent). The investigators concluded that 4F-PCC is an effective alternative to plasma for rapid VKA reversal in patients undergoing urgent surgical procedures.

Refaai MA, Goldstein JN, Milling TJ, et al. Randomized phase IIIb study of rapid vitamin K antagonist reversal in patients requiring an urgent surgical procedure: Four-factor prothrombin complex concentrate is superior to plasma. American Society of Hematology Annual Meeting. Oral and Poster Abstract 3588. Monday, Dec. 9, 2013.

KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of* International Blood Plasma News, *a blood products industry newsletter.*

BioProducts

New products in the marketplace.

Temperature-Sensitive Shipping

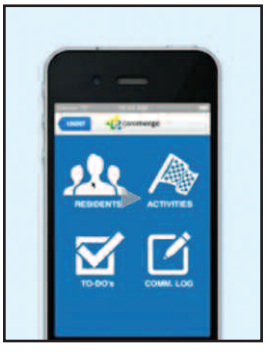
The Critical Cube is a temperature-sensitive carrier that moves freight in a dry van infrastructure. Using liquid CO2 and a digital controller, the unit can actively maintain a temperature down to minus 30 degrees Fahrenheit for up to five days (while maintaining a plus-or-equal-to-2 degrees Fahrenheit). It is large enough for a standard size pallet up to 60 inches tall with 77 cubic feet of loadable space. The technology is environmentally friendly and built entirely with U.S. Food and Drug Administration- and USDA-approved materials to move pharmaceuticals, chemicals and food products. Features include a locking mechanism to ensure the integrity of shipping security for the duration of the move and optional GPS tracking and temperature monitoring for highly sensitive shipments.

One Stop Critical, (888) 297-0496, www.onestopcritical.com

Hospital Readmission App

The new ReThink ReAdmissions app connects long-term care providers with hospitals, allowing information to flow from the hospital to the senior living or at-home care team, including necessary discharge instructions and critical medical information such as medication lists for the care transition. The technology helps hospitals reduce readmission from senior living facilities and patients who were discharged to their homes. "Twenty to 30 percent of all readmissions to hospitals come from senior living facilities, and reducing these readmissions is a daunting challenge," said Asif Khan, CEO of Carmerge. For the hospital, the discharge instructions are interfaced into the app, and the patient transition allows the hospital to transfer all relevant information to the specified senior living facility or home health agency.

Caremerge Technology, www.allscripts.com



Modern Patient Gowns

Patient Style offers hospital gowns with modern designs that are made of signature interlock fabric, innovative wrap-around designs and easy access features. The gowns are available in a tie or IV snap design, and they have an extra-large sweep so the patients' backsides are never exposed. The overlapping panels eliminate the need for "double" gowning, and the wrap-around design wraps in the back and ties at the side so patients can dress themselves easily, freeing nurses to focus on clinical care. In addition to basic hospital gowns, the company offers pediatric patient apparel, modesty gowns for the Muslim communities, specialty nursing gowns and wrap-around mammography tops. All garments provide comfort and modesty and are offered in fun, stylish prints.

Patient Style, patientstyle.com/index.html

Topical Analgesic

Salonpas Deep Relieving Gel is designed to penetrate deep to relieve the toughest muscle and joint pain. It is an easy-to-use topical analgesic that is fast-melting, quick-absorbing, clear, nongreasy and starts to deliver pain relief in seconds. It contains three active ingredients: camphor (3.1 percent), menthol (10 percent) and methyl salicylate (15 percent).

Hisamitsu America, www.salonpas.us/product/salonpas-deep-relieving-gel

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Clinical Research Manual

Author: U.S. Food and Drug Administration

The updated *Clinical Research Manual* for 2013 brings together guidance on everything from pharmacokinetics and study design, to recruitment, monitoring, human subject protections, statistics and budgeting. Both new and experienced trial managers can find the information they need to set up and run every phase of a clinical research program — from drug discovery through postmarketing surveillance — in the U.S. or abroad. Included are 20 chapters, each written by top experts from organizations involved in every aspect of clinical research, that provide practical hands-on advice, including how to plan international development of new medicines; specific steps for registering products in the United Kingdom and Europe; regulatory requirements in major markets, including the U.S. and Japan; how to recruit investigators; tips on good clinical research practice; tips on writing reports; and advice on effective budgeting of clinical research studies.
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Critical Care Market to 2019 — Growth from Factor Concentrates, New Indications and Increasing Demand for Albumin in Asia-Pacific

Author: Reportstack

The report provides in-depth analysis of the drivers and barriers that affect the global critical care market. The report includes data and analysis regarding the critical care market in leading geographical locations (U.S., U.K., Germany, France, Italy, Spain, Japan and Asia-Pacific countries, including India, China and Australia); annualized market data for the critical care market, including the individual markets for factor XIII concentrate, fibrinogen concentrate, antithrombin, prothrombin complex concentrate and albumin from 2006 to 2012, with forecasts provided up to 2019; market data on the geographical landscape and therapeutic landscape, including market size, market share, cost of therapy, sales volume and treatment usage patterns such as disease population, diagnosis population and prescription population; key drivers and restraints that have had a major impact upon the market; an overview of the competitive landscape of the global critical care market, including benchmarking for leading companies (CSL, Octapharma, Baxter, Grifols and LFB); and key M&A activities that took place in 2010 and 2011 in the critical care market.
www.sbwire.com/press-releases/critical-care-market-to-2019-growth-from-factor-concentrates-new-indications-and-increasing-demand-for-albumin-in-asia-pacific-388313.htm

Managing Physician Payment Disclosures

Author: U.S. Food and Drug Administration

By Sept. 30, drug- and devicemakers must report the types of financial arrangements they have with physicians and teaching hospitals. *Managing Physician Payment Disclosures* is designed to help organizations set up a compliant reporting program to withstand any challenges. In addition to providing key definitions on what information must be reported, it explains who qualifies under the law and must report, and who is exempt; how to build the "assumptions document" that will form the basis for the reporting strategy; special considerations for educating physicians and hospitals on implications of the rule; how to avoid simple mistakes that can result in failure to report; how to anticipate potential public relations and legal problems disclosure may create; and how to address and resolve complaints about data. Also included are details on questions likely to arise when implementing the reporting program, including: Are non-U.S. payments reportable? Must companies report payments occurring before a product is approved? Are consulting fees treated differently than gifts? Are drug samples considered items of value that must be reported? Are product discounts reportable? Are payments for treatment of adverse events reportable? Does the Sunshine Act preempt all state reporting requirements? And, many others.
www.fdanews.com/products/45538&hittrk=14109?utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=29450200m

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Medicare Reimbursement Rates* Rates are effective April 2014 through June 2014. ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$76.44	$75.21
CARIMUNE NF	CSL Behring	J1566	$60.09	$59.12
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$72.65	$71.49
GAMMAGARD LIQUID	Baxter	J1569	$78.33	$77.07
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$60.09	$59.12
GAMMAKED	Kedrion	J1561	$79.01	$77.74
GAMMAPLEX	Bio Products Laboratory	J1557	$73.63	$72.45
GAMUNEX-C	Grifols	J1561	$79.01	$77.74
OCTAGAM	Octapharma	J1568	$61.00	$60.02
PRIVIGEN	CSL Behring	J1459	$73.50	$72.33

** Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PIDD	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PIDD, ITP	3 g, 6 g, 12 g
FLEBOGAMMA 5% & 10% DIF Liquid	Grifols	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxter	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxter	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Laboratory	IVIG: PIDD, ITP	2.5 g, 5 g, 10 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PIDD	1 g, 2 g, 4 g, 10 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PIDD Primary immune deficiency disease

2014-2015 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Manufacturer	Product	Presentation	Age Group	Code
bioCSL	AFLURIA (IIV3)	5.0 mL multi-dose vial	9 years and older*	90658/Q2035
		0.5 mL single-dose syringe		90656
GlaxoSmithKline	FLULAVAL (IIV3)	5.0 mL multi-dose vial	3 years and older	90658/Q2036
	FLULAVAL QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	3 years and older	90688
	FLULAVAL QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
	FLUARIX QUADRIVALENT (IIV4)	0.5 mL single-dose syringe	3 years and older	90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 mL single-use nasal spray	2–49 years	90672
Novartis	FLUVIRIN (IIV3)	5.0 mL multi-dose vial	4 years and older	90658/Q2037
		0.5 mL single-dose syringe		90658
	FLUCELVAX (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661
Protein Sciences	FLUBLOK (RIV3)	0.5 mL single-dose vial	18–49 years	90673
Sanofi Pasteur	FLUZONE (IIV3)	5.0 mL multi-dose vial	6 months and older	Q2038
		0.5 mL single-dose syringe	3 years and older	90656
	FLUZONE QUADRIVALENT (IIV4)	5.0 mL multi-dose vial	6 months and older	90688
		0.25 mL single-dose syringe	6–35 months	90685
		0.5 mL single-dose syringe	3 years and older	90686
		0.5 mL single-dose vial	3 years and older	90686
	FLUZONE HIGH-DOSE (IIV3)	0.5 mL single-dose syringe	65 years and older	90662
	FLUZONE INTRADERMAL (IIV3)	0.1 mL single-dose microinjection system	18–64 years	90654

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 Cell culture-based trivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years.

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