Winter 2015

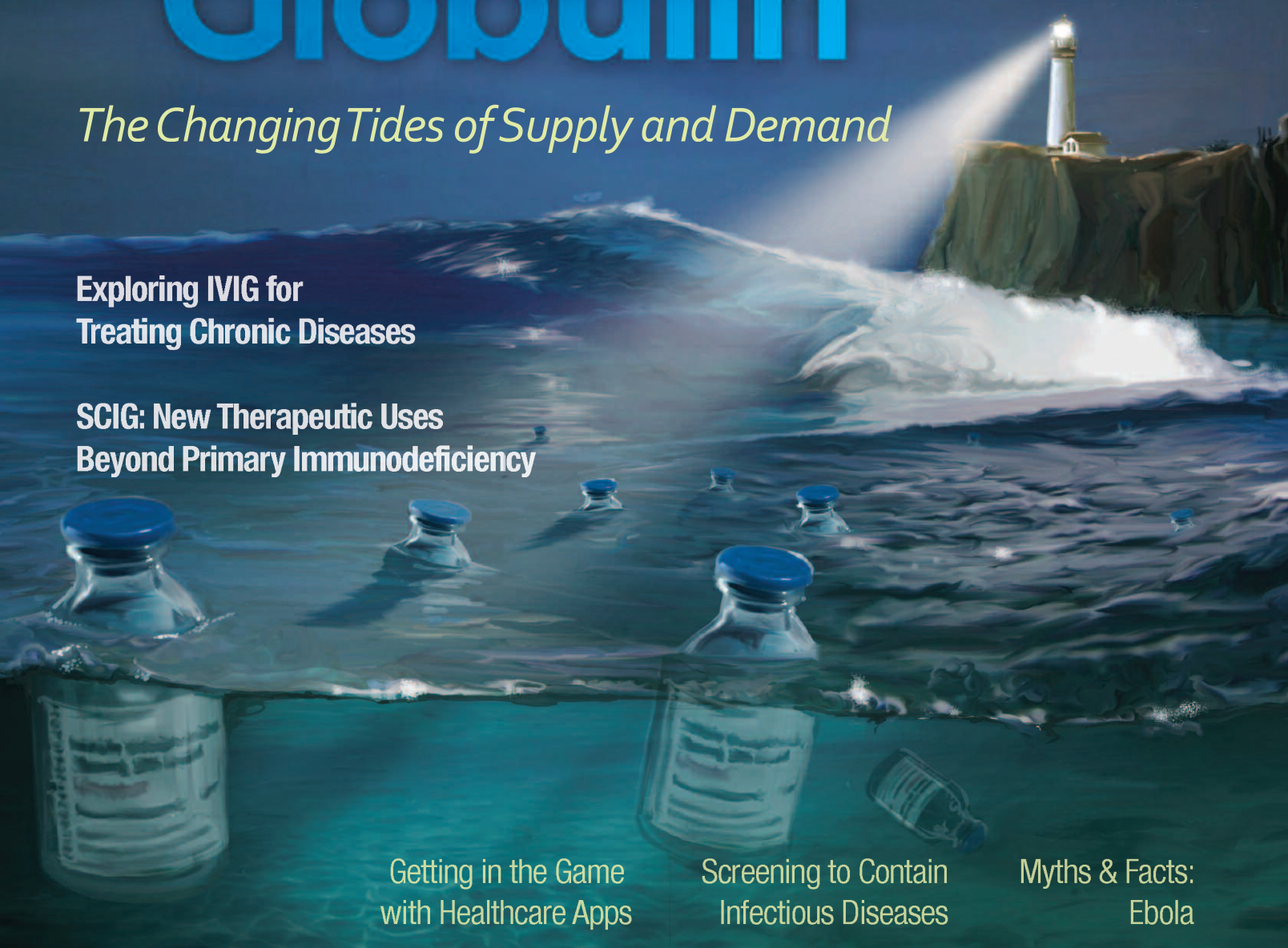
BioSupply Trends

Special Focus: PLASMA

Quarterly

Immune Globulin

The Changing Tides of Supply and Demand



Exploring IVIG for Treating Chronic Diseases

SCIG: New Therapeutic Uses Beyond Primary Immunodeficiency

Getting in the Game with Healthcare Apps

Screening to Contain Infectious Diseases

Myths & Facts: Ebola

Grifols Attacks Alzheimer's — Page 52

gamunex®-C
immune globulin injection (human), 10%
caprylate/chromatography purified

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GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) is indicated for the treatment of primary humoral immunodeficiency disease (PIDD), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Thrombosis may occur with immune globulin products, including GAMUNEX-C. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer GAMUNEX-C 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.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IVIG) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose. GAMUNEX-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.

GAMUNEX-C is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. It is contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity.

Severe hypersensitivity reactions may occur with IVIG products, including GAMUNEX-C. In case of hypersensitivity, discontinue GAMUNEX-C infusion immediately and institute appropriate treatment.

Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IVIG treatment, including GAMUNEX-C.

There have been reports of noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]), hemolytic anemia, and aseptic meningitis in patients administered with IVIG, including GAMUNEX-C.

The high-dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Because GAMUNEX-C is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Do not administer GAMUNEX-C subcutaneously in patients with ITP because of the risk of hematoma formation.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of GAMUNEX-C and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.

If signs and/or symptoms of hemolysis are present after an infusion of GAMUNEX-C, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

In clinical studies, the most common adverse reactions with GAMUNEX-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection-site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PIDD) and infusion-site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PIDD); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in 1 subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in 1 subject (in PIDD), and myocarditis in 1 subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

 October 2014 GX210-0914

Please see brief summary of GAMUNEX-C full Prescribing Information on adjacent page.

GRIFOLS

GAMUNEX®-C

Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX®-C, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including GAMUNEX-C. 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.**
- **For patients at risk of thrombosis, administer GAMUNEX-C 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.**
- **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. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

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

GAMUNEX-C is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

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

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy.
- Thrombosis has occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombosis; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload.
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Passive transfer of antibodies may confound serologic testing.

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

Serious adverse reactions which occurred in the clinical trials were an exacerbation of autoimmune pure red cell aplasia in one subject and pulmonary embolism in one subject with a history of PE. The most common adverse reactions observed in $\geq$ 5% patients were:

PI: Intravenous: Headache, cough, injection site reaction, nausea, pharyngitis and urticaria.
Subcutaneous: Infusion site reactions, headache, fatigue, arthralgia and pyrexia.

ITP: Headache, vomiting, fever, nausea, back pain and rash.

CIDP: Headache, fever, chills, hypertension, rash, nausea and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- The passive transfer of antibodies may transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella.

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

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

GRIFOLS

Grifols Therapeutics Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

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BioSupply Trends Quarterly

Winter 2015

Features

Special Focus: Plasma

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The Growth of the Plasma Market

THE NUMBER OF chronic illnesses treated with therapies manufactured from human plasma has been steadily growing in recent years, and manufacturers of immune globulin (IG) products in particular are rising to meet the demand. It is estimated that IG usage is growing at a rate of 6 percent to 8 percent each year; however, more accurate estimates may be as high as 10 percent to 15 percent. With 14 FDA-approved IG products currently on the market and a 15th on the way, one thing is certain: Increased demand for these life-giving products will require an increase in the raw plasma product.

In this annual plasma-themed issue of *BioSupply Trends Quarterly*, we take a critical look at the current plasma market, especially issues of supply and demand. The healthcare industry is currently experiencing an oversupply of IG, but is it possible another shortage is looming? History has shown that recalls and withdrawals can cause sudden and unexpected shortages without warning. In our article "Immune Globulin: Controlling Supply and Demand," we look at some of the reasons behind past shortages, assess where we are now and delve into what steps the industry is taking to help prevent another shortage.

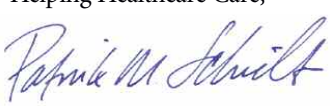
A significant factor concerning supply and demand in the plasma market is the growing global demand fueled by the rapidly expanding list of diseases and chronic conditions for which plasma derivatives are showing promise. Our article "Exploring the Power of IVIG" spotlights some of the current clinical studies using intravenous IG that are breaking new ground when it comes to treating chronic disease. Promising results are being seen in patients suffering from Alzheimer's, autism and even diabetes.

IG therapy for autoimmune and other neuromuscular disorders is most commonly administered intravenously. But recent studies show that the subcutaneous route is both as effective and more preferred by patients. In our feature "Subcutaneous Immune Globulin: New Therapeutic Uses Beyond Primary Immunodeficiency?" we learn that investigators across Europe recently have reported that SCIG may represent a better treatment option than IVIG for many patients with certain disease states. A very recently published Italian single-center experience compared IVIG and SCIG use in 61 patients with hypogammaglobulinemia secondary to chronic lymphocytic leukemia and nonHodgkins lymphoma, with results closely mirroring other findings: SCIG patients had fewer systemic adverse events, significantly higher IgG trough levels, reduced infectious events and improvement in quality of life.

Moving beyond the plasma market, if there was one healthcare headline that dominated the media in 2014, it was the Ebola epidemic. Dubbed the "deadliest Ebola outbreak in history," our article "To Screen or Not to Screen" explores how diseases like Ebola are spread across country borders and what guidelines and recommendations have been implemented to curb that spread. There's no debating how deadly Ebola is. Our Myths and Facts column takes a timely look at this frightening and widely misunderstood virus; the Centers for Disease Control and Prevention estimates that the number of Ebola cases could rise to as many as 1.4 million by early this year, but spreading even more quickly than the virus itself is fear due to a lack of understanding about what causes Ebola and how it is spread.

As always, we hope you find this issue of *BioSupply Trends Quarterly* educational, insightful and innovative. Looking to the future, we hope to continue to bring you the information and resources that are helpful to you in 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

Creative Director
Brian D. Miller

Artistic Director
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Graphic Artists
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Ben Drolet

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Contributing Writers
Keith Berman, MPH, MBA
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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

Drug Supply Chain Security Act In Effect as of January 1

On Jan. 1, Title II of the Drug Quality and Security Act (DQSA), known as the Drug Supply Chain Security Act (DSCSA), took effect. However, the U.S. Food and Drug Administration (FDA) will not be enforcing implementation of the transaction information, history and statements requirements until May 1. The DSCSA establishes a 10-year timeline for achieving an interoperable track-and-trace system for prescription drugs at the individual package level, as well as strengthens licensure requirements for wholesale distributors and third-party logistics providers and establishes nationwide drug serial numbers.

As of May 1, manufacturers and repackagers are required to capture the transaction history and movement of a pharmaceutical product through the supply chain by placing a unique product identifier on drug packages such as a bar code that can be read electronically. And, they are required to store that information for at least six years. They can choose, based on their facility's requirements, to maintain their records by 1) keeping packing slips, 2) maintaining shipping notification emails or 3) registering with Life Sciences Cloud, Tracelink's cloud-based technology platform (see Leadership Corner on page 56). Eventually, however, manufacturers and repackagers will be required to store the information in electronic format.

At the same time, wholesale distributors, dispensers and repackagers must develop verification methods to determine whether a product is a valid, suspect or illegitimate product. If they determine they are in possession of such a product, they must quarantine and promptly investigate it, and they must notify FDA and other stakeholders to prevent further circulation of potentially compromised medication. They also must respond within 48 hours to requests from federal or state officials — in the event of a recall or for the purpose of investigating a suspect product or an illegitimate product — for the transaction history of the pharmaceutical product.

The DQSA was signed into law on Nov. 27, 2013, to protect U.S. patients from ineffective, counterfeit, low-quality and unsafe drugs that pose serious public health safety concerns entering the market. The Act contains two parts: Title I applies to the compounding of human drugs pursuant to a prescription, while Title II pertains to the tracking and tracing of these drugs. ❖

Telehealth Payments and Domain to Expand Under Proposed CMS Rule

A 609-page proposed rule by the Centers for Medicare and Medicaid Services (CMS) would add to the list of Medicare-reimbursable telehealth activities, as well as pay for telehealth services in rural areas nearer big cities under a geographical expansion. The proposal would add annual wellness visits to the list of telehealth services for both the initial visit and subsequent visits if they include a personalized prevention plan of service. In addition, it would add psychoanalysis, family psychotherapy (both with and without the patient being present) and "prolonged service in the office or other outpatient setting requiring direct patient contact beyond the usual service." Payments for telehealth services would be afforded to patients in "rural census tracts" even if those tracts are within metropolitan statistical areas. Census tracts are composed of smaller census blocks and block groups and have, on average, about 4,000 inhabitants.

Existing CMS payment policy and the agency's new telehealth payment proposal model a telehealth policy guide approved in April by the Federation of State Medical Boards (FSMB), which says that a physician-patient relationship must be established for physicians to engage in telemedicine, but that a relationship can be initiated "whether or not there has been an encounter in person between the physician (or other appropriately supervised healthcare practitioner) and patient." In defining telemedicine, the FSMB states: "Generally, telemedicine is not an audio-only telephone conversation, email/instant messaging conversation or fax. It typically involves the application of secure videoconferencing or store-and-forward technology to provide or support healthcare delivery by replicating the interaction of a traditional encounter in person between a provider and a patient." Existing Medicare policy, the new rule says, mandates that telehealth includes "at a minimum, audio and video … permitting two-way, real-time interactive communication." Telephones and email "do not meet the definition of an interactive telecommunications system." Medicare permits payments for "store-and-forward" technology in demonstration projects in Alaska and Hawaii. ❖

New DEA Law Authorizes Drop-Off Sites for Unused Prescription Drugs

A new Drug Enforcement Administration (DEA) regulation allows pharmacies, hospitals, clinics and other authorized collectors such as long-term care facilities to serve as authorized drop-off sites for unused prescription drugs. The law builds on existing take-back programs launched by the DEA, including take-back events in April and September, as well as events over the past four years that have taken in more than 4.1 million pounds of prescription pills.

The new changes are expected to save lives and protect American families from the increased dangers of prescription drug misuse. In 2011, more than half of the 41,300 unintentional drug overdose deaths in the U.S. involved prescription drugs, and hazardous opioid pain relievers led to approximately 17,000 of those deaths. ❖

Supreme Court Upholds Exemption to ACA's Contraception Coverage Requirement

In June, the U.S. Supreme Court voted 5-4 to allow a key exemption to the Affordable Care Act's contraception coverage requirements, meaning closely held, for-profit businesses can assert a religious objection. Under the ACA, health insurance plans (except those that are grandfathered) are required to cover all U.S. Food and Drug Administration (FDA)-approved contraception methods (birth control pills, intrauterine devices and sterilization procedures) for women without any cost-sharing such as deductibles or co-payments. Employers with 50 or more workers that offer coverage that doesn't meet that standard would face fines of $100 a day per worker, and if they don't offer any coverage, they face a fine of $2,000 per employee per year.

The Supreme Court's ruling was in response to a lawsuit filed by Hobby Lobby Stores and Conestoga, both family-owned businesses, which argued that several types of contraceptives violate their owners' religious beliefs. According to them, they should be exempted from the requirement because of the 1993 Religious Freedom Restoration Act that says the government may not pose a "substantial burden" on the free exercise of religion unless that burden is the narrowest possible way to further a compelling government interest. The federal government and other advocates argued that only individuals — not corporations — can exercise religious rights.

While some analysts believe the ruling could open the door for employers to use religious objections to opt out of other areas of healthcare coverage, Justice Samuel Alito's decision went to lengths to limit the scope of the decision by writing: "This decision concerns only the contraceptive mandate and should not be understood to hold that all insurance-coverage mandates, e.g., for vaccinations or blood transfusions, must necessarily fall if they conflict with an employer's religious beliefs." ❖

HHS Awards Millions in Health Grants

Under the Affordable Care Act, the Department of Health and Human Services (HHS) awarded millions in health grants in 2014. In early 2014, $300 million was awarded to help the nation's community health centers expand service hours, hire more medical providers and add oral health, behavioral health, pharmacy and vision services. Today, nearly 1,300 health centers operate more than 9,000 service delivery sites that provide care to more than 21 million patients in every state, the District of Columbia, Puerto Rico, the U.S. Virgin Islands and the Pacific Basin.

In September, HHS released $65 million in Healthy Start grants to help 87 organizations in 33 states reduce high infant mortality rates and other health problems related to pregnancy and mothers' health. Healthy Start is targeted to the needs of vulnerable mothers and infants in areas of the country with disproportionately high rates of infant mortality. Twenty-two of these awardees serve rural communities, four serve the United States-Mexico border, and three programs serve a predominantly Native American population. In addition, 22 organizations are using the funds to create Healthy Start programs for the first time.

Also in September, $212 million in grants were awarded to all 50 states and the District of Columbia to support programs to prevent chronic diseases such as heart disease, stroke and diabetes. A total of 193 awards were made to states, large and small cities and counties, tribes and tribal organizations, and national and community organizations, with a special focus on populations hit hardest by chronic diseases. ❖

OPPS 2015 Final Rule: Impact from a Pharmaceutical Perspective

Reimbursement and revenue models in healthcare are changing with a move toward diversification in provision of service with payment for value and away from traditional fee-for-service. On Oct. 31, the Centers for Medicare and Medicaid Services (CMS) issued the calendar year 2015 Hospital Outpatient Prospective Payment System (OPPS) and Ambulatory Surgical Center Payment System Policy Changes and Payment Rates final rule [CMS-1613-FC]. OPPS covers all outpatient services offered by a facility, so it pertains to every patient who passes through a facility who is not considered an inpatient. Understanding these rules is essential, since many commercial payers base their payment decisions on CMS rules, and all code sets and descriptions are universal to all payers.

In August 2000, CMS implemented the prospective payment system now known as OPPS, which subsequently progressed toward the increased use of bundled payments or packaging and away from fee-for-service that individually pays for each item or service. CMS is very clear in stating its philosophy on "packaging," also known as bundling. According to CMS, "payment for multiple interrelated items and services into a single payment creates incentives for hospitals to:

• furnish services most efficiently and to manage their resources with maximum flexibility.

• maximize hospitals' incentives to provide care in the most efficient manner.

• use the most cost-efficient item that meets the patient's needs, rather than to routinely use a more expensive item, which often results if separate payment is provided for the items.

• effectively negotiate with manufacturers and suppliers to reduce the purchase price of items and services or to explore alternative group purchasing arrangements, thereby encouraging the most economical healthcare delivery.

• establish protocols that ensure that necessary services are furnished, while scrutinizing the services ordered by practitioners to maximize the efficient use of hospital resources."

CMS uses averaging to establish a payment rate that may be more or less than the estimated cost of providing a specific service or bundle of specific services for a particular patient. This occurs when data from higher-cost cases requiring many ancillary items and services is merged with data from lower-cost cases requiring fewer ancillary items and services. The packaging essentially includes all items and services that are typically integral, ancillary, supportive, dependent or adjunctive to a primary service.

Drug Reimbursement in 2015

As shown in Table 1, drugs, biologicals and radiopharmaceuticals will continue to be reimbursed in one of several ways as pass-through drugs, separately payable drugs and non-separately payable products that are bundled, or packaged, into reimbursement for the service or procedure. Bundling, or packaging, means there is no separate identified payment for the product. Because the category of pass-through drugs is designed for new products, the list is not static; each year, a number of products flow onto it and some off of it often with code (16 in 2015) and status indicator (SI) changes. A list of these pass-through drugs can be viewed at www.federalregister.gov/articles/2014/11/10/2014-26146/medicare-and-medicaid-programs-hospital-outpatient-prospective-payment-and-ambulatory-surgical.

Specific Covered Outpatient Drugs (SCODs)

Specific products costing more than $95 per day (up from $90 in 2014) with defined Healthcare Common Procedure Coding System codes, some of which may be brand-specific, fall under SCODs. Reimbursement is based on converting the actual dose of the drug given into CMS-defined billing units that are reimbursed at average sales price (ASP) plus 6 percent (sequestration then deducts approximately 2 percent). ASP methodology is based on a number of factors, including the sale price of the drug by the manufacturer to the distributor (not the purchase price); but, again in 2015, calculations do not include 340B sales price. Since billing unit calculation errors remain the biggest CMS-identified error, doses must be carefully converted into billing units. Under-reporting billing units results in both lower reimbursement, as well as misrepresentation of what it actually costs to treat a patient with these products. This is extremely important because this claims data is subsequently used to determine future rates.

What's Bundled and What's Not?

There are two different types of bundles for drugs, biologicals and radiopharmaceuticals. The first and

Table 1. OPPS 2015: Five Drug Payment Methods

easiest to understand is the non-separately payable category based on drug cost as defined by CMS (and not by what is actually paid or charged). This year, the cut-off has risen to $95 per day. The second is defined by services or procedures that include certain drugs regardless of cost. Correctly dispersing funds internally from this ever-growing category has huge implications.

Comprehensive Ambulatory Payment Classifications (C-APCs)

Consistent with the trend in past years, CMS is packaging more services into composite APCs. Effective Jan. 1, hospitals won't receive separate payment for argatroban, bivalirudin, clevidipine or topical thrombin "when administered to a patient receiving a comprehensive service," regardless of pharmaceutical cost.

Items and services packaged or included in payment for a primary service in the 2014 OPPS rule included five new categories of supporting items and services:

1) Drugs, biologicals and radiopharmaceuticals that function as supplies when used in a diagnostic test or procedure

2) Drugs and biologicals that function as supplies when used in a surgical procedure, including skin substitutes (skin substitutes were classified as either high or low cost and are packaged into associated surgical procedures with other skin substitutes of the same class)

3) Certain clinical diagnostic laboratory tests

4) Certain procedures described by add-on codes

5) Device removal procedures

In certain cases, a separate payment will be made if the item or service is furnished on a different date of service as the primary service.

Under the new C-APC payment policy, a single payment for each of 25 C-APCs covers all related or adjunctive hospital items and services provided to a patient receiving certain primary procedures that are either largely device-dependent or represent single-session services with multiple components. Items packaged for payment provided in conjunction with the primary service also include all drugs, biologicals and radiopharmaceuticals, regardless of cost, except those drugs with pass-through payment status and those that are usually self-administered, unless they function as packaged supplies.

CMS also will conditionally package all ancillary services assigned to APCs with a geometric mean cost of $100 or less prior to packaging as a criterion to establish an initial set of conditionally packaged ancillary service APCs. When these ancillary services are furnished by themselves, CMS will make separate payment for these services. Exceptions to the ancillary services packaging policy include preventive services, psychiatry-related services and drug administration services.

The drug administration exclusion is

important because even if the drug itself is not being paid for separately, its preparation and administration are being paid for separately through drug administration fee codes. Therefore, it's essential that these are correctly applied with the required documentation in place, and that they are traceable through the revenue cycle without problematic hard stop edits. The electronic medication administration record or electronic health record can be used to create accurate documentation, as well as a decision tree concerning which codes apply to which products. Remember, the administered drug must be billed for (even if it won't be paid separately or it's a zero-priced drug) in order for drug administration fees to be paid.

Collecting Data from Off-Campus Provider-Based Departments

The groundwork was laid for this new rule in 2014, when CMS requested public comments regarding the best method for collecting data that would allow it to analyze the frequency, type and payment for physicians' and outpatient hospital services furnished in off-campus provider-based hospital outpatient departments. This was precipitated by the increasing trend of hospitals purchasing specialty physician practices and then raising the prices for care, which caught the eye of federal regulators. That led CMS to establish a rule requiring the volume of outpatient care occurring in hospital-owned settings to be recorded.

CMS's analysis of vast volumes of claims data has shown a divide between Medicare payments for hospital outpatient services (generally higher) and those for the same services furnished in a freestanding clinic or physician's office (generally lower). As such, CMS intends to develop a better understanding of which practice expenses are typically incurred by the hospital, physicians and practitioners in a setting, and whether the facility and nonfacility site of service differentials adequately account for these costs.

Gathering information on the shift from physician practice site to hospital ownership is the first step. Data collection begins by requiring hospitals to report a modifier using a new place-of-service code on professional claims for services provided in an off-campus, provider-based hospital department. This data collection will be voluntary in 2015 and required in 2016.

Payers, including CMS's Medicare program, are experimenting with a variety of payment initiatives that partner with providers to control costs while improving quality and member satisfaction. The models have a variety of names — bundled payments, consolidated payments, payments for episode of care, a bundle of once-a-month, incremental payment, new patient payment or patient month payment — all designed to replace traditional fee-for-service payments, including drugs on a line-item basis. CMS describes its program as "packaged services in composite APCs." Regardless of which name is used, the basic principle remains the same: a fixed inclusive payment for a defined treatment, procedure or condition that is based on cumulated historical payments gleaned from claims data, as well as best practice from other sources.

If these payment initiatives are based on accurate data, well-designed and effectively implemented, they should be able to reward providers with strong financial incentives. Hospitals would be incentivized to work collaboratively with providers, and silos within the institution would be broken down from traditional roles and interests.

Healthcare providers should foster a discussion with their finance and revenue cycle teams about the need for transparent, realistic and defensible pricing of at least the pharmacy and drug administration components of the charge description master. If participating in the 340B program, providers should ensure that all requirements are being met and that there is a clear understanding of the eligible patient definition that is supported by their IT infrastructure. An accurate procedure-specific tally is essential because payments will be based on cumulated claims data from years past and may be adjusted for several factors. Billing accuracy, revenue cycle team skill and IT infrastructure robustness will all come into play as these rates are determined. ❖

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.*

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.

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Scholarship

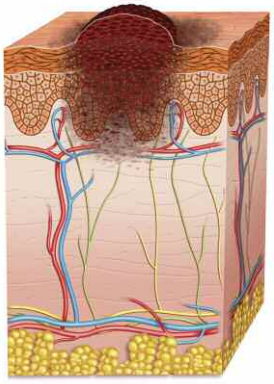
Eric Dostie Scholarship for Hemophilia Students Now Accepting Applications

Applications are now being accepted for the Eric Dostie Memorial College Scholarship, which is awarded to students who either have hemophilia or a similar bleeding disorder, or have a family member with a bleeding disorder. Ten students who can best demonstrate scholastic achievement, community service and financial need will each be awarded a $1,000 scholarship. Applicants must submit an essay describing how his or her education will be used to serve humankind and to encourage self-improvement and enchrichment. To be eligible, applicants must be U.S. citizens and enrolled full time in an accredited two- or four-year college program. The deadline to apply is March 1.

The Eric Dostie Memorial College Scholarship was created to honor the memory of Eric Dostie, a 5-year-old boy with hemophilia, who was tragically murdered Aug. 27, 1994. Eric's brief life forever touched many others with joy, humor and unending love. Eric used to tell his family that he might grow up to be a scientist and invent a cure for hemophilia in the form of a "chocolate pill." Although Eric's dream will never be realized, it has the chance to live on in the recipients of the award who pursue a college degree to broaden their education and career opportunities.

"Since the inception of the Eric Dostie Scholarship 10 years ago, we have provided scholarships to 100 students that have helped these bright, young, talented people succeed in their pursuit of higher education," said Patrick M. Schmidt, chief executive officer of FFF Enterprises, Inc. "FFF acknowledges the financial impact that a bleeding disorder can have on affected individuals and their families. This scholarship is about ensuring that a quality higher education remains within financial reach."

The scholarship is run by NuFACTOR, the specialty pharmacy of FFF Enterprises, Inc. Last year's scholarship recipients were Angela Kessler, Antonio Brown, Brandon Burnett, Calvin Dutcher, Evan Poole, Huda Ibramhin, Jonathan Lebron, Matthew Buck, Michael Zolonitsky and Patrick Klein. Visit the NuFACTOR Eric Dostie Memorial College Scholarship website at www.nufactor.com/EricDostieMemorial.aspx to learn more about the program and to request an application. Or, those interested can call (800) 323-6832, ext. 1300. ❖



Medicines

FDA Approves First Antibody-Based Melanoma Drug

The first drug in a new class of cancer medicines developed by Merck to treat melanoma, the most deadly form of skin cancer, has been approved by the U.S. Food and Drug Administration (FDA). FDA granted accelerated approval to Keytruda for treatment of melanoma that has spread or can't be surgically removed in patients previously treated with another drug. Known chemically as pembrolizumab, Keytruda is part of a new class of antibody-based (anti-PD-1) drugs that work by stimulating the immune system so it can better recognize and attack cancer cells.

Keytruda is administered intravenously every three weeks through a slow drip. It costs approximately $12,500 per month for many patients, similar to the price of many other new cancer drugs, and treatment lasts on average for just more than six months. In a study funded by Merck, one-third of 600 patients participating benefited from Keytruda, with 62 percent of those alive after 18 months. Chemotherapy drugs have an average survival of about nine months, while some newer cancer drugs keep patients alive for an average of 11 to 15 months. The overall survival rate for Keytruda hasn't been determined since most patients in the study are still being followed. Ninety percent of patients have had no side effects. However, in a small number of patients, it did have serious immune-related side effects, including hepatitis, colitis, thyroid problems and kidney inflammation.

Bristol-Myers Squibb Co. and a partner have a drug similar to Keytruda, called Opdivo, which was approved in Japan in July. They are seeking U.S. approval for it. ❖

Medicines

FDA Approves First Vaccine to Prevent Invasive Meningococcal Disease

The U.S. Food and Drug Administration (FDA) has approved Trumenba (Wyeth Pharmaceuticals), the first vaccine licensed in the U.S. to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B in individuals age 10 through 25. The approval was the result of three randomized studies conducted in the U.S. and Europe in approximately 2,800 adolescents. Among participants who received three doses of Trumenba, 82 percent had antibodies in their blood after vaccination that killed four different N. meningitidis serogroup B strains compared with less than 1 percent before vaccination. These four strains are representative of strains that cause serogroup B meningococcal disease in the U.S. The safety of Trumenba was assessed in approximately 4,500 individuals who received the vaccine in studies conducted in the U.S., Europe and Australia. The most commonly reported side effects by those who received the vaccine were pain and swelling at the injection site, headache, diarrhea, muscle pain, joint pain, fatigue and chills. ❖

Research

Immunization Rates Increase with Automated Flu Vaccination Tracking

Tracking influenza vaccination among healthcare personnel through an automated system enhances their immunization compliance while reducing their administrative burden, according to a study published in the November 2014 issue of *Infection Control and Hospital Epidemiology*. Developed by researchers in the Epidemiology and Infection Prevention Program at the University of California Irvine Health System, the system sends automated reminders to hospital staff and their supervisors at regular intervals prior to the required vaccination deadline. Through the system's intranet, hospital supervisors and department chairs can also review the current vaccine status of their employees to ensure their compliance.

Among the nearly 7,000 staff members covered under the mandatory policy, vaccination compliance rates increased from 58 percent to 85 percent within one year of the policy's implementation to 96 percent in three years. In addition, the automated system reduced the number of overtime

hours required for healthcare personnel to work on the mandatory vaccination program by 56 percent during the 2010-2011 and 2013-2014 influenza seasons.

"Mandatory vaccination programs help protect vulnerable patients but can be tremendously time- and resource-dependent," said study author Susan Huang, MD, MPH. "By successfully automating a system to track and provide feedback to healthcare personnel who have not received their seasonal flu vaccine, we are providing safer places for care and reducing the administrative burden of our mandatory vaccination program." ❖

Medicines

FDA Approves Baxter's Obizur for Acquired Hemophilia A

Obizur (antihemophilic factor [recombinant], porcine sequence) has been approved by the U.S. Food and Drug Administration (FDA) for treatment of bleeding episodes in adults with acquired hemophilia A (AHA). The drug is the first recombinant porcine factor VIII (FVIII) treatment approved for AHA that allows physicians to manage the treatment's efficacy and safety by measuring FVIII activity levels in addition to clinical assessments. Obizur replaces the inhibited human FVIII with a recombinant porcine sequence FVIII based on the rationale that it is less susceptible to inactivation by circulating human FVIII antibodies.

The approval is based on a Phase II/III clinical trial that examined the safety and efficacy of Obizur in the treatment of serious bleeding episodes in adults with AHA. All patients treated showed a positive response, meaning an effective or partially effective response with bleeding stopped or reduced and clinical improvement at 24 hours after the initial infusion. A total of 86 percent had successful treatment of the initial bleeding episode. Common adverse reactions observed in greater than 5 percent of the 29 patients in the clinical trial were development of inhibitors to porcine FVIII.

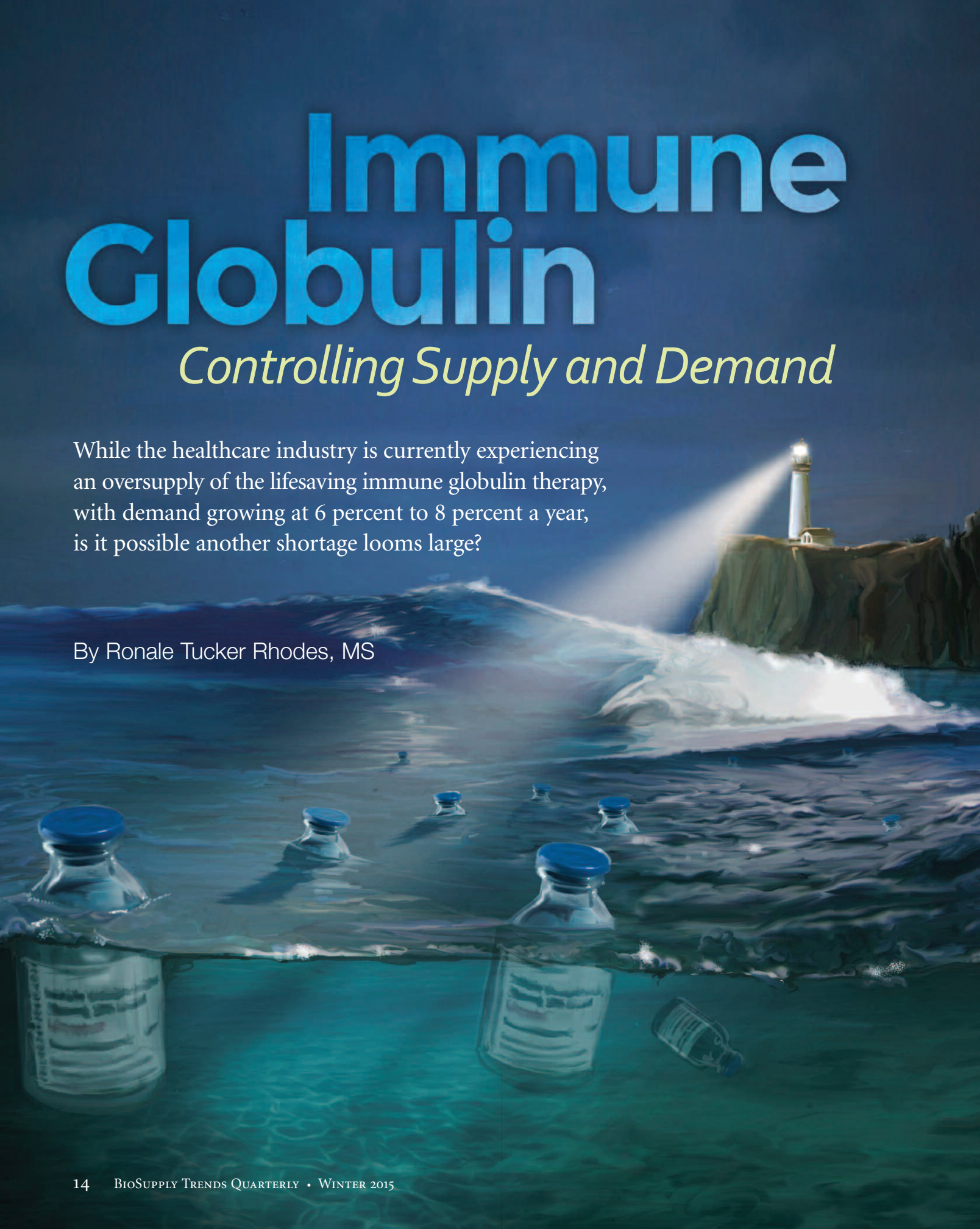
Obizur was granted orphan drug status by FDA, and its review was prioritized based on AHA's classification of a rare disease and the potential for the treatment to address an important unmet medical need. It is expected to be commercially available in the U.S. in early 2015 and is currently under regulatory review in Europe and Canada. ❖

Immune Globulin

Controlling Supply and Demand

While the healthcare industry is currently experiencing an oversupply of the lifesaving immune globulin therapy, with demand growing at 6 percent to 8 percent a year, is it possible another shortage looms large?

By Ronale Tucker Rhodes, MS



In March, the U.S. Government Accountability Office reported that the number of drug shortages has more than doubled since 2007.[1] Shortages of drugs, many of which treat life-threatening diseases, create public health threats and often lead to preventable deaths. In the mid- to late-90s, a major shortage of immune globulin (IG), a human blood product used primarily to treat immunodeficiences and autoimmune diseases, caused patients to go without treatment and risked their lives. Is it possible that another nationwide shortage of IG looms large? While it is often hard to predict if or when a shortage will occur, understanding what caused a past shortage, where we are now and what steps the industry is taking to help prevent another can help shed some light on the supply and demand of IG in the future.

A History of Supply and Demand

The IG market is a classic supply-and-demand situation. According to Chris Ground, chief operating officer at FFF Enterprises Inc., a supplier of critical-care biopharmaceuticals, plasma products and vaccines, "When supply is low, we refer to it as a short market, which means demand is higher than supply. When there is ample supply, it is known as a long market, one where demand isn't keeping pace with supply." Why a market switches from short to long and back again is primarily a result of current and predicted demand, but there are other reasons as well.

In 1997, then-U.S. Surgeon General David Satcher, MD, PhD, estimated a 20 percent shortage of intravenous IG (IVIG).[2] In 1998, the U.S. Food and Drug Administration (FDA) estimated the shortfall at 30 percent. Manufacturing standards violations and product recalls were the two major reasons for this shortage. FDA attributed approximately 60 percent of the decreased availability to production impediments related to compliance and approximately 20 percent to withdrawals of plasma products.[3] It all began in 1995, when FDA issued recommendations that plasma products made from pools later found to include a donor with a fatal and little-understood disease known as Creutzfeldt-Jakob disease (CJD) be withdrawn from the market. This resulted in both recalls and voluntary withdrawals. By 1997, industry records showed that the four manufacturers that produced the vast majority of IG — Bayer, Baxter Healthcare, Alpha Therapeutic and Centeon — had recalls and withdrawals totaling about 7 percent of the total supply.[4]

The shortage was addressed in two ways. In January 1998, FDA reminded physicians of the six approved uses for IVIG and recommended that priority for the therapy be given to patients who have FDA-approved indications. Then, a review of data from FDA, the National Institutes of Health and the Centers for Disease Control and Prevention suggested that the risk for transmission of classic CJD by blood products, if it existed, was considerably lower than the risk for harm to public health from CJD-related quarantines and withdrawals. So, in August 1998, the Surgeon General recommended that plasma derivatives, including IVIG, be withdrawn only if the blood donor developed new-variant CJD.[3]

Shortly after the FDA recommendation to withdraw IVIG due to CJD in 1995, FDA doubled its inspections of manufacturers of plasma products and discovered serious violations of manufacturing standards. As a result, every company in the business received warning letters citing numerous deficiencies.[5] Yet, while FDA allowed manufacturers to continue operating while addressing regulatory problems, some companies decided to stop release and distribution of IG and to shift resources to compliance correction. Centeon, in particular, decided to shut down production and didn't distribute product at all in 1997, accounting for 60 percent of the 20 percent product shortfall.[2]

Unfortunately, while supply was falling, demand was surging. Increased demand was a result of both new approved indications and an increase in off-label (non-FDA-approved) uses of IVIG. Medical studies found IVIG to be effective for treating several neuromuscular and other diseases. The Immune Deficiency Foundation and physicians at major centers estimated 50 percent to 70 percent of the drug was being prescribed for off-label use.[2]

The IG market is a classic supply-and-demand situation.

Export of IVIG was also another factor contributing to the shortage. FDA reported that exports accounted for up to 29 percent of distributed product, depending on the manufacturer. The International Plasma Products Industry Association reported that exports from the major U.S. fractionators increased from 1996 to 1997, accounting for about 20 percent of their marketed IVIG products.[2]

While there has not been a major shortage of IG since this one, there have been concerns. In 2005, the American Society of Health-System Pharmacists (ASHP) reported an impending shortage due to several factors. First, there was consolidation in the blood product industry when Baxter Healthcare and the American Red Cross pulled out of the plasma production market and three other suppliers cut production. In addition, most companies were gearing up to provide liquid preparations in place of their lyophilized powder preparations, which

resulted in a lag time in production while manufacturing practices were changed. And, growing use of IVIG continued at a rate of 5 percent to 10 percent annually, mostly due to new indications.[5]

In 2010, the market experienced a complete withdrawal of Octapharma's Octagam. Even though Octapharma was not one of the top-three producers of IVIG for the U.S., the voluntary withdrawal still affected the U.S. market since supplies from all markets were needed to fill the void of the loss of Octagam from the U.S., Australia and Europe.[6]

Plasma Collection and Manufacturing

Manufacturers estimate IG usage is growing at 6 percent to 8 percent each year; however, healthcare professionals assert that estimate is too low, and that a more accurate estimate is 10 percent to 15 percent.[7] Either way, an increase in demand for these products first necessitates an increase in the raw product: plasma.

In the United States alone, there were more than 29 million donations of plasma collected in 2013, according to the Plasma Protein Therapeutics Association (PPTA). This is more than double the increase of 12 million donations over the previous decade. Worldwide, the total annual demand for plasma by pharmaceutical companies that manufacture plasma-based therapies is about 38 million liters.[8] Most of the world's plasma is collected in about 400 plasma donation centers scattered throughout the U.S., with some of it exported to other countries. For instance, countries such as those in Europe are unable to pay for donations, which creates a demand for exportation from the U.S. The U.S. Centers (owned exclusively by plasma therapy manufacturers) pay between approximately $15 and $40 for a donation of plasma.

Once collected, plasma — 92 percent water and 8 percent proteins — must go through a fractionation process that separates and collects the individual proteins, of which 64 percent are albumin, 20 percent are immune globulin, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, C1 esterase inhibitor, etc.

As part of the industry's voluntary international standards program for manufacturers, known as the Quality Standards of Excellence, Assurance and Leadership (QSEAL), all plasma is held in inventory for 60 days before it can enter the manufacturing process. This allows for rigorous testing to identify, retrieve and destruct plasma donation from donors who are disqualified for various reasons such as having received a tattoo or piercing at the time of the original donation or failing to report foreign travel.[9] Most recently, due to the outbreak of Ebola, PPTA has endorsed the recommendation by the EU Center for Disease Prevention and Control that travelers or residents returning from Ebola virus disease-affected areas be deferred for donation of plasma for fractionation two months after return. PPTA says its voluntary inventory hold of all incoming plasma for fractionation of 60 days is adequate to allow for removal of a unit in question if necessary.[10]

Once the plasma is released from inventory, it is ready for fractionation. During the fractionation process, plasma is pooled from multiple donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit. The steps and regulations required to collect donated plasma and complete the manufacturing process that ultimately results in the final therapies takes between seven and nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, "it is the combination of time, temperature, pH and alcohol concentration [that] allows the extraction of the specific therapeutic proteins." At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by FDA and shipped between weeks 28 and 32 to the wholesalers and end users.[9]

The Current IG Market

In the U.S., there are currently seven companies — Baxter, Biotest Pharmaceuticals, BPL, CSL Behring, Grifols, Kedrion and Octapharma — that manufacture and market IG products administered intravenously (IVIG) and subcutaneously (SCIG). IVIG products include Carimune NF, Bivigam, Flebogamma 5% DIF, Flebogamma 10% DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam 5%, Octagam 10% and Privigen. SCIG products include Gamunex-C, Gammagard Liquid, Gammaked, Hizentra and HYQVIA. The newest entries to market are Bivigam in 2013 and HYQVIA in 2014.

A 15th IVIG product that is expected to enter the market is ADMA Biologics' RI-002. In December, the product demonstrated positive results and successfully achieved its primary endpoint in a Phase III trial in the U.S. for the treatment of primary immunodeficiency (PI). ADMA plans to report on additional secondary endpoints when the data is available, and it is currently assembling its biologics license application for planned submission to FDA during the first half of 2015.[11]

An additional two investigational SCIG products are also undergoing clinical trials. Baxter is in Phase II and III trials for its 20% SCIG to treat patients with PI.[12] Octapharma is scheduled to complete its Phase III clinical trial of Octanorm, a 16.5% SCIG to treat PI patients, in June 2016.[13]

With considerable growth over the past decade in the number

of companies that manufacture IG (from five to seven, and soon to be eight, despite a merger between two previous manufacturers) and the number of IG products (from 10 to 14, and soon to be 17) that are FDA approved to treat only six indications, the supply and demand outlook would appear to be optimistic. (Depending on the product, the six indications include PI, idiopathic thombocytopenic purpura, multifocal motor neuropathy, chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy.) But, medical evidence shows IG is beneficial for treating many off-label indications, which, according to past estimates, represent 50 percent to 80 percent of total IG use.[7] These indications include a host of autoimmune disorders such as Guillain Barré syndrome, multiple sclerosis, chronic fatigue syndrome, myasthenia gravis and Sjogren's syndrome that are now being routinely prescribed high doses of IVIG. And, even as the demand for plasma-based therapies continues to increase, several manufacturers are exploring new indications — two major ones being Alzheimer's disease and recurrent miscarriage.

Therefore, as the number of patients needing IG treatment continues to multiply as doctors prescribe IG for off-indicated uses and research expands to determine the effectiveness of IG to treat other conditions, the potential for a shortage heightens.

The Industry's Role in Ensuring Supply Meets Demand

Manufacturers strive to ensure that supply will meet demand. But, predicting how much IG to manufacture is challenging. For one, the fractionation process is lengthy, taking approximately seven to nine months from when an individual donates plasma to when the medication is ready for use. Therefore, says Ground, "manufacturers have to have a seven- to eight-month lead time to determine what the demand is going to be."

Global market dynamics, new indications and patient needs also make demand hard to predict. "As demand increases, manufacturers ramp up production, and at times, overshoot the estimated demand, which can result in a long market," explains Ground. "When this happens, manufacturers are forced to cool production until demand can catch up. And, when demand does catch back up with supply, a short market returns." To meet the different demands or to adjust capacity based on demand, manufacturers also can ship different parts of the protein product to different locations to ensure demand is met regardless of capacity constraints.

Currently, we're in a long market for IG, contributed to by the global demand for albumin, for which there is a shortage, especially from China, says Ground. When demand is high for one plasma protein therapy, enough plasma is available to increase capacity of other plasma protein therapies. In this case, since there is an increased need for plasma donations to try to meet the demand for albumin, the other proteins such as IG that are collected from plasma donations must also be fractionated into protein therapies or else they go to waste. "But, if the relative demand for IG can't keep up with the relative demand for albumin in the ratio in which they are manufactured," says Ground, "there is an oversupply."

Medical evidence shows IG is beneficial for treating many off-label indications, which, according to past estimates, represent 50 percent to 80 percent of total IG use.

The availability of plasma remains an uncertain limiting factor to increasing supply levels. To meet the demand for plasma protein therapies such as IG and albumin, manufacturers are continuing to expand their network of plasma collection centers. For instance, in just the past year, CSL Behring has opened 18 centers in the U.S. In October, the company and its subsidiary, CSL Plasma, saluted the contributions of plasma donors during International Plasma Awareness Week Oct. 12 through 18, at which they held a variety of activities in centers nationwide to promote greater understanding and appreciation among patients, employees and donors.[14] At the end of October, Grifols hosted a ribbon-cutting ceremony for its fifth Talecris Plasma Resources Center in El Paso, Texas. The $1.8 million, 15,800-square-foot facility includes new technologies and can accommodate 1,800 donors per week.[15] Grifols now has a network of 150 plasma donation centers across the U.S. Baxter Healthcare's BioLife Plasma Services also continues to expand its plasma collection centers throughout the U.S. with 13 centers having just opened or are scheduled to open within the next year.[16]

As the number of plasma donors increases, and as research for new indications for IG continues, manufacturers are expanding their plasma fractionation production facilities. CSL Behring will spend $450 million over the next few years to expand its production facilities in the U.S. and Australia, with

a $240 million investment into its Kankakee, Ill., facility that produces albumin and immune globulin and a $210 million investment into its Broadmeadows plant in Melbourne, Australia.[17] Grifols has also expanded its three manufacturing sites in Clayton, N.C., Los Angeles and Barcelona, Spain, the company's global headquarters. The expansions include a new, 185,000-square-foot fractionation facility in Clayton and a new facility in Los Angeles dedicated to the production of IG therapies. These new facilities have increased the company's capacity to fractionate plasma from 8 million liters per year to 12 million liters in 2015. Grifols also opened a new plasma testing lab in San Marcos, Texas, where every plasma donation undergoes rigorous scientific analysis prior to being approved for use in manufacturing.[18] And, according to a statement by Baxter Healthcare, the company is "in the process of building a new state-of-the-art fractionation and production facility in the U.S., with commercial production scheduled to begin in 2018. In addition, [the company has] established an agreement with Dutch company Sanguin to provide additional fractionation capacity to supplement Baxter's capacity."

Whether the market for IG is long or short, distributors become a management tool for allocating the drug in a responsible way, getting the product out to the most immediate need. "As a distributor, our goal is to work with the manufacturers and providers with an understanding of what the providers' immediate need is, especially during a very intense shortage," explains Ground. "In a long market, it becomes more interesting because the manufacturers are trying to get as much product out to market, and we become a buffering system between them and the end user. This also creates an environment in which the market has the opportunity to expand into new areas of therapeutic uses."

The Future of Supply

While there is currently no shortage of IG, history has shown that recalls and withdrawals can cause sudden and unexpected shortages at any time. Add to these possibilities the growing global demand and the list of indications currently being studied, and it's not a matter of if there will be a shortage, but when. For instance, had Baxter's study on IG to treat Alzheimer's disease met its endpoints, the industry would likely be facing a crisis right now. To be complacent and unprepared for such possibilities is to put patients' lives in danger.

"The wonderful thing about IG is its unwavering path toward dozens of undiscovered areas of therapeutic promise for thousands of patients globally," says Ground. "This is precisely why we must make every effort to be vigilant surrounding the global supply-and-demand ratio of IG and to work to try to keep those factors in balance. Being out of balance creates challenges either way. This, of course, is easier said than done, given the always present possibility of manufacturing issues. Yet, this is an inextricable fact of the plasma industry. We must strive to nurture demand, while delicately balancing this with managed increases in manufacturers' global capacity."[6] ❖

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

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Antihemophilic Factor/von Willebrand Factor Complex (Human)

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

- Control and prevention of bleeding in patients with hemophilia A
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with ALPHANATE should be discontinued, and emergency treatment should be sought.

Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** CSL Behring. Humate P Package Insert. August 2013; **3.** Octapharma. Wilate Package Insert. January 2012; **4.** Kedrion. Koate-DVI Package Insert. August 2012.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

Grifols Biologicals Inc.
5555 Valley Boulevard, Los Angeles, 90032 CA - USA Tel. 888-GRIFOLS (888 474 3657)
www.grifols.com

GRIFOLS

ALPHANATE®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])

Sterile, lyophilized powder for injection.

Initial U.S. Approval: 1978

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

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

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

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

Hemophilia A: Control and prevention of bleeding episodes

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

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

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, 1500 and 2000 IU FVIII in single dose vials.

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

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

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

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients has been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

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

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Pregnancy: No human or animal data. Use only if clearly needed.
- Pediatric Use: Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.

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Grifols Biologicals Inc.
5555 Valley Boulevard
Los Angeles, CA 90032, U.S.A.
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Subcutaneous Immune Globulin:
New Therapeutic Uses Beyond Primary Immunodeficiency?

While the intravenous route has been the standard method of IG therapy for autoimmune and other neuromuscular disorders, recent studies show that the subcutaneous route is both as effective and more preferred by patients.

By Keith Berman, MPH, MBA

While they have been available and increasingly popular in Europe over the last 25 years as replacement therapy for persons with primary immunodeficiency disorders (PIs),[1] the first subcutaneous immune globulin (SCIG) product wasn't approved for marketing in the U.S. until 2006. As recently as 2011, there was but a single SCIG brand — rather inconveniently formulated at the same 16 percent concentration as intramuscular immune globulin. Early on, some physicians recommended SCIG for carefully selected PI patients, but the vast majority continued to receive intravenous immune globulin (IVIG) every three to four weeks in a hospital outpatient clinic or physician office setting.

Thanks in part to a wave of published comparative studies, reviews and commentaries over the last several years, more U.S. immunologists and infectious disease specialists have become aware of specific advantages of SCIG in relation to IVIG for qualifying and motivated PI patients. Today, physicians can select from among five approved SCIG product options for their patients (Table 1), with at least two others reported to be in development. A steadily growing proportion of PI patients who require lifelong IG replacement therapy are newly initiating or switching to SCIG therapy, drawn in part by the obvious appeal of self-administering their therapy at home in lieu of hospital, office clinic or home nursing visits to receive IVIG therapy.

Risk of serious systemic adverse reactions is exceedingly low for currently licensed SCIG preparations.

With the benefit of years of experience with these products, investigators across Europe more recently have reported that SCIG may represent a better treatment option for patients chronically managed with IVIG for certain autoimmune neuromuscular diseases and secondary immunodeficiency disorders at risk for serious bacterial infections. Could self-administered SCIG represent a better option than IVIG for some patients with these disorders as well?

What Makes SCIG a Better Option for Some PI Patients?

To answer this question, it is important to consider why SCIG self-administration — typically using a programmable syringe infusion pump[2] — continues to attract a growing following among PI treatment specialists and patients.

Non-serious systemic adverse reactions are much less frequent with SCIG than IVIG therapy. Typically, smaller more frequent doses of SCIG act to moderate spikes and troughs in IgG serum concentration. The high supra-physiologic serum IgG peak that occurs immediately following IVIG infusion likely contributes to a two- to three-fold higher incidence of non-serious systemic adverse reactions — mainly headache, fatigue, pyrexia, chills, nausea and vomiting — than is seen following SCIG infusion.[3,4,5] Roughly one-half of patients newly starting SCIG experience generally minor local infusion site reactions — far more often than occurs with IVIG administration — but typical redness and swelling is transient and usually declines over time.

Risk of serious systemic adverse reactions is exceedingly low for currently licensed SCIG preparations. While serious systemic adverse events associated with IVIG therapy — primarily aseptic meningitis, thrombosis and hemolysis — are very uncommon (and often preventable with premedication and slowing of the infusion rate), they do occur and have been reported both in published clinical studies and retrospective chart reviews. By contrast, no serious systemic adverse reactions have occurred to date in licensing trials conducted for any currently available SCIG product. These findings are consistent with a number of published case series. Recent U.S. and Swedish studies in 47 and 60 PI patients, respectively, reported a combined total of more than 4,000 home-based SCIG infusions with no serious systemic adverse events.[6,7] An earlier large Scandinavian study documented just six moderate adverse systemic reactions and no severe or anaphylactoid reactions in 165 patients who received a total of 33,168 SCIG infusions.[8] Simply put, opting for SCIG therapy reduces a very low risk of serious systemic adverse events to an extremely remote risk.

SCIG offers an equally effective treatment option for patients with IVIG tolerability or venous access problems. A very small but significant proportion of patients repeatedly experience very unpleasant or debilitating adverse reactions to IVIG, which cannot be managed with premedication, a reduction in infusion rate or a change of product brand. Patients occasionally present with veins that are very difficult to access, necessitating surgical implantation of indwelling catheters that introduces its own potential infection risks. For these patients who are willing and capable of self-infusing at home, SCIG represents a safe and simple option to resolve these issues and continue to receive the full protective benefit of IG therapy.

Table 1. Licensed Subcutaneous Immunoglobulin Products

	HIZENTRA	HYQVIA	GAMMAGARD LIQUID	GAMUNEX-C	GAMMAKED
Manufacturer	CSL Behring	Baxter	Baxter	Grifols	Kedrion Biopharma
IgG concentration	20%	10%*	10%	10%	10%

**Co-administered following initial infusion of recombinant human hyaluronidase*

Table 2. Patient-Reported Preferences Following Experience with Both Hospital-Based IVIG Therapy and Home-Based SCIG Therapy

YEAR	COUNTRY	SUBJECTS	PREFERENCE
2006[25]	U.S./Canada	28	81% of patients preferred home-based SCIG
2008[26]	Sweden	12	100% of patients preferred home-based SCIG
2010[27]	Europe (multicenter)	82*	92% of patients preferred home-based SCIG

**Includes patients with both primary and secondary immunodeficiency disorders*

SCIG self-administration permits dosing schedule flexibility and results in fewer lost work and school days. IVIG therapy generally necessitates a clinic visit every three to four weeks. For non-elderly patients, those scheduled visits — including the infusion itself and post-infusion recovery and observation time — translate into lost work and school days. Self-administration of SCIG, by contrast, can be flexibly scheduled after school or work, during evenings or on weekends. Multiple studies have quantified important reductions in lost school and work days after switching from IVIG to SCIG.[9]

Patients who experience SCIG therapy consistently prefer it over IVIG. IVIG may be a better option for PI patients with good venous access who tolerate the product well, and who variously have poor manual dexterity, lack of motivation to take responsibility for self-treatment, or have expressed reluctance to deal with needles or the mechanics of self-infusion. But surveys of other patients who were able to switch to SCIG consistently document a strong preference for SCIG therapy (Table 2), as well as improved health-related quality of life (HRQL) measures.

An additional consideration when choosing between these two options is, of course, cost. Consistent with several European reports, two recent Canadian studies identified significant annual cost savings associated with home self-infusion of SCIG, driven by near-elimination of the need for infusion nursing and ancillary personnel.[10,11] These analyses are predicated on dosing SCIG equivalently to IVIG, a practice that also prevails in Europe. In the U.S., initial dosing instructions for four of the five available SCIG products* recommend boosting the total SCIG dose either by 37 percent (Gammagard Liquid, Gamunex-C and Gammaked) or by 53 percent (Hizentra) — with the objective of equalizing the estimated "area under the curve" (AUC) that corresponds with total circulating IgG over a specified period of time. However, available evidence, including a recent crossover study, suggests that dose-equivalent therapy with SCIG is as effective as IVIG for protection of PI patients against serious infections.[12] Possibly, the pharmacokinetics of SCIG — characterized by much less fluctuation in serum IgG and a significantly higher mean serum IgG trough level than IVIG — may help to offset the lower AUC profile of a dose-equivalent SCIG regimen.

SCIG for Autoimmune Neuromuscular Disorders and More

The multiple demonstrated advantages of SCIG therapy for qualified PI patients have not been lost on specialists who often prescribe IVIG as long-term maintenance therapy to manage certain autoimmune inflammatory neuromuscular disorders. Again, the Europeans have been out in front in investigating the feasibility of SCIG for a number of important conditions for which IVIG is already an established first-line therapy.

The Europeans have been out in front in investigating the feasibility of SCIG for a number of important conditions for which IVIG is already an established first-line therapy.

Chronic inflammatory demyelinating polyneuropathy (CIDP). Interest in SCIG as a treatment option for this disorder was signaled in 2008 with publication of case reports describing its effectiveness and good tolerability in CIDP patients already

*HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] full prescribing information recommends administering the product at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up.

successfully managed with IVIG.[13,14] In 2013, Danish investigators reported on a study that randomized 30 adult patients successfully managed on maintenance therapy with IVIG to either SCIG at a total dose corresponding to their pre-study IVIG dose or to subcutaneous saline.[15] The SCIG group actually experienced a modest increase in isokinetic muscle strength of 5.5 ± 9.5 percent ($P < 0.05$) as compared with an expected decline of 14.4 ± 20.3 percent ($P < 0.05$) in the saline placebo group. Various other key functional measures similarly improved following SCIG in relation to saline placebo.

This same Danish group then followed 17 CIDP patients, all of whom had previously responded to IVIG, for one year on SCIG maintenance therapy. SCIG preserved muscle strength and functional abilities.[16] "SCIG should be considered as an alternative in long-term treatment of CIDP patients," they concluded.

In crossover studies, weekly SCIG self-infusions have been consistently preferred by patients and have a sharply lower serious adverse event risk profile than IVIG therapy.

Very recently, an Italian research team has reported sustained clinical efficacy, as measured by the Overall Neuropathy Limitation Scale (ONLS), with SCIG therapy in a group of 66 CIDP patients previously managed with IVIG ($P= 0.018$). Just one subject experienced a worsening of symptoms over the four-month study period. Patients additionally reported an improvement in relation to IVIG therapy in their perception of the therapeutic setting.[17]

With support from CSL Behring, an ambitious 350-subject multicenter, prospective, randomized, double-blind, placebo-controlled trial now in progress will not only try to affirm the therapeutic equivalence of its 20 percent SCIG product, Hizentra, to IVIG, but will attempt to answer whether more aggressive maintenance dosing provides additional clinical benefit. Participating study sites in 15 countries are randomizing subjects with IVIG-dependent CIDP to receive "low dose" or "high dose" weekly SCIG infusions of 0.2 g/kg or 0.4 g/kg body weight, or to placebo infusions. This study is expected to be completed in November 2015.

Multifocal motor neuropathy (MMN). Hypothesizing that an equivalent dosage of SCIG is as effective as IVIG in patients with IVIG-responsive MMN, Danish investigators completed a randomized crossover study in nine subjects.[18] The two treatments were equally effective, with SCIG use additionally sparing subjects from "end-of-dose weakness" episodes that some experienced with IVIG therapy. Patient preference findings, however, were not in line with those expressed by PI patients, who strongly favor SCIG. Four of the nine subjects in this small MMN study preferred SCIG, three had no preference and two preferred IVIG. The reason could be traced at least in part to the study protocol: subjects had to self-infuse two to three times weekly.

A UK study of seven MMN patients on stable IVIG dosing who completed six months of once-weekly SCIG treatment again documented no change in muscle strength, disability, motor function or health status. With respect to HRQL, all seven rated SCIG home treatment as "extremely good." The investigators concluded that "MMN patients with stable clinical course on regular IVIG can be switched to SCIG at the same monthly dose without deterioration and with a sustained overall improvement in HRQL."[19] Sustained clinical efficacy with a stable ONLS score was very recently reported in a series of 21 MMN patients, just one experiencing worsening symptoms.[17]

Other neuromuscular disorders. At present, IVIG is first-line therapy for patients with steroid-resistant dermatomyositis (DM) and polymyositis (PM). Italian investigators recently reported that no relapse of disease occurred during weekly SCIG treatment of seven patients with severe idiopathic DM or PM previously on maintenance IVIG therapy over a median follow-up period of 14 ± 4 months.[20] Three of the seven patients were able to discontinue immunosuppressive drug therapy, and all were able to reduce their daily maintenance prednisone dose. A U.S. proof-of-concept study is set to enroll 10 IVIG-naïve adult subjects with DM this year to evaluate both changes in strength from baseline and participant preference for SCIG in relation to IVIG.[21]

Another newly organized single-center Phase 2 study at the University of Kansas will assess the safety and efficacy of SCIG in 25 subjects with myasthenia gravis who require maintenance IVIG therapy.

Wherever there is an autoimmune neuromuscular disorder or a disease commonly associated with secondary antibody immunodeficiency requiring chronic IVIG therapy, expect to see new case reports and small patient studies going forward. A prime example is the very recently published Italian single-center experience comparing IVIG and SCIG use in 61 patients with hypogammaglobulinemia secondary to chronic lymphocytic leukemia (CLL) and non-Hodgkins lymphoma (NHL). Unsurprisingly, their results closely mirrored findings in PI patient studies: fewer systemic adverse events, significantly

higher IgG trough levels, similar effectiveness in reducing infectious events and need for antibiotic coverage, and a decided improvement in quality of life-related parameters after the switch to SCIG.[22]

Older Age, Higher Dosage May Mean More SCIG Benefit

While SCIG therapy was originally tested in PI patients and has since become well accepted as a similarly effective alternative to IVIG with fewer adverse systemic effects, arguably the benefits of SCIG are even more important for patients with autoimmune neuromuscular disorders who require IG therapy. The PI IG-treated population includes all ages, but skews heavily toward children and younger adults. Patients with inflammatory neuromuscular conditions that require IVIG therapy, most prominently CIDP and MMN, are largely at the other end of the age spectrum. Most CIDP patients are over age 50 years, with many in their 60s, 70s and even 80s.[23] The mean age of onset of MMN is 40 years.[24] Of course, CLL and NHL patients on IVIG replacement therapy also comprise an older age demographic.

We know that older age and, in all likelihood, higher dose are among important risk factors for rare but well-documented thrombosis events following IG infusions. Persons whose neuromuscular disorders are managed with IVIG are generally older, and their average monthly dosage is at least two-fold higher than the average for persons with PI. In crossover studies, weekly SCIG self-infusions have been consistently preferred by patients and have a sharply lower serious adverse event risk profile than IVIG therapy. The convenience of SCIG for home infusion has taken an important leap forward with the recent approvals of every-two-week dosing for Hizentra and every-three-to-four-week dosing with HYQVIA.

As with PI, adoption of SCIG therapy will take time, but there now seems little doubt that it is an advantageous IG delivery option for properly selected patients with neuromuscular and secondary immunodeficiency disorders now chronically managed with IVIG. ❖

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.*

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Exploring the Power

Clinical studies using intravenous immune globulin therapy are breaking new ground when it comes to treating chronic disease; promising results are being seen in patients suffering from Alzheimer's, autism and even diabetes.

Immune globulin (IG) products from human plasma were first used in 1952 to treat patients with immunoglobulin deficiencies. Initially, treatment was administered intramuscularly, until intravenous methods were shown to be effective in autoimmune idiopathic thrombocytopenic purpura (ITP) in 1981. Experts later convened to discuss the treatment possibilities for patients with primary immunodeficiency disease (PI), and fascination with the miraculous plasma derivative has only increased in ensuing decades. Intravenous IG (IVIG) therapy has been the featured topic in thousands of case reports and studies, and in 2014, it was the subject of dozens of clinical trials.

Currently, IG is approved by the U.S. Food and Drug Administration (FDA) to treat a wide variety of diseases, with more than 75 percent of the IG in the U.S. administered to patients with autoimmune or inflammatory conditions.[1] FDA-approved indications for IG therapy include PI, idiopathic thombocytopenic purpura, multifocal motor neuropathy, chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy. The use of IVIG is also now accepted for patients undergoing allogeneic bone marrow transplantation and kidney transplantation when the recipient has a high antibody titer or when the donor's blood is ABO-incompatible. Additional approved indications with limitations include a variety of neuromuscular, hematologic and dermatologic conditions. But, there are a growing number of diseases and chronic conditions for which IVIG is showing promise when it comes to minimizing symptoms and improving the patient's quality of life.[1]

An Answer for Alzheimer's?

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the death of neurons; currently there is no cure for this disease. AD has been dubbed a 21st century epidemic, and according to the Alzheimer's Association, the disease affects one in nine people older than 65, and one in three people older than 85, although only between 2 percent and 7 percent of cases are diagnosed in the early stages. The World Health Organization estimates that 24.3 million people currently suffer from AD, with an increase of 4.6 million new cases each year.[2]

One area of growing interest is the potential use of IVIG to treat patients with AD. Pilot studies with the IVIG preparations Octagam (Octapharma) and

By Trudie Mitschang

# of IVIG

Gammagard (Baxter Healthcare) in individuals with mild-to-moderate AD suggested stabilization of cognitive functioning in these patients, and a Phase II trial with Gammagard reported similar findings. However, subsequent reports from Octagam's Phase II trial and Gammagard's Phase III trial found no evidence for slowing AD progression. Although these secondary findings reduced enthusiasm for IVIG as a possible treatment for AD, additional trials are still underway.[3]

As the world's third-largest manufacturer of plasma-derived medicines and a pioneer in the research and development of therapeutic alternatives, Grifols has been involved in ongoing research projects that explore the possibility of treating AD using plasma proteins. The company's AD research efforts currently focus on early diagnosis, treatment with albumin, and prevention and protection by means of vaccination. Currently, the company is working on the validation of a diagnostic kit and on the development of a potential AD vaccine.[4] (See "Saving the Aging Brain: Grifols Attacks Alzheimer's Disease Head-On" on page 52.)

In 2012, Grifols launched a two-year study into methods of treatment for AD. Known as the AMBAR (Alzheimer Management by Amyloid Removal) study, it investigates combined treatment using albumin plasmapheresis and IVIG at different nominal doses. The researchers are attempting to find synergies between the two treatments in order to reduce the frequency and volume of plasmapheresis, ultimately making the treatment experience more pleasant for patients and easier for medical professionals to administer.

Directed by Dr. Merce Boada, clinical head of the neurology service at the Vall d'Hebron Hospital in Barcelona, Spain, the AMBAR study includes 350 patients at the mild to moderate stage of the disease, randomly grouped into three treatment groups and a fourth control group. The treatment groups consist of plasmapheresis with 20% albumin and IVIG high dose; plasmapheresis with infusion of 20% albumin; and IVIG low dose and plasmapheresis with infusion of 20% albumin low dose. Patients will be treated with a prototype of a plasma developed with Fenwal that was specially adapted for the study.

According to Dr. Boada, "The AMBAR study opens up new prospects and hopes in dealing with an illness where success involves maintaining the quality of life of these patients. Despite the complexity of the study, the principal investigators are really keen to take part because they are aware that there are no simple treatments for Alzheimer's. They enjoy the challenge of offering new alternatives to patients and their families."[5]

One area of growing interest is the potential use of IVIG to treat patients with AD.

There is a growing interest in therapeutic strategies for the treatment of AD that focus on reducing the beta-amyloid peptide burden in the brain. In the last 10 years, Grifols has carried out two successful clinical trials that demonstrated the mobilization of beta-amyloid peptide in the blood of patients. The AMBAR study will allow researchers to confirm the tendency toward stabilization of the disease and to an improvement in the cognitive functions found in previous studies. Grifols plans to present the interim results of the AMBAR study by the end of 2015.[6]

Behavioral Improvements in Kids with Autism and PANDAS

More than one million Americans suffer from autism spectrum disorders, including an estimated one-half million people, mainly children, who have a clinical diagnosis of autism. Autism is generally identified by behavioral manifestations, rather than a specific pathology, and it is now widely accepted that autism is linked to autoimmune disorders.[7] As a result, researchers have been focusing on autoimmunity as a prime area for treatment breakthroughs.

IVIG was first used to treat autistic children in the mid-1990s by Dr. Sudhir Gupta at the University of California, Irvine. The study involved 10 children who each received IVIG therapy every four weeks for at least six months. Dr. Gupta stated: "A consistent (although variable) change was observed in calmer and improved social behavior, better eye contact, loss of echolalia and response to commands. The speech improved in terms of better articulation and improved vocabulary; however, little effect was observed on spontaneous meaningful speech in most patients. One of the patients almost completely recovered speech and another had marked improvement in speech. These two patients are attending regular school."[8]

IVIG was first used to treat autistic children in the mid-1990s.

Of note, for those children who did improve, the IVIG therapy not only improved the behavior of the children, but it also produced change in their antibody levels. Researchers also found that after the IVIG therapy, the antibody titers to myelin basic protein and neurofilament protein actually went down below the detection limit. This finding documented the therapeutic result of IVIG and encouraged further study.[9]

In March 2012, a National Institutes of Health (NIH) scientist and her colleagues launched a multi-site placebo-controlled study testing the effectiveness of IVIG for reducing obsessive compulsive disorder (OCD) symptoms in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). IVIG is used to treat other autoimmune illnesses and showed promise in a pilot study with PANDAS patients.[10] OCD is a common behavioral symptom in children diagnosed with PANDAS; previous human and animal research identified mechanisms by which strep-triggered antibodies mistakenly attack specific brain circuitry, resulting in obsessional thoughts and compulsive behaviors.

"Strep bacteria has evolved a kind of camouflage to evade detection by the immune system," said Susan Swedo, MD, of the NIH's National Institute of Mental Health (NIMH), who first characterized PANDAS two decades ago. "It does this by displaying molecules on its cell wall that look nearly identical to molecules found in different tissues of the body, including the brain. Eventually, the immune system gets wise to this 'molecular mimicry,' recognizes strep as foreign and produces antibodies against it; but because of the similarities, the antibodies sometimes react not only with the strep, but also with the mimicked molecules in the human host. Such cross-reactive 'anti-brain' antibodies can cause OCD, tics and the other neuropsychiatric symptoms of PANDAS. We predict that IVIG will have striking benefits for OCD and other psychiatric symptoms, and will prove most effective for children who show high levels of anti-brain antibodies when they enter the study."[10]

In another study, researchers investigated whether plasma exchange or IVIG would be better than a placebo in reducing the severity of neuropsychiatric symptoms in PANDAS patients. Of the 29 children in the study, 10 received plasma exchange (five single-volume exchanges over two weeks), nine received IVIG (1 g/kg daily on two consecutive days) and 10 received a placebo (saline solution given in the same manner as IVIG). Symptom severity was rated at baseline and at one month and 12 months after treatment. At one month, the IVIG and plasma-exchange groups showed striking improvements in OCD symptoms, and tic symptoms also were significantly improved with plasma exchange. Treatment gains were maintained at one year, with 14 (82 percent) of 17 children much or very much improved over baseline (seven of eight for plasma exchange, and seven of nine for IVIG).[11]

A Deterrent for Diabetic-Related Neuropathy

Diabetes mellitus (DM) is a chronic, lifelong condition that affects the body's ability to use the energy found in food. There are three major types of diabetes: type 1, type 2 and gestational. Diabetic neuropathy is a type of nerve damage that can occur in diabetic patients when high blood sugar injures nerve fibers, typically in the legs and feet. According to The Neuropathy Association, there are now between 15 million and 18 million Americans suffering from diabetic peripheral neuropathy (DPN) due to the increasing prevalence of diabetes. Sixty percent to 70 percent of the 25.8 million adults and children in the U.S. with diabetes have DPN.[12]

Depending on the affected nerves, symptoms of diabetic neuropathy can range from pain and numbness in the extremities to problems with the digestive system, urinary tract, blood vessels and heart. For some people, these symptoms are mild; for others, diabetic neuropathy can be painful and disabling.

Profilnine®
Factor IX Complex

Compare the price of PROFILNINE to other complex concentrates

PROFILNINE is a mixture of vitamin K-dependent clotting factors IX, II, X, and low levels of VII and is stable for 3 years at room temperature (provided that the storage temperature does not exceed 25 °C [77 °F]).

Potency	Diluent Size	NDC Numbers
500 IU FIX Range	5 mL	68516-3201-1
1000 IU FIX Range	10 mL	68516-3202-2
1500 IU FIX Range	10 mL	68516-3203-2

Important Safety Information

PROFILNINE® (factor IX complex) is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B). PROFILNINE contains non-therapeutic levels of factor VII and is not indicated for use in the treatment of factor VII deficiency.

Because PROFILNINE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The use of factor IX concentrates has historically been associated with development of thromboembolic complications, and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis, or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. PROFILNINE should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

After repeated treatment with PROFILNINE, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. As with intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, or manifestation of allergic reactions.

During post-approval use of PROFILNINE, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis of disseminated intravascular coagulation (DIC) have been reported.

Do not administer PROFILNINE at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Please see brief summary of PROFILNINE Package Insert on adjacent page.

Mix2Vial® is a registered trademark of Medimop Medical Projects, Ltd., a subsidiary of West Pharmaceutical Services, Inc.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

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Grifols Biologicals Inc.
5555 Valley Boulevard, Los Angeles, CA 90032 - USA Tel. 888-GRIFOLS (888 474 3657)
www.grifols.com

GRIFOLS

Profilnine®

Factor IX Complex

Solvent Detergent Treated/Nanofiltered

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

DESCRIPTION

Factor IX Complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine does not contain heparin and contains no preservatives. Profilnine contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.

Profilnine is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment have been incorporated into the Profilnine manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step.

The ability of the manufacturing process to eliminate virus from Profilnine was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvovirus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloved viruses.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo[a]	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Non-Env	Hepatitis B	NT	NT	≥ 5.3

[a] Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

INDICATIONS AND USAGE

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).

Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such products can potentially transmit disease: therefore the risk of infectious agents cannot be totally eliminated. The physician must weigh the risks and benefits of using this product and discuss these issues with the patient. Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX complex concentrates is recommended.

The use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. Profilnine should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Exercise caution when handling Profilnine due to the limited risk of exposure to viral infection. Discard any unused Profilnine vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse components.

Information for Patients

After repeated treatment with Profilnine, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. Patients must be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients must be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care if these symptoms occur.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine. It is also not known whether Profilnine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 have not been established. However, across a well controlled half-life and recovery clinical trial in patients previously treated with factor IX concentrates for Hemophilia B, the two pediatric patients receiving Profilnine responded similarly when compared with the adult patients.

ADVERSE REACTIONS

As with other intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling lethargy, hives, or manifestation of allergic reactions.

In addition, during post-approval use of Profilnine, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) have been reported. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

* Unit refers to International Unit in the labeling of Profilnine.

Rx only

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While not a treatment for diabetes itself, IVIG has proven effective in treating some forms of diabetic-related neuropathy, according to results of a study published in the *Archives of Neurology*. A separate study by the same group shows that chronic inflammatory demyelinating polyneuropathy (CIDP) is equally common in type 1 and type 2 diabetes patients, and much more common than in the general population. "We have the impression that clinically significant CIDP is a sufficiently common occurrence in patients with diabetes mellitus (DM) that it should be considered in the differential diagnosis of any diabetic patient with a worsening, relatively severe neuropathy, particularly where there is major motor involvement," writes Khema R. Sharma, MD, and colleagues from the University of Miami School of Medicine in Florida. "There is growing evidence that idiopathic CIDP and polyneuropathy in patients with DM that meets the electrophysiological criteria for CIDP (DM-CIDP) have many similarities."[13]

While not a treatment for diabetes itself, IVIG has proven effective in treating some forms of diabetic-related neuropathy.

Previous studies have confirmed that DM patients presenting with CIDP respond favorably to IVIG treatment, but until recently, there were few defined recommendations on how best to taper treatment regimen once patients begin to improve. A study published in February 2013 in the *Journal of the American Academy of Neuropathy* reviewed the effects of treating CIDP and dermatomyositis with low-dose IVIG as a monotherapy. The study followed seven CIDP patients and three dermatomyositis patients who were treated using weekly low doses of IVIG as a monotherapy (0.4 g/kg) started without loading doses and gradually tapered off treatment. The study concluded that 100 percent of patients showed significant improvement in all categories from baseline to endpoint; all patients showed improvement within the first 24 weeks of treatment, and 80 percent successfully reached a state of remission and were no longer receiving IVIG. The average length of treatment was 3.4 years for CIDP and 5.0 years for dermatomyositis.[14]

Promising Plasma Therapies Yet to Be Seen

Significant progress has been made in understanding the anti-inflammatory effects of IVIG in the treatment of autoimmune and chronic inflammatory disorders. It has been 30-plus years since it was first proven to provide protective antibody levels in PI patients, and since then, hundreds of studies and case reports have led to additional medical breakthroughs and potential uses for this miraculous plasma derivative. Currently, clinical trials are studying the possible benefits of IVIG therapy for diagnoses as diverse as fibromyalgia, narcolepsy and stroke.[15] While much has been accomplished, those on the frontlines of clinical research expect the most exciting clinical breakthroughs using IVIG and other plasma-based therapies to improve quality of life for patients are yet to be seen. ❖

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

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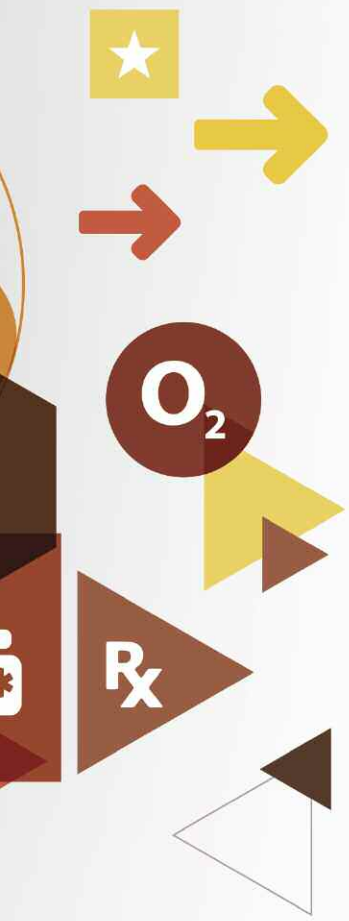
Game On!

Healthcare industry stakeholders are increasingly using diagnosis-specific apps and educational gaming platforms to engage with patients, encourage compliance and even manage treatment options.

The Age of Gamification

By Trudie Mitschang



Could an iPad detect Alzheimer's disease? A recent study intends to find out. Pharmaceutical giant Pfizer has partnered with therapeutic game developer Akili Interactive Labs to test whether a gaming platform used on iPhones and iPads can discern cognitive differences in healthy older adults at risk of developing Alzheimer's. Researchers at the Gazzaley Lab at the University of California, San Francisco, first developed the game's underlying mechanics that require players to steer around a track while shooting down road signs. The Pfizer study will build on the results of a previous study published in 2013[1] that found gaming techniques helped older people improve their capacity to multitask. The 2013 study also showed how patterns of brain activity changed as cognitive skills improved. "A tool that enables cognitive monitoring for the selection and assessment of clinical trial patients has the potential to be an important advance in Alzheimer's research and beyond," says Michael Ehlers, senior vice president and chief scientific officer in Pfizer's Neuroscience Research Unit.[2]

Gamification is a hot topic within the healthcare industry today, and by definition, it refers to the application of game-style mechanics and communication techniques that are used to motivate and engage audiences (in this case patients), while offering to solve problems in a fun way. Worldwide, an average of three billion hours is spent per week playing online games, and those numbers are rising. For pharma companies, gamification has tremendous potential, especially when it comes to encouraging adherence to treatment plans and patient education.

In the case of the Gazzaley study, researchers recruited 30 participants for each of six decades of life, from the 20s to the 70s, and confirmed that multitasking skills as measured by the game deteriorated linearly with age. They then recruited 46 participants aged 60 to 85 and put them through a four-week training period with a version of a game called NeuroRacer that increased in difficulty as the player improved. The results were encouraging; after training, subjects had improved so much that they achieved higher scores than untrained 20-year-olds, and the skill remained six months later without practice. Certain cognitive abilities such as working memory and sustained attention that were not specifically targeted by the game also improved and remained improved. Both skills are important for daily tasks — from reading a newspaper to cooking a meal.

Under the agreement with Akili Labs, Pfizer's clinical trial will assess healthy elderly patients whose brains show the presence or absence of amyloid (which may be an early marker of Alzheimer's) as determined by Positron Emission Tomography (PET) imaging. The trial will measure cognitive abilities at baseline and over the course of one month's game play with the NeuroRacer platform, renamed Project EVO. The objective is to evaluate Akili's platform as a biomarker or clinical endpoint for potential use in future Alzheimer's trials.

Project EVO for the Alzheimer's trial lends itself to the challenges faced by Alzheimer's patients, since the ability to pay attention, plan or make decisions are common symptoms of a number of degenerative diseases such as Alzheimer's, as well as psychiatric conditions like attention deficit hyperactivity disorder (ADHD), autism and depression.

Gamification and Education

For patients and providers alike, "learning by doing" is one of the most effective ways to absorb new or complex concepts. Syandus, a small experimental learning agency in Exton, Pa., recently pioneered a project for two large pharma companies to co-promote a drug for chronic obstructive pulmonary disease (COPD). The program features a simulation tool that lets physicians interact with a virtual patient and examine

the consequences of certain behaviors. The virtual patient can mirror an actual patient through the insertion of specific medical records, and the physician can tweak environmental variables and measure patient response and reaction. For example, a physician might introduce a drug therapy or adjust the number of cigarettes a patient smokes per day. This kind of engagement can help physicians better understand a disease while also creating valuable interactive exchanges between doctors and patients.[3] While not a game, per se, the COPD simulation program employs game technology by allowing physicians to make choices and see the results of those choices. "It's hard for a patient to really understand what's going on in their lungs, but when you go into the [simulation environment] and see a cross-section of what's happening when you breathe — here's the constriction that occurs — it helps to create a very vivid image of, 'this is where you are, and if you keep smoking it will get worse, so let me show you where it's going.' Being able to demonstrate disease progression visually is very important," says Doug Seifert, CEO at Syandus.[3]

Another pharma game billed as a cross between Pokemon and Facebook's FarmVille has also been garnering attention. Launched in 2013 by Boehringer Ingelheim, Syrum (a play on words for "serum") challenges players to discover new cures for diseases, create stable drug treatments and set up clinical trials in order to launch the drugs into the marketplace. Intended as a social game, Syrum combines elements of trading cards with Facebook functionality. Players use the social network's platform to earn in-game rewards and connect with their Facebook friends to collaborate on molecule development. Boehringer hopes to attract as broad an audience as possible, including players from industry, healthcare, patient groups, medical schools and beyond. "We built Syrum with a view to creating an ecosystem through which we could engage with people around education," explains John Pugh, director at Boehringer. Pugh says other goals include reputation management, market research and talent recruitment. "If FarmVille can reach 96 million people, and I can reach half of a percent of that, then I'll be really, really happy," he adds.[4]

Ward Round, a student-developed, problem-based learning application effectively pairs medical education tools with gamification principles. The app offers a medical learning experience in which the user is placed in the role of the doctor to solve clinical medical mysteries against the clock, adding gamification elements such as rewards and positive reinforcement. Medical specialties in the platform include cardiology, endocrinology, neurology and infectious disease. The question bank used in the Ward Round app was authored by Adrian Raudaschl, a graduate from Glasgow Medical School of Glasgow University, and case scenarios were verified by senior consultants in the relevant fields.[5]

Support for Patients and Caregivers

Gamification presents a distinct set of challenges in the healthcare arena, especially since providers are dealing with diseases that are anything but fun and games. Designing a game that is sufficiently serious but also engaging is no easy feat; for example, how do you use gaming techniques to engage patients battling cancer? HopeLab, a gamification pioneer, developed a popular program that does just that. Re-Mission targets adolescents and young adults with cancer and is played on tablets, laptops or smartphones. The game allows players to pilot a nanobot named Roxxi as she travels through the bodies of fictional cancer patients, destroying cancer cells, battling bacterial infections and managing side effects associated with cancer and cancer treatment.[6]

To create the game, HopeLab researchers, led by Dr. Pamela Kato, worked with video game developers, cancer experts, psychologists and young people with cancer. Research has demonstrated that specially designed games like Re-Mission can help drive positive behavior and potentially improve biological health. One study on the effects of Re-Mission published in the medical journal *Pediatrics* showed improved behavioral and psychological factors during cancer treatment.[6] According to the study, participants given Re-Mission maintained higher levels of chemotherapy in their blood and took their antibiotics more consistently than those in the control group, demonstrating the game's impact at a biological level. Participants given Re-Mission also showed faster acquisition of cancer-related knowledge and faster increase in self-efficacy. These results indicate that a carefully designed video game can have a positive impact on health behavior in young people with chronic illness. The study was the largest randomized, controlled study of a video game intervention ever conducted, following 375 teens and young adults with cancer at 34 medical centers in the United States, Canada and Australia during three months of cancer treatment. Participants were randomly assigned to receive PCs pre-loaded with a popular video game only (control condition) or that same control video game plus Re-Mission.[6]

When it comes to children and diseases, the management of care outside of the hospital setting often falls on parents. In these situations, parents can feel ill equipped and intimidated when it comes to administering needed medications. Scott Randall, CEO at BrandGames, recently launched a gamification project aimed at helping parents learn to correctly administer injections to their children.[7] "The risks involved in administering the medication are significant, and all patients get is this little box with a piece of rice paper in it, and it says, hold the syringe like this, put it together like this, do this, do that, and stick it in your kid's leg," says Randall. "They've never done this before, and now they have this hysterical child on their hands, and they're supposed to be administering the medication."

The idea for the game is built around the concept of a tutorial,

where users match the different steps in the process, assemble an interactive syringe, and then receive coaching on whether or not they've done it correctly. Game developers say the key performance metric in this instance is based on a reduction of adverse events.[7]

BrandGames has also created healthcare training for a nursing program at Johnson & Johnson, and pharma rep training for Daiichi Sankyo. "The idea is, how do you engage the doctor and how do you engage patients? When you're looking at patient outcomes, you have to give the patient the big picture of what the medication is doing. At the doctor's office, you get a Xerox of a Xerox of a Xerox. You go home with no emotional engagement; you have no context around your treatment. Without that, patients don't participate in their treatment, and outcomes are worse," says Randall.[7]

Patients who struggle with symptoms of chronic illness take an average of seven years to receive an accurate diagnosis. A new gamification platform called CrowdMed is seeking to significantly shorten that timeline. CrowdMed targets two different audiences: patients who have bounced from doctor to doctor without success, and those who want to help them. Patients who want to participate simply fill out a questionnaire that details their symptoms and case history. They can then submit their case for free or offer a "reward" to the medical detective who eventually solves their case. The second audience on CrowdMed are the self-appointed "detectives," an audience comprised of doctors, medical residents and laypeople who compete on a point system to try to come up with an accurate diagnosis.[8]

As far as incentives, CrowdMed provides cash rewards (keeping a 10 percent commission for the company) and the "feel-good factor" premise that by participating on the platform participants can make a difference in a stranger's life. In fact, CrowdMed's website recruits participants with this intriguing proposition: "As a Medical Detective, you can use your personal experience, intuition, and online research skills to help solve the world's most difficult medical cases. You can not only win cash, prizes, and status, but also help save lives."[9]

Getting In the Game

Pharma companies looking to gamify their brands might wonder where to start. Experts suggest making education and learning top priorities in any prospective gaming platform, and also encourage developers to spend ample time researching specific behaviors unique to their particular patient audience. One multimedia instruction guide to gamification produced by PMLiVE Publishers in association with Grey Healthcare Group, offers a helpful how-to manual for stakeholders interested in jumping on the gamification bandwagon. Authored by Dr. Kieran Walsh, clinical director at BMJ Learning, Andy Hastie, head of digital at Grey Healthcare Group, and Matthew Hunt, European head of planning at Grey Healthcare Group, the guide looks at how the pharmaceutical industry can utilize gamification theories and explores where the health benefits could lay. Structured as an easy-to-follow tutorial, topics include theories, dynamics, rules and practical applications for using gamification in healthcare. According to the study's authors, "As with any emerging discipline, there are many ways that it could develop, but at the very heart of it are some basic truths: People like challenges, they love rewards and they certainly enjoy sharing their success."[10]

Gamification can be a costly, time-consuming endeavor requiring a significant investment in research and design, coupled with a willingness to "think outside the box" when it comes to disease diagnosis and treatment. The Pfizer video game trial for Alzheimer's, for example, marked the first time a large pharmaceutical company evaluated a mobile video game as a clinical tool to determine early signs of neurodegenerative disease pathology.[2]

In addition to the Pfizer study, Akili Labs is also running trials with Duke University in children with ADHD; kids with autism spectrum disorders; college students in Vermont with autism, ADHD and other cognitive deficits; and two studies in people with depression. By examining outcomes in these and other studies, pharma companies, providers and other healthcare industry stakeholders will have an opportunity to evaluate their own objectives and determine if gamification techniques are a viable option for encouraging compliance, managing disease symptoms and, in some cases, offering opportunities for early intervention and treatment. ❖

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

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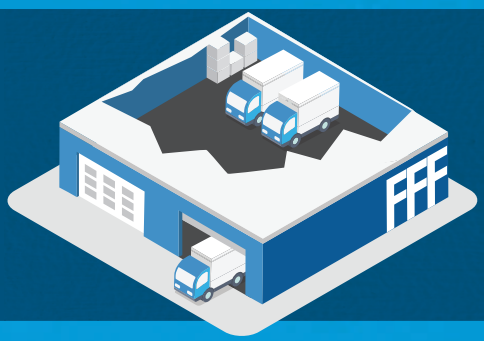

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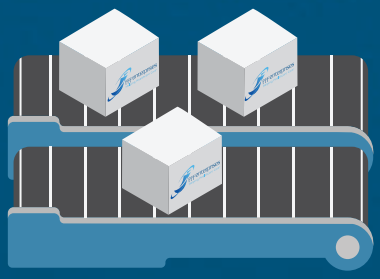

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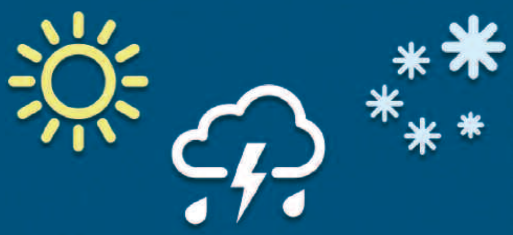

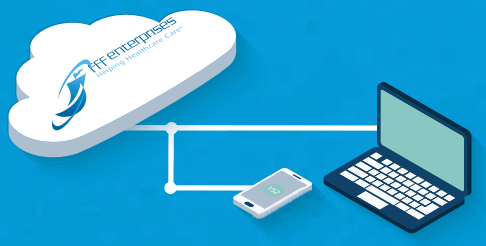

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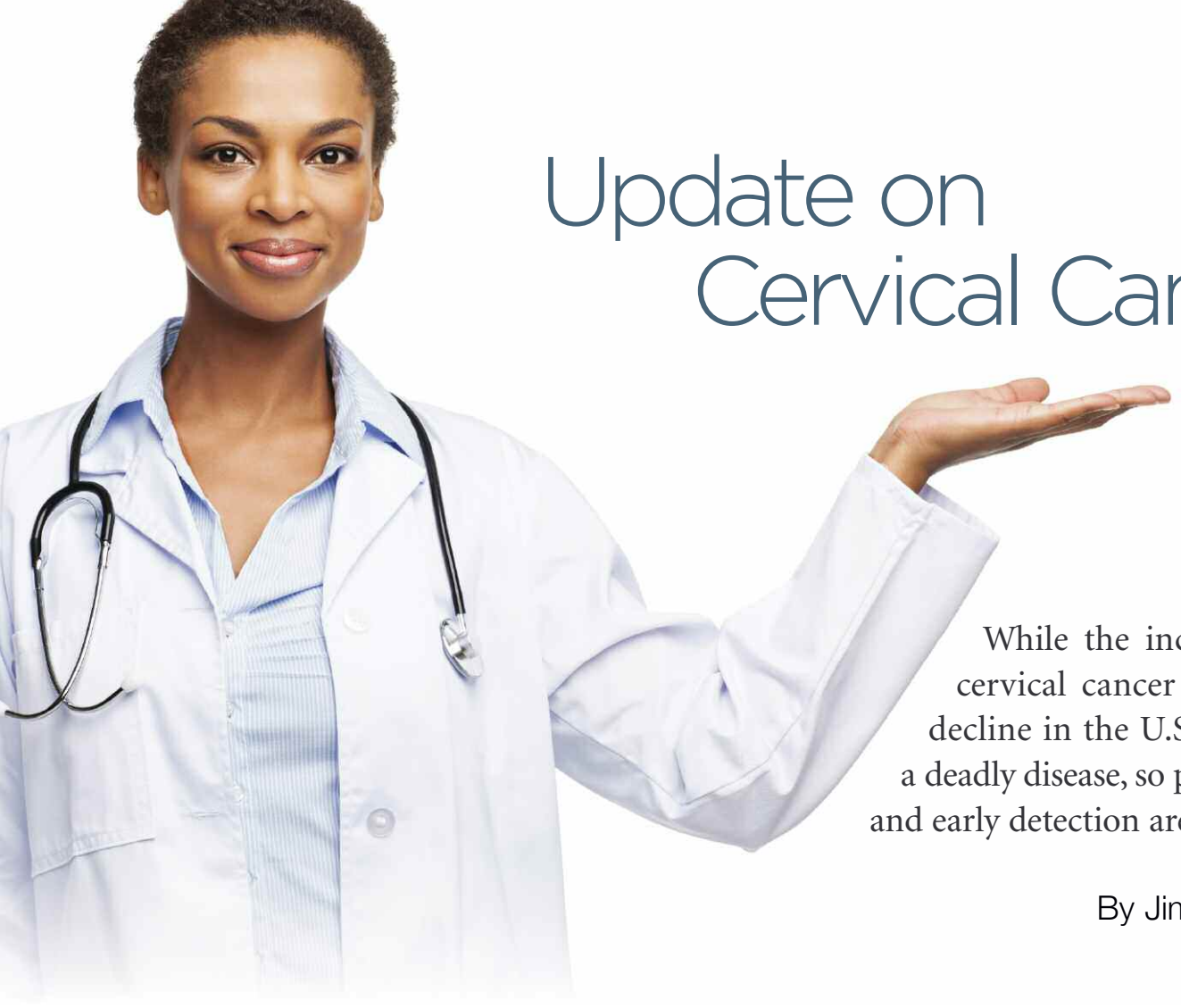

Update on Cervical Cancer

While the incidence of cervical cancer is on the decline in the U.S., it is still a deadly disease, so prevention and early detection are essential.

By Jim Trageser

In the United States, cancer of the cervix was once the most common type of cancer afflicting women.[1] And globally, it remains a lethal disease. However, a half-century of aggressive education campaigns and regular testing regimens in the U.S., combined with several recent technological advances in treatment and prevention, have resulted in a much lower rate of cervical cancer among American women than in previous generations. In fact, cervical cancer has decreased by 74 percent since 1955 and now represents less than 1 percent of all cancer diagnoses in the United States.[2] Today, American women who do develop a cervical cancer are far more likely to receive successful treatment and survive today, with death rates from cervical cancer continuing to decline at around 4 percent per year.[3]

Even with the relatively good news regarding modern medicine's ability to prevent and successfully treat cervical cancer, the sobering reality is that in 2010 (the most recent year for which statistics were available at press time), roughly 12,000 women in the U.S. were diagnosed with cervical cancer, while just under 4,000 cases resulted in death.[4] The World Health Organization estimates more than half a million women worldwide will develop cervical cancer this year.[5]

Even if it is no longer the killer it once was in the United States, a diagnosis of cervical cancer very much remains a tragedy for thousands of young women each year who see their dreams of starting or growing their families threatened, since cervical cancer and its treatments can leave a patient unable to bear children.

What Is Cervical Cancer?

The definition of "cervical cancer" is one based on the location of the growth; it is any malignancy that forms on the cervix.

The cervix is the connection between the uterus and the vagina. The lower portion of the cervix, nearest the vagina, is composed of squamous cells; the higher portion is made up of glandular cells. However, most cervical cancers arise in the transitional area, which is composed of both kinds. Malignancies of these two kinds of cells are responsible for nearly all cases of cervical cancer.

Squamous cell carcinoma arises from abnormal squamous cells, while precancerous glandular cells can develop into adenocarcinoma. More than 80 percent of cervical cancer diagnoses are of squamous cell carcinoma, and both of these types of cervical cancer typically develop from earlier precancerous abnormalities.

In addition, other types of cancers, including melanoma, sarcoma and lymphoma, do sometimes arise in the cervix, although this happens rarely.[6]

Symptoms of Cervical Cancer

Abnormal precancerous cells rarely manifest any noticeable symptoms. Only after the abnormalities have become cancerous do most symptoms arise. These may include irregular bleeding (outside normal menstrual cycles or following sex), abnormal discharge, pain during sex or unexplained changes in the menstrual cycle.[7]

Because symptoms do not typically appear until the disease is advanced, regular testing for cervical precancer has been recommended for women beginning in their 30s since the 1950s. The Papanicolaou test, more commonly known as a Pap smear, is the most common screening method for abnormal cell changes in the cervix.[8]

Diagnosing Cervical Cancer

Regular use of the Pap smear as an integral component of women's healthcare is primarily responsible for the massive decline in both cervical cancer cases and improved survival rates for those diagnosed. Yet, despite the decline, the American Congress of Obstetricians and Gynecologists (ACOG) issued new guidelines for cervical cancer screening in 2009, which resulted in a great deal of controversy in the medical community. ACOG's new guidelines changed from a Pap smear annually at age 18 or three years after becoming sexually active to a Pap smear annually beginning at age 21; an annual Pap smear for women ages 21 through 29 to a Pap smear every two years; and a Pap smear for women over age 30 every two to three years to only every three years (with the addition of an HPV test done at the same time as an option) if they have had three consecutive negative Pap smear results.[9]

During a Pap smear, cells are collected from the outer opening of the cervix. These cells are examined microscopically to determine if any are exhibiting signs of precancerous changes.[10] If any abnormalities are discovered, a more detailed examination is generally prescribed, including a biopsy, a visual examination or both.

Causes of Cervical Cancer

The vast majority of cervical cancer cases are caused by a strain of the human papillomavirus, or HPV. HPV is a sexually transmitted virus that is endemic among sexually active adults the world over.[11] It causes no symptoms of its own, and most women with HPV will not develop cervical cancer. Men with HPV most often exhibit no symptoms and typically have no idea they are infected.[12]

There are more than 150 strains of HPV, but four of them (types 16, 18, 31 and 45) are responsible for roughly 85 percent of cervical cancer cases. Other strains are also linked to cervical cancer (and yet others to genital warts in both men and women), and it is not unusual for sexually active adults to carry multiple strains without any symptoms.[13]

Other possible risk factors of cervical cancer include smoking, having multiple sexual partners, having HIV, giving birth three or more times or using oral contraceptives over a sustained period of time.[14] As with all cancers, other triggers likely exist that are not yet discovered or fully understood.

Treating Cervical Cancer

Treatment depends on the stage of the cancer or precancerous abnormality that is discovered, and the age of the patient.

For early or precancerous abnormalities, treatment generally consists of removing the abnormal or malignant tissue with electrical current (loop electrosurgical excision procedure, or LEEP) or laser, or freezing it to kill it.[15]

If the cancer is more advanced, then surgery is usually necessary to remove the cancer. The amount of tissue to be removed will depend on how far the cancer has spread, as well as the patient's hope to bear children in the future.

Preventing Cervical Cancer

With the overwhelming number of cervical cancer cases tied to HPV, recent prevention efforts have focused on inoculating against the virus. Since the introduction of HPV vaccines, infections rates have dropped by almost 50 percent.[16]

There are three vaccines currently available to protect against HPV: Cervarix (GlaxoSmithKline), Gardasil (Merck) and, now, Gardasil 9 (Merck). All are available for girls and young women and are administered in three timed doses. Gardasil also protects males from an HPV infection, which can also help in stopping the spread of the virus to their partners,[17] as well as protects against anal cancer, 92 percent of which is likely caused by HPV.[18]

These two vaccines have been effective, however, only against a handful of the more than 150 strains of HPV. Cervarix only protects against types 16 and 18.[19] Gardasil protects against types 6, 11, 16 and 18. While strains 16 and 18 are responsible for most causes of cervical cancer, types 6 and 11 cause an estimated 90 percent of genital warts.[20] Fortunately, in December, the U.S. Food and Drug Administration approved Merck's Gardasil 9, a 9-valent HPV vaccine for girls and young women ages 9 through 26 for prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic legions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. Gardasil 9 is also approved for boys 9 to 15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. According to Dr. Julie Gerberding, president of Merck Vaccines, with Gardasil

9, "there is an extraordinary opportunity to even further reduce the burden of HPV-related diseases and cancers in males and females."[21]

Each of these vaccines is most effective if administered before young people become sexually active and are thus exposed to HPV. They can be administered to adolescents beginning at age 9, although a window of 11 or 12 is recommended for the first dosage. However, as both vaccines inoculate against multiple strains of HPV, it is still recommended that women under the age of 26 and men under the age of 21 receive one of the vaccines. Even if young adults have been exposed to one strain, the inoculation offers the chance of building immunity to other types targeted by the vaccines.[22]

Using condoms has not yet been proven to be 100 percent effective at stopping the spread of the HPV virus; however, other studies have indicated that women who regularly have their partners use a condom during sex have a lower risk for developing cervical cancer.

Ongoing Research

Given the debilitating nature of cervical cancer, threatening to rob patients of the ability to bear children or remain sexually active (depending on the severity of the case and the nature of the treatment), ongoing research into its prevention remains a high priority, despite the relatively low rate of incidence compared with other cancers.

There are some promising studies currently being conducted to not only provide more effective protection against acquiring HPV or developing cervical cancer, but also to help the patient's body effectively fight a current case of cervical cancer or HPV infection. The American Cancer Society reports on a line of research to provide a vaccine to women already infected by HPV to help the body destroy the virus before it can cause cancer. Another promising line of research seeks to get the patient's body to destroy specific proteins unique to HPV in order to stop healthy cervical cells from changing to abnormal precancerous cells.

Other studies include applying the antiviral drug cidofovir on precancerous areas to stop HPV from reproducing; the American Cancer Society reports an early test shows some success. Another antiviral drug, imiquimod, is also being tested to fight cervical cancer by fighting the type of HPV that causes most cases.

Besides inoculations and antivirals, targeted therapy drugs are also being explored in the fight against cervical cancer. The noted anti-cancer drug Avastin, which helps block the formation of new blood vessels — thus starving or at least slowing malignancies — has been effective in treating advanced cervical cancer and is now being studied to determine if it can be used in treating earlier stage cervical cancers.[23]

More effective testing methods to improve early detection of abnormal cells in the cervix are also being developed. Earlier this year, the U.S. Food and Drug Administration approved the first HPV DNA test. Unlike the Pap smear, which involves visually inspecting sample cells microscopically to find abnormalities, the HPV DNA test scans a sample looking for the unique DNA signature of HPV. A positive response indicates the patient has one of the HPV strains linked with cervical cancer, allowing her physician to conduct a more careful follow-up exam to look for precancerous abnormalities.[24] ❖

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

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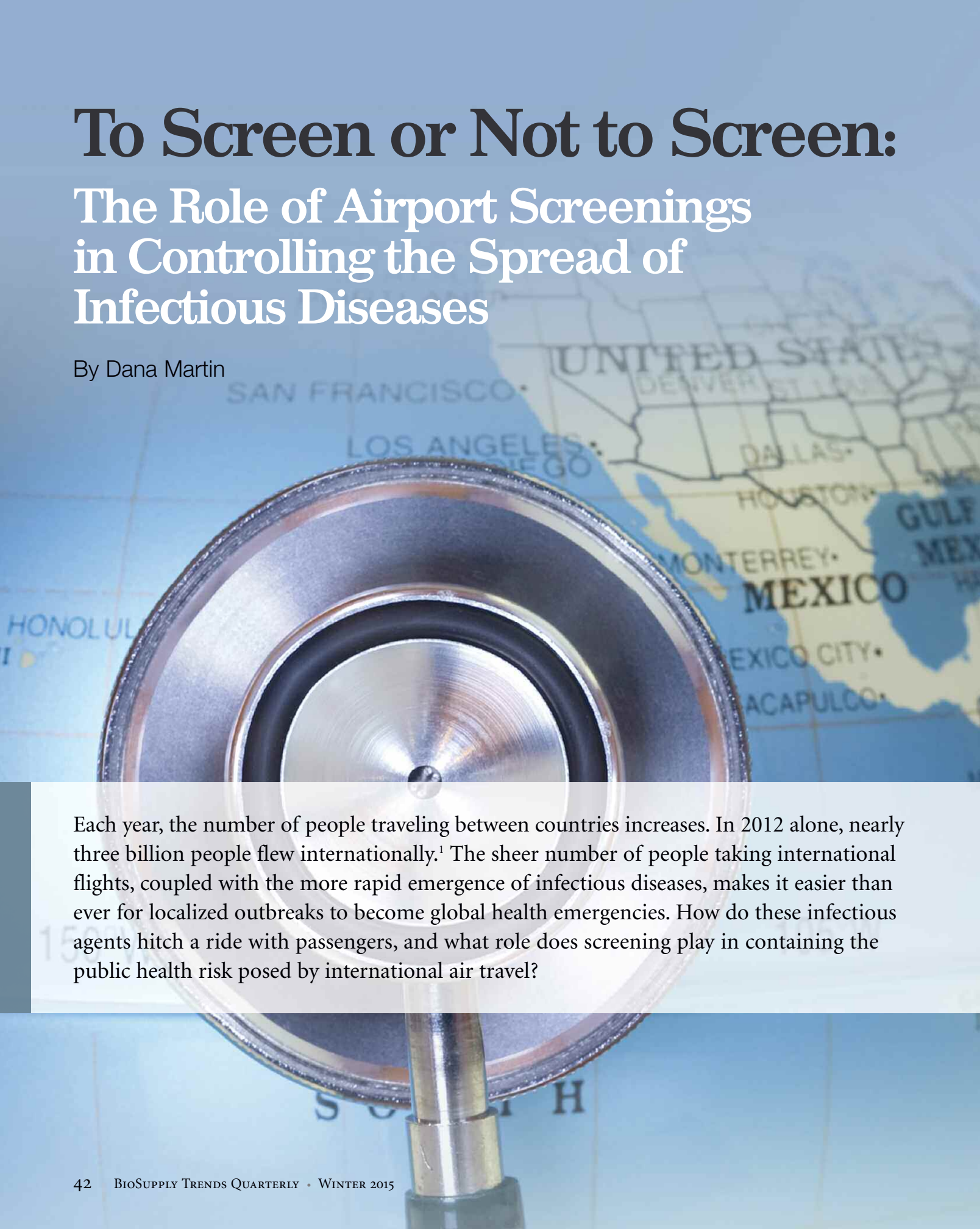
To Screen or Not to Screen:

The Role of Airport Screenings in Controlling the Spread of Infectious Diseases

By Dana Martin



Each year, the number of people traveling between countries increases. In 2012 alone, nearly three billion people flew internationally.[1] The sheer number of people taking international flights, coupled with the more rapid emergence of infectious diseases, makes it easier than ever for localized outbreaks to become global health emergencies. How do these infectious agents hitch a ride with passengers, and what role does screening play in containing the public health risk posed by international air travel?

In 2005, the World Health Organization (WHO) ratified changes to the 1969 International Health Regulations (IHR). The changes were designed to prevent, protect against, control and provide a public health response to the international spread of disease "in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade."[2] During the early phase of a pandemic, entry and exit screening can be made mandatory under the IHR. Such screenings are required as core capacities for designated airports so they can respond to events that may constitute a public health emergency of international concern.[3]

Aside from the IHR, there is no overarching body regulating screenings related to international travel. Many countries require screenings for specific situations, such as mandatory overseas medical examinations for immigrants and refugees before admission to the United States.[4] In its Travelers' Health website, the Centers for Disease Control and Prevention (CDC) outlines screening considerations for parasitic and nonparasitic infections in asymptomatic return travelers, noting that it has not put official guidelines or recommendations in place for those returning from international travel who have no symptoms of illness.[5]

Two Current Health Threats

The most notable current health threat is the much publicized Ebola outbreak in West Africa. In late September, CDC estimated that, with corrections made for underreporting, there could be 1.4 million cases of Ebola in Liberia and Sierra Leone by January.[6] One reason for this unprecedented growth is the fact that the virus has spread to major cities in five West African countries. In contrast, past outbreaks have been contained relatively quickly and have been restricted to remote areas. This spread into cities and across country borders makes the virus much more difficult to contain. While authorities are focusing on treatments and vaccines to control this outbreak, concern among the public over international travel, especially into and out of affected countries, is high. In response to the outbreak, WHO is recommending that affected countries carry out exit screening at international airports, seaports and major land crossings.[7]

Another current health threat is wild poliovirus. As of this writing, four countries are currently exporting the virus: Pakistan, Cameroon, Equatorial Guinea and the Syrian Arab Republic. In addition, six countries are infected with, but not currently exporting, the virus: Afghanistan, Ethiopia, Iraq, Israel, Nigeria and Somalia.[8] In May, the IHR Emergency Committee declared the virus a public health emergency and issued temporary recommendations for affected countries. For exporting countries, the recommendations include ensuring all residents and long-term visitors receive a dose of polio vaccine. For infected countries, the recommendations include encouraging residents and long-term visitors to receive a dose of polio vaccine prior to international travel. In an August follow-up meeting, the IHR Emergency Committee stated that the possible consequences of international spread had worsened since its May declaration, noting the increase in susceptible populations living in virus-free but conflict-torn areas where routine immunization services have deteriorated. The IHR extended its temporary recommendations and requested another reassessment in November.[8]

Not All Diseases Are Created Equal

Both Ebola and poliovirus raise numerous questions about the role of screening in international travel. For Ebola, the IHR is recommending exit screening in affected countries. For poliovirus, as of this writing, the IHR is recommending vaccination when traveling to and from affected countries. While screening has not been made mandatory in the latter case, the U.S. did implement mandatory screening for Ebola in October. Passengers who travel from nations struck by Ebola to Washington Dulles (Washington, D.C.), John F. Kennedy (New York), Newark Liberty (New Jersey), O'Hare (Chicago) and Hartsfield-Jackson (Atlanta) airports are now required to have their temperatures checked and fill out a health questionnaire.

Required and Recommended Travel Vaccinations

The International Health Regulations requires only two vaccinations as of this writing. Yellow fever vaccination is required for travel to certain parts of sub-Saharan Africa and South America, and the meningococcal vaccination is required by the Saudi Arabian government for travel during the period of the Hajj.[25] In addition, individual countries recommend numerous vaccines for travel to various parts of the world. For those traveling from the United States to other countries, the Centers for Disease Control and Prevention provides information about travel requirements and recommendations at its Travelers' Health webpage at wwwnc.cdc.gov/travel/destinations/list. This page also includes information for clinicians.

According to White House press secretary Josh Earnest, increased screening for Ebola at these airports will capture 94 percent of passengers arriving from African nations that are battling the virus.[9] Shortly after, Britain began screening travelers coming from Ebola-hit parts of West Africa at Heathrow and Gatwick airports and on Eurostar trains from Belgium and France.[10]

In late October, the Centers for Disease Control and Prevention (CDC) announced it will actively monitor individuals traveling from Liberia, Sierra Leone and Guinea for Ebola symptoms for 21 days after they enter the U.S. CDC Director Dr. Thomas Frieden said that travelers from the region will be required to take their temperatures twice a day and will be responsible for reporting their daily temperatures and any Ebola-related symptoms. State health departments will be responsible for enforcing the monitoring program, Frieden said.[11]

When an infectious disease emerges or experiences a resurgence, instinct tells us that every international traveler should be screened; otherwise, global travel will be unsafe. Taking this thinking to the extreme is what leads those like Donald Trump to make statements about the intrinsic lack of safety with regard to bringing a patient with Ebola into the United States for treatment as part of an appropriate medical evacuation. But even moderately concerned laypersons may believe a pandemic is just one flight away and that indiscriminate screening is the answer to the suppression of infectious diseases posing a worldwide threat.

According to WHO, infectious diseases seem to be emerging more quickly than ever. Nearly 40 new diseases have been discovered that were unknown a generation ago.[12] In addition, many diseases that were once under control are re-emerging.[2] To gain a better understanding of the applicability of airport screening in international travel for these diseases, it's important to understand that not all pathogens have the same microbiological characteristics. According to a retrospective evaluation of the A(H1N1) pandemic conducted by WHO, several factors need to be assessed to determine whether international passengers should be screened. These include the following:

- Will screening likely result in source control?
- If source control is not possible, is international export of the pathogen in question likely?
- What is the prevalence of infection and symptomatic disease in travelers?
- What is the clinical spectrum of illness, and can relevant illness be detected through direct observation, traveler health declarations, complementary tests or some combination of these approaches?
- What are the operating characteristics and limitations of available screening methods?
- What is the global epidemiologic pattern of the epidemic disease at the time when traveler screening is first contemplated?
- What are the opportunity costs of detecting other infectious diseases of lesser significance as a result of screening?
- What is the perceived contagiousness and severity of the epidemic disease, and what are its estimated health and economic effects?
- What is the availability and cost of effective methods for preventing or treating the epidemic disease?
- What are the projected public health benefits of health screening at airports relative to those that could be achieved by intervening at other international frontiers, domestic frontiers or both?[2]

Other factors to consider regarding the effectiveness of screening, especially with air travel, are the disease's incubation period and whether transmission is possible in the absence of symptoms.[3]

In the case of poliovirus, the expanded surveillance and screening recommended within exporting countries is not the same as entry or exit screening of international travelers at airports or other major crossing points. The former pertains to surveillance within a country rather than between country borders. Only two countries — the Kingdom of Saudi Arabia and India — currently have polio vaccination requirements for entry. Other countries have no entry requirements at this time but may put a requirement in place in the future.[13]

The European Centre for Disease Prevention and Control indicated last May that screening the polio vaccination status of travelers to Europe was not deemed necessary, stating: "There is evidence that the high vaccination coverage at the national level has prevented re-introduction [sic] of [wild poliovirus] — despite periodic detection in the EU."[14] This

helps explain why the IHR's temporary recommendations regarding vaccination target those who live in and travel to and from affected countries. Where vaccination coverage is high, what some call "herd immunity" takes hold, making it unlikely that the virus will spread even if it is reintroduced through international travel.

In the case of Ebola, after the meeting of the Ebola Emergency Committee under the IHR in early August, WHO provided recommendations to countries to help contain the current Ebola outbreak. One recommendation is that countries be prepared to detect, investigate and manage Ebola cases, including having the ability to identify and care for travelers coming from known Ebola-infected areas who arrive at international airports or major land crossing points with unexplained fever and other symptoms.[15] As noted above, WHO also recommended that anyone traveling from affected countries by air, sea or major land crossings be screened on exit.[7]

WHO issued a travel and transport update that outlines the risk of Ebola virus disease for various groups and details recommendations for public health authorities and the transport sector. The update states that the risk of Ebola transmission during commercial flights is low. That is because the disease cannot be spread while infected individuals are asymptomatic. In addition, the incubation period for the disease is relatively long (up to 21 days), which means the likelihood of developing symptoms during a flight is quite low. WHO does warn that infected individuals could travel long distances during the disease's incubation period without showing symptoms until they reach their destinations.[16] This is exactly what happened in Texas in late September, when the first case of Ebola in the United States was confirmed in a man who had recently flown to Dallas from Liberia. He became symptomatic only after his arrival. Because he was not symptomatic — and, therefore, not contagious — at the time of his flight, neither exit nor entry screening would have flagged him as infected. (In fact, he was screened on exit from Liberia but had no fever.)[17]

The WHO update adds that a passenger with Ebola symptoms could board a commercial flight without disclosing his or her health status. It reads: "It is highly likely that such patients would seek immediate medical attention upon arrival, especially if well-informed, and then should be isolated to prevent further transmission. Although the risk to fellow travellers [sic] in such a situation is very low, contact tracing is recommended in such circumstances."[16]

Lessons Learned from SARS and A(H1N1)

Not all infectious diseases will have the same profile as poliovirus, with its high level of vaccination coverage in unaffected countries, or as Ebola, with its low risk of transmission during international travel. We've already seen diseases that have a higher rate of transmission, including severe acute respiratory syndrome, also known as SARS. The international community learned just how quickly SARS could travel during the 2002–2003 outbreak. This outbreak led to 8,448 reported cases and 774 reported deaths. In a matter of weeks, the disease infected individuals in 37 countries, with a spread across four continents within three days by way of global air traffic. Before the outbreak subsided, affected countries included Canada, China, Singapore, the United States and Vietnam, in addition to the originating country, Hong Kong.[3,18,19]

In 2009, A(H1N1) went from posing a pandemic threat to being a full-blown pandemic in less than two months.[20] This

Air Travel Risks May Extend Beyond the Plane

Many travelers are concerned about their risk of contracting an infectious disease while on board an international flight. But, what about the areas in which air travelers spend time before and after their flights? Standing in airport lines, congregating at crowded gates, passing through jet bridges, waiting at baggage claim areas, passing through customs and taking public transit to and from the airport might put travelers at greater risk than their actual flights.

The authors of "Screening for Infectious Diseases at International Airports: The Frankfurt Model," published in *Aviation, Space, and Environmental Medicine*, posit that the transmission of diseases such as SARS and influenza, which have higher rates of transmission, are more likely to occur in areas proximal to the plane than on the plane itself. Their reasoning is that ventilation systems within the plane are often superior to those in the airport and its surrounding areas.

The authors propose several ways to curb the spread of infection in areas where people spend time before and after flights. First, ventilation systems in these areas should be optimized to help prevent the spread of droplet infections. Second, procedures that discourage the formation of lines such as at the boarding gate should be implemented. Third, jet bridges should have ventilation systems that flow toward the outside. And, fourth, aggressive air-sanitation measures should be installed.[3]

Passenger Misinformation: One Downside of Screening

On Sept. 30, Thomas Eric Duncan became the first person diagnosed with Ebola in the United States after traveling from Liberia to Dallas.[20,26,27] He underwent exit screening before leaving Liberia, which entailed filling out a questionnaire and undergoing three airport screenings that included temperature scans. He did not have a fever, and his questionnaire answers reportedly stated that he had not touched the body of someone who had died in an area affected by the disease. After he developed Ebola, news reports state that Duncan did in fact have contact with people afflicted with Ebola in Liberia, according to witness reports, including caring for an infected individual at a residence outside Monrovia.[27]

Duncan's case raises an important question with regard to airport screenings. When screening relies in part on passenger-supplied information, even the most comprehensive screening efforts can fail if a passenger provides erroneous information about his or her exposure risk. Though travelers have the potential to respond to screening questionnaires inaccurately, keeping borders open is paramount to allowing other countries access to them, which in turn facilitates efforts to help control the outbreak.[27] In an Oct. 2 Twitter chat on Ebola led by CDC experts, CDC Travelers' Health stated that people completing screenings don't always know when they've been exposed. It adds: "[Screening] doesn't need to be perfect to work."[28] Still, Duncan's story needs to be a larger discussion about taking measures to develop screening methods that are not undermined by unverifiable subjective information.

pandemic originated in Mexico but resulted in approximately 60.8 million cases, 274,304 hospitalizations, and 12,469 deaths in the United States alone, according to CDC.[21]

Both SARS and A(H1N1) are examples of infectious diseases with characteristics that differ from that of Ebola or poliovirus. Like Ebola, only those who are symptomatic can transfer SARS. But unlike Ebola, SARS can be passed through coughing and sneezing.[22] The incubation period for SARS is typically two to seven days,[22] compared with up to 21 days for Ebola. In the case of A(H1N1), like other flu viruses, those who are infected are contagious for up to one day before they become symptomatic.[3] A(H1N1) is thought to be spread by people with the virus when they cough, sneeze or talk.[23] The incubation period is about two days.[2] And, unlike wild-type poliovirus, people didn't have widespread protection in the form of a vaccine against SARS and A(H1N1) when they emerged. They were new viruses that populations had no protection against.

These differences in characteristics matter because, as noted above, responses to outbreaks, including international travel responses, must be based on the specifics of each infectious disease. For instance, the authors of a retrospective evaluation of the A(H1N1) pandemic concluded that exit screening at just six airports in Mexico would have caused the least disruption to international air traffic and would have allowed for the assessment of about 90 percent of all at-risk travelers. The authors are careful to note, however, that the relative benefits and costs of exit and entry screening are not fixed.[2]

Exit Screening vs. Entry Screening

Exit screening entails screening passengers at the point of departure from an affected area. Entry screening entails screening all passengers at the point of entry into a country. In many cases and as noted above, exit screening appears to confer more benefits than entry screening. During the A(H1N1) outbreak, indiscriminate entry screening, as opposed to exit screening, would have required assessing 67.3 million low-risk travelers at 1,111 international airports to ensure every at-risk traveler from Mexico was screened. Even targeted entry screening would have been cumbersome, requiring screening at 82 international airports in 26 countries.[2]

In terms of targeted screening, the authors of the retrospective evaluation postulate that, at the initial stages of a pandemic caused by a pathogen with a similar or longer incubation period than A(H1N1), the potential benefits of targeted entry screening over exit screening appear to be marginal because most flights have shorter durations than the incubation period.[2] In other words, those who are asymptomatic on exit screening will most likely still be asymptomatic if screened upon arrival at their destinations. Again, microbiological characteristics come into play. One example is that of travelers harboring infectious agents with very short incubation periods who are flying on long, nonstop intercontinental flights from areas with substantial epidemic activity. In these cases, targeted entry screening could be a reasonable addition to exit screening.[2]

In the case of Ebola, WHO is specifically recommending exit screening from affected countries as opposed to entry screening. The drawbacks of entry screening include its overall cost, its reliance on health and human resources that could otherwise

be focused on areas of greater need, and the difficulty of orchestrating consistent screening at all airports around the world.[2,16] At the same time, exit screening has its drawbacks: It places the screening burden on the affected country or countries while providing the benefits to other countries, and it becomes more difficult the closer an outbreak is to a major international hub.[2] Whether one or both are utilized, both exit and entry screening measures must abide by the IHR's mandate that unnecessary interference with international traffic and trade be avoided.

Managing Current and Future Threats

The role of entry and exit screening is complicated and comprises only one aspect of disease containment and control. There is no single approach to suppressing the spread of diseases that constitute international public health emergencies. Just as Ebola, wild poliovirus, SARS and (A)H1N1 are all distinct pathogens, distinct courses of action are required to contain them. The IHR works in real time to follow the evolution of diseases and the factors affecting their emergence and transmission.[24] In addition, retrospective analyses such as those carried out for (A)H1N1 and SARS allow more insight into the efficacy of responses to outbreaks, and provide information that can be used to help guide the management of future outbreaks. Ebola and poliovirus are not the first diseases to pose a global health threat, and they won't be the last. While responding to both diseases, the international community is learning even more about how to handle the next emergency that threatens public health. Ultimately, the question "to screen or not to screen" is not specific enough for any given threat. The international community needs to know who to screen, where to screen, when to screen, how to screen and if to screen — in addition to having the means to implement screenings and other protective measures on a global scale. ❖

DANA MARTIN *is a writer and editor in the Kansas City area who specializes in science, medicine and health.*

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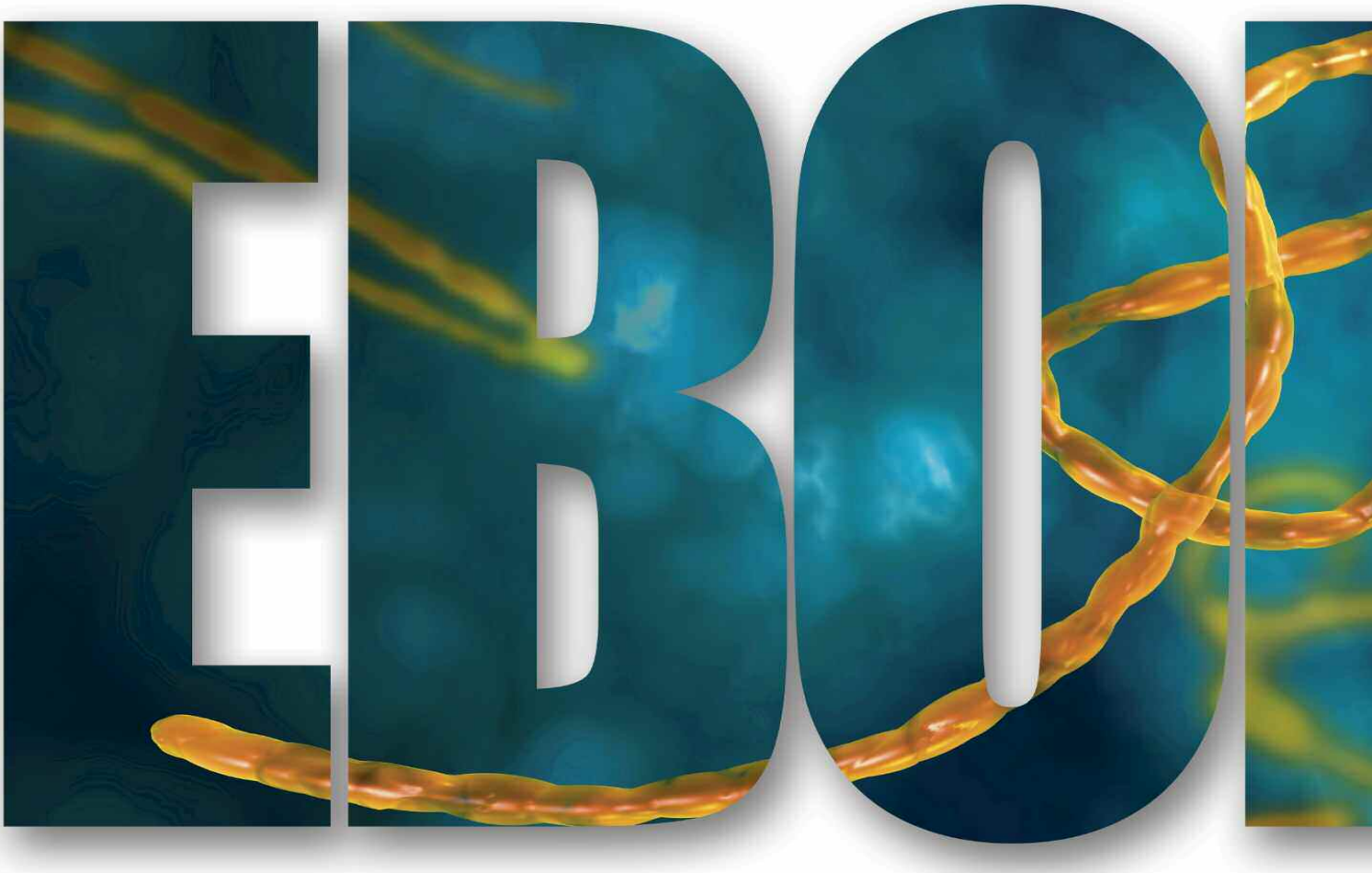
Myths and Facts:



A better understanding of Ebola, how it spreads and what's being done to curb it will help to quell the fear over this massive outbreak that has now crossed international borders.

It's being called the "deadliest Ebola outbreak in history." As of this writing, more than 14,000 people have become infected with the virus that began in four countries in West Africa, and more than 5,000 have died.[1] In August, experts at the World Health Organization (WHO) declared the Ebola epidemic an international health emergency requiring a coordinated global approach. It is a highly-infectious disease that, since November 2013, has been spreading within and, now, beyond the borders of West Africa. And, without additional interventions or changes in community behavior, the Centers for Disease Control and Prevention (CDC) estimated that the number of Ebola cases could rise to as many as 1.4 million in January.[2] But, spreading even more quickly than the virus itself is fear due to a lack of understanding about what causes Ebola and how it is spread — making the situation even more difficult to contain.

Separating Myth from Fact

Myth: All Ebola viruses are the same.

Fact: Ebola is one of five viruses that cause viral hemorrhagic fever, which takes over cells and replicates quickly, in turn "shutting down and misdirecting parts of the immune system and sending the rest into hyperdrive."[3] Four of the Ebola viruses can cause severe illness in humans and animals, and one causes illness in some animals but not in humans.[4] The five species of Ebola virus include Zaire, Bundibugyo, Sudan, Reston and Tai Forest, the first three of which have been associated with large outbreaks in Africa. The current virus in West Africa belongs to the Zaire species.[5]

Myth: This outbreak of Ebola is just like previous outbreaks.

Fact: The Ebola virus first appeared in 1976 in two simultaneous outbreaks, one in southern Sudan (now South Sudan)

By Ronale Tucker Rhodes, MS

and the other in northern Zaire (now the Democratic Republic of Congo) in a village near the Ebola River, after which it was named.[5] Prior to the current outbreak, there were 33 previous outbreaks of various Ebola viruses, all of which were contained and stopped in West Africa with far smaller death tolls than this one.[6] The current outbreak is the largest and most complex with more cases and deaths than all other outbreaks combined. It surfaced in late 2013 in Guinea in the rain forest close to the borders with Liberia and Sierra Leone.[3] And, it is spreading across land and air borders not just in West Africa,[5] but across continents, with the first reported case of Ebola diagnosed in the U.S. in September.[7] In October, the first transmission case outside of West Africa occurred in Spain when a nurse contracted the deadly virus after caring for a sick priest who had been flown back from West Africa for treatment.[8]

Myth: Ebola is a highly contagious disease.

Fact: While Ebola is extremely infectious, it is only moderately contagious. It is infectious because an infinitesimal amount can cause illness, and lab experiments show that even a single virus could cause a fatal infection. However, Ebola is not highly contagious because it is not a respiratory disease — one that can be transmitted through the air such as influenza or measles. In fact, because the Ebola virus doesn't travel far through the air like respiratory viruses, even sitting several rows away from an infectious person on a plane or in a room wouldn't put one at risk of transmission.[4] Ebola is also not a food-borne or water-borne illness, so it can't be transmitted through food or water.[9]

Ebola is introduced into humans through close contact with blood, secretions, organs or other bodily fluids of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rain forest. No one is sure when the current virus was first transmitted to humans or from what species, but it is thought to be a fruit bat.[3] The virus then spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with body fluids from an infected person, from objects (needles, sheets, clothing, etc.) contaminated by an infected person, as well as from direct contact with the body of a person who has died from Ebola. In West Africa, local customs concerning handling the dead have led to further infections. For some West Africans, the final farewell, one of the most important days of one's life, is a "hands-on, affectionate ritual in which the body is washed and dressed and, in some villages, carried through the community, where friends and relatives will share a favorite beverage by putting the cup to the lips of the deceased before taking a drink."[3]

For those who survive, Ebola remains infectious in them as long as their blood and body fluids, including semen and breast milk, contain the virus. For instance, men who have recovered from Ebola can still transmit the virus through their semen for up to seven weeks after recovery.[5,6]

Myth: Individuals who are not symptomatic for Ebola are still contagious.

Fact: Unlike measles or influenza, Ebola can't be transmitted until individuals present with symptoms. While symptoms typically appear between eight and 10 days after exposure to the virus, the actual incubation period — the time from virus infection to onset of symptoms — can span from two to 21 days. Initial symptoms of Ebola include the sudden onset of fever, fatigue, muscle pain, headache and sore throat. These are followed by vomiting, diarrhea, rash, symptoms of impaired kidney and liver function and, in some cases, both internal and external bleeding (e.g., oozing from the gums and blood in the stools).[5] Death can come within days from multiple organ failure.[3]

Myth: Ebola is easy to diagnose because those with the disease hemorrhage blood.

Fact: One of the more recognizable symptoms of Ebola is bleeding, but it doesn't always occur. That's what makes Ebola difficult to diagnose initially because in its early stages, it looks like the flu. One study found external bleeding in only 41 percent of cases.

When bleeding does occur, usually in the late stages of the disease, it happens in small amounts, and those who bleed aren't more likely to die than those who don't. Bleeding can occur externally from the eyes, nose, ears, mouth, rectum or at puncture sites such as from an IV, or it can occur internally.[6]

Ebola is diagnosed through an antibody-capture enzyme-linked immunosorbent assay (ELISA), antigen-capture detection tests, a serum naturalization test, a reverse transcriptase polymerase chain reaction (RT-PCR) assay, electron microscopy and virus isolation by cell culture. Lab findings include low white blood cell and platelet counts and elevated liver enzymes.[5]

Myth: The spread of this Ebola outbreak can't be stopped.

Fact: While there is serious concern about the spread of this Ebola outbreak, in previous outbreaks, health officials have successfully stopped the disease from spreading by finding patients, isolating them, finding everyone those original patients have contacted and keeping the patients isolated until they're no longer a threat.[6] However, there are many unique challenges to this particular outbreak. First, it wasn't until March — almost six months after the first case — that Ebola was identified as the disease in West Africa, at which time 49 cases, including 29 deaths (a case fatality ratio of 59 percent) had been reported. Second, the affected regions have impoverished healthcare infrastructures and a deep distrust of government, making it difficult for healthcare workers to carry out public health campaigns.[3] Last, the international response was delayed, giving the disease time to spread.[6]

However, in September, some scientists predicted that the outbreak would last another 12 to 18 months, which means it is expected to be contained. And, it should be noted that compared with other infectious diseases, Ebola is spreading much slower, with those infected transmitting the virus to only one or two other people on average, while each case of measles transmits to an average of 17 other people.[6] Yet, to slow the spread of Ebola and eventually stop it, the disease will need to be transmitted to fewer than one person.[3]

Myth: Ebola is a more dangerous virus than any other.

Fact: While Ebola has one of the highest death rates among infectious diseases, it kills far fewer people than many other diseases because it's not as contagious. For instance, an estimated 1.6 million people worldwide died of HIV and AIDS-related causes in 2012, according to WHO. CDC puts the average number of annual deaths from seasonal influenza in the United States somewhere between 3,000 and 49,000. CDC and WHO estimate that more than 600,000 people die each year worldwide from malaria. And, CDC reports an estimated 440,000 children who contract rotavirus die each year from complications, namely dehydration.[10]

Myth: Ebola is a death sentence.

Fact: Not everyone dies from Ebola. Throughout the history of Ebola outbreaks, the case fatality rate has hovered around 50 percent. As of this writing, the current outbreak has a case fatality rate of 53 percent.[11] Unfortunately, there is also no U.S. Food and Drug Administration-approved vaccine to prevent or drug to cure Ebola, either, although vaccines are in development and experimental drugs are being used to treat some patients. Currently, the standard treatment for Ebola remains supportive care, including balancing the patients' fluids with electrolytes, maintaining their oxygen status and blood pressure and treating them for any complicating infections.[12]

Researchers are working toward developing drugs to treat Ebola. One is ZMapp, developed by Mapp Biopharmaceutical Inc., a combination of three different monoclonal antibodies that bind to the protein of the Ebola virus. While ZMapp hasn't been tested in humans for safety or effectiveness, it has shown 100 percent effectiveness in 18 rhesus monkeys infected with Ebola.[12,13] At the time of this writing, very few doses of the drug had been manufactured, all of which had been distributed, including to two African doctors, a Spanish priest, who later died, and two U.S. aid workers, who recovered.[14]

Two doses of another experimental drug were given to the first patient diagnosed with Ebola in the U.S., who later died. Brincidofovir is an unapproved oral antiviral drug produced by Chimerix. Phase 3 clinical trials of the drug are being conducted to treat cytomegalovirus and adenovirus infections, and a Phase 1 clinical trial as a therapy for Ebola was expected to begin at the end of 2014.[15]

Finally, the National Institute of Allergy and Infectious Diseases (NIAID) has awarded $2.4 million to BioCryst Pharmaceuticals to test its experimental broad-spectrum antiviral called BCX4430 in monkeys. BCX4430 has already been successfully tested in monkeys for the treatment of Marburg.[16]

Myth: Ebola can't be prevented because attempts at developing a vaccine to date have been unsuccessful.

Fact: An Ebola vaccine may soon be reality. The National Institutes of Health (NIH) is partnering with several parties to develop an Ebola vaccine. Initial human testing of an investigational vaccine co-developed by NIAID and GlaxoSmithKline (GSK) to prevent Ebola began in September.[12] Containing no infectious Ebola virus materials, this vaccine is a chimpanzee adenovirus vector vaccine into which Ebola genes have been inserted. This gene inserts express a protein to which the body makes an immune response. Recently, it showed promise in a

primate model.[17] NIH has also partnered with a British-based international consortium to test the NIAID/GSK vaccine in healthy volunteers in the United Kingdom and in the West African countries of Gambia and Mali.[12]

NIH is also supporting Crucell's development of a multivalent Ebola/Marburg vaccine using recombinant adenovirus vector platforms and Profectus BioSciences's development of a recombinant vesicular stomatitis virus vectored Ebola vaccine. Additionally, NIH and the Thomas Jefferson University are collaborating to develop a candidate Ebola vaccine based on the established rabies vaccine.[12,17]

There also are other companies developing Ebola vaccines. With funds from the Department of Defense's Defense Threat Reduction Agency, Tekmira and Biocryst Pharmaceuticals have therapeutic candidates for Ebola in early development. The Department of Defense is also working with Newlink to develop an Ebola vaccine candidate.[12] In October, Protein Sciences announced it had been developing an Ebola vaccine with plans to deliver test samples to NIH in December.[18] And, last, Thailand's Siriraj Hospital claims it has developed a vaccine for Ebola.[19]

Dispelling the Myths Now

The only cure for Ebola right now is time. WHO released a plan to stop Ebola with a price tag of $490 million, which continues to increase as the outbreak progresses. Most of the funds will go to building treatment centers, hiring more staff and providing safe burials for victims in Sierra Leone, Liberia and Guinea — the three countries with the most infections.[20] In response, governments across the world have pitched in to help stop the outbreak.

In the U.S., efforts are being made to stop the virus from entering the country and to put plans in place for how to protect against it when it does. In October, airports in the U.S. began taking the temperatures of arriving passengers whose flight itineraries originated in West African countries.[21] Also in October, the American Association for Accreditation of Ambulatory Surgery Facilities began providing outpatient facilities with a preparedness checklist for Ebola, as well as facts about the virus.[22] And, the Centers for Disease Control and Prevention has posted a a special Web page that offers physicians the resources needed to be prepared for patients who might have the disease at www.cdc.gov/vhf/ebola/hcp/index.html.

Rapid progress is being made in the development of a drug to treat Ebola and a vaccine to protect against it. Until then, the only real way of curbing the fear about this frightening disease is to separate the myths from the facts.[1] ❖

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

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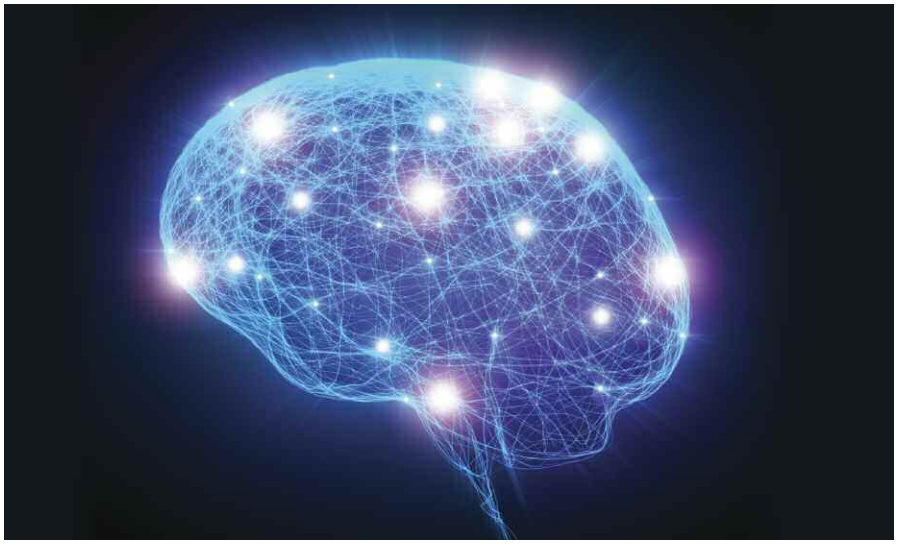
Saving the Aging Brain: Grifols Attacks Alzheimer's Disease Head-On

BY KEITH BERMAN, MPH, MBA



IT WAS OUR great fortune to have been born well into the 20th century. As recently as 1900, disease, poor nutrition and unsafe food and water limited U.S. life expectancy to less than 48 years. Since then, a myriad of 20th century advances in medicine, public health and sanitation have combined to dramatically extend average adult lifespan. People who reach 65 years of age can expect, on average, to live nearly 20 more years.[1]

But for an estimated five million Americans living with Alzheimer's disease (AD), an unrelenting decline in cognition, memory and capacity for self-care makes the last years of life anything but a blessing. Millions of others experiencing nagging signs of mild cognitive impairment must face each day wondering if they are gradually descending into a dark hell that will eventually rob them of their minds and their dignity.

Most chronic age-associated conditions are highly treatable. When diagnosed at an early stage, many are preventable, reversible or even curable. None of these positive scenarios currently applies for AD. A diagnosis cannot be made until the neurodegenerative process has advanced over many years to the point where frank evidence of dementia is apparent and much irreversible damage is done. Notwithstanding certain lifestyle choices that might mitigate disease risk (e.g., diet and exercise), Alzheimer's cannot be prevented; it will inevitably afflict one in nine persons over age 65 and one in three over age 85.[2] And once diagnosed, physicians can offer palliative drugs that may temporarily help control some symptoms, but nothing in their armamentarium to slow progression of the disease.

Numerous academic and industry teams are investigating early diagnostic tests, vaccines to delay or prevent progression to full-blown dementia, or treatments for persons already affected with mild to moderate AD. For nearly a decade, Grifols, the world's third largest manufacturer of plasma-based therapeutics and a leader in immunohematology and transfusion medicine diagnostics, has been patiently developing a novel approach to treatment of AD, based on plasma exchange and replacement with donor human albumin. Then on the eve of World Alzheimer's Day in September 2012, the Barcelona-based company announced a bold new "global" AD research and development strategy. Together with majority-owned Araclon Biotech, Grifols has committed to an extraordinarily ambitious three-pronged attack on this disease: early diagnosis, prevention and treatment.

Early Diagnosis: The ABtests

A 2004 spinoff of the University of Zaragosa, Araclon Biotech is developing two patented sandwich ELISA colorimetric test kits, dubbed ABtest 40 and ABtest 42, for direct determination of amyloid-β 40 and 42 peptides in blood. While their precise role is not fully understood, these

proteins have been clearly implicated in the pathophysiology of AD.

Many large multicenter initiatives have proposed elaborate models that exploit the most widely validated AD biomarkers — MRI, PIB-PET, FDG-PET and CSF levels of amyloid-β (Aβ), tau and phosphorylated-tau — to identify persons in early stages of AD. Unfortunately, this approach is hampered by practical considerations that severely limit their broad application. "The feasibility of these biomarkers for screening the general population once a preventive treatment has been developed also remains questionable," according to Araclon scientists.

Both because of their comparative simplicity and accumulating evidence that changes in brain Aβ are among the first detectable signs of disease onset, interest has turned to blood-based biomarkers, and the Aβ 40 and 42 peptides in particular. But different studies have yielded inconsistent results,[3,4] and variability in assay methods have been suggested as a reason.[5] Another potential confounder of these analyses is the fact that conventional tests measure only the Aβ peptides found free in plasma, which may be as little as 15 percent of total blood Aβ; the rest is bound to albumin and other plasma proteins, as well as to red blood cells.

A unique feature of Araclon's ABtest is its ability to quantify all Aβ peptide in blood — not just the free unbound portion in plasma. Using its battery of proprietary ABtest assays, the company recently identified four markers from the Aβ pool in blood that differed significantly between a group of MCI patients and a healthy control group, after adjusting for relevant demographic covariables.[6] Araclon is currently conducting studies involving more than 400 individuals with the goal of validating its ABtest kits as screening tools for diagnosis of early pre-symptomatic AD.

Active Immunization as a Preventive

In 1999, scientists at Elan Pharmaceuticals reported that injections of Aβ into a transgenic mouse model of AD resulted in virtually complete clearance of amyloid-β plaques, instantly suggesting an exciting new therapeutic approach.[7] The animals developed high titers of antibodies directed against Aβ, and in short order, Elan and Wyeth were at work on an Aβ vaccine. But the program was halted in 2002 when a few subjects experienced brain inflammation resembling aseptic meningoencephalitis, leading to the conclusion that the vaccine induced Aβ-reactive T cells that mediated widespread inflammation.[8]

More than a decade on, Araclon has readied a new and uniquely configured vaccine directed against Aβ1-40, the most abundant Aβ isoform in the brain and blood and known to form neurofibrillary tangle-like structures in persons with AD. Araclon scientists believe their ABvac40 vaccine, which consists of a short C-terminal fragment of Aβ1-40 cross-linked to a carrier protein and formulated with an alum-hydroxide gel adjuvant, will be far less apt to induce unwanted collateral effects that plagued the old Elan vaccine. Toxicology studies in rats and rabbits have revealed an excellent safety profile for ABvac40, with no signs of cerebral inflammatory activity.

In September 2013, a Phase 1 safety and tolerability study was approved by the Spanish Medicines Agency, and enrollment of patients with mild to moderate AD began in 2014. Ideally, if all goes as planned, physicians will utilize ABtest assays to help diagnose incipient disease years before progression to the clinical stage, and actively immunize these individuals with ABvac40 to prevent or delay AD.

The path to approval of the ABvac40 vaccine will be long and, given our limited understanding of AD pathophysiology, there is substantial risk that this and other prospective vaccines will come up short. Grifols and Araclon are undaunted; they have confidence in their science, and they recognize the enormity of the need. For individuals with early-stage AD and their families, the importance of a vaccine that can stave off its advance simply cannot be overstated.

The Powerful Logic of Plasma Exchange to Treat AD

The therapeutic principle underpinning Grifols' novel investigational AD treatment — essentially a modified regimen of plasmapheresis with albumin replacement — is elegantly simple and compelling. It is predicated on these observations:

- Available evidence suggests that certain Aβ peptides are neurotoxic; Aβ aggregates that accumulate as neuritic plaques are a histopathological hallmark of AD.
- It is now recognized that a chronic, mild pro-inflammatory state is correlated with the major degenerative diseases of the elderly, including AD.[9]
- Well-characterized mechanisms enable Aβ to cross from the circulation through the blood-brain barrier (BBB) into the brain, and to be cleared from the brain through the BBB and back into the circulation.
- As much as 90 percent of circulating Aβ peptide in healthy individuals is bound to albumin; albumin accounts for about more than one-half of total protein found in both blood and cerebrospinal fluid (CSF).
- Albumin undergoes glycation in normal aging, which attenuates its physiologic Aβ binding capacity; as a consequence, levels of toxic Aβ peptides may increase in the plasma and CSF.
- Glycation additionally attenuates the important antioxidant and anti-inflammatory functions of albumin.[10]
- Both brain and plasma levels of glycated albumin have been found to be significantly higher in persons with AD

than in age-matched controls.[11]

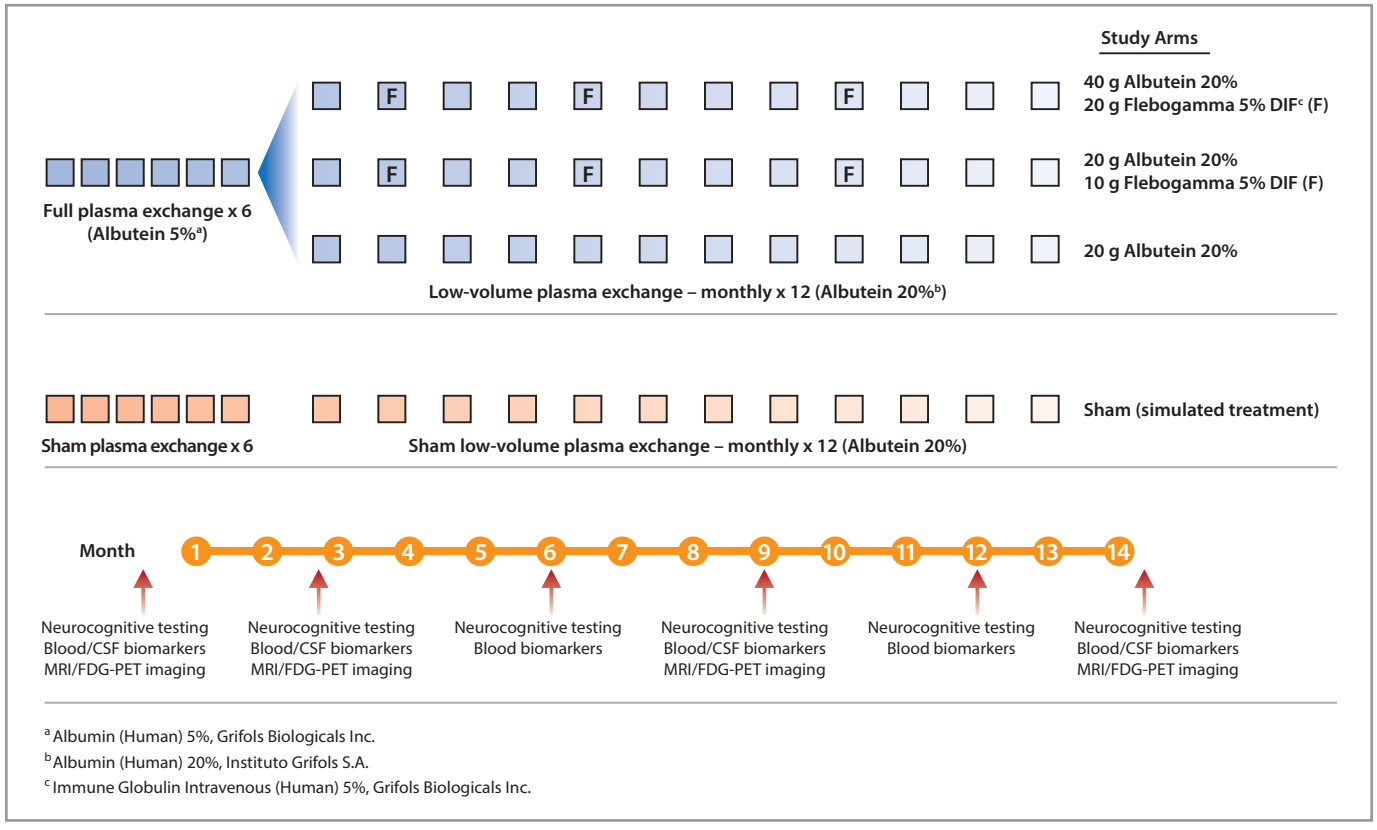
Plasmapheresis effects the removal of the patient's "old" and presumptively less functional glycated albumin, along with thousands of other plasma elements. It is replaced with five percent human albumin sourced from plasma collected from relatively young healthy adult donors. Preliminary research suggests that this purified replacement albumin retains its Aβ binding capacity but contains no quantifiable levels of Aβ. The process of albumin replacement and plasmapheresis (plasma exchange) is repeated multiple times, with the goal of reducing brain amyloid burden through exploitation of the dynamic equilibrium between brain, CSF and plasma Aβ. Each removal of old glycated, Aβ-saturated albumin from the circulation and replacement with fresh albumin acts to create a concentration gradient that promotes mobilization and transit of neurotoxic Aβ already resident in the brain and CSF across the BBB, and into the circulation until a new brain-CSF-plasma Aβ equilibrium is established.

Pilot and proof-of-principle studies. Over the last decade marked by much excitement (not to mention investor interest) surrounding large-scale clinical investigations of several highly touted monoclonal antibodies targeted against Aβ, Grifols has quietly advanced its plasma exchange/plasmapheresis research platform. In 2008, Grifols collaborator Dr. Mercè Boada and colleagues at the University Hospital Vall d'Hebron in Barcelona presented results of an exploratory study of plasma exchange in seven AD patients. At 12 months following a maximum of six treatment cycles over a 21-day period, neurocognitive retesting at 12 months revealed a strong trend toward stabilization of cognitive function. In a surprising additional finding, six of seven patients showed a significant increase in cerebral perfusion in the frontal and temporal areas of the brain.[12]

Shortly thereafter, Boada published interim results from a randomized, sham-controlled trial of 23 patients with AD, who underwent a total of 18 plasma exchange procedures in just over 20 weeks. Measured using two standard scales (ADAS-Cog and MMSE), again a trend toward cognitive function differences favoring the plasma exchange group persisted throughout treatment and continued to one year follow-up.[13]

The AMBAR trial. Having demonstrated that this procedure is feasible,

Figure 1. Grifols' Alzheimer Management by Albumin Replacement (AMBAR) Study Design



[a] Albumin (Human) 5%, Grifols Biologicals Inc.
[b] Albumin (Human) 20%, Instituto Grifols S.A.
[c] Immune Globulin Intravenous (Human) 5%, Grifols Biologicals Inc.

safe and shows promise of therapeutic benefit, Grifols initiated its pivotal Alzheimer Management by Albumin Replacement (AMBAR) study in early 2012. This ambitious clinical trial (Figure 1) reflects several significant refinements. Following an intensive treatment phase with six weekly "full volume" plasma exchanges, patients will be switched to monthly maintenance "low-volume" (650 to 800 mL) plasma exchanges (LVPEs). This faster "low volume" procedure was developed in collaboration with Fenwal, which has designed and provided a prototype plasmapheresis device specifically intended for this purpose.

A total of four study arms, including a sham treatment arm, will allow investigators to evaluate alternative 20 percent albumin replacement strategies in the LVPE treatment phase, as well as supplemental immunotherapy with intravenous immune globulin (IVIG).

Scheduled to enroll 350 subjects through the end of 2016, the AMBAR study is currently enrolling patients with probable mild to moderate AD in centers in Spain and the U.S.

When It Is Better to Partake Than to Understand

Aging is often not kind. But modern medicine has found innovative ways to replace many failing body systems: healthy transplanted organs and tissues, artificial hips and knees, insulin to replace non-functioning pancreatic islet cells, hemodialysis when kidneys can no longer filter waste products from the blood.

AD presents an unusually daunting challenge: At best, we still have only a foggy notion of its underlying pathophysiology, a reality brought into sharper focus by the spectacular failures of three humanized monoclonal antibodies along with a host of other narrowly targeted "magic bullet" treatments. But it isn't always necessary to understand, if observation teaches us how to treat. Human vaccine therapy traces its origins to the 18th century and Dr. Edward Jenner's chance observation that milk maids infected with cowpox were resistant to England's deadly smallpox epidemic; only centuries later would science explain how his crude cowpox vaccine actually works. In 1980, Swiss physicians were surprised to discover that human IVIG infusions in a boy with congenital agammaglobulinemia who happened to be also affected with immune thrombocytopenic purpura (ITP) dramatically increased his platelet counts; today, six IVIG products include an ITP indication. And, of course, plasma exchange is a standard first-line therapy for a number of serious autoimmune neurological disorders, even as its exact mechanisms of action remain a mystery.

In May 2014, Dr. Tony Wyss-Coray and colleagues at Stanford reported that exposure of old mice to plasma from young mice reversed "pre-existing effects of brain aging at the molecular, structural, functional and cognitive level."[14] Simple behavioral experiments confirmed that anatomical and biochemical changes in the hippocampus were accompanied by improved spatial learning and memory in the aged animals. "It was as if these old brains were recharged by young blood," Wyss-Coray said.

Imagine that. Well, Grifols and its research collaborators already have, applying their own twist on "young-for-old" plasma protein replacement to focus primarily on human albumin, the predominant circulating blood protein also known to be critical for toxic Aβ clearance. By the end of 2015, the company plans to present interim results from its AMBAR trial.

Should Grifols' novel plasma exchange-based approach prove to importantly slow AD progression, it could take many more years of study to elucidate exactly how it works. But we can be certain of one thing: Amid the rush to start treatment, neither affected patients nor their physicians or their loved ones will much care. ❖

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.*

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Leading Innovation and Supply Chain Safety

BY TRUDIE MITSCHANG

MAY 1, 2015, will mark a turning point in pharmaceutical supply chain security. With the phase-one implementation of the Drug Supply Chain Security Act (DSCSA), buyers and sellers of drug products will now be required to provide transactional data that will identify and trace drugs as they are distributed. (Enforcement of phase one of the DSCSA, originally scheduled for Jan. 1, was delayed until May 1.) Over a 10-year enactment period, the new law aims to ensure safe and efficient access to legitimate drugs, reduce the threat of counterfeits and facilitate more effective recalls down to the individual package level. A quick Google search of DSCSA provides numerous U.S. Food and Drug Administration (FDA) tutorials on the law's various phases and specifications, but search engines also consistently point to one trusted compliance solution provider: TraceLink.com.

As president and CEO of TraceLink, Inc., Shabbir Dahod leads a visionary team tasked with helping companies of all sizes meet the complex requirements of the DSCSA regulations. The law provides a national policy for combatting counterfeiting, theft and diversion in the pharmaceutical supply chain, and for a young company, TraceLink has quickly positioned itself as the go-to solution platform for end-to-end compliance. According to Dahod, the company's remarkable climb has been the result of innovative technology coupled with a well-defined vision and mission. "Although our company is five years old, the mission established by our core team began over a decade ago," explains Dahod. "There were 15 of us in a room discussing what we wanted this company to stand for. The vision was about building an integrated platform that would enable companies to share information, but the main focus, the human mission, was to protect patients from adulterated or counterfeit drugs."

Dahod says TraceLink employs a "people first" business philosophy that promotes transparency as one of its core values: "We are in the intellectual property business, and for me, people always come first. I look to hire the finest people and then give them operational transparency so they have access to the information they need to do their day-to-day jobs. Quality leadership comes down to this: You communicate the goals, cast the vision, create transparency and let people execute the vision to the best of their ability."

Compliance in the Cloud

Life Sciences Cloud, TraceLink's celebrated technology platform, enables manufacturers, wholesalers and pharmacies to instantly link to tens of thousands of trading partners. Built on the Amazon Web Services global cloud infrastructure, the cloud delivers on its promise to provide DSCSA compliance for all tracing, verification and serialization requirements. A single connection establishes compliance for the largest pharmaceutical company or the smallest pharmacy across all supplier and trading partner relationships. The innovative platform has been chosen by thousands of companies across the pharmaceutical supply chain, including FFF Enterprises, Inc., the nation's largest distributor of plasma products, vaccines and critical-care biopharmaceuticals. Companies like FFF have partnered with TraceLink to help streamline the compliance process and maintain uncompromised standards of patient safety and supply chain security. The platform has already been the recipient of numerous industry awards, including the Amazon AWS Global Start-Up Challenge grand prize and the Edison Award for innovation in health management. TraceLink's Life Sciences Cloud is already being used on a global scale to fight drug counterfeiting, protect product quality

Shabbir Dahod, CEO of Tracelink Inc., is spearheading a platform to meet the requirements of the Drug Supply Chain Security Act.

and reduce operational costs.

"We've delivered the only mature, field-tested platform that demonstrably minimizes the cost, risk and time involved in meeting DSCSA requirements," says Dahod. "The level of scale and complexity with track-and-trace regulations is high. Until recently, much of the supply network had been relying on paper transactions. The task at hand is to move the entire industry toward more efficient uses of technology."

The Road to Global Success

Throughout his 30-year career, Dahod has led innovation in the arenas of technology, business and management. While working at Layered Inc., he made a name for himself by developing an accounting package for the emerging Macintosh and Windows platforms. Later, he took a leap of faith and joined lead investor Paul Allen at his startup Asymetrix, establishing the company as a leader in multimedia authoring technology for computer-based learning. Dahod went on from there to lead collaboration and knowledge management initiatives at Microsoft. His career path led to several other successful start-ups, culminating in the 2003 founding of SupplyScape Corp., a leader in software solutions to safeguard the pharmaceutical supply chain. That company would provide the infrastructure that would later become TraceLink, Inc. With so many career milestones behind him, Dahod doesn't hesitate to say that it is his current endeavor that brings him the greatest sense of accomplishment. "I've been in the industry for 30 years and done everything from authoring applications to dealing with database modeling, but I think TraceLink is the achievement I'm most proud of," he says. "I feel like the human mission is really powerful — every day we know that what we are doing is going to save lives. If we are going to prosper as a society, we need to have established safety standards when it comes to the products we are consuming. I feel honored to be involved with a company that promotes both safety and innovation."

While much of TraceLink's early efforts focused on meeting the new U.S. track-and-trace requirements, the company's leading-edge technology is already leaving a significant global footprint. Looking to the future, Dahod sees TraceLink expanding throughout Europe and beyond; expansion plans are already underway in India and Brazil, with future collaborations planned in Korea, China, Singapore, Japan and Argentina. "We want to leverage this platform to drive greater efficiency within the industry," he says. "It will take significant effort, but once you are there, the opportunities are numerous."

Collaborative Leadership

According to Dahod, one of the biggest challenges during any innovation or growth phase happens internally. "You have to constantly shift and reinvent the idea, and doing so can take a toll on the team," he explains. During the initial phases of creating the TraceLink Life Sciences Cloud, for example, Dahod says he and his team met monthly to reevaluate what they'd learned and then assess what they were going to do with that knowledge. "I'm sure the team was wondering if I really knew where the product was going, and the answer at the time was no, I didn't," he says. "However, each change was methodical and based on actual input from test cases that we were running in the marketplace."

It is this type of collaborative leadership style that has driven Dahod's track record of success; the strength of his company's executive team speaks volumes about his own "lead by example" management style. For Dahod, the basic definition of leadership comes down to two words: vision and trust. He asserts that as a leader, you have to provide vision both to your customers and to the industry as a whole. Then, he explains, it is essential to build trust, whether it's with constituents, regulators or customers. "You conduct yourself with high levels of integrity and work very hard to implement the vision. You have to communicate honestly and openly at all times — we have to demonstrate leadership and then have the courage to lead." ❖

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

PTSD: A Patient's Perspective

BY TRUDIE MITSCHANG

According to the National Institutes of Health, approximately 7.7 million American adults age 18 and older suffer symptoms of post-traumatic stress disorder (PTSD). Thankfully, emerging treatments are providing relief and recovery, even in the most severe cases.

DELON BECKETT IS a soft-spoken, thoughtful man, with an easy sense of humor and a quick smile. But, less than a year ago, the married father of two was withdrawn, angry and suicidal. The Iraq War veteran was suffering from undiagnosed post-traumatic stress, and his life was slowly unraveling.

An Iraq War Veteran

Beckett began his tour of duty in August 2010, and although the 28-year-old did not see active combat, living under the constant barrage of mortar shells took an intense toll on his psyche. "When I went home on my first leave, something snapped. I was not excited to see my family, I was anxious and angry," he recalls. "When I returned, my platoon sergeant noticed a change in me and sent me to talk to one of the combat doctors."

Beckett was put on anti-depressants and anti-anxiety medication, and when his tour of duty ended, he was sent to a treatment center in Fort Irwin, Calif., for psychological evaluation. But, within two months, he was abruptly discharged and labeled "the VA's problem." "I had to wait a month to get into the VA program, and I had no access to my medications," he says. "That's when I started drinking, to cope with the withdrawal symptoms."

Beckett eventually began treatment through the VA and was prescribed a plethora of medications, including mirtazapine, bupropion and clonazepam (Klonopin) to address his depression, anxiety and sleep disorders. He also began seeing a counselor. But it was not until March 2014 that he faced the fact that he needed additional help. "The medications masked all my emotions so that all I could feel was rage," he explains "I was very withdrawn and could not handle more than a five-minute conversation with my wife. When I got word that one of my friends from my platoon had committed suicide, I hit rock bottom and wanted to kill myself too. That's when a mental health specialist employed by the VA told me about the Save a Warrior Program (SAW)."

Swapping Medication for Meditation

Started by veteran Jake Clark, the SAW program is an intensive five-day "war detox" for veterans suffering from PTSD. Featured in the CNN documentary "The War Comes Home," SAW combines an unconventional mix of equine therapy, transcendental meditation and trust-building exercises to help traumatized soldiers heal. Hosted at the scenic Big Heart Ranch in Malibu, Calif., the program has been extremely successful in providing a non-pharmaceutical model for helping traumatized veterans. The $1,200 cost of the program, which includes dormitory accommodations, is completely covered by corporate and other donations.

For Beckett (whose story is featured in the documentary), the program was transformative. He says he learned about the childhood issues that predisposed him to PTSD, and has been able to take responsibility for how his behavior has impacted his family. "It really is amazing what a horse can do for you!" he laughs. "The transcendental meditation was also incredibly impactful; since completing the program, I now meditate daily, and I believe it has kept me sober. I have not touched a drink since finishing the SAW program."

Delon Beckett is an Iraq War veteran who returned home from his tour of duty angry and suicidal.

Beckett is still in touch with his buddies, the veterans who completed the program with him, and he says the accountability and camaraderie have been a lifeline for him. He is completely off medications, continuing in family counseling, and for the first time in a very long time, optimistic about the future. "The SAW program put me on a path of self-discovery. Now I feel empowered to write my own story and pursue a career path that includes helping others," he says. "I don't have to live paranoid or self-conscious — I'm not scared anymore." ❖

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

PTSD: A Physician's Perspective

Dr. Alina Suris has developed a cellular therapy to treat PTSD for which she has won a George Winokur Research Award.

DR. ALINA SURIS is chief of psychology, mental health at VA North Texas Health Care System (VANTHCS) in Dallas. Last year, Dr. Suris and a team of researchers conducted two pilot studies exploring new ways to treat soldiers suffering from post-traumatic stress disorder (PTSD). Preliminary results show researchers were able to successfully interfere with traumatic memories at the cellular level, essentially altering the way individuals react when disturbing memories surface. While still in its infancy, the research holds promise; Dr. Suris has applied for grants from the Veterans Administration and the Department of Defense to conduct larger randomized trials. In October, Dr. Suris was the recipient of the George Winokur Research Award for her studies with PTSD.

BSTQ: Your research at the VANTHCS suggests doctors may one day be able to cure PTSD by erasing fears from a patient's mind. Tell us about that.

Dr. Suris: We're not erasing memories; we're quieting the emotions associated with those memories. You'll still have the memory, but your emotional response to that memory won't be so debilitating. For somebody with PTSD, they'll be able to remember their traumatic event, but it won't be overwhelming to them anymore.

BSTQ: Tell us about the role cortisol played in your research findings.

Dr. Suris: We know that when a traumatic memory is triggered, something happens at the cellular level. There's a chemical response that involves cortisol, a steroid hormone that is released by the body in response to stress — your heart may start to race, your palms may get sweaty. Veterans with PTSD have trouble mounting a cortisol defense to help them deal with memories that get triggered by certain cues, so our study posed the question: "What if we could interfere with that chemical response and intercept it before it really gets going?" We believe that by giving oral steroids, we may be able to supplement what the body needs to handle the traumatic memories in a more constructive way.

BSTQ: How was the study performed?

Dr. Suris: In one study, we asked veterans to write down their most terrifying battlefield experiences, the ones that inspired nightmares and invaded their daily thoughts. Those written memories were then reduced to a 30-second script that describes what happened and what the veteran was feeling in the moment. During a follow-up visit, we had them relax in a comfortable chair while wearing a headset. We administered either a glucocorticoid — a steroid medicine — or a placebo, and after a few minutes, played them an audio recording of their memory to see how they'd react.

BSTQ: What were the study's findings?

Dr. Suris: Veterans who received the steroid expressed significantly fewer PTSD symptoms, while those who were given a placebo continued to have significant symptoms such as avoiding places, people, activities or thoughts that reminded them of their trauma.

BSTQ: Can you explain the relationship between trauma and memory?

Dr. Suris: Research shows that when people have a trauma, that memory gets laid down in your brain. Then, every time you think about that memory, all those neurons and all those chemicals get excited again. And, when you're done, that memory gets laid down in the memory again.

In people without PTSD, the emotions accompanying a memory eventually fade. But for people with PTSD, the emotions don't fade and may even become more terrifying as time goes on.

BSTQ: The two most common therapies for treating PTSD are cognitive processing therapy and prolonged exposure therapy. What's the advantage of this new approach?

Dr. Suris: These are good, evidence-based therapies, and they are the best we have right now. But, what if 30 seconds and a pill would be just as effective? It would be quick, efficient and economical. Most important, it would likely be more palatable to veterans because of significantly less demand on their time in therapy. ❖

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

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BioResearch

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

IVIG and Prednisone Therapy May Improve Prospects of Live Birth in Patients with a History of Recurrent Pregnancy Loss

Danish investigators at University Hospital Copenhagen conducted a retrospective cohort study to evaluate live-birth outcomes following immunomodulation with intravenous immune globulin (IVIG) and prednisone during assisted reproductive technology (ART) in 52 patients between 2003 and 2012 with a history of at least three consecutive pregnancy losses after ART cycles. Specific ART methods included in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI). The live-birth rate per embryo transfer (ET) and cumulative live-birth rate after up to five embryo transfers was assessed in these women with recurrent miscarriage and implantation failure.

All study patients received one infusion of 24 to 25 grams of IVIG, given from five days before to one day after ET in the first IVF/ICSI cycle after referral. If the patient did not become pregnant in the first cycle with IVIG but had a new ET within three months, no further IVIG infusions were given before the next ET. If the patient did not become pregnant within three months after the first IVIG infusion, a new infusion was given in the first IVF/ICSI cycle after this period. In each IVF/ICSI cycle, 10 mg oral prednisone daily was given in accordance with a specified protocol.

Nineteen patients (36.5 percent) achieved a live birth after the first ET with immunomodulation, and a total of 32 patients achieved a live birth in the study period, resulting in a cumulative birth rate of 61.5 percent. There was no significant difference in baseline and immunological parameters between patients who achieved a live birth and those who did not. The live-birth rate after the first immunomodulated ART cycle in this patient series was higher than that reported in an earlier randomized placebo-controlled study evaluating single-therapy IVIG in Canadian patients with repeated IVF failure. The investigators speculate that the higher live-birth rate in this study could be attributable to the higher dose of IVIG or to the combined treatment with prednisone, but acknowledge that large randomized, placebo-controlled trials are needed to document the effect of isolated IVIG or combined IVIG/prednisone treatment for recurrent implantation failure.

Nyborg KM, Kolte AM, Larsen EC, et al. Immunomodulatory treatment with intravenous immunoglobulin and prednisone in patients with recurrent miscarriage and implantation failure after in vitro fertilization/ intracytoplasmic sperm injection. Fertil Steril *2014 Sep 23 [Epub ahead of print].*

Switching to Recombinant Factor IX Fusion Protein (rFIXFc) Results in Reduced Consumption and Lower Bleeding Rates

Transitioning from a prophylaxis regimen with conventional recombinant factor IX (rFIX) or plasma-derived factor IX (pdFIX) to prophylaxis with a recently approved long-acting recombinant factor IX fusion protein (rFIXFc, Alprolix) was associated with an overall 52 percent reduction in median weekly factor IX usage, according to an analysis of 26 children ≤12 years of age with severe hemophilia B. Median weekly consumption was reduced from 80.4 IU to 38.6 IU per kilogram (kg) of body weight (P <0.001). A subgroup analysis revealed that median pre-study weekly consumption was 105.1 IU/kg and 54.5 IU/kg for subjects using pre-study rFIX or pdFIX, respectively, which were respectively reduced to 42.5 IU/kg (P<0.001) and 37.6 IU/kg =0.110).

The most common pre-study dosing interval with conventional rFIX or pdFIX was twice weekly (73% of enrolled subjects). Subjects then initiated rFIXFc prophylaxis at a starting dose of 50 IU/kg every seven days; the dose was subsequently adjusted to maintain trough levels of 1 percent to 3 percent, or as clinically indicated. The annualized bleeding rate was reduced from 5.5 events pre-study with rFIX or pdFIX to 2.9 events on-study with rFIXFc (p=0.047).

Population pharmacokinetic modeling predicted that, in 95.4 percent of individuals receiving rFIXFc once weekly, factor IX levels would not dip below 1 percent at any time, compared with only 31.3 percent of individuals taking rFIX. This study was supported by the manufacturer of Alprolix (Biogen Idec), and study findings were presented by Biogen Idec investigators.

Powell J, Shapiro A, Ragni M, et al. Switching to recombinant factor IX Fc fusion protein prophylaxis results in fewer infusions, decreased factor IX consumption and lower bleeding rates. Br J Haematol *2014 Sep 11 [Epub ahead of print].*

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.

DNA-Based Diagnoses in Minutes

QuantuMDx Group has successfully produced its first fully integrated sample-to-result working prototype of Q-POC, a handheld lab that provides health workers with a tool to diagnose, manage, monitor and track emerging infections and drug resistance, and delivers DNA-based medical diagnoses in minutes. To run a sample-to-result molecular diagnostic test, the technician inserts a sample into the disease-specific cartridge, inserts the cartridge into Q-POC and presses the "Go" button on the touchscreen. Results and drug resistance information are displayed in 10 to 15 minutes, enabling immediate treatment and containment of infections. Each test costs just $5 to $20 depending on its complexity. It is designed for use in remote or resource-scarce settings, with no need for a stable electricity source or clean water. It features a user-friendly design with an intuitive touchscreen display and single-button operation and all reagents on board the disposable test cartridge.

QuantuMDx, (770) 321 8439, www.quantumdx.com/devices.html

Track Fitness with a Smartwatch

Apple's new smartwatch, named the Apple Watch, is a miniature computer that features a rectangular screen and a flexible design and comes in two sizes. A crown on the side acts as a digital dial, which can be turned to zoom in, and tapping the crown returns to the main menu. The watch can be attached to six strap styles, including a sport model. It relies on inductive charging (a form of wireless charging that requires a magnet that attaches to the back of the watch from another device) to replenish the battery. The smartwatch can run various apps such as a calendar, map navigation and a music player, and it includes Siri, Apple's tool for controlling the device with voice commands, which is activated by pushing on the crown. The watch will have a strong focus on health with an app called Fitness, which tracks statistics for different exercises, an accelerometer to track movements and a heart rate sensor to help measure intensity of workouts. Three versions of the watch will become available in 2015, including the Apple Watch, Apple Watch Sport and Apple Watch Edition, with pricing starting at $350.

Apple, (800) 692-7753, www.apple.com/watch

Dispose of Medicines Safely

The Pill Terminator is a safe, easy and affordable way to eliminate unwanted and unused prescription drugs. At approximately the size of a soft drink, it can eliminate up to 300 medium-sized pills or equivalent (capsules, liquids and powders). It uses a three-step procedure: pour in medications, add warm water and shake, and throw the container in the trash can. The Pill Terminator meets U.S. Food and Drug Administration and Environmental Protection Agency guidelines for disposal of prescription medications.

Pill Terminator, (732) 952-8800, pillterminator.com

More Plasma Rich Platelets

The new PRP (plasma rich platelets) kit is designed for use by orthopedists, veterinarians, dermatologists and plastic surgeons for use in shoulder, tendon and knee repairs, wound care and cosmetic procedures for acne scars, wrinkles, facial folds and hair loss. The kit is designed to be easier to use and more affordable. It fits most centrifuges and provides 1.2 million to 2 million platelets per micro liter, which is twice compared with other brands.

Physicians Products, (866) 704-8572, www.prpkits.com

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Ebola Information for Healthcare Workers and Settings

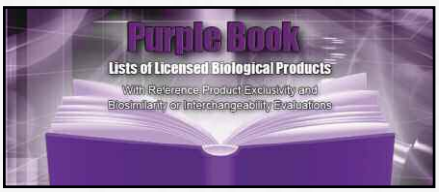
Author: Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) has posted a Web page that provides physicians with the resources needed to be prepared for patients who might have Ebola. Included are links to pages on guidance and recommendations, patient evaluation, laboratory, protecting healthcare workers, diagnosis and general information.

www.cdc.gov/vhf/ebola/hcp/index.html

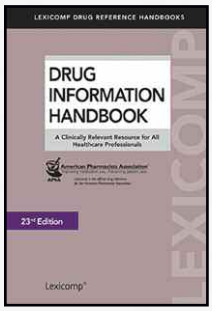
Purple Book

Author: U.S. Food and Drug Administration



Officially called the *Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, the Purple Book is a reference list for biologics that lists all brand products and any biosimilars with which they are interchangeable. Every biologic product is listed in the book along with date of licensure, whether it was evaluated for reference product exclusivity and when that exclusivity expires. The book also identifies whether the product is biosimilar to or interchangeable with another therapy. FDA will periodically update the book, which consists of two separate lists for the products overseen by the Public Health Service Act: one for biologics regulated by the Center for Drug Evaluation and Research and the other for those overseen by the Center for Biologics Evaluation and Research.

www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm



Drug Information Handbook, 23rd Edition

Author: Lexicomp

The 2014-2015 edition year of the *Drug Information Handbook*, now in its 23rd edition, follows a dictionary-like format with drug products organized alphabetically and cross-referenced by U.S. and Canadian brand names and index terms. Clinicians have access to more than 1,500 drug monographs, each offering up to 40 fields of information specific to a particular medication. New for this edition are 41 new drug monographs, two new fields (usual infusion concentrations pediatric and adult), nine new appendix topics (topical corticosteroids, injectable agents [non-insulin] for type 2 diabetes, oral anticoagulant comparison chart, oral antidiabetic agents comparison table, oral antiplatelet comparison chart, antithrombotic therapy in patients with atrial fibrillation, treatment of elevated INR due to warfarin, insulin products and reversal of oral anticoagulants) and four appendix updates (29 new drug monographs, new fields, renal function estimation in adult patients and immunization recommendations).

webstore.lexi.com/Store/Reference-Handbooks-for-Physicians/Drug-Information-Handbook

The Impact of Off-Label Promotion on Product Liability

Author: U.S. Food and Drug Administration

This report lays out a risk-management approach that addresses product liability concerns associated with off-label promotion in six key areas: policies and procedures, social media, compensation, training, monitoring and corrective action. It discusses what triggers 90 percent of product liability cases (it's not manufacturing or design flaws); common mistakes that lead to "failure to warn" claims in product liability lawsuits; how liability can arise even if your promotion includes warnings; how off-label promotion undermines the "learned intermediary" doctrine; why it's critical to inform doctors of product risks without promoting off-label uses; how FDA requirements differ from product liability laws; how to respond to unsolicited requests for off-label information; and more.

www.fdanews.com/products/48631?hittrk=14N21&utm_source=Real%20Magnet&utm_medium=Email&utm_campaign=58190956

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective January 1, 2015 through March 31, 2015.

Product	Manufacturer	HCPCS	ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$76.94	$75.70
CARIMUNE NF	CSL Behring	J1566	$53.46	$52.60
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$72.28	$71.12
GAMMAGARD LIQUID	Baxter	J1569	$78.31	$77.05
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$53.46	$52.60
GAMMAKED	Kedrion	J1599	$80.44	$79.15
GAMMAPLEX	Bio Products Laboratory	J1577	$71.83	$70.68
GAMUNEX-C	Grifols	J1561	$80.44	$79.15
OCTAGAM 5% & 10%	Octapharma	J1568	$77.74	$76.49
PRIVIGEN	CSL Behring	J1459	$73.31	$72.13

*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% DIF Liquid	Grifols	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			0.5 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, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PIDD	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Baxter	SCIG: PIDD	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 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 mL multi-dose vial	9 years and older*	90658/Q2035
		0.5 mL single-dose syringe		90656
GlaxoSmithKline	FLULAVAL (IIV3)	5 mL multi-dose vial	3 years and older	90658/Q2036
	FLULAVAL QUADRIVALENT (IIV4)	5 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 mL multi-dose vial	4 years and older	90658/Q2037
		0.5 mL single-dose syringe		90656
	FLUCELVAX (ccIIV3)	0.5 mL single-dose syringe	18 years and older	90661
Protein Sciences	FLUBLOK (RIV3)	0.5 mL single-dose vial	18 years and older	90673
Sanofi Pasteur	FLUZONE (IIV3)	5 mL multi-dose vial	3 years and older	90658/Q2038
			6-35 months	90657
		0.5 mL single-dose syringe	3 years and older	90656
	FLUZONE QUADRIVALENT (IIV4)	5 mL multi-dose vial	3 years and older	90688
			6–35 months	90687
		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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