

WINTER 2016

biosupplytrends

Special Focus: PLASMA

QUARTERLY

Biosimilars

Policy-Making Debate



The Role of
Nurse Practitioners in
the Healthcare System

The Growing Threat
of Superbugs

Myths and Facts
About Alzheimer's

Immunodeficiency
in Older Adults:
Case Studies

BabyBIG:
The Lifesaving Drug
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8 Critical Steps



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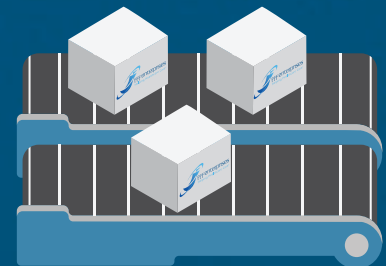


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About BioSupply Trends Quarterly

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Leveraging the Benefits of Biologic Medicines



PATIENTS DIAGNOSED with some of the most perplexing diseases — autoimmune disorders, cancer, immunodeficiencies — have few treatment options that work as well as biologics, the genetically engineered medications made from living organisms and their products, such as human and animal proteins. Typically injected or administered intravenously, biologics are by far some of the most expensive medications, costing patients upwards of \$45,000 a year. According to *World Biological Drugs Market 2013-2023*, published in May 2013, the world biological drugs market is estimated to top \$178 billion in 2017.

It's no wonder, then, why there is such a push to develop biosimilars, the cost-effective alternatives to biologics. After all, they are predicted to cost 20 percent to 30 percent less than their reference biologic products. What's even more important, with growing worldwide demand for biologics, biosimilars promise greater availability and increased treatment options. But, their introduction is not without challenges. In our cover feature "Future Biosimilars: Pros and Cons," we delve into key issues surrounding the U.S. Food and Drug Administration (FDA) policy-making decisions that are at the heart of the biosimilars debate. As FDA publishes its rules regarding biosimilars, at stake is their efficacy and safety that will be determined by the stringency of testing and dispensing requirements.

Also in this issue, we highlight a few disease states that are treated with specialty plasma products. The first, primary immunodeficiency disease (PI), comprises at least 176 hereditary disorders. According to the Immune Deficiency Foundation, some 50,000 individuals in the U.S. have been diagnosed with a PI. In our Patient and Physician Focus columns, we profile Brandon Dillon who was diagnosed in 2010 with the most common form of PI, common variable immunodeficiency. Brandon discusses how

he was ultimately diagnosed and how, with immune globulin therapy (a human plasma protein biologic) and great determination, he has gone from suffering recurrent illnesses to running marathons. On the flip side of Brandon's story, Dr. Terry Harville, immunologist and leading expert in the treatment of PI, discusses why he chose this specialty and how biologic therapies have evolved over the years to allow PI patients to lead relatively normal and active lives.

PIs typically are diagnosed when individuals are age 40 and under; however, it isn't uncommon for older adults to also be diagnosed with PIs, as well as secondary immunodeficiencies, many of which are also treated with biologics. In "Immunodeficiency in Older Adults," Dr. E Richard Stiehm, immunologist and professor of pediatrics, outlines case studies of the diagnosis of immunodeficiencies in seven older adults and how, in many of them, biologic therapies resulted in a positive prognosis.

Lastly, our article "BabyBIG: Definitive Early Immunotherapy for Infant Botulism," describes the 15-year effort to develop a hyperimmune globulin that spares infants long hospital stays and lengthy recovery periods complicated by serious adverse events. Discovered in 1976 as an entirely new disease pathway, infant botulism was found to infect infants lacking the adult bacterial flora to fight the disease, after they swallowed a few spores of *Clostridium botulinum*. Today, a single infusion of BabyBIG given to infants with laboratory-confirmed infant botulism neutralizes the neurotoxin.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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.

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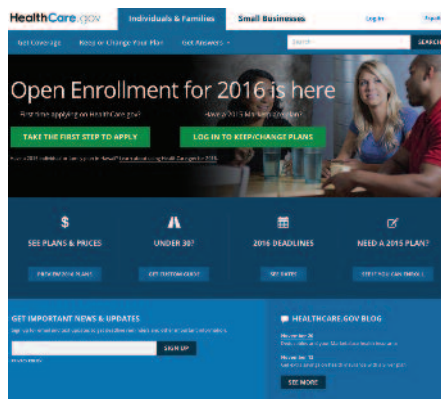


In October, President Obama signed a bill into law that will compensate patients for participating in clinical studies of rare diseases. An update to a 2009 law, the Ensuring Access to Clinical

Trials Act of 2015 will allow patients with rare diseases to collect up to \$2,000 per year without the compensation counting as income that could jeopardize eligibility for Supplemental Security Income and Medicaid. According to the National Organization for Rare Disorders, only a few hundred of the roughly 7,000 rare diseases in the U.S. have U.S. Food and Drug Administration-approved treatments.

The 21st Century Cures Act, which passed the House in May, also contains separate incentives for development of drugs for rare diseases. And, comparable legislation is being crafted by the Senate HELP Committee. ❖

Healthcare.gov Now Features Window Shopping Upgrades



Healthcare.gov, the main entry point for people seeking insurance in 38 states served by the federal exchange, features three new window-shopping features. The first allows consumers to see an estimate of total yearly costs for each health plan based on factors such as age, sex, income, ZIP code and how much

healthcare they expect to use. The cost-comparison tool takes into account premiums, as well as cost-sharing for services like office visits and the deductible. Since most people look only at premiums, this tool will be especially helpful for people with chronic illnesses who require regular follow-up by doctors and who might be better off paying a higher monthly premium for a plan with lower out-of-pocket costs.

A second feature allows individuals to enter the names of doctors and hospitals to receive a list of health plans in which those providers are in-network. Previously, consumers had to visit each insurer's website to determine which doctors and hospitals were in-network. And, a third feature allows people to find health plans that cover their prescription drugs. The open enrollment period for health plans on the exchanges opened Nov. 1 and closes Jan. 31. ❖

Senate's FDA Funding Bill Falls Short of What Was Requested



In July, the U.S. Senate Appropriations Committee approved the fiscal year 2016 appropriations bill to fund the U.S. Food and Drug Administration (FDA) but at levels far below what President Obama requested. The bill provides FDA with \$2.6 billion in discretionary funds, which is \$107 million less than proposed. Combining that with user fees, total FDA funding will be \$4.6 billion, an increase of \$116 million over fiscal year 2015.

The Senate's numbers are in line with those passed by the House Appropriations Committee. Under the House version, user fees for prescription drugs will increase from \$78 million to \$826 million, generic drug fees will increase from \$312 million to \$320 million, and biosimilars and biologicals will increase from \$21 million to \$21.5 million. A breakdown of user fees was not provided. The Senate bill also includes \$3 million to combat antibiotic resistance and \$2 million for the Precision Medicine Initiative (\$12 million and \$8 million less than requested, respectively). ❖

Federal Funds for Coordinated Care Go Unclaimed

Doctors who care for tens of millions of chronically ill Medicare patients are failing to take advantage of federal dollars intended to improve care and reduce hospital readmissions and overall costs, according to the Centers for Medicare and Medicaid Services (CMS). In 2015, the federal government began paying an average of \$42 per patient per month for non-face-to-face chronic-care management services such as consulting with other doctors caring for the same patient. But, according to CMS estimates, while 70 percent of Medicare beneficiaries (roughly 35 million) are eligible, reimbursement requests have been received for only 100,000 of them to date. And, that number could be even lower since some of the claims could be duplicates.

A number of possible reasons for not participating in the program have been suggested. First is that physicians must



get permission from patients who are responsible for a 20 percent co-pay each time the provider bills for services. A second is that CMS hasn't provided information on how to properly bill

under the codes. And, a third is a concern that the documentation workload to participate is not worth it for the money they would receive. However, a study from the Stanford University School of Medicine conducted in September, which looked at how much chronic-care management could affect the typical primary care practice, found substantial increases in annual revenue could be gained each year (as much as \$77,295) if practices used registered nurses to conduct annual wellness visits and used other staff to handle more frequent management. Another study by Smartlink released in October found that less than 20 percent of 300 physicians interviewed are currently participating in the chronic-care management program. But, those who are participating believe it is improving patient care. ❖

Federal Government Releases Claims and Payment Data

In an effort to make the opaque U.S. healthcare system more accountable, the federal government continues to release Medicare claims and payment information. The most recent reporting centered on 2013 Medicare Part D drug spending, inpatient and outpatient hospital charges, and payments to physicians. The goal of releasing the information is to give the public an opportunity to see how the government manages pharmaceuticals for seniors, as well as “facilitates a vibrant health data ecosystem, promotes innovation and leads to better-informed and more-engaged healthcare consumers,” said Niall Brennan, the Centers for Medicare and Medicaid Services’ (CMS) chief data officer.

CMS reported that in 2013, Medicare’s Part D prescription drug program spent \$103 billion. The data show the names, locations and specialties of physicians

and healthcare organizations who submitted drug claims to Medicare, as well as the names, costs and number of prescriptions for each individual drug. Medicare is projected to absorb \$76 billion of taxpayer money in 2015 (about 12 percent of Medicare spending) after accounting for premiums seniors pay, according to the Congressional Budget Office.

In June, CMS released three new sets of data. The latest data show what hospitals charged and what Medicare paid those hospitals for 100 of the most common inpatient stays and the 30 most common outpatient procedures. The inpatient data cover more than seven million discharges and \$62 billion of Medicare money. Physician data encompass 950,000 physicians, nurse practitioners and other providers and \$90 billion of Medicare funds. Spending on hospitals



and physician services makes up a majority of U.S. healthcare expenses. ❖

The Shift to Payment for Value Continues: OPPTS 2016 Final Rule

THE SHIFT TO ICD-10 that began Oct. 1 and the continuing shift in reimbursement models toward payment for value versus traditional fee-for-service have resulted in significant payment changes. Recently, the Centers for Medicare and Medicaid Services (CMS) issued the final 2016 hospital outpatient prospective payment system (OPPS) and ambulatory payment classification (APC) system policy changes and payment rates rule with comment period [CMS-1613-FC] on Oct. 30, 2015.

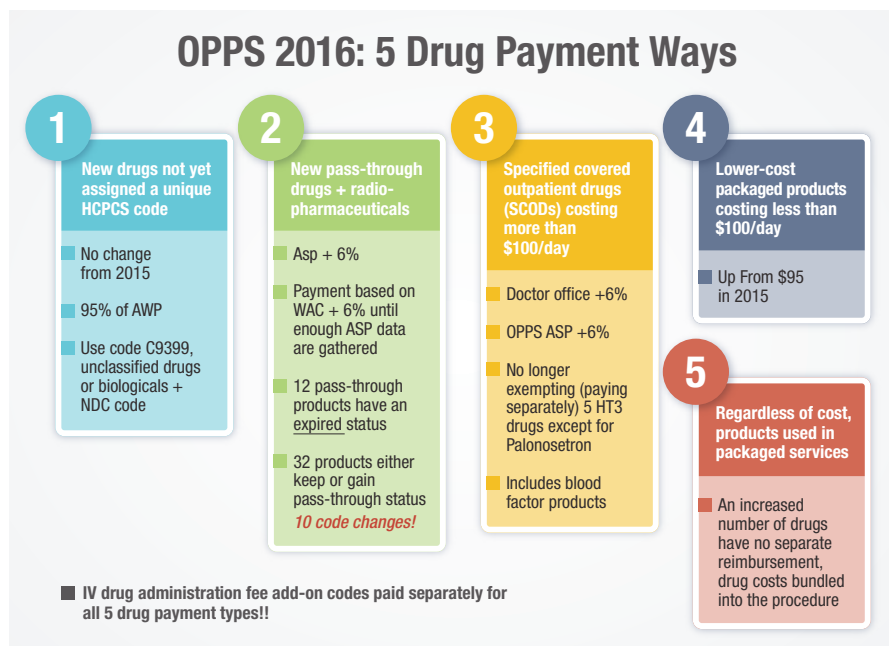
The OPPTS covers all outpatient services offered by a facility. Under the OPPTS, averaging is used to establish a payment rate that may be more or less than the estimated cost of providing a specific service or bundle of specific services for a particular patient. This occurs when data from higher-cost cases requiring many ancillary items and services is merged with data from lower-cost cases requiring fewer ancillary items and services. The packaged pricing includes all items and services that are typically integral, ancillary, supportive, dependent or adjunctive to a primary service. What is key to understand is that new rates are based on claims data whether for bundles or fee-for-service. Submitting missing or inaccurate data will result in an artificially low rate the next payment year.

Following are the changes under the final 2016 OPPTS rule. Understanding these changes is essential since many commercial payers base their decisions on those made by CMS, and all code sets and descriptions are universal to all payers.

Drug Reimbursement in 2016

As shown in Figure 1, drugs, biologicals and radiopharmaceuticals will continue to be reimbursed in one of several ways:

Figure 1.



as pass-through drugs, as separately payable drugs and as nonseparately payable products that are bundled or packaged into the reimbursement for the service or procedure. Bundling or packaging means there is no separate identified payment for the product, and disbursement of the bundled payment is left to the discretion of the facility. Because the category of pass-through drugs is designed for new products, the list is not static, and each year a number of products are added or removed with code (16 for 2016) and status indicator (SI) changes (Table 1).

Specific Covered Outpatient Drugs (SCODs)

Specific products costing more than \$100 per day (up from \$95 in 2015) with defined Healthcare Common

Procedure Coding System (HCPCS) codes, some of which may be brand-specific, fall into the SCOD group. Reimbursement is based on converting the actual dose of the drug given into CMS-defined billing units that are reimbursed at the 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 2016, calculations do not include the 340B sales price. Since billing unit calculation errors remain the biggest CMS-identified error, providers should carefully examine the conversion of doses into billing units. If billing units are underreported, facilities will receive less money since it

misrepresents what it actually costs to treat a patient. Providers need to remember that all claims data are subsequently used to determine future rates.

What's Bundled and What's Not

There are two different types of bundles under which drugs, biologicals and radiopharmaceuticals fall. The first and easiest to understand is the nonseparately payable category that is based on the drug cost as defined by CMS (not by what is actually paid or charged). In 2016, the cut-off rose to \$100 per day. The second type is defined by services or procedures that include certain drugs regardless of cost. Correctly disbursing funds internally from this ever-growing category has important implications.

Restructuring of APCs. CMS annually reviews and revises the OPSS APC groups to consider changes in medical practices and technologies and the addition of new services and cost data or other relevant information. This year, CMS has restructured, reorganized and consolidated APCs to create nine clinical APC families that will

include various surgical and diagnostic procedures.

Comprehensive APCs (C-APCs). C-APCs are APCs that provide for an encounter-level payment for a designated primary procedure, plus all adjunctive and secondary services provided in conjunction with the primary procedure. The current 25 C-APCs mostly include procedures for the implantation of costly medical devices. For 2016, CMS has added nine new C-APCs, including some surgical APCs and a new C-APC for comprehensive observation services. CMS also is collecting data through the use of an HCPCS modifier on all services related to a C-APC primary procedure that are reported on a separate claim. This data collection allows for the assessment of the costs of all adjunctive services related to C-APC services, even if reported on a separate claim.

To reiterate, the concept of packaging or bundling refers to all-inclusive Medicare payments for some of the most common tests and procedures instead of paying for the components separately. There are two major paths to

the march toward a true OPSS: 1) packaged payments for C-APCs within “clinical families,” and 2) packaged payments for certain ancillary services that are integral, supportive, dependent or adjunctive to a primary service. As expected and consistent with the trend set in past years, CMS is proposing to package more services into composite APCs. What this means for pharmacies is that effective Jan. 1, hospitals won't receive separate payment for abciximab, bivalirudin or mitomycin ophthalmic when administered to a patient receiving a comprehensive service, regardless of pharmaceutical cost.

Under the C-APC payment policy, a single payment for each of the 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

Table 1. Drugs and Biologicals with Pass-Through Payment Status 2016 and HCPCS Code Changes

CY 2015 HCPCS Code	CY 2016 HCPCS Code	CY 2015 Long Descriptor	CY 2016 SI	CY 2016 APC
C9022	J1322	Injection, elosulfase alfa, 1mg	G	1480
Q9970	J1439	Injection, ferric carboxymaltose, 1mg	G	9441
C9023	J3145	Injection, testosterone undecanoate, 1mg	G	1487
C9134	J7181	Injection, Factor XIII A-subunit (recombinant), per i.u.	G	1746
C9133	J7200	Factor IX (antihemophilic factor, recombinant) Rixibus, per i.u.	G	1467
C9135	J7201	Injection, Factor IX, fc fusion protein (recombinant), per i.u.	G	1486
C9021	J9301	Injection, obinutuzumab, 10 mg	G	1476
Q4121	Q4121	Theraskin, per square centimeter	G	1479
C9136	Q9975	Injection, Factor VIII, fc fusion protein (recombinant), per i.u.	G	1656
C9448	Q9978	Netupitant (300 mg) and palonosetron (0.5 mg)	G	9448

Table 2. New and Revised POS Codes Effective Jan. 1, 2016

Code	Descriptor
<ul style="list-style-type: none"> • POS 19 (new) Off Campus Outpatient Hospital 	A portion of an off-campus hospital provider based department that provides diagnostic, therapeutic (both surgical and nonsurgical), and rehabilitation services to sick or injured persons who do not require hospitalization or institutionalization.
<ul style="list-style-type: none"> • POS 22 (revised) On Campus Outpatient Hospital 	A portion of a hospital's main campus that provides diagnostic, therapeutic (both surgical and nonsurgical), and rehabilitation services to sick or injured persons who do not require hospitalization or institutionalization.

pass-through payment status and those drugs 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 continuing 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 the drug administration fee codes. It's essential that these are correctly applied with the required documentation in place and that it is traceable through the revenue cycle without problematic hard stop edits. It might help if providers use an electronic medical administration record or electronic health record to create accurate documentation, as well as a decision tree that shows which codes apply to which products.

Providers need to remember that they must bill for the drug administered (even if it won't be paid separately) for drug administration fees to be paid. This applies to white-bagged drugs, zero-priced drugs (such as patient assistance supplied drugs) and all drugs

where packages and bundles apply. Providers should also be aware of the 2016 APC renumbering that applies to each of the drug administration codes. They should also be aware that "chemo" includes traditional chemotherapy, immunotherapy, biologics and biosimilars (all considered complicated).

Changes to Place of Service (POS) Codes (MLN Matters number MM9231)

The POS code set provides care-setting information necessary to appropriately pay Medicare and Medicaid claims. To differentiate between on-campus and off-campus provider-based hospital departments, CMS has created codes for each effective Jan. 1 (Table 2). This code set was precipitated by the ever-increasing trend of hospitals purchasing specialty physician practices and then raising the prices for care to the extent that federal regulators opted not to turn a blind eye to the tactics.

A rare bipartisan budget agreement reached in late October included many automatic cuts. Due to reductions in Medicare payments for hospital-owned outpatient centers, payments would have to be at the lower outpatient fee schedules for physician offices and clinics. However, reductions would be only for new acquisitions; medical practices and clinics previously acquired or opened by hospitals would continue to be reimbursed at the higher rates, which was a compromise from the original proposal of capping all outpatient care delivered at hospital sites at the lower rates.

For pharmacists, this classification provides a clear pathway for data collection on pricing practices used in the two settings, especially when combined with 340B status. These codes are in response to CMS' plan to gather information on provider-based services. Effective Jan. 1, hospitals must start using a new modifier when billing for services rendered in provider-based departments, and physicians will use one of the two new POS codes. The mandate is seen as a possible precursor to reductions in payments to provider-based departments, which are higher than payments to freestanding clinics for the same services. See tinyurl.com/nv39mur for more details.

Providers should discuss with finance and revenue cycle teams the need for transparent, realistic and defensible pricing of at least the pharmacy and drug administration components of the charge description master. If a facility participates in the 340B program, it needs to ensure that all requirements are being met and that there is a clear understanding of the eligible patient definition that is supported by the IT infrastructure.

NOTICE Impacts Observation Patients

The Notice of Observation Treatment and Implication for Care Eligibility (NOTICE) Act requires hospitals to provide Medicare beneficiaries with written notification and a related verbal explanation at discharge or within 36 hours, whichever is sooner, if they

receive more than 24 hours of outpatient observation services. This applies to all Medicare patients when they receive observation care but aren't actually admitted to the facility. Unfortunately, this rarely happens now, and most patients are shocked when they receive their medical bills.

The new requirements stipulate that the notification must explain in easy-to-understand language why the patient was admitted to observation and the potential financial implications. The implications are more than just the hospital charges, since older adults admitted for observation often must pick up the costs of additional care at a skilled nursing facility. Medicare only covers those costs if the inpatient stay is at least three consecutive days, not counting observation days.

The Act also affects the packaging of observation services, which requires a new observation C-APC and inclusion into the payment virtually all associated services such as the emergency room visit, labs and radiology, including infusions and injections. Payment for observation services is \$2,111 with a new status indicator: J2.

For the pharmacist, this proposed rule has many implications, from re-examining drug distribution practices for observation patients to a revenue cycle standpoint and bundled payment fund distribution. Providers in facilities in the 340B program will need to pay attention to the implications of this proposed rule as well, much in the same way they do for surgical and diagnostic or treatment center locations serving both inpatients and outpatients. Managing utilization and controlling costs will be essential.

Bundled Payments for Knee and Hip Replacements

For knee and hip replacement surgeries, there is a unique five-year pilot program

for bundled payments that encompasses 75 different areas of the country and more than 800 hospitals. The program requires hospitals to partly repay the government if patients contract avoidable infections and other complications; rewards with extra payments if patients do not; treats the surgeries as one complete service instead of a collection of individual services; and holds hospitals accountable for care up to 90 days after discharge. More details can be read about this program at goo.gl/ZurYux. Robust information technology and revenue cycle infrastructures are essential to provide the crucial analytics that will be necessary for this program.

Medicare Add-On Payments to Hospitals for New Technology

Medicare covers costly treatments for chronic conditions treated in the inpatient setting through add-on payments that are petitioned by the drug manufacturer. The latest approval was given to Blincyto (Amgen) when CMS decided that the drug was a significant improvement over existing treatments. The new rule, published in the Federal Register on Aug. 17, explains that Medicare will allow for a “new technology add-on payment” to hospitals for a portion of that amount, up to \$27,000. The actual payment will depend on the duration of a patient's hospital stay.

New Rules Designed to Control Costs, Improve Quality

Payers, including CMS' Medicare program, are experimenting with a variety of payment initiatives that bring providers on board as partners to control costs while improving quality and member satisfaction. The models have a variety of names such as bundled payments, consolidated payments, payments for episode of care, a bundle of once-a-month, incremental

payment, new patient payment or patient month payment. They're all designed to replace traditional fee-for-service payments that pay for charges, including drugs, on a line-item basis. CMS describes their program as “packaged services in composite ambulatory patient classifications (APCs).” Regardless of the name being used, the basic principle remains the same: a fixed inclusive payment for a defined treatment or procedure or condition that is based on cumulated historical payments gleaned from claims data, as well as best practice from other sources.

If these initiatives are based on accurate data, are well-designed and effectively implemented, they should be able to reward effective 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 to accomplish this.

Of course, an accurate procedure-specific tally is essential. Actual payment is based on cumulated claims data from years past and may be adjusted for several factors. The accuracy of billing, the skill of the revenue cycle team and the robustness of the IT infrastructure are all coming into play as these rates are determined. ❖

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Correction

Incorrect Statistic Reported in Fall Issue of *BioSupply Trends Quarterly* Magazine

In the Fall 2015 issue of *BioSupply Trends Quarterly* on page 31 of the feature "The Perfect Storm for Patient-Centered Clinical Trials," it was incorrectly stated that "ResearchMatch now hosts 8,766

volunteers from 5,890 unique conditions and 832 rare conditions." That should read "ResearchMatch now hosts more than 84,000 volunteers from 5,890 unique conditions and 832 rare conditions." ❖

Research

FDA Approves NUWIQ to Treat Hemophilia A



Octapharma's NUWIQ, antihemophilic factor (recombinant), an intravenous therapy for adults and children living with hemophilia A, has been approved by the U.S. Food and Drug Administration (FDA). The approval includes on-demand treatment and control of bleeding episodes, routine prophylaxis to reduce the frequency of bleeding episodes and perioperative management of bleeding. NUWIQ is the first B-domain deleted recombinant factor VIII derived from a human cell line, not chemically modified or fused with

another protein.

The approval is based on positive results of clinical studies. An initial global study for NUWIQ of 22 (20 adults and two adolescents) previously treated patients using a one-stage clotting assay demonstrated a mean half-life of 17.1 hours in adults, 11.9 hours in children ages 2 years to 5 years, and 13.1 hours for children ages 6 years to 12 years. A second set of global clinical studies for NUWIQ evaluated the overall efficacy and tolerability in three prospective, open-label studies in previously treated patients with severe hemophilia A. Across these studies, a total of 135 patients with hemophilia A were treated with NUWIQ, including 74 adults, three adolescents between ages 12 years and 17 years, and 35 pediatric patients between ages 2 years and 11 years. Of these, spontaneous bleeds were rated as excellent or good in 92 percent of 32 adults and 97 percent of 59 children. The mean annualized bleeding rates for spontaneous bleeds during prophylaxis were approximately 1.5 in children and 1.2 in adults. In all studies, there were a total of seven reported adverse events, each of which occurred one time with a rate of 0.7 percent across all 135 patients. Events included paresthesia, headache, injection site inflammation, injection site pain, back pain, vertigo and dry mouth. ❖

Research

Serious Flu Risk Could Be Identified with Genetic Test

In August, a U.S.-Chinese research team pooled the results of four published studies that show among 445 people infected with either swine flu or H5N1 bird flu, those with a variant of a gene called IFITM3 were 24 percent more likely to have suffered a severe infection. Traditionally, those considered most in danger from the flu include individuals over age 65, pregnant women and those with underlying health problems such as asthma. But this new research suggests that many more people in the general population are prone to suffer badly with the flu if they have the variant IFITM3 gene. About one in 400 people carries the IFITM3 gene, which normally encodes a protein that helps the body's cells resist viral infection. But, the mutated version of the gene impairs the body's natural defense.

Paul Kellam, an expert in virus genomics at the Wellcome Trust Sanger Institute, says the gene variant could help doctors spot people who are not usually considered a risk, but are genetically susceptible to infection. "You can then start to stratify people ahead of time and prioritize them for vaccination," he said. Prioritizing people for the flu shot on the basis of their genetics could slash the number of cases of serious illness and save costs on hospital care. In addition, the discovery of the gene variant opens the door to new anti-viral drugs, said Kellam. A different study published in August showed that it might be possible to boost levels of the IFITM3 protein to make people more resistant to the flu. ❖

Sample 1. Serious Flu Risk Could Be Identified with Genetic Test. *The Guardian*, Sept. 7, 2015. Accessed at www.theguardian.com/science/2015/sep/08/serious-flu-risk-could-be-identified-with-genetic-test.

Research

Studies Suggest Flu Vaccine Is Long-Lasting and Reduces Hospitalizations

Two studies presented at the International Conference on Emerging Infectious Diseases show that the influenza vaccine can protect for six months, last throughout the flu season and reduce hospitalization in children.

In one study, outpatient data from inactive Department of Defense beneficiaries who attended outpatient facilities in San Diego and Great Lakes, Ill., was collected during four flu seasons from 2010-11 through 2013-14. Of the 1,720 participants, 75 percent were younger than 25 years and 55 percent were female, and complete data were available on 1,522 of them. Using outpatient febrile respiratory illness surveillance data to assess the effectiveness of the vaccine (taking into account age, calendar season and influenza season), they found that vaccine effectiveness ranged from 40 percent to 69 percent depending on the flu season. According to Jennifer Radin, PhD, from the U.S. Naval Health Research Center in San Diego, protection was consistent for 91 days to 180 days after vaccination for 60 percent of participants, but after 180 days, its effectiveness decreased to below 11 percent.

“Previous studies found that vaccine effectiveness drops off and does not provide significant protection after approximately 90 to 120 days,” said Dr. Radin. “However, many previous studies used very small sample sizes, and most were done outside of the United States.” She noted that “other countries have vaccine recommendations different than the United States, and sometimes use different flu vaccine compositions, making comparisons with previous studies somewhat difficult.” This study’s population matters because elderly people are particularly vulnerable to waning vaccine immunity over time, which is why a high-dose flu vaccine is recommended for them.

A second study looked at data on annual vaccination rates of children obtained from the National Immunization Survey and the Behavioral Risk Factor Surveillance System, which found that pediatric flu vaccination was directly associated with a reduction in hospitalizations in children and, indirectly, affected adults. Specifically, the study found that flu vaccination rates in children increased from 0 percent in 2000 to approximately

52 percent in 2012, after the U.S. Advisory Committee of Immunization Practices issued a recommendation for vaccination coverage of children younger than 5 years old. And, vaccination significantly reduced hospitalization for pneumonia, influenza and respiratory and circulatory diseases in those 19 years and younger. In adults aged 20 years to 49 years, influenza-related hospitalizations declined, consistent with indirect effects of the vaccine. “Our results suggest that the childhood influenza immunization program is effective in reducing the severe burden of influenza among children and, hence, the vaccination of this age group should be promoted,” said Cecile Viboud, PhD, from the division of epidemiology and population studies at the National Institutes of Health. “The recent decline in adult hospitalization rates is intriguing. Further research should evaluate whether this is due to herd immunity, declining influenza activity or unrelated long-term time trends.” ❖

Melville NA. Flu Vaccine Long Lasting, Study Suggests. *Medscape Medical News*, Sept. 10, 2015. Accessed at www.medscape.com/viewarticle/850817.

Insurance

CMS Announces Biosimilars Reimbursement Rule

At the end of October, the Centers for Medicare and Medicaid Services (CMS) issued final rules detailing how it will pay for services provided to Medicare beneficiaries in 2016. One of these rules was for Part B drugs for biosimilar biological products, which will be based on the average sales price of all biosimilar biological products included within the same billing and payment code.

The decision to group all biosimilars together under one payment calculation and billing code, while using a different

code for the reference product, has been met with disappointment by some in the healthcare industry because it is feared that the final rule will discourage “investment in biosimilar therapies, making it harder for patients to access these new more affordable products in the United States,” stated Chip Davis, president and CEO of the Generic Pharmaceutical Association (GPhA). “There is no scientific evidence that suggests it would be appropriate to blend all biosimilar products into a single payment calculation independent of the

reference product,” added Bert Liang, CEO of Pfenex Inc., and chairman of the Biosimilars Council, a division of GPhA. “While we appreciate CMS’ recognition that it would be premature to issue a rule regarding reimbursement for future interchangeable biosimilars, placing all non-interchangeable products in a single code independent of the reference product is still misguided. Non-interchangeable products are solely compared to the reference product, and not one another, making this arrangement highly unusual.” ❖

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

Please see BIVIGAM Important Safety Information and Prescribing Information on next page, including black box safety warnings, contraindications, and dosing.

*IVIG is also known as IGIV, Immune Globulin Intravenous (Human).

References: 1. Wasserman RL. A new intravenous immunoglobulin (BIVIGAM[®]) for primary humoral immunodeficiency. *Expert Rev Clin Immunol.* 2014;10(3): 325–337.
2. BIVIGAM [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; 2013.

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BIVIGAM® [Immune Globulin Intravenous (Human), 10% Liquid] Rx only

Brief summary: Consult the full Prescribing Information for complete product information

WARNING: THROMBOSIS, RENAL DYSFUNCTION, AND ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin (IGIV) products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose. For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM 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.

Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI).

Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions: Thrombosis: Thrombosis may occur following treatment with IGIV products, including BIVIGAM. 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. 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. For patients at risk of thrombosis, administer BIVIGAM 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. **Hypersensitivity:** Severe hypersensitivity reactions may occur with IGIV products, including BIVIGAM. In case of hypersensitivity, discontinue BIVIGAM infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. BIVIGAM contains trace amounts of IgA (≤ 200 micrograms per milliliter). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. BIVIGAM is contraindicated in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reaction. **Acute Renal Dysfunction and Acute Renal Failure:** Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering BIVIGAM. 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 blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer BIVIGAM at the minimum infusion rate practicable. **Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia:** Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including BIVIGAM. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events. **Aseptic Meningitis Syndrome (AMS):** AMS may occur infrequently with IGIV treatments including BIVIGAM. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. **Hemolysis:** IGIV products, including BIVIGAM, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration,¹³ and acute hemolysis, consistent with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these are present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. **Transfusion-Related Acute Lung Injury (TRALI):** Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support. **Transmissible**

Infectious Agents: Because BIVIGAM is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Biotech Pharmaceuticals Corporation at 1-800-458-4244. Before prescribing BIVIGAM, the physician should discuss the risks and benefits of its use with the patient. **Monitoring Laboratory Tests:** 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 blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. Because of the potentially increased risk of thrombosis with IGIV treatment, 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. If signs and/or symptoms of hemolysis are present after an infusion of BIVIGAM, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum. **Interference with Laboratory Tests:** After infusion of immunoglobulin, 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. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

ADVERSE REACTIONS: Serious adverse reactions observed in clinical trial subjects receiving BIVIGAM were vomiting and dehydration in one subject. The most common adverse reactions to BIVIGAM (reported in $\geq 5\%$ of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice. In a multicenter, open-label, non-randomized clinical trial, 63 subjects with PI, on regular IGIV replacement therapy, received doses of BIVIGAM ranging from 254 to 1029 mg/kg (median dose 462.8 mg/kg) every 3 weeks or 4 weeks for up to 12 months (mean 317.3 days; range 66 – 386 days). The use of pre-medication was discouraged; however, if subjects required pre-medication (antipyretic, antihistamine, or antiemetic agent) for recurrent reactions to immune globulins, they were allowed to continue those medications for this trial. Of the 746 infusions administered, 41 (65%) subjects received premedication prior to 415 (56%) infusions. Fifty-nine subjects (94%) had an adverse reaction at some time during the study. The proportion of subjects who had at least one adverse reaction was the same for both the 3- and 4-week cycles. The most common adverse reactions observed in this clinical trial were headache (32 subjects, 51%), sinusitis (24 subjects, 38%), fatigue (18 subjects, 29%), upper respiratory tract infection (16 subjects, 25%), diarrhea (13 subjects, 21%), cough (14 subjects, 22%), bronchitis (12 subjects, 19%), pyrexia (12 subjects, 19%), and nausea (9 subjects, 14%). Adverse reactions (ARs) are those occurring during or within 72 hours after the end of an infusion. In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of BIVIGAM infusions with one or more temporally associated adverse reactions was 31%. The total number of adverse reactions was 431 (a rate of 0.58 ARs per infusion).

Seven subjects (11.1%) experienced 11 serious ARs. Two of these were related serious Table: Adverse Reactions (ARs) (within 72 hours after the end of a BIVIGAM infusion) in $\geq 5\%$ of Subjects

ARs	No. Reporting ARs (% of Subjects) [n=63]	No. Infusions With ARs (% of Infusions) [n=746]
Headache	27 (43%)	115 (15.4%)
Fatigue	15 (24%)	59 (7.9%)
Infusion Site Reaction	5 (8%)	5 (0.7%)
Nausea	5 (8%)	8 (1.1%)
Sinusitis	5 (8%)	5 (0.7%)
Blood Pressure Increased	4 (6%)	5 (0.7%)
Diarrhea	4 (6%)	4 (0.5%)
Dizziness	4 (6%)	4 (0.5%)
Lethargy	4 (6%)	4 (0.5%)
Back Pain	3 (5%)	3 (0.4%)
Blood Pressure Diastolic Decreased	3 (5%)	5 (0.7%)
Fibromyalgia ^a	3 (5%)	17 (2.3%)
Migraine	3 (5%)	8 (1.1%)
Myalgia	3 (5%)	4 (0.5%)
Pharyngolaryngeal Pain	3 (5%)	3 (0.4%)

^aSymptoms occurring under pre-existing fibromyalgia

ARs (vomiting and dehydration) that occurred in one subject. One subject withdrew from the study due to ARs related to BIVIGAM (lethargy, headache, tachycardia and pruritus). All 63 subjects enrolled in this study had a negative direct antiglobulin (Coombs') test at baseline. During the study, no subjects showed clinical evidence of hemolytic anemia. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. During the clinical trial no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). There was a single positive finding for parvovirus (B19 virus) during the study. This subject came in contact with acute B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth's disease. There was no cluster (no other cases in other subjects) of B19 virus transmission with the IGIV batch concerned.

DRUG INTERACTIONS Live Virus Vaccines: Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response. The immunizing physician should be informed of recent therapy with BIVIGAM so that appropriate measures may be taken.

Research

New Study Shows No Link Between Vaccines and Autism

A study conducted between 2008 and 2014 at the Washington National Primate Research Center showed that vaccines did not cause any brain or behavioral changes in macaque monkeys. The study involved 79 infant male macaques aged 12 months to 18 months who were split into six groups. Two groups received thimerosal-containing vaccines (TCVs) for a child's complete vaccine schedule; two were given the measles, mumps and rubella (MMR) vaccine without TCVs; and two received saline injections as a control group. In each case, the monkeys were further split into subgroups: half were on an accelerated vaccination schedule recommended by the U.S. Centers for Disease

Control and Prevention in the 1990s, and half were on the recommended schedule from 2008. After receiving the vaccines, the monkeys were put together in cages to see if they exhibited any new autistic-like social behaviors such as fear, withdrawal, rocking, self-clasping and stereotypy (repetitive behavior), and it was found that their behavior remained unchanged.

The researchers also conducted post-mortem analyses of the primates' brains, after they had been euthanized, looking for brain abnormalities, including those in the volume and density of the cerebellum, amygdala and hippocampus region, which have been shown to have some variations in children with autism. In



addition, they looked at the numbers and size of Purkinje cells since some studies have shown there are fewer of these cells in the brains of children with autism. However, the researchers found no marked differences in the brains of monkeys in the vaccine groups compared with those in the control group. ❖

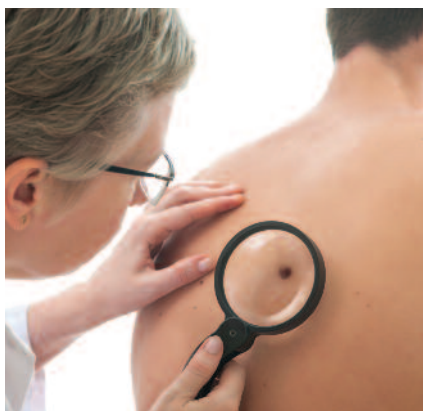
Gadad BS, Li W, Yazdani U, et al. Administration of Thimerosal-Containing Vaccines to Infant Rhesus Macaques Does Not Result in Autism-Like Behavior or Neuropathology. *Proceedings of the National Academy of Sciences*, Oct. 6, 2015. Accessed at www.pnas.org/content/112/40/12498.full.pdf.

Medicines

FDA Approves First-in-Class Treatment of Melanoma

Hailed as a major advancement in the fight against skin cancer, the U.S. Food and Drug Administration (FDA) has approved a new immune-based therapy for treating metastatic melanoma. Amgen's Imlygic (talimogene laherparepvec), commonly referred to as T-VEC, is among a new class of agents known as oncolytic virus immunotherapies. An oncolytic virus is one that preferentially infects and kills cancer cells. Imlygic is the first therapy in this class to receive FDA approval to treat melanoma.

Imlygic is a version of the herpes simplex virus that has been genetically modified to attenuate the virus, increase selectivity for cancer cells and secrete cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is a protein that is naturally secreted in the body that can promote an immune response. The virus invades both cancerous and healthy cells, but it



is unable to replicate in healthy cells, leaving them unharmed. Inside a cancer cell, the virus is able to replicate, secreting GM-CSF in the process. Eventually overwhelmed, the cancer cell ruptures, which destroys the cell and releases new viruses, GM-CSF and an array of tumor-specific antigens.

"Imlygic offers a two-pronged

approach for the treatment of metastatic melanoma. The combination of the virus with GM-CSF increases the drug's cancer-killing effect while activating the immune system to kill melanoma cells — even those that are distant from the treated tumor," said Lisa H. Butterfield, PhD, professor of medicine at the University of Pittsburgh and vice president of the Society for Immunotherapy of Cancer. "Imlygic also offers simple administration; it can be injected in an office visit and, importantly, has no serious side effects."

Prior to the approval of Imlygic, the therapy was extensively studied in clinical trials that indicated the treatment improved durable response rates in patients with advanced melanoma. Durable response rate is defined as partial or complete response to treatment lasting continuously for at least six months. ❖

Medicines

First Factor X Deficiency Bleeding Disorder Therapy Is Approved

In October, the U.S. Food and Drug Administration approved the first replacement therapy for hereditary factor X deficiency, coagulation factor X (Coagadex, Bio Products Laboratory), derived from human plasma. Coagadex is approved for individuals 12 years and older for on-demand treatment control of bleeding episodes, as well as for perioperative management of bleeding

in individuals with mild hereditary factor X deficiency. Factor X deficiency affects men and women equally. Prior to the approval of Coagadex, patients were generally treated with fresh frozen plasma or plasma-derived prothrombin complex concentrates; there was no specific coagulation factor replacement therapy available for patients with hereditary factor X deficiency. ❖

Medicines

FDA Approves Belbuca Buccal Film for Chronic Pain



The U.S. Food and Drug Administration has approved Belbuca (buprenorphine) buccal film for patients with severe chronic pain requiring daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is the first and only buprenorphine developed with a dissolving film that is absorbed through the inner lining of the cheek for chronic pain management.

Belbuca is a mu-opioid receptor partial agonist and a potent analgesic with a long duration of action that is delivered across the buccal mucosa. It is a Schedule III controlled substance, meaning it has been defined as having lower abuse potential than Schedule II drugs, a category that includes most opioid analgesics. Belbuca is expected to

become commercially available in the U.S. during the first quarter of 2016 in seven dosage strengths, allowing for flexible dosing ranging from 75 µg to 900 µg every 12 hours, and enabling physicians to individualize titration and treatment based on the optimally effective and tolerable dose for each patient.

The approval is based on two double-blind, randomized, placebo-controlled Phase III studies in patients with moderate to severe chronic low back pain. A total of 1,559 opioid-experienced and opioid-naive patients took part in the trials that included an open-label period in which patients were titrated to a tolerated, effective dose of Belbuca and then randomized to either continue to receive Belbuca or a placebo. In both studies, Belbuca demonstrated a consistent, statistically significant improvement in patient-reported pain relief at every week from baseline to week 12 compared with the placebo. The most common adverse reactions reported by fewer than 5 percent of patients were nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth and upper-respiratory tract infection. ❖

Medicines

FDA Approves First Combination Immunotherapy for Melanoma



In October, the U.S. Food and Drug Administration (FDA) approved Bristol-Myers Squibb's Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for the treatment of advanced melanoma. It is the first and only approved regimen of two immunotherapy agents in cancer. Opdivo (a PD-1 checkpoint inhibitor) and Yervoy (a CTLA-4 checkpoint inhibitor) are both a type of immunotherapy that acts to release the brakes on the immune system to recognize and mount an attack against cancer. Yervoy was approved by FDA in 2011 as the first therapy to show improved survival in patients with metastatic melanoma. Opdivo was approved in 2014 after showing impressive response rates in patients with previously treated unresectable or metastatic melanoma.

The approval is based on results from the CheckMate 069 study, a Phase II trial evaluating Opdivo plus Yervoy versus Yervoy alone in previously untreated patients with advanced melanoma. The study showed an increase in objective response rate with the Opdivo plus Yervoy regimen (60 percent) compared with Yervoy therapy alone (11 percent). Complete responses were reported in 17 percent of patients, while a partial response was observed in 43 percent of patients in the Opdivo plus Yervoy group. The Opdivo plus Yervoy combination therapy also resulted in a 60 percent reduction in the risk of progression compared with Yervoy alone. Progression-free survival was 8.9 months for the combination therapy compared with 4.7 months with Yervoy alone. ❖

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Future

By Meredith Whitmore

Biosimilars

Pros & Cons

As biosimilars are introduced into the U.S. market, it remains to be seen whether FDA guidances will ensure their safety and efficacy.

In this brave new world of medicines, more and more physicians are prescribing a biologic. Perhaps they have even witnessed a patient's remarkable transformation thanks to biologics such as Humira, Enbrel and Remicade. After months or years of debilitating chronic illness, the patient is now going back to work, experiencing less pain and even exercising again.

But maybe physicians have also seen the strain on a patient's face when he or she describes the cost of such life-changing drugs. Copays can cost \$1,500-plus out of pocket each month. What if, during an appointment, the patient finally asks if there's a less-costly but equally effective treatment? What's the answer for a patient who needs the higher quality of life that biologics provide, but without the devastating expense?

According to Industry Standard Reports, 46 percent of U.S. consumers have never heard of biologic medications, and only 38 percent know whether their prescription is a biologic or a chemical medication. That means they rely on their physicians to guide them through the maze of biopharmaceuticals. Unfortunately, 54 percent of primary health providers and 78 percent of pharmacists can't yet define "biosimilars."¹

What Are Biosimilars?

Biosimilar medications, sometimes called follow-on biologics, are considered the cost-effective alternative to biologics. They are roughly analogous to generic drugs in that they are a non-proprietary alternative to a name-brand medication. Unlike generics that are identical chemical formulations of the original medication, however, a biosimilar, due to its complex proteins, is highly similar to but not exactly the same as its reference biologic product.

While such medications have been available and successfully used in Europe and other parts of the world for at least nine years,² only one biosimilar, Zarxio (filgrastim-sndz), is available in the United States to date. But that will change. More and more biosimilars are lining up to be approved by the U.S. Food and Drug Administration (FDA). And while FDA develops guidances for biosimilars, these drugs remain a heated topic of debate. As such, physicians are wise to educate themselves about these medications now since they pose unique safety and legislative concerns.

Potential Pros of Biosimilars

Price. Perhaps the most anticipated advantage of a biosimilar is its lower cost, which ExpressScripts predicts will be at least 20 percent to 30 percent less than the cost of reference biologics.

By 2024, biosimilars in the United States are predicted to save \$250 billion. Currently, Zarxio (manufactured by Sandoz) costs 15 percent less than its reference product, Neupogen.^{3,4}

Some are skeptical of the potential savings, however. Among them is Frank Kopenski, principal actuary at Milliman actuarial group. "For a 10,000-lives employer with 2019 commercial healthcare expenditures of \$81.5 million, the 2019 total estimated savings is just \$635,925 or 0.8 percent of total healthcare spend assuming 30 percent total market penetration and 30 percent lower pricing of biosimilars," says Kopenski in a December 2011 study projecting biosimilar cost savings to employers. "The overall savings as a percentage of total healthcare costs resulting from biosimilars is likely to be small (i.e., less than 1 percent) given the relatively small frequency of members with high-cost conditions. At this level of savings potential, it is unlikely that employers will change benefit provisions to incent the use of biosimilars over biologics."⁵

Still, Julianna Reed, president of the Biosimilars Forum, says people must remember that biosimilars are not generic drugs. "It's important for physicians and patients to know how different biosimilars are and how much more rigorous the science is in their development. The cost of developing a biosimilar is so much higher than that of a generic — between \$100 million and \$200 million — that, initially, the first few products in the United States will not be the current generic model discount. That's what we've seen in Europe for the past nine years,"⁶ explains Reed. "Patients in the United States won't see great discounts until more and more biosimilar competitors come onto the market. This is exactly how the generic industry also started in its first years. It's important for folks to understand biosimilars are the very beginning of a very different pathway."

Availability and options. In some cases, biosimilars could offer greater availability than a reference product. If a biologic faces a shortage due to high demand or a lack of active ingredients, biosimilar manufacturing could alleviate the biologic's scarcity. Besides this, physicians want more options for patients, not fewer. Having biosimilars available, properly tested and used gives everyone more choice.

Potential Cons of Biosimilars

The drawbacks of biosimilar medications depend largely on what FDA's final guidances will be. Depending on the guidances' stringency, the cons could be devastating, hence the heated debate from numerous patient interest groups. If guidances are adequately strict, however, and clinical testing is effective, the risks will diminish significantly. It all remains to be seen,

but most patient groups and physicians are hopeful despite the following concerns.

Nomenclature. Biosimilar names, if not unique and nonproprietary, could be confusing for physicians and, as a result, harmful to patients. In the event of adverse reactions to drugs, biosimilar names that are too similar to a reference product could cause an inability to determine which biosimilar is problematic. “For example, ibuprofen, a generic of Motrin, is called only ibuprofen, without a unique name. If it caused adverse reactions in patients, how would we know if the problematic ibuprofen is from Walgreens or Sam’s Club or CVS?” explains Lawrence LaMotte, vice president of public policy for the Immune Deficiency Foundation (IDF). That’s a simple but clear analogy for a potentially serious problem. “We at IDF believe that labels must indicate that a drug is a biosimilar, and should indicate what the reference product is, at the very least. A biosimilar will not only not be identical to a reference product but will also not be similar to other biosimilars of the same reference product.”

The drawbacks of biosimilar medications depend largely on what FDA’s final guidances will be.

Many patient interest groups, including Lamotte’s, are thankful that FDA has begun to consider nomenclature more seriously. In its recently released guidance on nonproprietary naming, FDA states that distinguishable names, including four-letter suffixes based on the manufacturer’s name, will help in product identification, prescribing and dispensing. A manufacturer-specific suffix such as Zarxio’s -sndz (which stands for its manufacturer, Sandoz) not only ensures that doctors and pharmacists will know the products are not interchangeable, but makes drug companies accountable.

Extrapolation across indications. Just because a biologic is said to be effective in treating five different diseases does not mean that its biosimilar will be also. That assumption is dangerous for patients, many of whom have a 30 percent chance of experiencing adverse effects when taking any new biologic,⁷ let alone a drug that is merely similar to their biologic. “The idea that a similar drug, not an identical drug such as a generic, but a similar drug like a biosimilar, would be given indication extrapolation is

dangerous,” says Dr. David Charles, chairman of the Alliance for Patient Access. “Just imagine if you test the biologic in a condition like inflammatory bowel disease — do you really know it’s going to have similar efficacy in a condition like rheumatoid arthritis? No. The patient groups that are treated with biologics are so different that indication extrapolation is a concern. I think the FDA has a long way to go to offer more clarity.”

Katie Verb, associate director of policy and government relations at the Hemophilia Federation of America, agrees. “Our main concern with the FDA guidance is how it treats extrapolation across indications. A lot of biologics are approved to treat multiple diseases, and those approvals are based on clinical trials within each disease group,” says Verb. “The FDA seemed light on whether they would do that for biosimilars. The FDA guidance in 2012 took the patients’ safety into account more seriously. That guidance said more about extrapolation, and that there would need to be clinical data for each disease group. The 2015 guidance lightened up on that considerably, however. The 2012 guidance pointed out that there should be caution when it comes to extrapolation, and that caution indication for industry was taken out of the 2015 guidance.”

“You just can’t make that leap and assumption [of extrapolation across indications],” adds Lamotte. “That is an issue that needs to be better defined, and it has not yet been by the FDA. The scientific community and patient organizations have issues with that policy.”

Efficacy. At least one report has illustrated that biosimilars might not be as efficacious as their reference products. An Irish study on Inflectra, a biosimilar used to treat irritable bowel disease, found that 29 percent of patients who took it required surgery versus 0 percent of patients who took Remicade (infliximab), its reference biologic. In addition, 80 percent of the Inflectra group required hospital readmission versus 5 percent of the Remicade group. And 93 percent of the Inflectra group showed an increase in C-reactive protein (CRP), while 100 percent of the Remicade group had a decrease in CRP.⁸

Still, Dr. Charles is hopeful for the efficacy of future biosimilars. “How do we know, without clinical trials, that a biosimilar may not actually be better than its biologic? Some people are coming to the table as if the biosimilar will be only ‘just as good,’” he says. “Actually, they’re different products, and it’s possible that some biosimilars will have a better profile than the original. Maybe the biosimilar will treat the condition better, and maybe it has fewer side effects. But how do we know that? We will never know that unless these drugs are properly tested in clinical trials. I think we should come to the table with the notion that the biosimilar product is not the same and it may be

better. It's certainly possible. Why would we assume that the biosimilar is going to be merely the same or worse?"

Safety. In August, Indian pharmaceutical and biotechnology firm Intas Biopharmaceuticals stopped distribution of its injectable biosimilar, Razumab, after only two months on the market.⁹ Used to treat macular degeneration, the drug caused adverse reactions such as inflammation in patients' eyes. LaMotte expresses related concerns in the United States: "The question for us was: Does the FDA have enough inspectors around the world to inspect all these different manufacturers and get the required data in order to approve a biosimilar? There still isn't a good answer to this question."

Pharmacists' responsibilities and substitutions. Though laws differ from state to state, in many states, pharmacists may switch a drug to a generic instead of dispensing a name brand, and they may do so without informing physicians and patients. Because biosimilars are not identical to their reference biologics, switching from a biologic to a biosimilar, or vice versa, could pose considerable problems. Doctors must remember to write prescriptions clearly, blocking such substitutions by stating: "Dispense as written." Many patient interest organizations believe FDA must address this issue further.

Interchangeability. To be considered interchangeable, a biosimilar must be able to produce the same clinical result as a biologic in all patients without increasing the risk of side effects or lowering efficacy. There are currently no biosimilars that are interchangeable.

Considering that what is true of a biologic will likely be true of a biosimilar, however, Verb of the Hemophilia Federation of America says, "there's a really high immunogenicity portion of our patients. About 30 percent of our population develops an inhibitor while using a biologic. That means their bodies are basically eating their coagulation factor. There are a lot of issues for us, even in switching current FDA-approved biologics. There's anecdotal data in the community that switching drugs leads to a higher inhibitor development rate, so it becomes increasingly important for our population that they've got biologics that have gone through all these clinical trials and have gone through this huge approval system. Now there will be follow-on biosimilar products that might not be tested to the same strengths, so that for us is what causes a lot of the debate and the concern."

Today, there is no way to guarantee that a highly complex biosimilar will act exactly as its reference product biologic. Yet Dr. Charles remains hopeful that someday less complex biosimilars might be duplicated and considered interchangeable. "I don't think every biosimilar is so complex that there couldn't be one

that is duplicable," he says. "But how would you know that it's interchangeable? With detailed clinical trials to demonstrate that interchangeability, not just the assertion that it's interchangeable."

Time Will Tell

The pros and cons of biosimilars are still somewhat hypothetical, but significant, and as FDA irons out safety concerns, the future of the U.S. drug market will gradually emerge. New biosimilars under FDA review include Hospira's version of Amgen's Epogen, Celltrion's version of Remicade and Apotex's version of Neupogen.¹⁰ It is exciting to think of having more options for patients, but patient interest organizations remain hesitant with good reason.

"I think there's hope for biosimilars, and the community is looking forward to them, but a couple of things have to happen to ensure their safety," says Verb. LaMotte agrees: "We would love to have drugs on the market that cost less, because we're talking about expensive drugs. But we also want those drugs to be safe and effective, and that requires some assurance on the part of the regulatory body, and the drugs are going to be watched carefully. That is the FDA's number one concern, and they are raising these issues because they want safety and efficacy to be the number one priority." ❖

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Immunodeficiency



in Older Adults

Seven case studies unveil some of the immunodeficiencies affecting seniors.

By E Richard Stiehm, MD

Primarily immunodeficiency diseases (PIs) are common, believed to affect one in every 1,200 persons.¹ And, secondary immunodeficiencies, occurring as a result of age, illness, injury or medication, are considerably more common than PIs.²

In fact, every person has survived the immunodeficiency of the newborn, and the immunodeficiency of the aged, termed immunosenescence, will affect most of us in our senior years. Immunosenescence, which occurs in patients over age 60, includes new-onset, pre-existing and overlooked PIs, as well as secondary immunodeficiencies. Following are seven case studies that will examine these, the latter of which will include the immunodeficiency of older adults, their immune profile risk and some ways to delay aging, preserve immunity and live a long time.

Case 1: Shingles and Lymphopenia in a 69-Year-Old Woman

Mary, age 69 and retired from teaching, was doing well, enjoying gardening and walking her dog, when she developed painful shingles of the chest and upper arm. Nine years previously, she had received a shingles vaccine. The shingles occurred shortly after a prolonged viral respiratory infection with wheezing, which was treated with a course of steroids. Physical examination, except for the vesicular rash, was unremarkable. Her white blood count was 4,800 cells/uL with 15 percent lymphocytes. Immunoglobulins were normal, and antibodies to varicella were detectable but low. T and B cell subsets disclosed a CD3 total T cells of 450/uL (low), CD4 helper T cells of 85/uL (very low), CD8 cytotoxic T cells of 350/uL, CD19 B cells of 105/uL and CD16/56 natural killer cells of 72/uL. An extensive work-up for infectious disease was negative, including HIV by antibody and polymerase chain reaction testing. T cell proliferative studies were normal. Valacyclovir was given with rapid improvement. The varicella antibody titer increased dramatically, and she returned to her usual state of good health after three weeks.

Diagnosis: Idiopathic CD4 lymphocytopenia (ICD)

Comment: ICD is a heterogeneous illness first identified in 1992, when widespread lymphocyte subset phenotyping was conducted on people at risk for HIV/AIDS but who were not infected.³ Other apparently well patients, also negative for HIV, were then identified with CD4 levels less than 300 cells/uL, most without major illnesses or other immune abnormalities.^{4,5} Several ICD patients are older than 40 years, and some, like this patient, are over 60 years. Laboratory studies show only slight impairment of cellular immunity.

ICD patients are also identified following opportunistic infections with varicella/zoster Cryptococci and human papilloma virus.⁴ Others are identified with autoimmune disease such as Behcet's disease, vasculitis or thrombocytopenia. In a few patients, genetic testing has identified mutations linked to other immunodeficiencies.⁵ The prognosis is guarded with a long-term mortality of 15 percent among 40 patients

identified from 1991 to 2012; five remained asymptomatic.⁴ A few patients recover spontaneously.⁵

Case 2: Pneumonia and a Chest Mass in a 72-Year-Old Man

Thomas was in good health until a few years ago, when he developed a cough with sinusitis. He had a complete examination six years ago, including a normal chest X-ray. In the last few days, his cough worsened, and he developed a fever of 102 degrees Fahrenheit. His doctor noted some post-nasal drip and a few wheezes. Laboratory studies showed a slightly elevated sedimentation rate (31 mm/hour) but a normal complete blood count and chemistries.

A chest X-ray disclosed a symmetrical 6 cm in diameter anterior mediastinal mass. A CT scan suggested a thymic tumor. Further immune studies disclosed CD3 total T cells of 1,525 cells/uL, CD4 helper T cells of 550/uL, CD8 cytotoxic T

Immunosenescence, which occurs in patients over age 60, includes new-onset, pre-existing and overlooked PIs, as well as secondary immunodeficiencies.

cells of 780/uL and CD19 B cells of 85/uL (low). Immunoglobulins included an IgG of 220 mg/dl, IgM of 45 mg/dl and IgA of 30 mg/dl. Pneumococcal titers (despite a Pneumovax vaccine one year previously) were non-protective.

A complete thymectomy was performed, which revealed a spindle cell thymoma. The patient made an uneventful recovery. He was started on intravenous immune globulin (IVIG) therapy with clinical improvement.

Diagnosis: Immunodeficiency with thymoma (Good syndrome)

Comment: Immunodeficiency with thymoma was first described by Robert Good in 1954.⁶ The disorder primarily affects individuals between 40 years and 70 years. It is the only form of a primary late-onset antibody deficiency with low B cells. Most patients have mild to moderate hypogammaglobulinemia, variable defects of T cell immunity and a propensity to autoimmunity.⁷ Hypogammaglobulinemia is present in about 5 percent of all patients with thymomas.

Thymomas are also associated with myasthenia gravis and aplastic anemia, and, as in the immunodeficiency of Good

syndrome, are not reversed by thymectomy. The prognosis of patients with Good syndrome is favorable with IVIG therapy, unless the thymic tumor is malignant.

Case 3: A 74-Year-Old Woman on Immune Globulin Therapy for 24 Years

Jane, a 74-year-old screenwriter, was diagnosed with common variable immunodeficiency (CVID) 20 years previously because of frequent infections and a bout of pneumonia. She had an IgG of 310 mg/dl, IgM of 32 mg/dl and IgA of 18 mg/dl. Total B cells were normal, but there were decreased numbers of switched memory B cells (CD19+, CD27+, IgD-, IgM-). Antibody titers to prior vaccines were non-protective. T-cell numbers and function were normal. She was started on monthly intravenous immune globulin (IVIG), and four years ago, she switched to weekly subcutaneous IG infusions given at home.

In the last few months, Jane developed increasing fatigue, abdominal pain, intermittent diarrhea and a 10-pound weight loss. Her hemoglobin was 9.8 gm/dl, white blood count was 6,800 cells/uL and a normal differential. IgG was 705 mg/dL, IgM was 25 mg/dL and IgA was 20 mg/dL. The sedimentation rate was 64 mm/hr, and Coombs' test was negative. Stool was positive for blood.

A colonoscopy showed patchy infiltrates in the distal colon compatible with Crohn's disease. She was started on sulfasalazine and a tapering course of steroids with clinical improvement.

Diagnosis: CVID with Crohn's disease

Comment: CVID is the most common PI requiring lifelong IG therapy.⁸ The usual age of onset is between ages 20 years and 45 years, but it can present in children and older patients. Most patients live a normal life as long as they receive IVIG therapy. The outlook for prolonged survival is good with careful follow-up; the survival after 40 years is over 90 percent. The exception to this favorable outlook are patients with complications such as chronic lung disease, autoimmune disease, gastrointestinal or hepatic disease and malignancy; these patients have a 40-year survival of 42 percent compared with a 95 percent survival for CVID patients with infections only.⁹ Accordingly, all CVID patients must be monitored regularly for these complications.

Case 4: An Unrecognized Immunodeficiency in a 72-Year-Old Man with Seizures and Intellectual Disability

Steve, age 72, was a resident at a facility for mentally challenged adults ever since his caretaker brother died two years before. With an IQ of 72, Steve could manage the tasks of daily living but could not hold a job. He had successful heart surgery in the first year of life leaving him with a surgical scar but a well-functioning cardiovascular system.

He was brought to the emergency room because of a non-febrile seizure following a bout of gastroenteritis with diarrhea. Physical examination indicated short stature (5 feet, 2 inches),

slight microcephaly, indistinct speech, a midline thoracic surgical scar and a systolic heart murmur. Blood tests revealed hypocalcemia. An endocrinologist diagnosed late-onset hypoparathyroidism. A chromosome analysis revealed a 22q11.2 deletion. Immunoglobulins and lymphocyte subsets were normal. A head and neck surgeon identified a small cleft palate. He was started on calcium and vitamin D without recurrence of his seizures.

Diagnosis: DiGeorge syndrome (22q11.2 deletion syndrome) with normal immunity and late-onset hypoparathyroidism.

Comment: After Down syndrome, DiGeorge syndrome is the most common chromosomal abnormality (one per 6,000 live births).¹⁰ Most patients have a heterozygous chromosome deletion of 22q11.2, resulting in defects of the pharyngeal pouch system. The classic triad includes a hypoplastic thymus with cellular immunodeficiency, cardiac anomalies and hypocalcemia due to hypoparathyroidism. Distinctive morphologic features include low-set ears, ocular hypertelorism, palatal defects, tapered fingers and micrognathia.

The cellular immunodeficiency of DiGeorge syndrome can be profound (for example, the complete DiGeorge syndrome resembles severe combined immunodeficiency). In greater than 95 percent of cases, the immunodeficiency is mild and occasionally nonexistent.

Asymptomatic adult DiGeorge syndrome patients are often diagnosed because their child has DiGeorge syndrome. Other adults are identified because of cardiac conditions, speech and swallowing abnormalities, endocrinopathies or psychosocial problems. Many are in institutions, attending psychiatric clinics or in the criminal justice system.¹¹ The average IQ of adults with DiGeorge syndrome is 70. It may be the PI most often overlooked.

Case 5: A Common New-Onset PI in a 75-Year-Old Male

Edward, a 75-year-old physician, was healthy all of his life. He was up to date on all his vaccines, including the 23-valent polysaccharide pneumococcal vaccine (Pneumovax) given 10 years ago. But in the last year, he developed headaches, persistent sore throats, chronic sinusitis and purulent nasal discharge. His doctor found bilateral maxillary sinusitis on Waters view X-rays and started him on antibiotics. He improved with a two-week course of amoxicillin, but symptoms recurred when the medication was stopped.

Laboratory studies showed a normal complete blood count and an erythrocyte sedimentation rate of 21 (borderline high). IgG was 630 mg/dl, IgM was 134 mg/dl, IgA was 22 mg/dl and IgE was 45 IU/ml. Pneumococcal antibody titers showed protective titers to two of 23 serotypes. Following a repeat Pneumovax vaccine, five of 23 were protective. He was diagnosed with selective antibody deficiency (SAD).

The 13-serotype protein conjugate pneumococcal vaccine

(Pnevnar) was given; repeat titers showed that 10 of 23 were now protective, all of which were serotypes present in Pnevnrar. He was given a six-week course of antibiotics that cleared his sinusitis and then placed on prophylactic Azithromycin 250 mg three times weekly. This controlled his infections, and he has done well on this treatment.

Late-onset adult SAD is usually permanent, and may sometimes be the first manifestation of a global antibody deficiency.

Diagnosis: SAD

Comment: SAD, also termed impaired polysaccharide responsiveness, is probably the most common PI. It is particularly common in children 2 years to 6 years old and probably in individuals older than 60 years. SAD is characterized by frequent infections, normal immunoglobulins, intact cellular immunity, deficient antibody responses to polysaccharide vaccines, particularly Pneumovax, but normal responses to protein vaccines such as Pnevnrar, tetanus or measles.¹²

SAD is present in most infants for the first two years of life and was the impetus to develop protein-conjugate vaccines for pneumococcal and Haemophilus influenzae infections.

The characteristic clinical features are recurrent respiratory infections such as sinusitis, otitis and bronchitis. While younger children under age 6 years may recover spontaneously, late-onset adult SAD is usually permanent, and may sometimes be the first manifestation of a global antibody deficiency such as common variable immunodeficiency. The incidence of SAD increases gradually after age 60 years, suggesting that it is a feature of immunosenescence. SAD may be a component of other PIs, notably DiGeorge syndrome, selective IgA or IgM deficiencies, or combined immunodeficiencies.

Diagnosis is established by a diminished response to a majority of the serotypes in the Pneumovax vaccine (e.g., failure to develop a protective response — 1.3 ng/ml or higher).¹³ Treatment is antibiotics for each infection, or prophylactically, along with administration of two doses of the Pnevnrar vaccine. A few patients develop serious infections (pneumonia, mastoiditis) and may require immune globulin therapy.

Table 1. Major Causes of Secondary Antibody Deficiencies in Older Adults

- Leukemia and lymphoma, particularly chronic lymphocytic leukemia
- Gammopathies, including multiple myeloma and macroglobulinemia
- Monoclonal antibody therapy: rituximab, infliximab, others
- Corticosteroid therapy
- Immunosuppressive drug therapy
- Protein losing states
- Hemodialysis
- Pre- and post-organ transplantation
- Aging

Case 6: A Secondary Antibody Deficiency in a 68-Year-Old Man

Pedro is a 68-year-old retired house painter. On a routine blood count at age 65, he had a white blood count of 18,200 cells/uL with 72 percent lymphocytes. Physical exam revealed a few enlarged cervical nodes and a slightly enlarged spleen. A hematologist, after an extensive work-up including a bone marrow analysis, diagnosed chronic lymphocytic leukemia (CLL), and since he was asymptomatic, recommended close observation only.¹⁴ Six months ago, Pedro developed increasing fatigue, chronic bronchitis and sinusitis. His white blood count was 28,500 cells/uL with 82 percent lymphocytes, hemoglobin was 6 g/dL, IgG was 520 mg/dl, IgM was 52 mg/dl and IgA was 42 mg/dl. He was started on fludarabine and rituximab, as well as amoxicillin for his sinusitis.

After six months of therapy, Pedro's hemoglobin had increased to 12 g/dL, and his white blood count normalized. Because of persistent sinusitis and bronchitis, he was given a Pneumovax vaccine. One month later, his IgG was 250 mg/dl, IgM was 40 mg/dl and IgA was 45 mg/dl. Pneumococcal titers showed only one of 23 serotypes was protective. He was started on intravenous immune globulin (IVIg) therapy, with two infusions of 500 mg/kg three days apart, followed by repeat infusions of 500 mg/kg every four weeks. His IgG levels increased from 250 mg/dL to 720 mg/dL, but his B cells remained low. His sinusitis and bronchitis improved on this treatment.

Diagnosis: CLL with hypogammaglobulinemia, probably aggravated by rituximab

Comment: CLL is the most common leukemia in adults, accounting for 25 percent of all leukemias. It occurs primarily

in older adults and is more common in males. About 10 percent of CLL patients have hypogammaglobulinemia at presentation, which increases to 70 percent as the disease progresses. This is hastened and worsened by rituximab therapy, a monoclonal antibody to CD20 B lymphocytes, the precursor of the plasma cells that synthesize serum immune globulins. The hypogammaglobulinemia of rituximab is usually reversible when the drug is stopped.¹⁵ Lifelong IG therapy is effective in limiting infections in these patients. Some patients have subtle T cell defects that magnify the immunodeficiency.

CLL and other secondary antibody immunodeficiencies in older subjects are more common than PIs.¹⁶ Some of the major causes of secondary deficiency requiring IG therapy are listed in Table 1. Many more have T-cell deficiencies associated with cancer, steroids or other immunosuppressive therapy.

Case 7: An 88-Year-Old Hyperactive Man with a Worried Spouse

The wife of 88-year-old Arthur, despite his protests, brought him to the doctor because of his lifestyle. He had the habit of standing on a box, waving his arms and grimacing (smiles, frowns, joy, etc.). He continued this behavior for two or more hours at a time but never seemed tired or bored. He attracted a crowd to witness his behavior, and most were delighted with his antics. His wife worried about his health; she was sure he would become fatigued and catch something from the surrounding crowds. But he refused to stop, so she took him to his doctor.

He told the doctor that he was fully employed, exercised four hours a day, didn't smoke or drink, and was neither fat nor thin. His vaccines were up to date. The physical exam was unremarkable. Laboratory tests showed a normal complete blood count, chemistry panel and C-reactive protein. He had protective titers to tetanus, pertussis, pneumococci and varicella.

An immune profile risk assessment indicated a favorable profile: normal CD4 and CD8 cells, and a CD4:CD8 ratio of greater than 1.0.^{16,17} B cells were 320/uL, CD8+CD28-cells (memory cells) were normal, and an antibody titer to cytomegalovirus (CMV) was negative. Individuals with these features are likely to live to be 100.¹⁸

Diagnosis: Very healthy orchestra conductor

Comment: This man had the right demographics: Married, no bad habits, neither fat nor thin, well-immunized and an occupation that he loved and that fully engaged both his mind and body. He was an orchestra conductor.

Orchestra conducting is an occupation known for its longevity¹⁸ as exemplified by Arturo Toscanini conducting almost to the time of his death at age 87.

With advancing age, the immune system weakens, particularly the T cell system. The T cells are principally responsible for immunosurveillance (i.e., removing damaged cells that



Arturo Toscanini (1867-1957), famed Italian orchestra conductor, was known for his dynamic conducting almost to the end of his life. He conducted orchestras from all over the world with the exception of Italy and Germany during their fascist regimes. Because of poor eyesight, he memorized all the scores of the symphonies and operas that he conducted.

predispose to infection, cancer or autoimmunity). Alterations of the immune system with aging include thymic atrophy, decreased CD4 cells, increased CD8 cells, decreased naïve and increased memory cells, and elevated antibody titers to CMV.¹⁹ The latter suggests that immunosenescence is related to CMV reactivation, resulting in increased CMV cytotoxic T cells and elevated CMV antibody responses, to the detriment of responses to other antigens. CMV reactivation causes chronic inflammation leading to tissue and organ damage.

Table 2. Factors Associated with Longevity

- Old parents
- Eating right: fruits, vegetables and fish; consuming little red meat, dairy products and fried foods
- Exercising regularly, staying trim but not losing weight
- Striving to be happy, active and optimistic; staying engaged
- Avoiding falls
- Getting good medical care; maintaining vaccines
- Staying married; having a good income
- No smoking or illegal drugs, and consuming alcohol in moderation
- Being a world-famous orchestra conductor

Efforts to reduce the effects of aging are disappointing, although caloric restriction and moderate exercise have proven modest benefits. Dietary supplements (vitamins, probiotics, etc.) are not of proven benefit. The active ingredient in red wine (resveratrol) increases the life span of yeasts, worms and flies but not humans.²⁰

So if you want to live to be 100 with an intact immune system, first live to be 99. In the meantime, see Table 2 for some suggestions. ❖

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The Nurse

Licensed to do many of the same procedures as physicians — often at a lowered cost — nurse practitioners are increasingly poised to change the face of primary care.

By Trudie Mitschang

In 1965, the United States was in the early stages of significant political and social change. As anti-war protesters stormed the nation's capital and U.S. astronaut Edward White became the first American to walk in space, another first was quietly taking place in Boulder, Colo. Seeing the need for expanded education and training within the nursing profession, public health nurse Loretta Ford was collaborating with pediatrician Henry Silver to co-found the nation's first nurse practitioner program at the University of Colorado's Schools of Medicine and Nursing. "Here she is practicing in rural Colorado, she sees a need for a new pro-

feccion, a better way of doing things, something that could really enhance healthcare and bring healthcare to more people, and she created the whole profession," said Penny Kaye Jensen, DNP, former president of the American Academy of Nurse Practitioners.¹

Ford's program was successful, and decades later, nurse practitioner programs were cropping up all over the country. Today, the interest in and demand for the profession shows no signs of waning. According to the Bureau of Labor Statistics, the demand for all advanced practice registered nurses, including nurse practitioners (NPs), is expected to grow by 31 percent through the

year 2022, faster than average for all other occupations.² In fact, in early 2015, the American Association of Nurse Practitioners (AANP) released data showing that the number of nurse practitioners licensed in the United States has nearly doubled over the past 10 years alone, rising from approximately 106,000 in 2004 to 205,000 as of Dec. 31, 2014. “The explosive growth of the nurse practitioner profession is a public health boon considering our nation’s skyrocketing demand for high-quality, accessible care,” said AANP president Ken Miller, PhD, RN, CFNP, FAAN, FAANP. “The challenge now will be right-sizing state and federal laws such that all patients will have full and direct access to nurse practitioners, and these expert and dedicated clinicians will be able to provide care to the top of their education and clinical training.”³

The Expanding Role of the NP

Ford’s original vision for the profession she pioneered essentially encompassed four key components that offered NPs the opportunity to assess, diagnose, treat and evaluate. Fast-forward to 2016: With the demand for primary care services escalating in most states, more than 16 million individuals are expected to gain health insurance coverage thanks to the Affordable Care Act. Add to that a rapidly aging population with escalating healthcare needs, and it’s easy to see why many states

clinics, while RNs largely work in hospitals and surgical settings. But, perhaps the most significant difference between NPs and RNs lies in their day-to-day duties.⁶

Typical RN responsibilities include:

- monitoring patients
- recording and maintaining records
- ordering and interpreting diagnostic tests
- communicating with patients and families about care plans
- assisting physicians with exams and treatments

Typical NP responsibilities include:

- prescribing medications and monitoring side effects and drug interactions
- taking, analyzing and interpreting patient health histories in order to provide diagnoses
- creating individualized treatment plans
- diagnosing and treating acute illnesses
- monitoring and managing chronic illnesses

A Holistic Approach to Healthcare

In addition to providing excellent primary, acute and specialty care, NPs bring a unique perspective to health services because they place an equal emphasis on both care and cure. Ford’s original vision for the profession emphasized a holistic model of care, and according to the AANP, it’s a vision that continues

Practitioner *Will See You Now*

are considering options to expand the role of primary care providers, including expanding the scope of practice for NPs.⁴

Currently, NPs are the largest group of advanced practice registered nurses (APRNs), serving patients in a wide variety of settings under varying degrees of physician supervision.⁵ While both NPs and registered nurses (RNs) work closely with patients to monitor their health and provide care for acute and chronic illnesses, the work environments and responsibilities typically vary greatly between the two. The most significant differentiators between NPs and RNs are the educational requirements; RNs need, at minimum, an associate’s degree in nursing, while NPs require at least a master’s degree.

The working environment for NPs and RNs can also differ, with many NPs working in private practice and community

to be exemplified by a focus on wellness, disease prevention, education and counseling.⁶ “By providing both high-quality care and health counseling, NPs can lower the cost of healthcare for patients. For example, patients with NPs as their primary care provider have fewer instances of emergency room visits, shorter hospital stays and often have lower medication costs,” said Dr. Jensen. “This can be attributed to the fact that NPs partner with patients for their health and provide the necessary information so that they know when early intervention is needed.”⁷

This patient-centered approach to care has made NPs an increasingly preferred provider choice. A survey conducted by researchers at the University of Michigan using the U.S. Agency for Healthcare Research and Quality’s Consumer

Assessment of Healthcare Providers and Systems (CAHPS) questionnaire found that NPs outscored physicians on more than three-quarters of satisfaction questions. Of the 18 core questions, NPs had better scores than physicians on 15.⁸ In general, the findings indicated that NPs spend more time with patients, listen more closely, provide more feedback and show more respect for patients' opinions. Researchers were quick to note that physicians also scored well on the survey, averaging 7.2 out of 10, compared with 9.8 for NPs.⁹ "This adds to the evidence that NPs are able to work independently," stated researcher Susan Lyons, who is also a nurse at the university. "Patient satisfaction comes from respect and listening, fewer hospitalizations and fewer prescriptions. This is just more proof NPs can operate effectively independently without supervision by physicians."¹⁰

A survey found that NPs outscored physicians on more than three-quarters of satisfaction questions.

These survey results are not isolated. NPs routinely outscore other healthcare providers when it comes to patient satisfaction, primarily in their ability to listen and understand patients' concerns. A 2011 study showed only 50 percent of patients felt their physician providers "always" listened carefully, compared with more than 80 percent of patients with NP providers. Healthcare analysts agree that the trust factor between patient and provider is critical when it comes to engaging patients in their own healthcare. It is also a factor in patient compliance and consistency in scheduled follow-up and wellness visits — appointments that are critical for cost efficiency and healthcare quality.¹¹

Counting the Cost of Care

With healthcare costs on the rise, any practice model that reduces costs is worth a closer look. Several studies have demonstrated that NPs prove to be cost-effective providers. One 2009 study by the RAND Corp. projected that the increased use of NPs could save the state of Massachusetts between \$4 billion and \$8 billion over a 10-year period. Additional studies in California and North Carolina show comparable savings.¹⁰

Reductions in costs associated with broadening NPs' scope of practice are being documented across the U.S. In national retail clinics, for example, NPs provide the majority of the care, and cost savings have been significant. In one study, researchers compared insurance claims data for a two-week period for 9,503 patients who visited retail and nonretail clinics from 2004 through 2007. They compared costs in states that require NPs to be supervised by or collaborate with physicians, states that allow NPs to practice independently but not prescribe, and states in which NPs are allowed to practice and prescribe independently. They found that insurance claims for a two-week period were lower after retail clinic patient visits than after visits to other settings such as doctors' offices for the same conditions. Insurance expenditures for retail patient visits were even lower in states that allow NPs to practice independently. Payments for prescriptions were slightly higher in states where NPs are allowed to prescribe, according to the findings, but that increase in cost was mitigated by the lower cost of an NP practicing independently.¹¹

Cost of care aside, it is also less expensive to educate nurse practitioners. According to a 2011 article in the *New England Journal of Medicine*, "Between 3 and 12 nurse practitioners can be educated for the price of educating one physician." By avoiding the rising costs of medical school, NPs are also able to avoid the overwhelming amount of debt typically incurred by doctors. The average primary care physician leaves school with a burden of \$141,000, while an NP accrues approximately \$64,000 of debt.¹²

Of course, salary thresholds for NPs are lower than those for physicians; the average income for a physician is \$173,000 per year, whereas the average NP makes \$89,000. This large salary difference tends to reflect a difference in patient expenses between those who visit NPs versus primary care physicians. According to the National Nursing Centers Consortium, the average patient saves 20 percent by visiting a nurse practitioner over a physician.¹³

While all states regulate the degree of autonomy NPs are allowed, state laws in select areas of the country still restrict NPs from practicing to the full extent of their training, although the tide seems to be turning. Evidence from many studies indicates that primary care services such as wellness and prevention services, diagnosis and management of many common uncomplicated acute illnesses, and management of chronic diseases such as diabetes can be provided by NPs at least as safely and effectively as by physicians.¹⁴ After reviewing the issue, an Institute of Medicine panel supported this conclusion, calling for expansion of nurses' scope of practice in primary care.

Addressing the "Quality of Care" Debate

The trend toward NPs stepping into primary care roles is on

the rise, but not everyone favors the shifting roles. Some physicians' organizations argue that NPs cannot deliver primary care services that are as high quality or safe as those provided by physicians, citing the additional training required for a medical degree. In Virginia, for example, a 2010 proposal to expand the scope of practice for NPs was defeated after the state medical society raised safety concerns, citing NPs' "lack of training and coursework," and pushing instead for a greater focus on nurse education and clinical preparation.¹⁵ A medical society letter to the Joint Commission opposing the proposal stated: "Virginia must take all steps necessary to not only ensure access to care, but to ensure the delivery of quality care."¹⁵

Virginia is not the only state in conflict about expanding the role of NPs. In Florida, NPs have struggled for years to move from restrictive practice and licensure to full practice authority, and have consistently been met with opposition. In one case, a "fact sheet" was sent to members of the Florida Medical Association opposing the Independent Advanced Practice Registered Nurse bill. The reasons cited were major differences in educational preparation between NPs and physicians; concerns regarding NPs' ability to safely prescribe controlled substances and narcotics; shortage of physicians (should support initiatives to increase the number of physicians in the state); shortage of nurses (NPs will affect the future nursing workforce); inability to control healthcare costs (expansion of role may lead to the same NP reimbursement as physicians); and lack of physician oversight (concerns about the danger of less-qualified NPs practicing without supervision).¹⁵

Heated debates regarding these topics have brought the scope-of-practice issue to the forefront, with some legislators supporting the expanded role of NPs and others standing behind physician organizations that oppose broadening the scope of practice.

Despite a shortage of primary care providers, and the potential for NPs to step in and meet the demand for care, existing primary care physicians overwhelmingly do not support expansion of the roles and supply of NPs. A 2013 survey revealed that 70 percent of physician respondents agreed that nurse practitioners should practice to the "fullest extent of their education and training," but many did not agree with the prospect of NPs leading medical homes or receiving equal pay for providing similar service as physicians. In addition, physicians surveyed believed they provided better quality care to patients than their NP counterparts.¹⁵

Jan Tower, PhD, senior policy advisor for AANP, was not surprised by the findings of the survey, although she agreed with the recommendation for more professional education so the two opposing groups can better understand one another.

Dr. Tower also pointed out that the study was unclear as to how many of the physicians who responded actually worked with NPs.¹⁶ "The people who are most concerned about us are people who haven't worked with us," she said.

A Continued Rise in NP Services

The debate over the role of NPs in the healthcare delivery system in the U.S. will likely continue as the demand for healthcare services rises. Nevertheless, it remains clear that with research showing high patient satisfaction and lower cost of care, the number of NPs providing these necessary services will continue to increase. ❖

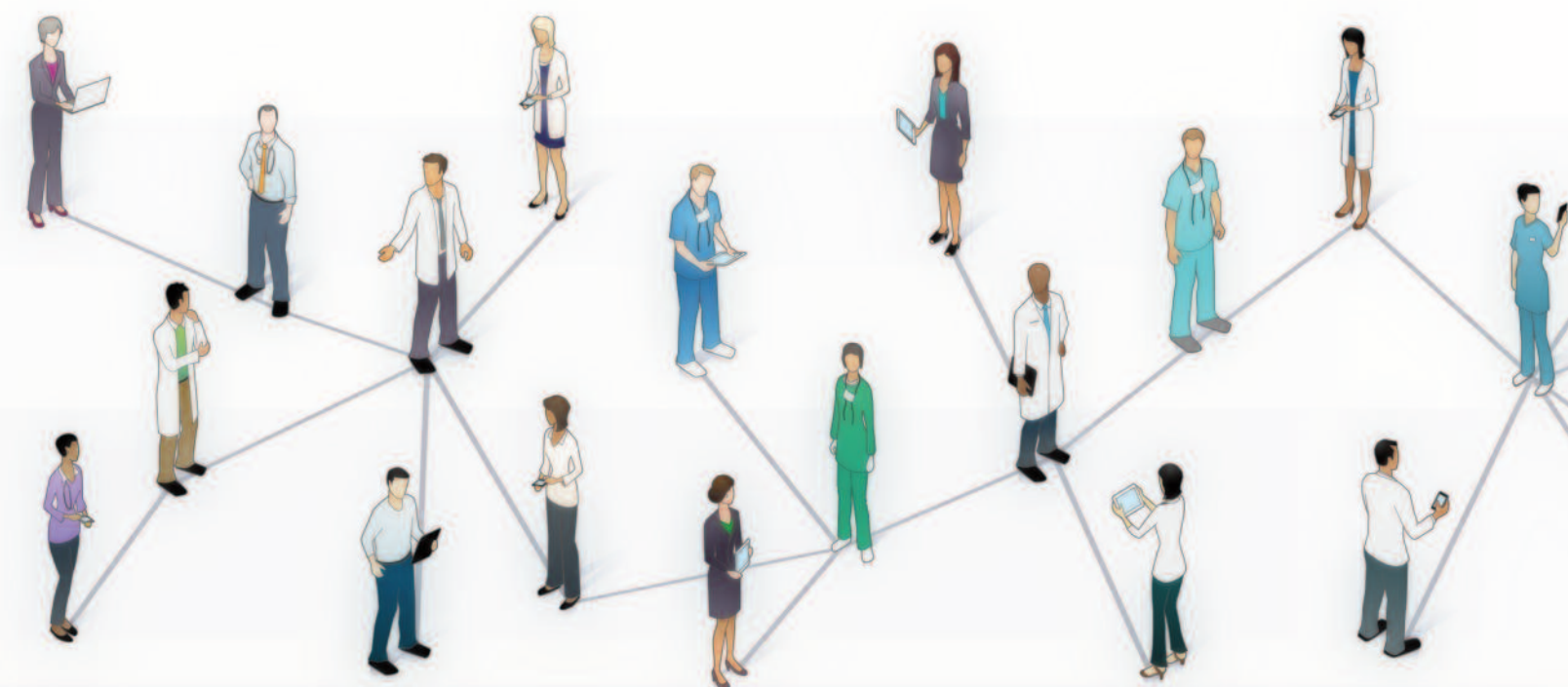
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How Crowdsourcing Is Changing Medicine

One physician. One patient. That's the model that has historically governed the doctor-patient relationship. But the iconic image of a doctor caring for a patient is shifting as more and more virtual entities crowd into the exam room. With the advent and ongoing evolution of crowdsourcing, there may be hundreds of other patients involved in one patient's care. Likewise, there may be dozens of healthcare providers weighing in to help a patient receive the care he or she needs. How is crowdsourcing informing the doctor-patient relationship, and how can healthcare providers be prepared for the ways in which crowdsourcing is changing the dynamics in medicine?



By Dana Martin

Crowdsourcing, a term first coined by Jeff Howe, a contributor to *Wired* magazine,¹ is most often associated with marketing and social media. A company might crowdsource its customers to decide on a new product launch, or a Twitter user might poll his or her followers for the best answer to a question. But crowdsourcing has other applications as well. The approach of widely canvassing a group in order to solve a problem or gain new insights is gaining popularity in

the medical community. Crowdsourcing is making a name for itself in medicine beyond the more traditional forms such as expert panels, case conferences, medical databases and polls in medical journals. Emerging technologies are making it easier than ever for patients to communicate with one another online and to participate in research, as well as for physicians to come together in virtual spaces with the shared goal of diagnosing and addressing difficult medical cases.

Peer Support

Peer support has existed in many real-world incarnations and predates the use of the term crowdsourcing. Patients who share the same diagnosis or who are all dealing with similar, often life-altering, symptoms may reach out to one another for the support and encouragement that only their peers can provide. These groups exist in communities across the country, and many are hosted and supported by local hospitals, churches, community centers and other local entities. Studies show that peer support is effective for patients with kidney disease, cancer, diabetes, heart disease, depression, HIV/AIDS, multiple sclerosis, brain injury, burns, amputation and numerous other health conditions.²

More and more, these peer support groups also exist online, where the number of participants is often much larger than it would be in a local support group, especially where rare diseases are concerned. With larger groups, more information can be shared

and solicited, which makes crowdsourcing possible in ways that might not have been feasible in the past. These days, even a patient with a rare disease can poll thousands of other patients with the same condition. This is an important shift. That same patient might not have another person in his or her community to share information with and request information from. Online peer support groups can confer many of the same benefits as in-person groups. One study whose objective was to test whether engaging

in an online patient community improves self-management and self-efficacy in veterans with epilepsy concluded that such an intervention increased epilepsy self-management and self-efficacy scores, with the greatest improvement occurring in information management behaviors.³

Peer support groups, especially those that include a large number of members, are an important consideration for those providing healthcare to patients. Members of peer support groups are often well-informed about their conditions and treatment options. “Dealing with a patient who is informed allows for more open communication between the doctor and the patient,” says Rick Kellerman, MD, FAAFP, a family physician

in Wichita, Kan. “The doctor can speak with the patient on a different level because he knows that the patient does have a body of information to draw from in relation to his own health.”⁴

At the same time, patients might be getting information from the group that counters their own physicians’ chosen courses of treatment. Informed and engaged patients require a different approach than those who learn about their conditions only from their healthcare providers. These patients will often ask more questions and demand more from their providers. In turn, providers need to be prepared to field questions, address proposed treatment options, explain why the given course of treatment has been chosen, and address any potential misinformation that has been gathered from fellow members of the support group. Such misinformation can arise because most online peer support groups are not mediated by healthcare professionals.⁵

Peer Support That Facilitates Research

An extension of peer support, patient-centered sharing networks such as Patients Like Me not only connect patients with one another in the ways that traditional support networks do, they also use the data they collect from patients to improve patient care, change the way the medical industry conducts research, and transform the way patients manage their conditions. The large amounts of data that Patients Like Me collects are aggregated and analyzed in order to give patients a collective voice that makes them the center of healthcare research and initiatives. One area in which Patients Like Me is leveraging this collective data is pharmaceutical research and evaluation. The data sets the company creates have been used to inform drug research. The company also wants patients to collaborate on developing outcome measures that evaluate the efficacy of new drugs. These measures would include elements that matter to those taking the medications. About a dozen pharmaceutical groups have already collaborated with Patients Like Me, including Merck and Novartis.⁶

In June, Patients Like Me announced another patient-centric initiative in the area of drug research. The company has signed a research collaboration agreement with the U.S. Food and Drug Administration (FDA) to determine how patient-reported data can give new insights into drug safety. The company and FDA will explore the potential of patient-generated data to inform regulatory review activities related to risk assessment and management. “Most clinical trials only represent the experience of several hundred or at most several thousand patients, making it impossible to anticipate all the potential side effects of drugs in the real world,” says Ben Heywood, co-founder and president. “Patient-generated data give a more complete picture about a drug’s safety by providing



a window into patients' lives and healthcare experiences over time. We're very encouraged by the FDA's action to evaluate newer sources of data to help identify benefits and risks earlier."⁷

Doctor Crowdsourcing by Patients

Another kind of crowdsourcing involves patients talking with a pool of doctors as opposed to their peers. CrowdMed, the first site of its kind, gives patients access to a team of medical professionals, including doctors, researchers and acupuncturists. Jared Heyman, the company's founder and CEO, created the CrowdMed website after his sister spent three years suffering from a chronic, undiagnosed medical condition. He says the average patient on CrowdMed has been ill for eight years and has already incurred \$60,000 in medical bills trying to reach a diagnosis by the time they reach the site. The site is not a replacement for visiting a physician. Rather, it is a tool that can help solve medical mysteries, according to Heyman. "We are definitely trying to shorten that path, from when a patient recognizes they have some type of illness that doesn't have a clear diagnosis, and to when they actually have the right answer," he says.⁸

SERMO, a crowdsourcing site for physicians, recently made news when a primary care doctor in Utah saved a boy's life after posting about his symptoms on the site.

One success story directly tied to the use of CrowdMed is that of Catherine Tan, who had a bicycle accident when she was a teenager. The resulting head injury left her with headaches and vision issues, but no effective treatment plan, even after \$250,000 had been spent on medical bills. Her mother shared Tan's story on CrowdMed, along with a \$400 award for an accurate diagnosis. The group of medical investigators on the site, whom Tan's mother describes as a community of young medical professionals who are reading and thinking in much more creative ways than the traditional medical establishment, determined that Tan did not have a concussion as a result of her accident but did have some brain damage.

She is now being treated at Cleveland Clinic. In relation to this success story, Heyman adds that the average case on CrowdMed is solved in just 75 days. One of Heyman's means for getting these speedy diagnoses is casting a bigger net than simply using the typical roster of medical doctors. Medical students, nurses, chiropractors and nutritionists can all weigh in, alongside physicians, in getting to the bottom of patients' difficult medical issues.⁹

While promising, models such as CrowdMed and those that may spring up in its wake are not without their drawbacks, chief among them concerns about privacy and medical errors.¹⁰ In addition, according to Darshak Sanghavi, a pediatric cardiologist and fellow of the Brookings Institution, some patients may not feel comfortable receiving a diagnosis by way of majority vote. This approach can feel impersonal. A better model, he notes, is having designated subspecialists review the information from those providing input.¹¹ CrowdMed's solution for providing context and limiting the flow of incoming information is to use a patented prediction market technology that collects and filters feedback from those who participate in the case, then provides a report with the best suggestions for further discussion with the patient's doctor. This isn't a doctor's distillation, but it is an innovative form of intelligent analysis that can be shared with the patient's doctor — as long as that doctor is open to reading and incorporating such feedback.

There's also the issue of additional costs associated with these sites, which may be prohibitive for some patients. Many have, however, already spent tens if not hundreds of thousands of dollars trying to get an accurate diagnosis and treatment plan, so the additional fees or monetary incentives are minuscule by comparison. Finally, there's the issue of platform. Those without access to the Internet or who are not Internet-savvy may not make use of online crowdsourcing tools. This includes nondigital natives such as older adults, who otherwise might be perfect candidates for such services.

Physician Crowdsourcing

SERMO, a crowdsourcing site for physicians, recently made news when a primary care doctor in Utah saved a boy's life after posting about his symptoms on the site.¹² The child, who had a persistent cough, coughed up a branchlike mass. Within two days, 231 doctors from the United States and the United Kingdom had responded with 16 possible diagnoses. One of those doctors made the right diagnosis, which was seconded by another SERMO user. The boy had an extremely rare respiratory condition and needed to be seen by a specialist immediately.

SERMO differs from CrowdMed because it's a resource for physicians to crowdsource other physicians, not for patients to make such inquiries. In this way, it functions more like an online extension of the more established forms of sharing and

collaborative problem-solving that exist in medicine. SERMO is designed to do what Dr. Sanghavi says is necessary for crowdsourcing to be at its most effective, which is getting the consensus of about 1,000 highly trained specialists.^{11,13} Under these conditions, even though many doctors will have the wrong answer, the plurality, Dr. Sanghavi points out, will hit the mark. “Debunking the myth of the lone maverick, health researchers suggest that groups of doctors outperform individuals not only in diagnosing problems but also in treating them,” he says.

One issue with sites such as SERMO is the overall lack of training in collaborative technologies on the part of physicians.¹⁴ Doctors receive little training in the use of social media sites such as Facebook and Twitter, and they don’t tend to spend a lot of time on these networks.^{14,15} Physician crowdsourcing sites have many of the same elements as public-facing social media outlets and may, therefore, encounter similar resistance with regard to their use. A 2012 article published in the *Journal of the American Medical Association* notes that the foundational values associated with the practice of medicine reinforce the independent, rather than the collaborative, model of care, even with regard to real-world social networking among physicians.¹⁶ It also takes time, including time away from other patients and from practice management, to incorporate crowdsourcing into one’s routine on a regular basis.

Making Room for Crowdsourcing

All the physician- and patient-led sources of information out there won’t help the physician who doesn’t allow the collaborative mindset into his or her work, the one who still wants to operate a solo practice in relative isolation and without the input of patients, other physicians or the wider healthcare community. A paradigm shift is required to incorporate any of these tools.

Dr. Sanghavi points out that even when new guidelines are agreed to through the most rigorous forms of physician-driven crowdsourcing — collective efforts that are published, widely distributed and nationally endorsed — they aren’t always followed. “Some doctors may honestly think the crowd is wrong, but more likely, they’re unaware of the fact that guidelines exist or they’re wedded to outmoded practices,” he says. According to the *New England Journal of Medicine*, guidelines for practice may predispose physicians to consider changing their behavior, but rapid change in actual practice may be unlikely unless disincentives are removed or there are other incentives for adopting the guidelines.^{11,13} By extension, emerging forms of online crowdsourcing, which aren’t published and don’t result in changes to policy guidelines, and also may carry no intrinsic incentives or barriers to disincentives, might be even more difficult to translate into changes in

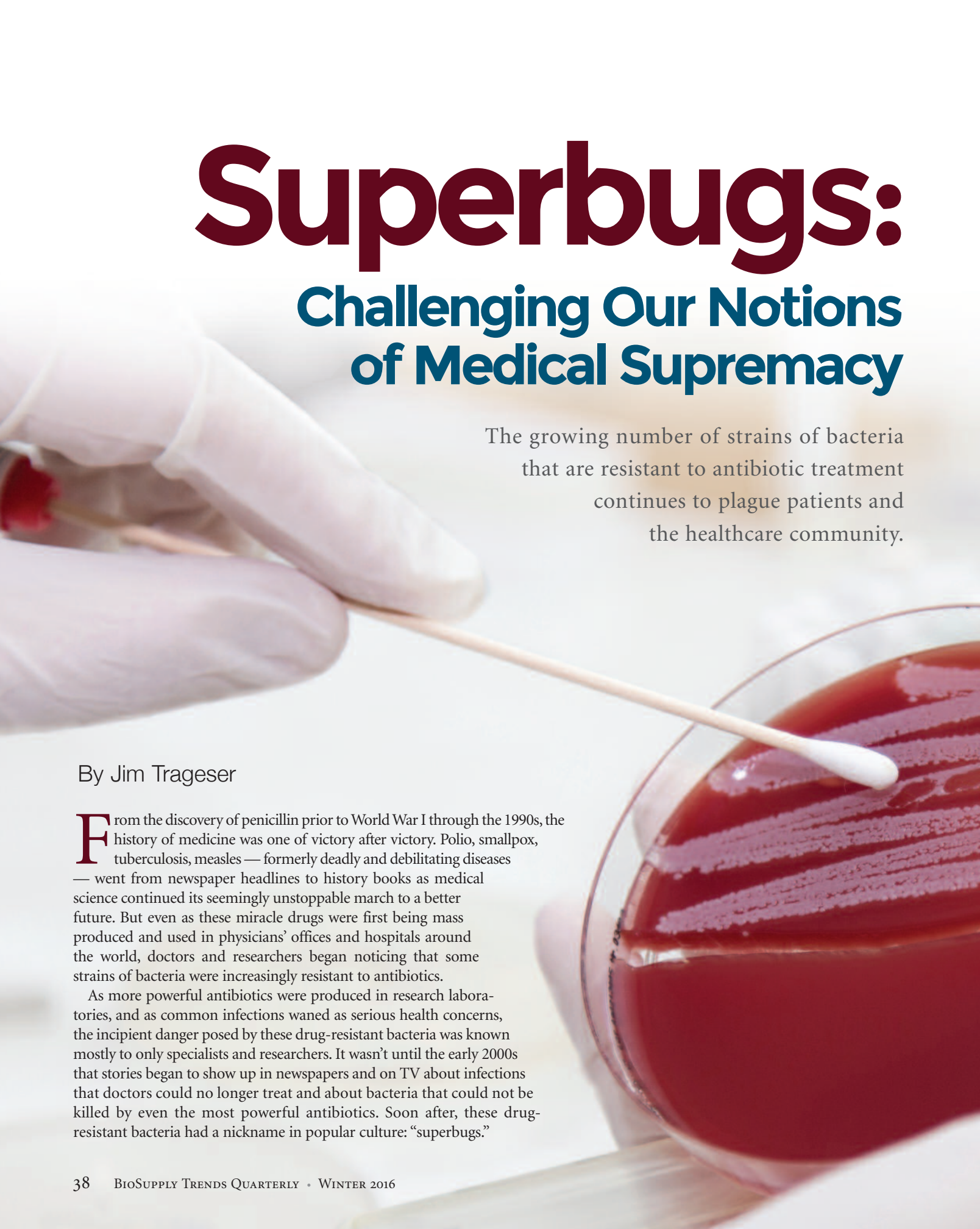
physician behavior. In addition, many of these forms of crowdsourcing are for rare or difficult-to-diagnose conditions, ones that may be less likely to apply to a physician’s broader patient base.

Even given the obstacles crowdsourcing faces, results such as those seen with Catherine Tan and the boy with the rare respiratory condition can’t be ignored, nor can the fact that we are living in an increasingly connected culture in which asking a larger group for advice on everything is the norm, even in medicine. Perhaps in the future, one-to-many relationships between patients and doctors will be as common, if not more common, than the one-to-one relationships that dominate today’s medical landscape. ❖

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Superbugs:

Challenging Our Notions of Medical Supremacy

The growing number of strains of bacteria that are resistant to antibiotic treatment continues to plague patients and the healthcare community.

By Jim Trageser

From the discovery of penicillin prior to World War I through the 1990s, the history of medicine was one of victory after victory. Polio, smallpox, tuberculosis, measles — formerly deadly and debilitating diseases — went from newspaper headlines to history books as medical science continued its seemingly unstoppable march to a better future. But even as these miracle drugs were first being mass produced and used in physicians' offices and hospitals around the world, doctors and researchers began noticing that some strains of bacteria were increasingly resistant to antibiotics.

As more powerful antibiotics were produced in research laboratories, and as common infections waned as serious health concerns, the incipient danger posed by these drug-resistant bacteria was known mostly to only specialists and researchers. It wasn't until the early 2000s that stories began to show up in newspapers and on TV about infections that doctors could no longer treat and about bacteria that could not be killed by even the most powerful antibiotics. Soon after, these drug-resistant bacteria had a nickname in popular culture: "superbugs."

Today, the Centers for Disease Control and Prevention (CDC) warns we may be heading back to a day when we do not have drugs available to treat infection: “Can you imagine a day when antibiotics don’t work anymore? It’s concerning to think that the antibiotics that we depend upon for everything from skin and ear infections to life-threatening bloodstream infections could no longer work. Unfortunately, the threat of untreatable infections is very real.”¹

What Are Superbugs?

It turns out that superbugs are likely an unavoidable part of using antibiotics to treat bacterial infections, which is endemic to the world we live in. Consider the combination of these factors: 1) the sheer number of disease-causing bacteria in the world; 2) random chance mutations to DNA that exist in all life on Earth; and 3) bacteria’s reproductive cycle, which is measured in hours, if not minutes. These add up to create a range of genetic diversity even among the same species of bacteria that is mind-bogglingly broad.

The fact is that no antibiotic yet approved is capable of killing all organisms in any bacterial infection, thus unavoidably leaving behind surviving organisms that have the ability to live even when swimming in the antibiotic. And, these survivors’ succeeding generations share their parents’ resistance to the drug, with far fewer non-resistant competitors with which they have to share resources.

Even as the lifesaving properties of penicillin were burnishing its reputation as a miracle of modern science in civilian hospitals in the years after World War II, almost immediately physicians began to notice that some bacterial infections that had previously responded well to penicillin treatment

no longer did.² Fortunately, most of these infections could still be successfully treated with newer drugs such as vancomycin (discovered in 1953) and methicillin (discovered in 1959). But already by 1961, bacterial infections that could not be stopped by either of these drugs had been found in Great Britain.³ The term “methicillin-resistant *Staphylococcus aureus*,” or MRSA, was coined to describe these bacteria.

Adding to the difficulty in devising drugs that can successfully treat infection is the fact that bacteria can share genetic material laterally (even across species) through the swapping of plasmids,⁴ allowing a resistant population of bacteria to replace a nonresistant one in days, if not sooner.

Today, in addition to MRSA, CDC lists a host of other resistant bacteria that pose a public health threat:¹

- vancomycin-resistant enterococcus
- extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae*
- multidrug resistant *Escherichia coli* and *Enterobacter*
- carbapenem-resistant *Pseudomonas aeruginosa*
- carbapenem-resistant *Klebsiella pneumoniae* (and *Klebsiella oxytoca*)

And, this is only a partial list.

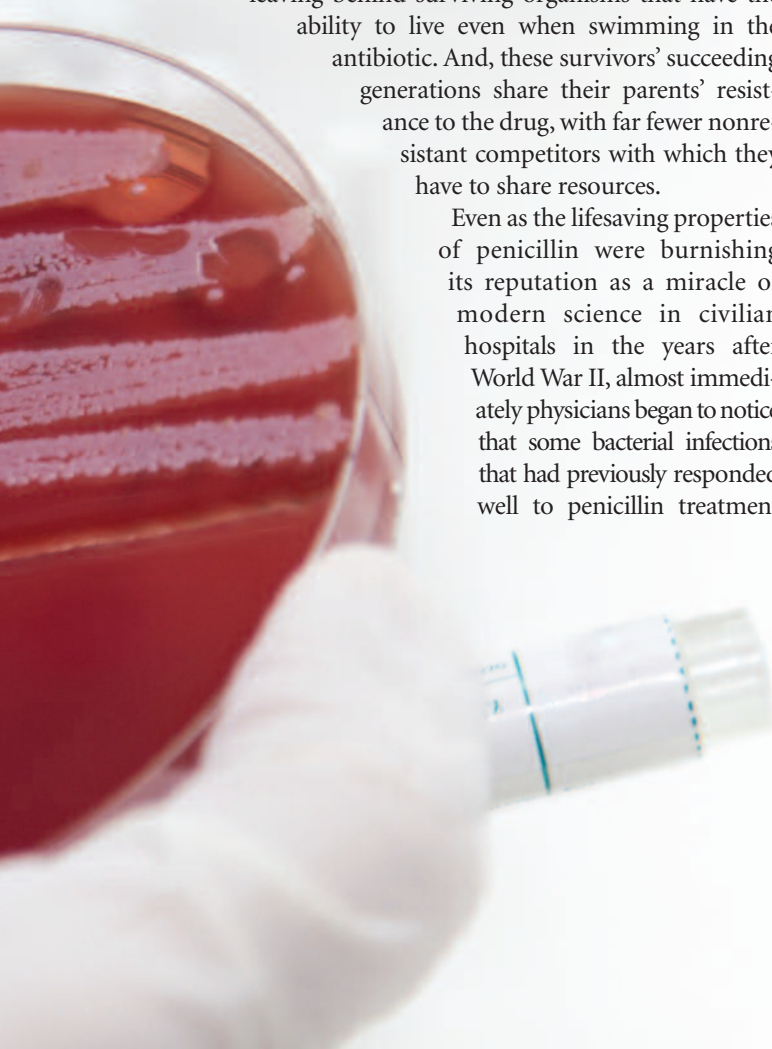
The Threat

CDC now lists superbugs as one of its top public health threats. A 2013 agency report states that some two million people a year are infected by resistant bacteria in the United States alone, and “at least 23,000 people die each year as a direct result of these antibiotic-resistant infections. Many more die from other conditions that were complicated by an antibiotic-resistant infection.... In addition, almost 250,000 people each year require hospital care for *Clostridium difficile* (*C. difficile*) infections. In most of these infections, the use of antibiotics was a major contributing factor leading to the illness. At least 14,000 people die each year in the United States from *C. difficile* infections.”⁵

In addition to tracking the types of bacteria that have growing populations of resistant members, CDC also now classifies resistant bacteria by the location where the infection was contracted: healthcare facilities, food supply or the community.

The agency has also prioritized the public health threat posed by different strains of resistant bacteria into three categories: urgent, serious and concerning.⁵ Those classified as urgent are considered a priority health threat requiring aggressive coordinated action to contain immediately. The three drug-resistant bacteria classified as urgent are:

- *C. difficile*
- carbapenem-resistant Enterobacteriaceae
- drug-resistant *Neisseria gonorrhoeae*



C. difficile causes severe and often fatal diarrhea, and the overall population of this bacteria is increasingly resistant to fluoroquinolone antibiotics, in addition to earlier drugs. Carbapenem-resistant Enterobacteriaceae causes dangerous bloodstream infections in hospitalized patients and has a 50 percent mortality rate. This species is resistant to all drugs currently in use. Both *C. difficile* and carbapenem-resistant Enterobacteriaceae are primarily contracted in healthcare settings. *Neisseria gonorrhoeae* is a sexually transmitted disease, with roughly 30 percent of all cases now showing signs of resistance to antibiotics.

In the United States alone, at least 23,000 people die each year as a direct result of these antibiotic-resistant infections.

The 12 pathogens classified by CDC as serious are not considered as critical a threat to public health as the above three, but they warrant serious attention by the medical profession to prevent them from becoming more prevalent:

- multidrug-resistant *Acinetobacter*
- drug-resistant *Campylobacter*
- fluconazole-resistant *Candida* (a fungus)
- extended spectrum β -lactamase producing Enterobacteriaceae
- vancomycin-resistant enterococcus
- multidrug-resistant *Pseudomonas aeruginosa*
- drug-resistant non-typhoidal *Salmonella*
- drug-resistant *Salmonella typhi*
- drug-resistant *Shigella*
- MRSA
- drug-resistant *Streptococcus pneumoniae*
- drug-resistant tuberculosis

Drug-resistant bacteria that are classified as concerning are being monitored in case they become more widespread. These include:

- vancomycin-resistant *Staphylococcus aureus*
- erythromycin-resistant group A *Streptococcus*
- clindamycin-resistant group B *Streptococcus*⁵

Viruses, Parasites and Other Infectious Agents

Just as bacterial populations can become resistant to antibiotics due to the inevitable survival of resistant organisms, so can other microscopic life forms that cause disease in humans. The 2013 CDC report on drug resistance specifically excluded

viruses and protozoa parasites, even while acknowledging that HIV and influenza virus populations are exhibiting signs of drug resistance, as are the protozoa that cause malaria.⁵ While the CDC report acknowledged the growing risk these resistant populations pose, it explained that they were beyond the scope of the report. (The one exception to this is fluconazole-resistant *Candida*, which CDC included because it is the leading source of bloodstream infections in healthcare settings.)⁶

Symptoms, Diagnosis and Treatment

The initial symptoms of resistant bacteria are no different from symptoms the same bacteria caused a century ago before the introduction of antibiotics, whether it's a skin infection, pneumonia, tuberculosis, etc. The diagnoses for these infections are also unchanged (although additional diagnostic tests to determine whether an infection is resistant are increasingly the norm when any of the above listed agents are suspected as the cause of the infection).

What has changed dramatically is the ability, or rather inability, of physicians to effectively treat the infection by killing the bacteria causing it. In many cases of resistant infection, if the infection does not respond to ever-more-aggressive antibiotic treatment, palliative care while the patient's own immune system battles the infection may be the only remaining option. Treatment regimens may also include additional procedures to ensure the resistant strain is contained and not spread to other patients.

Among the greatest challenges facing government health officials and healthcare professionals is that so many of these superbugs are firmly ensconced in hospitals and other healthcare facilities, where the most vulnerable patients are the most likely to contract them. As such, CDC's National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination provides clear guidelines on containing resistant infections in healthcare facilities. Mainly, the plan outlines the need for providing staff training and oversight with the goal of consistent usage of best practices so that a resistant strain does not spread.⁷ When resistant infections do spread, it is almost always due to a breach in standard operating procedures.

While hospitals and other medical facilities may remain the main battlefield in the war against resistant bacteria, a more recent front is the spread of resistant infections to the general population and the food supply. Of particular worry in the general population are resistant tuberculosis, resistant *Streptococcus pneumoniae*, skin infections caused by MRSA, and sexually transmitted gonorrhea.⁵ A notable example of this was the news in October last year that New York Giants' tight end Daniel Fells was diagnosed with a MRSA skin infection on his foot. After enduring seven surgeries to quell the infection that even spread to his lungs, he lost part of his foot and, of course, his football career.⁸

CDC lists four core approaches in its plan to combat resistant infections:

- Preventing infections and preventing the spread of resistance.
- Tracking resistant bacteria.
- Improving the use of today's antibiotics.
- Promoting the development of new antibiotics, and developing new diagnostic tests for resistant bacteria.

In addition to tracking incidences of resistant infections, CDC is working to improve the use of current generation antibiotics to maximize their efficiency. In particular, it is promoting its Get Smart program to encourage physicians to not overprescribe antibiotics in a variety of ways, from resisting patient demands for a prescription (as in the case of a cold, when an antibiotic will not help) to ordering lab tests to ensure a bacteria really is the cause.⁹ It is thought that overprescribing of antibiotics is a contributing factor in the rise of resistant populations.

The food supply is another worry for federal public health officials because antibiotics remain the single best tool for fighting dangerous intestinal tract infections. Historically, intestinal tract infections have been one of the leading causes of premature death — a trend only altered in the last century with the advent of antibiotics, refrigeration and safe food-handling procedures. Overuse of antibiotics in the agricultural sector could lead to resistant strains of salmonellosis and campylobacteriosis in the food supply, a trend CDC is working with the U.S. Food and Drug Administration (FDA) to counter.⁵

Prevention and Research

By tracking the source and severity of resistant bacterial populations, CDC hopes to slow their spread while promising that new research that may yet give physicians the upper hand in the battle against infectious bacteria has time to come to fruition.

Research into new antibiotics is showing promise as scientists learn more about how bacteria's internal processes operate at a molecular level. While penicillin was discovered to be an effective antibiotic decades before researchers understood the specifics of how it killed harmful bacteria while leaving other cells unharmed, today's researchers look for key moments in a bacterium's life cycle and then try to find methods of interfering with that critical function (much like research into treating cancers looks for weaknesses in a cancer cell's defenses at the molecular level).

While that basic research continues, pharmaceutical researchers also continue to look for antibiotics in the same place they found penicillin: nature. Many microbes such as bacteria, mold and protozoa defend themselves by emitting poisons. Labs around the world are busy growing samples of uncultured microbes harvested from nature.

In 2015, researchers announced the discovery of a new drug called teixobactin, which is produced by one of the many

bacteria researchers were cultivating. Teixobactin contains a molecule that interferes with the ability of some bacteria to maintain their cellular membrane. Initial tests show it to be 100 percent effective against some strains — meaning no resistance has yet been found.¹⁰

While tests continue on teixobactin (it is not yet approved for use), CDC notes that, overall, the number of new antibiotics introduced has been steadily declining over the past three decades. The last new antibiotic approved by FDA for use was ceftaroline in 2010. Before that was telavancin in 2008. Only six others have been approved since 2000.⁵

Teixobactin has only been shown to be effective against gram-positive bacteria, which means, if approved, it could be used to treat *C. difficile*, tuberculosis, MRSA and other dangerous diseases, but not many others caused by gram-negative bacteria. (Gram-negative or -positive refers to the results of a test using a specific stain to determine the type of membrane a cell has.)

Another drug in testing, brilacidin, has shown similar results in early testing and, if approved, would be used to treat skin infections.¹¹

Even if these two drugs are approved and prove effective against previously resistant strains, researchers warn that all it will take is one bacteria that is able to survive to start the cycle all over again. As such, it may turn out that resistance to antibacterial drugs is simply going to be part of the future medical landscape. ❖

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Myths and Facts: Alzheimer's Disease

Government and researchers continue to pursue plans and studies to gain a greater understanding of this devastating and deadly disease in order to prevent, treat and, ultimately, cure it.

By Ronale Tucker Rhodes, MS

It's an alarming statistic: 5.3 million Americans have Alzheimer's disease (AD).¹ But, that statistic belies reality: It's estimated that only one in four Americans with AD has been diagnosed.² It is a disease that develops in someone every 67 seconds. And, the figure rises each year, with an expected 7.1 million people with AD by 2025 — a 40 percent increase. As the numbers rise, so do the costs. In 2015, AD and other dementias cost the nation \$226 billion. That number in 2050 is expected to rise to \$1.1 trillion.¹

The sixth-leading cause of death in the U.S., AD affects twice the number of women as men and more African-Americans and Hispanics, even though there are more non-Hispanic whites living with the disease than any other racial or ethnic groups.¹ Sadly, how AD develops and how it impacts those living with it is clouded by many misconceptions about the disease, which stands in the way of helping those affected.

Separating Myth from Fact

MYTH: AD and dementia are the same disease.

FACT: While the terms “Alzheimer's” and “dementia” are often used interchangeably, they are very different. Dementia is an umbrella term for a group of symptoms that result in trouble

with learning and memory.³ And, dementia is caused by many things, including AD (as many as 50 percent to 70 percent of all dementia cases are caused by AD), Huntington's disease, Parkinson's disease and Creutzfeldt-Jakob disease. Some forms of dementia are temporary or they can be reversed, but with AD, that is not the case.⁴

MYTH: Memory loss is AD.

FACT: AD is much more than memory loss. Some memory loss is a normal part of aging. But, memory loss can also be caused by many other things such as medication side effects, vitamin deficiencies and other types of dementia.⁵

With AD, damage to the brain starts a decade or more before memory and other cognitive problems become evident, when people seem to be symptom-free. But, during this time, toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain, and once-healthy neurons stop functioning, lose connections with other neurons and die. The damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories, which can be one of the first signs of AD. But as more neurons die, additional parts of the brain are affected, and by the final stage of AD, damage is

widespread, and brain tissue has shrunk significantly.⁶

The Alzheimer's Association has identified 10 early signs and symptoms of AD: 1) memory loss, 2) challenges in planning or solving problems, 3) difficulty with completing familiar tasks, 4) confusion with time or place, 5) trouble understanding visual images and spatial relationships, 6) new problems with words in speaking or writing, 7) misplacing things and losing the ability to retrace steps, 8) decreased or poor judgment, 9) withdrawal from work or social activities and 10) changes in mood and personality.⁷

MYTH: All older adults develop AD.

FACT: While most people who develop AD are over age 65, AD isn't a normal part of aging. And, although a person's risk of developing AD doubles every five years after 65, nearly half of 85-year-olds don't have the disease.³

MYTH: Only seniors develop AD.

FACT: AD does most commonly occur in older adults, yet it can also affect people in their 30s, 40s and 50s. Approximately 90 percent of AD cases are called late-onset, meaning they occur after age 65. But, one in 10 cases occurs before age 65, known as early-onset AD.⁸

MYTH: AD is hereditary.

FACT: Less than 5 percent of all cases of AD are "familial Alzheimer's," a type that runs in families,³ but genes do play a role. Indeed, several genes associated with late-onset and early-onset AD have been identified in recent years.

In late-onset AD, the most common gene is apolipoprotein E (APOE), which has three common forms: APOE e2 is the least common and appears to reduce the risk of AD; APOE e4 is more common and appears to increase the risk of AD; and APOE e3 is the most common and doesn't seem to affect the risk of AD. The APOE gene can be inherited from both the mother and father. Inheriting at least one APOE e4 gene increases risk of developing AD. With two APOE e4 genes, the risk is even higher. Yet, not everyone who has one or two APOE e4 genes develops AD. What's more, the disease develops in people with no APOE e4 gene. In addition, with continuing research into the genetics of AD, five other genes have been identified. Some variations of SORL1 on chromosome 11 appear to be associated with AD. The CLU gene, which helps to regulate the clearance of amyloid-beta from the brain, suggests an imbalance that is central to the development of AD. A deficiency of the protein in the CR1 gene may contribute to chronic inflammation in the brain, which is a possible factor in the development of AD. The PICALM gene is linked to the communication process between the brain and nerve cells, suggesting the proper functioning of this gene is necessary. And, rare variants in the recently identified TREM2 gene, which regulates the brain's response to inflammation, are associated with an increased risk of AD.

Mutations in three genes that cause early-onset AD have also been identified: amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Mutations in these genes cause excessive amounts of the toxic amyloid-beta peptide protein, which cause tau protein malfunctions and the formation of neurofibrillary tangles that cause the brain cells to die.⁹

Most recently, a team of scientists discovered an immune system gene associated with higher rates of amyloid plaque buildup in the brains of AD patients and older adults at risk for the disease. Using positron emission tomography (PET) imaging in nearly 500 individuals, researchers assessed the levels of brain amyloid deposits at an initial visit and again two years later. Subsequently, a genome-wide analysis was conducted to identify genetic variants associated with the rate of plaque accumulation during the two-year window. As predicted, APOE e4 was found to be associated with higher rates of plaque buildup. But what was surprising is the finding that IL1RAP, which codes for the key immune signaling factor interleukin-1 receptor accessory protein, showed an independent and even stronger influence on amyloid accumulation. They also found that the amyloid-associated IL1RAP variant was associated with a lower level of microglial activity as measured by PET scans, greater atrophy of the temporal cortex (a region of the brain involved with memory), faster cognitive decline and greater likelihood among study participants of progression from mild cognitive impairment to AD.¹⁰

The truth is that experts don't really know what causes AD.

MYTH: AD can be caused by flu shots, depression, aluminum, silver fillings and aspartame.

FACT: The truth is that experts don't really know what causes AD. It's likely a mixture of genes, environmental factors and lifestyle. And, some research suggests it might be related to health conditions such as heart disease, high blood pressure and diabetes.¹¹

Depression can easily be mistaken for a cause of AD since it often occurs with symptom onset, and the changes in abilities brought on by AD cause fear.⁸

The theory that flu shots cause AD is due to the small amount of mercury in thimerosal, the preservative that is still contained in some flu vaccines. But, several studies debunk that theory and show that flu shots and other vaccines actually reduce the risk of AD and lead to overall better health.⁵ One study conducted in 2001 with 4,392 participants showed that

there was a decreased risk of developing AD for those who had received influenza immunizations, as well as for those who received vaccinations for diphtheria or tetanus (which were grouped together in the research) or poliomyelitis (polio). While it didn't actually show that the flu vaccine was what caused a lower risk of AD, it did indicate that those who received the vaccine were less likely to develop AD, and those who didn't were more likely to develop AD. In addition, a study published in the *Journal of the American Medical Association* in 2004 showed that annual flu shots for older adults were associated with a reduced risk of death from all causes.¹²

Mercury is also at the root of the theory that silver dental fillings increase the risk of AD. Silver fillings are made of an amalgam mixture that typically contains about 50 percent mercury, 35 percent silver and 15 percent tin. But, once again, studies show no relationship to AD. The most recent study was conducted in 2003, which found no connection between mercury-containing dental fillings and Alzheimer's or other neurological diseases.

Lastly, in May 2006, the U.S. Food and Drug Administration (FDA) reported that of the more than 100 laboratory and clinical studies conducted to determine if aspartame causes memory loss, none had presented any scientific evidence of it.⁵

The only conclusive diagnosis of AD is at death, when microscopic examination of the brain reveals the characteristic plaques and tangles.

MYTH: AD can be prevented.

FACT: It's really not yet known what can prevent AD, and there is certainly no single treatment to prevent it. It has been purported that taking supplements can help inhibit AD, but studies conducted on vitamins E, B and C, ginkgo biloba, folate and selenium have been inconclusive.¹³

Many things, however, can be done to protect the brain such as building brain power by learning new skills, exercising daily and maintaining a busy social life.³ The National Institute on Aging (NIA) and other public and private agencies have conducted observational and animal studies associated with changes in AD risk. In recent years, these studies have suggested there may be a connection between high levels of blood

cholesterol and the development of AD. On the flip side, some studies have shown that statins, the most commonly prescribed cholesterol-lowering drugs, may reduce the risk of dementia (although other studies have found no relationship). Yet, other studies have found that high levels of the amino acid homocysteine, which are known to increase heart disease risk, are associated with an increased risk of developing AD. Studies in mice have shown that the amino acid can make neurons stop working and die. A current NIA-funded study is investigating whether reducing homocysteine levels with folic acid and vitamins B6 and B12 supplements will slow the rate of cognitive decline in older adults with AD. But only future clinical trials will reveal whether any of these factors can help to prevent AD. And, those factors may vary from individual to individual, especially if a person has a risk factor gene.¹⁴

MYTH: There is a test for AD.

FACT: There is no test that can definitively diagnose AD. The only conclusive diagnosis of AD is at death, when microscopic examination of the brain reveals the characteristic plaques and tangles. However, to distinguish AD from other causes of memory loss, physicians rely on personal and medical history, blood tests, neurological tests and some imaging tests. The physical exam is used to determine overall neurological health by testing reflexes, muscle tone and strength, the ability to get up from a chair and walk across a room, sense of sight and hearing, coordination and balance. Blood tests help to rule out other causes of memory loss and confusion such as thyroid disorders or vitamin deficiencies. Neurophysical testing may include a brief mental status test or a more extensive assessment of thinking and memory. Magnetic resonance imaging can be used to rule out other conditions and to assess whether there is shrinkage in brain regions implicated in AD. Computerized tomography is used to rule out tumors, strokes and head injuries. And, a PET scan can show which parts of the brain aren't functioning well, with new techniques able to detect the levels of plaques and tangles in the brain.¹⁵

Researchers are also working to develop new diagnostic tools to help diagnose AD, including additional approaches to brain imaging, more sensitive tests of mental abilities and measurement of key proteins or protein patterns in blood or spinal fluid.¹⁵ Better testing is needed since a diagnosis of AD can be delayed or missed because it is often associated with the normal aging process, and early symptoms develop gradually.¹⁶ In fact, AD can develop 20-plus years before memory loss.³ AD can also be overdiagnosed because it mimics other conditions such as transient ischemic attack, depression, vascular dementia, Creutzfeldt-Jacob disease, brain tumor, hydrocephalus and other problems.¹⁶

This is why early detection is a key focus of research today. The earlier AD can be identified, the better the effectiveness of existing medications. At the University of Alberta, Canada, a

student has developed a potential new test that uses a form of protein analysis called liquid chromatography-mass spectrometry to analyze saliva samples to determine what substances are predominant in the saliva of AD patients. Results suggest that higher levels of certain substances present in the blood of AD patients can predict “worse episodic memory performance” and “slower speed in processing information.”

Other areas of research include sampling cerebrospinal fluid, which offers protection to the brain and spinal cord. And, PET scan technology has made it possible to isolate tau tangles in the brain to help understand how advanced a person’s disease may be. The scan can also be used to track inflammation, whose role in AD is still being investigated, as well as microglial cells, the brain’s immune cells, to get a better picture of brain health.¹⁷

MYTH: AD can be treated.

FACT: Currently, there is no treatment to indefinitely delay or stop the progression of AD. However, FDA has approved five medications that may help slow the progression of AD temporarily, but they work in only one in three people for a period of six months to a year.⁵ These drugs, which include donepezil (Aricept), galantamine (Razadyne), memantine (Namenda), rivastigmine (Exelon) and tacrine (Cognex), help with thinking, memory, language skills and some behavioral problems.¹¹

Because of the progress in understanding healthy brain function and what goes wrong in AD, there are some promising targets for next-generation drug therapies under investigation. These include trials for drugs targeting beta-amyloid (the chief component of plaques), tau protein (the chief component of tangles), inflammation (another key AD brain abnormality) and insulin resistance (the way brain cells process insulin may be linked to AD). There are also clinical trials in progress for brain imaging studies and testing of blood or spinal fluid to reveal AD biomarkers.

For individuals with rare genetic mutations, the Alzheimer’s Prevention Initiative (API) in Antioquia, Colombia, South America, is investigating the world’s largest family in which a gene for familial AD (also known as autosomal-dominant AD) has been identified. API’s first clinical studies will test therapies targeting beta-amyloid in family members who are known to have the AD-causing gene but who have not yet experienced symptoms.¹⁸

Several studies investigating the possibility of treating AD with intravenous immune globulin (IVIG) have shown mixed results. Both preclinical and clinical studies have shown that “IVIG has anti-amyloid and immune modulatory properties relevant to treating neurodegenerative disorders.” In early stage AD clinical trials, IVIG reduced cognitive decline and increased brain glucose metabolism. Unfortunately, IVIG failed to meet primary outcome objectives in the Phase III clinical trial in mild to moderate AD. However, positive cognitive signals were observed in pre-planned subgroup analyses among

APOE e4 carriers and moderately impaired AD patients. In these patients, biomarker studies revealed dose-dependent increases in plasma and cerebrospinal fluid immunoglobulins and decreases in beta amyloid-42 levels.¹⁹

While results of clinical trials to date don’t currently support the use of IVIG to treat AD, additional studies are being conducted. In October, researchers found that IVIG reduced brain atrophy and cognitive decline in patients in the early, pre-dementia phase of AD. The trial, administered from 2011 to 2013, included 50 patients aged 50 years to 84 years who were diagnosed with amnesic mild cognitive impairment due to AD. Participants were administered either IVIG or saline solutions every two weeks for a total of five infusions. Brain imaging was conducted at baseline, at 12 months and at 24 months. The images at 12 months for those who received IVIG showed less brain atrophy than those who were given the placebo. In addition, those who were treated with IVIG showed better cognitive testing results, and there were fewer conversions to dementia after 12 months. However, differences in the treatment groups faded by 24 months, which prompted the researchers to propose that annual infusions of IVIG may be necessary to sustain treatment effects. Additional research will be needed to prove this.²⁰

MYTH: AD symptoms are reversible.

FACT: AD is deterioration of the brain, and it can’t be reversed. In fact, no amount of effort such as physical activity or cognitive exercises will reverse AD. It is believed that those who think it is reversible may have known someone who was misdiagnosed with AD and then correctly treated for another condition such as thyroid problems, vitamin deficiency, depression and even medication. It’s also possible that people may misinterpret the advertising for AD disease medications, which provide a more subtle stabilization of symptoms rather than dramatic symptom relief.⁸

MYTH: An AD diagnosis means life is over.

FACT: Many people with AD can improve their quality of life and slow AD progression for years by eating a heart-healthy diet, exercising regularly, staying socially connected and doing things that challenge the brain.¹³ There are also other ways to improve daily life for those with AD. Keeping a routine helps because people with AD tend to prefer a familiar schedule and settings. Since crowds and noise can easily overwhelm people with AD, limiting the amount of sound and movement can help. Spending time on familiar tasks and hobbies can make them feel productive and happy. Caregivers can take some control of everyday choices to relieve the stress of making decisions. And, because people with AD can become more upset at night (called sundowning), caregivers can help by turning on more lights and showing concern by not dismissing fears.²¹

MYTH: AD isn’t fatal.

FACT: AD is the sixth-leading cause of death in the U.S., with

most people living only eight to 10 years after diagnosis. It is a progressive disease that causes people to forget to drink and eat, have trouble swallowing, can lead to a severe shortage of nutrients, can cause breathing problems and can lead to pneumonia. AD is also associated with high-risk behavior such as wandering into dangerous situations.¹¹

MYTH: Caregivers don't need help to care for their loved ones with AD.

FACT: Many caregivers, who are predominantly family members, don't ask for help for many reasons such as pride, sense of obligation or love. In 2014, friends and family of people with AD and other dementias provided an estimated 17.9 billion hours of unpaid care, with an estimated value of \$217.7 billion. Caring for a person with AD takes a devastating toll, with nearly 60 percent of caregivers rating their emotional stress as high or very high, and about 40 percent suffering from depression.¹

The reality is that caregivers can't do it alone. In fact, studies show that those who get a break provide better care than those who do not.⁸ Federal and state programs offer many resources for caregivers that can be found at www.alzheimers.gov/caregiver_resources.html. In addition, the Alzheimer's Association has a 24/7 support line at (800) 272-3900, and it can help caregivers find local support groups in their areas.

AD is the sixth-leading cause of death in the U.S., with most people living only eight to 10 years after diagnosis.

Dispelling the Myths Now

Developing treatments to slow or even cure AD is crucial. Without it, 28 million baby boomers will fall ill with AD by 2040, consuming 24 percent of Medicare spending, according to a report from the 2015 Alzheimer's Association International Conference.¹⁷

In recent years, both international and national efforts have recognized the public health importance of AD. In 2011, President Obama enacted the National Alzheimer's Project Act, which called for a National Advisory Council on Alzheimer's Disease Research and resulted in the development of a national plan to address AD each year for the effective prevention and treatment of AD by 2025. In 2012, the World Health Organization identified dementia as a public health priority.

And, to date, 40 states have developed plans to address AD.^{22,23}

Scientists have made remarkable progress in understanding AD in the last three decades, but there is much more to be accomplished. Through planning and research, it can only be hoped that we discover how AD can be prevented, treated and even cured. Until that happens, though, it's important for those affected to know the signs of AD and where to get help. ❖

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Beating the Odds with CVID

BY TRUDIE MITSCHANG

A diagnosis of primary immunodeficiency (PI) often leads to varying degrees of disability. For Brandon Dillon, it offered an opportunity to find untapped reserves of resilience.

AFTER A RELATIVELY healthy childhood, Brandon Dillon began coming down with multiple colds and respiratory infections as a young adult. For a decade, his health continued to deteriorate, and in October 2010, after a nasty bout of pneumonia that resulted in a six-month hospital stay, Brandon was diagnosed with common variable immune deficiency (CVID). At 37, Brandon was active, athletic and busy climbing the career ladder; it's an understatement to say he didn't have "time" for an immune disease. "Growing up, I hardly ever got sick," Brandon recalls. "Prior to my diagnosis, I battled the usual sinus infections that most of us with a primary immunodeficiency do, usually four or five per year. It seemed that every time I caught a cold, it would turn into an infection. This started happening when I was in my mid-20s. Years later, I was in the hospital being treated for a very severe case of pneumonia when I finally learned what was wrong with me."

Understanding CVID

There are more than 250 primary immunodeficiency diseases (PIs) recognized by the World Health Organization. CVID is a frequently diagnosed immunodeficiency, especially in adults, and is characterized by low levels of serum immunoglobulins and antibodies, which causes an increased susceptibility to infection. CVID is thought to be due to genetic defects, although the exact cause of the disorder is unknown in the large majority of cases. Compared with other human immune defects, CVID is

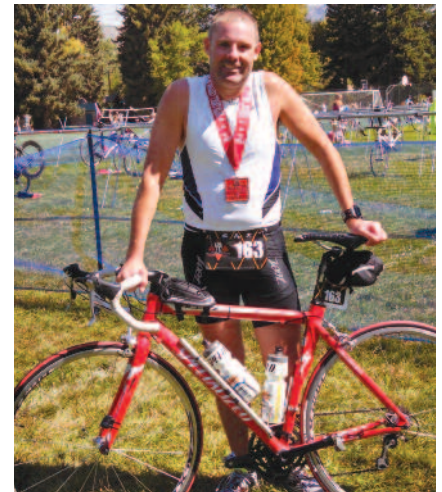
a relatively frequent form of PI, found in about one in 25,000 individuals.¹

Finding Strength Through Adversity

An avid cyclist prior to his diagnosis, Brandon approached his diagnosis with the same level of determination he used as a competitive athlete. A short six months after being diagnosed, he completed his first full marathon, coming in just short of his goal time. Today, Brandon is determined to live a full life and is passionate about inspiring others to pursue their own personal best. "After my diagnosis, I was at a follow-up visit with my immunologist, and he told me that the goal with my treatment is to die with CVID and not from CVID, and that there was no reason that I could not continue to participate in the activities I love," Brandon explains. "I took that literally, so when a friend asked me to run a full marathon with him that spring, I said yes."

Brandon's treatment plan includes intravenous immune globulin (IVIG) administered every four weeks in an infusion clinic, and so far, he's been fortunate to suffer few side effects. "Having CVID doesn't discourage me; if anything, it gives me more motivation," he says. "My hope is that others who have CVID or another PI, who think that life as they once knew it before diagnosis is over, can clearly see that it doesn't have to be."

Brandon is quick to add that running marathons isn't for everybody, noting that PI affects people differently: "I feel very fortunate that my body responds well to IVIG, and I'm still able to do the things I love."



Shortly after being diagnosed with common variable immune deficiency, Brandon Dillon completed his first full marathon, and he's not stopping there.

Although many PI patients struggle to maintain a busy schedule, Brandon currently works full time as a computer-aided design technician for a structural engineering company. He also recently competed in his first half distance triathlon. A proponent of patient support groups, Brandon credits the encouragement he has received from other CVID patients with keeping him motivated and optimistic. "I came across the group TriForBetter* online, and being a part of it has inspired me to keep up with my training and push myself to set higher goals," he explains. "Having the ability to see others who are dealing with the same illness that I am, living active lives, truly keeps me going." ❖

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

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*TriForBetter.com is an online patient support group founded by CVID patient David Brumley. The organization's mission is to inspire, equip and encourage those living with primary immunodeficiency disease.

Primary Immunodeficiency Disease: A Physician's Perspective



Dr. Terry Harville, a leading expert in the treatment of primary immunodeficiency diseases, was involved in the early stages of treatment options.

DR. TERRY HARVILLE is associate professor of pathology at the University of Arkansas for Medical Sciences (UAMS) and associate professor of pediatrics at the Arkansas Children's Hospital, both in Little Rock, Ark. In addition, he is medical director for the Special Immunology Laboratory and Molecular Diagnostics Laboratory at Arkansas Children's Hospital, and medical director for the Histocompatibility Laboratory and the Immunogenetics and Transplantation Laboratory at UAMS. Dr. Harville is considered a leading expert in the evaluation and treatment of patients with complex immune disorders.

BSTQ: Tell us about your background and experience treating primary immunodeficiency diseases (PI).

Dr. Harville: Before getting into medicine, it struck me as odd that we treated so many diseases by giving "poisons" to patients in hopes that they would kill the disease but not the patient. It

seemed that if we could manipulate the immune system, we could accomplish the goal of disease treatment without harm to the patient. Dr. Bob Good once described patients with immunodeficiencies as "experiments in nature" from whom we can learn and understand how the immune system works. All of this led me to become an immunologist. My initial work was primarily with the more severe immunodeficiencies and clinical practice of stem cell transplantation, primarily as inpatient care. My outpatient practice consisted of diagnosing the variety of immunodeficiencies that exist and especially diagnosing and treating patients with autoimmunities. In my current academic position, I teach, perform research and am the medical director of separate laboratories for the evaluation of patients for organ or hematopoietic stem cell transplantation and patients with suspected immune disorders.

We are in dire need to educate the medical community that PI is not "rare" but much more common than most have thought.

BSTQ: What are some of the "red flag" symptoms of PI?

Dr. Harville: Patients who present with numerous or unusual infections

should be immediately tested for PI, but it's possible that patients without obvious problems with infections may be developing autoimmune disorders only to later experience recurrent infections. These patients may have their recurrent infections ascribed to the treatment for their autoimmunity, further delaying diagnosis. At the time of this interview, more than 275 gene mutations have been identified that may result in immunodeficiency or autoimmunity, sometimes in the same patient. Therefore, an emerging concern is that patients may be in the gastrointestinal clinic for problems with inflammatory bowel disease, in the rheumatology clinic with arthritis or lupus disease features, or in the pulmonary clinic with lung disease, and may not be recognized as having PI.

BSTQ: What are some of the misconceptions about PI within the medical community?

Dr. Harville: Many think that PI occurs in as few as one per 100,000 or one per million in the population. This prevents most physicians from considering that PI is as common as other conditions. Currently, it is believed that common variable immunodeficiency may occur in approximately one per 10,000, and that clinically significant antibody deficiencies may be present in as many as approximately one per 3,000, about the frequency of conditions such as cystic fibrosis. Therefore, we are in dire need to educate the medical community that PI is not "rare" but much more common than most have thought.

Another major misconception is that antibiotics are sufficient to treat most patients with PI, and that expensive immune globulin (IG) replacement is not required. To adequately treat most

patients with antibody deficiency, IG replacement is required, and indeed, higher dosing is needed than what was previously thought to be sufficient.

BSTQ: How have treatment options evolved since you first began treating PI patients?

Dr. Harville: When I was beginning my training, we had intramuscular injections of gammaglobulin available, and testing was being done for the development of the intravenous (IV) forms. I participated in some of the testing for those “new” IVIG products. For safety issues, detergent treatment was developed for IVIG to inactivate enveloped viruses. And, other modalities were developed to ensure safety, including pasteurization and nanofiltration. Other proprietary viral inactivation components have also been

designed and tested. Thus, increased safety of the infused products derived from plasma has undergone tremendous change. Today, bone marrow stem cell transplantation for severe forms of PI has gone from arduous to routine, with 70 percent to 80 percent good outcomes improving to current outcomes in the high 90 percent range. Some transplants can be done essentially as outpatient procedures, decreasing the time required to be hospitalized.

BSTQ: What is the focus of current research?

Dr. Harville: Current research is focusing on identifying gene mutations that associate with PI. Now, patients can be stratified to study by the mutations present, as well as clinical features. I believe this will greatly push treatment options forward. A huge plus is that the

cost of the genetic studies is coming way down. Soon, a person may be able to have his or her entire genome sequenced for less than \$1,000. Currently, most immune testing costs more than this. With the proper computer analysis developed and available, all the genes associated with specific immune system activities and functions may be identified for each of us, and abnormalities may be more readily detected. Performed on infants, such testing may allow for identification of those at risk, who then can have appropriate further testing performed prior to complications of PI, and have the correct treatment started much sooner. ❖

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



Sponsor a child with hemophilia

It's rewarding and teaches unforgettable lessons

Facing another morning infusion, 10-year-old Andrew* looks at the picture of his beneficiary, 12-year-old Abil from the Dominican Republic, and sees Abil's swollen knees from repeated untreated bleeds. Each time this reminds Andrew just how fortunate he is to live in a country with factor.

Become part of our world family. A sponsorship is only \$22 a month!

A child is waiting for you at: www.saveonelife.net
Or email: contact@saveonelife.net

* name has been changed

BabyBIG: Definitive Early Immunotherapy for Infant Botulism

Behind this highly effective public service orphan drug is a remarkable story of innovation, faith and perseverance.

BY KEITH BERMAN, MPH, MBA

BOTULINUM TOXIN IS produced by the spore-forming, anaerobic bacterium *Clostridium botulinum* or other closely related bacterial species. It is the most poisonous substance known, natural or synthetic. The median lethal dose in adults is around one to two ten millionths of a gram when injected, or roughly 10 times that much when inhaled.¹ Once carried through the bloodstream to the peripheral neuromuscular synapses, botulinum toxin blocks release of the acetylcholine neurotransmitter to muscle, resulting in hypotonia and flaccid paralysis. Without aggressive, around-the-clock medical support, death from a lethal exposure to botulinum toxin usually results from airway obstruction due to paralysis of pharyngeal muscles that control swallowing and airway diameter.

The ultimate survivors, spores of *C. botulinum* can reside dormant for years in soil, dust and other unfriendly environments. The spores germinate, multiply and start to release the botulinum neurotoxin only when they find themselves in suitable anaerobic (oxygen-free) conditions combined with an adequate nutrient supply. Over the 150 years since the first complete description of the symptoms of victims of a “sausage poisoning” outbreak around 1820, the acute paralytic disorder known as botulism* referred only to the sequelae of ingesting botulinum toxin present in food in which *C. botulinum* had grown.

Modern food preservation and processing methods variously kill the spores, inhibit growth of the organism or inactivate the neurotoxin. As a result, foodborne botulism is an extremely rare event today in the U.S., with fewer than 30 instances reported annually.²

A New Host for an Old Disease

However, in 1976, a pair of case reports described six very young U.S. infants with symptoms consistent with botulism that prominently included weakness and descending flaccid paralysis.^{3,4} All presented with an additional symptom: constipation. Yet none of them had any known or suspected exposure to foodborne botulinum toxin. Testing of fecal samples by Thaddeus Midura, PhD, Stephen Arnon, MD, and colleagues at what is now the California Department of Public Health (CDPH) solved the mystery: both *C. botulinum* bacteria and botulinum neurotoxin were found in the stools of all six infants.

Infant botulism was immediately recognized as an entirely new disease pathway. It occurs in susceptible weeks- to months-



Source: CDPH/IBTPP

* From the Latin word “botulus,” meaning sausage.

old infants who swallow a few spores of *C. botulinum*. The intestinal tract of these young infants, who are still consuming only a very simple diet of breast milk or formula, lacks the adult-type inhibitory bacterial flora that arrive once the baby starts solid foods. In the absence of those inhibitory bacteria that would otherwise hold *C. botulinum* spores in check, the gut of the infected infant is, in essence, an incubator that allows the spores to germinate, propagate and secrete botulinum toxin.

Although infant botulism was newly recognized in 1976, the disease itself was not new. Earlier misclassified cases were identified on retrospective reviews, including one laboratory-confirmed case dating back to 1931.⁵ Over the years prior to 1976, cases had simply been improperly attributed to some other disease process. Less than



Source: CDPH/IBTPP

five years after the initial case reports, an epidemiological study conducted in California, where approximately half of U.S. cases are reported, found that about one in every 20 deaths reported as sudden infant death syndrome (SIDS) is actually caused by fulminant infant botulism.⁶

Over the ensuing 40 years, several thousand U.S. cases of infant botulism have been confirmed by fecal specimen testing. About 90 percent of the 100 to 150 cases reported annually occur in infants under 6 months of age; virtually all occur in babies under 1 year of age. In addition to California, case rates are much higher in a few other states, including Pennsylvania, Utah, Delaware and Hawaii. Soils in certain locations in

those states have been found to contain *C. botulinum* spores that manage to find their way into microscopic dust and honey, which parents are warned not to feed to their children prior to 1 year of age.

With timely clinical diagnosis (Table 1) and 24-hour intensive supportive care, nearly all affected infants survive and eventually fully recover. But the potency and unusually long duration of action of botulinum toxin⁷ prolongs the neuromuscular blockade, resulting in a disease course that is lengthy and potentially complicated by such serious adverse events as pneumonia, anemia, hyponatremia and urinary tract infection. Roughly half of infants will require mechanical ventilation at some point during their hospital stay; the average period of ventilator dependency for those who do is about four weeks. While highly variable depending on patient-specific factors and whether affected by type A or type B botulinum toxin, untreated infant botulism patients remain hospitalized for close to six weeks on average with supportive medical care alone.

Creating a Botulism Immune Globulin

An equine botulism antitoxin, first used in the 1960s to hasten the recovery of adult patients with severe foodborne botulism, was ruled out for infant botulism. Its risks of serious side effects, including serum sickness, anaphylaxis and lifelong sensitization to equine proteins, outweighed the presumptive benefits of neutralizing the botulinum toxin. A CDPH team led by Dr. Arnon decided to investigate a different approach: administration of an antitoxin purified from the plasma of toxoid-immunized human donors. Thus began a

Table 1. Clinical Signs and Symptoms of Infant Botulism^a

Early symptoms commonly noticed at home

- Constipation^b
- Lethargy
- Listlessness
- Poor feeding

Progressive signs and symptoms

- Expressionless face
- Feeble cry
- Ptosis (eyelids)
- Latent ophthalmoplegia
- Poor head control
- Generalized weakness and hypotonia
- Impaired gag, suck and swallow reflexes
- Fatigability of pupillary constriction

^aIn fulminant cases, the infant can be nursing normally six hours before becoming so floppy that acute meningitis may be the provisional diagnosis at first evaluation. Alternatively, the fulminant-onset patient may present as sudden cardiorespiratory arrest.¹⁰

^bThree or more days without defecation in a previously regular infant; a few patients (<5 percent) will not present with a history of constipation.

Table 2. Milestones in the Conceptualization and Gestation of BabyBIG⁸

Year	Event
1976	Infant botulism first identified as a distinct disease
1978	U.S. Army starts collecting hyperimmune plasma to prepare a botulism immune globulin (BIG) for military use against possible biowarfare
1988	With U.S. Army's agreement to supply BIG, CDPH successfully applies to FDA Office of Orphan Products Development for funds to conduct a pivotal trial of BIG
1990	Iraq invades Kuwait; U.S. Army redirects its entire supply of BIG to anticipated military needs in the Persian Gulf; CDPH statewide pivotal trial now without a product to test
1990	CDPH decides to create its own Botulism Immune Globulin Intravenous (Human) (BIG-IV). Starts collecting hyperimmune plasma from research staff and others already immunized with a CDC-supplied investigational botulinum toxoid
1992	Pivotal clinical trial of BIG-IV opened for planned enrollment of 120 infant botulism patients in 59 participating hospitals
1997	Pivotal clinical trial fully enrolled
1997	Analysis of findings shows that BIG-IV met primary and secondary endpoints; FDA authorizes open-label distribution in California
1998	FDA authorizes nationwide distribution of BIG-IV to infant botulism patients under treatment IND status, predicated on pivotal study findings and absence of an alternative treatment for this life-threatening condition
2000	A second lot of BIG-IV produced (licensure requirement) after securing IRB and FDA approvals to boost plasma donors with investigational botulinum toxoid
2003	FDA licenses BIG-IV to CDPH as BabyBIG for treatment of infant botulism types A and B

15-year odyssey (Table 2) that required Dr. Arnon and his colleagues to manage unforeseeable setbacks, navigate through a web of evolving laws and regulations, and enlist what amounted to an alphabet soup of federal and state government entities and altruistic volunteer plasma donors to produce and clinically test an experimental human botulinum antitoxin.

The initiative began with a major setback. In August 1990, just as organizational efforts were nearing completion for a randomized, placebo-controlled pivotal clinical trial of botulism immune globulin (BIG) to be supplied by the U.S. Army, Iraq invaded Kuwait. The Army redirected its entire supply of BIG to anticipated military needs in the Persian Gulf, and suddenly there was nothing to test.⁸

Not dissuaded, the CDPH, with support from the U.S. Food and Drug Administration (FDA) Orphan Drug Office, decided to create its own product to replace the Army's diverted BIG product. For a source of hyperimmune plasma, the CDPH relied on volunteer plasma donations from its own botulism research staff and others previously immunized with a botu-

linum toxoid product for occupational safety purposes. The product prepared from that plasma was dubbed BIG-IV.

The pivotal trial to evaluate BIG-IV in 59 participating California hospitals finally opened for patient enrollment in February 1992. Over the next five years, 122 infants with laboratory-confirmed infant botulism were randomized to receive a single dose of BIG-IV or placebo. As the antibody has a half-life of approximately 28 days and a large capacity to neutralize botulinum toxin, a single infusion was demonstrated to be sufficient to neutralize, for at least six months, all of the neurotoxin that might be absorbed from the infant's colon.

BIG-IV Proves Safe and Highly Effective

In May 1997, the study findings were unveiled. The mean length of hospital stay — the study's primary endpoint — was significantly reduced in patients given a single dose of BIG-IV (2.6 versus 5.7 weeks, $P < 0.001$). Essentially all of this reduction was reflected in a shorter mean intensive care unit (ICU) stay (1.8 versus 5.0 weeks, $P < 0.001$). The mean duration of

mechanical ventilation for the 59 patients requiring it also strongly favored the BIG-IV group (1.8 versus 0.4 weeks, $P < 0.001$), as did duration of tube or IV feeding (3.6 versus 10.0 weeks, $P < 0.001$).⁹

Earlier clinical diagnosis and administration of BIG-IV** directly translate into shortened hospitalization. The mean length of stay for patients administered BIG-IV within three days of admission was 2.0 weeks, compared with a mean stay of 2.9 weeks when given on days four to seven following admission ($P < 0.001$).

Not surprisingly, the adverse event rate was reduced by nearly one-half in the BIG-IV group (0.9 versus 1.7 events, $P < 0.04$). Anemia and urinary tract infection rates were significantly lower, with rates of other serious adverse events trending lower as well.

All of these clinical benefits translated into mean hospital charges per patient of \$74,800 in the BIG-IV group, 54 percent lower than mean charges of \$163,400 in the placebo group.

Finally in October 2003, an effort that began in 1988 with plans to test an Army BIG product culminated in the FDA's approval of Botulism Immune Globulin Intravenous (Human) (BIG-IV), trade named BabyBIG. The product license is held by the CDPH Infant Botulism Treatment and Prevention Program (IBTPP). BabyBIG is manufactured by Baxalta on a contract basis. It is distributed at the direction of IBTPP to hospitals throughout the U.S. and internationally by FFF Enterprises. As a not-for-profit, self-supporting state activity, IBTPP uses revenues eventually paid by health insurers for the product to fund its operations, including laboratory testing and 24-hour on-call availability of a physician botulism treatment specialist (see How to Contact the Infant Botulism Treatment and Prevention Program).

The Rewards of Staying the Course

Since IBTPP began supplying BabyBIG, it has carefully tracked patient outcomes and hospital charges, and documented that the product has spared infants more than 70 years of hospitalization (mostly in the ICU) and has reduced hospital charges by more than \$100 million.

Over a period of 15 years, BabyBIG was produced, clinically tested and licensed with a cash outlay of just \$10.6 million (in 2005 dollars).⁸ That shoestring budget does not, however, account for countless thousands of hours devoted by personnel at the CDPH and other collaborating agencies to make it all happen.

How to Contact the Infant Botulism Treatment and Prevention Program

- If you have a patient suspected of having infant botulism: (510) 231-7600, 24 hours a day, 7 days a week, 365 days a year
- For more information about infant botulism and securing BabyBIG: www.infantbotulism.org
- To send IBTPP non-urgent questions or comments: ibtpp@infantbotulism.org

“In my younger days, my avocation was mountain climbing,” Dr. Arnon shared with me in an interview. “Which, by definition, is always going uphill. In its own way, it was good preparation for the BabyBIG endeavor.” As a result of the perseverance and inventiveness of this state public health department, somewhere every few days a young infant paralyzed by the world's most potent toxin is discharged home weeks earlier and with a significantly lower risk of serious complications than he or she would have otherwise without BabyBIG treatment.

Without question, it was a mountain worth the climb. ❖

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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** As currently recommended for all new patients with a provisional clinical diagnosis, treatment with BIG-IV was started as early in the illness as possible to maximally neutralize the toxemia; it should not be delayed for laboratory confirmation of the clinical diagnosis.



BioResources

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Author: U.S. Food and Drug Administration

This new management report gives candid “what to do — and how to do it” advice, including the evolution of FDA’s thinking on the clinical requirements for showing biosimilarity, right up to and including the 2015 guidance; how participating in the FDA’s Biological Product Development Program is beneficial; the supporting clinical data that must be included in filings to gain approval quickly; the correct way to apply FDA’s latest recommendations for demonstrating that a proposed product is “highly similar” to a reference; how to effectively use key evaluations and modeling and simulation tools; and how to anticipate legal and regulatory hurdles such as patent and litigation issues, interchangeability and state substitution laws. Also included is a detailed review of four critical topics from the recent FDA guidance: 1) how to establish a step-wise approach to product development — the way FDA prefers; 2) the agency’s “totality of evidence” methodology for assessing 351(k) applications; 3) using foreign reference products and the need for bridge studies; and 4) how analytics should be designed for pharmacokinetics and pharmacodynamics.

www.fdanews.com/products/50902-strategies-for-biosimilars-approval-a-map-to-351k-success

to-electronic conversion will completely change and simplify existing procedures, processes and how information and data are handled. Specifically covered are how to convert a paper-based documentation system into an eDMS; the basic principles and functions of the eDMS — and what technical aspects to be concerned about; how to handle project management, validation and system selection when an eDMS is implemented; the links between document management and information and knowledge management; regulatory requirements to consider when an eDMS is implemented; why training management or other quality-relevant processes should be taken into account in an eDMS; how to define “the master document”; and what to think about in determining electronic data and electronic signatures.

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Find trial subjects using Social Media.

Using Social Media in Clinical Trial Recruitment

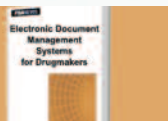
Using Social Media in Clinical Trial Recruitment

Author: U.S. Food and Drug Administration

Today, one in five sponsors uses social media to engage, recruit and retain subjects for clinical trials. This report is designed to help unsure clinical trial recruiters put aside their concerns and go ahead with social media recruiting of trial subjects. The report shows how other organizations are overcoming challenges and employing social media for increasingly successful recruitment. Also included is access to relevant survey results and social media tips and techniques being employed all around the country, including the importance of social media sharing and how it can supercharge recruiting efforts, results of a 1,000-patient survey that reveal clinical trial subjects’ online behaviors; the most effective social media techniques for reaching study subjects; how to avoid the “rookie mistakes” that drug companies make when they first use social media to recruit; where patients search for clinical trial information online; how to review social media efforts and make them more effective; what patients think about clinical trial sponsors and social media; and how to tell if there is overspending on social media campaigns.

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Let an expert guide you through your conversion from paper to a validated eDMS.



Electronic Document Management Systems for Drugmakers

Author: U.S. Food and Drug Administration

This new management report from FDAnews tackles the key concepts, various issues and tricky interrelationships with other systems that companies must deal with during a conversion to a validated eDMS. Expert author Markus Roemer explains how to begin making changes to a company’s documentation management — including both knowledge and information management — as well as to documents and records relating to SOP management, training management, changes, deviations, production and warehouse records, records from the laboratory sector and more. He also shows how a paper-

Short Course of IVIG May Slow Brain Atrophy and Conversion to Dementia in Persons with MCI Stage of Alzheimer's Disease



An exploratory controlled, randomized, double-blind study was conducted by investigators at the Sutter Neuroscience Institute in Sacramento to determine whether a single course of intravenous immune globulin (IVIG) influences the rate of brain atrophy and cognitive function in mild cognitive impairment (MCI) due to

Alzheimer's disease (AD). Fifty participants aged 50 years to 84 years with amnesic MCI were administered 0.4 g/kg of 10% IVIG or 0.9% saline every two weeks for a total of five infusions (2 g/kg total dose). Brain magnetic resonance imaging (MRI) was completed at baseline, 12 months and 24 months; average annualized percentage change in ventricular volume was computed as a measure of brain atrophy. Cognitive testing was completed at baseline and every four months thereafter.

At 12 months post-treatment, subjects in the IVIG group experienced significantly less brain atrophy (-5.87%) than those in the placebo control group (8.14%) ($p=0.037$, adjusted for MCI status); at 24 months, the relative reduction in brain atrophy in the IVIG group no longer reached statistical significance. Participants stratified into the late MCI stage who received IVIG performed better on AD Assessment Scale-cognitive subscale (ADAS-Cog; $p=0.011$) and Mini-Mental State Examination (MMSE; $p=0.004$) at one year; however, these differences were no longer present after two years. While after two years there was no difference in conversion to AD dementia between the IVIG and control groups, after one year there were fewer conversions from late MCI to AD dementia in the IVIG group (33.3%) when compared with the control group (58.3%).

This study provides limited evidence that a short course of IVIG given in the MCI stage of AD reduces brain atrophy, slows cognitive decline in late MCI and delays conversion to AD dementia for at least one year; however, its effect appears to wane by two years.

Kile S, Au W, Parise C, et al. IVIG treatment of mild cognitive impairment due to Alzheimer's disease: a randomized double-blinded exploratory study of the effect on brain atrophy, cognition and conversion to dementia. *J Neurol Neurosurg Psychiatry* 2015 Sep 29 [Epub ahead of print]

IVIG Used as First-Line Monotherapy Attenuates Statin-Triggered Autoimmune Myopathy

Statin-triggered autoimmune myopathy can occur in rare instances where muscle-related symptoms fail to resolve following stoppage of the medication. This condition is characterized by proximal muscle weakness, necrosis of muscle fibers, elevated serum levels of creatine kinase, and the presence of autoantibodies that recognize HMG-CoA reductase, the pharmacologic target of statins.

Among 82 patients with statin-triggered autoimmune myopathy at a single center, three patients with diabetes declined glucocorticoids because of concerns about potential side effects, but agreed to try monotherapy with intravenous immune globulin (IVIG), administered at a dose of 2 g/kg per month. Immediately pre-treatment, the mean creatine kinase level was 4919 ± 3523 IU per liter, and all three patients had documented weakness in the proximal arms and legs. After two or three rounds of IVIG monotherapy, the mean creatine kinase level declined to 1125 ± 1101 IU per liter, mean strength of arm abduction increased from 3.5 to 6.2 kg, and hip-flexion strength improved or normalized.

However, despite partial or full recovery of strength, two patients had persistent creatine kinase elevations, and all three continued to have positive titers for HMG-CoA reductase antibodies. According to the study authors, these findings suggest that IVIG may attenuate statin-treated autoimmune myopathy, allowing muscle regeneration to outpace muscle destruction, but may not completely abolish the pathophysiological processes that cause muscle damage. "Our experience suggests that monotherapy with IVIG may be considered as a first-line treatment for statin-triggered autoimmune myopathy," they concluded.



Mammen AL and Tziakou E. Intravenous immune globulin for statin-triggered autoimmune myopathy [letter]. *New Engl J Med* 2015 Oct 22;373:1680-2.

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Medicare IVIG/SCIG Reimbursement Rates

Rates are effective January 1, 2016, through March 31, 2016.

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Biotest Pharmaceuticals	J1556	\$77.72	\$76.47
CARIMUNE IVIG	CSL Behring	J1566	\$69.79	\$68.67
FLEBOGAMMA IVIG	Grifols	J1572	\$78.72	\$77.46
GAMMAGARD SD IVIG	Baxalta	J1566	\$69.79	\$68.67
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	\$74.62	\$73.43
OCTAGAM IVIG	Octapharma	J1568	\$84.88	\$83.52
PRIVIGEN IVIG	CSL Behring	J1459	\$76.51	\$75.28
HIZENTRA SCIG	CSL Behring	J1559	\$84.69	\$83.33
HYQVIA SCIG	Baxalta	J1575	\$108.30	\$106.56
GAMMAGARD LIQUID IVIG/SCIG	Baxalta	J1569	\$76.23	\$75.01
GAMMAKED IVIG/SCIG	Kedrion	J1561	\$83.53	\$82.19
GAMUNEX-C IVIG/SCIG	Grifols	J1561	\$83.53	\$82.19

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

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IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	6 g, 12 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PI	2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxalta	IVIG: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxalta	IVIG: PI, ITP, CLL, KD	5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Lab	IVIG: PI, ITP	5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PI	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Baxalta	SCIG: PI	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PI	1 g, 2.5 g, 5 g, 10 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PI, 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
PI Primary immune deficiency disease

2015-2016 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	5 years and older*	90658/Q2035
		0.5 ML prefilled syringes, 10-BX		90656
GlaxoSmithKline	FLULAVAL QUADRIVALENT (IIV4)	5 ML multi-dose vial	3 years and older	90688
	FLUARIX QUADRIVALENT (IIV4)	0.5 ML prefilled syringes, 10-BX		90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 ML live virus intranasal spray	2-49 years	90672
Novartis Vaccines	FLUCELVAX (ccIIV3)	0.5 ML prefilled syringes, 10-BX	18 years and older	90661
	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 years and older	90658/Q2037
		0.5 ML prefilled syringes, 10-BX		90656
Protein Sciences	FLUBLOK (RIV3)	0.5 ML single-dose vials, 10-BX	18 years and older	90673
Sanofi Pasteur	FLUZONE (IIV3)	5 ML multi-dose vial	3 years and older	90658/Q2038
		5 ML multi-dose vial	6-35 months	90657
	FLUZONE QUADRIVALENT (IIV4)	5 ML multi-dose vial	3 years and older	90688
		5 ML multi-dose vial	6-35 months	90687
		0.25 ML prefilled syringes, 10-BX	6-35 months	90685
		0.5 ML prefilled syringes, 10-BX	36 months and older	90686
		0.5 ML single-dose vials, 10-BX		90686
	FLUZONE INTRADERMAL QUADRIVALENT (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 years	90630
	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringes, 10-BX	65 years and older	90662

- 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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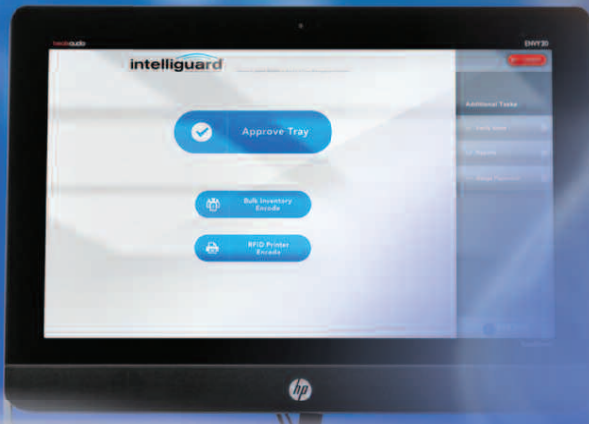


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