FALL 2019

biosupply trends

QUARTERLY

SPECIAL FOCUS:
INNOVATION

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The Technological Future of Medicine

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Alzheimer's Disease?

THE GROWING INFANT
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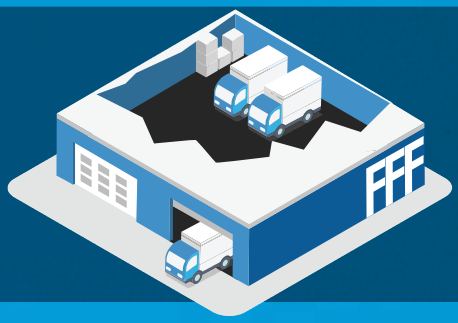

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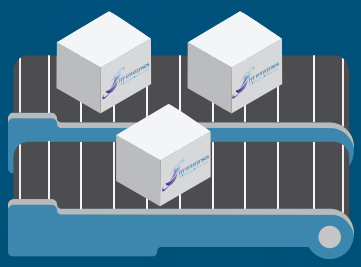

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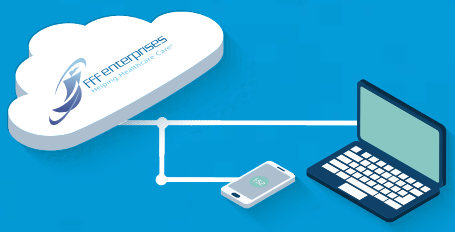

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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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Innovative Technologies Improve Patient Care

IT IS PREDICTED the global digital health market will reach $206 billion by 2020. According to MobiDev, a global software development company, the eight major technology trends to watch during the next two years include telemedicine, Internet of Medical Things, cloud computing, augmented and virtual reality, chatbots, predictive analytics, blockchain and, especially innovative for helping to improve the speed and accuracy of diagnosis and treatment, artificial intelligence (AI). It's a transforming time for our industry, allowing healthcare to boost performance and productivity, while at the same time delivering new patient-centric services.

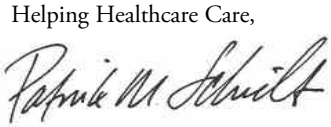
We are pleased to highlight in this innovation-themed issue some of the most recent developments in AI. As our article "The Future of Medicine with Artificial Intelligence" (p.18) explains, embracing AI is crucial to keep practitioners in touch with the industry. Today, much of AI's focus is on using machine learning, algorithms and software to assist healthcare professionals improve clinical results. Some of the more progressive technologies in place are the use of computer algorithms to earlier detect sepsis in hospital patients, predict the potential side effects of drug combinations, identify diabetic retinopathy, the most frequent cause of blindness in adults, and even monitor patients' vitals to help make diagnoses based on symptoms.

Strides are also being made, albeit slowly and with many setbacks, in developing vaccine technology to prevent Alzheimer's disease (AD). In our article "Stopping Alzheimer's with a Preventive Vaccine?" (p.22), we explain the two divergent camps of research: tauists who believe plaques and tangles are symptoms of AD and amyloidists who believe they are the cause. Of the more than 70 vaccines in development, we highlight the seven most promising. Yet, while many are hopeful the mystery behind this tragic disease that affects mostly seniors will one day be solved, it likely won't happen anytime soon.

While nutrition is often seen as a sideline healthcare issue, the link between nutrition and health may in fact be the next revolution in reversing DNA damage that causes disease. We take an in-depth look at the study of using nutrition to benefit health through the care and feeding of genes in our article "Nutrigenomics: How Genes and Nutrition Interact" (p.30). New technologies such as genetically modified organisms and 3D-printed foods could one day impact genetic expression and improve health outcomes, but will face many challenges, including environmental considerations, understanding personal genotypes, reliance on observational vs. experimental studies, and lack of patient and provider buy-in. To date, nutrigenomics has been investigated mostly in relation to obesity. But, it is hoped this form of personalized nutrition will one day provide individualized nutrition for better health.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

biosupply trends QUARTERLY

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

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New CMMI Direct-Contracting Pay Models Will Overhaul Fee-for-Service Models

The Centers for Medicare and Medicaid Innovation (CMMI) is introducing new pay models that will shift primary care from fee-for-service payments to a global fee model under which clinicians and hospitals could assume varying amounts of risk. The first model offers small primary care practices two options that come with a flat monthly fee per patient. Bonuses and penalties will depend on the practices' ability to keep their patients healthy and home. Larger practices and health systems will have additional choices that could result in higher payments but pose steeper risks. These include the professional option, under which providers assume 50 percent of the risk, including savings and losses, and the global option, under which providers take on full risk. There will also be a geographic option under which health systems and insurance plans could assume the risk for the total cost of primary care for communities within a particular region. All of the models, which are voluntary, will launch in January 2020 except the geographic option that is projected to begin in mid-2020.

According to Health and Human Services Secretary Alex Azar, the model will have providers competing for beneficiaries, thus motivating physicians and clinicians to keep patients happy enough to remain under their care. In addition, quality measures within Medicare will deter physicians or hospitals from preventing necessary hospitalizations. ❖

Luthi S. CMS to Launch New Direct-Contracting Pay Models in 2020. *Modern Healthcare*, April 22, 2019. Accessed at www.modernhealthcare.com/payment/cms-launch-new-direct-contracting-pay-models-2020?utm_source=modern-healthcare-am-tuesday&utm_medium=email&utm_campaign=20190423&utm_content=article1-headline.

FDA Seeks to Enhance Clinical Trial Diversity with New Guidance

Because there are still significant obstacles to increasing enrollment diversity in clinical trials, the U.S. Food and Drug Administration has issued draft guidance to overcome this. According to FDA, "Failure to include complex participants in a development program may lead to a failure to discover important safety information about use of the investigation drug in patients who will take the drug after approval. Broadening eligibility criteria, when appropriate, maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety."

To broaden eligibility criteria:

• Sponsors can examine each exclusion criterion to determine whether it is needed to help protect people's safety or to achieve the study objectives. If not, sponsors should consider eliminating the criteria or tailoring it as narrowly as possible. "For example, if there are unreasonable risks to participants with advanced heart failure, but enrollment of those with milder disease would be appropriate, the exclusion criteria should specifically define the population of heart failure participants that should be excluded," FDA said.

• Sponsors can consider using an adaptive clinical trial method that allows for prespecified trial design changes during the trial, including altering the trial population. "An adaptive design can start with a narrow population if there are concerns about safety and can expand to a broader population based on interim data from the trial, as well as external data," FDA said.

• Sponsors can account for logistical and other factors that could limit participation. For example, FDA suggested that when designing the study, sponsors could consider recruitment challenges that may occur because of the study's schedule. "Reduce the frequency of study visits to those needed to appropriately monitor safety and efficacy and consider whether flexibility in visit windows is possible and whether electronic communication (e.g., telephone/mobile telephone, secured electronic mail, social media platforms) or mobile technology tools can be used to replace site visits and provide investigators with real-time data," FDA said.

• Sponsors could offer financial reimbursements for travel and other costs associated with clinical trial participation. In addition, they should work directly with communities to address participants' needs, and to involve patients, patient advocates and caregivers in designing clinical trial protocols. "Patients may provide valuable insight into challenges and burdens and may be more willing to accept risk for a potential benefit as long as the risks are clearly communicated in the informed consent and the research team explains the risks," FDA said.

• Lastly, sponsors should consider recruiting clinical trial participants in diverse locations. "Make recruitment events accessible by holding them often, as well as offering them during evening and weekend hours," FDA said. "Consider holding the events in nonclinical but trusted locations (such as houses of worship) and social commercial venues (such as barbershops and beauty salons) as a means of connecting with diverse populations." ❖

FDA Issues Draft Guidance to Enhance Clinical Trial Diversity. Health IT Analytics, June 11, 2019. Accessed at www.distilnfo.com/lifesciences/2019/06/11/fda-issues-draft-guidance-to-enhance-clinical-trial-diversity.

HHS Grants Additional Money to Expand Access to Effective Opioid Treatment

The U.S. Department of Health and Human Services (HHS) released an additional $487 million to supplement first-year funding through its State Opioid Response (SOR) grant program. The second-year awards to states and territories are part of HHS's Five-Point Opioid Strategy to combat the opioid crisis. Combined with the $933 million already awarded, the total amount of SOR grants to states and territories totals more than $1.4 billion. The funding will expand access to treatment that works, especially to medication-assisted treatment (MAT) with appropriate social supports.

The State Opioid Response grants administered by HHS's Substance Abuse and Mental Health Services Administration (SAMHSA) aim to address the opioid crisis by increasing access to MAT using the three U.S. Food and Drug Administration (FDA)-approved medications for the treatment of opioid use disorder, reducing unmet treatment need and reducing opioid overdose-related deaths through the provision of prevention, treatment and recovery activities for opioid use disorder. "Strategies such as employing psychosocial supports, community recovery services and MAT using medicines approved by the FDA constitute the gold standard of treatment for opioid use disorders," said Elinore F. McCance-Katz, MD, PhD, assistant secretary for mental health and substance use. States and territories receive funding based on a formula, with 15 percent set aside for the 10 states with the highest mortality rates related to drug overdose deaths.

Other funding, including $50 million for tribal communities under the Tribal Opioid Response (TOR) grant program, has been awarded separately. These programs are built from the foundations laid in the $1 billion provided to states and territories through SAMHSA's Opioid State Targeted Response (STR) program. SAMHSA has complemented the work of the STR program with a national center of excellence that provides technical assistance and training to leverage local subject matter experts at the community level to sharpen treatment access and delivery. ❖

HHS Releases Additional $487 Million to States, Territories to Expand Access to Effective Opioid Treatment; 2019 SOR Grants Will Total $1.4 Billion. U.S. Department of Health and Human Services press release, March 20, 2019. Accessed at www.hhs.gov/about/news/2019/03/20/hhs-releases-additional-487-million-to-states-territories-to-expand-access-to-effective-opioid-treatment.html.

Universal Flu Vaccine Research Gets Boost with $30 Million Federal Grant

Cincinnati Children's Hospital has been awarded $30 million to research children's first exposures to influenza and how their immune system reacts to infection in the future with a goal of guiding the development of a universal influenza vaccine by providing a better understanding of the ideal strains to include. The funding is part of the National Institute of Allergy and Infectious Diseases' $140 million dedicated in 2019 for universal flu vaccine research.

The hospital's IMPRINT cohort study will include more than 2,000 sets of mothers and infants from Cincinnati and Mexico City (chosen because of its success with mother-infant cohort studies) who will receive weekly medical testing for at least three years to explore the emerging idea that a person's very first influenza virus exposure impacts the magnitude, durability and breadth of their immune response to all future flu exposures. Some questions that will be looked at include: Does a person have better resistance to future flu outbreaks if their first exposure was to a wild virus, or to weakened forms used in vaccines? How much does a person's future resistance depend on the specific strain of flu they encounter first? Or, if a person's immune system was primed by one strain, does that make it harder for their bodies to respond well to a vaccine that targets a different strain?

"We hope to better understand what the immunological responses to an influenza virus exposure in infants is in the context of infection compared to vaccination and then to determine the impact of this first exposure to the susceptibility and immunological responses to a second infection and/or vaccination," said Mary Allen Staat, MD, MPH, principal investigator. "It is likely that these initial immunologic responses initiated during infancy affect all subsequent responses to influenza exposures. The ultimate goal is to understand these responses so a more effective universal influenza vaccine can be developed."

Currently, the flu vaccine cannot be given to children younger than 6 months, and it does not have long durability; however, a universal flu vaccine could offer protection for people of all ages and could have a duration of at least one year and achieve more than 75 percent efficacy. Early estimates for the 2018-2019 influenza season have demonstrated a 47 percent overall efficacy, with "limited to no" protection for older adults, according to the Centers for Disease Control and Prevention. ❖

$30 Million Federal Grant Supports Universal Flu Vaccine Research. Haelio, May 7, 2019. Accessed at www.healio.com/pediatrics/influenza/news/online/%7B58c5933f-ed26-4b0e-bf24-8a2c901b74b9%7D/30-million-federal-grant-supports-universal-flu-vaccine-research.

CMS 2020 Proposed and Final OPPS and ASC Rules

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE CENTERS FOR Medicare and Medicaid's (CMS) proposed and final outpatient prospective payment system (OPPS) and ambulatory surgery center (ASC) rules take effect Jan. 1 (see Links for Rules and Fact Sheets). In response to the public outcry over healthcare expenses and pricing, the rules focus on transparency to reduce cost in a patient-driven healthcare system with reimbursement across the patient episodic care journey rather than on single encounters in healthcare facilities. Themes in the proposed rules are to continue to simplify electronic health records requirements, reporting and regulations; cut costs and save money by reducing operating costs and patient costs (the latter of which would go directly back to patients); and not losing focus on the opioid crisis.

Increasing Price Transparency of Hospital Standard Charges

An executive order titled "Improving Price and Quality Transparency in American Healthcare to Put Patients First" is designed to increase availability of meaningful price and quality information for patients. Its intent is transparency in healthcare pricing that is "critical to enabling patients to become active consumers so they can lead the drive toward value." The proposal builds upon the 2015 rule that required hospitals to make public their standard charges upon request and subsequently online in a machine-readable format beginning in 2019. The new requirements are broad, requiring each hospital operating within the U.S. to establish, update and make public a yearly list of the hospital's standard charges for items and services provided, including for diagnostic-related groups. Included are 1) definitions of "hospital," "standard charges" and "items and services"; 2) requirements for making public a machine-readable file online that includes all standard charges for hospital items and services; 3) requirements for making public payer-specific negotiated charges for a limited set of "shoppable" services that are displayed and packaged in a consumer-friendly manner; and 4) monitoring for and addressing hospital noncompliance, including issuing a warning notice, requesting a corrective action plan, imposing civil monetary penalties and a process for hospitals to appeal penalties.

OPPS Part B Drug Payment

CMS will continue to pay for Part B drugs in five ways divided into two categories: 1) separately payable with line-item reimbursement and 2) not separately payable without line-item reimbursement since payment is part of a bundle/package. Regardless of where the drug falls in these two categories, billing for every drug is a CMS requirement.

Separately payable line-item reimbursement drugs include:

1) New drugs not yet assigned a unique healthcare common procedure coding system code

2) New pass-through drugs, biologicals and radiopharmaceuticals

3) Specified covered outpatient drugs

Not separately payable with no line-item reimbursement (paid as part of a bundle/package) drugs include:

4) Lower-cost packaged products costing (proposed) less than $130 per day (up from $125 in 2019)

5) Regardless of cost, products used in policy packaged services. Payment for all packaged drugs, biologicals and radiopharmaceuticals is included in the services and procedures for which they are reported. These include:

- Diagnostic radiopharmaceuticals;
- Contrast agents;
- Anesthesia drugs;
- Implantable biologicals surgically inserted or implanted in the body through a surgical incision or natural orifice;
- Drugs, biologicals and radiopharmaceuticals used as supplies in a diagnostic test or procedure; and
- Drugs and biologicals used as supplies or implantable devices in a surgical procedure.

Some non-pass-through separately payable drugs paid for at average sales price (ASP) plus 6 percent minus 2 percent sequestration will expire in the quarter as close to three full years as possible after they were first covered for pass-through payment. The proposed rule lists 65 drugs with new/continuing pass-through status and six losing pass-through status that move from status indicator (SI) G (pass through) to SI K (separately payable) or SI N (items and services packaged into ambulatory payment classification rates). For 2020, new drugs and biologicals are paid at wholesale acquisition cost (WAC) plus 3 percent until ASP is available or 95 percent of average wholesale price (AWP) if WAC is unavailable.

Thresholds for separately payable drugs and biologicals increased to $130 per day based on ASP. These will continue to be paid at ASP plus 6 percent minus 2

percent sequestration under the 2013 statutory default payment policy. CMS will pay all non-pass-through separately payable therapeutic radiopharmaceuticals at ASP plus 6 percent minus 2 percent sequestration as well.

Providers should ensure all drugs with SI G, K and N are billed regardless of whether they are separately payable (which will be published in the updated Addendum B this fall). While it is common practice for some revenue cycle teams/billing services to put a hard stop on passing SI N-posted charges to payers, this behavior creates an inaccurate claims data file because the drug therapy and its costs are missing from the encounter. It also prevents payment of injectable drug administration charges because there is no drug listed as given.

Providers should also prepare for changes in their list of waste billing drugs. They should determine which of those on their current list have moved from K to N status and will no longer be eligible for waste billing as of Jan. 1.

Payment Rate Changes for Certain Medicare Part B Drugs Purchased by Hospitals Through 340B

OPPS payment rate changes apply only to 340B-eligible Medicare patients treated in an OPPS setting. The proposed 2020 OPPS rule keeps 2018 rates that cut reimbursement for 340B facilities, as well as the modifier requirement that identifies drugs with rate cuts. Products acquired under 340B will continue to be paid at ASP minus 22.5 percent, WAC minus 22.5 percent or 69.46 percent of AWP, as applicable. OPPS reimburses in five different ways (pass-through before and after ASP is established, separately payable and bundled or packaged either due to cost or statute). Only separately payable drugs (SI K) are affected; drugs on pass-through status (SI G) and vaccines continue to be excluded. Off-campus hospital departments defined as outpatient facilities located away from the hospital's main facility paid under physician fee service will also be subject to the reduction in 2020 and will be paid ASP minus 22.5 percent for drugs acquired through the 340B program.

CMS is continuing its policy to make all biosimilar biological products eligible for pass-through payment — not just the first biosimilar biological product for a reference product.

In a new twist and a move away from the national and local coverage determinations "honor system" concept, CMS proposes a prior authorization process for five categories of hospital outpatient department services: blepharoplasty, botulinum toxin injections, panniculectomy, rhinoplasty and vein ablation.

2020 proposals continue unpackaging and paying separately for the cost of nonopioid pain management drugs functioning as surgical supplies only in the ASC setting and not in the OPPS setting.

Hospital clinic visits will be reimbursed for site-neutral payments at the same rate as physician offices and other ambulatory facilities completing the process as in past years.

Sequestration remains in effect, and 2 percent will be deducted from every CMS payment to healthcare facilities. This applies only to the 80 percent CMS payment and not the 20 percent copay. Sequestration is the budget limit Congress created in the 2011 Budget Control Act when Republicans and Democrats couldn't agree on the best way to lower the deficit. While they did agree to use the threat of sequester to force themselves to reach an agreement, the threat didn't work, implementing the sequester to cut spending from 2013 through 2021. (Note: This may be extended by an additional two years to 2023.) This applies to each year's budget, cutting an equal amount from both mandatory discretionary budgets. Mandatory programs established by acts of Congress include Medicare, Social Security and the Affordable Care Act. Sequestration also sets caps on spending.

As healthcare facilities search for every opportunity to stabilize revenue and cut costs, they must understand drug payment rules and what to do to ensure payment. Additionally, moving forward with practice changes such as working with specialty pharmacies with white bagging and negotiating with private insurers is essential. ❖

Links for Rules and Fact Sheets

- Medicare OPPS and ASC Payment System Proposed Rule: www.federalregister.gov/ documents/2019/08/09/2019-16107/medicare-program-proposed-changes-to-hospital-outpatient-prospective-payment-and-ambulatory-surgical
- Medicare OPPS and ASC Payment System Fact Sheet: www.cms.gov/newsroom/ fact-sheets/cy-2020-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center

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

Streamlining Patient Visits

By Ronale Tucker Rhodes, MS

HEALTHCARE DELIVERY has become increasingly complex in the past couple of decades. According to Metaspire Consulting, a management consulting and coaching firm that offers process improvement consulting and training for companies in healthcare, "In the United States, the healthcare system is troubled by skyrocketing costs. In turn, the lack of affordability threatens the health, wellness and productivity for far too many."[1] The need, then, to deliver an efficient and effective healthcare delivery process is more important than ever. Following are some methods to help streamline patient visits.

Map the Patient Process

Process mapping, also known as patient journey mapping, outlines all of the patient touch points during each stage of the care journey. Practice Fusion, a cloud-based ambulatory electronic health records (EHR) platform in the U.S., suggests three ways to improve patient flow:[2]

1) *Establish practice buy-in.* Patient flow is a group staff effort. Therefore, to make staff understand the importance of improving patient flow, as well as the benefits for patients and staff such as getting home on time and generating higher income, need to be shared.

2) *Chart flow.* First, the bottlenecks to the patient care process need to be identified, and their underlying causes need to be understood. Flow mapping starts this process. Ideally, volunteers will visit the office as patients who take detailed notes about their appointments. The true purpose of these visits isn't shared with staff. Then, how much time each segment of the visit takes should be measured and charted, paying special attention to waiting times. The total time it takes from arrival to departure should be recorded, and these times should continue to be tracked to better understand the dynamics of the practice and identify the largest opportunities to improve patient flow.

3) *Address bottlenecks.* Once bottlenecks are identified, adjustments to the processes can be made. Practice Fusion has found the sources of most common bottlenecks are visit planning and office architecture. For instance, in many cases, critical tests or required documentation may be missing after a patient has already arrived for an appointment. To prevent this, it should be determined that all necessary information is available in patient charts the day prior to the appointment and, failing this, the appointment should be rescheduled. Providers and support staff can also review their schedules together to identify how to make a day run more smoothly. In addition, office layout is critical for optimal patient flow. For instance, the receptionist should be near the entrance and should be able to view the entire room; exam rooms should be in close proximity to the waiting area; patient traffic flow should move sequentially throughout a visit; and extra exam rooms should be available to handle patients during high demand.

The goal of process mapping is to deliver the same level of medical care to every patient, every time. Ultimately, mapping the patient journey accomplishes three things: improved outcomes for each

patient, enhanced patient experience and reduced costs.

Improve Scheduling

The appointment process can also be streamlined to help the office run efficiently, manage a steady flow of patients and increase the number of patients seen in a day. Spectrio, a company that helps create positive, memorable and informative patient experiences, suggests six steps to refine the process:[3]

1) *Offer multiple scheduling options.* These can include online scheduling via the provider's website or patient portals, as well as in-office appointment kiosks. Yet, even with the rise in digital platforms, offices must still manage incoming calls. And, if multiple appointments need to be scheduled, they should be arranged during a single call.

2) *Send scheduling and intake emails.* Help patients to remember appointments by sending welcome and reminder emails three to five days before and on the day of the appointment. These emails should detail copies of the forms and paperwork patients will need to have upon arrival. Also, patients need to be advised about what they need to bring to the appointment such as insurance cards, health records, etc.

3) *Create clear scheduling policies.* Scheduling policies allow the office to stick to appointment times and avoid gaps. Policies should include penalties for late arrivals and last-minute cancellations. And, patients should be told about the policies when they schedule and via appointment reminders.

4) *Keep staff on the same page.* One or two people should be trained to act as primary schedulers, and a standardized scheduling system that includes policies for appointment durations, provider availability and emergency appointment requests should be used. It can also help to use digital signage to keep track of patients' status (waiting, in exam room, with doctor, etc.).

5) *Minimize waiting times.* Appointments should not be double-booked, they should be scheduled according to anticipated appointment time, and time should be left for emergency appointments.

6) *Make it easier on providers.* Overbooking and overworking providers can be avoided by grouping similar patients or appointment times, scheduling downtime and factoring in providers' out-of-office time.

Leverage Technology

Technology can enable physicians to sit down with patients during an office visit to concentrate on their specific issues and needs, instead of focusing on using technology. While there are many ways to use technology, following are five ideas offered by IntakeQ, a company that emphasizes making a healthcare organization's intake process as smooth as possible:[4]

> The goal of process mapping is to deliver the same level of medical care to every patient, every time.

1) *Adopt an EHR system.* EHRs, available at every computer station, rid the office of paper, filing cabinets and time spent filing, sorting and searching for documents.

2) *Install a terminal in a convenient area of the office.* The terminal should have access to EHRs and a telephone so staff don't have to walk to offices. Alternatively, providers can utilize a tablet with access to the practice's electronic recordkeeping software so they can access and input information on the go.

3) *Standardize and make employee processes available on a computer.* For example, if an exam room is supposed to be set up in a specific way, a checklist can be created for the team to follow and electronically initial when the job has been completed.

4) *Send patient appointment reminders automatically with software.* Reminders can be sent by email, text message or prerecorded phone calls.

5) *Don't tolerate inadequate devices or outdated software.* New tools will require an investment, but they usually quickly pay for themselves in recovered time.

Streamlining Generates a Competitive Advantage

By streamlining patient office visits, physicians are both able to see more patients, which impacts the bottom line, and spend more time with patients, which results in higher quality care. Providers who can demonstrate they care about their patients' time, convenience and mobility by providing healthcare on patients' terms will enjoy a competitive advantage over those who don't. ❖

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

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Vaccines

Researchers Develop Vaccine Candidates to Prevent Epstein-Barr Virus

A National Institutes of Health research team has determined how several antibodies induced by Epstein-Barr virus (EBV) block infection of cells grown in the laboratory. They then used the information to develop novel vaccine candidates that, in animals, elicited potent anti-EBV antibody responses that blocked infection of cell types involved in EBV-associated cancers. One of the vaccine candidates is designed to elicit antibodies to gH/gL on epithelial cells, and the other is designed to elicit antibodies to gH/gL and another viral protein, gp42. When tested on mice and monkeys, each experimental vaccine induced antibodies that potently inhibited epithelial cell fusion. However, the vaccine containing gp42 induced stronger B cell fusion inhibitor antibodies.

Currently, there is no licensed vaccine for EBV, a virus associated with certain cancers (nasopharyngeal and gastric) of epithelial cells, which form the lining of the body's surfaces, as well as Birkitt and Hodgkin lymphomas, which are cancers of the immune system's B cells. Worldwide, approximately 200,000 cases of EBV-associated cancers occur annually, resulting in 140,000 deaths.

Previous research to develop a vaccine focused on a viral surface protein, gp350, that the virus uses to enter B cells. However, EBV infects both B cells and epithelial cells that line the mouth and upper throat, the latter of which are usually infected after contact with saliva from an EBV-infected individual. The new vaccine candidates could prevent EBV from fusing with both epithelial cells and B cells, thus providing protection independent of cell type. The team is planning to further develop one of the vaccine constructs that can be tested in humans. ❖

NIH Researchers Make Progress Toward Epstein-Barr Virus Vaccine. National Institutes of Health press release, April 9, 2019. Accessed at www.nih.gov/news-events/news-releases/nih-researchers-make-progress-toward-epstein-barr-virus-vaccine.

Patent

ADMA Biologics Receives U.S. Patent for Treatment and Prevention of Pneumococcal Infections

The U.S. Patent and Trademark Office has issued a patent to ADMA Biologics for methods of treatment and prevention of S. pneumonia infection. Specifically, the patent encompasses the method of preparing immune globulin (IG) via harvesting plasma from S. pneumonia-vaccinated healthy adult human donors and pooling that harvested plasma as the source for manufacturing a hyperimmune anti-pneumococcal IG containing elevated opsonic antibodies to a plurality of S. pneumonia serotypes. The patent also encompasses the prepared anti-pneumococcal IG, the method of treating S. pneumonia infection and the method of providing immunotherapy using the hyperimmune anti-pneumococcal IG.

The patent, which extends to March 2037, will enable ADMA to protect its proprietary rights while attracting collaborators interested in the development, marketing and commercialization of the needed therapeutic for treating and preventing infection of immune-compromised, immunodeficient and elderly patients who are poorly responsive to available S. pneumonia vaccines.

"This will be the first patent to issue in ADMA's immune globulin program tailored specifically to anti-pneumococcal hyperimmune globulin compositions and treatment modalities," said Adam Grossman, president and CEO of ADMA. "As stated in the National Foundation for Infectious Diseases, it is estimated that about one million U.S. adults get pneumococcal pneumonia each year, as many as 400,000 hospitalizations from pneumococcal pneumonia occur annually in the U.S., and about 5 percent to 7 percent of those who are hospitalized from it will die despite the widespread use of multiple vaccines for disease prevention." ❖

ADMA Biologics Granted U.S. Patent for Treatment and Prevention of Pneumococcal Infections. ADMA Biologics press release, Apr. 17, 2019. Accessed at www.apnews.com/Globe%20Newswire/7bac31b44e92146017aac5a12c3bd353.

Vaccines

Flu Pamphlet Impacts Parents' Decision to Vaccinate Kids

A new study by researchers at Columbia University has found handing a pamphlet about influenza (flu) to parents in pediatricians' waiting rooms can have a significant impact on increasing the uptake of the flu vaccine. The study included 400 parent-and-child pairs at pediatric clinics in northern Manhattan who answered a brief questionnaire to assess their attitudes toward the flu shot and the intent to vaccinate. One-third received a one-page handout with local information about the flu, another third received a one-page handout with national information about the flu, and the rest received usual care with no handout. Both handouts emphasized the risk of getting the flu, the seriousness of the disease and vaccine effectiveness. Providers were unaware of the parents' study participation.

Results showed nearly 72 percent of children whose parents were given either fact sheet were vaccinated before the end of the season compared to around 65 percent of those who received usual care. Parents who received the national handout were more likely to have their child vaccinated on the day of the clinic visit (59 percent) compared to those who didn't receive either handout (53 percent). Parents who had fewer concerns about vaccination were more likely to vaccinate their children by the end of the season (74 percent versus 59 percent of parents with significant concerns) and on the day of the clinic visit (59 percent and 45 percent), respectively. Approximately 90 percent of parents who said they planned to vaccinate their children did so by the end of the flu season. "We found that a low-cost handout that can be easily implemented in any pediatrics practice had a significant and meaningful impact on influenza vaccination in children," said Melissa Stockwell, MD, MPH, associate professor of pediatrics and population and family health at Columbia

University Vagelos College of Physicians and Surgeons and senior author of the paper.

Future studies will compare the effectiveness, cost-effectiveness and feasibility of different methods of delivering educational information about influenza, including handouts, text messages, video and interactive social media. ❖

Columbia University Irving Medical Center. Flu Fact Sheet for Parents Increases Vaccination Rate in Children. Medical Xpress, July 10, 2019. Accessed at medicalxpress.com/news/2019-07-flu-fact-sheet-parents-vaccination.html.

Research

Researchers Discover New, Rare Autoimmune Disease

A previously unknown autoimmune muscle disease involving sudden onset of debilitating muscle pain and weakness has been identified by researchers at Washington University School of Medicine in St. Louis, Mo. They named the disease large-histiocyte-related immune myopathy. According to the researchers, the syndrome can easily be mistaken for other muscle diseases that require different treatment, so the findings are expected to help physicians treat patients appropriately.

The study involved a retrospective review of records and muscle pathology of four patients whose clinical features included muscle pain and proximal, symmetric, moderate to severe weakness in the arms and legs progressing over one week to four weeks. Associated systemic disorders in the patients included anemia in all, and hemophagocytic lymphohistiocytosis, hepatic disease, Raynaud phenomenon, metastatic cancer and cardiomyopathy in one patient each. In addition, patients presented with very high serum creatine kinase levels ranging from 10,000 to 102,000 U/L. Three of the patients improved when treated with immunomodulating therapy such as steroids and have not relapsed since. The fourth was undergoing cancer treatment when the muscle symptoms developed, and he died due to cancer shortly afterward. ❖

Pestronk A, Sinha N, Alhumayyd Z, et al. Immune Myopathy with Large Histiocyte-Related Myofiber Necrosis. *Neurology*, April 9, 2019. Accessed at n.neurology.org/content/92/15/e1763.

Medicines

FDA Approves Pediatric Hexavalent Combination Vaccine

Sanofi and Merck's Vaxelis has been approved by the U.S. Food and Drug Administration. Vaxelis is a hexavalent vaccine indicated for the prevention of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive disease due to Haemophilus influenza type b. The vaccine is approved for use as a three-dose series in children ages 6 weeks to 4 years prior to the fifth birthday. It was developed as part of a joint partnership between Sanofi and Merck. However, commercial supply of the vaccine will not be available in the U.S. prior to 2020. ❖

FDA Approves VAXELIS, Sanofi and MSD's Pediatric Hexavalent Combination Vaccine. Global Newswire, Dec. 26, 2018. Accessed at finance.yahoo.com/news/sanofi-fda-approves-vaxelis-tm-193202061.html.

Vaccines

2018-19 Flu Season Separated by Two Waves Was Longest in Decade

The 2018-19 influenza (flu) season was both the longest in a decade and marked by two separate waves of influenza A, according to the Centers for Disease Control and Prevention (CDC). During the initial surge between October and mid-February, an H1N1 strain dominated, followed by an H3N2 strain beginning in mid-February that lasted through mid-May. The H3N2 strain is known to cause more severe symptoms than H1N1. "It was quite an unusual season in that we almost had two seasons in one," said Richard Webby, a flu scientist on the World Health Organization's influenza vaccine advisory board and a member of the St. Jude Children's Research Hospital's Department of Infectious Diseases. According to Webby, it's not unusual for an influenza A strain to be followed by a smaller wave of an influenza B strain; however, this longer-than-usual season had two almost similar peaks of activity from two strains of influenza A.

Despite its length and unusual pattern, CDC considers the season to be of only moderate severity both overall and for each age group. During the season in the U.S., the flu caused between 37.4 million and 42.9 million illnesses, between 531,000 and 647,000 hospitalizations and between 36,400 and 61,200 deaths. Deaths have markedly declined over the seasons, but the 2017-18 season was the deadliest in four decades with 80,000 deaths, including 180 children. By comparison, there were only 116 laboratory-confirmed deaths of children caused by the flu during the 2018-19 season. ❖

Scutti S. CDC: 2018-19 Flu Season Longer Than Usual. CNN, June 20, 2019. Accessed at www.ktvz.com/health/cdc-201819-flu-season-longer-than-usual/1087930177.

Vaccines

Genetics Linked to Immunity to Childhood Vaccines

A genome-wide study, conducted by researchers at the University of Oxford in the United Kingdom (U.K.), has linked a number of genetic variations with the level of protective antibodies generated following routine childhood immunizations. According to the researchers, further research may make it feasible to incorporate genetic tests into neonatal screening programs that can predict immunity to vaccines and, therefore, guide personalized vaccination regimens.

The two-stage genome-wide association study involving 3,602 children in the U.K. and the Netherlands investigated the link between genetic variation and levels of immunity to three routine childhood vaccinations: capsular group C meningococcal (MenC), Haemophilus influenzae type b (Hib) and tetanus toxoid (TT) vaccines. Results identified two genetic loci associated with the persistence of vaccine-induced immunity in immunized children. MenC immunity persistence was linked with single nucleotide polymorphisms (SNPs) in a region of the genome containing a family of signal-regulatory protein genes (SIRPA, SIRPB and SIRPG),

which are involved in immunological signaling. TT-specific immunity persistence was linked with SNPs in the human leukocyte antigen (HLA) locus, which contains the genes coding for HLA molecules that present peptides to T cells, which in turn induce B cells to produce antibodies. "We also identified a region within the HLA gene complex that contained SNPs associated with the persistence of TT-specific IgG," the researchers wrote. "Given their role, HLA genes have frequently been candidates in studies exploring the genetic determinants of vaccine responses."

According to the researchers, the identified variants will likely account for just a fraction of all the genetic determinants that impact on vaccine-induced immunity persistence. "In our study, we estimated the heritability of vaccine-induced immunity to vary from 14 percent to 81 percent," they noted. "TT immunity was estimated to be the most heritable of these measures … it is likely that the study of larger vaccine cohorts will yield more loci associated with immunity to vaccine antigens."

In addition, the researchers pointed out their study included primarily Caucasian children, so it is not clear whether the results would apply to different ethnicities. "We are now carrying out in-depth investigations into the biology of the genetic variants we described in this study," said Daniel O'Connor, PhD, a postdoctoral researcher at the department of pediatrics, University of Oxford, who is first author of the research team's published paper. "We also planned further research, in larger cohorts of children and other populations that benefit from vaccination, to further our understanding of how our genetic makeup shapes vaccine responses." ❖

Genetic Makeup Influences Immunity to Childhood Vaccines. *Genetic Engineering & Biotechnology News,* June 12, 2019. Accessed at www.genengnews.com/news/genetic-makeup-influences-immunity-to-childhood-vaccines.

Vaccines

Connecting with People Who Have Suffered from Diseases Can Change Attitudes Toward Vaccines

A study that tested whether vaccine-hesitant students who may be unfamiliar with the consequences of vaccine-preventable diseases (VPDs) might be swayed when confronted with the symptoms and dangers of VPDs found introducing them to people affected by VPDs can decrease vaccine hesitancy. The study, conducted by researchers in the Department of Microbiology and Molecular Biology at Brigham Young University (BYU), assessed 425 BYU students' attitudes about vaccines by surveys before and after interviews with individuals who experienced a VPD (students were picked since many will become future parents). Vaccine-hesitant students who conducted a VPD interview but received no additional vaccine educational materials were significantly more likely to become pro-vaccine (68 percent) than students who conducted an autoimmune interview and received no additional educational materials. Additionally, students whose interviewees experienced intense physical suffering or physical limitations or students who were enrolled in a course with intensive VPD and vaccine curriculum had significantly increased vaccine attitudes.

"It is possible to influence people's attitudes towards vaccines by showing the real-world consequences of not vaccinating," said Brian Poole, PhD, one of the researchers and an associate professor at BYU. "Since most people have not experienced the consequences of vaccine-preventable diseases, the minuscule risks of vaccination start to seem larger."

The World Health Organization recently listed vaccine hesitancy in its top 10 threats to global health, and the Centers for Disease Control and Prevention has warned the U.S. may soon lose its measles elimination status because of several urban-center outbreaks. According to Dr. Poole, urban areas are particularly vulnerable to the spread of infectious diseases. ❖

Johnson DK, Mello EJ, Walker TD, et al. Combating Vaccine Hesitancy with Vaccine-Preventable Disease Familiarization: An Interview and Curriculum Intervention for College Students. *Vaccines*, 2019, 7(2), 39. Accessed at doi.org/10.3390/vaccines7020039.

Gramigna J. Vaccine Attitudes Improve by Connecting with People Who Have Suffered from Diseases. Healio, June 7, 2019. Accessed at www.healio.com/pediatrics/vaccine-preventable-diseases/news/online/%7B93c64bdf-b24f-4c4f-8ddc-f5dbce2a49bb%7D/vaccine-attitudes-improve-by-connecting-with-people-who-have-suffered-from-diseases.

Medicines

FDA Approves Expanded Use of Doptelet to Treat Thrombocytopenia

The U.S. Food and Drug Administration (FDA) has approved an expanded indication for Dova Pharmaceuticals' Doptelet (avatrombopag) to treat adults with chronic immune thrombocytopenia who had an insufficient response to a previous treatment. Previously, Doptelet was approved to treat thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure. The company launched Doptelet commercially for immune thrombocytopenia purpura (ITP) in mid-July. According to a company statement, Doptelet will be priced similarly to other thrombopoietin receptor agonists used to treat ITP, and the company will continue to offer patient assistance and copay programs.

"ITP patients should work with their clinician to choose a therapy that supports their lifestyle and aims to achieve the best possible result to treat their ITP," said Caroline Kruse, president and CEO of the Platelet Disorder Support Association. "That's why having additional treatment options are so important. We are thrilled to have a new oral TPO-RA available for adult patients with ITP. Every new treatment provides more choices and new hope to our community." ❖

FDA Approves Application to Expand Doptelet for Autoimmune Bleeding Disorder. Dova Pharmaceuticals press release, July 22, 2019. Accessed at www.healio.com/hepatology/liver-injury-regeneration/news/online/%7Bf2345571-c88c-4c81-97f2-28dfb9104c11%7D/fda-approves-application-to-expand-doptelet-for-autoimmune-bleeding-disorder.

Vaccines

Campaign Launched to Remind Families Teens Need Second Meningitis Booster Shot

In response to Centers for Disease Control and Prevention (CDC) data that shows more than half of teens have not received the second recommended dose of the meningococcal meningitis vaccine, the National Meningitis Association has launched "16 Vaccine." The new educational campaign encourages more teens to get vaccinated with the booster dose to prevent meningitis. The campaign includes a library of social media posts and graphics on the16vaccine.org website to help people spread the word about getting teens a second dose of the MenACWY vaccine at age 16. While some parents are aware the first dose of the vaccine is needed at 11 years to 12 years of age, they don't know CDC recommends a second dose at age 16. ❖

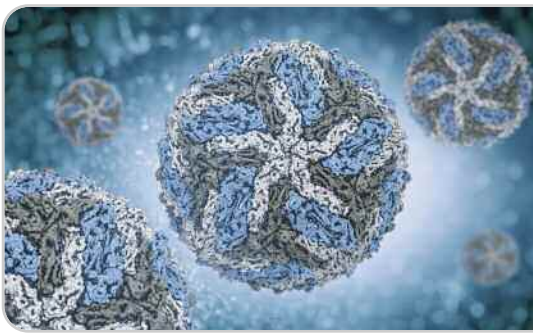
Stahl S. National Meningitis Association Launches '16 Vaccine' Campaign to Remind Families That Teens Need Second Booster Shot. CBS Philly, June 3, 2019. Accessed at philadelphia.cbslocal.com/2019/06/03/national-meningitis-association-launches-16-vaccine-campaign-to-remind-families-that-teens-need-second-booster-shot.

Vaccines

Sanofi Receives Narrow FDA Approval for Dengue Vaccine

The U.S. Food and Drug Administration (FDA) has given Sanofi SA's dengue vaccine Dengvaxia a narrow approval since the vaccine can cause severe infections in some people. According to FDA, Sanofi can sell the drug only to people age 9 years through 16 years who have laboratory confirmation of a previous dengue infection and live in areas where the disease is prevalent such as Puerto Rico, the U.S. Virgin Islands and American Samoa. It is not approved for individuals who have not previously been infected by one of the four types of the virus, which is spread by mosquitoes. Sanofi had sought broader approval of the vaccine to include people age 9 years through 45 years, but FDA excluded its use in adults after Sanofi disclosed Dengvaxia could increase the risk of severe dengue in children who had never been exposed to the virus, which triggered a government investigation in the Philippines where 800,000 school-aged children had already been vaccinated. "Today's FDA approval of Dengvaxia allows us to bring a critical medical prevention tool to at-risk populations, helping combat and prevent dengue, particularly among children, in U.S. dengue endemic areas," said David Greenberg, MD, Sanofi's regional medical head for North America.

In December, Dengvaxia won European approval for people age 9 years to 45 years living in endemic areas who have a documented prior infection. The World Health Organization said last spring that Dengvaxia should only be used on individuals with proven prior dengue exposure. ❖



Sanofi Wins U.S. Approval to Sell Dengue Vaccine But with Major Restrictions. Reuters, May 1, 2019. Accessed at www.reuters.com/article/us-usa-fda-sanofi-fr/sanofi-wins-u-s-approval-to-sell-dengue-vaccine-but-with-major-restrictions-idUSKCN1S74TI.

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The Future of Medicine with Artificial Intelligence

As AI continues to be used in healthcare settings, it is predicted those who don't embrace it could soon be out of touch with the medical industry.

By Meredith Whitmore

TO UNDERSTAND THE effect artificial intelligence (AI) will have on medicine, consider the following: Thirty-seven percent of healthcare professionals are using a form of AI in their work today. Eighty-eight percent of those who use it say AI improves patient care. Fifty-four percent expect widespread adoption of AI within the next five years.[1] The healthcare AI market is expected to surpass $34 billion by 2025.[2]

To put things another way, healthcare professionals who do not understand the monumental influence AI is beginning to wield will eventually find themselves out of touch with the industry. As one specialty publication elegantly states, for example: "Artificial intelligence will not replace radiologists, but radiologists who use AI will replace radiologists who don't."[3]

When considering AI in the medical industry, many might imagine iconic images from popular science fiction. After all, tricorders from the original "Star Trek" television series and medical robots from movies such as "Big Hero 6," "Interstellar" and "Star Wars: Episode III — Revenge of the Sith" are a bit advanced for today's AI capacities (more on that later). Still, AI is playing more and more of a role in healthcare, and often in ways that physicians do not always understand or recognize.

Today, much of the existing AI intricately synthesizes machine learning, complicated algorithms and software to approximate and even anticipate human thinking. As William Grambley, chief operating officer of Allazo Health, explains: "AI is not just creating a single formula. It's creating a complex set of relationships and then dynamically adjusting the formula based on any new data." Allazo Health, an AI-based company in New York City, helps healthcare stakeholders such as pharmacies, health plans and pharmaceutical companies to "intelligently drive their clinical outreach programs to improve clinical results."

Basics of AI

"There are so many places that AI is impacting people's lives that they may not even realize," Grambley explains. "The way Allazo uses it is primarily to analyze people's reactions to different kinds of clinical outreaches and programs, and therefore make predictions about what will happen if we run a certain clinical outreach program. As a piece of that, we're also predicting a clinical outcome independent of any outreach. I think there are a lot of places in healthcare where you'll start to see that. Examples include hospital readmissions or emergency room usage or things that in the near term impact utilization — but longer-term could be used to predict your individual risk of developing certain conditions based on how frequently you go to the doctor, the kinds of procedures you've had done in your life, the lab results you've gotten over time. If you can get that data over a large enough population and start to analyze it, you can create these types of machine-learning and AI models.

"You can imagine five or 10 years from now, when a doctor plugs in recent information about you into a system, and then the doctor says, 'The likelihood of you developing a certain disease is increased since last time, and here's what we could do differently.' That becomes a very different interaction than today, where I think most exchanges between physicians and others in the healthcare system are driven based on their training and knowledge, and not necessarily some kind of dynamic perspective of large population studies and other things that end up influencing an AI engine."

Yet, with emerging AI engines come ethical questions. "At what point do biases need to be controlled for or prevented from entering those kinds of engines?" Grambley asks. "You could imagine that demographic factors such as what ZIP code you live in, for example, could be a predictor of many things. Do you want that predictor to be used as part of a recommendation on a treatment path or recommendation of lifestyle changes?

"In healthcare, as in many other industries, there's always the question of: 'Are you focused on the maximum outcome, or are you focused on the most cost-efficient outcome?' I think that becomes particularly relevant in healthcare, where those two might not lead to the same answer. When you start to use these machine-learning or AI type of engines to decide things, the outcome you're trying to solve for needs to be very clear and understood. If you're trying to solve for the maximum outcome, then you're going to have a different set of expectations of a program than you may if you're trying to achieve the most cost-effective outcome. Again, as you're thinking about implementing an AI-type program, the trade-offs, in our case at Allazo, the client side, need to be really explicit, because if you don't explicitly make those decisions then the engine is going to try to maximize for what you tell it to. If you don't explicitly make a lot of decisions up front, it may not actually lead to what you're trying to do. When we work with clients, we end up spending a lot of time asking those questions. I think, just broadly in healthcare [with regard to AI] if you aren't explicit about what you're trying to do, then you may run into issues."

"For example," says Grambley, "if a client was trying to avoid patient emergency room usage, there are a lot of ways to address that. If you address it by somehow limiting access to it, that's not the right answer. You have to address it in a way that supports overall health for people and better decision-making about where they go, and lots of other things. Again, you need to be explicit about the constraints you're going to put on whatever the AI is going to produce. I think that becomes even more important in healthcare where you can get to unintended consequences if you don't think about what those could be explicitly up front."

Healthcare professionals who do not understand the monumental influence AI is beginning to wield will eventually find themselves out of touch with the industry.

Upcoming and Progressing AI Technologies

Beyond the technical and ethical discussions are research and development. Other companies are pioneering AI technology in addition to Allazo Health. Following are some of the most recent and exciting developments.

Early sepsis detection. With the assistance of AI, doctors at HCA Healthcare-affiliated hospitals are now detecting sepsis 18 hours earlier than the best clinicians at other facilities unaided by the same technology. The technology, called SPOT (Sepsis Prediction

and Optimization of Therapy), utilizes machine learning and manages algorithms based on patient vital signs, tests, nursing reports and other data that can prevent the dreaded, life-threatening condition from spreading. SPOT can identify at least one-third more sepsis cases that would not previously have come to caregivers' attention until it was too late. As a result, more than 5,500 lives have been saved over the last three years, and more than one million patients have been monitored by the technology. Considering sepsis is the 11th-leading cause of death in the U.S., the ninth-leading cause of death in all hospitals and the third-leading cause of death in intensive care units, SPOT is a remarkable and much-needed technology.[4]

With the assistance of AI, doctors at HCA Healthcare-affiliated hospitals are now detecting sepsis 18 hours earlier than the best clinicians at other facilities unaided by the same technology.

Breast cancer screening. In Europe, London-based Kheiron Medical Technologies recently launched Mia, a breast cancer screening tool that uses deep learning software. Mia is designed to analyze standard full-field digital mammograms and serve as a second reader for radiologists.[5] Kheiron claims clinicians will receive results "within seconds," directly into their existing workflows. Mia will also enable radiologists to "triage imaging studies before review so they can prioritize studies based on findings." A clinical study has shown Kheiron's software performs above the current average British benchmark for breast screening radiologists. The company is now launching new clinical evaluations across Europe and in the United States to improve its technology and assess the software's potential impact on breast screening around the world.[6]

Predicting medication side effects. Decagon is a cutting-edge AI-based technique developed to foresee potential side effects from millions of drug combinations.[7] As developers Marinka Zitnik, PhD, and Jure Leskovec, PhD, state: "Decagon's predictions have the potential to provide doctors with guidance on how to prescribe safe treatments by taking into account the patient's pharmacy and all drugs the patient currently takes. Predictions give clues about whether it is a good idea to prescribe a particular combination of drugs to a particular patient. Beyond giving clues and providing guidance to doctors, such predictions are also of interest to patients. That is because predictions about side effects associated with a particular combination of drugs can aid in self-care as patients can recognize unwanted effects early on. Ultimately, techniques like Decagon have the potential to give scientists and researchers guidance on designing new combinatorial drug therapies with fewer adverse side effects."

According to Drs. Zitnik and Leskovec, "Since the publication of Decagon, we have started working with Massachusetts General Hospital and Newton-Wellesley Hospital to test the utility of some of Decagon's predictions on real patient data. This clinical validation is currently ongoing, and we are validating predictions against classic drug-drug interaction markers, lab values and other surrogate measurements that are available in hospital clinics."

Upgrades to Decagon's machine learning algorithm are continually fine-tuned. "Decagon's algorithm is based on deep network embeddings, a flexible and recently invented computational paradigm that enables us to generate biologically meaningful machine-readable embeddings of drugs from large biomedical data," explain Drs. Zitnik and Leskovec. "We are now investigating those learned embeddings to provide interpretation for Decagon's predictions, and we are developing new means to design explainable models whose predictions are accurate and can be interpreted in the context of several decades worth of biomedical knowledge."

Diabetic retinopathy. Researchers using a deep machine learning algorithm are paving the way to detect diabetic retinopathy and macular edema in retinal fundus photographs. That's an exciting possibility in a world in which diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20 years to 74 years.[8]

In their study published in the *Journal of the American Medical Association*, researchers said the algorithm had "90.3 percent and 87.0 percent sensitivity and 98.1 percent and 98.5 percent specificity for detecting referable diabetic retinopathy, defined as moderate or worse diabetic retinopathy or referable macular edema by the majority decision of a panel of at least seven U.S. board-certified ophthalmologists." And, at the operating point selected for high sensitivity, the algorithm had "97.5 percent and 96.1 percent sensitivity and 93.4 percent and 93.9 percent specificity in the two validation sets." However, the researchers add "further research is necessary to determine the feasibility of applying this algorithm in the clinical setting and to determine whether use of the algorithm could lead to improved care and outcomes compared with current ophthalmologic assessment."[9]

Television Comes to Life

Getting back to the allusion to science fiction, an emergency room doctor literally developed a once-mythical tricorder first

DxtER, similar to the "Star Trek" tricorder seen in the 1960s television series, is a handheld device that helps doctors diagnose patients based on symptoms. It won the top prize at the Qualcomm Tricorder XPRIZE competition.

seen in the original 1960s "Star Trek" television series. Basil Harris, MD, a Philadelphia-based emergency room physician, decided to undertake a project to create the handheld diagnostic device called DxtER and enter it in the Qualcomm Tricorder XPRIZE competition at which he won the top prize. DxtER contains a digital stethoscope, an EKG sensor, a spirometer to measure lung function and a finger probe that measures glucose, white blood cell count and other blood tests. It continuously monitors a patient's vital signs and then asks questions through its smartphone or tablet app to better understand the symptoms. "It's doing exactly what I do in the ER," Dr. Harris explains. "It uses all of that objective information together in the way your doctor would to come up with a diagnosis." Dr. Harris hopes to keep the price around $200 once the device has received regulatory approval.[10]

The Future of AI?

Who knows what the future holds for AI in medicine. But, as we see here, what was once considered the impossible is no longer unachievable. Virtually anything can be created today with enough human determination, machine learning, technology and algorithms. The sky is no longer the limit. Today, it's more like the universe. And, 30 years from now, we will look back to marvel at how little we know today. ❖

MEREDITH WHITMORE is an English professor and freelance journalist in the Northwest.

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STOPPING **ALZHEIMER'S** WITH A **PREVENTIVE VACCINE?**

While several vaccines to prevent and treat AD are undergoing clinical testing, there is skepticism any will come to fruition after 40 years of therapy development failures.

By Diane L.M. Cook

AS BABY BOOMERS age, the number of people with Alzheimer's disease (AD) will skyrocket. According to the Alzheimer's Association, AD is the sixth-leading cause of death in the United States. Currently, 5.8 million Americans are living with AD, and that number is projected to rise to nearly 14 million by 2050.[1] And, because the rate of AD doubles every five years beyond age 65, the National Institute on Aging (NIA) says the number of people who will develop AD will exponentially increase.[2] These alarming statistics have prompted researchers to refocus their research on AD from drugs to vaccines with the hope to prevent, cure or slow it.

AD is a neurodegenerative brain disorder characterized by memory loss, cognitive impairment and functional decline. It is a very complex, multifaceted disease with no known singular cause. But, researchers have identified many potential causes of AD, including genetic, biological, lifestyle, environmental and comorbid conditions. Although AD symptoms typically present in people aged 65 years and older, it is suspected to be present up to 20 years prior to the onset of symptoms. After symptoms appear, AD can last anywhere from three or four years up to 10 years, depending on the time of diagnosis. AD is always fatal.

It was first described by Alois Alzheimer, MD, in 1906, but no progress was made on AD until 1974, when NIA was founded. NIA leads the nation in AD research by funding extramural research at universities and medical centers in the U.S. and around the world. Since NIA was formed, the AD field has progressed from the assumption the disease is a natural form of aging to a full-blown war on preventing and treating AD.[3]

Based on current vaccine research, two camps have emerged with opposing theories regarding the causes and symptoms of AD: amyloidists and tauists. Amyloidists believe plaques and tangles are the causes of AD; tauists believe plaques and tangles are the symptoms of AD.

According to Canaccord Genuity, a global, full-service investment banking and financial services company, there are currently 70 products in the AD clinical development pipeline of which 42 (60 percent) are small molecules and 28 (40 percent) are biologics. Biologics dominate the amyloid-beta (11 of 16; 69 percent) and anti-tau (9 of 13; 69 percent) approaches. Of these products, 16 rely on the amyloid-beta hypothesis and 13 rely on the anti-tau hypothesis. The amyloid beta-based products are farther along in the pipeline than the anti-tau products since the latter are relatively young. However, the amyloid-beta hypothesis is hanging by a thread after some recent drug failures, but it remains the single largest category in terms of the number of products still using that approach. But, now, there are signs this may change going forward.[4]

Following are some of the most promising AD biologic vaccine research projects:

AADvac-1

Axon Neuroscience has developed AADvac-1, an active immunotherapy vaccine that stimulates the patient's immune system to generate specific antibodies against diseased forms of the tau protein and, thus, protects the brain from neurodegeneration. AADvac-1 is intended to be a disease-modifying treatment for AD and aims to halt its progress.[5]

A first-in-man Phase I clinical trial was conducted with the vaccine from May 2013 to March 2015 on 30 patients with mild to moderate AD. The trial found the vaccine increased antibody titers with repeat injections, and mean Alzheimer's Disease Assessment Scale cognitive (ADAS-cog) scores remained stable over a six-month period. In addition, it had a favorable safety profile and excellent immunogenicity.[6]

In March 2016, a 24-month Phase II safety trial to evaluate the vaccine began to enroll 185 patients with mild to moderate AD. This trial is not trying to ascertain the presence of amyloid or tau pathology at study entry. Rather, it is comparing eight subcutaneous injections of 40 micrograms of the vaccine with the adjuvant aluminum hydroxide to placebo. The primary outcome is safety; secondary outcomes include cognitive and clinical batteries, as well as a measure of immunogenicity. It was slated to run until February 2019, but no results have yet been published.[6]

Based on current vaccine research, two camps have emerged with regard to the causes and symptoms of AD: amyloidists and tauists.

In June 2017, Axon Neuroscience started a two-year, open-label Phase I pilot trial of two doses of AADvac-1 in 30 people with nonfluent/agrammatic variant primary progressive aphasia between the ages of 18 years and 85 years. Participants are receiving either 40 or 160 micrograms of AADvac-1 in a series of six subcutaneous injections spaced six weeks apart, followed by five booster shots spaced 13 weeks apart. The trial will continue to run at three sites in Germany until July 2020.[6]

ABvac40

Araclon Biotech is developing an investigational, active immunotherapy vaccine called ABvac40. This vaccine is currently being evaluated in a Phase II multicenter, randomized, double-blind, placebo-controlled, 24-month study to investigate the safety,

tolerability and immune response of repeated subcutaneous injections in patients with amnestic mild cognitive impairment or very mild AD. The trial, which started recruiting in December 2017, is also evaluating responses at both the cognitive and molecular levels, providing the first data regarding a possible clinical impact.

Previous to this trial, the safety and tolerability of ABvac40 was evaluated in a Phase I trial in which the vaccine demonstrated a good safety and tolerability profile. While this Phase I blinded study did not evaluate the vaccine's efficacy, it produced an immune response in more than 87 percent of patients who received it.[7]

According to Jose Terencio, CEO of Araclon Biotech, "The innovative feature of this vaccine is the use of the C-terminus of the amyloid-β (Aβ) 40 peptide as an immunogen, a differentiated approach compared with other products in clinical development that are focused on Aβ 42 peptide. Aβ 40 peptide has been associated with plaque initiation and vascular amyloid deposition."

ACI-24 and ACI-35

AC Immune is currently developing two promising vaccine candidates: ACI-24 and ACI-35.

ACI-24 is a liposomal therapeutic anti-amyloid vaccine. In preclinical research, data demonstrated significant activity in plaque reduction and memory restoration. And, the vaccine had a favorable safety profile, characterized by a lack of observed local inflammation and a mechanism of action independent of inflammatory T cells. The Phase I/IIa study is complete, and results are scheduled to be published in 2019.

Novartis Pharmaceuticals Corp. is developing a vaccine called CAD106 designed to stimulate the production of antibodies against beta-amyloid while avoiding inflammatory T-cell activation.

A Phase II study of ACI-24 started in August 2018 to assess the vaccine's safety, tolerability, immunogenicity and target engagement of the vaccine's formulations in patients with mild AD. This trial seeks to confirm the positive trends on amyloid PET imaging observed in the previous Phase I/IIa study.[8]

ACI-35 is a liposomal therapeutic anti-tau vaccine. In preclinical testing in patients with mild to moderate AD, the vaccine induced an antibody response that was highly specific to misfolded and phosphorylated tau, which resulted in a significant reduction of phosphorylated tau and an improvement in cognitive clinical parameters. The Phase Ib study was considered safe and well-tolerated with no events related to central nervous center inflammation.

A Phase Ib/IIa study was announced in August. Based on the results of the Phase Ib study, in which a T-cell independent antibody response was indicated but lacked the boosting response desired for an optimal long-term and potentially preventive application, a new generation of the anti-tau vaccine was developed that demonstrated a high and boostable antibody response, which will be tested in this study.[8]

According to Andrea Pfeifer, CEO of AC Immune, "These two promising vaccine candidates were developed using the active immunization approach of our proprietary SupraAntigen vaccine discovery platform. This, along with the Morphomer small molecule discovery platform, forms the foundation of AC Immune's broad and robust pipeline. AC Immune's vaccines target AD through active immunization, where the immune system is stimulated to make its own antibodies against pathological proteins. The advantages of the SupraAntigen platform include a high selectivity for conformational targets and a favorable safety profile due to a T-cell independent mechanism of action, which does not trigger T-cell correlated inflammation. We are looking forward to further developing ACI-24 and ACI-35 through clinical trials, building on the promising results thus far."

CAD106

Novartis Pharmaceuticals Corp. is developing a vaccine called CAD106 designed to stimulate the production of antibodies against beta-amyloid while avoiding inflammatory T-cell activation. CAD106 is composed of a short fragment of beta-amyloid that includes only the amino acids 1 to 6. It is hoped the antibody response triggered by the vaccine will break down beta-amyloid plaques in a patient's brain and prevent new plaques from forming. Preclinical evidence gathered in animal studies suggests CAD106 can reduce beta-amyloid accumulation in the brain by inducing antibodies that interfere with beta-amyloid deposits and by binding to beta-amyloid aggregates.

Results of a Phase I study showed that, in people with mild to moderate AD, CAD106 induced titers that met prespecified responder criteria for an immune response while being generally safe and well-tolerated. Results of a Phase II study indicated antibody maturation and continued safety.

In November 2015, Novartis embarked on a Phase II/III study, called the Generation Study. This study is currently enrolling participants at sites across the U.S., Canada and Europe to test if CAD106 and another investigative medication, CNP520 from

Amgen, can prevent Alzheimer's in people ages 60 years to 75 years who are cognitively healthy but have two APOE4 genes. APOE4 is a variant of the APOE gene found in a number of Alzheimer's patients. People with two copies of the APOE4 gene variant are considered to be at high risk of developing mild cognitive impairment (a slight decline in cognitive ability, including thinking and memory skills) and/or dementia due to AD. One part of the study will compare 430 individuals given CAD106 as an injection to 260 individuals who will receive a placebo; another will compare 390 people treated with oral CNP520 against a placebo. The study will follow participants for at least 60 months (five years) and up to 96 months (eight years), and is expected to conclude in May 2024.[9,10]

According to Antonio Ligi, director of global external communications at Novartis, "We have recruited a sufficient number of subjects (65) for the CAD106 cohort to evaluate the effects on amyloid in the brain. We expect to conduct this assessment after two years of treatment at the latest. This is expected to take place in 2020. In parallel, we are working with Banner Alzheimer's Institute to evaluate whether there are further development options for CAD106."

DNA AB42

Scientists at the University of Texas Southwestern Peter O'Donnell Jr. Brain Institute led by Roger Rosenberg, MD, and Doris Lambracht-Washington, PhD, have developed a DNA vaccine called DNA AB42 that is on a short list of promising antibody treatments aimed at protecting against both types of proteins that kill brain cells as they spread in deadly plaques and tangles on the brains of AD patients. The idea for the vaccine was to start with DNA coding for amyloid and inject it into the skin rather than the muscle to produce a different kind of immune response. The injected skin cells make a three-molecule chain of beta-amyloid (AB42), and the body responds by producing antibodies that inhibit the buildup of amyloid and, indirectly, also of tau.[11]

The latest study, which consisted of four cohorts of between 15 and 24 mice each, showed a 40 percent reduction of Aβ 42 peptide and a 25 percent to 50 percent reduction of total tau and different phosphorylated tau molecules in mice compared with nonimmunized control animals. Plaque and Aβ peptide reductions in the brain were due to the anti-Aβ antibodies generated following the immunizations. Reductions of tau were likely due to indirect actions such as less Aβ in the brain resulting in less tau kinase activation. The vaccine did not induce inflammatory T-cell responses.[12]

One strategy still being tested for clinical benefits involves producing the antibodies in the lab and injecting them into the body. Allowing the body to produce its own antibodies through active immunization would be the preferable strategy since the vaccine would be more accessible and less expensive. It also produces a wider variety of antibody types than the preformed antibodies containing only one specific antibody.[11]

According to Dr. Rosenberg, "The DNA AB42 vaccine differentiates itself from other AD vaccines currently being researched in that it targets both amyloid and tau, it elicits a different immune response that might be safe for humans, and it produces its own antibodies through active immunization. I'm hopeful this vaccine can prevent or slow the progression of AD, and plans are now underway to obtain funding to test it in humans."

UB-311

United Neuroscience is developing an anti-amyloid endobody vaccine called UB-311. This synthetic peptide vaccine couples a helper T-cell epitope designed with United Biomedical's UBITh platform to the amino acids 1-14 in the beta amyloid protein, packaged in a proprietary delivery system. The approach aims to stimulate a T-helper type 2 regulatory immune response over a T-helper type 1 pro-inflammatory response, and to avoid cross-reactivity with similar endogenous antigens.[13]

A peer-reviewed paper on preclinical studies in small animals, baboons and macaques reported the vaccine generated N-terminal anti-amyloid antibodies, which neutralized amyloid toxicity and promoted plaque clearance. The paper also claimed the vaccine evoked no anti-amyloid cellular responses in a transgenic mouse model for AD, and both acute and chronic dosing were safe and well-tolerated in cynomolgus macaques.

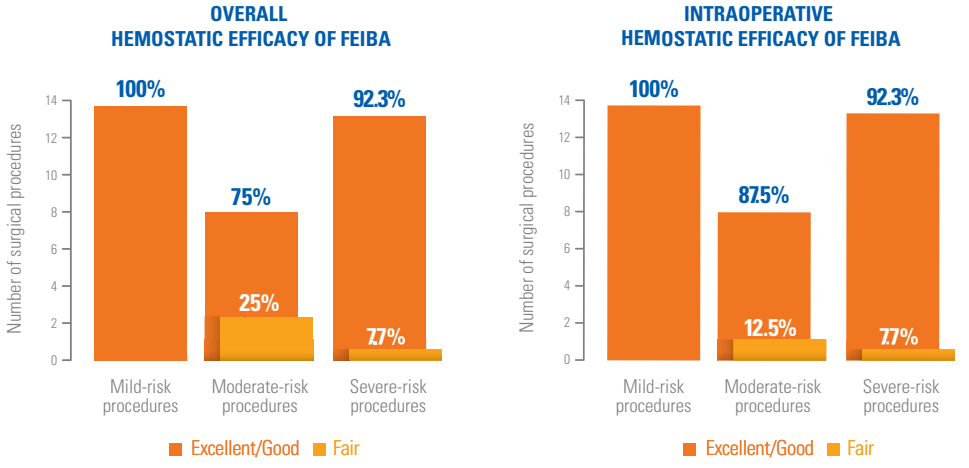
In a Phase I clinical trial, the UB-311 vaccine was tested on patients with mild to moderate AD to determine safety, tolerability and immunogenicity. Results concluded the vaccine was safe, well-tolerated and produced a specific antibody response in all par-

On hand to meet surgery demands[1]

BE PREPARED WITH FEIBA®

FEIBA is the only FDA-approved treatment for patients with hemophilia A and B with inhibitors, for prophylaxis, on-demand, and surgery.

FEIBA effectively maintained bleed control perioperatively[2]



91% Overall efficacy was rated as excellent or good for 91% of surgical procedures (n=34)[2]

94% Intraoperative efficacy was rated as excellent or good for 94% of surgical procedures (n=34)[2]

ADVERSE EVENTS IN THE STUDY

Treatment-Related: 1 serious AE, a case of a clot in an arteriovenous fistula, occurred during a moderate-risk surgery; 1 nonserious AE, a case of postoperative anemia, occurred after a severe-risk surgery[2]
Not Treatment-Related: 2 serious AEs; 1 case of anemia and 1 case of hemarthrosis; each occurred during severe-risk surgeries[2]

STUDY DESIGN

The SURgical Interventions with FEIBA (SURF) study was an open-label, prospective, non-interventional, observational, post-authorization study, specifically designed to clinically evaluate the perioperative use of FEIBA and accumulate a database of experience with perioperative FEIBA treatment that can be used to identify best practices in the surgical hemostatic management of hemophilia patients with inhibitors. This study evaluated outcomes for 35 surgical procedures in 24 patients. Of the surgeries performed, the risk level was considered severe for 13 procedures, moderate for 9 procedures, and mild for 13 procedures. The SURgical interventions with FEIBA (SURF) study, hemostatic efficacy was defined as follows: **Excellent** = hemostatic expectations were met or exceeded in light of previous experience with bypassing agents **Good** = efficacy was "somewhat less than expected" but still adequate compared with previous bypassing therapy **Fair** = hemostasis was significantly less than expected compared with previous bypassing therapy.[2]

FEIBA
[anti-inhibitor coagulant complex]

Keep FEIBA on hand to meet demands
before, during, and after surgery

FEIBA [Anti-Inhibitor Coagulant Complex] Indications and Detailed Important Risk Information

FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VIII or coagulation factor IX.

Detailed Important Risk Information for FEIBA

WARNING: EMBOLIC AND THROMBOTIC EVENTS

- **Thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA, particularly following the administration of high doses (above 200 units per kg per day) and/or in patients with thrombotic risk factors.**
- **Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events.**

CONTRAINDICATIONS

FEIBA is contraindicated in patients with:

- History of anaphylactic or severe hypersensitivity reactions to FEIBA or any of its components, including factors of the kinin generating system
- Disseminated intravascular coagulation (DIC)
- Acute thrombosis or embolism (including myocardial infarction)

WARNINGS AND PRECAUTIONS

Thromboembolic events (including venous thrombosis, pulmonary embolism, myocardial infarction, and stroke) can occur, particularly following the administration of high doses (>200 units/kg/day) and/or in patients with thrombotic risk factors.

Patients with DIC, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with recombinant factor VIIa have an increased risk of developing thrombotic events due to circulating tissue factor or predisposing coagulopathy. Potential benefit of treatment should be weighed against potential risk of these thromboembolic events.

Infusion should not exceed a single dose of 100 units/kg and daily doses of 200 units/kg. Maximum injection or infusion rate must not exceed 2 units/kg/minute. Monitor patients receiving >100 units/kg for the development of DIC, acute coronary ischemia and signs and symptoms of other thromboembolic events. If clinical signs or symptoms occur, such as chest pain or pressure, shortness of breath, altered consciousness, vision, or speech, limb or abdomen swelling and/or pain, discontinue FEIBA and initiate appropriate diagnostic and therapeutic measures.

WARNINGS AND PRECAUTIONS (continued)

Safety and efficacy of FEIBA for breakthrough bleeding in patients receiving emicizumab has not been established. Cases of thrombotic microangiopathy (TMA) were reported in a clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding following emicizumab treatment. Consider the benefits and risks with FEIBA if considered required for patients receiving emicizumab prophylaxis. If treatment with FEIBA is required for patients receiving emicizumab, the hemophilia treating physician should closely monitor for signs and symptoms of TMA. In FEIBA clinical studies TMA has not been reported.

Hypersensitivity and allergic reactions, including severe anaphylactoid reactions, can occur. Symptoms include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension. Reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. If signs and symptoms of severe allergic reactions occur, immediately discontinue FEIBA and provide appropriate supportive care.

Because FEIBA is made from human plasma it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

ADVERSE REACTIONS

Most frequently reported adverse reactions observed in >5% of subjects in the prophylaxis trial were anemia, diarrhea, hemarthrosis, hepatitis B surface antibody positive, nausea, and vomiting.

Serious adverse reactions seen are hypersensitivity reactions and thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

DRUG INTERACTIONS

Consider possibility of thrombotic events when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used with FEIBA. No adequate and well-controlled studies of combined or sequential use of FEIBA and recombinant factor VIIa, antifibrinolytics, or emicizumab, have been conducted. Use of antifibrinolytics within approximately 6 to 12 hours after FEIBA is not recommended.

Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab.

Please see FEIBA Brief Summary of full Prescribing Information on following page.

References: 1. FEIBA Prescribing Information. **2.** Négrier C, Lienhart A, Numerof R, et al. SURgical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia.* 2013;19:e143-e150. **3.** Rota M, Cortesi PA, Crea R, Gringeri A, Mantovani LG. Thromboembolic event rate in patients exposed to anti-inhibitor coagulant complex: a meta-analysis of 40-year published data. *Blood Adv.* 2017;1(26):2637-2642.

Takeda

FEIBA (anti-inhibitor coagulant complex)

for intravenous use, lyophilized powder for solution

Brief Summary of Prescribing Information: Please see package insert for Full Prescribing Information

WARNING: EMBOLIC AND THROMBOTIC EVENTS

- **Thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA, particularly following the administration of high doses and/or in patients with thrombotic risk factors.**
- **Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events.**

INDICATIONS AND USAGE

FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VIII or coagulation factor IX.

CONTRAINDICATIONS

- Known anaphylactic or severe hypersensitivity reactions to FEIBA or any if its components, including factors of the kinin generating system.
- Disseminated intravascular coagulation (DIC).
- Acute thrombosis or embolism (including myocardial infarction).

WARNINGS AND PRECAUTIONS

Embolic and Thrombotic Events

Thromboembolic events (including venous thrombosis, pulmonary embolism, myocardial infarction, and stroke) can occur with FEIBA, particularly following the administration of high doses (above 200 units per kg per day) and/or in patients with thrombotic risk factors [see *Adverse Reactions*].

Patients with DIC, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with recombinant factor VIIa have an increased risk of developing thrombotic events due to circulating tissue factor or predisposing coagulopathy. Potential benefit of treatment with FEIBA should be weighed against the potential risk of these thromboembolic events.

Monitor patients receiving more than 100 units per kg of body weight of FEIBA for the development of DIC, acute coronary ischemia and signs and symptoms of other thromboembolic events. If clinical signs or symptoms occur, such as chest pain or pressure, shortness of breath, altered consciousness, vision, or speech, limb or abdomen swelling and/or pain, discontinue the infusion and initiate appropriate diagnostic and therapeutic measures.

The safety and efficacy of FEIBA for breakthrough bleeding in patients receiving emicizumab has not been established. Cases of thrombotic microangiopathy (TMA) were reported in a clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding following treatment with emicizumab. Consider the benefits and risks with FEIBA if considered required for patients receiving emicizumab prophylaxis. If treatment with FEIBA is required for patients receiving emicizumab, the hemophilia treating physician should closely monitor for signs and symptoms of TMA. In FEIBA clinical studies thrombotic microangiopathy (TMA) has not been reported.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions, including severe anaphylactoid reactions, can occur following the infusion of FEIBA. The symptoms include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension. These reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of FEIBA and provide appropriate supportive care.

Transmission of Infectious Agents

Because FEIBA is made from human plasma it may carry a risk of transmitting infectious agents, e.g., viruses, and the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process [see *Description* in full prescribing information]. Despite these measures, the product may still potentially transmit human pathogenic agents. There is also the possibility that unknown infectious agents may still be present.

All infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare providers to Baxalta US Inc., at 1-800-423-2090 (in the U.S.) and /or to FDA Med Watch (1-800-FDA-1088 or www.fda.gov/medwatch).

Presence of Isohemagglutinins and Interference with Laboratory Tests

FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

ADVERSE REACTIONS

The most frequently reported adverse reactions observed in >5% of subjects in the prophylaxis trial were anemia, diarrhea, hemarthrosis, hepatitis B surface antibody positive, nausea, and vomiting.

The serious adverse reactions seen with FEIBA are hypersensitivity reactions and thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety assessment of FEIBA is based on the review of the data from two prospective clinical trials in which FEIBA was used for the treatment of acute bleeding episodes and a prospective trial that compared the use of FEIBA prophylactically versus on-demand treatment.

The adverse reactions reported from two prospective clinical trials in which FEIBA was used for the treatment of acute bleeding episodes were chills, chest pain, chest discomfort, dizziness, dysgeusia, dyspnea, hypoesthesia, increase of inhibitor titer (anamnestic response), nausea, pyrexia, and somnolence. Specifically, the first trial was a multicenter randomized, double-blind trial in 15 hemophilia A subjects with inhibitors to factors VIII. The second trial was a multicenter FEIBA study conducted in 44 hemophilia A subjects with inhibitors, 3 hemophilia B subjects with inhibitors and 2 acquired factor VIII inhibitor subjects. Of the 489 infusions used to treat acute bleeds during the second trial, 18 (3.7%) caused minor transient reactions of chills, fever, nausea, dizziness and dysgeusia. Out of 49 subjects, 10 (20%) had a rise in their inhibitor titers after treatment with FEIBA. Five of these subjects (50%) had increases that were, tenfold or more, and 3 (30%) of these subjects received factor VIII or IX concentrates within 2 weeks prior to treatment with FEIBA. These anamnestic rises were not associated with decreased efficacy of FEIBA.

Table 1 lists the adverse reactions in >5% of subject reported in the randomized, prospective prophylaxis trial comparing FEIBA prophylaxis with on-demand treatment in 36 hemophilia A and B subjects with inhibitors to factors VIII or IX. The trial population included 33 (92%) subjects with hemophilia A and 3 (8.3%) subjects with hemophilia B. Four (11%) subjects were ≥7 to <12 years of age, 5 (14%) were ≥12 to <16 years of age, and 27 (75%) were ≥16 years of age. A total of 29 (80.6%) subjects were Caucasian, 3 (8.3%) Asian, 2 (5.6%) Black/African American, and 2 (5.6%) other. The subjects received a total of 4,513 infusions (3,131 for prophylaxis and 1,382 for on-demand).

Table 1 Prophylaxis Study Adverse Reactions (ARs) in >5% of Subjects

MedDRA System Organ Class	Adverse Reaction	Number of ARs	Number of Subjects	Percent of Subjects (N=36)
Blood And Lymphatic System Disorders	Anemia	2	2	5.6
Gastrointestinal Disorders	Diarrhea	2	2	5.6
	Nausea	2	2	5.6
	Vomiting	2	2	5.6
Investigations	Hepatitis B Surface Antibody Positive	4	4	11.1
Musculoskeletal And Connective Tissue Disorders	Hemarthrosis	5	3	8.3

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of FEIBA. Because post-marketing reporting of adverse reactions is voluntarily and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Blood and Lymphatic System Disorders: disseminated intravascular coagulation

Cardiac Disorders: tachycardia, flushing

Respiratory, Thoracic, and Mediastinal Disorders: bronchospasm, wheezing

Gastrointestinal Disorders: abdominal discomfort

Skin and Subcutaneous Tissue Disorders: pruritus

General Disorders and Administration Site Conditions: malaise, feeling hot, injection site pain

DRUG INTERACTIONS

Concomitant Medications

Consider the possibility of thrombotic events when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. No adequate and well-controlled studies of the combined or sequential use of FEIBA and recombinant factor VIIa antifibrinolytics, or emicizumab have been conducted. Use of antifibrinolytics within approximately 6 to 12 hours after the administration of FEIBA is not recommended.

Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab when FEIBA was used as part of a treatment regimen for breakthrough bleeding (see *Warnings and Precautions* above; see also Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med* 2017:377:809-818).

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ticipants tested. In a Phase II clinical trial, patients with a clinical diagnosis of mild AD were assessed for the primary outcomes of safety, tolerability and immunogenicity and the secondary outcomes of cognitive, functional, global and neuropsychiatric.[14] Results showed UB-311 generated antibodies to specific beta-amyloid peptides and fibrils, and there was no decrease in antibody levels in patients who were older. Results also showed PET imaging of beta-amyloid clumps and genetic screening for the APOE4 gene can help identify people with mild cases of AD.[15] In addition, results of a top-line Phase IIa study showed UB-311 met the primary aims of safety and immunogenicity with a 96 percent response rate.[16]

A Research Paradigm Shift?

Unfortunately, as promising as the results of these vaccines sound, many in the field are not convinced all or even any of these AD vaccines will be effective for humans. To date, there has not been a single vaccine that either targets the toxic proteins amyloid or tau that has made it beyond a Phase III clinical trial. In fact, a recent study found "the attrition rate for AD treatment is high, with 72 percent of agents failing in Phase I, 92 percent failing in Phase II and 98 percent failing in Phase III in the period observed [from 2002 to 2012]." Further, "the failure rate since 2002 (excluding agents currently in Phase III) is 99.6 percent."[17]

What's needed in AD research is a paradigm shift, says Zaven Khachaturian, former director of the Office of Alzheimer's Research at the National Institutes of Health, former director of the Division of Neuroscience at NIA, and now senior science advisor of the Alzheimer's Association, Editor-in-Chief of *Alzheimer's & Dementia*, the journal of the Alzheimer's Association, and president of the Campaign to Prevent Alzheimer's Disease by 2020. "The current research on Alzheimer's disease, based on current prevailing ideas, theories, paradigms and promising leads, have not yielded any positive results in the last 40 years. The problem is that this is a very complex disease, and this field does not have any single theory that encompasses all of the well-documented facts about the spectrum of Alzheimer's disease. Therefore, novel research projects need to be developed to find a primary intervention that will reverse, prevent or cure Alzheimer's disease."

In the current approach to conducting AD research, Khachaturian says, "The traditional approach, based on reductionistic logic, to untangle the complexity of a biological system, is not adequate by itself to explain the behavior of the higher levels of organization of the system." In addition, says Khachaturian, novel approaches to conducting AD research are needed to discover new, novel primary interventions: "Current models and/or modeling systems used to understand the complex neurobiological mechanism that underlie the neurodegenerative processes associated with dementia-Alzheimer syndrome are not adequate for developing effective treatments. There is a need for new or different modeling systems that incorporate concepts derived from systems theory."[18]

"After 40 years of consistent therapy development failures, I am skeptical about any positive reports based on early preliminary animal studies or early clinical trials. There have been too many promising ideas that did not come to fruition. However, I remain optimistic about any potential promising interventions, pending successful demonstration of efficacy in a well-powered and controlled clinical trial," adds Khachaturian.

Unfortunately, as promising as the results of these vaccines sound, many in the field are not convinced all or even any of these AD vaccines will be effective for humans.

Until the crucial missing piece of the AD puzzle is found, it could be several years or even decades before a vaccine is developed that will prevent, cure or slow the progression of this fatal disease. ❖

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Nutrigenomics:
How Genes and Nutrition Interact

Is personalized nutrition the next revolution in managing health? While its study is on the rise and holding great promise, it faces challenges, including whether individuals will embrace it.

By Amy Scanlin, MS

THE PROMISE OF nutritional interventions tailored to one's specific needs has, until recently, been difficult to realize. More than just "eating right for better health," using nutrition to benefit health through the care and feeding of genes, though still in its infancy, is an exciting field of study seeing exponential growth. It has long been theorized dietary choices have a direct impact on whether genes, or genetic mutations, are turned on or off, although a firm grasp of just how that interaction might play out has been elusive. Still, the evidence of some kind of link between people's genes and the foods they consume is there.

Familiar examples of genetic interactions include otherwise apparently healthy individuals who consume vast quantities of foods widely known to cause adverse health outcomes with no ill effect. Yet, others who seem to make all the right choices develop disease nonetheless. The question, then, is "Does diet have a direct impact on an individual's genetic expression, and if so, how does that effect differ from person to person?"

Science's understanding of diet's effects on genes has evolved from merely studying individual single nucleotide polymorphisms (SNP) to studying whole genomes.[1] And, it is hoped that as

nutrigenomics (how genes, nutrition and the environment interact) evolves, diet-related diseases will be able to be prevented using genetic testing to predict health risks and offer a tailored approach to a person's diet based on their specific needs and genetic makeup. It is known diet can affect genomic mutations in vivo and in vitro at the base chromosomal level,[2] but how?

In addition to nutrigenomics, research is focusing on metabolomics, or how the molecular composition of foods and the chemical process of metabolism lead to the potential for gene expressions. The concept is enticing. While genes account for only 5 percent to 10 percent of the risks linked to diet-related diseases,[3] SNP biomechanic pathways account for 90 percent of genetic variation. Further, studies assessing genetic risk scores as aggregates of information from multiple SNPs is evolving.[4] Understanding how to apply nutrigenomics at the individual level may someday enable nutritional interventions aimed at preventing and even reversing DNA damage as opposed to diagnosing and treating disease. This means our understanding of the effects of eating too much or too little of certain nutrients can ultimately have lasting positive impacts on health choices.

Challenges of Personalized Nutrition

Personalized nutrition comes with many challenges, including a lack of general consensus on how to define it and what constitutes it. For instance, personalized nutrition must take into consideration environmental factors such as smoking, pollution, physical activity and the nutritional quality of foods. What makes personalized nutrition personal is that each individual's nutritional needs differ. What is a "normal" nutrient requirement for one may be completely unhealthy for another. Hence, the challenge of translating large amounts of study data into something meaningful and individualized persists.

To date, there have been few large-scale, long-term, randomized studies evaluating the links between diet and genes, in part because dietary recall is largely observational and difficult to reproduce. Adding to the complexity are genetic variations and environmental considerations that must be factored into the study design, meaning both diet and genotype must be controlled to truly study the effects of diet on chronic disease. Therefore, for the foreseeable future, it is expected observational studies will continue to be the predominant line of human study, which can provide associations but not much in the way of causation.

Even with the strides made in understanding diet and genes, developing exact and appropriate personalized nutrition plans could be elusive until individuals know their own personal genotype. But, the problem lies in provider and patient buy-in to act on the potential benefits of nutrigenomics. A Greek survey showed that although 80.5 percent of nutritionists and doctors reported a willingness to recommend a nutrigenomics analysis, only 17 percent had actually done so.[5]

Some argue the public isn't ready for personalized nutrition. Yet, others say we now know enough about developing personalized nutrition to benefit patients. For instance, genetic information can be used to create some dietary recommendations, even if it isn't yet tailored to a point where diet can influence genes.

Food Choices and DNA

In a practical sense, genetic variations are directly related to energy balances, and they play out in a multitude of ways from appetite, food preferences, insulin signaling, inflammation, the formation of fat cells and metabolism. This means a person's weight and body composition are functions of more than just how many calories they burn in relation to how many calories they consume.[4]

While science has linked genetics and dietary choices for some conditions such as celiac disease and lactose intolerance, this knowledge is just the tip of the iceberg. The interplay of DNA sequence variations of SNPs, ribonucleic acid (RNA) and how dietary choices alter our risk for disease is seen, though not understood, in numerous examples such as the connection between folate and riboflavin, both of which can catalyze a reaction of the methylenetetrahydrofolate reductase (MTHFR) gene. Folate is a substrate for MTHFR, and riboflavin is a cofactor of MTHFR. In some homozygous carriers of the C677T polymorphism, high intake of these two nutrients could cause developmental defects, but also subsequent protection from certain cancers. Additionally, calcium intake may enhance the effects of a diet high in folate, while a diet high in riboflavin may exacerbate the effects of a diet low in folate. This may explain higher cancer rates among those who consume more red meat (high in riboflavin), more alcohol (which deletes folate) and fewer vegetables (high in folate).[2]

Personalized nutrition comes with many challenges, including a lack of general consensus on how to define it and what constitutes it.

Nutrigenomics has thus far been most widely studied in relation to obesity. For instance, findings such as a link between SNPs and the obesity-associated protein FTO demonstrate high-protein diets result in the loss of more body fat for those with one specific FTO variation, but they have little impact on those without it.

And, Mediterranean diets have been found to be most effective in controlling obesity and protecting against type 2 diabetes in groups with one type of SNP of the FTO gene, but not another.[6]

These examples demonstrate that without knowing an individual's genetic makeup, today's recommendations of which type of diet to follow is largely based on generalized recommendations. However, as more nutrition-related SNPs are identified, recommendations can become more tailored and more effective, which should increase patient motivation for compliance as the implications of dietary choices become clearer.[4]

The Science of Food

Foods and beverages are also being analyzed in great chemical detail to understand how their micronutrients and bioactive substances impact both gene expression and genome health. With thousands of DNA alterations and damage from environmental factors occurring daily, quick repair of DNA is critical. Diets and lifestyle choices can provide some of the needed repairs. Additionally, it is thought diet may be able to compensate for inherited defects in DNA repair mechanisms and may be able to stabilize the genome from further disrepair once genetic alterations have occurred. Therefore, scientists must look more broadly at how multiple nutritional imbalances impact the genome.[2]

Until a more complete picture emerges of how diet impacts genes that then impact health, the question remains: "Will people follow that advice?"

Foods produced or altered in laboratories have been questioned for their authenticity and health benefits, but what if they were supplemented with the extra dose of whatever vitamin or mineral is largely missing in an individual's diet? Or, what if food was produced without a substance toxic to one's system? Would that food be considered the wave of the future?

Food that can be 3D printed is in rapid research and development, and someday, it may be able to solve many of the consumption challenges individuals face. From pureed food for those with chewing challenges to gourmet chocolates for the discerning palate, this newer technology (which today is in its infancy) may hold the key to solving for missing nutritional links, while at the same time reducing food waste. 3D printers, which create foods from substances in powder and oil forms housed in cartridges (that forms a gel when combined with water) may be able to create nutritious foods. And, future generation printers may be able to individualize nutrients to meet consumer needs, offering an entirely new tailored approach.

Of course, the idea of printing food is a lot more challenging than printing plastic. Food ingredients interact with each other differently, layers of ingredients may need to be cooled before the next layer is added, and the number of ingredient cartridges needed to create something as simple as a vegetable could be in the millions, making them cost-prohibitive. However, as technology improves, many feel 3D printing can someday be a missing link that marries personalized data and the kitchen.[7]

Preferences Take the Cake

So, what does the future of food look like? From genetically modified organisms (GMO) to non-GMOs to 3D-printed foods, the culinary world is on the cusp of new technologies to enable specific choices that will catalyze specific chemical reactions that can impact our genetic expression and conceivably improve health outcomes. As scientists work to find new techniques for food production and nutritional enhancements, our understanding of how to use food for specific genetic manipulation will someday intersect.

Of course, until a more complete picture emerges of how diet impacts genes that then impact health, the question remains: "Will people follow that advice?" Humans are finicky eaters, and food-consumption choices are often based on factors and preferences other than nutrition. Tastes are discretionary, but availability, cost and access to foods that can most benefit individuals can, in some cases, be prohibitive.

Still, the future of nutrigenomics holds great promise. As healthcare costs continue to soar and access to care in remote areas continues to be a challenge, patients will one day be able to, with the watchful eye of their providers, make more intentional dietary choices for the better care and feeding of their genes. ❖

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The Growing Need for **Supportive Care in Oncology**

Organizations are making strides to reduce the many barriers to palliative care for cancer patients.

By Diane L.M. Cook

EARLY CANCER DETECTION and better treatment options have resulted in more people surviving cancer and living longer with their posttreatment symptoms. Now, as baby boomers enter their senior years, there continues to be an explosion in the number of aging adults diagnosed with and surviving cancer. And, however positive this phenomenon might seem, it has contributed significantly to the growing need for supportive care in oncology.

According to the Centers for Disease Control and Prevention, "In 2015, the latest year for which incidence data are available, 1,633,390 new cases of cancer were reported, and 595,919 people died of cancer in the United States."[1] The upside to this statistic is, of the 1,633,390 new cancer cases, 1,037,471 people survived. This means for every year that passes, there are more than one million more people living with cancer and their posttreatment symptoms who require some level of supportive oncology care.

Unfortunately, the current healthcare system is ill prepared for this onslaught of new oncology patients. Even though major strides have been made in the palliative care field — there were only 658 hospitals (50 or more beds) with a palliative care team in 2000 compared with 1,831 hospitals with a palliative care team in 2016 (a 178 percent increase) — there still exist myriad barriers to supportive care in oncology.[2]

Diane Meier, MD, FACP, FAAHPM, director at the Center to Advance Palliative Care (CAPC), says the main barriers to palliative care include a lack of physician understanding of what palliative care is and when to refer; a lack of public understanding of what palliative care is; an inadequate skilled workforce pipeline in which there are more patients than trained health professionals to care for them; inadequate financing; and outdated policies that fail to address the changing needs of an aging and chronically ill patient population.

Palliative vs. Hospice Care

The World Health Organization's outdated definition of "palliative care"[3] still defines it as a pathway to dying, which perpetuates the misperception of many oncologists and their patients that palliative care is the same as hospice care. This misperception can result in oncologists failing to refer patients to palliative care at the right time or not referring them at all. It can also result in patients failing to request palliative care if and when they decide they want and need it.

Today's definition of palliative care is distinctly different from hospice care. Palliative care is intended to be provided at any point during an illness with the goals of providing comfort, quality of life and support to patients and their families. Palliative care can begin at any time and at any stage of illness, whether the illness is curable, chronic or life-threatening, at the discretion of physicians and patients.[4]

On the other hand, hospice care provides comfort when there are no longer curative options available or when patients have chosen not to pursue curative or aggressive treatment because side effects outweigh benefits. Eligibility for hospice care requires two physicians to certify a patient has less than six months to live, if the illness were to follow its natural progression.[4]

The Palliative Care Framework

The palliative care framework includes many services provided by an interdisciplinary team that consists of physicians, nurses, social workers, therapists, home health aides, volunteers, spiritual counselors and bereavement counselors who work together to provide symptom relief and pain management, and to alleviate psychosocial distress to cancer patients during and after treatment. These services are provided in diverse care settings such as hospitals, nursing homes, assisted living facilities, long-term care facilities

or patients' residences.

The main purpose of palliative care is to improve communication between patients, caregivers and healthcare providers. Cancer patients who receive supportive oncology care can expect to remain comfortable by preventing or relieving their pain and suffering; improving their quality of care while reducing medical costs; and receiving psychological and spiritual care.[4]

The benefits of palliative care also include fewer tests and treatments that can be invasive and costly and cause additional anxiety and stress for patients, shorter or fewer hospital stays, fewer emergency room visits, fewer intensive care unit admissions on hospital readmission, and more procedures that can be performed at home (such as intravenous and drug treatments).

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Guidelines for Quality Palliative Care

The National Consensus Project for Quality Palliative Care, comprising 16 national organizations with extensive expertise in palliative care and hospice, recently updated its *National Consensus Project Clinical Practice Guidelines for Quality Palliative Care* in 2018. These guidelines, endorsed by more than 80 national organizations, establish a comprehensive foundation for gold-standard palliative care for people living with a serious illness, regardless of diagnosis, prognosis, age or setting.

This fourth edition expands upon the original guidelines first developed in 2004 that described core concepts, structures and processes necessary for quality palliative care, including eight domains of practice. It also expands upon clinical and organizational strategies, screening and assessment elements, practice examples, tools and resources.[5]

Models of Palliative Care

CAPC's three levels of palliative care. CAPC, a national member-based nonprofit organization dedicated to increasing the availability of quality palliative care services for people living with a serious illness, developed a provider-based model for primary, secondary and tertiary palliative care. The model focuses on palliative care services according to level of patient complexity and setting. Primary palliative care is provided by primary care providers, oncologists and others, and includes services all clinicians should be able to deliver, including symptom management and communication skills. Secondary palliative care is provided to patients when their symptoms are especially complex or difficult to manage. And, tertiary palliative care is indicated for patients with the most complex supportive care needs, which includes the roles of conducting research and educating the next generation of physicians and other professionals.[6]

The Bow Tie Model of 21st Century Palliative Care. Philippa Hawley, BMed, FRCPC, division head in the Department of Palliative Care at the British Columbia Cancer Agency in Vancouver, B.C., Canada, proposes the Bow Tie Model to describe palliative care. This new model acknowledges the duality of an approach that prepares patients for the worst (death) but still allows hope for the best (cure). It consists of two overlapping triangles that resemble a bow tie, with an arrow pointing from left to right. The first triangle represents disease management, and the second triangle is palliative care. The base of the palliative care triangle (end of the model) includes both death and survival as possible outcomes. The arrow indicates this is a dynamic process with a gradual switch in focus. The key difference between this and traditional models is survivorship is included as a possible outcome. This model permits the early acceptance of a care pathway where the two approaches to care are integrated from the time of diagnosis, when the ultimate outcome (death or survivorship) may be too frightening for the patient to contemplate.[7]

Born out of the Bow Tie model is the term "survivorship." According to Dr. Hawley, survivorship "is starting to be used in reference to a type of service overlapping with or including palliative care."[7] She says a palliative approach to care is particularly important when the prognosis of a patient is uncertain and survivorship is a possibility. "Survivorship refers to a distinct phase in the illness trajectory between cessation of attempts to cure the disease and transition back to normal life or as near to a person's normal as possible," says Dr. Hawley. "Learning to live with stable illness may be one state of survivorship, and cure is not necessarily required. People who have been cured of a serious illness may be irreversibly damaged by the disease or its treatment, and may require significant multidisciplinary care to achieve their full subsequent potential." Dr. Hawley believes the suffering of patients who enter the "limbo" of survivorship should be acknowledged, and palliative care specialists should have the skills to contribute to the care of these patients.[8]

The PACSSI model. Joseph Rotella, MD, MBA, HMDC, FAAHPM, chief medical officer for the American Academy of Hospice and Palliative Medicine (AAHPM), who works to improve the care of patients who have serious illnesses, says current fee-for-service payment mechanisms also pose a key barrier to expanding

access to palliative care. In an effort to remove this barrier, AAHPM, an organization created in 1988 for healthcare providers who specialize in hospice and palliative medicine, proposed an alternative payment model that would support community-based palliative care called Patient and Caregiver Support for Serious Illness (PACSSI). PACSSI is one of two initiatives under AAHPM's *Payment Reforms to Improve Care for Patients with Serious Illness*. "We believe the PACSSI model holds great promise for both improving quality of care for Medicare beneficiaries with serious illness and reducing costs for the Medicare program," says Dr. Rotella.[9]

Mitigating a Skilled Workforce Shortage

AAHPM believes palliative care providers and organizations are integral to meeting the "triple aim" of better care for individuals, improved health of populations and lower growth in healthcare expenditures. The organization refers to recent studies that have demonstrated high-quality palliative care not only improves quality of life and patient and family satisfaction, but can also prolong survival.[10]

According to Dr. Rotella, "There are increasing numbers and needs of Americans living with serious or complex chronic illnesses, and the realities of the care pose challenges for their families. Because the number of people living with serious and complex chronic illness is expected to skyrocket over the coming decades, our nation needs to expand its capacity to train both palliative care specialists and all other clinicians who care for them."

For instance, AAHPM's policy statement says by 2050, the population age 65 years and older is projected by the U.S. Census Bureau to be 83.7 million, almost double that of 2012. As the population ages, an increasing number of people will be living with serious, complex and chronic illness. And, according to the Medicare Payment Advisory Commission, in 2010, more than two-thirds of Medicare beneficiaries had multiple chronic conditions, while 14 percent had six or more. Treatment of chronic and serious illnesses such as heart disease and cancer now accounts for nearly 93 percent of Medicare spending.[10]

Unfortunately, says AAHPM, there is a large gap between the number of healthcare professionals with palliative care training and the number required to meet the needs of the growing population of individuals with serious illness or multiple chronic conditions.[11] In 2010, AAHPM estimated 6,000-plus full-time equivalents, or 8,000 to 10,000 physicians, were required to meet then-current staffing needs in palliative care and hospice programs, with up to 18,000 physicians needed if all hospices and palliative care programs used exemplary staffing models. These scenarios did not take into account future expansion of need due to population growth and aging or expansion of palliative care services into community settings such as nursing homes, homecare and office practices, all of which can be expected to exacerbate the hospice and palliative medicine workforce shortage.[10]

To mitigate this skilled workforce shortage, AAHPM developed a bill titled the Palliative Care and Hospice Education and Training Act (PCHETA), which was reintroduced into the U.S. House of Representatives on Jan. 17. This bill includes the establishment of palliative care and hospice education centers, physician training, academic career awards, workforce development, career incentive awards, nurse training, palliative care education and awareness, and enhanced research. AAHPM and its stakeholder partners are focused on securing support from Energy and Commerce Committee members to quickly advance PCHETA.[12]

A Needed Paradigm Shift

Although strides are being made in the palliative care field, supportive care in oncology still requires a paradigm shift if it is ever expected to be considered an essential element of quality medical care for people who have serious, complex or multiple illnesses, regardless of their age, stage of illness, number of illnesses or care setting in which they reside.

"Increasing access to high-quality palliative care is a social transformation of profound importance to our health system, our nation and to people living with a serious illness and their families," says Dr. Meier. "The goal now is to standardize timely access to quality palliative care for all who can benefit."[13] ❖

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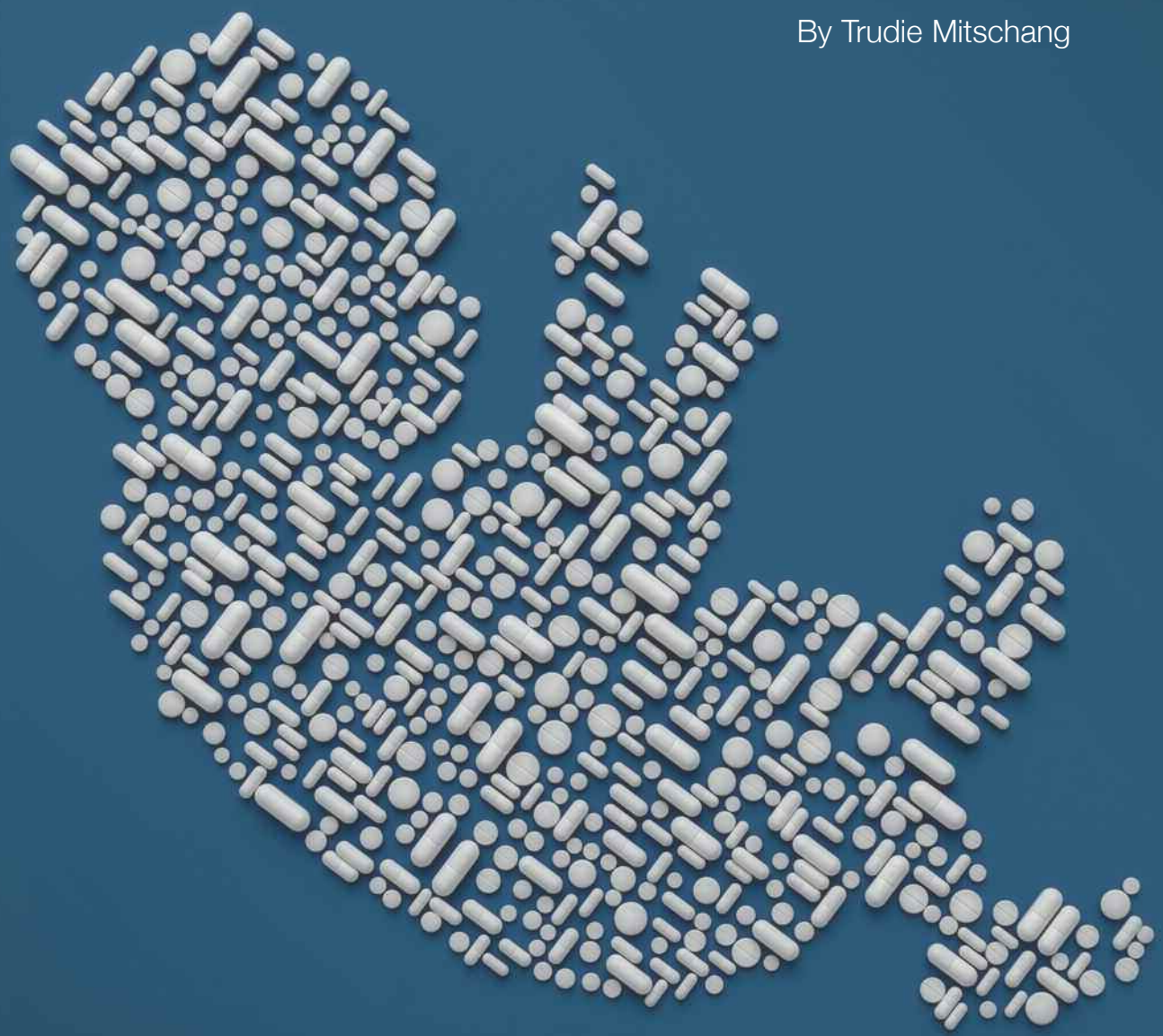
OPIOID DEPENDENCE IN INFANTS:

As medical professionals and policymakers grapple with the rapidly expanding and increasingly urgent healthcare dilemma of addicted newborns, the youngest victims of the opioid epidemic are crying for answers.

By Trudie Mitschang



A GROWING CRISIS

IT IS ESTIMATED one baby is born every hour in the United States with a dependence on opiate drugs. This heartbreaking epidemic is complex and not easy to treat. Because the birthing process brings an abrupt cessation of the opioid, these tiny addicts immediately go into withdrawal. Symptoms may include crying for hours due to pain and discomfort as their bodies adjust. Not surprisingly, they often are fussy and difficult to calm. The official diagnosis of infant drug withdrawal is neonatal abstinence syndrome (NAS), and sadly, the health impact on these children can be significant and lifelong. "There are studies that show an increased risk of congenital heart defects in babies exposed to codeine in the first trimester, but in general, the chronic use of opioids in pregnancy increases the risk for fetal growth restriction, placental abruption (the separation of the placenta from the uterine wall), preterm delivery and fetal death," said James J. Steigerwald, MD, a member of the OB Hospitalist Group at Memorial Hospital in Colorado Springs, Colo.[1]

NAS was first formally described in the 1970s by Philadelphia pediatrician Loretta Finnegan, MD, yet all these decades later, it remains a challenging condition to diagnose and report. For one thing, although a woman's drug use during pregnancy can be confirmed by testing the baby's urine and first bowel movement, withdrawal exhibits a cluster of symptoms easily mistaken for other maladies. The hallmark symptoms are shrill, inconsolable crying and tremors, but the baby may also suffer muscle spasms, convulsions, vomiting, diarrhea, insomnia, trouble feeding, fever, nasal stuffiness, scratching, yawning and sweating, making a straightforward diagnosis difficult at best. In addition, infants whose mothers also took stimulants such as cocaine or methamphetamines typically don't display the classic signs of withdrawal from prescription opioids and heroin, complicating diagnosis and treatment. "One of the problems with the diagnosis of NAS is that there is no national or state guidance on when to code it," said Debra Bogen, MD, a pediatrician and NAS expert at Children's Hospital of Pittsburgh of UPMC. "It's a messy term." Pennsylvania state health official Rachael Levine, MD, agrees: "NAS is a clinical diagnosis. It involves lab testing. But some of the symptoms are nonspecific in terms of a jittery baby. It is not always obvious and can be challenging."[2]

Adding to challenges with diagnosis and treatment plans, the sheer number of cases continues to rise, potentially overwhelming hospitals ill-equipped to handle them. According to *U.S. News & World Report*, the national rate of babies born with NAS increased fivefold from 2000 to 2012. Additionally, 27 in every 1,000 babies were admitted to neonatal intensive care units (NICUs) suffering from NAS in 2013, compared with seven in every 1,000 in 2004, according to a study published in the *New England Journal of Medicine*.[3]

An Emphasis on Integrative Care

Opioids include various prescription medications such as Vicodin, Percocet, Norco, Lortab, codeine, oxycodone, hydrocodone and Dilaudid. But, when it comes to opioid dependence in infants, the list also includes nonprescription drugs such as heroin. Sadly, babies born with NAS may also have been exposed to medication-assisted therapy used to treat their mother's opioid addiction, including drugs like Suboxone or methadone, adding yet another layer of complexity to the growing healthcare crisis. When it comes to treatment, most NAS babies require decreasing doses of morphine or methadone until withdrawal symptoms subside, although some infants have attained sufficient relief with a regimen of cuddling and swaddling.

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Dr. Steigerwald notes that despite the hurdles, there are treatment options, although until recently, the choices were extremely limited. "Treatment for the newborn usually consists of giving them opiates and gradually weaning down the dose."

With escalating caseloads around the country, researchers have been seeking more effective treatment options. Rather than a one-size-fits-all approach, a 2018 study states the effective management of NAS requires a coordinated "cascade of care," from prevention through long-term follow-up. Researchers who participated in the study identified four essential areas with the potential to improve care for this increasingly common complication of opioid use. "Greater resources, coordination and cross-disciplinary education are urgently needed across the cascade of care to effectively address NAS," stated Jennifer L. Syvertsen, PhD, MPH, of the University of California, Riverside, and colleagues at the University of Southern California.[4]

In their study, researchers conducted in-depth interviews with 18 central Ohio healthcare providers caring for infants and families affected by NAS. Ohio has among the highest rates of opioid use and NAS in the United States. Informed by analysis of the provider interviews, the researchers listed the following interrelated components for effective treatment:

• *Prevention.* Care begins with preventing the misuse of opioids and other drugs. Preventive efforts should encompass the "social determinants of health" such as poverty, lack of education and limited opportunities.

• *Prenatal care and drug treatment.* The study stressed the need for supportive care for pregnant women using opioids rather than punitive approaches. While comprehensive care programs have yielded promising results, NAS can occur even in infants born to mothers receiving recommended medication-assisted treatment for opioid use disorder.

• *Labor and delivery.* Infants must be monitored for signs of NAS, with treatment if needed; providers stressed that consistency in following protocols is critical to reducing infant length of stay in the hospital. Programs to sensitize staff and mitigate stereotyping attitudes toward mothers of babies with NAS have also led to better care. One challenge identified in rural areas, for example, is that the infant often has to be transported to a NICU, creating barriers to mother-infant bonding.

• *Aftercare.* Supportive aftercare includes access to drug treatment and social services, monitoring the child's development and providing a healthy home environment for the infant to thrive. While services are typically available for pregnant women, all too often they shut down after delivery.

"Our current focus on the period of pregnancy alone is insufficient to address the complexity of NAS," Dr. Syvertsen explained. The study goes on to highlight the need for programs and policy at each stage of treatment, toward the critical goal of stemming the tide of NAS. "Unless we make a serious political commitment to create fair drug policy, adapt a more integrative approach to addressing NAS and adequately support the initiatives that we know can work, NAS incidence will continue to rise and devastate communities."

Blaming and Shaming: Addressing the Stigma

Historically, a significant impediment to better care for babies with NAS has been the tendency to blame their mothers for using illegal substances while pregnant. Stephen Patrick, MD, MPH, MS, a neonatologist at Monroe Carell Jr. Children's Hospital at Vanderbilt University, says among people with substance use disorders, "there's no population that's more stigmatized than pregnant women," adding there is a sense of "How could you do this to your baby?"[5]

Hendrée Jones, PhD, executive director of the University of North Carolina Horizons Program, which offers mothers with substance use disorders intensive treatment, psychiatry, case management, therapy and other services, agrees. "There is a tremendous amount of blaming and shaming and stigma," she says. "Unfortunately, that is something that has not changed at all in the 25 years I've been in the field." Tragically, this stigma and the resulting shame drive a woman from the very treatment that could help her and her unborn child.

Now the medical director at Wellbridge Addiction Treatment and Research in New York, Harshal Kirane, MD, had previously worked and done research at the epicenter of what may be one of the worst areas of opioid addiction in Staten Island, N.Y. He recently led an assessment that evaluated the attitudes of physicians from all fields across the Northwell Health System. The survey assessed clinician attitudes and

practices in treating opioid dependence, and the data directly influenced an expanded framework now being used to address treatment at the hospital level. "There remains inadequate physician training in addressing pain management, and that's certainly true in obstetrics and gynecology, which means substance abuse issues are often not screened for or addressed in preventative ways," he explains. "Once someone is pregnant with an opioid addiction, the situation rapidly deteriorates each day treatment is delayed. A woman struggling with this disorder feels stigmatized, is afraid, and in the process of avoiding care for her addiction, is also not accessing basic care for her pregnancy. By the time of delivery, the situation is much more dire than if these issues had been addressed way upstream."

Recognizing the scope of the problem, a multidisciplinary team spearheaded by Salem Magarian, MD, at East Cliff Family Health Center in Santa Cruz, Calif., has developed a care model worth a second look. This comprehensive treatment approach involves a network of agencies throughout the county. The result is an innovative, voluntary prenatal program in which every pregnant woman can access home visits and drug and alcohol counseling without facing judgment or fear of repercussion. In a typical scenario, a social worker gets to know mothers before they deliver and helps support them while their babies are in the NICU. Nurses are trained to provide comfort care to babies going through withdrawal, keep them in quiet rooms and teach their mothers how to swaddle them with skin-to-skin contact. In addition, the team developed a weaning protocol. Every baby who exhibited signs of serious withdrawal was put on the same small dose of morphine, which increased up to a certain limit until the baby stabilized. Babies who were stable for 48 hours were sent home to wean.

While there hasn't yet been a peer-reviewed investigation into the model developed in Santa Cruz, the limited data thus far seems to support the approach. Nationally, babies with NAS tend to stay in the hospital an average of 3.5 times longer than other newborns. Under this program, stays for impacted infants in the NICU dropped from 14 days to nine. In addition fewer babies returned to the emergency room while more of the mothers remained in long-term recovery.[5]

In another notable treatment model at Yale New Haven Children's Hospital, under the guidance of Matthew Grossman, MD, doctors implemented the "eat/sleep/console" system, in which they put babies who had been exposed to opioids in utero in low-stimulation rooms with their parents sleeping in the hospital. Babies were comforted frequently, but only given morphine on select occasions. According to a study published in the journal *Pediatrics* last year, the percentage of infants being treated with morphine dropped from 98 percent to 14 percent, and the average stay decreased from 22 days to six.[5]

"I absolutely see these programs having tremendous merit," says Dr. Kirane. "The emphasis of addiction treatment in pregnancy has to move toward a more humanistic, interdisciplinary approach to care. When an entire team can be mobilized to support a new mother in this delicate and vulnerable time, it seems to be a really powerful opportunity to meet a very complex need."

With escalating caseloads around the country, researchers have been seeking more effective treatment options.

Hope on the Horizon

As various stakeholders seek alternatives to traditional opioid treatment for newborns, there are many emotional, ethical and legal considerations. Questions include whether criminal penalties should be lessened or eliminated for women whose infants are exposed to opioids, or whether policymakers should destigmatize substance use disorder for pregnant women and treat it as a chronic medical condition instead. The latter would allow those who are suffering from opioid addiction to receive behavioral therapy and medication-assisted treatment, also known as a whole-patient approach.

"As far as the management of NAS, it has remained an area of limited innovation beyond engaging mothers in opioid replacement therapies during pregnancy," adds Dr. Kirane. "Even with these treatments, the infant will still present with NAS; however, in contrast to infants born to mothers who never engaged in any type of treatment during pregnancy, the severity and other health consequences of NAS is much more problematic than when it's unfolding in an anticipated and controlled manner." ❖

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Update on **Toxic Shock Syndrome**

While TSS is not as common as it was when first discovered, it remains a serious, life-threatening complication of certain types of infections that can be fatal.

By Jim Trageser

THE PUBLIC FIRST learned of toxic shock syndrome (TSS) not from the healthcare community but from television news anchors. In 1978, public health officials traced an outbreak of fatal staphylococcal infections in women and teen girls to a new line of super-absorbent tampons. James K. Todd, MD, a Denver pediatrician, had coined the phrase "toxic shock syndrome" earlier that year after another outbreak of staph infections led to blood poisoning from toxins produced by the bacteria. As news reports of women contracting the disease after using the new tampons spread across the country, TSS entered the public consciousness.

Although no longer the feared infection it was in the late 1970s and early 1980s, it remains a dangerous condition that strikes unexpectedly and affects otherwise healthy patients. Today, about half of all TSS cases remain associated with tampon use, with the remaining cases the result of other staph infections caused by burns, cuts, insect bites and intravaginal birth control devices.

TSS is a fairly rare condition with estimates ranging from three cases per 100,000 people to even lower. The TSS Information Service (a program funded by personal hygiene companies in Great Britain) says there are approximately 40 cases per year in the United Kingdom, two to three of which are fatal.[1] Even in cases not involving menstruation, women are three times more likely than men to contract TSS for reasons not entirely understood.[2]

What Is TSS?

Similar to scarlet fever, TSS is a secondary condition caused by a bacterial infection. Symptoms of TSS and the damage it causes to the body are a result of toxic poisons secreted by bacteria during an infection.

While the underlying cause of TSS is generally a staph infection, it can also be caused by a Streptococcus pyogenes (or group A Streptococcus) infection. This is often referred to as streptococcal toxic shock-like syndrome, or STSS.[3] An even rarer form of TSS, but one that is much more virulent, is caused by toxins secreted by the bacteria Clostridium sordellii or Clostridium perfringens.[4]

Both Staphylococcus aureus and Streptococcus pyogenes are normal denizens in human bodies that live on the skin, in the nasal passages and in the vaginal canal. About one-third of people have the staph bacteria living on them, causing no symptoms or health problems. And, while the strep bacteria is less common, it is still found on a significant swath of the population without incident. It is not entirely clear what causes these organisms to experience sudden, explosive growth, but when they do, the amount of toxins they normally produce as part of their life cycle similarly spike, leading to the rare case of TSS if those toxins end up in the bloodstream.

Both clostridium species are also part of the human microbial flora. Up to 10 percent of females harbor Clostridium sordellii with no ill effects, generally in the vaginal canal.[5] And, Clostridium perfringens is a normal part of the human intestines' microbial biome.

During an infection, TSS or its related syndromes can develop only if the toxins enter the bloodstream. Once the toxins spread through the body, they cause hypotensive shock. As blood pressure drops, the brain, heart, lungs, kidneys and other organs don't get enough oxygen to function normally, so the body begins to shut down, just as it does when it experiences any other kind of shock.[6]

Causes of TSS

As mentioned earlier, TSS was first seen during an outbreak of staph infections among women using a new type of highly absorbent tampon in 1978. But it has since been found to also occur following staph infections in wounds, cuts and burns, pneumonia and even bone infections.[3]

With the new tampons, the bacteria was able to grow exceptionally well in the menses collected in the tampon. Leaving one in for more than eight hours seems to be a highly correlative risk factor.[7] Also, the process of inserting and removing tampons creates microabrasions on the vaginal wall, allowing the toxins to enter the bloodstream. In the case of burns and cuts, the bacteria that normally live on the surface of the skin can begin to grow more rapidly once they are able to penetrate the body's normal protective coating via the wound, where they also have access to the circulatory system.

STSS is most often associated with chickenpox or a skin infection, or in patients with compromised immune systems.[4]

While both Staphylococcus aureus and Streptococcal pyogenes produce a variety of toxins that can cause illness if they enter the bloodstream (such as enterotoxin, which causes most cases of food poisoning), the main culprit in TSS is TSS toxin.[8] This is a superantigen that causes the body to react by releasing massive amounts of cytokines (regulatory proteins that trigger the production of T helper cells), which then leads to systemic shock as blood pressure drops.

With Streptococcal pyogenes, the main culprits are pyrogenic exotoxin A and pyrogenic exotoxin B.[9] These have a very similar reaction to the body's defense system to the TSS toxin, with the overproduction of T cells causing the body to go into shock.

A study in 2004 found some rare cases of STSS caused by group B streptococcus (Streptococcus agalactiae).[10]

TSS cases caused by Clostridium sordellii are quite rare, but generally prove fatal. Clostridium sordellii produces a hemorrhagic toxin and a lethal toxin, both of which are very difficult to counteract.[11] These infections have been documented to have led to the death of women shortly after childbirth, following elective abortion and after miscarriage. In addition, newborns have had the infection enter via their umbilical cord stump.[12] Researchers are not sure why postabortion women are three times more likely for the clostridium bacteria to colonize in their vaginal canal compared to other nonpregnant women.[13]

Symptoms of TSS and the damage it causes to the body are a result of toxic poisons secreted by bacteria during an infection.

Although all three types of TSS (TSS, STSS and clostridium) are caused by bacterial infection, it is not considered an infectious disease since it cannot spread from patient to patient.

Symptoms and Progression of TSS

The Mayo Clinic lists the following as typical symptoms of TSS:[14]

- High fever
- Sudden drop in blood pressure
- Vomiting or diarrhea
- Rash that looks like sunburn and often appears on the soles or palms
- Muscle aches

- Seizures
- Headaches
- Red eyes, mouth or throat
- Redness around the vaginal opening
- Confusion

Symptoms generally manifest within about two days of the underlying infection's beginning.[4] It is recommended that anyone exhibiting any of these symptoms who has an open wound, a skin infection or is using a tampon or intravaginal birth control method (a diaphragm, cervical cap, sponge) seek emergency treatment immediately.[14]

The range of symptoms of STSS are similar, but not identical:[4]

- Severe pain at the site of the infection
- Difficulty breathing
- Bruising
- Low blood pressure
- Unusual bleeding

Anyone exhibiting these symptoms following chickenpox or a skin infection, or suffering from a compromised immune system, should likewise seek immediate emergency care.

If left untreated, low blood pressure associated with TSS and STSS may result in additional symptoms as the condition progresses: Skin may begin to slough off from the palms and soles, urine output may decline and the individual may feel listless and lack energy. Both TSS and STSS can progress rapidly, and death may occur within hours if not promptly treated.

STSS is most often associated with chickenpox or a skin infection, or in patients with compromised immune systems.

Clostridium sordellii nearly always starts with an infection in the uterus, and the toxins spread to the bloodstream from the uterine walls. These infections generally do not cause a fever. Instead, symptoms may include:[4]

- Abdomen tender to the touch
- Abdominal swelling
- High red and white blood cell counts
- Influenza-like symptoms
- Elevated heart rate

Similar to TSS and STSS, this form of toxic shock can advance rapidly, with progression measured in hours or days.

Diagnosing and Treating TSS

Diagnosing any of the three variants of TSS is based on recent health history and a blood or swab culture from an obvious or suspected site of infection.[15] If diagnosis is made in a nonacute setting, transfer to a hospital should be arranged immediately due to the rapid progression of the syndrome.

In cases in which a tampon or intravaginal contraceptive is being used, it should be removed immediately if the patient has not already done so. If TSS is likely the result of a burn or wound, the affected areas should be cleaned and disinfected.

Once a blood or swab test has confirmed the presence of one of the bacteria that can lead to TSS, an antibiotic can be prescribed to help reduce the source of infection. Additional tests may then be ordered to determine how far the toxins have advanced in the body. These tests may include a chest X-ray, CT scan or lumbar puncture to determine how well the patient's organs are functioning.[16]

Depending on the progression of the poisoning from the toxins, medication to raise blood pressure may be indicated. If the kidneys are struggling due to shock, dialysis may be necessary. Oxygen assistance can help with breathing difficulties, and a blood transfusion can help lower toxin levels. Intravenous immune globulin (IVIG) may also be prescribed to help the individual's immune system fight the infection.[17] In extreme cases, surgery may be necessary to remove dead tissue and prevent gangrene.

Today, despite advances in detection, diagnosis and treatment, the mortality rate for TSS is still between 5 percent and 15 percent.[4]

Preventing TSS

Using low-absorbency tampons and changing tampons regularly will greatly reduce the chance of contracting TSS. Using menstrual pads instead of tampons can lower it even more. Britain's National Health Service also provides these additional tips:[18]

- Seek medical care whenever a burn or wound shows signs of infection.
- Avoid inserting bandages or packing material to treat a nosebleed.
- Always wash hands before and after inserting or removing a tampon.
- Never use more than one tampon at a time.
- Women who have previously had TSS should avoid using tampons and intravaginal contraceptives in the future.
- Carefully follow instructions on how long to leave in intravaginal contraceptive devices.

TSS and STSS caused by Clostridium sordellii and Clostridium perfringens are not easily prevented since the triggers that cause these infections to bloom are not well understood.

Recurrent infections are an issue for anyone who has had TSS

or STSS, with some studies indicating up to 30 percent of individuals will have a second bout of TSS.[7]

Ongoing Research

Given the rarity of TSS and its two related variants, it is perhaps not surprising there are very few ongoing studies evaluating the disease. In fact, fewer than a half-dozen are listed on ClinicalTrials.gov.

The most promising study was conducted in 2016 at the Medical University of Vienna in Austria. The double-blind trial tested the efficacy of a TSS toxin variant in stimulating an immune response in 46 study subjects. No participants developed TSS in the study, and all of those given the toxin developed immunity. The study's authors felt these results warranted further investigation to see if a vaccine could be developed.[19]

The Hospices Civils de Lyon in France is preparing a study to test how effective IVIG treatment is in preventing organ damage during TSS in children. This study is still listed as active, but is not yet ready to recruit participants.[20]

Research into the underlying infections that lead to TSS is far more extensive, particularly for Staphylococcus aureus, with several hundred recent or ongoing studies. Among the more interesting are:

- Using RNA blood markers to identify Staphylococcus aureus infections in patients (France)
- Mother-to-infant transmission of Staphylococcus aureus (Israel)
- Nasal carriage of Staphylococcus aureus in healthcare settings (France)
- Potential methods of decolonizing patients of Staphylococcus aureus before surgery (France)
- Reducing transmission of Staphylococcus aureus in surgical settings (University of Iowa)

There are also several potential vaccines being investigated, and dozens of studies are looking at treating a Staphylococcus aureus infection with a variety of antibiotics, all of which could, if proven effective, find their way into emergency room protocols for treating TSS.

Among the other causes of TSS variants, Streptococcal pyogenes has six recent or ongoing trials listed. The Centre for Clinical Studies in Victoria, Australia, is presently recruiting for a study on a potential vaccination. The Butantan Institute in Brazil is also recruiting for a study into a possible vaccination based on a synthetic polypeptide. Another study is looking into the effectiveness of various antibiotic treatments.

Clostridium sordellii and Clostridium perfringens have been the subject of only one recent study conducted six years ago, which sought to determine a baseline for what percentage of women carry the bacteria in their vagina or rectum.[21]

Looking Ahead

Since the initial outbreak of TSS in the late 1970s, manufacturers of tampons have changed their design and construction, which has greatly reduced the incidence of TSS caused by Staphylococcal aureus. However, the condition still arises occasionally, requiring patients to seek emergency care immediately.

STSS and the clostridium variants remain rare, but they also occur in otherwise healthy patients and are thus impossible to predict and simply have to be dealt with like any other medical emergency.

While research may eventually bring about a vaccine for TSS and even STSS, for the foreseeable future, physicians will continue to emphasize hygienic best practices with tampons and intravaginal devices, as well as how to care for burns and other open wounds. And, patients with compromised immune systems should be attentive to all possible symptoms so infections can be addressed swiftly to avoid potentially fatal reactions to bacterial toxins. ❖

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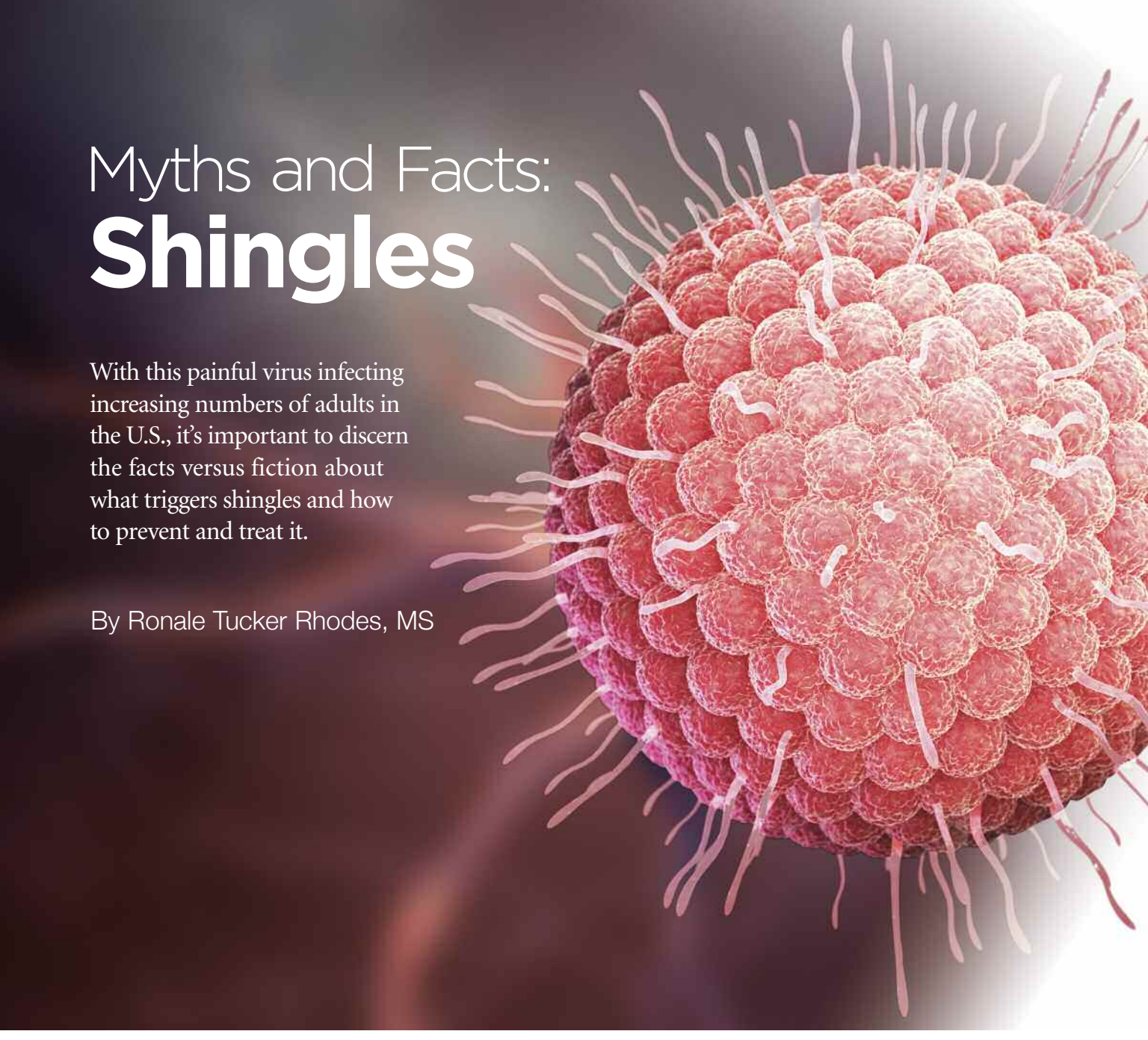
Myths and Facts: **Shingles**

With this painful virus infecting increasing numbers of adults in the U.S., it's important to discern the facts versus fiction about what triggers shingles and how to prevent and treat it.

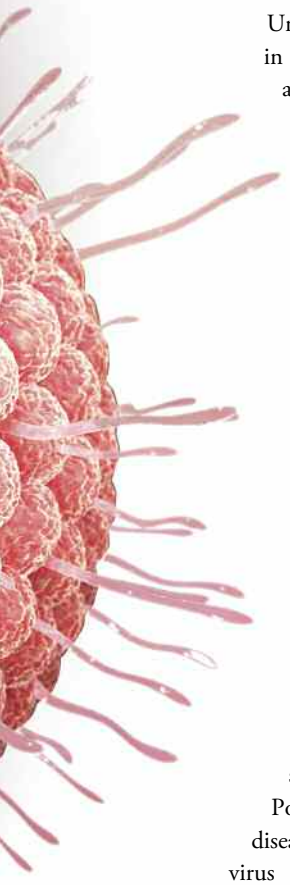
By Ronale Tucker Rhodes, MS



PEOPLE OFTEN DESCRIBE shingles as the most unbearable pain ever experienced — pain they wouldn't wish on their worst enemies. Its symptoms include a mix of electrical shock and small needles against the skin, accompanied by muscle pain and exhaustion. People with shingles find it extremely painful to wear clothes, and they can't tolerate being touched.[1]

Also known as herpes zoster, shingles is an infection of an individual nerve and the skin surface that is supplied by that nerve. It is caused by varicella-zoster virus (VZV), the same virus that causes chickenpox. Once a person is exposed to VZV, the virus can lay dormant in the body for years.[2]

Today, almost one in three people in the U.S. will develop shingles during his or her lifetime, with an estimated one million cases each year.[3] While shingles is uncommon in children, it can occur at any age, with approximately one million cases of pediatric shingles occurring in the U.S. each year.[4] And, the older one gets, the higher the risk of getting shingles. In fact, a person's chance of getting the virus increases with each passing year, especially after age 40. According to the National Institute of Neurological Disorders and Stroke, a person who is 60 years old is 10 times more likely to develop shingles than a child who is 10 years old.[5] In fact, half of the population who lives to 85 years of age will experience shingles during their lifetime.[6] In addition, approximately 1 percent to 4 percent of people with shingles, many of whom are older adults and 30 percent of whom have a weakened or suppressed immune system, must be hospitalized for complications.[3]



Unfortunately, shingles is increasing among adults in the U.S., and this upturn has been gradual over a long period of time.[3] Therefore, it is important people understand the many myths and misconceptions surrounding the illness.

Separating Myth from Fact

Myth: Shingles is the same as chickenpox.

Fact: Shingles and chickenpox are both caused by VZV, which belongs to a group of viruses called herpes (this is why shingles is also known as herpes zoster). However, shingles and chickenpox are not the same illness. Chickenpox is a milder illness that mainly affects children, while shingles results from reactivation of the virus. After a person recovers from chickenpox, the virus remains dormant in the body's central nervous system. But, under the right circumstances, the herpes zoster virus can reactivate and travel down nerve fibers. While the causes of reactivation are unclear, it is believed to happen when something weakens the immune system. Possible triggers could include older age; other diseases such as cancer, human immunodeficiency virus (HIV) or AIDS; cancer treatments such as chemotherapy and radiation therapy that lower a person's resistance to disease; stress or trauma; medications (especially immunosuppressive drugs) used to treat patients after an organ transplant; and children who had chickenpox in infancy or whose mothers had chickenpox late in pregnancy.[2,6]

Myth: Only elderly people get shingles.

Fact: It is true people's risk of getting shingles increases as they get older, but anyone at any age can get it. Currently, about half of all shingles cases occur in people over age 60 years, which means the other 50 percent occurs in younger individuals. In fact, the incidence of shingles in those younger than 60 years old seems to be on the rise, although the cause is unknown. According to Niket Sonpal, MD, an assistant professor of clinical medicine at Touro College of Osteopathic Medicine in New York City, people whose immune systems are compromised due to a condition such as HIV or taking immune-suppressing medication to keep them from rejecting a transplanted organ are certainly at greater risk.[7]

A recent study shows a cancer diagnosis of any kind, which can occur in any age group, is associated with an approximately 40 percent increase in risk for developing shingles compared to those without cancer. The large prospective study expanded on previous research by examining the risk of shingles before and after a new cancer diagnosis and across a range of cancer types among approximately 240,000 adults in Australia from 2006 to 2015. Patients with a blood-related, or hematological, cancer diagnosis had a more than three-fold higher risk of developing shingles than people without cancer. And, individuals with a diagnosis of cancer related to a solid tumor had a 30 percent higher shingles risk compared to someone with no cancer. The study also found the higher risk for shingles among patients with blood cancers was present in the two years before their cancer diagnosis. However, for patients with solid tumors, the higher risk of developing shingles appeared to be largely associated with receiving chemotherapy after their diagnosis, rather than the cancer itself.[8]

Older adults *are* more prone to herpes zoster ophthalmicus (HZO) (occurring when shingles gets in the eyes) that can lead to corneal scarring and blindness. According to research at the Kellogg Eye Center in Vancouver, Canada, occurrences of HZO among a group of 21 million adults tripled during a 12-year period, occurring in 9.4 cases per 100,000 people at the beginning of the study period and growing threefold to 30.1 cases per 100,000 by the end of the study period. The study also showed HZO may be more of a problem for women and adults over age 75 (53 cases per 100,000).[9]

Myth: People who have never had chickenpox can't get shingles.

Fact: Because shingles is caused by a reactivation of the chickenpox virus, it would make sense that if people haven't had chickenpox, they can't get shingles. However, getting the chickenpox (varicella) vaccine exposes people to the virus that causes both chickenpox and shingles. "The varicella vaccine is a live, attenuated virus, so if you've gotten it, you have the virus in your body, same as if you'd had chickenpox," said Richard Lorraine, MD, a shingles specialist and researcher in Harleysville, Pa. In short, the vaccine makes people immune to chickenpox, but it leaves people at risk for shingles. Unfortunately, no one knows what the odds of shingles are in this case since the varicella vaccine is only 20 years old.[7]

Shingles and chickenpox are not the same illness.

Myth: The increase in shingles cases is caused by the chickenpox vaccine.

Fact: It has been suggested that since the chickenpox vaccine boosts a person's immunity to VZV and reduces the risk of VZV reacting as shingles, then fewer children with chickenpox could theoretically lead to an increase in shingles in adults. However, research conducted by the Centers for Disease Control and Prevention (CDC) counteracts that theory, which found 1) shingles rates started increasing before the chickenpox vaccine was

introduced in the U.S., and 2) shingles rates did not occur faster after the routine chickenpox vaccination program started. Increases in shingles has also been occurring in other countries without routine chickenpox vaccination.[3]

What's more, the rate of shingles in children in the U.S. has been declining since the routine chickenpox vaccination program began. This is because the varicella vaccine is a weakened strain of VZV, which is less likely to reactivate as shingles than the wild-type VZV. Therefore, since children are less likely to become infected with wild-type VZV, they are at a much lower risk of shingles.[3]

Myth: Shingles is contagious.

Fact: VZV can spread from a person with active shingles and cause chickenpox in someone who had never had chickenpox or received the varicella vaccine; however, shingles itself cannot be passed from one person to another. Furthermore, VZV from a person with shingles is less contagious than the virus from someone with chickenpox. However, there are some individuals who are more susceptible to infection, including people who have medical conditions that keep their immune systems from working properly such as certain cancers like leukemia and lymphoma, HIV, and those who receive drugs that keep their immune systems from working properly such as steroids and drugs that are given after organ transplantation.[10]

During the blister phase of shingles, VZV can spread through direct contact with fluid from the rash blisters. It is not infectious before blisters appear or once the rash crusts. To avoid infecting another person with VZV during the blister phase, CDC recommends covering the rash, avoiding touching or scratching the rash, washing hands often, and avoiding contact with the following individuals until the rash crusts:[10]

- pregnant women who have never had chickenpox or the varicella vaccine;
- premature or low birth weight infants; and
- people with weakened immune systems such as those receiving immunosuppressive medications or undergoing chemotherapy, organ transplant recipients and people with HIV infection.

Myth: Rash is the biggest complication of shingles.

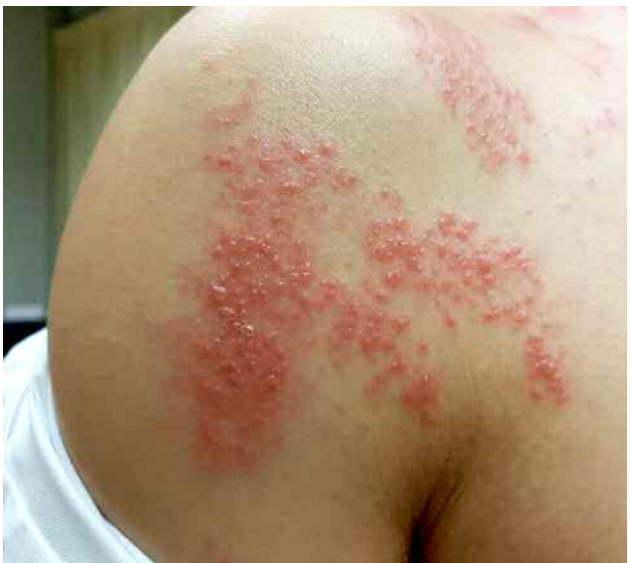
Fact: While rash is the defining characteristic of shingles, it is by far not the most troubling complication. Rather, pain associated with shingles that can begin two days to four days before the rash and last sometimes up to a year or more can be severe. Pain lasting after the rash is known as postherpetic neuralgia (PHN), which occurs when the damaged nerve sends impulses to the brain coded as "throbbing pain." PHN is often described as burning, stabbing, throbbing and/or shooting pain. In addition to pain, other symptoms include long-term nerve pain, fever, headache, chills, upset stomach, muscle weakness, skin infection, scarring and decreased or loss of vision or hearing.[6,7] As mentioned previously, shingles can get into the eyes, which can lead to corneal scarring and blindness.[9]

Myth: There is nothing people can do to avoid getting shingles.

Fact: Vaccination is the best way to avoid getting shingles. This means children should receive the chickenpox vaccine, and adults should receive one of the two U.S. Food and Drug Administration-approved shingles vaccines: zoster vaccine live (ZVL, Zostavax), which has been in use since 2006, and recombinant zoster vaccine (RZV, Shingrix), which has been in use since 2017 and is recommended by the CDC's Advisory Committee on Immunization Practices as the preferred shingles vaccine.[10]

Researchers at the Kaiser Permanente Center for Health Research found children who receive the varicella vaccine are significantly less likely to contract pediatric shingles. In the study, the researchers looked at the incidence rates of herpes zoster (shingles) overall per 100,000 person-years, including by age and gender. "We saw the highest rates of herpes zoster in the early years of the study, when there was a higher proportion of children, particularly older children, who had not received the varicella vaccine," said Sheila Weinmann, PhD, lead investigator of the study. What's more, the researchers found the rate of herpes zoster among children who were unvaccinated climbed from 2003 to 2007 and then declined sharply through the end of the study period (perhaps related to the introduction of the second vaccine dose beginning in 2007). And, increasing rates of vaccination over the study period reduced the risk of contracting herpes zoster overall for all children, including those who were unvaccinated.[4]

In adults, CDC recommends healthy adults age 50 years and older receive two doses of RZV to protect against shingles and its complications, and those age 60 years and older receive either RZV or ZVL, although RZV is preferred.[6] A systematic review of clinical studies conducted in 2018 involving more than two million patients aged 50 years and older found RZV 85 percent more effective in reducing shingles cases than ZVL, but it also carried a 30 percent greater risk of site-adverse events such as redness or swelling. However, there were no statistically significant differences between the two vaccines for serious adverse events and deaths.[11]



Myth: People can't get shingles if they've been vaccinated against it.

Fact: While the shingles vaccine greatly reduces the risk of getting shingles, it doesn't drop the odds to zero. Instead, it reduces the risk by about 50 percent and significantly reduces the chance of serious complications. The vaccine's protection lasts approximately five years, which is why CDC recommends individuals 60 years and older get vaccinated.[7]

Myth: People can get shingles only once.

Fact: While shingles doesn't recur in most people, it can come back a second and, rarely, a third time. In the first several years, chances of shingles recurring are lower than it is for people who have never had shingles. But, over time, chances of a recurrence go up. One study found that within seven years, the odds of a recurrence may be almost 5 percent, which is about the same as the odds of getting shingles the first time.

Recurrence most often occurs in people with weakened immune systems. But, recurrence also occurs in people with healthy immune systems who are female and/or who had severe pain from shingles that lasted more than 30 days. If shingles does recur, it is likely to return in a different part of the body. For instance, if a person had it on the right side of the stomach, it might come back on the left side or on the face, chest, neck or back.[12]

Myth: There is no treatment for shingles except enduring the course of the virus.

Fact: The severity and length of a shingles outbreak can be reduced if an antiviral drug is prescribed within the first three days of an outbreak. Antiviral drugs include acyclovir (Zovirax), famciclovir (Famvir) and valacyclovir (Valtrex). In addition, medicines can be prescribed to help lessen the pain such as:

- Lidocaine skin patches that can be worn on the affected area;
- 8 percent capsaicin (an extract of chili peppers) skin patches;
- Anti-seizure drugs such as gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica);
- Antidepressants such as duloxetine (Cymbalta) and nortriptyline (Pamelor); and
- Opioid painkillers.[13]

Lastly, symptoms can be eased by keeping the rash dry and clean to reduce the risk of infection, wearing loose-fitting clothing for comfort, avoiding rub-on antibiotic creams or adhesive dressings that can slow the healing process, and using products such as Calamine lotion to soothe and relieve itching.[2]

Dispelling the Myths Now

The National Institute of Neurological Disorders and Stroke currently funds and conducts research on a wide range of neurological disorders such as shingles to understand their causes and to develop and improve ways to diagnose, treat and prevent them. Medical research on shingles has two main goals: 1) to develop drugs to fight the disease and to prevent or treat its complications, and 2) to understand the disease well enough to prevent it, especially in people at high risk. To achieve these goals, more needs to be learned about VZV and its effects, including how it becomes latent in nerve cells, what induces it to become active again and how such reactivation can lead to PHN and other complications.

While rash is the defining characteristic of shingles, it is by far not the most troubling complication.

In addition, clinical trials involving the zoster virus and PHN may lead to better understanding of shingles and identify potential treatments. These studies are in need of both healthy individuals and people with disorders to advance the understanding of diseases and how to treat them.[14]

While studies of shingles and ways to prevent and treat it continue, the established facts about the virus can help individuals to better protect themselves against it and its complications, as well as how to treat it should they be one of the growing number of adults affected. ❖

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

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Agents That Block Plasma IgG Recycling: The Next Big Thing for IgG Antibody-Mediated Diseases?

By Keith Berman, MPH, MBA

HERE IS A question that just might stump you: Is it possible a single monoclonal antibody-based therapeutic could effectively treat disorders as diverse as myasthenia gravis (MG), autoimmune mucocutaneous blistering diseases and immune thrombocytopenic purpura (ITP)? The answer is yes.

At least three investigational agents, all of which target neonatal Fc receptor (FcRn) on the surface of blood vessel endothelial cells, are currently in clinical testing. These FcRn inhibitors define a potential new therapeutic class that, if proven safe and effective, could represent an important new treatment option for IgG autoantibody- and alloantibody-mediated diseases known to respond to administered IgG or to therapeutic plasma exchange.

FcRn Plays the Long-Acting Game

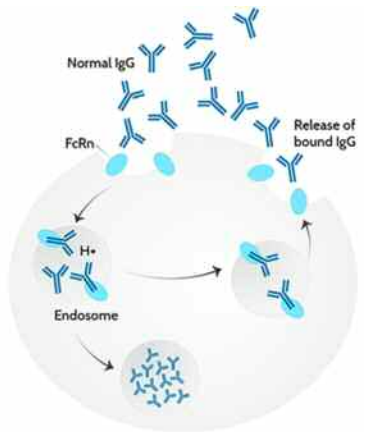
After human albumin, which accounts for more than two-thirds of total plasma protein, the four immunoglobulin classes (IgA, IgE, IgG and IgM) comprise the next most abundant plasma protein component. IgG alone accounts for 75 percent of circulating immunoglobulin and roughly 15 percent of total plasma protein. Combined, IgG and albumin account for a remarkable 80 percent to 90 percent of plasma protein.

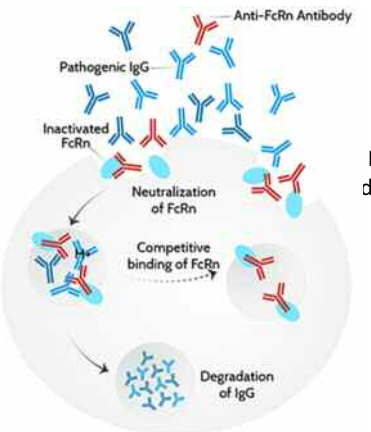
To maintain this high plasma IgG concentration, a "recycling" mechanism evolved that protects it from cellular catabolism, thus extending its total circulating half-life to 19 days to 23 days, compared to just five days to six days for IgA and IgM.[1] That mechanism (Figure) is mediated by FcRn, a surface blood endothelial protein first identified for its role in the facilitated transport of IgG from the mother to the fetus or neonate (thus its name).

FcRn interacts with the constant tail region — the Fc region — of plasma IgG and internalizes it into recycling endosomes, protecting the IgG from degradation by cellular lysosomes. Still complexed with FcRn, IgG contained in endosomes migrates to the cellular surface, where by exocytosis it is released back into the

Figure. (1) Endothelial Cell FcRn-Mediated Recycling of Plasma IgG and (2) Blockade of Plasma IgG Recycling by FcRn Inhibitor Antibody

(1) Plasma IgG taken up by endothelial cells binds to FcRn, which protects the IgG from lysosomal degradation and recycles it back to the circulation





(2) Anti-FcRn antibody competitively binds FcRn, resulting in IgG degradation *(including pathogenic IgG autoantibodies)* and reduced rate of return to the circulation

circulation. In short, FcRn rescues IgG from cellular catabolism and recycles it into the circulation; thus the prolonged 19- to 23-day half-life.*

Drug development scientists eventually figured out this FcRn-mediated IgG recycling functionality can be "hijacked" to extend the half-life of therapeutic proteins with short intravascular persistence, in particular those that must be infused on an ongoing basis. Two such products, chronically self-administered by persons with hemophilia A and B to prevent bleeds, are ELOCTATE, a B-domain-deleted factor VIII:Fc featuring a 50 percent longer half-life than factor VIII alone, and ALPROLIX, a factor IX:Fc with a threefold longer half-life than factor IX alone. Sometimes referred to as "biobetters," these and other Fc fusion proteins significantly reduce the burden of self-injections and improve patient treatment compliance.

The Conceptual Basis for FcRn Inhibitors

The IgG-protective role of FcRn was first characterized more than 20 years ago by investigators who documented abnormally short IgG half-lives in genetically manipulated mice that don't express FcRn.[2,3] These FcRn "knockout mice" typically have fourfold to fivefold lower levels of circulating IgG as normal mice,[4] and injected IgG is rapidly cleared. Study of a rare human genetic syndrome involving FcRn-disabling mutations further supports the role of FcRn as a homeostatic regulator of IgG levels: In two affected siblings from a consanguineous marriage, their abnormally low expression of FcRn correlated with a very low plasma level of IgG.[5]

It is also well-documented that FcRn is saturable by IgG. High administered doses of exogenous IgG in the form of intravenous immune globulin (IVIG) or subcutaneous immune globulin (SCIG) competitively saturate FcRn receptors, resulting in much-increased cellular catabolism of circulating endogenous IgG and a corresponding drop in endogenous IgG levels. FcRn saturation is a well-recognized mechanism of action of polyvalent human IG products: High-dose administered IgG equally drives down circulating levels of pathogenic IgG autoantibodies.[6]

Finally, there is a long-established treatment modality — therapeutic plasma exchange (TPE) — that effectively treats certain IgG-mediated disorders by physically reducing plasma IgG levels through 1:1 replacement of blood plasma with 5 percent human albumin. A single TPE procedure, with 1.5 plasma volumes replaced with 5 percent human albumin, acutely lowers plasma IgG by about 75 percent, followed by IgG synthesis-driven rebound.[7] Patients commonly undergo five to six TPE procedures to drive down circulating levels of pathogenic IgG, with intermittent repeated TPE procedures to maintain the treatment effect. Both IG therapy and TPE have been shown to be similarly effective for treatment of three IgG autoantibody-mediated disorders: chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome and MG.[8,9]

Motivated by this understanding, several research teams have designed monoclonal antibodies that target FcRn and block its IgG recycling functionality. The objective is fundamentally the same as TPE: to acutely or chronically reduce circulating levels of pathogenic IgG autoantibodies — whether characterized or not — that mediate disease.

Table. FcRn Inhibitor Products Currently in Development

Company	Product Identifier and Description	Current Development Status
Argenx (Netherlands/Belgium)	**ARGX-113 (efgartigimod)** Anti-FcRn monoclonal antibody fragment	**Generalized myasthenia gravis (gMG)**: In Phase III clinical testing **ITP**: In Phase II clinical testing **Pemphigus**: In Phase II clinical testing **CIDP**: Phase II clinical trial expected to start before year-end 2019
Momenta Pharmaceuticals (U.S.)	**M281 (nipocalimab)** Anti-FcRn monoclonal antibody	**gMG** **HDFN**† **wAIHA**† } In Phase II clinical testing
UCB Pharma (Belgium)	**UCB7665 (rozanolixizumab)** Anti-FcRn monoclonal antibody	**gMG** Phase II study completed; Phase III gMG clinical trial now in progress **CIDP**: In Phase II clinical testing **ITP**: In Phase II clinical testing

†HDFN = hemolytic disease of fetus and newborn; wAIHA = warm autoimmune hemolytic anemia

FcRn Inhibitors in Development

Three companies are currently evaluating or planning to evaluate their investigational anti-FcRn monoclonal antibody or antibody fragment products for the treatment of a half dozen immunity-based disorders (Table). All of these products selectively block FcRn-mediated IgG recycling, with the goal of reducing circulating levels of pathogenic IgG antibodies to achieve a prespecified therapeutic benefit.

Argenx. This Dutch/Belgian clinical-stage biotechnology firm is developing efgartigimod (ARGX-113), a first-in-class antibody fragment that competitively

** FcRn additionally binds and facilitates recycling of circulating human albumin, which has a similar 19- to 21-day half-life.*

binds FcRn in the same fashion as endogenous IgG. With repeated dosing, Argenx's investigational FcRn inhibitor rapidly depletes circulating levels of IgG antibodies by as much as 85 percent. Argenx has completed a Phase I safety trial in healthy volunteers and is currently evaluating ARGX-113 for the treatment of four autoimmune disorders:

• *Generalized MG (gMG).* In a report in *Neurology* published in June, Phase II study findings in 24 patients randomized to ARGX-113 or placebo showed this investigational FcRn inhibitor was safe and well-tolerated, with a rapid decrease in IgG and anti-AChR autoantibody levels. All four efficacy scales demonstrated 75 percent of patients showed "a rapid and long-lasting disease improvement."[10]

To fully evaluate ARGX-113's efficacy, safety and tolerability, Argenx's new randomized, double-blind, placebo-controlled Phase III ADAPT trial is currently recruiting up to 150 gMG patients at multiple sites in the U.S. and Europe.

• *ITP.* A randomized, double-blind, placebo-controlled Phase II trial is currently recruiting approximately 36 European patients to receive one or two doses of ARGX-113, in addition to standard-of-care treatment (e.g., oral corticosteroids, thrombopoietin receptor agonist). Initial testing has documented platelet count improvements across doses and ITP patient classifications, correlating with reduction in IgG levels.

• *Pemphigus.* A Phase II open-label, noncontrolled clinical trial is now recruiting 12 participants to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of ARGX-113 in patients with mild to moderate pemphigus vulgaris and pemphigus foliaceus.

> "Motivated by this understanding, several research teams have designed monoclonal antibodies that target FcRn and block its IgG recycling functionality."

A seminal 2005 study[11] showed experimental FcRn-deficient mice were resistant to cutaneous blister-inducing IgG antibodies, and levels of these pathogenic antibodies were significantly reduced relative to wild-type mice injected with them. Further, administration of high-dose human IgG (HDIG) drastically reduced circulating pathogenic IgG levels and prevented blistering, while in FcRn-deficient mice, no additional protective effect with HDIG was seen.**

Argenx is planning to launch a Phase II proof-of-concept trial to evaluate ARGX-113 for the treatment of CIDP before the end of this year.

Momenta Pharmaceuticals. Cambridge, Mass.-based Momenta has developed nipocalimab (M281), a fully human anti-FcRn IgG1 monoclonal antibody. A randomized, double-blind, placebo-controlled Phase I trial in 50 healthy volunteers established multiple weekly doses achieved mean IgG reductions of about 85 percent from baseline, which were maintained at greater than or equal to 75 percent from baseline for up to 24 days. M281 was well-tolerated with no serious or severe adverse events and a low incidence of infection-related adverse events comparable to placebo treatment.[12]

The company is currently in progress with Phase II trials evaluating M281 for the treatment of three disorders:

• *gMG.* This Phase II randomized, double-blind, placebo-controlled study, dubbed the "Vivacity-MG" study, is evaluating M281 in 60 U.S., Canadian and European patients with gMG, who have had an inadequate response to standard-of-care treatment.

• *Hemolytic disease of the fetus and newborn (HDFN).* In the instance of HDFN, the causal factor is not autoantibodies but one of three maternal alloantibodies (anti-RhD, anti-Rhc and anti-Kell) transferred to the fetus in utero. These alloantibodies attack fetal red blood cells, often resulting in serious morbidity or mortality. There are currently limited treatment options for HDFN, which affects an estimated 4,000 to 8,000 pregnancies each year in the U.S.

Momenta's Phase II multinational open-label "Unity" study will enroll 15 pregnant women at high risk for early onset severe HDFN to receive intravenous infusions of M281. Its effectiveness will be assessed by examining the percentage of participants with a live birth at or after a fetal gestational age of 32 weeks, without the need for an intrauterine transfusion through their entire pregnancy. With the goal of expediting its development for this clinical application, the U.S. Food and Drug Administration (FDA) has granted Fast Track Designation for M281 for treatment of HDFN.

• *Warm autoimmune hemolytic anemia (wAIHA).* Again with the support of FDA Fast Track Designation, Momenta has launched an adaptive Phase II/III

*** The investigators further concluded these findings both 1) support an FcRn saturation/pathogenic IgG degradation mechanism for high-dose IVIG in autoimmune skin blistering diseases, and 2) rule out the possibility that IVIG contains anti-idiotypic antibodies that neutralize blistering disease-inducing IgG antibodies.*

clinical study to assess Momenta's M281 product for the treatment of this rare autoantibody-mediated hemolytic disease. There are no approved treatments for wAIHA.

The adaptive design allows for modification of the study protocol based on interim analyses of the data. If successful, this Phase II/III study could serve as a pivotal study, making M281 the first labeled treatment option for wAIHA.

Momenta expects to report top-line data from its gMG study in the second or third quarter of 2020, and from its HDFN and wAIHA studies in 2021.

UCB Pharma. Focused on treatments for immune and neurological disorders, this large multinational biopharmaceutical firm is currently investigating its high-affinity subcutaneous anti-FcRn monoclonal antibody, rozanolixizumab (UCB7665),[13] in two autoimmune neurological disorders:

• *gMG.* In late 2018, UCB completed and reported top-line findings from a Phase II randomized, placebo-controlled proof-of-concept study in 43 North American and European patients. The study compared three infusions of placebo or UCB7665 administered over a four-week period, followed by a second dosing phase with continued observation until day 99. Infusions were safe and well-tolerated with clinically meaningful improvements seen across several prespecified disease-related endpoints over the entire duration of the study.

A 240-subject placebo-controlled Phase III study is now in progress to assess the safety and efficacy of two different dosages of UCB7665 in two dosage regimens in adult patients with gMG. This study is expected to be completed in early 2021.

• *CIDP.* A Phase II randomized, placebo-controlled study is currently enrolling 34 U.S. and Belgian CIDP patients to evaluate the efficacy, safety and tolerability of UCB7665.

• *ITP.* Earlier this year, UCB reported Phase II study findings in 54 primary ITP patients treated with UCB7665.[14] No serious treatment-related adverse events or treatment discontinuations due to adverse events were reported. The platelet response increased with increasing dose intensity: 33 percent at the 4 mg/kg and 7 mg/kg doses, 50 percent at the 10 mg/kg dose and 67 percent at the 15 mg/kg dose. Based on these findings, study investigators are now dosing ITP patients at once-weekly doses of 20 mg/kg.

Gazing Into the Future

Whether these FcRn inhibitors are safe and effective for the treatment of gMG, CIDP, ITP, pemphigus, wAIHA, HDFN and potentially other IgG autoantibody- and alloantibody-mediated autoimmune disorders obviously awaits results of ongoing and future patient trials. But if shown to be safe and effective, these agents could be a viable therapeutic option for certain patients currently treated with IG and plasma exchange.

Individual patient considerations and published clinical outcomes will always dictate the treatment prescribed for a particular disease. But if shown to be safe and effective, FcRn inhibitors could be a viable treatment option in particular for patients with IG tolerability issues, as well as for those who are poor TPE candidates due to difficult venous access or some other contraindication.

Will FcRn inhibitors prove to be effective for just a few isolated disorders, or for a diverse spectrum of IgG antibody-mediated diseases? Or, will they end up falling short of expectations? As pivotal study results are reported over the next two to three years, we can look forward to the much-anticipated answers. ❖

"Whether these FcRn inhibitors are safe and effective obviously awaits results of ongoing and future patient trials."

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. He also serves as editor of *International Blood/Plasma News*, a blood products industry newsletter.

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After losing his hand, wrist and partial forearm in an accident, Dr. Robert Doty struggled with the decision to undergo multiple surgeries to reestablish function of his limb or to amputate.

Prostheses: *A Patient's Perspective*

By Trudie Mitschang

AFTER LOSING HIS arm in a freak accident, Robert Doty, MD, became actively involved in educating and providing support for people with upper limb loss, in addition to advocating for prosthetic parity at the state and federal levels. Dr. Doty served as the chair of the Upper-Limb Loss Advisory Council for the Amputee Coalition of America.

BSTQ: Tell us about your background.

Dr. Doty: I am a physician who spent 30 years in practice. My specialty was emergency medicine, so trauma was not an unfamiliar occurrence. However, I did not expect to experience trauma of my own. When a hydraulic lift holding a car above me failed, gravity took over. As two objects cannot occupy the same space at the same time, and the car had considerably more mass and inertia than me, I was, quite literally, dealt a losing hand, including a wrist and partial forearm.

BSTQ: What happened at the hospital?

Dr. Doty: After battling the car for hours, I managed to get loose and find help. While I was being treated at the hospital, a deputy retrieved my arm from the site, and we were flown to another hospital where a surgical team reattached the arm during a 22-hour surgery. This included reconstruction of the radius, but the ulna was too badly damaged to reconstruct. (The radius and the ulna are the outer and inner bones of the forearm, respectively.) The cut through the arm was relatively "clean," but the impact of the brake disc and wheel assembly had shattered the bone above the amputation.

BSTQ: What led to your decision to amputate?

Dr. Doty: I underwent treatment, including extensive physical therapy, several orthotics and continuous passive motion machines. Though the hand remained, there was no functional nerve return, sensory or motor. Worse, with a useless hand and a weak, painful wrist, I couldn't use the remaining portion of the arm and shoulder, so they also were wasting from disuse. I was considering a series of surgeries, but the likelihood of any sustained improvement was remote. Finally, with the insight and agreement of my orthopedic surgeon, I underwent a therapeutic amputation. Suddenly, what had been a painful, disappointing and frustrating period of my life began to improve dramatically.

BSTQ: How did getting a prosthesis improve your quality of life?

Dr. Doty: With my prosthesis, the list of things I could do again was staggering. Most significant by far were the improved ability to feed and dress myself, drive, tie knots, open containers, use tools and take care of my home. I also wasted less time having to wait for someone to help me. Although my prosthetic hand could never give me the function I had before the injury, it was light-years ahead of anything I could have hoped for with the reattached arm and hand.

BSTQ: Tell us about your work with amputees.

Dr. Doty: Since being thrust into the world of amputation and prosthetics, my learning curve has been steep, but interesting and enlightening. I have met and worked with many amputees, occupational therapists, prosthetists and others in the field. I've participated in and led a number of presentations, seminars and lectures.

BSTQ: As a physician, what challenges did you recognize in the medical community regarding this topic?

Dr. Doty: I think doctors struggle to avoid focusing on the specific injury or disease and can lose focus on the patient as a whole. This tendency has worsened with the development of specialties and subspecialties. Doctors tend to feel we have failed or given up on our patients. Of course, this is not always possible or rational. Doctors also have difficulty giving up the battle and moving on if we experience some initial successes. This not only exhausts the doctor's resources, but more importantly, the patient's.

BSTQ: Are insurance considerations a factor?

Dr. Doty: If the surgeon knows insurance will pay many times over for serial surgeries but will not cover the patient for far less expensive prosthetic options, it can influence the decision process.

BSTQ: What about statistics regarding patient noncompliance?

Dr. Doty: A number of poorly understood statistics sometimes deter surgeons in upper-extremity cases. One stat is that 50 percent of upper-extremity amputees with prostheses don't wear them. This is certainly not what I've experienced. In some cases, patients may not have the experience or knowledge to recognize a poorly fitting or nonfunctioning prosthesis. Patients may give up, thinking it's their fault, or they may give up because no one knowledgeable counsels them. It is essential for upper-extremity amputees to follow up with a prosthetist experienced with their level of amputation. ❖

Prostheses: *An Expert's Perspective*

After losing both legs below the knees to bacterial meningitis, Don Cummings earned a degree in prosthetics and orthotics and now works with pediatric patients who have lost limbs.

DON CUMMINGS became interested in the field of prosthetics in 1978 when, as a freshman in college, he lost both legs below the knees to bacterial meningitis. In 1981, he received a Bachelor of Science degree in generic special education from the University of Texas at Dallas, and in 1984, he earned a Bachelor of Science in prosthetics and orthotics from the University of Texas Southwestern Medical Center. He is an Association of Boards of Certification-certified and Texas-licensed prosthetist.

BSTQ: Tell us about your work in the field of prosthetics.

Don: I work in a pediatric orthopedic nonprofit hospital in its prosthetics department. We attend interdisciplinary clinics with the surgeons, personal trainers, occupational therapists, nurses and psychologists, and we hold three prosthetic clinics a month during which we see about 20 to 25 children per clinic. Our patients range from infants to 18 years, with about 70 percent having a congenital limb difference, and the remaining 30 percent losing limbs either to cancer, disease or trauma. We are part of a full orthotics and prosthetics department, so we have a mix of practitioners who either work exclusively in prosthetics or who are certified in both orthotics and prosthetics.

BSTQ: What does your work entail?

Don: Our staff sees patients in clinic, and based on a prescription generated in that setting, we cast, design, fit, align, fabricate, deliver and provide all adjustments and follow-up on site. We have a full lab to fabricate prostheses, including carbon laminations and thermoplastic. My work involves seeing patients, attending clinics, fitting, aligning, trouble-shooting, making growth adjustments, and really getting to know my patients and their families because I spend a lot of time with them. I also document and submit insurance codes for billing, and work with insurance companies. Also, I have some administrative responsibilities, including submitting an annual budget and attending a lot of meetings. However, it is the patient care I most enjoy.

BSTQ: What surprises you the most about how the field has evolved?

Don: The introduction of 3D printing and its gradual advancement as a possible means of fabricating structurally strong prostheses with lots of unique artistic esthetics has been interesting to follow. It's not there yet for routine rapid fabrication of highly durable prostheses, but I think it will be in a few years. Developments in technology have evolved quickly since wounded warriors began returning home with amputations and more federal and private research has become available. Recently, microprocessor knees and myoelectric hands have advanced quite a bit with more options than ever before. In general, the greatest advancements have been in socket technology, lots of different material options, and carbon fiber or fiberglass composites used in feet, pylons, knees, etc., which have provided patients with more dynamic feet, running blades and all sorts of components to match their needs.

BSTQ: What's your opinion about recent developments such as prosthetics with nerve detectors and consciously controlled limbs?

Don: It's exciting to watch research and development in this area. But, it takes a while for this research to filter down to the pediatric level. We would love to see true sensation easily integrated in a noninvasive way for upper-limb prostheses. I think the function would be much better, and acceptance of upper-limb prostheses for children born with absent hands might improve greatly if they had true sensory feedback. Myoelectric arms using surface electrodes that pick up EMG signals from muscles to control a hand or elbow have advanced quite a bit in recent years, but again, mostly in adult-sized hands. All the advancements are fun to watch and to get excited about, but the biggest challenge will be keeping them affordable so the technology is practical and available to as many people who need it. It can be very frustrating as a patient to find your insurance company considers an emerging technology that you would benefit from experimental or not medically necessary.

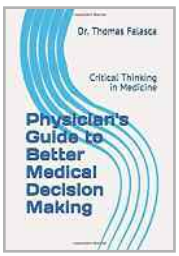
BSTQ: What do you find most rewarding about working with younger patients?

Don: Kids are generally on the upswing physically and so a prosthesis is a positive thing in most cases that enables them to be active and pursue their goals and dreams as they grow up. Pediatric and adolescent patients challenge us to find creative ways to enable them to participate in a wide array of activities. We make a lot of activity-specific prostheses such as for riding a bicycle, playing a guitar or other instrument and, of course, for running track or participating in sports. Also, I love that kids are honest and straightforward and generally tell it like it is, but are also very adept at telling whether we're being honest. So it's good to be able to shoot straight when we're communicating. Kids see the world with fresh eyes, and that's enjoyable. And, in general, they are enthusiastic and moving forward, so our practice is a positive upbeat place. ❖

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

Physician's Guide to Better Medical Decision Making: Critical Thinking in Medicine

Author: Thomas Falasca



This book is written for physicians, medical students and health professionals to identify and remedy factors leading to hazardous and costly medical decision errors. It features experimental evidence showing how specific influences lead to bad medical decisions, effective identification tools for flawed medical decisions derived from a varied range of disciplines, practical and specific countermeasures to the influences facilitating poor medical decisions and numerous medical examples. The book synthesizes experimental research and methods from diverse fields, including perceptual psychology, cognitive psychology, illusion management, experimental design, medication testing and approval, formal logic, mathematical statistics and civil law. It then applies these results specifically to the making of sound medical decisions.

www.amazon.com/Physicians-Better-Medical-Decision-Making/dp/1733587403/ref=sr_1_44?keywords=physicians&qid=1559751890&s=books&sr=1-44

Relapsing Polychondritis Poster

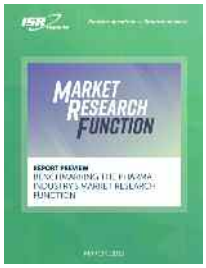
Author: Relapsing Polychondritis Awareness and Support Foundation (RPASF)

To equip physicians with the knowledge necessary to spot relapsing polychondritis (RP), RPASF has created a new resource that is unique in two important ways. First, it condenses the available information on RP into succinct, memorable categories, including common symptoms, possible complications, a diagnostic checklist and information specifically for physicians and healthcare professionals. And, for potential patients, it provides a list of support groups. Second, it uses information from an increasingly collaborative group of RP researchers, which is critical for a rare disease with limited literature, some of which is outdated.

www.polychondritis.org/wp-content/uploads/2019/05/Relapsing-Polychondritis-RP-Poster.pdf

Benchmarking the Pharma Industry's Market Research Function

Author: ISR Reports



ISR's *Benchmarking the Pharma Industry's Market Research Function* report is designed to be used as a tool for readers at pharma companies to compare their market research functions to those of other pharmaceutical organizations. Market researchers in pharmaceutical organizations play an important role in collecting, interpreting and disseminating data and findings to appropriate stakeholders throughout the company. To gain a better grasp on the market research function, ISR conducted five in-depth interviews and 31 online surveys with experienced market researchers in the biopharmaceutical space. Research subjects shared their insights on the types of research performed, how their market research function is structured and outsourcing behavior.

isrreports.com/reports/benchmarking-the-pharma-industrys-market-research-function/?&utm_source=blast&utm_medium=email&utm_campaign=050919-3-A&utm_content=35062755

Surviving the New FDA Inspection Plan: A Drugmaker's Guide to Working with the Agency

Author: U.S. Food and Drug Administration

This guide explains FDA's integrated approach and how to make the most of the agency's quality priorities and inspection procedures. Included are how investigators prepare for an inspection and what resources they use to understand a product and its manufacturer; the different types of inspections and when they occur; how FDA classifies each inspection (no action, voluntary action or official action needed); the roles and responsibilities of integrated assessment team members; flowcharts that show the process for each inspection type; and the specific regulations that apply to each FDA inspection requirement.

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Patients on IVIG Therapy for Neurological Disorders Successfully Transitioned to SCIG Therapy

Canadian investigators at Ottawa Hospital have reported a very high success rate with a nurse-led individualized program to facilitate a smooth transition in patients with neurological disorders from chronic intravenous immune globulin (IVIG) to subcutaneous immune globulin (SCIG) treatment. Recognizing a large injection volume can be overwhelming and a barrier to successful SCIG treatment, this program involved a lead nurse who provided two or more individual educational sessions on SCIG administration, established a written transition plan and liaised with physicians.

The mean prior IVIG treatment duration in 19 participating patients was 31.5 months (range four months to 98 months). Referral diagnoses included myasthenia gravis (n=9), multifocal motor neuropathy (MMN) (n=5), chronic inflammatory demyelinating polyneuropathy (n=4) and Lambert-Eaton myasthenic syndrome (n=1). All patients were initially able to switch to SCIG, with a retention rate of 17 out of 19 (89.5 percent) at six months and 15 out of 19 (78.9 percent) at 12 months.

Overall, 79 percent and 68.4 percent of patients perceived their neurological symptoms either did not change or improved at six months and 12 months, respectively. Two patients reverted back to IVIG treatment due to worsening of their symptoms at two

months and three months, while two others required supplemental IVIG infusions. Three of the four patients who failed to stay on SCIG treatment alone had MMN. In addition, four of the six patients who reported worsening neurological symptoms had MMN; there were only five MMN patients participating in total. The investigators propose "the SCIG dosage could be too low in our MMN patients."

Suleman A, Theoret L, Bourque P, et al. Evaluation of a personalized subcutaneous immunoglobulin treatment program for neurological patients. Can J Neurol Sci *2019 Jan 19 [Epub ahead of print].*

SCIG with Recombinant Human Hyaluronidase Is Safe and Preferred vs. IVIG by Some Multifocal Motor Neuropathy Patients

A team of Dutch investigators enrolled 18 multifocal motor neuropathy (MMN) patients on intravenous immune globulin (IVIG) treatment in a prospective open-label study to evaluate the comparative safety of treatment with 10% human immune globulin whose subcutaneous administration is facilitated with recombinant human hyaluronidase (fSCIG) (HyQvia).

Patients remained on IVIG treatment for three visits over 12 weeks, followed by a second 36-week study phase during which they received fSCIG treatment at an equivalent dose and frequency for three more visits, followed by self-administration of fSCIG at home. Outcome measures included safety, muscle strength, disability and treatment satisfaction.

Switching to fSCIG reduced the systemic adverse event rate (IVIG 11.6 vs. fSCIG 5.0 adverse events per person-year; $p < 0.02$), and increased the number of local injection site reactions (IVIG 0 vs. fSCIG 3.3 local reactions per person-year; $p < 0.01$). Overall, no significant difference in muscle strength or disability was found between IVIG and fSCIG. Citing improved independence and treatment scheduling flexibility, eight of the 17 patients (47 percent) who completed the study perceived fSCIG as optimal treatment, and all eight continued with fSCIG following study completion.

The investigators concluded fSCIG is a safe alternative for patients with MMN on IVIG treatment. Additionally, "fSCIG could be a favorable option in patients who prefer self-treatment and more independence, and in patients who experience systemic adverse events on IVIG or have difficult intravenous access."

Herraets IJT, Bakers JNE, van Eijk RPA, et al. Human immune globulin 10% with recombinant human hyaluronidase in multifocal motor neuropathy. J Neurol *2019 July 19 [Epub ahead of print].*

Medicare Immune Globulin Reimbursement Rates

Rates are effective Oct. 1, 2019, through Dec. 31, 2019

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$71.17	$70.03
	GAMMAGARD SD	Takeda	J1566	$122.41	$120.44
	GAMMAPLEX	BPL	J1557	$91.65	$90.18
	OCTAGAM	Octapharma	J1568	$71.37	$70.22
	PANZYGA	Octapharma	J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$80.24	$78.96
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$74.94	$73.73
	GAMMAKED	Kedrion	J1561	$78.28	$77.02
	GAMUNEX-C	Grifols	J1561	$78.28	$77.02
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$137.87	$135.66
	HIZENTRA	CSL Behring	J1559	$104.37	$102.70
	HYQVIA	Takeda	J1575	$145.56	$143.23

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

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** ASP-based Medicare payment rate not yet available; payment rate assigned by your Medicare Administrative Contractor.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g
	PANZYGA Liquid, 10%	Octapharma	PI, ITP	2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	5 g, 10 g, 20 g
			SCIG: PI	
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 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

2019–2020 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

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