

Immune Globulin

Access, Billing and Reimbursement

Reducing Drug Waste
IN THE SUPPLY CHAIN

ADDRESSING THE OVERUSE AND
Misuse of Antimicrobials

HOW TO LOWER THE
Risks of Anaphylaxis

MYTHS AND FACTS ABOUT
Bipolar Spectrum Disorder

*Secondary Antibody
Deficiency Driving
IG Demand* p.40



8 Critical Steps

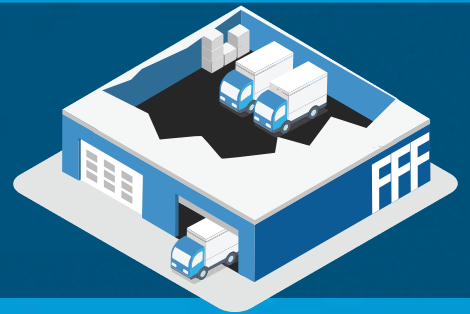


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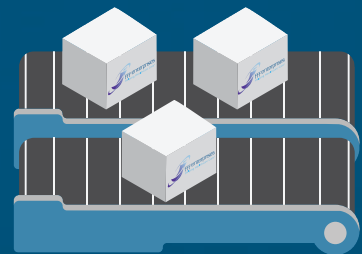


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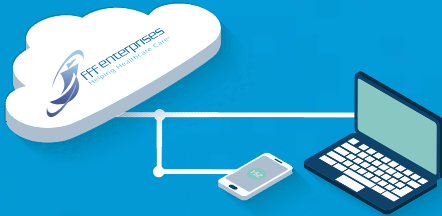


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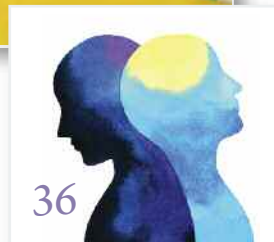


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The Challenges of Drug Accessibility

JUST MORE than a decade ago, the Secretary-General of the United Nations reported that over one-third of the world's population (approximately two billion people) did not have sufficient access to essential medicines. Thankfully, in the U.S., medicines are far more available than in developing countries. However, we still experience access issues due to a variety of factors, including shortages, reimbursement problems and waste, all of which are topics of discussion in this issue.

We begin with an analysis of the current plasma-derived immune globulin (IG) shortage. Beginning last April, many patients across the country began to hear the IG product used to treat their life-threatening illness was limited or stopped altogether. Yet, as we explain in our article "The Current Challenge of Immune Globulin Access" (p.16), official acknowledgment of the shortage and an explanation of its origin didn't materialize until August, when the U.S. Food and Drug Administration released an explanatory statement. As of this writing, nine of the 16 available IG products are affected by this shortage caused mainly by an ever-increasing demand for the treatment, which continues to grow more than 8 percent a year. Demand is fueled by a number of factors, including an increase in the number of autoimmune, inflammatory, immunodeficiency and other immune-mediated disorders; more aggressive treatment of autoimmune neurologic diseases with high-dose IG; a surge in demand in other countries; and, most recently, an increase in the number of secondary antibody deficiencies and a growing geriatric population with weakened immune systems prone to antibody deficiency disorders. And, while there is no prediction about when the IG shortage will end, the number of plasma collection facilities is on the rise, manufacturers are optimizing IG production capacity, and organizations are suggesting ways manufacturers and healthcare providers can mitigate the current situation.

Even when available, the high cost of IG products often results in reimbursement denial by payers, leaving patients without needed treatment. To help providers who prescribe and administer IG products, our article "A Guide to Immune Globulin Billing and Reimbursement" (p.20) offers a roadmap to avoiding reimbursement pitfalls. Included is information about which diagnoses are reimbursable for treatment, which require pre-authorization, how to effectively bill for treatment and how to file an appeal if denied.

Regrettably, waste is often an unfortunate outcome when medicines expire before they can be used, which is extremely costly to the healthcare profession. As such, it is vitally important medications are properly managed to ensure they don't become short-dated, which occurs when they near their expiration date and are not yet consigned to a buyer. Our article "Short-Dated Products: Reducing Unsalable Returns and Supply Chain Waste" (p.24) discusses industry safeguards to protect product from becoming short-dated, as well as considerations for handling inventory such as with smart systems on a consignment basis to minimize the risk of short-dated product returns. A consignment strategy can streamline and automate inventory management processes and reduce carrying costs for specialty pharmaceuticals. This approach allows hospitals to store products in their pharmacies and pay for them only when they are used. A revolutionary cost-saving idea!

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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

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\$1 Billion Grant Awarded to Fight Addiction and Chronic Pain



The National Institutes of Health (NIH) has awarded \$945 million to battle addiction and chronic pain. The grant will be used to fund research by 375 grantees in 41 states designed to guide future efforts. Some of the research projects include one to Dartmouth College to study ways of initiating drug treatment in hospital emergency rooms rather than days later at treatment centers, a second that will help a small company test a device worn on the wrist to detect biomarkers for stress and cravings to determine how long people need to continue treatment, a third that will look at best practices for the care of hundreds of thousands of infants who have been born to mothers who use opioids during pregnancy, and a fifth that will test the effectiveness of acupuncture on low-back pain for which Medicare will now pay.

The grant is part of the \$9 billion Congress has devoted to treatment and prevention of opioid abuse in the last three years, which is funded under the NIH's Helping to End Addiction Long-Term initiative. ♦

Bernstein L. NIH Awards Nearly \$1 Billion in Research Grants to Battle Addiction, Chronic Pain. *The Washington Post*, Sept. 26, 2019. Accessed at www.washingtonpost.com/health/nih-awards-nearly-1-billion-in-research-grants-to-battle-addiction-chronic-pain/2019/09/26/7470cfd4-e06e-11e9-be96-6adb81821e90_story.html?hpid=hp_hp-top-table-main-drug-abuse%3Ahomepage%2Fstory&utm_campaign=KHN%3A%20Daily%20Health%20Policy%20Report&utm_content=77383959&utm_medium=email&utm_source=hhs_email

CMS Finalizes Rule for Cuts to Medicaid DSH Payments

The Centers for Medicare and Medicaid Services (CMS) published a final rule for calculating state Medicaid disproportionate share hospital (DSH) cuts in the amount of \$4 billion in 2020 and \$8 billion for each subsequent year through 2025. The method considers the rate of uninsured in each state, the number of Medicaid inpatients, the level of uncompensated care in the state and other budget neutrality factors.

The DSH health reform methodology encourages states to target remaining DSH payments to hospitals caring for the most low-income patients by incorporating five factors:

- An adjustment factor to impose smaller reductions on low-DSH states;
- An adjustment factor to impose larger reductions on states with low uninsured percentages (UPF);
- An adjustment factor to impose larger reductions on states that do not target DSH funds to hospitals that treat a high

volume of Medicaid inpatients (HMF);

- An adjustment factor to impose larger reductions on states that do not target DSH funds on hospitals with high levels of uncompensated care (HUF); and
- An adjustment factor to account for certain waiver states that used DSH dollars for coverage expansion.

CMS finalized its proposal to change the weights for the three targeting factors that were previously equally weighted: UPF, HMF and HUF. The UPF adjustment factor would receive a 50 percent weight, with HMF and HUF receiving 25 percent. CMS also finalized a state-specific cap to limit the annual DSH allotment reduction to 90 percent of a state's original unreduced DSH allotment for that fiscal year. ❖

Brady M. The CMS Finalizes Rule for Cuts to Medicaid DSH Payments. *Modern Healthcare*, Sept. 23, 2019. Accessed at www.modernhealthcare.com/payment/cms-finalizes-rule-cuts-medicaid-dsh-payments?utm_source=modern-healthcare-alert&utm_medium=email&utm_campaign=20190923&utm_content=hero-readmore.

Schwartz R. CMS Finalizes Methodology for Oct. 1 Medicaid DSH Cuts. America's Essential Hospitals, Sept. 24, 2019. Accessed at essentialhospitals.org/policy/cms-finalizes-methodology-oct-1-medicaid-dsh-cuts.

FDA Issues Final Guidance on Biosimilar Interchangeability

The U.S. Food and Drug Administration (FDA) released guidelines on the studies companies need to conduct to show their biosimilar is interchangeable with a biologic. Currently, biosimilars can't automatically be substituted by a pharmacy for a brand product without FDA's interchangeability designation. And, while there are 24 approved biosimilar drugs (as of this writing), there are no FDA-approved interchangeable biosimilars on the market. This is because while federal law created a pathway for interchangeability, drug companies have been seeking greater guidance from FDA.

“Today’s final guidance gives an overview of important scientific considerations in demonstrating interchangeability with a

reference product, and explains the scientific recommendations for an application or a supplement for a proposed interchangeable product,” said acting FDA Commissioner Ned Sharpless.

The guidance is part of a larger action plan by FDA to spread biosimilar use. Currently, only one company, Boehringer Ingelheim, is pursuing FDA approval for an interchangeable biosimilar for the arthritis drug Humira, one of the top-selling drugs in the world.

The guidance document can be downloaded at www.fda.gov/media/124907/download. ♦

King R. FDA Finalizes Guidance to Spur Biosimilar Availability. *Modern Healthcare*, May 10, 2019. Accessed at www.modernhealthcare.com/operations/fda-finalizes-guidance-spur-biosimilar-availability.

CMS Finalizes Rule for Programs of All-Inclusive Care for the Elderly

The Centers for Medicare and Medicaid Services (CMS) has finalized a rule to update and modernize the Programs of All-Inclusive Care for the Elderly (PACE) that reflects updates based upon best practices in caring for frail and elderly individuals. PACE provides comprehensive medical and social services to certain frail, elderly individuals who qualify for nursing home care but, at the time of enrollment, can still live safely in the community.

The final rule provides administrative flexibility and regulatory relief for PACE organizations. Previously, team members could serve in only one role on the team. Now, one individual can fill two separate roles on the team under certain circumstances to better meet participants' needs and participate in more aspects of participants' care. It will allow certain nonphysician primary care providers to provide some

services in place of primary care physicians.

The rule also strengthens protections and improves care for PACE participants. It clarifies that PACE organizations offering qualified prescription drug coverage must comply with Medicare Part D prescription drug program requirements unless the requirement has been waived; implements changes related to PACE enforcement actions, including sanctions and civil money penalties, to strengthen CMS's ability to hold PACE organizations accountable for providing quality care and protecting PACE participants from harm; and adds language to help ensure individuals with a conviction for a criminal offense relating to physical, sexual or drug or alcohol abuse or use will not be employed by a PACE organization in any capacity where their contact with patients would pose a potential risk.

In addition, the rule provides greater operational flexibility, removes redundancies and outdated information, and codifies existing practice of relying on automated review systems for processing initial applications to become a PACE organization and expansion applications for existing PACE organizations. And, it modifies the PACE regulations to eliminate the need for PACE organizations to request waivers for a number of the most commonly waived provisions. Finally, it includes important clarifications to enrollment policies, quality improvement and other requirements for PACE organizations, resulting in more consistent, transparent and comprehensible regulations and guidance. ❖

Programs of All-Inclusive Care for the Elderly (PACE) Final Rule (CMS-4168-F). Centers for Medicare and Medicaid Services press release, May 28, 2019. Accessed at www.cms.gov/newsroom/fact-sheets/programs-all-inclusive-care-elderly-pace-final-rule-cms-4168-f.

CMS Enacts Medicare, Medicaid and CHIP Fraud-Fighting Rules

A final rule that went into effect Nov. 4 strengthens the Centers for Medicare and Medicaid Services' ability to stop fraud before it happens. Program Integrity Enhancements to the Provider Enrollment Process "creates several new revocation and denial authorities to bolster CMS's efforts to stop waste, fraud and abuse. Importantly, a new "affiliations" authority in the rule allows CMS to identify individuals and organizations that pose an undue risk of fraud, waste or abuse based on their relationships with other previously sanctioned entities. For example, a currently enrolled or newly enrolling organization that has an owner/managing employee who is "affiliated" with another previously revoked organization can be denied enrollment in Medicare, Medicaid and CHIP [Children's Health Insurance Program] or, if already enrolled, can have its enrollment revoked because of the problematic affiliation.

In addition to the affiliations component, CMS has enacted other measures to revoke or deny Medicare enrollment if:

- A provider or supplier circumvents program rules by coming back into the program, or attempting to come back in, under a different name (e.g., the provider attempts to "reinvent" itself);
- A provider or supplier bills for services/items from noncompliant locations;
- A provider or supplier exhibits a pattern or practice of abusive ordering or certifying of Medicare Part A or Part B items, services or drugs; or
- A provider or supplier has an outstanding debt to CMS from an overpayment that was referred to the Treasury Department.

In addition, the new rule gives CMS the ability to prevent applicants from enrolling in the program for up to three years if a provider or supplier is found to have submitted false or misleading information in its initial enrollment application. And, it expands the re-enrollment bar that prevents fraudulent or otherwise problematic providers from re-entering the Medicare program. CMS can now block providers and suppliers who are



revoked from re-entering the Medicare program for up to 10 years, whereas they were previously prevented from re-enrolling for only up to three years. Lastly, if a provider or supplier is revoked from Medicare for a second time, CMS can block that provider or supplier from re-entering the program for up to 20 years. ❖

CMS Announces New Enforcement Authorities to Reduce Criminal Behavior in Medicare, Medicaid and CHIP. Centers for Medicare and Medicaid Services press release, Sept. 5, 2019. Accessed at www.cms.gov/newsroom/press-releases/cms-announces-new-enforcement-authorities-reduce-criminal-behavior-medicare-medicare-and-chip.

Complying with Rules Ensures Reimbursement for Drugs

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

ALTHOUGH STEEPLY rising healthcare costs can be attributed to many complex interconnected factors, and with payment models continuing to evolve to cope with this cost burden, it is payers that often dictate reimbursement. In many cases, payers decide which expensive high-investment drugs will be reimbursed and under what circumstances.

For private insurance carriers and Medicare Advantage (MA) Parts B and D plans, the prior authorization (PA) process guides payment decisions. For traditional Medicare Part D plans, PA guides payment decisions as well. However, for traditional Medicare Part B plans, local coverage determinations (LCDs) and national coverage determinations (NCDs) guide payment decisions. Now, in the proposed 2020 outpatient prospective payment system rules, the Centers for Medicare and Medicaid Services (CMS) is considering PA for specific current procedural terminology codes covering five categories of hospital outpatient department services: blepharoplasty, botulinum toxin injections, panniculectomy, rhinoplasty and vein ablation. See Table for the similarities and differences between PAs and NCDs/LCDs.

For plans that require PA, providers must ask permission before drug administration to obtain payment. To date, however, Medicare uses the honor system to determine whether providers adhere to its requirements for specific drug use. For LCDs and NCDs, payment for drugs is determined after the fact by Medicare Administrative Contractors (MACs) representing CMS, and payment may be denied if the rules are not followed. As such, clinicians must understand which products are affected, how to document completely and thoroughly, and how to

code correctly. Specifics for each affected drug are published on each MAC website at go.cms.gov/1VN8JkX.

The Medicare Coverage Database (www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx) contains all NCDs and LCDs, local articles and proposed NCD decisions. It also includes several other types of national coverage policy-related documents, including national coverage analyses, coding analyses for labs, Medicare Evidence Development and Coverage Advisory Committee proceedings, and Medicare coverage guidance documents.

Although clinicians are often outraged by the loss of control that comes with outside entities dictating payment terms that impact care, they must balance their need to be fiscally responsible with making decisions that may result in no payment. This is especially true since Medicare Advantage, which represents one-third of all Medicare patients, moved to step therapy with accompanying mandatory PAs on Jan. 1, 2019, for both Part B and Part D drugs.

NCDs, LCDs, PAs and ICD-10: Understanding the Vital Links

To ensure reimbursement, NCDs, LCDs and PAs require an ICD-10 code that supports use of the product in question. ICD-10 codes for LCDs and NCDs can be obtained from the provider's MAC website, and the ICD-10 codes for PA can be obtained from payers. Providers should be sure ICD-10 codes documented in the chart support the codes the revenue cycle team is expected to apply. And, this information should be updated when new drugs are released, new payment decisions are made and ICD-10 code revisions are

published. For optimal results, the clinical and technical staff should practice in a cross-functional manner with patient navigators to ensure compliance with expensive specialty drugs and biologicals. This means remembering to provide the required electronic health record (EHR) documentation before the drug order is written and before the drug is prepared and administered. Equally important is ensuring PAs remain a permanent part of the record in real time for auditing purposes.

Consider three key points that can determine the path of an appropriate drug for a patient that results in success (payment) or failure (payment refused for lack of medical necessity):

1) Patient registration

- Success: The payer data is available to the pharmacy at order entry.
- Failure: The pharmacy doesn't know the payer.

2) Computerized physician order entry (CPOE) file

- Success: The PA/LCD/NCD information is included in the CPOE file.
- Failure: Neither the provider nor the pharmacy is aware of the requirements, and the PA/LCD/NCD is not included in the CPOE file.

3) Physician order entry

- Success: The physician is aware of the PA/LCD/NCD requirements, and EHR charting is thorough and complete for optimum ICD-10 code assignment.
- Failure: The physician charts scantily, and the revenue cycle team assigns codes that don't meet payer requirements.

Obstacles to Overcome

A dilemma often arises when a patient is treated for an off-label indication that is supported by the literature. While

Table. Similarities and Differences Between PAs and NCDs/LCDs

	Prior Approval (PA)	National/Local Coverage Determination (NCD/LCD)
Need patient's payer status?	Yes	Yes
Drug tagged in CPOE/PDM?	Yes	Yes
Link to actual rule needed?	Yes	Yes
Rule requirements	Ask permission first before drug administration	Understand and follow requirements; document completely and thoroughly; code correctly and as required
Payment	Only if permission is given first, otherwise denied for lack of medical necessity	Determined after the fact and may be denied for lack of medical necessity if all rules are not followed

off-label treatment may be sufficient grounds for payment denial, it is possible denials can be overturned with the help of patient and billing assistance programs offered by pharmaceutical companies. Another helpful resource is the pharmacy's familiarity with CMS-approved compendia, which can be used to support a billing claim for a pharmaceutical with a reimbursable Healthcare Common Procedure Coding System code used for an off-label indication.

Five drug compendia are identified as authoritative sources for the benefit of anti-cancer drugs. However, each MAC may have its own requirements for use, which can be found on its website. For instance, some may use evidentiary levels of efficacy discussed in these compendia to determine whether a drug may be covered for a given indication. CMS-approved authoritative compendia are listed in the CMS Internet Only Manual (IOM) Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5 at www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.

For all drugs, including anti-cancer drugs, and in the absence of any statutory, CMS or MAC exclusion of a drug or specific drug indication, MACs may recognize an indication to be medically accepted if the indication is:

- FDA-approved for the drug at the FDA-published dose and frequency; or
- Listed in one or more of the approved

compendia with an appropriate level of evidence of efficacy; or

- Recognized, following Medicare review of the peer-reviewed literature, as an appropriate treatment (the requester is expected to provide significant peer-reviewed full articles to the contractor for review) *and* the use is not listed as unsupported, not indicated or not recommended (or equivalent terms) in any of the compendia. Any such listing precludes reimbursement for the drug.

Financial Advocacy

Unfortunately, many facilities treat financial advocacy in a disjointed, understaffed fashion with no one area ultimately responsible and little documentation to support the entire effort across the continuum of care. This is a problem because the complexity of PAs, especially for oncology and other immunologic agents, has increased significantly. To gain better perspective, facilities need to determine whether what they are doing now is working or whether their denial rate is climbing. They must also determine if their systems are robust enough to withstand the addition of Medicare Advantage patients. Furthermore, their systems need to be up-to-date and timely, and EHR systems must be optimized to improve patient flow, reduce patient expense and increase assistance program enrollment.

To develop and strengthen the team, facilities can track write-offs and denials, many of which will be coded “no authori-

zation” or “lack of medical necessity” despite the drug being a valid choice for a patient's condition. It may not be that the choice of product was the problem, but rather how it was handled and/or documented in the EHR, resulting in an incomplete or faulty claim. By ensuring these problems don't occur, both the patient and facility will benefit in measurable ways.

Resisting Change Not an Option

Is your facility flexible or rigid? Can it respond quickly to changing environments and new government mandates? Have you positioned your clinical and technical staff to practice in a cross-functional manner along with the rest of the financial advocacy team to ensure compliance? Rigid adherence to policies, practices and formularies will significantly impair facilities in the current rapidly changing healthcare environment. ♦

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.

Internet of Things (IoT) in the Healthcare Setting

By Ronale Tucker Rhodes, MS



POWERED BY satellites and landlines, Internet of Things (IoT) dates back to 1962 with the advent of the Internet as part of the Defense Advanced Research Projects Agency. One of the first examples of IoT involved a Coca-Cola machine located at Carnegie Mellon University that programmers connected to the Internet to check if drinks were available and if they were cold before making the trip to get them. But, IoT wasn't officially named until 1999, and by 2013, it had evolved into a system that used multiple technologies ranging from the Internet to wireless communication, micro-electromechanical systems and embedded systems, among others.¹

While IoT is difficult to precisely define, Kevin Ashton, an expert on digital innovation, is credited with the first version's definition in 1999 in the *RFID Journal*: "If we had computers that knew everything there was to know about things — using data they gathered without any help from us — we would be able to track

and count everything, and greatly reduce waste, loss and cost. We would know when things needed replacing, repairing or recalling, and whether they were fresh or past their best." Essentially, IoT is anything that can be connected digitally to communicate in an intelligent fashion.²

IoT in Healthcare

IoT has changed the world, influencing the way people live and work. Officially, IoT in the U.S. healthcare system mainly started with the Health Information Technology for Economic and Clinical Health Act in 2009 that stimulated the adoption of electronic health records and supporting technology, allowing patients to be more engaged in their treatment. Today, IoT in healthcare is projected to transform the industry. Grand View Research released a report showing global IoT devices in the healthcare market were valued at \$58.4 billion in 2014, and in 2020, they will reach nearly \$410 billion.³ And, in 2017, research from Aruba

Networks found that by 2019, 87 percent of healthcare organizations would have adopted IoT technology, with 73 percent of applications used for remote patient monitoring and maintenance, 50 percent for remote operation and control, and 47 percent for location-based services.^{4,5}

What's driving this growth? First, major companies such as Medtronic Inc., Philips, Cisco Systems, IBM Corp., GE Health and Microsoft are developing products specifically for medical applications. Second is the growing prevalence of chronic diseases and an aging population prone to chronic diseases that are spurring governments to develop digital health solutions to improve access to healthcare services and decrease costs.³ In addition, there is increasing demand from consumers for remote and home health devices.⁴

IoT in Action

The range of IoT applications in healthcare is vast, especially when including personal healthcare, the pharmaceutical industry, healthcare insurance, remote telehealth services, facilities, robotics, biosensors, smart beds, smart pills, etc. Yet, today, the majority of IoT devices in use can be divided into three major groups: wearable external devices, implanted medical devices and stationary medical devices.

Wearables are typically biosensors that monitor physiological data with remote/wireless communication. With wearable devices, medical professionals can get a more detailed understanding of their patients' conditions. Some examples:

- The Proteus Digital Health Feedback System is a wearable sensor or patch that gathers information from a digestible sensor that is consumed alongside oral medication. The digestible sensor is made of magnesium and copper and is activated

when it gets wet in the stomach. The wearable sensor is secured on the patient's torso and collects information from the activated digestible sensor in the stomach, including when the medication was ingested and activity level and rest patterns of the patient. The wearable sensor then relays the captured information to the patient's mobile device, which can then be shared with healthcare providers via a web-based portal.⁶

- Zephyr Anywhere's BioPatch is a device attached to a patient's chest that helps track a patient's condition minute-by-minute instead of the usual four- to eight-hour interval while at the hospital. If there is a dip in their health or condition, nurses and doctors are notified immediately from the patch to a smartphone.⁷

The adoption of implanted devices is still in its infancy, but in essence, they replace, support or enhance biological structures such as implantable infusion pumps, cardiac pacemakers, etc. Some examples:

- The Eversense Continuous Glucose Monitoring System is an implantable, fluorescence-based sensor, a smart transmitter worn over the sensor to facilitate data communication and a mobile app. The sensor, inserted subcutaneously in the upper arm by a physician via a brief in-office procedure, displays glucose values, trends and alerts. The data is then transmitted to an external transmitter that can be monitored by a healthcare professional.⁸

- Researchers at the Georgia Institute of Technology have created a new medical sensor to treat brain aneurysms. The device, which is battery-less, is a capacitive sensor with an inductor that is implanted in the blood vessels of the human brain to help doctors assess any abnormalities that can cause patient death.⁹

Stationary devices can be used for clinical operations such as telehealth, connected imaging, lab tests, imaging, etc. Some examples:

- AirFinder is a real-time location system that uses open-source iBeacon, Bluetooth

Low Energy technology and Symphony Link integration to track supplies in an operating room or throughout an entire hospital or facility.³

- Microsoft's Power BI collects and analyzes electronic health records (EHRs) and then pairs the information with open data sources to allow users to visualize data and explore service area patterns. Power BI brings data together on one platform so a network of doctors can share EHR data or metrics to better predict, for example, when flu season will hit and how severe strains might be.¹⁰

IoT's Increased Need for Security

With 30 percent of healthcare organizations using IoT for sensitive information, there is a need to balance utility and security.⁴ Even with secure methods to communicate information to the cloud, the information is vulnerable to hackers. To counter risks, the U.S. Food and Drug Administration (FDA) has published numerous guidelines to establish end-to-end security for connected medical devices, and these devices will likely continue to be regulated.

In 2018, FDA issued the *Medical Device Cybersecurity Regional Incident Preparedness and Response Playbook* that outlines a framework for health delivery organizations and other stakeholders to plan for and respond to cybersecurity incidents around medical devices, ensure effectiveness of devices and protect patient safety. It is intended to supplement existing health delivery organization emergency management and/or incident response capabilities with regional preparedness and response recommendations for medical device cybersecurity incidents. Specifically, it identifies how hospitals and other organizations can develop a cybersecurity preparedness and response framework, which starts with conducting device inventory and developing a baseline of medical device cybersecurity information.¹¹

The playbook can be downloaded at www.mitre.org/publications/technical-papers/medical-device-cybersecurity-regional-incident-preparedness-and.

Unlimited Benefits of IoT

Possibly more than any other industry sector, healthcare has the most potential for IoT use. Its benefits include reduced costs, increased efficiency, upgraded management of drugs and medication adherence, reduced errors and waste, improved treatment outcomes, enhanced data access, more personalized care and fewer hospital and doctor visits. Yet, inherent to these benefits come security risks that could expose healthcare organizations and patients to cyber mischief and attack. To counter these vulnerabilities, FDA and organizations responsible for creating IoT devices are forward-thinking to make safety and security a priority. ❖

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

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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. ❖

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Research

HPV Vaccine Exceeds Expectations by Providing Herd Immunity

A new study shows the human papillomavirus (HPV) vaccine is far more effective than expected, with benefits extending beyond those who receive the vaccine. Specifically, the study showed vaccination not only reduces rates of HPV infection and the presence of precancerous cells in the cervix in people who receive the vaccine, it also reduces rates of HPV-related diseases in people who are not vaccinated.

The study, which expanded upon a 2015 meta-analysis that looked at the real-world effects of the vaccine, included a total of 65 studies that spanned eight years and included more than 60 million people living in 14 countries. Each study measured either changes in the number of new HPV infections, genital warts diagnoses or cases of abnormal cells associated with cervical cancer in countries before and after they adopted routine HPV vaccination in girls. (Two countries included in the analysis, the U.S. and Australia, also recommend the vaccine for boys.)

Researchers found there was a significant decrease in the prevalence of two strains of



HPV that cause 70 percent of cervical cancers, HPV 16 and 18. In addition, there was a decrease in the prevalence of precancerous cells in the cervix, which can develop into cancer. In countries where at least half the population actually received the vaccine, researchers saw evidence of herd immunity, meaning there was a decrease in the prevalence of HPV-related diseases even among those who weren't vaccinated since vaccination leads to fewer

HPV hosts. They also saw a decrease in genital warts diagnoses among unvaccinated boys and older women. And, among girls within the age groups targeted for vaccination, there were fewer diagnoses of three HPV strains that the vaccine does not specifically protect against, a phenomenon called cross-protection. Countries in which people in multiple age groups received the vaccine also saw a greater decrease in HPV-related disease.

"The impact of the HPV vaccination has actually exceeded expectations," said Lauri Markowitz, associate director of science for HPV at the Centers for Disease Control and Prevention, who worked on the study. "The trials showed that HPV vaccines are very effective, and data from the real world has confirmed that." ❖

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Medicines

FDA Approves Octaplas to Treat Pediatric Patients Who Require Multiple Coagulation Factor Replacement

A revised product label for Octapharma USA's Octaplas (pooled plasma [human] solvent/detergent treated solution for intravenous infusion) to treat critically ill pediatric patients who require replacement of multiple coagulation factors has been approved by the U.S. Food and Drug Administration (FDA). Approval was based on a prospective, open-label, multicenter, single arm, post-marketing study that assessed 50 pediatric patients age 16 years and younger (37 neonates/infants less than 2 years; and 13 children/adolescents age 2 years to 16 years). Study participants included 40 cardiac surgery patients, five liver transplant/dysfunction patients, four sepsis-related coagulopathy patients and one patient with hypoxic encephalopathy. Patients were dosed based on body weight,

and doses were adjusted as needed. There were no hyperfibrinolytic or treatment-related thromboembolic events reported by investigators. Overall safety was assessed by investigators as "excellent" for all 50 patients. Hemostatic parameters as measured by international normalized ratio, prothrombin time, activated partial thromboplastin time and thromboelastography were within expected ranges following use of Octaplas.

"The results of this study provide clinical evidence supporting the use of Octaplas in critically ill pediatric patients with acquired deficiencies who require replacement of multiple coagulation factors due to liver disease or who are undergoing cardiac or liver transplant surgery," said Octapharma USA President



Flemming Nielsen. "The results of the present study and those of previous studies comparing Octaplas with fresh frozen plasma support its use in this patient population." ❖

Octapharma USA: FDA Approves New Octaplas® Product Label. Octapharma press release, May 22, 2019. Accessed at www.businesswire.com/news/home/20150309005120/en/Octapharma-USA-FDA-Approves-Octaplas-License-Supplement.

Medicines

Octapharma Introduces New SCIG Product and IgCares Program

At the Immune Deficiency Foundation (IDF) National Conference in June, Octapharma introduced its newest product, Cutaquig (immune globulin subcutaneous [human] 16.5% solution) for subcutaneous infusion indicated for treatment of primary humoral immunodeficiency (PI) in adults. The company also launched its free IgCares program, an initiative managed through the community portal at www.IgCares.com providing a safety and sustainability service that transforms medical waste into energy; Octapharma donations to PI nonprofit organizations; access to educational and informational resources for PI patients; and personal connections to peers, the PI community and patient advocates. "Multiple clinical trials have demonstrated the safety and efficacy of Cutaquig in treating PI in adults, so we are pleased to introduce the product," said Octapharma USA President Flemming Nielsen. "We

are excited to launch IgCares as well because it provides Cutaquig patients with benefits through educational and community resources, as well as support for patient organizations and the environment."

IgCares enables patients to return product materials at no cost, keeping their medical waste out of landfills. With each monthly shipment of Cutaquig, patients will receive a custom sharps container for needles and other medical waste and an additional box for product shipping materials. "The IgCares initiative helps protect the environment by transforming medical waste into energy," added Nielsen. "Everything patients return will be repurposed into an industrial material used to generate electricity for homes and businesses."

The IgCares initiative also lets patients access educational and informational resources, including a wide range of tips, tactics and tools to succeed in the patient

treatment journey. Its portal also connects patients with peers, the PI community and patient advocates who are available to answer questions. Patients earn points through IgCares every time they fill a prescription, complete educational activities, track their treatment and participate in the sustainability program. They can convert their points into a charitable donation by Octapharma made to one of four PI community organizations, including IDF, the Jeffrey Modell Foundation, the Foundation for Primary Immunodeficiency Diseases and the International Patient Organisation for Primary Immunodeficiencies.

Cutaquig is available through four distribution partners: Nufactor, Healix, KabaFusion and Main Bridge Health Partners. ❖

Octapharma Introduces Cutaquig & IgCares. Sponsors IDF National Conference. BusinessWire, June 27, 2019. Accessed at finance.yahoo.com/news/octapharma-introduces-cutaquig-igcares-sponsors-153500478.html.

Medicines

New Rabies Calculator Helps Providers Treat Patients Exposed to Rabies

Kedron Biopharma has created the KEDRAB Dose Calculator to help healthcare providers treat rabies exposures. The free, easy-to-use online tool prompts healthcare providers to input the weight of a patient who has been exposed to rabies, and the tool then calculates the precise KEDRAB dose needed.

KEDRAB is a human rabies immune globulin (HRIG) indicated for post-exposure prophylaxis (PEP) of rabies infection. Administered concurrently with a full course of rabies vaccine, HRIG is an important component of rabies PEP for previously unvaccinated persons. PEP is a highly effective treatment regimen issued by the Centers for Disease Control and Prevention and the Advisory Committee

on Immunization Practices (ACIP). Rabies is almost always fatal when left untreated. However, by administering rabies PEP promptly and properly, healthcare professionals can prevent the onset of rabies symptoms. When administered according to ACIP guidelines, PEP is essentially 100 percent effective in preventing human rabies.

“Rabies is a medical urgency and care should not be delayed. Because rabies is a fatal disease, there is no room for treatment error when a person exposed to rabies presents at the emergency room or clinic,” said Peter Costa, MPH, MCHES, AVES (Hon), rabies immunoglobulin brand director at Kedron Biopharma. “The KEDRAB Dose Calculator was created to

help clinicians quickly and accurately dose KEDRAB, which is a critical component of the rabies post-exposure prophylaxis regimen.” ♦

New KEDRAB Dose Calculator Launches to Help Hospitals in Treating Rabies Exposures. Kedron Biopharma press release, Aug. 7, 2019. Accessed at finance.yahoo.com/news/kedrab-dose-calculator-launches-help-110000984.html.

Vaccines

NIH to Evaluate Experimental Adjuvants for Seasonal Influenza Vaccine



The National Institutes of Health (NIH) is conducting an early-stage clinical trial to evaluate the safety and efficacy of two licensed seasonal influenza vaccines administered with or without novel adjuvants. Adjuvants are more likely to produce a stronger immune response to the vaccine, thus providing better protection. The two novel adjuvants being tested in the study have demonstrated promise in enhancing

the immune response to influenza vaccines in animal models. Both were also shown to be well-tolerated when given in conjunction with either Flublok or Fluzone in additional animal models.

The Phase 1 trial will enroll 240 healthy adults between 18 years and 45 years at eight vaccine and treatment evaluation units comprised of a network of clinical trial sites funded by the NIH’s National Institute of Allergy and Infectious Diseases. During the 18-month trial, participants will be randomized to receive one dose of the Northern Hemisphere 2018-2019 influenza seasonal version of either Fluzone quadrivalent influenza vaccine or Flublok quadrivalent influenza vaccine administered alone or in combination with either the AF03 or the Advax CpG55.2 adjuvant. Participants will then be required to return to the clinic for regular visits for at least 57 days to be evaluated for adverse effects and to collect blood samples to track

vaccine-related immune responses. Ninety days after vaccination, all volunteers will receive a dose of the 2019-2020 seasonal quadrivalent influenza vaccine without adjuvant and will be observed for adverse effects. Those who received Fluzone initially will receive the updated Fluzone vaccine, and those who received Flublok will receive the updated Flublok vaccine. At the final clinic visit one year after participants’ first vaccination, investigators will conduct a final blood draw and will ask for a total account of any adverse effects.

Investigators are hopeful the completed study will provide more information on the safety and immunogenicity of adjuvanted seasonal influenza vaccines. Specifically, they hope to determine the best combination of vaccine and adjuvant needed to provide robust immunity. ♦

Fleming M. Study to Evaluate Experimental Adjuvants for Seasonal Influenza Vaccine. Contagion Live, Aug. 12, 2019. Accessed at www.contagionlive.com/news/study-to-evaluate-experimental-adjuvants-for-seasonal-influenza-vaccine.

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The Current Challenge of Immune Globulin Access

Understanding the factors contributing to the current shortage of immune globulin could help to address a crisis that threatens dire consequences for patients.

By Ronale Tucker Rhodes, MS

ACCORDING TO THE University of Utah Drug Information Service, as of Sept. 30, 2019, there were 265 active drug shortages in the U.S., up from 224 during the same period in 2018 and 174 in 2017.¹ While all drug shortages can have a significant impact on patient care, “medically necessary” medicines such as immune globulin (IG) that treat rare, serious, genetic and life-threatening illnesses and have few to no alternative treatment options can result in chronic debilitation, permanent physical damage and even death. Today, IG is in short supply with no clear indication of when the shortage will resolve. In turn, treatment for some patients is either being limited or stopped altogether. So, what is causing this shortage? And, what is being done to respond to the crisis?



IG Access: A History Lesson

Since the first U.S. Food and Drug Administration (FDA)-approved intravenous IG (IVIG) product in 1981, there has been only one major shortage of IG in the U.S., which was due to product recalls, manufacturing standards violations and product export.

It began in 1995, when FDA issued recommendations that plasma products made from pools later found to include a donor with a fatal and little-understood disease known as Creutzfeldt-Jakob disease (CJD) be withdrawn from the market, which resulted in recalls and voluntary withdrawals. By 1997, four manufacturers that produced the vast majority of IG — Bayer, Baxter Healthcare, Alpha Therapeutic and Centeon — had recalls and withdrawals totaling approximately 7 percent of the total IVIG supply. This part of the shortage was addressed when a review of data from FDA, the National Institutes of Health and the Centers for Disease Control and Prevention suggested the risk for transmission of CJD by blood products, if it existed, was considerably lower than the risk for harm to public health from CJD-related quarantines and withdrawals, causing the Surgeon General to recommend plasma derivatives, including IVIG, be withdrawn only if the blood donor developed new-variant CJD.

Shortly after its recommendation to withdraw IVIG due to CJD, FDA doubled its inspections of plasma products manufacturers and discovered serious violations of manufacturing standards. While every manufacturer received warning letters citing numerous deficiencies, FDA allowed manufacturers to continue operating while addressing the problems. Yet, although some companies decided to continue operations, others decided to stop release and distribution of IVIG and shift resources to compliance correction. Centeon, in particular, decided to shut down production and didn't distribute product at all in 1997, accounting for 60 percent of the 20 percent shortfall. At the same time supply was diminishing, demand was surging because of new approved indications and an increase in off-label (non FDA-approved) uses. In fact, the Immune Deficiency Foundation and physicians across the country estimated 50 percent to 70 percent of IVIG was being prescribed off-label.

Another contributing factor to the shortage was export of IVIG. FDA reported exports accounted for up to 29 percent of distributed product, depending on the manufacturer. And, the International Plasma Products Industry Association reported exports from the major U.S. fractionators increased from 1996 to 1997, accounting for approximately 20 percent of their marketed IVIG products.²

Since this shortage, there has yet to be another until now.

The Reasons Behind Drug Shortages

Since 1999, FDA has been working with the healthcare industry and patients to prevent and mitigate shortages of medically necessary drugs. FDA considers a drug medically necessary if it “is

used to treat or prevent a serious disease or medical condition and for which no acceptable drug alternative is available in adequate supply.”

The top reason for drug shortages involves quality concerns caused by manufacturing issues of delays/capacity (64 percent), but a lack of raw material (27 percent), boost in drug demand (5 percent) and lack of financial incentive to continue production (2 percent) can also affect drug availability.³ Clearly, the reasons behind the previous IG shortage lend credence to these statistics.

Since 1999, FDA has been working with the healthcare industry and patients to prevent and mitigate shortages of medically necessary drugs.

IG Shortage: What's Available?

Currently, there are 16 IG products marketed by seven manufacturers: Asceniv (IVIG 10%), Bivigam (IVIG 10%), Cutaquig (subcutaneous IG [SCIG] 16.5%), Cuvitru (SCIG 20%), Flebogamma DIF (IVIG 5% and IVIG 10%), Gammagard Liquid (IVIG 10% and SCIG 10%), Gammagard S/D (IVIG 5%, low IgA), Gammaked (IVIG 10% and SCIG 10%), Gammaplex (IVIG 5% and IVIG 10%), Gamunex-C (IVIG 10% and SCIG 10%), Hizentra (SCIG 20%), Hyqvia (SCIG 10%), Octagam (IVIG 5% and IVIG 10%), Panzyga (IVIG 10%), Privigen (IVIG 10%) and Xembify (SCIG 10%). These products — manufactured by ADMA Biologics, BioProducts Laboratory, CSL Behring, Grifols, Kedrion, Octapharma and Takeda — are deemed medically necessary drugs to treat many diseases for which it is the only therapy.

IVIG and SCIG are approved by FDA to treat these diseases: chronic inflammatory demyelinating polyneuropathy, chronic lymphocytic leukemia (CLL), immune thrombocytopenic purpura, Kawasaki disease, multifocal motor neuropathy and primary immunodeficiency disease (PI). But, as mentioned previously, IG products are also prescribed to treat a host of off-label diseases and conditions, including autoimmune disorders, neurological diseases and secondary antibody deficiencies (SAD), among others.

With the number of IG products almost double that available 10 years ago, healthcare providers, hospitals and medical systems are grappling with how to optimize limited supplies for patients. The current supply of IG began to diminish in April 2019, when

some patients were told their product was unavailable. Then, FDA confirmed this shortage in a statement dated Aug. 12, 2019.⁴

IG products affected by the shortage include Bivigam, Cuvitru, Flebogamma DIF, Gammagard Liquid, Gamunex-C, Hizentra, Hyqvia, Octagam and Privigen.⁵

Demand Is Outpacing Production

While manufacturers and distributors of IG products have always contracted with one another to deliver product based on historic usage and future projections to curtail shortages, today's production capacity is mainly inadequate not due to manufacturing issues, but rather a significant increase in demand. Since FDA approved the first IVIG product in 1981, IG has experienced a sustained record of near-continuous demand growth. Today, demand for IG products continues to grow more than 8 percent a year. In 2018, as it has over each of the past several years, demand for IG products grew by more than 7 million grams. Collectively, IVIG and SCIG product shipments in 2018 approached 88 million grams.⁶

Today, the demand for IG products continues to grow more than 8 percent a year.

According to Keith Berman, MPH, MBA, a blood products expert and editor of *International Blood/Plasma News*, "The clinical utility of IG across an ever-broadening spectrum of serious or life-threatening autoimmune, inflammatory, immunodeficiency and other immune-mediated disorders continues to be documented in patient studies and case reports now numbering in the thousands." In addition, Berman says, there is a trend toward more aggressive treatment with high-dose IG in autoimmune neurologic diseases in particular; a steadily increasing proportion of patients being treated with long-term IG; and a growth in worldwide demand for IG products. For instance, there is a surge in IG demand in many countries in Southeast Asia, accounting for 18 percent of the market in 2014, and worldwide demand growing at an average rate of 9 percent between 2008 and 2016.⁷

In addition to many disease states now being treated with IG therapy, one of the primary drivers of heightened IG demand is SAD. According to an article in *Frontiers of Immunology*, the prevalence of SAD is estimated to be 30 times more common than PI (the disease for which the first IVIG product was approved and for which all IG products on the market today are indicated). Common causes of SAD include hematological malignancies such

as CLL or multiple myeloma and their treatments, as well as side effects of many immunosuppressive agents and procedures involved in solid organ transplantation. According to the article's authors, "It is becoming increasingly important to address the unmet [treatment] needs of this growing patient population," which is progressively being treated with IG therapy.⁸ (See Secondary Antibody Deficiency: A Key Driver of IG Demand (p.40) for more in-depth information about treating SAD with IG.)

Another primary driver of increased IG therapy demand is the growing geriatric population, which is prone to antibody deficiency disorders due to weakened immune systems. According to the U.S. Census Bureau, the number of people aged 65 years and older in the U.S. was approximately 46.2 million in 2014, and their numbers are expected to reach 98 million by 2060.⁹

To address this demand growth, Berman says, IG manufacturers must 1) forecast and invest in plasma collection facilities to ensure sufficient additional donor plasma is available to process into IG products, and 2) plan, invest and provide adequate lead time to construct and secure regulatory approval to operate new or expanded fractionation (how plasma is manufactured into IG products) and related IG production facilities.⁷

A Need for More Plasma

According to Berman, "More than 90 percent of the global supply of plasma for fractionation comes from 'source plasma,' which is typically collected from remunerated donors in dedicated licensed centers that use automated apheresis equipment to perform plasmapheresis to separate and retain only the plasma portion of donor blood. The balance of the plasma supply comes from 'recovered plasma' separated from whole blood donations that is not needed for direct transfusion into hospital patients."¹⁰

Once collected, plasma (comprised of 92 percent water, 7 percent proteins and 1 percent other solutions) must go through a fractionation process that separates and collects the individual proteins, of which 64 percent are albumin, 20 percent are IgG, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, CI esterase inhibitor, etc., to produce plasma therapies such as IG, clotting factor, etc.

To try to meet the current demand for IG products, industry is growing the number of plasma collection facilities. Between 2004 and 2014, the global supply of plasma intended for fractionation doubled to nearly 40 million liters. And, in the U.S., there were 737 plasma collection centers in 2018 versus just 478 in 2014,¹¹ at which more than 48 million donations of plasma were collected.¹²

Yet, despite this growth in plasma collection, Berman says, "IG product supplies here in the U.S. and internationally were — and continue to be — tight, as plasma raw material supply and IG products manufactured from it just manage to keep pace with

worldwide demand growth.”⁹ In fact, he says, to keep pace with demand will require new and expanded plasma collection centers, as well as additional equipment and staff. For instance, it was calculated that an additional three million plasma donations were needed just in 2018.⁷

Optimizing IG Production

With increased plasma collection also comes the need for increased production of IG products, which is a very complicated, costly and lengthy process. After plasma is released to manufacturers, it must go through a fractionation process in which plasma that is pooled from multiple donors is processed to extract specific therapeutic proteins, which are then subjected to various purification methods and viral inactivation and removal processes to ensure their safety and efficacy. The steps and regulations required to collect donated plasma and complete the manufacturing process that results in the final therapies take between seven and 12 months. As the Plasma Protein Therapeutics Association (PPTA) points out, this is what “sets the production of plasma protein therapies apart from chemical pharmaceuticals and other biologics whose manufacturing processes are much more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall cost.”¹³

And, IG manufacturers are stepping up to the plate. They have been investing substantially in research and technologies to increase the quality of proteins extracted from plasma, known as the “yield,” to create new and more effective therapies.¹⁴ The original Cohn fractionation process developed in the 1940s resulted in a significant loss in IgG-containing donor plasma. But, since the 1990s, manufacturers’ modifications to their purification processes improved the yield of IgG per liter of plasma. According to Patrick Robert, PhD, of the Marketing Research Bureau, “Over the last 25 years, plasma processing advances have improved IgG yield by roughly 60 percent on average, from 2.5 grams per liter to 4 grams or more per liter today.”⁷ Efforts continue on behalf of manufacturers to invest in new production capacity to keep ahead of forecasted future IG demand growth. And, as stated previously, the number of IG products on the market has almost doubled today compared to just 10 years ago as a result.

Meeting Patient Needs

The growing number of illnesses IG is used to treat (PPTA reports a 66 percent increase in distribution of IG therapy between 2012 and 2018 across North America and Europe), less-than-optimal plasma supply and the complicated manufacturing process all contribute to today’s IG shortage. In response, the healthcare industry is taking steps to optimize limited supplies for patients, including lowering doses, delaying treatments, prioritizing based on medical need and using alternative therapies when those exist.¹⁵

On another front, several organizations are making efforts to improve the current situation. PPTA has been working with some manufacturers to assist healthcare providers in obtaining specific products needed by patients. FDA is helping manufacturers mitigate the supply situation. It is exploring ways to improve the

With increased plasma collection also comes the need for increased production of IG products, which is a very complicated, costly and lengthy process.

manufacturing yield of IG products, as well as encouraging healthcare providers, hospitals and medical systems to prospectively devise an evidence-based approach to deciding which patients will receive priority treatment. Too, it has suggested hospitals and other medical systems consider a second IG product contract to improve resilience during and after the shortage.⁴ ♦

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

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A Guide to Immune Globulin Billing and Reimbursement

These guidelines are intended to assist providers in following proper procedures and submitting required documentation to ensure payment for IG therapy.

By Abbie Cornett, Michelle Greer, RN, Ronale Tucker Rhodes, MS, and Leslie J. Vaughan, RPh

GETTING REIMBURSED for expensive immune globulin (IG) therapies can be challenging and frustrating for providers for a couple of reasons. First, what is required when submitting a claim may vary depending on the insurer. Second, denial often occurs due to lack of pre-authorization and incomplete and/or inaccurate claims submission requirements. Following is a guide to assist providers to ensure they are reimbursed for the cost of these medications.

When Is IG Treatment Covered?

IG is approved by the U.S. Food and Drug Administration (FDA) to treat primary immunodeficiency diseases (PIs), immune-mediated thrombocytopenia purpura, Kawasaki disease, chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy. However, many other diagnosed indications not FDA-approved for IG therapy may also be reimbursable.

To determine whether the cost of IG therapy will be reimbursed, providers administering the therapy should conduct a thorough benefits investigation for a patient prior to initiating therapy. This investigation will reveal whether the payer requires a patient to use a preferred provider, whether pre-authorization is necessary and whether IG therapy falls under the patient's prescription benefit or major medical benefit. In addition, it will reveal the patient's deductible under the major medical benefit and how much has been satisfied, the maximum patient responsibility and how much has been satisfied, what the plan pays (percentage) and the site-of-care (which may include the patient's home, the physician's office or a hospital outpatient infusion suite) and in-network options. Once the benefits investigation is complete, providers will be informed about their options before moving forward with the therapy.

Obtaining Pre-Authorization

Years ago, pre-authorization for IG therapy was not routinely required, but today it is generally required by most commercial payers and by Medicare Part D plans. Once authorization has been given by a payer, treatment can begin. Typically, pre-authorization is obtained by providers based on information provided by the prescriber.

Prior authorization and insurance coverage for IG vary based on the patient diagnosis, where the patient will be infused, who will be submitting claims for the infusion and by the type of payer source. There are many differences between commercial insurance and Medicare. For example, commercial insurance companies typically will reimburse for IG to treat many disease states regardless of whether they are designated as FDA-approved. On the other hand, Medicare Part B will reimburse IG for most diagnosis codes in the physician office or hospital outpatient setting. But in the homecare setting, Medicare Part B reimburses for only 24 specific diagnosis codes (which is new since prior to August 2019, Medicare B reimbursed for only 14 diagnosis codes at home). Also, Medicare Part D may reimburse for additional diagnosis codes in the home (Table 1).

When obtaining pre-authorization, providers must accurately report a patient's diagnosis, symptom or complaint codes to the highest level of specificity. In addition, all diagnoses generally must be substantiated through clinical and diagnostic documentation. This may include office notes and/or a history and physical, lab work, procedures performed during the work-up, and any medications tried and failed, not tolerated or contraindicated. In addition, results of any prior response to IG therapy should be provided if applicable.

The No. 1 reason for delaying an authorization is incomplete clinical information from the prescriber. Clinical information for

Table 1. Medicare B Diagnosis Codes Covered at Home (not exhaustive)

ICD-10 Code	Description
D80.0	Hereditary hypogammaglobulinemia
D80.2	Selective deficiency of immunoglobulin A [IgA]
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.5	Purine nucleoside phosphorylase [PNP] deficiency
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	DiGeorge syndrome
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B or T cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
G11.3	Cerebellar ataxia with defective DNA repair
Other Codes Commonly Covered	
G61.0	Guillain-Barré syndrome
G61.81	Chronic inflammatory demyelinating polyneuropathy
G62.81	Critical illness polyneuropathy
G60.8	Other hereditary and idiopathic neuropathies
G99.0	Autonomic neuropathy in diseases classified elsewhere
G60.9	Hereditary and idiopathic neuropathy, unspecified
G90.9	Disorder of the autonomic nervous system, unspecified
G70.0	Myasthenia gravis without exacerbation
G70.01	Myasthenia gravis with acute exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G73.1	Lambert-Eaton syndrome in neoplastic disease
G70.81	Lambert-Eaton syndrome in other diseases classified elsewhere
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.20	Polymyositis, organ involvement unspecified
G73.7	Myopathy in diseases classified elsewhere
G25.82	Stiff-person syndrome
G35	Multiple sclerosis
H46.9	Unspecified optic neuritis
G37.9	Demyelinating disease of central nervous system, unspecified
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
D89.9	Disorder involving the immune mechanism, unspecified
L10.0	Pemphigus vulgaris
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L13.8	Other specified bullous disorders
L88	Pyoderma gangrenosum

Table 2. Manufacturer Contacts for Billing Assistance

- ADMA Biologics (Asceniv, Bivigam): www.admabiologics.com
- Bio Products Laboratory (Gammaplex): www.gammaplex.com/gammaplex-10-reimbursement-support
- CSL Behring (Hizentra, Privigen): www.cslbehring-us.com/Products/Universal-Billing-Codes.htm
- Grifols (Flebogamma DIF): (888) 474-3657, reimbursementsupport@grifols.com
- Grifols (Gamunex-C): www.gamunex-c.com/en/hcp/gamunex-financial-support
- Grifols (Xembify): www.xembify.com/en/hcp
- Kedrion (Gammaked): www.kedrionusa.com
- Octapharma (Cutaquig): www.cutaquigus.com/hcp/usage/diagnostic-billing-codes
- Octapharma (Octagam): www.octagamus.net
- Pfizer (Panzyga): www.pfizer.com/products/product-detail/panzyga
- Takeda (Gammagard Liquid, Gammagard S/D): www.gammagard.com/healthcare-professionals/ordering-andreimbursement/billing-instructions.html
- Takeda (Hyqvia): www.hyqvia.com

PI patients should include the history of infections (type, treatment, occurrence), Ig levels (IgG and subclasses IgM and IgA), vaccination response (failure to show a response to pneumococcal, tetanus and diphtheria vaccines) and other tests depending on the type of immune deficiency.

For neuromuscular diagnoses, results of tests such as a nerve conduction, electromyogram (EMG), muscle biopsy and spinal tap may be required. For example, for CIDP patients, documentation required to approve IG may include an EMG, nerve conduction studies, cerebral spinal fluid tests and a history of symptoms, as well as a complete neurological examination.

Every payer, whether private or government, has different guidelines for approving IG. Some are very simple, and others are very detailed. If it is determined the diagnosis is within a payer's guidelines and proof of that diagnosis is submitted, IG should be approved.

Billing for Reimbursement

Billing codes for reimbursement are the responsibility and liability of the providers of IG therapy, including the drug, supplies and nursing costs (if applicable). Codes should include, but are not limited to, national drug codes, ICD-10-CM codes and Healthcare Common Procedure Coding System codes.

For a Medicare patient infusing IG in the home, nursing is 100 percent covered under Medicare Part A when the nursing is provided by a Medicare-certified home health agency if the physician certifies the patient is homebound. If a patient is not deemed homebound, the cost for a nurse to visit the home may be billed to the patient. However, on Jan. 10, 2013, the Medicare IVIG Access Act was enacted, which provided for a demonstration project to examine the benefits of providing coverage and payment for items and services necessary to administer intravenous IG (IVIG) in the home for PI patients. In addition, as a result of the 21st Century Cures Act, there is now coverage when a nurse is in the home to administer subcutaneous IG via a pump. This coverage for nursing is limited to the 24 diagnosis codes covered by

Medicare Part B.

Because the duration of authorization differs from payer to payer, deadlines for obtaining authorizations and for billing must be adhered to. Prior to pre-authorization, the payer may require evidence of a positive response to IG, which may be documented in the form of an exam performed by the physician or by lab work. If deadlines are met and the proper billing procedures are used, IG therapy should be reimbursed without issues. Some manufacturers have coding guides or reimbursement staff to assist with billing codes (Table 2).

Filing an Appeal

There is always a chance authorization may not be granted for IG. When a payer denies authorization for IG therapy, the prescriber will receive a letter stating the denial and the reason. If this happens, an appeal can be made. Instructions on how to appeal are always included in the denial letter.

The first thing that should be checked prior to filing an appeal is whether the proper codes were submitted on the claim. If they were correct, the provider can appeal by submitting a letter of medical necessity (LMN) or requesting a peer-to-peer review between the prescriber and a medical director from the insurer.

The LMN should state the medical necessity of IG therapy particular to the diagnosis, as well as provide evidence-based medical data that pertain to the physician's diagnosis. Evidence-based medical data can often be obtained by conducting a search of medical journals that substantiate the effectiveness of IG therapy for a particular disease state. In addition, the LMN should indicate the failure or intolerance of other therapies. And, if there is a prior response to IG therapy, that should be included.

In some cases, rather than a written appeal, a conversation known as a peer-to-peer review may be better, especially for complex cases. In this situation, the prescribing physician and the insurance company's medical director can discuss the justification for IG therapy. The denial letter provides instructions for requesting a peer-to-peer review.

It's important to note that under the Affordable Care Act, there are new health insurance appeal rules that apply to health plans created or purchased after March 23, 2010.¹ Specifically, when a payer denies payment for a treatment or service, an appeal can be requested, and the payer is required to review its decision. For plan years or policy years beginning on or after July 1, 2011, when the payer denies a claim, it must notify the patient of the reason the claim was denied, the patient's right to file an internal appeal, the right to request an external review if the internal appeal is unsuccessful, and the availability of a consumer assistance program (if the state in which the patient resides has one).

When an internal appeal is filed, the payer must give a decision within 72 hours after receiving the request when appealing the denial of a claim for urgent care, within 30 days for denials of nonurgent care not yet received, or within 60 days for denials of services already received. If after an internal appeal the payer still denies the request for payment or services, an independent external review by an organization that will decide whether to uphold or overturn the payer's decision can be requested. If the external review organization overturns the payer's denial, the payer must reimburse the claim.

The internal appeals rights under the Act take effect when the plan starts a new plan year or policy year on or after Sept. 23, 2010. The external review rights took effect Jan. 1, 2012.

Accuracy and Timing Are Crucial

Patients who rely on IG therapy could be placed at great risk of medical complications should they be denied coverage. With the prohibitively high cost of IG therapy, most patients are unable to afford the drug without coverage. What's more, when an appeal is necessary, patients, physicians and infusion providers all face financial hardship with time-consuming delays in the appeals process. Therefore, accurate and thorough authorization and error-free billing practices will provide a win-win situation for all when this critical lifesaving therapy is needed. ❖

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Editor's note: This article has been updated from the original published in the February-March 2013 issue of IG Living magazine.



Sponsor a child with hemophilia

It's rewarding and teaches unforgettable lessons

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

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

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

* name has been changed

Short-Dated Products:

Reducing Unsalable Returns and Supply Chain Waste

The glut of soon-to-expire products within the pharmaceutical supply chain is a costly problem impacting multiple stakeholders, but smart technology and innovative inventory management systems offer cost-saving solutions.

By Trudie Mitschang



LIKE MANY OTHER industries, manufacturers of pharmaceutical products have historically created return policies that offer customers credit for unsold items, assuming those product returns meet specified guidelines. In general, six scenarios would support a pharmaceutical manufacturer accepting a product back from regular distribution channels: The product has expired; a research-and-development failed batch is identified; a product is recalled either by the U.S. Food and Drug Administration (FDA) or the manufacturer; a product is withdrawn by FDA; the product has damaged packaging; or the product is identified as short-dated.¹

Products are considered short-dated when they are nearing their expiration date and are not yet consigned to a buyer. In an inventory management system, this product would be flagged for return, and the process could begin anywhere from less than six months to 18 months from expiration, depending on manufacturer requirements for the product.

But what are the drivers that cause an excess of short-dated products to become unusable within the supply chain? A report by Healthcare Distribution Management Association (HDMA) suggests increasingly streamlined return processes may have resulted in an overdependence on returns rather than a more proactive inventory management effort. Other influencing factors include the specific guidelines each entity practices when managing inventory flow. “Retailers often pull short-dated products off the shelf 90 days prior to expiration. Distributors usually work with a six-month window (shipping at seven months). Biotech or specialty products generally have shorter shelf lives, e.g., three months,” states the HDMA report. “In addition, some states may have requirements regarding the date on which the prescription is filled as it relates to expiration date. These conditions and practices can result in expired products being returned to manufacturers for credit after being held in a ‘morgue’ inventory location until they expire.”¹

Drug waste due to product expiration dates can be extremely costly, particularly at the hospital level. For example, according to sources at Newton-Wellesley Hospital in Massachusetts, the facility is able to return some expired drugs for credit, but in 2017 alone, it had to destroy nearly \$200,000 worth of outdated medication. And, a commentary in *Mayo Clinic Proceedings* cited comparable losses at Tufts Medical Center in Boston. Extrapolating those costs for hospitals nationwide, it amounts to nearly \$800 million annually, not including the costs of expired drugs at long-term-care facilities and retail pharmacies and those still sitting forgotten in consumer medicine cabinets.²

Even given those statistics, a follow-up report by HDMA indicates the true cost impact of short-dated products may frequently be underestimated: “Most trading partners underestimate the true cost of returns. The projected value of all prescription products returned in the U.S. for which manufacturer credit is

requested is between \$2.6 and \$4.2 billion (1 percent to 2 percent of manufacturer selling units), the vast majority of which are either ‘outdated’ or ‘short-dated’ (72 percent).”³

Understanding Industry Safeguards

Drug expiration dates reflect the time period during which the product is known to remain stable, meaning it retains its strength, quality and purity when it is stored according to label guidelines. FDA regulations require drug applicants to provide stability testing data with a proposed expiration date and storage conditions when they submit an application for FDA approval of their drug. This testing provides confidence that the product will meet the applicable standards of strength, quality and purity throughout its shelf -life.

Products are considered short-dated when they are nearing their expiration date and are not yet consigned to a buyer.

Industry safeguards that address the problem of short-dated products also include processes that ensure pharmaceutical shipments operate on a “first-expiration-first-out” schedule, with products shipped according to the proximity of their expiration dates. This assures older inventory is moved first and also creates an efficient stock rotation system. Additionally, as referenced in the HDMA report, distributors normally ship product with at least six months remaining until the expiration date.⁴

Another option that exists when short-dated products are flagged for return involves donation to charitable organizations. Often, these nonprofits collect short-dated pharmaceuticals donated by manufacturers and distribute them to low-income, uninsured patients. In fact, there are specific pharmaceutical donation and reuse programs that allow unused prescription drugs to be donated and redispensed to patients. Such drug repository programs began with state legislative action in 1997, and as of fall 2018, there were 38 states and Guam with enacted laws for donation and reuse.⁵

Still, the problems created by short-dated products and their resulting returns or donation impact numerous industry stakeholders, including distributors, manufacturers, healthcare providers and service providers. And, while there are product- and demand-related drivers of soon-to-expire pharmaceutical returns,

there are also potential process improvements that may address and reduce the quantity of short-dated products that are returned, including the adoption of track-and-trace technologies designed to enhance inventory management. Indeed, pharmaceutical track-and-trace regulations have been taking shape for several years. Industry guidelines enacted in 2017 require U.S. manufacturers to serialize products using 2-D bar codes and a unique identifier that includes product ID, serial number, expiration date and lot number. And, by 2023, regulations that are a part of the Drug Supply Security Act require each bottle or package of a drug be trackable to the original manufacturer.⁶

Considerations for a Consignment Strategy

Specialty pharmaceuticals pose unique challenges when it comes to inventory management. By 2021, the specialty market is expected to make up 50 percent of total pharmaceutical spend, or \$285 billion. In comparison, this market accounted for only 28 percent of pharmaceutical spend in 2011 and 39 percent in 2016, according to a Drug Channels Institute report.⁷

One of the key issues surrounding high-cost specialty therapies is unpredictable demand, which requires a different inventory strategy than traditional pharmaceuticals. To minimize the risk of short-dated product returns, some health systems are increasingly turning to a consignment model to better manage these specialty drugs, a move that can also reduce costs. IQVIA Institute for Human Data Science⁸ noted specialty drugs represent 60 percent of invoice spending and 2.3 percent of standard unit volumes in nonretail settings. With a higher invoice cost comes higher inventory carrying costs, and hospital pharmacies cannot afford to let costly specialty drugs expire. Some medications may also be cold chain products requiring refrigeration, so pharmacies must additionally plan for proper storage to avoid waste.

*Return systems for
short-dated products serve
several useful purposes,
the most important of which
is to protect patient safety.*

With that in mind, a consignment strategy can streamline and automate inventory management processes and reduce carrying costs for specialty pharmaceuticals. The approach allows hospitals to store products in their pharmacies and pay for them only when they are used.

In a webinar discussion sponsored by Ohio-based Cardinal Health, the organization outlined its approach to utilizing the consignment model and described how radio-frequency identification (RFID)-enabled consignment solutions can help reduce waste. “If you buy too much, you could risk waste due to expiration. If you buy too little, you could risk not having a product for a patient,” said James Roof, national director of consignment and technology programs. “Consignment ensures you have the products you need at the right time without incurring costs due to waste.”

The Cardinal Health Consignment Program uses RFID technology to monitor inventory in real time, set par levels based on actual pharmacy usage and send alerts for recalled products. Consigned inventory can be tracked and traced within a cloud-based platform, which allows health systems to gain real-time visibility into inventory levels. And, if there are multiple facilities in a network, consigned products can be transferred within the network.⁷

Another smart system worth noting was developed by FFF Enterprises, a nationwide distributor of plasma products, vaccines and biopharmaceuticals. The system, known as Verified Inventory Program-Consignment (VIPc), is a streamlined inventory management solution designed for high-value and critical-care products. This RFID-based consignment solution tracks and monitors products and the conditions in which they are stored. The cabinets are monitored by FFF Enterprises’ VIPc team on a 24/7 basis for both temperature and inventory. In the event of a temperature excursion, the team responds immediately to ensure product integrity is not compromised. Likewise, when product is loaded or removed from the cabinet, the RFID technology updates the inventory of the cabinet without any manual intervention on the part of the customer. Throughout each day, the facility’s staff can dispense product from the cabinet as it is needed for patient dosing, and once a minimum par level (a minimum quantity of a given item that must be kept on hand) is reached, an alert will go to the VIPc team, and replenishment will arrive the next day.

From a waste-management perspective, the VIPc team proactively monitors product expiration to ensure these high-cost critical-care products do not become short-dated. In the event a customer is unable to use a product and it is projected to become short-dated, the team will reach out to facilitate return of the product well before it reaches its expiration date so it can be sent to a customer who can immediately use it. The team then replenishes that facility’s cabinet with longer-dated product.

Currently, VIPc is being used in acute facilities and hospital pharmacies, particularly for coagulation factors, which are costly and have unpredictable usage, but are critical to have on hand when lifesaving situations arise. Other specialty products at risk of becoming short-dated can be stored using VIPc, including treatments for

snake bites, heart attacks, strokes and even cataract surgeries.

FFF also pioneered an innovative solution specifically for vaccine storage. MinibarRx (MBRx) was developed in 2013 as a stand-alone joint venture of affiliates of Minibar Systems (the world's largest maker of refrigerated platforms to the hospitality industry) and InstantDx (a leader in electronic prescribing and healthcare-transaction services). MBRx streamlines the process of purchasing, storing, administering and billing for refrigerated vaccines in physician offices, retail pharmacies and nonacute, ambulatory surgery centers and urgent care facilities.

As an affiliate, FFF Enterprises provides the MBRx refrigerators with the vaccines it distributes and automates the MBRx process using its proprietary software that sets a reorder point for each refrigerated vaccine at each location based on average usage. To avoid product expiry, electronic notifications are communicated to providers starting 45 days prior to the medication's expiration date. An LCD screen on the unit also displays all vaccines close to expiring for proper management. As an additional safeguard, if a product does expire before being used, the LED indicator light on the dispenser will turn red to indicate not to use the product. And, if the product is removed for use, an alarm will sound triggering an email notification. The product would then be returned for possible credit based on the manufacturer's guidelines.

According to Shay Reid, chief operating officer who leads development of the smart refrigerator technology at FFF, MBRx also complies with the Centers for Disease Control and Prevention's regulatory requirements for storage and handling of vaccines and biologics, creating what is essentially a worry-free system for inventory purchase and management. Reid notes that MBRx also has some unique differentiators compared to other smart refrigeration technologies. "MBRx does not require any additional product labeling such as the use of RFID tags. It is also an interactive technology capable of presenting temperature and inventory information on screen to the user, as well as directing the user to dispense first expiring products to help eliminate product expiry in the machine," he explains. "Additionally, MBRx's unique design helps to maintain the correct temperature and block light even when the main door is open, which serves to further protect the very sensitive inventory the machine dispenses without limiting accessibility."

Pursuing Innovation and Safety

Return systems for short-dated products serve several useful purposes, the most important of which is to protect patient safety, and any efforts to minimize returns must keep end-user well-being at the forefront of proposed innovation. Given the complexity of the issue and the multiple product-related and demand-related drivers, clearly, there is no one-size-fits-all solution to reducing the number of short-dated products in the supply chain. Process improvements and technological advances are definitely steps in

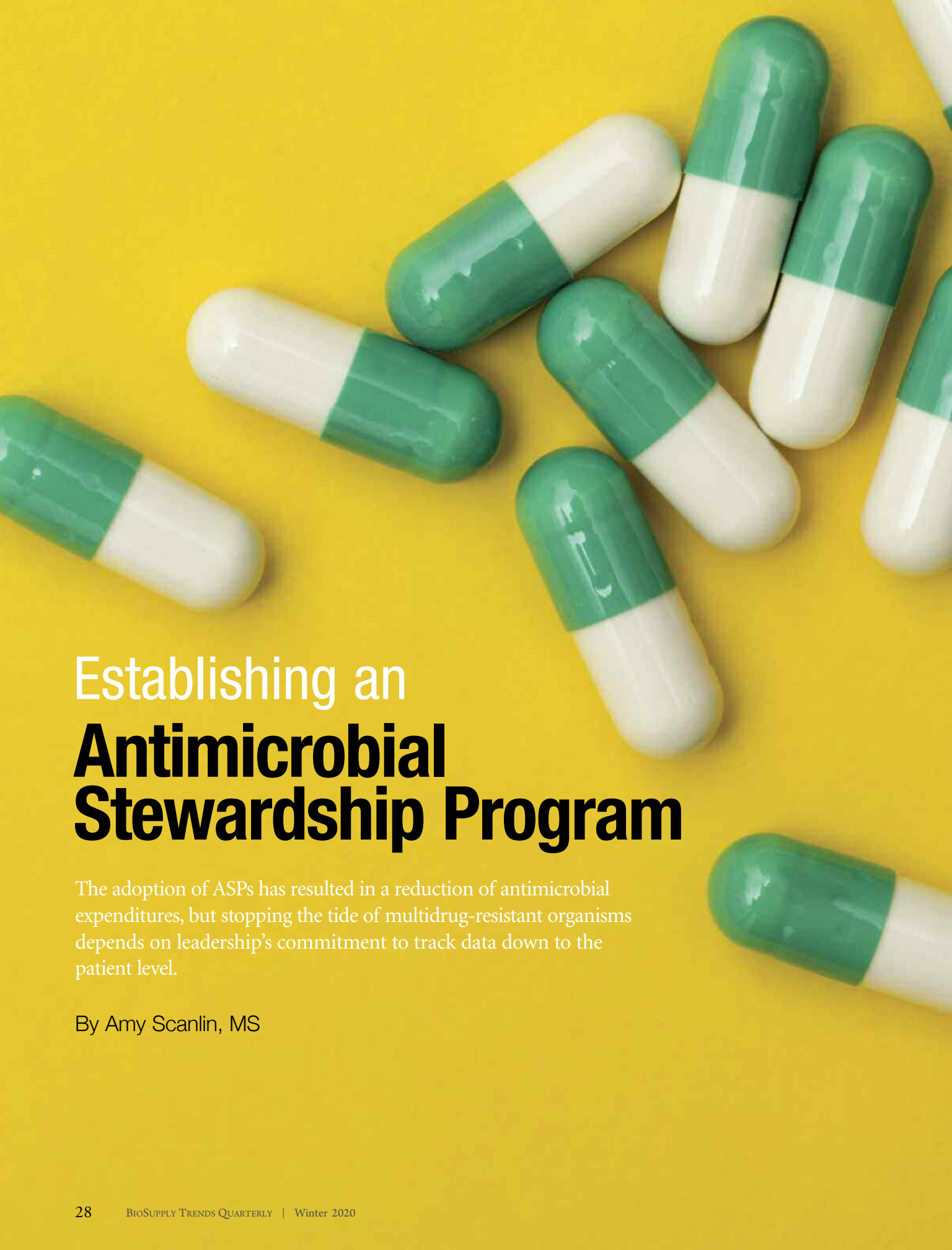


the right direction, and moving forward, a collaborative effort spearheaded by manufacturers, distributors, retailers and dispensers alike has the potential to reduce the overall quantity of expired and soon-to-expire pharmaceutical products; reduce total supply chain costs associated with unsalable returned goods; and preserve or improve the safety and security of the healthcare supply chain. ♦

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Establishing an **Antimicrobial Stewardship Program**

The adoption of ASPs has resulted in a reduction of antimicrobial expenditures, but stopping the tide of multidrug-resistant organisms depends on leadership's commitment to track data down to the patient level.

By Amy Scanlin, MS

THE CENTERS FOR Disease Control and Prevention (CDC) estimates more than two million patients in the U.S. become infected and 23,000 die from drug-resistant infectious organisms each year.¹ The overuse and misuse of antimicrobials, a contributing factor to multidrug resistant organisms (MDROs), is one of the most pressing concerns challenging the healthcare industry today. As infectious organisms adapt to the very drugs designed to kill them, antibiotics and antimicrobials are rendered ineffective and a vulnerable population is at greater risk. Beyond the potential for serious side effects and adverse reactions that could occur with any drug, patients who become infected with MDROs require longer and more expensive hospital stays and risk long-term consequences and even death.

It is estimated between 20 percent to 50 percent of antibiotics prescribed in U.S. acute care hospitals are either unnecessary or used inappropriately.¹ Therefore, to gain a foothold on MDROs, numerous programs have been launched, including a partnership between the U.S. and European Union (EU) that outlines the urgency, need for collaboration and steps for antimicrobial oversight. The role of antimicrobial stewardship programs (ASPs) (coordinated programs that educate and improve prescription practices of antibiotics and antimicrobials to optimize clinical outcomes) affects the entire healthcare spectrum, from physicians to pharmacists, nursing staff and patients, and ASPs encompass specific and actionable steps to reduce risk and identify areas of improvement.

Since MDRO and antimicrobial misuse was first identified, multiple international stakeholders joined to combat the problem. In the 13 years since CDC published its 2006 guideline “Management of Multi-Drug Resistant Organisms in Healthcare Settings,” its resources have been enhanced by the National Strategy on Combating Antibiotic Resistant Bacteria through Executive Order 13676 signed in 2014 by President Obama and the March 2015 National Action Plan for Combating Antibiotic-Resistant Bacteria, as well as position papers and additional action plans by organizations such as the Association for Professionals in Infectious Control and Epidemiology (APIC), the American Pharmacy Association (APhA) and Pew Charitable Trust, not to mention the Transatlantic Task Force on Antimicrobial Resistance joint declaration formed between the EU and the U.S. This international collaboration highlights the global urgency since a 2014 report commissioned by the Wellcome Trust and United Kingdom Prime Minister suggested that, without intervention, 10 million lives could be lost by the year 2050.²

The ease and frequency of global mobility means easier transmission of newly emerging infectious diseases, including new drug-resistant bacteria, says Sarah M. Bishop, MSN, APRN, CCNS, CIC, director of infection prevention and control at the University of Louisville Hospital and a member of APIC’s Communications Committee: “A new disease can be transmitted

from one side of the globe to your hospital doorstep in just one plane ride. The ever-present threat of global disease transmission translates into a need for healthcare facilities to be vigilant about screening and identification of newly emerging antibiotic-resistant bacteria based on travel history, exposure to healthcare in other countries and contact with others who may be in those risk categories. Healthcare facilities should collaborate with their infection preventionists (IPs) to design effective screening methods and develop communication tools to share information on current global disease threats.”

Closer to home, state, local and other federal agencies, as well as healthcare collaboratives, help in facilitating programs and tracking progress. Together, these resources demonstrate the immense challenge of gaining a foothold and how critical it is to do so.

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The Challenge

While antibiotics have transformed healthcare, over time that transformation has come at a cost. Half of all hospital patients receive antibiotics that are most commonly prescribed for lung infections (22 percent), urinary tract infections (UTI) (14 percent) and suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infections (17 percent). By one account, a third of antibiotics prescribed in hospitals for UTIs include a potential error. And, there are other concerns such as patients receiving powerful broad-range antibiotics are up to three times more likely to become infected with another even more drug-resistant germ. It is estimated a reduction in high-risk antibiotic prescriptions by 30 percent can lower deadly diarrheal infections by 26 percent.³ *Clostridium difficile* infections (CDIs), a potentially deadly outcome of antibiotic use, are a high priority since they affect more than 500,000 patients each year and cause more than 15,000 deaths in the U.S. alone.⁴

The danger is especially pronounced for patients who are immunocompromised because their reduced ability to fight infections makes them at even greater risk of complications and death associated with drug-resistant infections.

The complexity of healthcare decisions, particularly if starting antibiotic treatment prior to diagnostic testing, can be a daunting life-or-death situation. Providers may feel pressure to prescribe antibiotics from patients who do not understand the requirements of their care or the implications of inappropriate antibiotic use. Providers themselves may use outdated practices or misunderstood information about antibacterial recommendations. Even staffing shortfalls may put undue pressure on facilities of all sizes to meet a growing demand for patient care.

However, there is evidence ASPs work. Antimicrobial expenditures, which were on the increase by 14.4 percent annually in the years preceding the development of ASPs, decreased by 9.75 percent the year after implementation, and they remain stable, with an overall cost savings of \$1.7 million.⁵

Meta-analysis shows ASPs reduce infections and colonization with multidrug-resistant gram-negative bacteria and extended-spectrum β -lactamase-producing gram-negative bacteria, as well as MRSA and CDI infection rates. Patient outcomes are improved, adverse events are lessened and antibiotic-resistant organisms are reduced. Equally important, ASPs used in conjunction with other infection prevention control methods such as hand hygiene are even more effective than ASPs alone.²

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“Everything plays together,” says Michael Klepser, PharmD, FCCP, at the Ferris State University College of Pharmacy and APhA spokesperson. “Stewardship is not just about cost-containment. It really does optimize therapy and patient outcomes.”

Changing prescribing practices and the culture of care can be hard, but both are critical to reducing dependence on antimicrobials, the emergence of new MDROs, as well as ensuring patients are best cared for in the immediate and long-term by preventing infections.

The Core Elements of an ASP

With multiple stakeholders invested, there are numerous resources to complement the CDC’s Core Elements of Hospital Antibiotic Stewardship Program for hospitals, long-term care and outpatient facilities. Core elements include:

- With key buy-in and proactive leadership, IPs, physicians,

nurses, pharmacy leaders, laboratory staff and all parties with roles to play in infection prevention and control will be well-equipped to understand, promote and implement ASP best practices. An ideal team, says Klepser, would see both a pharmacist and physician trained in IP in leadership roles with coordination of laboratories, infection control, etc.

- Leadership will create an air of accountability to ensure each party has support necessary to perform critical ASP duties and hold them to a standard of care.

- A commitment to ensuring drug expertise, whether through an in-house pharmacist trained in ASP or outsourced pharmacist via telemedicine, hospital collaboratives or by other methods, is critical to patient care and program success. In support of this effort, documentation of dose, duration and indication for all antibiotics must be captured.

- All parties must take action for ASP to be a success. Nurses are a fantastic frontline resource working with IPs and physicians in initiating pre-antibiotic cultures, antimicrobial reviews and antibiotic reconciliation between care transitions.

- Surveillance tracking of antibiotic use and infection trends either by the CDC National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance module or some other means will help to ensure efforts are applied consistently, as well as to identify any prescribing trends and to assess the effectiveness of ASP implementation. “There are different things you can look at,” says Klepser. “Depending on the institution, you may look at CDI infections, decreased length of hospital stays or antibiotic reduction.” No matter which parameter or combination is chosen, says Klepser, “it is all about improving patient outcomes.”

- The reporting of timely, nonpunitive data and trends to providers, facilities and board of directors provides important information on antibiotic use, rates of CDI infections and, in the event of MDRO identification, how it is contained.

- Finally, ensuring education about ASPs is continual, frequent and specific to each job function concerning how the overall program ties together is imperative to foster a supportive team environment. “There are certificate programs,” says Klepser. Widely known for pharmacists is the Society of Infectious Disease Pharmacists antimicrobial stewardship certificates for both long-term and acute care.

Supplemental Support

Beyond the CDC’s core elements, APIC, the Society for Healthcare Epidemiology of America and the Society of Infectious Disease Pharmacists recommend additional elements of a timely diagnosis by a microbiological laboratory that can provide clear-cut information as to whether the patient is infected, what the pathogen is and the susceptibility of the organism, and that can translate the results into day-to-day infection management.

In many cases, the source of the outbreak can be tracked in

just a few days. And, because diagnostics are improving rapidly and infections can morph quickly, it is important results are interpreted by a clinical microbiologist who can further advise what they mean.²

It is common practice for patients to be started on antibiotics while the results of diagnostic tests are pending. However, what should also be common practice is revisiting the use of that antibiotic once results are in, which does not always happen. Within 48 hours of initiating antibiotics, physicians should consider whether diagnostic tests confirm the patient has an infection that can be treated with antibiotics and, if so, whether the antibiotic currently prescribed is the right one administered by the safest route.

Without question, smaller and more rural health clinics may find staffing challenges complicate their ability to create an ASP. However, these facilities are not alone, and they are encouraged to reach out to their state hospital associations, state and local health agencies and even telemedicine options to identify already existing ASPs with which they can collaborate.

Tracking Progress

Comparative data is a critical component to assess the execution and success of an ASP. Although it is difficult to attribute specific individual modifications to multifactorial antibiotic-resistant infections, an accounting of how antibiotics are used and the rate of which and where MDROs are identified can help facilities and the larger community understand progression and progress. “It is important to have measurable goals, accurate performance data and an effective method to provide feedback to frontline clinicians on how their prescribing practices align with overall stewardship goals,” says Bishop.²

Facilities should track both their compliance with set ASP protocols, as well as evidence of their effects. Laboratory reports are key to this effort, and those facilities that use offsite services are encouraged to include stewardship efforts in their contracts. Once data is collected, IPs and hospital epidemiologists can audit and analyze data.

Whether using a facility-specific tracker or one linked to a larger metadata registry, it is important the data collected and analyzed are of value to the facility and its staff. Days of therapy (DOT), rather than antibiotic expenditures, is considered to be most valuable for stewardship efforts. It should be noted antibiotic expenditures are an ineffective way of tracking stewardship efforts since they do not always correlate to antibiotic use. The CDC’s NHSN includes an antibiotic use option whereby systems can be configured to include electronic medication administration records, and barcoding medication records can be reported using an HL7-standardized clinical document architecture. NHSN will automatically collect and report monthly DOT data, which can be analyzed in aggregate or by specific agents and facility locations. As more facilities come online, CDC will begin providing risk-adjusted facility benchmarks for antibiotic use.¹

Once data is collected and analyzed, the collective healthcare team

can begin to see trends in treatment recommendations, administration information, diagnostics and patient progress. The distilling of data is where the team approach of stewardship can be most telling. For example, are antibiotics being commonly prescribed and/or misprescribed for certain conditions? Once diagnostic test results are in, is the treatment reevaluated? Should antibiotic time-outs be implemented, and if they are, are they adhered to? How often are unnecessary and duplicate therapies being prescribed? How can inpatient facilities work with outpatient facilities to coordinate patient care?

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Compliance

As healthcare organizations and governments hone their focus on the challenge of antibiotic resistance and implementation of ASPs, compliance requirement considerations are already in development. For example, since 2016, the Centers for Medicare and Medicaid Services (CMS) has required long-term care facilities to update their infection prevention programs, including the appointment of a designated person in charge of them. Requirements have since been expanded to include ASP protocols and monitoring of antibiotic use. CMS has also proposed an infection control conditions-of-participation rule that requires ASPs in all acute care and critical access hospitals, approval of which is pending. And, in 2017, the Joint Commission Antimicrobial Stewardship Standard began requiring hospitals, critical access hospitals and nursing facilities to implement ASPs and form multidisciplinary teams, which include IPs, to oversee them.

The success of ASP will ultimately depend on leadership commitment, its trickle-down effect and the execution of sound collaboration and the distillation of data at the patient level. ❖

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Update on Anaphylaxis

Responding to the growing number of people affected by food allergy anaphylaxis, researchers are seeking ways to reduce the risk and severity of this condition.

By Diane L.M. Cook

IN THE LAST decade, the number of cases of anaphylaxis has dramatically escalated in the United States. According to an article titled “Trends in Emergency Care for Anaphylaxis,” between 2008 and 2016, emergency department visits for anaphylaxis increased 1.9-fold among adults and 3.2-fold among children.¹ The U.S. Food and Drug Administration (FDA) estimates food-induced anaphylaxis results in 30,000 emergency room visits, 2,000 hospitalizations and 150 deaths each year.² And, while eliminating anaphylaxis is unlikely despite studies to determine its triggers, researchers are pursuing methods of reducing the risk posed by this allergic reaction.

What Is Anaphylaxis?

Anaphylaxis is an extreme, sometimes life-threatening allergic reaction to an antigen such as food (milk, eggs, fish, shellfish, tree nuts, peanuts, wheat or soybeans), drugs (penicillin, aspirin, ibuprofen or anesthesia), insect bites (bees, wasps, hornets, yellow jackets or fire ants) or latex (disposable gloves, intravenous tubes, syringes, adhesive tapes or catheters) to which the body has become hypersensitive. Food allergy is the most common culprit of anaphylaxis.

When a severe, life-threatening reaction to an allergen occurs, symptoms usually present within five minutes to two hours after contact with the allergen. Symptoms generally affect two or more of these body systems:³

- Skin: hives, swelling (face, lips, tongue), itching, warmth, redness
- Respiratory: coughing, wheezing, shortness of breath, chest pain/tightness, throat tightness, hoarse voice, nasal congestion or hay fever-like symptoms (runny itchy nose and watery eyes, sneezing), trouble swallowing
- Gastrointestinal: nausea, pain/cramps, vomiting, diarrhea
- Cardiovascular: paler than normal skin color/blue color, weak pulse, passing out, dizziness or light-headedness, shock
- Other: anxiety, sense of doom (the feeling that something bad is about to happen), headache, uterine cramps, metallic taste

Allergic reactions among people vary from mild to severe to anaphylactic, and people may not react the same way twice. Reactions typically follow a uniphasic course (peaking within 30 minutes to one hour after symptoms appear and resolving either spontaneously or with treatment within the next 30 minutes to one hour). However, 20 percent will be biphasic (having a



recurrence of anaphylaxis after appropriate treatment). When a biphasic reaction occurs, the second phase usually occurs after an asymptomatic period of one hour to eight hours, but there may be a 24-hour delay. Protracted anaphylaxis (a recurrence of anaphylactic symptoms several hours after successful treatment in the absence of a new exposure to a triggering antigen) may persist beyond 24 hours.⁴ In rare cases, anaphylaxis can be fatal.

Diagnostic Criteria

Symptoms of anaphylaxis vary and can be difficult to recognize. People who experience one of three of the following conditions may be having an anaphylactic reaction: symptoms within minutes to several hours after coming into contact with an allergen, two or more of the typical symptoms of anaphylaxis and a drop in blood pressure.

Allergies can be diagnosed by an allergist or an immunologist with a skin prick test, an oral food challenge (OFC), an OFC with naked milk and egg products, and/or specific IgE (sIgE) testing and allergen-specific IgG testing. Test results can differentiate between a sensitivity and a true allergy.⁵

Causes of Food Allergies

According to the National Institute of Allergy and Infectious Diseases (NIAID), food allergies develop when a person consumes or comes into contact with an allergen, and the immune system makes an antibody called immunoglobulin E (IgE), which circulates through the blood and attaches to immune cells called mast cells and basophils. While this initial exposure does not cause an allergic

reaction, subsequent contact with the same allergen may allow previously created IgE antibodies to recognize it, which can then launch an immune response that can result in a severe allergic reaction. However, some people make IgE antibodies against certain foods without developing an allergy, while others still may develop only a mild allergy compared to those who experience severe reactions.⁶

In the United States and other parts of the developed world, food allergy has been growing in prevalence.⁷ According to a recent survey, more than 10 percent of U.S. adults (more than 26 million people) are estimated to have a food allergy.⁸

Risk Factors for Anaphylaxis

Certain people are more at risk for food allergies than others. Risk factors include:³

- Age: Food allergy is more common in young children than in older children or adults.
- Family history: A person is more likely to have a food allergy if his or her parent or sibling has one.
- Another food allergy: An individual who has a food allergy is at greater risk for developing another.
- Related medical conditions: A person's risk is increased if he or she has an allergic disease such as asthma, eczema or hay fever.

Although a severe or fatal anaphylactic reaction can happen at any age, teenagers and young adults with food allergies are at highest risk of fatal food-induced anaphylaxis. And, individuals with food allergies who also have asthma may be at increased risk for severe or fatal food allergy reactions.⁹



Food allergy typically occurs with comorbid conditions. For instance, food-allergic children are two times to four times more likely than those without food allergies to have related conditions such as asthma (4.0-fold), atopic dermatitis (2.4-fold) and/or respiratory allergies (3.6-fold).⁵

Treating Anaphylaxis

Current prevailing treatments for anaphylaxis are to prevent it by avoiding triggers and to administer epinephrine as soon as symptoms present if an anaphylactic reaction occurs. Doctors also strongly recommend patients who have experienced an anaphylactic reaction be transferred to a hospital for further treatment, including observation for biphasic or protracted anaphylaxis.

While there is no cure for food allergy or anaphylaxis, some experimental immunotherapies might decrease symptoms in people with food allergies, thereby reducing the risk or severity of a reaction.

Current prevailing treatments for anaphylaxis are to prevent it by avoiding triggers and to administer epinephrine as soon as symptoms present if an anaphylactic reaction occurs.

According to Food Allergy Research and Education (FARE), the world's largest private funder of food allergy research, which has invested more than \$90 million to study allergic reactions and discover life-changing treatments, three types of immunotherapy to treat food allergies have made significant progress in human clinical trials:

- 1) Oral immunotherapy in which the allergen is eaten;
- 2) Sublingual immunotherapy in which the allergen is placed under the tongue; and
- 3) Epicutaneous immunotherapy in which the allergen in a dermal patch is applied to the skin.

A fourth type of immunotherapy, subcutaneous immunotherapy (SCIT), has made less progress in clinical trials, but, more recently, new efforts are underway to develop safer SCIT methods.¹⁰

Ongoing Research

Nurry Hong, FARE's chief of strategy and innovation, explains the current research landscape for anaphylaxis: "There are many ways to potentially prevent the onset of severe anaphylaxis, including food allergy. The two primary approaches being tried can be generally segmented into two buckets. Bucket one is to disrupt the specific mechanisms that are involved in causing an anaphylactic reaction. And, bucket two is to modulate the body's immune system to try and regulate the underlying causes that lead to an IgE-mediated condition.

"There is a growing drug pipeline in bucket one disrupting the mechanisms of anaphylaxis. The leader is Xolair (omalizumab), which is an anti-IgE molecule already on the market and approved for asthma and urticaria. Xolair is being developed now for food allergy. The success of Xolair is creating a growing pipeline of alternative ways of inhibiting IgE. Essentially, there is interest to develop a better drug profile than Xolair. Researchers are looking at both IgE and non-IgE mechanisms. In the latter category, the emerging targets are various receptors on mast cells that may inhibit their function, as well as various mechanisms that have been used in other diseases, including cancer. Siglecs [sialic acid-binding immunoglobulin-type lectins] are a popular type of receptor on mast cells being targeted, but there are other cell types and receptors also being researched.

"In bucket two, in modulating the body's immune system, there is a lot of activity going on within atopic disease. There is a common underlying immune response in all of these conditions (Th2 response), which share some similar characteristics. Based on our knowledge across these diseases, there is a growing pipeline trying to treat these conditions with either monotherapy or combination drug therapies. The classes of therapies include immunotherapy, biologics, microbiome-based therapeutics and various small molecule drugs.

"There are many targets that are emerging. Immunotherapy has been available for many years, but is just emerging as an FDA-regulated therapy for food allergy. Biologics targeting various immune-regulating cytokines are another big class emerging (anti-IL-4, IL-13, IL-5, IL-33, IL-25 and TSLP, among others). Researchers are also trying to identify ways to 'upregulate' the immune system so the body can defend and retrain itself to the antigen to be nonresponsive. Microbiome plays a role in this latter category, as do other novel targets being explored."

Scientists are in the very early stages of conducting novel research on receptors being investigated for their ability to inhibit histamine release. Preliminary research shows certain receptors inhibit the rapid release of inflammatory mediators such as histamine, prostaglandins, leukotrienes, tryptase and cytokines, which could potentially reduce the risk and severity of anaphylactic reactions.

Recent research also shows engagement of a mast cell

inhibitory receptor can block human mast cell allergic activation and protect mice from anaphylaxis. Anti-siglec-8 antibodies are in clinical trials for various diseases, including mast cell diseases. Following are results of several recent research projects on the receptors siglec-3 and siglec-8 and the enzyme Bruton's tyrosine kinase (BTK):

- According to a recent study conducted on siglec-3, scientists demonstrated liposomal nanoparticles bearing an allergen and a high-affinity glycan ligand of the inhibitory receptor CD33 profoundly suppressed IgE-mediated activation of mast cells, prevented anaphylaxis in mice with mast cells expressing human CD33, and desensitized mice to subsequent allergen challenge for several days. The results demonstrated the potential of exploiting CD33 to desensitize mast cells to provide a therapeutic window for administering allergen immunotherapy without triggering anaphylaxis.¹¹

- In another recent study conducted on siglec-8 (AK002), results showed AK002 selectively evokes potent apoptotic and antibody-dependent cellular cytotoxicity activity against eosinophils and prevents systemic anaphylaxis through mast cell inhibition.¹²

- In a study on potential applications of BTK inhibitors for the prevention of allergic reactions, the scientists explain that BTK is an enzyme located downstream of Fc ϵ RI and is essential for Fc ϵ RI-mediated activation of mast cells and basophils. According to the scientists, the importance of BTK in mediating systemic allergic responses is demonstrated by earlier studies showing BTK-deficient mice have impaired anaphylaxis in a model of passive cutaneous anaphylaxis.¹³

- Research shows drugs that target the BTK enzyme are very effective at blocking anaphylaxis. Currently, there are two FDA-approved BTK inhibitors for use in humans — ibrutinib and dasatinib — that are used to treat cancer. There are also three other BTK inhibitors in development — acalabrutinib, zanubrutinib and PRN1008 — currently in clinical trials.¹³

- A study on the potential applications of BTK inhibitors for the prevention of allergic reactions provided encouragement for the concept that BTK inhibitors can inhibit or reduce the severity of anaphylactic reactions.¹³

Future Outlook

Although scientists might not discover a cure or preventive therapy for anaphylaxis or food allergy, they are optimistic they will discover therapies in the future that will reduce the risk or severity of anaphylaxis.

“We are very hopeful that there will be many more options to treat conditions with IgE-mediated anaphylaxis both to stop the specific mechanisms involved but also to better retrain the immune system to be less desensitized,” says Hong. “We believe the future will require many different mechanisms and

combinations of therapies to treat all patients. There will not be one solution that works for all, or at least that would not be a realistic expectation. Our hope is that immunotherapy for food allergy continues to proliferate, providing an option to achieve a baseline of protection.

“Xolair or other anti-IgE therapies should get approved in the next wave of innovations for food allergy (they are already available for other diseases), along with various biologics targeting key immune functions like IL-4. We believe there is a way to improve on therapy where some patients may be able to achieve relearned tolerance or effectively are nonreactive for sustained periods of time. The research is starting to emerge to potentially make treatment much more effective than what is available today.

“However, we still have a lot to learn about IgE-mediated anaphylaxis. The known mechanisms and targets are only the beginning, and we will elucidate even more targeted approaches to safely stopping anaphylaxis in the future.”

Looking ahead, researchers will continue the pursuit of preventive therapy for anaphylaxis, as well as its major cause: food allergy. Lowering the risk and decreasing the severity of anaphylaxis would greatly reduce the high numbers of emergency room visits, hospitalizations and deaths that occur each year from this life-threatening condition. ♦

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Myths and Facts: **Bipolar Spectrum Disorder**

A great deal of stigma surrounds this disorder due to a misunderstanding of what it is and how effectively it can be treated and managed.

By Jim Trageser



A DISEASE DEFINED by its symptoms rather than by the underlying cause, bipolar spectrum disorder refers to a family of classifications used to describe abnormally changing moods that include both highs (manic) and lows (depression). The disorder can range from mild symptoms that do not interfere with a person's ability to function in daily life to a deeply debilitating condition that in extreme cases requires hospitalization to effectively treat.

While the specific causes behind bipolar disorders aren't precisely known, the symptoms are well enough described that an accurate diagnosis can be made in nearly all cases. Common symptoms that may lead a physician to make a diagnosis of a bipolar spectrum disorder are bouts of depression alternating with periods of mania (high energy). This is distinct from what is referred to as unipolar depression, also known as major depressive disorder, in which there are no manic episodes.

Symptoms of what we today call bipolar spectrum disorder were first noted in the first century AD by Greek physician Aretaeus of Cappadocia.¹ However, his belief that these seemingly disparate symptoms shared a common cause did not become widely accepted until the mid-19th century. In 1854, a rough approximation of our modern understanding of the disease was separately described by French physicians Jules Baillarger and Jean-Pierre Falret as “dual-form insanity” and “circular insanity,” respectively. A half-century later, German psychiatrist Emil Kraepelin differentiated bipolar disorder from schizophrenia based on its episodic nature, coining the term “manic-depressive psychosis.”² But, it was only in the 1960s that manic-depressive disease was itself differentiated from depressive psychosis — giving us our contemporary model of bipolar vs. unipolar disorders.

While there is no cure for bipolar spectrum disorder, with modern treatment options, most patients can lead productive, healthy lives. Symptoms can be controlled or decreased via medication, and patients can learn proven coping mechanisms to help them navigate the emotional swings that accompany a bipolar disorder.

One stumbling block that keeps many patients from seeking treatment from their physician, though, is the continuing prevalence of many myths and misconceptions still associated with bipolar disorder, leading to the condition a stigma that many patients want to avoid.

Separating Myth from Fact

Myth: Bipolar syndrome is an extremely serious mental illness.

Fact: While some patients obviously exhibit more serious symptoms than others, Amit Anand, MD, of the Cleveland Clinic points out: “We have learned over the last few decades that milder forms of bipolar disorder are much more common. Most people with bipolar disorder live in the community and may never be admitted to a psychiatric hospital.”²

Myth: Bipolar disorder is a single condition.

Fact: The disease is properly known as bipolar spectrum disorder, a description of a range of similar conditions of varying severity. Four distinct types of bipolar disorder are currently recognized:³

- **Bipolar I:** With this disorder, manic episodes last a week or longer, coupled with multiple episodes of major depression; or symptoms are debilitating to the point hospitalization is required. During manic episodes, patients may engage in risky behavior. Serious cases may involve hallucinations or breaks from reality during a manic episode.

- **Bipolar II:** This is similar to bipolar I, but manic episodes are not as pronounced (hypomania). It is not a milder form of bipolar I, but rather a separate related condition.⁴

- **Cyclothymic:** With this type, numerous manic and depressive episodes occur over a period of two years, but the episodes are not severe enough to warrant a diagnosis of bipolar I or II.

- **Unspecified bipolar disorders:** Symptoms of these disorders do not match any of the other three definitions.

Myth: Researchers know the cause of bipolar spectrum disorder.

Fact: To date, scientists do not know what exactly causes bipolar spectrum disorder. Studies indicate it is likely a combination of factors: family history, brain structure, emotional distress and/or substance abuse.⁴ Genes play a role, but in roughly 20 percent of identical twins, one may have bipolar disorder while the other does not, so genetics are clearly not the sole determining factor.³

While there is no cure for bipolar spectrum disorder, with modern treatment options, most patients can lead productive, healthy lives.

Researchers continue to search for the combination of risk factors and triggers that can lead to the onset of bipolar disorder in the hope understanding the cause may lead to a cure or even prevention.

Myth: Bipolar disorder is a “fake” disease, a handy excuse for people who don't want to deal with their mood swings.

Fact: According to the National Institutes of Health, “Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels and the ability to carry out day-to-day tasks.”³ Those suffering from

bipolar disorder are often unable to adequately function during an episode, whether it is manic or depressive. The disorder costs, on average, more than 65 lost work days annually per patient in the United States, or about a 25 percent drop in productivity per patient in an average year.⁵

According to the National Institutes of Health, “Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels and the ability to carry out day-to-day tasks.”

In some instances, those with bipolar I may suffer psychosis during a manic episode, and may require hospitalization to prevent them from causing harm to themselves or others. A manic or hypomanic episode will feature at least three of these symptoms:⁴

- Overly energetic or anxious
- Abnormally upbeat
- Lowered need for sleep
- Racing thoughts
- Difficulty focusing or concentrating
- More talkative than normal
- Overly risky behavior

A major depressive episode will include many of these symptoms:⁴

- Feeling helpless
- Decreased energy
- Sleeping more than normal
- Heightened sense of guilt
- Lower self-esteem
- Indecisiveness
- Fixation on death or suicide
- Unexplained weight loss or weight gain

A diagnosis of a bipolar disorder follows very clearly delineated criteria. And, when properly diagnosed, the disease responds positively to treatment. A physician who suspects bipolar disorder will work with a patient to answer the following questions:

- Have you experienced any episodes as described above?

- Is there a family history of bipolar disorders?
- How much alcohol or other drugs do you use?

A physical exam will be ordered to look for any other possible causes of symptoms such as a thyroid condition.⁶ A referral to a psychiatrist will also generally be made to further explore the patient’s symptoms and possible underlying causes.

Myth: It is easy for doctors to determine if a patient has a bipolar disorder.

Fact: It can take several months or longer to arrive at a definitive diagnosis. Making a diagnosis of a bipolar disorder is as much a process of elimination as discovery. Whenever a physician suspects the possibility of a bipolar disorder, the first order of business is to look for other causes of symptoms. Once those have been eliminated, the doctor and patient can begin looking for confirmation of a bipolar disorder.

While there is no single test to diagnose a bipolar disorder, protocols are well-established and described in *Diagnostic and Statistical Manual of Mental Disorders* published by the American Psychiatric Association.

After a physical and a family history have been conducted and no other cause for symptoms has been discovered, a physician will request a patient keep a mood diary, making daily note of moods for weeks or even months. And, family members and friends may, with the patient’s approval, be asked about their observations of any mood changes.

Bipolar I and II diagnoses are fairly straightforward due to their distinctive manifestation of symptoms; the other subsets can be more challenging to differentiate from related illnesses such as attention deficit hyperactivity disorder and borderline personality disorder.⁷

In addition, many bipolar disorder patients also suffer from other physical or mental ailments, with anxiety disorders and substance abuse among the top concurrent afflictions, which can make it more difficult to isolate the specific cause of symptoms.³

Myth: Bipolar disorder is very common.

Fact: Most studies indicate less than 5 percent of the population suffers from a bipolar disorder at any point in their lives.³ During any one year in the United States, approximately 2.8 percent of the population has a bipolar disorder. There is little difference between genders or among age or ethnic groups.⁸

However, among those diagnosed with a bipolar disorder, 82.9 percent were assessed as having a serious impairment — the highest of any mental illness.³ Yet, it is also known those with milder forms are less likely to seek medical help, request a diagnosis or accept treatment, so it is likely this statistic is skewed since those with more serious cases are the most likely to seek treatment and be diagnosed.⁷

Myth: Bipolar disorder cannot be effectively treated.

Fact: While there is no cure for bipolar disorder, most cases can be effectively treated. Mood stabilizers can help prevent or lessen

episodes of mania and depression, psychotherapy can provide the tools needed to more successfully manage symptoms, and lifestyle changes such as exercise and diet can assist in managing symptoms.

Lithium is the most common mood stabilizer, which has been used to treat bipolar disorder since the 1950s. It is a long-term maintenance treatment, and it is only effective when consistently used — particularly between episodes when patients feel fine and may think they don't need medication. Other mood stabilizers include valproic acid, carbamazepine and lamotrigine, all of which are anticonvulsants originally developed to treat epilepsy but later discovered to be effective in treating bipolar disorder.⁶

When mood stabilizers are not able to prevent a depressive or manic episode from occurring, the specific symptoms of an episode may be treated with secondary drugs. For instance, antipsychotics can be used during manic episodes, and may include aripiprazole, olanzapine, quetiapine or risperidone. During depressive episodes, antidepressants may be prescribed, but care must be taken since many bipolar disorder patients react differently to antidepressants than do those suffering from other types of depressive disorders.

While medications can help tremendously in evening out episodes of bipolar disorder, they are always used in conjunction with psychotherapy. In fact, therapy is a main component of any treatment regimen for bipolar disorder. Working with patients to help them identify triggers, establish regular routines for sleep and exercise, and manage their emotions can assist in leveling some of the highs and lows.³ Family therapy can also provide patients' loved ones with support and help them understand the disorder.

Myth: Young people do not develop bipolar disorders.

Fact: The percentage of young people developing bipolar disorders is similar to adults: about 2.9 percent. Statistically, among teens, girls are slightly more likely to develop a bipolar disorder than are boys (3.3 percent vs. 2.6 percent).⁹

There are some other differences between younger bipolar disorder patients and adults. Adults tend to endure more depressive episodes than do children or teens,¹⁰ and adolescents are more likely to have a bipolar disorder in conjunction with another condition such as attention deficit hyperactivity disorder.

Myth: Bipolar disorder patients have regular cycles of mania and depression.

Fact: Episodes of mania and depression are irregularly timed and often chaotic, and they may even overlap.²

Myth: Artistic personalities with a bipolar disorder will lose their creativity if treated.

Fact: Best-selling author Marya Hornbacher was told this myth when she was diagnosed with a bipolar disorder. However, once she began treatment, she found her ability to maintain focus and a work discipline improved tremendously, with no loss of creativity. "I was very persuaded I would never write again when

I was diagnosed with bipolar," she wrote. "But before [being diagnosed], I wrote one book; and now, I'm on my seventh. When I was working on my second book, I was not yet treated for bipolar, and I wrote about 3,000 pages of the worst book that you have ever seen in your life. And then, in the middle of writing that book, which I just somehow couldn't finish because I kept writing and writing and writing, I got diagnosed and I got treated. And the book itself, the book that was ultimately published, I wrote in 10 months or so. Once I got treated for my bipolar, I was able to channel the creativity effectively and focus."¹¹

Myth: Bipolar patients are always either on a high or a low.

Fact: Most bipolar patients will go through long periods of calm without any episodes.¹¹ And, those being treated with mood stabilizers are even more likely to have significant stretches with no episodes.

Dispelling the Myths Now

Given the high risk of attempted suicide associated with bipolar disorder — 33 percent of bipolar I and 36 percent of bipolar II patients¹² — the importance of physicians proactively discussing mood disorders with their patients and working with them to accurately diagnose and treat any symptoms cannot be overstated.

Studies reveal many patients are wary of asking for help dealing with mood disorders for fear of being stigmatized. They may fear ridicule, social isolation or loss of employment. For those who may worry about a mood disorder but resist exploring their symptoms, numerous advocacy organizations can help them learn more about bipolar spectrum disorder and the options available to them, including:

- Depression and Bipolar Support Alliance: dbsalliance.org
- International Bipolar Foundation: ibpf.org
- International Society for Bipolar Disorders: isbd.org ♦

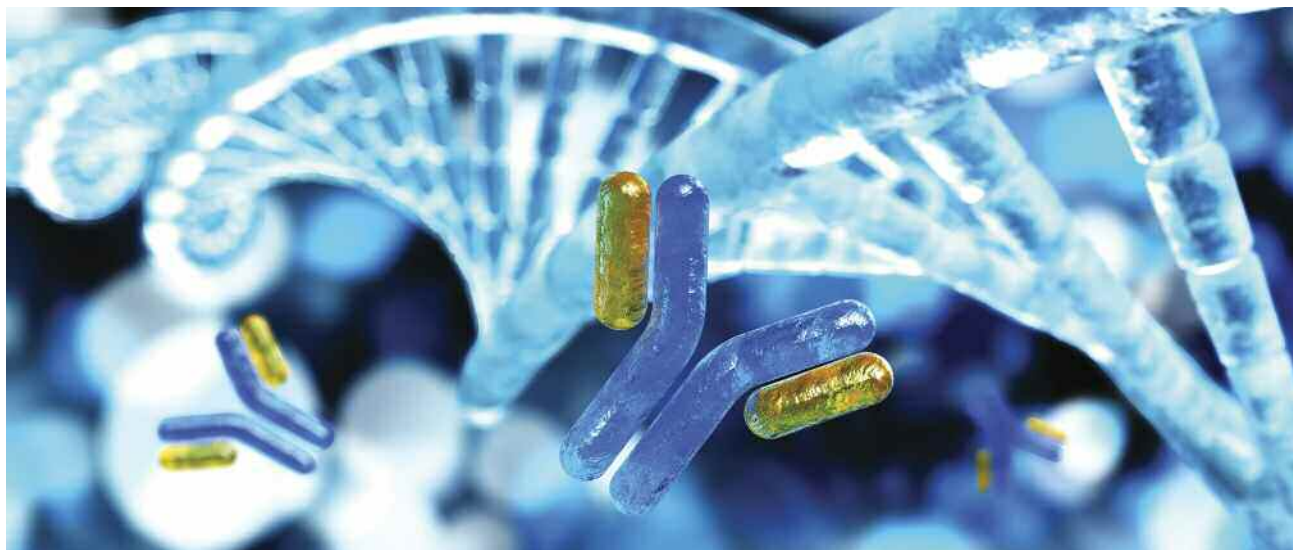
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Secondary Antibody Deficiency: A Key Driver of IG Demand

By Keith Berman, MPH, MBA



THE FIRST POLYVALENT intravenous immune globulin (IVIg) product was approved in the U.S. for treatment of primary humoral immunodeficiency disorders (PI) in 1981. Nearly four decades later, PI still accounts for more than 20 percent of the nearly 90 million grams of IVIg and subcutaneous IG (SCIG) administered in the U.S. last year,^{1,2} as newly identified cases continue to add to the PI patient population on chronic IgG replacement therapy.

Similarly, the efficacy of IVIg therapy for several autoimmune neuropathies — chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, myasthenia gravis and Guillain-Barré syndrome — was documented in numerous studies in the 1980s and 1990s.^{3,4,5,6} Human IG preparations have been standard therapy for these disorders, which collectively account for about 40 percent of total IG usage, for many years.

But as long as new patients starting on treatment outnumber those who discontinue therapy, growth in IG utilization for these disorders is likely to continue.

Much the same applies for most significant autoimmune hematologic, dermatologic and rheumatologic diseases for which IG has been part of the standard treatment armamentarium for many years. However, for many of these disorders — examples include Kawasaki disease, immune thrombocytopenic purpura, pemphigus/pemphigoid and antirejection therapy for solid organ or hematopoietic stem cell transplantation (HSCT) — patients typically require just one or perhaps a few courses of IG treatment. Consequently, the contribution of these typically rare conditions to growth in IG utilization tends to be relatively modest, as there is no chronically treated patient “base” on which demand builds year after year.

All of this has raised an intriguing question for IG product manufacturers tasked with forecasting future demand to decide how much to invest in costly new plasma collection and processing capacity. Since PI and autoimmune neuropathy, which collectively comprise around 60 percent of the IG market, are “maturing” indications for IG therapy, and IG usage growth is limited for most other rare, short-term IG clinical applications, how do we account for nearly 8 percent average annual growth in demand for IG products over the last five years? To put it into clearer perspective, year-over-year IG demand has now reached 7 million grams, more than double the annual growth rate of about 3 million grams just a decade ago.

Several lines of evidence point to the emergence of an important new contributor to IG demand growth: secondary or “acquired” hypogammaglobulinemia associated with potent immunosuppressive

drugs and cytotoxic B cell-targeted biologics now in common use to treat hematologic malignancies, as well as other hematologic and immune-mediated disorders.

Acquired Secondary Antibody Deficiency (SAD) in Hematological Disease

Hypogammaglobulinemia and serious infections secondary to intrinsic disease and/or immunosuppressive drug therapy is a leading cause of death in patients with B cell chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL) and plasma cell myeloma (multiple myeloma). Early studies in the 1980s showed prophylactic IVIG can significantly reduce the incidence of major infection in high-risk CLL and plasma cell myeloma patients, but subsequent analyses of these findings did not support a survival benefit or overall improved quality of life when taking into consideration the increased prevalence of IVIG-related adverse events.^{7,8} Existing practice guidelines recommend IVIG therapy only for hypogammaglobulinemic patients with recurrent bacterial infections and documented failed antibody response against diphtheria, tetanus or pneumococcal vaccines.⁹ Historically, prophylactic IVIG has been selectively prescribed for these hematologic malignancies, and until very recently had been estimated to account for little more than 5 percent of U.S. IG demand.¹

Then, in 1997, the U.S. Food and Drug Administration approved rituximab (Rituxan), a cytolytic mouse/human monoclonal antibody that targets the CD20 antigen present on all peripheral B cells, for relapsed or refractory low-grade or follicular CD20+ B-cell NHL. Rituximab is now indicated for treatment of essentially all B-cell malignancies, including B-cell CLL, as well as for several autoimmune disorders, including granulomatosis with polyangiitis, pemphigus vulgaris and rheumatoid arthritis. New

combinations of immunosuppressive drugs and rituximab continue to be investigated to identify the most optimal treatment regimens for CLL and for follicular, mantle cell, diffuse large B cell and NHLs; well over 200 clinical trials are currently evaluating rituximab in the U.S. and internationally.

protective effect of IG replacement therapy has been documented in patients with hematological malignancies accompanied by iatrogenic SAD. Below are examples of studies assessing the value of IG in patients with CLL and NHL:

- Of 132 CLL patients enrolled in a study evaluating ibrutinib, a tyrosine

“Year-over-year IG demand has now reached 7 million grams, more than double the annual growth rate of about 3 million grams just a decade ago.”

Repeated treatment courses and maintenance therapy with rituximab and other potent anti-B cell agents can prolong the duration of remission and the time between relapses. However, they have been shown to be frequently associated with sustained hypogammaglobulinemia and ablation of a functional antibody response to vaccine challenge. Usually co-administered or sequentially administered with other cytotoxic drugs, repeated or long-term rituximab in particular can result in both a variably lower serum IgG concentration and an impaired proliferative B cell response to microbial attack. As the treatment duration is extended and/or as the disease becomes more advanced, the hypogammaglobulinemia defect tends to worsen, increasing the risk of septicemia, cellulitis and serious infections of the respiratory and urinary tract.¹⁰ The hypogammaglobulinemia and recurrent infections commonly seen in patients treated with B cell-depleting therapies have been characterized as a “common variable immunodeficiency (CVID)-like clinical and immunologic phenotype.”¹¹

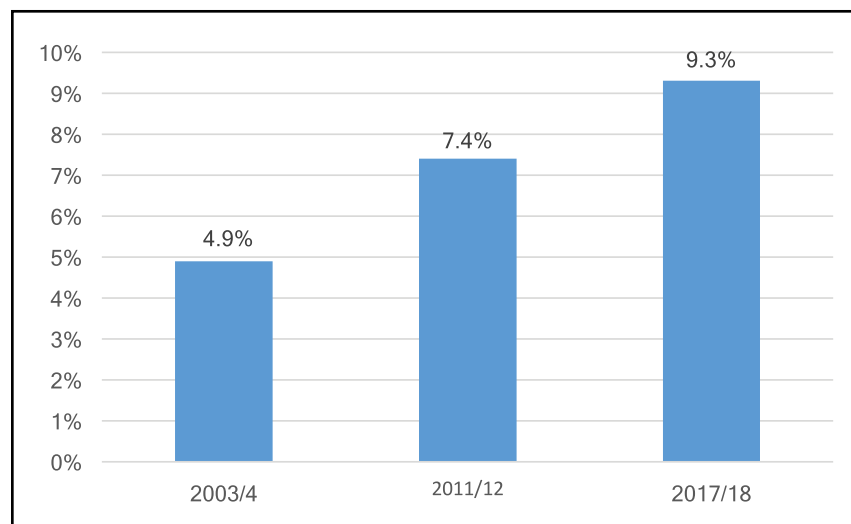
As with CVID and other PIs, the

kinase inhibitor, IVIG supplementation was administered in 16 percent of previously treatment-naïve participants, and in 53 percent of patients with advanced disease and those receiving rituximab.¹²

- In a large series of 211 NHL patients treated with rituximab, de novo hypogammaglobulinemia developed in 39 percent of those whose serum IgG level was previously normal, while it was exacerbated in 72 percent of those who had baseline hypogammaglobulinemia. Exposure also to fludarabine or other purine analogue was associated with increased risk of developing hypogammaglobulinemia. Patients who received rituximab as maintenance therapy had a higher likelihood of developing hypogammaglobulinemia than those receiving it as immunotherapy (54 percent vs. 33 percent). Of the 14 patients who required IVIG, 11 (79 percent) received multiple courses of rituximab, whereas just three patients (21 percent) received IVIG after only one course.¹³

In addition to rituximab, there are now several other licensed anti-CD20 monoclonal antibodies, each of which targets

Figure 1. Percentage of IG Administered for Treatment of Secondary Antibody Deficiency in Four Eastern Provinces in Canada, 2003/4 to 2017/18



a different B cell epitope. Ofatumumab (ARZERRA) is approved for the treatment of previously untreated CLL, obinutuzumab (GAZYVA) for the treatment of CLL and follicular lymphoma, and tositumomab (BEXXAR) for the treatment of NHL, including patients with rituximab-refractory NHL. As with rituximab, the labeling for these products includes warnings about risks of serious infections.

SCIG as an IgG Replacement Alternative

IVIG has historically been the standard IG replacement therapy for hypogammaglobulinemia secondary to B cell lymphoproliferative disorders. However, the same advantages that make SCIG administration popular for qualifying patients with PI — a lower rate of systemic adverse events, lower overall cost of care and improved health-related quality of life^{14,15} — may apply as well for patients with SAD who require prolonged IgG replacement therapy.

In a recent retrospective review of patients with lymphoproliferative disorders

(B cell CLL and NHL), Italian investigators documented similarly low rates of serious and overall bacterial infections with either IVIG or SCIG treatment. But systemic reactions, in particular fever (33 percent vs. 7 percent) and dyspnea (9 percent vs. 0 percent), were less frequent in those receiving SCIG. Premedication was required in 17 of 33 patients receiving IVIG, compared to one of 61 patients receiving SCIG. Most patients who shifted from IVIG to SCIG reported improved quality of life in their questionnaire responses. Tellingly, just two of 33 patients who were crossed over to SCIG returned to IVIG therapy.¹⁶

For some patients there is yet another very tangible benefit with SCIG use beyond the advantages of time-flexible, home-based self-infusion: avoidance of venous access problems that are often a major concern in patients treated with chemotherapy. SCIG infusion can potentially obviate the need to surgically place central and peripheral venous access devices for IVIG infusions, thus reducing the risk of access-related bloodstream infections.

A Growing Piece of the IG Usage Pie

Several reviews cited in this article support the presumption that SAD is an important contributor to growing IG demand, both here in the U.S. and internationally. Population-based longitudinal IG utilization data that might verify and provide a sense of the magnitude of its contribution are not available for the U.S., but our Canadian neighbors have systematically captured and reported diagnosis-specific IG utilization in four eastern provinces,* with a population exceeding three million lives, for well over a decade.

Figure 1 identifies the percentage of IG provided for SAD disorders over a six-month baseline period from Oct. 1, 2003, to March 31, 2004, in four eastern Canadian provinces,¹⁷ and again over one-year periods in fiscal 2011/12 and 2017/18. While IG prescribing patterns in this limited population does not necessarily reflect U.S. prescribing patterns, the direction over time is still instructive: As a share of all IG directed to patients, IG for patients with SAD nearly doubled from 4.9 percent in 2011/12 to 9.3 percent in 2017/18.^{18,19}

Australia, a country with per capita IG usage similar to the U.S., also tracks its utilization of IG by diagnostic categories. According to single-month data for August 2019 (Figure 2),²⁰ “acquired hypogammaglobulinemia,” including patients with hematological malignancies and those post-HSCT, accounted for nearly 24 percent of IG utilization nationwide. All other patients with secondary hypogammaglobulinemia accounted for more than 4 percent of IG usage, for a combined total of 28 percent.

Remarkably, the number of grams of IG administered to Australians for acquired or secondary hypogammaglobulinemia in August 2019 was 2.5-fold larger than the

* The Atlantic provinces of Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and New Brunswick.

number of grams administered for all PIs. Medical practice patterns in Australia and the U.S. undoubtedly differ; Australia's National Blood Authority has defined detailed patient eligibility criteria for IG access, while in the U.S., patient eligibility for IG is conditional on individual coverage policies of hundreds of health insurers. Nevertheless, the Australian experience strongly implies SAD now accounts for a considerable share of total IG usage here in the U.S.

Other Disorders That May Boost Need for IG

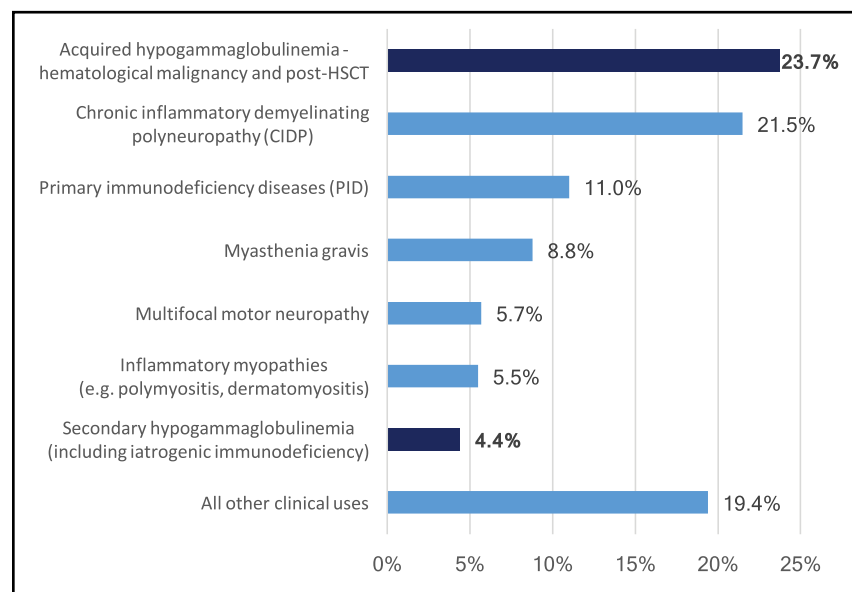
Already estimated to be 30 times more common than PI, the prevalence of treatment-induced SAD can be expected to increase going forward. In addition to CLL, lymphomas and plasma cell myeloma, an ever-expanding number of new B cell-targeted biological response modifiers and other immunosuppressive therapies are in use or are being evaluated as primary or maintenance therapy for a range of other clinical disorders, including:²¹

- Acute and chronic myeloid leukemia
- Myelodysplastic syndrome
- Waldenstrom macroglobulinemia
- Post-hematopoietic stem cell transplant
- Post-solid organ transplant
- Rheumatological disorders (e.g., rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica)
- Neurological disorders (e.g., autoimmune encephalitis, myasthenia gravis, relapsing-remitting multiple sclerosis, neuromyelitis optica)

With the benefits of more aggressive B cell-ablative treatments comes a cost in serious infections and hospitalization. For patients rendered unable to mount a protective IgG antibody response, and for whom antibiotic prophylaxis proves inadequate, prophylactic IG replacement therapy is clearly indicated.

The plasma therapeutics industry is continuously working to expand its production capacity to address this growing demand. Like blood itself, when IG is needed, there is simply no substitute. ❖

Figure 2. Australian Immune Globulin Use in Grams by Clinical Indication, August 2019



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Nichole Howson felt the effects of bipolar disorder when she was a teenager, but it wasn't until she was 20 that she was diagnosed. Fortunately, Nichole got the treatment she needed and is now a successful businesswoman and helps others with the disorder.

SURVIVOR IS the word that comes to mind when describing Nichole Howson. Diagnosed with bipolar disorder at 20 years old, Nichole overcame multiple setbacks and a suicide attempt, and today, she runs a social media marketing company and manages a team of freelancers. In her spare time, Nichole volunteers for nonprofits and teaches free workshops in her local community. She's also the founder of Defying Shadows, a website for mental health bloggers.

BSTQ: How old were you when you suspected you had mental health issues?

Nichole: I was a preteen when it started to show, and I was between 14 years old and 16 years old when I was first diagnosed with anxiety (and depression a few years later). The rest we wrote off as being a "normal teenager." Looking back on certain times of my life, I know I was dealing with a manic episode or severe depression. We cannot change what is in the past, but if we had known I was struggling with bipolar disorder at that time, we would have done many things differently.

BSTQ: At what age were you accurately diagnosed?

Nichole: I was diagnosed when I was 20.

Bipolar Disorder: *A Patient's Perspective*

By Trudie Mitschang

BSTQ: How did living with bipolar disorder affect your relationships?

Nichole: Some of my most strained relationships were a result of my untreated condition. I have to own up for the decisions and actions I have taken, but we know this disorder caused a lot of problems between me and my siblings, family and friends. It still affects my relationships at times, but being self-aware really helps.

BSTQ: What was your original treatment plan, and how has it changed over the years?

Nichole: Medication was the first step. I went through a wellness program that taught me coping skills and techniques. I also went through counseling. My treatment plan is an ongoing process. Right now, it's a combination of counseling, dialectical behavior therapy and medication.

BSTQ: How has counseling helped?

Nichole: I have been in counseling since I was a teen and continue to go on a monthly basis. Counseling doesn't work for everyone, but I find it helpful to talk through my problems, feelings and thoughts. Counseling gives people an outlet to say whatever they need to say without damaging a relationship. It also helps build all sorts of skills such as communication, problem-solving, mindfulness, emotion management and so much more. Finding the right counselor for what a person is dealing with is crucial. I've been to six different counselors and each served a different purpose.

BSTQ: Tell us about when you hit rock bottom and attempted to take your own life. Was there a trigger?

Nichole: The only trigger was not

understanding what was happening to me. I knew something was wrong, but I didn't know what, and I felt like it was my fault. I just wanted it to stop. I didn't have the resources to get help, and I didn't feel like I had any other options.

BSTQ: How did you get your life back on track?

Nichole: With a *ton* of support from my parents, and then my friends. They fought for me when I couldn't fight for myself. I went through the programs and followed the treatment plan, and things started to fall back into place over time.

BSTQ: Do you feel there is still a stigma associated with bipolar disorder?

Nichole: One hundred percent! There are so many common misconceptions around it in the media, so it makes those difficult to debunk when music and movies being produced are inaccurately showcasing what it looks like.

BSTQ: What are your goals and hopes for the future?

Nichole: I just want to keep growing as a person. I want to continue growing my business. And, I want to continue to use my story to help others. If I can help one person, it makes it worth it.

BSTQ: What advice do you have for others?

Nichole: If you feel something is wrong, speak to a medical professional as soon as possible. There are crisis centers and phone helplines available 24/7. Do not feel ashamed of having these emotions or problems. Bottling them up or blowing them off won't help you get better. Do not be afraid to speak out about your disorder. Know that it is not your fault, and nothing you did has caused this to happen to you. ♦



Dr. Sudhakar Selvaraj specializes in treating adult patients with mental disorders, including the severely disabling condition known as bipolar disorder.

SUDHAKAR SELVARAJ, MD, PhD, is an assistant professor in the Department of Psychiatry and Behavioral Sciences at McGovern Medical School at The University of Texas Health Science Center at Houston. He is active in several professional organizations, including the American Society of Clinical Psychopharmacology, Houston Academy of Medicine and more. He has also received several awards and honors throughout his career, including the 2016 Dean's Teaching Excellence Award.

BSTQ: For those not familiar, can you define bipolar disorder?

Dr. Selvaraj: Bipolar disorder is a serious illness characterized by recurrent periods of changes in mood, activity and energy levels, and sleep patterns. At one extreme, individuals may suffer from mania symptoms that include elevated mood or irritable mood, increased activity levels and poor sleep or less need for sleep. With mania, patients may feel they have more energy, and they may feel grandiose about their ability. During periods of depression, individuals may feel sad and tired, and they sleep less or more. There are also cognitive symptoms such as difficulty making decisions and thinking things over again and again. Sometimes, patients may have both of the depression and mania symptoms, called "mixed." Bipolar disorder is a severely disabling condition for many patients for long periods and sometimes many episodes throughout life. Many patients do well with

Bipolar Disorder: *A Physician's Perspective*

treatment and continue to function well and achieve their life potential.

BSTQ: How is bipolar disorder diagnosed?

Dr. Selvaraj: Bipolar disorder is diagnosed mainly based on clinical symptoms and history and an assessment performed in the clinic by psychiatrists or mental health clinicians. Sometimes, the diagnosis may need several visits. Currently, there are no tests available to diagnose bipolar disorder.

BSTQ: What are some barriers to accurate diagnosis?

Dr. Selvaraj: Delays in seeking help with mental health difficulties is a very important barrier to be addressed. Stigma about mental illness, availability of mental health resources, costs, family and social perception are all factors that impact accurate and early diagnosis. Also, many symptoms overlap with other psychiatric conditions such as anxiety, depression, attention deficit hyperactivity disorder, substance abuse, etc. People often experience depression or other symptoms for a longer period before being diagnosed with bipolar disorder. For accurate diagnosis, patients have to be carefully followed for a long period. More research is needed to improve the early and accurate diagnosis of this condition.

BSTQ: Can you tell us about treatment strategies?

Dr. Selvaraj: Education about the illness, involving the patient and family in treatment planning, appropriate choice of medications, and making sure the patient is in a safe place and takes part in treatment are the key points of treatment. For mania symptoms, the standard treatments are use of a mood stabilizer or antipsychotic medication. Lithium is one of the gold standards in treating bipolar disorder since it works for both treating and preventing mania and preventing depression, but it is not as good at treating acute depression.

There are also other drugs used to treat mania, usually antiepileptic drugs such as sodium valproate, carbamazepine and

lamotrigine. Antipsychotic drugs or lamotrigine are increasingly used for treating depression symptoms in bipolar disorder. Traditional antidepressants are only given along with mood stabilizers or antipsychotic medications to reduce the risk of flipping the depression into mania symptoms.

Continuing medication for long periods may be necessary to prevent relapses. And, education about helping to recognize life stressors, developing strategies to cope with stress, maintaining a healthy lifestyle (exercise, sleep hygiene, avoiding excess alcohol use and illegal drug use, etc.) are very important.

BSTQ: What are the newer developments in the treatment of bipolar disorder?

Dr. Selvaraj: A lot of research is being conducted to improve the early diagnosis of this condition in childhood and adolescence. We are beginning to understand how this illness overlaps with many other conditions and how symptom dimensions emerge early in life. Many researchers are interested in the course of early symptoms and are incorporating digital strategies such as using smartphones to monitor symptoms. In addition, smartphone-based apps are improving educational aspects and providing self-help psychological treatments that are improving the ways people seek treatment.

BSTQ: What role does the patient play in a successful treatment plan?

Dr. Selvaraj: The patient's awareness of symptoms and illness and their motivation to get better are vital in the successful outcome of bipolar disorder treatment. Therefore, patients should be involved in decision-making from the beginning to improve their participation in treatment. They need to be comfortable with treatment approaches — not only about medications but also understanding the illness and the ways to reduce the risk of relapses. ❖

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

Supplier Assessment Checklists: A Tool for Vetting Vendors and Contractors

Authors: Christine Oechslein and Cornelia Wawretschek



Supplier Assessment Checklists: A Tool for Vetting Vendors and Contractors includes two checklists — the API and Excipient Supplier Checklist and the Contract Manufacturing and Analysis Checklist — written by two industry experts with more than 30 years of combined experience: Pharmacist Christine Oechslein, who provides internal good manufacturing practices (GMP) training for pharmaceutical companies, manufacturers of active ingredients and suppliers, and Cornelia Wawretschek, a quality assurance consultant, who advises pharmaceutical and biotechnology companies during the development and update of pharmaceutical quality systems. Included in the checklists are how to make sure suppliers are compliant with pertinent GMP regulations and standards; how to determine if their failure investigation processes are adequate; how to assess the training of their personnel; what standard operating procedures to review; and how to evaluate a contract manufacturer that doesn't have a site master file. The checklists can be adapted to meet companies' needs, as well as to form the base of documentation on individual suppliers and contractors.

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Immune-Checkpoint Drugs in Oncology: Analytical Tool

Author: Research and Markets



This handbook is written for business developers, business intelligence/clinical intelligence operatives or clinical developers who need a competitive edge in their immune-checkpoint drug surveillance and intelligence. It covers deals and collaborations; new technologies/drugs (emerging from patents, grants, abstracts, etc.); funding, grants and initial public offerings; filings and approvals; latest clinical trial development and results; newly launched clinical trials; conference coverage of the world's 12 leading meetings in oncology; and quarterly and annual reporting. It comes with one year of online access to twice-weekly updates in both contents and features, pipeline alerts and online support.

www.prnewswire.com/news-releases/oncology-immune-checkpoint-drugs-analytical-tool-300862412.html

Nursing 2020 Drug Handbook

Author: Lippincott



This fourth edition of the drug handbook contains completely updated nursing-focused drug monographs featuring more than 3,700 generic, brand-name and combination drugs in an A-to-Z format; 34 new U.S. Food and Drug Administration (FDA)-approved drugs, including 31 complete monographs tabbed and conveniently grouped in a "new drugs" section for easy retrieval; more than 8,100 clinical updates with new dosages and indications, Black Box warnings, adverse reactions, nursing considerations, clinical alerts and patient teaching information; ISMP-recommended tall-man lettering for look-alike and sound-alike drugs; a special focus on U.S. and Canadian drug safety issues and concerns; and a photoguide insert with images of 455 commonly prescribed tablets and capsules. Also included is a free companion toolkit available online through NDHnow.com that includes monthly FDA updates featuring newly approved drugs, indications and warnings; pharmacology videos, audio pronunciation guide and English-Spanish translator; equianalgesic dosing guidelines for opioid drugs; mechanisms and sites of action graphics for selected drugs; and NCLEX-style questions, free continuing education tests and bonus discounts.

www.amazon.com/Nursing2020-Drug-Handbook-Nursing/dp/1975109260/ref=sr_1_1?keywords=pharmaceutical+references&qid=1571060350&s=books&sr=1-1

The Engaged Caregiver: How to Build a Performance-Driven Workforce to Reduce Burnout and Transform Care

Authors: Joseph Cabral, Thomas H. Lee and Martin Wright

Written by a team of thought leaders with expertise in healthcare workforce engagement and cultural development, *The Engaged Caregiver* shows leaders, managers and frontline providers how to recognize early signs of burnout and turn it around; address staff more effectively to keep them engaged; build strong, reliable teams with a sense of purpose; map their organization's core values and get everyone on board; create a positive culture that's cohesive, inclusive and resilient; develop highly effective leadership and organizational systems; hire, engage and manage talent strategically and successfully; promote diversity, equity and inclusion in the workplace; and leverage data to drive improvements throughout the organization. The guide provides an actionable plan for creating a resilient work culture that empowers caregivers and gives them the support they need to fulfill the patient promise with every care experience, every day.

www.amazon.com/Engaged-Caregiver-Performance-Driven-Workforce-Transform/dp/1260461297/?ef=sr_1_9?keywords=pharmaceutical+references&qid=1571061003&s=books&sr=1-9

Emicizumab Prophylaxis Combined with ITI Effective in Pediatric Patients with Severe Hemophilia A and Inhibitors

Researchers at Emory University have described successful use of a novel treatment regimen, dubbed the “Atlanta Protocol,” that involved concomitant use of Hemlibra (emicizumab) prophylaxis and immune tolerance induction (ITI) to treat pediatric patients with severe hemophilia A and inhibitors. The study group included seven children between 21 months and 12 years of age. This modified treatment strategy combines recombinant factor VIII (FVIII) or plasma-derived FVIII products to manage inhibitor levels, while Hemlibra is prophylactically administered at the same time to prevent or stop bleeding.

Six patients used three different recombinant FVIII products at 100 IU/kg three times per week, and one used a plasma-derived FVIII product at an initial dose of 50 IU/kg three times per week. Over the median 35-week follow-up period, three children experienced no bleeding events, and inhibitors were cleared or reduced to unmeasurable titers (<0.6 Chromogenic Bethesda Units per mL) in three of the seven children. Four others experienced a total of nine bleeding events, but no thrombotic events occurred in any patient.

Six children underwent surgery during the study, with no major complications or excess bleeding during or after surgery. While concluding that “immune tolerance induction while on



emicizumab prophylaxis is a feasible approach in pediatric patients with inhibitors,” the investigators acknowledged prospective studies will be necessary to compare treatment outcomes to standard ITI regimens.

Batsuli G, Zimowski KL, Tickle K, et al. Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis. Haemophilia 2019 Sep;25(5):789-96.

Anti-Influenza Hyperimmune Immune Globulin Not Effective in Hospitalized Adults with Influenza Infection



Encouraged by nonrandomized studies and small clinical trials suggesting convalescent plasma or anti-influenza hyperimmune intravenous immune globulin (hIVIG) might have clinical benefit, a multinational team conducted a randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of hIVIG (in conjunction with standard care) in adults hospitalized with laboratory-confirmed influenza A or B infection.

Patients were eligible if they had a National Early Warning (NEW) score of 2 points or greater at the time of screening, onset of symptoms no more than seven days before randomization, and were expected to be hospitalized more than 24 hours. The investigational hIVIG product was manufactured using high-titer anti-influenza plasma collected either from fractionated whole blood or

by plasmapheresis from U.S. and Canadian volunteers. Donors and plasma units were selected on the basis of increased hemagglutination inhibition antibody titers against contemporary vaccine strains.

In 308 patients enrolled in 34 sites between December 2014 and May 2018, hIVIG treatment produced a robust rise in hemagglutination inhibition titers against influenza A, and smaller rises in influenza B titers. Through 28 days of follow-up, 47 (30 percent) of 156 patients in the hIVIG group and 45 (30 percent) of 152 patients in the placebo group had the composite safety outcome of death, a serious adverse event or a grade 3 or 4 adverse event (hazard ratio 1.06, 95% confidence interval, 0.70-1.60; $p=0.79$).

On the basis of the primary ordinal outcome of clinical status at day seven (ranging in severity from death to postdischarge resumption of normal activities), hIVIG was not superior to placebo for adults hospitalized with influenza infection. In contrast with a negative finding in patients with influenza A, antibody affinity analyses identified a clinical benefit for patients with influenza B, but confirmation is warranted with a further randomized controlled trial.

Davey RT Jr, Fernández-Cruz E, Markowitz N, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. Lancet Respir Med 2019 Sep 30 [Epub ahead of print].

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2020, through March 31, 2020

	Product	Manufacturer	HCPSC	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	\$71.55	\$70.40
	GAMMAGARD SD	Takeda	J1566	\$126.38	\$124.35
	GAMMAPLEX	BPL	J1557	\$92.45	\$90.97
	OCTAGAM	Octapharma	J1568	\$76.43	\$75.21
	PANZYGA	Pfizer	J1599	**	**
	PRIVIGEN	CSL Behring	J1459	\$81.69	\$80.38
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	\$79.84	\$78.56
	GAMMAKED	Kedrion	J1561	\$80.69	\$79.40
	GAMUNEX-C	Grifols	J1561	\$80.69	\$79.40
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	\$140.10	\$137.85
	HIZENTRA	CSL Behring	J1559	\$104.95	\$103.27
	HYQVIA	Takeda	J1575	\$146.35	\$144.00
	XEMBIFY	Grifols	90284/J3590	**	**

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

Calculate your reimbursement online at www.FFFenterprises.com.

** 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%	Pfizer	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	
SCIG	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
	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
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 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)	SANOPI 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)	SANOPI 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)	SANOPI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOPI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOPI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOPI 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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