SPRING 2021

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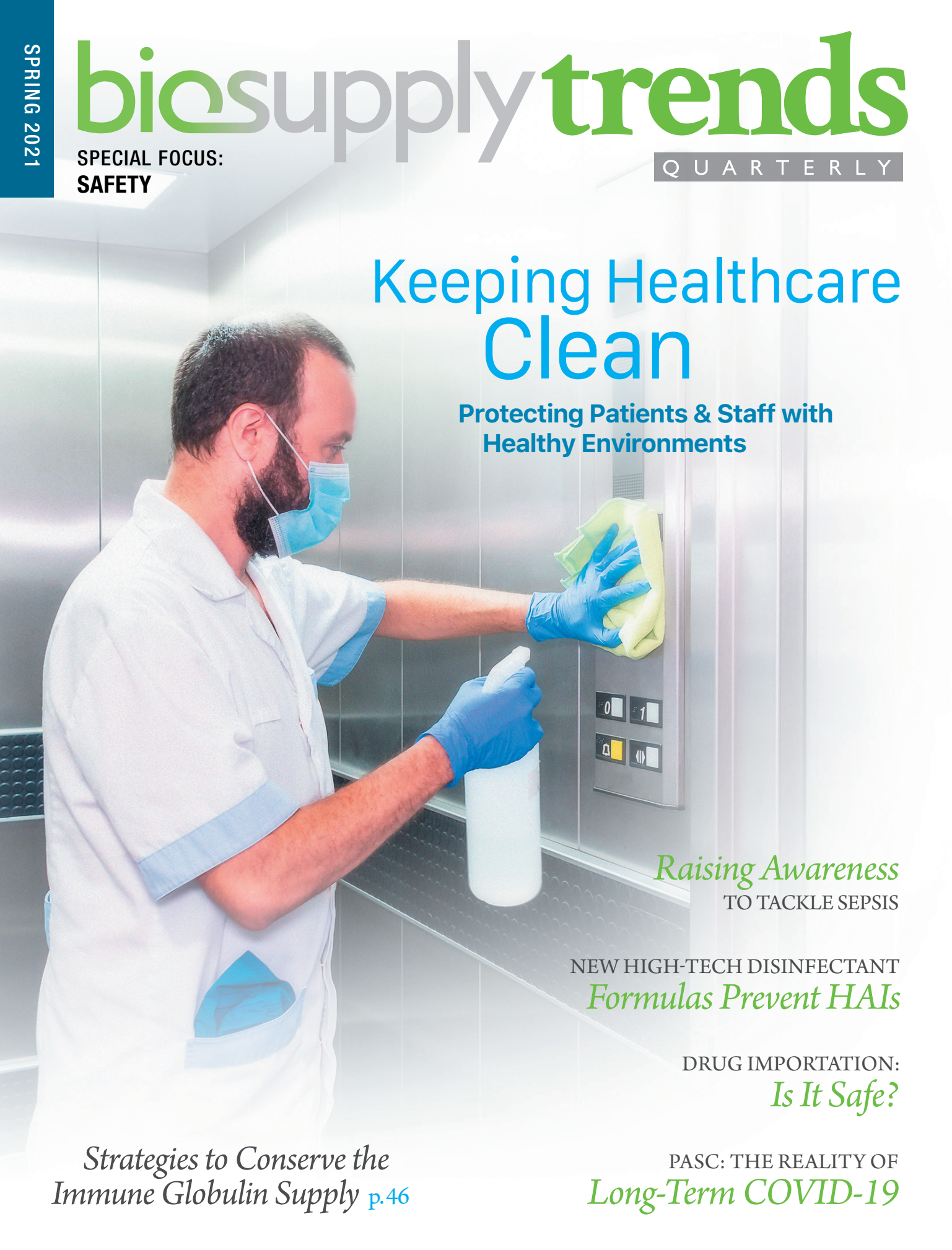
QUARTERLY

SPECIAL FOCUS:
SAFETY



Keeping Healthcare Clean

Protecting Patients & Staff with Healthy Environments

Raising Awareness
TO TACKLE SEPSIS

NEW HIGH-TECH DISINFECTANT
Formulas Prevent HAIs

DRUG IMPORTATION:
Is It Safe?

Strategies to Conserve the Immune Globulin Supply p.46

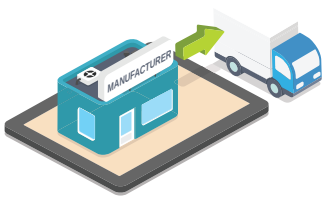
PASC: THE REALITY OF
Long-Term COVID-19

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

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STEP 3

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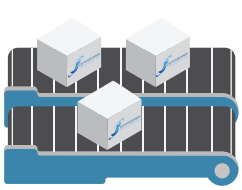
FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

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STEP 5

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STEP 6

Methods of Delivery

We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

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In compliance with U.S. Drug Supply Chain Security Act (DSCSA) requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History, and Transaction Statement.

STEP 8

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

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Features

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The Heightened Importance of Cleanliness for Patient Safety

ACCORDING TO the World Health Organization, it is estimated one in every 10 patients is harmed while receiving hospital care caused by a range of adverse events, with nearly 50 percent of them preventable.[1] Regrettably, deficiency in cleanliness is one of the leading causes of adverse events, most notably healthcare-associated infections (HAIs). For instance, the Office of Disease Prevention and Health Promotion reports that at any given time, about one in 25 patients has an infection related to hospital care, leading to tens of thousands of deaths and costing billions of dollars each year.[2]

Indeed, environmental cleaning is critical to the health and safety of patients, as well as staff. And, without strict cleaning standards in place, pathogens can be hard to overcome and result in deadly outbreaks. In our article "Cleanliness Guidelines for Healthcare Settings" (p.18), we outline the types of standard operating procedures needed, including training, monitoring, feedback and safe handling instructions. And, we emphasize the importance of focused leadership since responsibility for patient and staff safety relies on adequately planning and executing the expected standard of care.

For the last several years, sepsis has been recognized as a growing HAI that occurs in at least 1.7 million hospitalized adults in the U.S. annually, resulting in 270,000 deaths. As we explain in our article "Tackling Sepsis in Hospitals" (p.26), sepsis is an extreme response to infections caused by many different types of pathogens, and it can be very difficult to recognize and diagnose. We take a look at the successful types of awareness and education campaigns, protocols and state-of-the-art tools healthcare organizations in the U.S. have developed to lower the risk and incidence of sepsis, as well as the number of deaths.

In today's environment, there is a new addition to the list of HAIs: the SARS-CoV-2 virus that causes COVID-19, another highly infectious pathogen that not only can be transmitted through person-to-person contact, but can remain on surfaces for up to 72 hours. That's why, as we discuss in our article "What's New in Antiviral/Antibacterial Disinfectants?" (p.22), we point out a growing need to produce more protective disinfectants. And, while this is true for all classifications (critical, semicritical and noncritical) of medical equipment and devices, items that fall under the noncritical classification are most vulnerable because they are often overlooked, and staff charged with cleaning them are typically unsupervised. Fortunately, researchers are investigating new products that will last longer and provide greater protection, and some of them are currently on the market.

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

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

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FDA Takes Actions to Help Lower U.S. Prescription Drug Prices

The U.S. Department of Health and Human Services and the U.S. Food and Drug Administration (FDA) took actions to help provide safe, effective and more affordable drugs to American patients as part of the Safe Importation Action Plan, fulfilling the aspect of the July Executive Order on drug pricing to complete the rulemaking to allow states to import certain prescription drugs from Canada.

The final rule implements a provision of federal law that allows FDA-authorized programs to import certain prescription drugs from Canada under specific conditions that ensure the importation poses no additional risk to the public's health and safety while achieving a significant reduction in the cost of covered products to the American consumer. The final guidance for industry describes procedures drug manufacturers can follow to facilitate importation of prescription drugs, including biological products, that are FDA-approved, manufactured abroad, authorized for sale in any foreign country and originally intended for sale in that foreign country.

The rule allows states (including the District of Columbia and territories), Indian tribes and — in certain future circumstances — pharmacists and wholesalers, to submit importation program proposals to FDA for review and authorization. An importation program can be co-sponsored by a state, Indian tribe, pharmacist or wholesaler. Referred to as Section 804 Importation Programs, these programs will be managed by the respective sponsor and any co-sponsors and authorized by FDA to facilitate the importation of certain prescription drugs that are approved in Canada and, with appropriate labeling, meet the conditions of an FDA-approved drug application. Eligible prescription drugs would have to be relabeled with the required U.S. labeling and undergo testing for authenticity, degradation and to ensure the drugs meet established specifications and standards. These programs will also have to demonstrate significant cost reductions of the covered products to the American consumer.

The final guidance describes procedures for a drug manufacturer to obtain a National Drug Code (NDC) for certain FDA-approved prescription drugs, including biological products and combination products, that were originally manufactured and intended for sale in that foreign country. The use of an additional NDC for these products may allow greater flexibility for drug companies to offer these products at a lower price than what their current distribution contracts require. Prescription drugs, including biological products, imported under the pathway described in the final guidance could be available to patients in a variety of settings, including hospitals, healthcare provider offices or licensed pharmacies, and would include the FDA-approved labeling (including prescribing information).

"Today's action is an important part of FDA's priorities to promote choice and competition. The Safe Importation Action Plan aims to clearly describe procedures to import drugs that would lower prices and improve access while also maintaining the high quality and safety Americans expect and deserve," said FDA Commissioner Stephen M. Hahn, MD. "The FDA will continue to assess and act on opportunities to increase competition in the prescription drug market and help reduce the cost of medicines." ❖

FDA Takes Actions to Help Lower U.S. Prescription Drug Prices. U.S. Food and Drug Administration press release, Sept. 24, 2020. Accessed at www.fda.gov/news-events/press-announcements/fda-takes-actions-help-lower-us-prescription-drug-prices.

NIH Launches Database to Track Neurological Symptoms Associated with COVID-19

Researchers at NYU Grossman School of Medicine have created a database to collect information from clinicians about COVID-19-related neurological symptoms, complications and outcomes, as well as COVID-19 effects on pre-existing neurological conditions. The COVID-19 Neuro Databank/Biobank (NeuroCOVID), which will be maintained by NYU Langone Health in New York City, will be a resource of clinical information, as well as biospecimens from people of all ages who have experienced neurological problems associated with SARS-CoV-2 infection. The database is supported by the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS).

"We know that COVID-19 can disrupt multiple body systems, but the effects of the virus and the body's response to COVID-19 infection on the brain, spinal cord, nerves and muscle can be particularly devastating, and contribute to persistence of disability even after the virus is cleared," said Barbara Karp, MD, program director at NINDS. "There is an urgent need to understand COVID-19-related neurological problems, which not uncommonly include headaches, fatigue, cognitive difficulties, stroke, pain and sleep disorders, as well as some very rare complications of serious infections."

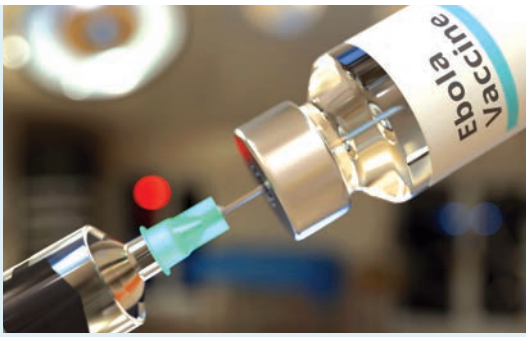
Healthcare providers and participating clinical sites across the United States are invited to use the web-based data portal to submit de-identified information into the database, along with relevant biospecimens collected during research studies or from previous clinical procedures and tests.

Information to be collected in the database includes neurological symptoms, comorbidities, disease course, complications, sequelae and outcomes. A Global Unique Identifier will be used to recognize data and biospecimens from each individual with no personally identifying information collected or stored in the database.

NeuroCOVID can be accessed by scientists for research studies on preventing, managing and treating neurological complications associated with COVID-19. The database may provide insight into how COVID-19 affects the nervous system, and how common, or rare, such complications are. ❖

NIH Launches Database to Track Neurological Symptoms Associated with COVID-19. National Institutes of Health press release, Jan. 26, 2021. Accessed at www.nih.gov/news-events/news-releases/nih-launches-database-track-neurological-symptoms-associated-covid-19.

NIAID Awards Soligenix $1.5M to Support COVID-19 and Ebola Vaccine Development



The U.S. National Institute of Allergy and Infectious Diseases (NIAID) has awarded a $1.5 million grant to Soligenix Inc. to aid manufacture, formulation and characterization of COVID-19 and ebola virus disease vaccine candidates. These candidates will be pursued in conjunction with the CoVaccine HT adjuvant, and the money will support the adjuvant's immune characterization that has shown unique potency and the ability to enable thermostabilization in subunit vaccines, allowing vaccines to avoid the need for cold chain storage and shipping.

Sologenix is working on a COVID-19 vaccine candidate known as CiVax, which is heat stable and has shown potential to produce a significant immune response. "We are appreciative of the continued support provided by NIAID for our thermostabilization program," said Christopher Schaber, PhD, president and CEO of Soligenix. "This SBIR grant award will further advance our studies with the CoVaccine adjuvant, as well as our CiVax and filovirus vaccine programs. We remain dedicated to progressing our public health solutions business segment and look forward to accelerating our CiVax program in particular with this funding."

One of the major hindrances for vaccines is their ability to be transported and stored. Even among the first COVID-19 vaccines to be approved in the United States, significant logistical challenges may be seen due to cold chain requirements demanding cold temperatures to maintain stability. However, with the CoVaccine adjuvant platform, single vaccines are possible with stable temperatures of up to 104 degrees Fahrenheit.

With this grant funding, Soligenix will pursue detailed immunogenicity assessments of CoVaccine along with either the SARS-CoV-2 Spike protein antigen — for COVID-19 — or the Zaire ebolavirus glycoprotein antigen — for Ebola. Testing will be conducted on both mice and nonhuman primates. ❖

Galford C. Soligenix Wins $1.5M NIAID Award to Support COVID-19, Ebola Vaccine Development. Homeland Preparedness News, Jan. 27, 2021. Accessed at homelandprepnews.com/stories/59628-soligenix-wins-1-5m-niaid-award-to-support-covid-19-ebola-vaccine-development.

Preparing for Possible Drug Pricing Changes

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE COVID-19 pandemic that has pushed the U.S. healthcare system to its limits and crippled the economy has brought stark attention to the need for new legislation to lower medication prices. Such legislation could address lowering the acquisition price of medicines or lowering reimbursement for medicines when the federal or state government is the payer. In either case, the benefit to patients is reduced co-pays and other savings. In late July 2020, four executive orders addressing drug pricing were signed, each addressing a different aspect, with one limited to just two drugs and the others broader in scope. This column addresses one of those known as the Most Favored Nations (MFN) model.

The release of the interim final rule of the MFN model in late fall with a Jan. 1, 2021, start date was met with immediate criticism and pushback from a variety of stakeholders, as well as a flurry of lawsuits resulting in a temporary hold. The model tackled the issue of drug pricing by lowering reimbursement of drugs, leaving it to healthcare facilities to negotiate lower prices with manufacturers and suppliers. The fate of the MFN rule will be determined by the current administration that can eliminate it, appeal the California preliminary injunction or do nothing. Despite a comment period that ended Jan. 26, implementation has been blocked by federal courts. In addition, a court in Maryland has issued a temporary restraining order, and courts in New York and California have granted preliminary injunctions.

Even if the MFN model is eliminated, drug pricing is extremely likely to be addressed in the near future as either a revised version of the MFN model and/or applying other creative approaches

to lowering drug prices in the U.S. Yet, regardless of what approaches are taken, healthcare organizations will have to calculate the financial impact of the new ruling(s) and the benefit to patients in the form of lower co-pays. They also will have to determine what operational changes may need to be made to their supply chain, pricing structure or other revenue cycle services. And, this will entirely depend on access to accurate data and an understanding of their payer structure for drugs and biologicals.

What Is the MFN Model?

Skipping the normal rulemaking process, which allows for public comment, the Centers for Medicare and Medicaid Services (CMS) issued an "interim final rule" typically reserved only for rules that need to be enacted quickly. This rule creates a new mandatory payment model for separately payable Part B drugs that ties reimbursement to prices other countries (i.e., most favored nations) pay for the same drugs. The rule applies only to traditional fee-for-service Medicare beneficiaries; it does not apply to those who have private insurance. The administration is pushing the rule to lower traditional Medicare drug spending.

The rule, which was set to take effect Jan. 1, proposes to restrict costs for the top-50 physician-administered Medicare Part B drugs, which account for almost 80 percent of Part B spending, to no more than the lowest price drug manufacturers receive in other similar countries. Specifically, it would have replaced the existing average sales price (ASP) plus 6 percent formula with a new formula based on international pricing information from an index of 22 different countries. The new formula applies to Medicare-participating physicians, nonphysician practitioners, supplier groups (such as group practices), hospital outpatient departments (including 340B-covered entities, ambulatory surgical centers and other providers) and suppliers that receive separate Medicare Part B fee-for-service payment for the model's included drugs. Excluded from the new formula are cancer hospitals, children's hospitals, critical access hospitals, rural health centers, federally qualified health centers, Indian Health Service facilities, and providers in the Maryland Total Cost of Care model that has an annual global budget for healthcare spending. Additionally, participants can request exemption based on financial hardship.

Under the rule, CMS will pay for the 50 costliest Medicare Part B drugs, 38 of which are oncology-related, "at comparable amount to the lowest adjusted price paid by any country in the Organization for Economic Co-operation and Development that has a gross domestic product (GDP) per capita that is at least 60 percent of the U.S. GDP per capita." After a price is established, the model will phase pricing in with the applicable ASP by 25 percent per year for performance years one through three

and reach 100 percent by performance years four through seven. The goal is to give providers "time to adjust to the model payment amounts and formulas." Complicating this fluctuation, CMS will replace the 6 percent add-on payment with a flat fee add-on payment regardless of product cost calculated quarterly at 6.1 percent of the 2019 historical spending on all MFN drugs and adjusted every year based on inflation. The per-dose add-on payment for the first quarter of 2021 will be $148.73. If a drug is in short supply, the price will revert to ASP.

Implications of the MFN Model

Manufacturers' prices remain the same and won't be lowered to compensate for the MFN price. The goal is to involve group purchasing organizations to determine any anticipated decreases in contracted costs effective the new start date that parallels decreased reimbursement for MFN model drugs for traditional Medicare beneficiaries. Therefore, providers may have to develop mechanisms such as rebates or discounts with manufacturers. Success will depend on providers negotiating drug prices down to meet reduced reimbursement levels, but it's unclear whether or by how much manufacturers will actually lower prices they charge healthcare providers. If unsuccessful, providers will have to choose whether to offer the drugs at a financial loss. Beneficiaries will pay lower coinsurance for these high-cost Part B drugs, and they will not pay coinsurance on the add-on payment.

The pharmaceutical and finance teams will bear responsibility for determining the impact on facility/system income. This begins with categorizing the MFN drug list by which ones will affect each area of the facility/system, eliminating those that are not relevant, and determining usage of the remaining relevant drugs by traditional fee-for-service Medicare patients, as well as any covered by commercial payers that use Medicare as their payment. And, this will require a thorough understanding of the terms of each commercial payer agreement. For instance, it will need to be determined whether, in managed care contracting, there are third-party payer contracts with statements that pay for outpatient drugs covered by Medicare or that use Medicare payment rates as a basis for the contract.

Another crucial determination will be how much lost income will result from payer reimbursement directly to the facility, as well as how much lost income will result from co-pay amounts for add-on fees. And, consideration must be given to lost income from using MFN versus ASP (Note: 340B facilities paid the lower of MFN versus ASP minus 22.5 percent). Waste billing will also be affected, so lost income from this must be considered as well.

Even though many sites use billed charges when creating proformas, these are irrelevant when comparing MFN versus ASP. Rather, to determine the true impact, a comparison of actual Medicare (and commercial) payments versus MFN payments must be made.

The pharmaceutical and finance teams must also consider payment reductions in the 340B program. The same basic understanding of which patients are covered by which payers (commercial or government) using which drugs in which site of care need to be applied to analyzing the impact of payment reductions for 340B drugs used to treat 340B-eligible Medicare patients when treated in a 340B-eligible outpatient prospective payment system (OPPS) setting. Additionally, only certain drugs, in this case those with status indicator (SI) K, are affected. Therefore, analysis should begin with accessing the list of SI K drugs from CMS Addendum B, and then determining which ones are used in the facility's OPPS setting. Pass-through drugs (SI G) are exempt from this payment reduction.

In the final analysis, every one of these changes depends on knowing who the payer is for every patient and having clean accurate data, as well as access to files that hold the information on targeted drugs. ❖

Resources

- MFN Part B drugs and biologicals interim final rule FAQ sheet: www.cms.gov/newsroom/fact-sheets/fact-sheet-most-favored-nation-model-medicare-part-b-drugs-and-biologicals-interim-final-rule
- MFN model initiative: innovation.cms.gov/initiatives/most-favored-nation-model
- MFN model interim final rule with comment period: innovation.cms.gov/media/document/mfn-ifc-rule
- Revised list of drugs: innovation.cms.gov/innovation-models/most-favored-nation-model

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.

Enhancing Doctor-Patient Communication with Technology

By Ronale Tucker Rhodes, MS

IN 2016, a study of physicians showed nearly two-thirds believe they deliver quality care. Yet, the same study found only 40 percent of patients believe that is the case. And, 81 percent of patients expressed dissatisfaction with their care experience.[1] What's more, an analysis of 35,000 online physician reviews showed 96 percent of recorded complaints were related to poor communications or poor customer service rather than a physician's demeanor, diagnostic skills or a diagnosis.[2]

Unfortunately, while the medical profession has made great strides in debuting better practice management systems, cutting-edge diagnostic tools and emerging care models that pay for quality of care rather than volume of care, this is not so for communications strategies. So, how can facilities improve their doctor-patient communications? The consensus: patient portals and communication platforms that include options for text and social media.[2]

Patient Portals

Patient portals are an important tool for improving communication between physicians and patients, but they also empower patients to become more engaged in managing their care.[3] Specifically, they offer the following benefits:[4]

1) *A secure messaging center.* Through portals, patients can ask questions they feel are urgent or that they might have left out during their in-person visit. Such service is one of the quickest ways to build patient trust and improve patient retention rates since the more quickly physicians respond to patients' questions through their portal, the more patients feel physicians are listening to and care about their health concerns and goals.

2) *Access to personal health information.* Patient portals provide the quickest way to communicate test and lab results and for patients to view and understand their personal health information (PHI). This access can help them to understand where improvements in their routines can be made and discuss with their physicians how to accomplish their goals.

3) *Engaging care head-on.* By accessing PHI, patients are often inspired to tackle their care head-on. Patient portals inspire patients to work more closely with their physicians to stay compliant with their annual care and testing, visit more regularly and remain compliant with follow-up care, leading to improved outcomes.

4) *Understanding medical expenses.* Patients can now view, understand and plan for their medical expenses, as well as pay their bills to prevent being overwhelmed by any costs. Portals also enable patients to pay by credit card and avoid having delinquent accounts.[3]

Texting

While patient portals have become an important tool, twice as many patients prefer texting, according to a survey by DrFirst, a provider of e-prescribing and patient medication management solutions. The online survey that included responses from 199 patients who visit the doctor at least once every six months found they favor receiving information via secure text messages when in-person visits and phone calls are not an option. Further, the respondents said they would like the ability to communicate via secure text messaging with a family member's care team if that loved one were ill. "The survey results confirm our observation that patients want to be more engaged in their care and desire more options for interacting with their healthcare providers using the same communication methods they regularly use in every other part of their life," said G. Cameron Deemer, president of DrFirst. "Clinicians who use secure text messaging to connect with patients and their family members can improve patient satisfaction, drive medication adherence and empower patients to be more actively involved in their health and wellness."[5]

There are four major benefits of developing a secure message system (SMS) program:[6]

1) *Reduced missed appointments.* A study found using text reminders reduced the number of missed patient appointments by 12 percent. Sending a text to patients the day before an appointment reminds them

they are scheduled to come into the office.

2) *Improved patient support.* SMS programs can also be used for general patient support — from prescription pick-ups and renewals to announcements about flu shots and other practice news. Texting also works as two-way communication, allowing patients to ask questions or share concerns.

3) *Better patient-doctor communication.* While physicians must be careful about the information sent in texts due to confidentiality and legal issues, texts can enhance patient-doctor communication. For instance, patients can text the office if they have a question, and the office can contact them through a more secure channel. Or, the practice can contact patients via text stating they need to contact the office. In addition, a study found texting patient results for nonurgent blood tests reduced the number of appointments by 600 per year.

4) *Reduced costs.* SMS programs can also reduce a practice's overall budget by saving resources wasted due to missed appointments and by freeing up employees' time by automating communications such as prescription and appointment reminders. The latter can be accomplished by signing up for a texting service, which typically costs just a few cents to send a text. And, many services offer monthly deals for higher volumes of messages.

Social Media

The increasing usage of social networks among physicians and patients has had a positive impact on overall healthcare quality. For instance, social media contributes to how patients choose healthcare providers, with a PricewaterhouseCoopers report finding 41 percent of patients allow social media content to impact their choice of hospital or physician. In addition, a study conducted at the University of Groningen in the Netherlands that analyzed more than 1,700 articles found patients' use cases of social media are divided into six categories: emotional, informational, esteem, network support, social comparison and emotional expression. And, these categories affect their relationship with healthcare providers in various ways such as leading to more equal communication between patients and doctors, contributing to increased switching of doctors, developing more harmonious doctor-patient relationships and resulting in suboptimal interactions between doctors and patients.[7]

Social media also develops a sense of community. By connecting patients with others at the same care facility or receiving guidance toward the same health goals, social media can help build a network of people supporting each other toward better health. In addition, since patients use social media and blog sites to get healthcare information, they can improve patient education and health literacy.[8]

Addressing Privacy and Security Concerns

Unfortunately, new technology also comes with privacy and security vulnerabilities. For instance, patient portals carry risks for physicians, including compromised patient information when shared online, patient misinterpretation of test results and notes, raised anxiety levels among patients when viewing clinical notes and test results, a poor medium for informing patients about certain situations such as when providing a serious diagnosis, and the need to get informed consent from patients to use a patient portal to share information with the healthcare team. Therefore, doctors are advised to use robust security and privacy protections, manage expectations, write clear and concise notes, draw attention to important information or desired actions, highlight patient accomplishments, keep their language professional, provide additional information and ensure follow-up plans are clearly visible.[3]

In addition, SMS programs can have issues with security and Health Insurance Portability and Accountability Act (HIPAA) compliance. In fact, The Joint Commission has banned physicians from using traditional SMS for any communication that contains electronic PHI or includes an order for a patient to a hospital or other healthcare provider, and violations can result in hefty fines. Therefore, it's imperative for physicians to communicate within a HIPAA-compliant platform. This is also true for emails. Lastly, when using social media sites, questions related to treatment are best answered with a direct response. And, employees' social networking use during work hours should be monitored since there are many ways in which misuse could result in employer fault under HIPAA.[9] ❖

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

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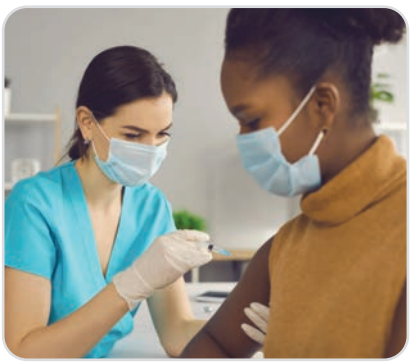
Research

Flu Vaccine May Reduce COVID-19 Infection Rates and Severity

A recent study shows the odds of testing positive for COVID-19 were reduced in patients who received an influenza (flu) vaccine compared to those who did not by 24 percent. It also found those who tested positive for COVID-19 were less likely to require hospitalization or mechanical ventilation and had a shorter hospital length and stay.



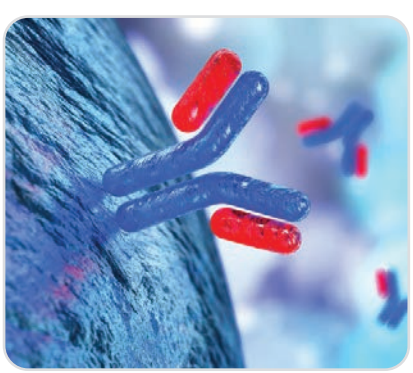
In the retrospective cohort study, 27,201 patients were tested for COVID-19. The primary outcome was comparison of positive COVID-19 testing in those who received the flu vaccine versus those who did not. Secondary end points in patients testing positive for COVID-19 included mortality, need for hospitalization, length of stay, need for intensive care and mechanical ventilation. Results showed the odds of testing positive for COVID-19 were reduced in patients who received a flu vaccine compared to those who did not, vaccinated patients testing positive for COVID-19 were less likely to require hospitalization or mechanical ventilation, and they had a shorter hospital length of stay.

According to the researchers, the study shows a flu vaccine is associated with decreased positive COVID-19 testing and improved clinical outcomes, and it should be promoted to reduce the burden of COVID-19. ❖

Conlon A, Ashur C, Washer L, et al. Impact of Influenza Vaccine on COVID-19 Infection Rates and Severity. *American Journal of Infection Control*, Feb. 22, 2021. Accessed at www.ajicjournal.org/article/S0196-6553(21)00089-4/fulltext.

Guidelines

Octapharma Releases New Guidelines on Use of IG Replacement Therapy to Treat SAD



Octapharma has released new expert consensus guidelines on the use of immune globulin replacement therapy (IGRT) to treat patients with haematological malignancy and secondary antibody deficiencies (SAD).

The guidelines were developed by a task force of eight experts in immunology and haemato-oncology on key aspects of IGRT, which were reviewed by a panel of 32 European experts. This consensus recommendations for SAD due to haematological malignancies include: measurement of IgG levels at the beginning of anti-cancer treatment; initiation of IGRT in patients who have received appropriate anti-infective therapy during or after a single severe infection or during recurrent or persistent infections when IgG levels are less than 4 g/l or if test immunization has failed; initiation of IGRT with a minimum IgG dose of 0.4 g/kg body weight every three to four weeks or stopping IGRT after at least six months without infections and concomitant evidence of immunological recovery. A total of 21 consensus statements emphasize the importance of IGRT for patients with SAD who experience severe, recurrent or persistent infections and provide guidance on initiation, dosing and discontinuation of IGRT, as well as measurement of IgG levels and the use of subcutaneous IG therapy. The publication is available through open access at "Treating Secondary Antibody Deficiency in Patients with Haematological Malignancy: European Expert Consensus" in the *European Journal of Haematology*.

According to Stephen Jolles, lead author of the publication and professor at the Immunodeficiency Centre for Wales in Cardiff, United Kingdom, "Developing consensus guidelines for the use of IGRT in secondary antibody deficiency (SAD) aims to address a major need for treatment recommendations for patients with haematological malignancies and SAD. IGRT can reduce morbidity and mortality in a selected group of these patients, and it is important that physicians have consistent guidance on defining this group and managing infection risk." ❖

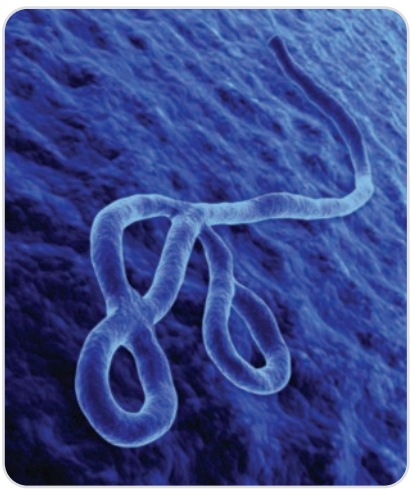
Recommendations on Treatment of Secondary Antibody Deficiency in Patients with Haematological Malifnancies. Octapharma press release, Feb. 19, 2021. Accessed at financialpost.com/pmn/press-releases-pmn/business-wire-news-releases-pmn/octapharma-new-consensus-recommendations-on-treatment-of-secondary-antibody-deficiency-in-patients-with-haematological-malignancies.

Medicines

FDA Approves First Treatment for Ebola Virus

The U.S. Food and Drug Administration (FDA) has approved Inmazeb (atoltivimab, maftivimab and odesivimab-ebgn), a mixture of three monoclonal antibodies, as the first treatment for Zaire ebolavirus (Ebola virus) infection in adult and pediatric patients. Inmazeb targets the glycoprotein that is on the surface of Ebola virus. Glycoprotein attaches to the cell receptor and fuses the viral and host cell membranes, allowing the virus to enter the cell. The three antibodies that make up Inmazeb can bind to this glycoprotein simultaneously and block attachment and entry of the virus.

Approval was based on evaluation of 382 adult and pediatric patients with confirmed Zaire ebolavirus infection in one clinical trial (the PALM trial) and as part of an expanded access program conducted in the Democratic Republic of the Congo (DRC) during an Ebola virus outbreak in 2018-2019. In the trial, led by the U.S. National Institutes of Health and the DRC's Institut National de Recherche Biomédicale with contributions from several other international organizations and agencies, 154 patients received Inmazeb (50 mg of each monoclonal antibody) intravenously as a single infusion, and 168 patients received an investigational control. The primary efficacy endpoint was 28-day mortality. The primary analysis population was all patients who were randomized and concurrently eligible to receive either Inmazeb or the investigational control during the same time period of the trial. Of the 154 patients who received Inmazeb, 33.8 percent died after 28 days, compared to 51 percent of the 153 patients who received a control. In the expanded access program, an additional 228 patients received Inmazeb. The most common symptoms experienced while receiving Inmazeb included fever, chills, tachycardia (fast heart rate), tachypnea (fast breathing) and vomiting; however, these are also common symptoms of Ebola virus infection. Patients who receive Inmazeb should avoid the concurrent administration of a live vaccine due to the treatment's potential to inhibit replication of a live vaccine virus indicated for prevention of Ebola virus infection and possibly reduce the vaccine's efficacy.



"Today's approval highlights the importance of international collaboration in the fight against Ebola virus," said John Farley, MD, MPH, director of the Office of Infectious Diseases in the FDA's Center for Drug Evaluation and Research. "The urgent need for advanced therapies to combat this infectious disease is clear, and today's action is a significant step forward in that effort." ❖

FDA Approves First Treatment for Ebola Virus. U.S. Food and Drug Administration press release, Oct. 14, 2020. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-ebola-virus.

Research

Flu Vaccine Reduces Risk of Respiratory Morbidity and Mortality in Autoimmune Rheumatic Diseases

A new study shows inactivated influenza (flu) vaccine is associated with a reduced risk for respiratory morbidity and mortality in patients with autoimmune rheumatic diseases (AIRDs). In the study, data from 30,788 adults with AIRDs treated with immunosuppressive drugs in the three-month period before Sept. 1, 2006, through 2009, and Sept. 1, 2010, through 2015, were assessed for the effectiveness of the inactivated flu vaccine in preventing influenza-like illnesses, lower respiratory tract infection, pneumonia, chronic obstructive pulmonary disease (COPD) exacerbations and death. Results showed vaccination reduced the risk for hospitalizations with pneumonia, COPD exacerbations, all-cause mortality and death due to pneumonia in those flu seasons. In addition, vaccination reduced the risk for primary care consultation for flu-like illness when the analysis was restricted to the period when flu viruses circulated. When seasons with exposure to sulfasalazine alone were excluded, these associations did not change. However, the inactivated flu vaccine did not reduce the risk for primary consultations for lower respiratory tract infection and COPD exacerbations.

Data was taken from the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics and Office for National Statistics databases. ❖

Kumar D. Influenza Vaccine Associated with Reduced Respiratory Morbidity, Mortality Risk in Autoimmune Rheumatic Diseases. Rheumatology Advisor, April 2, 2020. Accessed at www.rheumatologyadvisor.com/home/general-rheumatology/influenza-vaccine-associated-with-reduced-respiratory-morbidity-mortality-risk-in-airds.

Research

NIH Researchers Discover Autoimmunity Is on the Rise

Researchers at the National Institutes of Health (NIH) have found autoimmunity, a condition in which the body's immune system reacts with components of its own cells, appears to be increasing in the U.S. Specifically, they found the prevalence of antinuclear antibodies (ANA), the most common biomarker of autoimmunity, was significantly increasing in the U.S. overall and particularly among certain groups, including males, non-Hispanic whites, adults 50 years and older and adolescents.

In the study that included 14,211 participants 12 years and older in the U.S. National Health and Nutrition Examination Survey, scientists used immunofluorescence, a technique that uses fluorescent dye to visualize antibodies, to examine the frequencies of ANAs in subjects from three time periods. They found ANA prevalence for 1988 through 1991 was 11.0 percent, while it was 11.5 percent from 1999 through 2004 and 15.9 percent between 2011 and 2012. The percentages corresponded to 22, 27 and 41 million affected individuals, respectively. Young people ages 12 years to 19 years had the largest ANA increases in the study, going from a two-fold to a three-fold increase over the three time frames. According to the researchers, since people have not changed much genetically during the past 30 years, it's possible changes in lifestyle or the environment may be involved in ANA increases.

"The reasons for the increases in ANA are not clear, but they are concerning and may suggest a possible increase in future autoimmune disease," said corresponding and senior author of the study Frederick Miller, MD, PhD, deputy chief of the Clinical Research Branch at the National Institute of Environmental Health Sciences. "These findings could help us understand more about the causes of the immune abnormalities and possibly learn what drives development of autoimmune diseases and how to prevent them."

The researchers say they hope a national registry of autoimmune diseases will be established so they can examine changes over time, define geographic hotspots and eventually understand what is causing them. ❖

National Institutes of Health. Autoimmune Conditions Are On the Rise, April 9, 2020. Accessed at www.technologynetworks.com/immunology/news/autoimmune-conditions-are-on-the-rise-333244.

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Research

New Vaccine Could Protect Infants Against Infection in the Presence of Maternal Antibodies

Researchers at the University of Pennsylvania School of Medicine have found a specialized modified-RNA (mRNA) influenza vaccine successfully protected young mice against the infection in the presence of maternal antibodies, suggesting the protection occurred because the vaccine programs cells to constantly churn out new antigens for a prolonged period of time rather than delivering a one-time shot of a viral protein. Developing effective vaccines that protect infants in the presence of maternal antibodies has been difficult because the antibodies can bind to vaccines and prevent them from eliciting good immune responses.

For this study, the researchers used a nucleoside-modified mRNA encapsulated in a lipid nanoparticles (mRNA-LNP) vaccine. In the past, this vaccine, which expresses hemagglutinin (HA) proteins, elicited robust antibody responses and protected adult animals from influenza. To determine its ability to overcome maternal antibodies, the researchers first established a mouse model to show how the antibodies protect young mice against influenza and how they inhibit immune responses elicited by conventional vaccinations. Next, they tested the mRNA vaccine platform in the mouse model and found it elicited very strong antibody responses, both in the presence and absence of maternal antibodies, and protected the mice from the virus. The vaccine essentially "slips under the radar," gets into cells, and then starts continuously producing the antigen for the immune system to respond to in what's called "prolonged germinal center reactions," said Scott E. Hensley, PhD, an associate professor of microbiology. The finding suggests maternal antibodies eventually drop below a certain level and the antigen is still there to generate an immune response from the child.

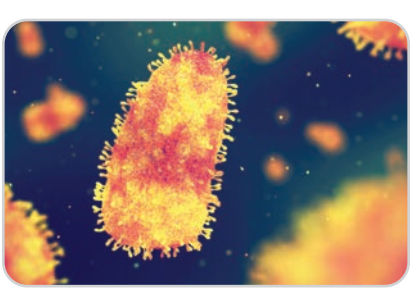
"Around the world, every year, many young infants become infected and often die from infections because of a lack of effective vaccines to protect them earlier in life," said Drew Weissman, MD, PhD, a professor of infectious diseases in the Perelman School of Medicine at the University of Pennsylvania. "mRNA-based vaccines could potentially help prevent that. What's more, it would not only be effective against influenza but also other pathogens, as the vaccine's platform is easily adaptable to different antigens." "It could be a real game-changer," said Dr. Hensley. "Imagine a world where an infant is born or comes into the clinic very early in life and can receive vaccines that have antigens not just for the flu but a multitude of different pathogens. Wouldn't that be something?" ❖

University of Pennsylvania School of Medicine. New Vaccines to Protect Infants Against Infections. Science Daily, Jan. 8, 2020. Accessed at www.sciencedaily.com/releases/2020/01/200108160336.htm.

Research

KEDRAB Is Safe and Effective in Pediatric Patients Exposed to Rabies

A new study has found Kedrion Biopharma's KEDRAB 150 IU/mL (HRIG150, rabies immune globulin [human]) is a well-tolerated and effective post-exposure prophylaxis in patients 17 years and younger who have been exposed to rabies. In the study, 30 participants received 20 IU/kg HRIG150 infiltrated into the detectable wound site(s), with any remainder injected intramuscularly, concomitantly with the first of a four-dose series (days 0, 3, 7 and 14) of rabies vaccine. Rabies virus neutralizing antibody (RVNA) titers and tolerability were assessed on day



14 following administration. Participant safety was monitored for 84 days. No serious adverse events, rabies infections or deaths were recorded. Twenty-one participants (70.0 percent) experienced a total of 57 treatment-emergent adverse events (TEAEs) within 14 days following administration. Twelve participants (40.0 percent) experienced a total of 13 adverse events deemed treatment-related. All TEAEs were mild in severity. On day 14, 28 participants (93.3 percent) had RVNA levels of ≥0.5 IU/mL.

The study was the first trial of human rabies immune globulin in children. ❖

Hobart-Porter N, Stein M, Toh M, et al. Safety and Efficacy of Rabies Immunoglobulin in Pediatric Patients with Suspected Exposure. *Human Vaccines & Immunotherapeutics,* DOI: 10.1080/21645515.2020.1854000. Accessed at www.tandfonline.com/action/showCitFormats?doi=10.1080%2F21645515.2020.1854000&area=0000000000000001.

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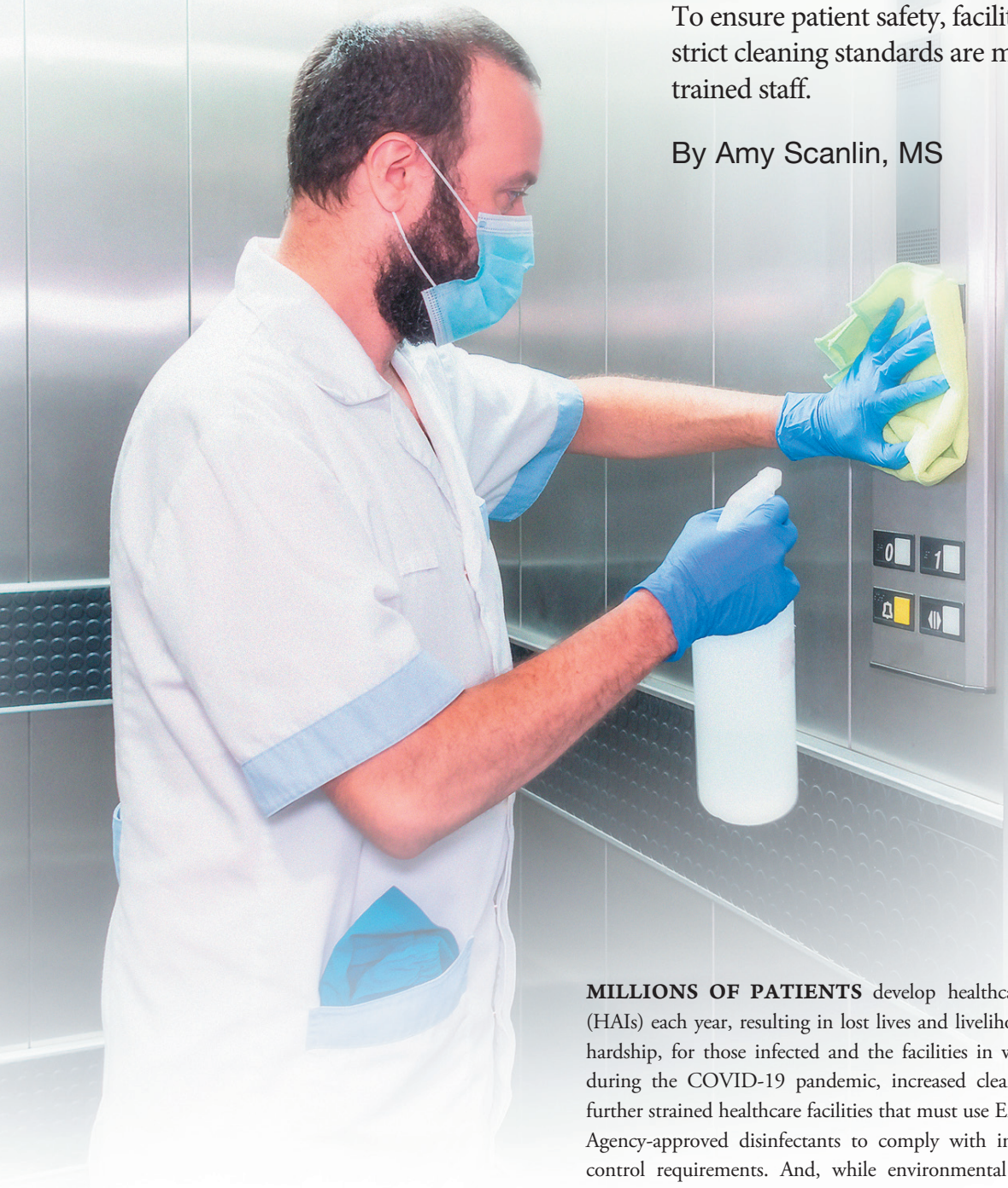
Cleanliness Guidelines for Healthcare Settings

To ensure patient safety, facilities must require strict cleaning standards are met by properly trained staff.

By Amy Scanlin, MS



MILLIONS OF PATIENTS develop healthcare-associated infections (HAIs) each year, resulting in lost lives and livelihoods, as well as financial hardship, for those infected and the facilities in which they occur. Now, during the COVID-19 pandemic, increased cleaning requirements have further strained healthcare facilities that must use Environmental Protection Agency-approved disinfectants to comply with infection prevention and control requirements. And, while environmental cleaning is admittedly not a sexy topic, often overshadowed by new equipment and breakthrough treatments, it is critical to the safety of patients and hospital staff.

Unfortunately, this obscure topic often remains invisible until deadly outbreaks of methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, Clostridioides difficile and others occur. And, once pathogens take hold, they can be hard to overcome. In the right conditions, pathogens can survive on surfaces for months, hiding in cracks and crevices, and they can infect new hospital room occupants following discharge of an infected patient, even after cleaning has been performed. In fact, about one in 31 hospital patients develops at least one HAI. And, infection risks are significantly higher for patients housed in rooms previously occupied by those with an HAI. Unfortunately, environmental surfaces aren't the sole culprit when it comes to pathogen-spread infections. According to the Centers for Disease Control and Prevention (CDC), on average, healthcare providers clean their hands less than half the time they should.[1] Another problem contributing to pathogen spread? Clean supplies housed in dirty storage.

Clean Versus Dirty

"I see the same issues repeatedly," says Peggy Luebbert, MS, CIC, CHSP, CBSPD, an infection preventionist consultant with APIC Consulting Services, a subsidiary of the Association for Professionals in Infection Control and Epidemiology. "More often than not, no matter the type of facility, storage and separating clean from dirty, including instruments and supplies, is the challenge." Luebbert says, too frequently, building design just doesn't incorporate enough clean storage: "It's always a struggle."

Since COVID-19, the storage problem has worsened, and it was particularly bad early on when limited supply availability prompted stockpiling. As new supplies came in, and with limited storage capacity, deliveries found their way to any available space, including attics, basements, garages and closets not suitable for storing clean supplies before being used. "These are key problems when talking about infections," explains Luebbert.

Cleaning and clean storage are the two key areas on which Luebbert first focuses when problem-solving, particularly when an infection isn't caused by a single source such as a germ or healthcare provider. "The interesting thing," she explains, "is when people bring supplies in, if they had just left them sealed in the cardboard box, it may have been OK to store in a dirty area. But, once the box is opened, whatever is inside must be stored in a clean area with controlled traffic. I've seen clean supplies stored near a time clock! No! Don't do that!" Once a box of clean supplies is opened or stored in a dirty area, its contents must be thrown away.

You Don't Know What You Don't Know: SOPs

Standard operating procedures (SOPs) are comprehensive measures outlining specific requirements at every step of the process, from receipt of materials, to sorting and storage of everything from equipment to supplies, as well as the appropriate standard precautions, including cleaning and disinfecting protocols.

SOPs are intended to be instructional. Therefore, the literacy level and language of those following them should be taken into consideration, as well as definitions of technical terms and acronyms. Infographics are often necessary to minimize user confusion and maximize compliance with expectations.

Detailed environmental cleaning policies as outlined in SOPs must be adequate, effective, regularly practiced, reviewed and, importantly, revised as needed.

On the environmental cleaning front, detailed SOPs should include:

- Approved cleaning products and vendors
- The quantities in which cleaning products will be purchased, maintained and stored
- Location of safety data sheets (in close proximity to the products)
- Proper hand hygiene before and after cleaning tasks
- Approved and required personal protective equipment (PPE) by task
- Instructions for donning and doffing PPE
- Step-by-step instructions for all cleaning processes, including preparations of products, listed in sequential order of use, based on the product's manufacturer instructions
- Safe disposal of soiled cleaning equipment and supplies
- How to handle emergencies such as chemical spills, etc.

Detailed environmental cleaning policies as outlined in SOPs must be adequate, effective, regularly practiced, reviewed and, importantly, revised as needed against new and emerging CDC, U.S. Food and Drug Administration (FDA) and Occupational Safety and Health Administration (OSHA) regulations that govern disinfection interventions. As protocols and products evolve, human factors such as staffing, workflow, supervision and

collaboration between support services and clinical staff must evolve with them to ensure best practices.

As part of an SOP, employee monitoring against standards should be clearly articulated, including by whom, at what frequency and how feedback will be communicated. Employee monitoring, as well as surface monitoring, is at the heart of ensuring compliance with standard precautions and the development of staff training.

The robustness of any cleaning and disinfecting program is directly related to the specificity of the applicable information in the SOPs, the thoroughness of training for those who will perform the tasks and the priority placed on environmental cleaning by leadership.

Top-Down Approach

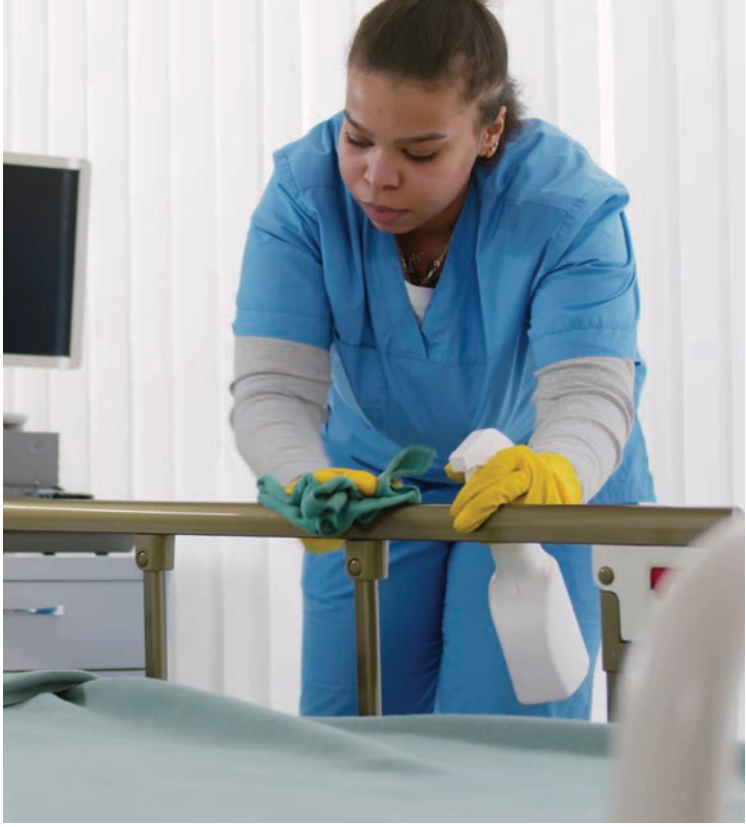
The ultimate responsibility for environmental awareness and best practices lies with facility leadership. Reporting lines and accountability may demonstrate who performs what tasks, but leadership demonstrates the expected standard of care through planning and execution. Funding is always a significant hurdle, too, so from an environmental standpoint, consideration must be given to ensure:

- Adequate staffing (including contingencies)
- Appropriate supplies and equipment
- Facility infrastructure design and maintenance (such as clean storage)
- Training and assessments for all staff according to clearly defined performance expectations

Additionally, ancillary costs such as the printing of training materials and posters, software licensing, support for online training programs and administrative costs of documentation and record keeping in accordance with any regulatory requirements or human resource policies must be taken into consideration.

Whether cleanliness regimens are handled by employees, are contracted out or are a hybrid (such as facility employees who are recruited by a staffing company that specializes in environmental cleaning), CDC, FDA and OSHA requirements and other applicable government standards (such as state standards) should be clarified so expectations and standards are clear.

Leadership must also ensure a watchful eye on facility requirements and needed improvements. As an example, even the most advanced cleaning products will be rendered ineffective in the presence of turbid water in which suspended particles such as dirt can reduce the effectiveness of detergents and disinfectant solutions. Likewise, wastewater considerations must be taken into account to protect healthcare facilities and surrounding communities.



Training, Monitoring and Feedback

Environmental staff should be trained on their job descriptions, SOPs pertaining to their jobs, expectations and performance standards and the mechanisms by which they will be evaluated. In addition to understanding how to perform their jobs, these staff members should perform only those duties for which they have been trained. This means those who have not been trained to clean high-risk areas should not be assigned this duty.

Staff must also receive information about how to identify the various chemical and pathogen hazards to which staff will be exposed, as well as how to protect themselves with PPE. And, they must understand the logic of not only what they are asked to do but why, explains Luebbert. Otherwise, they may not understand the seriousness of their tasks and training. For instance, she says, staff must have answers to why linty towels are a big deal and why it is important to cover their hair. She also recommends that once a facility retains good staff, it should do everything possible to keep them since one of the biggest breakdowns with cleaning and disinfecting is losing trained staff: "Remember, they could get a job anywhere — a hotel, a casino — places with a lot less body fluid. Keeping good staff comes down to respecting good staff. Support them as they do their jobs. Help them understand why they do what they do and why [the facility doesn't] cut corners." A good relationship works both ways, she adds, and "people love their environmental services person. Don't even think about moving them to another area! I always say, from an infection control perspective, 'If housekeeping's not happy, Peggy's not happy.'"

Once trained, monitoring is a critical component of effective

cleaning and disinfecting programs, and staffing levels are a critical component of monitoring. There must be clear and defined lines of accountability, functional reporting and responsibilities for all staff. The supervisor-to-cleaner ratio should allow for routine and regular performance observations, with performance intervals consistently maintained to accurately track and benchmark. If resources allow, CDC guidelines recommend in-patient settings include a monitoring program that covers 10 percent to 15 percent of beds on a weekly basis, and outpatient settings monitor either 10 percent to 15 percent of procedural areas on a weekly basis. Better yet, if resources allow, outpatient settings should monitor 25 percent of procedural areas weekly so the entire facility is monitored monthly.[2]

While visual inspections are the simplest method for evaluating cleanliness, quantitative feedback provides confirmation, albeit at additional cost and turnaround time. Aerobic colony counts in which cultures are collected and processed, even if they are not immediate, are one option. Or, more rapid feedback can be obtained via UV light inspections and bioluminescence-based adenosine triphosphate assays. In either case, reputable laboratories should be used to obtain valid and verifiable results.

Third-party observers may be enlisted for independent assessments as well. Key questions Luebbert asks when she arrives at a facility include:

- Why are you doing that?
- What disinfectant are you using?
- How will you dilute it?
- What is its expiration date?
- What is its kill time?
- What surfaces do housekeeping, environmental services and nursing staff clean?

Also, she advised, "Ask, 'who cleans the bed? Who cleans under the bed? Who cleans the infusion pump?' Oftentimes, the answer ends up being 'everyone thought someone else was cleaning it.'"

Feedback helps to further competency and effectiveness of both staff and the procedures they perform. Whether formal or informal, feedback is the basis for improved training. Much like SOPs, training documentation demonstrates compliance. These records must include dates, content, the trainers' names and those being trained. An evaluation of the content is also helpful. Refresher trainings and competency assessments should be conducted at least annually, and always before introducing new environmental cleaning supplies or equipment.

Safe Handling Instructions

Laundering of reusable linens in a healthcare setting is highly recommended. From soiled linens (bedding, isolation gowns) to protective clothing worn by environmental workers, universal precautions must be used when receiving, handling and laundering.

Accrediting organizations such as the Healthcare Laundry Accreditation Council (HLAC) set standards by which both in-house and contracted laundering facilities agree to operate to sanitize reusable linens. Expectations go beyond the use of chemical additives and hot water during the wash cycle and extend to equipment design, adherence to OSHA requirements, personnel training, quality monitoring and more. Unless the textiles have been exposed to an infectious agent that would render them unusable, protocols designed by HLAC and similar organizations are sufficient to protect patients and healthcare staff, as well as those workers who handle laundry.

Remember, once items have been laundered, sanitized and packaged in sealed wrapping, they must be handled and stored in such a way that maintains their integrity and avoids environmental contamination until they are ready for use.

Cleanliness in healthcare settings is as important as the care provided to patients.

Cleanliness Ensures a Healthy Environment

Cleanliness in healthcare settings is as important as the care provided to patients. By adhering to federal standards implemented by CDC, FDA and OSHA, as well as private collaboratives such as APIC and HLAC that determine best practice standards, providers, environmental services and cleaning staff can ensure facilities are safe for the most vulnerable populations. Understanding and executing appropriate SOPs, correctly preparing and using approved cleaning and disinfecting solutions, and ample space and safe work areas — all under competent and engaged leadership — can instill confidence and a healthy environment for all. ❖

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What's New in Antiviral/ Antibacterial Disinfectants?

Spurred by the COVID-19 pandemic, researchers are developing new formulas that will last longer and provide greater protection with some new products already on the market.

By Jim Trageser

THE COVID-19 PANDEMIC has persisted far longer than anticipated, along with the resulting shutdowns of nonessential businesses in many jurisdictions. Accordingly, many medical facilities have seen their cleaning practices turned upside down. Reduced operating hours and social distancing requirements have disrupted normal staff scheduling, including those members responsible for keeping facilities clean. Staffing levels have also been unsettled by employees required to self-quarantine due to COVID-19 exposure or to care for infected family members. Other employees who live with high-risk family members have taken voluntary leave or even changed careers to reduce the risk of exposing their loved ones.

At the same time medical facility managers are juggling staffing disruptions, the highly infectious nature of the SARS-CoV-2 virus, including its ability to survive on surfaces for up to 72 hours, means those medical facilities that remain open or have reopened must directly address this new threat, in addition to adhering to their existing environmental cleaning practices. The good news is that as high-tech disinfectants continue to be developed and marketed, preventing healthcare-associated infections (HAIs) from environmental sources is becoming both easier and less labor-intensive.

Preventing HAIs and COVID-19

HAIs are one of the top risks for healthcare practices. The three legs of an effective plan to prevent infections in medical offices, hospitals, clinics or other healthcare settings are proper patient care, consistent staff hygiene (including the proper use

of personal protective equipment) and effective equipment and environmental cleaning that includes disinfecting and sterilization as appropriate.

But just having an anti-infection plan in place[1] isn't sufficient. It is likely every medical facility in the country now has a well-designed set of protocols established to prevent HAIs. In fact, the U.S. Centers for Disease Control and Prevention (CDC) has been emphasizing the need to combat HAIs for the past 13 years, since initiating the multi-agency Federal Steering Committee for the Prevention of HAIs in 2008.[2]

But a plan only works when it is followed consistently, and humans are fallible in this regard. Attention spans wander, focus drifts and emergencies and crises arise. CDC reports a significant portion of HAIs comes not from medical procedures, but from environmental contamination.[3] And, earlier studies indicate most infections occur with an approved plan in place that is not consistently followed.

Fortunately, new technologies are coming to market that protect against human inconsistency. The latest disinfectants can provide protection for weeks or even months, reducing the need to have daily or even hourly disinfection procedures in place. However, it remains important for facility management to be aware of the different classes of disinfectants, how they are regulated by different government agencies, and how each type of product fits into a facility's overall anti-infection plan.

Classes of Equipment to Be Cleaned

CDC utilizes Spaulding's Classification of Equipment and Medical Devices as the basis for all its disinfection and sterilization standards.[4] The system organizes equipment and devices into critical, semicritical and noncritical classes.

Critical items are those that come into contact with exposed patient tissue or the vascular system, bypassing the body's normal defenses. These items — scalpels, catheters, implants, etc. — must be sterilized before each use. (Sterilization in this context is defined by CDC as having removed or killed not only all bacteria, fungi and viruses, but also bacterial and fungal spores.) Steam or hydrogen peroxide plasma are recommended methods of sterilization, but liquid sterilants can be used on equipment that is heat-sensitive.

Semicritical items come into contact with mucus membrane or skin that has scrapes or scratches. These items — esophageal probes, rectal probes, diaphragm-fitting rings, dental tools, etc. — must be free from all microorganisms, although they don't need to be sterilized. This level of treatment for semicritical items, which allows for spores to remain, is defined by CDC as "high-level disinfection."[5]

Everything else in a medical facility is categorized as a noncritical item, although these items are broken down further into patient-care items (bedpans, crutches, blood-pressure cuffs, etc.) and environmental surfaces (bedside tables, bed rails, chairs, doors, floors, etc.).

This last category is one that is often overlooked in medical facilities. While the critical and semicritical equipment used by medical professionals is incorporated into daily quality control processes, noncritical equipment is often maintained and cleaned by custodial staff with no direct medical supervision.

Exploring New Options

Most hospital-grade disinfectants used to clean noncritical equipment and infrastructure fall into a handful of categories: alcohols, bleaches, phenolics, ammonium and benzalkonium chloride. (To be listed as "hospital grade," a product must show efficacy against both Pseudomonas aeruginosa and Staphylococcus aureus.[6]) Each of these disinfectants chemically interacts with the molecules of a bacteria, fungi or virus to kill it. These same properties can pose significant health risks if a person accidentally ingests or inhales too much of them, so accidental poisonings are rare but not unprecedented.

The latest disinfectants can provide protection for weeks or even months, reducing the need to have daily or even hourly disinfection procedures in place.

Now, there is a new alternative for noncritical equipment that attacks bacteria and fungi physically rather than chemically through the use of tiny, microscopic spikes that puncture the membranes of any single-cell organisms that fall onto a surface treated with the product. Jason Winkleblech, vice president of infection control products for FFF Enterprises, the nation's leading supplier of critical-care biopharmaceuticals, plasma products and vaccines, says FFF will be distributing one of these new classes of biostatic surface treatments known as Penetrexx Antimicrobial. "The surface treatment product creates a colorless, odorless, positively charged polymer that bonds to a treated surface," explains Winkleblech. "That treated surface looks like a field of spikes, if you will. The spikes will puncture the cell

membrane and render the microorganisms dead.

"It's really the missing step in any good cleaning and disinfecting protocol. You clean to remove dirt and grime, you disinfect to kill everything on the surface and then you apply this product on the surface after disinfecting to create this long-term active antimicrobial shield. It doesn't lose its strength; it's a mechanical interaction, not a chemical reaction. The barrier will only be degraded by extended contact. If you apply it to a door handle that's constantly being touched, that layer will break down in time."

Interestingly, nonabrasive cleaning of treated surfaces won't degrade the product's protective shield. In fact, regularly removing grime and dead microbes from surfaces will prolong the life of the treatment by keeping the microscopic spikes clear for the next group of microbes to fall upon. And, due to the way human skin is structured, the spikes will not scratch or irritate anyone coming in contact with a coated surface. The caveat, though, is since this product is not an antiviral, other products need to be used in conjunction with it to protect against viral transmission, including SARS-CoV-2.

Most hospital-grade disinfectants used to clean noncritical equipment and infrastructure fall into a handful of categories: alcohols, bleaches, phenolics, ammonium and benzalkonium chloride.

According to Winkleblech, with regular light cleaning of treated surfaces, Penetrexx Antimicrobial can remain effective for three months after application. And, once it has been applied and dried, there is no risk of exposure to staff or patients.

Types of Cleaners

Winkleblech points out that while the U.S. Food and Drug Administration handles the certification process for antibiotics and some products used to sterilize or provide a high-level disinfection of medical instruments and other equipment that comes in direct contact with patient tissue, the Environmental Protection Agency (EPA) oversees facility cleaning products used to disinfect noncritical equipment on the CDC list. But, he adds, facility managers need to be sure the products used to clean floors, doorknobs, countertops and other public areas meet EPA standards for the specific application for which they are being used. (EPA maintains the lists of products approved for use versus specific pathogens.[7])

For its part, EPA notes that due to the nature of healthcare, cleaning staff is often required to disinfect patient rooms or common areas where feces, urine or even blood may have been spilled. In addition to fully removing the waste and any other dirt using an approved disinfectant to kill germs, facility managers must also ensure they are complying with the Occupational Safety and Health Administration's requirements for occupational exposure to bloodborne pathogens. Also, when disposing of urine, waste or bodily fluids, staff must conform to the Resource Conservation and Recovery Act.[7]

The types of hospital-grade disinfectants approved by EPA for use in environmental cleaning are:

Alcohol. Alcohols kill cellular organisms (bacteria, fungi) by dissolving their outer membrane. Ethyl alcohol can also disable many classes of viruses, and isopropyl alcohol is highly effective against lipid viruses.[8] Alcohols tend to disinfect rapidly, but have little long-lasting effect since they evaporate quickly as well; therefore, surfaces being disinfected with alcohol will need frequent applications.

Alcohol-based disinfectants are highly toxic if accidentally ingested, highly flammable and can mar the surface of some materials. As such, they should be tested on a small sample of a surface before being used.

When used as a hand sanitizer, alcohol-based products are very effective and quick-acting, but they generally must be reapplied frequently, which can lead to dry and even chapped hands among users.

Phenolics. These hydrocarbons, chemically similar to alcohols, work by penetrating the cellular wall and bonding with various enzymes inside of a bacteria or fungus. They are also effective as virucides. If they are used to clean areas where infants are treated, the surfaces must be thoroughly cleaned following the disinfection.[8]

Bleaches. Bleaches work by causing a chemical reaction to the proteins of microbes, similar to cooking: They cause the proteins to "unwind" and stop working. As in frying an egg, the process cannot be undone by the microorganism. Bleaches can take longer to disinfect than alcohols, and they can discolor materials with which they come into contact.[8] Hydrogen peroxide, a weak bleach, has shown to be effective at decontaminating soiled fabrics in patient rooms. Bleaches should not be used as hand sanitizers.

Ammonium. These are ions of ammonia whose mode of disinfecting is not as well understood as that of alcohols and bleaches. It is thought ammonium kills microorganisms by disrupting cellular membranes or penetrating the membrane and reacting with various cellular enzymes.[8] They are effective against bacteria, fungi and viruses, but not all ammonium variants are equally effective against all pathogens. One quaternary ammonium cation, benzalkonium chloride, has been approved by CDC as a hand sanitizer effective at killing the SARS-CoV-2 virus, along with those that contain at least 60 percent ethanol or 70 percent isopropanol as active ingredients.[9]

Benzalkonium chloride. Popularly known as BKC, BZK or BAC, benzalkonium chloride is the active ingredient in MediDefense mPulse Hand Sanitizer, another product FFF Enterprises distributes. "These BZK-based hand sanitizers don't dry your skin," explains Winkleblech. "Folks who work in the medical field are constantly using hand sanitizer, and their skin becomes dry, cracked and uncomfortable." And, he adds, unlike the alcohol-based sanitizers, the MediDefense mPulse product is nonflammable and hypoallergenic: "It doesn't strip away natural oils, it can last longer and it's approved for food handling."

Revealing Research

While a wide swath of effective products to disinfect common areas and other noncritical environments in healthcare facilities already exists, many products have significant risks in terms of toxicity or discoloring equipment on which they are applied. Others are only effective for a short time, requiring frequent reapplications, and most require keeping surfaces moist for up to a few minutes to effectively kill all microbes. But, some promising research may help to solve these issues.

A research team at the University of Central Florida is working on a spray-on nanoparticle disinfectant that would work almost instantly, and then leave behind a disinfecting film that would be nontoxic to people and nondetectable to touch or the naked eye.[10] And a team at the Technion Israel Institute of Technology in Haifa, Israel, has been studying antiviral polymers that can effectively kill viruses for two weeks or more from a single application.[11]

Another study, jointly conducted by EPA and New York City's Metropolitan Transportation Authority, field-tests current EPA-authorized disinfectants for long-term effectiveness. While no new products are currently being tested, any current disinfectants that show effectiveness will be allowed to update their labeling and marketing.[12]

In Hong Kong, researchers building on previous antibacterial polymers have developed a heat-sensitive antiviral polymer named MAP-1. When the polymer coating detects a rise in temperature, which could indicate the surface is being touched by a hand, it releases antivirals. The scientists at Hong Kong University of Science and Technology say the polymer has been shown to be active for 90 days after application.[13]

Finding the Right Products Is Key

As with all aspects of managing medical operations — whether a primary care practice, an urgent care clinic or other type of facility — a mountain of regulatory red tape is associated with developing and implementing an environmental cleaning plan as part of a larger facility cleaning plan.

While there are plenty of products available to fulfill every requirement, finding the right products to fulfill facilities' cleaning protocols is the first challenge. And, learning about newer products with longer efficiency can help with both labor costs and consistent compliance.

Winkleblech says his team at FFF Enterprises works with clients to help them navigate the maze of regulations surrounding environmental cleaning and disinfecting in medical settings. "We want to provide that sense of security and confidence, as well as improve navigation for our customers in this antimicrobial space," he explains. "We understand there can be a lot of challenges in this marketplace, and we strive to ensure our products are properly registered and marketed." ❖

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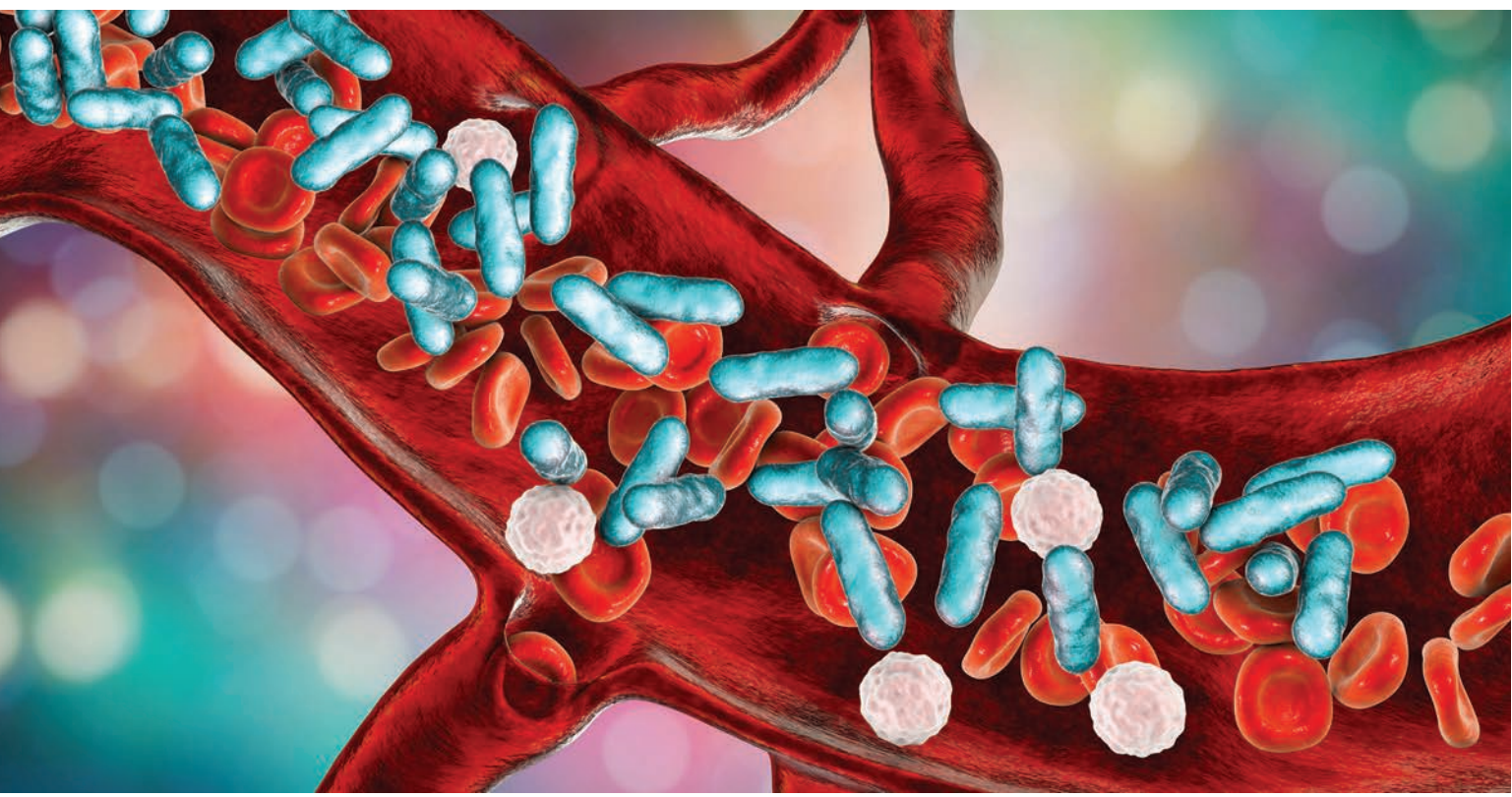
Tackling Sepsis in Hospitals

By raising awareness and developing tools to detect sepsis earlier, healthcare organizations save lives from this often-deadly infection.

By Diane L.M. Cook



THE STATISTICS ARE grim. Each year in the United States, at least 1.7 million adults develop sepsis, and nearly 270,000 of them die as a result of it. What's more, one study showed one in three patients who died in a hospital had sepsis;[1] however, 86.8 percent of hospital sepsis cases are present on admission.[2] Whether patients have sepsis upon entering a hospital or contract it while staying there, these statistics illuminate more must be done to recognize the symptoms of sepsis earlier, confirm diagnosis faster and treat the infection more aggressively to save more lives.

According to the Centers for Disease Control and Prevention (CDC), sepsis is the body's extreme response to an infection. It is life-threatening, and without prompt treatment, often rapidly leads to tissue damage, organ failure and death. Almost any type of infection can trigger sepsis, but those often linked to it occur in the lungs, urinary tract, skin and gut. The most frequently identified pathogens that cause infections that can develop into sepsis include Staphylococcus aureus (staph), Escherichia coli (E. coli) and some types of Streptococcus (strep).[3]

While anyone can get an infection and almost any infection can lead to sepsis, those at higher risk of infection and sepsis are adults 65 and older, people with chronic medical conditions (especially diabetes, lung disease, cancer and kidney disease), those with weakened immune systems, sepsis survivors and children younger than 1 year old. Signs and symptoms of sepsis can include any one or a combination of symptoms, including confusion or disorientation, shortness of breath, rapid heart rate or low blood pressure, fever, shivering or feeling very cold, extreme pain or discomfort and/or clammy or sweaty skin.[3]

Fortunately, several organizations are currently tackling this serious infection in hospitals with significant results.

Augusta Health

Augusta Health, a nonprofit hospital located in Virginia's Shenandoah Valley, prides itself on providing patients with excellent care using state-of-the-art technology. In 2015, Augusta Health established a Sepsis Task Force to find ways to reduce sepsis mortality, which began by researching more efficient ways to detect it. Penny Cooper, DHSc, director of data science and governance at Augusta Health, says, "Since early identification of sepsis remains the greatest barrier to compliance with recommended evidence-based bundles, Augusta Health's objective was to improve the early identification and treatment of sepsis by developing an automated sepsis screening tool."

The tool, which the hospital launched in May 2016 in its emergency department, employs an algorithm that analyzes patient clinical data to determine when a patient shows signs of becoming septic. Based on standard sepsis screening measures, an alert is activated when two or more variables (body temperature, pulse, respiratory rate and white blood cell count) register outside of the normal range and when one or more variables from an additional group (systolic blood pressure and mean arterial pressure check, lactate level or creatinine level) fall outside of the normal range.[4]

Since the sepsis mortality rate rises significantly each hour when treatment is delayed, the algorithm automatically runs every 15 minutes. When the parameters trigger an alert, a secure text is delivered directly to the emergency department charge nurse's cell phone. If the patient is determined to be septic after an assessment, the charge nurse alerts the entire hospital via an overhead communication. The house supervisor, a phlebotomist and a pharmacist respond to the page by going to the emergency department and assisting with lab work, rapid administration of antibiotics and documentation.[4]

In March 2020, Augusta Health started to work with its ICU staff on a handoff sepsis checklist to ensure all components of sepsis screening are completed in a timely manner. However, because the ICU staff at Augusta Health found it difficult to identify "time zero," the Sepsis Task Force is revisiting this item to develop a matrix for its ICU staff. If this matrix works well, the hospital will implement it for other units in the patient tower.

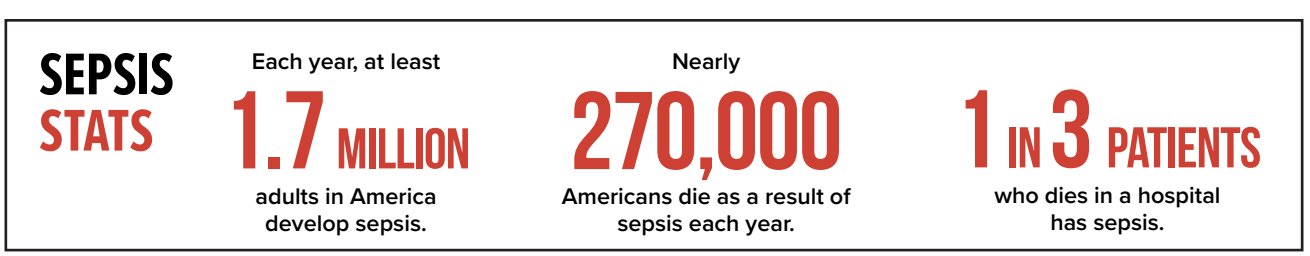
In addition to providing continuing education on sepsis compliance to its hospital staff and physicians, Augusta Health has promoted its automated sepsis screening tool to other hospitals in the state for which it has received recognition. The sepsis screening tool was named Health Quality Innovator of the Year for Data-Driven Care in 2018,[5] and it won the Virginia Patient Safety Summit Performance Improvement award in 2020.

"Our automated sepsis screening tool has significantly reduced Augusta Health's overall sepsis mortality rates," says Dr. Cooper. "By subtracting the actual mortality rate from the expected mortality rate, we estimate that 300-plus lives have been saved since the automated sepsis screening tool's initial implementation in the second quarter of 2016. We expect to continue our automated sepsis screening tool's use to readily identify the patients with sepsis and begin treatments in a more timely fashion."

CDC

As part of CDC's goal to provide health information that protects the nation against expensive and dangerous health threats, the agency has developed a guidance document and campaign to help healthcare professionals tackle sepsis in hospitals.

According to CDC, because there is no confirmatory diagnostic test for sepsis, diagnosis requires clinical judgment based on evidence of infection and organ dysfunction. Therefore, in 2018, CDC developed the Hospital Toolkit for Adult Sepsis Surveillance to help healthcare professionals assess adult sepsis incidence within their facilities. "We have been encouraged to hear that the toolkit is already being used by hospitals to track healthcare facility-level sepsis incidence and outcomes," says Raymund Dantes, MD, MPH, at Emory Healthcare and medical advisor to CDC's sepsis team, who helped develop the toolkit. "This shows that ongoing tracking of sepsis using electronic health records is feasible, can be incorporated into healthcare quality improvement initiatives aimed at driving sepsis rates down, and will be used to assess how well local sepsis prevention, early recognition and treatment programs are reducing the devastating impact of sepsis in their communities."[6]



In addition, CDC's Get Ahead of Sepsis campaign is a national educational effort that emphasizes the importance of early recognition, timely treatment, reassessment of antibiotic needs and prevention of infections. The infographic for this campaign outlines how healthcare professionals can get ahead of sepsis with four easy steps: 1) Know the signs and symptoms of sepsis; 2) Act fast if you suspect sepsis; 3) Prevent infections by following infection control practices and ensure patients receive recommended vaccines; and 4) Educate patients and their families about preventing infections, keeping cuts clean and covered until healed, managing chronic conditions, recognizing early signs and symptoms of worsening infection and sepsis, and seeking immediate care if sepsis presents.

If healthcare professionals suspect sepsis, they should: 1) Immediately alert the clinician in charge; 2) Start antibiotics as soon as possible in addition to other therapies appropriate for the patient; and 3) Check patient progress frequently.[3]

HCA Healthcare

Founded in 1968 and based in Nashville, Tenn., HCA Healthcare is one of the nation's leading providers of healthcare services comprising 2,000 sites of care, including 187 hospitals in 21 states and the United Kingdom. HCA Healthcare is a learning health system that uses the significant data it collects from approximately 35 million annual patient care encounters to inform and improve care for patients. Its national clinical data warehouse, which receives information from electronic health records (EHRs), is the heart of HCA Healthcare's data ecosystem that has the ability to aggregate and analyze data streams in real time and feed tools that provide actionable information to health professionals.

Using this information, HCA Healthcare's clinical experts, data scientists and programmers developed Sepsis Prediction and Optimization of Therapy (SPOT), an algorithm-driven, real-time monitoring system that uses predictive analytics to help clinicians "spot" potentially deadly sepsis infections. SPOT was developed over a two-year period from 2017 to 2019, with enterprise-wide rollout completed in 2019. To date, SPOT has been employed to treat 2.5 million patients and has helped save an estimated 8,000 lives in the last five years.

SPOT continuously monitors vital signs, lab results, nursing reports and other data that can inform treatment and recognizes critical data points in patients' EHRs. It links algorithmic sepsis detection with clinical workflow and quickly alerts care teams to important, often subtle changes in a patient's condition, so they can take appropriate action. Although SPOT does not make decisions, it does monitor patients in the background and brings vital, accurate and up-to-date information to the healthcare professionals who make decisions.[7]

According to HCA Healthcare, since the symptoms of sepsis are similar to those of many other illnesses, diagnosing it can be very challenging. However, studies have shown with early recognition followed by aggressive treatment, patient survival can increase significantly because sepsis mortality increases 4 percent to 7 percent every hour it goes undetected.[7]

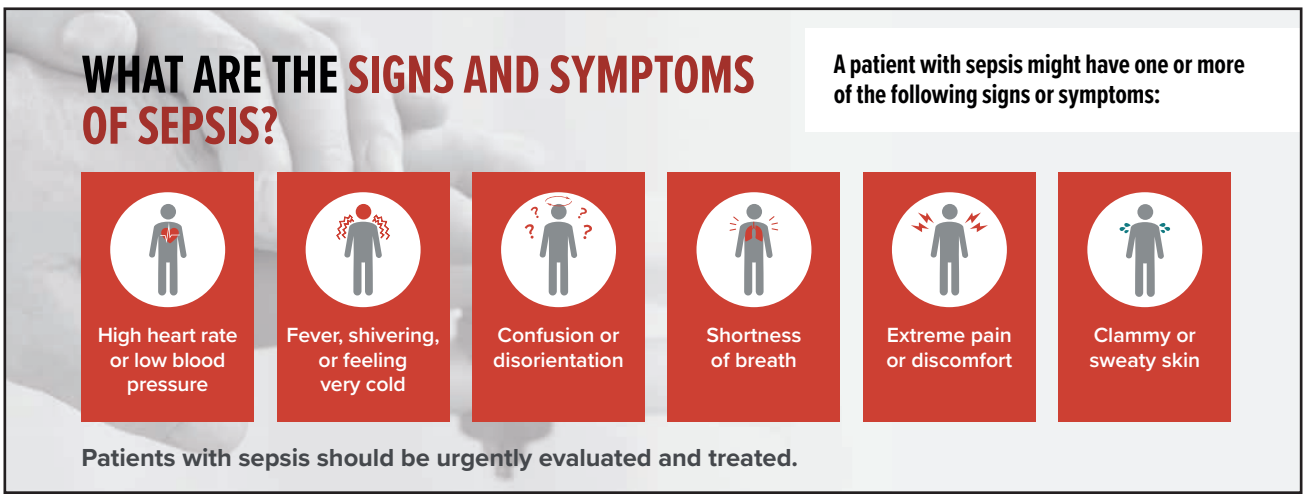
In 2019, HCA Healthcare received the John M. Eisenberg Patient Safety and Quality Award from The Joint Commission and National Quality Forum for SPOT, which can signal potential sepsis six hours earlier than traditional screenings.[8]

Jonathan Perlin, MD, HCA Healthcare's chief medical officer and president of the Clinical Operations Group, says, "With sepsis, minutes matter, and just as we've improved safety in our homes with smoke detectors that 'sniff out' possible fire, HCA Healthcare's SPOT technology now helps detect sepsis earlier, accelerating treatment, improving the care provided to our patients and thereby saving lives."

Sepsis Alliance

In 2007, Carl Flatley, DDS, MSD, founded Sepsis Alliance in memory of his daughter, Erin Kay Flatley, who died unnecessarily from sepsis in 2002. The organization produces information and educational material to raise public awareness about sepsis and to help healthcare professionals provide information to the public when sepsis strikes.

In 2011, Sepsis Alliance designated September as Sepsis Awareness Month[9] to bring healthcare professionals and community members together in the fight against it. Sepsis Awareness Month is a national observance in which Sepsis Alliance spends the month working intensely to raise awareness, including hosting community events and its annual Sepsis Heroes



gala, and providing toolkits for heath systems and hospitals to spread the word in their facilities. Sepsis Alliance also releases its annual Sepsis Awareness Survey every September. According to the organization, sepsis awareness has increased by 31 percent since 2012, when Sepsis Alliance conducted its first online survey. And since 2003, sepsis awareness has risen from 19 percent to 71 percent.[10]

Because adults, especially those over 65, are particularly susceptible to sepsis, Sepsis Alliance launched its "It's About TIME" campaign in 2019 to make sepsis symptoms more memorable. As a result, when adults potentially have sepsis, they will know when to seek emergency medical care. The acronym TIME stands for T (temperature: higher or lower than normal), I (infection: may have signs and symptoms of an infection), M (mental decline: confused, sleepy, difficult to rise) and E (extremely ill: severe pain, discomfort, shortness of breath). The campaign encourages people who experience a combination of these symptoms to seek urgent medical care, call 911 or go to a hospital with an advocate and ask: "Could it be sepsis?"[11]

Sepsis Alliance also founded "Erin's Campaign for Kids" in memory of Erin, which aims to combat the high incidence and mortality rates of sepsis among children. The campaign creates awards and training programs for nurses and other health professionals to help identify and treat sepsis that causes more than 18 child deaths per day or 6,800 child deaths per year.[12]

To coincide with Sepsis Awareness Month, Sepsis Alliance also created Sepsis Heroes in 2011, another annual event that honors patients, doctors, nurses, hospitals and associations making a significant contribution to sepsis awareness and education among the public and healthcare professionals.[13]

Thomas Heymann, president and CEO of Sepsis Alliance, has led the organization's efforts to launch the Sepsis Alliance Clinical Community, a network that provides sepsis best practice resources and guidance to health professionals in the United States, which is led by a team of expert nursing leaders with critical experience in caring for sepsis patients and developing and implementing sepsis protocols. The community is also led by the Sepsis Alliance Institute, which has awarded more than 18,500 continuing education contract hours to thousands of medical professionals, and Sepsis Alliance Voices, a new platform for national and state advocacy.

According to Heymann, "Sepsis is the number one cause of death in U.S. hospitals and it is a national health crisis. The work Sepsis Alliance does will help save lives by raising awareness of sepsis as a medical emergency."

Ohio Hospital Association

Established in 1915, the Ohio Hospital Association (OHA) represents the interests of 14 health systems and 240 hospitals across the state. Hospitals include acute care facilities, long-term acute care facilities and those specializing in psychiatry, rehabilitation, specialty surgery and pediatrics.

In 2015, to celebrate its 100th birthday, OHA decided to form the Institute for Health Innovation to acknowledge this milestone, choosing sepsis as one area that Ohio hospitals desperately needed to focus on. The institute developed the Statewide Sepsis Initiative (SSI), which starts with participating hospitals performing a gap analysis to evaluate their individual performance with early recognition and early intervention and identify opportunities for improvement. Key tenets of SSI are to: 1) Collect, analyze, monitor and report sepsis mortality-related data; 2) Design and provide pertinent monthly evidence-based continuing education programs addressing current trends in sepsis care, leveraging regional, state and national subject matter experts;

Sepsis Screening Tools

1) Baxter's Starling Fluid Management Monitoring System provides a dynamic assessment of fluid responsiveness used to guide treatment in sepsis patients to determine whether to administer fluid or increase vasopressors: USStarling.Baxter.com
2) SeptiCyte's SeptiCyte RAPID uses a patient's immune system for rapid and accurate diagnosis and can determine sepsis with certainty in just one hour: Septicyte.com
3) Inflammatix's InSep Acute Infection & Sepsis Test is a blood test that can identify sepsis quicker, distinguish between a bacterial or a viral infection, and classify its severity: www.inflammatix.com
4) ThermoFisher Scientific's BRAHMS PCT (Procalcitonin) biomarker assay aids differential diagnosis of bacterial infection and sepsis and provides expanded insight to aid clinicians in reducing antibiotic use: Thermofisher.com/aboutsepsis
5) CytoSorbents Corp.'s CytoSorb modulates the excess immune response and contributes to circulatory stabilization to increase the chance of recovery: www.cytosorb.com (Note: CytoSorb is not yet approved by the U.S. Food and Drug Administration (FDA). FDA has given emergency use authorization for use of CytoSorb in COVID-19 patients only.)
6) T2Biosystems T2 Bacteria detects bacterial or fungal pathogens that lead to sepsis: www.t2biosystems.com
7) GenMarkDx's ePlex Blood Culture Identification Panels identify more than 95 percent of the pathogens that can cause bloodstream infections: GenMarkDx.com

3) Collaborate with provider groups and other state and national quality initiatives; 4) Assess and address healthcare provider needs related to the timeliness and accuracy of diagnosing sepsis; and 5) Target efforts toward early and appropriate treatment of sepsis not present at time of admission.

OHA staff, including nurses and physicians, work with hospital staff and clinicians who lead the focus on sepsis. Educational sessions are also conducted virtually via teleconference and webinars. So far, 125 hospitals are participating in the five-year program, and it is hoped that eventually the majority of the state's more than 200 hospitals will participate.[14]

One of the goals in OHA's 2019-2021 strategic plan is for SSI to continue its efforts to reduce sepsis mortality to a rate of 14.9 percent by the end of 2021. In the past year, OHA says more than 45,000 sepsis encounters have occurred in Ohio hospitals and, of those, it estimates 5,480 lives were saved from sepsis due to SSI.

In September 2020, the Sepsis Alliance named OHA as a Sepsis Hero in recognition for its work in reducing sepsis mortality by raising awareness and improving management throughout Ohio.[15] And, in support of Sepsis Alliance's Sepsis Awareness Month, OHA has been working with the Ohio governor's office for the past five years to officially proclaim September as Sepsis Awareness Month.

John Palmer, director of media and public relations at OHA, says, "Through ongoing focused efforts, the OHA's Statewide Sepsis Initiative will continue its work toward further decreasing sepsis mortality through early recognition and through early, appropriate intervention. Increasing community awareness, providing continuing education programming, partnering with Sepsis Alliance and monitoring our progression are examples of strategies that we will continue to utilize."

Awareness and Tools Reduce Incidence and Death

It is hoped that with continued sepsis awareness and education, together with new protocols and state-of-the-art tools, healthcare professionals will continue to help patients lower their risk and incidence of sepsis, and most importantly, greatly reduce the number of deaths caused by sepsis every year in the United States. ❖

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Importing Drugs: Is It Safe and Responsible?

As Americans continue to grapple with the skyrocketing costs of prescription drugs, many are turning to other countries to access medications they need at prices they can afford.

By Trudie Mitschang

PURCHASING PRESCRIPTION drugs imported from other countries has long been controversial. The allure of significant cost savings often fuels demand, while the potential health risks have driven legal restrictions and widespread government crackdowns over the years. But, whether these purchases are illegal or not, faced with the rising costs of pharmaceuticals, millions of Americans regularly buy drugs outside the U.S., typically online or while traveling abroad. In a 2016 Kaiser Health Tracking Poll, a whopping 80 percent of respondents said they or someone in their household had at some point imported a drug.[1] Another recent University of Florida study found 1.5 percent of adults — more than two million Americans — purchase their prescription drugs from outside the U.S. to save money.[2] And study researchers cautioned that numbers are likely to rise with the rapid growth in unemployment related to the COVID-19 pandemic and subsequent loss of health insurance for many Americans. "With the economic and health consequences of COVID-19 disproportionately impacting minority and low-income populations, more people in those groups may be seeking an alternative way to meet their medication needs," said the study's lead author Young-Rock Hong, PhD, MPH, an assistant professor of health services research, management and policy at the UF College of Public Health and Health Profession.

Dr. Hong notes that in recent years, a number of proposals have been discussed as strategies to counteract increases in drug pricing. For example, last year, the Trump administration announced plans to allow importation of drugs from Canada in an effort to stimulate price competition. The U.S. Food and Drug Administration (FDA) also introduced the Safe Importation Action Plan, with proposed pathways to allow for the safe importation of drugs originally intended for foreign markets. If finalized, the plan would permit U.S. consumers to purchase certain drugs from Canada. But the question remains: Is it safe?

Counting the Cost of Counterfeits

Many people assume if drugs are imported from a highly developed neighbor like Canada that safety risks will be minimal. But experts say not necessarily. While Canadian regulators ensure the safety and authenticity of medicines entering their market and intended for use by Canadian patients, they do not apply those same standards for medicines intended for export only. In a statement on the topic, the Canadian government said, "Health Canada does not assure that products being sold to U.S. citizens are safe, effective and of high quality, and does not intend to do so in the future."[2]

According to FDA reports, while nearly half of imported drugs claim to be Canadian or from Canadian pharmacies, 85 percent of such drugs were actually from different countries. Given that drugs imported from abroad lack oversight by any health authority, there is a high likelihood such drugs — if not counterfeit — could nonetheless be mishandled or could display deceptive or incorrect packaging and labeling.[3]

Many people assume if drugs are imported from a highly developed neighbor like Canada that safety risks will be minimal.

The World Health Organization (WHO) conservatively estimates one in 10 medications sold in the world is substandard or falsified. According to a report by WHO, 10 percent of drugs worldwide and approximately 50 percent consumed in developing nations are counterfeit.[4] One of the challenges is that in the absence of FDA's oversight and proper enforcement of laws developed for patient safety, which is undermined by drug importation, these products could easily infiltrate the pharmaceutical supply chain, with potentially life-threatening consequences. FDA has repeatedly stressed it cannot ensure the safety of imported drugs, which begs the question from a patient perspective: Is the cost savings worth the risk?

Here are some important considerations:

- Evidence suggests some drugs shipped to the U.S. from Canada have their origins in other countries with amenable regulatory systems like Pakistan and Bulgaria.
- Counterfeiters are getting more sophisticated with their technology. In 2015, for example, a Canadian online pharmacy was fined $78 million for conspiring to allegedly smuggle unapproved and mislabeled prescription drugs into the U.S.[5] That same year, FDA and Interpol confiscated fake drugs from as many as 1,000 websites.[6]
- According to The Alliance for Safe Online Pharmacies, there are at least 35,000 illegal online pharmacies at any given time that do not comply with laws and pharmacy standards.[7]
- Imported medications and their ingredients, although legal in foreign countries, may not have been evaluated for safety and effectiveness in the U.S. These products may be addictive or contain other dangerous substances.

• The medication's label, including instructions for use and possible side effects, may be in a language individuals do not understand, or the label may make medical claims and suggest specific uses not adequately evaluated for safety and effectiveness.

• An imported medication may lack information that would permit someone to be promptly and correctly treated for a dangerous side effect caused by the drug.

The Skyrocketing Cost of Prescriptions

In data analyzed from a 2015-2017 National Health Interview Survey, participants were asked if they had purchased prescription drugs from countries outside the U.S. to save money. Those who had were more likely to be older, be an immigrant and have inadequate insurance coverage and financial constraints that impact their ability to refill prescriptions. They were also more likely to use the Internet for healthcare information.[1] "Patients might not be getting what they think they are getting," said the UF study's co-author Juan Hincapie-Castillo, PharmD, PhD, an assistant professor of pharmaceutical outcomes and policy in the UF College of Pharmacy. "This is particularly dangerous to patients needing medications with a narrow therapeutic index. In other words, a medication with a small dose deviation can result in severe adverse events."[1]

Still, many believe the risk is worth the cost savings. Amanda Mazumder, a 27-year-old graphic designer in St. Paul, Minn., began buying birth control pills online when she became frustrated by the cost of her prescription. She couldn't afford to pay $150 a month for her birth control, but found an online Canadian pharmacy that sold her a three-month supply for $60. And, Los Angeles resident Bobby Grant has relied on foreign pharmacies for years to get medicine for his partner's severe asthma. Grant travels internationally for his job, and each time he's in Mexico or France, he buys 10-packs of inhalers and 20-packs of nebulizer solution for a fraction of what they would cost in the U.S. — medications costing $300 a month if purchased here. Grant estimates he saves at least $2,500 a year by buying the drugs overseas.[8]

Mazumder and Grant are far from alone. Research shows people who have imported medicines range from college students in their 20s to retirees in their 80s. Their purchases include medications to treat chronic conditions — such as high blood pressure and thyroid problems — and acute problems such as sinus infections and acne.

Of course, safety isn't the only concern for people who purchase drugs from other countries. According to FDA, it is illegal for Americans to import drugs into the U.S. for personal use. The law isn't rigorously enforced, in part because it is difficult to monitor the entry of medicine in suitcases and small packages. But, in 2015, FDA implemented a rule that would give government border inspectors expanded authority to destroy drugs imported for personal use at their point of entry. Yet, as Mazumder and Grant prove, when people are desperate, they are willing to risk breaking the law.[8] "The reality is that literally millions of people get their medications this way each year, and they are either saving a lot of money or they are getting a drug they wouldn't have been able to get because prices are too high here," says Gabriel Levitt, president of PharmacyChecker.com, an online company that allows people to compare prescription drug prices among international and U.S. pharmacies.[9]

For people with diabetes, for example, the inability to pay U.S. prices for insulin can be a matter of life and death, which is why so many families look to Canada or Mexico and are willing to break the law if it means staying alive. Robin Cressman, who was diagnosed with type 1 diabetes in 2012 and has become a vocal advocate for lower drug prices, says even with insurance, she was paying $7,000 a year out of pocket for the two insulin drugs she needs: Lantus and Humalog. At one point, her credit card debt hit $30,000. Then, while on an outing in Tijuana, Mexico, she popped into a few pharmacies to see if they stocked her medications. With little fanfare, she says, she was able to buy both

drugs over the counter for less than 10 percent of what they cost her at home. "I left Tijuana that day absolutely trembling because I could not believe how easy it was for me to get my insulin," she says, "but also how little money it cost and how badly I was being extorted in the U.S."[9]

Colorado First of Several States to Pioneer Drug Importation Program

In January, Colorado became the first state to formalize a prescription drug importation program. "We're a pioneering state," said Kim Bimestefer, head of Colorado's Department of Health Care Policy and Financing. "We lead. We're not shy about being first into the gate and figuring this out. We want to bring the savings to Colorado."[10]

Bimestefer's department is in charge of creating the importation program and is soliciting bids from Canadian wholesalers to purchase drugs for the Colorado market, as well as importers to package and distribute the drugs. The state will also hire a company to handle administration of the program, including compliance monitoring. It hopes to have all three vendors in place by fall 2021. "We're confident that what we're putting together works within the guidelines established by Canada," Bimestefer says, adding that the financial savings for Colorado are in brand name drugs. Her department compared the cost of 50 popular drugs in Colorado with the cost of the same drugs in Canada and found Coloradans pay, on average, 63 percent more. "Our consumers and employers are paying 20 times more the price than Australia is for the same thyroid medication. That's not OK. So, we want to take the same drugs, with the same FDA approval, and just bring them in through a different pathway that allows us to bring so much more savings."

The state's plan is to hire a wholesaler, importer and compliance vendor by this fall and begin importing drugs from Canada, and possibly France and Australia, by 2023. Bimestefer says the draft proposal the state sent to the federal government (which will have final say) includes at least 167 drugs.

Colorado is not alone in its efforts to formally launch an importation program. Florida, Vermont, New Hampshire and Maine are also moving ahead with plans to import prescription drugs from Canada, a strategy approved last year by former President Donald Trump.[11] While it remains unclear whether the Biden administration will support the proposed plan, Trish Riley, executive director of the National Academy for State Health Policy, said states have worked hard to set up procedures to ensure drugs coming from Canada are as safe as those typically sold at their local pharmacy. She noted that many drugs sold in the U.S. are already made overseas.

Riley acknowledged the Biden administration could choose not to defend the importation rule in the Pharmaceutical Research and Manufacturers of America court case or ask for an extension to reply to the lawsuit. "Right now, it's murky," she said of figuring out what the Biden team will do.[11]

In January, Colorado became the first state to formalize a prescription drug importation program.

Discussion and Policy Changes Are Needed

Clearly, more discussion and policy changes are needed, including a willingness by all stakeholders to address the root causes and issues surrounding unaffordable medication costs. With more Americans anticipated to purchase prescriptions outside the U.S. in the coming months and years, patient education and stringent quality control measures are more important than ever. "Patients should be informed of the potential risks they can encounter," Dr. Hong said, "and policies that seek to pursue drug importation should reinforce quality assurance and strict monitoring processes to promote safe administration of imported medication in the U.S. market."[1] ❖

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Long-Term Effects of COVID-19

By Meredith Whitmore

Long-haul COVID, now termed PASC, is a very real effect of the SARs-CoV-2 virus, but few physicians are familiar with the symptoms and where to send patients for treatment.

"I WAS A healthy, active person with no health problems," Jenifer Johnston told ABC News affiliate KATU, in Portland, Ore. "I was happy, and now I can barely walk." Johnston contracted the SARs-CoV-2 virus in March 2020. A year later, she is adjusting to life with long COVID, or "long-haul" COVID-19 symptoms as some in healthcare phrase it. Even now, she suffers from shortness of breath, lack of endurance and cognitive issues such as severe short-term memory loss and anxiety that were not present prior to her illness.[1] Unfortunately, she is far from alone.

Perhaps you have seen patients such as Johnston at your own healthcare facility. Or, perhaps you have seen them unknowingly, unaware their symptoms are actually COVID-19-related, occurring weeks and months after their recovery from the initial COVID-19 infection.

Regrettably, few physicians are yet aware that long-haul symptoms can occur even months after the infection, and the long-term problems such as brain fog and fatigue are often misdiagnosed or even dismissed. Pediatric nurse Jennifer Minhas, another COVID-19 survivor, is one example of this. Last year, she experienced new symptoms, including severe fatigue, heart palpitations and chest pain, four weeks after she had recovered from the initial illness. When she sought medical help for the issues, her primary care physician told her she was just being overly anxious. According to Minhas, "That wasn't what I needed to hear."[2]

In fact, it is not what any "long-hauler" needs to hear. Somewhere between 10 percent and 30 percent of COVID-19 sufferers experience long-term side effects (the actual percentage is unknown since the illness is still relatively new and data are still being gathered). After months of being labeled "long COVID," in February, Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, revealed its new official name: post-acute sequelae of SARS-CoV-2 (PASC) infection.[3] PASC symptoms can include chest pain, heart palpitations, orthostatic intolerance, crushing fatigue, brain fog, anxiety, inability to concentrate, lingering cough, lack of endurance, memory problems, depression and many others since the list of reported symptoms is vast, complex and seemingly ever-growing.

Observations from the Johns Hopkins COVID Clinic

PASC clinics are being launched around the United States to help COVID-19 patients cope with the aftermath of this vicious illness. The Johns Hopkins School of Medicine's Post-Acute COVID-19 Team (JH PACT) is one of, if not the most well-

established, such clinics. It is perhaps the longest running in the country, having opened its doors in April 2020, when doctors first recognized the need for a multidisciplinary, collaborative, ambulatory framework that supports COVID-19 survivors.

Alba Azola, MD, a physical medicine and rehabilitation specialist, assistant professor at the Johns Hopkins School of Medicine and co-director of the PACT clinic, says, "We knew from work in our institution that patients who have prolonged intensive care unit (ICU) stays present with post-intensive care syndrome, affecting mental health and causing cognitive as well as physical impairments, including chronic fatigue, nerve damage, critical illness myopathy, anxiety, depression, post-traumatic stress disorder, and impaired attention and memory. Because of the pandemic, we realized we were going to have an influx of patients who were going to have prolonged hospital stays who were going to need pulmonary, as well as rehabilitative care. So with that in mind, we decided to start creating a system to provide the needed services. That's how our PACT clinic came about."

And doctors at JH PACT soon noticed something unexpected. "We quickly started seeing that not only patients who had ICU stays had long-term symptoms," Dr. Azola says, "but we also started seeing that patients who did not require hospitalization also presented with long-term, lingering symptoms. Then, the clinic started seeing both types of patients. In terms of the symptoms, they present a little differently. In the cases that had a severe COVID 19 [illness] with prolonged mechanical ventilation, they will present with severe deconditioning and muscle weakness, in part from requiring paralyzation for venting and being bedbound for weeks. In this population, we usually start the rehabilitation in the ICU, and some may require subsequent admission to an inpatient rehabilitation unit. Once we see them [as an] outpatient, we continue to progress them with outpatient physical, occupational and speech therapy to continue to recover endurance and build strength. A lot of them present with cognitive impairment — mainly memory deficits, deficits in concentration and brain fog. There's another group of patients, and these are the patients who did not stay in the hospital who also present with chronic fatigue, palpitations, deconditioning and quite a bit of cognitive impairment when it comes to memory and higher-level cognitive tasks. They also present with difficulty in tolerating changes in position or posture, or postural orthostatic tachycardia syndrome (POTS)-like symptoms."

Tae Chung, MD, a physical medicine and rehabilitation specialist and an assistant professor of physical medicine and rehabilitation and neurology at the Johns Hopkins University School of Medicine, is founder of the POTS clinic at Johns Hopkins. He says POTS is largely misunderstood in general, and now that many long-hauler COVID sufferers are displaying POTS-like symptoms — or "COVID POTS" — he wants to raise awareness about this disorder. Dr. Chung says he sees many long-haulers present with "a lot of severe fatigue and brain fog, which are very typical symptoms of POTS. And though there is no official data or solid research just yet, surveys and several publications indicate that more than 90 percent of COVID long-haulers were either asymptomatic or had very mild infections of COVID-19. These are not patients who were in the ICU." He also expects to see many more such patients, which he adds, "is truly scary."

"POTS is a true neurological disorder, though many doctors do not recognize it and even dismiss it," he says. "It takes, on average, six years for a patient to be diagnosed with POTS, even though POTS is one of the most typical reasons for chronic fatigue and brain fog, which are so common today." And as for how POTS might play a role in COVID-19, Dr. Chung says, "I see a large number of patients who present with POTS-like symptoms in the clinic now because of COVID-19. There is good evidence that POTS is basically a sympathetic neuropathy of denervation. And that denervation affects blood volume, among other things, causing dizziness, fainting, chronic fatigue and brain fog, all of which are seen in typical POTS and COVID POTS. Though there is not yet research to back this theory up, what I have observed makes me wonder whether there is something very specific about the virus that causes COVID-19, since I have never seen this many patients come in with POTS-like symptoms after having the flu, for example. The COVID-19 virus seems to directly infect the sympathetic nerves, which causes blood vessels to contract differently, negatively affecting blood regulation and leading to COVID POTS."

Regrettably, few physicians are yet aware that long-haul symptoms can occur even months after the infection, and the long-term problems such as brain fog and fatigue are often misdiagnosed or even dismissed.

Nisha Gilotra, MD, assistant professor of medicine at the

Johns Hopkins School of Medicine in the division of cardiology, echoes Dr. Chung's observation with regard to COVID's ability to directly infect tissues and damage blood vessels, adding her own perspective on heart involvement. "We are learning more and more every day in terms of how the virus responsible for COVID-19 can affect the heart," she explains. "There is much more to it than its ability to affect the respiratory system. It can actually enter the cells in the heart directly and affect the heart in a multitude of ways. In the acute setting, because of the systemic inflammation, it can cause an inflammatory cardiomyopathy or something called myocarditis, a condition garnering a lot of attention in the media and in scientific studies. We're learning that myocarditis is probably less commonly occurring than we think, and that this virus has the ability to actually affect the blood vessels more so in the heart, like it does in the rest of the body, and cause damage to the heart that way by disrupting the surface of the blood vessels. This can lead to a number of different things clinically, with one of them being blood clots."

"For patients who have had COVID-19, who don't have a cardiac history," Dr. Gilotra adds, "my colleagues and I are seeing long-hauler syndrome or long COVID syndrome, where the symptoms can often be nonspecific. They can cover a lot of organ systems, and present with fatigue, shortness of breath, palpitations and dizziness, among other manifestations. It could be the respiratory system, the cardiovascular system or neurologic. And so, what's been important for us, my colleagues and I, is to really have a multidisciplinary approach to patients so that we're taking all of the organ systems into account. We're also trying to recognize when it would be appropriate to do further evaluation from a cardiac perspective. There is more and more data coming out of MRI and other imaging studies where, in patients who otherwise don't have cardiac issues, the rate of cardiac involvement in a minor infection is very, very low, so keeping that in mind."

Post-COVID Syndrome?

No one expected post-polio syndrome to afflict polio sufferers many decades after they contracted and survived the polio virus. Is it possible a post-COVID syndrome could attack in a somewhat similar manner, even if PASC abated decades prior? "That's the big question," Dr. Azola explains. "That is something that we, by following the patients, researching the natural history of their disease and getting a biorepository of samples, we can identify different biomarkers that could help us understand what patient factors, as well as viral factors, are affecting the people who have long-term symptoms. We are meeting with a group of infectious disease doctors who started very early with intervention for outpatients, or patients who were never hospitalized but sought treatment for COVID, whether it was convalescent plasma or monoclonal antibody. These specialists want to collaborate with us to help look at that population to see how treatments can impact it as well. So there's a lot of work to be done, and we don't have the answers right now, but we are trying to come up with the questions and find ways to make better-informed decisions and better counsel patients."

What Else Should Physicians Know?

Soo-Yeon Kim, MD, a physiatrist, director of musculoskeletal medicine in the Johns Hopkins Musculoskeletal Center and co-director for the PACT clinic, explains how important it is for primary care physicians and other healthcare professionals to understand patients do suffer symptoms even months after COVID-19, even if they were initially asymptomatic. "It's real, and awareness is really important," she says, explaining Johns Hopkins has seen many long-haul COVID patients arrive at PACT from other healthcare facilities because their primary care physician or other doctors did not believe them regarding long-term symptoms. They were dismissed and sometimes even belittled. "Healthcare providers should be aware of the long-haul symptoms and find resources around their region to help their patients," she explains. "Many primary care physicians are not really familiar with these types of symptoms, and at times they mismanage them or think that the patient is normal when they are not. This leads patients to experience more anxiety and depression, thinking that they are crazy. But when patients

present with cognitive symptoms and mental health issues months later, don't assume that they are crazy. Just because their labs and studies might be normal, these patients are telling the truth, and they are genuinely suffering. We just don't know the exact mechanism of COVID-19 yet, but don't underestimate the effects of COVID. Initially, when ICU patients are discharged, they are so happy that they survived, but they don't realize the long-term effects of it. And months later, they're learning their judgment and memory are not as good as before, which is very discouraging."

Dr. Azola is just as passionate about telling physicians and other healthcare workers that long COVID is real. "A lot of patients find that some healthcare providers don't necessarily believe what the patient is feeling or experiencing," she says, "and it can be debilitating to the point where they have physical difficulty going back to work, for example. And it can be difficult for them to find providers who understand that these are real side effects of having the infection. So, I think that it's important to have an awareness that there are a significant group of patients who will continue to present long-term symptoms after the infection, and that there are ways we can support their recovery and help them recuperate and get back to their normal lives. I think providers should be aware and should be able to direct their patients to find the providers who are treating this, because there are ways that we can help them cope and help them compensate and get back to more normalcy. Anywhere they will let me speak, I will try to spread the word. This is a real collection of symptoms, and these patients need help."

Dr. Kim also stresses the importance of physiatrists who work in the relatively underpublicized medical field of physical medicine and rehabilitation. "A lot of people think COVID-19 affects primarily the lungs, and it's a respiratory disease," Dr. Kim explains. "They all think that this is a medical condition, so they run labs and images and all that. Actually, what we're seeing more is that after they recover from the infection, what long-haulers really need is functional recovery or cognitive recovery. And the people who are specialized in that are physiatrists. We are the ones who can manage all of the symptoms, and I think people will need more awareness of this field and [need to know] where to go to when those symptoms happen. Primary care physicians might not know this yet."

The Future

During 2020, medicine meant constant discovery for healthcare workers who fought to treat COVID-19 and learn more about its mechanisms and symptoms. The world, too, has been focused on keeping the virus at bay through masks, social distancing and handwashing, among other preventive measures. And a year into this process, medical professionals now know much more as data are multiplying and studies continue.

What does the future hold for both long-haulers and COVID-19 research and treatment? Dr. Gilotra is hopeful. "I think that we are, as a profession, evolving our focus in the pandemic," she says. "The last year has been dedicated to prevention and treating patients who are acutely ill, figuring out when to test patients, when to clear them, etc. But I think this next phase is really going to focus on the long-term consequences of COVID-19 infection, ranging from cardiovascular complications to respiratory, to psychosocial impacts. I think we've yet to learn a lot more about what the longer-term impact is going to be. We will advocate for the profession to dedicate efforts to this very important aspect of COVID-19."

"Healthcare providers should be aware of the long-haul symptoms and find resources around their region to help their patients."

Indeed, now that long-term symptoms of COVID-19 have been identified as PASC, Dr. Fauci said the National Institutes of Health (NIH) has been granted $1.15 billion in funding over the course of four years to look at PASC, how it affects the population, and how many people have it. "It's very difficult to treat something when you don't know what the target of the treatment is," said Dr. Fauci. "And, that's the reason why it's extremely important to take a look at these individuals, not only the scope of this and not only, you know, the depth and breadth of the symptoms, but also to try and have some correlate that actually is the pathophysiological correlate."[3] ❖

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Myths and Facts: **Antibiotics**

To staunch the growing threat of antibiotic resistance, the medical profession is pivotal in properly prescribing antibiotics and educating patients about their appropriate use.

By Ronale Tucker Rhodes, MS

ANTIBIOTICS ARE MAJOR lifesavers in medical history, helping to save millions of lives globally. They can be loosely defined as the variety of substances derived from bacterial sources (microorganisms) that control the growth of or kill other bacteria. More recently, synthetic antibiotics (usually chemically related to natural antibiotics) have been produced that accomplish comparable tasks. Classification of antibiotics is based on their chemical structure (Figure), with the level of effectiveness, toxicity and side effects rendered by the same structural group. There are two types of antibiotics: bactericidal, which kill bacteria, and bacteriostatic, which halt the growth of bacteria. In addition, antibiotics' bacterial spectrum can be either broad to protect against a range of microorganisms or narrow, and they can be administered either orally or by injection.[1]

Prior to the 20th century, infections now considered straightforward to treat such as pneumonia and diarrhea caused by bacteria were the No. 1 cause of human death in the developed world. Then, in the late 19th century, Paul Ehrlich, a German physician, noted certain chemical dyes colored some bacterial cells but not others, concluding it must be possible to create substances that can kill certain bacteria selectively without harming other cells. In 1909, Ehrlich developed the first modern antibiotic when he discovered a chemical called arsphenamine was an effective treatment for syphilis. But, it wasn't until more than 30 years later that the word "antibiotics" was first used by Ukrainian-American inventor and microbiologist Selman Waksman, who in his lifetime discovered more than 20 antibiotics.

In 1928, Alexander Fleming accidentally discovered penicillin when, upon returning from a holiday in Suffolk, he noticed a fungus, Penicillium notatum (P. notatum), had contaminated a culture plate of Staphylococcus bacteria he had accidentally left uncovered. Fleming isolated and grew the mold in pure culture, and he found that P. notatum proved extremely effective even at very low concentrations, preventing Staphylococcus growth even when diluted 800 times, and was less toxic than the disinfectants used at the time. By D-Day in 1944, penicillin was being widely used to treat troops for infections both in the field and in hospitals throughout Europe. And by the end of World War II, penicillin was nicknamed "the wonder drug" and had saved many lives.[2]

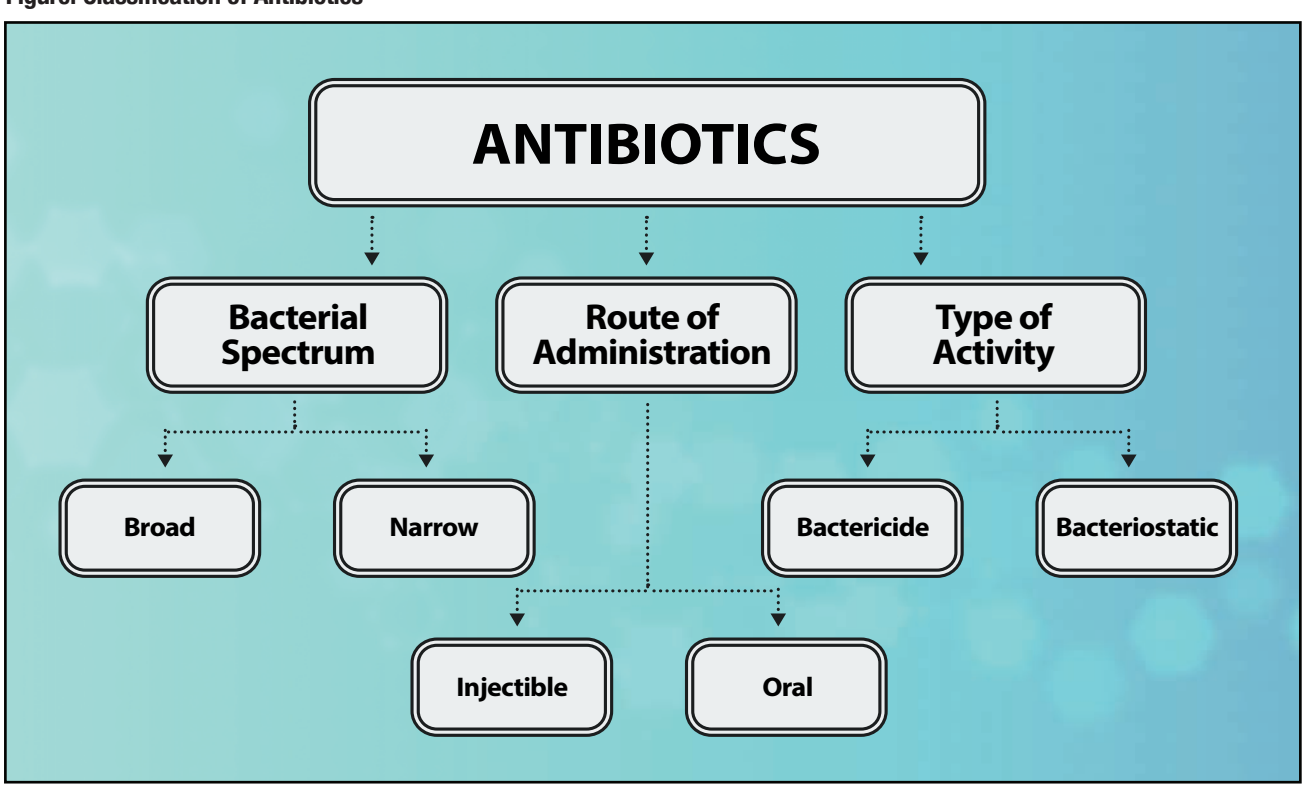
According to the Centers for Disease Control and Prevention's (CDC) "Antibiotic Use in the United States, 2020 Update: Progress and Opportunities," the number of antibiotics dispensed per 1,000 population in outpatient pharmacies across U.S. states in 2018, for which the most recent data are available, ranged from 450 to nearly 1,200. What's more, the report emphasized that antibiotics continue to be prescribed unnecessarily. To combat this excess, antibiotic stewardship programs (improving how antibiotics are prescribed and used) are increasingly being implemented to optimize treatment of patients who have infections and, thus, protect them from harm. Still, the myths surrounding the prescribing and use of antibiotics continue to threaten the population from the growing threat of antibiotic resistance.[3]

Separating Myth from Fact

Myth: All antimicrobial agents are antibiotics.

Fact: This is a common misconception. Antimicrobials (anti-infectants) are medicines that act across a wide range of organisms, including bacteria, viruses, fungal, protozoa and helminths, that interfere with the vital functions of pathogens, without affecting the host cell. Antibiotics belong to a subcategory of antimicrobials and are prescribed to treat infections caused by bacteria. Antibiotics have the ability to kill and stop the growth of bacteria, and are prescribed based on the likely organisms involved, prevalence of the resistance of the organism, relevant pharmacology and presence of allergy or host factors that may modify pharmacology, the degree of the severity, urgency and the availability of the culture and sensitivity results. Antibiotics are also prescribed to treat systemic infections, postoperative infections and during surgical procedures that are more than four hours of duration, neurosurgeries, cardiothoracic surgeries, implants and in immune compromised patients.[4]

Figure. Classification of Antibiotics[1]



Myth: Antibiotics should be prescribed for all infections.

Fact: Antibiotics are not the correct choice for all infections. For example, most sore throats, cough and colds, influenza (flu) or acute sinusitis are viral in origin (not bacterial) and do not respond to antibiotics. These viral infections are self-limiting, meaning an individual's own immune system will usually kick in and fight the virus off.[5] Unfortunately, the majority (64 percent) of respondents in 12 countries surveyed by the World Health Organization said they believe viruses such as colds and flu can be treated with antibiotics.[6] In fact, using antibiotics for viral infections can increase the risk for antibiotic resistance, lower the options for future treatments if an antibiotic is needed, and put a patient at risk for side effects and extra cost due to unnecessary drug treatment.

The top-10 infections for which antibiotics can and should be prescribed are acne, bronchitis, conjunctivitis (pink eye), otitis media (ear infection), sexually transmitted diseases, skin or soft tissue infection, Streptococcal pharyngitis (strep throat), traveler's diarrhea, upper respiratory tract infection and urinary tract infection.[5]

Myth: Antibiotics should not be taken by pregnant women and young children.

Fact: Antibiotics are commonly prescribed during pregnancy; however, the specific medication must be chosen carefully since some antibiotics are OK to take during pregnancy, while others are not. Safety depends on various factors, including the type of antibiotic, when in the pregnancy the antibiotic is taken and for how long, how much antibiotic is taken and what possible effects it might have on the pregnancy.

Some believe those with food allergies shouldn't take antibiotics; however, food allergies are not a contraindication to antibiotics.

Antibiotics generally considered safe during pregnancy include penicillins (amoxicillin, ampicillin); cephalosporins (cefaclor, cephalexin); erythromycin; and clindamycin. Yet, there are other antibiotics believed to pose risks during pregnancy. For example, tetracyclines can discolor a developing baby's teeth, and they aren't recommended for use after the 15th week of pregnancy.[7]

Babies and toddlers can and should take antibiotics to treat a bacterial infection such as a urinary tract infection or bacterial sinusitis. However, since antibiotics also remove some good bacteria (as well as the bacteria causing the infection), they can put children at risk for severe diarrhea caused by Clostridium difficile (C. diff). In fact, the risk for C. diff diarrhea can last for a few weeks, even after a child has stopped taking antibiotics.[8]

What's more, a recent study conducted at Rutgers University found children under 2 years old who take antibiotics are at greater risk for childhood-onset asthma, respiratory allergies, eczema, celiac disease, obesity and attention deficit hyperactivity disorder. In the study, the researchers looked at 14,572 children born in Olmsted County, Minn., between 2003 and 2011, 70 percent of whom received at least one antibiotic prescription during their first two years, primarily for respiratory or ear infections. They found antibiotics were associated with metabolic diseases (obesity, overweight), immunological diseases (asthma, food allergies, hay fever) and cognitive conditions or disorders (attention deficit hyperactivity disorder, autism), but effects varied among the different antibiotics. For instance, cephalosporins were associated with the most risk for multiple diseases, and uniquely autism and food allergies. Researchers also found risk increased with more courses of antibiotics and when given earlier in life — especially within the first 6 months. According to the study's authors, the findings are consistent with the hypothesis that the composition of the microbiome — the trillions of beneficial microorganisms that live in and on our bodies — plays a critical role in the early development of immunity, metabolism and behavior.[9]

Myth: Antibiotics should not be taken by those with allergies.

Fact: Some believe those with food allergies shouldn't take antibiotics; however, food allergies are not a contraindication to antibiotics. That said, it is possible for people to have an allergic reaction to an antibiotic. Signs of a mild allergic reaction include red, itchy, flaky or swollen skin; a flat, red area on the skin covered with small bumps; and hives. Severe allergic reactions include skin that blisters or peels, vision problems, severe swelling or itching, toxic epidermal necrolysis and anaphylaxis, which results in throat tightness, trouble breathing, tingling, dizziness and wheezing.

In addition, there are some issues that can increase the risk of an allergic reaction to antibiotics such as other allergies (for instance, to cats), a family history of antibiotic allergies, frequent use of antibiotics and a long-term illness that makes the immune system more sensitive.[10]

Myth: Antibiotics don't cause side effects.

Fact: All medications have side effects, including antibiotics. Antibiotic allergies or hypersensitivity reactions are some of the most common side effects of antibiotics leading to emergency room admission. Other common side effects include mild skin rash, soft stools or short-term diarrhea, upset stomach and nausea,

loss of appetite, and fungal (yeast) vaginal infections or oral thrush. Other more severe antibiotic side effects in addition to severe allergic reaction are severe watery or bloody diarrhea, C. diff, stomach cramps and yeast infections in the mouth or vagina (white discharge and severe itching in the vagina or mouth sores or white patches in the mouth or on the tongue).[11]

Myth: Antibiotics can be discontinued after symptoms subside.

Fact: No, and yes. For years, individuals have been told that if antibiotics are stopped early or if doses are missed, the amount of antibiotic available to kill the bacteria isn't enough and the bacteria are still able to replicate. In addition, it's easier for bacteria to become resistant if there is too little antibiotic present, so individuals should always complete their full course of antibiotics and shouldn't discontinue them even if they feel better.[6]

Yet, despite how widespread and deep-rooted this belief is, Brad Spellberg, MD, professor of clinical medicine at Keck School of Medicine at the University of Southern California, and chief medical officer at Los Angeles County+University of Southern California Medical Center in Los Angeles, advises "there are no data to support that continuing antibiotics past resolution of signs and symptoms of infection reduces the emergence of antibiotic resistance. To the contrary, studies have repeatedly found that shorter-course therapies are less likely to select out for antibiotic resistance, which is consistent with fundamental principles of natural selection. Every randomized clinical trial that has ever compared short-course therapy with longer-course therapy, across multiple types of acute bacterial infections (including cellulitis, acute bacterial sinusitis, community-acquired pneumonia, nosocomial pneumonia/ventilator-associated pneumonia, complicated urinary tract infections and complicated intra-abdominal infections), has found that shorter-course therapies are just as effective. When evaluated, shorter-course therapies have resulted in less emergence of resistance." So, Dr. Spellberg proposes a new antibiotic mantra: Shorter is better! "Patients should be told that if they feel substantially better, with resolution of symptoms of infection, they should call the clinician to determine whether antibiotics can be stopped early," he explains. "Clinicians should be receptive to this concept, and not fear customizing the duration of therapy.[12]

Myth: It's OK for individuals to take others' leftover antibiotics.

Fact: Despite being told to finish the course of antibiotics, patients often fail to do so, leaving them with unused antibiotic prescriptions. But, individuals should not take antibiotics that are left over from past treatments or offered by family and friends for two specific reasons: 1) antibiotics past their date are more likely to cause resistance since the active ingredient may be impaired, and 2) the antibiotic may not be the correct one for the infection, and if so, the infection will be treated incorrectly, increasing the chance of the bacteria becoming resistant.[6]

Myth: Antibiotics can help with COVID-19 symptoms.

Fact: The SARS-CoV-2 virus, which causes COVID-19, is a virus and will not respond to antibiotics. However, antibiotics are being studied for the treatment of COVID-19. This is the case for azithromycin, which has anti-inflammatory effects and may help reduce an overactive immune response to COVID-19. Specifically, researchers are looking into the effects of the combination of hydroxychloroquine, an anti-malarial drug (hydroxychloroquine has been found to have anti-SARS-CoV activity in test tube experiments), and azithromycin.

Results from one small-scale study that looked at the effects of hydroxychloroquine and azithromycin on people receiving hospital treatment for COVID-19 in France showed hydroxychloroquine significantly reduced the viral load or eliminated the coronavirus. And, the addition of azithromycin increased the effectiveness of hydroxychloroquine. However, another study that looked at 1,438 people receiving hospital treatment for COVID-19 in New York, all of whom had similar age, race and time of starting treatment, found treatment with hydroxychloroquine and azithromycin did not improve outcomes, and increased the risk of cardiac arrest. Since then, the U.S. Food and Drug Administration has revoked the emergency use authorization for hydroxycholoroquine.

Nevertheless, doctors are prescribing antibiotics to those with COVID-19. This treatment is needed when the virus causes a

respiratory infection that can weaken the immune system, which can increase the risk of getting a bacterial infection that can be harder to fight off. Some doctors also prescribe antibiotics to people with COVID-19 to prevent or treat secondary bacterial infections such as bacterial pneumonia.[13]

Myth: People's bodies become resistant to antibiotics.

Fact: It's not the body but rather the bacteria that becomes resistant to an antibiotic. Antibiotic resistance happens when the germs no longer respond to the antibiotics designed to kill them, which means the germs are not killed and continue to grow.

Myth: Antibiotic resistance only happens when they are taken repeatedly.[14]

Fact: Antibiotic resistance can occur whenever an antibiotic is taken, whether it is a single course or multiple repeat courses. The more courses taken, the more resistance can occur. But that doesn't mean it doesn't occur with a single course. In addition, a single course of antibiotics can lead to life-threatening unwanted side effects and potentially catastrophic changes to the normal bacteria that live in our guts. The imbalance can allow dangerous bacteria like C. diff to predominate and cause severe diarrheal illness.[6]

Myth: The medical profession is responsible for antibiotic resistance.

Fact: According to CDC, approximately 47 million unnecessary antibiotics are prescribed to patients each year. Yet, while many people quickly associate the health sector alone with the rise of antibiotic resistance, other industries have been influential, too. For example, agricultural professionals once regularly used antibiotics to promote animal growth, a practice that is now prohibited.

There are measures the medical profession can take to reduce the number of unnecessary antibiotic prescriptions. For instance, one case study of a rapid testing system that confirms cases of respiratory viruses in less than an hour shows using such methods could reduce the instances of people getting antibiotics when they don't need them. And, if doctors don't have access to such tests, they should resist pressure from patients who ask for antibiotics in cases where they're not warranted. That often means educating patients about how antibiotics don't treat viral infections and giving them suggestions of interventions that should help.[15]

Antibiotic stewardship, the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients, is another method for reducing unnecessary antibiotics use. According to the American Academy of Pediatrics (AAP), antibiotic stewardship is dedicated to using antibiotics only when necessary, and using the appropriate spectrum of activity, dose, route and duration of therapy to optimize clinical outcomes while minimizing harm. In January, the AAP Committee on Infectious Diseases and Pediatric Infectious Diseases Society published a new policy statement regarding antibiotic stewardship in pediatrics.[16]

Dispelling the Myths Now

The key to curbing the growing threat of antibiotic resistance involves spreading the word about responsible antibiotic prescribing and use. Held annually since 2015, World Antimicrobial Awareness Week is a global campaign that aims to increase awareness of antimicrobial resistance worldwide and to encourage best practices among the general public, health workers and policymakers to avoid the further emergence and spread of drug-resistant infections. Also in November each year, the U.S. Antibiotic Awareness Week is held as an annual observance that gives participating organizations an opportunity to raise awareness of the importance of appropriate antibiotic use to combat the threat of antibiotic resistance. As part of this effort, the CDC's Be Antibiotics Aware is an educational effort that provides partners with up-to-date information to help improve human antibiotic prescribing and use in the United States.[17] ❖

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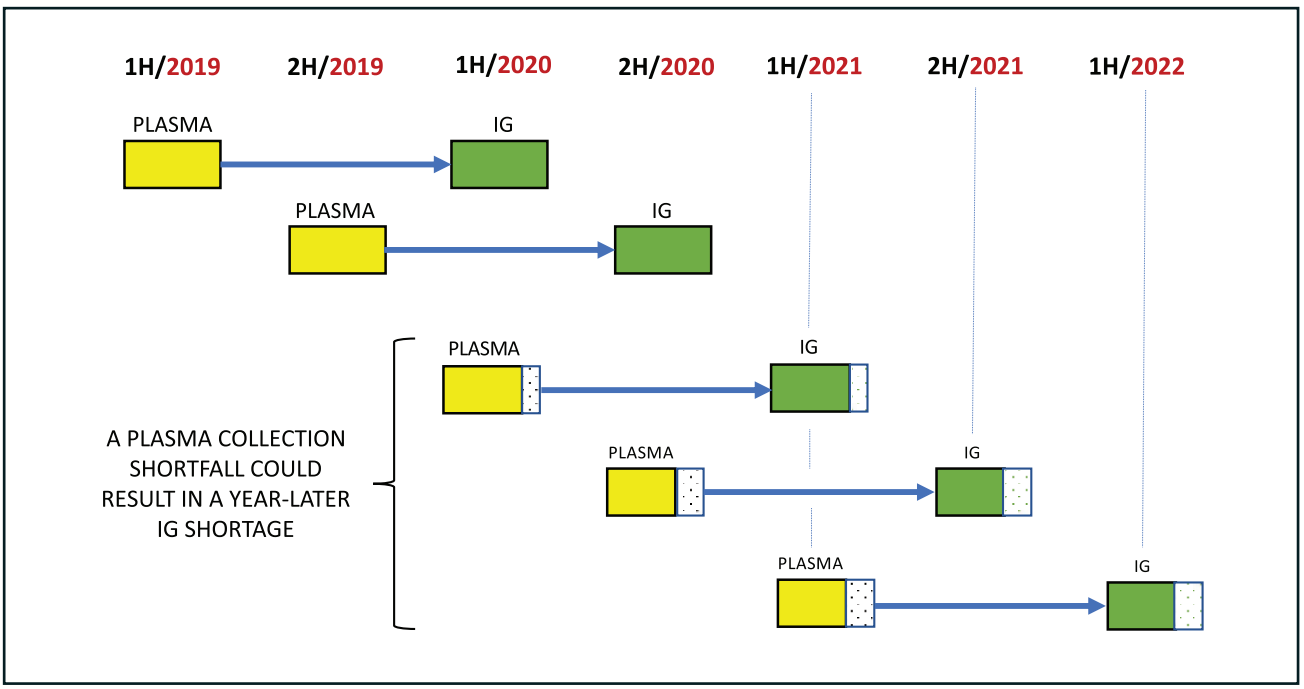
In Case of a Shortage: Strategies to Conserve the Immune Globulin Supply

By Keith Berman, MPH, MBA

SINCE MARCH of last year, the COVID-19 pandemic has forced cancellations of thousands of blood drives and dissuaded many would-be donors from visiting their local community blood center. While the resulting drop in the blood supply has been mitigated in part by public appeals for blood donation, millions of Americans are well-acquainted by now with the primary tactic hospitals have employed to ensure adequate inventories of blood to meet critical and emergency needs: cancellations of elective surgeries. At the peak of the pandemic last year, an estimated 340,000 elective surgeries were cancelled each week,[1] many of which would have required transfusions of blood that blood banks did not have on hand.

U.S. donations of plasma intended for further processing into polyvalent immune globulin (IG) and other therapeutic proteins have similarly been heavily impacted by the pandemic. But while hospitals have been able to contract their blood usage by simply postponing elective surgeries until supplies improve, simply cancelling or deferring IG treatments for patients who require it for

Figure 1. Simplified Model Depicting the Potential Effect of a Pandemic-Related Plasma Shortage on IG Product Supply



This model excludes multiple other variables influencing IG supply, including demand fluctuations, shifts of manufacturer inventory to or from international markets, etc.

humoral immunodeficiency disorders or a host of severely debilitating autoimmune or inflammatory diseases is not an option. What, then, can be done in the event of a severe shortage of IG products, whose production is entirely reliant on a continuous supply of IgG-rich plasma donated at more than 800 dedicated U.S. collection facilities?

At this writing, there is no IG shortage, and the potential for a shortage situation remains hypothetical. Despite months-long periods of sharp declines in plasma collections last year, both intravenous IG (IVIG) and subcutaneous IG (SCIG) have generally remained in good supply over the more than yearlong course of the pandemic. Unquestionably, cancelled clinic visits that would otherwise have generated diagnoses and new orders for IG have played a role. But the real answer to this medical challenge is related to the complexity and protracted length of time required to process plasma into IgG and other therapeutic proteins.*

According to the Plasma Protein Therapeutics Association, between seven months and 12 months are required to manufacture a single batch of IG, from the pooling of thousands of donor units to shipment of the product in its final container form. In addition, plasma units are quarantined in a frozen state for a minimum of 60 days before they are released for manufacture.[2]

How does that long production time frame affect IG supply in the context of the current COVID-19 pandemic? The highly simplified model in Figure 1 tracks just a few batches of plasma, each on its roughly one-year journey to become an IVIG or SCIG product. We see in Figure 1 that IG delivered in 2020 — the first year of the pandemic — was produced from plasma collected a year earlier in 2019, well before the COVID-19 crisis came along to dissuade donors from visiting their local plasma collection center.

But starting in March 2020, pandemic-related concerns and public orders restricting mobility resulted in a substantial drop in donations. By mid-May 2020, some reports suggest that total volume was down as much as 30 percent, according to Patrick Schmidt, CEO of FFF Enterprises, a leading plasma products distributor. "There was a bit of a resurgence in donations over the summer when cases were down, but now we're in a much more difficult time, and donations will likely decline again," he added in a recent interview.[3]

** e.g., human albumin, C1 esterase inhibitor, alpha1-proteinase inhibitor, fibrinogen*

Figure 2. Examples of Ideal and Adjusted Body Weight-Based Dosing of IVIG (1 g/kg) Prescribed for Overweight or Obese Adults

Patient	IVIG Dosage Basis	IVIG Dose	
5'10" 95 kg adult male	Actual body weight (ABW): 95 kg	95 g	Dose Reduction
	Ideal body weight (IBW): 50 kg + [2.3 kg x (height in inches – 60 inches)] = 73 kg	73 g	23%
	Adjusted body weight (adjBW):* IBW + [0.4 x (ABW - IBW)] = 82 kg	82 g	14%
5'5" 75 kg adult female	Actual body weight (ABW): 75 kg	75 g	Dose Reduction
	Ideal body weight (IBW): 45.5 kg + [2.3 kg x (height in inches – 60 inches)] = 57 kg	57 g	24%
	Adjusted body weight (adjBW):* IBW + [0.4 x (ABW - IBW)] = 64 kg	64 g	13%

*Some institutions calculate adjBW with the following formula: IBW + [0.5 x (ABW – IBW)].

Those shortfalls in plasma collections in 2020 will directly translate into lower IG production as we advance through 2021. Again, however, other mitigating factors could minimize or entirely prevent an IG shortage, the most important of which is constrained IG utilization as some patients on chronic IG therapy may skip or delay their outpatient infusion visits, and others who would otherwise have been prescribed IG therapy put off scheduling appointments to see a specialist.

Whether ongoing plasma supply shortages ultimately result in IG supply shortages remains to be seen, but the prospect itself returns us to the original question: What can be done in the circumstance of an IG undersupply — without compromising patient care?

Dosing with Ideal or Adjusted Body Weight Spares IVIG

Infused IVIG is known to mainly accumulate in blood plasma, with much less distribution in body tissues and minimal distribution in fat tissue.[4] As a consequence, when an overweight or obese patient (generally defined as a body mass index [BMI] ≥ 30 kg/m2) is dosed with IVIG in accordance with his or her actual body weight (ABW), the resulting serum IgG level is elevated above that of a nonoverweight patient who receives the same weight-based dose. As pointed out in a statement by the Society of Critical Care Medicine, "obese patients who are dosed at ABW may be put at additional risk for adverse reactions due to excess plasma concentration."[5] Partly for this reason, IVIG clinical trials typically exclude individuals with a BMI above a specified threshold.

A report by a large U.S. immunology clinic providing chronic IVIG therapy to obese and nonobese primary immune deficiency (PI) patients appears to validate this effect of excess adiposity on IgG serum levels. As a result of this clinic's general policy to "cap" monthly dosage, the mean monthly IVIG dose for patients with a BMI ≥30 kg/m2 was 14 percent lower than the monthly dose for those whose BMI was under 30 kg/m2 (0.54 g/kg versus 0.63 g/kg). Yet the mean serum IgG levels for obese and nonobese patients were about the same (882.2 mg/dL versus 903.4 mg/dL).[6]

For overweight and obese patients, many academic medical centers now utilize either a calculated ideal body weight (IBW) or adjusted body weight (adjBW) to arrive at an IVIG dose. Figure 2 provides examples of how ABW may be converted to either an IBW or an intermediate adjBW as the basis for IVIG dosing, an approach sometimes referred to as "precision dosing." A simple patient height-based equation — the Devine Formula — is most commonly used to calculate patient IBW,[7] which can be further adapted to specify an adjBW that falls between ABW and IBW. The Ontario Regional Blood Coordinating Network provides a widely referenced online tool, using inputs of patient height and weight, to generate IBW, adjBW (called "dosing weight") and IVIG dose calculated using the dosing weight.[8]

adjBW or IBW-based IVIG dosing is a standard practice in a number of countries, including Canada, Australia and the United Kingdom.[9,10] According to the most recent survey by the U.S. Centers for Disease Control and Prevention (CDC) in 2016, 72 percent of U.S. adults are now classifiable as overweight or obese, up

significantly from 64 percent in 1999.[11] Consistent with these U.S. figures, a group of Canadian provinces reported that, in fiscal 2019, adjBW was utilized to reduce administered dosages in 64 percent of all patients (817/1,270) receiving IG therapy. This use of adjusted "dosing body weight" translated into 14 percent overall savings in IG grams and associated cost.

Pharmacists at Brigham and Women's Hospital applied IBW-based dosing for all inpatient IVIG orders over a period of one year.[12] For the majority of cases (142/265; 54 percent), IVIG was prescribed for hypogammaglobulinemia with recurrent infections in oncology and bone marrow transplant patients. The mean patient IBW and ABW were 63.3 ± 10.5 kg and 77.3 ± 9.2 kg, respectively. Using IBW for dosing, a total of 15,383 grams of IVIG was dispensed over the one-year period, which was 3,880 grams or 20 percent less than the gram total had dosing been based on actual patient body weight.

In a retrospective analysis of all IVIG doses administered over a recent five-year period, investigators at MD Anderson Cancer Center concluded that use of an adjBW-based dosing formula would have yielded a 24 percent reduction in dispensed IVIG grams.[13] Astonishingly, their calculations found that use of IBW would have reduced dispensed IVIG grams by nearly 36 percent. "IVIG dosing optimization through the use of alternative dosing weights represents a significant source of waste reduction and cost reduction," the study authors concluded.

Those shortfalls in plasma collections in 2020 will directly translate into lower IG production as we advance through 2021.

An obvious presumption behind these IVIG dose-sparing strategies is that circulating IgG levels and bioavailability that roughly approximates a standard dose in lean individuals will provide similar therapeutic benefit. A team at the University of North Carolina Medical Center put this question to the test with a lookback at actual patient outcomes data. Of 209 consecutive IVIG infusion encounters in adults with hematologic malignancies, 125 were dosed traditionally by ABW, while 84 others were dosed in accordance with an IBW- or adjBW-based formula. No differences were seen in 30-day infection rates between the precision dosing and the traditional ABW-based dosing methodology (15.5 percent versus 16 percent, respectively); 60-day infection rates were similar as well.

Figure 3. Indications for Use of IVIG in the UK Prioritized by Red-Blue-Grey Color-Code Scheme

Color Code	Meaning/Usage Priority
Red	A disease for which IG treatment is considered the highest priority because of risk to life without treatment.
Blue	A disease for which there is a reasonable evidence base, but where other treatment options are available. The use of IVIG in these indications should be modified in times of shortage.
Grey	Indications for which evidence is weak, in many cases because the disease is rare. IVIG treatment should be considered on a case-by-case basis, prioritized against other competing demands.

IG dosing based on IBW or ABW has particularly been embraced by hospitals as a significant cost-saving opportunity. But in the potential context of a national IG shortage situation, its value as a safe and effective means to conserve IG applies equally for the roughly 50 percent of patients who receive their treatments at home or in other nonhospital settings.

Titrating IG Dose for Each Patient

While oral and most injectable medications are typically prescribed at the dosage recommended in the package insert, it makes sense to individualize the dosage of IG when it is used as chronic immunomodulatory or IgG replacement therapy. For most patients on chronic IG therapy, the recommended dosage should serve as a starting point.

Each patient metabolizes infused IgG at a different rate. In particular, when IVIG or SCIG is prescribed as long-term replacement therapy for new patients with a PI, the dosage can be initially adjusted to achieve the desired serum IgG trough level. Prescribing information for most IVIG and SCIG products further recommend dosage adjustments as needed to attain an optimal protective response. This practice, as opposed to simply prescribing a "standard" dose that turns out to be effective for the patient, can help minimize wastage of excessive IG, reduce the likelihood of side effects and shorten infusion time or frequency of infusion sessions.

When the immunomodulatory properties of IG are exploited to treat disabling chronic immune neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy, clinicians most commonly like to continue with the standard maintenance dose (e.g., 1 g/kg for CIDP) and increase the time interval between infusions to find the longest interval that will maintain remission without relapse. This strategy may allow discontinuation of IVIG treatment altogether for some patients who remain in clinical remission.[14]

A special consideration with CIDP is the unfortunately commonplace misapplication of this diagnosis, followed by inappropriate prescribing of high-dose IVIG therapy. Clinical and electrodiagnostic evaluations of 59 consecutive patients diagnosed with CIDP and referred by community neurologists to an academic center found 47 percent of them failed to meet diagnostic criteria for the disorder.[15] A separate expert assessment of case records for 248 patients with presumptive immune neuropathies who received home-based IVIG treatment determined only 32.2 percent actually had an immune neuropathy and were appropriate candidates for IVIG therapy. Another 46.4 percent had neuropathies that were not immune-mediated.[16] Consistent with these findings, just 36.7 percent of cases with reviewable records actually responded to IVIG therapy. Plainly, there is an opportunity to avoid wastage of IVIG by first subjecting potential treatment candidates to more stringent diagnostic assessments.

Prioritizing Better Supported Use

In the commonplace circumstance when one or more IG product brands are temporarily unavailable, providers are well-accustomed to being asked to switch affected patients to a different brand in good supply. Separately, challenges securing and processing enough additional plasma to keep pace with 8 percent to 9 percent annual demand growth[17] have created intermittent shortages that have affected many providers over the last several years. But we have never experienced the kind of severe, protracted IG supply shortage situation that could potentially arise from the pandemic-caused decline in plasma collections that began more than a year ago in March 2020. A scenario of this nature could require pharmacists and physicians to make many difficult decisions about which patients do and do not receive IG therapy.

To rationalize IG utilization in the context of budgetary or supply constraints, a number of countries with national healthcare systems have formalized this process, assembling expert panels that review

and grade the available evidence supporting IG use across a wide spectrum of clinical indications.[18,19] The *UK's Clinical Guidelines for Immunoglobulin Use*, for example, employs a color-code scheme to assign a priority to each clinical use (Figure 3), and whether IG is recommended for short-term or long-term use, or both. Particularly helpful is the "blue" prioritization, which identifies clinical indications for which other treatment options are available and whether the use of IG "should be modified in times of shortage."[20]

In the U.S., these and other helpful published guidelines can assist individual provider organizations in making informed decisions about which patients should receive priority for IG therapy in the event of a severe shortage. The American Academy of Allergy, Asthma & Immunology, for example, has conducted a comprehensive review of evidence that assigns indications to one of four categories: definitely beneficial, probably beneficial, may provide benefit and unlikely to be beneficial.[21]

Fortunately, many providers, including large tertiary care hospitals in particular, have already visited this issue to address past shortage situations. "We prioritize patients with chronic immune deficiency, life-threatening conditions such as immune thrombocytopenic purpura, Guillain-Barré syndrome and Kawasaki disease, versus indications where there are effective alternatives — for example, multiple sclerosis," noted the Mayo Clinic's vice chair for pharmacy supply solutions Eric Tichy, PharmD, in a recent interview with *Pharmacy Practice News*.[22]

It Comes Down to the Plasma

Patient advocacy organizations and plasma collection centers from coast to coast have boosted appeals for donors during the ongoing pandemic, reminding prospective donors of the value of their gift of plasma, and providing assurances that donating plasma is safe. The Immune Deficiency Foundation, for example, has launched an initiative called "PlasmaHero" to educate the general public about the critical need for plasma and to connect potential donors with resources to get started.[23] All indications suggest these efforts are helping to convince more donors to return or step up to donate plasma for the first time.

Yet the concern remains that many months of sharply lower plasma collection activity already caused by the COVID-19 pandemic may yet impact IG supply as we continue into 2021. Without question, the best and surest way to avert or at least mitigate an impending IG shortage tomorrow is to take advantage of measures we know from experience can help to conserve more of this precious product today. ❖

For overweight and obese patients, many academic medical centers now utilize either a calculated ideal body weight or adjusted body weight to arrive at an IVIG dose.

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Melissa DuBay, who is still experiencing the effects of systemic inflammatory response syndrome and sepsis caused by a dental procedure, feels lucky to be alive.

Sepsis: *A Patient's Perspective*

By Trudie Mitschang

IT ALL happened so fast," recalls sepsis survivor Melissa DuBay. "I had a dental crown that broke at the base, and because it was incorrectly seated, I was told they would have to extract the molar. I had the extraction done on May 5, 2020. I remember it took the endodontist a very long time to extract the tooth, and we now know that's when the strep bacteria that led to sepsis likely entered my bloodstream."

One month after her dental procedure, Melissa awoke with a fever, body aches and pain, and her doctor immediately recommended she get tested for COVID-19. She tested negative, but her symptoms continued to worsen. "I was taking 1,000 mg of Tylenol every six hours four times a day. It would bring the fever down to 99 and then it would shoot back up to 103. I was barely hungry and very weak," she says. "On the second day, I got up to let my dog out and passed out, and as I crashed to the floor, I broke my nose. I reported this to my primary care doctor who said I probably had low blood pressure and should keep trying to hydrate."

By the evening of day three, Melissa was still experiencing high fever and chills. That's when she made the lifesaving decision to call the nurse's help line. After describing her symptoms, she was advised to go to the emergency room (ER) where she underwent an abdominal ultrasound. She was eventually diagnosed with systemic inflammatory response syndrome (SIRS) and sepsis. But because of COVID-19 restrictions, Melissa was alone in the ER and had difficulty processing her dire diagnosis. "I was mentally confused and shivering from the fever," she explains. "I had no idea what SIRS or sepsis was, or what that meant for me. I really wished I could have a family member with me."

A subsequent CT scan found Melissa had an enlarged liver with three large abscesses plus a moderately distended gallbladder. "By mid-June, I underwent a procedure called thoracentesis that drained a liter of fluid from my chest wall," she says. "I was in the most pain I'd ever had in my life — all while still experiencing fever and intense chills." Melissa's pain was so intense doctors alternated Dilaudid with Percocet just to take the edge off. In addition, she was continually flushed with IV fluids. "I went into the hospital at 159 pounds and left weighing 207 pounds just from the water retention," says Melissa.

After two excruciating weeks, Melissa was finally allowed to go home and was assigned visiting nurses. She was also given a midline IV for antibiotics and an oral antibiotic, Lasix for fluid retention and Percocet for the pain.

During her long road to recovery, Melissa says she was too weak to stand in the shower or even walk to the kitchen to eat. She used a shower chair and needed her meals prepared while she regained her strength. Additional troubling side effects were disorientation, mental confusion and memory loss. In total, it took five weeks for Melissa to begin to regain her strength. But the lingering effects of sepsis have been devastating, she explains: "I lost all of the water weight and continued to lose weight, eventually getting down to 135 pounds. At 5 foot 8 inches, I looked like a skeleton. I didn't feel stronger until about September, and at that point, I had shed half of my hair."

Melissa says she also experiences post-traumatic stress disorder from any hint of illness now: "I am a diabetic, and we tend to be more prone to infection, so now I always worry that sepsis could occur again from a dental procedure, a bladder infection or something else."

During her long road to recovery, Melissa says she was too weak to stand in the shower or even walk to the kitchen to eat.

Melissa lives with lingering pain with every deep breath, and when she laughs, sneezes or even hiccups; doctors say it is likely due to the scar tissue in her lung and liver. "I'm told I may need to accept the fact that this is a permanent way of life for me," says Melissa. "I still consider myself lucky because if I hadn't gotten to the ER on day three of the fever, it might have been too late. My hair is finally showing new growth, so I'm happy about that! But at the end of the day, I'm thankful to be alive." ❖

Sepsis: *A Physician's Perspective*

Dr. Rahul Kashyap is a proponent of using smart technology to detect sepsis and improve treatment outcomes.

Rahul Kashyap, MD, MBA, is a clinical research scientist and assistant professor at the Mayo Clinic in Rochester, Minn.

BSTQ: What is sepsis?

Dr. Kashyap: When a person gets an infection, the body releases chemicals into the bloodstream to fight off the infection. In some cases, those chemicals can trigger inflammation throughout the body. That inflammatory response is sepsis. If it's not treated promptly, sepsis can progress, lowering blood pressure and making it hard for blood to reach vital organs. As a result, the heart, lungs, brain and kidneys all can be damaged. If it continues, sepsis can develop into septic shock, a life-threatening situation in which organs begin to fail and blood pressure drops even more dramatically. Any kind of infection can trigger sepsis. But certain infections such as pneumonia, abdominal or kidney infection and infections that affect the blood are more likely to cause sepsis.

BSTQ: Who is most at risk for developing sepsis?

Dr. Kashyap: Age is a significant risk factor. The elderly and the very young are at higher risk because the immune system tends to be weaker in elderly adults, and it's not fully developed in infants. Other people with weak immune systems are more vulnerable to sepsis, too. Many people have weakened immune systems due to medical conditions, putting them at higher risk. A severe illness that requires hospitalization also can lead to problems with a person's immune system, raising the sepsis risk.

BSTQ: How is sepsis diagnosed?

Dr. Kashyap: Sepsis develops quickly, and it can be difficult to identify in its early stages. Symptoms include high fever, fast heart rate and rapid breathing. As sepsis worsens, it can trigger an abrupt change in mental status such as disorientation or confusion. A significant decrease in urine production usually is a sign that sepsis is affecting the kidneys and other vital organs. If someone who has an infection begins to experience sepsis symptoms, it is critical he or she gets medical care right away. Hospital staff members watch patients closely for sepsis, particularly those in the emergency department and in ICUs. Patients diagnosed with sepsis receive plenty of IV fluids and are immediately given antibiotics.

BSTQ: How is sepsis treated?

Dr. Kashyap: People who have sepsis may require hospitalization. In addition to antibiotics and hydration, other medications may be used to treat symptoms such as low blood pressure. People whose conditions progress to septic shock often require care in an ICU, where they receive oxygen and bolus IV fluids. They also may need a machine to help them breathe. The longer sepsis is allowed to progress, the higher the chances it will become life-threatening. Research has shown, however, that if treatment is started within the first few hours from the time sepsis begins, the death rate from sepsis falls significantly. That makes early, aggressive treatment of sepsis crucial. If it is caught quickly, sepsis often can be managed effectively.

BSTQ: What drives your interest in effectively treating sepsis?

Dr. Kashyap: Sepsis has been listed as one of the top 10 causes of death — not only globally by the World Health Organization, but also by U.S. hospitals. There's an unwritten rule in the ICU: Unless it's otherwise ruled out, you assume sepsis in every single patient you treat. I have personal reasons as well. I lost my grandfather five years ago because of sepsis. While I had done some work before that experience, I'm a bit more passionate about it now in terms of seeing how we can find a cure. One of the questions I have is: How can we use technology and make sure there's enough knowledge around sepsis signs and symptoms?

BSTQ: How do you think technology can be harnessed to treat sepsis?

Dr. Kashyap: Smart technology use can help not only with sepsis predication and detection, but also with sepsis treatment and outcome improvement. Machine learning algorithms can use vast information from electronic medical charts, deploy an early alert system for new sepsis diagnosis, and indicate failure to meet sepsis treatment guidelines. Smart technology monitoring in the critical care setting has potential for improved compliance with treatment, thus improving mortality rates. When pairing sepsis recognition technology with a sepsis response team, the death rates could be brought down substantially. ❖

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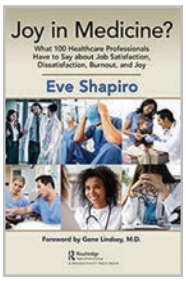
TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Joy in Medicine? What 100 Healthcare Professionals Have to Say about Job Satisfaction, Dissatisfaction, Burnout, and Joy

Author: Eve Shapiro

Eve Shapiro has been writing about patient-centered care, physician-patient communication and relationships between doctors and their patients since 2007. In this book, she turns her attention to those on the healthcare delivery side of this interaction, in which healthcare professionals share their enthusiasm, joys, frustrations, disappointments, insights, advice, stories, fears and pain, explaining how it looks and feels to work in healthcare today no matter who you are, where you work or what your position is in the organizational hierarchy.



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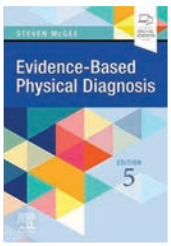
Planning During a Pandemic: Economic Scenario Planning Helps Companies Navigate the COVID Economy

Author: Prevedere

Companies must contend with an unprecedented level of uncertainty and flux. As we head into the 2021 planning cycle, every business wants to know how the pandemic will affect next year's numbers and how the company can adjust accordingly and dynamically. This new whitepaper discusses how a data-driven, artificial intelligence-powered solution can help project future business outcomes for three plausible macroeconomic scenarios; utilize a combination of economic data, econometric modeling and senior economic expertise to ensure the validity of outlooks; and improve 2021 planning, guidance and risk management with a clearer view of performance.

www.prevedere.com/economic-scenario-planning/economic-scenario-planning-whitepaper

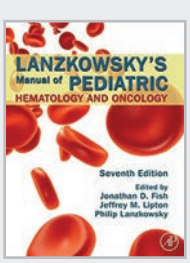


Evidence-Based Physical Diagnosis, 5th Edition

Author: Steven McGee, MD

Evidence-based insights into physical signs have evolved and progressed greatly over the past few years, further defining how physical findings identify disease, solve clinical problems and forecast patient outcomes. *Evidence-Based Physical Diagnosis, 5th Edition*, is an up-to-date, authoritative resource for guidance on interpreting physical signs, enabling physicians to determine the most appropriate physical finding to confirm a diagnosis. Incorporating more than 200 new studies, this definitive text helps physicians glean the most from what they hear, see and feel at the bedside — information that, combined with modern technologic testing, will grant clinicians the keys to outstanding patient care.

www.amazon.com/Evidence-Based-Physical-Diagnosis-Steven-McGee/dp/032375483X



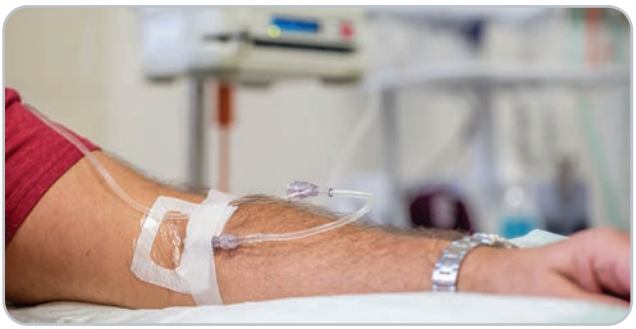
Lanzkowsky's Manual of Pediatric Hematology and Oncology, 7th Edition

Editors: Jonathan D. Fish, Jeffrey M. Lipton and Philip Lanzkowsky

Lanzkowsky's Manual of Pediatric Hematology and Oncology, Seventh Edition, remains the go-to clinical manual for the treatment and management of childhood cancers and blood disorders. It is a comprehensive book on patient management, replete with algorithms and flow diagrams, and includes a new section on vascular anomalies. Reflecting the considerable advances in the treatment and management of hematologic and oncologic diseases in children, the seventh edition of this successful clinical manual is entirely updated to incorporate all current treatment protocols, new drugs and management approaches. Its concise and easy-to-read format, again, enables readers to make accurate diagnoses and treatment decisions without having to reference larger medical textbooks.

www.amazon.com/Lanzkowskys-Manual-Pediatric-Hematology-Oncology/dp/0128216719

Lower, More Frequent Dosing of IVIG-Dependent CIDP Patients Does Not Improve Efficacy or Safety in CIDP



High peak serum immunoglobulin G (IgG) levels associated with infrequent high doses of maintenance intravenous immune globulin (IVIG) treatment may not be needed for effective treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), but may cause side effects and result in lower IgG trough levels than more frequent divided IVIG dosage regimens. A team of Dutch investigators conducted a randomized trial to learn whether lower, more frequent IVIG dosing — associated with more stable IgG levels and higher trough levels — might improve efficacy or reduce side effects.

Twenty-five IVIG-dependent CIDP patients were randomized to a placebo group that received their full, individually established IVIG dose at their usual interval, followed by a placebo infusion at one-half of the usual interval. Intervention group patients received one-half of their usual dose at one-half their usual interval, with the half repeated at the end of their usual interval. After a wash-out phase, patients were crossed over to the alternative treatment regimen. The primary outcome was handgrip strength. Secondary outcomes included health-related quality of life, disability, fatigue and side effects.

At baseline, patients had individually adjusted IVIG dosages ranging from 20 grams to 80 grams, and intervals ranging from 14 days to 35 days. In the 22 patients who completed both treatment periods, there was no significant difference in handgrip strength change from baseline between the established dosage regimen and the lower, more frequent dosage regimen. Nor were there significant differences in side effects or any of the secondary outcomes. The investigators concluded lower, more frequent dosing does not further improve the efficacy of IVIG in stable IVIG-dependent CIDP patients, or result in fewer side effects.

Kiutwaard K, Brusse E, Jacobs BC, et al. Randomized trial of intravenous immunoglobulin maintenance treatment regimens in chronic inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol *2021 Jan;28(1):285-96.*

Plasma Exchange May Slow Alzheimer's Disease Cognitive and Functional Decline: Phase 2b/3 Clinical Study Findings

Patients with mild to moderate Alzheimer's disease treated with therapeutic plasma exchange (TPE) outperformed placebo group patients on co-primary cognitive and activity-of-daily-living endpoints, according to complete findings from the Grifols-sponsored AMBAR study. The working hypothesis for this experimental intervention is that repeated removal of albumin bound to the suspected pathogenic agent (amyloid beta), replaced by fresh albumin, can facilitate removal of amyloid beta from the cerebrospinal fluid and the brain itself.

Initiated in 2012, this Phase 2b/3 study randomized 347 patients on a 1:1:1:1 basis to a control (placebo) sham procedure arm and three active treatment arms, all of which received a series of six TPE treatments with 5 percent albumin replacement, followed by 1) monthly low-volume plasma exchange (LVPE) with infusion of 20 grams of albumin, 2) LVPE with infusion of 20 grams of albumin alternated with infusions of 10 grams of intravenous immune globulin (IVIG) or 3) LVPE with infusion of 40 grams of albumin alternated with 20 grams of IVIG.

At 14 months from baseline compared to the placebo group, TPE-treated patients experienced 52 percent lesser decline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) score ($P = 0.03$) with a strong trend for lesser deterioration in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) ($P = 0.06$). TPE-treated patients also scored better on the Clinical Dementia Rating Sum of Boxes (CDR-sb) (71 percent less decline; $P = 0.002$) and ADCS-CGIC scales (100 percent less decline; $P < 0.0001$). The subset of TPE-treated patients with moderate disease had 61 percent better scores on ADCS-ADL and ADAS-Cog, while the subset with mild disease did not significantly improve.

"This trial suggests that plasma exchange with albumin replacement could slow cognitive and functional decline in Alzheimer's disease, although further studies are warranted," the investigators concluded.

Boada M, López OL, Olazarán J, et al. A randomized, controlled clinical trial of plasma exchange with albumin replacement for Alzheimer's disease: Primary results of the AMBAR study. Alzheimers Dement *2020 Oct;16(10);1412-25.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective April 1, 2021, through June 30, 2021

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$963.54	$948.09
IVIG	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
IVIG	FLEBOGAMMA	Grifols	J1572	$72.16	$71.00
IVIG	GAMMAGARD SD	Takeda	J1566	$128.43	$126.37
IVIG	GAMMAPLEX	BPL	J1557	$102.54	$100.89
IVIG	OCTAGAM	Octapharma	J1568	$84.04	$82.69
IVIG	PANZYGA	Pfizer	90283/J1599	**	**
IVIG	PRIVIGEN	CSL Behring	J1459	$86.07	$84.69
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$92.22	$90.74
IVIG/SCIG	GAMMAKED	Kedrion	J1561	$93.04	$91.55
IVIG/SCIG	GAMUNEX-C	Grifols	J1561	$93.04	$91.55
SCIG	CUTAQUIG	Octapharma/Pfizer	90284/J3590	**	**
SCIG	CUVITRU	Takeda	J1555	$140.06	$137.81
SCIG	HIZENTRA	CSL Behring	J1559	$112.27	$110.47
SCIG	HYQVIA	Takeda	J1575	$147.32	$144.96
SCIG	XEMBIFY	Grifols	J1558	$149.76	$147.36

* 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.FFEnterprises.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
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
IVIG	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g
IVIG	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
IVIG	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
IVIG	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g
IVIG	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g, 30 g
IVIG	PANZYGA Liquid, 10%	Pfizer	PI, ITP	2.5 g, 5 g, 10 g, 20 g, 30 g
IVIG	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 SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
IVIG/SCIG	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	5 g, 10 g, 20 g
IVIG/SCIG	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma/Pfizer	PI	1 g, 2 g, 4 g, 8 g
SCIG	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g
SCIG	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 4 g PFS
SCIG	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g
SCIG	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
PFS Prefilled syringes

2021-2022 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
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
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	2 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	2 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

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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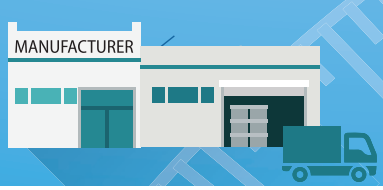

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