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Pulmonary telerehab for COPD: Promising, more data needed

BY WALTER ALEXANDER

As COVID-19 cedes its pandemic-scale status to the past, its wake is revealing surprises and raising questions, particularly in relation to pulmonary medicine. The need for isolation at COVID's outset kept many millions at home, creating conditions favorable for the rapid expansion of technologies that were taken up quickly in telehealth applications. The need was overwhelming. But just how effective telehealth actually is at replacing on-site programs for COPD pulmonary rehab has remained a research challenge, although results from early studies show unmistakable value. Creating conditions conducive to research into the strengths

and weaknesses of pulmonary rehab, and determining how research can be applied effectively, remain formidable challenges.

Early studies of telehealth pulmonary rehab have not uncovered any glaring erosion of pulmonary rehab's well-established benefits. But, at the same time, the relatively young field of pulmonary telerehab for COPD has lacked coordinated efforts to determine its key practices and the instruments for measuring them, both basic elements for pursuing research questions.

A 2021 American Thoracic Society workshop report (AE Holland, <https://doi.org/10.1513/AnnalsATS.202102-146ST>) identified essential components of a pulmonary rehab model

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Digital inhaler discontinuations: Not enough uptake of device

BY WALTER ALEXANDER

On the heels of the January 2024 announcement by GlaxoSmithKline that its Flovent inhalers are being discontinued, Teva's recent announcement that it will discontinue US distribution of its Digihaler® products is adding concern and complication to patients' and physicians' efforts to manage asthma symptoms.

"It is unfortunate to hear more asthma inhalers are being discontinued," said Asthma and Allergy Foundation of America (AAFA) President and CEO Kenneth Mendez. The impact of Teva's June 1 discontinuations of its Digihaler portfolio (ProAir Digihaler, AirDuo Digihaler, and ArmonAir Digihaler), he added, is only partially softened by Teva's reassurance that its still-available RespiClick devices deliver the same drug formulations via the same devices as the ProAir and AirDuo products — without the digital aspect key to the Digihaler portfolio.

Digital app companion to inhaler

The digital components of the AirDuo Digihaler (fluticasone propionate and salmeterol)

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An NP's role as advocate for health policy and patient care

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through an online Delphi process involving about 50 international experts. Components ultimately included those with median scores of 2 or higher (strongly agree or agree that the item is essential) and high consensus (interquartile range, 0). Thirteen essential components fit into four categories (Patient Assessment, Program Components, Method of Delivery and Quality Assurance). The Patient Assessment category included seven items: (1) An initial center-based assessment by a health care professional, (2) An exercise test at the time of assessment, (3) A field exercise test, (4) Quality of life measure, (5) Dyspnea assessment, (6) Nutritional status evaluation, and (7) Occupational status evaluation. The Program Components: (8) Endurance training and (9) Resistance training. The Method of Delivery: (10) An exercise program that is individually prescribed, (11) An exercise program that is individually progressed, and (12) Team includes a health care professional with experience in exercise prescription and progression. The single Quality Assurance item: (13) Health care professionals are trained to deliver the components of the model that is deployed.

Cochrane Library review

“To date there has not been a comprehensive assessment of the clinical efficacy or safety of telerehabilitation, or its ability to improve uptake and access to rehabilitation services for people with chronic respiratory disease,” stated the Cochrane Collaboration NS Cox et al 2021 “Intervention Review” (<https://doi.org/10.1002/14651858.CD013040.pub2>). Using their own databases (eg, Cochrane Airways Trials Register) and others, the authors included controlled trials published up to November 30, 2020 with at least 50% delivered by telerehab. The authors’ analysis of 15 studies (with 32 reports) including 1904 participants (99% with COPD): “There was probably little or no difference between telerehabilitation and in-person pulmonary rehabilitation for exercise capacity measured as 6-Minute Walking Distance (mean difference 0.06 meters (m), 95% confidence interval (CI) -10.82 m to 10.94 m).” They reached the same conclusion for quality of life and for breathlessness. Completion of rehab programs, however, was more likely with telerehab at 93% versus 70%

for in-person rehabilitation. No adverse effects of telerehab were observed over and above those for in-person or no rehab. An obvious limitation of the findings is that the studies all pre-date COVID-19, which would have introduced very significant disincentives for in-person rehab completion.

An older (2016) international randomized controlled study (Zanaboni et al, <https://doi.org/10.1186/s12890-016-0288-z>) comparing long-term telerehab or unsupervised treadmill training at home with standard care included 120 participants with COPD and had 2 years of follow-up. Telerehab consisted of individualized treadmill training at home. Participants had scheduled exercise sessions supervised by a physiotherapist via videoconferencing following a standardized protocol. Participants in the unsupervised training group were provided with a treadmill only to perform unsupervised exercise at home. They also received an exercise booklet, a paper exercise diary to record their training sessions, and an individualized training program but without regular review or progression of the program. For the primary outcomes of combined hospitalizations and emergency department presentations, incidence rates of hospitalizations and emergency department presentations were lower with telerehab (1.18 events per person-year; 95% CI, 0.94–1.46) and with unsupervised training group (1.14; 95% CI, 0.92–1.41) than in the control group (1.88; 95% CI, 1.58–2.21; $P < .001$) compared with intervention groups. Both training groups had better health status at 1 year, achieved, and maintained clinically significant improvements in exercise capacity.

Access to pulmonary rehab

Continuing evidence of telerehab benefits is good news, especially in light of impediments to attendance at in-clinic programs. However, persisting access issues remain for substantial portions of eligible populations, according to a recent (2024) cross-sectional study (PA Kahn, WA Mathis, [doi:10.1001/jamanetworkopen.2023.54867](https://doi.org/10.1001/jamanetworkopen.2023.54867)) looking at travel time to pulmonary rehab programs as a marker for pulmonary rehab access. The report, based on US Census designations (lower 48 states and Washington, D.C.) found while 80.3% of the population lives in urban or

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inhalation powder and ArmonAir Digihaler (fluticasone propionate) inhalation powder, both maintenance inhalers for patients 12-years or older with asthma, include built-in wireless technology that connects to a companion mobile app. Their triggers for recording data on inhaler use are either the opening of the inhaler cap or the patient's inhalation. The devices detect, record, and store data on inhaler use and peak inspiratory flow.

Also, they can remind the patient how often the devices have been used, measure inspiratory flow rates, and indicate when inhalation technique may need improvement. Data are then directly sent to the Digihaler app, giving discretion to patients as to whether or not their data will be shared with health care providers.

When patients share their device-recorded data, Teva sources state, providers can more objectively assess the patients' inhaler use patterns and habits to determine if they are using them as prescribed, and through inspiratory flow rates, judge whether or not patients may need inhaler technique coaching.

Possibility for objective data

"I was excited about the Digihaler when it was first launched," said Maureen George, RN, PhD, of Columbia University School of Nursing, New York, "because it gave very good objective feedback on patients' inhaler technique through peak inspiratory flow. It showed whether they missed doses or if there

were patterns of increased use with increased symptoms.

"Inhaled medications are the only therapy that — if you inaccurately administer them — you don't actually get any drug, at all," she said. "If you don't get the drug into the target organ, the lungs, you don't get symptom relief, nor disease remission. Actually, most patients use their devices incorrectly, and most health care professionals can't demonstrate correct delivery technique. At the pharmacy, you're unlikely to see a real pharmacist, and more likely to see just a cashier. No other product that I know of has offered that degree of sophistication in terms of the different steps of inhaler technique."

CONNECT2: Better asthma control at 24 weeks

Benefits in asthma control for the Digihaler system have been confirmed recently in clinical research. The CONNECT2 trial (Mosnaim GS et al. doi: 10.1016/j.jaip.2023.11.037) compared asthma control with the Digihaler system (DS) versus standard of care (SoC) in patients 13 years or older with uncontrolled asthma (Asthma Control Test [ACT] score < 19). Investigators randomized them open-label 4:3 to the DS (n = 210) or SoC (n = 181) for 24 weeks. Primary endpoint assessment of the proportion of patients achieving well-controlled asthma (ie, an ACT score ≥ 20 or increase from baseline of ≥ 3 units at week 24) revealed an 88.7% higher

probability that DS patients would have greater odds of achieving asthma control improvement at week 24, with 35% higher odds of asthma control in the DS group. Also, clinician-participant interactions, mostly addressing poor inhaler technique, were more frequent in the DS group. Six-month adherence was good (68.6%, vs 79.2% at month 1), and reliever use at month 6 was decreased by 38.2% from baseline in the DS group.

Lack of inhaler uptake

"It made me sad to hear that it was going away. It's a device that should have been useful," Dr. George said, "but the wonderful features that could have come at an individual level or at a population health level just were never realized. I don't think it was from lack of trying on the company's part, but when it was launched, insurance companies wouldn't pay the extra cost that comes with having an integrated electronic monitoring device. They weren't convinced that the return on investment down the road from improved disease control and fewer very expensive acute hospitalizations was worth it. So the uptake was poor."

Where does this leave patients? The AAFA lists in detail alternatives to Teva's discontinued devices (community.aafa.org/blog/teva-digihaler-discontinued), naming quick-relief inhalers and inhaled corticosteroids, noting where dosing, devices, or active ingredients vary from the Teva products. ■

TELEREHAB continued from previous page

suburban areas within a 30-minute drive of a pulmonary rehab program, travel time exceeds that in rural and other sparsely populated areas with more than 14 million people residing in areas demanding more than 1 hour for travel. A further analysis showed nearly 30% of American Indian and Alaska Native populations live more than 60 minutes from a pulmonary rehab program. Aside from the obvious restraints for homebound patients, those lacking transportation, or who need medical transport, other impediments inhibit on-site pulmonary rehab attendance, said Corinne Young, MSN, FNP-C, FCCP. Ms. Young is the director of Advance Practice Provider and Clinical Services for Colorado Springs Pulmonary Consultants, president and founder of the Association of Pulmonary Advance Practice Providers, and a member of the *CHEST Physician* Editorial Board. "I have some patients who say, 'There's no way I could do onsite pulmonary rehab because of my knee, or back, or shoulder.' But in their own home environment they may feel more comfortable. They may be willing to try new things at their own pace, whereas,

for them a program may feel too regimented." For others, Ms. Young said, aspects of a formal program are a clear plus factor. "They love to hear their progress at the end of — say a 12-week program — where their virtual respiratory therapist records and reports to them their 6-minute walk and other test results. Feedback is a great reinforcer."



Ms. Young

Quality of life improvements, Ms. Young commented, were one of the very impressive benefits that appeared in the initial studies of pulmonary rehabilitation for COPD patients. "Being patient-centric, you want to improve quality of life for them as much as possible and we see telerehabilitation as a great opportunity for many," she added.

"I would like to see head-to-head data on outpatient versus at-home pulmonary rehabilitation on hospitalizations, time to exacerbation, and, of course, mortality. We have all that for outpatient rehab, but it would be great to be able to compare them. Knowing that would

influence what we recommend, especially for patients who could go either way. Also, you have to assess their motivation and discipline to know who might be more appropriate for unsupervised pulmonary rehabilitation."

The current reality for Ms. Young is that in her Colorado Springs vicinity, she knows of no telerehab programs being offered. While there are contract telerehab providers, Young said, and her organization has been approached by one, none are licensed in Colorado, and telerehab is not a billable service.

"As of yet, I'm not aware of any telemedicine pulmonary rehab available at our institution," said pulmonologist Mary Jo S. Farmer, MD, PhD, FCCP, Associate Professor of Medicine at UMass Chan Medical School – Baystate, Springfield, MA, and a member of the *CHEST Physician* Editorial Board. A brief internet search identified a telerehab contract provider only in Arizona. Reimbursement will also be a major concern, Ms. Young said. While a physician virtual visit for education may be billable, telerehab reimbursement is new territory. "How that all is going to work out is a big unknown piece," she said.

Minimal components

Effective pulmonary telerehab programs, Ms. Young said, need to provide exercise with an aerobic device, either a treadmill, a stationary bike or even an under desk foot pedal, and some resistance training (elastic bands, or weights, for example). "But 50% of pulmonary rehabilitation is education about breathing techniques, pursed-lip breathing, and pulmonary nutrition." Also essential: one-on-one discussion with a qualified medical practitioner who checks on oximeter use, inhaler technique, and titrating oxygen therapy. "At our elevation of 6,500 feet, most of our patients are on that." Optimal frequency of encounters between providers and remote patients has to be elucidated by future research, Ms. Young said. She commented further, "With outpatient pulmonary rehab there often isn't a lot of one-on-one, but rather a big group of people exercising at the same time. I think actually there may be the potential to have more individualization with pulmonary telerehabilitation. But the barriers, the reimbursement/financial part, and the red tape and bureaucracy have to be worked on." ■

Do patients benefit from cancer trial participation?

BY DEEPA VARMA

According to a new study, it's widely believed that patients with cancer benefit from access to investigational drugs. However, that belief does not align with trial findings. The study looks at survival rates and toxicity. Overall, patients with solid tumors who receive an investigational cancer drug experience small progression-free survival (PFS) and overall survival benefits but much higher toxicity than those who receive a control intervention.

Do the benefits outweigh the risks?

The view that patients with cancer benefit from access to investigational drugs in clinical trials is widely held but does not necessarily align with trial findings, which often show limited evidence of a clinical benefit. It is important to note most investigational treatments assessed in clinical trials fail to gain regulatory approval. However, the minority that are approved tend to offer minimal clinical benefit, experts explained. "We believe our

findings are best interpreted as suggesting that access to experimental interventions that have not yet received full FDA approval is associated with a marginal but nonzero clinical benefit," the authors wrote.

Meta-analysis of more than 100 trials

To estimate the survival benefit and toxicities associated with receiving experimental treatments, researchers conducted a meta-analysis of 128 trials comprising 141 comparisons of an investigational drug and a control treatment, which included immunotherapies and targeted therapies. The analysis included 42 trials in non-small cell lung cancer (NSCLC), 37 in breast cancer, 15 in hepatobiliary cancer, 13 in pancreatic cancer, 12 in colorectal cancer, and 10 in prostate cancer, involving a total of 47,050 patients.

The primary outcome was PFS and secondary outcomes were overall survival and grades 3-5 serious adverse events.

Modest improvement, and increased adverse events

Overall, the experimental treatment

was associated with a 20% improvement in PFS (pooled hazard ratio [HR], 0.80), corresponding to a median 1.25-month PFS advantage. The PFS benefit was seen across all cancer types, except pancreatic cancer. Overall survival improved by 8% with experimental agents (HR, 0.92), corresponding to 1.18 additional months. A significant overall survival benefit was seen across NSCLC, breast cancer, and hepatobiliary cancer trials but not pancreatic, prostate, colorectal cancer trials.

Patients in the experimental intervention group, however, experienced much higher risk for grade 3-5 serious adverse events (risk ratio [RR], 1.27), corresponding to 7.40% increase in absolute risk. The greater risk for serious adverse events was significant for all indications except prostate cancer (RR, 1.13; 95% CI, 0.91-1.40). Study authors noted, "Although our findings seem to reflect poorly on trials as a vehicle for extending survival for participants, they have reassuring implications for clinical investigators, policymakers, and institutional review boards," the researchers said, explaining that this "scenario allows

clinical trials to continue to pursue promising new treatments — supporting incremental advances that sum to large gains over extended periods of research — without disadvantaging patients in comparator groups."

Heterogenous studies, drugs

Study limitations include that there was high heterogeneity across studies due to variations in drugs tested, comparators used, and populations involved. The use of comparators below standard care could have inflated survival benefits. Additionally, data collected from ClinicalTrials.gov might be biased due to some trials not being reported. Renata Iskander, MSc, of McGill University, Montreal, Quebec, Canada, led this work, which was published in *Annals of Internal Medicine*. Canadian Institutes of Health Research supported this work; authors received grants for this work from McGill University, Rossy Cancer Network, and National Science Foundation. One author received consulting fees outside this work. The other authors declared no competing interests. ■



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Lung cancer screening: All about patient selection

BY ELENA RIBOLDI

A study conducted in the United States showed that many individuals undergo lung cancer screening despite having a higher likelihood of experiencing harm rather than benefit. Why does this happen? The authors of the study, which was published in *Annals of Family Medicine* (doi: 10.1370/afm.3081) interviewed 40 former military personnel with a significant history of smoking. Though the patients presented with various comorbidities and had a limited life expectancy, the Veterans Health Administration had offered them lung cancer screening.

Of the 40 respondents, 26 had accepted the screening test. When asked why they had done so, they responded, "to take care of my health and achieve my life goals," "because screening is an opportunity to identify potential issues," "because it was recommended by a doctor I trust," and "because I don't want to regret not accepting it." The respondents did not consider

their poor health or life expectancy. The screening was also welcomed because low-dose computed tomography (LDCT) is a noninvasive test. However, many participants were unaware the screening needed to be repeated annually and further imaging or other types of tests could follow LDCT, such as biopsies and bronchoscopies.

Many did not recall discussing with the doctor the potential harms of screening, including overdiagnosis, stress due to false positives, and complications and risks associated with investigations and treatments. Informed about this, several patients stated they would not necessarily undergo further tests or antitumor treatments, especially if invasive.

The authors of the article emphasized the importance of shared decision-making with patients who have a marginal expected benefit from screening. Guidelines advise against screening individuals with limited life expectancy and multiple comorbidities because the risk-benefit ratio is not favorable. ■

Novel ENV-101 associated with improved lung function in idiopathic pulmonary fibrosis

BY NEIL OSTERWEIL

FROM ATS 2024

SAN DIEGO — Patients with idiopathic pulmonary fibrosis (IPF) had significant improvements in lung function and reversal of lung fibrosis measures after 12 weeks of therapy with an investigational inhibitor of the Hedgehog signaling pathway.

Early efficacy data from a phase 2a safety trial suggest that the novel oral agent, dubbed ENV-101, is associated with improvements in forced vital capacity (FVC) and other measures of lung function, and may be a disease-modifying therapy for IPF, according to Toby M. Maher, MD, PhD, director of the interstitial lung disease program at Keck School of Medicine, University of Southern California, Los Angeles. Dr. Maher presented the results at the American Thoracic Society's international conference.

"Historically, we've not been seeing improvements in FVC, which is what we've been seeing [with ENV-101], and I think it's conceivable that you can get remodeling of early areas of fibrosis in the lung," Dr. Maher said.

"We know from histology studies that if you look at IPF lungs, you'll see areas of end-stage fibrosis. But even in advanced disease you'll see areas where the lung is relatively well preserved and there's early fibrosis, so I think it's conceivable that there is remodeling of some of those early areas of fibrosis," he said.

Vital pathway

The Hedgehog pathway is highly conserved in evolution. The cell-signaling pathway is active embryogenesis, tissue proliferation, and organ development. There is also evidence to suggest that in adult the pathway becomes reactivated following tissue injury, as can occur in lung epithelia, Dr. Maher explained.

Although as the word "idiopathic" in IPF indicates the etiology of the disease is unknown, investigators have found that in IPF repetitive epithelial injury to lung tissue leads to activation of the Hedgehog pathway. Hedgehog signaling in turn induces formation and activation of myofibroblasts that lay down fibrotic matrix and contract lung tissue, leading to significant impairments in gas

exchange, Dr. Maher said.

ENV-101 blocks Hedgehog from binding to the PTCH1 receptor, preventing release of the zinc-finger protein GLI1 from the kinase complex into the cell cytoplasm. With signaling blocked, myofibroblasts undergo apoptosis instead of initiating wound repair as they



Dr. Maher

normally would, thereby eliminating an evident mechanism of IPF pathology, he explained.

Study details

In the phase 2a trial, investigators enrolled patients with IPF who were not taking antifibrotic agents and who had a percent predicted FVC greater than 50%, predicted diffusing capacity for carbon monoxide (DLCO) of at least 35%, and life expectancy of more than 1 year.

The patients were randomized to receive 200 mg oral ENV-101 daily (18 patients) or placebo (15 patients) for 12 weeks.



Sample scan of IPF sourced from Wikimedia Commons

"We know from histology studies that if you look at IPF lungs you'll see areas of end-stage fibrosis, but even in advanced disease you'll see areas where the lung is relatively well preserved ... I think it's conceivable that there is remodeling of some of those early areas of fibrosis."

– Dr. Maher

The primary endpoint of the trial was safety of the experimental agent. A previous phase 1b study of a different Hedgehog inhibitor — vismodegib (Erivedge), in combination with the antifibrotic agent pirfenidone (Pirespa) — in patients with IPF was discontinued because of poor tolerability.

deaths and no clinically significant findings on labs, vital signs, electrocardiograms, or physical exam.

Efficacy endpoints

An analysis of the secondary efficacy endpoints showed a 1.9% mean improvement in FVC from baseline among patients assigned to ENV-101, compared with a mean decline of 1.3% of patients assigned to placebo ($P = .035$).

Patients on the active drug also had a 200-mL mean increase in total lung capacity, compared with a mean decline of 56 mL for patients on placebo ($P = .005$).

In addition, high-resolution CR studies showed a 9.4% absolute decrease from baseline in quantitative interstitial lung disease with ENV-101, vs. a 1.1% increase among controls, a 2% absolute decline from baseline in quantitative lung fibrosis compared with a 0.87% increase with placebo, and a 4.6% absolute decrease from baseline in quantitative ground glass, compared with an increase of 0.29% with placebo.

Bad taste a good sign?

Reinoud Gosens PhD, University of Groningen, the Netherlands, who co-moderated the session but was not involved in the study, questioned whether the dysgeusia seen in patients who received ENV-101 might be related to the dysgeusia seen in clinical trials of P2X3 receptor antagonists for cough.

"I was wondering if there would be a mechanistic overlap between Hedgehog inhibition and cough, which would be quite relevant for IPF," he said.

The increase in FVC seen with ENV-101 and with the investigational agent buloxibutid, a novel angiotensin II type 2 receptor agonist described in a separate presentation by Dr. Maher, suggests that these drugs may have the ability to help remodel damaged lungs, Dr. Gosens said.

Investigators are currently planning a phase 2 dose-ranging trial (WHISTLE-PF) in patients with IPF or progressive pulmonary fibrosis.

The phase 2a trial was supported by Endeavor BioMedicines. Dr. Maher disclosed consultancy or speaker fees from Endeavor and others. Dr. Gosens had no relevant disclosures. ■

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PULMONARY MEDICINE

National mine safety group issues rule to reduce silica exposure

BY HEIDI SPLETE

The Mine Safety and Health Administration (MSHA) has announced a final rule designed to protect miners from the dangers of exposure to silica dust, according to a press release from the US Department of Labor. Respirable crystalline silica, also known as silica dust or quartz dust, is a carcinogen associated with a range of serious health conditions including silicosis, lung cancer, progressive massive fibrosis, chronic bronchitis, and kidney disease.

The MSHA final rule reduces

the permissible exposure limit of respirable crystalline silica to 50 micrograms per cubic meter of air for a miner's full-shift exposure, which was calculated as an 8-hour time-weighted average. If a miner's exposure exceeds this limit, mine operators must take immediate action to comply with it, according to the new final rule.

"It is unconscionable that our nation's miners have worked without adequate protection from silica dust despite it being a known health hazard for decades," said Department of Labor acting

SILICA continued on following page

Priya Balakrishnan, MD, MS, FCCP, comments:

The recent tightening of the respirable crystalline silica exposure limit is vital in our fight to protect miners. The boom of silica mining over the past few decades has been driven by the consumerism of products like stone-washed jeans, cosmetics, computer hardware, and engineered stone counter tops leading to the resurgence of many conditions associated with silica exposure. Examples include silicosis, chronic obstructive pulmonary disease, tuberculosis, and a wide range of autoimmune conditions like systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. Unfortunately, we are seeing younger miners exposed to higher levels of respirable silica dust when more efficient highwall drills and blasters are used in larger surface mines. Modern mining and drilling techniques, while highly effective, generate excessive respirable silica dust affecting not only miners, but also mine operators, and nearby residential communities. The best treatment for many, if not all diseases, remains prevention, and ideally elimination of exposure or causative agents. Thus, the new MSHA rule is a welcome change in



the right direction to protect lung health and the lives of our patients. What we can do better when seeing patients is to emphasize the importance of respirator use and adherence

to workplace safety measures. Utilizing validated questionnaires like the Dust Exposure Life-Course Questionnaire in patients of high-risk occupations may improve diagnostic yield of occupational disorders. Usage of screening tools among

family members of patients with high-risk occupations, for example those who perform laundry activities of dusty clothing, may unmask daily-life sources of respirable silica dust. Over the next few decades new drugs currently under investigation and development targeting common dysregulated pathways of autophagy, apoptosis, and pyroptosis implicated in autoimmune disease and silicosis will provide an array of treatment options for our patients. Until then, the focus remains in education, advocacy, and prevention.

See doi:10.1097/ACI.0000000000000966 for further information on silicosis and autoimmune disease.

Dr. Balakrishnan is a member of the CHEST Physician Editorial Board.

Drug prototype shows potential for stem cell treatment of pulmonary disease

BY HEIDI SPLETE

A drug prototype showed promise for treating pulmonary disease by stimulating new stem cell growth to repair damaged tissue, based on a proof-of-concept study. In many pulmonary diseases, insufficient stem cells allow damage to progress, but researchers have developed a lung-targeted, drug-like small molecule to stimulate lung stem cell growth, according to data published in *Proceedings of the National Academy of Sciences*.

Michael J. Bollong, PhD, associate professor in the department of chemistry at Scripps Research, San Diego, and colleagues used ReFRAME, a drug repurposing library and database created by the Calibr-Skaggs Institute for Innovative Medicines (the drug discovery arm of Scripps Research) to test existing drugs as foundations to promote stem cell growth and repair in the lungs. “At present, there are no drugs which promote regenerative

repair of the lung,” Dr. Bollong said. “This is especially important in idiopathic pulmonary fibrosis [IPF], as this disease is driven by an insufficiency of the stem cell population of the lower airway, alveolar type 2 cells (AEC2s), to proliferate and to regenerate the gas exchange epithelium,” he said. The researchers identified dipeptidyl peptidase 4 (DPP4) inhibitors as potential tools to help promote production of stem cells in the lower airway called AEC2s. Dysfunction of AEC2 is thought to play a key role in the pathogenesis of IPF, the researchers noted. They created a new and highly soluble DPP4 inhibitor (NZ-97) that could be administered via intratracheal injection.

In a mouse model of lung disease, NZ-97 induced the growth of AEC2 cells and improved damaged lung tissue. In addition, 1 month of treatment with 0.5 mg/kg of NZ-97 every fourth day showed no detectable changes in alveolar structure, increased inflammation, or cellular hyperplasia. The NZ-97 prototype

drug is chemically similar to CMR316, a clinical drug candidate from researchers at Calibr-Skaggs that is scheduled to start a phase 1 clinical trial later in the summer of 2024, Dr. Bollong said.

Meeting the need for regenerative treatment

The ongoing research into NZ-97 may address the need for regenerative therapies in pulmonary disease, said Dharani K. Narendra, MD, FCCP, of Baylor College of Medicine, Houston, Texas, and a member of the *CHEST Physician Editorial Board*. “Identifying DPP4 inhibitors, particularly NZ-97, as potential agents for expanding type 2 alveolar epithelial cells (AEC2s) represents a promising therapeutic strategy to stimulate the regeneration of damaged alveolar epithelium,” she said. “The AEC2s play a crucial role in lung repair, and targeting these could potentially ameliorate various lung diseases that currently lack effective treatments,” she explained. “DPP4 inhibitors are

well-established in diabetes management and have known biological actions; however, the successful repurposing and effectiveness of NZ-97 in promoting lung repair are surprising to some extent,” Dr. Narendra said. “This surprise stems from this medication’s novel application and efficacy in a pulmonary context, showing significant potential where traditional DPP4 inhibitors required higher, potentially unsafe doses to achieve similar effects,” she said.

If successful, NZ-97 could offer substantial clinical benefits for treating pulmonary diseases such as IPF and other conditions involving alveolar damage. More research on NZ-97 is needed in order to identify potential barriers to its use, Dr. Narendra said. “Further studies are needed to evaluate the long-term effects of NZ-97, understand its mechanisms in human lung tissue, and determine its safety and efficacy in clinical settings.”

Dr. Narendra had no financial conflicts to disclose. ■

SILICA *continued from previous page*

secretary Julie Su. “The Department of Labor has taken an important action to finally reduce miners’ exposure to toxic silica dust and protect them from suffering from preventable diseases,” she said.

The final rule requires mine operators to prevent miners’ overexposures by using engineering controls and to use environmental evaluations and dust samplings to monitor their exposures. The rule also updates standards for respiratory protection to include the latest advances in equipment and practices to safeguard miners against a range of airborne hazards including silica dust, diesel particulate matter, and asbestos.

In addition, the rule requires metal and non-metal mine operators to establish medical surveillance programs and provide periodic health examinations to minors at no cost, similar to existing programs for coal miners. Implementation of the rule will result in approximately 1,067 lifetime avoided deaths and 3,746 lifetime avoided cases of silica-related illness, according to MSHA.

“Congress gave MSHA the authority to regulate toxic substances to protect miners from health hazards and made clear that miners’ health and safety must always be our first priority and concern,” said Chris Williamson, assistant secretary for mine safety and health, in the press release. “No miner should ever have to sacrifice their health or lungs to provide for their family,” he said. ■

Waistline tied to asthma attacks risk

BY HEIDI SPLETE

A recent study links waist size and a higher risk for asthma attack. After adjustments, the likelihood of asthma attacks was 1.06 times higher for every 5-cm increase in waist circumference in adults with asthma.

BMI earlier tied to asthma

Previous research supports a link between increased body mass index (BMI) and asthma, but the association between abdominal obesity and asthma attacks has not been well studied.

The researchers in the current study reviewed data from the National Health and Nutrition Examination Survey for 5,530 adults with asthma in the United States. Adults in the study were divided into groups based on whether they did or did not experience asthma attacks.

The median age of the study population was 43 years, the median waist circumference was 98.9 cm, and the median BMI was 28.50.

More waist inches = asthma attacks

Overall, patients who reported asthma attacks had a significantly higher waist circumference than those without asthma attacks (median, 102.6 cm vs 97.3 cm, $P < .001$).

The association between increased waist circumference and increased odds of asthma attack was significant across non-adjusted, minimally

adjusted, and fully adjusted models (odds ratios, 1.7, 1.06, and 1.06, respectively). In fact, each 5-cm increase in waist circumference was associated with a 1.06 times higher likelihood of an asthma attack after full adjustment for BMI-defined obesity, age, gender, race/ethnicity, education, poverty income ratio, smoking status, and metabolic syndrome.

The relationship between increased likelihood of asthma attacks and increased waist circumference persisted in subgroup analyses based on gender, age, and smoking status.

Importance of waist size

“Our study underscores the critical role of waist circumference measurements in the routine health evaluations of individuals diagnosed with asthma, highlighting its inclusion as an essential aspect of comprehensive health assessments,” the researchers wrote.

The study findings were limited by several factors including the use of existing database questions to evaluate asthma attacks, a lack of data on the specificity of triggers of asthma exacerbations, and an inability to distinguish the severity of asthma attacks.

The study was published online in *BMC Public Health*. The lead author was Xiang Liu, MD, of Qingdao Municipal Hospital, Qingdao, China. The study received no outside funding. The researchers had no financial conflicts to disclose. ■

Antibiotics in LRTI: No benefit

BY DIANA SWIFT

Antibiotics had no measurable effect on the severity or duration of coughs due to acute lower respiratory tract infection (LRTI, or acute bronchitis), a prospective study found. In fact, those receiving an antibiotic in the primary- and urgent-care setting had a small but significant increase in overall length of illness (17.5 vs 15.9 days; $P = .05$) — largely because patients with longer illness before the index visit were more likely to receive these drugs. The study adds further support for reducing the



Dr. Merenstein

prescription of antibiotics for LRTIs.

“Importantly, the pathogen data demonstrated the length of time until illness resolution for those with bacterial infection was

the same as for those not receiving an antibiotic versus those receiving one (17.3 vs 17.4 days),” researchers led by Daniel J. Merenstein, MD, a professor and director of research programs, family medicine, at Georgetown University Medical Center in Washington, wrote in the *Journal of General Internal Medicine* (doi: 10.1007/s11606-024-08758-y).

Patients believed an antibiotic would shorten their illness by an average of about 4 days, from 13.4 days to 9.7 days, whereas the average duration of all coughs was more than 2 weeks regardless of pathogen type or receipt of an antibiotic. “Patients had unrealistic expectations regarding the duration of LRTI and the effect of antibiotics, which should be the target of antibiotic stewardship efforts,” the group wrote.

LRTIs can, however, be dangerous, with 3%-5% progressing to pneumonia, “but not everyone has easy access at an initial visit to an x-ray, which may be the reason clinicians still give antibiotics without any other evidence of a bacterial infection,” Dr. Merenstein said in a news release.

No effect on duration

The current study looked at 718 patients (mean age: 38.9 years, 65.3% female), of whom 207 received an antibiotic and 511 did not. Of those with baseline data,

29% were prescribed an antibiotic at baseline; 85% received amoxicillin-clavulanate, azithromycin, doxycycline, and amoxicillin. Antibiotics had no effect on the duration or overall severity of

cough in viral, bacterial, or mixed infections. Receipt of an antibiotic did, however, reduce the likelihood of a follow-up visit: 14.1% vs 8.2% (adjusted odds ratio, 0.47; 95% confidence interval, 0.26-0.84)

— perhaps because it removed the motivation for seeking follow-up. Antibiotic recipients were more likely to receive a systemic corticosteroid (31.9% vs 4.5%, $P < .001$) and were also more likely to receive an

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albuterol inhaler (22.7% vs 7.6%, $P < .001$).

Jeffrey A. Linder, MD, MPH, a primary care physician and chief of internal medicine and geriatrics at Northwestern University Feinberg School of Medicine in Chicago, agrees antibiotics do not speed healing in most LRTIs. “Forty years of research show antibiotics do not

make acute bronchitis go away any faster,” Dr. Linder said, who was not involved in the current study. “There’s even growing evidence that a lot of pneumonia is viral as well, and 10 or 20 years from now we may often not be giving antibiotics for pneumonia because we’ll be able to see better if it’s caused by a virus.” A 2018 review by Dr. Linder

reported 46% of antibiotics were prescribed without any infection-related diagnosis code and 20% without an office visit.

“Serious cough symptoms and how to treat them needs to be studied more, perhaps in a randomized clinical trial as this study was observational and there haven’t been any randomized trials looking at this

issue since about 2012,” Dr. Merenstein said.

This research was funded by the Agency for Healthcare Research and Quality. The authors have no conflicts of interest to declare. Dr. Linder reported stock ownership in pharmaceutical companies but none that make antibiotics or infectious disease drugs. ■

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Automated tool reduces antibiotic prescribing rates

BY BRITTANY VARGAS

An algorithm-driven risk assessment embedded in an electronic health record

(EHR) helped clinicians reduce inappropriate broad-spectrum antibiotic prescribing by 28.4% in patients with pneumonia, according to a study published in *JAMA*.

The randomized control trial included more than 96,000 adult patients with non-life threatening pneumonia (doi:10.1001/jama.2024.6248) in 59 hospitals

owned by HCA Healthcare across the country. Researchers analyzed baseline prescribing behaviors over an 18-month period starting in April 2017, and data from a

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15-month period of implementation of the new antibiotic system starting in April 2019.

They focused on the use of broad-spectrum antibiotics during the first 3 days of hospital admission, before microbiologic test results came back, and when clinicians are likely to err on the side of caution and prescribe one

of the drugs, according to lead author Shruti K. Gohil, MD, MPH, associate medical director of epidemiology and infection prevention, infectious diseases at the University of California Irvine School of Medicine. “When a patient comes in with pneumonia...it’s precisely because we are concerned that our patients have a multidrug-resistant organism

that we end up using broad-spectrum antibiotics,” she said.

Despite growing awareness of the need to reduce unnecessary antibiotic use, clinicians have still been slow to adopt a more conservative approach to prescribing, Dr. Gohil said. “What physicians have been needing is something to hang their hat on, to be able to say, ‘Okay, well,

this one’s a low-risk person,’” Dr. Gohil said.

The trials compared the impact of routine antibiotic activities with a stewardship bundle, called INSPIRE (Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection). Both groups received educational materials, quarterly coaching calls, prospective evaluations for antibiotic use, and were required to select a reason for prescribing an antibiotic. But prescribers in the intervention group took part in monthly coaching calls and feedback reports. In addition, if a clinician ordered a broad-spectrum antibiotic to treat pneumonia or outside of the intensive care unit within 72 hours of admission, an EHR prompt would pop up. The pop-up suggested a standard-spectrum antibiotic instead if patient risk for developing a multidrug-resistant (MDRO) version of either condition was less than 10%.

An algorithm used data from the EHR calculated risk, using factors like patient demographics and history and MDRO infection at the community and hospital level. Prescribing rates were based on the number of days a patient received a broad-spectrum antibiotic during the first 72 hours of hospitalization. For the pneumonia intervention group, rates dropped by 28.4% (RR, 0.72; 95% CI, 0.66-0.78; $P < .001$). “We cannot know which element — prompt, education, or feedback — worked, but the data suggests the prompt was the main driver,” Dr. Gohil said.

The prompt “is your easy button,” said Paul Pottinger, MD, professor of medicine at the Division of Allergy and Infectious Diseases at the University of Washington Medical Center in Seattle, who was not involved with either study. “The researchers made it simple, fast, and straightforward, so people don’t have to think about it too much.”

The studies showed similar safety outcomes for the control and intervention groups. Among patients with pneumonia, the average days to ICU transfer were 6.5 for the control group and 7.1 for the intervention group. “[This study] shows us this tool can be refined and made even more precise over time,” Dr. Pottinger said.

The study was funded by the US Centers for Disease Control and Prevention and was led by the University of California Irvine, Harvard Pilgrim Healthcare Institute, and HCA Healthcare System. Authors report funding and support outside the submitted work; a full list can be found with the original article. ■

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CRITICAL CARE COMMENTARY

Hospital-onset sepsis: Why the brouhaha?

BY SIDDHARTH P. DUGAR, MD, FCCP;
NAMITA JAYAPRAKASH, MBBC;
RONALD REILKOFF, MD; AND
ABHIJIT DUGGAL, MD, MPH, MSC

A 47-year-old woman with a history of cirrhosis is admitted with an acute kidney injury and altered mental status. On the initial workup, there are no signs of infection, and dehydration is determined to be the cause of the kidney injury. There are signs of improvement in the kidney injury with hydration. On hospital day 3, the patient develops a fever (101.9°F) with accompanying leukocytosis to 14,000. Concerned for infection, the team starts empiric broad spectrum antibiotics for presumed spontaneous bacterial peritonitis. The next day (hospital day 4), a rapid response evaluation is activated as the patient is demonstrating increasing confusion, hypotension with a systolic blood pressure of 70 mm Hg, and elevated lactic acid. The patient receives 1 L of normal saline and transfers to the ICU. The new critical care fellow, who has just read up on sepsis early management bundles, and specifically the Severe Sepsis and Septic Shock Management Bundle (SEP-1), is reviewing the chart and notices a history of multidrug-resistant organisms in her urine cultures from an admission 2 months ago. They ask of the transferring team, “When was time zero, and was the 3-hour bundle completed?”

Sepsis is recognized as a medical emergency, which, without a prompt response, causes significant morbidity and mortality. In the United States alone, more than 1.7 million adults develop sepsis, with approximately 270,000 deaths and \$57 billion in aggregate costs annually. The excessive cost, both of human life and monetary, has led to the commitment of significant resources to sepsis care. Improved recognition and timely intervention for sepsis have led to noteworthy improvement in mortality. Most of this effort has been directed toward patients with sepsis diagnosed in the emergency department (ED) who are presenting with community-onset sepsis (COS). A new entity, called hospital-onset sepsis (HOS), has been described recently, defined by the Centers for Disease Control and Prevention (CDC) as both infection and organ dysfunction developing more than 48 hours after hospital admission.

A systematic review of 51 studies found approximately 23.6% of all sepsis cases are HOS. The proportion of HOS is even higher (more than 45%) in patients admitted to the ICU with sepsis. The outcome for this group remains comparatively poor. The hospital mortality among patients with HOS is 35%, which increases to 52% with progression to septic shock compared with 25% with COS. Even after adjusting for baseline factors that make one prone to developing infection in the hospital, a patient developing HOS has three-times a higher risk of dying

compared with a patient who never developed sepsis and two-times a higher risk of dying compared with patients with COS. Furthermore, HOS utilizes more resources with significantly longer ICU and hospital stays and has five-times the hospital cost compared with COS.

The two most crucial factors in improving sepsis outcomes, as identified by the Surviving Sepsis Campaign guidelines, are: 1) prompt identification and treatment within the first few hours of onset and 2) regular reevaluation of the patient's response to treatment.

Prompt identification

Diagnosing sepsis in the patient who is hospitalized is challenging. Patients admitted to the hospital often have competing comorbidities, have existing organ failure, or are in a postoperative/intervention state that clouds the application and interpretation of vital sign triggers customarily used to identify sepsis. The positive predictive value for all existing sepsis definitions and diagnostic criteria is dismally low. And while automated electronic sepsis alerts may improve processes of care, they still have poor positive predictive value and have not impacted patient-centered outcomes (mortality or length of stay). Furthermore, the causative microorganisms often associated with hospital-acquired infections are complex, are drug-resistant, and can have courses which further delay identification. Finally, cognitive errors, such as anchoring biases or premature diagnosis closure, can contribute to provider-level identification delays that are only further exacerbated by system issues, such as capacity constraints, staffing issues, and differing paces between wards that tend to impede time-sensitive evaluations and interventions.

Management

The SEP-1 core measure uses a framework of early recognition of infection and completion of the sepsis bundles in a timely manner to improve outcomes. Patients with HOS are less likely than those with COS to receive Centers for Medicare & Medicaid Services SEP-1-compliant care, including timely blood culture collection, initial and repeat lactate testing, and fluid resuscitation. The Surviving Sepsis Campaign has explored barriers to managing HOS. Among caregivers, these include delay in recognition, poor communication regarding change in patient status, not prioritizing treatment for sepsis, failure to measure lactate, delayed or no antimicrobial administration, and inadequate fluid resuscitation. In one study, the adherence to SEP-1 for HOS was reported at 13% compared with 39.9% in COS. The differences in initial sepsis management included timing of antimicrobials and fluid resuscitation, which accounted for 23% of observed greater mortality risk among patients with HOS

At the system level, survival from sepsis is determined by the speed with which complex medical care is delivered and the effectiveness with which resources and personnel are mobilized and coordinated.



Dr. Dugar

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compared with COS. It remains unclear how these recommendations should be applied and whether some of these recommendations confer the same benefits for patients with HOS as for those with COS. For example, administration of fluids conferred no additional benefit to patients with HOS, while rapid antimicrobial administration was shown to be associated with improved mortality in patients with HOS. Although, the optimal timing for treatment initiation and microbial coverage has not been established.

The path forward

Effective HOS management requires both individual and systematic approaches. How clinicians identify a patient with sepsis must be context-dependent. Although standard criteria exist for defining sepsis, the approach to a patient presenting to the ED from home should differ from that of a patient who has been hospitalized for several days, is postoperative, or is in the ICU on multiple forms of life support. Clinical medicine is context-dependent, and the same principles apply to sepsis management. To address the diagnostic uncertainty of the syndrome, providers must remain vigilant and maintain a clinical “iterative urgency” in diagnosing and managing sepsis. While machine learning algorithms have potential, they still rely on human intervention and interaction to navigate the complexities of HOS diagnosis.

At the system level, survival from sepsis is determined by the speed with which complex medical care is delivered and the effectiveness with which resources and personnel are mobilized and coordinated. The Hospital Sepsis Program Core Elements, released by the CDC, serves

SEPSIS continued on following page

FROM THE PRESIDENT

Complementing, not competing

BY JACK D. BUCKLEY, MD,
MPH, FCCP

As we enter summer, it's hard to believe that we're halfway through my presidency. Registration for CHEST 2024 (October 6 to 9) is now open, and October will be here before we know it. We're thrilled to host the CHEST Annual Meeting in Boston for the first time ever and hope to see you there to experience all that the meeting has to offer.

I'm happy to share that we

received more than 4,000 abstract and case report submissions from clinicians at all stages of their careers, and, for the first year, we had a dedicated category to solicit submissions from physician assistants (PAs), nurse practitioners (NPs), respiratory therapists, and other members of the broader health care team.

In both my practice and my time as CHEST President, I've been reflecting on the benefits of the multidisciplinary team—especially in the ICU. Because this is a setting that relies heavily on a team aspect, every member of the care team is a great asset.

CHEST is working to ensure that all integral members of our professional health care teams have the resources they need to best serve our



Dr. Buckley

patients. We encourage advanced practice providers (APPs) to apply to serve on our committees during the current open call, and we recently launched a dedicated column, called APP Intersection, within this publication to elevate diverse perspectives. I anticipate more is on the horizon.

Our future is ripe with opportunities to better serve the whole care team—MDs, PAs, NPs, and more...

In my experience, I have seen tremendous success in partnering with and complementing each other, rather than competing for space when caring for a patient. Each and every one of us shares the same goal of providing the best patient care, and we each bring our own strengths.

Our future is ripe with opportunities to better serve the whole care team—MDs, PAs, NPs, and more—and it starts with recognizing the needs of everyone within the organization. To help CHEST better serve our members, I encourage you to scan the QR code to take a short survey about your professional

hurdles. And please, do not hesitate to contact me (president@chestnet.org) with suggestions or just to introduce yourself.

All the best,
Jack



SEPSIS *continued from previous page*

as an initial playbook to aid hospitals in establishing comprehensive sepsis improvement programs.

A second invaluable resource for hospitals in sepsis management is the rapid response team (RRT). Studies have shown that resolute RRTs can enhance patient outcomes and compliance with sepsis bundles; though, the composition and scope of these teams are crucial to their effectiveness. Responding to in-hospital emergencies and urgencies without conflicting responsibilities is an essential feature of a successful RRT.

Often, they are familiar with bundles, protocols, and documentation, and members of these teams can offer clinical and/or technical expertise as well as support active participation and reengagement with bedside staff, which fosters trust and collaboration. This partnership is key, as these interactions instill a common mission and foster a culture of sepsis improvement that is required to achieve sustained success and improved patient outcomes. ■

All references available online at chestphysician.org.

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PULMONARY PERSPECTIVES®

Military burn pits: Their evidence and implications for respiratory health

BY ZACHARY A. HAYNES, MD,
AND JOEL ANTHONY
NATIONS, MD, FCCP

Military service is a hazard-ridden profession. It's easy to recognize the direct dangers from warfighting, such as gunfire and explosions, but the risks from environmental, chemical, and other occupational exposures can be harder to see.

Combustion-based waste management systems, otherwise known as “burn pits,” were used in deployed environments by the US military from the 1990s to the early 2010s. These burn pits were commonly used to eliminate plastics, electronics, munitions, metals, wood, chemicals, and even human waste. At the height of the recent conflicts in Afghanistan, Iraq, and other southwest Asia locations, more than 70% of military installations employed at least one, and nearly 4 million service members were exposed to some

degree to their emissions.

Reports of burn pits being related to organic disease have garnered widespread media attention. Initially, this came through anecdotal reports of post-deployment respiratory symptoms. Over time, the

Research on outcomes related to burn pit exposure is challenging given the heterogeneity in exposure volume. Much of the research is retrospective and subject to recall bias.

conditions attributed to burn pits expanded to include newly diagnosed respiratory diseases and malignancies. The composition of burn pit emissions sparked concern after fine particulate matter, volatile

organic compounds, dioxins, and polycyclic aromatic hydrocarbons were detected. Each has previously been associated with an increased risk of respiratory disease or malignancy.

Ultimately, Congress passed the 2022 Promise to Address Comprehensive Toxins (PACT) Act, presumptively linking more than 20 diagnoses to burn pits. The PACT Act provides countless veterans access to low-cost or free medical care for their respective conditions.

What do we know about burn pits and deployment-related respiratory disease?

Data from the Millennium Cohort Study noted an approximately 40% increase in respiratory symptoms among individuals returning from deployment but no increase in the frequency of diagnosed respiratory diseases. This study and others definitively established a temporal relationship between deployment and respiratory symptoms. Soon after, a retrospective, observational study of service members with post-deployment respiratory symptoms found a high prevalence of constrictive bronchiolitis (CB) identified by lung biopsy. Patients in this group reported exposure to burn pits and a sulfur mine fire in the Mosul area while deployed. Most had normal imaging and pulmonary function testing before biopsy, confounding the clinical significance of the CB finding. The publication of this report led to increased investigation of respiratory function during and after deployment.

In a series of prospective studies that included full pulmonary function testing, impulse oscillometry, cardiopulmonary exercise testing, bronchoscopy, and, occasionally, lung biopsy to evaluate post-deployment dyspnea, only a small minority received a diagnosis of clinically significant lung disease. Additionally, when comparing spirometry and impulse oscillometry results from before and after deployment, no decline in lung function was observed in a population of service members reporting regular burn pit exposure. These studies suggest that at the



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population level, deployment does not lead to abnormalities in the structure and function of the respiratory system.

The National Academies of Sciences published two separate reviews of burn pit exposure and outcomes in 2011 and 2020. They found insufficient evidence to support a causal relationship between burn pit exposure and pulmonary disease. They highlighted studies on the composition of emissions from the area surrounding the largest military burn pit in Iraq. Levels of particulate matter, volatile organic compounds, and polycyclic aromatic hydrocarbons were elevated when compared with those of a typical American city but were similar to the pollution levels seen in the region at the time. Given these findings, they suggested ambient air pollution may have contributed more to clinically significant disease than burn pit emissions.

How do we interpret this mixed data?

At the population level, we have yet to find conclusive data directly linking burn pit exposure to the development of any respiratory disease. Does this mean that burn pits are not harmful?

Not necessarily. Research on outcomes related to burn pit exposure is challenging given the heterogeneity in exposure volume.

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Top reads from the *CHEST* journal portfolio

Malnutrition in critically ill patients, MODE trial findings, and guideline alignment in COPD

Journal *CHEST*[®]

The Association Between Malnutrition and High Protein Treatment on Outcomes in Critically Ill Patients

By: Charles Chin Han Lew, PhD, et al

Current international critical care guidelines based on expert opinion recommend high protein treatment (average 1.6 g/kg/d) for critically ill patients diagnosed with preexisting malnutrition to improve clinical outcomes. This multicenter, randomized controlled clinical trial investigated the effects of high vs usual protein treatment in 1,301 critically ill patients across 16 countries. Preexisting malnutrition was independently associated with the primary outcome of slower time to discharge alive (TTDA) (adjusted hazard ratio, 0.81; 95% CI, 0.67-0.98). However, high protein treatment in patients with and without preexisting malnutrition was not associated with TTDA (adjusted hazard ratios of 0.84 [95% CI, 0.63-1.11] and 0.97 [95% CI, 0.77-1.21]). Furthermore, no effect modification was observed (ratio of adjusted hazard ratio, 0.84; 95% CI, 0.58-1.20).

Most importantly, this study demonstrated an association between malnutrition and slower TTDA; however, this association was not modified by high protein treatment. This research challenges current international critical care nutrition guidelines.

– Commentary by Mary Jo S. Farmer, MD, PhD, FCCP, Member of the *CHEST Physician* Editorial Board



Dr. Farmer

CHEST[®] Critical Care

Protocol and Statistical Analysis Plan for the Mode of Ventilation During Critical Illness (MODE) Trial

By: Kevin P. Seitz, MD, et al

The Mode of Ventilation During Critical Illness (MODE) trial is a cluster-randomized, multiple-crossover pilot study conducted in a medical ICU exploring how different mechanical ventilation modes affect ventilator-free days in critically ill patients. This trial aims to determine which ventilation mode maximizes the days patients spend alive without invasive ventilation. By switching between ventilation modes each month, the study ensures a thorough assessment under uniform clinical conditions. The trial's protocol and statistical analysis plan were defined before the end of enrollment, which bolsters the rigor, reproducibility, and transparency of the findings. Initial findings indicate the necessity for an expanded, multicenter trial to definitively identify the optimal ventilation mode, as current data do not universally prefer one method over others. This research has significant implications for clinical practice, potentially altering mechanical ventilation guidelines and improving patient outcomes by reducing the time spent on mechanical ventilation.

– Commentary by Dharani Narendra, MD, FCCP, Member of the *CHEST Physician* Editorial Board



Dr. Narendra

CHEST[®] Pulmonary

Guideline Alignment and Medication Concordance in COPD

By: Meredith A. Chase, MD, MHS, et al

This study aligns with prior research showing lack of compliance between physician prescriptions and the Global Initiative for Chronic Obstructive Lung Disease strategy's recommendations. The inappropriate use of maintenance inhalers and the excessive use of inhaled corticosteroids are contributing factors to the skyrocketing expenses of managing COPD.

There are a number of factors that are difficult to address. First, primary care providers (PCPs) are less knowledgeable about the recommendations and guidelines than specialists are. Second, managed care companies are sometimes reluctant to refer patients to a specialist, resulting in delayed diagnosis or misdiagnosis and mismanagement. Third, managed health care organizations have limited drugs for managing COPD on their formularies, limiting the ability of the provider to prescribe guideline-recommended treatments. Lastly, the number of primary care doctors is decreasing, which is influencing patients' ability to connect with a clinician with the clinical expertise to assist them.

Future studies should focus on solutions that could lessen these obstacles.

– Commentary by Humayun Anjum, MD, FCCP, Member of the *CHEST Physician* Editorial Board



Dr. Anjum

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Much of the research is retrospective and subject to recall bias. Relationships may be distorted, and the precision of reported symptoms and exposure levels is altered. Given these challenges,

The DoD and VA have dedicated large portions of their research budgets to investigating the impacts of exposures during military service and optimizing the care of those with respiratory symptoms.

it's unsurprising that evidence of causality has yet to be proven. In addition, some portion of service members has been diagnosed with respiratory disease that could be related to burn pit exposure.

What is now indisputable is that deployment to southwest Asia leads to an increase in respiratory complaints. Whether veteran respiratory symptoms are due to burn pits, ambient pollution, environmental particulate matter, or dust storms is less clinically relevant. These symptoms require attention, investigation, and management.

What does this mean for the future medical care of service members and veterans?

Many veterans with post-deployment respiratory symptoms undergo extensive evaluations without obtaining a definitive diagnosis. A recent consensus statement on deployment-related respiratory symptoms provides a framework for evaluation in such cases. In keeping with that statement, we recommend veterans be referred to centers with expertise

in this field, such as the Department of Veterans Affairs (VA) or military health centers, when deployment-related respiratory symptoms are reported. When the evaluation does not lead to a treatable diagnosis, these centers can provide multidisciplinary care to address the symptoms of dyspnea, cough, fatigue, and exercise intolerance to improve functional status.

Despite uncertainty in the evidence or challenges in diagnosis, both the Department of Defense (DoD) and VA remain fully committed to addressing the health concerns of service members and veterans. Notably, the VA has already screened more than 5 million veterans for toxic military exposures in accordance with the PACT Act and is providing ongoing screening and care for veterans with post-deployment respiratory symptoms. Furthermore, the DoD

and VA have dedicated large portions of their research budgets to investigating the impacts of exposures during military service and optimizing the care of those with respiratory symptoms. With these commitments to patient care and research, our veterans' respiratory health can now be optimized, and future risks can be mitigated. ■

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NETWORKS

Early-life infections and pediatric OSA, cardiopulmonary exercise testing, and more

CRITICAL CARE NETWORK Mechanical Ventilation and Airways Management Section

Electrical impedance tomography: Visualization and integration of the impact of mechanical ventilation

Lung protective ventilation (LPV) is the cornerstone to minimizing ventilator-induced lung injury. Hence, LPV is associated with better survival in patients both with and without ARDS.

Continuous monitoring of the tidal volume, plateau pressure, and positive end-expiratory pressure (PEEP) is crucial to maintain LPV. Electrical impedance tomography (EIT) is a noninvasive, radiation-free, imaging method of the electrical conductivity distribution inside the human body. Integrating EIT into invasive mechanical ventilation allows imaging of the regional lung ventilation as affected by the mechanical ventilation

settings as well as the patient position. It can also provide a personalized approach to determining the optimum ventilatory settings based on individual patient conditions.



Dr. Zaaqoq

Optimum PEEP titration is crucial to prevent lung collapse as well as overdistension. In a single-center, randomized, crossover pilot study of 12 patients, optimum PEEP titration was carried out using a high PEEP/FiO₂ table vs EIT in moderate to severe ARDS. The primary endpoint was the reduction of mechanical power, which was consistently lower in the EIT group. EIT also allows the assessment of regional compliance of the lungs. There are reports regarding the superiority of regional compliance

of lung over global compliance in achieving better gas exchange, lung compliance, and weaning of mechanical ventilation. EIT could assess the patient's response to prone positioning by illustrating the change in the functional residual capacity between supine and prone positioning. In addition, by visualization of the ventilated areas during spontaneous breathing and reduction of pressure support, EIT could help in weaning off the mechanical ventilation.

In conclusion, EIT can be a tool to provide safe and personalized mechanical ventilation in patients with respiratory failure. However, there are limited data regarding its use and application, which might become an interesting subject for future clinical research.

All references available online at chestphysician.org.

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CHEST INFECTIONS AND DISASTER RESPONSE NETWORK Pediatric Chest Medicine Section

Severe early-life respiratory infections heighten pediatric OSA risk

Children with severe lower respiratory tract infections (LRTIs) within the first 2 years of life had a 2.06-fold increased risk of developing pediatric OSA by age 5, according to a study comparing patients hospitalized with LRTI to controls without severe LRTI. Prior studies linked LRTI and OSA, but the impact of LRTI severity was unknown. Using a case-control design, researchers analyzed data from 2,962 children enrolled in the Boston Birth Cohort (BBC): 235 children with severe LRTIs and 2,333 controls. They used Kaplan-Meier survival estimates and Cox proportional hazards models to evaluate the risk of OSA.

Compared with patients with severe
NETWORKS continued on following page

APP INTERSECTION

An NP's role as advocate for health policy and patient care

BY ALANNA KAVANAUGH, EDD(C),
FNP-BC, MSN, BSN, CCRN

In the intricate tapestry of health care, the roles of advanced practice registered nurses, also known as nurse practitioners (NPs), have evolved beyond the confines of clinical settings. Once solely seen as caregivers at the bedside, these nursing professionals now stand at the forefront of advocacy, policymaking, and patient empowerment.

The journey into the realm of nursing often begins with a passion for healing and caring for others. However, for many, this path frequently leads to overcoming barriers to patient care, restrictions to practice, and lengthy red tape in the face of care teams that do not fully understand the scope and role of the NP.

Delving into health policy intricacies, efforts focus on understanding how legislative decisions directly impact patient care. Involvement in advocacy aims to improve health care access, promote patient-centered policies, and reduce disparities in the workforce and patient care.

Achieving sound primary care for people with multiple comorbid conditions requires the skills and abilities of all members of the health care workforce, including NPs. NPs have assumed an increasing role in recent decades as primary care providers for people with chronic diseases, while national trends show few physicians entering and staying in

primary care. NPs are the nation's fastest-growing primary care workforce, with nearly 90% of them trained to deliver primary care. Yet, NPs continue to experience reduced reimbursement for services compared with their physician counterparts.

Barriers to practice reduce the productivity and capacity of these health care professionals. Not permitting NPs to practice to the full extent of their licensure and education decreases the types and amounts of health care services that can be provided for people who need care. As noted in the *Future of Nursing 2020-2030* report, this restriction also has significant implications for addressing the disparities in access to health care between rural and urban areas. A recent systemic review revealed that full practice authority is associated with higher numbers of NPs in rural areas and in primary care where there is a shortage of physicians. Full practice authority is associated with increased access to care and utilization of health care services, lower cost of care, and no decrease in quality of care. As stated in the *National Council of State Boards of Nursing 2022 Environmental Scan*, regulators and nurse leaders are responsible for upholding rules and regulations of nursing practice as well as ensuring that standards of care are met and patients are protected.

Of equal importance is regulator awareness of the degree to which barriers continue to impact NP practice and limit aspects of care that directly



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influence care quality and access. Nursing leaders can have a significant impact on removing non-regulatory barriers to practice, such as changing outdated hospital bylaws that restrict NP practice. In turn, regulators can support efforts to remove unnecessary barriers to NP practice.

Fueled by experience in reduced practice, NPs become catalysts for change, transcending the role of health care providers. At the core of the NP role lies a commitment to patient advocacy. Beyond diagnosing and treating illnesses, NPs champion patients' rights, ensuring their voices in health care decision-making. Advocacy efforts range from expanding access to essential services to promoting preventive care and fighting discrimination. By embracing roles as caregivers and agents of change, NPs can help the health care system emerge equitable, accessible, and patient-centric. ■

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NETWORKS *continued from previous page*

LRTIs, controls were more likely to have been full-term births, delivered vaginally, and breastfed. The OSA rate was significantly higher among children with severe LRTIs compared with controls (14.7% vs 6.8%). In the adjusted model controlling for relevant maternal and infant covariables, severe LRTI was significantly associated with increased OSA risk (HR, 2.06; 95% CI, 1.41-3.02; $P < .001$).



Dr. Montgomery

Other factors such as prematurity (HR, 1.34; 95% CI, 1.01-1.77; $P = .039$) and maternal obesity (HR, 1.82; 95% CI, 1.32-2.52; $P < .001$) were also associated with increased OSA risk.

Maria Gutierrez, MD, of the Division of Pediatric Allergy, Immunology, and Rheumatology at Johns Hopkins University School of Medicine in Baltimore led the research. The study was published in *Pediatric Pulmonology* (2023 Dec 2. doi: 10.1002/ppul.26810). Study limitations included the use of electronic medical record data and potential lack of generalizability. The BBC is supported by the NIH.

All references available online at chestphysician.org.

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THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK Pleural Disease Section

Primary vs secondary: A review of pneumothorax management

Optimal management of primary spontaneous (PSP) and secondary spontaneous pneumothorax (SSP) remains an area of ongoing debate, with both CHEST and the British Thoracic Society (BTS) offering guidelines to address management decisions.

The consensus for treatment of PSP depends on the size of the pneumothorax; if smaller than 2-3 cm, the patient can be observed for 3-6 hours and if radiographically stable, can discharge home with close (within 48 hours) follow-up and repeat chest radiograph (CXR). If symptomatic or large, an intervention is recommended or home discharge with a Heimlich valve and close follow up (48 hours) with interval CXR. For the management of SSP, it is recommended that the patient remain hospitalized, with a lower threshold



Dr. Iyer

to intervene with chest tube placement.

Both the 2001 CHEST guidelines and 2010 BTS guidelines recommend the use of a small bore pigtail catheter (<14 Fr) for management of PSP. Expert consensus and retrospective studies recommend the use of a large bore chest tube (>28 French) in patients with secondary spontaneous pneumothorax and concomitant hemothorax, empyema, large air leaks, or mechanical ventilation.

For patients requiring pleurodesis, talc slurry is frequently used due to it being widely available and inexpensive. However, talc is associated with impurities and has been associated with severe pain, fever, dyspnea, and pneumonitis. Other agents such as doxycycline have been studied but overall data is lacking. One study comparing doxycycline solution with talc slurry showed less recurrence of pneumothorax with talc as compared with doxycycline with no difference in side effects.

All references available online at chestphysician.org.

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DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK Pulmonary Physiology and Rehabilitation Section

Machine learning meets cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is a clinically useful modality to discriminate between cardiac, pulmonary, and musculoskeletal limitations to physical exertion. However, it is relatively underutilized due to the lack of local expertise necessary for accurate interpretation. Several studies



Dr. Salmon



Dr. Shumar

have explored automation of CPET interpretation, the most notable of which utilized machine learning.

Recently, Schwendinger et al. investigated the ability of machine learning algorithms to not only categorize (pulmonary-vascular, mechanical-ventilatory, cardiocirculatory, and muscular), but also assign severity scores (0-6) to exercise limitations found in a group of 200 CPETs performed on adult patients referred to a lung clinic in Germany. Decision trees were constructed for each of the limitation categories by identifying variables with the lowest Root Mean Square Error (RMSE), which were comparable to agreement within expert interpretations. Combining decision trees allowed for a more comprehensive analysis with identification of multiple abnormalities in the same test. A major limitation to the study is limited applicability to general patient populations without



Dr. Russo



Dr. Zeba

suspected lung disease. This bias is reflected in the decision tree for cardiovascular limitation that relied on VO_2 peak and FEV_1 alone. The authors were unable to construct a decision tree for muscular limitations due to a lack of identified cases.

Overall, these results suggest that refinement of machine learning algorithms built with larger heterogeneous data sets and expert interpretation can make CPETs accessible to the nonexpert clinician as long as test quality can be replicated across centers.

All references available online at chestphysician.org.

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PULMONARY VASCULAR AND CARDIOVASCULAR NETWORK Pulmonary Vascular Disease Section

Right heart catheterization practice patterns in pulmonary hypertension in the US

In the right clinical scenario, three key hemodynamic components obtained by right heart catheterization



Dr. Bajwa



Dr. Pettigrew

(RHC) define precapillary pulmonary hypertension (PH) warranting vasodilator treatment: mean pulmonary arterial pressure >20 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood units. While these cutoffs are straightforward, a gap in practical application is evidenced by considerable variability in how PH providers perform and interpret RHC hemodynamic information.

A recent survey of 145 PH providers conducted by CHEST's Pulmonary Vascular Disease Section shed light on the current RHC practices in the US. Regarding the respondents' characteristics, 85% were in the 30-60 age range, 68% were males, and 71% were pulmonologists. About half of the providers perform the RHC themselves. Most review the hemodynamic tracings, but up to 21% rely on the final report alone. Regarding PCWP, most (86%) obtain it during end-expiration, but only 42% routinely measure a PCWP saturation for confirmation. When faced with PVR discrepancies between thermodilution and indirect Fick (IFick), up to 30% chose either IFick or didn't know which one to trust. Nearly 20% repeat the RHC at least annually, and 80% whenever the patient declines.

This study provides the largest reported data on real-world RHC practices by PH physicians in the US. We found significant variability in hemodynamic interpretation. Standardization of RHC performance and hemodynamic evaluation is crucial to ensure appropriate PH management.

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Jumpstart your AI learning: The very best tools

BY JULIE STEWART

Like it or not, artificial intelligence (AI) is coming to medicine. For many physicians, it's already here. More than a third of physicians use AI in their practice, and 94% of health care companies, according to Morgan Stanley, use some kind of machine learning.

"It's incumbent on physicians, as well as physicians in training, to become familiar with at least the basics [of AI]," said internist Matthew DeCamp, MD, PhD, an associate professor in the Center for Bioethics and Humanities at the University of Colorado Anschutz Medical Campus, Aurora, Colorado. Understanding AI can help you leverage it safely and effectively, and "make better-informed decisions about whether or not to use it in [your] practice," Dr. DeCamp said.

"Frankly, the people who are deciding whether to implement algorithms in our day-to-day lives are oftentimes not physicians," noted Ravi B. Parikh, MD, an assistant professor at the University of Pennsylvania and director of augmented and artificial intelligence at the Penn

Center for Cancer Care Innovation, Philadelphia. Yet, physicians are most qualified to assess an AI tool's usefulness in clinical practice.

In fact, the best starting place for your AI education is your own institution. Find out what AI tools your organization is implementing.

"Getting involved with your hospital data governance is the best way not only to learn practically what these AI tools do, but also to influence the development process in positive ways," Dr. Parikh said.

Then, consider these resources to build your AI knowledge.

Get a lay of the land: Free primers

Many clinical societies and groups have put out AI primers. The following were recommended or developed by experts, and all are free:

- The American Medical Association's (AMA's) framework for advancing health care AI lays out actionable guidance. Ask three key questions, the AMA recommends: Does it work? Does it work for my patients? Does it improve health outcomes?
- The Coalition for Health AI's

Blueprint for Trustworthy AI Implementation Guidance and Assurance for Healthcare provides a high-level summary of how to evaluate AI in health care, and steps for implementing it.

- The National Academy of Medicine's draft code of conduct for AI in health care proposes core principles and commitments, which "reflect simple guideposts to guide and gauge behavior in a complex system and provide a starting point for real-time decision-making."
- Health AI Partnership (a Duke Health and Microsoft collaboration) outlines eight key decision points to consider at any stage of AI implementation, whether you're planning how to use it or you want to improve it. The site also provides a breakdown of standards by regulatory agencies, organizations, and oversight bodies.

Make the most of conferences

Next time you're at a conference, check the agenda for AI sessions. "For someone who's interested in this, I would be looking for content in my next national meeting

because, undoubtedly, it's going to be there," Dr. DeCamp said. In a fast-moving field like AI, it's a great way to get fresh, up-to-date insights.

Listen to podcasts

The New England Journal of Medicine's free monthly podcast, AI Grand Rounds, is good for researchers and clinicians "looking to see both where the field is going [and to hear] a retrospective on big-name papers," Dr. Parikh said.

To learn about the challenges of applying AI to biology: Listen to Daphne Koller, PhD, founder of AI-driven drug discovery and development company, insitro. For insights on the potential of AI in medicine, tune into the episode with Eric Horvitz, MD, PhD, Microsoft's chief scientific officer.

Consider a class

Look for courses that focus on AI applications in clinical practice rather than a deep dive into theory. Be wary, Dr. DeCamp said, of corporate-funded training that centers on one product, which could present conflicts of interest. ■



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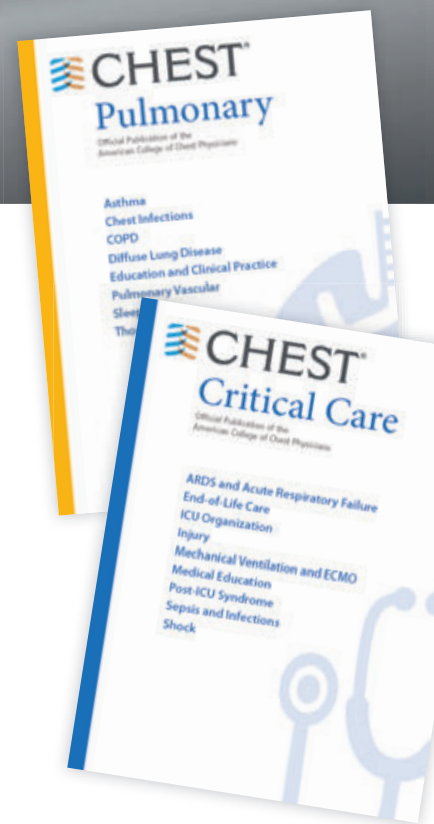


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Innovations that will soon change your practice

BY ERIC SPITZNAGEL

Medical innovations don't happen overnight — but in today's digital world, they happen pretty fast. Some are advancing faster than you think. We're not talking theory or hoped-for breakthroughs in the next decade. These technologies are already a reality for many doctors and expected to grow rapidly in the next 1-3 years.

Are you ready? Let's find out.

1. Artificial intelligence (AI) medical scribes

You may already be using this or, at the very least, have heard about it. Physician burnout is a growing problem, with many doctors spending 2 hours on paperwork for every hour with patients. But some doctors, such as Gregory Ator, MD, chief medical informatics officer at the University of Kansas Medical Center, Kansas City, Kansas, have found a better way.

"I have been using it for 9 months now, and it truly is a life changer," Dr. Ator said of Abridge, an AI helper that transcribes and summarizes his conversations with patients. "Now, I go into the room, place my phone just about anywhere, and I can just listen." He estimated the tech saves him between 3 and 10 minutes per patient. "At 20 patients a day, that saves me around 2 hours," he said.

Bonus: Patients "get a doctor's full attention instead of just looking at the top of his head while they play with the computer," Dr. Ator said. "I have yet to have a patient who didn't think that was a positive thing."

Several companies are already selling these AI devices, including Ambience Healthcare, Augmedix, Nuance, and Suki, and they offer more than just transcriptions, said John D. Halamka, MD, president of Mayo Clinic Platform, who oversees Mayo's adoption of AI. They also generate notes for treatment and billing and update data in the electronic health record. "It's preparation of documentation based on ambient listening of doctor-patient conversations," Dr. Halamka explained. "I'm very optimistic about the use of emerging AI technologies to enable every clinician to practice at the top of their license."

Patricia Garcia, MD, associate clinical information officer for ambulatory care at Stanford Health Care, has spent much of the last year co-running the medical center's pilot program for AI scribes, and she's so impressed with the technology that she "expects it'll become more widely available as an option for any clinician that wants to use it in the next 12-18 months."

2. Three-dimensional (3D) printing

Although 3D-printed organs may not happen anytime soon, the future is here for some 3D-printed prosthetics and implants — everything from dentures to spinal implants to prosthetic fingers and noses.

"In the next few years, I see rapid growth in the use of 3D printing technology across orthopedic surgery," said Rishin J. Kadakia, MD, an orthopedic surgeon in Atlanta. "It's becoming more

common not just at large academic institutions. More and more providers will turn to using 3D printing technology to help tackle challenging cases that previously did not have good solutions."

Dr. Kadakia has experienced this firsthand with his patients at the Emory Orthopaedics & Spine Center. One female patient developed talar avascular necrosis due to a bone break she'd sustained in a serious car crash. An ankle and subtalar joint fusion would repair the damage but limit

Health care systems are just beginning to explore the potential of drone deliveries, for everything from lab samples to medical and surgical supplies.

her mobility and change her gait. So instead, in August of 2021, Dr. Kadakia and fellow orthopedic surgeon Jason Bariteau, MD, created for her a 3D-printed cobalt chrome talus implant.

The technology is also playing a role in customized medical devices — patient-specific tools for greater precision — and 3D-printed anatomical models, built to the exact specifications of individual patients. Mayo Clinic already has 3D modeling units in three states, and other hospitals are following suit. The models not only help doctors prepare for complicated surgeries but also can dramatically cut down on costs. A 2021 study from Durham University reported that 3D models helped reduce surgery time by between 1.5 and 2.5 hours in lengthy procedures.

3. Drones

For patients who can't make it to a pharmacy to pick up their prescriptions, either because of distance or lack of transportation, drones — which can deliver medications onto a customer's backyard or front porch — offer a compelling solution.

Several companies and hospitals are already experimenting with drones, like WellSpan Health in Pennsylvania, Amazon Pharmacy, and the Cleveland Clinic, which announced a partnership with drone delivery company Zipline and plans to begin prescription deliveries across Northeast Ohio by 2025.

Health care systems are just beginning to explore the potential of drone deliveries, for everything from lab samples to medical and surgical supplies — even defibrillators that could arrive at an ailing patient's front door before an emergency medical technician arrives.

According to a 2022 survey from American Nurse Journal, 71% of nurses said that medical courier delays and errors negatively affected their ability to provide patient care. But with drone delivery, "lab samples can be sent for processing immediately, on-demand, resulting in faster diagnosis, treatment, and ultimately better outcomes," said Hillary Brendzel, head of Zipline's US Healthcare Practice.

4. Portable ultrasound

Within the next 2 years, portable ultrasound — pocket-sized devices that connect

to a smartphone or tablet — will become the "21st-century stethoscope," said Abhilash Hareendranathan, PhD, assistant professor in the Department of Radiology and Diagnostic Imaging at the University of Alberta, in Edmonton, Alberta, Canada.

AI can make these devices easy to use, allowing clinicians with minimal imaging training to capture clear images and understand the results. Dr. Hareendranathan developed the Ultrasound Arm Injury Detection tool, a portable ultrasound that uses AI to detect fracture.

"We plan to introduce this technology in emergency departments, where it could be used by triage nurses to perform quick examinations to detect fractures of the wrist, elbow, or shoulder," he said.

More pocket-sized scanners like these could "reshape the way diagnostic care is provided in rural and remote communities," Dr. Hareendranathan said, and will "reduce wait times in crowded emergency departments." Bill Gates believes enough in portable ultrasound that last September, the Bill & Melinda Gates Foundation granted \$44 million to GE HealthCare to develop the technology for under-resourced communities.

5. Virtual reality (VR)

When RelieVRx became the first US Food and Drug Administration (FDA)-approved VR therapy for chronic back pain in 2021, the technology was used in just a handful of Veterans Affairs (VA) facilities. But today, thousands of VR headsets have been deployed to more than 160 VA medical centers and clinics across the country.

"The VR experiences encompass pain neuroscience education, mindfulness, pleasant and relaxing distraction, and key skills to calm the nervous system," said Beth Darnall, PhD, director of the Stanford Pain Relief Innovations Lab, who helped design the RelieVRx. She expects VR to go mainstream soon, not just because of increasing evidence that it works but also thanks to the Centers for Medicare & Medicaid Services, which recently issued a Healthcare Common Procedure Coding System code for VR. "This billing infrastructure will encourage adoption and uptake," she said.

Hospitals across the United States have already adopted the technology, for everything from childbirth pain to wound debridement, said Josh Sackman, the president and cofounder of AppliedVR, the company that developed RelieVRx. "Over the next few years, we may see hundreds more deploy unique applications [for VR] that can handle multiple clinical indications," he said. "Given the modality's ability to scale and reduce reliance on pharmacological interventions, it has the power to improve the cost and quality of care."

Other VR innovations are already being introduced, from the Smileyscope, a VR device for children that's been proven to lessen the pain of a blood draw or intravenous insertion (cleared by the FDA last November) to several platforms launched by Cedars-Sinai. "There may already be a thousand hospitals using VR in some capacity," said Brennan Spiegel, MD, director of Health Services Research at Cedars-Sinai. ■

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