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2022 - Pros and Cons in General Internal Medicine and Geriatrics

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1. The COVID-19 epidemic has now entered its third year with its effects still being felt across the world. In many countries, there have been an alarming trend of waning vaccine efficacy paired with the emergence of variants with stronger immune escape and transmission ability. The XBB.1.5 omicron subvariant is raising concerns of a potential surge in COVID-19 cases as it sweeps across US. XBB.1.5 is also considered as the most transmissible subvariant that has been detected yet. Cov- 2 BQ.1 in Europe and Cov- 2 XBB in Asia, were thought as two of the most dangerous subvariants. The results of current research showed that Cov- 2 BQ.1, BQ.1.1, XBB and XBB.1 have the strongest immune escape to neutralizing antibodies induced by almost all variants, including BA.5.

The effectiveness of the latest bivalent mRNA vaccine and all therapeutic antibodies so far were decreased or disappeared to these subvariants, which meaning that people who have been vaccinated or infected may be reinfected. This consistent challenging of our pre-established immune barriers has driven the need for new, innovative vaccine modalities that overcome the hurdles of existing vaccination programs (1).

A recent breakthrough in COVID vaccine research is the regulatory approval of inhaled vaccine described to effectively induce comprehensive immune protection in response to SARS-CoV-2 after just one breath, swiftly followed by another inhaled aerosol vaccine indicated for restricted use in emergency situations. The advent of this new administration modality directs our attention to the comparison between inhaled vaccines and conventional intramuscular vaccines.

For the latter vaccines, the standard method in predicting efficacy is through the evaluation of neutralizing-antibody levels, while cellular immunity is evaluated by antigen-specific T cell response and cytokine secretion. Conversely, the proposed efficacy of inhaled vaccines stems from the stimulation of mucosal immune response alongside humoral and cellular responses. Overall, it might be easy to jump to the conclusion that inhaled vaccines will be the future route of administration for vaccines. However, as stated by Jansen et al. (2) more research regarding lung delivered mRNA vaccines is worthwhile. Future studies should further characterize immunological responses and safety aspects, and work toward inhalable formulations that are well tolerated also by patients suffering from lung diseases. Waiting for further researches to improve the protection against respiratory infections, during a period in which both the Delta and Omicron variants were circulating, SARS-CoV-2 booster vaccination was associated with significant reductions in SARS-CoV-2 infections, hospitalizations, and the combined end point of hospitalization or death among residents of two US nursing home systems (3).

2. Does severe COVID-19 disease accelerate brain aging?

Severe COVID-19 triggers aging-like changes in the brain's frontal cortex region, resulting in cognitive deficits. Although COVID-19 is primarily a respiratory disease, neurological symptoms and cognitive decline have been also reported in a subpopulation of infected Sars-CoV-2 individuals, despite the absence of detectable virus in brain tissue. In a recent article published

in Nature Aging, researchers found that severe coronavirus disease 2019 (COVID-19) triggers aging-like changes in the brain's frontal cortex region, resulting in cognitive deficits.

A neurological follow-up of individuals who recovered from COVID-19 is recommended and suggest potential clinical value in modifying risk factors to reduce the risk or delay the development of aging-related neurological pathologies and cognitive decline (4).

3. Our understanding of the microbiome and its implications for human health and disease continues to develop

At present, faecal microbiota transplantation (FMT) is not approved by the US Food and Drug Administration for any indication in the USA, but can be reserved for patients with multiple recurrent C. difficile episodes. Moreover, there is also increasing evidence for the efficacy of FMT in inducing remission for mild–moderate ulcerative colitis and many other conditions, such as: Crohn's disease, functional gut disorders, metabolic syndrome, modulating responses to chemotherapy, and eradication of multidrug resistant organisms, and the gut–brain axis.

FMT involves the selection of a healthy donor and the preparation of a minimally manipulated suspension of feces, comprising a complete contingent of microbes, including bacteria, viruses, and fungi. The transplantation of an entire gastrointestinal microbiome carries the risk of transmission of pathogenic organisms, both known and unknown. Donor screening of known organisms is routinely undertaken, but unknown infections remain an unquantifiable risk. Further, many concerns related to pathophysiological, methodological, and mechanistic factors require an explanation.

An update on the current knowledge in this fast-growing field has been reported by Waller et al. (6).

4. Many **functional limitations** exist in individuals with **Parkinson disease** prior the diagnosis , compared with the general population. Collecting responses to survey questions addressing dexterity, eating, mobility, mood, pain, sleep, speech, strength, and vision, suggests that individuals with prodromal or unrecognized Parkinson disease may have greater impairment in activities involving mobility and strength up to 3 years prior to diagnosis. Early identification of prodromal symptoms may facilitate timely global intervention to improve function (7).

5. Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Many patients with COPD go undetected for multiple reasons, including under recognition of mild symptoms (e.g., dyspnea) or nonspecific symptoms (e.g., fatigue). Screening or active case finding (e.g., spirometry based on systematically assessing for symptoms, risk factors, or both) for COPD can detect persons otherwise not diagnosed as part of routine care; however, it is yet unclear if increased detection of persons with unrecognized symptoms improves patient health outcomes and sometimes , particularly in older person, can provide a bad diagnosis and care. Bronchodilators with or without inhaled corticosteroids can reduce COPD exacerbations and tiotropium can improve health-related quality of life in adults with moderate COPD. Overall, there was no consistent benefit observed for any type of nonpharmacologic intervention across a range of patient outcomes. Two large observational studies in a screen-relevant population demonstrated an association of the initiation of a long-acting muscarinic antagonist or long-acting beta agonist with the risk of a serious cardiovascular event in treatment-naïve patients and an association of inhaled corticosteroids use with the risk of developing diabetes. The findings of this targeted evidence update of pharmacologic treatment are still largely limited to persons with moderate airflow obstruction, and there are no consistent benefit observed for a range of nonpharmacologic interventions in mild to moderate COPD or in minimally symptomatic persons with COPD (8).

6. Still trying to find the right oxygenation target in critically ill patients

Two trials showed no benefit to targeted titration of oxygen in the intensive care unit. Invasive mechanical ventilation in critically ill adults involves adjusting the fraction of inspired oxygen to maintain arterial oxygen saturation. The oxygen-saturation target that will optimize clinical outcomes in this patient population

remains unknown. In a pragmatic, cluster-randomized, cluster-crossover trial conducted in the emergency department and medical intensive care unit at an academic center, adults who were receiving mechanical ventilation were assigned to a lower target for oxygen saturation as measured by pulse oximetry (SpO_2) (90%; goal range, 88 to 92%), an intermediate target (94%; goal range, 92 to 96%), or a higher target (98%; goal range, 96 to 100%). The primary outcome was the number of days alive and free of mechanical ventilation (ventilator-free days) through day 28. The secondary outcome was death by day 28.The median number of ventilator-free days was 20 in the lower-target group, 21 in the intermediate-target group, and 21 in the higher-target group (P = 0.81). In-hospital death by day 28 occurred in 281 of the 808 patients (34.8%) in the lower-target group, 292 of the 859 patients (34.0%) in the intermediate-target group, and 290 of the 874 patients (33.2%) in the higher-target group. The incidences of cardiac arrest, arrhythmia, myocardial infarction, stroke, and pneumothorax were similar in the three groups (9).

In conclusion, among critically ill adults receiving invasive mechanical ventilation, the number of ventilator-free days did not differ among groups in which a lower, intermediate, or higher SpO_2 target was used.

7. Screening for prostate cancer is burdened by a high rate of overdiagnosis. The most appropriate algorithm for population-based screening is unknown. In a trial a to of 66 of the 11,986 participants in the experimental group (0.6%) received a diagnosis of clinically insignificant prostate cancer, as compared with 72 of 5994 participants (1.2%) in the reference group, a difference of −0.7 percentage points. Clinically significant cancer that was detected only by systematic biopsy was diagnosed in 10 participants in the reference group; all cases were of intermediate risk and involved mainly low-volume disease that was managed with active surveillance. The avoidance of systematic biopsy in favor of MRI-directed targeted biopsy for screening and early detection in persons with elevated PSA levels reduced the risk of overdiagnosis by half at the cost of delaying detection of intermediate-risk tumors in a small proportion of patients (10).

8. Frailty is a multidimensional state of increased vulnerability and frail patients are at increased risk for poor surgical outcomes. Prior research demonstrates that rehabilitation strategies deployed after surgery improve outcomes by building strength. The feasibility and impact of a novel, multi-faceted prehabilitation intervention (PI) for frail patients before surgery was evaluated in patients who undergone major abdominal, urological, thoracic, or cardiac surgery.

PI started in a supervised setting to establish safety and then transitioned to home-based exercise with weekly telephone coaching by exercise physiologists, and included: strength and coordination training, respiratory muscle training, aerobic conditioning, nutritional coaching and supplementation. PI length was tailored to the 4–6 week time lag typically preceding each participant's normally scheduled surgery. Functional performance and patient surveys were assessed at baseline, every other week during PI , and then 30 and 90 days after surgery. 43 patients completed baseline assessments; 36 (84%) completed a median 5 weeks (range 3–10) of PI before surgery; 32(74%) were retained through 90-day follow-up. Between baseline and day of surgery, timed-up-and-go decreased 2.3 seconds, gait speed increased 0.1 meters/second, six-minute walk test increased 41.7 meters, and the time to complete 5 chair rises decreased 1.6 seconds (P: ≤0.007). Maximum and mean inspiratory and expiratory pressures increased 4.5, 7.3, 14.1 and 13.5 centimeters of water, respectively (P: ≤0.041). Thus PI is feasible before major surgery and achieves clinically meaningful improvements in functional performance that may impact postoperative outcomes and recovery (11).

9. Low 25-hydroxyvitamin D levels have been associated with frailty and pre-frailty in several observational studies of community-dwelling adults. However, the benefits of supplemental vitamin D3, marine omega-3 fatty acids, and a simple home exercise program (SHEP) on frailty prevention in generally healthy community-dwelling older adults are unclear. In a three-year, double-blind, randomized controlled trial among 1,137 older adults, the combined interventions of daily supplemental 2000 IU vitamin D3 plus daily 1g marine omega-3 plus SHEP had significant benefits with regard to the risk of becoming pre-frail over 3

years. Further investigation is warranted to determine whether the combined benefits of the interventions are superior compared to a healthy and active lifestyle including a comparative amount of dietary omega- 3s and regularly physical exercise in this target group (12). Moreover, the U.S. Preventive Services Task Force found inadequate evidence to make recommendations about most vitamins and minerals for primary disease prevention (13).

10. The use of **hormone therapy** is recommended by clinical practice guidelines to manage menopause-associated symptoms. In the past, hormone therapy also has been prescribed for the prevention of common chronic diseases such as cardiovascular disease, osteoporosis (and subsequent fractures), cognitive impairment, and some types of cancers in persons with and without menopausal symptoms. It is uncertain whether hormone therapy should be used for the primary prevention of chronic conditions such as heart disease, osteoporosis, or some types of cancers. To update evidence twenty trials and 3 cohort studies were considered. Participants using estrogen only compared with placebo had significantly lower risks for diabetes over 7.1 years and fractures over 7.2 per 10 000 persons. Risks per 10 000 persons were statistically significantly increased for gallbladder. Use of hormone therapy in postmenopausal women for the primary prevention of chronic conditions was associated with some benefits but also with an increased risk of harms. More research is needed to addresses whether age or the timing of initiation of hormone therapy with respect to menopause affects health outcomes, benefits and harms of menopausal hormone therapy in different population groups, and the comparative benefits and harms of different formulations and treatment durations of menopausal hormone therapy (14).

11.Doxycycline is often **a last-choice agent for managing community-acquired pneumonia** (CAP),and guidelines do list doxycycline as a treatment option for outpatient with CAP, but the recommendation is rated as conditional with low quality of evidence A meta-analysis of six randomized clinical trials compared doxycycline with other agents in 834 adult outpatients and inpatients, none of whom required intensive care. Comparators were 3 macrolides (roxithromycin, spiramycin, and erythromycin) and 3 fluoroquinolones (ofloxacin, fleroxacin, and levofloxacin). Outcomes including length of stay, treatment expense, and adverse events were similar. Doxycycline is consistently active against all common typical and atypical bacterial causes of pneumonia, is inexpensive, offers twice-daily dosing, has a favorable side-effect profile, and achieves unusually high penetration into lung tissue and especially into alveolar macrophages. Further, the drug's use appears to entail an unusually low risk for *Clostridioides difficile* infection, and it might have intrinsic anti-inflammatory properties as well. In the end, a familiarity with local resistance patterns will be the clinician›s best tool when considering its use (15,16).

12.Is regular use of phosphodiesterase type 5 inhibitors (PDE5Is) associated with an increased risk for serous retinal detachment (SRD), retinal vascular occlusion (RVO), and ischemic optic neuropathy (ION) in older men?

A number of case reports and small epidemiologic studies have evaluated the risk of ocular adverse events associated with the use of PDE5Is. However, results have been conflicting, and epidemiologic data on the risk of serous retinal detachment (SRD) and retinal vascular occlusion (RVO) were not conclusive. Recently a large cohort study on 213 033 men receiving PDE5Is, including sildenafil, tadalafil, vardenafil, and avanafil, found an increased risk of SRD, RVO, and ION associated with the use of PDE5Is. Etminan et al.(17) have suggested that individuals who regularly use PDE5Is should be cognizant of ocular adverse events associated with these drugs and alert their physicians if they experience any visual deficits.

13.What is the time to benefit of intensive blood pressure treatment in adults 60 years and older?

Recent guidelines recommend a systolic blood pressure (BP) goal of less than 150 mm Hg or even 130 mm Hg for adults aged 60 years or older. However, harms from intensive BP treatments occur immediately (e.g., syncope, fall), and benefits for cardiovascular event reduction emerge over time. Therefore, harms with low chance of benefit need to be clearer, particular-

ly for those with limited life expectancy. In the Chen et al. (18) analysis, findings suggest that for patients 60 years and older with hypertension, intensive BP treatment may be appropriate for some adults with a life expectancy of greater than 3 years but may not be suitable for those with less than 1 year (18). In conclusion, the degree to which an individual patient will benefit from intensive BP control will likely depend on their risk profile and potential harm.

14. Is chlorthalidone superior to hydrochlorothiazide for preventing major adverse cardiovascular events in patients with hypertension?

In this large pragmatic trial of thiazide diuretics at doses commonly used in clinical practice, patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non-cancer-related deaths than patients who received hydrochlorothiazide. No differences between-groups were observed regarding the occurrence of any of the components of the primary outcome. The incidence of hypokalemia was higher in the chlorthalidone group than in the hydrochlorothiazide group (6.0% vs. 4.4%, P: <0.001)(19).

15. Video Capsule Endoscopy (VCE) is an effective, noninvasive modality for small bowel (SB) investigation and its use in older adults is rising. Nevertheless, data in octa-nonagenarians regarding diagnostic yield and motility are lacking. A study evaluated and compared safety and efficacy of VCE between age subgroups of older adult patients.In octa-nonagenarians, VCE was safe as in younger older-adults with a higher diagnostic yield of significant and treatable conditions. To my knowledge, this study is the first to characterize VCE performance in subgroups of older adult patients. In conclusion VCE is safe and effective in patients who are 80 or older (20).

16. Deprescribing: why, when and where?

Deprescribing is the medically supervised tapering or cessation of medications that are no longer needed or beneficial, including medications that are potentially inappropriate (PIMs), time delimited, ineffective, or that do not align with goals of care.

Scalable deprescribing interventions may reduce polypharmacy , adverse drug events (ADEs), and the use of PIMs. Does clinical decision improve deprescribing of PIMs and postdischarge ADEs in older adults?

A cluster randomized multicenter trial of 5 698 hospitalized participants found that providing electronically generated deprescribing reports did not have a significant impact on ADEs within 30 days despite increased deprescribing at discharge. The findings indicate that clinical decision support during hospitalization improves deprescribing but has little impact on medication harms in the short term.

However, this intervention effectively stopped PIMs, with no evidence of increased harm. Short-term ADEs may not be the ideal outcome to measure to capture the benefits of deprescribing during an acute care hospitalization. In common practice physicians may be reluctant to alter long-term outpatient therapies managed by other prescribers, particularly if they do not follow patients. Not all settings of care include routine pharmacist or geriatrician subspecialties to support interprofessional care, and some prescribers fear that stopping or reducing a drug can lead to adverse effects., despite deprescribing opportunities, therapeutic inertia is common; true even for low-risk drugs with no withdrawal concerns and more so for drugs with higher risks of harm. Unfortunately even when adverse events occur, opportunities to deprescribe are not always recognized and acted on. That's a great problem in older care (21).

17. The use of artificial intelligence (AI) in medicine and healthcare has been praised for the great promise it offers, but has also been at the centre of heated controversy. AI can benefit future healthcare, increasing the efficiency of clinicians, improving medical diagnosis and treatment, and optimising the allocation of human and technical resources.

The EU has made significant investments in AI in recent years, but inequalities persist between different European countries. The AI divide can be explained by structural differences in research programmes and technological capacities, as well as by varying levels of investment from the public and private sectors. Future

strategy should include concrete actions to boost the technological research and industrial capacities of all EU countries in the field of AI for healthcare, developing specific programmes, implementing coordination of activities, thereby supporting common guidelines and approaches. Infrastructure projects should be established specifically for those countries that have limited research and data availability, to enhance training capacities and human capital, with measures and policy options to minimise the risks and maximise the benefits of medical AI, including multi-stakeholder engagement through increased transparency and traceability, in-depth clinical validation of tools, and clinical competence (22).

18. Is music a medicine?

Are music-making and listening interventions associated with positive changes in health-related quality of life (HRQOL)? A systematic review and meta-analysis of 26 studies comprising 779 individuals found that music interventions were associated with statistically and clinically significant changes in mental HRQOL, both preintervention to postintervention as well as when music interventions were added to treatment. These results suggest that associations between music interventions and clinically significant changes in HRQOL are demonstrable in comprehensive reviews of previous studies. Increasing evidence supports the ability of music to broadly promote well-being and HRQOL. Nevertheless, the magnitude of music's positive association with HRQOL is still unclear, particularly relative to established interventions, limiting inclusion of music interventions in health policy and care (23).

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