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Top 10 Infectious Diseases Articles in 2023

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In 2023, at least 10 practice-changing studies on the prevention and treatment of a broad range of infectious diseases were published. Advances in prevention include studies of new vaccines to reduce the incidence of respiratory syncytial virus (RSV) infections in infants and older adults. Respiratory syncytial virus infections cause significant morbidity in infants and elders. In 2 industry-sponsored studies, the efficacy of a bivalent perfusion-stabilized F glycoprotein RSV vaccine was evaluated in pregnant women (to prevent disease in their infants) and in older adults, which led to the FDA (Food and Drug Administration) approval and Advisory Committee on Immunization Practices recommendations for these vaccines (1).

In another trial, post-exposure prophylaxis (PEP) with doxycycline (DOXY) prevented bacterial sexually transmitted infections (STIs). With the rising incidence of bacterial STIs in many countries, particularly among men who have sex with men (MSM) and transgender women, better interventions are needed. Post-exposure prophylaxis with DOXY after condomless sex was shown to be beneficial against syphilis and chlamydia but not gonorrhea in a study conducted in France. Researchers have evaluated the same strategy in MSM or transgender women who were on pre-exposure prophylaxis (PrEP) or were living with HIV (PLWH) in the US. A total of 501 participants (327 [PrEP group] and 174 [PLWH group]) were randomized to a single 200-mg dose of DOXY PEP or standard of care (SOC) without DOXY. The primary endpoint was a diagnosis of a new bacterial STI per follow-up quarter (2). In this open-label randomized trial, post-exposure DOXY significantly reduced bacterial STI incidence in at-risk MSM and transgender women who were on PrEP or were living with HIV.

Another study led the FDA to approve letermovir for the prevention of cytomegalovirus disease in high-risk kidney transplant recipients. Cytomegalovirus (CMV) seronegative recipients of kidney transplants from seropositive donors are at high risk for donor-to-recipient transmission of CMV and subsequent CMV disease. Universal prophylaxis with valganciclovir is highly effective in preventing CMV disease during the early post-transplant period, but leukopenia is common, resulting in discontinuation of prophylaxis or changes to the immunosuppressive regimen. Letermovir is a CMV-specific antiviral approved for prophylaxis after a stem cell transplant. Now, researchers report the results of a randomized non-inferiority trial comparing letermovir to valganciclovir in CMV seronegative recipients of kidneys from seropositive donors. In this randomized trial, letermovir was as effective as — but better tolerated than — valganciclovir (3).

This year also saw the publication of one of the most important HIV clinical trials of the last decade — REPRIEVE — which showed that even those people with HIV (PWH) who are at low to moderate risk for cardiovascular disease (CVD) benefit from starting a statin. People with HIV are at higher risk for CVD than those without HIV; moreover, the atherosclerotic cardiovascular disease (ASCVD) risk score used to decide when to start a statin may underestimate the likelihood of CVD events in PWH. To assess whether statins should be used for primary prevention in PWH with risk scores below those recommended for the general population, investigators conducted the REPRIEVE trial in 7700 PWH aged 40–75 who were receiving antiretroviral therapy and had low-to-moderate CVD risk. All enrolled patients had 10-year ASCVD risk scores $< 15\%$ (mean, 4.5%), and nearly all had LDL < 160 mg/dL (median 108 mg/dL). A randomized trial demonstrates that even those PWH at low-to-moderate risk for CVD benefit from starting

pitavastatin as a lipid profile-lowering drug (4).

Another study led to FDA approval of new antimicrobial therapeutics: Sulbactam-durlobactam for treating carbapenem-resistant *Acinetobacter baumannii* infections caused by carbapenem-resistant *A. baumannii* (CRAB) have limited therapeutic options. Sulbactam-durlobactam (sul-dur) is a β-lactam-β-lactamase inhibitor (BL/BLI) combination recently approved by the FDA for patients with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) caused by *A. baumannii-A. calcoaceticus* (ABC). Sulbactam, a BLI developed >40 years ago, was often combined with ampicillin; however, some *Acinetobacter* strains produce β-lactamases that can inactivate sulbactam. Durlobactam is a novel non-β-lactam BLI that is a potent inhibitor of β-lactamases found in CRAB; as such, durlobactam protects sulbactam from hydrolysis by these enzymes. In an international phase 3 trial across 59 sites, investigators randomized 177 hospitalized adults with documented HABP/VABP due to ABC to receive sul-dur or colistin. Both groups also received imipenem/cilastatin. This newly approved combination offers a practice-changing upgrade for treating patients with serious carbapenem-resistant *A. baumannii* infections (5).

Another new advancement is rezafungin, a once-weekly echinocandin for treating invasive candidiasis. Echinocandin antifungals are the first choice for the therapy of invasive candidiasis, although current formulations require daily dosing. Rezafungin, a new echinocandin with a broad range of activity and a half-life of 133 hours, may present advantages over the available echinocandins. A consortium of international investigators performed a multicenter, prospective, double-blind, non-inferiority phase 3 study from October 2018 through August 2021 to assess weekly IV rezafungin compared with daily IV caspofungin followed by optional step-down oral fluconazole in adult patients with Candidemia or invasive candidiasis. Participants received treatment for a minimum of 14 days. The study was funded by the manufacturer of rezafungin. In a phase 3 trial, weekly rezafungin was non-inferior to daily caspofungin, followed by optional fluconazole with a 14-day global cure and 30-day all-cause mortality (6).

In addition, it is noted that oral microbiota therapy has been used to prevent recurrent *Clostridioidesdifficile* infection. Standard treatments for *C. difficile* infection (CDI), while highly effective for resolving the initial episode, are limited by frequent recurrence (probably due to persistent disruption of the intestinal microbiome). Fecal microbiota therapy (FMT) after CDI treatment is recommended for patients with multiple episodes. Fecal microbiota therapy may be difficult to access when stool banks or directed donors supply the fecal material. These processes occur in a confusing regulatory environment with little standardization and often at significant expense to the patient, as payers generally do not cover the cost of products obtained from stool banks (7).

Another spotlighted study examines the efficacy of an all-oral bedaquiline-containing regimen for the treatment of multidrug-resistant TB. The incidence of resistant TB continues to rise worldwide, in part because treatment protocols are prolonged, complex, and painful, all potentially leading to medication failures. Several small single-nation studies have found that bedaquiline-based regimens appear effective for these infections. Researchers sponsored by the United States Agency for International Development (USAID) and the manufacturer of bedaquiline have performed a randomized, phase 3, non-inferiority, unmasked study — STREAM stage 2 — on the treatment of multidrug-resistant TB in seven countries between March 2016 and January 2020. In a multinational open-label trial, an all-oral 9-month bedaquiline-containing regimen and a 6-month bedaquiline regimen with injectable kanamycin were superior to a 9-month control injectable regimen (8).

The rebound of SARS-CoV-2 happens even in those who do not receive treatment. Symptom rebound and reversion to positive test results after viral clearance may take place following nirmatrelvir-ritonavir treatment. Still, rebound in non-treated individuals has received little research attention. In the ACTIV-2/A5401 trial, researchers analyzed data from 563 recipients of placebo who had mild-to-moderate COVID-19. The goal was to evaluate the natural course of viral and symptomatic rebound. The subjects recorded their symptoms every day for 28 days, and anterior nasal swabs were collected daily for 14 days and on the 21st and 28th days. Transient viral or symptomatic rebound was seen in one-third of the participants who had untreated mild-to-moderate COVID-19 (9). In a new guideline for diagnosis and management of diabetes-related foot infections (DFI), the incidence of DFI is increasing in parallel with the rising global prevalence of diabetes and is associated with significant morbidity and mortality. Recommendations were recently updated by the International Working Group on the Diabetic Foot/Infectious Diseases Society of America (IWGDF/IDSA) to guide the management and diagnosis of DFI (10).

As in the past, the breathtaking advances during 2023 highlight the dynamism of the field of infectious diseases — while portending that we are likely to see continued and accelerating progress in the years to come.

Footnotes

Authors' Contribution: Masoud Mardani is the only author of the article and the study was solely carried out by the author.

Conflict of Interests: The author is the EIC of the journal.

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