

# What's Hot in Clinical Infectious Diseases? 2019 IDWeek Summary

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The year 2019 brought about a multitude of innovations in clinical infectious diseases. With the continued rise of antimicrobial resistance (AMR), advances in diagnostics and newly available antibiotics offer additional strategies for combating this threat, but the broken antibiotic market serves as an impediment to further developments. The IDSA and other stakeholders are working to create novel pull incentives to stabilize the pipeline. Ongoing needs include developing optimal stewardship practices, including by using narrow-spectrum antibiotics and shorter durations of therapy. In the area of solid organ transplantation, early data from transplanting Hepatitis C virus (HCV)-infected organs are encouraging and the American Society of Transplantation (AST) released new guidelines addressing several key issues. Lastly, 2019 saw a resurgence in Measles emphasizing the importance of vaccination.

Leading existential threats to human health in 2019 include climate change, overpopulation, and antimicrobial resistance (AMR). In selecting topics for “What’s Hot in Clinical Infectious Diseases” at IDWeek 2019, we focused on the pivotal issue of AMR and conducted a review of several other timely topics in clinical infectious diseases.

## COMBATTING ANTIMICROBIAL RESISTANCE

Each year in the United States, at least 2 million people are infected with antibiotic-resistant bacteria, and that number is increasing. In 2013, 23 000 people died from infections due to resistant pathogens [1], but that number has increased to an estimated 162 000 deaths in 2018 [2]. There are several potential avenues to combat this evolving threat. Rapid diagnostic tests can lead to early identification of pathogens, allowing for early change to targeted therapy with a reduction in exposure to unnecessary antibiotics. Studies have shown that rapid diagnostics improve clinical outcomes, but only if they are coupled with stewardship interventions that properly interpret results and apply them to treatment decisions [3].

## NEW DIAGNOSTIC TESTS

Fragments of genomic DNA from pathogens causing infection at various locations in the body can be extracted as circulating free DNA (cfDNA) in purified plasma [4]. A new metagenomics test, called the “Karius test” (named after the sponsor company), can identify and quantify the microbial cfDNA from 1250 clinically relevant bacteria, DNA viruses, fungi, and eukaryotic parasites [5]. A recent clinical validation study looking at 350 patients found that the Karius test had 93.7% agreement when compared with initial blood cultures for identifying an infectious cause in patients with suspected sepsis [5]. Additionally, in patients who had received antibiotics within the prior 2 weeks, the Karius test had a 28% higher diagnostic yield than all other microbiologic tests combined. Although this test can identify a greater number of etiological causes of sepsis than standard-of-care testing, limitations remain. The current turnaround time for this test is roughly 53 hours, which is too long for the diagnosis of serious infections, and the test only targets DNA, which overlooks many clinically relevant RNA viruses. Additionally, the specificity of this test is relatively low (63% for the diagnosis of sepsis). Because of this potential for false-positive results, the test could be useful for ruling out infection in certain scenarios, such as suspected sepsis or in immunocompromised patients with nonspecific symptoms.

Metagenomic next-generation sequencing (NGS) can identify nucleic acid from a plethora of bacterial, viral, fungal, and parasitic organisms with a single assay. For conditions like neuroinflammatory disease, where there is limited availability of cerebrospinal fluid (CSF) samples, the ability to identify a broad range of pathogens in a single test could prove to be valuable. A recent multicenter prospective study used metagenomic NGS in addition to conventional testing in evaluating 204

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patients for meningoencephalitis. Of the 58 infections identified, 13 (22%) were identified by NGS alone and 19 (33%) were identified by both NGS and conventional testing. Among the remaining 26 infections that were diagnosed by clinical testing only (NGS negative), 11 were diagnosed by serologic testing only, 7 were diagnosed from tissue samples other than CSF, and 8 were not detected in the CSF due to low titers. Although this test may improve diagnostic yield in certain scenarios, it has limitations. High host DNA in CSF samples, particularly with >200 cells per cubic milliliter, leads to reduced sequencing depth and decreased sensitivity of the test. This test also has the potential to identify organisms of unclear clinical significance. Clinical metagenomic NGS represents another new diagnostic tool that could be useful in guiding earlier targeted treatments, but the preferred application and patient population are yet to be determined.

These and other new tests show promise in that we may soon be able to reliably identify causative pathogens earlier in the course of disease. The current lack of specificity emphasizes the importance of diagnostic stewardship to guide appropriate use of laboratory testing and ensure optimal clinical management in order to limit the spread of resistance.

## NEW ANTIBIOTICS

As antimicrobial resistance increases, research and development for new antibiotics have stagnated. In 2010, the Infectious Diseases Society of America (IDSA) issued a call for 10 new efficacious and safe antibacterial agents by the year 2020 [6]. Thankfully, at the time of this writing, there have been 13 new systemically available antibiotics approved for marketing by the US Food and Drug Administration (FDA) since that declaration. Although success in the labeled indications is a welcome advance for our patients and allows a path to making these medicines available, there has been some disappointment with the fact that some of these drugs have not achieved indications in the areas of greatest need, such as in treating infections due to carbapenem-resistant gram-negative bacteria. Here we present data regarding several of the most recently approved drugs with a focus on their potential capability for treatment of multidrug-resistant pathogens.

Omadacycline is an aminomethylcycline antibiotic agent, derived from the tetracycline class, that overcomes the efflux and ribosomal protection mechanisms of tetracycline resistance. It has no cross-resistance with  $\beta$ -lactams, aminoglycosides, polymyxins, or fluoroquinolones and can be administered orally or intravenously. Omadacycline is active against methicillin-resistant *Staphylococcus aureus* (MRSA), typical bacterial respiratory pathogens, and atypical organisms, including *Legionella pneumophila*, *Mycoplasma pneumonia*, and *Chlamydia pneumoniae*. It was approved by the FDA in 2018 for treatment of community-acquired bacterial pneumonia (CABP)

and acute bacterial skin and skin structure infections (ABSSSIs) [7]. The OPTIC trial compared omadacycline and moxifloxacin for the treatment of CABP. Early clinical response rates at 72 to 120 hours were similar (81.8% omadacycline vs 82.7% moxifloxacin, respectively), and the criteria for noninferiority were met [8]. It is important to note, however, that there were more deaths in the omadacycline group (8 deaths) compared with the moxifloxacin group (4 deaths). Omadacycline is also active against *Enterobacteriaceae* and *Acinetobacter baumannii* and has shown some efficacy in the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter* species [9]. Two separate phase 2 studies assessing the efficacy of omadacycline in the treatment of urinary tract infections (cystitis in 1, pyelonephritis in the other) were recently completed [10]. In both studies, omadacycline had similar clinical success rates compared with either nitrofurantoin or levofloxacin, but microbiological responses were generally lower in the omadacycline group than in the comparators. Based on these results, the sponsor is reportedly considering a study of different dosing regimens in this indication.

Imipenem/relebactam (IMI/rel) is a combination of the carbapenem imipenem-cilastatin and relebactam, a novel non- $\beta$ -lactam, small-molecule  $\beta$ -lactamase inhibitor (BLI) that inhibits class A carbapenemases and class C cephalosporinases. IMI/rel is active against *Pseudomonas* spp., organisms producing extended-spectrum  $\beta$ -lactamase enzymes (ESBLs), and some carbapenem-resistant *Enterobacteriaceae* (CREs); this drug is not active against metallo- $\beta$ -lactamase-producing organisms. IMI/rel was initially FDA approved for complicated urinary tract infections (cUTIs) [11] and complicated intra-abdominal infections (cIAIs) [12]. The RESTORE-IMI 1 trial compared IMI/rel with colistin + imipenem for the treatment of imipenem-nonsusceptible bacterial infections [13]. In this study, 31 of 47 enrolled patients (66%) were included in the modified microbiologic intent-to-treat (mMITT) population. Favorable overall response was similar between the IMI/rel and colistin + imipenem groups (71.4% IMI/rel vs 70% colistin + imipenem). IMI/rel-treated patients had lower 28-day mortality (9.5% IMI/rel vs 30% colistin + imipenem) and lower treatment-related nephrotoxicity (10% IMI/rel vs 56% colistin + imipenem), though no inferential testing was performed in this study. Success was similar for patients with HABP/VABP (87.5% IMI/rel vs 66.6% colistin + imipenem), cIAI (0% IMI/rel vs 0% colistin + imipenem), and cUTI (72.7% IMI/rel vs 100% colistin + imipenem). A study of IMI/rel vs piperacillin/tazobactam for HABP/VABP has been completed [14]; we await peer review and publication.

Lefamulin is a pleuromutilin, a new antibiotic class that inhibits the bacterial 50S ribosomal subunit at the peptidyl transferase center. This molecule has activity against both typical and atypical CABP pathogens, including MRSA, and both oral and intravenous formulations are available. In 2018, lefamulin was

approved by the FDA for the treatment of CABP based on data from 2 trials. The LEAP 1 trial compared intravenous lefamulin and moxifloxacin ± linezolid for the treatment of moderate to severe CABP. Early clinical response rates were similar at 96 to 120 hours (87.3% lefamulin vs 90.2% moxifloxacin/linezolid) [15]. Both groups received a minimum of 3 days of intravenous therapy with an option to switch to oral treatment. The LEAP 2 trial compared 5 days of oral lefamulin with 7 days of oral moxifloxacin and found similar early clinical response rates at 96 hours (90.8% lefamulin vs 90.8% moxifloxacin-treated patients) [16]. Higher rates of adverse events were reported in the lefamulin group (32.6% lefamulin vs 25.2% moxifloxacin), particularly diarrhea (12.2% lefamulin vs 1.1% moxifloxacin) and nausea (5.2% lefamulin vs 1.9% moxifloxacin) [16].

Plazomicin is an aminoglycoside with bactericidal activity against ESBL-producing pathogens, fluoroquinolone-resistant and aminoglycoside-resistant gram-negative bacilli (GNB), and GNBs that produce ampC cephalosporinases, carbapenemases, and metallo-β-lactamase-producing organisms. Data from the EPIC trial showed that plazomicin was noninferior to meropenem in the treatment of cUTI, with similar rates of composite cure at day 5 (88% plazomicin vs 91.4% meropenem) and higher rates of microbiologic eradication at days 15 to 19 (81.7% plazomicin vs 70.1% meropenem) [17]. The CARE trial was designed to compare a plazomicin-based regimen with a colistin-based regimen in the treatment of serious CRE infections. After screening >2000 patients, only 39 were enrolled [18]. The trial was discontinued prematurely. No formal hypothesis testing was performed, but data did show numerically greater success and survival among plazomicin-treated patients (all-cause mortality at 28 days: 24% plazomicin vs 50% colistin-based therapy). Among patients with bloodstream infections, death from any cause at 28 days or clinically significant disease-related complications occurred in 2 of 14 patients (14%) who received plazomicin and in 8 of 15 (53%) who received colistin-based therapy. Serious adverse events occurred less frequently in the plazomicin group than in the colistin group (50% plazomicin vs 81% colistin-based therapy). Although these data did not prove adequate for FDA approval, they provide clinicians with relevant information, especially when faced with multidrug-resistant infections.

Cefiderocol is a siderophore cephalosporin with a similar chemical structure to that of cefepime and ceftazidime but with the addition of a catechol moiety that chelates free iron [19]. This allows the molecule to be actively transported across the outer membrane via the bacterial iron transport system. It has broad activity against aerobic gram-negative bacteria, including *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Cefiderocol is stable against all classes of beta-lactamases, including metallo-carbapenemases, and the siderophore moiety allows for efficient cell entry that can overcome porin channel mutations and efflux pump overproduction. In a study of 448 patients with cUTI,

73% of patients treated with cefiderocol had resolution of symptoms and eradication of the bacteria after 7 days compared with 55% of patients who received imipenem-cilastatin [20]. The CREDIBLE-CR study compared cefiderocol with the best available therapy for CRE infections including HABP/VABP, cUTI, and bloodstream infection. Although the numbers were small in each group, all-cause mortality was higher in the cefiderocol group with HABP/VABP and bloodstream infection (not UTI) [21]. These data led to the approval of cefiderocol in October 2019 for the treatment of cUTI [22], along with a label warning of cefiderocol's higher all-cause mortality when compared with other antibiotics observed in the CREDIBLE-CR study [23].

## CHALLENGES WITH ANTIBIOTIC DEVELOPMENT

With 13 new systemically available antibiotics becoming available from 2010 to 2019, the IDSA's 10 × '20 goal has been achieved and progress has been made. The less good news, however, is that these medications are entering a struggling market. The sales of these newly FDA-approved drugs are low, and 1 company, Achaogen, filed for bankruptcy protection in April 2019, shortly after the FDA approval of their drug. News of this bankruptcy sent a chill to the antibiotic marketplace and further decreased interest in supporting antibiotic research and development. Large numbers of antibiotic researchers have been let go in recent years. This has accelerated dramatically in the last few months. Reasons for this broken market are complex and include the relatively low price of antibiotics and the fact that they are held in reserve in the interest of good stewardship and preserving their efficacy. We and others have called for a rapid "fix" of the broken antibiotic market via pull incentives [24, 25].

Other challenges identified include the fact that most of these agents are modifications of existing classes of antibiotics rather than truly novel agents with distinct mechanisms of action. As seen in the examples above, it is difficult for new antibiotics to achieve indications for MDR organisms given the small number of cases identified despite screening large numbers of patients. As a result, the IDSA is working closely with other national organizations and the US federal government (FDA, Centers for Disease Control and Prevention [CDC], National Institute of Allergy and Infectious Diseases, etc.) on initiatives to streamline clinical trials for agents that treat serious or life-threatening infection with unmet medical needs [24, 26].

## SHORTER IS BETTER

While we await newer agents, we need to employ better strategies for preserving the efficacy of existing antimicrobials. Shorter courses of antibiotics provide less selection pressure and can decrease the emergence of antibiotic resistance. Thus, it is imperative to employ good stewardship practices by using narrow-spectrum antibiotics, shorter durations of therapy,

and oral rather than parental therapy when possible. Multiple RCTs have shown that 3- to 5-day courses of antibiotic therapy are at least as effective as 7- to 14-day courses for CABP and that 8 days is as effective as 15 days for VABP [27]. This trend has also been demonstrated in other infections. Yahav et al. showed that after achieving clinical stability and source control, 7 days of antibiotic therapy was not inferior to 14 days in patients with gram-negative bacteremia (mostly caused by *Enterobacteriaceae*) [28]. Ihm et al. showed that longer treatment courses were not associated with lower treatment failure rates for patients with skin and soft tissue infections [29]. Similarly, Germanos et al. showed that men with uncomplicated UTI did not benefit from antibacterial therapy longer than 7 days [30]. Despite the plethora of gathering evidence, short-course antibiotic therapy remains underutilized. In fact, national societal guidelines still recommend using traditional longer treatment durations, and the FDA still requires companies to compare antimicrobial agents using traditional durations. With antimicrobial resistance on the rise, it is imperative that we limit excessive antibiotic use, reduce selection pressure, and employ proper antibiotic stewardship.

### ORAL STEP-DOWN THERAPY

Several studies suggest that early switch to oral therapy may also be safe and effective in certain populations. The OVIVA trial randomized patients with bone and joint infections to receive either early switch from intravenous (IV) to oral antibiotic therapy or standard IV antibiotic therapy for 6 weeks. Treatment failure within 1 year was similar in both groups, occurring in 14.6% of those in the intravenous group and 13.2% in the oral step-down group [31]. The POET trial compared single-agent intravenous therapy with partial combination step-down oral therapy in the treatment of both native and prosthetic valve endocarditis of the left side of the heart [21]. The primary composite outcome included death, unplanned cardiac surgery, embolic events, and relapse of bloodstream infection and was similar in both groups (12.1% in the intravenous group vs 9.0% in the oral therapy group). In a recent study of patients with MRSA bloodstream infection who cleared blood cultures during hospitalization, step-down to oral outpatient antibiotic therapy was associated with similar clinical failure rates at 90 days when compared with outpatient intravenous antibiotic therapy (13.8% oral step down vs 14.9% parenteral therapy) [32]. It is likely premature at this time to recommend a widespread early switch to oral therapy, but these studies show promising data on the role of oral antibiotic therapy in the future.

### TRANSPLANTATION

#### Solid Organ Transplant Guidelines

With the growing number of adult solid organ transplant recipients, infections are increasingly recognized as a major

cause of morbidity and mortality with potentially devastating consequences. Continuous efforts are being made to improve our understanding of risk factors, treatment paradigms, and preventative strategies for this unique patient population. The American Society of Transplantation published updated guidelines for 2019, and several recent studies have provided new insights [33].

Transplant recipients are at increased risk of vaccine-preventable diseases. It is optimal for patients to receive the full complement of recommended vaccines before transplantation, as vaccine response can be diminished in the setting of immunosuppression. There is growing evidence that immunization following transplantation may be safe and efficacious. A recent multicenter prospective cohort study in adult solid organ transplant recipients showed that the administration of inactive influenza vaccine within 6 months after transplantation, and even as early as 1 month post-transplant, was safe and as immunogenic as vaccination thereafter [34]. Additionally, use of adjuvanted vaccine or high-dose influenza vaccine was associated with significantly greater seroconversion rates and antibody titers as compared with unadjuvanted or standard-dose vaccine, respectively [35]. Traditionally, only inactivated vaccines could be administered to patients after they received transplants, and live vaccines were generally contraindicated. However, with continuing outbreaks of measles being reported worldwide, earlier vaccination in pediatric select transplant recipients may be warranted. Recent studies have shown that administration of measles vaccine in pediatric solid organ transplant recipients is safe and efficacious [35]. It is important to note that the ability to mount an immune response will be impacted by the type and amount of immunosuppression after organ transplantation.

Although primary varicella zoster virus (VZV) infection is now uncommon with the institution of routine childhood vaccination, re-activation of VZV occurs in 8%–11% of transplant recipients within the first 4 years post-transplantation [36]. Oral antiviral therapy is appropriate for localized nonsevere dermatomal zoster not affecting the eyes or facial nerve in immunocompromised patients [37, 38]. Immunosuppression also increases the risk of multidermatomal or disseminated zoster infection, and these patients should still receive IV acyclovir. Both the IDSA and AST recommend herpes zoster (HZ) vaccination in VZV-seropositive pretransplant patients  $\geq 50$  years of age, at least 4 weeks before transplantation. The updated AST guidelines recommend the adjuvanted subunit HZ vaccine (Shingrix, GlaxoSmithKline, Brentford, United Kingdom) due to superior efficacy seen in the general population. For select low-risk kidney transplant recipients at risk for VZV reactivation who were not vaccinated pretransplant, a recent phase III trial demonstrated safety and immunogenicity with the adjuvanted subunit HZ vaccine post-transplantation [39]. Some

centers are recommending pretransplantation vaccination before heart, liver, and lung transplant with the adjuvanted subunit HZ vaccine for varicella-immune patients.

*Toxoplasma gondii* is a parasitic infection that can have a significant impact on transplant outcomes. Due to its predilection for heart muscle, all potential heart transplant donors and recipients are routinely screened for toxoplasma immunoglobulin G (IgG). However, a recent study has shown that, despite lower risk of transmission in non-heart transplant recipients, the morbidity and mortality of toxoplasmosis remain high [40]. It is therefore recommended to screen all potential solid organ donors and recipients for toxoplasma IgG. In high-risk heart transplant recipients (D+/R-), lifelong prophylaxis is now recommended due to frequent reports of toxoplasmosis after cessation of chemoprophylaxis. In fact, in all high-risk solid organ transplant recipients (D+/R-), chemoprophylaxis for toxoplasma should be considered. We note that these studies were conducted mostly in the EU, where *T. gondii* infection is more prevalent. The updated AST guidelines offer more relevant updates (<https://onlinelibrary.wiley.com/toc/13990012/2019/33/9>).

#### **Hepatitis C–Infected Organ Transplantation**

There are more than 113 000 patients awaiting transplantation in the United States, and >12 000 of those people died in 2018 before they were able to undergo transplantation [41]. There has also been an increasing proportion of potential donors infected with hepatitis C virus (HCV) related to the opioid epidemic. Tremendous advances in HCV therapy with pan-genotypic direct-acting antiviral agents (DAAs) that can achieve sustained virologic response and cure have raised the possibility of using HCV-positive organs for transplantation. In a recent open-label pilot trial, Woolley et al. [42] enrolled 44 patients awaiting heart and lung transplantation to receive HCV-mismatched organs. Patients preemptively received sofosbuvir-velpatasvir for 4 weeks, starting within hours after transplantation. Of the 44 patients enrolled, 42 had a detectable HCV viral load immediately post-transplantation, confirming uniform and predictable HCV infection in this setting. Data are available for the first 35 patients enrolled, and all 35 patients had an undetectable viral load and excellent graft function at 6-month follow-up. There were no treatment-related serious adverse events reported. There were more cases of acute cellular rejection in the HCV-infected lung transplant recipients than in the cohort of patients receiving lung transplants from donors who were not infected with HCV.

Although the early results from this study and other similar studies [43–47] are promising, a great deal remains unknown. As of yet, there are no data regarding long-term mortality or long-term graft survival. It is unclear if patients will be at increased risk of cardiovascular disease or fibrosing cholestatic hepatitis. The optimal treatment strategy regarding timing and

duration of direct-acting antiviral therapy for transplant recipients is unknown. Acute HCV infection, even when being actively treated, can cause immune activation, leading to organ rejection and opportunistic infection. Although there are still many questions, the accumulating reports of successful outcomes are encouraging and warrant further consideration. Incorporating HCV-positive donors into the donor pool would provide much-needed access to organs for many patients awaiting transplantation.

#### **Measles**

Measles is a highly contagious virus that was declared eliminated in the United States in 2000. It is characterized by acute febrile illness and maculopapular rash, but it can lead to severe complications including pneumonia, encephalitis, and even death. Unvaccinated and underimmunized subpopulations are particularly at risk for large measles outbreaks, which can require considerable resources to control. According to the CDC's Morbidity and Mortality Report, there had been 704 reported cases from January 1–April 26, 2019, which was the largest number of cases reported in a single year since 1994 [48]. Of those 704 cases, 503 (71%) occurred in unvaccinated persons. Thirteen outbreaks, accounting for 663 cases, were reported, and 6 of those outbreaks, accounting for 620 cases, were associated with underimmunized close-knit communities.

According to the CDC, during January 1–October 3, 2019, there were 1250 reported cases of confirmed measles. Transmission of measles occurs through person-to-person contact and airborne spread. As we enter the height of influenza season, we can expect a similar uptrend in cases of measles. Misinformation has contributed significantly to the decreasing vaccination rates, leaving these communities vulnerable. With the growing number of measles outbreaks both in the United States and worldwide, vaccination is critical to limiting transmission. Physicians should make every effort to ensure that their patients are up to date with measles-mumps-rubella (MMR) vaccinations.

#### **CONCLUSIONS**

The year 2019 saw a number of advances in clinical infectious diseases. Antimicrobial resistance continues to threaten modern health care. Advances in diagnostic testing and antimicrobial drugs provide hope for meeting this challenge, but the broken antibiotic market threatens the availability of precious newly approved antibiotic medicines. Pull incentives are needed in the short term to provide a path for keeping antibiotics available for our patients. It is more important than ever to employ good stewardship practices by using narrow-spectrum antibiotics, shorter durations of therapy, and oral rather than parenteral therapy when possible. In the realm of solid organ transplantation, new guidelines have been

introduced, and the practice of transplanting HCV-infected organs is advancing. Finally, and perhaps most disturbingly, measles has made a resurgence, emphasizing the importance of vaccination.

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