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*[By e-mail submission jvselby@pcori.org]*

Joseph V. Selby, MD, MPH
Executive Director
Patient-Centered Outcomes Research Institute (PCORI)
5185 MacArthur Boulevard, NW
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Washington, DC 20016

RE: Infectious Diseases Research Opportunities at the Patient-Centered Outcomes Research Institute

Dear Dr. Selby:

IDSA represents more than 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, chronic viral hepatitis, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and finally emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Zika virus disease, and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

For patients suffering from chronic illnesses, such as diabetes or cancer, complications from infection can add significant patient morbidity and lead to poor outcomes. Since its formation in 2010, the Patient-Centered Outcomes Research Institute (PCORI) has become a leader in supporting comparative effectiveness research. In 2014, IDSA highlighted the importance of PCORI supported research in addressing the challenged faced by patients who have or may contract an infectious disease. Multi-drug resistant microbes, healthcare-associated infections, and emerging infectious diseases all remain major challenges to patient care, and require strong, patient-engaged research to assess the effectiveness of new advances in clinical care.

IDSA has continued to promote awareness of PCORI funding to our members. Our recent efforts include a joint IDSA-PCORI webinar on opportunities in PCORI ID funding as well as creating an IDSA resource web-page for members interested in pursuing PCORI funding. We have continued our engagement with PCORI, and are happy to see the inclusion of community acquired pneumonia (CAP) as a research

in PCORI's cycle 2 funding announcement. We remain eager to work with PCORI leaders to increase the appreciation for how infectious diseases (ID) research aligns with PCORI's research priorities and review criteria.

Below we have highlighted five priority ID comparative effectiveness research topics that our society believes address several of the major challenges faced by patients suffering from infectious diseases.

**Comparing watchful waiting versus empiric antimicrobial therapy for patients with asymptomatic bacteriuria**

Asymptomatic bacteriuria is a common condition, especially among older patients, those with diabetes mellitus, long-term care facility residents, and those with long-term indwelling catheters. When correctly recognized as asymptomatic bacteriuria, high-quality evidence is available to guide clinicians to the appropriate response—which is to not administer antimicrobials. Unfortunately, non-specific and vague symptoms are often elicited from patients, leading to circumstances where some are interpreted as symptomatic urinary tract infection (UTI) and treated with antimicrobials. In addition, largely because of the absence of high quality comparative data, many providers err on the side of antimicrobial treatment instead of observing patients with non-specific symptoms and bacteriuria.

Outside of two specific circumstances (pregnancy and prior to urologic surgery), antimicrobials prescribed for asymptomatic bacteriuria have no proven benefit, and instead can result in adverse drug events. Antimicrobial treatment of asymptomatic bacteriuria often delays identification of underlying cause of symptoms, leading to negative patient outcomes. Non-indicated antibiotic therapy also fuels the continued emergence of antimicrobial-resistant bacteria. Most episodes of bacteriuria are caused by Gram-negative organisms, some of which are treatable only with poorly-tolerated toxic antimicrobials.

There is a need for high-quality data which can inform providers about the lack of effect of antibiotic therapy for the management of patients presenting with non-specific symptoms and evidence of bacteriuria, but without any of the classic symptoms of UTI. The optimal study design is a randomized trial comparing observation/supportive care vs. empiric antimicrobial therapy. If antimicrobial treatment for patients with nonspecific symptoms and bacteriuria confers no benefit, this would help to limit a substantial amount of antimicrobial use, adverse events, and selection for antimicrobial resistance. With limited new antimicrobial drugs in the development pipeline, efforts to eliminate unnecessary antimicrobial use are vital to preserve current agents for when they are clearly needed.

**Comparing strategies that address barriers to access for screening and treatment of chronic hepatitis C virus infection**

Chronic hepatitis C virus (HCV) is the leading cause of cirrhosis in the United States and is associated with substantial morbidity and mortality. IDSA applauds PCORI's strong focus on improving HCV patient treatment outcomes by funding three HCV research trials. PCORI recently engaged IDSA on future HCV studies, such as a randomized trial to determine if there are rapid

benefits from treatment of HCV for symptoms such as fatigue, depression, mental fogginess, ability to function, and quality of life in patients at low risk for progression to serious liver injury in the near future. IDSA is concerned that these trials will result in withholding curative treatment and clinically-important information from patients in the early stages of HCV infection, and strongly urges the PCORI to consider other research that can improve HCV patient treatment outcomes.

One alternative is comparing strategies that overcome barriers to HCV treatment. Improved therapeutic regimens have the promise to cure almost 95% of infected individuals, but their impact will be limited in the absence of screening to identify infection along with easily accessible treatment. Many barriers exist to screening and treatment access, ranging from medical decision-making, proper testing and counseling surrounding the infection and disease, and the administrative know-how to authorize approval of medications. Provider access may be limited by issues such as workforce capacity, insurance restrictions and geographic distance. Geographic distance is a major issue particularly for patients residing in suburban or rural areas or in prison settings. As a result of these barriers, substantial numbers of patients go both without diagnosis or treatment to cure chronic HCV infection.

Many established methods exist to address the problem of access, including, telemedicine, virtual consults, and increasing workforce capacity via methods such as Project ECHO. Telemedicine is a longstanding approach that has been used, particularly in prison settings. Virtual consults or "econsults" may become more prevalent, especially with the onset of compatible and comprehensive electronic health records (EHRs). Project ECHO pursues a model that equips local providers with the expertise to deliver comprehensive care of HCV.

Each of these methodologies may achieve excellent viral outcomes, but it is unknown whether these approaches affect differentially longer-term outcomes such as durable lifestyle changes or medical outcomes including reinfection and hepatocellular carcinoma prevention/surveillance. Engagement with HCV care has often offered other opportunities for health improvement, such as colon cancer screening, smoking cessation, and prevention of other infections. These approaches may differ between patients in terms of their satisfaction with their care, the degree of monitoring necessary and time off from work and other responsibilities while on therapy. Comparing these approaches may reveal differences in patient-related outcomes that focus on the greater impact of these therapies that go beyond viral cure.

**Effective use of Telemedicine-enabled ID-led Outpatient Parenteral Antimicrobial Therapy (OPAT) to affect positive patient outcomes**

In 2007 over 42,000 patients acquired infection as a result of inpatient medical care, accounting for 0.2% of all hospital stays. These hospital acquired infections result in prolonged hospital stays that increase the risk of additional complications, particularly for elderly patients, who represent half of all cases. One alternative to continued in-hospital treatment is outpatient parenteral antimicrobial therapy (OPAT), where intravenous (IV) antimicrobial therapy is administered at home or in alternate care settings, administered either by a healthcare practitioner or the patient. First introduced in the 1970s, OPAT has since been a standard of care for patients requiring long-term intravenous antibiotic therapy. OPAT has evolved over decades to demonstrate effectiveness in allowing for timely hospital discharge and hospital admission/readmission avoidance. However,

not every health care system has established an OPAT program, and across OPAT programs, there is significant variability in terms of resources and capabilities.

With the evolution towards patient-centered, value-based health care, the demand for OPAT is increasing. Telemedicine adapted to OPAT, along with the novel deployment of a multidisciplinary team under ID specialists leadership may lead to improved outcomes across a variety of healthcare settings. With this treatment approach, patients have access to telemedicine guided OPAT outside of the clinic, with the capability for continued communication between the patient and provider to address patient's concerns, ensure care continuity, adherence to treatment protocol, and avoidance of complications. While this new approach is likely to be of great value to patients, we lack data on whether telemedicine adapted OPAT results in improved patient outcomes compared to traditional OPAT guidelines. Research directly comparing these two approaches would help identify the OPAT approach of greatest value to patients and also provide guidance to healthcare providers who currently lack established OPAT programs.

**Comparative effectiveness of antimicrobial stewardship strategies for outpatient prescribing for Uncomplicated Acute Respiratory Tract Infections**

Each year in the United States, antibiotic resistant bacteria infect 2 million people, resulting in 23,000 deaths. The large volume of outpatient antibiotic use likely contributes to the rise of antibiotic resistance. In particular, uncomplicated acute respiratory tract infection (RTI) accounts for approximately 70% of primary diagnoses in adults who visit ambulatory care offices with a chief symptom of cough. Despite guidelines recommending no antibiotic treatment for uncomplicated acute RTIs, most outpatient antibiotic prescriptions in the United States are for acute RTIs. Estimates indicate that 50% of this prescribing is unnecessary, resulting in adverse events such as allergic reaction or *Clostridium difficile* infection as well as the rise of antimicrobial resistance.

The National Action Plan for Combatting Antibiotic Resistant Bacteria (CARB) calls for antimicrobial stewardship programs (ASP) in all healthcare facilities, including the ambulatory setting. Several systematic reviews have examined a variety of strategies to better improve antimicrobial stewardship for outpatient care. Several more decentralized strategies include interactive educational meetings for physicians, outreach visits and physician reminders, and patient-based interventions such as the use of delayed prescriptions for infections for which antibiotics are not immediately indicated. With the widespread adoption of EHRs, more centralized stewardship processes have been examined, including approaches where "antibiotic justification notes" must be entered in a patient's medical record when antibiotics are not clearly called for in the diagnosis, as well as reviews of antimicrobial prescribing relative to peers to identify and educate consistent over-prescribers.

While research examining these approaches show promise in reducing antibiotic prescribing, we lack systematic data comparing whether the most successful de-centralized and centralized stewardship strategies not only result in lower antibiotic prescribing, but also lower adverse outcomes rates and lead to greater patient satisfaction. Research comparing these strategies can help identify the most effective approaches to not only reduce inappropriate antibiotic usage for the benefits of society as a whole, but also improve individual patient outcomes.

**Comparing beta-lactam beta-lactamase inhibitor combinations vs. alternative therapy in the treatment of Multidrug Resistant (MDR) infections**

The introduction of novel beta-lactam beta-lactamase inhibitor therapies (ceftazidime/avibactam and ceftolozane/tazobactam ) promise to provide clinicians with an unprecedented opportunity to treat highly drug resistant Gram negative bacterial infections. These two novel agents, recently approved by the FDA to treat complicated intra-abdominal and urinary tract infections, have demonstrated enhanced microbiological efficacy against many pathogens resistant to our current antibiotic armamentarium (e.g., piperacillin/tazobactam resistant *Escherichia coli*, carbapenemase producing *K. pneumoniae*-KPCs, imipenem resistant *P. aeruginosa*). Clinicians are now are faced with extremely difficult choices as the speed with which drug resistance emerges outpaces our ability to conduct clinical trials comparing treatment efficacy. Current studies comparing carbapenems vs. beta-lactam beta-lactamase inhibitors in the treatment of infections caused by extended-spectrum beta-lactamase producing Gram negative bacteria have thus far yielded controversial results. The role of expanded spectrum cephalosporins has also received a lot of attention.

With the recent release of these two agents (ceftazidime/avibactam and ceftolozane/tazobactam) we have an unprecedented opportunity to design comparative effectiveness trials looking clinical outcomes in patient populations with infections caused by highly drug resistant bacteria before widespread inappropriate use has already occurred.

**Conclusion**

Our society hopes PCORI considers these research topics as it prioritizes its future funding. We look forward to continuing to work with PCORI on tackling the many challenges patients face, including those from infection. If you should have any questions, please contact Greg Frank, PhD, IDSA's program officer for science and research policy at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Johan S. Bakken, MD, PhD, FIDSA
IDSA President