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IDSA
Infectious Diseases Society of America

July 28, 2009

Dennis M. Dixon, PhD
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
6610 Rockledge Drive
Room 4218
Bethesda, MD 20892

Dear Dr. Dixon:

We are writing on behalf of the Infectious Diseases Society of America (IDSA) to continue our dialogue with the National Institute of Allergy and Infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID) on the urgency of the antimicrobial resistance problem and the need for high quality experimental data to support ongoing efforts to optimize the use of antimicrobial agents in the community and hospital settings. At this time, we respectfully submit a proposal for three clinical trials designed to study the comparative effectiveness of different methods to improve the practices of health care providers who prescribe antimicrobial agents.

In IDSA's previous communications with DMID/NIAID, we suggested three clinical studies aimed at answering important questions regarding optimal duration of antimicrobial therapy in treating skin and soft tissue infections, the need for antimicrobial therapy in treatment of otitis media and the need for combination therapy in the treatment of community-acquired pneumonia. Our goal in suggesting those studies was to prompt the conduct of specific trials comparing the effectiveness of different therapeutic strategies designed to minimize unnecessary antimicrobial use and the resulting selective pressure favoring the emergence and spread of antimicrobial resistance. We were gratified that the three previous proposals informed a recent NIAID Broad Agency Announcement (BAA) and that such trials are currently in development. IDSA considers the collaboration that informed the BAA to be an outstanding example of how the "point of care" expertise of IDSA's members can augment NIAID's expertise in developing clinical trials. We are optimistic that the results of these trials, and other comparative effectiveness trials to come, will provide a solid evidence base upon which to build programs to improve antimicrobial prescribing practices in this country and throughout the world.

Programs designed to optimize the use of antimicrobial agents fall under the general heading of "antimicrobial stewardship." One of the fundamental limitations of stewardship programs has been the lack of credible evidence to support many of the recommendations made. The proposals that informed the BAA were an attempt to address this deficiency by yielding data that could

credibly support shortening, narrowing or eliminating antimicrobial courses for common infectious diseases. The availability of these data will be a critical component of reducing antimicrobial selective pressure, but it will not be sufficient by itself to effectively change the antibiotic prescribing practices of health care providers, the majority of whom do not have specific expertise in the area of antibiotics or treatment of bacterial infections.

As a complement to the clinical data to be provided by the planned studies under the BAA, it is critical that we also develop an evidence base that supports positive changes in prescribing practices. The three new studies IDSA members are now proposing represent the product of extensive discussions involving members of the IDSA Research on Resistance Work Group (RRWG) along with invited experts in the area of antimicrobial stewardship. The studies have been carefully chosen to address the shortcomings of the current antimicrobial stewardship literature, an area of inquiry in which available data are most commonly derived from small local studies or efforts to reduce the cost of antibiotics to individual institutions. As with the previously suggested clinical studies, these suggestions represent trials that will yield critically important information, but are unlikely to be feasibly supported by individual health care institutions, industry or private foundations. The three trials are:

1. A multi-center, randomized controlled trial comparing the impact of a "downstream" antimicrobial stewardship program with standard hospital practice.
2. A multi-center, prospective observational study to establish a relationship between antimicrobial exposure (appropriate or inappropriate) and adverse events broadly defined.
3. A multi-center, prospective interventional study to determine whether educating health care providers regarding adverse events will impact overall antimicrobial prescribing practices.

A detailed document explaining the rationale and proposed methods for conducting these studies is enclosed with this letter.

IDSA values our close working relationship with NIAID. Given our shared expertise in the field of antimicrobial resistance, we look forward to working with you on these and other issues.

Should you have any questions, please feel free to contact Padma Natarajan, MPH, MS, IDSA's program officer for science and research, at pnatarajan@idsociety.org or (703) 299-1216.

Sincerely,

Edward N. Janoff, MD
Chair, IDSA Research Committee

Louis B. Rice, MD
Chair, IDSA Research on Resistance Work Group

cc: Anthony S. Fauci, MD, Director
H. Clifford Lane, MD, Director, Office of Clinical Research (OCR)/NIAID
Carole Heilman, PhD, Director, NIAID/DMID
Barbara Mulach, PhD, Director, Office of Scientific Coordination and Program Operations, DMID/NIAID

Enclosure: IDSA Proposal for Three Randomized Multi-Centered Controlled Trials to be Sponsored by NIAID with the Goal of Optimizing Antimicrobial Prescribing Practices

Infectious Diseases Society of America (IDSA)
IDSA represents more than 8,600 infectious diseases physicians and scientists devoted to patient care, education, research, prevention and public health. Our members include leaders and experts in the field of influenza, bioemergency preparedness and biodefense, HIV/AIDS, immunizations, pneumonia, tuberculosis, meningitis and new and emerging infections, such as antibiotic-resistant bacteria.

Proposal for Three Randomized, Multi-Centered Controlled Trials to be Sponsored by the National Institutes of Allergy and Infectious Diseases (NIAID), with the Goal of Optimizing Antimicrobial Prescribing Practices

Infectious Diseases Society of America (IDSA)

July, 2009

Developed by the IDSA Research on Resistance Work Group Members and Invited Experts:

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Trial #1: The impact of an antimicrobial stewardship program on hospital antimicrobial exposure

A multi-center, randomized controlled trial comparing the impact of a "downstream" antimicrobial stewardship program with standard hospital practice

State the question that needs to be asked – Do antimicrobial stewardship programs have the effect of decreasing overall antimicrobial exposure in the hospital setting?

Describe the gap in our current knowledge regarding these questions – The broad applicability of "downstream" antimicrobial stewardship programs has not been demonstrated. By "downstream" we mean programs in which an individual knowledgeable about antimicrobial therapy (generally, but not necessarily, an infectious diseases trained pharmacist) reviews antimicrobial prescriptions after initiation and makes recommendations for modifications in therapy based on microbiological and clinical data. Effectiveness of these programs has been demonstrated in smaller studies, generally involving single medical centers, leading to reluctance on the part of many medical centers to accept the generalizability of the results. A multi-center study would test the applicability of stewardship principles on a broader scale.

Antimicrobial stewardship programs that involve patient-level interaction have taken two forms. One form is the prior approval approach, in which antimicrobial agents are restricted for use, requiring approval of an authority before they may be used by physicians and other health care providers. These programs have been shown to be effective in smaller, local studies, but have the potential to create discomfort among prescribers who are reluctant to cede control over therapeutic interventions when their patients are severely ill. "Downstream" programs avoid this complication by allowing the managing physician more freedom with initial prescriptions, choosing instead to intervene when a period of time sufficient to determine whether the patient is likely to benefit from prolonged antimicrobial therapy has passed. Smaller studies that have shown positive effects of such interventions emphasize the importance of obtaining support from the hospital's varied stakeholders (e.g., prescribers, pharmacists, administrators, etc.) before the intervention is initiated.

Outcomes in studies of downstream programs in the past have generally focused on a lowering of antimicrobial costs to the institution. While a reduction in costs is a worthy goal, cost containment can be achieved in ways that do not necessarily reduce antimicrobial selective pressure and the complications associated with antimicrobial use. The goal would be to focus the antimicrobial stewardship program around principles designed to reduce overall antimicrobial selective pressure, such as targeting antimicrobial therapy to isolated pathogens, minimizing duplicative therapies and insuring that antibiotics are administered at the appropriate dose and for the appropriate length of time. Outcomes measured should be those directly related to these principles, as well as 30-day mortality, length of stay, length of intensive care unit (ICU) stay, readmission rates and need for antifungal therapy. User perception surveys would also be incorporated to assess the acceptability of the interventions.

Describe issues that have complicated these studies in the past, and suggest ways in which those issues can be overcome with a different study design, etc. – Previous studies have suffered from quasi-experimental study designs, most commonly before-after designs that determine the impact of interventions on antimicrobial costs. The limitations of such designs are primarily that they are prone to unidentified confounding factors that complicate the ability to establish an association between the intervention and the result. Moreover, most previous studies have occurred in single centers, raising questions about the generalizability of the findings. The proposed study would be a multi-center, randomized, controlled design in which the randomizations would occur both within and between medical centers, allowing a substantial increase in the power of the study. Centers would be solicited that did not have existing downstream antimicrobial stewardship programs, but which could have a variety of other measures in place to curb antimicrobial use or reduce the transmission of infectious agents. The impact of the interventions could then be assessed both within the institution and between institutions.

Define the bottom line that these studies will address – the yield at the end that will make the studies a worthwhile endeavor – The study will allow us to make evidence-based recommendations on the role of downstream antimicrobial stewardship programs. As health care dollars become increasingly scarce and as regulatory agencies (both government and non-government) further define the type of programs required for hospitals to be in compliance with their evolving requirements, it is critical that the evidence base for the benefits of the programs be strong and that we understand both the direct and the unintended effects of regulatory requirements. As an example, the performance measure that patients with a diagnosis of pneumonia be given antibiotics within four hours of arrival in the emergency area was well intentioned, but led to algorithms that encouraged the overuse of potent and broad-spectrum antibiotics. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) is specifically requesting information about antimicrobial stewardship programs in hospitals. It would be of significant help to know the anticipated effect of these programs so that they can be adequately evaluated.

Trial #2: Determine the risk of adverse events associated with exposure to antimicrobial agents in the hospital setting

A multi-center, prospective observational study to establish a relationship between antimicrobial exposure (appropriate or inappropriate) and adverse events broadly defined

State the question that needs to be asked – What are the overall risks of adverse events associated with the decision to administer antimicrobial agents in the healthcare setting?

Describe the gap in our current knowledge regarding these questions – While estimates of complications and adverse events exist regarding the administration of individual antibiotics, it is extremely difficult to quantify the risk of adverse events associated with using antimicrobial agents in the hospital. For example, it is reasonable to presume that the administration of antimicrobial agents in combinations may be associated with a higher rate of complications or adverse effects than the administration of each of the agents alone. Such a synergistic interaction could occur through a broadening of antimicrobial spectrum (perhaps increasing the risk for diarrhea, fungal infections or *Clostridium difficile* colitis), through drug interactions that could increase the serum concentrations of one or both drugs or through the additive effects of similar toxicities (such as combining vancomycin and gentamicin leading to synergistic renal toxicity). The absence of data on adverse effects associated with our current patterns of hospital antimicrobial use makes it extraordinarily difficult to determine an accurate risk-benefit ratio when considering administering antimicrobial agents to hospital inpatients. Recent data indicate that adverse reactions to antibiotics are common causes of emergency room visits in all age groups[1], and the most common cause of medication adverse reactions in the pediatric population[2].

The aim would be to perform a study that would focus on two different goals over a range of institutions. The first goal would be to prospectively evaluate antimicrobial prescriptions in the inpatient setting. Given the frequency of antimicrobial prescriptions in the hospital (60% of inpatients receive antibiotics at one large city hospital – Henry Chambers, M.D., personal communication), feasibility would dictate that only a defined percentage of patients receiving antibiotics would be studied (perhaps 25%). Based on predefined criteria and principles, each antimicrobial course would be judged appropriate or inappropriate based on correlation with microbiological data, optimal dose and acceptable duration. Adverse events would be prospectively assessed and would include diarrhea, rash (including Stevens-Johnson syndrome), renal insufficiency, *Clostridium difficile* colitis, elevated liver function tests, unexplained fever, bone marrow toxicity or anaphylaxis. Patients would be contacted after discharge 30 days post initiation of antimicrobial agents to determine whether any of these complications occurred after discharge and to determine whether a readmission to the hospital was required.

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[1] Shehab N, Patel PR, Srinivasan A, Budnitz DS: **Emergency department visits for antibiotic-associated adverse events**. *Clin Infect Dis* 2008, **47**:735-743.

[2] Le J, Nguyen T, Law AV, Hodding J: **Adverse drug reactions among children over a 10-year period**. *Pediatrics* 2006, **118**:555-562.

The primary outcome would be any event listed above in the thirty days following initial prescription of antimicrobial agents. There would be no attempt to associate specific adverse effects to specific antimicrobial agents, since it is presumed that the majority of patients would be exposed to more than one antibiotic, in addition to many other agents. It would be worth discussing whether a control group of patients that do not receive antimicrobial agents would be identifiable. It is possible that a control group would be difficult to identify, since patients who proceed through hospitalization without receiving antimicrobial agents are likely to be considerably different in many respects than those who receive them. It may be possible to get around this by using a dose-response analysis of the group that receives antibiotics. In other words, do patients who receive more antibiotics (dose, duration, number of antibiotics) have more adverse events than those patients who receive less?

Describe issues that have complicated these studies in the past, and suggest ways in which those issues can be overcome with a different study design, etc. – Knowledge of the risks for adverse reactions associated with receipt of different antibiotics are generally derived from registration studies in which the populations are narrowly defined and the drug exposures are necessarily discreet. This does not reflect the true situation in hospitals, where many patients are given antibiotics for vague indications and the rule is to prescribe multiple antimicrobial agents at the same time. Many other studies have attempted to assess the frequency of adverse events, but they are retrospective, with limitations based on chart accuracy and a lack of follow-up data. Our goal is to derive a real-world assessment of risk for many of these adverse events, so that some value can be used to define the "risk" side of a risk-benefit calculation when antimicrobial prescriptions are considered.

Define the bottom line that these studies will address – the yield at the end that will make the studies a worthwhile endeavor – Underlying the antimicrobial prescribing practices in the United States and in hospitals worldwide is a baseline assumption that administration of an antimicrobial agent is at worst a therapeutically neutral choice ("it may help, but it won't hurt"). This philosophy is one of the most difficult cultural issues for antimicrobial stewardship programs to overcome. Data such as those to be derived from this study would provide an excellent basis upon which stewardship programs could frame the issue of antibiotic administration. In many respects, this study is the equivalent of clinical studies designed to determine optimal therapy lengths, etc. Without carefully derived data, we cannot hope to counteract cultural norms.

Trial #3: Determine the impact of feedback of individualized data on generalized adverse event and *C. difficile* colitis rates on prescribing practices in the hospital setting.

A multi-center, prospective interventional study to determine whether educating health care providers regarding adverse events will impact overall antimicrobial prescribing practices

State the question that needs to be asked – Will the feedback of individual patient data (provider-specific *C. difficile* and adverse event rates) alter the prescribing patterns of individual practitioners?

Describe the gap in our current knowledge regarding these questions – Data on surgical complication rates have been shown to impact surgical practices when the information is individualized. There are no data examining the efficacy of similar measures on the prescription of antimicrobial agents in the hospital setting.

The proposed study is conceived as a follow-up study to study #2 above. While the baseline data for study #2 is being acquired, focus testing would be performed by educational experts to determine the optimal method of communicating information regarding specific complications to individual practitioners. This testing is required to minimize the chance that a negative result in these studies would be attributable to the method of communication, rather than to the data communicated. Once the optimal education method is defined and the baseline data from study #2 is available, these data will be communicated with prescribers in a defined fashion, along with education regarding optimal use and dosing of antimicrobial agents.

The primary outcome in this study would be changes (yes/no) in the prescribing patterns of practitioners to whom feedback is given relative to prescribers who are not given such feedback. Data on changes (if any) in antimicrobial prescribing practices would be measured over a defined time period to determine whether the feedback of data is associated with sustained changes in prescribing patterns by individual physicians. Rates of complications, as those acquired in study #2, could then be calculated prospectively to see whether changes in prescribing habits, if any, are associated with changes in the rate of complications in patients cared for by the study subjects. One issue of importance in this study is to identify a group of practitioners for whom prescriber-specific data would be feasible and relevant. For obvious reasons, hospitals that rely exclusively on house-staff run services would not be optimal, given the itinerant nature of the prescribers. Many hospitals, including academic hospitals, are now moving toward systems in which many services are covered by full-time hospitalists. Hospitalists would be an ideal study group, and could potentially be the best ombudsmen to further promote provider-specific feedback in the future.

Describe issues that have complicated these studies in the past, and suggest ways in which those issues can be overcome with a different study design, etc. – The major issue that has complicated such studies in the past is identifying a group of physicians to target for individual feedback. As noted above, these techniques have been used with success to change the practices of surgeons, but in this instance it is easy to link a specific surgical practice to the surgeon. As noted above, it may be that

hospitalists would be the most appropriate target population for antimicrobial prescribers in the modern hospital setting.

Define the bottom line that these studies will address – the yield at the end that will make the studies a worthwhile endeavor – Obtaining prescriber specific data and feeding it back to individual physicians is often difficult and resource-intensive. It is therefore critical for us to determine whether this strategy is truly able to change prescribing patterns in a manner that will result in reduced overall complications and *C. difficile*. As a follow-up study to study #2, this is the perfect setting to ask this important question that will inform stewardship strategies into the future.