Infectious Disease Treatment Guidelines Weakened By Paucity of Scientific Evidence

Daniel M. Keller, PhD

November 13, 2009 (Philadelphia, Pennsylvania) — Two separate analyses presented here at the Infectious Diseases Society of America (IDSA) 47th Annual Meeting revealed that most of the society's treatment guidelines are based on expert opinion, nonrandomized trials, and case studies. Only about 15% of the guidelines are supported by randomized controlled trials (RCTs), considered the highest level of evidence. Nonetheless, more than 40% of the guidelines' recommendations were classified as class A, the strongest level of treatment recommendation, according to Dong Lee, MD, and colleagues from the Division of Infectious Diseases and HIV Medicine at Drexel University College of Medicine in Philadelphia, Pennsylvania.

Between 1994 and April 2009, IDSA issued 68 guidelines on 52 different topics (there have been 2 more since April). Most were published in *Clinical Infectious Diseases*. Of the 52 current guidelines, Dr. Lee's team analyzed the 30 that followed IDSA's standard grading system to evaluate the class of clinical recommendations and the strength of the supporting evidence underlying them.

"Our analysis revealed that more than half were based on expert opinion or not supported by properly controlled trials," Dr. Lee announced. In an oral presentation, he reported that the 30 guidelines he analyzed contained a mean of 47 recommendations (range, 14 to 150). Recommendations ranged from class A (should always be offered) to class C (optional). The quality of evidence ranged from level I, consisting of 1 or more properly conducted RCTs, to level III, the opinion of respected authorities, based on clinical experience. Level II evidence is derived from 1 or more properly controlled trials without randomization.

The guidelines revealed a total of 589 class A recommendations. "Ideally, all should be [supported by] level I evidence," Dr. Lee said. "However, a class A recommendation was supported by level I evidence only in 25% [of cases]." The rest were based on level II (40%) or level III (35%) evidence. Of all the guidelines evaluated, a median of 41% of recommendations were class A, but level I evidence supported them only 14% of the time.

Guidelines for common conditions were often based on fairly strong evidence. The recommendations that are most supported by level I evidence are in the guidelines for tropical medicine (41% of recommendations), intra-abdominal infection (39%), and asymptomatic bacteriuria (38%). "Influenza or Group A *Streptococcus* guidelines had less than 20% of level III evidence," possibly because of the high prevalence of these diseases and the ease of designing studies, Dr. Lee reported.

He explained the lack of RCTs for some conditions, saying that certain infections occur rarely or present in heterogeneous forms, making it difficult to design a study. Furthermore, in some cases it might be unethical to conduct such a trial, and at times certain knowledge based on sound clinical judgment will never be tested in RCTs. Finally, funding to do trials might be lacking.

"Although a randomized controlled trial is referred to as level I evidence, not all RCTs are created equal," he warned. "Some choose surrogate markers, others choose patient-centered outcomes. Well-designed nonrandomized trials may provide more information than certain randomized controlled trials, but I do think that a randomized controlled trial minimizes bias and does deserve the high levels of evidence."

Dr. Lee summarized his presentation, saying that of the 1408 guideline recommendations he reviewed, "more than half were based on level III evidence, which is from expert opinion or not supported by properly controlled trials. Level I evidence was only 15%." He said his study should help to point out where evidence is lacking and to suggest areas for further research.

Physicians and trainees should not just look at guidelines, but should also examine the strength of the evidence on which they are based, he advised. "When clinicians are using the guidelines, they should not assume that they are all based on well-designed studies. . . . Clinicians should remain cautious when using current guidelines as the sole source for guiding patient care."

A second presentation supported the findings of Lee and coworkers. Abdur Khan, MD, assistant consultant at King Fahad Medical City in Riyadh, Saudi Arabia, presented his results in a poster session. Of the 65 IDSA guidelines, encompassing 6667 recommendations, issued between March 1994 and July 2009, he and his colleagues evaluated the 44, comprising 4206 recommendations, that were posted on the IDSA Web site at the end of July.

They, too, found that, overall, the strength of the recommendations did not correlate with the available evidence. Level I evidence was the basis for only 15% of the guidelines, which is in agreement with the findings that Lee and colleagues reported. Thirty percent of the evidence was level II.

"Around 55% of the guidelines had a level of evidence of III, which was based on expert opinion," Dr. Khan told *Medscape Infectious Diseases*, "but the class C recommendations [are] only 12%." Guidelines for the treatment of fungal infections had the weakest supporting evidence; 46.5% to 89.5% of the recommendations were based on level III evidence.

Although the highest levels of evidence generally led to class A recommendations (25.9%), these strongest recommendations were most often based on lesser levels of evidence (36.3% on level II; 37.8% on level III).

Commenting on the studies' findings, Richard Whitley, MD, professor of pediatrics, microbiology, medicine, and neurosurgery at the University of Alabama at Birmingham and president of IDSA, told *Medscape Infectious Diseases* that "one always has to be concerned when we don't have randomized controlled trials that provide evidence-based medicine to write guidelines. Without a shadow of a doubt, the best evidence comes from controlled clinical trials that are adequately powered with a sample size to answer the targeted question." But he noted that sometimes expert opinion or small uncontrolled studies have to suffice if there are not enough patients to conduct better trials.

In some situations, less than level I data can be powerful, Dr. Whitley observed. He cited the example that neuraminidase inhibitors can decrease mortality from influenza in elderly individuals. This finding was based on retrospective reviews of databases of Kaiser Permanente and other managed health care systems, he explained.

Looking forward, he said, "guidelines don't necessarily just teach how to take care of patients. They identify areas for future investigation . . . because they tell us where the vagueness is and where we have to move forward." This information can then be brought to the attention of the leadership of the National Institute of Allergy and Infectious Diseases so that they can fund studies and to the attention of the US Food and Drug Administration, which has funds to study targeted issues.

Dr. Whitley emphasized that "guidelines shouldn't be just for patients in the United States. They should be for patients around the world." As such, IDSA and the European Congress of Clinical Microbiology and Infectious Diseases will try to work on guidelines together, and IDSA will also work with Canadian colleagues "so that we can provide a level of care that's standardized around the world," he said. "Certainly, that's optimistic."

Neither of these studies received funding. Dr. Lee and Dr. Khan have disclosed no relevant financial relationships. Dr. Whitley reports being on the board of directors of Gilead Sciences and is a consultant for 3-V Biologics and Chimerix; his other consulting, review, advisory panel positions, investigator, or speaker honoraria relationships include Juvaris, Primus, Inhibitex, and JID.

Infectious Diseases Society of America (IDSA) 47th Annual Meeting: Abstract 1324. presented November 1, 2009; Abstract LB-31, presented October 31, 2009

Authors and Disclosures

Journalist

Daniel M Keller, PhD

Daniel M. Keller is a freelance writer for Medscape.

Daniel M. Keller has no disclosures.