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Antimicrobial stewardship research: where do we go from here?

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The rising tide of antimicrobial resistance, coupled with a paucity of new drug development, has led to increasingly clamorous calls for improved antimicrobial stewardship to reduce the oft-cited 30-50% rate of inappropriate antimicrobial therapy.[cite CDC, Obama, WHO, NHS, TransAtlantic] Much attention has been given as to what interventions stewardship programs should pursue to achieve specific objectives such as adherence to local guidelines, use of pathogen-directed therapy, discontinuation of therapy when infection is found to be unlikely, timely parenteral to oral conversion and appropriate duration of therapy. However, there is substantial uncertainty in the degree to which specific interventions (e.g., drug restrictions, audit and feedback, computerized decision support systems) achieve these objectives, in how to assure that interventions are successfully implemented, and whether successful interventions sustainably reduce antimicrobial use and lead to improvements in meaningful patient-level (e.g., adverse events, mortality) and societal (costs and bacterial resistance) outcomes. [Cochrane, ESP]

In this issue of *The Lancet Infectious Diseases*, Schuts, *et al*, instead of taking the usual approach of focusing on what interventions best achieve stewardship objectives, focus instead on the effect of meeting these objectives. The authors identified 14 objectives (compiled via expert Delphi procedures and guideline review) and exhaustively reviewed the literature to find studies which evaluated the impact of meeting each of these objectives on patient and societal outcomes. In doing so, the authors have assembled a comprehensive and well-organized compendium that identifies the gaps in data linking

stewardship objectives to practical outcomes. Unfortunately, the studies examined by Schuts, *et al*, were largely of poor quality, owing to inconsistency, indirectness, and imprecision in data reporting, and overall high risk of bias. Nevertheless, the demonstration of decreased mortality (risk ratio 66%) with achievement of de-escalation of therapy based on culture results (derived from 25 studies in diverse clinical settings) is provocative. Their other major result, i.e., that decreased mortality was associated with guideline-concordant prescribing of empiric antimicrobial therapy (40 studies) was largely driven by studies of community-acquired pneumonia, corroborating findings of a Cochrane review which found that interventions aimed to increase appropriate prescribing for pneumonia reduced mortality.

(Davey2013)

So how can we advance the science of antimicrobial stewardship? Clearly there is a need for more randomized multihospital trials to test the effectiveness of interventions on achieving stewardship outcomes and the subsequent effect on clear and meaningful clinical outcomes. Specifically, robust demonstration of direct clinical benefit to individual patients whose care is impacted by stewardship interventions can provide a powerful counter-argument to healthcare providers who view stewardship interventions as being designed more for overall societal benefit by reducing population level rates of antimicrobial resistance or *Clostridium difficile* infection than for providing value to their individual patient.

Furthermore, although Schuts, *et al*, considered the impact of achieving stewardship objectives in isolation, in practice interventions are likely to be bundled. When measuring the impact of bundles, we suggest that one needs to consider where planned stewardship activities affect the timeline of a prescribed course of antimicrobial therapy: the initial timeframe when decisions are made as to whether to start therapy and during which an empiric regimen is selected (*Choice*), the time period in which emergent microbiologic data and the clinical course allows for initiation of pathogen specific therapy or discontinuation of therapy in persons found not to have an infection(*Change*), and the final time frame in

which the total duration and route of administration of therapy is decided upon (*Completion*). This characterization will allow for not only determination of where along the antimicrobial prescribing timeline interventions can most effectively effect improvement in more global outcomes but will also allow for development of more sophisticated outcome metrics tailored specifically to each of these branch or decision points of therapy.

In summary, this systematic review and meta-analysis of the association between addressing specific antimicrobial stewardship objectives and outcomes serves as a novel complement to previous reviews by focusing on “what to do” rather than “how to do it.” While the data supporting their efficacy are far from ideal, interventions that encourage guideline-concordant therapy and de-escalation as appropriate are likely to be good starting points for any healthcare system starting an antimicrobial stewardship program.