

Antimicrobial Stewardship: What Works?

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As antimicrobial stewardship programs are established, they start by implementing various interventions recommended by organizations such as the Centers for Disease Control and Prevention and the Infectious Diseases Society of America. Although these interventions often seem commonsensical, the empiric evidence for their efficacy is often absent, inadequate, or equivocal.

Schuts and colleagues (1) performed a systematic review and meta-analysis designed to assess the available evidence regarding the effect of antimicrobial stewardship interventions on clinical outcome such as mortality and length of stay, the occurrence of adverse events, costs, and effects on antibacterial resistance. Although the overall quality of evidence in the available studies was low and the heterogeneity between studies was moderate to high, some conclusions were sturdy enough to support the likely value of specific individual interventions.

Of 40 studies examining the effects of adherence to guidelines for the empiric administration of antimicrobials, all of which were observational and subject to bias, 37 reported associated mortality and 31 of these found an association with reduced mortality. The result was statistically significant in 14 of the 31. Similarly, 17 of 24 such studies reported a reduced length of stay and this was significant in 8 of the 17.

De-escalation of therapy based on culture results was assessed in 24 observational studies with high risk of bias that were judged to be of poor quality. Nineteen of the 24 assessed mortality and 17 of these reported an association of de-escalation with lowered mortality. Overall, the results demonstrated a relative risk (RR) reduction of 66% (RR, 0.44; 95% confidence interval [CI], .30–.66; $P < .0001$). Nine of 10 observational studies found de-escalation to be associated with reduced length of stay, but this was statistically significant in only 2. The only prospective randomized study reported a numerically greater intensive care unit and hospital length of stay in those subject to de-escalation, but the difference was not statistically significant.

Conversion from intravenous to oral antibiotic administration was examined in 18 studies and, although 13 were randomized controlled trials, their overall quality was low because of small sample size and a high risk of bias. There was no consistent effect on outcomes such as cure or mortality, but there was evidence of an association with reduced cost and length of stay. Nine of 16 studies of therapeutic drug monitoring (TDM) were observational. TDM was not associated with a difference in mortality, but there was a possible reduction in length of stay.

Complete discontinuation of empiric antibiotic administration in response to a lack of evidence of the presence of infection was analyzed in just 3 studies (including 2 randomized trials) and their overall quality was low to moderate. There was no difference in clinical outcomes, but 2 of the studies with randomization found an associated reduced intensive care unit length of stay, with statistical significance achieved in 1 study. One of the randomized studies also found reduced costs and antibiotic resistance rates.

Antibiotic restrictions were evaluated in 30 studies, 29 of which were observational, and the general quality of the evidence was judged to be low. The overall effect on mortality was limited and nonsignificant. Reduced costs were reported in 10 of 11 studies. In general, microbial resistance to restricted antibiotics was significantly decreased, although a few studies reported contemporaneous increased resistance to nonrestricted antibiotics.

Five of 7 studies that assessed the relationship of bedside infectious diseases consultations to mortality reported a decrease that was significant in 3, but the overall result was not significant—a finding that is likely indicative of a favorable effect given the obvious bias toward consultation for sicker patients. In addition, a sensitivity analysis (2) examining patients with bacteremia due to *Staphylococcus aureus* found a relative risk reduction of 66% (RR, 0.34; 95% CI, .15–.75; $P = .008$).

In summary, this critical review provides support for a number of common stewardship interventions. Following guidelines in the administration of empiric antibiotics, de-escalation, intravenous to oral conversion, TDM, antibiotic restrictions, and infectious diseases consultations are each associated in many studies with improved clinical outcomes, as well as reduced costs and frequency of adverse events. Following guidelines for empiric therapy as well as de-escalation appeared to also be associated with reduced mortality.

This study concluded that bedside infectious diseases consultations were associated with reduced mortality in patients with *S. aureus* bacteremia. This finding was robustly enforced by a study that was published after the literature review performed for this meta-analysis was completed [1]. That 6-center observational study of 847 patients with *S. aureus* bacteremia found that consultation was associated with significantly reduced in-hospital mortality as well as earlier hospital discharge.

Another important lesson to be learned from this meta-analysis, besides its bolstering of support for elements of antimicrobial stewardship, is that we need higher-quality studies in the field.

1. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2016 Mar 2. pii:S1473-3099(16)00065-7. doi:10.1016/S1473-3099(16)00065-7.
2. Bai AD, Showler A, Burry L et al. Impact of infectious disease consultation on quality of care, mortality, and length of stay in *Staphylococcus aureus* bacteremia: results from a large multicenter cohort study. *Clin Infect Dis* 2015; 60:1451–61.