Antimicrobial Stewardship: What Works?


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 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 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.

Reference

A New *Borrelia* Species Causing Lyme (-Like) Disease


From 2003 and 2014, the Mayo Medical Laboratories tested 100 545 clinical specimens submitted for diagnostic testing for Lyme disease using a real-time polymerase chain reaction (PCR) assay that targets the chromosomal *oppA1* gene specific for *Borrelia burgdorferi* sensu lato. Melting temperature analysis of the amplicon was used to differentiate it into genospecies. Sequencing of additional multiple genes was also performed.

Of 9197 blood, synovial fluid, cerebrospinal fluid, and tissue specimens from residents of Minnesota, Wisconsin, and North Dakota submitted from 1 January 2013 to 30 September 2014 for PCR testing, 102 were positive for *B. burgdorferi* sensu lato. An additional 6 specimens (5 blood, 1 synovial fluid) had an atypical melting temperature, something not detected among 24 786 specimens collected from residents of 44 other states during that time period or among 66 562 from all states in the previous 8 years.

All 5 patients with atypical results had either a known or probable tick exposure. Five of the 6 presented with fever, while 1 patient had monoarticular arthritis of the knee. Two patients had encephalopathy. One had a macule at the site of a possible tick bite, 1 had erythema migrans, and 2 had multiple macular lesions. Lymphopenia was present in 4 of 5, mild thrombocytopenia in 2 of 5, and elevated serum hepatic aminotransferases in 2 of 3 patients.

Motile spirochetes were observed at a concentration of approximately $8.5 \times 10^4$/mL in a blood sample obtained 1 day after the onset of illness in 1 patient. The median *oppA1* gene copy number in the 5 blood specimens of PCR-positive patients was 180 times higher than that in 13 specimens that tested positive for *B. burgdorferi* sensu stricto tested during the same time period.

Antibody tests for *B. burgdorferi* sensu stricto were frequently positive in these patients. They were, however, negative on specimens obtained on days 1–3, but the C6 enzyme immunoassay was positive in all 4 patients whose specimens were obtained >3 days after the onset of illness. Immunoglobulin M immunoblots of specimens obtained 8–32 days after illness onset were positive in 3 patients. The *B. burgdorferi* sensu stricto immunoglobulin G immunoblot was, however, positive only for the single patient with >30 days of untreated illness.

Four patients recovered after receiving doxycycline and 1 after ceftriaxone therapy. The patient with knee arthritis had persistence of joint pain after doxycycline treatment.

The novel organism, provisionally named *Borrelia mayonii*, was detected in host-seeking *Ixodes scapularis* ticks collected from presumed exposure sites of 2 patients in Wisconsin, with 4% and 5% infection rates in nymphs and adults, respectively. This, together with subsequent experimental work demonstrating that *I. scapularis* is able to serve as a vector of *B. mayonii*, indicates that it is a primary vector for infection of humans with this novel spirochete [1].

Reference

Published by Oxford University Press for the Infectious Diseases Society of America 2016. DOI: 10.1093/cid/ciw169