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Drug Use in Infection Control – Is More Less?

Major challenges face infection control – an increasing population of immunocompromised patients, increasing use in hospitals and clinics of invasive devices and procedures, and increasing presence of multiply resistant bacteria, fungi, and viruses. Since antimicrobial drugs are the primary weapons we have used to combat unwanted microbes, it seems natural that the response to these threats has been the more aggressive prophylactic use of these agents – topically, systemically, and incorporated within indwelling devices. But will this approach reduce the incidence of nosocomial infection? Or can technologic advances, newer immunologic products, and different strategies, better help to achieve the broad objectives of preventing microbial colonization of the host, lessening host risk factors, and augmenting host defenses?

The report by *Bonten* et al. [1] on selective decontamination of the gastrointestinal tract (SDD) in this issue of INFECTION is a prime example of aggressive antimicrobial drug use as a strategy to improve upon past efforts to reduce infection risk. Topical application of antibiotics to the oropharynx and stomach, with or without a short course of systemic antibiotics, was first popularized in the Netherlands to control patients' endogenous microflora. As in the *Bonten* paper, prior studies demonstrated a reduction in the overall incidence of nosocomial infection, particularly gram-negative pneumonia [2,3]. *Bonten* tried to overcome one of the major perceived shortcomings of previous SDD studies, i. e. "assuring" the diagnosis of pneumonia, by obtaining lower respiratory tract specimens for culture via protected specimen brushes. Despite this effort to improve upon study design, the lack of a control group in the *Bonten* trial makes it difficult to evaluate. In addition, unanswered questions which still plague SDD include the potential to foster the development of multiply resistant gram-negative and gram-positive bacteria; the value of SDD in reducing mortality in the intensive care unit (ICU); and "cost-effectiveness" of this aggressive form of infection control [3].

In a broader context, SDD is part of a growing literature on more aggressive use of antimicrobial agents to control microbial colonization of patients and/or to lessen device-related risk factors. Systemic antimicrobial prophylaxis has been advocated for relatively simple and clean surgical procedures [4]. Antibiotics have been bonded (through ionic interactions) onto vascular catheter surfaces [5], administered systemically to patients with vascular catheters [6], or simply allowed to dwell within the lumens of intravascular catheters [7]. Silver-impregnated subcutaneous cuffs have been used to decrease the incidence of catheter-related infection, but may also predispose patients to fungal colonization [8]. Urinary catheters which continuously release silver ions may have been designed to eradicate bacteria multiplying within biofilms, and therefore prevent recurrent bacteriuria [9].

While a major emphasis has been placed on the use of antimicrobials to reduce colonization and/or infection risk, a better understanding of factors determining colonization could lead to infection control strategies that do not rely on antibacterials. For example, reducing bacterial growth in the stomach – and thus lessening the risk of bacterial aspiration pneumonia – by maintaining the natural gastric acidity of the stomach has been advocated, although there is still debate about the effect of this intervention on risk of infection [10]. Knowledge of the electrostatic interactions between bacteria and biomaterials has led to the recognition that microbes with an overall net negative charge (e. g., staphylococci and *Candida albicans*) will not adhere to vascular catheters with slight negative electric currents flowing through them [11].

Advances in biotechnology have moved us closer to the next step in the scientific sophistication of infection control – the modulation of patients' immune systems. Reviews of immune modulator drug studies in the 1970–80s showed that the data were not strong enough to recommend routine use of these agents [12,13]. Major problems included inconsistent effectiveness in reducing infections and inadequate study designs. Studies in the 1990s of immune globulin and antibody directed against bacterial endotoxin are still surrounded by much uncertainty [14]. For example, although intravenous use of standard immune globulin significantly decreased the incidence of nosocomial infections in low birth weight neonates and high risk postsurgical patients, the benefits in neonates have not been consistently substantiated. Also, it is unclear why a hyperimmune globulin which was expected to be at least as efficacious as standard immune globulin, did not confer the same protection as did the latter agent in surgical patients.

Most recently, recombinant DNA technology has resulted in the commercial availability of growth factors, such as human granulocyte-macrophage and human granulocyte colony-stimulating factor, which augment the proliferation and function of white blood cells and may lower infection risk in some patients undergoing chemotherapy [15].

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Other areas of current immunoprophylaxis research include studies of vaccines to enhance the secretion of protective mucosal antibodies, particularly secretory IgA [16], and studies of the role of other cytokines, such as interleukins and interferon gamma, to enhance host defenses and/or augment the protective effects of vaccines [17–19].

Although immunologic strategies are intriguing approaches to infection control, several factors still preclude their use. First, they have not always led to consistent reductions in infection or mortality. Second, much needs to be learned about the optimal dosage regimens for these agents, their toxicities, and their potential deleterious effects on the immune system [14,18,20]. Third, the protective effects of active immunization with vaccines may be limited by the inherent delay in antibody response and failure of some immunosuppressed patients to mount an adequate response. Fourth, the overall impact on clinical outcome requires careful assessment, since one problem may be replaced by another. For example, invasive *Pseudomonas aeruginosa* infections were lessened in burn victims by immunotherapy, only to be replaced by *Klebsiella pneumoniae* infections [21]. Finally, because of the enormous expense associated with immunotherapies, a major challenge will be to identify prospectively patient groups who will benefit most; although even the optimum end point of "benefit", e. g., infectious complications, survival, duration of hospitalization, cost of immunotherapy etc., is not uniformly agreed upon.

Given the options, what drugs should we be using in hospitals today for infection control? First, we must not underestimate the potential of "aggressive" antimicrobial prophylaxis to foster the development of widespread microbial resistance or the potential toxicities associated with immunoprophylactic strategies [14,18,20]. Second, we favor limiting the use of antimicrobial prophylaxis to short courses (1–3 doses) for traditionally high-risk procedures; limiting the use of device-related innovations to those shown by repeated, well designed, controlled trials, to be "cost- effective;" and limiting immunoprophylaxis to those settings where the cost and benefits have been carefully evaluated. Third, broadened use of SDD should be avoided until results of ongoing multi-center ICU trials are available that will allow better definition of which groups (e. g., previously healthy trauma patients and some post-operative patients) will benefit. Finally, and most importantly, we must not lose sight of the need to continually remind our colleagues of the enduring value of soap and water.

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