EDITORIALS

Team-Based Prevention of Catheter-Related Infections

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Each year, 36 million patients are admitted to acute care hospitals in the United States, staying for 164 million days.[1] Eleven percent (18 million days) of these hospitalizations are spent in intensive care units (ICUs). For 54% of the days (9.7 million) that patients are in ICUs, central venous catheters remain in place for the infusion of medications and fluids. Regrettably, the use of these devices results in 48,600 associated bloodstream infections (5 per 1000 catheter-days).[2] The leading pathogens, in descending order, are coagulase-negative staphylococci, *Staphylococcus aureus*, enterococcus species, and candida species. Morbidity is significant with bloodstream infections. At least 5% of patients whose condition meets the criteria for sepsis will have the acute respiratory distress syndrome, and at least 15 to 20% will have disseminated intravascular coagulation, acute renal failure, or shock, alone or in combination, while in the hospital.

The epidemiologic concept of attributable mortality has been advanced to distinguish deaths directly due to catheter-related bloodstream infection from those due to the underlying disease. In historical cohort studies in which infected patients are tightly matched to noninfected control subjects, estimates of excess (attributable) deaths in ICUs have been as high as 35% (17,000 deaths yearly).[3] These figures represent the portion of the total deaths that can be maximally influenced by the use of effective antimicrobial agents or maximally prevented (Fig. 1).

Cumulative data on pathogenesis focus on the role of contamination by organisms residing on the hands of health care workers and the skin of patients. Microorganisms gain access to the bloodstream intraluminally through the connecting ports of the catheter or extraluminally at the exit site, at the interface between the catheter and the patient's skin. Since bacteria and yeast can traverse both the inner and outer surfaces of the catheter, the use of chemically bonded materials has been recommended to reduce infection rates. On the basis of current data on pathogenesis, prevention strategies have become a major issue in the quality of care.

In 1966, Avedis Donabedian elegantly defined the architecture of quality-assurance programs as having three platforms: structure, process, and outcome.[4] This seminal partition influenced medical care worldwide. Early quality-assurance

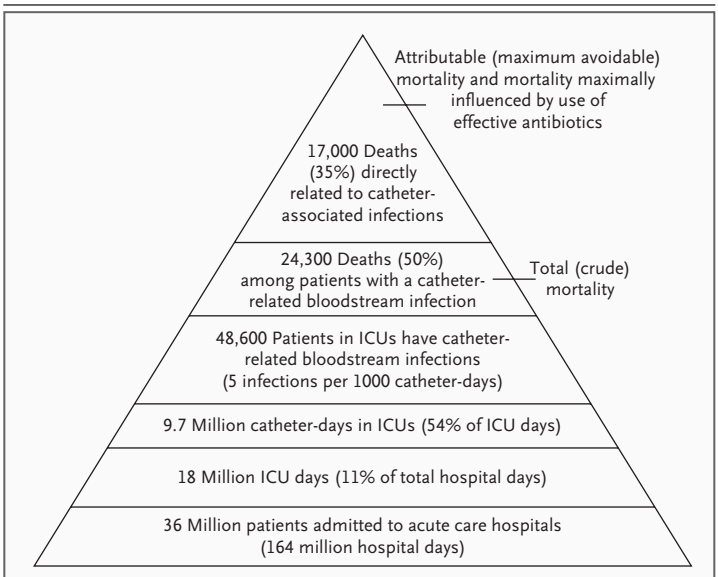

Figure 1. Annual Patient Stays in the 6000 Acute Care Hospitals and Associated ICUs in the United States.

About half the days patients spend in ICUs (ICU days) are associated with the use of a central venous catheter and therefore with a risk of subsequent bloodstream infection (five infections per 1000 catheter-days).

programs in U.S. hospitals were centered on infection-control activities. Specifically, the efforts of the Centers for Disease Control and Prevention (CDC) in the 1970s sparked the development of infection-control expertise, the use of uniform definitions of nosocomial infections, and concurrent surveillance activities. Subsequently, the Study on the Efficacy of Nosocomial Infection Control identified structures and processes linked to reduced infection rates.[5]

In the classic 1972 book titled *Effectiveness and Efficiency*, Archie Cochrane stressed the importance of cost–benefit analysis and randomized, controlled clinical trials for prioritizing investments in health care.[6] He used the word "efficiency" to mean the benefits measured in community practice, in contrast to observations from clinical trials. Given a world with limited resources, Cochrane recommended medical interventions only when the evidence of their value was substantial.

In 1988, an independent panel of experts was charged by the Agency for Healthcare Research and Quality with systematically reviewing intervention studies and grading the evidence of improved outcomes: level A indicated high-quality, randomized, controlled trials or meta-analyses; level B, well-designed, nonrandomized clinical trials, clinical cohort studies, and case–control studies; and level C, expert consensus or opinion. A similar system was adopted by the University of Oxford Centre for Evidence-Based Medicine, which designated levels 1a and 1b for systematic reviews of multiple and individual randomized clinical trials, respectively. Subsequently, the CDC modified this classification, designating a category of IA for interventions "strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies."[7]

Against this background, in this issue of the *Journal* Pronovost and colleagues describe a remarkable interventional cohort study involving 103 ICUs in 67 hospitals with more than 375,000 catheter-days of observation.[8] Five of the CDC's category IA recommendations were championed by local team leaders at the ICUs, and during the 18 months after implementation of the study intervention, the median rate of catheter-related bloodstream infection fell from 2.7 (mean, 7.7) to 0 (mean, 1.4) per 1000 catheter-days — a 66% reduction.

In this study, the structure of the intervention involved daily commitment to a culture of safety, ongoing surveillance by trained infection-control personnel, and a supportive central education program. The five components of the intervention involved the following processes: appropriate hand hygiene, use of chlorhexidine for skin preparation, use of full-barrier precautions during the insertion of central venous catheters, use of the subclavian vein as the preferred site for insertion of the catheter, and the removal of unnecessary central venous catheters.

The improved outcomes were very likely causally related to these processes. The improvement temporally followed the implementation of the intervention, there was biologic plausibility, and the outcomes had a large effect that was sustained over months. The lack of randomization, control subjects, and microbiologic data and the uncertainty about the effect of other specific interventions might suggest an across-the-board improvement that was due more to attention being focused on an important issue than to the specific interventions. Yet even if we ascribed 15 percentage points to such an effect,[9] a 50% reduction in the rate of infection would still remain.

This quasi-experimental study would warrant the designation of level B evidence by the U.S. Preventive Services Task Force and the Centre for Evidence-Based Medicine. We would like to have known the validity of the institutional surveillance systems, the frequency of use of chemically bonded (with antimicrobial agents) vascular catheters during the study period, the rate of compliance with specific recommendations, and the influence on mortality. Yet the real-world efficiency — in Cochrane's lexicon — of the intervention was extraordinary, an "A" according to most standards. The story is compelling and the costs and efforts so relatively minor that the five components of the intervention should be widely adopted. We can no longer accept the variations in safety culture, behavior, or systems of practice that have plagued medical care for decades. Imagine the effect if all 6000 acute care hospitals in the United States were to show a similar commitment and discipline.

There is much to criticize about U.S. health care, including its fragmentation, high costs, impersonal delivery, and adverse events. In contrast, a focus on quality could be a unifying concept, part of a new, team-based professionalism using evidence-based systems and caring behavior that consistently lead to safety and comfort for patients.

Dr. Wenzel reports serving on advisory boards for Pfizer and Replidyne and receiving research support from Pfizer. No other potential conflict of interest relevant to this article was reported.

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Targeted Therapy for Metastatic Breast Cancer

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Metastatic breast cancer is incurable, so most oncologists favor sequential chemotherapy with one agent at a time over concurrent therapy with multiple agents.[1] The use of single agents on a sequential basis can control the growth of metastases and improve the quality of life without a detrimental effect on survival. This conventional practice is about to change as a result of the development of new targeted agents for cancer.[2]

These targeted therapies — drugs that are specifically designed to block one or more critical pathways involved in cancer-cell growth and metastases — have led to major advances in the treatment of breast cancer and other malignant conditions. The development of these therapies stems from advances in molecular biology that have permitted the identification of qualitative and quantitative differences in gene expression between cancer cells and normal cells.[3] The new agents range from antibodies that form complexes with antigens on the surface of the cancer cell to small molecules that have been engineered to block key enzymatic reactions. The interaction of the antibody or drug with its target inhibits pathways that are essential for cell proliferation or metastasis or activates pathways that culminate in cell death (apoptosis). Since these targets are usually specific for or overexpressed in cancer cells, the new agents generally have fewer side effects than most conventional chemotherapeutic agents, and when the targeted agents are combined with single-agent chemotherapy, toxicity is only minimally increased. Thus, combinations of targeted and conventional chemotherapeutic agents may improve the response to treatment without a major increase in side effects.

The epidermal growth factor receptor stands at the origin of a major signaling pathway involved in the growth of breast cancer.[4] Two of the four transmembrane glycoprotein receptors in this pathway, epidermal growth factor receptor type 1 (HER1) and epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu or ErbB2), are promising targets for new treatments. In about 20% of patients with breast cancer, the tumor overexpresses HER2. Trastuzumab, a humanized monoclonal antibody that targets the extracellular domain of HER2, is effective as adjuvant therapy and as treatment for metastatic disease in patients with HER2-positive breast cancer. Lapatinib, an orally administered small-molecule inhibitor of the tyrosine kinase domains of HER1 and HER2, has antitumor activity when used as a single agent in patients with HER2-positive inflammatory breast cancer or HER2-positive breast cancer with central nervous system (CNS) metastases that are refractory to trastuzumab. This finding is important because HER2-positive tumors frequently spread to the CNS, where the tumor is sheltered from trastuzumab and most chemotherapeutic agents.

In this issue of the *Journal*, Geyer and colleagues report on a study that expands the indications for lapatinib.[5] In their trial, 324 patients with locally advanced or metastatic breast cancer that had progressed after initial chemotherapy plus trastuzumab were randomly assigned to receive treatment with the oral fluorouracil prodrug