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Drug eluting antimicrobial vascular catheters: Progress and promise☆

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ABSTRACT

Vascular catheters are critical tools in modern healthcare yet present substantial risks of serious bloodstream infections that exact significant health and economic burdens. Drug-eluting antimicrobial vascular catheters have become important tools in preventing catheter-related bloodstream infections and their importance is expected to increase as significant initiatives are expanded to eliminate and make the occurrence of these infections unacceptable. Here we review clinically significant and emerging drug-eluting antimicrobial catheters within the categories of antibiotic, antiseptic, novel bioactive agents and energy-enhanced drug eluting antimicrobial catheters. Important representatives of each category are reviewed from the standpoints of mechanisms of action, physical–chemical properties, safety, in vitro and clinical effectiveness.

Contents

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1. Introduction

The scope of this review is vascular catheters that elute antimicrobial agents to prevent infectious complications. The review is not intended to be encyclopedic, but rather to survey significant themes centered on different classes of drugs used in developing drug-eluting vascular catheters with a focus on those that have made a clinical impact. Vascular catheters have become indispensable devices for providing medical care to patients. For the critically ill, they are lifelines for providing nutrition, medications, blood products, hydration and diagnostics [1,2]. These catheters also remain an important mode of vascular access for hemodialysis and emergency medicine [3]. The increasing use of vascular catheters has led to the development of different types of specialized catheters with optimized designs to meet specific needs. Some design variables include multiple lumens to accommodate different functions as well as to administer incompatible drugs, cuffed catheters to reduce infection and obtain better anchoring, as well as vascular ports that eliminate the continuous conduit extending from outside the body to inside of blood vessels. Examples of widely used specialized catheters are dialysis catheters, central venous catheters (CVCs) and ports [4]. Within each category there are further varieties; for example CVCs can be peripherally inserted, subclavian, jugular or femorally inserted [5]. Vascular catheter designs have evolved over time to more optimally meet vascular access needs as well, as to reduce complications associated with insertion and placement in the desired position in the vascular tree [6]. Vascular catheters are used for both short and long durations, and need to sustain both low and high pressures, so different materials for fabricating vascular catheters have been introduced [7]. These include silicone, as well as polyurethanes. Over time, different polyurethanes have been introduced to improve stability and vascular compatibility [8]. Despite the vascular access benefits provided by vascular catheters they also serve as a portal for entry into the bloodstream of pathogenic bacteria and fungi [9].

In the United States, 15 million CVC days occur in intensive care units (ICUs) each year [10]. Unfortunately, 80,000 catheter-related bloodstream infections (CRBSIs) occur in ICUs each year, while more than 250,000 cases of bloodstream infections have been estimated to occur annually, if entire hospitals are assessed [11,12]. Additionally, several studies have revealed a temporal relationship between CVC duration, or dwell time, and both catheter colonization and CRBSI [13]. The prolongation of catheterization by 1 day was determined to increase the risk of CRBSI by 1.08 times (95% CI 1.02–1.15, $p = 0.004$) [14]. The median and interquartile range of periods of use related to CRBSI were calculated at 12 and 6–24 days, respectively [15]. The National Healthcare Safety Network (NHSN) report during 2009–2010, revealed that the most commonly encountered organisms causative for CVC-related infections were Gram-positive cocci 51% (coagulase-negative *Staphylococci* 20.5%, *Enterococcus* spp. 18.1%, and *Staphylococcus aureus* 12.3%), Gram-negative rods 26% (*Klebsiella* spp. 7.9%, *Enterobacter* spp. 4.5%, *Escherichia coli* 4.0%, and *Pseudomonas* spp. 3.8%), and *Candida* spp. 15% [16]. Throughout the past two decades the rate of Gram-positive cocci infections has decreased from 63.4% to 50.9%, while Gram-negative rods have increased from 14.4% to 25.6%, as well as *Candida* spp. from 8% to 14.6% [17–19]. Of interest, the International Nosocomial Infection Control Consortium report, which included 503 ICUs in developing nations worldwide, found that the pooled rate of CRBSI was 4.9 per 1000 central line days, almost five fold higher than the rate of comparable hospitals in the United States (0.9 per 1000 central line days) [20]. These infections independently increase hospital costs and length of stay, but have not generally been shown to independently increase mortality [21]. The cost of these infections is substantial, both in terms of morbidity and financial resources expended, ranging from $12,000 to $56,000 per infection [22–25].

In 2002, the National Quality Forum (NQF) endorsed a list of "Serious Reportable Events" and the term "Never Event," in reference to particularly shocking medical errors that should never occur was established [26]. In late 2008, following this trend, the Centers for Medicare & Medicaid Services (CMS) adjusted its payment policy regarding "preventable" hospital acquired infections, including central line-associated bloodstream infection (CLABSI) [27]. Under this policy, hospitals no longer receive payment for certain clinical complications deemed preventable, that occurred during the hospitalization and were not present at the time of admission. Never Events are also being publicly reported, with the goal of increasing responsibility and improving the quality of care. Health care facilities are accountable for correcting systematic problems that contributed to the event. Since the implementation of the CMS policy, many states and private insurers have adopted similar policies. Although the implication of the policy is that all infections are preventable, not all infections are preventable to the same degree [28]. Nonetheless, hospitals and practitioners are under increasing pressure to decrease their CLABSI rates down to zero [29].

As CRBSIs are believed to be due to bacterial colonization of the intravascular portion of the catheter that occurs during insertion, or the migration of microbes from the skin or catheter luers, guidelines for the placement and care of CVCs have been developed and are continuously updated [21]. These guidelines are intended to provide evidence-based recommendations for preventing intravascular CRBSI. Major areas of emphasis include (a) educating and training healthcare personnel who insert and maintain catheters; (b) using maximal sterile barrier precautions during central venous catheter insertion; (c) using a 0.5% chlorhexidine skin preparation with alcohol for antisepsis; and (d) avoiding routine replacement of central venous catheters as a strategy to prevent infection. Additionally, the introduction of checklists and central line "bundles," along with educational programs, have been shown to improve outcomes and increase adherence to best practices [30–32]. Unfortunately, despite the above preventive measures, achieving a CRBSI rate near zero has become very difficult. Therefore the Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA) with the Infectious Disease Society of America (IDSA) advocate as a category IA recommendation, that if the rate of infection is not decreasing despite adherence to other strategies, in patients whose catheter is expected to remain in place >5 days, based on several randomized controlled trials (RCTs) [33], the use of catheters coated with antiseptics or antibiotics for adults should be encouraged [21,34].

2. Non-eluting antimicrobial catheters

Prior to commencing the review of drug eluting antimicrobial vascular catheters, it is worth noting that non-eluting antimicrobial catheters have also been a subject of significant research. Non-eluting catheters might in theory have longer antimicrobial durabilities (by removing the limitation of exhausting available antimicrobial agents in eluting catheters through the process of elution) and less toxicity [35]. One approach to non-eluting antimicrobial catheters has been to prepare surfaces that repel or prevent attachment to microbes due to unfavorable surface chemistries. These include stealth surfaces such as fluoropolymer coatings, hydrogel coatings or biomimetic surface coatings [36–38]. These also include surface geometries that inhibit colonization by having unfavorable surface ridges and topologies [39]. In