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# Antimicrobial efficacy of the CLAVE® Connector using silver-saturated fluid path elements

## Background

Contamination of vascular access devices remain a substantial risk to patients in today's healthcare environment. The CDC estimates that there are a minimum of 250,000 incidents of Catheter Related Bloodstream Infections (CRBSI) annually in the United States.[1] Those patients that develop CRBSI may incur extended hospital stays and an increased risk of long term health effects and mortality. The treatment of CRBSI carries substantial cost to the Healthcare provider, placed at an average cost of $56,000 USD per incidence.[2] The Centers for Medicare Reimbursement (CMS) recently identified CRBSI (also defined as 'Vascular Access Device Related Infection'), as one of the listed preventable medical errors. CMS enacted a ruling in October of 2008 that will result in reimbursement for the treatment of CRBSI to cease in their fiscal year of 2009.

In a 1996 Special Communication, Pearson et al, identified two primary points of entry for bacteria in a central venous catheter; the extraluminal, or dermal entry point for the catheter, and the intraluminal, or hub of the catheter through which clinicians administer fluids and medications. This report went on to suggest that the hub is the more likely culprit for bacterial entry when the catheter dwell time exceeds ten days.[3] In 1993 the CLAVE NeedleFree Connector was developed to protect the hub and intraluminal pathway of catheters. The CLAVE is a microbiologically and mechanically closed connector which permits access to the catheter via use of a needlefree luer lock connection. The Antimicrobial CLAVE is a device that incorporates silver-saturated fluid path elements, housed in the traditional CLAVE design. The Antimicrobial CLAVE has been developed to reduce bacterial contamination on the swabbing surface and in the fluid path, which serves as the portal for entry to the catheter. This paper discusses the evolution of the needlefree connector market since the introduction of the CLAVE, how the unique design of the CLAVE can positively impact the prevention of bacterial colonization of the catheter, and lastly, the findings of investigations that demonstrate a greater than 4-log reduction in both gram negative and gram positive bacteria in an all new Antimicrobial CLAVE.

[1] Kluger DM, Maki DG. The relative risk of intravascular device related bloodstream infections in adults. Abstract of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. ASM 199:514.

[2] Dimick JB. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. *Arch Surg*, 2001; 136: 229-243.

[3] Pearson ML. Special Communication; Guideline for the prevention of intravascular device-related infections. Part I; Intravascular device-related infections: An Overview. *AJIC*, 1996; 24: 262-93.

## Introduction: The Evolution of NeedleFree

Central Venous Catheters (CVC) are widely used in healthcare today to facilitate the treatment of patients at inpatient hospital facilities, outpatient clinics and even in the patient's home.  While these catheters are often providing life-saving fluids and medications, they are also associated with serious infectious complications. In a recent study, Safdar and Maki found that preventative measures used at the catheter insertion site were largely unsuccessful at reducing CRBSI. Their conclusion supports that as much as 60% of CRBSI likely originates from the intraluminal pathway, or through the catheter hub.[4]

Protection of the catheter hub is solely accomplished by use of a capping device, most commonly known as a needlefree connector (NC), coupled with specific nursing protocols for handling that NC. The introduction of the first standalone NC that did not require needles or cannulas for IV access was the CLAVE Connector in 1993. Since then there have been as many as twenty different NCs introduced in the United States, including devices that exhibit positive pressure and most recently neutral NCs, such as the MicroCLAVE®.

The incentive for companies to develop NCs after the CLAVE, came with the onset of recommendations to use devices which aid in the prevention of needlestick injury, ultimately becoming a Federal OSHA Mandate in 2000, known as the Bloodborne Pathogens Standard. While use of these devices resulted in substantial gains towards the reduction of needlestick injury for healthcare workers, their designs did not incorporate robust infection control features which might protect the catheter from contamination and therefore, the patient against potential CRBSI.

In the late 90's reports started coming out about NCs causing an increase in CRBSI which were ultimately linked to capped NCs. Since then, the market has become almost exclusively capless, or what are now known as one-piece, swabable NCs. Swabable implies that if you use a 70% Isopropyl swab to wipe the injection site of an NC, bacteria will be removed such that the access point for the intraluminal pathway of a CVC is protected. The majority of today's market uses a one-piece swabable NC, with the CLAVE Connector being the largest stakeholder.

More recent reports linking swabable NCs with an increase in CRBSI started surfacing in about 2005. Since then, there have been a number of public statements and terms used in published works that implicate certain features such as 'Positive Pressure' or 'Mechanical Valve' as being associated with CRBSI. Yet, despite attempts by certain investigators and the promotional efforts of particular device manufacturers, no single design feature or broad classification can be used to indict a device as the culprit behind an increase in CRBSI. Each NC has a very unique design with complex componentry, functions and features that make up the finished device. It is therefore necessary to consider each device as a whole, and not as a single feature or classification. Further to this concept, it was recently recommended by Mermel and Marschall that NCs should  'involve fail-safe engineering advances aimed at further mitigation of the risk of infection in the complex hospital environment in which they are used'.[5]

In addition, no single feature including an antimicrobial additive, is capable of significantly reducing CRBSI in isolation of robust infection control policies and practices. The NC is only a component in the infection control bundle, which also includes such important practices as the care and maintenance of CVCs and the protocols associated with handling the NCs used to protect them.

## The CLAVE Connector

The CLAVE was developed in the early 90s as a Microbiologically and Mechanically Closed Connector. Its primary intent was to replace the popular pre-slit, blunt cannula systems of the time. Clincians were asking for a simplified system which didn't require multiple parts and pieces to use. The CLAVE design simply took the once external blunt cannula, and integrated it into the split septum, so one could access with any standard male luer. Further, while the CLAVE has undergone numerous incremental improvements over the last decade, the reversed, split-septum technology remains as the foundation of its design today.

The CLAVE is the most widely used and published NC on the market today. Various studies have shown that terminating the use of the CLAVE in favor of an alternative NCs has resulted in a temporal increase in CRBSI.[6,7] Results demonstrated that upon returning to the CLAVE, the facility was able to return to their baseline infection rate or better. Other studies have shown that the CLAVE will independently reduce catheter hub colonization on central venous catheters.[8] Catheter hub colonization is a recognized and acceptable surrogate endpoint for CRBSI development.[8] Additionally, a comparative in-vitro study found that the CLAVE was the least likely of nine other commercially available NCs to permit the transfer of bacteria into the fluid path.[9] The heart of the CLAVE design is the reversed, split-septum technology which provides the dedicated internal fluid path. This feature can be found in all variations of the CLAVE including the MicroCLAVE, the Y-CLAVE and the Antimicrobial CLAVE.

## The Antimicrobial CLAVE

The Antimicrobial CLAVE was developed to provide another tool in the fight against CRBSI. While the CLAVE reversed, split-septum technology remains the key factor for the prevention of catheter contamination, the antimicrobial additive provides additional benefit. This premise is based on the notion that if the injection site and fluid path, which are constantly exposed to manipulation, include a feature to combat bacterial contamination; then subsequent contamination of the intraluminal fluid path may be limited.

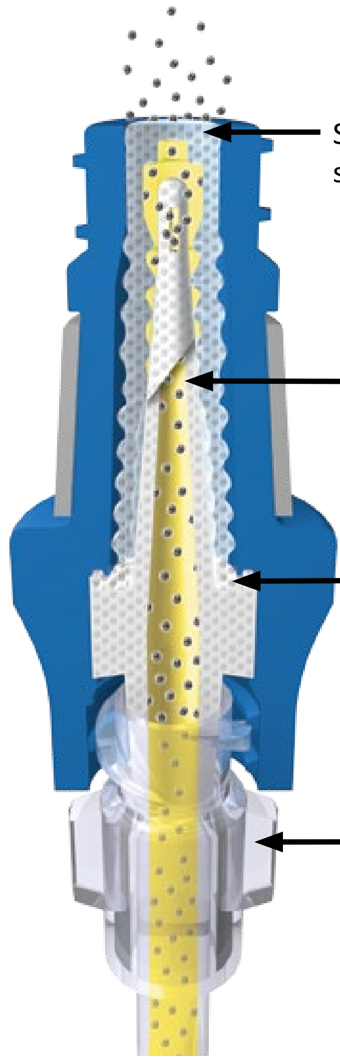
## Methods

An exhaustive development program was completed to determine the best agent with the greatest efficacy and least risk, as well as a method of manufacturing to ensure proper release and distribution of the agent in the clinically important components. This research determined that the following attributes are required:

- The agent must be widely accepted in clinical practice and have no measurable incidence of adverse reactions in patients.
- The agent must be integral to the componentry and not an add-on or coating that has the risk of wearing off.
- The agent must demonstrate clinical efficacy of greater than a 4-log kill factor for gram negative and gram positive bacteria.
- The agent's efficacy must be established for a 96-hour period, in accordance with CDC guidelines, when subjected to a simulated use model.

All components which have communication with the fluid path of the CLAVE were considered. This includes the internal blunt cannula and split septum. The housing is not in communication with the fluid path and therefore was determined to be outside the scope of consideration. Two proprietary formulations of ionic silver that are compatible with the unique CLAVE components were selected. These formulations were integrated into the materials of the split septum and the internal blunt cannula. This process of integration ensures complete saturation of the component and even distribution throughout, while also providing scratch resistant antimicrobial protection over the useful life of the device. This proprietary process allows for the proper 'elution' of the silver ions so that they can exit the component and enter the fluid path where any bacteria present will be exposed to the silver ions.

## Antimicrobial CLAVE: Internal Fluid Path Operation




In order to establish antimicrobial efficacy the FDA was consulted in regards to their draft publication, *Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents (2007).* It was determined that efficacy testing must be done on a finished device in a simulated use model. Four organisms were selected for study which represent commonly found bacteria in the healthcare environment. Efficacy was required for a period of 96-hours, as that is a minimum use life common to NCs. The four organisms used in this testing were:

*Staphylococcus aureus* (ATCC #6538)
*Staphylococcus epidermidis* (ATCC #35984)
*Klebsiella pneumoniae* (ATCC #4352)
*Pseudomonas aeruginosa* (ATCC #9027)

## Procedures

For a 96-hour period, the fluid path of each study device was inoculated with a 5-log concentration of the specified organism. Total bacterial counts were measured at four unique time points over the 96-hour period. This model was selected to demonstrate the durability and efficacy of the antimicrobial agent for the useful life of the device.

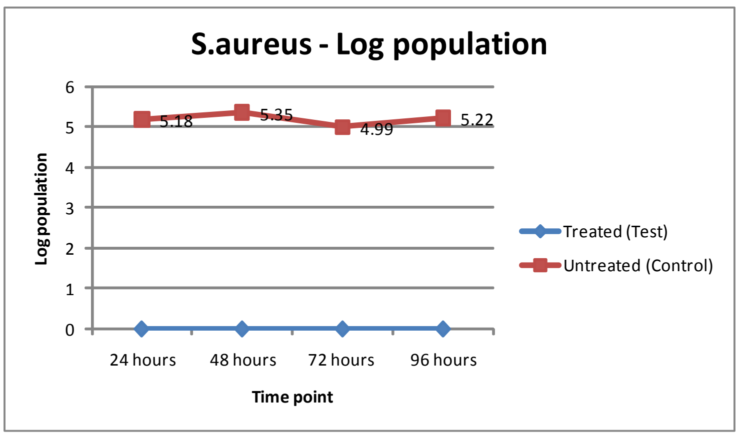
Antimicrobial efficacy was measured in terms of total log reduction in bacterial counts. Antimicrobial CLAVE test devices and standard CLAVE control devices were used for each bacterial model. The reduction was calculated by comparing the inoculated count, to the number of bacteria recovered from the study devices at various time points. The following charts show the antimicrobial efficacy of the Antimicrobial CLAVE as compared to the standard CLAVE, for each of the test microorganisms over time.

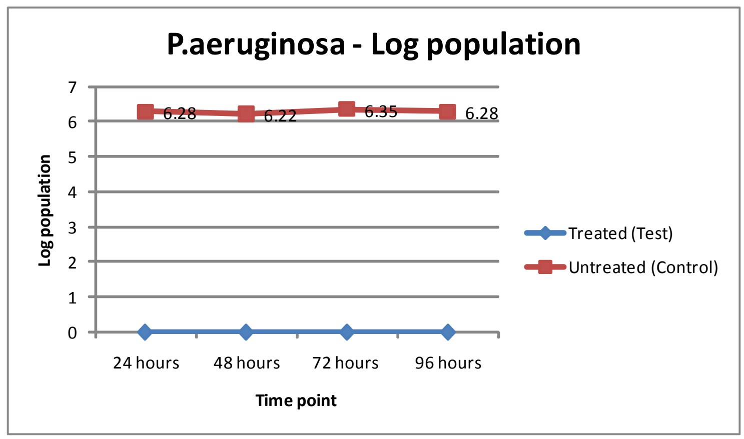
## Conclusions

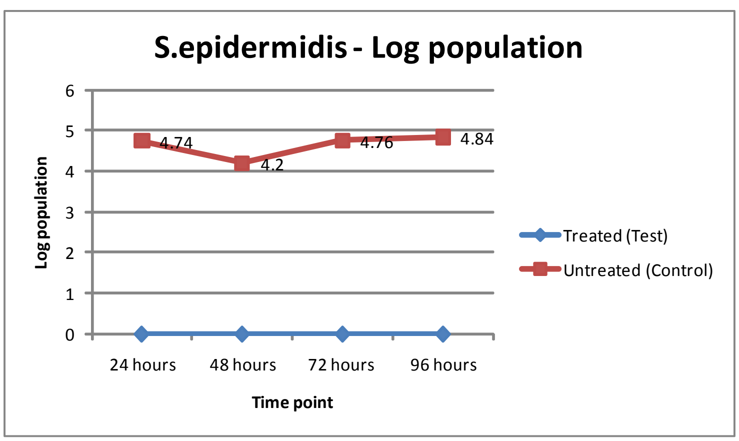
For all four bacterial strains, there was a significant reduction in the total bacteria counts on the Antimicrobial CLAVE devices for the simulated model of repeated contamination. The Antimicrobial CLAVE was capable of providing a minimum 4-log kill factor, or 99.99% efficacy, against all four strains of bacteria at various time points.

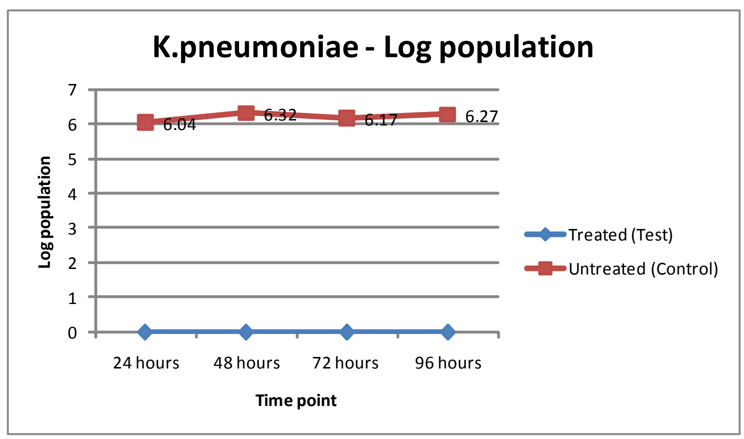
In all cases the Antimicrobial CLAVE was effective at significantly reducing the number of bacteria for an extended 96-hour use life. The proprietary ionic silver formulation and mode of integration into the finished device was proven to be effective in a worst case model.

The Antimicrobial CLAVE can limit bacterial colonization of the catheter, however the internal fluid path design and proper adhearance to an infection control bundle, remain important for limiting CRBSI.





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