Review of Central Venous Catheter-Related Infections and UV-C as a Potential Solution

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Abstract

Central venous catheters (CVCs) are indispensable medical devices that are utilized in clinical settings globally. Though CVCs provide life-saving functions, they are highly susceptible to bacterial colonization that eventually leads to catheter-related bloodstream infection (CRBSI). Existing strategies in hospitals such as standard sterilization protocols have not been effective in significantly lowering the rate of CRBSIs in the past decade. The use of ultraviolet (UV) light as a source of microbial disinfectant is historically known. In particular, UV-C light has been shown to effectively eradicate bacteria, including strains that are difficult to kill with antibiotics. Many studies show that multiple logs-reduction in bacterial colonization after UV-C exposure can be achieved.

With the emergence of light emitting diodes (LEDs) that deliver UV-C, the idea of applying UV-C energy to sterilize catheters has become more practical to implement due to their small size and low power consumption implement. In addition to its efficacy against bacteria, UV-C has also been shown to have little to no negative health effect on human tissues and minimal photochemical effect on infusates commonly delivered through CVCs. Altogether, UV-C light has a promising application in the prevention of CRBSIs that is not only effective but safe.

Keywords: sterilization, central venous catheters (CVC), ultraviolet light (UV), infections, catheter related bloodstream infection (CRBSI), hospital-acquired infection (HAI), bacteremia, sepsis, intensive care unit (ICU), hemodialysis, chemotherapy

Central venous catheters (CVCs) are indispensable medical devices that are utilized in clinical settings globally. They have diverse functions including delivering fluids or medications, drawing blood for testing, and monitoring central venous, pulmonary artery, and pulmonary capillary wedge pressures. CVCs are commonly used by cancer patients receiving chemotherapeutic drugs, end-stage renal disease patients requiring hemodialysis, and chronically ill patients needing long-term parenteral nutrition. 48% of patients in the intensive care unit (ICU) receive CVCs. CVCs remain in place for longer periods of time (weeks to 6 months) than other venous access devices like peripherally inserted central catheters (PICCs), which remain in place form days to week making them more prone to infections.1

Though CVCs provide life-saving functions, they are highly susceptible to bacterial colonization that eventually leads to biofilm formation. Approximately 64% of hospital-acquired infections (HAIs) globally are attributed to bacterial biofilm formation on medical devices and implants. In the U.S., 250,000 annual cases of bloodstream infections are associated with catheters, 90% of which are due to central venous catheters.2 The sheer magnitude of CRBSIs causes inevitable yet avoidable financial burdens on hospitals and additional health burdens on patients. Over 80,000 cases alone appeared in ICUs and were associated with increased lengths of hospital stays by up to 20 days and an additional $56,000 per case in cost of care.3 Collectively, CRBSIs in the United States are associated with an average mortality rate of 25% and total cost of $7 billion.2
Existing strategies, such as the central line bundle, have not been entirely effective in preventing CRBSIs. They have instead created a sterilization gap that must be closed in order to reduce mortality rates and costs associated with CRBSIs. This review discusses the origins of CRBSIs, its monetary and personal impact on patients and hospitals, and potential areas of improvement in the clinical setting.

The prevention and management of catheter-related bloodstream infections (CRBSIs) is a significant public health challenge that must be tackled by clinical settings worldwide. This review examines the strategy of using ultraviolet light as a possible method to fill in the catheter sterilization gap and reduce the risk of CRBSIs in catheterized patients. Firstly, a summary will be provided of bacterial infection pathology and factors also to CRBSIs, to establish a ground of certain criteria required in designing a solution to prevent CRBSIs. The paper will present feedback on how catheter sterilization may be improved in the future and the necessary steps that must be taken in order to bring the rate of CRBSIs down significantly. Next, the paper will introduce existing strategies that are being used in clinical settings to prevent CRBSIs and detail the advantages and disadvantages of each preventative solution. The paper will conclude with the introduction and assessment of ultraviolet energy as an effective and safe means to lower CRBSI rates.

A. Components of Central Venous Catheters

Central venous catheters (CVCs), also known as central catheters or central lines, are tubes that pass through the internal jugular vein in the chest, subclavian or axillary vein in the chest, or the femoral vein in the groin. CVCs can be tunneled or nontunneled. Non-tunneled CVCs are inserted directly into the vein, whereas tunneled CVCs are inserted from a separate entry/exit site on the skin that is not directly at the site of the vein.1 Implanting a tunneled CVC under the skin confers stability, and they are therefore preferred over longer term treatment options. However, despite these differences, the components of most catheters remain fairly standardized.

All CVCs have hubs, which are found at the end of the device. Hubs represent the junction point between the catheter and the external environment. External medical devices such as syringes attach at this point to administer fluids, drugs, or nutrition. In clinical settings, either a regular cap or an ethanol-impregnated cap is attached to the hub to provide a physical barrier between the catheter and external environment. Catheters also contain clamps that prevent the backflow of fluid. On CVCs, clamps are located outside the patient’s body on the portion of the catheter that is not tunneled. Additionally, CVCs can contain multiple lumens, or channels through which different fluids pass on their way in and out of the body. This allows a single CVC to serve multiple purposes.

To insert a CVC, the skin is cleaned and a local anesthetic is applied. To identify the location of the target vein, an ultrasound device is used. A hollow needle is advanced through the skin until blood is aspirated; this step is also used to distinguish venous blood from arterial blood. The line is then inserted; the blunt guidewire is first passed through the needle and the needle is subsequently removed. A dilator is used to open up the insertion pathway. The central line is next passed over the guidewire before the wire itself is removed. The lumens of the CVC are aspired to ensure their correct positioning within the vein and also flushed. A chest x-ray is conducted soon after surgery to ensure that the line is located in its correct position and pneumothorax has not occurred.1

CVCs have a recommended dwell time of 5 to 10 days.4 However, CVC dwell time ranges depending on various factors such as type of catheter use and hospital setting. One study found that CVC dwell time ranged from 3 to 98 days, with a mean of 28 days for hemodialysis patients.5

B. Sources of Catheter-Related Infections

To effectively prevent CRBSIs, it is important to gain a comprehensive understanding of how infections occur. As seen in Figure 1, there are multiple sources of CRBSIs. They include endogenous skin microflora from the patient, exogenous microflora from the healthcare personnel, contaminated infusates like fluids and medications, and contaminated disinfectants at the skin. Bacteria primarily gain access to the catheter via external migration from the skin or internal migration from the catheter hub. Contaminated infusates account for less than 1% of CRBSIs while bacteria from the patient’s skin or contaminated disinfectants entering from the skin exit site only pose a significant threat during the first week post-implantation until a fibrin sheath forms over the entry site.1 In an effort to prevent bacterial entry through the exit site, a Dacron cuff is placed close to the hub of the tunneled catheter. This cuff helps induce the formation of a fibrotic barrier that mechanically prevents bacterial entry into the patient’s bloodstream. Exit site infections are commonly associated with short-term catheters.

Colonization of hubs, with subsequent bacterial ingress into the catheter lumen, is considered the cause of approximately 54% of post-insertion infections.4 Another study evaluating long-term catheter-related infections found two-thirds of infection cases to be due to intraluminal sources, which includes the hub.7 Dwelling times of approximately up to 14 days may be primarily associated with extraluminal routes such as from the skin. However longer dwelling times are associated with intraluminal routes, especially the hub.5 The hub is a common site for infection because it is the primary connection between the catheter and other medical devices like syringes or needleless connectors. Therefore, it is frequently handled by healthcare personnel and is susceptible to bacteria from unsterilized hands, skin, or clothing. As seen in Figure 1, the hub is a significant target site for preventative strategies.

These human factors, while universal and commonplace, are often the original source for the contaminants that infect CVCs and lead to subsequent CRBSIs. For instance, proper hand decontamination and hygiene greatly minimizes the risk of contaminant transmission.6 Evaluation of an acute-care ward revealed that 84% of sampled clinical equipment such as syringe drivers, drug trolleys, and drip stands had levels of organic soil beyond the standard protocol.10 Only a small amount of Clostridium difficile (C. difficile) spores or...
**Staphylococcus aureus (S. aureus)** bacteria is required to cause contamination and infection. In regards to catheters specifically, compliance with proper catheter handling remains a problem. Even though overwhelming evidence recommends the discontinuation of changing CVCs at predetermined time intervals, the practice has still been adopted in approximately 15% of hospitals in the United States. In another study, 44.8% of CVCs were associated with breaches in proper catheter care such as the incorrect placement of catheter caps. Hygiene measures have been difficult to enforce in hospitals due to a variety of reasons. Recently, nurses have been given more responsibilities that were originally given to doctors, such as intravenous line insertion and catheter manipulation. Given the added burden of new specialized tasks, it is not difficult to imagine that nurses may inadvertently neglect to thoroughly clean the catheter. Moreover, studies have shown that scrubbing catheter hubs itself may be inadequate as a means of decontamination. Microorganisms may remain on internal CVC surfaces that cannot be reached by the disinfectants used. Other types of pathogens require longer exposure times to antimicrobial disinfectants to ensure proper sterilization.

The central line bundle, a strategy that utilizes techniques including hand hygiene, personal protective equipment, chlorhexidine skin antisepsis, and optimal catheter site selection, has proven difficult to enforce in healthcare settings. Achieving 100% compliance among physicians and nurses is not feasible and opens the door for potential infections in susceptible patients. A 2011 study by Furuya et al found that at least 95% compliance is needed to lower CRBSI rates, but only 38% of ICUs in the U.S. reported high enough compliance.

Thus, it is quite imperative that medical devices be designed with the possibility for human errors occurring in mind. Ideally, these devices should provide continuous and effective protection against contaminants. Infections from central lines are associated with increased mortality rates and costs. The relative risk for developing CRBSIs is 64 times greater in CVCs than in peripheral venous catheters. Therefore, there is a critical need to reduce this exceptional risk, especially in places like intensive care units, where CVCs are often placed to deliver drugs and/or fluids and to access the bloodstream.
C. Pathogenesis of CRBSIs

It has been shown that indwelling vascular catheters and can become contaminated with microflora within 24 hours of implantation. If bacteria do make their way into the lumen, the solid-liquid interface of the catheter inside vasculature is an ideal environment for their growth. Bacteria can adhere to the catheter surface, forming what is known as biofilm. This refers to the sessile lifestyle that aggregates of bacteria or other microbial cells that can adapt to once they are irreversibly attached to a surface. Biofilm is characterized by surface-attached microbes encased in a matrix of extracellular polymeric substance (EPS), a structure comprised of mostly polysaccharides and other organic compounds that maintain the vitality of biofilms.15

Biofilm on catheter surfaces often lead to CRBSI and is notoriously known for its difficulty in treating. It is therefore imperative to understand the factors and stages of biofilm formation to target or prevent biofilm from causing infection.

C.1. Bacterial Movement and Entry

The primary source of CRBSIs is external microbes that gain access into the bloodstream through the catheter hub migrating towards the venous end of the catheter, which is rich in nutrients and an attractive environment for bacteria. Bacteria migration rates depend on factors such as surface material property and bacterial strain.16 Wilkins et al. found that *Escherichia coli* (*E. coli*) had high motile tendency and one of the highest migration rates among the bacteria species studied.16 Wolfe found that wild-type *E. coli* migrates at 0.8 cm/h in semi-solid agar after a 7 hour colonization period. The migration rate is slower on harder surface materials.17 On glass surfaces, the observed *E. coli* migration rate was similar to previous studies at 0.9 cm/h, but required up to 18 hours of colonization period before migration occurred. In addition, the bacteria generation period is approximately 20 minutes for *E. coli*.18

Table 1 presents migrational behavior of different bacterial strains on polyethylene and polypropylene surfaces. Due to the fact that polyethylene is a commonly used material for the cannula section of CVCSs, the table gives a relatively accurate indication of migration potential of bacteria from the hub to the venous end of CVCSs. Similar to Song’s study, Wilkins also noted negligible movement of *Staphylococcus aureus* on both polyethylene and polypropylene surfaces.16

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Polyethylene</th>
<th>Polypropylene</th>
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</thead>
<tbody>
<tr>
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<td>2.83</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>0.83</td>
<td>0.33</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>0.67</td>
<td>0.83</td>
</tr>
<tr>
<td><em>Branhamella catarrhalis</em></td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Initially, the microbial cells are transported to the conditioning layer by physical forces or bacterial appendages. The adhesion of bacteria depends on local environmental factors such as available energy, surface functionality, bacterial orientation, temperature, and pressure condition. A fraction of the microbial cells reaching the surface are reversibly absorbed through by van der Waals forces, steric interactions, and electrostatic interaction, collectively known as the DVLO (Derjaguin, Verwey, Landau and Overbeek) forces. If the repulsive forces are greater than the attractive forces, the bacteria will detach from the surface. Given that the activation energy for desorption of bacteria is low, desorption is favorable and likely to occur. The adsorbed microbial cells secrete high molecular weight natural polymers, known as the extracellular polymeric substances, into the environment. The extracellular polymeric substances then aggregate due to hydrogen bonding to form a highly hydrated viscoelastic gel matrix.19 To deal with environmental stress, the matrix responds by exhibiting elastic tension due to the polymeric entanglement, entropic, and weak hydrogen bonding forces; viscous damping caused by polymeric friction and hydrogen bond breakage; and polymers alignment in shear direction.20

Over time, a number of reversibly adsorbed cells remained intact and become irreversibly adsorbed. The physical appendages of bacteria overcome the repulsive forces of the conditioning layer. Subsequently, the appendages interact with the bulk lattice of the conditioning layer to facilitate chemical reactions such as oxidation, hydration, and bacteria-surface bond strengthening.19 After a period of growth and aggregation, biofilm undergoes a period of maturation and sporulation with the mature biofilm may detach and disperse, colonizing in other areas. Eventually the death phase occurs, during which the breakdown of biofilm is observed. The polysaccharides that hold the biofilms together are broken down by the enzymes produced by the microbial cells. Simultaneously, the operons coding for flagella, an apparatus used for motility, are up-regulated, and the genes coding for porins are down-regulated causing a dispersion of the indwelling bacteria. This would then conclude the genetic cycle for biofilm adhesion and cohesion.20

C.2 Biofilm Development and Dispersion

Biofilm grows on a conditioning layer composed of either inorganic or organic particles that modify the underlying substrate to facilitate bacterial accessibility. The conditioning layer interacts with the substrate and provides anchorage and nutrients, thus promoting bacterial growth.19

C.3. Treating Biofilm: Challenges and Complications

Biofilm is particularly troublesome to treat because it renders the patient’s immune response impenetrable and it can
become resistant to antibiotics. This stems from increased resistance markers found in biofilms and reduced diffusion due to the bulk EPS. In addition, the metal ions that gather at biofilm sites and low pH can contribute to antibiotic inactivation.15

Though the exact mechanisms of antibiotic resistance within biofilms remain unknown, common hypotheses are that biofilms may slow the distribution of antibiotics due to charge interaction and matrix viscosity.19 As a result, it becomes more difficult to remove biofilms using simple antimicrobial strategies. Physical forces must be applied to remove the biofilm, which creates an additional risk of biofilm remnants traveling through the bloodstream and lodging elsewhere in the body. This can lead to downstream health consequences.

Several concerns have been raised about the possibility of fluid flow through the catheter applying enough shear stress on biofilm to disrupt it. Detachment of biofilm from the catheter surface and subsequent release of planktonic microbes downstream the catheter is a critical issue that can lead to the spread of infection.17

The mechanism of bacterial attachment depends on protein interactions between bacterial receptors and ligand proteins on the attachment surface through electrostatic, van der Waals, and hydrophobic interactions. At shear stresses of 1 - 60 dynes/cm², the detachment rate is approximately 0.1% of bacterial colony per second for S. aureus on a collagen surface.22 In another study on Pseudomonas aeruginosa (P. aeruginosa), shear stress in similar magnitudes reduces the number of attachments events, but increases the adhesion time to surface and therefore creates higher infection potency.23 Stewart explains that mechanical biofilm failure, that is a failure to adhere to a surface, results from applying a shear stress that is greater than the biofilm failure strength. Biofilm failure strengths can be as high as 104 to 105 Pa (for S. epidermidis) and as low as 101 Pa (for a combination of various bacteria). By comparison, catheters apply a shear stress of approximately 101 to 102 Pa on biofilm.24

Further studies on the effect of shear stress due to fluid flow, bacterial movement, and resulting infection is necessary to establish a better understanding. Nevertheless, it is clear that in preventing CRBSIs, the detachment of biofilm or its colonies from the catheter surface either through natural biofilm stage progression or applied shear stress (due to fluid injection) must not occur. In the worst case scenario where biofilm begins to form on the catheter surface, a fluid injection through the catheter must not dislodge the biofilm and send the indwelling bacteria downstream toward the venous end of the catheter. This characteristic is important in designing a catheter sterilization method. It provides evidence that sterilization applied to local regions of the catheter is sufficient to prevent CRBSIs. Biofilm before maturation is relatively stationary and thus a small but focused sterilization zone at the site of the biofilm formation is adequate.

To combat biofilms, the primary strategy physicians use is to remove and replace the infected catheter entirely. This, however, creates financial and personal stresses to the patient and delays treatment for the patient’s pre-existing condition. The time between removal and reinsertion of a CVC may be greater than four days.25 In addition, the procedure of removing CVCs may lead to complications such as air embolism, catheter fracture, and hemorrhage.26 Such complications may be associated with a 57% mortality rate.27 Removal followed by reinsertion of CVCs in a different vascular site also may not be possible. Septic patients such as cancer patients may not have an additional vascular site available for reinsertion.28 Scientists have also questioned the efficacy of catheter removal as a way of addressing catheter-related infections. In one study, 41.5% of patients that underwent CVC re-insertion were found to have recurrent catheter-related infections.29

Following the formation of biofilm on the catheter surface and bacterial migration into the patient’s body, bacteremia, or bacterial presence in the bloodstream, will manifest. In this early stage, the patient will not exhibit any noticeable symptoms. However, bacteremia will occasionally lead to sepsis. Sepsis is a serious, systemic response to the bacteria in the bloodstream that triggers a host of symptoms like fever, weakness, a rapid heart rate, and an increased number of white blood cells.30 Sepsis decreases the host inflammatory response, potentially limiting the viability of the immune system to counteract the infection.31 Sepsis can also result in tissue hypoperfusion or organ dysfunction (i.e., severe sepsis) and in some cases septic shock, a state of dangerously low blood pressure causing end-organ damage and death.30

Given the severe complications and risks associated with biofilm and its removal, it is therefore critical to target and eliminate bacteria before they form these biofilm complexes and become resistant to common clinical strategies.

D. Diagnosis of CRBSIs

Common clinical signs of CRBSIs are inflammation or pus generation at the catheter insertion site. Other symptoms include fever, chills, and hypotension with no other apparent source of infection but the catheter.4 Relying on these clinical observations alone is not a specific or sensitive way to diagnose a CRBSI. In a study of 1353 CVCs conducted in a university hospital, 73% of the 11 patients with CRBSI had no signs of local inflammation; however, purulence at the insertion site had a higher positive predictive value, so removal of device was recommended. In addition, blood cultures may be drawn from the patient’s peripheral sites and then compared with blood drawn from the infected catheter. If the catheter cultures are positive and the peripheral cultures are negative, a line infection is suspected. This method for verifying catheter infection is inaccurate, though, having a high false-positive rate because bacteria from other sources can also result in a positive test result.4

The diagnosis of CRBSIs is difficult and often relies on clinical suspicion. Therefore, removal and replacement of the CVC is usually the most utilized option.

E. Current Strategies to Prevent CRBSIs

In the U.S., the main measure for preventing CRBSIs in the clinical setting is the central line bundle. Developed by the Institute for Healthcare Improvement (IHI), this series of
evidence-based practices is believed to reduce rates of CRBSIs. It includes hand hygiene, full barrier precautions and personal protective equipment, chlorhexidine skin antisepsis, optimal catheter selection, and optimal catheter site selection. The central line bundle, while commendable in its intentions, has proven difficult to enforce in healthcare settings.32 This is primarily because healthcare personnel in ICUs across the U.S. are not achieving a high enough compliance needed to lower infections rates.13

Gap analysis has identified inadequate catheter maintenance as a significant cause of CRBSIs. Researchers found that caregivers did not consistently scrub the hub with alcohol for the required 15 seconds before accessing the line.32 Nevertheless, when experimenters tried to educate nurses on how to perform the established protocols to scrub the catheter hubs, the infection rate did not improve.

One step in the protocol is allowing the chlorhexidine to fully dry before inserting the line. If healthcare workers do not comply with this procedure, then optimal disinfection will not be achieved. Additionally, chlorhexidine, while it has been shown to be effective against gram-positive organisms such as staphylococci, may not be as effective against gram-negative bacilli and fungi such as the Candida species.33 This can also serve as a barrier against achieving complete disinfection through the IHI bundle strategy.

Central venous catheters with needleless connectors are particularly difficult to clean. Hospital standard protocols of cleaning needleless connectors with 70% alcohol may be ineffective if the connectors are heavily contaminated. One study demonstrated that when needleless catheter connectors heavily contaminated with Enterococcus faecalis were subjected to 70% alcohol cleaning, an alarming 67% of connectors transmitted bacteria (25,000 to 442,000 colony forming units) across the membrane of the connector.34

Material scientists and physicians have also considered modifying the materials that make up the body of catheters. By accounting for issues like biocompatibility, biofunctionality, and chemical inertness, they have designed new device surfaces that prevent bacterial adhesion. Nonfouling biomaterials help minimize protein adsorption and microbial adhesion. These approaches combine at least one of the following two mechanisms: resistance to adhesion of bio-contaminants and degradation of bio-contaminants. Strategies aimed at preventing adhesion include using the addition of PEG or oligo(ethylene glycol) groups and smart or stimuli-responsive materials. However, the disadvantage of these anti-adhesive catheter materials is their inability to eradicate bacteria.10

Strategies aimed at degrading bio-contaminants have utilized either a released-based approach or a non-released-based approach; in the released-based approach, scientists have used silver, antibiotics or antiseptics, and nitric oxide. In the non-released-based approach, scientists have used surfaces functionalized with polycations or antimicrobial peptides (AMPs), photoactive surfaces, and coatings containing enzymes that degrade bacterial strains.6

Although antimicrobial-coated catheters, such as those made from silver, heparin, and antibiotics like chlorhexidine, were made in an effort to limit microbial growth, they are associated with several disadvantages. A 2009 review found that antimicrobial coatings did not significantly reduce bloodstream or exit site infections, nor reduce all-cause mortality rates.35 Another demonstrated a high colonization rate for antimicrobial coating catheters; 40 out of 101 catheters were colonized and 12 catheter-related infections were identified, six of which were caused by Gram-positive organisms, one fungal, and five Gram-negative organisms.36 Alternatively, another study found that antimicrobial coatings had limited microbicidal effects, lower than a 2-log pathogen reduction. Interestingly, these values were obtained from tests on pathogens that exclude notoriously antimicrobial-resistant C. difficile spores and norovirus.37 Antimicrobial coatings have also been shown to be toxic and cause allergies.37

Modified catheter materials have other limitations. They are associated with increased cost and necessitate replacement of existing catheters in hospitals, which must be accounted for when conducting a cost-benefits analysis. Additionally, antimicrobial coatings can lead to increased bacterial resistance, which is an already rampant problem in clinical settings across the world.38 Finally, coatings tend to not last for the lifetime of the product and wear off or peel.39

In vascular catheters, Staphylococcus species that form biofilms were shown to acquire resistance against antibiotics like methicillin and vancomycin.40 In another case, researchers discovered that triclosan-coated antifungal catheters led to bacterial resistance. It was found that 12.5% of Staphylococcus epidermidis isolates collected from blood cultures of patients had tolerance to triclosan. When non-tolerant isolates were passaged in the presence of triclosan in vitro, tolerance also developed.41 Silver-coated catheters lead to bacterial tolerance and resistance, requiring the addition of diffusible microbes such as rifampin that can also lead to resistance.10

To minimize contamination of catheter access ports, hospitals and healthcare settings are utilizing novel protective barriers like the needleless connector system and disinfecting port protectors. The needleless connector system was created to decrease hub manipulation by healthcare workers and lower contamination rates. This device allows fluid to enter via a straight path after which a silicone seal becomes activated to close the path and limit blood exposure. A research study conducted by DaVita Clinical Research found that the needleless connector coating catheters; 40 out of 101 catheters were colonized and 12 catheter-related infections were identified, six of which were caused by Gram-positive organisms, one fungal, and five Gram-negative organisms. Another study found that antimicrobial coatings had limited microbicidal effects, lower than a 2-log pathogen reduction. Interestingly, these values were obtained from tests on pathogens that exclude notoriously antimicrobial-resistant C. difficile spores and norovirus. Antimicrobial coatings have also been shown to be toxic and cause allergies.

The disinfecting port protector is a plastic threaded device that attaches directly to the catheter port and holds a solution of 70% isopropyl alcohol. This device sterilizes the hub for a certain period of time and act as a short-term barrier, which is...
at most 1 week, against invading bacteria when the catheter is not in use. Each time the catheter is accessed, this device must be replaced. Research studies have found that the use of ethanol-impregnated caps may reduce infection rates. A study conducted in a tertiary referral trauma center found that the rates of catheter-related bloodstream infections decreased from 1.5±0.37 to 0.88±0.62 over a 12-month period after device implantation.\(^\text{41}\)

However, the use of alcohols such as ethanol and isopropyl alcohol has also been linked to increased biofilm production in common pathogens like \textit{S. aureus}\(^\text{34}\). After exposing this strain to clinically relevant concentrations of alcohol (i.e. >40%), biofilm production was found to have increased.\(^\text{44}\) This is a significant finding because alcohols are widely used in clinical settings as a cutaneous disinfectant and in catheter lock solutions as a means to prevent CRBSIs. If alcohols are instead contributing to the problem, this heightens the need to find an alternative solution. Moreover, the ethanol-impregnated cap only offers discontinuous sterilization; the cap must be removed when catheter access is required, leaving the port largely unprotected against bacteria from the external environment when the catheter is being used. Though healthcare personnel are encouraged to wipe the port with an alcohol wipe prior to catheter use, this additional sterilization is often found to be inadequate. Wright et al. found that ethanol caps cost hospitals an average of $2.07 per catheterized patient per day; this amounts to $755 per catheterized-patient year.\(^\text{46}\)

Another strategy being implemented in clinical settings is prophylactic intraluminal antimicrobial lock (AML) therapies. AML consists of instilling a disinfectant solution into the intraluminal section of a catheter between treatments to sterilize the interior surface area of the catheter. The use of this strategy has been controversial due to the emergence of antibiotic-resistant strains of bacteria. A study conducted by Landry et al found that although AML reduced CRBSIs by 95% in more than 1,400 patients, strains of gentamicin-resistant organisms emerged after 4 years of AML use.\(^\text{49}\) Another study that utilized taurolidine, an antimicrobial agent that affects bacterial cell walls, found that though this AML strategy reduced CRBSIs, taurolidine also increased the need for thrombolytic therapy. Specifically, heparin had to be administered as well.\(^\text{45}\) Finally, AML has not been shown to effectively eradicate bacteria found in biofilms, which are notoriously ten-to 1,000-fold more resistant to antibiotics.\(^\text{48}\)

### F. Use of UV-C as a Disinfectant

The potential application of UV-C as a sterilization method in catheters will be explored. The efficacy of germicidal properties of UV-C were evaluated in relevant test conditions. These included bacterial strains commonly found in hospitals and catheters, such as \textit{S. aureus}. Because UV-C applied to catheters is a relatively novel concept, studies were chosen in which UV-C light was applied to pathogens on surfaces, as opposed to pathogens in other mediums such as air, in order to most accurately draw conclusions about UV-C disinfection for catheter surfaces.

Table 2 below gives a brief summary of UV-C potency in bacterial disinfection in water medium. UV-C sterilization of microorganisms in water medium is a poor approximation of the dosage required for surface sterilization under direct UV light due to relatively lower transmission of ultraviolet light through water medium, but nonetheless demonstrates a useful benchmark of UV sterilization dosage for transparent liquid mediums.

#### F.1 Historical Background

The use of UV to disinfect microbes has a long history that dates back to 1878 when germicidal effects of UV were first discovered,\(^\text{49}\) followed by a Nobel prize-winning invention of UV therapy to treat lupus vulgaris in 1903.\(^\text{50}\) UV has been used as a sterilization means for numerous applications, ranging from inactivation of contaminants in food\(^\text{51, 52}\) and water purification\(^\text{53, 54}\) to air disinfection in hospital rooms\(^\text{39}\) and maintaining sterility in laboratory biosafety cabinets.\(^\text{56}\)

In recent years, the hospital setting has become a notorious breeding ground for some of the most virulent strains of

<p>| Table 2. A summary of UV-C sterilization studies. Bacteria are submerged in water medium, and are exposed to different dosages of UV-C. The rightmost column shows the percent of bacterial inactivation as a result of UV-C exposure on the bacterial strain. The data is compiled by Song et al.(^\text{54}) in Application of ultraviolet light-emitting diodes (UV-LEDs) for water disinfection: A review. |</p>
<table>
<thead>
<tr>
<th>UVC wavelength (nm)</th>
<th>Bacterial strain</th>
<th>UV-C dosage (mJ/cm2)</th>
<th>% inactivation</th>
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</thead>
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<tr>
<td>250</td>
<td>Bacillus subtilis</td>
<td>59.2</td>
<td>99.90%</td>
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<tr>
<td>254</td>
<td>Mesophilic bacteria</td>
<td>0.73</td>
<td>84.15%</td>
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<td>E. coli</td>
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</table>
antibiotic-resistant bacteria. They can remain on hospital room surfaces long after the infected patient has left and incoming patients can become readily exposed to these microbes. Common vegetative strains include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Acinetobacter* spp. These types of bacteria can remain on surfaces for days or weeks. *C. difficile* spores can also persist on surfaces for up to 5 months.67

In an effort to combat this environmental contamination, hospital administrators have been applying ultraviolet (UV) light to sterilize the hospital environment. The World Health Organization (WHO) Global Solar UV Index (UVI) divides UV into three bands based on wavelength: the A band is 315-400 nm, B band is 280-315 nm, and C band is 100-280 nm. C band or UV-C light is considered to be in the germicidal range because of its ability to damage DNA and RNA of microbes.36, 37 The specific mechanism of UV-C sterilization is that it induces the formation of pyrimidine dimers from thymine and cytosine. These dimers can then cause breaks in microbial DNA that make genetic reproduction impossible.58 Consequently, microorganisms are destroyed or no longer able to grow or reproduce.58 The historical use of UV-C in hospitals makes it an appealing choice when tackling the problem of CRBSIs. UV-C has also been recognized as being less carcinogenic than UV-B. Moreover, the use of UV-C has been deemed favorable when the target microorganisms are capable of antibiotic resistance.61

In order to achieve a 4 log inactivation (99.99%) of bacteria, the U.S. Food and Drug Administration (FDA) suggests a dosage of 40 mJ/cm² UV-C light to be exposed to a surface. Table 3 below shows the UV-C exposure necessary for inactivation of several common strains of bacteria involved in CRBSIs, as required for the U.S. FDA.61

Many studies have shown that UV-C can target a wide array of microorganisms such as MRSA, VRE, *Acinetobacter*, and *C. difficile* in both non-clinical, experimental conditions and real-world clinical settings.62 In clinical settings, an automated UV-C emitter can reduce the bioburden of these bacteria. An Ultraviolet Area Sterilizer device has been shown to greatly reduce the spore viability of *Bacillus atrophaeus* and *Bacillus anthracis* on nonreflective surfaces a period.63 Other products that utilize UV-C sterilization in clinical settings include a pulsed-xenon device for patient rooms sterilization and UV-C reflective paint coatings to sterilize entire hospital room surfaces.64

### Table 3. Necessary UV-C exposure needed for 4-log inactivation of common strains of bacteria involved in CRBSIs. This data is according to the FDA.

<table>
<thead>
<tr>
<th>Organism Causing CRBSI</th>
<th>% of Total CRBSI</th>
<th>UV-C Exposure (mJ/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococcus</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>12.4</td>
<td>5-11</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5.5</td>
<td>11</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>4.9</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>8.9</td>
<td>n/a</td>
</tr>
</tbody>
</table>

In a study conducted by Lin et al, UV-C was found to be effective against bacteria on catheters. Catheters primarily colonized with coagulase-negative staphylococci (60%) and *S. aureus* (33%) were treated with UV-C delivered by fiber optics at a range of doses of 40 to 1,300 mJ/cm². Results demonstrated a statistically significant reduction in viable bacteria of greater than 99.5% compared to the no treatment group. A 100% eradication was achieved in 57% of the samples.65

UV-C has also been shown to successfully eradicate bacteria on surfaces in laboratory settings. One study investigated the efficacy of UV-C using an automated handheld device with a radiant dose of 100 mJ/cm² at 185-230 nm. Significant reductions were found in *C. difficile*, MRSA, and VRE contamination by 4.4 log₁₀ colony forming unit (CFU), 5.4 log₁₀ CFU and 6.9 log₁₀ CFU, respectively on inoculated plastic Petri dishes. At a lower radiant dose of 30 mJ/cm², more than a 3 log₁₀ CFU reduction was obtained for MRSA and VRE. However, eradication of *C. difficile* was less than a 3 log reduction.66 In a separate study, an automated room decontamination device that emits UV-C was analyzed. A UV-C dose of 22 mJ/cm² was delivered by the device on laboratory bench tops inoculated with various pathogens and strains. Average log₁₀ CFU/cm² reductions were found to be greater than 2-3 for *C. difficile* spores and MRSA and greater than 3 to 4 for VRE.67

UV-C was also found to be effective at disinfecting portable medical equipment and hospital rooms. At 100 mJ/cm², UV-C emitted resulted in a 3.2 log₁₀ CFU reduction of *C. difficile* spores on surfaces at four different healthcare sites: the call light, bedside table, telephone and bed rail.68 A different UV-C emitting device delivering a UV-C dose of 22 mJ/cm² was able to reduce *C. difficile* cultures by 80% at these same four sites. The device also reduced MRSA and VRE cultures by 93%. Moreover, in comparison to routine hospital cleaning, the edges of bedside tables, which are frequently touched and not readily accessible to cleaning, experienced a reduction of MRSA from 18% to 0% after UV-C exposure.69

The feasibility of implementing ultraviolet environmental disinfection (UVD) in high-risk areas was evaluated in an academic medical center. A pulsed xenon UVD machine emitting UV-C was placed in various high-risk areas such as patient rooms and bathrooms. The duration of UV light was determined based on room size and UVD machine position. UVD corresponded to a statistically significant decrease in infection from 2.67 cases to 2.14 cases per 1,000 patient-days, or a 20% reduction, of hospital-acquired multiple-drug-resistant organisms and *C. difficile*.80

A review article by Dai et al. found promising evidence that UV-C may be useful in treating local infections.81 For example, 100% eradication of Gram-positive cocci commonly found in wound infections was achieved upon delivering a minimum of 5 seconds of UV-C at 5 mW/cm², in other words a dose of 25 mJ/cm².82 Researchers also showed different UV-C doses for total 10 minutes on surgical wound sites after total joint arthroplasty surgeries. They found that 0.1 mW/cm² (dose of 60 mJ/cm²) and 0.3 mW/cm² (dose of 180 mJ/cm²) reduced mean bacterial CFUs by 87% and 92%, respectively, compared to the no
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S. aureus after exposure durations of greater than 5 seconds.74 A 7- to 8-log CFU/mL pulse was delivered to bacteria in a suspension of agar-seeded Bacillus globigii. Another study evaluated the ability of UV-C to disinfect different strains of bacteria has highlighted its well-established efficacy as a disinfectant. However, evidence has indicated that UV-C may have a reduced penetration ability through organic matters and opaque materials.72

F.2 Pulsed Vs. Continuous UV-C

The UV-C delivery method may be important in optimizing bactericidal efficacy. Research suggests delivering UV-C in short energy bursts may be superior to continuous irradiance. Umezawa et al. compared the sterilization efficacy of pulsed and continuous UV-C and found pulsed UV-C to be more effective. A handheld device delivering pulses of UV-C every 1/30,000 seconds with an energy output of 3.17 J per flash. Continuous UV-C was applied using a handheld wand with 250 µW/cm². A duration of 5 seconds of pulsed UV-C at a 5 cm distance was able to reduce bacterial growth by 2 log for all tested bacterial species commonly found in hospitals, such as P. aeruginosa, E. coli, S. aureus, Acinetobacter baumannii, amikacin and ciprofloxacin-resistant A. baumannii, multidrug-resistant Pseudomonas aeruginosa (MDPR), MRSA, and Bacillus cereus. In contrast, identical conditions utilizing continuous UV-C radiation were only sufficient in obtaining a 2 log reduction for bacterial strains: P. aeruginosa and MDPR. Evaluated in clinical settings, pulsed UV-C radiation also decreased the amount of bacteria present on the surfaces of various apparatuses in the ICU and emergency ward. In addition, nurses halved the time spent decontaminating surfaces when using pulsed UV-C instead of ethanol wipes.73

A separate investigation tested the efficacy of pulsed UV light on the inactivation of S. aureus. A dose of 5.6 J/cm² per pulse was delivered to bacteria in a suspension of agar-seeded for a total duration of up to 30 seconds. A 7- to 8-log CFU/mL reduction was observed for both suspended and agar-seeded of S. aureus after exposure durations of greater than 5 seconds.74

Another study evaluated the ability of UV-C to disinfect Bacillus globigii using either pulsed or continuous radiation. Continuous UV-C achieved a 6 log CFU reduction faster than pulsed UV-C, requiring a total exposure time of 840 seconds as opposed to 5,000 seconds. However, pulsed UV-C only required 365 J/m² to attain 6 log inactivation while continuous UV required 665 J/m².75

F.3 LEDs as a Source of UV-C Irradiation

Light Emitting Diodes (LEDs) recently emerged as a new source of UV light in the past decade and have been met with great interest as a promising technology in the sterilization field.74 UV LEDs offer advantages over the traditional UV mercury lamps, including their faster startup time due to the elimination of a warm-up time, small size, durability, relatively low power requirements and environmental friendliness with the absence of mercury.76 The features make LEDs an attractive choice for inclusion in minimally-invasive sterilization devices applied in clinical settings. They meet important criteria such as patient comfort and performance reliability. LEDs are made from semiconductors. The recombination of electrons and holes at the p-n junction of the LED semiconductor leads to emission of UV light.54 Peak wavelengths of UV LEDs are determined by the semiconducting materials such as gallium nitride, aluminium gallium nitride and aluminum nitride.54

UV-C LEDs appear to have comparable, if not better, germicidal effects against bacteria compared to UV-C lamps. Samples of pathogens (S. aureus, Klebsiella pneumoniae, and Enterococcus faecium) commonly found in surgical site infections were exposed to UV-C with either a mercury lamp or LED at doses of 15, 30, or 40 mJ/cm². At the same the UV-C doses, no significant differences were found in pathogen survival rates between the two UV-C sources.77 Nevertheless, it is important to note that although both sources irradiated UV-C light, the wavelengths emitted were slightly different (254 nm and 270 nm for the lamp and LED, respectively). Alternatively, other studies found evidence that UV LEDs may even be more effective at bacterial inactivation than UV lamps. Bacteria (E. coli, Salmonella enterica serovar Typhimurium, and Listeria monocytogenes) were exposed to UV-C from LEDs or lamps, both at intensities of approximately 4 µW/cm². A UV-C range of doses from 0.1 to 0.7 mJ/cm² using LEDs resulted in inactivation rates that were significantly higher than those from UV lamps. For example at 266 nm, a dose of 0.7 mJ/cm² reduced bacteria counts by at least a 5.3 log reduction with LEDs but at most a 3.06 log reductions with lamps.61

Dean et al. used a device with a UV-C LED to treat corneal microbial infections. A wavelength of 265 nm and intensity of 1.93 mW/cm² was emitted on four bacterial strains of S. aureus, E. coli, P. aeruginosa and Streptococcus pyogenes in agar plates. A 100% growth inhibition of all bacterial strains after a minimum of 1 second exposure time was found, corresponding to a UV-C dose of 1.93 mJ/cm².78 Another study examined the efficacy of UV-C from LEDs in decontaminating stethoscopes. The LEDs had a peak wavelength at 275 nm and average power of 2.4 mW. Prior to testing, two UV-C LEDs were subjected to 1668 five-minute cycles, simulating prolonged usage. Afterwards, a stethoscope was used on a volunteer followed by 5 minutes of UV-C irradiation from the LEDs at a distance of 11 to 23 mm. This resulted in a statistically significant reduction from 104 CFUs to 15 CFUs when one LED was used and to 12 CFUs when the two LEDs were used. Similarly, when evaluated in a laboratory setting, there were statistically significant bacterial reductions on stethoscope membranes inoculated with S. aureus and E. coli.79

Overall, the accumulated results from these studies demonstrate that pulsed UV-C from LEDs is an effective means of disinfection.
G. Health Concerns

The high energy of ultraviolet light raises numerous concerns on human health. Studies show that UV-C may affect certain parts of the body more than others.

As briefly alluded to in the previous section, UV-C has potential applications in treating wound infections by promoting wound healing without bringing harm to mammalian cells.22 UV-C light has been found to promote wound healing in various ways such as stimulating wound contractions, triggering the release of growth factors, and aiding endothelial cell proliferation.12 Though DNA lesions from mouse skin abrasions were observed after a 3.24 J/cm² dose of UV-C, these lesions were repaired within 72 hours.13 Photochemical reactions in the skin occurs when UV is transmitted through the skin to the peripheral blood capillaries. The transmission of UV-C through skin varies with wavelength with a 15% transmission through the human stratum corneum was found at 297 nm compared to a 72% transmission at 536 nm.40

In the corneal infection study previously mentioned, a UV-C dose of up to 57.95 mJ/cm² resulted in no significant differences of the alive to dead ratio of human corneal cells as compared to the non-UV-C treated control group.75 Boettner and Wolter discovered evidence that the cornea transmits light from 300 to 2,500 nm, which is above the UV-C spectrum. The majority of the transmission (84%) occurs outside of the ultraviolet-C range at 650 to 850 nm.41

The effect of UV-C on blood components is also of concern. UV-C irradiation on platelets at a dose of 1500 J/m² was observed to lead to platelet aggregation. The mechanism at which aggregation occurs was shown to be due to UV-C reducing disulfide bonds that play a role in regulating integrin conformation, resulting in activation of an integrin called αIIbβ3.23 In another study, H. Turker exposed Swiss albino mice to UV-C at 0.14 mW/cm² for 8 hours daily (4,032 mJ/cm² per day) over 60 days using a UV lamp. Significant decreases (p < 0.001) in hemoglobin and neutrophil concentrations were observed in the UV treated group compared to the untreated controls. Significantly increased levels of white blood cells, hematocrit, lymphocyte, and eosinophil were also found. Differences in various hematological parameters between the UV-treated group and the control group were observed after 15 days of UV exposure at a dose of 60 J/cm².83

In a similar study involving the same investigator, 60 female Swiss Albino mice were exposed to UV-C at 0.14 mW/cm² for 8 hours daily over 75 days. Measuring blood and urine parameters revealed that UV-C significantly affected renal function (p < 0.01) since the first data collection time point of 7 days, which translates to a UV-C dose of 28 J/cm². Hepatic functions were only significantly affected (p < 0.01) after the 75th day with a total UV-C dose of 302 J/cm².84

On the other hand, evidence suggests that UV-C doses below 50 mJ/cm² do not alter the quality of blood platelets.83 Another study exposed platelet concentrates (PCs) to UV-C irradiation. A UV-C dose of 400 mJ/cm² had little impact on in vitro parameters measuring PC quality, such as pH and platelet aggregation. Over 6 days, pH increased from 7.1 to 7.3 for untreated PCs, but remained constant for UV-C-treated PCs. Metabolic activity as measured by increases in glucose consumption and lactate accumulation levels was greater in treated PCs. UV-C also increased CD62 expression and annexin V binding. Higher or similar amounts of aggregation were also observed.89

Ozone is an extremely strong oxidant that can attack the human respiratory tract at levels greater than 0.1 ppm. Ozone naturally decays to O₂ but may form CO₂ in the presence of organic matter. Ozone may be generated by the dissociation of oxygen molecules exposed to UV.77 According to Eliasson and Kogelschatz, the UV light must have enough energy (i.e. wavelengths should be below 242 nm) to dissociate oxygen molecules, but should not contain too much energy (i.e. wavelengths should not be less than 103 nm) to cause ionization.88 Ozone is destroyed at wavelengths of 250 to 260 nm.89 Therefore, little to no ozone generation is expected with UV-C wavelengths.

As demonstrated, research in the area of UV effects on human cells and tissue is scarce. More detailed investigations with a wide range of factors, such as UV-C dose and wavelength on various cell types and in different test conditions, are called for.

H. Interactions between UV-C and Drugs

Reactions induced by UV radiation occurs when drug molecules or sensitizers absorb photons of specific wavelengths, causing an excitation from their ground state to reactive excited states. Photochemical reactions may involve multiple competing reaction pathways. Oxygen is a commonly found key player in photochemical reactions that involve consumption of oxygen and/or oxidation. Following absorption of UV photons and a transition to an excited state, the molecule dissipates energy to return back to the more stable ground configuration. Several possible photo-reactions can occur including fluorescence and photoionization. During the excited state of the drug, direct reactions can occur such as photodehalogenation. Photodehalogenation is the loss of a halogen substituent to light. Drugs with chlorine aromatic substituents are particularly likely to undergo photodehalogenation. Photosensitization can also occur, in which the reactivity of a species is transferred through a means other than absorption. The most common type is photosensitized oxidation.89

Few studies on the interaction between specific drugs and UV-C light have been carried out. This may be partially due to the fact that wavelengths in the UV-C range must be artificially generated and are not typically found in natural sunlight.80

However, certain drugs have been shown to have photosensitivity to UV-A and/or UV-B light. Phototoxicity is a subset of photosensitivity that occurs when cell damage results from compounds exposed to light. On the other hand, photoallergic reactions are related to the immune response.91 Table 4 lists out examples of drugs from a review by Lugovic et al. that may be administered intravenously and are associated with photosensitivity.92 Whether or not the drugs are affected by light in the UV-C range specifically is unconfirmed.
Next, certain drugs and chemicals commonly used in CVCs will be evaluated to determine how UV-C irradiation may impact them.

**Ethanol:** Ethanol is expected to remain stable in the presence of UV-C in normal hospital settings. Under ambient pressure lower than 300 bars (3 MPa), Ceppatelli et al. exposed samples of liquid ethanol to wavelengths of 514.5 to 350 nm for 5 to 10 hours using a 500 mW laser. Ethanol remained stable for wavelengths greater than 458 nm. Reactivity occurred at 350 nm and an irradiance of approximately 0.6 kW/cm², which is an extremely high UV dose of at least 10.8 MJ/cm². Common reactions were the splitting of C-O and O-H bonds that resulted in radical species. At pressures in the megapascal scale, the main product that resulted from ethanol reactivity was molecular hydrogen. However, it is important to note that the wavelengths in the study were longer than those in the UV-C range. It is uncertain the extent to which results may be extrapolated to UV-C conditions.

Furthermore, ethanol combined with UV-C has been found to create synergistic disinfectant effects. A combination of UV-C and ethanol corresponded with greater log reductions of bacterial CFUs. For example, a 3.74 log CFU/mL was observed following combined UV-C (504 mJ/cm²) and 50% ethanol solution treatment of S. aureus, a bacterial strain tested with the highest resistance to both disinfection methods. This is greater than the colony reductions using either UV-C light or ethanol alone. The results suggest UV-C does not affect the disinfecting potency of ethanol, and may even enhance it.

**Chlorhexidine:** Upon exposure to sunlight, chlorhexidine digluconate solutions was observed to turn yellow and darken. Impurities were generated after 69 hours of sunlight irradiation, most impurities were a direct result of sunlight cleaving the carbon-chloride bond of the molecule’s aromatic group. Nevertheless, it is important to note that sunlight mostly consists of UV-A and UV-B wavelengths and not UV-C. In addition, the temperature during experimentation was 32°C and therefore the results may have been partially due to thermal effects. Chlorhexidine has also been observed to maintain and even increase its germicidal effects when used in conjunction with UV-C. Applying 15 mJ/cm² of UV-C alone was found to be more effective than using 0.05% chlorhexidine in reducing CFU counts of S. aureus, K. pneumonia, but not E. faecium on canine skin. However, when E. faecium samples were treated to both UV-C and chlorhexidine, bactericidal synergy effects were observed.

**Saline:** Both log phase and stationary phase MRSA samples in increasingly concentrated sodium chloride solutions demonstrated greater sensitivity to the germicidal effects of UV-C. Sodium chloride concentrations ranged from 1.37 to 2.5 M. Therefore increasing ionic strength may decrease the required UV-C dose needed to achieve bacterial eradication.

**Heparin:** Glycosaminoglycans including heparin are photosensitive to UV. Exposure of dilute aqueous heparin-Ca²⁺ salt to ultraviolet light leads to depolymerization of heparin. It was observed that degradation occurred through two different processes: hydrogen abstraction at 184.9 nm of light or through photosensitive to UV. Exposure of dilute aqueous heparin-Ca²⁺ salt to ultraviolet light leads to depolymerization of heparin. It was observed that degradation occurred through two different processes: hydrogen abstraction at 184.9 nm of light or through glycosidic bond dissociation resulting in free radicals at 194.2 nm. Heparin photodegradation led to decreased anticoagulant properties and “cationic dye binding power of the polyanion”.

With the exception of glycosaminoglycans, UV-C appears to have no damaging effects on the drugs reviewed. However, due to the scarcity of studies, UV-C effects on drugs cannot be reached conclusively and more research is needed in the field. When determining UV effects on certain drugs, it is also important to keep in mind certain test conditions such as UV wavelength and dose.

In a study by Reddick et al., the rate of fluid flow through central venous catheter varies between 69.4 - 117.3 mL/min due to gravity alone. The variation in fluid flow rate depends on the number of lumens in the catheter and size. Taking into account the addition of a pressure bag within the intravenous device system, the flow rate increases by 56 - 80% to 116.1 - 211.1 mL/min. Again, this is dependent on the length and width of the cannula of the catheter. According to Reddick, a 14G 150 mm Vygonz ‘Leadercath’ (single lumen Seldinger technique central venous catheter) has a fluid flow rate of 117.3 mL/min due to gravity. With such a level of flow rate, any fluid that

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**Table 4. Examples of medication that may induce phototoxic and/or photoallergic responses**

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug</th>
<th>Phototoxic</th>
<th>Photoallergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Tetracyclines (doxycycline, tetracycline)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal Anti-Inflammatory Drugs</td>
<td>Ibuprofen</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cancer Treatments</td>
<td>Epidermal growth factor receptor inhibitors</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRAF inhibitors (vemurafenib, dabrafenib)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Itraconazole</td>
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<td>X</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Others</td>
<td>Para-aminobenzoic acid</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
passes through the central venous catheter containing a UV-C sterilization mechanism will be exposed to a UV dosage in the 0.1 mJ/cm² order of magnitude, assuming a UV-C LED output power of 1-2 mW. This should ensure negligible disruption on the fluid traveling within the CVC.

Conclusion

It is widely accepted that careful disinfection of environmental surfaces in hospital settings can lower infection rates among patients. However, achieving this optimal disinfection can be difficult. This may stem from a number of reasons including failure to follow the manufacturer’s or institute’s protocols for disinfectant use and the emergence of antimicrobial-resistant strains of bacteria. Existing strategies to prevent CRBSIs have introduced elements of human error that are difficult to bypass without expensive monitoring and surveillance.

After accounting for the suboptimal disinfection that occurs in hospital settings and the limitations of strategies used to combat CRBSIs, a need has been identified to close the sterilization gap for central venous catheters. We call for an improved technology that will automatically and continuously sterilize catheter ports with minimal input from healthcare workers. The application of UV-C energy, which has historically been used in clinical settings but not yet applied in the context of central venous catheter hub, may eliminate the gaps generated by existing preventive strategies. It removes the manual aspect of other forms of decontamination, such as applying liquid disinfectants or alcohol caps and thus reduces the possibilities of infection or transmission of pathogens. Additionally, UV-C can be localized at the hub so as to protect both healthcare personnel and patients from unwanted exposure. Overall, a technology utilizing UV-C represents a practical solution for busy workplaces such as the intensive care or surgical units in a hospital.

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References


