ZOLL

Temperature Management White Paper

Intravascular Temperature Management Does Not Increase the Rate of Catheter-Related Bloodstream Infection

Abstract

This whitepaper examines the risk factors for catheter-related bloodstream infection (CRBI) and central line-associated bloodstream infection (CLABSI) resulting from central venous catheter (CVC) placement. Therapeutic hypothermia products are compared for the rates of catheter-related complications between surface cooling methods and intravascular temperature management (IVTM). A summary of peer-reviewed publications from clinical studies shows that the rates of CRBI and CLABSI were 0.4% with IVTM, 1.4% with standard CVC without hypothermia, and 3% in hypothermia with surface cooling plus standard CVC. Additionally, a randomized controlled trial comparing patients receiving IVTM cooling to patients receiving surface cooling and central lines found that there was no difference in the rate of infection between the two groups. These results demonstrate that the use of therapeutic hypothermia induced by an IVTM cooling catheter is not associated with increased incidence of catheter-related infection.

Key Takeaways

1. The rate of CRBI for a general critically ill patient population is 1.4%.
2. The rate of CRBI for patients receiving therapeutic hypothermia after cardiac arrest with surface cooling is 3%.
3. The rate of CRBI for patients receiving therapeutic hypothermia after cardiac arrest with ZOLL IVTM is 0.4%.
4. An RCT comparing standard surface cooling to ZOLL IVTM found no difference in the rate of occurrence of CRBI (Surface: 4.2% vs IVTM: 1.3%, p = not significant).
5. The rate of CRBI is not worse for femoral central line placement when compared to subclavian or jugular central lines.
6. Use best practice sterile barriers (cap, mask, sterile gown, sterile gloves, and a sterile full-body drape) to reduce or eliminate CRBI.
7. Be aware of the CRBI risk factors like prolonged hospitalization before catheter insertion, male gender, multiple CVCs, catheter duration (with the risk increasing with CVC dwell time) and parenteral nutrition administration.

Introduction

Central venous catheters (CVC) and interventional procedures are essential to manage patients who have been resuscitated from cardiac arrest or are critically ill, but catheters are not without risks. To improve patient outcomes and reduce healthcare costs, catheter-related bloodstream infection (CRBI) and central line-associated bloodstream infection (CLABSI) have received recent attention. To decrease the prevalence of these infections, healthcare organizations in the U.S. and Europe have published evidence-based clinical practice guidelines for CVC use[1-7], which can be very helpful to clinicians trying to reduce risk factors for catheter-related infection.

What are the risk factors for CRBI and CLABSI?

The catheter insertion process and its post-insertion maintenance, especially for CVCs, have the greatest impact on the overall risk of CRBI and CLABSI[8,9]. Some adult surgical patients in burn or trauma critical care units are at higher risk of infection than patients in other ICU units[10]. Underlying diseases or conditions – hematological and immunological deficiencies, cardiovascular disease, and gastrointestinal diseases – have also been associated with an increased risk for CLABSI[10-13]. Other risk factors include:

- Prolonged hospitalization before catheter insertion[13]
- Male gender[14, 15]
- Multiple CVCs[13, 14, 16]
- Catheter duration, with the risk increasing with CVC dwell time[11, 12, 13, 17, 18]
- Parenteral nutrition administration[9, 11, 13, 17, 19, 20]
- Lack of maximal sterile barriers (cap, mask, sterile gown, sterile gloves, and a sterile full-body drape) for catheterization or guidewire exchange[21,22]

CVCs can become contaminated with microorganisms via two major routes[5, 23-26]:

1. Extraluminal: The patient's skin organisms at the insertion site can migrate along the surface of the catheter into the cutaneous catheter tract surrounding the catheter, resulting in colonization at the catheter tip. Among patients whose catheter is in place for a short period of time, this is the most common source of infection.
2. Intraluminal: The most common cause is direct contamination of the catheter or contamination at some point along the fluid pathway when the IV system is manipulated (as might occur when healthcare personnel have hand contact with IV solution connection sites, access hubs, needleless connectors, or tubing junctions); the patient's own body fluids or skin can also serve as the contamination source. Intraluminal contamination has been associated with more prolonged catheter dwell time (in place for more than 10 days) and with tunneled CVCs such as Hickman and Broviac-type catheters and peripherally inserted central catheters (PICCs).

Critically ill patients require a CVC due to severity of their condition and the needs of intervention for treatments. Approximately 250,000 CLABSI cases (80,000 in the ICU) occur in hospitals in the United States annually[1]. Published studies showed an average CLABSI occurrence rate of 1.4% (0.3%-7.7%) for all CVCs[27]. Table 1 shows the combined total number of catheters and CLABSI events from subclavian, internal jugular (IJ) and femoral insertion sites.

Table 1: Summary of studies of CVC and CLABSI events

First Author	Year	RCT/C	Country	Patients	Number of catheters	Number of CLABSI	Occurrence rate
Goetz[28]	1998	C	USA	ICU & Ward	300	8	2.7%
Lorente[29]	2005	C	Spain	ICU	2,595	53	2.0%
Deshpande[30]	2005	C	USA	ICU	551	3	0.5%
Nagashima[31]	2006	C	Japan	ICU & Ward	767	59	7.7%
Gowardman[32]	2008	C	Australia	ICU	413	2	0.5%
Gamacho-Montero[33]	2008	C	Spain	ICU	1,598	61	3.8%
LeMaster[34]	2010	C	USA	ER	575	7	1.2%
Harrisen[35]	2010	C	Wales	ICU	9,571	31	0.3%
Merrer[36]	2001	RCT	France	ICU	270	3	1.1%
Parienti[37]	2008	RCT	France	ICU	736	8	1.1%
Overall occurrence rate					**17,376**	**235**	**1.4%**

C = case series, RCT = randomized controlled trial

Peripherally inserted Central Venous Catheters (PICCs) are not superior to centrally inserted catheters in terms of the reduction in bloodstream infections. Safdar et al[38] reported in a prospective and randomized trial that the PICCs had a similar rate of CRBI compared to conventional CVCs (2.4% vs 3.9%). Table 2 lists of published studies on the incidence rate of CRBI with different routes of insertion[39].

Table 2: Catheter-related bloodstream infection in non-hypothermia population[39]

Access site	Patients with CVCs	Number of CVCs	Ratio # of cath vs. of Pts	# of patients with CRBI
Peripheral	257	331	1.29	2
Subclavian	321	432	1.35	5
Jugular	618	698	1.13	4
Femoral	111	147	1.32	5
Total	1,307	1,608	1.23	16
Population				1,307
Occurrence rate				**1.2%**

In summary, the average rate of CRBI in generally critically ill patients is about 1.4%.

Do femorally inserted CVCs have a higher rate of infection?

The femoral vein is the primary site of catheterization for interventional procedures. The decision regarding the preferred site for placement of a CVC is complex and based on the skill of the clinician, the availability of ultrasound-guided placement, the risk of bleeding, and other complications (i.e. pneumothorax or hemothorax), as well as the urgency of placement. In emergent and high-risk situations, the femoral route is often chosen due to the ease and perceived less insertion caused complications[2, 40].

While some guidelines recommend using "the insertion site associated with the least likelihood of injury (jugular, femoral, subclavian)"[2], many of the clinical practice guidelines recommend that the femoral site be avoided due to the perceived higher risk of CRBI associated with this site. Recommendations released in 2011 by the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (CDC) state that one should "avoid using the femoral vein for central access in adult patients" as a Class 1A recommendation[1]. Several studies have been conducted in the past to examine this recommendation. One such study is a recent NEJM publication by Parienti et al, which gives further details on the rates of complications reports for three CVC insertion sites (subclavian, jugular, and femoral)[41]. In this multicenter randomized trial, 2352 catheters were placed and randomly assigned in a three-choice, 1:1:1 scheme. The rates of CVC infection are reported in this study as 0.5%, 1.4%, and 1.2% for subclavian, jugular, and femoral sites respectively, which are consistent with the average CRBI rate of 1.4% in the critical care population.

Although Parienti et al found that the subclavian insertion site was associated with a lower risk of CRBI compared to jugular and femoral sites, there are a number of key points of note in the results. First, chlorhexidine dressing and bathing, which is considered a Category 1 CDC guideline[1], was used in less than 50% of the study population. The authors acknowledge that this was a study limitation and could potentially influence the outcomes in this trial. Secondly, the overall rate of complications (summation of CRBI, deep vein thrombosis, and mechanical events) for the three insertion sites in this trial was similar (subclavian 3.1%, jugular 3.8%, femoral 3.3%), and according to the authors, these results suggest that an ideal site for CVC insertion does not exist[41]. In choosing a CVC insertion site, it is important to consider the overall rate of complication, which has a greater impact than a single type of complication (i.e., mechanical complication such as pneumothorax). Lastly, the results show that femoral insertion site had the lowest rate of insertion failure (5.3%) compared to jugular (7.7%) and subclavian (14.7%) insertion sites. Thus, the ease of insertion should also be considered when selecting a CVC site.

Marik, et al performed a systematic review of the literature and meta-analysis comparing the risk of CRBI for catheters placed in the femoral vein, compared with catheters placed in the subclavian or IJ vein[42]. Data from 10 clinical studies, including two randomized trials, for a total of 113,690 catheter days were examined. Overall, there was no significant difference in the risk of CRBI for the femoral site compared with the subclavian site (RR 1.75; 95% CI 0.80–3.8, p = 0.16); however, heterogeneity was noted in this analysis, largely explained by two outlying studies (Lorente and Nagashima). When these two studies were removed from the meta analysis, there was no heterogeneity (RR 1.02; 95% CI 0.64-1.65, p=0.92). Meta-regression showed a significant relationship between the risk of infection and the year of publication (p = 0.01), with the earlier studies favoring the IJ site. However, the main finding of this meta-analysis was that recent studies demonstrate no difference in the risk of CRBI between the femoral, subclavian, and IJ sites. Therefore, the authors conclude that "the 1A recommendation to avoid the femoral site for the placement of a nontunneled short-term central venous catheter is not supported by the literature"[1,5]. Furthermore, the authors note that the overall risk of CRBI has decreased over time and attribute this improvement to better risk-reduction procedures, including the use of full drapes, masks, gloves, and chlorhexidine for skin preparation along with strict adherence to aseptic precautions.

The Marik meta-analysis is further supported by the results of a study by Casanegra et al., which found that the overall risk of CVC-related infection was 0.6 per 1,000 catheter days, with no difference in the risk of infection regardless of insertion site[43].

Does intravascular temperature management have a higher risk compare to standard central line?

Therapeutic hypothermia and feedback-controlled patient temperature has become routinely used in the ICU setting for patients with a wide range of neurological injury (cardiac arrest, acute ischemic stroke, traumatic brain injury, reduction of intracranial pressure, etc.). With promising results from various clinical studies, therapeutic hypothermia is increasingly recognized as an effective agent for treatment of several critical disease states. Therapeutic hypothermia is currently a Class I recommendation for the post-resuscitation treatment of patients who achieve return of spontaneous circulation but remain comatose after out-of-hospital cardiac arrest[44]. In addition, therapeutic hypothermia is a Class I recommendation for newborns with neonatal hypoxic ischemic encephalopathy[45] Therapeutic hypothermia is also associated with a significant decrease in the incidence of intracranial hypertension[46-50].

Studies using hypothermia after cardiac arrest have suggested that reaching target temperature sooner may allow for hypothermia to be even more beneficial than has already been demonstrated[44]. The same applies to studies using hypothermia after neonatal hypoxia ischemia[45]. Additionally, studies using therapeutic hypothermia after traumatic brain injury suggest that patients may have higher chances of reducing mortality when hypothermia is maintained for more than 48 hours[51]. Given the unavoidable delays in the discovery, resuscitation, and transport of patients with cardiac arrest, stroke, or traumatic brain injury, it is very likely that significant secondary injury has already occurred by the time hypothermia is initiated. The sooner the patient is cooled to target temperature, the more likely he or she is to benefit from the therapy[52,53]. Importantly, it has been documented that precise control of target temperature can improve neurological outcome[54]. Cooling blankets, ice packs, gel pads, and other external methods are clinically inefficient, labor intensive, and hinder access to critically ill patients who require constant care[55]. In a study of therapeutic cooling using ice packs and cooling blankets, Holzer reported that target temperature was reached in only 30% of patients[56]. Another observational cohort study involving 1,036 patients reported similar findings[57]. Surface cooling failure (target temperature was not reached) occurred in nearly one-third of patients, the failure rate even higher with obese patients and patients who underwent percutaneous coronary intervention, both common among patients who have been resuscitated[57].

Compared to skin surface cooling, intravascular temperature management (IVTM) systems rapidly reach target temperature and precisely maintain patient core temperature. One publication showed that the target temperature (33°C) was reached in a mean time of 64 minutes[56], while another study found that 98% of patients cooled with an IVTM system were maintained at target temperature, compared with only 50% of patients cooled using surface methods[58]. IVTM not only provides ease of use but demonstrate good outcomes both short- and long-term, compared with surface cooling[59].

It has been well described that the risk of infection increases during post-resuscitation care of patients treated in intensive care units[60,61]. Furthermore, hypothermia has been shown to decrease host immunity, which has the potential for an increased propensity for infection[62,63]. Recently, cardiac arrest survivors undergoing therapeutic hypothermia using skin surface cooling have been shown to have an increased risk of infection-related complications[64,65].

As clinicians consider the use of therapeutic hypothermia and managing fever, they must carefully weigh the risks as well as the potential benefits of the therapy. Like any interventional procedure, IVTM involves insertion of a catheter into the superior vena cava via the subclavian vein, internal jugular vein, or into the inferior vena cava via the femoral vein and therefore carries the potential for central venous catheter-related complications. However, this potential is relative, since most patients who would be considered candidates for therapeutic hypothermia require central venous access anyway, by virtue of their critical medical condition.

The reported CRBI rate with IVTM cooling catheters is very low. The likely reasons are that the catheter is placed using sterile technique and the indwelling time is short. To date, there have been a number of peer-reviewed publications on the use of IVTM to treat patients who suffered cardiac arrest, ischemic stroke, trauma, and other diseases. These studies prospectively and specifically evaluated catheter-related complications including CRBI, and the rate of occurrence for such complications is low at 0.4% (Table 3).

Table 3: Rate of catheter-related complications among patients treated with intravascular temperature management (IVTM).

First Author	Study Type	Disease	Number of Patients	Catheter Location	Number of Bacteremia	Number of CRBI
Horn[66]	Prospective	Stroke	20	Femoral	1	0
Levi[67]	Single Arm	Acute Cervical Spinal Cord Injury	35	Femoral	2	0
Patel[68]	Single Arm	Cardiac Arrest	115	Femoral	1	0
Lopez-de-Sa[69]	RCT	Cardiac Arrest	36	Femoral	Not Reported	0
Lundbye[70]	Prospective	Cardiac Arrest	52	Femoral	Not Reported	0
Tømte[71]	Single-Center Observational	Cardiac Arrest	72	Femoral	Not Reported	0
Gillies[55]	Retrospective Cohort Study	Cardiac Arrest	42	Femoral	0	0
Allen[72]	Prospective	OPCAB*	38	Femoral	0	0
Pichon[73]	Prospective	Cardiac Arrest	40	Femoral	5	0
Arrich[74]	Registry	Cardiac Arrest	374	Femoral	Not Reported	Not Reported
Holzer[75]	Prospective	Cardiac Arrest	97	Femoral	0	0
Keller[76]	Prospective	SAH**, vasospasm and ICP control	100	Femoral	3	3
Götberg[77]	Prospective	AMI***	20	Femoral	Not Reported	0
Steinberg[78]	RCT	Cerebral aneurysm surgery	88	Femoral	1	0
Total			**1,129**		**13**	**3**
Population					**575**	**755**
Occurrence Rate					**2.3%**	**0.4%**

OPCAB = off-pump coronary bypass, SAH = subarachnoid hemorrhage, AMI = acute myocardial infarction

Reporting on CRBI from studies evaluating cardiac arrest patients receiving therapeutic hypothermia with surface cooling methods are somewhat inconsistent and under reported. The resuscitated patients in these trials invariably receive standard CVCs to deliver vasopressors as well as withdrawing blood due to vasoconstriction from peripheral vessels. Several trials in surface cooling showed sepsis and bacteremia rate between 7% to 13%[56,65,79,80]. One French study in 334 post-cardiac arrest patients cooled with external forced cold air showed a 3% line-related infection rate and 8% bloodstream infection rate[63] (Table 4). Cardiac arrest patients receiving therapeutic hypothermia with surface cooling do get central line-related infections.

Two randomized studies (Tomte & Pittl[81]) compared ZOLL IVTM to surface cooling using the Bard Arctic Sun product and found no difference in either sepsis nor bacteremia (10% with Bard Arctic Sun and 9% with ZOLL IVTM) as well as no statistical difference in antibiotic use (85% with Bard Arctic Sun, 77% with ZOLL IVTM, p=0.218).

Table 4: Rate of catheter-related complications among patients treated with external or surface cooling device

First Author	Study Type	Disease	Number of Patients	Surface Cooling Device	Number of sepsis or bacteremia	Number of CRBI
Holzer[56]	Randomized	Cardiac arrest	135	Forced cold air	17	NA
Nielsen[79]	Observational	Cardiac arrest	765	Surface (85%) & IVTM (15%)	31	NA
Heard[80]	Randomized	Cardiac Arrest	61	Arctic Sun & Cincinnati	4	1
Tømte[71]	Single-Center Observational	Cardiac arrest	92	Arctic Sun	9	NA
Jarrah[65]	Retrospective	Cardiac arrest	69	Arctic Sun	NA	6
Clifton[82]	Randomized	Brain injury	46	External	13	NA
Kory[83]	Retrospective	Cardiac arrest	65	External and lavage	8	NA
Mongardon[64]	Retrospective	Cardiac arrest	334	Forced cold air	35	8
			1,567		117	15
Population					**1,498**	**464**
Occurrence rate					**8%**	**3%**

Summary of studies regarding CRBI and CLABSI showed a rate of 0.4% with IVTM, a rate of 1.2% with standard CVC but in critically ill patients not receiving hypothermia and 3% in patient receiving hypothermia with surface cooling plus standard CVCs.

Product Surveillance Data

Post-market surveillance of IVTM catheters based on the manufacturer's internal complaint database shows an infection rate of 5 out of 171,000 catheters sold between May 2009 and July 2015 (0.003%)[84]. Although underreporting of complaints from hospitals is possible, even an underreporting rate of 100x less than actual would show an infection rate of less than the 0.4% reported in Table 3.

Conclusion

Critically ill and post-cardiac arrest patients admitted to the intensive care unit are prone to nosocomial infections, mostly due to their underlying critical status, stress-induced decreased cell-mediated immunity, translocation of bacteria from the gastrointestinal tract due to mesenteric ischemia, as well as the use of interventional procedures when managing their care[25]. Institutions should follow CDC recommendations, which include strict hand hygiene, using maximum barrier precautions during catheter insertions, skin cleansing with chlorhexidene, and prompt removal of the catheter after use. Institutional implementation of standard protocols that incorporate these measures may have contributed to the recently observed reduced incidence of CLABSI overall. Moreover, a recent study showed that the administration of prophylactic antibiotics in order to prevent aspiration pneumonia during post-resuscitation treatment of cardiac arrest survivors may have contributed to the absence of CLABSI[68].

Importantly, therapeutic hypothermia using a ZOLL IVTM cooling catheter placed in the femoral vein is not associated with increased incidence of catheter-related infection[68]. A 296 patient randomized controlled trial comparing ZOLL IVTM catheter to standard surface cooling and specifically evaluating central line-related infections, found no difference in the rate of occurrence between groups[85]. When IVTM cooled patients are compared general critically ill patient populations who receive central lines, the rate of infections with IVTM is the same and numerically lower. Conversely, the rate of central line-related infections during therapeutic hypothermia with surface cooling appears numerically greater than the general critically ill population. In short, the demonstrable benefits of IVTM should not be withheld for concern of central line infections, as they do not occur at a higher rate in practice.

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Table 5. CDC 2011 Recommendations for Skin Preparation

There are a number of resources with instructions for central line placement and maintenance to prevent CLABSI, and these are detailed below.

Per CDC guidelines[1], the recommendations for skin preparation along with the level of evidence for each step are as follows:

- Prepare clean skin with an antiseptic (70% alcohol, tincture of iodine, or alcoholic chlorhexidine gluconate solution) before peripheral venous catheter insertion. Category IB
- Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before central venous catheter and peripheral arterial catheter insertion and during dressing changes. If there is a contraindication to chlorhexidine, tincture of iodine, an iodophor, or 70% alcohol can be used as alternatives. Category IA
- No comparison has been made between using chlorhexidine preparations with alcohol and povidone-iodine in alcohol to prepare clean skin. Unresolved issue.
- No recommendation can be made for the safety or efficacy of chlorhexidine in infants aged <2 months. Unresolved issue
- Antiseptics should be allowed to dry according to the manufacturer's recommendation prior to placing the catheter. Category IB

Table 6. CDC 2011 Recommendations for Catheter Site Dressing Regimens

The CDC guidelines also provide recommendations regarding catheter site dressing regimens, along with the level of evidence for each[1]:

- Use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site. Category IA
- If the patient is diaphoretic or if the site is bleeding or oozing, use a gauze dressing until this is resolved. Category II
- Replace catheter site dressing if the dressing becomes damp, loosened, or visibly soiled. Category IB
- Do not use topical antibiotic ointment or creams on insertion sites, except for dialysis catheters, because of their potential to promote fungal infections and antimicrobial resistance. Category IB
- Do not submerge the catheter or catheter site in water. Showering should be permitted if precautions can be taken to reduce the likelihood of introducing organisms into the catheter (e.g., if the catheter and connecting device are protected with an impermeable cover during the shower). Category IB
- Replace dressings used on short-term CVC sites every 2 days for gauze dressings. Category II
- Replace dressings used on short-term CVC sites at least every 7 days for transparent dressings, except in those pediatric patients in which the risk for dislodging the catheter may outweigh the benefit of changing the dressing. Category IB
- Replace transparent dressings used on tunneled or implanted CVC sites no more than once per week (unless the dressing is soiled or loose), until the insertion site has healed. Category II
- No recommendation can be made regarding the necessity for any dressing on well-healed exit sites of long-term cuffed and tunneled CVCs. Unresolved issue
- Ensure that catheter site care is compatible with the catheter material. Category IB
- Use a sterile sleeve for all pulmonary artery catheters. Category IB
- Use a chlorhexidine-impregnated sponge dressing for temporary short-term catheters in patients older than 2 months of age if the CLABSI rate is not decreasing despite adherence to basic prevention measures, including education and training, appropriate use of chlorhexidine for skin antisepsis, and MSB. Category 1B
- No recommendation is made for other types of chlorhexidine dressings. Unresolved issue
- Monitor the catheter sites visually when changing the dressing or by palpation through an intact dressing on a regular basis, depending on the clinical situation of the individual patient. If patients have tenderness at the insertion site, fever without obvious source, or other manifestations suggesting local or bloodstream infection, the dressing should be removed to allow thorough examination of the site. Category IB
- Encourage patients to report any changes in their catheter site or any new discomfort to their provider. Category II

Table 7. Patient Safety Movement (APSS) 2014 Recommendations for Prevention of CLABSI

Practice Plan[86]: Use of current evidence-based guidelines and/or implementation aids regarding the prevention of CLABSIs

- Create line cart that contains all needed supplies
- Wear sterile clothing – as mask, gloves and hair covering – and cover patient with a sterile drape, except for a very small hole where the line goes in. Maintain strict aseptic technique when placing the line.
- Wash hands with soap and water or an alcohol cleanser
- Ultrasound guidance should be used for all non-emergent internal jugular line placements.
- Before the procedure, perform a “time-out”
- Place patient in trendelenburg position (< 0 degrees)
- Clean patient’s skin at the insertion site with chlorhexidine.
- Avoid veins in arm and leg, which are more likely to get infected than veins in chest.
- Ensure line aspirates blood to prevent hemothorax
- Apply a sterile dressing to the site
- Check the line for infection each day and remove the line when no longer needed.

Table 8. Selected International Resources for CRBI Prevention

There are several resources from international governmental bodies pertaining to the prevention of CRBI:

European Centre for Disease Prevention and Control (ECDC):

- http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/guidance-infection-prevention-control/Pages/guidance-prevention-control-infections-caused-by-multidrug-resistant-bacteria-and-healthcare-associated-infections.aspx

Ireland – CVC maintenance bundles:

- http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/CareBundles/CentralVascularCathetersCVCs/MaintenanceofCVCs/File,4124,en.pdf

Germany – Resources from the Robert Koch Institute:

- http://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Clostridium.html#doc2393684bodyText25
- http://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Kommission/Downloads/MRSA_Rili.pdf?__blob=publicationFile