Product Monograph

TauroSept®
The Medical Solution for Treatment and Prevention of Catheter Infections
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Introduction

The medical care of patients in intensive care, haemo-oncology and dialysis units and other medical facilities necessitates the implantation of central venous access devices (CVADs). These are used to deliver liquids, medication, blood products and parenteral nutrition and to carry out test taking and haemodialysis/haemofiltration. The use of CVADs can lead to an array of complications of which infection is the most significant. Examples of this include local and systemic infections, such as infection of the insertion site, septic thrombophlebitis, endocarditis and CVAD-related bacteraemia (catheter-related bloodstream infection or CRBSI). The numerous preventive measures introduced in recent years have partly affected the high incidence of CRBSI \(^1\), \(^2\) but despite the highly effective antimicrobial substances available, the lethality rate for CRBSI remains between 5% and 25%\(^3\), \(^4\).
Catheter-related bloodstream infections (CRBSI)

Definition
The definition of a catheter-related bloodstream infection or more recently used Central Line-associated Blood Stream Infection CLABSI as defined by the CDC (Centers for Disease Control, Atlanta, USA) is a clinical definition and based on microbiological criteria on the one hand (a single blood culture for organisms not commonly present on the skin and two or more blood cultures for organisms commonly present on the skin) and clinical signs on the other (fever, chills and fever and/or hypotension), in a patient who has a central line at the time of infection or within the 48-hour period before development of infection. The infection cannot be related to any other infection the patient might have and must not have been present or incubating when the patient was admitted to the facility.

Epidemiology
Conclusions can only be partly drawn from literature that concerns itself with the incidence of catheter-related infection. This is due to the inconsistent use of definition, heterogeneous patient groups (surgical patients, burn patients, tumour patients, etc.), the use of various types of catheter with different indwelling periods, as well as the varying measures taken to prevent infection.

The incidence of CRBSIs in intensive care units in the USA is between 0.7 and 5.5 episodes per 1,000 catheter days, and in Europe between 1.5 and 4.6 episodes per 1,000 catheter days depending on the ward. CRBSI constitutes a major clinical and economic problem. Despite general hygienic measures and programs with certain reductions in the infection rates, it is estimated that 80,000 episodes of CRBSI occur annually on intensive care units in the United States. If all hospital wards, not just the intensive care units, are considered, the total number of CRBSI episodes in one year would be closer to 250,000.

Each episode of CRBSI is estimated to cost the US health care system $2,000 – $45,000, depending on the source of data. This costs the US economy and health care system between $296 and $2,300 million per annum.

Pathogenesis
Biofilm plays a major role in the development of catheter-related infections. The new definition of a biofilm is a microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription. Almost all vascular catheters are contaminated with micro-organisms after a short indwelling period. Within 24-hours following CVAD insertion biofilm develops on the catheter surfaces. A biofilm develops when the attached cells excrete polymers that facilitate adhesion, matrix formation, and alteration of the organism’s phenotype with respect to growth rate and gene transcription. The physical and genetic profiles of micro-organisms within the protected biofilm community are profoundly different from their existence as unprotected independent (planctonic) cells. During the first stage of biofilm formation, bacteria accumulate on the surface of biomaterials...
and excrete polysaccharides. Because the device is in direct contact with the bloodstream, the surface becomes coated with platelets, plasma, and tissue proteins such as albumin, fibrinogen, fibronectin and laminin. These materials act as conditioning films; S. aureus adheres to proteins such as fibronectin, fibrinogen and laminin, and S. epidermidis adheres only to fibronectin. The organisms may also produce adhesins. In a second stage the microorganisms settle in this biofilm increase adhesion, growth and aggregation of cells into micro colonies which protect them against the immune system’s defence mechanisms (phagocytosis, antibodies) and impede treatment with antibiotics. The structural characteristic of biofilm that has the greatest impact on the outcome of chronic bacterial infections, such as native valve endocarditis, is the tendency of individual micro colonies to break off and/or detach when their tensile strength is exceeded. This detachment of preformed micro colonies containing sessile cells in the antibiotic-resistant biofilm phenotype poses a very serious risk of infective emboli in the first capillary bed that is encountered. The nature of biofilm structure and the physiological attributes of biofilm organisms confer an inherent resistance to antimicrobial agents, whether these antimicrobial agents are antibiotics, disinfectants or germicides. Mechanisms responsible for resistance may be one or more of the following: (i) delayed penetration of the antimicrobial agent through the biofilm matrix, (ii) altered and slower growth rate of biofilm organisms, and (iii) other physiological changes due to the biofilm mode of growth. The extracellular polymeric substances constituting this matrix present a diffusion barrier for antibiotics. Another pathogen of intravascular catheter insertion is thrombosis, which is particularly associated with catheters indwelling for prolonged periods of time. This is due in part to binding of host proteins such as fibrinogen, fibronectin, thrombospondin etc. Thrombosis itself is a potentially life-threatening complication as this may lead to pulmonary embolism and death. Also, thrombosis has been shown to dramatically increase the risk of catheter related blood-stream infection because many microbial pathogens avidly bind to thrombus thus allowing them to tightly adhere to the catheter surface in the bloodstream.

The adherence of pathogens to certain materials is dependent on the physical characteristics of the catheter, such as surface texture and electric charge as well as the bacteria’s surface properties (e.g. hydrophobia). For example, hydrophobic Staphylococci and Candida species colonize catheters made of polyvinyl chloride (PVC) and silicone more frequently than catheters made of Teflon or polyurethane. Colonization and biofilm formation may occur within 3 days of catheterization. Raad et al. also showed that catheters in place for less than 10 days tended to have more extensive biofilm formation on the external surface of the catheter; for longer-term catheters (up to 30 days), biofilm were more extensive on the internal lumen.

Transmission routes
Bacteria can enter the bloodstream using the external catheter surface or through the lumen of the catheter (Fig. 1).
If bacteria reach the catheter tip, they can migrate retrograde along the internal/external surfaces of the catheter that are not yet colonized. The patient’s skin and the translocation of bacteria through a needle puncture or bacterial migration from another focus of infection (e.g. a skin/tissue foot infection) can be considered the primary source of colonization which leads to contamination of the external surfaces of the CVAD.

Colonization of the internal surface of the CVAD can be caused by manipulation leading to contamination of the CVAD’s extensions or by contaminated infusions and infusion sets. In a recent study, lumen colonization is cited as the origin of bacteraemia in all patients with CRBSI. The bacteria discovered at the catheter insertion site were mostly identical to the bacteria found on/in the catheter. This proves the fact that skin
germs do appear to settle on the luminal and extra luminal surfaces of a CVAD during insertion. Jeske et al. found in a study that the skin germs on the implantation sets and CVADs that led to a CRBSI were identical.

Risk factors
Several factors that contribute to the risk of venous catheter-related infections are discussed in the literature. The CVAD's indwelling period is important, prolongation of catheterization, catheterization in emergent conditions increases the risk for a CRBSI as well as the frequency of manipulation (e.g. taking blood, injections), and the insertion site location.

The use of the femoral vein for central venous access in adult patients should be avoided. Preferred is the use of a subclavian site, rather than a jugular or a femoral site, in adult patients to minimize infection risk for CVAD placement. Additionally, the administration of high caloric parenteral nutrition appears to be significant for an increased rate of CRBSI. It is still not clear whether the application of multi-lumen catheters increases the risk of catheter-related infections. Based on older non-randomized studies, the use of single-lumen catheters (if possible) has always been recommended. A meta-analysis of 15 studies suggests that the risk of infection from multi-lumen catheters when compared to the risk from single-lumen catheters is only slightly higher.

O’Grady et al. in the guidelines for the prevention of intravascular catheter-related infections 2011 from CDC have identified other risk factors like, catheter material and the intrinsic virulence factors of the infecting organism combined with adherence properties and the ability to produce biofilm.

Spectrum of pathogens
Gram-positive pathogens are responsible for 50% to 70% of all catheter-related bacterial infections. Staphylococcus epidermidis and other coagulase-negative staphylococci are the most common micro-organisms followed by Staphylococcus aureus and Candida spp. In a European CRBSI prevalence study, Gram-positive cocci could be detected in 71%, Gram-negative rods in 22% and yeasts in 7% of all cases.

The five most common micro-organisms were coagulase-negative staphylococci (34%), Staphylococcus aureus (17%), Enterobacter spp. (9%), Candida spp. (9%), Klebsiella spp. (6%), Pseudomonas spp. (6%) and Enterococcus spp. (6%). Although coagulase-negative staphylococci were the pathogens isolated most commonly in EU countries, S. aureus was predominant in non-EU countries (39% vs. 13%).

Similar pathogens are being found in the U.S. Of the CLABSIs reported to CDC and the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) database, respectively the most commonly reported causative pathogens remain coagulase-negative staphylococci, Staphylococcus aureus, Enterococci and Candida spp. Gram-negative bacilli accounted for 19% and 21%. Antimicrobial resistance has been and still is an increasing problem, particularly in ICUs. Methicillin-resistant Staphylococcus aureus (MRSA) now account for more than 50% of all Staphylococcus aureus isolates obtained in
ICUs. The incidence however, of MRSA CLABSIs has decreased in recent years, perhaps as a result of prevention efforts. For Gram-negative rods, antimicrobial resistance to third generation cephalosporin among Klebsiella pneumoniae and E. coli has increased significantly as has imipenem and ceftazidime resistance among Pseudomonas aeruginosa. Candida spp. are increasingly noted to be fluconazole resistant.

Diagnostics
Diagnostic measures for detecting a catheter infection should be initiated immediately if an infection is suspected. The clinical symptomatic can be characterized by the clinical signs and symptoms of a bloodstream infection (temperature > 38.5°C, chills, hypotension, tachycardia, elevated white blood cell count and/or CRP rise) in absence of hypovolemia and a cardiac event, without any other focus for infection than the central line. A urinary specimen and chest X-ray can be performed to exclude other infection foci. Further investigation involving several diagnostic procedures is required. Diagnosing a venous catheter-related infection involves eliminating the possibility of another source of infection by clinical and operative examination. This includes taking blood cultures from the patient's CVAD and from a peripheral vein and inoculating the samples into aerobic and anaerobic blood cultures for further microbiological examination (aerobic, anaerobic and fungal). If the catheter is removed, the catheter tip should be microbiologically examined using a semiquantitative or quantitative method (e.g. Maki's, Cleri flush or Brun-Buisson technique). Quantitative blood culturing techniques have been developed as an alternative for the diagnosis of catheter-related bloodstream infection in patients for whom catheter removal is undesirable because of limited vascular access. This technique relies on quantitative culture of paired blood samples, one of which is obtained through the central catheter hub and the other from a peripheral venopuncture site. In most studies, when blood obtained from the CVAD yielded a colony count at least 5–10-fold greater than that for blood obtained from a peripheral vein, this was predictive of catheter-related bloodstream infection.

Prevention
The longer the catheter indwelling time, the greater the danger is of a catheter-related infection (CRBSI) developing. Rule one for prevention must be keeping the catheter indwelling time to an absolute minimum. Other important preventive measures include a strict aseptic technique when inserting the catheter, the avoidance of unnecessary catheter manipulation, asepsis when taking blood and injecting via the catheter, sterile dressings and the reduction of connectors and 3-way valves to a minimum. Proper training of medical staff helps reduce CRBSIs considerably. The results of two clinical studies have shown that regularly replacing CVADs (on a weekly basis) does not reduce the frequency of CRBSIs.

The latest generation of catheters have an antimicrobial layer that reduces the microbial colonization of catheters. Recently developed catheters with a double coating of minocycline and rifampicin have proved their antimicrobial effectiveness, even
against Candida. The routine application of these coated catheters is a contentious issue and can cause even further microbial resistance, and they should only be used, if at all, for special patient groups and in high-risk situations. Conventional preventative measures should be used instead to keep CVAD-related infections to an absolute minimum before coated catheters are used.

The so-called antimicrobial lock represents a promising preventative measure in the fight against catheter-related infections. This technique involves instilling an antimicrobial solution in the catheter lumen. The solution is left in the catheter lumen for a specific length of time (usually 6–12 hours) and is then removed. The effectiveness of antimicrobial locks in preventing catheter-related infections has been proven in a number of clinical studies. A number of antibiotics were suggested in preventing CRBSI. Vancomycin-heparin solution and vancomycin-ciprofloxacin-heparin solution are two examples. Vancomycin is a risk factor in the development of vancomycin-resistant Enterococci and should not be used routinely. Minocycline-EDTA solution (M-EDTA) has also shown itself to be microbial active against most of the microorganisms that cause CRBSI.

In general routine use of antibiotic solutions preventively in catheters will cause resistance within 3–6 months. Without any real evidence base heparin or saline solution are mostly used today as catheter lock solutions. However, an anticoagulant is not always needed and there is evidence that heparin supports microbial growth in solutions and in biofilm. Sometimes heparin is combined with antimicrobial instillation solutions to prolong the catheter’s patency but heparin is not always compatible with antibiotic solutions. There is also the theoretical risk of a heparin-induced thrombocytopenia (HIT) developing when heparin is used.

Lately a new generation of catheter lock solution has been developed which causes no resistance over long term use and is efficient against all microbes even in existing biofilm. The catheter lock solution TauroSept® contains 2% taurolidine and can be used both in preventing catheter infections over long time or saving already infected catheters of having to be explanted.

**Therapy**

If a patient already has a CRBSI usually IV antimicrobial therapy is initiated with only marginal short-lasting success caused by resistance forming, endotoxins release, cytokine enhancement and biofilm formation. Multiple resistant germs are a major problem (MRSA, VRE, VISA and VRSE).

Therefore the use of antimicrobial therapy should be narrowed and consideration given for a lock therapy in order to avoid the change and removal of the implanted device.

TauroSept® containing 2% taurolidine can be instilled in already infected catheters and port systems in order to prevent an explantation.
Summary

- Catheter-related bloodstream infection (CRBSI) represents a major clinical and economic problem.

- CRBSI continues to cause considerable morbidity, mortality and increased cost of treatment, even though a considerable number of prophylactics are available and are partially in use.

- To reduce the incidence of CRBSI in any meaningful way, the existing prevention and treatment strategies must be optimized.

- Recent microbiological studies indicate that most incidents of CRBSI originate on the internal surfaces of CVADs.

- Progress in the area of antimicrobial lock solution techniques should in the future lead to more effective prevention and therapy of CRBSI.

- TauroSept® containing 2% taurolidine can be instilled in already infected catheters and port systems in order to prevent an explantation.\(^ {51,52}\)
The medical device TauroSept®

› TauroSept® is an antimicrobial solution (lock solution) for the prevention and treatment of catheter-related infections and is intended for instillation in intravenous catheters between treatments.

› TauroSept® contains the antibacterial chemotherapeutic agent taurolidine. Taurolidine differs from antibiotics in that it reacts chemically with the cell wall. It possesses a broader antibacterial and antimycotic spectrum of activity than the conventional antimicrobial agents currently available.

› It is also effective against methicillin-resistant and vancomycin-resistant bacteria (MRSA, VISA and VRE). Because of its chemical mechanism of action, development of resistance is unlikely and has not yet been observed.

› Taurolidine, even in low concentrations, causes loss of fimbriae and flagella in bacteria which inhibits or makes bacterial adherence to surfaces impossible. It has been suggested that the anti-adherence properties of taurolidine might well stop the formation of biofilm.

› Taurolidine influences no main blood coagulation factors in vivo that might be clinically relevant.

› Due to the strength of its effective mechanism, the medical device TauroSept® (taurolidine 2%) represents a promising alternative to conventional antibiotic instillation solutions in the prevention and treatment of CRBSI.
Chemistry
TauroSept® contains a 2% taurolidine solution (0.2 g / 10 ml), Sterile Water for Injection, 5% Polyvinylpyrrolidone (PVP) and traces of hydrochloric acid or sodium hydroxide for adjusting the pH value to 7.3.

Taurolidine
Chemical formula: C$_{7}$H$_{16}$N$_{4}$O$_{4}$S$_{2}$
Chemical name: Bis-(1,1-dioxo-perhydro-1,2,4-thiadiazinyl-4-) -methane
Molecular weight: 284.37

TauroSept® exists in equilibrium with taurultam and N-methylol-taurultam in aqueous solution.

TauroSept® (taurolidine 2% solution in 6 ml or 10 ml vials) is certified as a Class III medical device (Annex II, Section 4.1, Council Directive 93/42/EEC).
**Clinical pharmacokinetics**

TauroSept® is intended for instillation in central vascular access devices. Since this type of application is extracorporeal, the pharmacokinetics of taurolidine is of limited clinical relevance because only minute amounts are likely to enter the body. Therefore, the pharmacokinetics is only briefly discussed below.

**Distribution**
Plasma protein binding is approximately 40%.

**Metabolism**
Taurolidine and taurultam are quickly metabolized to taurinamide, taurine and CO₂ (Fig. 2). Taurolidine exists in equilibrium with taurultam and N-methylol-taurultam in aqueous solution.

**Elimination**
The half life of the terminal elimination phase ($T_{1/2}$) of taurultam is about 1.5 hours, that of the taurinamide metabolite about 6 hours. 25% of the taurolidine dose applied is renally eliminated as taurinamide and/or taurine.

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**Fig. 2. Mechanism of action and metabolism of taurolidine.**

- Tauroline
- Taurultam
- Methylol-taurultam
- Methylol-taurinamide
- Taurinamide
- Taurine + CO₂
- H₂N-CH₂-CH₂-SO₂-NH₂
- Active methylol-Group
**Mechanism of action**

TauroSept® contains the active ingredient taurolidine, a derivative of the aminosulphonic acid taurine. Taurolidine is a unique antimicrobial agent with a broad antibacterial and antymycotic spectrum of activity.\(^{54,55,56,57}\)

In contrast to most antibiotics, taurolidine acts by a non-selective chemical reaction. During the metabolism of taurolidine to taurinamide and ultimately taurine and water, methylol groups are liberated that chemically react with the mureins in the microbial cell wall and with the amino and hydroxyl groups of endotoxins and exotoxins. This results in denaturing of the complex polysaccharide and lipopolysaccharide (LPS) components of the microbial cell wall and in the inactivation of susceptible endo- and exotoxins. Resistance development to this mode of action has not been demonstrated and is unlikely to develop.\(^{54,56,71}\)

**Inhibition of microbial adherence**

During the development of taurolidine it was discovered that it possesses properties other than antimicrobial that are clinically relevant to the control of microbial infections. It could also be shown that taurolidine inhibits the adherence of microbes to human epithelial tissue and biomaterials in vitro.\(^{61}\)

Gorman et al. proved that taurolidine reduces the ability of clinical Candida albicans, E. coli and Staphylococcus saprophyticus urine isolates to adhere to human epithelial cells. Treatment of either epithelial cells or micro-organisms with taurolidine resulted in reduced adherence of microorganisms.\(^{62}\) The anti-adherence effect was time-dependent, requiring a contact time of 15–30 minutes to reach its maximum level of effectiveness. However, E. coli lost its flagella and fimbriae (and its pathogenicity) after an exposure time of just 4 minutes.\(^{63}\)

**Properties**

- Scanning electron micrograph of E. coli in culture medium (15x10^3)

- Before exposure to taurolidine 2% solution: Normal E. coli.

- 4 minutes after exposure to taurolidine 2% solution: Loss of flagella and fimbriae.

This effect, while in part possibly destroying or removing some of the fimbriae (and flagella), predominantly causes the fimbriae to be compressed to the bacterial cell surface or become agglutinated to the extent that adherence is reduced.
With regard to the distinction between Gram-negative fimbriated bacteria and Gram-positive non-fimbriated bacteria and species such as non-fimbriated Candida albicans; all these organisms adhere to epithelial cells and exhibit reduced adherence in the presence of taurolidine. This shows that taurolidine exerts its anti-adherence activity primarily via a chemical modification of outer surface structures such as fimbriae, causing agglutination and thus “disappearance” of the structure.

The effect of taurolidine on these structures which contribute an important role in the initiation of infection and in determining the pathogenicity of the organism, shows clear evidence of one aspect of the agent’s mechanism of action in preventing infection or reducing its severity.

Finally, it can be argued on the basis of these experimental studies that the anti-adherence properties of taurolidine counteract the formation of biofilm.

**Inhibition of staphylocoagulase induced coagulation**

Taurolidine inhibits, depending on concentration the pathologically-shortened coagulation caused by staphylocoagulase that cannot be inhibited by heparin. The results can be explained by a transfer of methylol groups to residues of arginine and histidine in the active region. Taurolidine potentially reduces the risk of pathological coagulation at the catheter tip and the complications caused when clotting leads to lumen occlusion. Staphylocoagulase is a crucial pathogenic feature of Staphylococcus aureus and other staphylococci which display a high affinity for the synthetic surfaces found in catheters, which they often colonize.

As yet, no blood coagulation dysfunction linked to taurolidine has been observed in human trials.

**Antimicrobial activity**

During the metabolism of taurolidine to taurinamide and ultimately taurine and water, three active N-methylol groups (CH2) are liberated that chemically react with the free amino groups (mureins) in the microbial cell wall. The microbial mureins are cross linked with methylene bridges, which alter their physical properties.

Electron microscopy of aerobic organisms for example Streptococcus pyogenes typically demonstrates the effect of exposure to 2% taurolidine, where the spherical cell structures have been broken down completely. With E. coli the bacteria become elongated and lose their capacity to divide and with it their pathogenic or invasive properties.

The in vitro killing time is 15 to 30 minutes, whereas the killing time for an antiseptic is by definition less than 5 minutes. Therefore taurolidine is not by definition an antiseptic but rather a local and systemic antimicrobial chemotherapeutic agent.

Taurolidine has a broad antimicrobial spectrum of activity that is effective against aerobes and anaerobes, Gram-negative and Gram-positive bacteria as well as yeasts and moulds in vitro. Taurolidine is also effective against methicillin-resistant and vancomycin-resistant bacteria (MRSA, VISA and VRE).
Fig. 3. Mechanism of action of taurolidine. 

**Diagram:**
- **Radiomarkers:**
  - Mureins
  - Exotoxins/Proteins
  - Endotoxins (LPS-Protein-Lipid-Complex)
  - Mureins
  - Exo-/Endotoxins
  - Mureins
  - Toxins

**Mechanism of action:**
- Irreversible methylol transfer to the bacterial cell wall and to the endo- and exotoxins.

**Chemical Structures:**
- Taurolidine
- Taurinamide
- Taurine

**Equations:**
- Taurolidine + H₂O → Exit
- Mureins + H₂N - CH₂ - CH₂ - SO₂ - NH₂ → Exit
- Taurinamide: H₂N - CH₂ - CH₂ - SO₂ - NH₂
- Taurine: H₂N - CH₂ - CH₂ - SO₃H

**Notes:**
- Taurolin®
- Taurolidine
The range of minimum inhibitory concentration (MIC) for anaerobic bacteria is between 0.03–0.6 mg/ml, for aerobic bacteria between 0.5–5 mg/ml and for fungi between 0.3–5 mg/ml. Table 1 provides an overview of the in vitro effectiveness of taurolidine against different microorganisms.

When exposed to a taurolidine 1% solution, Escherichia coli, Pseudomonas aeruginosa, Proteus spp., Enterococcus feacalis and Staphylococcus aureus die within 15–30 minutes.

TauroSept® contains taurolidine in a 2% concentration, equivalent to 20 mg/ml. This concentration easily exceeds the MIC for each microorganism. Development of resistance against taurolidine has not yet been observed and is unlikely to occur because of taurolidine’s chemical mechanism of action. In a recently published microbiological study by Sherertz et al., a number of instillation solutions were tested for their effectiveness against microorganisms that grow in biofilm; included were Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa and Candida albicans.

1 cm long segments of Hickman catheters that were incubated with different germs at 37°C were used in the test. Afterwards, the catheter segments were washed with phosphate buffered saline (PBS) and subsequently incubated for 0, 2,

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>MIC50 (mg/ml)</th>
<th>Microorganisms</th>
<th>MIC50 (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. aureus</td>
<td>0.25 – 0.5</td>
<td>Serratia marcescens</td>
<td>0.125 – 0.5</td>
</tr>
<tr>
<td>Staph. epidermidis</td>
<td>0.125 – 0.25</td>
<td>Acinetobacter spp.</td>
<td>0.5</td>
</tr>
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<td>Enterococcus faecalis</td>
<td>0.25</td>
<td>Moraxella catarrhalis</td>
<td>0.5</td>
</tr>
<tr>
<td>Strep. pyogenes</td>
<td>0.125</td>
<td>Pseudomonas aeruginosa</td>
<td>0.5 – 1.0</td>
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<tr>
<td>Strep. pneumoniae</td>
<td>0.125</td>
<td>Bact. fragilis</td>
<td>0.06 – 0.25</td>
</tr>
<tr>
<td>Strep. viridans</td>
<td>0.125 – 0.25</td>
<td>Bact. thetaiotaomicron</td>
<td>0.06 – 0.125</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>0.5</td>
<td>Burkholderia cepacia</td>
<td>0.3</td>
</tr>
<tr>
<td>E. coli</td>
<td>0.25 – 0.5</td>
<td>Clostridium difficile</td>
<td>0.125</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
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<td>Clostridium perfringens</td>
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</tr>
<tr>
<td>Klebsiella oxytoca</td>
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<td>Corynebacterium jeikeium</td>
<td>0.25</td>
</tr>
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<td>Enterobacter cloacae</td>
<td>0.25 – 0.5</td>
<td>Peptostrep. anaerobius</td>
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<td>Enterobacter aerogenes</td>
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<td>Peptococcus sp.</td>
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<td>Fusobacterium sp.</td>
<td>0.06 – 0.125</td>
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<td>Proteus mirabilis</td>
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<td>Candida albicans</td>
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<td>Proteus vulgaris</td>
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<td>Candida glabrata</td>
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<td>Morganella morganii</td>
<td>0.25 – 0.5</td>
<td>Candida tropicalis</td>
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</table>
4 and 24 hours at 37˚C with the instillation solutions vancomycin, ciprofloxacin, minocycline, minocycline-rifampicin, ciprofloxacin-rifampicin, vancomycin-rifampicin, ethanol, EDTA, minocycline-EDTA and taurolidine 2%. The segments were washed several times afterwards, put into a growth medium briefly and then placed in a dilution series on blood agar plates. Colony counts were carried out after a 24-hour incubation period.

Vancomycin, the most tested instillation solution of all, proved to be the least effective overall. In contrast, taurolidine, minocycline-EDTA, ciprofloxacin-rifampicin, minocycline-rifampicin and ethanol turned out to be most effective against the germs that were used in the test.

Ciprofloxacin-rifampicin and minocycline-rifampicin were applied in pharmacologically effective concentrations which can lead to the development of resistant strains.

Taurolidine is appreciably more effective in an acid environment (pH5) than at pH7 or 8. Mermel also evaluated the changes in pH on the MIC of taurolidine with VRE and found a reduction in MIC with decreasing pH changes. Additionally, taurolidine is not inactivated by biological fluids containing protein, such as peritoneal fluid, wound secretion, pus or blood. The activity of taurolidine is effectively increased when taurolidine solution is pre-warmed to

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<table>
<thead>
<tr>
<th>Species / Strains</th>
<th>Taurolidine MIC (mg/l)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Broth Alone</td>
</tr>
<tr>
<td>Vancomycin-Resist. Enterococcus</td>
<td></td>
</tr>
<tr>
<td>VRE 495</td>
<td>100</td>
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37°C; this effect is attributed to an acceleration of the reaction between the active methylol compounds and the bacterial cell wall which reduces the killing time.

**Anti endotoxin activity**
Lipopolysaccharides (LPS) in Gram-negative bacteria endotoxins are among the most poisonous substances known. They are essential weapons that enable the micro-organisms to eliminate the host body defences and then initiate its invasion; they are a causative factor in the rapid build up of resistance to antibodies. The toxic component Lipid A possesses two free amino groups, which react non selective and chemically with the methylol groups in tauroidine, through cross linking.

E. coli endotoxin was administered intravenously to mice at a dose range of 15 to 120 mg/kg. Tauroidine (0.1 ml of a 2% solution in 5% PVP) was administered i.v. 5 minutes before, after and together (mixed in vitro) with endotoxin. Tauroidine exerted significant protection from the lethal effects of endotoxin when given after endotoxin; this effect was enhanced when given before. There was complete protection when tauroidine was mixed with endotoxin (15 to 60 mg/kg) in vitro prior to administration.\(^\text{72}\)

The lethal effect of intravenous administration of *Bacteroides fragilis* crude endotoxin (0.1 ml of autoclaved bacterial suspension) was prevented by the i.v. administration of tauroidine (0.1 ml of a 2% solution in 5% PVP) immediately following, or mixed together, with the crude endotoxin.\(^\text{72}\)

During observations, both in vitro and in vivo of the release of large amounts of free endotoxin following initial antibiotic administration, the anti endotoxin activity of tauroidine has been examined with the emphasis on antibiotic-induced endotoxin liberation\(^\text{57}\). For each antibiotic tested the endotoxin concentration after growth in the additional presence of sub-inhibitory concentrations of tauroidine, represented a 20-fold reduction in endotoxin concentration.

**Anti exotoxin activity**
Tauroidine reacts in vitro with the exotoxins of *S. aureus*. These include highly toxic polypeptides from 18 amino acids. The main point of attack is the ε-amino group of lysine, which is readily cross-linked. *S. aureus* has the ability to release a toxin; staphylocoagulase, that combines with prothrombin to produce a complex that promotes coagulation with the eventual formation of insoluble fibrin.

This activity of staphylothrombin, unlike that of thrombin, is not inhibited by heparin. Further coagulase induced thrombi show an increased resistance to the fibrinolytic process. The ability of *S. aureus* to develop an enveloping fibrin barrier as a protection against the hosts defence mechanism emphasises the pathogenic importance of staphylocoagulase. As staphylocoagulase is the major characteristic of the pathogenic *staphylococcus* species we assume that its inactivation is an important feature of the efficiency of tauroidine in the treatment or staphylococcal infections.\(^\text{65,73}\)
Summary

› Taurolidine exhibits antibacterial and antimycotic activity against a wide spectrum of microorganisms.

› Taurolidine inhibits in vitro the adherence of microbes to human epithelial tissue and biomaterials. It is conceivable that this acts against biofilm formation.

› TauroSept® is effective against aerobes and anaerobes, Gram-negative and Gram-positive bacteria, killing them in less than 30 minutes.

› TauroSept® is also effective against methicillin-resistant and vancomycin-resistant bacteria.

› TauroSept® is effective against yeasts and moulds.

› TauroSept® performed better than vancomycin during microbiological tests on catheter segments incubated with biofilm-forming bacteria.

› TauroSept® neutralises endo- and exotoxins produced by the microbes and released during treatment with antibiotics.

› TauroSept® has been observed to date.

› Taurolidine inhibits the pathologically-shor- tened coagulation caused by staphylocoagulase. By exploiting this property of taurolidine, it might be possible to reduce the risk of pathological coagulation phenomena, particularly at the catheter tip.
Toxicology

TauroSept® is meant for instillation in catheter systems. This means that the toxicology of taurolidine is of limited clinical relevance here because the application is extracorporeal and only minute amounts are ever likely to enter the bloodstream. For this reason, the toxicology data for taurolidine that follows has been kept brief.

Toxic studies

Acute and subacute toxicity
Taurolidine distinguishes itself by having a relatively low acute and subacute toxicity. Excitation, exophthalmos and ataxia were observed in mice during intravenous infusion of taurolidine. The LD50 was >4050mg/kg (with water as a solvent). Intravenous infusion of taurolidine in a dose range of 200–800 mg/kg resulted in a NOAEL (No Observed Adverse Effect Level) of <800 mg/kg.

Intravenous injection of 400 mg/kg taurolidine into mice over a 10-day period caused irritability, spastic movement and lachrymation during the injections.

Chronic toxicity
Intravenous injection of 80 mg/kg taurolidine into rats over a 30-day period caused no change of behaviour in the animals, and there were no signs of direct toxicity.

Reproduction toxicity
No effects were observed on the reproductive performance of rats and rabbits that received intra peritoneal daily doses of taurolidine up to 600 mg/kg during segment I, II and III studies. There were also no signs of a teratogenic potential.

Mutagenicity
There were no signs of mutagen activity of taurolidine in an Ames test with Salmonella strains and a mouse micronucleus test.

Local tolerance and sensitization potential
The repeated application of taurolidine 2% to the shaved skin of guinea pigs caused neither irritation nor a sensitization of the skin. After an intradermal application of taurolidine 2%, some of the laboratory animals had mild to moderate reactions, but sensitization of the skin did not occur. The epidermal application of taurolidine 3% caused a mild erythema in some of the laboratory guinea pigs.

Summary

› Taurolidine, when intravenously applied, has a relatively low acute, subacute and chronic toxicity.

› Taurolidine has no mutagenic potential and exhibited no teratogenic effects in animal tests.

› Topical application of taurolidine does not cause sensitization of the skin.
Prevention and therapy of CRBSI

Jurewitsch et al. first described a case in 1998 in which a taurolidine 2% lock was instilled in a central venous catheter\textsuperscript{75}. A 29-year-old male patient with short bowel syndrome receiving total parenteral nutrition (TPN) was admitted to hospital 18 times in 9 years for treatment of recurring CRBSI. He was treated on each occasion with antibiotics, and the catheter was replaced 10 times. The patient was instructed to instil 1.5 ml taurolidine 2% in his catheter every time he finished his TPN. He continued to do this for 2 years. The incidence of CRBSI decreased from 8.5 to 1.5 episodes per 1,000 catheter days compared to the period before application of taurolidine.

In a pilot study carried out by Koldehoff & Zakrzewski, a taurolidine-Ringer’s 0.5% solution was instilled in the catheters of 11 oncology patients with a CRBSI who were not responding to systemic antibiotic therapy\textsuperscript{76}. The taurolidine-Ringer’s solution was allowed to remain in the catheters for 24 hours. In addition, all patients were treated with systemic antibiotics. All CRBSI episodes were successfully treated without having to replace a single catheter. Three patients who suffered a recurrent CRBSI were also successfully treated. There were no undesirable effects.

In an open clinical study carried out by Jurewitsch et al., the effectiveness of a taurolidine 2% solution in preventing CRBSI in patients receiving parenteral nutrition via a subclavian catheter was studied. Seven patients were included in the study that had experienced general malaise and/or chills and fever for a period of 1–6 months before inclusion.

If a CRBSI was diagnosed, the patients received a systemic antibiotic therapy and an intra-luminal instillation of antibiotics in accordance with the results of the sensitivity test.

Whilst participating in the study, the patients had to instil 3 ml taurolidine 2% every 12 hours when their total parenteral nutrition (TPN) was finished. Each catheter was flushed before the next TPN.

During the period prior to entering the study, the 7 patients had an average of 10.8 episodes per 1,000 catheter days. During the study, the incidence of infection fell to 0.8 per 1,000 catheter days. The number of infection-free catheter days was significantly higher when taurolidine was used compared to the period before therapy (p = 0.016)\textsuperscript{77}.

In 2009 Weber et al. investigated the option of a conservative i.v. port-a-cath maintaining, endoluminal, antiseptic local therapy in a selected number of patients with microbiologically detected infection of the i.v. port-a-cath using 2x5.0ml taurolidine 2.0%/d for 3 days an accompanying clinical observation of initial therapeutic use and its effect. Thereafter, microbe detection was again compared between blood culture and the port-a-cath catheter. From 2002 to 2005, overall 1588 i.v. port-a-caths were implanted at the Department of General, Abdominal and Vascular Surgery (University Hospital, Magdeburg, Germany). In total, 117 patients (69 females vs. 48 males; sex ratio, 1.44:1) with complications and subsequent indication for an explantation of the i.v. port-a-cath were observed (most frequent cause: infection of the i.v. port-a-cath, 40%).
Taken together, 10 patients underwent systematic administration of 2% taurolidine and follow-up investigation: In 8 of 10 patients (success rate, 80%), the infection of the i.v. port-a-cath could be successfully treated with taurolidine administration as described and, in addition, the threatening explantation of the i.v. port-a-cath could be avoided. Bisseling et al. 2010 carried out a randomized study with 30 patients with home parenteral nutrition (HPN) who had had recurrent CRBSIs. Thirty patients from one referral centre for intestinal failure were enrolled after developing a catheter-related bloodstream infection. Following adequate treatment, either with or without a new access device (tunnelled catheter or subcutaneous port), these patients were randomized to continue HPN using heparin (n = 14) or taurolidine (n = 16) as catheter lock. Whereas in controls 10 reinfection were observed, in the taurolidine group during 5370 catheter days only 1 reinfection occurred (mean infection-free survival 175 (95% CI 85-266; heparin) versus 641 (95% CI 556-727; taurolidine) days; log-rank p < 0.0001). No side effects or catheter occlusions were reported in either group. Moreover, after crossing-over of 10 patients with infections on heparin to taurolidine, only 1 new infection was observed.

Taurolidine lock dramatically decreased catheter-related bloodstream infections when compared with heparin in this high-risk group of HPN patients.

Summary

- TauroSept® alone and if indicated and necessary in combination with systemic antibiotics is suitable for prevention and treatment of catheter infections and prevents the usual necessity of removing the permanent catheter or extend its dwell time.
- TauroSept® can be used long term for the prevention of CRBSI, by patients with permanent intravenous catheters without any microbial resistance.
Clinical safety

When TauroSept® is instilled correctly in the central vascular access devices, no undesirable effects should occur. There are no risks or pharmacological interactions when used simultaneously with antibiotics.

An intraperitoneal application of taurolidine or an incorrect subcutaneous/intramuscular injection can cause an acute burning sensation. This pain reaction can lead, in the case of patients who are not anaesthetized or when too little anaesthesia has been used, to increased or decreased blood pressure with corresponding change in the patient’s pulse.

The risk of undesirable effects when TauroSept® is instilled is very low because very small volumes are used for catheter instillation and it is very unlikely that the contents of the catheter will enter the patient’s bloodstream. The low concentration and low volume mean that clinically relevant undesirable effects are improbable.

The accidental intravenous injection of a whole 10 ml vial of TauroSept® into a human would be equivalent to 200 mg taurolidine or 3 mg/kg approximately. Gong et al. administered 5.0 g of taurolidine in 250 ml of 5% polyvinylpyrrolidone in water over 2, 1, or 0.5 hours by intravenous infusion in 18 healthy volunteers in a parallel-group design. All subjects noted discomfort at the infusion site, although there were no serious adverse events 53.

In tests on animals, necrosis and scarring were observed after subcutaneous and intramuscular application.

Indication and application

Indication
TauroSept® is intended for instillation in central vascular access devices (CVAD) between treatments to prevent bacterial and fungal growth as well as to maintain device patency and to avoid formation of biofilm in the catheter lumen leading to infection.

Product information
TauroSept® is a heat sterilized medical device and comes supplied as a clear, sterile, non-pyrogenic solution. It comes in glass vials that each contains 6 ml or 10 ml solution.

Instructions for use
› Always follow the individual catheter manufacturer’s instructions for use carefully.
› The recommended priming volumes for each individual catheter must be strictly adhered to.
› Use 10 ml of sterile physiological saline to flush the catheter before instilling TauroSept®.
› Draw the required amount of TauroSept® from the vial with a sterile syringe and use it to fill the catheter lumen with solution.
› Allow TauroSept® in the catheter to work for at least 30 minutes or until the next treatment.
› Aspirate TauroSept®, if possible, and dispose of it as prescribed before using the catheter for the next treatment.
Precautions and contraindications

Precautions
› TauroSept® should never be injected systemically.
› TauroSept® should be used with precaution in the case of patients with a known predisposition to allergies.
› TauroSept® should never be mixed with oxidizing substances such as Dakin’s solution (sodium hypochlorite), povidone iodine or hydrogen peroxide because of the risk of it oxidizing to formic acid. These substances are normally used on the skin surrounding the insertion site and not on the actual catheter, meaning any risk is extremely low.
› TauroSept® was shown not to influence the activity of heparin in in-vitro studies, animal tests and clinical trials involving a limited number of patients. A recombinant tissue plasminogen activator (Alteplase, r-tPA) was successfully used in clinical practice when a thrombolytic intervention was needed during taurolidine instillation.
› TauroSept® should be instilled in the catheter as described in the instructions for use provided by the catheter manufacturer. Failure to follow the instructions for use carefully can lead to an accidental systemic injection of TauroSept®.
› The TauroSept® solution should only be instilled once, and the aspirated remainder should be disposed of in the prescribed manner.
› TauroSept® should not be used if the sealing cap is damaged in any way.
› TauroSept® should never be stored in the refrigerator.

Contraindications
Contraindications for TauroSept® are unknown to date.
TauroSept® is a heat sterilized medical device and comes supplied as a clear, sterile, non-pyrogenic solution. The vials contain 6 ml or 10 ml taurolidine 2% solution.

**Package size of TauroSept®**
5 vials with 6 ml or 10 ml taurolidine 2% solution

**Storage**
TauroSept® should be stored horizontally at temperatures between 15 and 30°C. TauroSept® should never be stored in the refrigerator. The TauroSept® solution should only be instilled once and the aspirated residual solution from the catheter should be discarded in the manner described in the waste management guidelines that apply.

**Shelf life**
4 years for unopened vials.

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**General product information**

TauroSept® is an innovative catheter lock solution that

› considerably reduces the risk of infection during intravenous catheter use, counteracts bacterial adherence, and possesses both antimicrobial spectrum and anti-staphylocoagulase potential.

› has a very broad spectrum of antibacterial and antimycotic activity enabling it to prevent CRBSI or treat it effectively.

› is not expected to develop antimicrobial resistance because its antimicrobial effectiveness stems from a chemical reaction with the cell wall of the microbe.

› counteracts the colonization of the catheter with bacteria and fungi, reducing the risk of infection.

› is registered as a medical device.

› stands out from antibiotic instillation products because of its ability to neutralize endo and exotoxins.

› delivered promising results during clinical trials that studied its effectiveness in the prevention and treatment of CRBSI in patients with permanent catheters.
References


