

ANTIMICROBIAL PROPHYLAXIS AND INFECTION CONTROL IN CASES OF MECHANICAL CARDIAC SUPPORT DEVICES

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Summary

Ventricular assist devices (VADs) for patients with severe heart failure are improving, and there are increasing numbers of implants, as device therapy enters the era of permanent use (i.e. destination therapy). The device-related infection of implanted pumps and sepsis remain important risk factors for death, and once infections are established on biomaterial surfaces, they usually persist despite prolonged antimicrobial therapy.

Biofilm forming is the crucial moment in the pathogenesis of many subacute and chronic bacterial infections, including the infections connected with a foreign body. Biofilm is a significant clinical problem. Its eradication by conventional antimicrobial agents is rather complicated, as it disposes of several mechanisms for developing resistance to antibiotics. The role of persisting cells is crucial in the context of the tolerance of bacterial biofilm towards antimicrobials. The mechanism for biofilm forming and the consequential antimicrobial resistances are the key to developing new therapeutic strategies.

Therefore, adherence to evidence-based infection control and prevention guidelines, meticulous surgical technique and optimal post-operative surgical site care form the foundation for VAD-associated infection prevention.

Keywords: ventricular assist device; infection; biofilm; antimicrobial therapy; prevention guidelines

INTRODUCTION

The most frequent complications of ventricular assist devices (VAD) are bleeding, infection, thromboembolism, renal failure, haemolysis and neurological dysfunction. Bleeding and infection are the most prevalent and immediate complications [1].

Infection frequency in patients in need of a VAD is presumed to be over 35 % [2]. Within the first three months (peak in the third week) following the operation, 28 % of patients suffer from infections [3,4]. According to the *REMATCH trial* (the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure), the mortality caused by sepsis equals 41 % [5].

Besides the risk factors (gender; obesity; smoking; chronic obstructive pulmonary disease - COPB; Low Cardiac Output State; *Diabetes mellitus*; corticosteroid therapy; renal and hepatic insufficiency) [6] and the prevention of infections common for all cardiac surgical patients (urinary tract infection – UTI [7]; ventilated associated pneumonia – VAP [8]; catheter-related bacteraemia – CRB; sepsis), for patients with mechanical cardiac support devices, characteristic are also several additional specific factors. These factors are as follows: the prevention of infections connected with the mechanical cardiac support pump / device (VAD); the pre-, intra- and post-operative management; and the very origin of VAD infections related to biofilm forming.

MECHANICAL CARDIAC SUPPORT DEVICE (*Ventricular Assist Device – VAD*)

First generations of implantable pulsative VADs (*Heart Mate I*) had – though having enhanced the haemodynamics in cardiac surgical patients – also contributed to developing frequent infections (18–80 %) [3,9,10]. High infection frequency (among other factors) has initiated the development of new generations of rotational, non-pulsative pumps (*Heart Mate II*), the introduction of which aimed at reducing the infection frequency (by 13–27 %). Differences between the older and the newer pumps, in favour of the latter ones, are further manifested in the following: size and weight (1/7 smaller and 1/4 lighter); operation scale (as opposed to extensive operation and large haematoma at the pump site, the infection frequency is much lower when the pump is smaller); thinner, more flexible and impregnated cuffs have replaced the earlier inadequately immobilised, non-flexible and large drivelines that had often resulted in ascendant infections. Consequently, with regard to the pump site and the pump of the first generation itself, secondary infections and pump infections ending in bacteraemia had occurred more frequently, unlike *Heart-Mate-II*-related infections, which – according to Lahpor – do not exceed the range 0–3 % [11].

PRE-, INTRA- AND POST-OPERATIVE MANAGEMENT

Pre-operative infection control includes the patient-related procedure and the setting of the central venous catheter, while following the CDC 2009, Guideline for the Prevention of Intravascular Catheter-Related Infections [12].

Full patient preparation for the operation comprises the following: eradication of chronic infections / focus; decolonisation of the skin by the means of antiseptic polyhexadine-based cleansing; eradication of the nasal carrier *Staphylococcus aureus* MRSA by applying antibiotic prophylaxis; elimination of superfluous medical devices (urinary catheter, central venous line, etc.); prevention of the aspiration of stomach content (in case of intubation) and decubitus; maintenance of oral hygiene; control of the blood glucose level accompanied by adequate diet [6].

The staff should maintain maximal hand hygiene (in accordance with the WHO Guidelines on Hand Hygiene in Health Care) both before and after the contact with a patient during all procedures, as well as pre-, intra- and post-operatively; this is of crucial importance for the prevention of hospital infections [13]. Antimicrobial prophylaxis is tailored to institutional surveillance cultures, and a patient's culture results in doses adjusted for renal and hepatic function: Vancomycin (15 mg/kg, i.v. one hour pre-operatively, every 12 x 48–72 hours) – covered gram-positive bacteria; Levofloxacin (500 mg i.v. Q12 x 48–72 hours) – for gram-negative bacilli / capable of penetrating into the area of inflammation (macrophages); Rifampicin (600 mg PO 1–2 hours pre-operatively, daily x 48–72 hours) – due to small molecule, capable of penetrating into the biofilm; Fluconazole 400 mg i.v. pre-operative and each day x 48h – covered *Candida* spp.; Mupirocin 2 % nasal ointment pre-operatively and twice daily x 5 days – decolonisation of the staphylococcal nasal carrier (REMATCH trial) [5].

The intra-operative infection control includes the operating room, the operating field and the mechanical cardiac support device / pump itself.

In the operating room, the staff hand hygiene has to be harmonised with the European norms – EN 12791: 2005 Surgical hand disinfection [13,14,15]; apart from limited movement of the staff in the room, it is also recommended to use a *HEPA filter* for maintaining ultra-clean air during the surgical implantation procedure [6, 16, 17].

The operating field, apart from prior antiseptic cleansing (with chlorhexidine or iodoform) and polyalcohol antiseptics, is to be covered with sterile coverings.

VAD itself should be opened only immediately before the operation; using meticulous surgical technique (careful haemostasis – avoiding the pump site haematoma), it is to be implanted and immobilised, and a drain should be placed [16].

In post-operative infection control, the most critical component is driveline immobilisation (care), as this is the place where the initial contamination – colonisation – infection (usually by the saprophyte flora of the patient's skin) most frequently occurs. It is therefore very important to instruct patients on the following issues: minimisation of driveline exit site trauma; importance of personal hygiene and life environment cleanliness; adequate diet and nutritional support [18]; and the control of blood glucose level [19]. It is further of major importance to terminate the peri-operative prophylaxis after 48 hours, and to introduce – in accordance with microbiological cultures – the antimicrobial therapy, with the aim of avoiding an increasingly frequent medical problem – the emergence of multiresistant organisms (Extended Spectrum Beta Lactamasis *Enterobacteriaceae* – ESBL; Vancomycin Resistant *Enterococcus* – VRE) [20,21].

Driveline exit site care includes: dressing technique; antiseptic cleansing; avoiding shower for the first 30 days (later using a special shower set); if any clinical signs of infection emerge, a surrounding skin swab after bandaging is taken, as well as the aspiration of the wound secretion for microbiological analysis, i.e. isolation and identification of agents with the accompanying sensitivity test.

INFECTION

Post-operative VAD infection includes the already mentioned driveline site on the skin, the VAD site, and the infection of the inner pump surface.

Infections may be caused in the following ways: by intra-operative inoculation (in the rarest number of cases); haematogenously (seldom) as a result of haematogenous spreading of catheter-related bacteraemia (CRB); as a consequence of secondary bacteraemia caused by either ventilated associated pneumonia (VAP) or urinary tract infection.

The most frequent late infection occurs however as a result of the spreading of the initial driveline colonisation to the pump site. It is an ascendant bacterial colonisation of the saprophyte flora not only to the driveline, but also to the inflow / outflow cannulas, accompanied by biofilm / glycocalyx forming. The colonisation becomes an infection spreading to the pump site, which – depending on the size – contains non-drained blood (haematoma), i.e. a potential medium for microorganisms. From the pump site, the infection spreads to the pump itself, i.e. further to the blood stream as bacteraemia / sepsis.

Except from VAD infections, in some patients, deep sternotomic wounds connected with purulent mediastinitis or a necrosome of the thoracic wall may develop.

Biofilm

According to the *National Institutes of Health*, biofilm production is regarded an important medical term, as it is a part of over 80 % of all the microbial infections in the human body [22].

It is in the nature of 99 % of bacteria to form biofilm, and the most common microorganisms, responsible for two thirds of infections connected with a foreign body, are biofilm-forming bacteria – staphylococci (*Staphylococcus aureus*, *S. epidermidis*, *S. lungdunensis*), followed by *Pseudomonas aeruginosa* and *Enterococcus* spp, and, in cases of fungus infections, *Candida* spp.

The mentioned saprophyte flora, which initiates the colonisation, consists mainly of staphylococci (coagulase-negative and *Staphylococcus aureus* / MRSA), which – within a very short time period (24 hours) – initiate the “good biofilm” forming, as protection from the pathogenic flora. A longer time period is needed for biofilm forming in gram-negative bacteria (e.g. *Pseudomonas aeruginosa*).

The majority of chronic infections are connected with the forming of biofilm adhered to the native tissue, the mucous surface or the wound tissue: e.g. cystic fibrosis and *Pseudomonas aeruginosa*; endocarditis of native valves; middle ear infection; periodontitis; etc.

However, biofilm is much more frequently an agent causing non-eradicated infections connected with a foreign body, i.e. the forming of extracellular matrix (glycocalyx) at the surface of medical products (implants) in the human body; e.g. urinary catheters (10-30 %); mechanical ventilation (9-27 %); central venous catheter (3-8 %); vascular grafts and coronary bypasses (1-5 %); pacemakers (1-7 %); and other various kinds of implants / prosthetic devices – breasts, joints, intra-ocular lenses, etc. (1-3 %). According to Lynch [23], infection frequency associated with the implantation of the mechanical cardiac support devices (VAD) is the highest: 25-50 %.

In order to enable the direct visualisation of the three-dimensional structure of bacterial biofilm, the *Center for Genomic Sciences* has developed a new diagnostic protocol – the *Confocal laser scanning microscopy (CLSM)*, based on 16S rRNA [24], and the *Fluorescence in situ hybridization (FISH)* method, which have in the recent years helped creating a better understanding of these types of infections [25].

Biofilm – depending on the sort, type and surrounding – consists of bacteria within and surrounding the glycocalyx. The bacteria at the bottom of biofilm (in anaerobic conditions) are the reason why the antibiotic therapy may be extremely resistant (low-level penetration of antibiotic / antifungal medications; protection from phagocytosis); biofilm-producing bacteria may be extremely difficultly cultivated by using the traditional microbiological methods [26].

The antimicrobial therapy in cases of infections associated with biofilm is based on the result of a conventional antibiogram of the planctonic bacteria. However, this sensitivity is not equal, even if the agents within the biofilm are. The bacteria within the biofilm are 100–1,000 times more resistant than the planctonic bacteria; the antibiotic is therefore active against the latter bacteria, but not against the biofilm; this makes the treatment of patients suffering from implant infection unsuccessful [27]. None of the so-far known antibiotics (except for peroral Rifampicin, which should always be combined with other antimicrobial drugs) have managed to be active against hibernating bacteria within the biofilm; only the new lypopeptide, Daptomycin, has been successful. Due to its extremely swift bactericidal acting by causing the bacterial membrane of the agent – gram-positive bacteria – to break, Daptomycin is antimicrobially active against the stationary bacterial phase of the agents, i.e. the biofilm [28,29].

AGENTS CAUSING VAD INFECTIONS

Staphylococcus aureus and coagulase-negative staphylococci (CoNS) are the most frequent agents of driveline exit site and pump site infections. In doubt of an infection, not only must the microbiological analysis be done without delay, but also the urgent direct gram-medication taken, so that the empirical antimicrobial therapy might be commenced as soon as possible. Agents causing infections in intra-vascular devices resulting in VAD bacteraemia are, apart from the already mentioned gram-positive cocci, *Candida*, *Pseudomonas aeruginosa* and other multiresistant microorganisms.

The prevalence of enterococcal device colonisation in Herrmann's study [17] may be explained by the high incidence of thromboembolism of small bowel arteries. Due to the virulent factors and primary pathogenic nature, infections caused by *S. aureus* usually develop in the early post-operative period as acute, and are accompanied by common inflammation symptoms. Infections caused by *Staphylococcus epidermidis* and other CoNS are in most cases – due to the low-level invasiveness of the agents and the slow development of the clinical inflammation symptoms – recognised only several months after the operation.

THERAPY

Apart from the surgical procedure (in case of the pump site infection, incision is obligatory) and the antibiotic therapy in the treatment of such infections, in cases of the presence of *Staphylococcus aureus*, aerobic gram-negative bacilli and *Candida* spp., the VAD implant has to be removed as well. The supportive surgical therapy is *Vacuum Assisted Closure – V.A.C.*, which accelerates wound healing and granulation production, and eliminates excess liquid from the wound surface and the skin lobe.

Table 1.

Supervision culture	Urine	Blood culture	Wound Tissue	Part of prosthesis	Bronchoaspirate Sputum	Others	Serology
30/10/2008 SURGERY							
<input checked="" type="checkbox"/>					10/08 B*. <i>E.coli</i> , <i>P. aeruginosa</i>		<input checked="" type="checkbox"/>
11/08 – MEROPENEM, VANCOMYCIN, FLUCONAZOLE							
			12/08 <i>St. epidermidis</i>		11/08 St. <i>Candida albicans</i>	11/08 VC‡ <i>E.coli</i>	
		03/09 <i>Stenotrophomonas maltophilia</i>		03/09 <i>St. pidermidis</i>		03/09 D** <i>Corynebacterium</i>	
03/09 – VANCOMYCIN, CIPROFLOXACIN							
	04/09 <i>Proteus mirabilis</i>		04/09 <i>Corynebacterium</i>				
		07/09 <i>S.aureus</i>					
07/09 - CLOXACILLIN							
	08/09 <i>P.aeruginosa</i>				08/09 B. <i>P. aeruginosa</i>		
08/09 - MEROPENEM							

ABBREVIATIONS: – Satisfactory supervision culture; B* – bronchoaspirate; ST – sputum; VC‡ – top venous catheter; D** – top drain
10/08 – month/year

Table 2. M.B. – op. LVAD 18. 06. 2009. / exitus 20. 06. 2009.

Supervision culture	Urine	Blood culture	Wound Tissue	Part of prosthesis	Bronchoaspirate Sputum	Others	Serology
14/01/ <i>St. aureus</i> N■		☒	☒	☒		☒	☒
25/01/ <i>Morganella morganii</i> <i>Enterococcus faecalis</i>							
08/06 / <i>St. aureus</i> N■							
16/06/ CEFAZOLIN 18/ 06 /09 SURGERY							
19/06/ <i>Enterobacter</i> N■ <i>cloacae</i> <i>P. aeruginosa</i> S§ <i>Enterococcus</i> spp.					19/06/ B* - <i>P. aeruginosa</i>		
19/06/ MEROPENEM							

ABBREVIATIONS: ☒ – No indications for taking; N■ – nose; B* – bronchoaspirate, S§ – skin (hurdle) 14/01/- day/month/

Table 3. S.B. – op. LVAD 28. 10. 2009.

Supervision culture	Urine culture	Blood culture	Wound Tissue	Part of prosthesis	Bronchoaspirate Sputum	Others	Serology
<input checked="" type="checkbox"/>	10/09 E. coli	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>
26/10/ – 04/11/ – CIPROFLOXACIN							
27/10/ – VANCOMYCIN							
28/10/09 SURGERY							
01 – 09/11/ – CEFAZOLIN							
			06/11/ <i>St. epidermidis</i>			10/09 D Coagulasa negative staphylococci	
	11/09 <i>E. coli</i>		11/09/ <i>St. epidermidis</i>				
15 – 21/11/ – AMOXYCILLIN/ CLAVULANIC acid							
23/11/ – 03/12/ – VANCOMYCIN							
			22,23,24,26/11/ <i>St. epidermidis</i> 23,24,26 /11/ <i>Corynebacterium</i>				

ABBREVIATIONS: – Satisfactory supervision culture; – No indications for taking; D** – top drain
10/09 – month/year; 26/10/ – day/month

Table 4.

Supervision culture	Urine	Blood culture	Wound Tissue	Part of prosthesis	Bronchoaspirate Sputum	Others	Serology
☑	☑	☒	☒	☒	☒	☑ ☑	☒
17/02/ - VANCOMYCIN 1g in 20.00 h							
18/02/2010 – SURGERY							
18 – 21/02/ – VANCOMYCIN RIFAMPICIN FLUCONAZOLE							
22 – 24/02/ – CEFAZOLIN							

ABBREVIATIONS:

☑ – Satisfactory supervision culture; ☒ – No indications for taking; D** – top drain

17/02/ - day/month/

Along with a carefully chosen antimicrobial therapy according to the agent antibiogram, in cases of gram-positive cocci, which are also the most frequent, it is relevant to prescribe the antibiotic that is active against biofilm. In referential literature, there are frequent mentions of using Rifampicin in combination with Cloxacillin, Vancomycin, Linezolid or Fucidic acid in the staphylococcal biofilm therapy [30,31].

In his work, Beiras-Fernandez [2] mentions the currently most efficient antibiotic for treating multiresistant gram-positive biofilm-related VAD infections – the already mentioned Daptomycin. In a retrospective study, 9 patients suffering from post-implantation VAD infections were analysed. In as much as 83 %, infection agents were gram-positive cocci (33 % Methicillin Resistant *Staphylococcus aureus* – MRSA; 25 % *Enterococcus faecium*; 12,5 % Methicillin Resistant *Staphylococcus epidermidis* – MRSE; 12,5 % Methicillin Sensitive *Staphylococcus aureus* -MSSA); out of this number, in 66 %, catheter-related infections were present. Therapy with Daptomycin was empirically initiated in all cases. Successful outcomes were reported in seven subjects (78 %), with two patients succumbing due to multiorgan failure related to their heart condition prior to completing the therapy.

DUBRAVA CLINICAL HOSPITAL

In the Dubrava Clinical Hospital, four patients received mechanical circulatory support in the period between October 2008 and February 2010; one patient was implanted Paracorporal VAD, and the others Left VAD).

Prior to the VAD implantation, each of the hospitalised patients underwent, inter alia, microbiological screening: nose, pharynx, skin (axilla, inguinal region, anus / perineum) swabs, and urine culture. In accordance with a patient's clinical state and if indicated, following samples were taken pre- and / or post-operatively: haemoculture; bronchial aspirate / sputum; wound swab / tissue / part of a prosthetic device; other material – e.g. drain peak; drain content; central venous catheter peak; catheter-surrounding skin swab, etc. In some patients, serology to: *Cytomegalovirus*, *Ebstein Barr* virus and *Toxoplasma* was indicated as well. The entire microbiological control and the samples taken (according to time periods) in all four cases may be seen in Tables 1–4. Usual peri-operative prophylaxis was prescribed routinely, in accordance with the REMATCH trial [5], except for substituting Levofloxacin (which is not registered in Croatia) by Ciprofloxacin, in cases where the control swabs were satisfying. Where not, the chosen antimicrobial therapy (see Tables 1–4) was introduced even prior to the operation, and changed during the post-operative stay in accordance with a patient's clinical state and the results of the microbiological analyses of the samples.

The final outcome of the medical treatment of the four patients with mechanical cardiac support device implants was that two of the patients died, while in the other two cases, the operations were successfully performed; in one of the latter cases, heart transplantation was consequently performed as destination / end therapy.

The first patient (G.K., Table 1), though the mechanical heart was removed by using intensive haemodynamic monitoring and applying carefully chosen, state-of-the-art antimicrobial therapy, died due to septic shock. The second patient (M.B., Table 2) also died, only two days following the operation, due to sepsis of unknown aetiology. The third patient (Š.J., Table 4) was released from hospital soon after the operation; the patient's general state was stable, all the control cultures were satisfying, and the patient received adequate and carefully chosen antimicrobial therapy based on the microbiological samples. The fourth patient (S.B., Table 3), with both pre- and post-operative states being stable, ended the hospitalisation in December 2009; eight months following the VAD implantation, in June 2010, heart transplantation was successfully performed.

CONCLUSION

Microbes are ubiquitous in the environment and pose a constant threat to the well-being of the patients with implanted VAD. The infection prevention and control according to the *Evidence based guidelines*, along with the regulation of the pre-operative risk factors, are therefore important factors in the context of patient prepara-

tion for the mechanical circulatory support. Meticulous surgical technique, optimal post-operative care of the surgical site and driveline immobilisation, avoiding the emergence of trauma, and applying healthy diet assure the success of the operation. Thanks to the today's correct approach in treating VAD infections and the new bactericidal antimicrobial medications, the outcome of the therapy applied in cases of patients with chronic LVAD infections has become successful in an increasing number of cases. In future, this will surely be further supported by enhancing the VAD hardware with antiseptic dressing and biomaterial resistant to biofilm forming, as well as by developing completely implantable systems with transcutaneous energy transmission to eliminate the need for percutaneous driveline. Such VAD technology will probably result in the reduction of morbidity by preventing the colonisation of microorganisms, leading consequently to the reduction of biofilm-related infections and the related unnecessary antibiotic therapy.

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Sažetak

Antimikrobna profilaksa i kontrola infekcije kod mehaničke potpore srca

Danas je sve većem broju bolesnika sa teškim zatajenjem srca, zbog napretka tehnologije omogućeno privremeno ili trajno liječenje uređajem (pumpom) za mehaničku potporu srca (VAD).

Infekcije implantiranih srčanih pumpi i sepsa ostaju važnim faktorom rizika za smrt. Kad se na površinama biomaterijala utvrdi postojanje infekcija one perzistiraju unatoč produljenoj antimikrobnoj terapiji.

Formiranje biofilma je presudni korak u patogenezi mnogih subakutnih i kroničnih bakterijskih infekcija, a osobito infekcija povezanih sa stranim tijelom. Biofilm je signifikantan klinički problem. Teško se eradicira konvencionalnim antimikrobnim lijekovima, jer posjeduje nekoliko mehanizma stvaranja antibiotske rezistencije. Perzistirajuće stanice imaju glavnu ulogu u toleranciji bakterijskog biofilma prema antimikrobnom lijeku. Mehanizam stvaranja biofilma i posljedice antimikrobne rezistencije biti će ključ za razvoj novih terapijskih strategija.

Dakle, poštivanje dokazima utemeljene kontrole infekcija uz smjernice za prevenciju istih, pedantna kirurška tehnika i optimalna njega postoperativnog kirurškog mjesta čine temelje za prevenciju infekcija povezanih s VAD-om.

Ključne riječi: VAD; infekcija; biofilm; antimikrobna terapija; smjernice za prevenciju infekcija