Non-antibiotics that may influence Central Line-Associated Bloodstream Infection (CLABSI)

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PhD thesis

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I. Introduction

Central line-associated bloodstream infection (CLABSI) is one of the most severe forms of hospital acquired infections. Central venous lines have been gaining importance in the rapidly evolving contemporary medicine. Different therapeutic modalities, like total parenteral nutrition (TPN), chemotherapy for malignancies, and renal replacement therapy, are inconceivable without central venous accesses. We could not find any accurate data regarding the use of central venous lines in Hungary; however, different studies have given some insight into central line consumption in the UK (200000 / year) and the US (5 Million / year). According to the literature, the incidence of CLABSI is between 9-26% (0.4-24 case / 1000 catheter days) dependent on patient cohort, the country where the survey has been done, and the preventive bundles applied. CLABSI may increase mortality by 7 – 56% and additional therapeutic costs as well. CLABSI can be the most expensive Hospital Acquired Infection as its additional cost can be as high as $45000. Central Venous Line-Associated Infections caused by bacteria can be originated from the patient (endogenous) or from the surrounding environment (exogenous). The defensive mechanisms of the skin breaks during central venous catheter placement; therefore, during the procedure, bacteria can be introduced into the deeper subcutaneous tissues as well as through the site of the puncture. CLABSI can be caused by contaminated infusions, giving sets, and bolus injections. These sets and infusions can get contaminated during their preparation or while getting changed. Central Venous Catheters could get infected from other infectious sources of the body through the haematogenous pathway. When bacteria reach the central venous catheter, they adhere to it and colonize it while forming a biofilm on the catheter surface. Once the biofilm is being formed, it can be very challenging to treat as it is difficult for the antibiotic to penetrate the material of the biofilm. There are bacteria in different metabolic states, from active to dormant, rendering them less susceptible or more resistant to treatment. Therapy of such a complicated infection can be challenging and may well end up in catheter removal eventually. New therapeutic methods were introduced to treat the cannula associated infection and keep the catheter in place. This approach can be beneficial in patients who need long term catheters with limited central venous access. The most common bacteria that can cause CLABSI are gram-positive coagulase-negative Staphylococcus (CoNS) 34.1%; Enterococcus spp. 16%; *Staphylococcus aureus* 9.9%; and gram-negative Klebsiella spp. 5.8%; Enterobacteriaceae 3.9%; *Pseudomonas aeruginosa* 3.1%; *Escherichia coli* 2.7%; Acinetobater spp. 2.2%. Candida in 11.8% and other bacteria in 10.5% of the CLABSI cases

were present. Frequently used intravenous medications can easily get contaminated during the preparation process either on the wards or in the anaesthetic room with an overall incidence of 5-44%. On opening the glass vials without cleaning them, little contaminated particles can fall into the intravenous solution that can be the cause of severe infections in case the actual medication supports bacterial growth. According to the literature and our findings, some medication does not support bacterial growth or even have bactericide properties hence safe to use them from that perspective.

In our anaesthetic practice, we tend to draw up some medications at the beginning of the shift (atropine, glycopyrrolate, ephedrine). We may use them later on in case of an emergency. Unused medicine quite often ends up in the bin at the end of the day. That policy can lead to substantial additional costs added to the anaesthetic expenditure. Since the central venous devices play a pivotal role in treating the patients in need and the treatment of a CLABSI can be extremely challenging, not to speak of the complications, it is better to prevent it than treat it. There are several options to prevent CLABSI from happening. The first element is the continuous education of the staff. Other measures like hand hygiene, strict infection control during preparation of infusions and medications, introduction and application of central venous catheter care bundles. The development of CLABSI can be influenced by the fixation and dressing, as well as the material of the catheter (PVC, polyurethane, teflon, impregnated with silver or antibiotics). There are also patient-related factors such as age, the immune or metabolic status, and comorbidities of the patient. Lock therapy can be a preventive and therapeutic tool in the case of CLABSI. Antibiotic and non-antibiotic drugs can be used alone or in combination in the lumen of the cannula during intervals between therapy sessions to prevent CLABSI. The most often used and investigated antibiotics are gentamycin, tobramycin, minocycline, vancomycin, cefotaxime, and cefazoline. The frequent deployment of antibiotics can easily lead to bacterial resistance. To avoid the development of resistance, we can use non-antibiotics to enhance the effect of antibiotics, especially in biofilms. Heparin, citrate, ethanol, taurolidine, methylene-blue, parabens have been used either alone or in combination with antibiotics. Although their use has contributed to reducing the development of CLABSI, none of them have been proven to be satisfactorily effective.

II. Objectives

1/ We aimed to determine the contamination rate of infusions at a university department of intensive care.

2/ Determine which medications support or inhibit bacterial growth if contaminated.

3/ Determine which bacteria contaminate the infusions at the bedside at a university department of intensive care.

4/ Investigate whether there is any connection between the bacteria isolated from the infusions collected at the bedside and the bacteria isolated from patients' blood samples.

5/ Investigate bacterial growth in atropine.

6/ Investigate bacterial growth in glycopyrrolate.

7/ Investigate bacterial growth in amiodarone.

8/ Determine the minimal inhibitory concentration (MIC) value of amiodarone.

III. Material and methods

Isolation of bacteria from syringes collected from a university department of intensive care.

One hundred and fifty-five 50 mL syringes were collected that were used at the intensive care unit. The infusions were used for 14 – 72 hours. The staff was not informed of the aim of the study. One drop was spread on the surface of agar and eosin-methylene blue agar at the lab. Following 24 and 48 hours' incubation at 37°C the isolated bacteria were identified with standard microbiological methods. Antibiotic susceptibility was also determined. Bacteria isolated from syringes were compared with bacteria isolated from blood samples of the same patient by antibiotic sensitivity and RAPD-PCR.

Medications administered from the collected syringes were: amiodarone 12 mg mL^{-1}, furosemide 1 mg mL^{-1}, noradrenaline 60 µg mL^{-1}, adrenaline 60 µg mL^{-1}, bupivacaine 0.125%, sufentanil 1 µg mL^{-1}, metoprolol 0,1 mg mL^{-1}, insulin 1 unit mL^{-1}, propofol 2%, potassium chloride 20 mg mL^{-1} and morphine 1 mg mL^{-1}.

Medications, infusions, culture media, and bacteria for the investigation of bacterial growth in atropine, glycopyrrolate, and amiodarone

Investigated medications:

- atropine sulphate (Atropine Sulphate Injection BP®, B. Braun Melsungen AG, Berlin, Germany, 600 µg mL^{-1});
- glycopyrronium bromide (Robinul®, Anpharm, Croydon, UK, 200 µg mL^{-1});
- amiodarone hydrochloride (Cordarone®, Sanofi Aventis, Budapest, Hungary, 50 mg mL^{-1});
- glucose 5% (Glucose B. Braun 50 mg/ml infusion, B. Braun Melsungen AG, Melsungen, Germany),
- sodium chloride 0.9% (NaCl 0,9% Fresenius infusion, Fresenius Kabi Deutschland GmbH, Bad Homburg v.d.H., Germany)
- Mueller-Hinton agar (Bio-Rad, Marnes-la-Coquette, France)
- eosin-methylene blue agar (Bio-Rad, Marnes-la-Coquette, France)

Investigated bacterial strains

Laboratory reference strains

S*taphylococcus aureus* ATCC (American Type Culture Collection) 23923,
Staphylococcus epidermidis ATCC 35984
Escherichia coli ATCC 25922,
Pseudomonas aeruginosa ATCC 27853,
Klebsiella pneumoniae ATCC13883.

Clinical isolates

S. epidermidis
metallo-beta-lactamase producing (MBL) *P. aeruginosa*,
methicillin resistant *S. aureus* (MRSA),
extended-spectrum beta-lactamase (ESBL) producing *E. coli*,
extended-spectrum beta-lactamase (ESBL) producing *K. pneumoniae*,
multidrug-resistant *Acinetobacter baumannii* (MDR)

Investigation of bacterial growth in atropine, glycopyrrolate, and amiodarone

Mueller-Hinton liquid culture media were inoculated with the investigated strains and incubated at 37°C overnight. Then the culture was set at 0,5 McFarland density. This means 1,5 – 3 x 10^8 mL^{-1} colony forming units (cfu). All strains were further diluted in saline. The starting cfu was 10^3 – 10^4 mL^{-1}. The bacteria were kept at room temperature. Following stirring (vortex) 10 µL from the culture was taken and spread on MH agar plate immediately, and at 15, 45, 60 minutes, 2, 3, 4, 6, 12, or 24 hours. After 24 hours' incubation at 37°C the cfu was counted. The results are average ± SD.

Bacterial growth in glucose 5% and MH liquid media served as control. The sterility test of atropine, glycopyrrolate, and amiodarone ampoules, and that of the control solutions was also done by incubating them for 24 and 48 hours' at 37°C.

We had three parallel investigations for all medications.

Determination of amiodarone MIC

The suggested method of the "Clinical and Laboratory Standards Institute" was modified to determine the MIC value in glucose 5% that is the recommended diluent for amiodarone. The strains were cultured in Mueller-Hinton agar then it was set to McFarland 0,5 in saline. Amiodarone was diluted in glucose 5% in 96 wells plates and bacterium suspension containing 10 μL ~$5x10^4$ cfu was added. The plates were incubated at 37°C for 24 hours. For the determination whether it was bactericidal or bacteriostatic effect 10 μL from each wells was spread on Mueller-Hinton agar.

Statistical analysis

Statistical analysis was performed by using analysis of variance. Individual comparisons between group means were made with the Scheffé test. $P < 0.05$ was regarded as significant.

IV. Results

Isolation of bacteria from syringes used at an intensive care unit

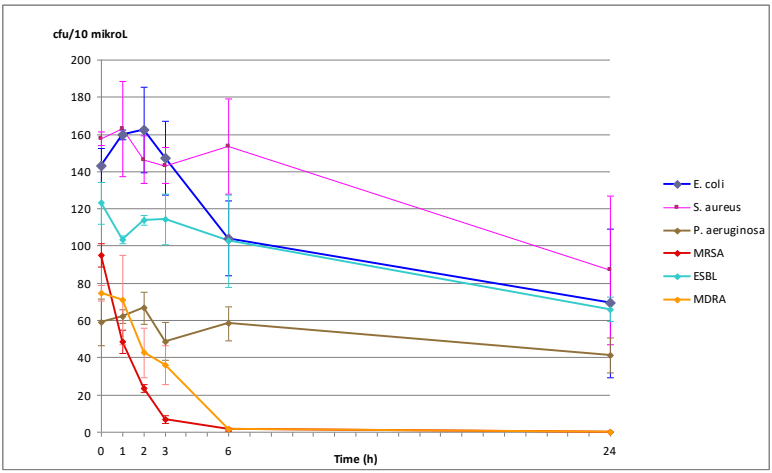
The contamination rate of the collected syringes and giving sets (amiodarone 12 mg mL^{-1}, furosemide 1 mg mL^{-1}, noradrenaline 60 μg mL^{-1}, adrenaline 60 μg mL^{-1}, bupivacaine 0.125%, sufentanil 1 μg mL^{-1}, metoprolol 0,1 mg mL^{-1}, insulin 1 unit mL^{-1}, propofol 2%, potassium chloride 20 mg mL^{-1}, morphine 1 mg mL^{-1}) was 16%. Seventy-eight percent of the isolated bacteria was *P. aeruginosa*, the rest *A. baumannii* and coagulase negative staphylococcus. There was no growth from the amiodarone, potassium chloride or morphine syringes. Most of the contaminations was detected in the insulin syringes. In 46% of cases the same bacterium was isolated from the syringes and from patients' blood cultures.

The impact of atropine-sulphate on bacterial growth at room temperature

The tested atropine ampoules were sterile. The investigated strains showed normal growth in Mueller-Hinton liquid media.

Atropine did not influence the growth of *S. aureus*, *E. coli* ESBL, and *P. aeruginosa*, the cfu did not change significantly. The cfu of the MRSA strain significantly decreased after 2 hours' incubation and that of *A. baumannii* after 3 hours. By the end of the experiment (24 hours' incubation) both the MRSA and the *A. baumannii* MDR strains were killed. There was no increase of the cfu in the case of any of the investigated strains in atropine sulphate 0,6 mg mL^{-1} (Figure 1).

Figure 1. Bacterial growth in atropine 600 µg mL^{-1} at room temperature



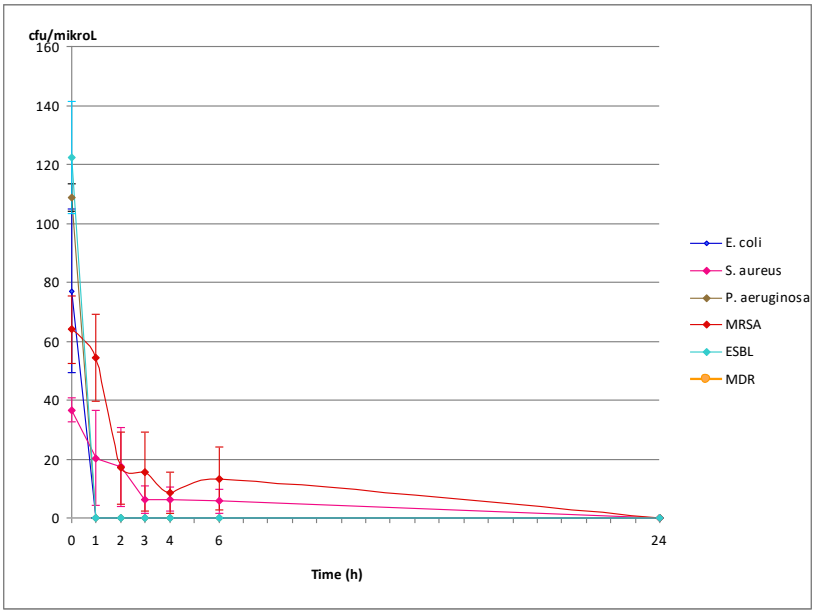
The cfu of *S. aureus*, *E. coli* ESBL and *P. aeruginosa* did not change significantly, while that of MRSA decreased after 2 hours', A. baumannii MDR after 3 hours' compared to baseline. The results are the average of 3 measurements ± S.D. $P<0,05$.

The impact of glycopyrronium bromide on bacterial growth at room temperature

The tested glycopyrrolate ampoules were sterile. The investigated strains showed normal growth in Mueller-Hinton liquid media.

The cfu of MRSA significantly decreased after 2 hours that of the other strains after 1 hour (Figure 2).

Figure 2. Growth of bacteria in glycopyrronium bromide 200 µg mL^{-1} at room temperature



The cfu of all strains significantly decreased following 1 hour. The results are the average of 3 measurements ± S.D. P<0,05.

Growth of bacteria in amiodarone at room temperature

All examined strains grew on MH agar. During the sterility tests we did not find any growth from the amiodarone ampoules and from glucose 5% solution. The cfu of all strains decreased in glucose 5% but there were living cells at the end of the experiment. This pattern agrees with previous reports.

Amiodarone showed a fast acting (within 1 minute) antibacterial activity against ATCC *E. coli*, *P. aeruginosa*, *K. pneumoniae* strains and against the clinical isolates of *P. aeruginosa* and *A. baumannii*. The cfu of ATCC *S. aureus* and the clinical isolate *S. epidermidis*, and *E. coli* significantly decreased to zero in 15 minutes while the cfu of ESBL *K. pneumoniae* within 45 minutes (Table 1, 2). All cfu numbers were significantly less after 1 and 15 minutes in amiodarone than the starting cfu or the cfu in MH or glucose 5% at the same time.

Table 1. Growth of ATCC reference strains in amiodarone 0.6 mg mL^{-1} at room temperature

	Growth in amiodarone (0.6 mg mL^{-1})				
	ATCC reference strains				
Time (min)	*S. aureus* ATCC 23923	*S. epidermidis* ATCC 35984	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*K. pneumoniae* ATCC 13883
0	83.6±11	138±14	13±0.6	33.3±1.5	51±1
1	4.6±4.0	5 ± 0	0	0	0
15	0	0	0	0	0
45	0	0	0	0	0
60	0	0	0	0	0

Cfu numbers of ATCC reference strains following 1, 15, 45, or 60 minutes incubation in amiodaron 0.6 mg mL^{-1} (diluted in glucose 5%) at room temperature ± SD. The cfu numbers of *S. aureus* and *S. epidermidis* were significantly less at 1 minute than at the starting time and in MH or glucose 5% at 1 minute. $P<0.05$ was considered significant.

Table 2. Growth of clinical isolates in amiodarone 0.6 mg mL^{-1} at room temperature

	Growth in amiodarone (0.6 mg mL^{-1})				
	Clinical isolates				
Time (min)	*S. epidermidis*	*P. aeruginosa* MDR	*E. coli* ESBL	*K. pneumonia* ESBL	*A. baumannii* MDR
0	265 ± 7	93 ± 1	58±4.4	89.6±6	147±4
1	18 ± 3,6	0	3,3±2,1	7,3±4,9	0
15		0	0	0,6±1,1	0
45		0	0	0	0
60		0	0	0	0

Cfu numbers of clinical isolates following 1, 15, 45, or 60 minutes incubation in amiodaron 0.6 mg mL^{-1} (diluted in glucose 5%) at room temperature ± SD. All cfu numbers were significantly less at 1 and 15 minutes than at the starting time and in MH or glucose 5% at the corresponding times. $P<0.05$ was considered significant.

MIC values of amiodarone in glucose 5%

The MIC values of the examined strains in amiodarone diluted in glucose 5% are between < 0,5 and 32 μg mL^{-1} (Table 3, 4).

Table 3. The MIC values of ATCC reference strains in amiodarone (in glucose 5%)

Minimal inhibitory concentration	Clinical isolate
<0,5 μg mL^{-1}	*S. aureus* ATCC 23923
	S. epidermidis ATCC 35984
	P. aeruginosa ATCC 27853
0,5 μg mL^{-1}	*E. coli* ATCC 25922
32 μg mL^{-1}	*K. pneumoniae* ATCC 13883

The MIC values of ATCC reference strains in amiodarone 5% at 37ºC.

Table 4. MIC values of clinical isolates in amiodarone

Minimal inhibitory concentration	Clinical isolate
<0.5 μg mL^{-1}	*A. baumannii* MDR
	S. epidermidis
	P. aeruginosa
32 μg mL^{-1}	*K. pneumoniae* ESBL
	E. coli ESBL

Minimal inhibitory concentrations of amiodarone diluted in glucose 5% at 37ºC against clinical isolates

MIC values of amiodarone diluted in glucose 5%
<0.5 μg mL^{-1} against *S. aureus*, *S. epidermidis*, *P. aeruginosa* and *A. baumannii*,
0.5 μg mL^{-1} against *E. coli* (ATCC 25922),
32 μg mL^{-1} against *K. pneumoniae* (ATCC13883), *K. pneumoniae* ESBL, and *E. coli* ESBL strains.

A. baumanni and *P. aeruginosa* are non-fermenting strains that may contribute to the low MAC aginst these strains

The above values are bactericidal against *S. aureus* and *A. baumannii* while bacteriostatic against the other strains.

V. Discussion

CLABSI is one of the most severe forms of hospital-acquired infections. Central venous catheters have played a pivotal role in a broad spectrum of patient management. Total parenteral nutrition, management of sepsis, chemotherapy, and renal replacement therapy are vital areas where central venous access is indispensable.

Multiple factors can contribute to the development of CLABSI, such as intrinsic and extrinsic factors. A less known segment of the latter has been the subject of my research.

Several publications have explored the rate of contamination of a broad spectrum of medicines, but their results were inconclusive. Some studies have not taken the antibacterial effect of certain medications into account; hence their outcome was biased due to the low contamination rate. According to the latest results based on samples collected in theatres and on the wards, the used intravenous medications are regarded as high risk in terms of infection control as they easily can get contaminated while being used with an incidence of 5-44%.

Only one study on intensive care related contamination of medicines has been published so far in the literature. The contamination rate was found to be 22-44%. They were modelling in six hospitals of preparing infusions without attaching them to the patients and incubated the solutions on 37 C for seven days. After the incubation period, they analysed bacterial growth. The weakness of this study was that the used medicines were not noted; therefore, it is hard to extrapolate its results to the contamination rate in the daily routine.

Our publication has described the first study that was based on real-life data processing from an active intensive care unit. We have collected used syringes for three months. Results have shown the challenges of infection control during the handling of medicines from drawing them up or prepare an infusion to connect them to the patients. Breaches of protocols can happen at any level of this complicated process. The intensive care team was blinded to our study, so they followed their regular protocol, and the preparation of the medicines has been made in the usual way. Samples were collected for a more extended period; therefore, we managed to see the results of the work of a larger cohort of nurses.

The overall contamination rate has been found to be 16% that correlates with the previously published results.

The most common pathogen that had been isolated in our cohort was *P. aeruginosa*, which is different from the findings of previous studies. The most likely reason for that may be that we took our samples directly from the patients or connected equipment on intensive care.

Our study shows that certain medicines, including amiodaron, has never shown any contamination.
Comparing bacterial traces of the samples from the medicines and the hemocultures of the patients using RAPD-PCR, we found that there was a match in 46% of the cases.

Data regarding the effect on bacterial growth of drugs that we are currently using in our daily practice in anaesthetics and intensive care are scarce. The importance of this topic came to light in 1991 when contamination of propofol during the drawing up process caused severe infections in patients.
The effect on bacterial growth of the ever often used glycopyrrolate and atropine has not been explored yet. In Hungary, we use the glycopyrrolate quite rarely, but in Western-Europe, Australia, and North-America, it is considered to be common practice in reversing the effect of muscle relaxants, as it does not cause tachycardia as often as atropine.
It is a habit in our anaesthetic practice that we usually draw up atropine before the start of a list and keep the syringe until the end of the list or even the next day. According to our results, it can be considered as a safe practice from an infection control point of view.
While the investigated bacterial strains of *S. aureus*, E. coli, *P. aeruginosa*, and *A. baumannii* were unable to grow, the growth of MRSA and MDR strains have significantly reduced after two hours, and there were no viable bacteria after 24 hours.
However, in glycopyrrolate, the number of CFU was found to be significantly reduced after one hour, and there was no growth after 24 hours.

A possible way to reduce the extrinsic component of bloodstream infections in the operating theatre is to discard all unused syringes at the end of each case. On the other hand, this practise has effects on hospital finance. Keeping the unused syringes that were prepared under strict hygienic regulations and do not support bacterial growth we could save significant amount of money. One of these medications is atropine (in many countries glycopyrrolate as well) that is drawn up before the first case in every operating theatre for the sake of patient safety. We rarely use them and waste at the end of the list.
There are a few papers dealing with the financial aspect of the prepared but unused medications. A study observed the proportion of the used and wasted medications (atracurium, thiopental, succinylcholine, propofol, midazolam, rocuronium) in the operating theatres for one year in the US and found that 39 to 71% of the medications were wasted. In this way 26% of the value of anaesthetic drugs was wasted. A resent prospective study analysed the utilization of medications during 98 surgeries. The results were devastating:

95% of adrenaline, 92% of succinylcholine, 92% of lidocaine, and 81% atropine that were prepared were wasted. This meant 46% of the whole anaesthetic drug expenditure. A French study evaluating 27.000 operations in 2012 revealed that only 7% of the patients received atropine but a dose was prepared for all cases. This kind pf waste affects not only Europe and the US. A prospective study published in 2017 from India examining 677 cases reported that 37% of atropine was thrown away.

Only one study dealt with glycopyrrolate, the waste was 45%. Our results suggest that the prepared atropine and glycopyrrolate may be safely stored at room temperature for at least 24 hours. It could not cause an infection risk as the cfu of the contaminated bacteria remains the same or decreases.

In a previous study we investigated the contamination rate of medications used on an ICU, that was not known before. We noticed that there was no growth from the amiodarone syringes. Then we investigated bacterial growth in amiodarone in vitro. Our results revealed that amiodarone has a fast acting bactericidal effect against the investigated strains. It killed *P. aeruginosa* and *A. baumannii* within 1 minute in the highest dilution that can be used in clinical practice. We did not find growth after 15 minutes in the case of *S. aureus*, and *E. coli*, and after 45 minutes *K. pneumoniae* ESBL was killed as well.

To the best of our knowledge this is the first study investigating the impact of amiodarone on the growth of human pathogenic bacteria including multidrug resistant strains and determined amiodarone MIC.

Intravenous amiodarone is usually administered through a central venous line frequently for days. One of the complications of the use of central lines is bloodstream infections that increases mortality and expenses. Its frequency can be as high as 24 cases / 1000 cannula days and is influenced by the age of the patient, the anatomical site of the cannula (subclavian, jugular vein vs. femoral vein), the disease, and the location of the patient (home, general hospital ward or ICU) and weather preventive hospital bundles are used or not. Intrinsic and extrinsic factors can be found in the pathomechanism. Contaminated infusion is a possible extrinsic factor. Our results suggest that amiodarone is unlikely to be responsible for CLABSI as bacteria that may contaminate it will be killed within 45 minutes. The MIC of amiodarone against the examined reference strains and clinical isolates is low; it is between $<0{,}5 - 32\ \mu g\ mL^{-1}$.

There are numerous ways to reduce the incidence of CLABSI. The use of cannulas impregnated with antibacterial solutions, antibacterial dressings, education of staff, adherence to hygienic rules belong to them.

Another approach is to lock the cannula with antibiotics and anticoagulants, or without anticoagulants when not in use. Gentamicin, tobramycin, minocyclin, cefotaxim, vancomycin and cefazolin are the most frequently used antibiotics. The use of antibiotics always rise the possibility of the appearance of resistant strains. Another way to reduce CLABSI is the use of non-antibiotics that has antibacterial properties. Amongst others heparin, citrate, ethanol, taurolidine, parabens and methylene-blue were applied alone or in combination. Most of the studies investigating the effect of the above solutions reported beneficial results but none of them solved the problem of CLABSI and they may have side effects like influencing the clotting system, causing protein precipitation, damaging cannula material or may lead to liver dysfunction.

Amiodarone is a well-known antiarrhythmic medication. The initial intravenous dose is 5 mg/kg body weight, and the daily dose can be as high as 1,2 grams. That is higher by orders of magnitude than the MIC of amiodarone against the investigated human pathogens. This may make amiodarone a suitable catheter lock. It is suggested to withdraw the catheter lock before reuse of the central line but it may be missed or not done thoroughly. In the case of amiodarone even if we don't do it properly only a fraction of the therapeutic dose will be given to the circulation.

There are other medications used in anaesthesia and intensive care that have beneficial side effects. Further research is needed to agree whether amiodarone may provide some protection from CLABSI or not.

VI. New results

1/ The bacterial contamination of in use syringes at a university multidisciplinary intensive care unit is 16%.

2/ At a university multidisciplinary intensive care unit *Pseudomonas aeruginosa* is responsible for the contamination of intravenous medications in 70%.

3/ Atropine does not support the growth of ATCC reference strains and the growth of clinical isolates (*E. coli, P. aeruginosa, K. pneumoniae, A. baumannii*).

4/ Glycopyrrolate has antibacterial property against the investigated ATCC reference strains and clinical isolates (*E. coli, P. aeruginosa, K. pneumoniae, A. baumannii*).

5/ Amiodarone has a fast bactericidal effect against the investigated ATCC reference strains and clinical isolates (*E. coli, P. aeruginosa, K. pneumoniae, A. baumannii, S aureus, S. epidermidis*).

6/ The MIC value of amiodarone is between <0.5 μg mL^{-1} és 32 μg mL^{-1} for the investigated ATCC reference strains and clinical isolates (*E. coli, P. aeruginosa, K. pneumoniae, A. baumannii, S. aureus, S. epidermidis*).

VII. List of publications

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Publications related to the Thesis IF: 6,149

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