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Review

The Biofilm Eradication Using Gentamicin and Anticoagulants as Catheter-Related Infection Prophylaxis in Hemodialysis Patients : A Systematic Review

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The use of double lumen catheters as a means of hemodialysis access is commonly accompanied with the use of gentamicin as an antibiotic lock. Other antibiotics and anticoagulants are often added to increase the efficacy of gentamicin in order to reduce catheter-related infection and to prevent biofilm formation. This review aimed to evaluate the following: 1) the use of gentamicin in eliminating catheter-related infection and reducing biofilm formation in hemodialysis catheters, 2) the efficacy of additional antibiotics in combination with gentamicin, and 3) the effect of additional anticoagulants to complement the efficacy of gentamicin as the main prophylactic antibiotic lock. We sorted through data from 242 PubMed and ScienceDirect studies, which were then short-listed to 33 studies. Next, they were grouped, extracted, and analyzed qualitatively to fulfil the objectives of this review. Consequently, the use of a gentamicin-lock solution was shown to reduce the incidence of bacteremia; however, it was not strong enough to inhibit the growth of infectious microbes and formation of biofilms. Several bacteria, such as *Staphylococcus aureus*, *Staphylococcus epidermidis, Escherichia coli,* and *Klebsiella pneumoniae*, have been reported as infectious agents. Combination with other antibiotics also provided no effect in reducing bacterial growth and biofilm formation in catheters. Furthermore, the additional anticoagulants (trisodium citrate and EDTA) were reported to be effective in enhancing the efficacy of gentamicin in avoiding catheter-related infection, bacterial growth, and biofilm formation; thus, the use of gentamicin can be rationalized.

Keywords: **Antibiotic lock, biofilm, catheter-related infection, gentamicin, anticoagulant, hemodialysis**

Introduction

In Indonesia, over 30.000 patients registered as hemodialysis patients. In 2015, 76% hemodialysis (HD) patients were using AV-shunt as their vascular access, about 8% still using central venous catheter (CVC) [1]. There is an increasing percentage of CVC usage compared to report made in 2012 [2]. The use of CVC is often associated with higher risk of Catheter-related infection (CRI) [3]. CRI is known as a major complication which increases morbidity and mortality in HD patients with CVC [4–6]. There is a report that 48% of tunneled CVCs become infected after 6 months of insertion and the number is increasing in linear trends [7]. The use of CVC make the HD patients more prone to infection, which could increase the inpatient management cost and reduce the patient's quality of life [4, 8].

The first research question is the CRI relationship with

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biofilm unyielding to antibiotics. All indwelling vascular catheters are usually colonized by microbes within 24 h after insertion [9]. The formation of biofilm on external and internal surface of vascular catheter is suspected as an important role in the colonization process. Endoluminal biofilm is thought to be more important in the development of infection, which also could be modified with endoluminal antibiotic lock [10]. The ability to prevent or clean up the biofilm is highly sought by combining the best catheter-lock solution. Gentamicin (GM) is widely used as the component of antibiotic lock solution (ALS). But cocktails of several antibiotics as ALS is also proposed in some trials [11–15]. It seems that GM alone is not efficient enough in eliminating biofilm.

The second research question is the effort to find the best way in preventing CRI in HD patients with indwelling catheter. Several studies evaluate the use of ALS which is effective in CRI prevention [6, 16, 17]. Although those studies report the promising outcome of ALS use, KDIGO nor KDOQI still not recommend ALS as prophylaxis. But recently, the Infectious Diseases Society of America includes ALS in their guideline as an option in both prevention and treatment for catheter-related infection [13]. Therefore, ALS is possible as prophylaxis for CRI prevention in HD setting.

The third research question is the routine use of antibiotic and anticoagulant combination as ALS. Anticoagulant is used to fill the dead space of CVC after every hemodialysis session to maintain its patency [18]. Three anticoagulants are reported, namely heparin, trisodium citrate (TSC), and EDTA. The use of a dilute heparin solution is the most common method of "locking" a catheter since the use of intermittent catheters began in early 1970s [18]. Lately TSC and EDTA are introduced as the substitute. In some trials, TSC and EDTA show a promising activity in biofilm eradication [19–22]. Hence, TSC and EDTA have the potential as a better anticoagulant alternative in preventing CRI.

The objectives of this systematic review were to do in depth evaluation of the efficacy of GM lock in preventing catheter-related infection and biofilm formation on catheter lumen; the effect of additional antibiotics beside GM; and the effect of heparin, TSC and EDTA as the additional anticoagulants in combination with GM. In this review we evaluate and compare the emergence of GM resistancy, CRI reduction, and biofilm eradication.

Materials and Methods

Searching strategy

The literature search was done by two authors, independently, using PubMed and Science Direct databases. Search was conducted between January 1st to February 1st 2018. The following keywords were used as search terms : [(Gentamicin AND antibiotic lock AND hemodialysis)] OR [(Gentamicin AND hemodialysis AND catheter-related infection)] OR [(antibiotic lock AND hemodialysis AND catheter-related infection)].

Screening and selection

The author uploaded the search result to EndNote (ver. X8, Clarivate Analytics, USA) reference management, then removed the duplicates, selecting relevant title, and grouped according to objectives of this study view. The inclusion criteria are every study which using GM as their ALS component with the purpose as prophylaxis in HD patients. The exclusion criteria are the use of GM as treatment in CRI, the use of ALS in critical care setting, the spectroscopy analysis of GM, and meta-analysis of ALS. Studies were eligible only of publication in English. All studies that included after selection were reviewed independently by authors in full articles to determine its relevance. Every disagreement in inclusion were determined via discussion.

Content analysis

Each author extracted qualitative data from each included articles to a Microsoft Office Excel workbook and then both authors reviewed the data in the discussion. Any discrepancies were discussed and solved by consensus. The data which extracted from the included studies were the efficacy of GM to eradicate bacteria and biofilm, the effect of the additional antibiotic beside GM, and the benefit of anticoagulant added in ALS. After extracted, the data arranged in certain order to be analyzed descriptively and examined the pattern.

Results and Discussion

Our searching and screening strategy identified 33 articles (Fig. 1). Most of the articles reported a clear effect of GM as antibiotic lock and its combination with other antibiotic and anticoagulants. Most articles reported the

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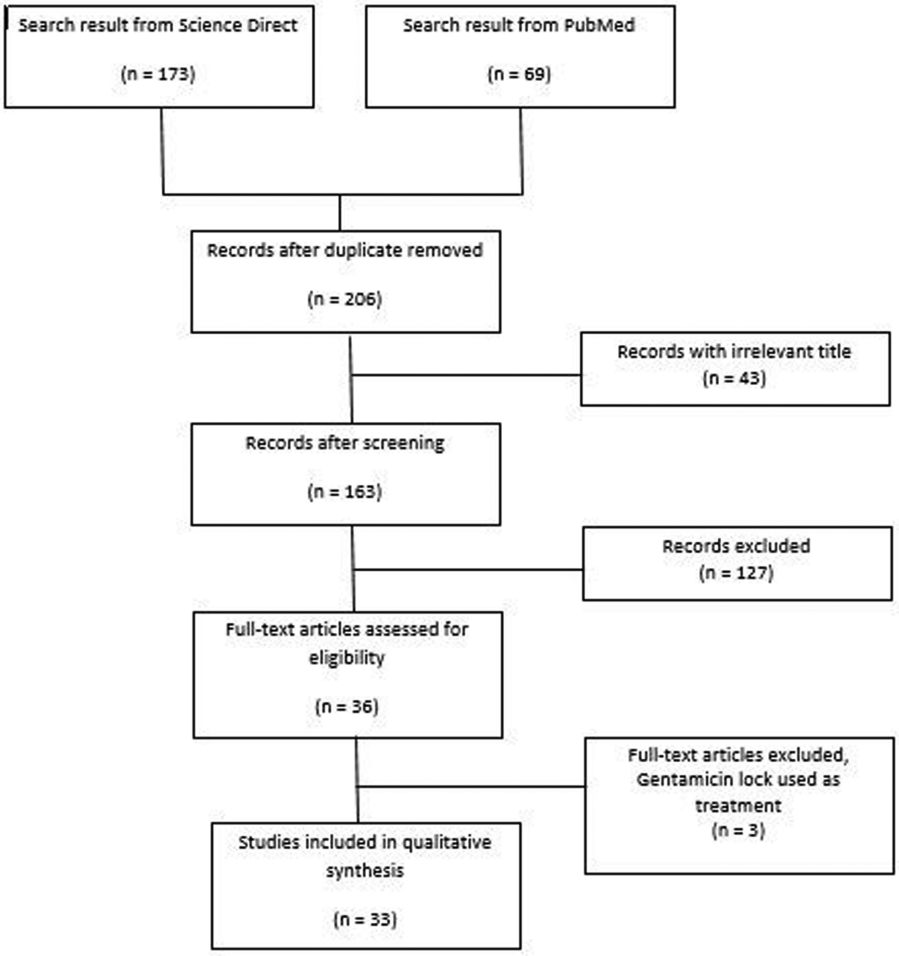

Fig. 1. Flow diagram of the article selection process (PRISMA).

positive effect of the use of GM which could be enhanced by the addition of other antibiotic, and by anticoagulants to achieve reduction in CRI and eradication of biofilm. This chapter is divided into three sections according to the three objectives as mentioned previously in the introduction.

CRI and biofilm formation on hemodialysis catheter under GM as ALS

The pathogenesis of CRI is initiated with colonization of microbes on the surface of CVC lumen and continued with biofilm formation [23, 24]. The most common route of bacterial contamination in long-term catheters is through the hub, which supports ALS as a suitable treatment method [17]. ALS is initially described the late 1980s as closing the catheter and exposing its internal surface to a high concentration of appropriate antibiotic to eradicate the colonizing microbes [17, 25].

Staphylococcus aureus is the most common etiology of the CRI in either the presence or absence of GM (Table 1 and 2). Even after ALS application, the most common microbes are Gram positive (Table 2). *S. aureus* and coagulase-negative *Staphylococci* are the predominant bacteria. The predominant yeast is *Candida albicans*. Members of *Enterobacteriaceae* and *Pseudomonas aeroginosa*, Gram negative bacteria, are reported to cause severe infection [11, 13, 26].

Biofilm formation is measured in several studies as positive or negative (presence or absence). Its eradication is aimed by applying components of ALS. From ten studies, only two of them reported the absence of biofilm on catheter after applying GM [27, 28]. Eight studies report the inability of GM as single agent in eliminating biofilm [12, 14, 26, 29–32]. We assume that GM alone is ineffective in biofilm eradication. It needs to be incorporated with

Table 1. Microbial distribution before ALS.

No	Literatures	Gram positive						Gram negative			Yeast
		CoNS*	*S. aureus*	*S. epidermidis*	*Enterococcus* sp	*Streptococcus* sp	Others	*Enterobacteria-ceae*	*Pseudomonas* sp	Others	*Candida* sp
1	Abbas *et al.* (2009)	+	+			+		+			
2	Chow *et al.* (2010)	+	+								
3	Dogra *et al.* (2002)		MRSA	+							
5	Goh *et al.* (2017)	+	MRSA							+	
6	Kim *et al.* (2006)		+	+							
8	Moore *et al.* (2004)		MRSA, MSSE		VRE, VSE		+	+	+	+	+
9	Moran *et al.* (2011)		MRSA	+	+	+		+	+		+
12	Silva *et al.* (2013)	+	+								

Note : *CoNS = Coagulase negative *Staphylococci*

Table 2. Microbial distribution after ALS.

No	Antibiotic lock solution	Gram positive						Gram negative			Yeast		Literatures
		CoNS	*S. aureus*	*S. pyogenes*	*Enterococcus* sp	*Streptococcus* sp	Others	Entero-bacteriaceae	*Pseudomonas* sp	Others	*Candida* sp	Others	
1	Gentamicin & heparin	+	+	+	+	+		+		+			Abbas *et al.* (2009)
		+	+					+					Chow *et al.* (2010)
			+		+								Silva *et al.* (2008)
			+										Zhang *et al.* (2009)
		+	MRSA		+	+	+						Landry *et al.* (2010)[ł]
			+					+	+				Filiopoulos *et al.* (2011)
		+	+				+			+	+		Goh *et al.* (2017)
2	Gentamicin & citrate		MRSA		VRE, VSE		+	+	+	+	+		Moore *et al.* (2014)
			MRSA		+		+	+	+			+	Moran *et al.* (2012)
		+	+							+			Goh *et al.* (2017)
3	Gentamicin, cefazolin, & heparin		+										Kim *et al.* (2006)
			MRSA										Silva *et al.* (2013)
4	Taurolidine & citrate		+										Filiopoulos *et al.* (2011)

Note : *CoNS = Coagulase negative *Staphylococci* ; ł = all bacteria is gentamicin resistant

another substance to sterilize the CVC lumen.

When GM combined with anticoagulant as ALS, its application is seemed to reduce the incidence of CRI in all studies (Table 3). Before ALS, the rate of CRI range from 0.4 to 13.11 per 1000 catheter days. The rate after ALS was reduced from 4.54 to zero per 1000 catheter days. To magnify the significance, we calculated the percentage of the reduction. The result was the reduction of CRI ranged from 31 to 100%.

The CRI reduction under various GM dosage, additional antibiotic, and anticoagulant is shown in Fig. 2. When combined with TSC as ALS, the CRI reduction is not affected with the dosage of GM. Some studies use the combination of TSC and GM with GM dose ranged from 0.32 to 40 mg/ml [8, 10, 33–35]. The similar result also showed in combination of GM and Heparin. Although it seems that 1 mg/ml GM with heparin gave the lowest CRI reduction compared to higher GM dose [36]. Several studies reported the benefit of ALS use with Kaplan-Meier method [4, 10, 33–35, 37–44]. The Kaplan-Meier method is used to present the cumulative infection-free catheter survival, with or without ALS. All of the studies showed significantly

Table 3. List of studies with CRI rates and ALS combination.

No	Literatures	No. cath.[1]	No. patients[2]	Duration (months)	Catheter-related infection (/1000 catheter days)		CRI reduction (%)	Gentamicin (mg/ml)	Other antibiotic (mg/ml)	Heparin (IU/ml)	TSC (%)
					Before ALS[3]	after ALS[4]					
1	Abbas *et al.* (2009)	404	320	42	0.90	0.62	31.11	1		5000	
2	Al-hwiesh *et al.* (2008)	86	69	18	11.69	4.39	62.44	40	vancomycin 25	5000	
3	Al-hwiesh *et al.* (2007)	81	63	12	13.11	4.54	65.4	40	vancomycin 25	5000	
4	Chow *et al.* (2010)		75	14	4.6	1.5	67.4	5		5000	
5	Dogra *et al.* (2002)	112	83	26	4.2	0.3	92.85	40			3.13
6	Feely *et al.* (2007)		33	24	9.10	1.04	88.6	5		5000	
7	Filiopoulos *et al.* (2011)	150	119	20	9.92	2.74	72.4	40		5500	
						3.67	63		taurolidine 1.35%		4
8	Goh *et al.* (2017)		64	60	1.42	0.66	53.3	5		1000	
						0.16	88.73	1.6			4
9	Kim *et al.* (2006)		120	24	3.12	0.44	85.9	5	cefazoline 10	1000	
10	Landry *et al.* (2010)		1863	48	17	0.83 [a]	95.11	4		5000	
						1.2 [b]	92.9				
11	McIntyre *et al.* (2004)		50	14	4	0.3	92.5	5		5000	
12	Moore *et al.* (2004)	1350	555	34	1.68	0.45	73.21	0.32			4
13	Moran *et al.* (2011)		303	56	0.91	0.28	69.2	0.32			4
14	Nori *et al.* (2006)		62	7	0.4	0	100	4			3.13
15	Pervez *et al.* (2002)	55		16	2.11	0.62	70.6	40			4.6
16	Silva *et al.* (2008)	141	116	24	1.78	0.16	91	5.2		4347	
17	Silva *et al.* (2013)	325	233	26	1.74	0.57	67.2	5	cefazoline 10	5000	
18	Venditto *et al.* (2010)	265		18	2.9[c]; 3.4[d]	0.4	86.2-88.2	10		5000	
19	Zhang *et al.* (2009)		140	30	0.67	0.06	91	4		5500	

Notes :
1 : number of catheter included in the study;
2 : number of patients included in the study;
3 : data taken before intervention using ALS;
4 : data taken after intervention ALS;
a : end of 1st year;
b : end of 4th year;
c : heparin;
d: citrate

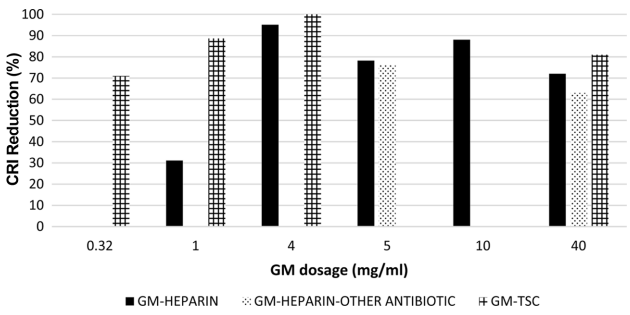

Fig. 2. The histogram of CRI reduction from various GM dose in combination with heparin, other antibiotics, and TSC.

higher cumulative infection-free survival in the group with GM as ALS. With this information, GM used as prophylactic ALS seemed to give benefit in HD patients.

It is interesting to know that a lot of HD facilities use GM as their antibiotic component. From all of articles included in this review, only several mentioned the reason behind antibiotic selection in their studies. GM broad spectrum activity is mentioned as the reason of selection in five studies [8, 37, 39, 41, 44]. Two studies mentioned GM as a better option for gram-negative bacteria, especially if there is a distinct percentage of nosocomial infection by Gram negative bacteria [10, 28]. Three studies mentioned cost

and availability as the reason of GM usage for antibiotic lock solution [10, 39, 41]. One study had to switch their protocol to GM-heparin lock because their previous ALS were using Minocycline-EDTA [45]. Minocycline-EDTA was no longer available in the market and the alternative was too expensive. The use of Linezolid was reported in two studies, in comparison with GM. Linezolid has the spectrum towards most Gram positive organism, include beta-lactam resistant and glycopeptide resistant [26, 28]. One study tested Ciprofloxacin in their study because of Ciprofloxacin sporadic use against gram-negative organism [28]. The use of GM seems superior in terms of spectrum and sustainability which makes GM a preferred antibiotic for long-term use.

The problem with the use of antibiotics, GM in this case, is the emergence of resistant behavior of several isolates of *Enterococcus* sp. and *S. aureus* in clinical setting (nosocomial) [46–49]. This is a major concern for the CDC and the primary reason for the lack of a recommendation in the use of any prophylactic antibiotic lock [33].

From the studies we included in this review, the results in emergence of GM resistance are varied in three reports [33, 45, 50]. Two studies mention the emergence of GM resistant bacteria. The first study reported that isolates of coagulase-negative *Staphylococci* (CoNS), *Streptococcus viridans*, and *Enterococcus* sp. are resistant to GM after GM-heparin lock protocol [50]. The second study reported the appearance of GM resistant *Enterococcus* sp. [45]. But 20% of *Enterococcus* isolates in their hospital already resistant to GM and the sensitivity for *Enterococcus* isolate prior to antibiotic lock usage is unknown. The first and second studies are different with third study. The third study reported the significant decrease of GM resistant incidence during gentamicin-lock period [33].

The possible explanation of these findings is that the emergence of GM-resistant bacteria has a connection with the predominant bacteria in the health care facility. Many pathogenic bacteria, either GM sensitive or resistant are nosocomial bacteria. The GM sensitive are suppressed, and the resistant are survived. This makes the use of GM alone is not strong enough to eradicate the growth of GM resistant [45, 50]. Therefore, several research later tried to find the effect of additional antibiotic beside GM.

The efficacy of gentamicin with addition of other antibiotics

In order to overcome the emergence of GM resistancy as discussed in the previous section, other antibiotics is added in combination with GM. Two antibiotics are commonly used, i.e. vancomycin, and cefazoline (Table 3). Only four trials combine GM with another antibiotics [4, 42, 51, 52]. But the CRI reduction by combining GM-anticoagulant with other antibiotics is average compared to GM-anticoagulant only (Table 3).

Some guidelines recommend empirical systemic treatment with vancomycin and an aminoglycoside to provide broad spectrum cover for Gram positive and Gram negative bacteria [53]. The combination of vancomycin and GM is used in two studies [51, 52]. Cefazoline and GM are combined as ALS because cefazoline is found to be empiric antibiotic of choice in dialysis unit with low MRSA rate, and GM is the empiric antibiotic to Gram negative bacteria [4, 42].

An important information is the reason for not using vancomycin as ALS. General use of vancomycin has risk of gylcopeptide resistance and is no longer recommended [25]. Since vancomycin is also used as independent predictor for the acquisition of vancomycin-resistant *Enterococcus*, its application as lock agent is discouraged [9]. Two studies described vancomycin as unable to penetrate biofilm in a demonstration by confocal microscopy [12, 28]. One study further explained that vancomycin penetrates the biofilm slowly, producing gradual exposure to the sessile microbial cells, which may promote stress-induced mechanism of resistance to the selected glycopeptides [12]. The vancomycin ability in biofilm disruption might be expected to enhance GM efficacy. But the combination of these antibiotic is not excelled compared to GM combination with only anticoagulant in reducing CRI (Fig. 2). In addition, one study clearly reports combination of other antibiotic with GM is ineffective to eradicate biofilm model [15].

The enhancement of GM efficacy by additional anticoagulants

As discussed before, the use of antibiotics cocktail is inadequate. To increase the efficacy of GM, the addition of anticoagulants is proposed. Anticoagulant as a component of lock solution is necessary to maintain the patency of catheter during the interdialytic period [9, 18]. The most common anticoagulant is heparin. Heparin is inexpensive and available in most HD facilities. Research published in 1980 showed that, in laboratory test, heparin concentration less than equal to 500 units per mL inhibited the growth of

many microbes in a brain-heart infusion broth [18]. It is suggested that any antimicrobial activity related to heparin may be due to its preservative content in the solution [18]. Up until now, heparin instillation remains the gold standard for anticoagulant of catheter locking [9].

In contrast to the suggestion above, heparin has several drawbacks such as prolonged bleeding, incompatibility with other drugs, and heparin-induced thrombocytopenia which can alter the patient's quality of dialysis [3, 9, 18]. One study reported the biofilm eradication after GM-heparin application [54]. Besides them, one study described that heparin stimulates the growth of biofilm from cell-to-cell interaction after primary attachment [55]. The problem of biofilm formation indicates that an alternative is needed. Trisodium citrate (TSC) and Ethylenediaminetetraacetic acid (EDTA) are promoted as anticoagulant with antimicrobial activity.

Both TSC and EDTA are known as strong cation chelator [20, 22, 56]. It has been shown that divalent cations can stimulate cell-to-cell adhesion. Thus promote aggregation through the shared binding of divalent cations by cell wall theicoic acids which increasing the number of organism adhering to a finite surface area [20]. Mg^{2+} and Ca^{2+} are involved in growth and differentiation of numerous bacterial strains. Magnesium increases adhesion and slime production while calcium is involved in morphogenesis and development of extracelullar matrix of biofilm [13, 20]. Both TSC and EDTA were found to increase the permeability of the outer membrane of microbe thereby increasing their susceptibility to antimicrobial agents [20]. With this ability, TSC and EDTA are used in combination with antibiotics as ALS [8, 10, 11, 13, 30, 31, 33–35].

Four randomized trials use combination of GM and TSC [10, 34, 35, 38]. Depending on its concentration, for example 15 and 30%, TSC significantly reduced the number or colony-forming units of *S. aureus*, *S. epidermidis*, and *E. coli*. In 30% concentration, *C. albicans*, and *P. aeruginosa* colonies are reduced over a period 24 h [20]. Lower concentration of citrate (2.2 to 15%) are known to have antimicrobial activity against Gram-positive bacteria only, particularly *S. aureus* and *S. epidermidis* [38]. The TSC is superior in reducing catheter related bacteremia and intraluminal catheter biofilm when compared to heparin [22, 56]. But one death case reported after injection of 46.7% TSC, made Food and Drug Administration ban the use of TSC in concentration above 4% [22].

Despite the death report, TSC seemed to be used in some HD facilities as a routine anticoagulant, in combination with gentamicin. The concentration used in the studies was between 3.13% to 4.6%, since higher concentration was considered dangerous for regular use [35]. As mentioned before, all of the studies reported the reduction of CRI incidence in the group with gentamicin-TSC as the ALS [8, 10, 33–35, 38].

EDTA is used in the therapy for hypercalcemia and lead poisoning. EDTA destabilizes the biofilm matrix and enhances detachment of cells from the biofilm which in turn inhibits the biofilm formation [13, 19, 20, 31]. EDTA is also known to release endogenous phospholipases which changes in the outer membrane of Gram-negative bacteria and inhibits the export of wall mannoproteins required for cell wall formation of fungal species [19]. The efficacy of tetrasodium EDTA in killing and removing biofilms from the catheter lumen is known [19, 20]. Three studies combined GM with EDTA and reported that the combination have the most potent activity against all organism tested in their experiments [13, 30, 31]. One study even mentioned that the EDTA-GM group was the most active combination towards the GM-resistant strain [31].

The use of other anticoagulant as heparin substitute is also looked for their ability to eradicate biofilm. Four studies report the biofilm eradication is happened after the exposure of GM combined with anticoagulant other than heparin [13, 30, 31, 55] One study reported the efficacy of GM-TSC combination [55]. Three studies reported the superiority of GM-EDTA combination in biofilm eradication [13, 30, 31]. These suggest that the addition of TSC or EDTA to the GM as catheter lock has the potential to eradicate biofilm in catheter

Catheter-related infection (CRI) is the major problem in CVC use for hemodialysis. The use of catheter lock should be accompanied with the prevention of bacteremia, biofilm formation, and infection. The use of GM alone in ALS is not enough. But GM efficacy is not intensified with additional antibiotics. Nevertheless, TSC and EDTA emerge as appropriate anticoagulants which able to promote the biofilm eradication. The improvement in biofilm eradication would enhance the reduction of CRI. Further research direction is necessary in developing several antibiotic lock solution by using GM and different anticoagulant.

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Conflict of Interest

The authors have no financial conflicts of interest to declare.

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