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REVIEW

A Narrative Review of Experimental Models to Study Vascular Grafts Infections

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Background: Many experimental models have been developed to decipher the mechanisms of vascular graft and endograft infections (VGEIs), and to elaborate strategies to prevent or treat their occurrence. A systematic literature research was conducted to identify the most accurate models for studying VGEIs, depending on the research question.

Methods: A narrative literature search was conducted using the MEDLINE and Cochrane databases, with no set limit on the date of publication, up to 10 August 2021. *Ex vivo*, *in vitro*, and *in vivo* animal studies on VGEIs, published in English or French, were selected. Cross references retrieved from selected articles on PubMed database were also included. Data on microorganisms and grafts studied, details of experimental models, and of graft implantation and removal in animal studies were collected.

Results: A total of 243 studies were included in the review after reading the full length articles: 55 *in vitro* studies, 169 animal studies, 17 studies which used both *in vitro* and animal models, and two *ex vivo* studies. Many differences in model characteristics were seen. The main *in vitro* model was the incubation of a graft sample in a bacterial solution, used to study the first steps of infection. In animals, vascular large animal models (dogs and pigs) were the most commonly described but supplanted over time by extravascular and particularly subcutaneous mouse and rat models, which have been reported increasingly over the last few years. In animal models, antibiotic prophylaxis and therapy were rarely administered (27.4% and 19.9%, respectively), and vascular reconstruction after VGEIs even less frequently (9.8%).

Conclusion: Despite protocol discrepancies, it was possible to dinstinguish three main experimental models (i.e., in vitro and in vivo vascular models, and extravascular models), which all remain of interest to study specific phases of VGEIs.

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INTRODUCTION

Vascular graft and endograft infections (VGEIs) are associated with high morbidity, mortality, and relapse rates.[1] Consensus guidelines on VGEIs have been published by the American Heart Association in 2016,[2] and by the European Society for Vascular Surgery in 2020.[1] However, many issues remain unresolved owing to the paucity of robust evidence and the heterogeneity of published studies,[1] especially with regard to the anti-infectious treatment of VGEIs, notably the molecules associated with the best outcomes, their activity in biofilm, and treatment duration.

Experimental clinical studies are very heterogeneous. The first experimental study was conducted on dogs by in 1958.[3] Many studies on graft infectability or VGEI treatment in experimental models have since been published. These studies have been partly summarised in two well conducted literature reviews, which focused on *in vivo* models to study vascular graft coating and silver coated grafts for the prevention of VGEIs.[4,5] However, so far there has been a lack of a reviews of VGEI and graft infectability models.

A narrative literature review was performed in order to summarise all models described in experimental VGEI studies, and to identify the most suitable ones for studying VGEIs, depending on the research question.

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METHODS

The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines,[6] and the PICO strategy (patient population [P], intervention [I], comparison [C], and outcomes [O]), which was used to structure and respond to the research question. The PICO criteria was 'Which experimental models (I) are the most accurate (C) to investigate the unresolved issues on pathophysiology and treatment (O) in VGEIs field (P)'?

Search strategy and information sources

A duplicate electronic literature search was conducted by two authors (M.P. and C.C.) using the MEDLINE and Cochrane databases, with no limit on the date of publication. Disagreements were resolved by consensus. If consensus was not achievable, an opinion was sought from a third author (X.B.). An updated search was performed on 10 August 2021. The search terms were: "vascular graft infection", combined, by mean of the Boolean operator "AND", with "animal study", "animal model", "in vitro study", or "in vitro model" The MeSH terms "blood vessel prosthesis" AND "infections" AND "models, animal", and "blood vessel prosthesis" AND "infections" AND "in vitro techniques" were also used. For each included article, the reference list and the first 20 related articles in PubMed were screened to retrieve potentially relevant articles.

Eligibility criteria and study selection

Studies were selected according to the following criteria. Only *in vitro* and *in vivo* animal studies on VGEIs and graft infectability, published in English or French, were selected. Clinical studies on human and experimental studies on other device infections were excluded. Studies were first selected on a title and abstract basis, then on full text. Duplicates were discarded.

Data collection process

Data were extracted by M.P. and C.C. From each study, information on the source (main author, journal, and year of publication), microorganisms and grafts studied, details of experiments and analysis performed were collected. For animal studies, the animal characteristics, details of graft implantation, whether antibiotic prophylaxis or anti-infectious therapy was administered, and the delays between graft implantation, infection, and graft explantation were recorded. The focus was on the model details; the results of the studies were not analysed.

RESULTS

A total of 243 articles were included in the comprehensive review: 55 *in vitro* studies, 169 animal studies, 17 that used both *in vitro* and animal models, and two *ex vivo* studies (Fig. 1). The models created to reproduce VGEIs are summarised in Fig. 2.

In vitro models

In vitro models are summarised in Table 1 and detailed in Supplementary Table 1. Five *in vitro* models were identified with lots of different experimental protocols (Supplementary Table 1). The model used most often was graft incubation in a microbial culture.[7] This simple model allowed the study of

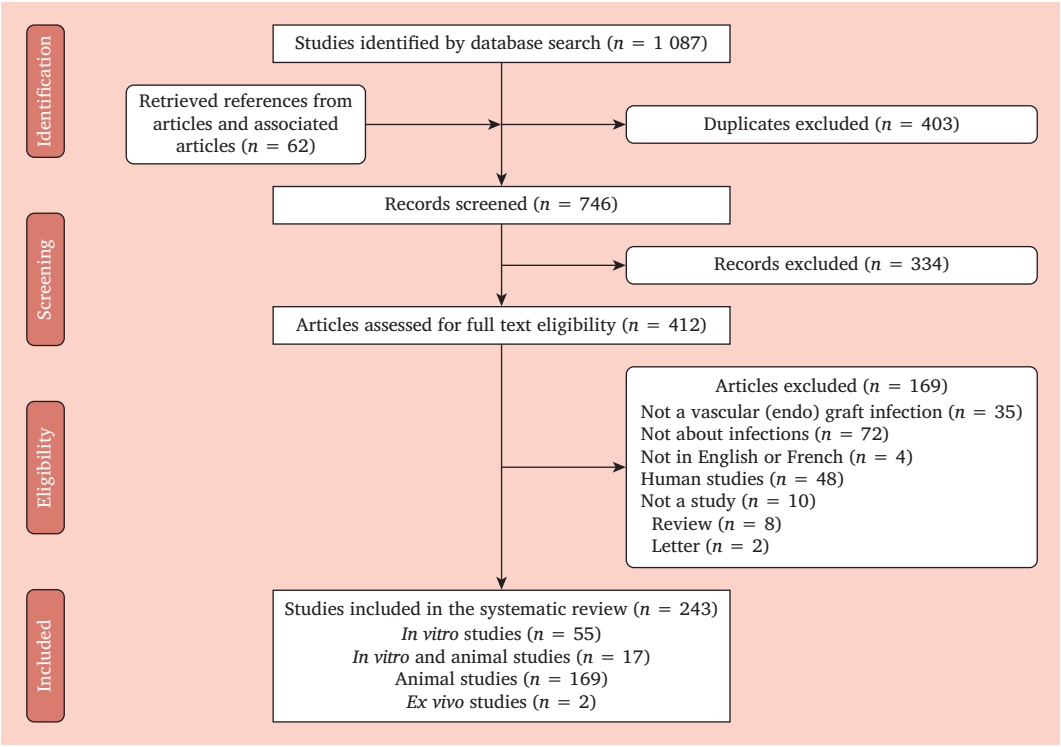

Figure 1. Flow chart of the study according to the PRISMA guidelines.

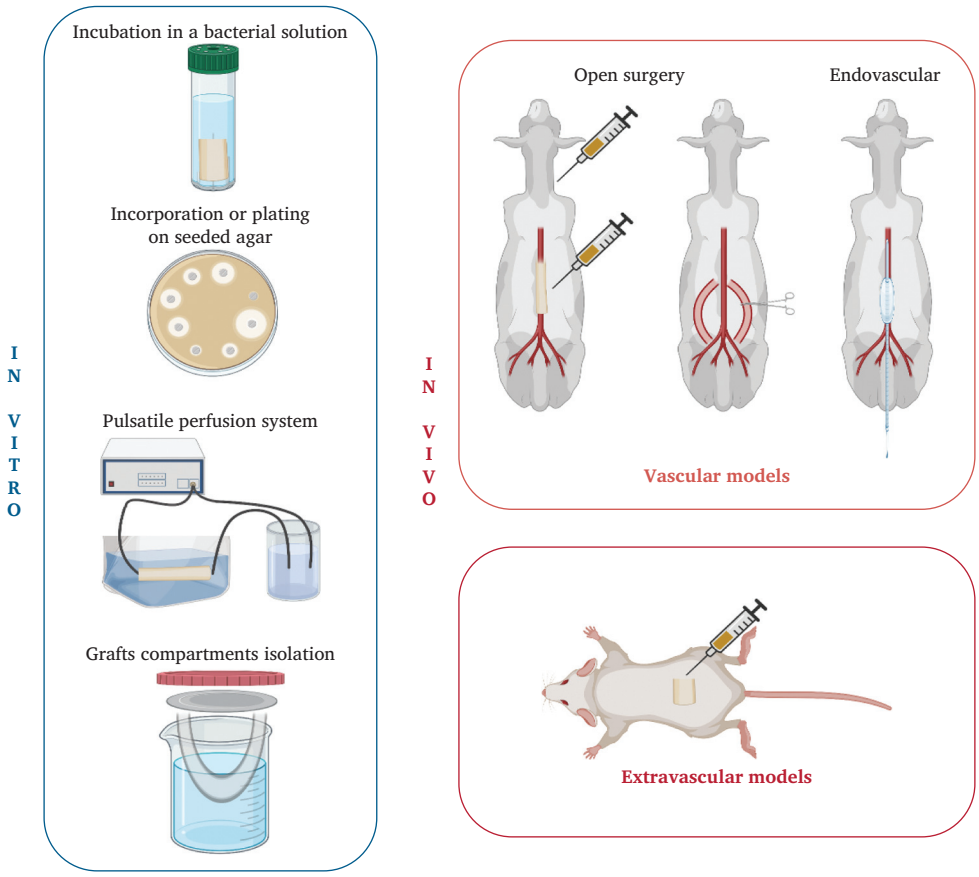

Figure 2. Summary of *in vitro* and *in vivo* models of vascular and endovascular graft infections (created with BioRender.com).

graft infectability and infection with low costs, high reproducibility, and could easily be reproduced in different experimental conditions. More often used in the 1980s and 1990s but less employed nowadays, models using inclusion or plating on a seeded agar were especially used for graft infectability study.[8] The third most frequently encountered model was the perfusion system, used for reproducing blood flow and studying bacterial adherence under shear stress and flow conditions.[9] Other *in vitro* models were rarely described (Supplementary Table 1). All these *in vitro* models were useful for the study of graft infectability and the first stages of infection, adhesion, and biofilm formation (Table 2). Thanks to their low cost, which makes conducting a large number of experiments easier, these models remain far from the real conditions in humans. Indeed, there was a lack of cellular environment, immune system, and blood flow, with the exception of rarely described perfusion systems. Therefore, conclusions from these *in vitro* studies required caution.

IN VIVO MODELS

Animal models are summarised in Table 1 and detailed in Supplementary Table 2.

Animal species

Many different animals have been used for research on VGEIs, despite differences among animal species in terms of infection susceptibility. For example, haematogenous aortic graft infection was more frequent in dogs than pigs.[10] Initially, the most frequently encountered animals were dogs (72 studies; 38.7% of animal studies).[11] Pigs then became preferred over dogs, notably because their cardiovascular system has many similarities to that of humans ($n = 28$; 15%).[12,13] However, some authors have described some differences from humans. For instance, in pigs, neointima development is completed within four weeks, whereas in humans and dogs, development of neointima in polyester grafts may take months or even years and does not always cover the graft completely.[14] More recently, smaller animals such as rats and mice ($n = 51$ and $n = 12$ [27.4% and 6.5%], respectively)[15,16] have been studied more frequently.

These *in vivo* models have been useful to study VGEIs in a cellular environment that is similar to that of humans, and to allow a more reliable approach to the study of the efficacy of antimicrobial molecules. However, the use of animal models remains difficult owing to the high cost, especially when dealing with large animals, in addition to ethical issues around animal testing. These drawbacks limit the number and therefore the reproducibility of animal studies.

Graft implantation

Vascular models. Vascular models have been elaborated in large animals, especially dogs, pigs, and sheeps, almost

Table 1. Main characteristics of experimental models of vascular graft and endograft infections.

Model	Graft types	Microorganisms	Inoculum	Implantation	Localisation	Inoculation	References
In vitro (72 studies)	Biological and synthetic, impregnated or not	Gram positive and negative bacteria, *Candida* spp.	10^4—10^8 CFU/mL	In a bacterial solution (89.1%) On seeded agar (32.7%) Pulsatile perfusion system ($n = 5$) Graft surface isolated from lumen ($n = 2$)	NA	Graft incubation in a bacterial solution Seeded agar Through perfusion solution (animal blood or bacterial solution)	[7—9,15,25]
Ex vivo ($n = 2$)	Explanted vascular grafts from patients, biological and synthetic	Anaerobes Gram positive and negative bacteria	NA	Open surgery	Aortic and peripheral grafts	NA	[29,30]
In vivo							
Vascular ($n = 122$)	Biological and synthetic, impregnated or not	Gram positive and negative bacteria	10^2—10^9 CFU/mL	Arterial (63.7% of animal studies): open surgery ($n = 113$) or endovascular ($n = 6$) or both ($n = 1$) Vena cava ($n = 2$) Arteriovenous shunt ($n = 1$)	Abdominal (47%) and/or thoracic aorta (3.8%) Peripheral arteries: limb, carotid artery (12.9%) Vena cava ($n = 2$)	Either locally and/or systemic bacteraemia Faecal contamination Bacterial translocation Pre-infected graft	[3,12,13,31]
Extravascular ($n = 66$)	Biological and synthetic, impregnated or not	Gram positive and negative bacteria	10^1—10^9 CFU/mL	Subcutaneous (33.5%) Submuscular ($n = 1$) Retroperitoneal ($n = 1$) Intraperitoneal ($n = 2$)	SC: back most often, rarely abdomen or groin SM: next to spinous processes IP: iliac fossa, caecal area	Locally most often Rarely systemic bacteraemia	[15,20]

CFU = colony forming unit; NA = non-applicable; SC = subcutaneous; SM = submuscular; IP = intraperitoneally.

Table 2. Main characteristics of the three experimental models of vascular graft and endograft infections (*in vitro*, *in vivo* vascular and extravascular models).

Models	Advantages	Weaknesses	Checklist Specific	General
In vitro	First stages of infection, adhesion, and first steps of biofilm formation study High number of experiments Possible fluid flow conditions: pulsatile perfusion system	Far from real conditions in humans, no cellular environment, no immune system		Use reference strains and VGEI clinical strains Use a standardised inoculum to induce infection
In vivo	Closer to human VGEIs: immune system, cellular environment Relevant to study antimicrobial therapy	Ethics on animal testing High costs	Stick as closely as possible to clinical practice: • Antibiotic prophylaxis before graft implantation • Anti-infectious treatment combined with the surgical strategy when VGEI treatment is investigated	
Vascular	The most realistic: fluid flow condition and high shear stress, cellular environment, fibrin deposit, potential thrombosis, endothelialisation Both surgical and endovascular graft implantations, both local and haematogenous infection induction can be studied Possible in small animals (carotid catheter) Mechanical properties of infected grafts can be analysed Relevant to study graft replacement in case of VGEI	Complex experimental conditions Most often large animals: higher costs and smaller number of tested animals compared with smaller animals		
Extravascular	Reproduces infections from the wound or an adjacent infectious focus, especially in peripheral grafts Small animals: larger number of animals, useful to compare several anti-infectious treatment regimens	Low shear environment which might influence biofilm formation Different cellular and biochemical environment compared with vascular models		

VGEIs = vascular graft and endograft infections.

always in an arterial position. These models are difficult to set up, especially in small animals, where smaller graft segments were usually implanted, such as aortic patchs. In these small animals, technical errors were more frequent, notably haemorrhage from the inferior vena cava.[17] Catheters can also be implanted in mice carotid arteries, which might be less invasive and easier to achieve.[18] Vascular *in situ* reconstruction to treat VGEIs was only evaluated in 9.8% of the vascular model studies and was associated with systemic antibiotic therapy in only five studies. Only two studies analysed surgical debridement of perigraft infected tissues combined with antibiotic therapy.

Vascular models are the closest to real conditions, as they reproduce more accurately the cellular environnement and the fluid flow conditions of implanted vascular grafts. They allow the study of different ways of infection, peri-operatively or post-operatively, and through distant or local microbial contamination in addition to offering the possibility of evaluating several surgical strategies, either for graft implantation or VGEI treatment.

Extravascular models

As they offer an easier access to the graft, subcutaneous models have been largely used in recent studies (33.5% of all animal studies), especially in rats and mice,[15] and more rarely in rabbits and pigs. A segment of graft was often implanted in a subcutaneous pocket on the animal's back, rarely in the anterior abdominal wall, in the groin, or in other extravascular locations (Supplementary Table 2). Despite different cellular and shear environments *vs.* grafts implanted into arteries, these extravascular models might reproduce quite faithfully some specific situations encountered in VGEIs, such as infections occurring from the wound or an adjacent infectious focus, especially in peripheral grafts (Table 2).

Local and systemic prophylaxis and therapy

Antibiotic prophylaxis was administered in only 27.4% of animal studies, either locally,[19] at the surgical site, or in the wound after closure, or systemically.[12] Systemic antibiotic therapy was administered in only 19.9% of animal studies,[20] most often started peri-operatively or just after the onset of infection. The duration of antibiotic therapy varied but often corresponded to the delay of explantation after the induction of infection (two days to three weeks). Sometimes, antibiotic therapy or prophylaxis was combined with an antibiofilm drug. Several studies also evaluated local devices releasing antibiotics or antiseptics. When grafts were implanted into arteries, antiplatelet therapy was rarely administered (6% of all vascular models, mainly aspirin), sometimes before graft implantation.[21] Rarely, immunosuppression was induced by specific drugs (see Supplemantary Table 3).[22]

Infection induction modalities

Grafts were infected either before implantation by incubation in a bacterial solution, or after, by systemic or local routes. Direct inoculation of the graft surface by a bacterial culture was favoured in subcutaneous models, mimicking the infection process, which often starts along the external surface of the vascular prosthesis, especially in peri-operative infections and contiguous spread from a nearby focus of infection but less often along the endoluminal layer by haematogenous spread from a distant focus.[15] Rarely, a faecal solution was inoculated on the graft, either directly, by mimicking a faecal contamination or through digestive translocation induced by a systemic inflammatory response syndrome.[23] These last inoculation methods did not allow the quantification of the microbial inoculum, thus limiting experimental reproductibility between animals.

Several studies involved the inoculation of the bacterial culture immediately after graft implantation, mimicking a peri-operative contamination, especially locally and more rarely by a bacteraemia.[24] Nevertheless, the delay between graft implantation and infection varied considerably from 30 minutes to several months. Authors also compared different delays in infection in order to assess differences in infectability according to graft age, whether its incorporation to the aortic wall was good enough, and to evaluate the impact of endothelialisation and pseudo-intimal coverage on older grafts. Explantation delays also varied among studies, between two hours and several weeks, thus enabling the study of both acute and chronic infections.

MICROORGANISMS INVESTIGATED

Infections were quasi-exclusively monomicrobial, mostly with *Staphylococcus aureus*, but many other bacteria have been studied (Supplementary Table 2). Polymicrobial infections were rare, despite being a rather frequently encountered situation in aortic VGEIs. Of note, bacterial solution concentrations differed between studies (10^2—10^9 colony forming units/mL) and were sometimes compared before selecting the optimal concentration able to provoke graft infection but not the death of the animal, and to determine the median infective dose. These 'optimal' concentrations were different between studies, depending on the type of contamination, the bacteria involved, and the animal model.

Microorganisms were retrieved either from reference collections or clinical sources, mainly from bacteraemia, and also from endocarditis or vascular infections. Both strain types are interesting: the reference strains allow comparison between studies and clinical strains often come directly from patients' samples and are therefore closer to real conditions in terms of adhesion and biofilm formation. However, microbial inoculum should be standardised for each experimental conditions, in order to be able to compare studies results.

TYPE OF GRAFTS STUDIED

Graft segment length was influenced by animal model but was often short compared with grafts implanted in humans, which might lead to better healing than expected in humans. Therefore, studies only seldom used longer graft

segments to better mimic human situation in thoraco-abdominal bypasses (25—30 cm length).

EVOLUTION OF EXPERIMENTAL MODELS

Since the first animal model of VGEI elaborated in dogs in 1958 by Harrison,[3] and the first *in vitro* perfusion system created by Goëau-Brissonière et al. in 1980,[25] experimental models have evolved. In animal models, small animals have gradually replaced large ones, allowing the use of larger cohorts with a higher reproducibility. Consequently, vascular models have been progressively superseded by extravascular ones, which technically are less difficult to achieve. Regarding *in vitro* models, graft incubation in a bacterial solution was the most frequently used. Alongside the evolution of these models, the methodological approaches employed for infectability analysis have greatly evolved in the last few years, notably in the microscopy and imaging fields.[15,18]

DISCUSSION

A narrative review was conducted on experimental models used for VGEI studies. In total, 243 studies were included, mostly on animal models, and detailed the experimental conditions of those most frequently used. Over the years, most *in vitro* and animal studies have focused on graft infectability, trying to identify the best graft materials to prevent and treat VGEIs. However, studies were disparate in terms of models used and analyses performed and were therefore not comparable. Many studies were published years ago, when no guidelines on animal experimentation were available.[26]

Three main model types were identified: *in vitro*, and vascular and extravascular studies, which have different applications in VGEI studies. The three model types are complementary as they allow the study of different infection stages, and are summarised in Table 2, along with their main advantages, weaknesses, and the criteria that should be considered. Despite technical difficulties, vascular models have many advantages: they reproduce the cellular environment of VGEIs more accurately and they also expose the graft to high shear stress, which has been correlated with biofilm formation. Indeed, fluid flow condition seems to be a dominant factor that influences the number of attached bacteria, as well as biofilm structure. Bacterial growth rate, morphology, size, density, and metabolism are also affected by a high shear environment. Indeed, strains of *Staphylococcus epidermidis* isolated from high shear environments are more capable of biofilm synthesis and graft adhesion than strains isolated from low shear environments.[27] In these particular cases, biofilm might provide protection against shear flow. Therefore, subcutaneous models probably provide less reliable information on biofilm synthesis and antimicrobial treatment efficacy, but they can still reproduce quite accurately peripheral graft infections from wounds or peri-operative infections.[15]

Technical difficulties and the many issues raised regarding legislation of animal experiments and ethics should prompt the innovation and development of new models, both *in vitro models* which could better mimic human conditions, and less invasive animal models such as vascular models of carotid catheters, which might be easier to achieve and could be a compromise between vascular models in large animals and subcutaneous models in smaller ones.[18] Lastly, alternative technologies to avoid animal testing, such as *in vitro* perfusion models, which need further development to better mimic human VGEIs, or computer simulation, will hopefully increase in the coming years.[28] Moreover, there were notably few animal studies combining graft removal and anti-infectious therapy. The majority of studies investigated peri-operative contamination and graft infectability rather than VGEI treatment. However, no matter which infection step is under evaluation, experimental conditions should be as close as possible to real life conditions. Therefore, antibiotic prophylaxis should be performed systematically according to the current consensus. Moreover, when VGEI treatment is investigated, an anti-infectious therapy should be administered and more systematically associated with vascular reconstruction, as is currently recommended in clinical practice.[1]

Finally, *in vitro* models remain interesting for studying the early stages of infection, particularly microbial adhesion and the first steps of biofilm formation on vascular grafts.

Conclusion

The three experimental models (i.e., *in vitro*, vascular, and extravascular), are complementary and should therefore be combined in future studies according to the infection step to be investigated. It is noteworthy that the impact of antimicrobial treatment on the development of resistance and biofilm formation remains largely unknown and should be given priority in future VGEI research studies.

FUNDING

None.

CONFLICTS OF INTEREST

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvsvf.2022.03.002.

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