Journal of Parenteral and Enteral Nutrition
Volume 00 Number 0
xxx 2018 1–11

DOI: 10.1002/jpen.1039
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Effect of Delaying Replacement of Parenteral Nutrition Intravenous Administration Sets: Preclinical Experiments and a Dynamic Laboratory Model of Microbial Colonization

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Abstract

Background: Recommendations prescribe daily intravenous administration set (IVAS) replacement for parenteral nutrition (PN) comprising intravenous fat emulsions (IVFE) due to risk of micro-organism growth and resultant central-line associated bloodstream infections (CLABSIs), but system disconnection for this practice may allow contamination and CLABSIs. *Materials and Methods:* Laboratory experiments and model development were used to simulate PN administration after contamination from healthcare workers' hands. This study observed the growth of micro-organisms known to cause CLABSIs in a variety of PN and other IV fluids and developed a model to investigate the effect of delaying IVAS replacement on microbial growth for up to 7 days. *Results:* Micro-organisms grew at different rates and were affected by solution type. In static experiments, growth was supported in IVFE and all-in-one PN, but suppressed in 50% glucose. Growth patterns were consistent over time for *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Candida albicans* in IVFE, all-in-one PN, and 0.9% sodium chloride in both static and dynamic experiments. *C. albicans* grew exponentially to clinically significant numbers in all-in-one PN and IVFE IVAS after 30 hours, but negligible growth of *S. epidermidis* or *S. aureus* occurred for 7 days. *Conclusion:* All-in-one PN and IVFE support the *C. albicans* growth after minimal initial contamination, with micro-organisms migrating from the fluid bag to the central venous access device. Improved aseptic nontouch technique during clinical practice is vital to prevent contamination. Daily IVAS replacement of for all-in-one PN and IVFE should continue until the safety of prolonging IVAS replacement is confirmed by randomized trials. (*JPEN J Parenter Enteral Nutr.* 2018;00:1–11)

Keywords

parenteral nutrition; intravenous administration set; venous access; laboratory model

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Financial disclosure: This work was supported by an American Society of Parenteral and Enteral Nutrition Society Rhoads Research Foundation Grant and a Baxter Investigator Initiated Research Grant. Nicole Gavin received a PhD scholarship from the National Health and Medical Research Council Centre of Research Excellence in Nursing at Griffith University, Brisbane, Australia, and the Royal Brisbane and Women's Hospital Foundation.

Conflicts of interest: N.G. received educational funding and honoraria from ICU Medical and Hospira as part of the AVATAR group and the Cancer Nurses' Society of Australia Vascular Access Device and Infusion Therapy Specialist Practice Network. S.K., as part of the AVATAR group, received unrestricted research grants and consultancy monies for project management and lectures from Becton Dickinson Medical for work unrelated to this study. Griffith University has received the following on behalf of G.R.-B.: unrestricted research grants from 3M, B. Braun, and BD/Carefusion and consultancy payments from 3M, Becton Dickinson, ResQDevices, and Medline for educational lectures based on her research. In 2015–2017, Griffith University received unrestricted investigator-initiated research or educational grants on behalf of C.M.R. from the following manufacturers: 3M, Adhezion, Angiodynamics, Bard, Baxter, B. Braun, Becton Dickinson, Centurion Medical Products, Cook Medical, Entrotech, Flomedical, ICU Medical, Medical Australia, Medtronic, Smiths Medical, Teleflex. In 2015–2017, Griffith University received consultancy payments on behalf of C.M.R. from the following manufacturers: 3M, Bard, B. Braun, BD, ResQDevices, Smiths Medical. D.M. and M.A.C. have no conflicts of interest to report.

accepted for publication October 23, 2017.

This article originally appeared online on xxxx 0, 2018.

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Clinical Relevancy Statement

Poor hand hygiene and aseptic nontouch technique may contribute to central-line associated bloodstream infections. We are challenging the age-old belief that all-in-one parenteral nutrition or intravenous fat emulsions increase infection risk over other fluids. These laboratory findings are a first step to examining whether daily intravenous administration set replacement may be putting our patients at more risk.

Introduction

Vascular access devices (VAD) are ubiquitous in healthcare. They enable the continuous infusion of parenteral nutrition (PN), intravenous (IV) fluids and medications, and blood sampling, all infused through an intravenous administration set (IVAS). However, VADs and IVASs are major risk factors for hospital-acquired infections. Approximately half of all *Staphylococcus aureus* bacteremias are associated with VADs.[1,2] The highest bloodstream infection (BSI) incidences are in patients with central venous access devices (CVADs), commonly used for the delivery of PN. Approximately 1.3%–26.2% of patients receiving PN will develop a BSI.[3]

As a result of their association with BSI, CVADs and IVAS used for the delivery of PN have unique management protocols. These protocols recommend that PN containing intravenous fat emulsions (IVFE) be administered through a designated single-lumen CVAD and that IVASs be replaced every 24 hours.[4-6] This is based on nonanalytic studies and expert opinion. In contrast, an IVAS not used for PN containing IVFE or blood products, such as 50% glucose and amino acid solutions, should be replaced no more frequently than every 96 hours.[4,7] This recommendation is supported by a Cochrane Review.[8]

IVASs typically consist of tubing, fluid bags, burettes, extension sets, 3-way taps, and needleless connectors. These components are packaged separately and need to be assembled by hand at each IVAS replacement. Extrinsic contamination of the intraluminal VAD and IVAS may also occur during routine clinical practice and patient care due to poor hand hygiene and/or inadequate decontamination of the IVAS.[9] Contaminants may be micro-organisms present on the patient or healthcare workers or the environment.[10] If micro-organisms enter an IVAS, they may attach to and colonize the internal (intraluminal) surfaces, establishing a biofilm. Biofilms are a complex micro-ecology that exhibit surface attachment, the development of an extracellular polymeric substance that provides an ideal environment for the exchange of genetic material and cell dispersal or detachment.[11] This biofilm may then act as a seed for a catheter line–associated bloodstream infection (CLABSI). Alternatively, the micro-organisms may migrate through the IVAS into the VAD and enter the bloodstream directly.

Although current recommendations prescribe daily IVAS replacement for PN delivery, the handling of the IVAS for this procedure may itself be a contributor to CLABSI. IVAS replacement requires manipulation at the lumen hub closest to the bloodstream. If aseptic nontouch technique is poor, then the daily PN IVAS replacement may cause hub contamination and, in turn, intraluminal contamination of the CVAD.[12,13] The total number of colony forming units (CFU) recovered from 5 fingertips ranges from 0 to 300 CFU.[14] The average number of viable bacteria colonies transferred from ungloved fingertips ranges from 4 to 20 CFU per minute during skin contact, direct patient contact, blood sampling, and IV injection or care.[14] With increasing rates of hospital-acquired infections in clinical settings and an increase in the use of VADs, including CVADs, it is imperative that risk factors associated with CLABSI and the methods used to reduce these risks be identified and evaluated.

Laboratory experiments and models can be the first step to answering a clinical problem that involves a host-pathogen response. Previous researchers have developed laboratory models to simulate PN administration[15,16]; however, none have investigated the effect of touch contamination from healthcare workers' hands on micro-organism growth in fluids over time. Merlino and colleagues[15] simulated a 9-hour contaminated PN infusion for 3 days and found that all organisms grew exponentially, a period defined by cell doubling or otherwise known as the logarithmic phase. However, extremely high numbers of organisms were used for contamination, which likely does not generalize to contamination from the hands of healthcare workers. Mershon and colleagues[16] developed a model using fewer colonies and simulated PN infusion for 3 days. This study did not use a control solution but, rather, varied the concentration of glucose. The authors found that a 0.22 μM filter effectively removed *Staphylococcus epidermidis*, *Escherichia coli,* and *Candida albicans* from contaminated PN. Current infection control and PN guidelines[5-7] do not recommend filters to be used solely for CLABSI prevention; thus research using nonfiltered models is also an important gap. However, filters are effective at eliminating or reducing the infusion of particulates, microprecipitates, micro-organisms, pyrogens, and air.[5]

In the past 30 years, there have been many changes to PN manufacturing, the materials used in CVAD and IVAS components, understanding of the pathogenesis of CLABSI, and the host–pathogen interaction. In previous laboratory studies,[15,16] PN was prepared daily by the hospital pharmacy under sterile conditions in a laminar flow cabinet. PN is available as commercially manufactured in a 3-in-1 bag or in separate component infusions (glucose, IVFE, and amino acids). Thibault and Pichard[17] reviewed the safety

of nutrition support in intensive care units and highlighted that the advances made in commercially available all-in-one PN solutions meant that studies performed pre-1990 did not reflect current practice. In 1991, needleless connectors were introduced to IVAS to reduce needle-stick injuries, but in some cases they have been associated with increased catheter-related bloodstream infections and CLABSI.[18]

In this article, we describe laboratory experiments including a dynamic model to simulate PN administration and contamination from healthcare workers' hands. In the first instance, the growth properties of pathogens known to cause CLABSI were observed in commonly used hospital IV solutions, including all of the component parts of PN. A model was then used specifically to explore the growth properties of pathogens in the solution bags and IVASs and whether this was influenced by the duration of IVAS use to understand the likely efficacy of current 24-hour replacement policies.

Materials and Methods

Design

This study included preclinical laboratory experiments and dynamic IVAS model development to simulate PN administration and contamination from healthcare workers' hands and the effect over time. The micro-organisms used were derived from patients, not laboratory reference strains, and therefore initial growth curve experiments were undertaken to establish a baseline for growth.

Aims

This study aimed to (1) observe the growth of micro-organisms known to cause CLABSI in a variety of PN solutions and other IV fluids and (2) develop an IVAS model to investigate the effect of the duration of IVAS use on micro-organism growth.

Hypotheses

It was hypothesized that (1) the micro-organisms tested would grow at different rates; (2) the growth of micro-organisms would vary in different solutions; (3) if the previous hypotheses were correct, it was conjectured that the micro-organisms would follow that same growth trajectory in the IVAS model when compared with the static experiments; and (4) growth at the distal needleless connector of the IVAS model in the first 24 hours would be representative of the subsequent days' growth.

Microbiological Strains

Bacterial isolates representing 3 species (*S. aureus, S. epidermidis, Streptococcus pyogenes,* and *Pseudomonas aeruginosa)* were used in addition to *C. albicans*. The isolates were obtained from a biobank of specimens collected from patients at the Royal Brisbane and Women's Hospital (Queensland, Australia). These bacterial species were chosen because they represent species commonly responsible for CLABSI. The isolates were grown on the appropriate agars: *S. aureus, S. epidermidis,* and *S. pyogenes* were initially grown on horse blood agar plates (Oxoid, Inc. [Ottawa, Ontario] blood agar base, product number CM0055; and Equicell defibrinated horse blood, product number E-HBD); *P. aeruginosa* on cetrimide agar (Oxoid pseudomonas cetrimide agar, product number CM0579); and *C. albicans* on Sabouraud dextrose agar (Oxoid Sabouraud dextrose agar; product number CM0041).

Phase 1. Micro-Organism Growth in PN and Other Intravenous Therapy Solutions

The growth of all micro-organisms was assessed in 6 solutions representing PN and/or its component parts and 4 control solutions. After growing overnight, 1 colony of each species was transferred to 5 mL of prewarmed TSB (Becton Dickinson [Franklin Lakes, NJ] Bacto tryptic soy broth without dextrose, product number 286220) and incubated at 37°C overnight at 200 revolutions per minute (RPM). The next day, the suspensions were centrifuged at 3000 RPM, the supernatant removed, and the pellet washed in 5 mL of phosphate buffered saline (Invitrogen [Carlsbad, CA], product number 003002). After a second washing, micro-organisms were resuspended in 20 mL of phosphate buffered saline. Of this suspension, 1 mL was inoculated into 20 mL of the following prewarmed solutions: TSB; 0.9% sodium chloride (Baxter International Inc. [Deerfield, IL] sodium chloride 0.9%, product number AHB1324); 5% glucose (B. Braun [Melsungen, Germany] 5% glucose IV infusion british pharmacopoeia (BP), product number AUST R 49332); sterile water (Baxter water for injections BP, product number AHB0304); all-in-one PN (Baxter QH Central Parenteral Nutrition + Calcium, product number TCB-50-CA); IVFE (Baxter clinoleic 20%, product number FDB89503B); amino acids with electrolytes (Baxter synthamin 17 [amino acid 10%], IV infusion with electrolytes, product number AHA6921); amino acids without electrolytes (Baxter Synthamin 17 [amino acid 10%], IV infusion without electrolytes, product number AHA6920); 50% glucose (Baxter 50% glucose IV infusion BP, product number AHB0253); and amino acids with electrolytes plus 50% glucose.

The suspensions were incubated at for 24 hours at room temperature (23°C–25°C) in static conditions to represent solutions hanging on a pole at a patient's bedside. Aliquots were recovered at 0, 4, 8, and 24 hours, serially diluted, plated onto appropriate agar, and incubated overnight. The total CFU at each time point was then determined for each species in each solution. Data are presented as the

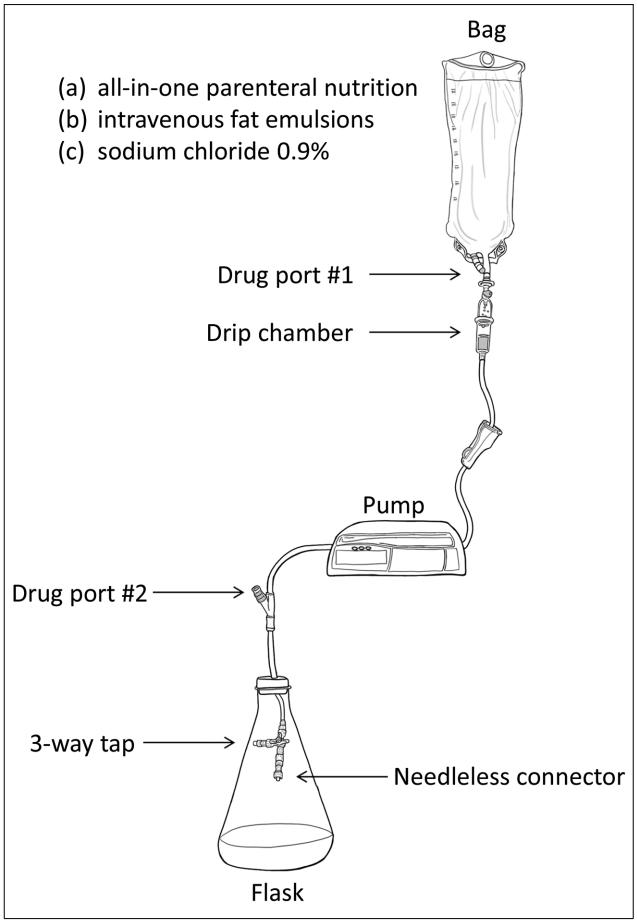

Figure 1. Intravenous administration set model.

percentage change in growth compared with CFU recovered at 0 hours. All experiments were undertaken in duplicate.

Phase 2. Development of a Dynamic Model of IVAS Contamination

This experiment was designed to contaminate the fluid bags with a clinically relevant number of colonies informed by the results of the phase 1 experiment. The model was intended for use with low numbers of micro-organisms, mimicking the numbers of organisms observed by contamination from healthcare workers' hands. Less than 100 colonies were used to contaminate the fluid bag in each experiment.

The dynamic IVAS model developed here consisted of the fluid bag, IV tubing (B. Braun Infusomat Space Line, product number 8700110SP), 3-way tap (B. Braun discofix C, product number 14/1892047), and needleless connectors (CareFusion [San Diego, C.A.] Needle-Free Value, product number 14115115) set up as per normal hospital practice for the continuous delivery of IV fluids and solutions (see Figure 1). To collect micro-organisms migrating down the tubing, the distal end of the IVAS model passed through a sterile bored bung into a sterile conical flask. In the clinical setting, the needleless connector at the distal end of the model would connect to the patient's CVAD. Fluid bags used in the IVAS model contained all-in-one PN, IVFE, or sodium chloride. For contamination experiments, 30 mL of fluid was removed from the fluid bag via the drug port 1 (see Figure 1) using the aseptic nontouch technique, and 100 μL of bacterial or fungal suspension containing <100 CFU inoculated into the bag via the same drug port. This drug port was then flushed with 30 mL of fluid. After letting the bag rest for 1 hour, it was connected to the IVAS, the IVAS was primed, and an IV pump (B. Braun Infusomat Space, product number 8713070) delivered the contents of the fluid bag for 24 hours. The model fully replicated fluid flow rates and bag and component changes as carried out in clinical settings. IVFE were delivered at 20 mL/hour; the PN and the 0.9% sodium chloride were delivered at 40 mL/hour. The IVAS remained in place for up to 7 days, with fluid bags replaced only when empty and using the aseptic nontouch technique. Aliquots of 1 mL were collected from drug port 1 at 0, 2, 6, 24, and 26 hours to ascertain growth in the fluid bags. The aliquot at 26 hours was to establish the sterility of the new fluid bag being connected to the existing IVAS. Aliquots of 1 mL were collected from the needleless connector on the distal end of the 3-way tap at 0, 2, 6, and 24 hours after initial contamination. The samples were also collected at 2, 6, and 24 hours after the bag replacement. These samples were collected to determine the migration of micro-organisms from the solution to the distal needleless connector. These samples were centrifuged, the supernatant was removed, and the pellet was resuspended in 100 μL of phosphate buffered saline. The suspension was subsequently plated onto horse blood agar or Sabouraud dextrose agar and incubated overnight at 37°C CFU. All experiments were undertaken in duplicate.

Ethical and Safety Considerations

This study was approved by the Human Research Ethics Committee of the Children's Health Services Queensland HREC/13/QRCH/185 and Griffith University, Brisbane NRS-41-14-HREC. There was no direct patient involvement in this study.

Results

Phase 1. Growth of Micro-Organisms in the Presence of PN and Control Solutions

The growth rates for the 5 micro-organisms in PN and the other solutions are presented in Figure 2 (A: *S. aureus*; B: *S. epidermidis*; C: *P. aeruginosa*; D: *S. pyogenes*; and E: *C. albicans*). All micro-organisms entered thelogarithmic

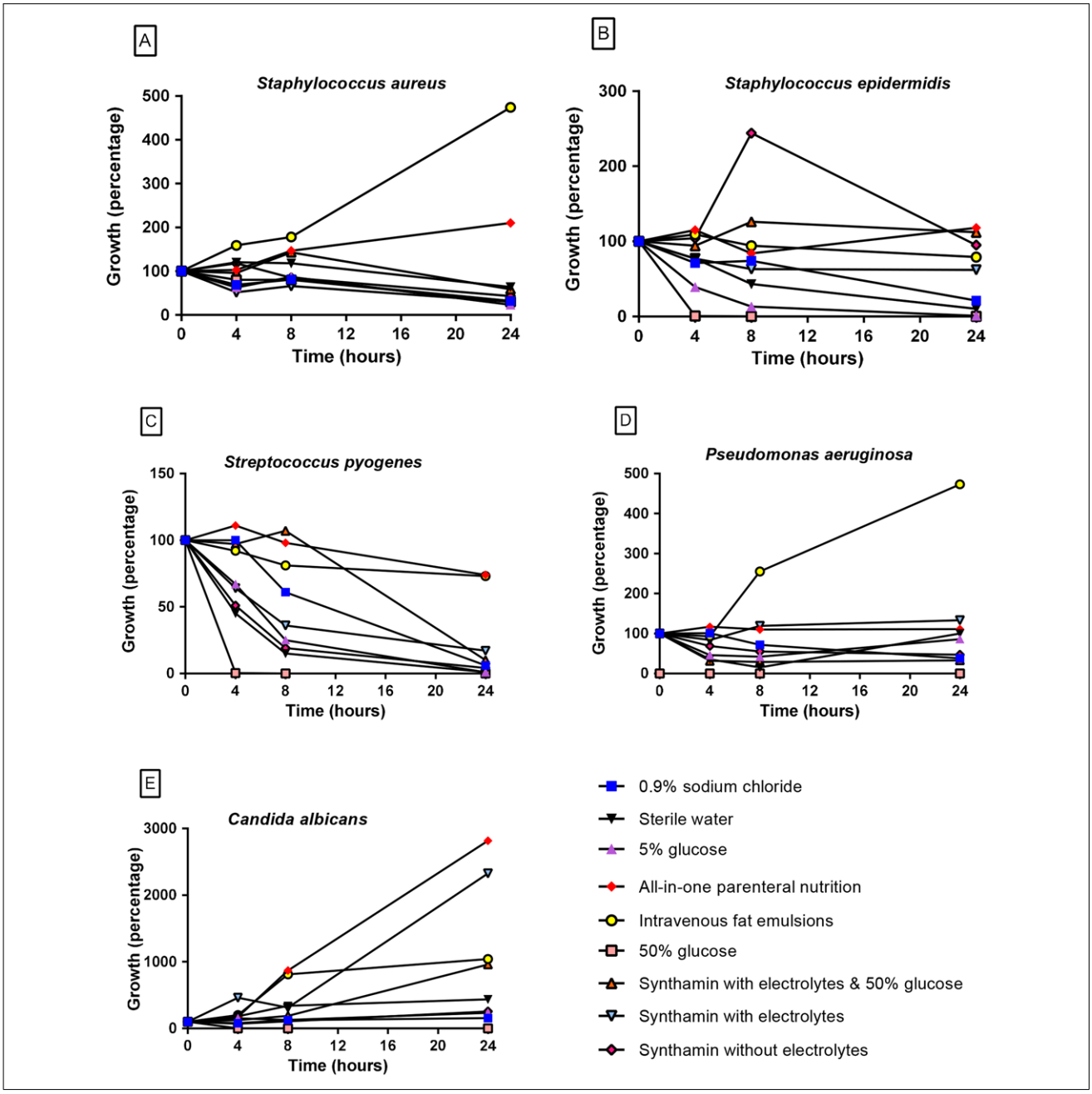

Figure 2. Growth of micro-organisms in static experiments.

phase when grown in in TSB (data not shown). In contrast, all micro-organisms except for *S. aureus* were nonviable in 50% glucose. *S. aureus* also grew in both IVFE and all-in-one PN. *C. albicans* entered the logarithmic phase in all solutions tested except 50% glucose where cell death occurred within 4 hours. *P. aeruginosa* entered te logarithmic phase in IVFE. *S. epidermidis, S. aureus, S. pyogenes,* and *P. aeruginosa* survived in all other solutions, but growth was suppressed.

Phase 2. IVAS Model

Number of colonies counted at drug port 1 in the first 24 hours. No colonies of *S. epidermidis*, *S. aureus*, or *C. albicans* were observed from drug port 1 in the first 24 hours in the sodium chloride 0.9% solution. However, these 3 micro-organisms were present in the cultures from the all-in-one PN and IVFE solution at drug port 1 within the first 24 hours. See Tables 1–3 for results.

Table 1. Growth of *Staphylococcus epidermidis* in Dynamic Intravenous Administration Set Model..

Number of colonies inoculated into solution bag at drug port 1																						
Experiment 1			51		69		75		82						Dilutions plated out in quadruplicate							
Experiment 2			4		7		8		9													
Number of colonies counted at drug port 1																						
Sodium chloride 0.9%						All-in-one parenteral nutrition						Lipids										
	Hours						Hours						Hours									
	0	2	6	24	26		0	2	6	24	26		0	2	6	24	26					
Experiment 1	0	0	0	0	0	Experiment 1	0	0	0	0	0	Experiment 1	0	0	0	3	0					
Experiment 2	0	0	0	0	0	Experiment 2	0	0	1	0	0	Experiment 2	0	0	0	0	0					
Number of colonies counted at distal needleless connector																						
	Hours																					
	0	2	6	24	26	30	48	50	54	72	74	78	96	98	102	120	122	126	144	146	150	168
Sodium chloride 0.9%																						
Experiment 1	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
All-in-one parenteral nutrition																						
Experiment 1	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lipids																						
Experiment 1	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

A dash (–) indicates no colonies counted on agar.

Table 2. Growth of *Staphylococcus aureus* in Dynamic Intravenous Administration Set Model..

Number of colonies inoculated into solution bag at drug port 1				
Experiment 1	27	33	34	34
Experiment 2	2	4	6	7

Number of colonies counted at drug port 1																					
Sodium chloride 0.9%						All-in-one parenteral nutrition							Lipids								
	Hours						Hours							Hours							
	0	2	6	24	26		0	2	6	24	26			0	2	6	24	26			
Experiment 1	0	0	0	0	0	Experiment 1	0	0	0	0	0	Experiment 1		0	0	0	29	0			
Experiment 2	0	0	0	0	0	Experiment 2	2	0	0	0	0	Experiment 2		0	0	0	4	0			

Number of colonies counted at distal needleless connector																						
	Hours																					
	0	2	6	24	26	30	48	50	54	72	74	78	96	98	102	120	122	126	144	146	150	168
Sodium chloride 0.9%																						
Experiment 1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
All-in-one parenteral nutrition																						
Experiment 1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lipids																						
Experiment 1	–	–	–	7	5	5	–	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	6	–	–	3	1	–	–	–	–	–	–	–	–	–	–	–	–	–

A dash (–) indicates no colonies counted on agar.

Table 3. Growth of *Candida albicans* in Dynamic Intravenous Administration Set Model..

Number of colonies inoculated into solution bag at drug port 1

Experiment 1	12	15	16	20
Experiment 2	5	7	8	13

Number of colonies counted at drug port 1

Sodium chloride 0.9%						All-in-one parenteral nutrition						Lipids					
	Hours						Hours						Hours					
	0	2	6	24	26		0	2	6	24	26		0	2	6	24	26
Experiment 1	0	0	0	0	0	Experiment 1	0	0	0	0	0	Experiment 1	0	0	0	253	0
Experiment 2	0	0	0	0	0	Experiment 2	0	0	0	1	0	Experiment 2	0	0	0	58	0

Number of colonies counted at distal needleless connector

	Hours																					
	0	2	6	24	26	30	48	50	54	72	74	78	96	98	102	120	122	126	144	146	150	168
Sodium chloride 0.9%																						
Experiment 1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Experiment 2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	34	4
All-in-one parenteral nutrition																						
Experiment 1	–	–	–	–	–	2	260	53	253	180	404	820	60	2676	3208	2960	3864	5890	5964	5440	4808	6512
Experiment 2	–	–	–	1	–	–	140	48	60	694	2288	2760	2984	1004	1716	5568	3312	2136	3956	2640	2430	2720
Lipids																						
Experiment 1	–	–	–	–	1	5	90	32	157	22	600	1736	1696	481	103	681	2056	1228	5128	1052	13	2008
Experiment 2	–	–	–	1	–	–	34	56	204	161	466	1480	2760	2224	3368	4176	4224	4720	2072	4160	3600	976

A dash (–) indicates no colonies counted on agar.

Number of colonies counted at the distal needleless connector. For *S. epidermidis*, bacteria were observed at the distal needleless connector when the IVFE IVAS was first connected and then at 54 hours in both the all-in-one PN and 0.9% sodium chloride. No growth was observed from 3 days until the end of the experiment at 7 days. For *S aureus*, bacteria were detected at 24, 26, 30, 48, 50, and 54 hours in IVFE. No growth was observed in the IVFE from 3 days until the end of the experiment at 7 days. No growth at any time point was observed at the distal end of the sodium chloride or all-in-one PN tubing. For *C. albicans*, 1 colony was grown from the IVFE and all-in-one PN tubing at 24 hours. Growth was subsequently observed in the IVFE and all-in-one PN at each time point after 48 hours. Growth (34 and 4 colonies) was observed in the sodium chloride tubing at 150 and 168 hours (in the 7th day) after 6 days of no growth in 1 experiment. Refer to Tables 1–3 for tabulated summaries.

Discussion

This study observed the growth of a selection of micro-organisms known to cause CLABSI in a variety of PN solutions and other IV fluids under both static conditions and in a dynamic IVAS model. Quality controls were demonstrated with all micro-organisms entering the logarithmic phase in TSB. As hypothesized, each of the 5 species tested grew at different rates, and growth was affected by the different solutions. In general, growth was supported in IVFE and all-in-one PN and suppressed in 50% glucose when tested in static conditions. There was consistency in the growth patterns over time of *S. epidermidis, S. aureus,* and *C. albicans* in IVFE, all-in-one PN, and 0.9% sodium chloride. This is important because it demonstrates the consistency of micro-organism growth in the static experiments and the dynamic conditions of the IVAS model. In the dynamic IVAS model, only 1 or 2 colonies of *S. epidermidis* were observed in all 3 solutions tested in the first 3 days, and not thereafter; the IVFE promoted *S. aureus* growth up to 3 days, and not thereafter. However, *C. albicans* grew exponentially after 2 days in the IVFE and all-in-one PN, and this continued for 7 days. The number of colonies recovered using *C. albicans* in the model would be clinically meaningful and cause a BSI. Our experiments and the IVAS model tested 1 micro-organism at a time and therefore may not always reflect the clinical setting where multiple micro-organisms may enter solution through staff handling of IVAS. Interactions between micro-organisms can create a microecology where individual organisms may not be able to exist in isolation.[19] In addition, this IVAS model did not deploy surface conditioning to promote a biofilm but, rather, contaminated directly into the IV fluids. Despite these limitations, these results reinforce the capacity of PN and its component parts to support and promote the growth of a major pathogen—*C. albicans.* Our results indicate that touch contamination of all-in-one PN or IVFE IVAS causes minimal growth for up to 30 hours but then exponential and potentially harmful growth from 2 days onward. Our findings support the current recommendations that IVASs used to infuse saline and other fluids can be used for longer periods, but that IVASs used for PN and IVFE benefit from replacement after 24 hours to remove infusions that may have been contaminated in the previous 24-hour period.[4,6-8]

Skin microbiota is made up of many micro-organisms that can be commensals, mutualistic (when both organisms benefit from the interaction), or pathogenic. Some micro-organisms, such as *P. aeruginosa*, can inhibit the growth of *Staphylococcus* and *Candida* but can themselves become pathogenic. Today, most PN is manufactured commercially rather than in hospital pharmacies, which has contributed to a reduction in infusate colonization and consequently CLABSI.[20,21] Therefore, the contaminating pathogens are usually extrinsic to the manufacturing processes. Pathogens are present on healthcare workers' hands, patient skin, and the environment. Consequently, impeccable infection prevention practices are required when handling the IVAS. If this could be guaranteed, clinicians may not need to replace IVASs containing IVFE every 24 hours, but unfortunately this is difficult to achieve consistently. If hand hygiene and decontamination of needleless connector practices are impeccable, then it may be safe to extend the frequency of IVAS replacement for PN containing IVFE beyond 24 hours. Infection control, VAD, and nutrition guidelines could advocate the requirement for increased vigilance in infection prevention practices when replacing IVAS for all-in-one PN and IVFE and replacing these IVASs when a patient develops signs of sepsis (pyrexia, tachycardia, tachypnoea, hypotension, oliguria). Replacing the all-in-one PN and IVFE IVAS, and any additional IVAS connected to the same lumen, in this clinical scenario would remove any potentially colonized IVASs and prevent further colonization of the CVAD.

Ullman and colleagues[8] undertook a Cochrane Review examining the optimal timing for IVAS replacement. A total of 8 randomized controlled studies were reviewed, and 5 studies adequately described whether participants had received PN to undertake a subgroup analysis. Patients receiving PN were more likely to develop catheter-related bloodstream infections if their IVAS were replaced less frequently (risk ratio 1.25; 95% CI, 0.12–12.91; $P = .85$), although the confidence intervals were wide and the comparison underpowered to statistically detect clinically important differences. Only 1 small study[12] ($n = 52$) focused solely on patients receiving PN, and this was considered at high risk of bias due to lack of description of the random sequence generation or allocation concealment methods, and more patients were randomized to the experimental group.

Our study provides new and valuable data that confirms the merit and ethical utility of laboratory studies as an important step prior to conducting randomized controlled trials on infection endpoints. We have developed an effective dynamic IVAS model that can be used in future infection prevention studies to examine the initial effect of new devices or practices on colonization of the IVAS, CVAD, and CLABSI risk.

With regard to other fluids such as sodium chloride, our data suggest that even the current recommendation for 4-day to 7-day IVAS replacement is conservative and that routine replacement could safely occur every 7 days because we observed effectively no growth during the 7-day experiment. In the Cochrane Review,[8] there was no statistically significant difference in catheter-related bloodstream infections for patients not receiving PN who had their IVAS replaced less frequently (risk ratio 0.65; 95% CI, 0.13–3.23; $P = .60$). Our results are consistent with this lack of effect. We believe it is important that an adequately large, good-quality randomized controlled trial examines the safety of reducing the frequency of routine IVAS replacement for non-IVFE infusions.

The static experiments and dynamic IVAS model were used to evaluate the likely migration of micro-organisms in the context of poor hand hygiene and aseptic nontouch technique during clinical practice and to question the effectiveness of restricting PN containing IVFE to 24 hours. This dynamic IVAS model could be developed further to incorporate surface conditioning to examine the development of biofilms on the distal needleless connector and how this community is disrupted during continuous IV infusion and routine flushing. It could not account for additional patient factors such as immune suppression, exposure to antimicrobial therapy, or migration from the gastrointestinal tract into the bloodstream and to the VAD. There is a need for further research in the clinical environment to understand the interplay between PN, poor practice, and patient factors, and this would provide robust evidence for clinical practice guidelines. One such clinical question that requires answering with definitive evidence is the use of filters in PN administration. Such models are vital because it is not possible to undertake these experiments in the clinical setting or knowingly expose patients to suboptimal care. This model thus provides important evidence on the potential impact of poor hand hygiene and aseptic nontouch technique practices by healthcare workers. Research conducted using models can inform studies that examine current practice or new techniques and thus provide data to safely translate knowledge from the laboratory bench to patient bedside and ultimately inform policy and practice.

We have undertaken experiments under static conditions and then established and validated a dynamic IVAS model to evaluate the migration of micro-organisms known to cause CLABSI in the context of poor hand hygiene and aseptic nontouch technique during clinical practice, particularly with PN and IVFE. We have provided evidence that clinicians should follow the current guidelines to replace IVAS containing all-in-one PN and IVFE every 24 hours until the safety of prolonging IVAS replacement is confirmed by randomized controlled trials. Additional educational campaigns are needed to reinforce to healthcare workers and patients the high risk of *Candida* growth in these infusions.

Acknowledgments

The bacterial samples were collected from the following 2 National Health and Medical Research Council–funded clinical trials: (1) Intravascular Device Administration Sets: Replacement After Standard Versus Prolonged Use: The RSVP Trial (APP1008428) and (2) Securing All intraVenous devices Effectively in Hospitals: The SAVE Trial (APP1041910). The fungal sample was collected from the Central Pathology Laboratory at the Royal Brisbane and Women's Hospital, Queensland Pathology. Many thanks to Marie Greco, medical illustrator at the Clinical Multimedia Unit, Royal Brisbane and Women's Hospital, for the figure of the intravenous administration set model.

Statement of Authorship

N. Gavin, D. McMillan, S. Keogh, M. A. Choudhury, and C. M. Rickard contributed to conception and design of the research. N. Gavin, D. McMillan, S. Keogh, M. A. Choudhury, G. Ray-Barruel, and C. M. Rickard contributed to acquisition, analysis, or interpretation of the data. N. Gavin drafted the manuscript. D. McMillan, S. Keogh, M. A. Choudhury, G. Ray-Barruel, and C. M. Rickard critically revised the manuscript. N. Gavin, D. McMillan, S. Keogh, M. A. Choudhury, G. Ray-Barruel, and C. M. Rickard agree to be fully accountable for ensuring the integrity and accuracy of the work. N. Gavin, D. McMillan, S. Keogh, M. A. Choudhury, G. Ray-Barruel, and C. M. Rickard read and approved the final manuscript.

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