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Growth of Staphylococcus aureus *in Diprivan and Intralipid*

Implications on the Pathogenesis of Infections

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Background: **The incidence and severity of infections are increased when Intralipid or Diprivan are administered to patients. Intralipid promotes infection, presumably by inhibiting the reticuloendothelial system, thereby suppressing the host's constitutive immunity, whereas Diprivan supposedly promotes infection by supporting bacterial growth and increasing the inoculating dose. This study considers whether bacterial replication alone in Intralipid and Diprivan adequately explains the increased risk of infection associated with these agents or whether other factors might also be involved.**

Methods: ***Staphylococcus aureus*** **was cultured in 10% Intralipid or Diprivan at clinically relevant conditions or in Intralipid containing 0.005% (w/v) sodium EDTA, a current additive, to measure growth. To determine whether Intralipid affected infection, New Zealand white rabbits were injected intravenously with *S. aureus* with or without Intralipid. Twenty-four hours later, bacteria in lung, liver, spleen, and kidney tissues were enumerated.**

Results: ***S. aureus*** **failed to grow in Diprivan or Intralipid containing 0.005% EDTA. Whereas *S. aureus* did replicate in plain Intralipid, growth was delayed until the bacteria conditioned the media. Once initiated, growth was slow at clinically relevant temperatures. The administration of Intralipid to rabbits significantly increased the recovery of staphylococci from the kidneys, $P < 0.001$, relative to the other tissues 24 h after an intravenous inoculation with *S. aureus,* compared with rabbits receiving *S. aureus* with no Intralipid.**

Conclusions: **These results suggest that Diprivan, and possibly Intralipid, represent poor media for the growth of *S. aureus* and may promote infection through mechanisms other than increased inoculum size. (Key words: Bacterial growth; culture; temperature; propofol.)**

IN 1991, six months after gaining the approval of the Food and Drug Administration, Diprivan (Zeneca, Wilmington, DE; a preparation of propofol, in a 10% Intralipid vehicle [Abbott Laboratories, Abbott Park, IL]) was implicated in several staphylococcal and fungal infections reported from four geographically separate areas of the United States.[1] Supplies of Diprivan from the manufacturer were found to be sterile, but lapses in sterile technique during preparation of the drug for administration were documented by the Centers for Disease Control (CDC).[1] *In vitro* growth studies showed that low inocula of *Staphylococcus aureus* (10-100 colony forming units [CFU]/ml) replicated in Diprivan at 34°C, reaching concentrations of 10^5 or 10^6 CFU/ml in 24 h.[1] It was therefore assumed that Diprivan had served as a growth medium for the bacteria, resulting in the administration of overwhelming numbers of microorganisms to patients. However, the number of bacteria in Diprivan at the time of its administration has never been determined, and there is some evidence that bacterial replication in Diprivan is limited in clinical settings.

Diprivan uses a 10% emulsion of Intralipid as a vehicle for the anesthetic propofol, and Intralipid itself is associated with a significantly increased risk of staphylococcal and fungal infections in pediatric[2,3] and adult[4-7] populations when used for parenteral nutrition. The

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most commonly implicated organisms in infections related to Intralipid are *S. aureus*[1-3] and fungi, in particular, *Candida albicans*,[1,5] particularly when there is direct contact between Intralipid and the microbe.[2-8] This association seems to hold whether Intralipid is given for parenteral nutrition or as a component of Diprivan.

The increased incidence of infection after the administration of Intralipid has been attributed to a depression of reticuloendothelial function.[9-11] In an effort to describe how Intralipid impedes the constitutive immunity of the host, the effects of Intralipid on phagocytosis,[9-13] chemotaxis,[14,15] and oxidative function[9,16] were evaluated. The influences of Intralipid on bacterial killing[9,15] and inhibition of lymphocyte blastogenesis to specific antigens[16] also were studied.

Suppressed reticuloendothelial function and a generalized depression of the innate immunity of the host would be expected to result in diverse infections from the many organisms encountered by patients in the hospital. Yet *S. aureus* and *C. albicans* remain the leading infectious agents associated with Intralipid and Diprivan, accounting for a disproportionate number of infections. Hence, divergent hypotheses have been suggested as explanations for what may be a common phenomenon. As a result, infection control measures may not be aimed at the most relevant factors in Diprivan- and Intralipid-associated infections.

These studies were conducted to determine whether *S. aureus* would grow in Intralipid or Diprivan sufficiently during clinically relevant conditions to reach overwhelming numbers. We also evaluated whether Intralipid could promote systemic infection by *S. aureus* in a rabbit model. The formulation of Diprivan was changed in 1994 when 0.005% (w/v) sodium EDTA was added to the product. Because many studies that investigated these issues were conducted before 1994, we also used Intralipid with and without 0.005% sodium EDTA in our experiments.

Methods

Preparation of Bacteria

S. aureus isolated from a wound, and strain 17, which was used in the original growth studies reported by the Centers for Disease Control,[1] were used in these experiments. Bacteria were maintained in L broth (LB) or on L agar (containing 1.5% [w/v] agar). Stock cultures were stored at −70°C in LB containing 35% (v/v) glycerol. Bacteria were incubated in LB at 37°C overnight without agitation, and the next morning a 1-ml aliquot was inoculated into 24 ml fresh LB and grown at 37°C with agitation for approximately 4 h to ensure that the bacteria were growing exponentially. Bacterial density was then estimated by optical density at 600-nm wavelength. The *S. aureus* culture was centrifuged at 13,800*g* for 10 min at ambient temperature, and the bacterial pellet was suspended in 25 ml phosphate-buffered saline with 0.01% (w/v) gelatin. Serial dilutions of the bacteria were made to achieve appropriate concentrations of bacteria. A 0.1-ml aliquot was plated to measure the CFU/ml.

Effects of Temperature on Growth of S. aureus *in Intralipid and Diprivan*

To determine the effect of temperature on the growth kinetics of *S. aureus*, 25 ml Intralipid, Diprivan, or LB was inoculated with 0.1 ml phosphate-buffered saline with 0.01% (w/v) gelatin containing 500–1,500 CFU of *S. aureus*. The lipid cultures (Intralipid and Diprivan) were incubated at clinically relevant temperatures 16°C and 17.5°C (operating room temperatures), 22.5°C (ambient temperature), or 30°C (previous methods of others) for 24 h. These cultures were maintained in 50-ml plastic conical centrifuge tubes with the lids loosely closed to simulate the environmental conditions of clinical infusions. To determine the number of viable bacteria, 0.1 or 0.2 ml of the cultures, or appropriate dilutions thereof, was plated in duplicate at frequent intervals for up to 24 h.# We compared the growth rate of *S. aureus* in Intralipid and Diprivan with the growth rate in the rich medium LB at each temperature. Repetitions were performed for each experiment to ensure that growth counts were consistent and reproducible.

Analysis of the Lag Period after Transfer of Exponential Cultures in Intralipid

To evaluate the extended lag phase in the growth of *S. aureus* in lipids compared to LB, *S. aureus* was grown in LB to achieve an exponential growth phase, as described previously. A 0.1-ml suspension (10^5 CFU/ml) of *S. aureus* in phosphate-buffered saline was added to 25 ml Intralipid (10^2 CFU final concentration) and incubated at 22.5°C. Every 2 h for 12 h and then at 4-h intervals up to 48 h, 0.5 ml Intralipid culture was sampled for CFU, as described previously. Twenty-four hours after inoculation, a sample of the first culture was mixed with an equal volume of saline and was vortexed vigorously for 5 min to disperse the bacteria, and 0.5 ml was trans-

Duplicate plates were made to ensure that bacterial counts were accurate.

ferred to 35 ml Intralipid to yield a bacterial concentration of approximately 10^3 CFU/ml. Bacterial growth in the second culture was measured by frequent plating, as described previously.

To determine whether limiting carbon dioxide in the Intralipid growth media contributed to the observed lag phases, Intralipid containing 0, 10, and 100 mM sodium bicarbonate was prepared by adding 8.4% (w/v) sodium bicarbonate to the second cultures. Because the bicarbonate solution contributed less than 1% of the final volume of the culture, Intralipid was not diluted appreciably.

Effects of Intralipid on Rabbit Infection with S. aureus

After approval was obtained from the University of Florida's Institutional Animal Care and Use Committee, male New Zealand white rabbits (3.0 kg) were injected intravenously *via* the ear vein with 5×10^7 CFU *S. aureus* suspended in 1 ml Intralipid (n = 6) or saline (n = 6). A third group of animals (n = 6) was injected intravenously with 1 ml Intralipid 1 min before intravenous injection of 5×10^7 CFU *S. aureus* suspended in saline. Serial blood samples were obtained from the contralateral ear vein immediately before, immediately after, and at 1, 5, 10, 20, 60, and 120 min after inoculation. Intravenous cannulae were removed from the ears, and the animals were returned to their cages and given free access to food and water. Twenty-four hours after inoculation, the rabbits were anesthetized, and biopsies of the liver, lung, spleen, and kidneys were obtained. The tissues were weighed, homogenized in 5 ml phosphate-buffered saline with 0.01% (w/v) gelatin at 4°C, and 0.1 ml was plated for quantitative colony count. The remainder of the sample was stored at 4°C for further dilution or concentration to quantify CFU.

Statistical Analysis

Bacterial Growth. We measured and analyzed the doubling time during the exponential phase of growth and the minimal lag period necessary before exponential growth occurred. The minimum lag period was defined as the time preceding the first statistically significant doubling of CFU/ml after inoculation. The doubling time during exponential phase growth was determined by plotting the $\log_{10}$ CFU/ml *versus* time and identifying that portion of the growth curve after the lag phase when at least three points formed a line. Linear regression was used to determine the slope of that line, and the slope was transformed to a doubling time. When more than three points could be chosen to determine the line, and therefore the doubling time (slope), the three points along the line with the highest correlation coefficient were used.

Distribution of S. aureus *in Tissues of Rabbits*

The data for the number of bacteria recovered from tissues 24 h after inoculation are presented as the "Infection Index." Animals received slightly different numbers of *S. aureus* (1.5×10^7-1.5×10^8 CFU), and the weight of the rabbits varied by approximately ± 400 g. To normalize for these factors, we present the data as the Infection Index (recovered CFU/g of tissue)/(inoculated CFU/g body weight). Repeated-measures analysis of variance was performed comparing the vehicle (saline *vs.* Intralipid *vs.* Intralipid pretreatment) and number of bacteria recovered from tissues (liver, spleen, lung, and kidney) after performing a log transformation with the raw data to stabilize variance. The Tukey multiple pair-wise comparison procedure was used to maintain an experiment-wise significance level of 0.05 for pair-wise comparisons among means.

Results

Growth of S. aureus *in Intralipid from L Broth*

The doubling times of both *S. aureus* strains in LB at 37°C were similar: approximately 27 min. When exponential phase LB cultures at 37°C were diluted into fresh LB, there was no lag phase. We then evaluated the growth kinetics of *S. aureus* in Intralipid at various temperatures (fig. 1, table 1). Growth kinetics of *S. aureus* PL001 and strain 17 were similar; we present only our most complete data from PL001. Growth in Intralipid was highly erratic, with many experiments failing to achieve replication at any temperatures; we present only those data from the experiments in which the most reproducible and rapid growth occurred. Lag phases were generally longer and growth rates were slower at lower temperatures. At 16°C, the temperature of our operating rooms, there was no net growth even 25.5 h after inoculation of Intralipid.

At 30°C, lag phases ranged from 3 h to 6 h (≤ 4 h for 8 of 12 runs), during which there was a decrease in CFU/ml. After this lag period, there was a rapid increase in CFU/ml over the next 2 h, which was not sustained (fig. 1). Cultures then settled into a net doubling time of 3.0 ± 0.4 h (fig. 1). Although it appears that the staphylococci replicated more rapidly at 22.5°C than at 30°C

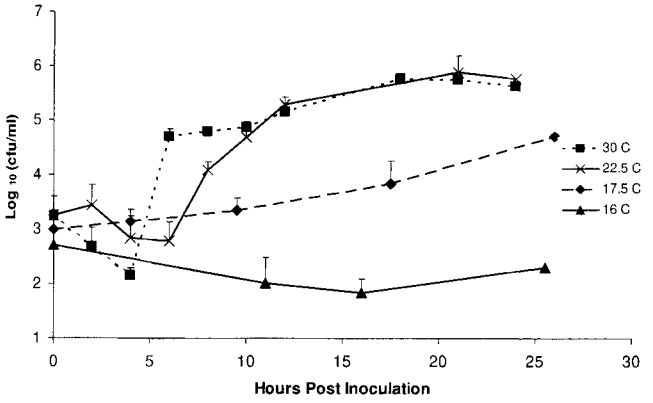

Fig. 1. Growth of *S. aureus* PL001 in Intralipid at various temperatures. Bacteria were grown to exponential phase in L broth, suspended in phosphate-buffered saline with 0.01% (w/v) gelatin, and then inoculated into Intralipid at the indicated temperatures. Initial bacterial concentrations for the representative experiments shown were approximately 10^3 CFU/ml. Intralipid cultures were sampled at various times, diluted, and plated to enumerate CFU/ml.

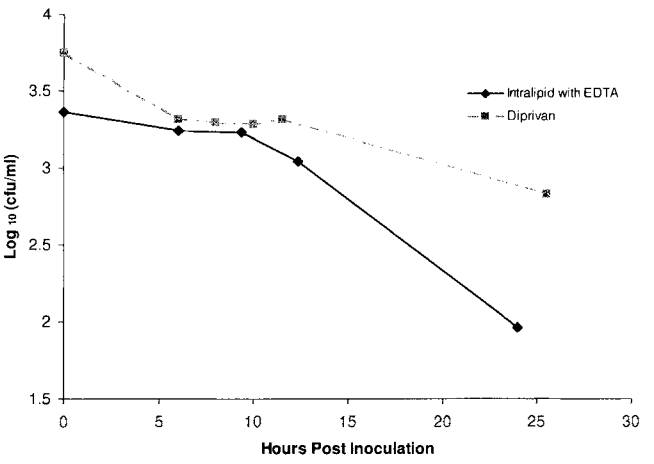

Fig. 2. Lack of growth of *S. aureus* PL001 in Diprivan or Intralipid containing 0.005% EDTA. Bacteria were grown to exponential phase in L broth, suspended in phosphate-buffered saline with 0.01% (w/v) gelatin, and then inoculated into Diprivan or Intralipid containing 0.005% EDTA at 22.5°C. Initial bacterial concentrations for the representative experiments shown were between 10^3 and 10^4 CFU/ml. Cultures were sampled at various times, diluted, and plated to enumerate CFU/ml.

(table 1), it should be noted that the maximal cell densities in Intralipid at 22.5°C and 30°C were attained with roughly the same kinetics (fig. 1). We therefore reported the sustainable doubling times.

Growth of S. aureus *in Diprivan and Intralipid Plus 0.005% Sodium EDTA from L Broth*

We consistently observed a steady drop in the CFU/ml of *S. aureus* in the current preparation of Diprivan at all temperatures (22.5°C is shown in fig. 2). We added 0.005% sodium EDTA to Intralipid, and, at all temperatures studied, the addition of EDTA to Intralipid abolished its ability to serve as a growth medium for *S. aureus* (data for 22.5°C are shown in fig. 2).

Analysis of Secondary Lag Phases in Intralipid Cultures

When 24-h Intralipid cultures of *S. aureus* growing exponentially at 22.5°C were transferred to fresh Intralipid at a 1:50 dilution, we observed a second lag phase of at least 8 h (fig. 3). Secondary lag phases were not observed at transfer of *S. aureus* cultures from LB to LB at 37°C, and only a 20-min lag in bacterial growth occurred at 22.5°C for LB (data not shown).

Because the initial growth of bacteria in poor media can be limited by the availability of carbon dioxide, which is involved in lipid metabolism, we precondi-

Table 1. Summary of Growth Kinetics in Intralipid

	17.5°C (n = 8)	22.5°C (n = 9)	30°C (n = 12)
Doubling time (h) (±SD)	5.22 ± 0.48	1.54 ± 0.34	3.00 ± 0.36
Minimum lag time (h) (range)	4–8	3–8	3–6

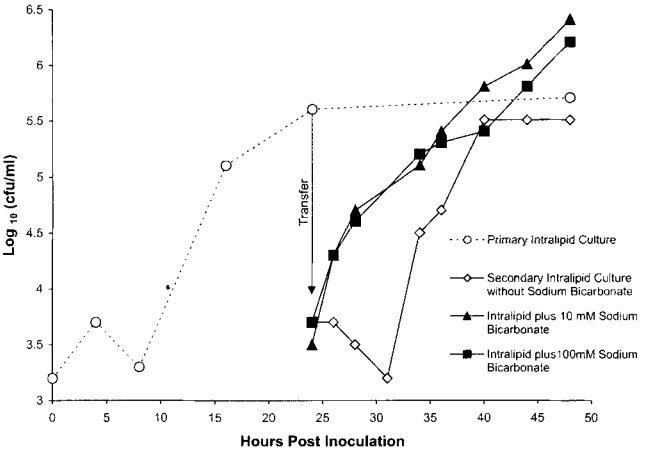

Fig. 3. Analysis of lag phase during transfer of *S. aureus* from exponential growth in Intralipid to fresh Intralipid. The primary culture of *S. aureus* in Intralipid was prepared as for figure 1. At 24 h postinoculation (arrow), when bacterial density was approximately 10^5 CFU/ml, a portion of the primary culture was diluted into secondary Intralipid emulsions containing 0, 10, or 100 mM sodium bicarbonate. Bacterial growth in all cultures was measured by dilution and plating. This figure is a representative curve for one run.

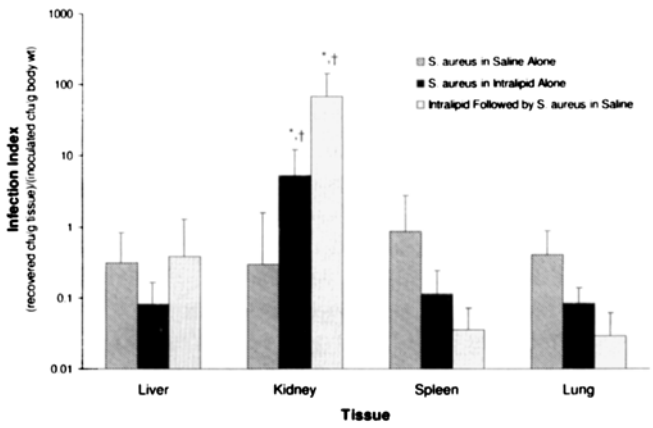

Fig. 4. Intralipid affects the tissue distribution of *S. aureus* in intravenously inoculated rabbits. Rabbits were injected intravenously during the following conditions: *S. aureus* in saline alone, *S. aureus* in Intralipid alone, or Intralipid followed immediately with *S. aureus* in saline. Twenty-four hours later, the rabbits were anesthetized, tissues were harvested, and bacterial CFU/g was enumerated by quantitative plating of homogenates. The data are represented as Infection Index [(recovered CFU/g tissue)/(inoculated CFU/g body weight)] to compensate for slightly different inocula and body weights of rabbits. *Infection Index for kidneys from both Intralipid-treated groups were not significantly different from each other, but were †significantly different ($P < 0.0001$) from kidneys in the absence of Intralipid.

tioned the second Intralipid culture with sodium bicarbonate as a source of carbon dioxide. The addition of 10 or 100 mM bicarbonate eliminated the lag phase during transfer from the initial Intralipid culture (fig. 3).

Effects of Intralipid on Infection of Rabbits

When bacteria were suspended in saline and rabbits received no Intralipid, bacteria were recovered from the spleen, liver, lung, and kidney equally (fig. 4). In the presence of Intralipid, the distribution of the bacteria 24 h postinoculation was shifted to the kidneys ($P < 0.0001$). This was true whether the animal received the Intralipid immediately before or simultaneously with the bacteremia.

Discussion

Before Intralipid- and Diprivan-associated infections can be effectively controlled, the basis for the infections must be understood. Recent studies have focused on the ability of Diprivan to serve as a growth medium for bacterial pathogens,[17-20] but these studies have not always evaluated bacterial growth at clinically relevant temperatures. We therefore measured the replication of *S. aureus* in Diprivan and Intralipid at clinically relevant temperatures of 16°C and 17.5°C (operating room temperatures), 22.5°C (ambient temperature), and 30°C to mimic previous studies by others.[17,21] We did not observe replication of *S. aureus* in Diprivan at any of these temperatures (fig. 2). Because previous reports from other laboratories described replication of *S. aureus* in Diprivan,[1,17-19] and because the formulation of Diprivan was changed in 1994 to include 0.005% w/v sodium EDTA, we used Intralipid without EDTA and with 0.005% EDTA added as an approximation of the original preparation and its reformulation.

In Intralipid, we observed a temperature-dependent lag phase before bacterial replication, followed by slow and erratic growth (table 1 and fig. 1). The extended lag phase after inoculation of *S. aureus* into Intralipid is consistent with data from Crocker *et al.*,[22] who reported a colony count equal to the inoculating dose after 6 h of incubation in Intralipid at 25°C. Sosis and Braverman[19] grew *S. aureus* in Diprivan (before 1994) at 27°C and found that the bacteria had not doubled after 6 h, whereas Tessler *et al.*[18] showed that *S. aureus* had not doubled 8 h after inoculation in Diprivan at 25°C. Arduino *et al.*[17] similarly reported growth curves showing lag periods exceeding 6 h at 30°C. One study showed almost immediate growth by *S. aureus* at 20°C,[20] but the bacteria were not removed from their initial growth medium before inoculation in Diprivan, which could have precluded a lag phase because the bacteria essentially were in dilute broth. Hence, our data are consistent with virtually all previous studies with respect to the presence and duration of the lag period.

Once initiated, *S. aureus* grows poorly in Intralipid. Our studies reveal a doubling time of 1.5 h at 22.5°C. Crocker *et al.*[22] and Mally *et al.*[21] reported doubling times of nearly 3 h for *S. aureus* in Intralipid at 25°C, whereas Arduino *et al.*[17] showed that the doubling time of *S. aureus* in Diprivan (before 1994) was approximately 2 h at 30°C. Our shorter doubling times undoubtedly arise from the manner in which they were calculated. Unlike previous investigations, we did not simply average the doubling time over 24 h. Rather, we chose three time points after the lag period from which to generate a regression line with the highest correlation coefficient and used the slope of that line to compute the doubling time for the most rapid and sustainable growth period.

Lag phases occur either because the bacteria must adjust to the media or because the bacteria must alter the media. During transfer of *S. aureus* from exponentially growing Intralipid cultures into fresh Intralipid, the lag

phase recurred (fig. 3). Because the staphylococci were adapted to Intralipid and were growing exponentially before transfer, we suspected this second lag phase occurred while the bacteria conditioned the medium before exponential growth ensued. Bacteria need a finite concentration of carbon dioxide to grow because carbon dioxide is a nonconsumed reactant of lipid metabolism.[23] We postulated that the growth of *S. aureus* might be limited until sufficient carbon dioxide accumulated in the medium from bacterial metabolism to allow the bacteria to enter the exponential growth phase. We tested this hypothesis by adding sodium bicarbonate to provide an immediate source of carbon dioxide to Intralipid. Addition of bicarbonate nearly abolished the lag period during transfer from a primary Intralipid culture in exponential phase of growth to fresh Intralipid (fig. 3).

Our data show a lag period in excess of 6 h, a doubling time of 1.5 h at 22.5°C (5 h at 17.5°C), and a maximal concentration of approximately 1×10^6 CFU/ml, which is consistent with four previous studies that evaluated the growth of *S. aureus* in Intralipid and Diprivan before its reformulation in 1994.[1,17,20–22] These data suggest that contamination of Diprivan with small numbers of staphylococci should not create an overwhelming inoculum for patients, either in the operating room or in other hospital units. Interestingly, the manufacturers of these products recommend that the drugs be administered within 6 h of preparation, presumably to prevent potential microbial replication from reaching clinically significant levels.[24]

The original report of Diprivan-related infections stated that the same syringe of Diprivan was used throughout the day in the operating room.[1] In none of the cases was the syringe held overnight and used the following day. If the lag phase for growth is at least 6 h (certainly longer at typical operating room temperatures of 16°C to 17.5°C), and the doubling time is more than 4 h, it is difficult to understand how the bacteria could have multiplied over the original contamination to more readily infect patients. Furthermore, the Centers for Disease Control documented that all of the cases were related to the use of 60-ml syringes in syringe pumps. Even if the patients were small (50 kg) and the infusion rates necessary were low ($100\ \mu g \cdot kg^{-1} \cdot min^{-1}$), the syringe would have to be refilled every 2 h. Our data indicate that *S. aureus* grows poorly during transfer to fresh Intralipid. Therefore, adding fresh Diprivan to a syringe, analogous to diluting the remaining bacteria, should result in another extended lag period.

The possibility of the Intralipid in Diprivan affecting the host was evaluated using a rabbit model for staphylococcal infection. Equal doses of *S. aureus* suspended in either Intralipid or saline were administered to rabbits intravenously and were cleared from the blood equally well (in less than 10 min). However, rabbits given *S. aureus* in Intralipid appeared to become more ill, more rapidly than those who received the bacteria in saline. Although this observation was qualitative only, the quantitative distribution of bacteria differed significantly when rabbits were exposed to Intralipid (fig. 4). In the absence of Intralipid, *S. aureus* delivered in saline was recovered about equally from reticuloendothelial tissues (liver and spleen), lung, and kidney, whereas *S. aureus* delivered in either Intralipid or in saline 1 min after pretreatment of rabbits with Intralipid was primarily recovered from the kidney (fig. 4). It is conceivable that *S. aureus* delivered with Intralipid may be preferentially distributed to the kidney rather than to tissues in which they would normally be destroyed. If this is true, then bacteria may escape destruction *in vivo* and compromise the animal from a relatively sequestered nidus. It is interesting to note that Curry and Quie[25] also reported that bacteria were recovered most often from the kidneys of patients who had infection after the administration of Intralipid, although these cultures were obtained postmortem.

Based on our data, we question whether simple bacterial multiplication to increase the inoculating dose can adequately explain the increased incidence of infection associated with the clinical use of Diprivan or Intralipid. Other investigators also have questioned how well bacteria actually grow in Diprivan during clinical conditions;[26] yet many practitioners simply use Diprivan immediately after it is prepared before growth can occur, believing this will alleviate the potential for infection. Our findings strongly suggest that Intralipid affects the distribution of the bacteria *in vivo* and by doing so potentially increases their virulence. How the altered distribution of bacteria contributes to the risk of infection associated with Intralipid and Diprivan is not known. Nevertheless, the results of our studies suggest that changing the means by which lipid-based infusions are handled before administration may not entirely solve the problem of the infections associated with the use of these agents. Further studies in specific pathogen-free rabbits are needed to evaluate this completely. In the mean time, greater care may be needed for general infection control in patients receiving these infusions, because the host defenses or some other aspect of the

host-pathogen relationship may be disturbed by Intralipid and Diprivan.

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